NATIONALE VERSORGUNGS LEITLINIEN

Nationale VersorgungsLeitlinie

Hypertonie

Recherchedokumentation + Evidenztabellen

Version 1.0

AWMF-Register-Nr. nvl-009

Träger:

Bundesärztekammer

Kassenärztliche Bundesvereinigung

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

BUNDESÄRZTEKAMMER KBV AWMF

Inhaltsverzeichnis

1 Recherchestrategien

1.1 Leitlinien

Leitlinienrecherche AWMF

Die Leitlinien-Recherche in der Datenbank der AWMF wurde am 10.03.2020 vom Ärztlichen Zentrum für Qualität (ÄZQ) durchgeführt. Es wurden Leitlinien mit Schnittstellen zum Thema „Hypertonie“ gesucht. Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und unter Recherchestrategien dargelegt.

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

Suchdatum: 10.03.2020
Leitliniensuche unter www.awmf.org/leitlinien/leitlinien-suche.html nach „Hypertonie“
Treffer: 198
Davon relevant: 3 (195x thematisch nicht passend)

Name	Register-nummer	Status	Gültigkeit	Hypertonierelevante Themen	Link
Erkrankungen der Nierenarterie	004 - 008	S2k	29.11.2022	Sekundäre Hypertonie - Nierenarterienstenose > Diagnostik > Therapie	https://www.awmf.org/leitlinien/detail/ll/004-008.html
Hausärztliche Risikoberatung zur kardiovaskulären Prävention	053-024	S3	30.12.2021		https://www.awmf.org/leitlinien/detail/ll/053-024.html
Schlaganfall: Sekundärprophylaxe ischämischer Schlaganfall und transitorische ischämische Attacke	030-133	S3	30.01.2020	Kapitel 4 - Besserung MACE durch antihypertensive Therapie nach Schlaganfall - Zielwerte nach Schlaganfall - Zielwerte nach Schlaganfall + Diabetes	https://www.awmf.org/leitlinien/detail/ll/030-133.html

1.2 Gezielte Recherche

Epidemiologische Daten im Deutschen Versorgungskontext

RKI: DEGS, GEDA EHIS 2014/15

Versorgungsatlas

Nationale Kohorte: keine Publikationen zur Epidemiolgie der Hypertonie identifiert, bisher (Stand:05.04.2020) Publikation zur Methodik der Blutdruckmessung vorhanden:

- Jaeschke, L., Steinbrecher, A., Greiser, K.H. et al. Erfassung selbst berichteter kardiovaskulärer und metabolischer Erkrankungen in der NAKO Gesundheitsstudie: Methoden und erste Ergebnisse. Bundesgesundheitsbl 63, 439–451 (2020).
- Schikowski, T., Wigmann, C., Fuks, K.B. et al. Blutdruckmessung in der NAKO – methodische Unterschiede, Blutdruckverteilung und Bekanntheit der Hypertonie im Vergleich zu anderen bevölkerungsbezogenen Studien in Deutschland. Bundesgesundheitsbl 63, 452–464 (2020). https://doi.org/10.1007/s00103-020-03109-8

Zitat	Erhebung	Datenbasis	Maßzahlen
Neuhauser H, Kuhnert R, Born S. 12-Monats-Prävalenz von Bluthochdruck in Deutschland. Journal of health monitoring 2017; 2(1):57–63. [1]	GEDA-EHIS 2014/15	Querschnittstudie Befragungssurvey	12-Monatsprävalenz
Neuhauser H, Sarganas G. Hoher Blutdruck: Ein Thema für alle. GBE kompakt 2015; 6(4):1–10. [2]	DEGS 1 BGS 1998	Quer- und Längsschnitterhebung Untersuchungssurvey	Punktprävalenz
Holstiege J, Akmatov MK, Steffen A, et al. Diagnoseprävalenz der Hypertonie in der vertragsärztlichen Versorgung – aktuelle deutschlandweite Kennzahlen. 2020 (Versorgungsatlas-Bericht; Nr. 20/01) [cited: 2020-03-26]. [3]	Sekundärdatenanalyse	vertragsärztliche Abrechnungsdaten	Diagnoseprävalenz

1.3 strukturierte Recherche (2019)

PICO-Frage

P erwachsene Patienten mit arterieller Hypertonie

I jegliche diagnostische, medikamentöse, nicht medikamentöse Intervention

C jeglicher diagnostische, medikamentöse, nicht medikamentöse Vergleich

O muss in Auftaktsitzung priorisiert werden

S systematische Übersichtsarbeiten, HTA

Z keine Einschränkung

Datenbanken der Cochrane Library (08.10.2019)

Nr.	Suchfrage	Anzahl
#12	**#10 in Cochrane Protocols**	**43**
#11	**#10 in Cochrane Reviews**	**566**
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9	92149
#9	#7 AND #8	23591
#8	((high OR elevat* OR rais*)):ti,ab,kw (Word variations have been searched)	299394
#7	("blood pressure"):ti,ab,kw (Word variations have been searched)	85144
#6	MeSH descriptor: [Blood Pressure] explode all trees	26865
#5	(antihypertens*):ti,ab,kw	18905
#4	(antihypertensive):ti,ab,kw (Word variations have been searched)	18800
#3	(hypertens*):ti,ab,kw	62117
#2	(hypertension):ti,ab,kw (Word variations have been searched)	62097
#1	MeSH descriptor: [Hypertension] explode all trees	16863

Cochrane Reviews • Review • Protocol	 566 43

NICE (09.09.2019)

Nr.	Suchfrage
Suchbegriffe	hypertension OR blood pressure

Nr.	Suchfrage
Suchzeitraum	Keine Einschränkung
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	356
Eingeschlossene Treffer	3 - NICE guidance [NG136] mit 9 Evidence reviews The following documents contain the evidence that was used to develop the 2019 recommendations: • Diagnosis • Monitoring • Initiating treatment • Targets • Step 1 treatment • Step 2 and step 3 treatment • Step 4 treatment • Relaxation therapies • Same-day specialist review - Interventional procedures guidance [IPG533]: https://www.nice.org.uk/guidance/ipg533 - Interventional procedures guidance [IPG418]: https://www.nice.org.uk/guidance/ipg418
2. Filter	NICE advice
Treffer	140
Eingeschlossene Treffer	0
3. Filter	NICE pathways
Treffer	89
Eingeschlossene Treffer	1 (https://pathways.nice.org.uk/pathways/hypertension)

Anzahl der Treffer nach Titelscreening: 12

IQWiG (10.09.2019)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	Keine Einschränkung
Suchbegriff: Hypertonie	
Treffer	72
Eingeschlossene Treffer	11
Suchbegriff: Hypertonus	
Treffer	5
Eingeschlossene Treffer	0
Suchbegriff: Bluthochdruck	
Treffer	21
Eingeschlossene Treffer	0
Suchbegriff: hypertension	
Treffer	27
Eingeschlossene Treffer	0
IQWiG-Infodienst	

Nr.	Suchfrage
Suchbegriffe: Bluthochdruck, Hypertonie, Hypertonus	
Treffer	1
Eingeschlossene Treffer	0

Anzahl der Treffer nach Titelscreening: 11

Datenbanken der AHRQ (10.09.2019)

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	12	0
Technology Assessment Program (completed)		10	1
EPC Evidence-based	Hypertension	7	2
	Blood pressure	30	2

Anzahl der Treffer nach Titelscreening: 4

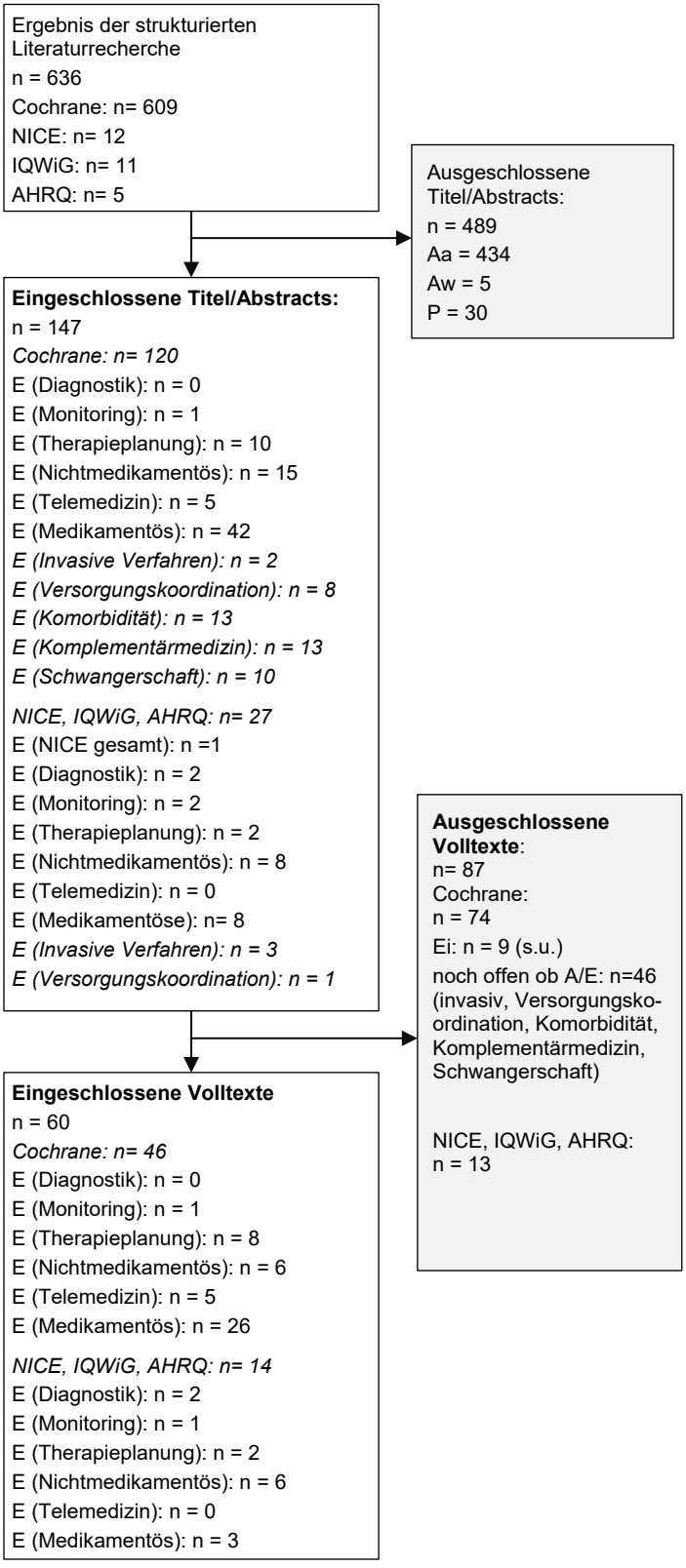
Übersicht der eingeschlossenen Treffer

Aggregierte Evidenz	Anzahl
Cochrane Datenbanken	609
NICE	12
IQWIG	11
AHRQ	4

Screening

E	PICO erfüllt
P	Protokoll
Aa	PICO nicht erfüllt
Aw	zurückgezogen
Z (TiAb)	Relevanz der Themen muss erst in LL-Gruppe geklärt werden - Primärprävention des art. Hypertonus oder - Primärprävention von CV-Erkrankungen oder - Perioperatives Management m.H.v Antihypertensiva bei heterogener Population
Z (VT)	Zurückgestellt, weil: - SR mit ähnlicher Fragestellung und aktuellerem Suchzeitraum und/oder besser methodischer Qualität vorliegend oder - PICO allenfalls indirekt passend, kann ggf. im Nachgang gesichtet werden: falls sich zum Thema eine Recherchefrage ergibt, kann z.B. die das Vorgehen des CR adaptiert werden oder von der AG erneut die Extrapolierbarkeit der Ergebnisse geprüft werden

Flowchart



*Hinweis: nicht alle Themen, die zunächst im Titel-Abstract-Screening eingeschlossen wurden, konnten 2019 für die Arbeitsguppenarbeit genutzt werden; diese Themen werden voraussichtlich zu einem späteren Zeitpunkt ergänzt

Ei: ausgeschlossene, interessante zusätzliche Treffer:

- Aung K. Thiazide diuretics and the risk of hip fracture. Cochrane Database Syst Rev 2011(10):CD005185. dx.doi.org/10.1002/14651858.CD005185.pub2. https://www.ncbi.nlm.nih.gov/pubmed/21975748.
- Bahiru E. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. Cochrane Database Syst Rev 2017; 3(3):CD009868. dx.doi.org/10.1002/14651858.CD009868.pub3. https://www.ncbi.nlm.nih.gov/pubmed/28263370.
- Diao D. Pharmacotherapy for mild hypertension. Cochrane Database Syst Rev 2012(8):CD006742. dx.doi.org/10.1002/14651858.CD006742.pub2. https://www.ncbi.nlm.nih.gov/pubmed/22895954.
- Lip GY. Antiplatelet agents and anticoagulants for hypertension. Cochrane Database Syst Rev 2011(12):CD003186. dx.doi.org/10.1002/14651858.CD003186.pub3. https://www.ncbi.nlm.nih.gov/pubmed/22161375.
- Lv J. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev 2012; 12(12):CD004136. dx.doi.org/10.1002/14651858.CD004136.pub3. https://www.ncbi.nlm.nih.gov/pubmed/23235603.
- Musini VM. Pharmacotherapy for hypertension in adults 60 years or older. Cochrane Database Syst Rev 2019; 6(6):CD000028. dx.doi.org/10.1002/14651858.CD000028.pub3. https://www.ncbi.nlm.nih.gov/pubmed/31167038.
- Musini VM. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Cochrane Database Syst Rev 2017; 8(8):CD008276. dx.doi.org/10.1002/14651858.CD008276.pub2. https://www.ncbi.nlm.nih.gov/pubmed/28813123.
- Taverny G. Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. Cochrane Database Syst Rev 2016; 3(3):CD011745. dx.doi.org/10.1002/14651858.CD011745.pub2. https://www.ncbi.nlm.nih.gov/pubmed/26961575.
- Wong GW. Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension. Cochrane Database Syst Rev 2014(11):CD007450. dx.doi.org/10.1002/14651858.CD007450.pub2. https://www.ncbi.nlm.nih.gov/pubmed/25427719.

1.4 strukturierte Recherche (Update 2021)

PICO-Frage Hypertonie

P erwachsene Patienten mit arterieller Hypertonie

I jegliche diagnostische, medikamentöse, nicht medikamentöse Intervention

C jeglicher diagnostische, medikamentöse, nicht medikamentöse Vergleich

O muss in Auftaktsitzung priorisiert werden

S systematische Übersichtsarbeiten, HTA

Z keine Einschränkung

Datenbanken der Cochrane Library (26.03.2021)

Nr.	Suchfrage	Anzahl
#11	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 in Cochrane Protocols (Filter ab 01/09/2019)**	**11**
#10	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 in Cochrane Reviews (Filter ab 01/09/2019)**	**97**
#9	#7 and #8	26020
#8	(high OR elevat* OR rais*):ti,ab,kw (Word variations have been searched)	325527
#7	("blood pressure"):ti,ab,kw (Word variations have been searched)	93273
#6	MeSH descriptor: [Blood Pressure] explode all trees	27658
#5	(antihypertens*):ti,ab,kw	19721
#4	(antihypertensive):ti,ab,kw (Word variations have been searched)	19602
#3	(hypertens*):ti,ab,kw	65746
#2	(hypertension):ti,ab,kw (Word variations have been searched)	65721
#1	MeSH descriptor: [Hypertension] explode all trees	18789

Cochrane Reviews	
• Review	97
• Protocol	11

NICE (15.03.2021)

Nr.	Suchfrage
Suchbegriffe	hypertension OR blood pressure
Suchzeitraum	from September 2019
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0

Anzahl der Treffer nach Titelscreening: 0

IQWiG (15.03.2021)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	09.2019-15.03..2021
Suchbegriff: Hypertonie	
Treffer	4
Eingeschlossene Treffer	0
Suchbegriff: Bluthochdruck	
Treffer	4
Eingeschlossene Treffer	0

Anzahl der Treffer nach Titelscreening: 0

Datenbanken der AHRQ (20.04.2021)

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen (2019-2021)	92	0*
Technology Assessment Program (completed)		3	0

Anzahl der Treffer nach Titelscreening:

*in progress: Screening for Hypertension in Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force Date: June 2020 EPC Type: In Progress EPC Name: AHRQ

Übersicht der eingeschlossenen Treffer

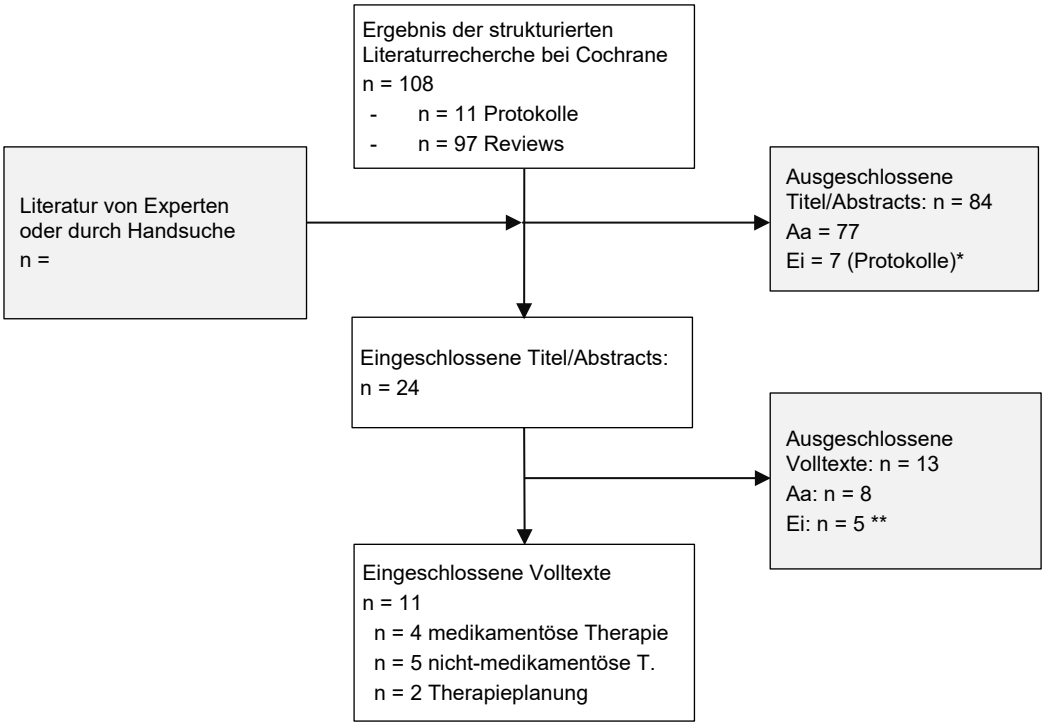
Aggregierte Evidenz	Anzahl
Cochrane Datenbanken	
NICE	0
IQWIG	0
AHRQ	0

Screening

E	PICO erfüllt
P	Protokoll
Aa	PICO nicht erfüllt

E	PICO erfüllt
P	Protokoll
Aw	zurückgezogen
Z	

Flowchart



*Hinweis: in der Suche in der Cochrane Datenbank fanden sich die folgenden Protokolle

- Lunny C. First-line drug classes for hypertension in adults: A network meta-analysis. Cochrane Database of Systematic Reviews 2020; 19(5):579. dx.doi.org/10.1002/14651858.CD013741.
- Luo HC. Blood pressure lowering efficacy of drugs inhibiting the renin-angiotensin system as second-line therapy for primary hypertension. Cochrane Database of Systematic Reviews 2020; 12(9):1053. dx.doi.org/10.1002/14651858.CD007188.pub2.
- Finizola RM. Pharmacotherapy for hypertension-induced left ventricular hypertrophy. Cochrane Database of Systematic Reviews 2019; 17(7):S0735-S1097. dx.doi.org/10.1002/14651858.CD012039.pub2.
- Doogue R. Self-monitoring for improving control of blood pressure in patients with hypertension. Cochrane Database of Systematic Reviews 2021; 57(1):29. dx.doi.org/10.1002/14651858.CD010311.pub2.
- Smart NA. Isometric exercise training for hypertension. Cochrane Database of Systematic Reviews 2020; 25(10):1360. dx.doi.org/10.1002/14651858.CD013803.
- Cameron M. Community and home-based exercise for the prevention and treatment of hypertension. Cochrane Database of Systematic Reviews 2020; 36(3):533. dx.doi.org/10.1002/14651858.CD013752.
- Bensaaud A. Dietary Approaches to Stop Hypertension (DASH) for the primary and secondary prevention of cardiovascular diseases. Cochrane Database of Systematic Reviews 2020; 141(8):1552. dx.doi.org/10.1002/14651858.CD013729.

**Hinweis: identifizierte interessante Arbeiten, die zunächst nicht den Einschlusskriterien entsprachen

Schwangerschaft/Monitoring Blutdruck

- Ashworth DC. Setting and techniques for monitoring blood pressure during pregnancy. Cochrane Database Syst Rev 2020; 8(8):CD012739. https://www.ncbi.nlm.nih.gov/pubmed/32748394.

Medikamentöse Therapie / Aldosteronantagonisten zusätzlich zu RAS – Vorbeugen einer verschlechterten Nierenfunktion

- Chung EY. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev 2020; 10(10):CD007004. https://www.ncbi.nlm.nih.gov/pubmed/33107592.

Medikamentöse Therapie / CCB bei Patient*innen mit dialysepflichtiger, chronischer Niereninsuffizienz

- Mugendi GA. Calcium channel blockers for people with chronic kidney disease requiring dialysis. Cochrane Database Syst Rev 2020; 10(10):CD011064. https://www.ncbi.nlm.nih.gov/pubmed/33000470.

Multimorbidität

- Smith SM. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2021; 1(1):CD006560. https://www.ncbi.nlm.nih.gov/pubmed/33448337.

Komplexe Interventionen (“community pharmacy”)

- Steed L. Community pharmacy interventions for health promotion: Effects on professional practice and health outcomes. Cochrane Database Syst Rev 2019; 12(12):CD011207. https://www.ncbi.nlm.nih.gov/pubmed/31808563.

Cochrane Evidence by topic: https://www.cochrane.org/search/site/hypertension?solrsort=ds_published+desc

1.5 strukturierte Recherche (Update 2022)

PICO-Frage

P	erwachsene Patienten mit arterieller Hypertonie
I	jegliche diagnostische, medikamentöse, nicht medikamentöse Intervention
C	jeglicher diagnostische, medikamentöse, nicht medikamentöse Vergleich
O	muss in Auftaktsitzung priorisiert werden
S	systematische Übersichtsarbeiten, HTA
Z	ab 26.03.2021

Datenbanken der Cochrane Library (26.03.2021 - 14.02.2022)

Nr.	Suchfrage	Anzahl
#11	**#10 ab 2021-03-26**	**42**
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 in Cochrane Reviews, Cochrane Protocols	692
#9	#7 and #8	27676
#8	(high OR elevat* OR rais*):ti,ab,kw (Word variations have been searched)	351616
#7	("blood pressure"):ti,ab,kw (Word variations have been searched)	98482
#6	MeSH descriptor: [Blood Pressure] explode all trees	28387
#5	(antihypertens*):ti,ab,kw	20484
#4	(antihypertensive):ti,ab,kw (Word variations have been searched)	20358
#3	(hypertens*):ti,ab,kw	69331
#2	(hypertension):ti,ab,kw (Word variations have been searched)	69303
#1	MeSH descriptor: [Hypertension] explode all trees	19463

Cochrane Reviews • Review • Protocol	 42 0

NICE (15.03.2021 - 14.02.2022)

Nr.	Suchfrage
Suchbegriffe	hypertension OR blood pressure
Suchzeitraum	from March 2021
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	2
Eingeschlossene Treffer	1#
2. Filter	NICE advice
Treffer	0
Eingeschlossene Treffer	0
2. Filter	NICE quality standard
Treffer	1

Anzahl der Treffer nach Titelscreening: 2#

- Hypertension in pregnancy Quality standard Published: 16 July 2013 www.nice.org.uk/guidance/qs35 Last updated: 23 July 2019
- Hypertension in pregnancy: diagnosis and management NICE guideline Published: 25 June 2019 www.nice.org.uk/guidance/ng133 /
- https://pathways.nice.org.uk/pathways/hypertension-in-pregnancy

  Evidence Review von Relevanz: Hypertension in pregnancy [A] Evidence review for interventions for chronic hypertension NICE guideline NG133 June 2019 https://www.nice.org.uk/guidance/ng133/evidence/a-interventions-for-chronic-hypertension-pdf-6836186126

  weitere zur Info: (Evidence reviews – June 2019)

  In 2019 we reviewed the evidence in the following areas and made recommendations (labelled [2019]):

  A. Interventions for chronic hypertension

  B. Monitoring gestational hypertension

  C. Prediction of complications in pre-eclampsia

  D. Interventions for pre-eclampsia

  E. Postnatal management of hypertension

  F. Advice at discharge

  G. Assessment of proteinuria

IQWiG (15.03.2021 – 14.02.2022)

Nr.	Suchfrage
Filter	Projekte, Abschlussberichte, Dossierbewertungen, Rapid Reports
Suchzeitraum	03.2021 – 11.02.2022
Suchbegriff: Hypertonie	
Treffer	0
Eingeschlossene Treffer	0

Nr.	Suchfrage
Suchbegriff: Hypertonus	
Treffer	0
Eingeschlossene Treffer	0
Suchbegriff: Bluthochdruck	
Treffer	0
Eingeschlossene Treffer	0
Suchbegriff: hypertension	
Treffer	0
Eingeschlossene Treffer	0
IQWiG-Infodienst **Suchbegriffe:** Bluthochdruck, Hypertonie, Hypertonus	
Treffer	0
Eingeschlossene Treffer	0

Anzahl der Treffer nach Titelscreening: 0

Datenbanken der AHRQ (20.04.2021 - 14.02.2022)

Kategorien	Suchbegriffe/ Filter (Keine Einschränkung des Zeitraums)	Treffer	Eingeschlossene Treffer
Full research report	Sichtung der Ergebnisliste ohne Eingabe von Suchbegriffen	1	1
Technology Assessment Program (completed)		0	0
EPC Evidence-based	Hypertension	0	0
	Blood pressure	0	0

Anzahl der Treffer nach Titelscreening: 1 (Hypertension in Adults: Screening. https://www.uspreventiveservicestaskforce.org/uspstf/document/final-evidence-review/hypertension-in-adults-screening)

Hinweis: Management of Chronic Hypertension During Pregnancy. Report Type: Evidence Reports. Affiliation: University of Texas Health Sciences Center. Report Status: Final. August 2000

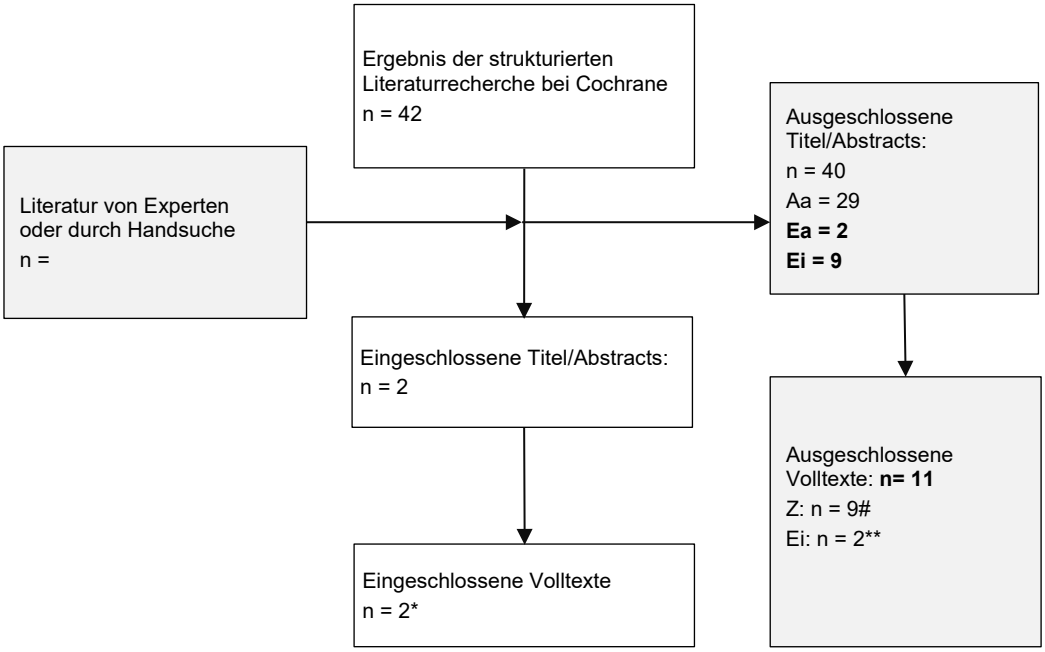
Übersicht der eingeschlossenen Treffer

Aggregierte Evidenz	Anzahl
Cochrane Datenbanken	13
NICE	2
IQWIG	0
AHRQ	1

Screening

E	PICO erfüllt
P	Protokoll
Aa	PICO nicht erfüllt
Aw	zurückgezogen
Z	

Flowchart



Cochrane Hypertension, „Our Evidence": https://hypertension.cochrane.org/our-evidence
n=80 Cochrane Reviews; n=2 new (Stand 23.02.2022):
Calcium channel blockers versus other classes of drugs for hypertension
Calcium supplementation for prevention of primary hypertension)

* Pisano A. Renal denervation for resistant hypertension. Cochrane Database Syst Rev 2021; 11(11):CD011499. https://www.ncbi.nlm.nih.gov/pubmed/34806762.

Zhu J. Calcium channel blockers versus other classes of drugs for hypertension. Cochrane Database Syst Rev 2022; 1(1):CD003654. https://www.ncbi.nlm.nih.gov/pubmed/35000192.

➔ *Interessante oder zurückgestellte Treffer der vorherigen strukturierten Recherchen 2019 und 2021 wurden ebenfalls themenbezogen berücksichtigt (Dokumentation s. dort)*

** interessant, aber nicht im aktuellen Themenbereich diskutiert (Ei):

Cunningham EL. Pharmacological treatment of hypertension in people without prior cerebrovascular disease for the prevention of cognitive impairment and dementia. Cochrane Database Syst Rev 2021; 5(5):CD004034. https://www.ncbi.nlm.nih.gov/pubmed/34028812.

Leache L. Pharmacotherapy for hypertension-induced left ventricular hypertrophy. Cochrane Database Syst Rev 2021; 10(10):CD012039. https://www.ncbi.nlm.nih.gov/pubmed/34628642.

zurück gestellt:

Palmer MJ. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev 2021; 3(3):CD012675. https://www.ncbi.nlm.nih.gov/pubmed/33769555.

McMahon EJ. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev 2021; 6(6):CD010070. https://www.ncbi.nlm.nih.gov/pubmed/34164803.

Hartmann-Boyce J. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2021; 9(9):CD010216. https://www.ncbi.nlm.nih.gov/pubmed/34519354.

Maagaard M. Interventions for altering blood pressure in people with acute subarachnoid haemorrhage. Cochrane Database Syst Rev 2021; 11(11):CD013096. https://www.ncbi.nlm.nih.gov/pubmed/34787310.

Pattanittum P. Roselle for hypertension in adults. Cochrane Database Syst Rev 2021; 11(11):CD007894. https://www.ncbi.nlm.nih.gov/pubmed/34837382.

Sasongko TH. Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease. Cochrane Database Syst Rev 2021; 12(12):CD009191. https://www.ncbi.nlm.nih.gov/pubmed/34932828.

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Cormick G. Calcium supplementation for prevention of primary hypertension. Cochrane Database Syst Rev 2022; 1(1):CD010037. https://www.ncbi.nlm.nih.gov/pubmed/35014026.

Naude CE. Low-carbohydrate versus balanced-carbohydrate diets for reducing weight and cardiovascular risk. Cochrane Database Syst Rev 2022; 1(1):CD013334. https://www.ncbi.nlm.nih.gov/pubmed/35088407.

1.6 PICO-Frage EKG

Welche diagnostische Genauigkeit besitzt das EKG zur Detektion einer linksventrikulären Hypertrophie bei Patienten mit Hypertonie?

Population	Patienten mit gesicherter Diagnose art. Hypertonie ohne Komorbiditäten
Indextest	EKG
Referenztest	Echokardiographie, ggf. MRT und CT
Endpunkte	Sensitivität und Spezifität für die Diagnose der linksventrikulären Hypertrophie
Fallzahl	≥100
Publikationsdatum	ab 2010

Medline via Pubmed (www.pubmed.gov) (20. April 2020)

Nr.	Suchfrage	Anzahl
#17	**Search (#15 AND #16)**	**561**
#16	Search ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR (predictive[Title/Abstract] AND value*[Title/Abstract]) OR predictive value of tests[MeSH Term] OR accuracy*[Title/Abstract]))	2043336
#15	Search #6 AND #11 AND #14	2867
#14	Search (#12 OR #13)	38013
#13	Search ((((((left[Title/Abstract]) AND ventric*[Title/Abstract]) AND hypertroph*[Title/Abstract])))) OR (((restrict*[Title/Abstract]) AND ((function*[Title/Abstract]) OR capacit*[Title/Abstract])) AND ((left[Title/Abstract]) AND ventric*[Title/Abstract]))	33540
#12	Search Hypertrophy, Left Ventricular[MeSH Terms]	13827
#11	Search (#7 OR #8 OR #9 OR #10)	252082
#10	Search EKG[Title/Abstract]	2880
#9	Search ECG[Title/Abstract]	62333
#8	Search Electrocardiogra*[Title/Abstract]	94961
#7	Search Electrocardiography[MeSH Terms]	202967
#6	Search (#1 OR #2 OR #5)	586283
#5	Search #3 AND #4	180053
#4	Search ((((high[Title/Abstract]) OR elevate*[Title/Abstract]) OR raise*[Title/Abstract]) OR increase*[Title/Abstract])	8040703
#3	Search "blood pressure"[Title/Abstract]	300228
#2	Search hypertens*[Title/Abstract]	432273
#1	Search hypertension[MeSH Terms]	252064

Anzahl der Treffer: 561

Anmerkungen

- MeSH-Term „hypertension“ enthält den MeSH-Term für „blood pressure, high“
- „High“ kann nicht trunkiert werden, da mehr als 600 Variationen
- Diagnostik-Filter der McMaster Universität mit bester Balance zwischen sensitivität und Spezifität genutzt

Datenbanken der Cochrane Library (20. April 2020)

Nr.	Suchfrage	Anzahl
#21	**#19 AND #20**	**60**
#20	#7 AND #11 AND #15	395
#19	#16 OR #17 OR #18	92763
#18	((sensitiv* OR (predictive AND value*) OR accuracy*)):ti,ab,kw	92341
#17	MeSH descriptor: [Predictive Value of Tests] explode all trees	6814
#16	MeSH descriptor: [Sensitivity and Specificity] explode all trees	15119
#15	#12 OR #13 OR #14	2579
#14	((restrict* AND (function* OR capacit*) AND left AND ventric*)):ti,ab,kw	220
#13	((left AND ventric* AND hypertroph*)):ti,ab,kw	2390
#12	MeSH descriptor: [Hypertrophy, Left Ventricular] explode all trees	870
#11	#8 OR #9 OR #10	27585
#10	(electrocardiography):ti,ab,kw (Word variations have been searched)	11579
#9	((Electrocardiogra* OR ECG OR EKG)):ti,ab,kw	27480
#8	MeSH descriptor: [Electrocardiography] explode all trees	8729
#7	#1 OR #2 OR #3 OR #6	91301
#6	#4 AND #5	44537
#5	((high OR elevate* OR raise* OR increase*)):ti,ab,kw	514561
#4	("blood pressure"):ti,ab,kw	87224
#3	(hypertension):ti,ab,kw (Word variations have been searched)	62111
#2	(hypertens*):ti,ab,kw	62132
#1	MeSH descriptor: [Hypertension] explode all trees	17628

Anzahl der Treffer: 60

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane Datenbanken	Summe
RCTs	561	60	**621**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

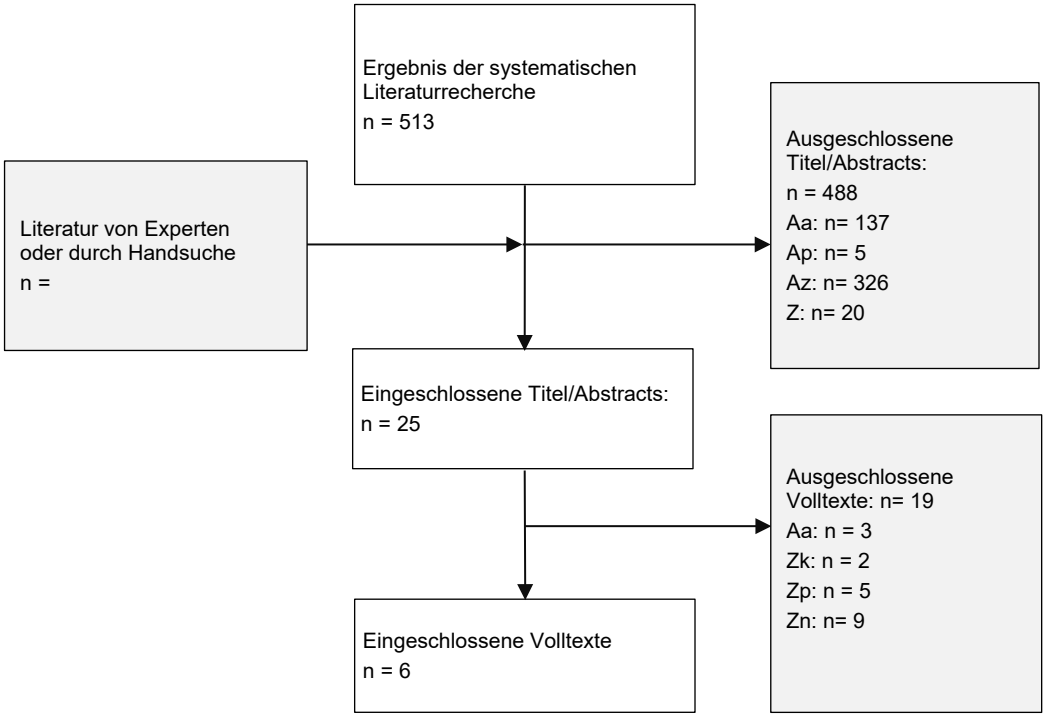
A1 (Dubletten): 42

A2 (nicht englisch/deutsch): 62

A3 (Conference Abstracts): 4

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 513

Flowchart



Legende:

Aa	thematisch nicht passend (PICO)
Zp	zurückgestellt, da general population untersucht bzw. andere Besonderheiten der Population nicht passend
Zf	zurückgestellt, da Fallzahl <100
Zk	zurückgestellt, da Relevanz des untersuchten EKG-Kriteriums nachrangig
Zn	zurückgestellt, da Nebenaspekt untersucht wird, der zur Beantwortung der Schlüsselfrage nicht relevant
Ad	Doppelpublikation, nicht erhältlich
Ap	anderer Publikationstyp, anderer Studientyp
Aw	zurückgezogen
Az	anderer Veröffentlichungs-, Recherchezeitraum
As	andere Sprache als Englisch oder Deutsch
Aq	schwache methodische Qualität
Av	Systematische Übersichtsarbeit mit gleicher Fragestellung und aktuellerem Suchzeitraum vorhanden

1.7 PICO-Frage Mikroalbuminurie

Zunächst wird auf Basis systematischer Übersichtsarbeiten nach folgenden Fragestellungen gesucht:

1. Sind **Mikroalbuminurie und Proteinurie** prognostische Faktoren für kardiovaskuläre Folgeerkrankungen bei Patienten mit der Diagnose Hypertonie?
2. Wie ist die diagnostische Genauigkeit der Bestimmung der **Mikroalbuminurie** mittels einer Point-of-Care-Messung im Vergleich zur Laborbestimmung?
3. Ist die **Mikroalbuminurie** ein geeigneter Parameter für die Therapiesteuerung bei Patienten mit Hypertonie?

Hätte die Suche nach aggregierter Evidenz keine Ergebnisse erbracht, hätte für die Fragestellungen 1 und 2 auf Primärstudienbasis gesucht werden können.

PICO-Frage: Systematische Übersichtsarbeiten

Population: Patienten mit der Diagnose Hypertonie ohne Komorbiditäten

Parameter: Proteinurie, Mikroalbuminurie, Albumin-Creatinin-Ratio (ACR) (= Marker 1)

Studientyp: systematischen Übersichtsarbeiten

Endpunkte: zu 1 und 3: MACE: Myokardinfarkt, Schlaganfall, Tod

zu 2: Sensitivität, Spezifität, diagnsotische OR, PPW, NPW

PICO-Frage: Prognosestudien

Population: Patienten mit der Diagnose Hypertonie ohne Komorbiditäten

Parameter: Mikroalbuminurie, Albumin-Creatinin-Ratio (ACR) (= Marker 2)

Studientyp: prognostische Studien

Endpunkte: MACE: Myokardinfarkt, Schlaganfall, Tod

PICO-Frage: Diagnosestudien

Population: Patienten mit der Diagnose Hypertonie ohne Komorbiditäten

Indextest: Mikroalbuminurie, Albumin-Creatinin-Ratio (ACR) in Point-of-care-Messung

Referenztest Mikroalbuminurie, Albumin-Creatinin-Ratio (ACR) in Laborbestimmung

Studientyp: diagnostische Studien

Endpunkte: Sensitivität, Spezifität, diagnsotische OR, PPW, NPW

Medline via Pubmed (www.pubmed.gov) (22. April 2020)

Nr.	Suchanfrage	Results
#15	**Search (#11 AND #14) NOT (#9 OR #13)**	**1073**
#14	Search sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR (predictive[Title/Abstract] AND value*[Title/Abstract]) OR predictive value of tests[MeSH Term] OR accuracy*[Title/Abstract]	2044153
#13	**Search ((#11 AND #12) NOT #9)**	**1381**
#12	Search prognos*[Title/Abstract] OR (first[Title/Abstract] AND episode[Title/Abstract]) OR cohort[Title/Abstract]	1098986
#11	Search #6 AND #10	9871
#10	Search "albuminuria"[MeSH Terms] OR albuminuria[Title/Abstract] OR microalbuminuria[Title/Abstract] OR micro albuminuria[Title/Abstract] OR "albumin creatinine ratio"[Title/Abstract] OR "albumin to creatinine ratio"[Title/Abstract] OR ACR[Title/Abstract] OR UACR[Title/Abstract]	33412
#9	**Search (#6 AND #7 AND #8)**	**573**
#8	Search (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab]	449884

Nr.	Suchanfrage	Results
	OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	
#7	Search "albuminuria"[MeSH Terms] OR albuminuria[Title/Abstract] OR microalbuminuria[Title/Abstract] OR micro albuminuria[Title/Abstract] OR "albumin creatinine ratio"[Title/Abstract] OR "albumin to creatinine ratio"[Title/Abstract] OR ACR[Title/Abstract] OR UACR[Title/Abstract] OR "proteinuria"[MeSH Terms] OR proteinuria[Title/Abstract]	78763
#6	Search #1 OR #2 OR #5	586494
#5	Search #3 AND #4	180114
#4	Search high[Title/Abstract] OR elevate*[Title/Abstract] OR raise*[Title/Abstract] OR increase*[Title/Abstract]	8044011
#3	Search "blood pressure"[Title/Abstract]	300318
#2	Search hypertens*[Title/Abstract]	432435
#1	Search hypertension[MeSH Terms]	252164

Treffer: 573 SR; 1381 prognostische Studien; 1073 diagnostische Studien

Datenbank Epistemonikos (22. April 2020)

Nr.	Suchanfrage	Results
1	(title:(albuminuria) OR abstract:(albuminuria)) OR (title:(microalbuminuria) OR abstract:(microalbuminuria)) OR (title:(micro albuminuria) OR abstract:(micro albuminuria)) OR (title:("albumin creatinine ratio") OR abstract:("albumin creatinine ratio")) OR (title:("albumin to creatinine ratio"[) OR abstract:("albumin to creatinine ratio"[)) OR (title:(ACR) OR abstract:(ACR)) OR (title:(UACR) OR abstract:(UACR)) OR (title:(proteinuria) OR abstract:(proteinuria)) AND (title:(hypertens*) OR abstract:(hypertens*))	189

Treffer: 189 SR

Datenbanken der Cochrane Library (23.04.2020)

Nr.	Suchfrage	Anzahl
#18	**((#11 AND #16) NOT #17) NOT "conference abstract":pt**	**174**
#17	**(#11 AND #12) NOT "conference abstract":pt**	**193**
#16	#13 OR #14 OR #15	92764
#15	MeSH descriptor: [Predictive Value of Tests] explode all trees	6814
#14	MeSH descriptor: [Sensitivity and Specificity] explode all trees	15119
#13	(sensitiv* OR (predictive AND value*) OR accuracy*):ti,ab,kw	92342
#12	(prognos* OR (first AND episode) OR cohort):ti,ab,kw	89471
#11	#7 AND #10	2234
#10	#8 OR #9	8072
#9	((albuminuria OR microalbuminuria OR micro albuminuria OR "albumin creatinine ratio" OR "albumin to creatinine ratio" OR ACR OR UACR)):ti,ab,kw	8072
#8	MeSH descriptor: [Albuminuria] explode all trees	1268
#7	#1 OR #2 OR #3 OR #6	91652
#6	#4 AND #5	45035
#5	((high OR elevat* OR raise* OR increase*)):ti,ab,kw	522138

Nr.	Suchfrage	Anzahl
#4	("blood pressure"):ti,ab,kw	87224
#3	(hypertension):ti,ab,kw (Word variations have been searched)	62111
#2	(hypertens*):ti,ab,kw	62132
#1	MeSH descriptor: [Hypertension] explode all trees	17628

Treffer: 193 prognostische Studien; 174 diagnostische Studien

Übersicht der eingeschlossenen Treffer

	Medline	Cochrane Daten-banken	Epistemonikos	Summe
Aggregierte Evidenz	573	-	189	**762**
Prognosestudien	1381	193	-	**1574**
Diagnosestudien	1073	174	-	**1247**

Aggregierte Evidenz:

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 162

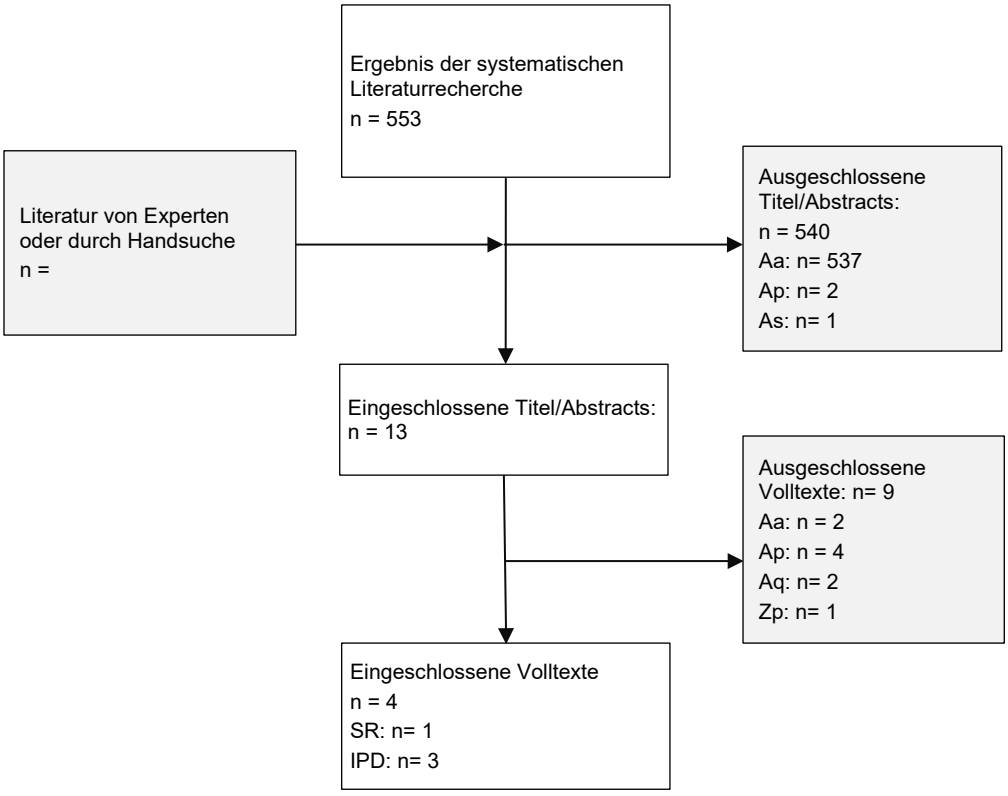
A2 (nicht englisch/deutsch): 47

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 553

Prognostische Studien: nicht gesichtet

Diagnostische Studien: nicht gesichtet

Flowchart systematische Übersichtsarbeiten (Stand: 06.01.2021)



Legende

Aa	Thema nicht passend (PICO)
Ap	Studientyp nicht passend
As	Sprache nicht englisch oder deutsch
Aq	Qualität nicht ausreichend
Zp	zurückgestellt, da Population nicht hypertoniespezifisch
SR	systematischer Review
IPD	Individualdaten-Metaanalyse

1.8 PICO-Frage Motivational Interviewing

Kann die motivierende Gesprächsführung (motivational interviewing) die Arzt-Patienten-Kommunikation bei Patienten mit Hypertonie verbessern?

Population	Patienten mit Hypertonie
Intervention	motivierende Gesprächsführung (motivational interviewing)
Vergleich	communicative strategies, behaviour change technique, patient centered counselling
Endpunkte	1. Gesundheitswissen, -Kompetenz, Adhärenz
	2. Sekundärfolgen bzw. langfristige Endpunkte
Studientypen	systematische Übersichtsarbeiten, ggf. im zweiten Schritt RCTs

Medline via Pubmed (www.pubmed.gov) (1. Juli 2020)

Nr.	Suchfrage	Anzahl
#14	**Search: (#10 AND #12) NOT #13 Sort by: Most Recent**	**111**
#13	**Search: #10 AND #11 Sort by: Most Recent**	**13**
#12	Search: ((((((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) OR "randomized"[Title/Abstract]) OR "placebo"[Title/Abstract]) OR "clinical trials as topic"[MeSH Terms:noexp]) OR "randomly"[Title/Abstract]) OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) Sort by: Most Recent	1,201,430
#11	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt]) Sort by: Most Recent	460,607
#10	Search: #6 AND #9 Sort by: Most Recent	244
#9	Search: #7 OR #8 Sort by: Most Recent	13,020
#8	Search: (motivation*[Title/Abstract]) AND (interview*[Title/Abstract]) Sort by: Most Recent	12,622

Nr.	Suchfrage	Anzahl
#7	Search: motivational interviewing[MeSH Terms] Sort by: Most Recent	1,824
#6	Search: #1 OR #2 OR #5 Sort by: Most Recent	592,349
#5	Search: #3 AND #4 Sort by: Most Recent	181,833
#4	Search: blood pressure[tiab] Sort by: Most Recent	303,045
#3	Search: (((((high[Title/Abstract]) OR elevate*[Title/Abstract]) OR raise*[Title/Abstract]) OR increase*[Title/Abstract]) Sort by: Most Recent	8,154,257
#2	Search: hypertens*[Title/Abstract] Sort by: Most Recent	437,149
#1	Search: hypertension[MeSH Terms] Sort by: Most Recent	253,619

Anzahl der Treffer: 13 Aggregierte Evidenz; 111 RCTs

Epistemonikos (01.07.2020)

Nr.	Suchanfrage	Results
1	(title:((title:(((high OR elevat* OR raise* OR increase*) AND (blood pressure)) OR hypertens*) OR abstract:(((high OR elevat* OR raise* OR increase*) AND (blood pressure)) OR hypertens*)) AND (title:(motivat* AND interview*) OR abstract:(motivat* AND interview*))) OR abstract:((title:(((high OR elevat* OR raise* OR increase*) AND (blood pressure)) OR hypertens*) OR abstract:(((high OR elevat* OR raise* OR increase*) AND (blood pressure)) OR hypertens*)) AND (title:(motivat* AND interview*) OR abstract:(motivat* AND interview*)))) Filter: systematic reviews	3

Psyndex via PubPsych (01.07.2020)

Nr.	Suchanfrage	Results
1	((((high OR elevat* OR raise* OR increase*) AND (blood pressure)) OR hypertens*) AND (motivat* AND interview*)) AND DB="PSYNDEX"	8

Datenbanken der Cochrane Library (01.07.2020)

Nr.	Suchfrage	Anzahl
#13	**#11 NOT "conference abstract":pt in Trials**	**287**
#12	**#11 NOT "conference abstract":pt in Cochrane Reviews, Cochrane Protocols**	**1**
#11	#7 AND #10	329
#10	#8 OR #9	5471
#9	(motivation* AND interview*):ti,ab,kw	5471
#8	MeSH descriptor: [Motivational Interviewing] explode all trees	798
#7	#1 OR #2 OR #3 OR #6	93079
#6	#4 AND #5	45697
#5	((high OR elevat* OR raise* OR increase*)):ti,ab,kw	532545
#4	("blood pressure"):ti,ab,kw	88632
#3	(hypertension):ti,ab,kw (Word variations have been searched)	63097
#2	(hypertens*):ti,ab,kw	63120
#1	MeSH descriptor: [Hypertension] explode all trees	17779

Cochrane Reviews • Review • Protocol	 1 0
Trials	287

Übersicht der eingeschlossenen Treffer

	Medline	Epistemonikos	Psyndex	Cochrane Datenbanken	Summe
Aggregierte Evidenz	13	3		1	17
RCTs	111			287	398
Sonstige			8		8
Gesamt					**423**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 115

A2 (nicht englisch/deutsch): 1

A3 (Conference Abstracts): 5

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 302

Screening

Ea: aggregierte Evidenz

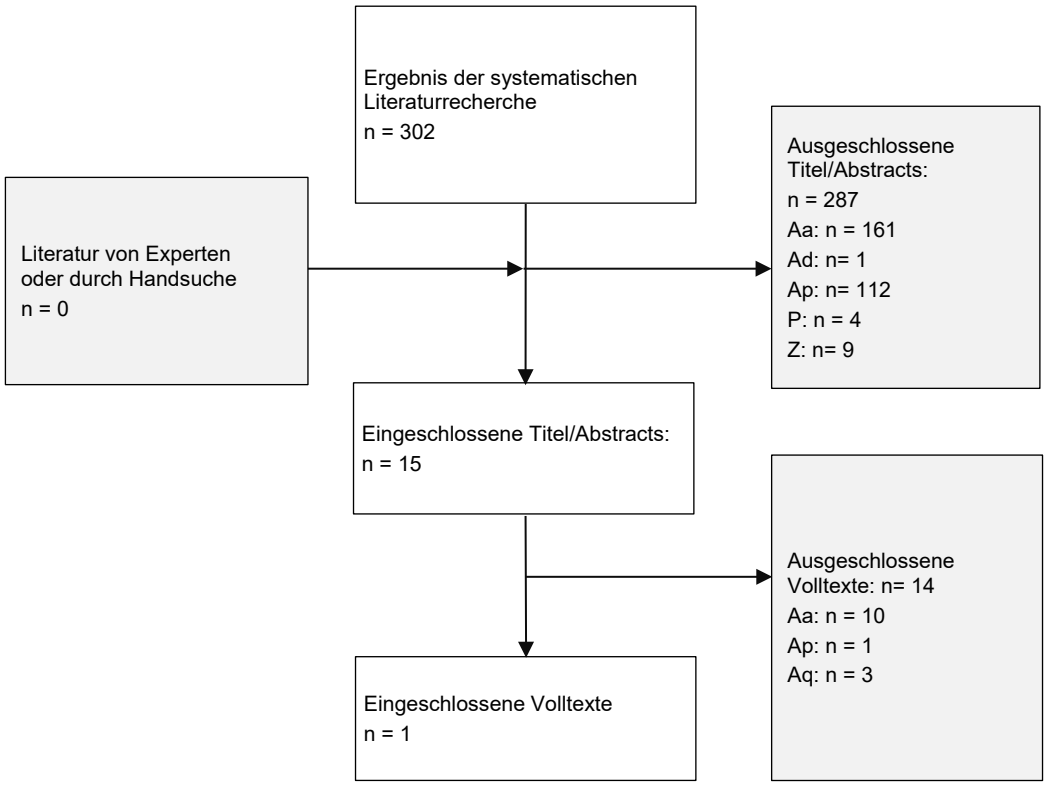
E1: alle Komponenten erfüllt (PICO)

E2: Population mit einer Komorbidität oder komplexe Intervention

Z: Population unspezifisch oder nur Surrogatendpunkte ausgewertet

P: Protokoll der letzten 5 Jahre, im Verlauf ggf. prüfen, ob mittlerweile veröffentlicht

Flowchart (Stand 06.01.2021)



Ausschlussgründe: Aa: Fragestellung bzw. PICO, Ap: Studientyp, Ad: Dublette, Z: Population unspezifisch oder nur Surrogatendpunkte ausgewertet, P: Protokoll

1.9 PICO-Frage körperliche Aktivität

Vorüberlegungen

Der Rapid Report des IQWiG ([A05-21D] Steigerung der körperlichen Aktivität bei essenzieller Hypertonie - Rapid Report) bildet die Evidenzgrundlage. Da der Suchzeitraum (02/2009) weit in der Vergangenheit liegt, entschied sich die Arbeitsgruppe, ein Recherche-Update auf Basis von systematischen Übersichtsarbeiten durchzuführen. Dazu wurde die Recherchestrategie des IQWiG adaptiert.

Primär relevant sind Arbeiten mit patientenrelevanten Endpunkten. Sollten diese nicht identifiziert werden, können Arbeiten mit Surrogatendpunkten herangezogen werden. Alternativ können ausgewählte Interventionen auf Primärstudienbasis recherchiert werden. Eine Auswahl der klinisch relevanten Interventionen ist aufgrund der hohen Trefferzahl einer übergeordneten Recherche notwendig.

PICO-Frage

Wirksamkeit und Sicherheit von Interventionen zur Steigerung der körperlichen Aktivität.

P: Erwachsene Patient*innen mit essentieller Hypertonie

I: Steigerung der körperlichen Aktivität, Dauer ≥ 24 Wochen

C: keine Steigerung der körperlichen Aktivität

O: 1. Kardiovaskuläre Mortalität, Gesamtmortalität, Lebensqualität, Morbidität,

2. Blutdruck

S: systematische Übersichtarbeiten ab 02/2009

Anmerkung zu Post-hoc-Veränderung der PICO-Fragestellung:

I: Für die Untersuchung der Effekte auf den Surrogatendpunkt Blutdruck genügte eine Studiendauer ≥ 4 Wochen (siehe auch Screening)

Medline via Pubmed (www.pubmed.gov) (28.10.2020)

Nr.	Suchterm	Filter
#16	**Search: #11 AND #14 Filters: from 2009/2/1 - 3000/12/12 Sort by: Most Recent**	**865**
#15	Search: #11 AND #14 Sort by: Most Recent	1,049
#14	Search: #12 OR #13 Sort by: Most Recent	282,697
#13	Search: meta-analysis[tiab] OR metaanalysis[tiab] OR "Meta-Analysis" [Publication Type] Sort by: Most Recent	187,158
#12	Search: (((systematic review[tiab] OR systematic literature review[tiab] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[tiab] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt] Sort by: Most Recent	177,867
#11	Search: #4 AND #10 Sort by: Most Recent	52,158
#10	Search: #5 OR #6 OR #7 OR #8 OR #9 Sort by: Most Recent	1,373,987
#9	Search: exercise*[TIAB] Sort by: Most Recent	302,380
#8	Search: (training*[TiAB] AND aerobic*[tiab]) OR (training*[TIAB] AND strength*[TIAB]) OR (training*[TIAB] AND physical[TIAB]) OR (training*[TIAB] AND endurance[TIAB]) OR (training*[TIAB] AND resistance[TIAB]) Sort by: Most Recent	81,902
#7	Search: (physical activity[TIAB] OR physical activities[TIAB] OR physical inactivity[TIAB] OR physical inactivities[TIAB]) Sort by: Most Recent	121,074

Nr.	Suchterm	Filter
#6	Search: (walk*[TIAB] OR swim*[TIAB] OR jogg*[TIAB] OR sport*[TIAB] OR cycle[TIAB] OR cycling[TIAB] OR run[TIAB] OR runn*[TIAB] OR fitness[TIAB] OR gymnastic*[TIAB] OR Tai chi[TIAB] OR Tai-chi-chuan[TIAB]) Sort by: Most Recent	945,036
#5	Search: exercise[MeSH Terms] OR exercise therapy[MeSH Terms] OR Physical Education and training[MeSH] OR sports[MeSH Terms] OR Swimming[MeSH] OR bicycling[MeSH Terms] OR walking[MeSH Terms] OR Gymnastics[MeSH] OR Tai Ji[MeSH] OR Yoga[MeSH] Sort by: Most Recent	346,058
#4	Search: #1 OR (#2 AND #3) Sort by: Most Recent	647,392
#3	Search: high[Title/Abstract] OR elevate*[Title/Abstract] OR raise*[Title/Abstract] OR increase*[Title/Abstract] Sort by: Most Recent	8,345,461
#2	Search: "Blood Pressure"[Mesh] OR blood pressure[tiab] Sort by: Most Recent	456,421
#1	Search: hypertension[MeSH Terms] OR hypertens*[Title/Abstract] Sort by: Most Recent	501,395

Anzahl der Treffer: 865 Aggregierte Evidenz

Epistemonikos (28.10.2020)

Nr.	Suchfrage	Anzahl
#1	(advanced_title_en:((((high OR elevat* OR raise* OR increase*) AND blood pressure) OR hypertens*) AND ((training* AND aerobic*) OR (training* AND strength*) OR (training* AND physical) OR (training* AND endurance) OR (training* AND resistance) OR (physical activity OR physical activities OR physical inactivity OR physical inactivities) OR (walk* OR swim* OR jogg* OR sport* OR cycle OR cycling OR run OR runn* OR fitness OR gymnastic* OR Tai chi OR Tai-chi-chuan))) OR advanced_abstract_en:((((high OR elevat* OR raise* OR increase*) AND blood pressure) OR hypertens*) AND ((training* AND aerobic*) OR (training* AND strength*) OR (training* AND physical) OR (training* AND endurance) OR (training* AND resistance) OR (physical activity OR physical activities OR physical inactivity OR physical inactivities) OR (walk* OR swim* OR jogg* OR sport* OR cycle OR cycling OR run OR runn* OR fitness OR gymnastic* OR Tai chi OR Tai-chi-chuan)))) [Filters: classification=systematic-review, protocol=no, min_year=2009, max_year=2021]	411

Übersicht der eingeschlossenen Treffer

	Medline	Epistemonikos	Summe
Aggregierte Evidenz	865	411	**1276**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 287

A2 (nicht englisch/deutsch): 41

A3 (Conference Abstracts): 7

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 941

Screening

Das Screening erfolgte schrittweise.

Im ersten Schritt wurden systematische Reviews (SR) mit patientenrelevanten Endpunkten gesucht. Es wurden SR identifiziert, die jedoch teilweise keine relevanten Primärstudien fanden.

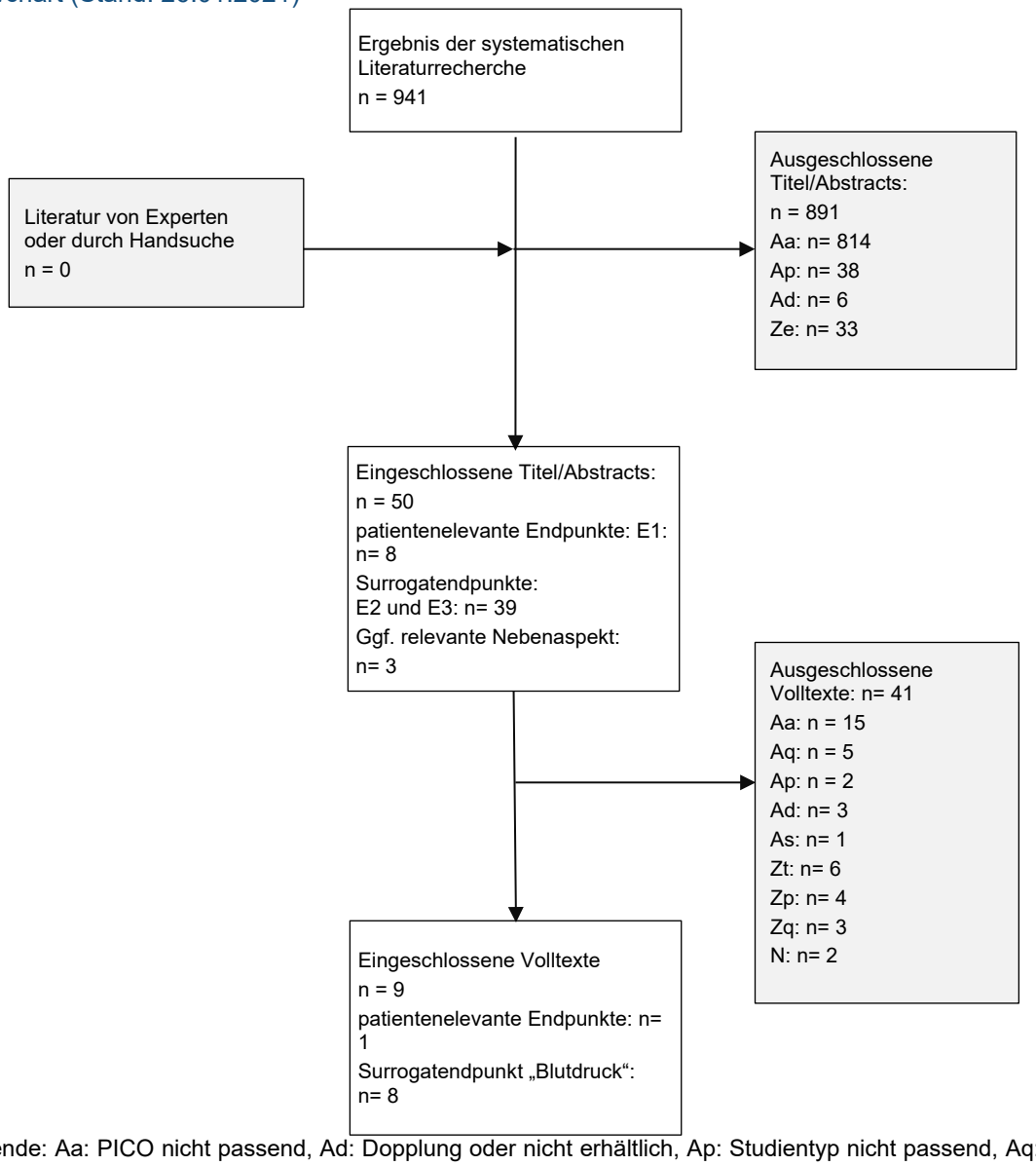
In einem zweiten Schritt wurden SR mit dem Surrogatendpunkt Blutdruck herangezogen. Die Interventionen wurden vorab von der Gruppe entsprechend ihrer Versorgungsrelevanz im schriftlichen Umlauf priorisiert. Eingeschlossen wurden SR mit den Interventionen „moderate intensity continuous training“, „aerobic training“, „high intensity interval training“, „running“, „walking“ und „tai chi“.

Es konnten keine SR identifiziert werden, die in ihren Einschlusskriterien eine Studiendauer von ≥ 24 Wochen definierten. Die Leitliniengruppe entschied sich daher, die PICO-Fragestellung anzupassen und auch SR einzuschließen, die eine Studiendauer von ≥ 4 Wochen untersuchten.

Im dritten Schritt wurden SR zum Thema „resistance taining“ und „strength training“ eingeschlossen.

Wurden mehrere SR zu einer Fragestllung indentifiziert, wurde die aktuellste mit der besten AMSTAR-II-Bewertung eingeschlossen.

Flowchart (Stand: 26.01.2021)



Legende: Aa: PICO nicht passend, Ad: Dopplung oder nicht erhältlich, Ap: Studientyp nicht passend, Aq: Qualität nicht ausreichend, As: Sprache nicht englisch oder deutsch, N Nebenaspekt, Ze: zurückgestellt, weil Surrogatendpunkt für weniger versorgungsrelevante Intervention untersucht, Zp: zurückgestellt, weil Population nicht hypertoniespezifisch, Zt: zurückgestellt, weil aktuellere systematische Übersichtsarbeit zu ähnlicher Fragestellung identifiziert und herangezogen wurde, Zq: zurückgestellt, weil systematische Übersichtsarbeit zu ähnlicher Fragestellung mit besserem methodischen Vorgehen identifiziert und herangezogen wurde

Liste der im Volltextscreening ausgeschlossenen Publikationen

Referenz	Grund	Kommentar VT
Conn VS. Meta-analysis of interventions to increase physical activity among cardiac subjects. Int J Cardiol 2009; 133(3):307–20. https://www.ncbi.nlm.nih.gov/pubmed/18582959.	Aa	Population nicht hypertoniespezifisch

Referenz	Grund	Kommentar VT
Lauche R. Efficacy of **Tai Chi and qigong** for the prevention of stroke and stroke risk factors: A systematic review with meta-analysis. Medicine (Baltimore) 2017; 96(45):e8517. https://www.ncbi.nlm.nih.gov/pubmed/29137055.	Zq	**Zurückgestellt** - keine Primärstudien gefunden, die patientenrelevanten Endpunkte untersuchten - für Auswertungen zum Surrogatendpunkt "Blutdruck" wird Hartley et al. herangezogen. Suchzeitraum zwar älter aber Methodik transparenter - Sprache: engl. und dt.
Schultz MG. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: A systematic review and meta-analysis. Am J Hypertens 2013; 26(3):357–66. https://www.ncbi.nlm.nih.gov/pubmed/23382486.	N	Nebenaspekt ggf. in Rationale im HG-Text verwendbar
Smart NA. An evidence-based analysis of managing hypertension with isometric resistance exercise-are the guidelines current? Hypertens Res 2020; 43(4):249–54. https://www.ncbi.nlm.nih.gov/pubmed/31758166.	Ap	post-hoc-Analyse zu ID 30830
Zheng G. **Tai chi** chuan for the primary prevention of stroke in middle-aged and elderly adults: A systematic review. Evid Based Complement Alternat Med 2015; 2015:742152. https://www.ncbi.nlm.nih.gov/pubmed/25784950.	Zp	**Zurückgestellt** Ergebnis aus Sicht der AG nicht extrapo-lierbar Studie von Han et al. nicht identifizierbar Ergebnisse für EP Blutdruck nicht verwend-bar, da Studien mit unter-schiedlichen Populationen gepoolt
Echouffo-Tcheugui JB. Association of Physical Activity or Fitness With Incident Heart Failure: A Systematic Review and Meta-Analysis. Circulation. Heart failure 2015; 8(5):853–61. https://www.ncbi.nlm.nih.gov/pubmed/26175539.	Aa	Kohortenstudien eingeschlossen, ohne Subgruppenanalysen für Pat. mit Hypertonie
Milton K. Review of the epidemiological evidence for physical activity and health from low- and middle-income countries. Glob Public Health 2014; 9(4):369–81. https://www.ncbi.nlm.nih.gov/pubmed/24697197.	Aa	Versorgungssituation nicht vergleichbar: low- and middle-income countries
Patnode CD. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2017; 318(2):175–93. https://www.ncbi.nlm.nih.gov/pubmed/28697259.	N	Nebenaspekt ggf. in Rationale im HG-Text verwendbar
Zhong D. Tai Chi for Essential Hypertension: A Systematic Review of Randomized Controlled Trials. Curr Hypertens Rep 2020; 22(3):25. https://www.ncbi.nlm.nih.gov/pubmed/32124064.	Zq	**Zurückgestellt** AG entscheidet sich nach klinischer Sichtung des SR, den Cochrane-Review von Hartley et al. heranzuziehen. Der Suchzeitraum ist zwar älter aber die Methodik transparenter.
Leal JM. Effectiveness of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training in Hypertensive Patients: A Systematic Review and Meta-Analysis. Curr Hypertens Rep 2020; 22(3):26. https://www.ncbi.nlm.nih.gov/pubmed/32125550.	Aq	4 kritische Kriterien nicht erfüllt
Noone C. Comparative efficacy of exercise and antihypertensive pharmacological interventions in reducing blood pressure in people with hypertension: A network meta-analysis. Eur J Prev Cardiol 2020; 27(3):247–55. https://www.ncbi.nlm.nih.gov/pubmed/31615283.	Ap	Netzwerkmetaanalyse
Liang H. Effects of Tai Chi exercise on cardiovascular disease risk factors and quality of life in adults with essential hypertension: A meta-analysis. Heart Lung 2020; 49(4):353–63. https://www.ncbi.nlm.nih.gov/pubmed/32171586.	Zt	Zurückgestellt: SR mit ähnlicher Frage und aktuellerem Suchzeitraum

Referenz	Grund	Kommentar VT
Murtagh EM. The effect of walking on risk factors for cardiovascular disease: An updated systematic review and meta-analysis of randomised control trials. Prev Med 2015; 72:34–43. https://www.ncbi.nlm.nih.gov/pubmed/25579505.	Aa	Population: apparently sedentary but otherwise healthy at baseline
Hanson S. Is there evidence that walking groups have health benefits? A systematic review and meta-analysis. Br J Sports Med 2015; 49(11):710–5. https://www.ncbi.nlm.nih.gov/pubmed/25601182.	Aa	Population: nicht HTN-spezifisch Studiendauer 3 Wo bis 1 Jahr
Maturana FM. Effectiveness of HIIE versus MICT in Improving Cardiometabolic Risk Factors in Health and Disease: A Meta-analysis. Med Sci Sports Exerc 2020. https://www.ncbi.nlm.nih.gov/pubmed/32890201.	Aa	Dauer >/= 2 Wochen - Population fraglich HTN-spezifisch - Subgruppenanalysen für folgende Populationen: healthy-population, overweight/obese cardiac rehabilitation, metabolic syndrome and T2D
Way KL. The effect of high Intensity interval training versus moderate intensity continuous training on arterial stiffness and 24h blood pressure responses: A systematic review and meta-analysis. J Sci Med Sport 2019; 22(4):385–91. https://www.ncbi.nlm.nih.gov/pubmed/30803498.	Aa	Population nicht HTN-spezifisch (siehe Baseline-Charakteristika im Supplement)
Kelley GA. Brief Report: Exercise and Blood Pressure in Older Adults-An Updated Look. Int J Hypertens 2018; 2018:6548659. https://www.ncbi.nlm.nih.gov/pubmed/30510795.	Ad	Hauptpublikation: Herrod PJ. (ID 30740)
Wen H. Reducing effect of aerobic exercise on blood pressure of essential hypertensive patients: A meta-analysis. Medicine (Baltimore) 2017; 96(11):e6150. https://www.ncbi.nlm.nih.gov/pubmed/28296729.	Aq/ Zt	4 kritische Kriterien nicht erfüllt, u.a. kein RoB angewandt
Huang G. Controlled aerobic exercise training reduces resting blood pressure in sedentary older adults. Blood Press 2013; 22(6):386–94. https://www.ncbi.nlm.nih.gov/pubmed/23550511.	Aa	Studiendauer: >2 Wochen Population: Ältere Gesunde (Most of the studies (91 %) provided information on comorbidities with reporting all subjects healthy)
Guan Y. Effects of Tai Chi on essential hypertension and related risk factors: A meta-analysis of randomized controlled trials. J Rehabil Med 2020; 52(5):jrm00057. https://www.ncbi.nlm.nih.gov/pubmed/32338292.	Zt	Zurückgestellt: - SR mit ähnlicher Frage und aktuellerem Suchzeitraum
Wu Y. Tai Ji Quan as antihypertensive lifestyle therapy: A systematic review and meta-analysis. J Sport Health Sci 2020. https://www.ncbi.nlm.nih.gov/pubmed/32360952.	Aa	Studiendauer nicht in Einschlusskriterien definiert und nicht in Baseline-Tabelle berichtet (siehe Suppl)
Cornelissen VA. Endurance exercise beneficially affects ambulatory blood pressure: A systematic review and meta-analysis. J Hypertens 2013; 31(4):639–48. https://www.ncbi.nlm.nih.gov/pubmed/23325392.	Aa	Population: gesunde Erwachsen
Liu D. The Efficacy of Tai Chi and Qigong Exercises on Blood Pressure and Blood Levels of Nitric Oxide and Endothelin-1 in Patients with Essential Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med 2020; 2020:3267971. https://www.ncbi.nlm.nih.gov/pubmed/32802122.	Zq	**Zurückgestellt** AG entscheidet sich nach klinischer Sichtung des SR, die beiden Cochrane-Reviews von Hartley heranzuziehen Die Suchzeiträume ist zwar älter aber die Methodik transparenter AMSTAR: 2 kritische Kriterien nicht erfüllt (Protokoll, Liste der exkludierten PS)
Lian Z. Effects of Tai chi on adults with essential hypertension in China: A systematic review and meta-analysis. European Journal of Integrative Medicine 2017; 12:153–62. www.sciencedirect.com/science/article/abs/pii/S1876382017301051.	Zt	SR mit ähnlicher Fragestellung und aktuellerem Suchzeitraum vorhanden
Wang J. Tai chi for essential hypertension. Evid Based Complement Alternat Med 2013;	Zt	SR mit ähnlicher Fragestellung und aktuellerem Suchzeitraum vorhanden

Referenz	Grund	Kommentar VT
2013:215254. https://www.ncbi.nlm.nih.gov/pubmed/23986780.		
Herrod PJ. Exercise and other nonpharmacological strategies to reduce blood pressure in older adults: A systematic review and meta-analysis. J Am Soc Hypertens 2018; 12(4):248–67. https://www.ncbi.nlm.nih.gov/pubmed/29496468.	Zp	Population nicht HTN-spezifisch (siehe Baseline-Charakteristika) verschiedene komolexe Interventionen untersucht
Lee L-L. The effect of walking intervention on blood pressure control: A systematic review. Int J Nurs Stud 2010; 47(12):1545–61. https://www.ncbi.nlm.nih.gov/pubmed/20863494.	Aa	Population nicht HTN-spezifisch >> keine Subgruppenauswertung für HTN-Population
Batacan RB, JR. Effects of high-intensity interval training on cardiometabolic health: A systematic review and meta-analysis of intervention studies. Br J Sports Med 2017; 51(6):494–503. https://www.ncbi.nlm.nih.gov/pubmed/27797726.	Aa	Population gemischt, keine HTN-spezifische Auswertung
Lee MS. Tai chi for lowering resting blood pressure in the elderly: A systematic review. J Eval Clin Pract 2010; 16(4):818–24. https://www.ncbi.nlm.nih.gov/pubmed/20557410.	Zt	SR mit ähnlicher Fragestellung und aktuellerem Suchzeitraum vorhanden
Oliver-Martínez PA. Chronic effects and optimal dosage of strength training on SBP and DBP: A systematic review with meta-analysis. J Hypertens 2020; 38(10):1909–18. https://www.ncbi.nlm.nih.gov/pubmed/32890263.	Aa	nicht klar beschrieben, dass nur Pat. mit bestehender HTN eingeschlossen wurden - Patientencharakteristika in Baseline-Tabelle nicht berichtet, keine Subgruppenanalyse erstellt pretension levels of the intervention groups, the mean SBP was 128 mmHg (94–155mmHg) and the mean DBP was 75mmHg (57–98mmHg).
López-Valenciano A. Updated systematic review and meta-analysis on the role of isometric resistance training for resting blood pressure management in adults. J Hypertens 2019; 37(7):1320–33. https://www.ncbi.nlm.nih.gov/pubmed/30624369.	Ad/ Aa	7 studies were carried out with pre or hypertensive participants and 9 studies were performed with normotensive participants. Moderatoranalyse für HTN in Baselinetabelle geht hervor, welche Studien HTN-Population: - die Handgrip-Studien sind bis auf eine Ausnahme (Badrov) alle auch in die Metaanalyse von Loaiza-Betancur et al (ID 30832) eingeschlossen, daher ist dieser SR für das Handgriptraining nicht relevant. Zudem sind zwei Studien zu „leg extension“ eingeschlossen, diese sind beide bei Prä-HTN-Patienten durchgeführt worden (n= 50) eine der Studien hat 2 Interventionsarme, aus den Baselinetabellen bzw. dem Forest plot geht nicht hervor, welcher Arm welchem Ergebnis zuzuordnen ist
Smart NA. Effects of isometric resistance training on resting blood pressure: Individual participant data meta-analysis. J Hypertens 2019; 37(10):1927–38. https://www.ncbi.nlm.nih.gov/pubmed/30889048.	Zp	nur 109 von 326 Teilnehmer*innen hatten eine HTN (siehe Tabelle 2) --> keine Subgruppenanalyse für HTN-Patienten präsentiert, Supplement nicht verfügbar
Domingos E. Blood pressure response between resistance exercise with and without blood flow restriction: A systematic review and meta-analysis. Life Sci 2018; 209:122–31. https://www.ncbi.nlm.nih.gov/pubmed/30086274.	Aa	- Studiendauer nicht beschrieben - "akute" Effekte der Intervention ermittelt, RR-Messungen zumeist direkt nach der Intervention - eine Studie hat "chronic effects" untersucht [11], diese wurde bei normotensiven Patient*innen durchgeführt
Farah BQ. Acute and Chronic Effects of Isometric Handgrip Exercise on Cardiovascular Variables in Hypertensive Patients: A Systematic Review. Sports (Basel) 2017; 5(3). https://www.ncbi.nlm.nih.gov/pubmed/29910415.	Zt	aktuellere systematische Übersichtsarebit mit ähnlicher Fragestellung vorhanden cardiovascular parameters = office BP, Herzfrequenz, systemic vascular resistance (n = 1), cardiac index (n = 1)

Referenz	Grund	Kommentar VT
		by means of impedance cardiography, and rate pressure product (n = 1).
Neto GR. Effects of resistance training with blood flow restriction on haemodynamics: A systematic review. Clin Physiol Funct Imaging 2017; 37(6):567–74. https://www.ncbi.nlm.nih.gov/pubmed/27095591.	Zp	weder in Einschlusskriterien noch in Baseline-Tabelle HTN-Status berichtet, keine Subgruppenauswertung für Pat. mit bestehender HTN identifiziert chronic effects nur in 2 Studien evaluiert: (Fahs et al., 2012 (= 46 young men); Ozaki et al., 2013 (= 19 young men),
Sousa EC de. Resistance training alone reduces systolic and diastolic blood pressure in prehypertensive and hypertensive individuals: Meta-analysis. Hypertens Res 2017; 40(11):927–31. https://www.ncbi.nlm.nih.gov/pubmed/28769100.	Aq	keine Qualitätsbewertung der eingeschlossenen Studien vorgenommen.
Casonatto J. The blood pressure-lowering effect of a single bout of resistance exercise: A systematic review and meta-analysis of randomised controlled trials. Eur J Prev Cardiol 2016; 23(16):1700–14. https://www.ncbi.nlm.nih.gov/pubmed/27512052.	Aa	healthy adults - nur eine einmalge Intervention betrachtet - Endpunkt: Post-exercise BP
Carlson DJ. Isometric exercise training for blood pressure management: A systematic review and meta-analysis. Mayo Clin Proc 2014; 89(3):327–34. https://www.ncbi.nlm.nih.gov/pubmed/24582191.	Aq	3 kritische Kriterien nicht erfüllt und Suchstrategie nicht nachvollziehbar, zudem nur Suche in peer-reviewed journals investigated the effects of isometric exercise on blood pressure in healthy adults
Lima AH. Efeito da fadiga induzida pelo treino de força na resposta da pressão arterial em sujeitos hipertensos: Uma revisão sistemática. Motricidade 2013; 9(1):23–30. go.gale.com/ps/anonymous?id=GALE%7CA334486380&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=1646107X&p=IFME&sw=w.	As	Sprache
Rossi AM. The evolution of a Canadian Hypertension Education Program recommendation: The impact of resistance training on resting blood pressure in adults as an example. Can J Cardiol 2013; 29(5):622–7. https://www.ncbi.nlm.nih.gov/pubmed/23541664.	Ad	inhlatliche Dopplung - aus Supplement geht hervor, dass nur 3 Studien mit Patienten mit HTN eingeschlossen wurden, alle drei sind auch in (ID 30825: Macdonald HV) eingeschlossen und ausgewertet
Owen A. Effect of isometric exercise on resting blood pressure: A meta analysis. J Hum Hypertens 2010; 24(12):796–800. https://www.ncbi.nlm.nih.gov/pubmed/20182455.	Aq	- keine Qualitätsbewertung der eingeschlossenen Primärstudien - anhand Einschlusskriterien und Baseline-Charakteristika wird nicht klar, ob Patienten alle mit HTN

1.10 PICO-Frage Einnahmezeitpunkte

Schlüsselfrage: Einnahmezeitpunkte (morgens, abends, mehrfach) → Recherche adaptiert nach Zhao et al. Cochrane 2011 https://pubmed.ncbi.nlm.nih.gov/21975743/ (dort Suche bis Oktober 2009; n=21 klinische Studien mit n=1.993 eingeschlossen (angiotensin-converting-enzyme inhibitors - ACEI (5 trials), calcium-channel blockers - CCB (7 trials), angiotensin II receptor blockers - ARB (6 trials), diuretics (2 trials), alpha-blockers (1 tri beta-blockers (1 trial)) → keine der eingeschlossenen Studien berichtete über die in der Übersichtsarbeit definierten primären Endpunkte, mit Ausnahme einer Blutdrucksenkung)

P: Patienten mit (arterieller) Hypertonie

I: antihypertensive Wirkstoffe (mit unterschiedlichen Einnahmezeitpunkten (morgens, abends, mehrfach))

C: Kohortenstudien (Langzeitbeobachtung)

O: [keine Einschränkung] bzw. Tod; Herzinfarkt; Schlaganfall

→ zweistufiges Vorgehen: SR zu RCT und ggf. Einschränkung der betrachteten Endpunkte in RCT bzw. ggf. Kohortenstudien

Medline via Pubmed (www.pubmed.gov) (14. Juni 2021)

Nr.	Suchanfrage	Results
#22	**#19 AND #20**	**268**
#21	**#17 AND #20**	**185**
#20	"Mortality"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR mortalit*[Text Word] OR fatalit*[Text Word] OR death[Text Word] OR “myocardial infarction*”[Text Word] OR “heart attack*”[Text Word] OR stroke*[Text Word] OR apoplex*[Text Word]	2,384,991
#19	**(#13 AND #18) NOT #15**	**1,257**
#18*	cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	2,858,072
#17	**(#13 AND #16) NOT #15**	**1,116**
#16	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))	1,274,817
#15	**#13 AND #14**	**150**
#14	(systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	521,131
#13	#11 AND #12	4,402
#12	"2009/11/01"[Date - Publication] : "3000"[Date - Publication]	11,903,098
#11	#1 AND #9 AND #10	11,882
#10	“Chronotherapy”[Mesh] OR chronopharm*[Text Word] OR chronomodulat*[Text Word] OR chronotherap*[Text Word] OR morning*[Text Word] OR day[Text Word] OR am[Text Word] OR diurnal*[Text Word] OR daytime*[Text Word] OR awak*[Text Word] OR evening*[Text Word] or bedtim*[Text Word] OR night*[Text Word] OR nocturnal*[Text Word] or pm[Text Word]	1,404,011
#9	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	572,604
#8	"Diuretics"[Mesh] OR "Diuretics" [Pharmacological Action] OR diuretic*[Text Word] OR thiazide*[Text Word] OR Bendroflumenthazide[Text Word] OR Hydroflumethazide[Text Word] OR Hydrochlorothiazide[Text Word] OR Chlorothiazide[Text Word] OR Polythiazide[Text Word] OR Trichlomethazide[Text Word] OR Cyclopenthazide[Text Word] OR Methylclothiazide[Text Word] OR Cyclothiazide[Text Word] OR Mebutizide[Text Word] OR Quinethazone[Text Word] OR Clopamide[Text Word] OR Chlorthalidone[Text Word] OR Mefruside[Text Word] OR Clofenamide[Text Word] OR Metolazane[Text Word] OR Meticrane[Text Word] OR Xipamide[Text Word] OR Indapamide[Text Word] OR Clorexolone[Text Word] OR Fenquizone[Text Word] OR Furosemide[Text Word] OR Bumetamide[Text Word] OR Piretanide[Text Word] OR Torasemide[Text Word] OR Azosemide[Text Word] OR “etacrynic acid”[Text Word] OR “tienilic acid”[Text Word] OR Muzolimine[Text Word] OR Etozoline[Text Word] OR Spironolactone[Text Word] OR “potassium canrenoate”[Text Word] OR Canrenone[Text Word] OR Eplerenone[Text Word] OR Amiloride[Text Word] OR Triamteren[Text	116,331

* University of Texas: https://libguides.sph.uth.tmc.edu/search_filters/pubmed_filters

Nr.	Suchanfrage	Results
	Word]	
#7	“Calcium Channel Blockers”[Mesh] OR “Calcium Channel Blockers”[Pharmacological Action] OR (“calcium channel”[Text Word] AND (antagonist*[Text Word] OR blocker*[Text Word])) OR Amlodipin[Text Word] OR Felodipin[Text Word] OR Isradipin[Text Word] OR Nicardipin[Text Word] OR Nifedipin[Text Word] OR Nimodipin[Text Word] OR Nisoldipin[Text Word] OR Nitrendipin[Text Word] OR Lacidipin[Text Word] OR Nilvadipin[Text Word] OR Manidipin[Text Word] OR Barnidipin[Text Word] OR Lercanidipin[Text Word] OR Clinidipin[Text Word] OR Benidipin[Text Word] OR Clevidipin[Text Word] OR Verapamil[Text Word] OR Gallopamil[Text Word] OR Diltiazem[Text Word]	116,648
#6	“Adrenergic beta-Antagonists"[Mesh] OR “Adrenergic beta-Antagonists”[Pharmacological Action] OR (beta*[Text Word] AND (blocker*[Text Word] OR antagonist*[Text Word])) OR Alprenolol[Text Word] OR Oxprenolol[Text Word] OR Pindolol[Text Word] OR Propranolol[Text Word] OR Timolol[Text Word] OR Sotalol[Text Word] OR Nadolol[Text Word] OR Mepindolol[Text Word] OR Carteolol[Text Word] OR Tetratolol[Text Word] OR Bopindolol[Text Word] OR Metipranolol[Text Word] OR Bupranolol[Text Word] OR Penbutolol[Text Word] OR Cloranolol[Text Word] OR Carazolol[Text Word] OR Bunitrolol[Text Word] OR Practolol[Text Word] OR Metoprolol[Text Word] OR Atenolol[Text Word] OR Acebutolol[Text Word] OR Betaxolol[Text Word] OR Bevantolol[Text Word] OR Bisoprolol[Text Word] OR Celiprolol[Text Word] OR Esmolol[Text Word] OR Epanolol[Text Word] OR Atenolol[Text Word] OR Nebivolol[Text Word] OR Talinol[Text Word] OR Landiolol[Text Word] OR Labetalol[Text Word] OR Carvedilol[Text Word]	220,255
#5	"Angiotensin Receptor Antagonists"[Mesh] OR ((“angiotensin receptor*”[Text Word] OR “angiotensin II receptor*“[Text Word]) AND (antagonist*[Text Word] OR blocker*[Text Word])) OR ARB[Text Word] OR Losartan[Text Word] OR Eprosartan[Text Word] OR Valsartan[Text Word] OR Irbesartan[Text Word] OR Tasosartan[Text Word] OR Candesartan[Text Word] OR Telmisartan[Text Word] OR Olmesartan[Text Word] OR Azilsartan[Text Word] OR Fimasartan[Text Word]	37,922
#4	“Adrenergic alpha-Antagonists”[Mesh] OR “Adrenergic alpha-Antagonists”[Pharmacological Action] OR alpha-blocker*[Text Word] OR alpha-antagonist*[Text Word] OR “alpha-adrenergic receptor*”[Text Word] OR Prazosin[Text Word] OR Indoramin[Text Word] OR Trimazosin[Text Word] OR Doxazosin[Text Word] OR Urapidil[Text Word] OR Bunazosin[Text Word] OR Terazosin[Text Word]	65,280
#3	„Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors”[Pharmacological Action] OR ((„angiotensin converting enzyme”[Text Word] OR „angiotensin-converting-enzyme”[Text Word] OR ACE[Text Word]) AND inhibitor*[Text Word]) OR Captopril[Text Word] OR Enalapril[Text Word] OR Lisinopril[Text Word] OR Perindopril[Text Word] OR Ramipril[Text Word] OR Quinapril[Text Word] OR Benazepril[Text Word] OR Cilazapril[Text Word] OR Fosinopril[Text Word] OR Delapril[Text Word] OR Moexopril[Text Word] OR Zofenopril[Text Word]	66,322
#2	"Antihypertensive Agents"[Mesh] OR antihypertensive*[Text Word] OR anti-hypertensive*[Text Word]	97,750
#1	((Hypertension[Mesh]) OR (hypertens*[Text Word])) OR (("blood pressure*"[Text Word]) AND (high[Text Word] OR elevate*[Text Word] OR raise*[Text Word] OR increase*[Text Word]))	682,481

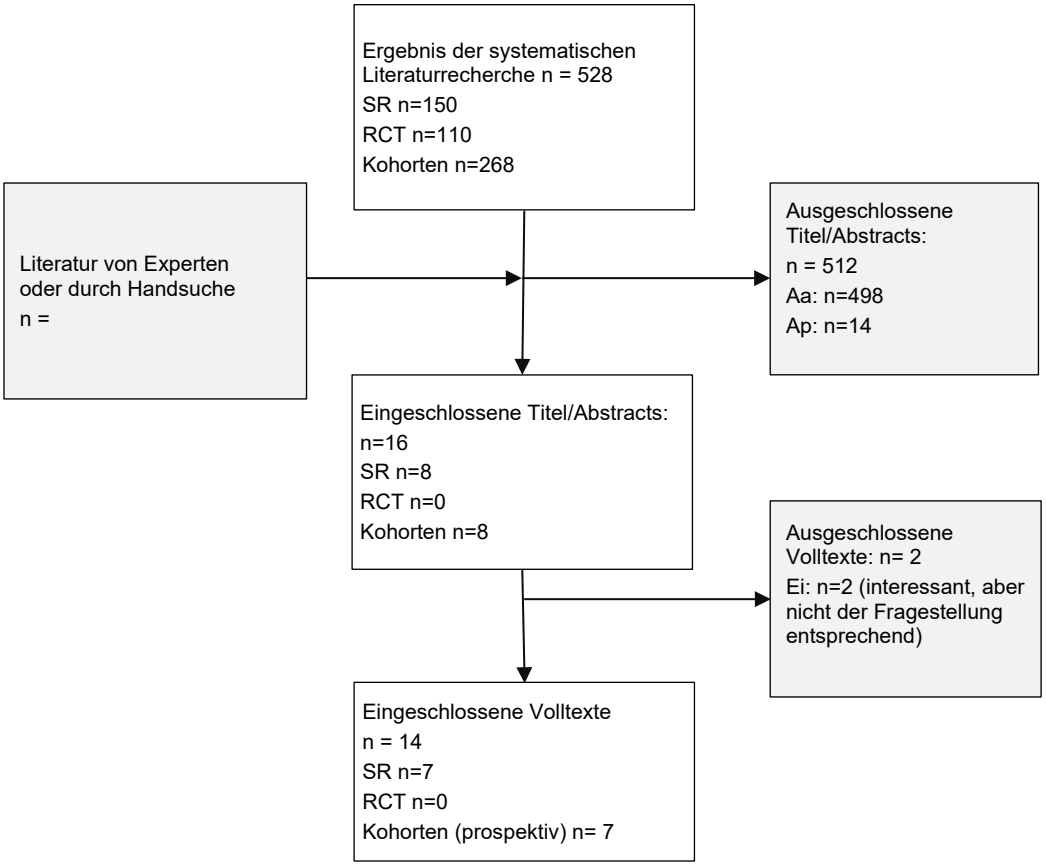
Übersicht der eingeschlossenen Treffer

	Aggregierte Evidenz	Klinische Studien	Kohorten Studien	Dubletten	Summe
Medline	150	185	268	**75**	**528**

Einschluss E	**Fragestellung passend** **Studientyp passend**	
Ausschluss A	Aa	thematisch nicht passend: andere Erkrankung, andere Fragestellung, anderes Thema
	Ap	Publikationstyp/ Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch

	Az	falscher Zeitraum: Zeitraum zu weit zurückliegend (vor …), bislang nur Protokoll veröffentlicht o. Ä.
	Aw	withdrawn
	Aq	schwache methodische Qualität
	K	Konferenzabstract

Flowchart systematische Übersichtsarbeiten (Stand: 16.06.2021)



1.11 PICO-Frage Kombinationstherapie mit Diuretika

Schlüsselfrage: Soll die Antihypertensiva-Kombinationstherapie als fixe Kombination erfolgen?

P: Patienten mit arterieller Hypertonie

I: antihypertensive Wirkstoffe in der fixen Kombination mit Diuretika

C: freie Kombination (Kohortenstudien (Langzeitbeobachtung))

O: [keine Einschränkung]

(Einschränkung des Publikationszeitraums: die letzten 10 Jahre; Grund: u.a. Beobachtungszeiträume)

(Hinweis: Adjustierung bzw. Matchingverfahren zulässig)

Medline via Pubmed (www.pubmed.gov) (24. Juni 2021)

Nr.	Suchanfrage	Results
#15	**#13 AND #14**	**478**

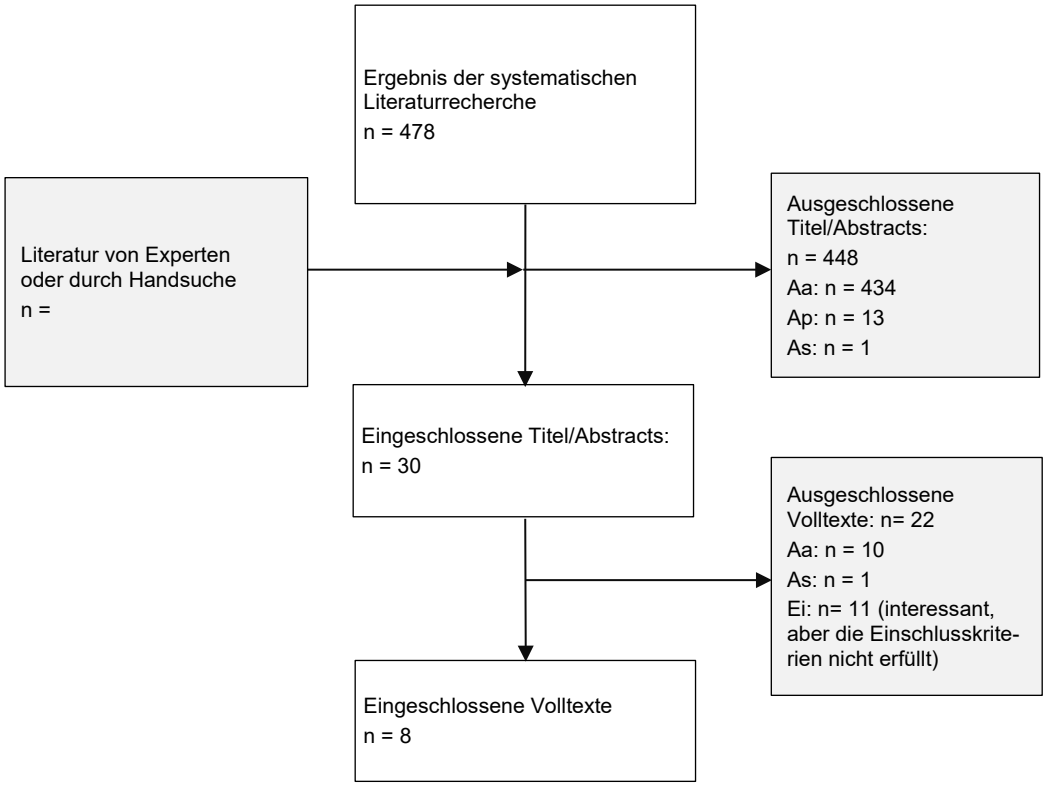
Nr.	Suchanfrage	Results
#14	"2011/01/01"[Date - Publication] : "3000"[Date - Publication]	11,903,098
#13	#11 AND #12	1,291
#12*	cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	2,858,072
#11	#1 AND #8 AND #9 AND #10	7,621
#10	“fixed-dose”[Text Word] OR “fixed dose”[Text Word] OR combin*[Text Word]	2,302,698
#9	"Diuretics"[Mesh] OR "Diuretics" [Pharmacological Action] OR diuretic*[Text Word] OR thiazide*[Text Word] OR Bendroflumenthazide[Text Word] OR Hydroflumethazide[Text Word] OR Hydrochlorothiazide[Text Word] OR Chlorothiazide[Text Word] OR Polythiazide[Text Word] OR Trichlomethazide[Text Word] OR Cyclopenthazide[Text Word] OR Methylclothiazide[Text Word] OR Cyclothiazide[Text Word] OR Mebutizide[Text Word] OR Quinethazone[Text Word] OR Clopamide[Text Word] OR Chlorthalidone[Text Word] OR Mefruside[Text Word] OR Clofenamide[Text Word] OR Metolazane[Text Word] OR Meticrane[Text Word] OR Xipamide[Text Word] OR Indapamide[Text Word] OR Clorexolone[Text Word] OR Fenquizone[Text Word] OR Furosemide[Text Word] OR Bumetamide[Text Word] OR Piretanide[Text Word] OR Torasemide[Text Word] OR Azosemide[Text Word] OR “etacrynic acid”[Text Word] OR “tienilic acid”[Text Word] OR Muzolimine[Text Word] OR Etozoline[Text Word] OR Spironolactone[Text Word] OR “potassium canrenoate”[Text Word] OR Canrenone[Text Word] OR Eplerenone[Text Word] OR Amiloride[Text Word] OR Triamteren[Text Word]	116,331
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	486,351
#7	“Calcium Channel Blockers”[Mesh] OR “Calcium Channel Blockers”[Pharmacological Action] OR (“calcium channel”[Text Word] AND (antagonist*[Text Word] OR blocker*[Text Word])) OR Amlodipin[Text Word] OR Felodipin[Text Word] OR Isradipin[Text Word] OR Nicardipin[Text Word] OR Nifedipin[Text Word] OR Nimodipin[Text Word] OR Nisoldipin[Text Word] OR Nitrendipin[Text Word] OR Lacidipin[Text Word] OR Nilvadipin[Text Word] OR Manidipin[Text Word] OR Barnidipin[Text Word] OR Lercanidipin[Text Word] OR Clinidipin[Text Word] OR Benidipin[Text Word] OR Clevidipin[Text Word] OR Verapamil[Text Word] OR Gallopamil[Text Word] OR Diltiazem[Text Word]	116,648
#6	“Adrenergic beta-Antagonists"[Mesh] OR “Adrenergic beta-Antagonists”[Pharmacological Action] OR (beta*[Text Word] AND (blocker*[Text Word] OR antagonist*[Text Word])) OR Alprenolol[Text Word] OR Oxprenolol[Text Word] OR Pindolol[Text Word] OR Propranolol[Text Word] OR Timolol[Text Word] OR Sotalol[Text Word] OR Nadolol[Text Word] OR Mepindolol[Text Word] OR Carteolol[Text Word] OR Tetratolol[Text Word] OR Bopindolol[Text Word] OR Metipranolol[Text Word] OR Bupranolol[Text Word] OR Penbutolol[Text Word] OR Cloranolol[Text Word] OR Carazolol[Text Word] OR Bunitrolol[Text Word] OR Practolol[Text Word] OR Metoprolol[Text Word] OR Atenolol[Text Word] OR Acebutolol[Text Word] OR Betaxolol[Text Word] OR Bevantolol[Text Word] OR Bisoprolol[Text Word] OR Celiprolol[Text Word] OR Esmolol[Text Word] OR Epanolol[Text Word] OR Atenolol[Text Word] OR Nebivolol[Text Word] OR Talinol[Text Word] OR Landiolol[Text Word] OR Labetalol[Text Word] OR Carvedilol[Text Word]	220,255
#5	"Angiotensin Receptor Antagonists"[Mesh] OR ((“angiotensin receptor*”[Text Word] OR “angiotensin II receptor*“[Text Word]) AND (antagonist*[Text Word] OR blocker*[Text Word])) OR ARB[Text Word] OR Losartan[Text Word] OR Eprosartan[Text Word] OR Valsartan[Text Word] OR Irbesartan[Text Word] OR Tasosartan[Text Word] OR Candesartan[Text Word] OR Telmisartan[Text Word] OR Olmesartan[Text Word] OR Azilsartan[Text Word] OR Fimasartan[Text Word]	37,922
#4	“Adrenergic alpha-Antagonists”[Mesh] OR “Adrenergic alpha-Antagonists”[Pharmacological Action] OR alpha-blocker*[Text Word] OR alpha-antagonist*[Text Word] OR “alpha-adrenergic receptor*”[Text Word] OR Prazosin[Text Word] OR Indoramin[Text Word] OR Trimazosin[Text Word] OR Doxazosin[Text Word] OR Urapidil[Text Word] OR Bunazosin[Text Word] OR Terazosin[Text Word]	65,280
#3	„Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors”[Pharmacological Action] OR ((„angiotensin converting enzyme”[Text Word] OR „angiotensin-converting-enzyme”[Text Word] OR ACE[Text Word]) AND inhibitor*[Text Word]) OR Captopril[Text Word] OR Enalapril[Text Word] OR Lisinopril[Text Word] OR Perindopril[Text Word] OR Ramipril[Text Word] OR Quinapril[Text Word] OR Benazepril[Text Word] OR Cilazapril[Text Word] OR Fosinopril[Text Word] OR Delapril[Text Word] OR Moexopril[Text Word] OR Zofenopril[Text Word]	66,322
#2	"Antihypertensive Agents"[Mesh] OR antihypertensive*[Text Word] OR anti-hypertensive*[Text Word]	97,750
#1	((Hypertension[Mesh]) OR (hypertens*[Text Word])) OR (("blood pressure*"[Text Word]) AND	682,481

* University of Texas: https://libguides.sph.uth.tmc.edu/search_filters/pubmed_filters

Nr.	Suchanfrage	Results
	(high[Text Word] OR elevate*[Text Word] OR raise*[Text Word] OR increase*[Text Word]))	

Einschluss E	Fragestellung passend Studientyp passend	
Ausschluss A	Aa	thematisch nicht passend: andere Erkrankung, andere Fragestellung, anderes Thema
	Ap	Publikationstyp/ Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum: Zeitraum zu weit zurückliegend (vor …), bislang nur Protokoll veröffentlicht o. Ä.
	Aw	withdrawn
	Aq	schwache methodische Qualität
	K	Konferenzabstract

Flowchart systematische Übersichtsarbeiten



1.12 PICO-Frage Low-Ceiling-Diuretika

Schlüsselfrage: unterscheiden sich die Low-Ceiling-Diuretika (Thiazide) von anderen Low-Ceiling-Diuretika (ohne Thiazide; Sulfonamide C03BA) in der Wirksamkeit und Sicherheit

P: Patienten mit (arterieller) Hypertonie

I: C03A Low-Ceiling-Diuretika, Thiazide: Hydrochlorothiazide OR Bendroflumethazide OR Bemetizide

C: C03B Low-Ceiling-Diuretika, excl. Thiazide bzw. C03BA Sulfonamide: Chlorthalidone OR Indapamide OR (Xipamide)

O: Mortalität (Tod), kardiovaskuläre Morbidität (Myokardinfarkt, Apoplex – Schlaganfall, Herzinsuffizienz, Herzrhythmusstörungen), Sicherheit, (Blutdruck)

→ Vorschlag zweistufiges Vorgehen: SR zu RCT und ggf. update RCT bzw. ggf. Kohortenstudien

Hinweis: Chlorthalidon vs. Indapamid wurde ebenfalls als Vergleich gesucht (2. Recherchearm)

Medline via Pubmed (www.pubmed.gov) (22. Juli 2021)

Nr.	Suchanfrage	Results
#14	**(#8 AND #13) NOT #10**	**59**
#13	cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	2,885,772
#12	**(#8 AND #11) NOT #10**	**148**
#11	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))	1,282,606
#10	**#8 AND #9**	**38**
#9	(systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	528,532
#8	**#6 OR #7**	**443**
#7	(#1 AND #3 AND #4) NOT #6	27
#6	#1 AND #2 AND #5	416
#5	#3 OR #4	3,337
#4	Xipamide[Mesh] OR Xipamide[Text Word] OR Indapamide[Mesh] OR Indapamide[Text Word]	1,512
#3	Chlorthalidone[Mesh] OR Chlortalidone[Text Word] OR Chlorthalidone[Text Word]	1,943
#2	Hydrochlorothiazide[Mesh] OR Hydrochlorothiazide[Text Word] OR Bendroflumethazide[Text Word] OR "dehydrosanol" [Supplementary Concept] OR Bemetizide[Text Word]	9,224
#1	((Hypertension[Mesh]) OR (hypertens*[Text Word])) OR (("blood pressure*"[Text Word]) AND (high[Text Word] OR elevate*[Text Word] OR raise*[Text Word] OR increase*[Text Word]))	685,928

Datenbanken der Cochrane Library (22.07.2021)

Nr.	Suchfrage	Anzahl
	#24 In Cochrane RCT NOT	**682**
	#24 in Cochrane Protocols	**0**
	#24 in Cochrane Reviews	**1**
#24	#21 NOT #22	684
	#23 In Cochrane RCT NOT	**168**

Nr.	Suchfrage	Anzahl
	#23 in Cochrane Protocols	**0**
	#23 in Cochrane Reviews	**1**
#23	#20 NOT #22	169
#22	(conference abstract):pt	178278
#21	#6 AND #12 AND #19	725
#20	#6 AND #9 AND #19	182
#19	#12 OR #15 OR #18	1482
#18	#16 OR #17	660
#17	(Indapamide):ti,ab,kw	660
#16	MeSH descriptor: [Indapamide] explode all trees	300
#15	#13 OR #14	53
#14	(Xipamide):ti,ab,kw	53
#13	MeSH descriptor: [Xipamide] explode all trees	23
#12	#10 OR #11	794
#11	(Chlortalidone OR Chlorthalidone):ti,ab,kw	794
#10	MeSH descriptor: [Chlorthalidone] explode all trees	428
#9	#7 OR #8	3996
#8	(Hydrochlorothiazide OR Bendroflumethazide OR Bemetizide):ti,ab,kw	3961
#7	MeSH descriptor: [Hydrochlorothiazide] explode all trees	2093
#6	#1 OR #2 OR #5	99268
#5	#3 and #4	48723
#4	(high OR elevat* OR raise* OR increase*):ti,ab,kw	580847
#3	("blood pressure"):ti,ab,kw	94831
#2	(hypertens*):ti,ab,kw	67272
#1	MeSH descriptor: [Hypertension] explode all trees	19004

Epistemonikos (https://www.epistemonikos.org/) (23. Juli 2021)

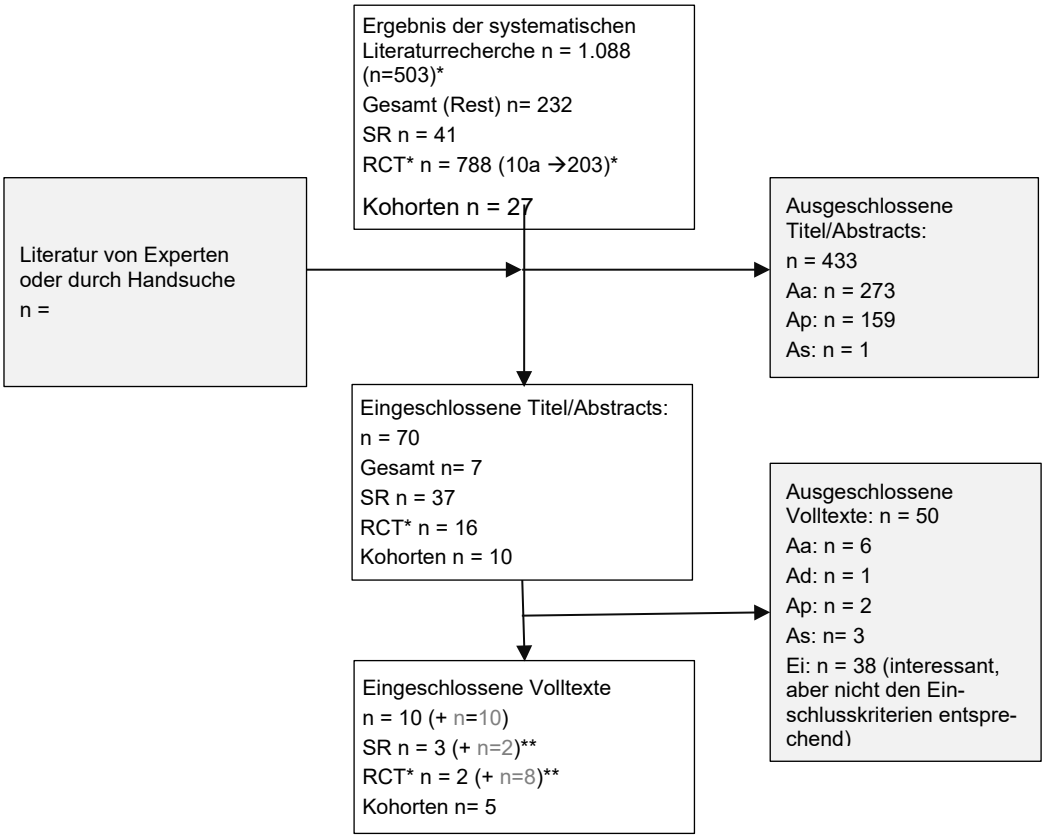
Nr.	Suchanfrage	Results
	#2 Filters Systematic Review	**9**
#2	(title:(hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*))) OR abstract:(hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))) AND (title:(Chlortalidone OR Chlorthalidone) OR abstract:(Chlortalidone OR Chlorthalidone)) AND (title:(Xipamide OR Indapamide) OR abstract:(Xipamide OR Indapamide))	10
	#1 Filters Systematic Review	**27**
#1	(title:(hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*))) OR abstract:(hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))) AND (title:(Hydrochlorothiazide OR Bendroflumethazide OR Bemetizide) OR abstract:(Hydrochlorothiazide OR Bendroflumethazide OR Bemetizide)) AND (title:(Chlortalidone OR Chlorthalidone OR Xipamide OR Indapamide) OR abstract:(Chlortalidone OR Chlorthalidone OR Xipamide OR Indapamide))	44

Übersicht der eingeschlossenen Treffer

	Gesamt	Aggregierte Evidenz	Klinische Studien	Kohorten Studien	Summe
Medline	443	38	148	59	**688**
Cochrane	-	1 + 1	168 + 682	-	**852**
Epistemonikos	-	36	-	-	**36**
Dubletten	211	35	95 + 115	32	**488**

Summe	232	41	788	27	**1.088**

Flowchart systematische Übersichtsarbeiten (Stand: 30.07.2021)



Eingeschlossene Studien:
SR: [4–6]
RCT*: [7,8] **
Kohorten: [9–13]

*Hinweis: RCT Screening für die letzten 10 Jahre, da Fragestellung in Übersichtsarbeiten teilweise beantwortet
**Hinweis: zudem wurden 2 SR [14,15] und 8 RCT [16–23] ermittelt, die Kombinationen von Chlorthalidon oder Hydrochlorothiazid mit Sartanen bzw. Indapamid oder Hydrochlorothiazid mit ACE Hemmern verglichen

Einschluss E	Fragestellung passend Studientyp passend	
Ausschluss A	Aa	thematisch nicht passend: andere Erkrankung, andere Fragestellung, anderes Thema
	Ap	Publikationstyp/ Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum: Zeitraum zu weit zurückliegend (vor …), bislang nur Protokoll veröffentlicht o. Ä.
	Aw	withdrawn
	Aq	schwache methodische Qualität
	K	Konferenzabstract

1.13 PICO-Frage Renale Denervation

SR

Schlüsselfrage: Wirksamkeit und Sicherheit der renalen Denervation bei Patienten mit (resistenter) arterieller Hypertonie

P: Patienten mit (resistenter) arterieller Hypertonie

I: Renale Denervation

C: Placebo bzw. Scheinintervention oder Standardverfahren

O: Mortalität (Tod), kardiovaskuläre Morbidität (Myokardinfarkt, Herzinsuffizienz, Herzrhythmusstörungen), Sicherheit, (Blutdruck)

→ Fragen:

- Verfahren nach „Ersttherapie“?
- Add-on?
- Zu betrachtende Endpunkte

Hinweis: der GBA hat am 20.08.2015 ein Beratungsverfahren zur sympathischen renalen Denervation zur Behandlung der schweren resistenten Hypertonie (§ 135 SGB V) eingestellt (www.g-ba.de/bewertungsverfahren/methodenbewertung/54/)

Medline via Pubmed (www.pubmed.gov) (23. August 2021)

Nr.	Suchanfrage	Results
#5	**Search: #3 AND #4**	**193**
#4	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	534,038
#3	Search: #1 AND #2	7,560
#2	Search: Denervation[Mesh] OR Ablation Techniques[Mesh] OR ((renal[tiab] OR catheter[tiab] OR radiofrequenc*[tiab] OR ultrasound[tiab]) AND (ablation[tiab] OR denervation[tiab])) OR sympathectom*[tiab] OR RDN[tiab] OR RSDN[tiab]	213,696
#1	Search: ((Hypertension[Mesh]) OR (hypertens*[tiab])) OR (("blood pressure*"[tiab]) AND	637,379

Nr.	Suchanfrage	Results
	(high[tiab] OR elevate*[tiab] OR raise*[tiab] OR increase*[tiab]))	

Datenbanken der Cochrane Library (23. August 2021)

Nr.	Suchfrage	Anzahl
#15	**(#6 AND #13) NOT (conference abstract):pt in Cochrane Protocols**	**0**
#14	**(#6 AND #13) NOT (conference abstract):pt in Cochrane Reviews**	**8**
#13	#7 OR #8 OR #11 OR #12	14888
#12	(sympathectom* OR RDN OR RSDN):ti,ab,kw	589
#11	#9 AND #10	6031
#10	(ablation OR denervation):ti,ab,kw	9937
#9	(renal OR catheter OR radiofrequenc* OR ultrasound):ti,ab,kw	113937
#8	MeSH descriptor: [Ablation Techniques] explode all trees	5934
#7	MeSH descriptor: [Denervation] explode all trees	4689
#6	#1 OR #2 OR #5	99791
#5	#3 and #4	48971
#4	(high OR elevat* OR raise* OR increase*):ti,ab,kw	585089
#3	("blood pressure"):ti,ab,kw	95406
#2	(hypertens*):ti,ab,kw	67624
#1	MeSH descriptor: [Hypertension] explode all trees	19076

Epistemonikos (https://www.epistemonikos.org) (23. August 2021)

Nr.	Suchanfrage	Results
	#1 Filters Systematic Review	**93**
#1	(title:((title:((hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))) OR abstract:((hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))))) AND (title:(((renal OR catheter OR radiofrequenc* OR ultrasound) AND (ablation OR denervation)) OR sympathectom* OR RDN OR RSDN) OR abstract:(((renal OR catheter OR radiofrequenc* OR ultrasound) AND (ablation OR denervation)) OR sympathectom* OR RDN OR RSDN))) OR abstract:((title:((hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))) OR abstract:((hypertens* OR (("blood pressure*") AND (high OR elevate* OR raise* OR increase*)))))) AND (title:(((renal OR catheter OR radiofrequenc* OR ultrasound) AND (ablation OR denervation)) OR sympathectom* OR RDN OR RSDN) OR abstract:(((renal OR catheter OR radiofrequenc* OR ultrasound) AND (ablation OR denervation)) OR sympathectom* OR RDN OR RSDN))))	201

NICE (23. August 2021)

Nr.	Suchfrage
Suchbegriffe	denervation
Suchzeitraum	Keine Einschränkung
1. Filter	guidance (clinical guidelines, diagnostic guidance, NICE guidelines, Public health guidelines, Technology appraisal guidance, interventional procedure guidance, medical technology guidance, safe staffing guideline, social care guideline) published
Treffer	2
Eingeschlossene Treffer	1 IPG418. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. 23 January 2012.

Nr.	Suchfrage
	https://www.nice.org.uk/guidance/ipg418 / https://www.nice.org.uk/guidance/ipg418/evidence/overview-pdf-438572845

Anzahl der Treffer nach Titelscreening: 1

IQWiG (23. August 2021)

Nr.	Suchfrage
Filter	Projekte, Projekte und Ergebnisse
Suchzeitraum	Keine Einschränkung
Suchbegriff: Renale Denervation, Denervation	
Treffer	2
Eingeschlossene Treffer	0
Suchbegriff: Bluthochdruck, Hypertonie, Hypertonus	
Treffer	18
Eingeschlossene Treffer	0

Anzahl der Treffer nach Titelscreening: 0

GBA (23. August 2021)

Nr.	Suchfrage
Suchbegriff: Renale Denervation, Denervation	
Treffer	17
Eingeschlossene Treffer	1 Methodenbewertung zur katheterbasierten sympathischen renalen Denervation zur Behandlung der schweren resistenten Hypertonie. Vom 20. August 2015. https://www.g-ba.de/richtlinien/7/

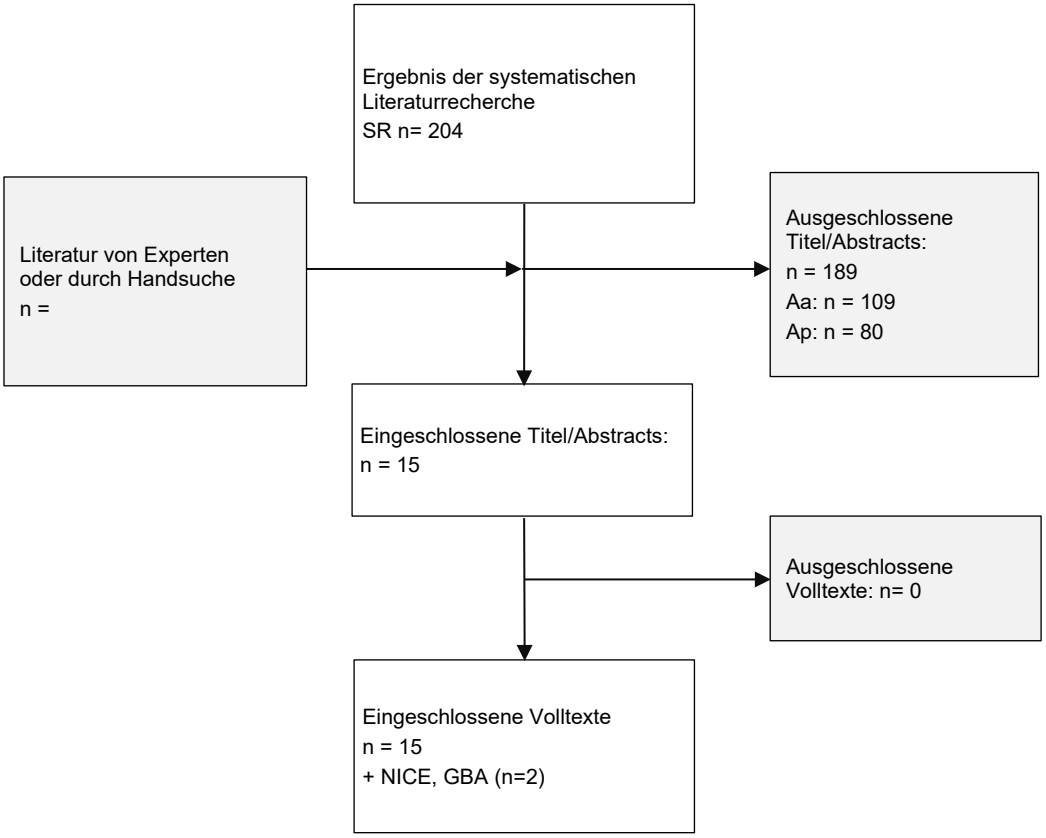
Anzahl der Treffer nach Titelscreening: 1

Übersicht der eingeschlossenen Treffer

	Aggregierte Evidenz
Medline	193
Cochrane	8
Epistemonikos	93
Summe	**294**

Dubletten:	58
Conference Abstracts/Poster:	8
Nicht engl./de:	24
Anzahl eingeschlossener Treffer:	**204**

Flowchart systematische Übersichtsarbeiten (Stand: 13.10.2021)



Einschluss E	Fragestellung passend Studientyp passend	
Ausschluss A	Aa	thematisch nicht passend: andere Erkrankung, andere Fragestellung, anderes Thema
	Ap	Publikationstyp/ Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum: Zeitraum zu weit zurückliegend (vor …), bislang nur Protokoll veröffentlicht o. Ä.
	Aw	withdrawn
	Aq	schwache methodische Qualität
	K	Konferenzabstract

Primärstudien

Schlüsselfrage: Wirksamkeit und Sicherheit der renalen Denervation bei Patienten mit (resistenter) arterieller Hypertonie

P: Patienten mit (resistenter) arterieller Hypertonie

I: Renale Denervation

C: Placebo bzw. Scheinintervention oder Standardverfahren bzw. gegeneinander

O: Mortalität (Tod), kardiovaskuläre Morbidität (Myokardinfarkt, Apoplex – Schlaganfall, Herzinsuffizienz, Herzrhythmusstörungen), (Sicherheit), (Blutdruck)

→ Vorschlag zweistufiges Vorgehen: update RCT (ab März 2014: Publikationsdatum der SYMPLICITY HTN-3 Studie, 2014*) bzw. ggf. Kohortenstudien mit eingeschränkter Endpunktbetrachtung (Mortalität, Morbidität, s.u.)

Medline via Pubmed (www.pubmed.gov) (17. Mai 2022)

Nr.	Suchanfrage	Results
#11	**Search: #7 AND #8 Filters: from 2014/3/1 - 3000/12/12 - Kohorten**	**243**
#10	**Search: #3 AND #4 Filters: from 2014/3/1 - 3000/12/12 - RCT**	**442**
#9	Search: #7 AND #8	404
#8	Search: "Mortality"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR mortalit*[Text Word] OR fatalit*[Text Word] OR death[Text Word] OR "myocardial infarction*"[Text Word] OR "heart attack*"[Text Word] OR stroke*[Text Word] OR apoplex*[Text Word] OR "heart failure"[Text Word] OR "cardiac failure"[Text Word] OR "myocardial failure"[Text Word] OR "arrhythmia*"[Text Word] OR "atrial fibrillation"[Text Word]	2,796,848
#7	Search: (#3 AND #5) NOT #6	981
#6	Search: #3 AND #4	732
#5	Search: cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]	3,078,879
#4	Search: (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))	1,342,802
#3	Search: #1 AND #2	7,836
#2	Search: Denervation[Mesh] OR Ablation Techniques[Mesh] OR ((renal[tiab] OR catheter[tiab] OR radiofrequenc*[tiab] OR ultrasound[tiab] OR neurotoxic*[tiab] OR chemical*[tiab] OR alcohol*[tiab]) AND (ablation[tiab] OR denervation[tiab])) OR sympathectom*[tiab] OR RDN[tiab] OR RSDN[tiab]	223,271
#1	Search: ((Hypertension[Mesh]) OR (hypertens*[tiab])) OR (("blood pressure*"[tiab]) AND (high[tiab] OR elevate*[tiab] OR raise*[tiab] OR increase*[tiab]))	660,155

Datenbanken der Cochrane Library (17. Mai 2022)

Nr.	Suchfrage	Anzahl
#14	**(#6 AND #13) NOT (conference abstract):pt in Trials; Filter year first published 2014**	**482**
#13	#7 OR #8 OR #11 OR #12	15679
#12	(sympathectom* OR RDN OR RSDN):ti,ab,kw	616
#11	#9 AND #10	6443
#10	(ablation OR denervation):ti,ab,kw	10330
#9	(renal OR catheter OR radiofrequenc* OR ultrasound OR neurotoxic* OR chemical* OR alcohol*):ti,ab,kw	187325
#8	MeSH descriptor: [Ablation Techniques] explode all trees	6208
#7	MeSH descriptor: [Denervation] explode all trees	4959
#6	#1 OR #2 OR #5	103695
#5	#3 and #4	50720
#4	(high OR elevat* OR raise* OR increase*):ti,ab,kw	609344

* Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. New England Journal of Medicine 2014;370:1393-401. https://pubmed.ncbi.nlm.nih.gov/24678939/

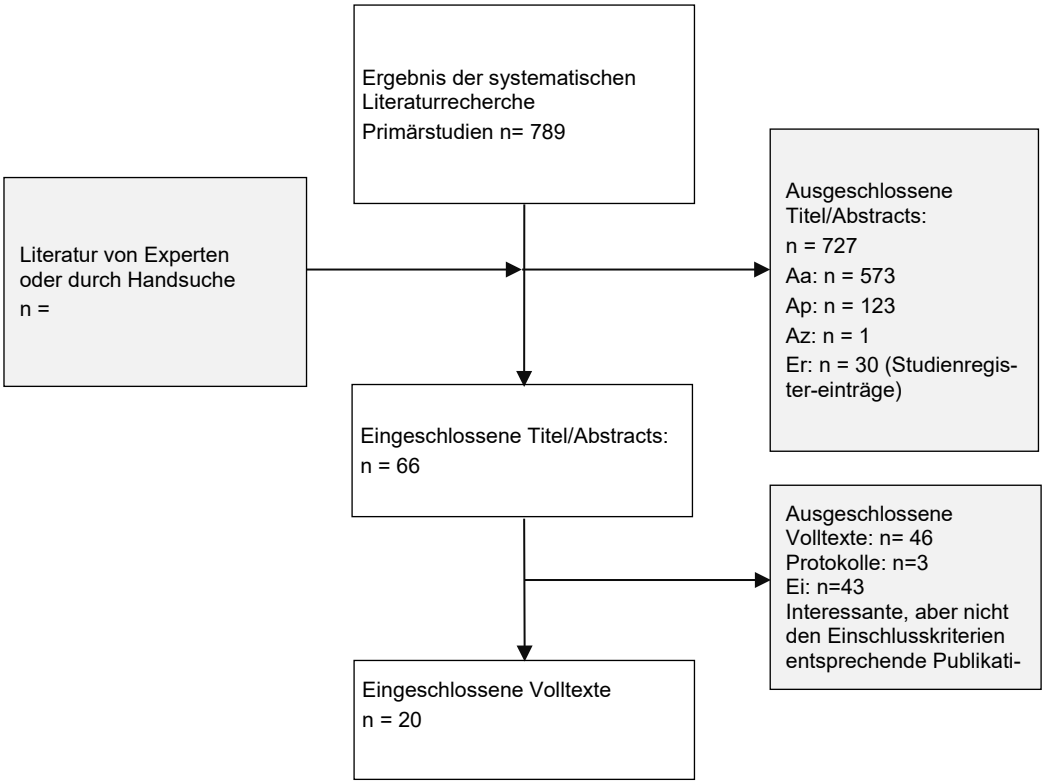
Nr.	Suchfrage	Anzahl
#3	("blood pressure"):ti,ab,kw	99119
#2	(hypertens*):ti,ab,kw	70360
#1	MeSH descriptor: [Hypertension] explode all trees	19722

Übersicht der eingeschlossenen Treffer

	RCT	Kohortenstudien	GESAMT
Medline	442	243	
Cochrane	482	-	
Summe	**924**	**243**	**1167**

Dubletten aufgrund 1. Recherche nach SR:	160
Dubletten:	172
Conference Abstracts/Poster:	38
Nicht engl./de:	8
Anzahl eingeschlossener Treffer:	**789**

Flowchart systematische Übersichtsarbeiten



Einschluss E	Fragestellung passend Studientyp passend	
Ausschluss A	Aa	thematisch nicht passend: andere Erkrankung, andere Fragestellung, anderes Thema
	Ap	Publikationstyp/ Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum: Zeitraum zu weit zurückliegend (vor …), bislang nur Protokoll veröffentlicht o. Ä.
	Aw	withdrawn
	Aq	schwache methodische Qualität
	K	Konferenzabstract

2 Evidenztabellen Epidemiologie

2.1 Handsuche/ Literaturlistensuche

NCD Risk Factor Collaboration (NCD-RisC) Lancet 2021 worldwide hypertension prevalence (1990-2019, cohort)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021 Sep 11;398(10304):957-980. doi: 10.1016/S0140-6736(21)01330-1. Epub 2021 Aug 24. https://pubmed.ncbi.nlm.nih.gov/34450083/ [24]	**Background** we aimed to measure the prevalence of hypertension and progress in its detection, treatment, and control from 1990 to 2019 for 200 countries and territories **Design** - data from 1990 to 2019 on people aged 30-79 years from population-representative studies with measurement of blood pressure and data on blood pressure treatment - collated by the NCD Risk Factor Collaboration (NCD-RisC) - for 200 countries and territories (referred to as countries hereafter) - Bayesian hierarchical model to estimate the prevalence of hypertension (fitted using Markov chain Monte Carlo (MCMC) algorithm) - the model allowed for trends over time to be non-linear and to vary by age **Inclusion and exclusion criteria** - hypertension: systolic blood pressure ≥140 mm	n=1202 studies (carried out from 1990 to 2019) n=104 million participants - n=986 (82.1%) studies with information on previous diagnosis **Results** - global age-standardised prevalence of hypertension in 2019 (adults, 30-79 years of age): o women: 32% (95% CI 30-34) o men: 34% (95% CI 32-37) - stable global prevalence in relation to 1990: 32% women vs. 32% men - decrease in high-income contries and increase, or at best remained unchanged, in most low-income and middle-income countries - number of people aged 30-79 years with hypertension doubled from 1990 to 2019, from 331 (95% credible interval 306-359) million women and 317 (292-344) million men in 1990 to 626 (584-668) million women and 652 (604-698) million men in 2019, despite stable global age-standardised prevalence - in 2019, age-standardised hypertension prevalence was lowest in Canada and Peru for both men and women; in Taiwan, South Korea, Japan, and some countries in western Europe including Switzerland, Spain, and the UK for women; and in several low-income and middle-income countries such as Eritrea, Bangladesh, Ethiopia, and Solomon Islands for men	ROB nicht anwendbar Funding: WHO; The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.	als Handsuche aus der Konsultationsphase; nach besprechung in der Leitliniengruppe Aufnahme als redaktionelle Ergänzung: kurze Textergänzung (aktuelle epidemiologische Daten, welche die weltweite Relevanz der Hypertonie im Zeitverlauf darlegt); https://pubmed.ncbi.nlm.nih.gov/34450083/

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	Hg, diastolic blood pressure ≥90 mm Hg, or taking medication for hypertension - (1) data were collected using a probabilistic sampling method with a defined sampling frame; - (2) data were from population samples at the national, sub-national (covering one or more sub-national regions), or community (one or a small number of communities) level; - (3) systolic blood pressure and diastolic blood pressure were measured; and - (4) data on hypertension treatment were available **Outcome** **primary:** - prevalence of hypertension - the proportion of people with hypertension who reported a previous hypertension diagnosis (detection), - who were taking medication for hypertension (treatment), - and whose blood pressure was controlled (control)) - also report the proportion of people with hypertension who were undiagnosed or untreated with systolic blood pressure 160 mm Hg or greater or diastolic blood pressure 100 mm Hg or greater	- hypertension prevalence surpassed 50% for women in two countries and men in nine countries, in central and eastern Europe, central Asia, Oceania, and Latin America - globally, 59% (55-62) of women and 49% (46-52) of men with hypertension reported a previous diagnosis of hypertension in 2019, and 47% (43-51) of women and 38% (35-41) of men were treated - control rates among people with hypertension in 2019 were 23% (20-27) for women and 18% (16-21) for men - in 2019, treatment and control rates were highest in South Korea, Canada, and Iceland (treatment >70%; control >50%), followed by the USA, Costa Rica, Germany, Portugal, and Taiwan - treatment rates were less than 25% for women and less than 20% for men in Nepal, Indonesia, and some countries in sub-Saharan Africa and Oceania - control rates were below 10% for women and men in these countries and for men in some countries in north Africa, central and south Asia, and eastern Europe - treatment and control rates have improved in most countries since 1990, but we found little change in most countries in sub-Saharan Africa and Oceania. Improvements were largest in high-income countries, central Europe, and some upper-middle-income and recently high-income countries including Costa Rica, Taiwan, Kazakhstan, South Africa, Brazil, Chile, Turkey, and Iran. Hypertension treatment cascade in 2019 (Figure 3):		

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
		High-income western: women - 73% (95% CI 69-78) diagnosed o 27% (95% CI 22-31) not diagnosed o 10% diagnosed, but not treated - 64% (95% CI 58-69) treated o 21% treated but not controlled - 43% (95% CI 35-50) controlled Men - 69% (95% CI 65-73) diagnosed o 31% (95% CI 27-35) not diagnosed o 11% diagnosed, but not treated - 58% (95% CI 53-63) treated o 21% treated, but not controlled - 37% (95% CI 30-43) controlled **author interpretation:** Improvements in the detection, treatment, and control of hypertension have varied substantially across countries, with some middle-income countries now outperforming most high-income nations. The dual approach of reducing hypertension prevalence through primary prevention and enhancing its treatment and control is achievable not only in high-income countries but also in low-income and middle-income settings.		

3 Evidenztabellen Früherkennung (Stand: 27.01.2021)

3.1 Screening

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
High Blood Pressure in Adults: Screening [25] https://www.ncbi.nlm.nih.gov/books/NBK269495/	2014	low	**Fragestellungen:** 1. Does screening for high BP reduce CVD and mortality in adults age 18 years or older? 2. What is the best way to screen for high BP in adults in the primary care setting? a. How accurate are clinic-based BP measurement methods (e.g., manual vs. automated) in provisionally diagnosing hypertension within a single visit?	**Allgemeines:** - 1 trial examining the benefits of screening for high BP (KQ 1) - 7 studies examining the diagnostic accuracy of clinic-based BP measurements and protocols - 15 studies examining the predictive value of clinic-based and other BP measurements (i.e., ABPM and HBPM)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
pdf/Bookshelf_NBK269495.pdf			b. What screening protocol characteristics within a single visit (e.g., sitting quietly for 5 minutes, number of readings) define the best diagnostic accuracy? 3. What is the best way to confirm hypertension in adults who initially screen positive for high BP? a. How well do ABPM and HBPM methods predict CV events compared with clinic-based methods? What confirmation protocol characteristics define the best prediction of CV events? Which methods and associated protocols best predict CV events*? b. How accurate are other noninvasive BP measurement methods in establishing or confirming the diagnosis of hypertension compared with these best methods and associated protocols? Does diagnostic accuracy vary by protocol characteristics (i.e., number of visits)? c. Does changing the measurement method from that used during the initial screening improve diagnostic accuracy for some specific patient subgroups (e.g., those with suspected white coat hypertension†)? 4. What is the clinically appropriate rescreening interval for patients who have previously been screened and found to have normal BP? a. What is the shortest interval in which clinically significant, diagnosed hypertension may develop? b. Does the rescreening interval vary by patient characteristics? 5. What are the adverse effects of screening for high BP in adults? **Suchzeitraum:** 2003-02/2014 **Population**: ≥ 18y **Indextest/ Referenztest:** siehe Fragestellung Studientyp: RCTs and CCTs (KQs 1 and 5) and cohort studies (KQ 5 only); for diagnostic accuracy longitudinal cohort studies	- 27 studies examining the diagnostic accuracy of other BP measurement methods - 40 studies evaluating rescreening for high BP in adults - 9 studies examining the harms of screening for high BP **Ergebnisse:** - One randomized, controlled trial (39 clusters; n=140,642) of a Canadian BP screening program (adults ≥ 65 y) reported 3.02 fewer annual hospital admissions for CV disease per 1,000 persons in the intervention group compared with the no screening group - 3 studies, automated oscillometric office BP results showed a range of sensitivity (51%–68%) for elevated BP, defined by manual mercury sphygmomanometry, but more consistent specificity (97%–98%) and positive predictive value (PPV) (76%–84%). - ABPM predicted long-term CV outcomes independently of office BP (HR range, 1.28 - 1.40, 11 studies). - Across 27 studies, 35% - 95% of persons with an elevated BP at screening remained hypertensive after nonoffice confirmatory testing. - CV outcomes in persons who were normotensive after confirmatory testing (isolated clinic hypertension) were similar to outcomes in those who were normotensive at screening. - In 40 studies, hypertension incidence after rescreening varied considerably at each yearly interval up to 6 years. - Intrastudy comparisons showed at least 2-fold higher incidence in older adults, those with high-normal BP, overweight and obese persons, and African Americans. - 4 trials found no significant differences in psychological distress or quality of life after patients were labeled as hypertensive or prehypertensive. - 1 cohort study reported significantly increased absenteeism up to 4 years after labeling compared with the year before. - 3 cohort studies reported significant sleep disturbances associated with ABPM use and 1 study reported that a significant proportion of ABPM users experienced pain, skin irritation, and overall discomfort. - Discomfort and restrictions in daily activities were more frequently reported with ABPM than HBPM in one study	

4 Evidenztabellen Diagnostik (Stand: 27.01.2021)

4.1 Diagnostik

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [A] Evidence review for diagnosis [26] https://www.nice.org.uk/guidance/ng136/evidence/a-diagnosis-pdf-6896748206 Freier Volltext	2019	low	**Fragestellungen:** *1. Diagnostic clinical effectiveness: In adults with suspected primary hypertension, what is the best method of measuring blood pressure (home, ambulatory or clinic measurement) to establish the diagnosis and prevent cardiovascular events?* **Suchzeitraum:** bis 10/2018 **Population:** Adults (> 18 y) with suspected primary hypertension **Intervention:** methods of measuring BP followed by appropriate treatment based on the BP measurement (test + treatment): Home measurement (HBPM) without telemonitoring, HBPM with telemonitoring, Ambulatory measurement (ABPM), Clinic or office measurement (CBPM), Pharmacy measurement **Vergleich:** each other **Endpunkte** (at ≥ 12 months): *Critical:* All-cause mortality, HrQoL, Stroke (ischaemic or haemorrhagic), Myocardial infarction (MI) *Important*: Heart failure needing hospitalisation, Vascular procedures (including coronary and carotid artery procedures), Angina needing hospitalisation, Intolerance to device **Studientypen:** RCTs, SR *2. Diagnostic accuracy: In people with suspected hypertension, which test is most accurate in identifying whether hypertension is present, as indicated by the reference standard, ambulatory blood pressure measurement?* **Suchzeitraum**: bis 10/2018 **Population:** Population: Adults (over 18 years) with suspected primary hypertension **Intervention:** Home measurement (HBPM) without telemonitoring, HBPM with telemonitoring,	**Zu Fragestellung 1:** keine Studien identifiziert **Zu Fragestellung 2:** **Baseline-Informationen** - 13 Studien identifiziert, 11 für Evidenzsynthese nutzbar - 3 diagnostic tests evaluated **Art der Blutdruckmessung/ des Telemonitorings** - siehe Appendix D (S. 61f/104) o. Detailaufbereitung **Home BP measurement without telemonitoring** - 4 studies, n=963: specificity 84%; sensitivity of 90%; diagn. threshold ≥135/85 mmHg (very low quality) - 1 study, n=340: specificity 62.4%, sensitivity 84%; study could not be combined in the meta-analysis, as 2x2 table values or prevalence were not reported (Low quality) - 1 study, n=203: specificity 81%, sensitivity 71%, diagn. threshold ≥130/85 mmHg (Very low quality) - 1 study, n=203: specificity 90%, sensitivity 63%, diagn. threshold ≥130/80 mmHg (Very low quality) - 1 study, n=47: HBPM with a wrist cuff, specificity 70%, sensitivity 100%, diagn. threshold ≥135/85 mmHg (Moderate quality) - 1 study, n=43: HBPM with a wrist cuff and position sensor specificity 76%, sensitivity 100%, diagn. threshold ≥135/85 mmHg (Moderate quality) **Home BP measurement with telemonitoring:** - 3 studies, n=539: specificity 63%, sensitivity of 80% diagn. threshold ≥135/85 mmHg (Very low quality) **Clinic BP measurement** (alle: diagn. threshold ≥140/90 mmHg)**:** - 3 studies, n=1,250: specificity 76%, sensitivity of 81%, (Very low quality) - 1 study, n=340: specificity 89.3%, sensitivity of 41.4%, using 2. and 3. readings over 3 days (Low quality) - 1 study, n=340: specificity 78.7%, sensitivity 61.1%, using 2. - 6. readings over 3 days (Low quality) - 1 study, n=340: specificity 59%, sensitivity 44.4%, using 1. reading from day 1 only (Low quality)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Clinic or office measurement (CBPM),Pharmacy measurement **Reference standard:** ABPM (daytime or 24 hour) **Endpunkte:** Critical: Sensitivity, Specificity, Raw data to calculate 2x2 tables to calculate sensitivity and specificity Important: AUC, Likelihood ratios, Predictive values **Studientypen**: Cross-sectional, diagnostic accuracy observational cohort studies, SRs of observational cohort		

4.2 Detailaufbereitung Diagnostik (bereits bearbeitet)

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
den Hond Querschnittstudie	247	People with a diastolic office BP >95 mmHg	**HBPM** - digital BP monitor - brachial artery - morning (06.00-10.00h), evening (18.00-22.00h) - 3 readings after 5 minutes of rest - sitting position. - Diagnostic threshold: 135/85 mmHg	**24 hour ABPM** - oscillometric Space-Labs 90207 monitors - 15-minute intervals: 08.00-22.00 h - 30 minute intervals: 22.00-08.00h - Daytime and nighttime ABP: time-weighted means of the readings obtained from 10.00-20.00 h and from 00.00-06.00 h - Diagnostic threshold: 135/85 mmHg	-	Unclear if participants were already diagnosed with hypertension
Gerc 2000 Retrospektive Kohorte	1466	Consecutive people referred to a hypertension clinic	**Clinic BPM** - Nurse-measured BP - 3 times - sitting position - Y-tube connecting sphygmomanometer and recorder - Korotkoff phases I and V used to identify SBP and DBP values - Mean value reported	**Daytime ABPM** - Vorab: Abgleich 3 automatischer Messungen mit denen des Pflegepersonals. Wenn Differenz wiederholt >5mmHg: Ausschluss - 12h daytime period (≥ 10/12 h): ABPM every 20 minutes - performed on working days - routine activities - unusual physical exercise avoided - diagnostic threshold 140/90 mmHg but also reported statistical measures with threshold of 135/85, which was used.	-	People under the age of 18 also included; proportion not specified
Gill 2017 Querschnittstudie	551	Hypertensive people recruited from primary care	**1. Index test: HBPM (with telemonitoring).** - Threshold >135/85 mmHg - Participants fitted with device - Home measurements: 2x/morning and evening for 1	**Daytime ABPM** - ambulatory monitor - Readings: half-hourly intervals during day (07.00-23.00h); hourly overnight	k.A.	Unclear if participants were taking antihyper-

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
			week, - first days readings discarded - mean of remaining readings calculated. - minimum of 12 readings were considered valid if there were ≥ 4 days readings using average except the 1st day's readings. **2. Index test: CBPM** - 6 sets of CBPM taken by nurse at 3 clinic visits - first CBPM: simultaneously on both arms - non-dominant arm unless difference in SBP was > 20mmHg between arms, it was measured in arm with higher reading. - Mean of 2nd and 3rd readings over 3 days - Threshold >140/90 mmHg. **3. Index test: CBPM** - Durchführung analog 2. Index test - Mean of 2nd to 6th readings over 3 days - Threshold >140/90 mmHg. **4. Index test: CBPM** - Durchführung analog 2. Index test - first reading from the first day - Threshold >140/90 mmHg.	- mean daytime BP calculated. - ABPM readings: valid if there were ≥ 14 daytime (07.00-23.00h) readings/person - Threshold >135 mmHg SBP/85 DBP		tensive medication
Mansoor 2004 Querschnitt-studie	48	People referred to health centre with an office BP >140/09 mmHg	**HBPM (with telemonitoring)** - taught by nurses: measure BP and check devices' accuracy. - sit quietly for 5 minutes beforehand - large cuff used for mid-arm circumference >34cm. - 3 readings 07.00-22.00h for 7 days. - device set to allow readings at 1-minute intervals - Threshold SBP >135 mmHg.	**daytime ABPM** - device. - studied on a typical workday - ≥ 75% of readings had to be valid for a participant to be included, with < 3-hour gap without a reading/hour - Participant diaries: check sleep times, calculate nighttime averages. - Threshold >135 mmHg SBP or >85 DBP daytime readings.	Index Test - trans-telephonic BP device that transmitted data over analogue telephone lines.	Unclear if participants were already diagnosed with hypertension
Mutlu 2016 Querschnitt-studie	160	Adults that were eligible for ABPM; baseline BP unclear	**HBPM** - People were instructed on how to measureBP - informed to visit pharmacy to have their BP checked (1 day of measurement) - Diagnostic threshold 130-135/85 mmHg	**24-hour ABPM** - diagnostic threshold 125-130/80 mmHg - no further details	-	Diagnosis prior to study is unclear
Nunan 2015 Querschnitt-	247	SBP between 130–179 mmHg	**HBPM with telemonitoring:** - 2-7 day; 1-5 day; 2-5 day or 1-5 day measurement - 5minute seated test: identify which arm should be	**Daytime hour ABPM** - undertaken after index test - using clinically validated monitor	Indextest: - automated	Participants already diagnosed

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
studie			used for HBPM. - non-dominant arm was used (if difference of ≥ 10 mmHg SBP between arms, highest reading used) - 6 sequential measurements separated by a 1-minute rest using same device. - self-monitored BP daily for 28 days - 2 readings morning and 2 evening - 1-3 minute gap between 1st and 2nd and following a 5 minute seated rest - Threshold 135/85 mmHg.	- 07.00-23.00h: readings half-hourly - 23.00-07.00h: readings hourly - Threshold 135/85 mmHg.	sphygmomanometer paired to mobile phone via Bluetooth - transmit BP readings securely to a dedicated web database. - Email alerts automatically generated for critically high or low BP values.	with hypertension or receiving antihypertensive treatment were excluded
Ozdemir 2000 Querschnitt-Studie	126	Eligible renal transplant donors in an outpatient department	**CBPM** - Measurements during clinical visits prior to start of ABPM - 3 consecutive measurements - mean of 3 recorded	**24-hour ABPM** - Fully automatic Accutracker II used. - 06.00-23.00h: readings every 20 minutes - 23.00-06.00h: readings every 45 minutes - educated how to improve measurements - if > 10% of measurements unsuccessful: re-evaluated with ABPM.	-	Population not 'suspected hypertension'; mix of hypertensive and normotensive
Park 2017 Querschnitt-studie	319	Clinic blood pressure above 140/90 mmHg	**HBPM** - Measurements: 7 consecutive days, ended on morning of day 8 - 3 different diagnostic thresholds: (1) SBP ≥135 mmHg and/or DPB ≥85 mmHg (2) SBP ≥130 mmHg and/or DBP ≥85 mmHg (3) SBP ≥130 mmHg or DBP ≥80 mmHg	**24-hour ABPM** - Readings started on 8th day for 1 day - Measurements on non-dominant arm - automated oscillometric device - measurement interval: 30 minutes - valid = readings for > 70% of attempts with ≥14 daytime and 7 nighttime readings. - Diagnostic threshold: 24-h average of ≥130 mmHg SBP and/or ≥80 mmHg DBP	-	Population not 'suspected hypertension'
Shimbo 2009 Querschnitt-studie	229	Normotensive or Stage 1 hypertensive (140–159 mmHg/90–99 mmHg)	**HBPM** - over a 10-week period - automatic HBP monitor - modem provided a telephone link to server located at measurement centre. - time and date stamp for each reading, stored 125 readings in memory - 3 HBPM: 4 days a week (morning + evening) - additional HBPM mid-day: 2 days/ week - total of 36 measurements/ week - analysis used first 12 values (in line with minimum required as per AHA systematic review) - hypertension threshold ≥ 135/85 mmHg	**Daytime ABPM** - first visit: ABPM was initiated over a period of 36h - 75% of these recordings, ABPM took BP readings every 30 minutes - remaining recordings were taken at 15-minute intervals (between 06.00-22.00) - Only first 24h of measurements: included in analysis. - ABPM repeated at week 4 and week 8 (but not used in analyses). - ≥ 135/85 mmHg for hypertension threshold.	-	Unclear if participants diagnosed prior to study or on antihypertensive medication. Participants with a normotensive office BP excluded (after being included in the study initially, n=145)

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
Stergiou 2000 Nicht-randomisierte Studie	142	clinic DBP of 90–115 mmHg, diagnosis of hypertension was questionable	**HBPM** - 3 workdays/week for 2 weeks, - duplicate morning and evening measurements - after 5 minutes of sitting, 1 minutes between recordings.	**ABPM** - every 20 minutes for 24 hours	-	2-week washout period. CBPM were also taken but not compared to reference standard therefore results not extracted for this arm.
Uen 2002 RCT (cross-over)	46	Participants either normotensive SBP <140 mmHg, or hypertensive.	**HBPM** - wrist device with position sensor - duration 16 days, - 8 days using each home BP device. - Measurements: 2x morning and 2x evening. - Only stored data were used **CBPM** - sitting at 2-minute intervals - auscultatory BP measurement device - 2 office measurements/arm were performed at study entry.	**24-hour ABPM.** - Recorded on days 8 and 9. - Measurements: during working days -BP measured at 15 minute intervals from 07.00-22.00 and 20-minute intervals at night classified as hypertensive if: • SBP ≥130 mmHg or DBP ≥80 mmHg for 24-hour BP measurement • SBP ≥135 mmHg or DBP ≥85 mmHg for daytime values of 24-hour BP measurement • SBP ≥135 mmHg or DBP ≥85 mmHg for self-BP measurement • SBP ≥140 mmHg or DBP ≥90 mmHg for office measurements.	-	Diagnosis and anti-hypertensive treatment unclear.
Ungar 2004 Querschnittstudie	388	People being referred to an outpatient clinic for suspected or established hypertension	**CBPM** - standard Cuff used - larger cuff if arm circumference > 32 cm - 2 measurements taken 24h apart after ≥ 10 minutes of sitting - 3rd measurement taken if first 2 differed by > 5 mmHg - Threshold ≥ 140/90 mmHg	**Daytime ABPM** - oscillometric device - cuff placed on non-dominant arm - 3 cuff sizes used based on arm circumference - daytime: every 15 minutes - nighttime: every 20 minutes - on a working day - arm in a relaxed and stable position during measurements - record their activities - Threshold ≥ 135/85 mmHg.	-	Participants: a subgroup of original study not taking antihypertensive medication
Zhuo 2009 Querschnittstudie	126	SBP ≥ 130 mmHg and < 160 mmHg (DBP 80–100 mmHg)	**HBPM** - Automatic device used - self-measurements taken at 1-minute intervals - after 10 minutes of rest in a quiet room. - 2nd and 3rd measurements at each measurement	**24-hour ABPM.** - threshold in prehypertensive population (according CBPM): based on a 24-hour ambulatory threshold: ≥ 130/80 mmHg. - threshold in hypertensive population (according	-	Not ‘suspected hypertension’ population

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
			were averaged. - between 06.00-08.00h and 18.00-20.00h - Diagnostic threshold ≥138/85 mmHg	CBPM): based on daytime measurement: ≥ 135/85 mmHg. - Oscillomertic device - non-dominant arm - over 24-hour period - throughout normal daily activities (had to stay still with forearm extended during measurement). - 07.00-22.00h: 30-minute intervals - 22.00-07.00h: 1-hour intervals - If < 80% of readings available: participants not included in analysis - maximum of 2 h allowed to be unaccounted for in 24-hour period.		

4.3 EKG

Methodische Bewertung: QUADAS-II

Zitat	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Calderon A. Detection of left ventricular hypertrophy by different electrocardiographic criteria in clinical practice. Findings from the Sara study. Clin Exp Hypertens 2010; 32(3):145–53. (Publikation zur Beurteilung der Methodik: #30655) [27]	unklar	gering	unklar	unklar	unklar	gering	unklar
Shao Q. Newly proposed electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in a Chinese population. Ann Noninvasive Electrocardiol 2019; 24(2):e12602. [28]	gering	gering	gering	gering	unklar	gering	gering
Gosse P. ECG detection of left ventricular hypertrophy: The simpler, the better? J Hypertens 2012; 30(5):990–6. [29]	unklar	unklar	unklar	unklar bis hoch	gering	gering	gering
Mahn JJ. Test characteristics of electrocardiography for detection of left ventricular hy-	gering	gering	unklar	gering	unklar	gering	gering

Zitat	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
pertrophy in asymptomatic emergency department patients with hypertension. Acad Emerg Med 2014; 21(9):996–1002. [30]							
Jiang X. Electrocardiographic criteria for the diagnosis of abnormal hypertensive cardiac phenotypes. J Clin Hypertens (Greenwich) 2019; 21(3):372–8. [31]	gering	unklar	unklar	unklar	gering bis unklar	gering	gering
Kuhl JT. Left ventricular hypertrophy identified by cardiac computed tomography and ECG in hypertensive individuals: A population-based study. J Hypertens 2019; 37(4):739–46. [32]	unklar	unklar	unklar	unklar	gering	gering	gering

Evidenztabelle

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
ID 30361 Shao Q. Newly proposed electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in a Chinese population. Ann Noninvasive Electrocardiol 2019; 24(2):e12602. [28] https://www.ncbi.nlm.nih.gov/pubmed/30281188. Freier Volltext	2019	**Fragestellung:** to investigate the correlation of these novel ECG criteria in the diagnosis of LVH with hypertensive patients in a Chinese population. **Population:** - n= 235 - hospitalized hypertensive patients (defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, or any type of antihypertensive medication) **Indextest:** - 12-Kanal-EKG: Cornell Voltage Criteria, Sokolow–Lyon voltage criteria, newly proposed SD + SV4 Kriterium **Referenztest:** - Transthoracic echocardiography used to diagnose LVH - defined as interventricular septum and LVr posterior wall thickness > 11 mm each **ausgewählte Ausschlusskriterien:** - atrial or ventricular arrhythmias - complete left or right bundle branch block, - inability to obtain or unclear echocardiographic images, - a history of myocardial infarction, - ventricular paced rhythm. **Studientyp:** Querschnittstudie	**ausgewählte Baseline-Charakteristika:** - 116 hypertensive patients with LVH (50% male; mean age 65.7 y), - 119 hypertensive patients without LVH (48.7% male; mean age 64.9 y) - groups comparable in baseline characteristics - exception: higher incidences of stroke and renal insufficiency in LVH group **Ergebnisse** **-** higher voltage values in the LVH group vs. non-LVH group in: - newly proposed (SD + SV4; 2.35 ± 0.95 vs. 1.47 ± 0.61) - Cornell limb lead criteria (RavL + SV3; 1.68 ± 0.61 vs. 1.25 ± 0.51). - Sokolow–Lyon criteria (SV1 + RV5) no significant difference between groups (2.09 ± 0.86 vs.1.90 ± 0.71). **Sensitivität:** - Cornell limb lead criteria (male: 55.2%; female: 56.9%) - Sokolow–Lyon criteria (male: 63.8%; female: 51.7%). - newly proposed criteria (male: 65.5%; female:81.0%), S**pecificity** - Cornell limb lead criteria (male: 75.9%; female: 94.0%) - Sokolow–Lyon criteria (male: 56.9%; female: 59.0%) - newly proposed criteria (male: 74.1%; female: 77%) **AUC:** - novel criteria, values of ≥2.6 mV for male (AUC: 0.772; 95% CI: 0.687–	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
		Land: China **Studienzeitraum:** 2017-2018	0.856) and ≥2.1 mV for female subjects (AUC: 0.832; 95% CI: 0.757–0.906) were considered positive for LVH (Figures 2 and 3). - Cornell limb lead criteria predicted LVH at lower values (males: 2.04 mV; females: 1.71 mV) than in the guidelines (2.8, 2.0 mV, respectively). - same phenomenon in the standard of the Sokolow–Lyon criteria (males: 2.05 mV; females: 1.95 mV).	
ID 30363 Jiang X. Electrocardiographic criteria for the diagnosis of abnormal hypertensive cardiac phenotypes. J Clin Hypertens (Greenwich) 2019; 21(3):372–8. [31] https://www.ncbi.nlm.nih.gov/pubmed/30706989. Freier Volltext	2019	**Fragestellung:** aims to compare the diagnostic value of single and combined ECG criteria for ECHO LVH and LAE. **Population:** - patients with hypertension - aged between 30 and 65 years - urban community of Beijing. **Indextest:** - EKG mit 18 Scores **Referenztest:** - Echo - LVM by cube formula: 0.8 × 1.04 × [(IVSd+LVIDd+PWTd)3 − LVIDd3] + 0.6g and indexed to body surface area (LVMI) - Left atrial volume indexed by body surface area (LAVI). **ausgewählte Ausschlusskriterien:** - secondary or suspected secondary hypertension - heart failure - LVEF < 50%, - angina pectoris, myocardial infarction, PCI with stent or coronary artery bypass graft surgery, - CV diseases, atrial fibrillation, left bundle branch block, cardiac valve diseases, cardiomyopathy - pregnancy **Studientyp:** Querschnitt **Land:** China **Zeitraum:** 2017-2018	**ausgewählte Baseline-Charakteristika:** - 152 hypertensive patients - average age of 58 y, - 29% male and 71% female subjects. - mean duration of HTN: 10 years. - patients with obesity: 24%. - The proportion of patients with ECHO LVH was 14% **Ergebnisse** - sensitivity of SD+SV4 was highest (29%; 95% CI: 12%, 52%) **Sensitivität:** Cornell Voltage Criteria: 3/21 (14%) 95%KI 3.8%, 37% Cornell voltage Duration Product: 5/21 (24%) 95%KI 9.1%, 47.5% Sokolow-Lyon: 3/21 (14%), 95% KI 3.8%, 37% **Spezifität:** Cornell Voltage Criteria: 129/131 (98%) 95%KI 94%, 99.7% Cornell voltage Duration Product: 128/131 (98%) 95%KI 93%, 99% Sokolow-Lyon: 128/131 (98%), 95%KI 93%, 99% **AUC:** Cornell Voltage Criteria: 0.71 (0.58-0.84) Cornell voltage Duration Product: 0.72 (0.59-0.85) Sokolow-Lyon: 0.71 (0.59-0.83)	
ID 30364 Kuhl JT. Left ventricular hypertrophy identified by cardiac computed tomography and ECG in hypertensive individuals: A population-	2019	**Fragestellung:** - to identify individuals with LVH using both cardiac CT and ECG and to explore potential differences between these phenotypical distinct diagnostic modalities **Population:** - Subpopulation der Copenhagen General Population Study - untreated hypertension (≥ 140/90 mmHG) - > 40y - normale Nierenfunktion	**ausgewählte Baseline-Charakteristika:** - Gesamt: 4942 participants, - davon: 1347 untreated hypertension - in this group: - 61,7 +/- 9,7y - history of CV-Disease: 52 (4%) - 13% presented with anatomical LVH by CT and 10% by ECG with an overlap of 4% **Ergebnisse**	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
based study. J Hypertens 2019; 37(4):739–46. [32] https://www.ncbi.nlm.nih.gov/pubmed/30817455. Kein freier Volltext		**Indextest:** - 12-Kanal-EKG **Referenztest:** - CT (vorab Betablocker, Nitro) **ausgewählte Ausschlusskriterien:** - tachy- or bradyarrhythmias - atrial fibrillation and flutter, - bundle branch block, - sekundärer oder tertiäre4 AV-Block - ventricular rhythm (QRS> 120ms) - pacemaker rhythm - delta waves - premature atrial or ventricular complexes **Studientyp:** Stichprobe aus einer Querschnittstudie **Land:** Dänemark **Zeitraum:** 2010	**Sensitivität:** Cornell Voltage Index: 9,0% [5,9-12,0] Cornell voltage Duration Product: 13,0% [9,0-17,4] Sokolow-Lyon-Index: 20,3% [15,6-25,4] **Spezifität:** Cornell Voltage Criteria: 98,8% [98,3-99,3] Cornell voltage Duration Product: 96,7% [96,1-97,3] Sokolow-Lyon-Index: 95,6% [94,9 - 96,4] **PPV:** Cornell Voltage Index: 53,3% [35,0-70,9] Cornell voltage Duration Product: 37,1% [25,8-49,7] Sokolow-Lyon-Index: 41,4% [31,7-51,6] **NPV:** Cornell Voltage Criteria: 87,8% [87,4-88,2] Cornell voltage Duration Product: 88,0% [87,5-88,6] Sokolow-Lyon-Index: 88,8% [88,1-89,5] >> zur Info: auch Kombinationen der Scores ausgewertet (siehe Tab. 4 Seite 8/9)	
ID 30355 Mahn JJ. Test characteristics of electrocardiography for detection of left ventricular hypertrophy in asymptomatic emergency department patients with hypertension. Acad Emerg Med 2014; 21(9):996–1002. [30] https://www.ncbi.nlm.nih.gov/pubmed/25269580. Freier Volltext	2014	**Fragestellung:** to evaluate diagnostic test characteristics of 3 validated ECG criteria for the diagnosis of LVH in undifferentiated, asymptomatic ED patients with HTN. **Population:** - hypertensive patients - recruited from the ED of a single tertiary care facility - asymptomatic ED patients with HTN was enrolled. - Patients who were ≥35 years of age - SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg on 2 separate readings **Indextest:** - EKG - Cornell voltage, Cornell product, Minnesota Code **Referenztest:** - Echo - interventricular septal or posterior wall thickness ≥ 1.3 cm, LV mass ≥ 225 g (male) or ≥ 163 g (female), or LV mass indexed to height raised to the power of 2.7 ≥ 48 g/m2.7 (male) or ≥ 45 g/m2.7 (female). **ausgewählte Ausschlusskriterien:** - dyspnea or chest pain as chief complaint; - known history of heart failure, coronary artery disease, cardiomyopathy, renal failure, or valvular heart disease; - exertional or nocturnal dyspnea identified as a secondary	**ausgewählte Baseline-Charakteristika:** - 161 patients screened - LVH: 89 subjects (55.2%, 95% CI = 47.6% to 62.8%). - African American (93.8%), mean (SD) age of 48.4 years (±8.5) years. - history of HTN (93.8%); 68.3% on antihypertensive therapy at baseline. - History of stroke: 15 (9,3%) **Ergebnisse** **Sensitivität** - Cornell Criteria 25.4% (15.3–37.9) - Cornell Product 25.4% (15.3–37.9) **Spezifität** - Cornell Criteria 50% (67.6–93.2) - Cornell Product 75% (19.4–99.4)	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
		complaint during a comprehensive review of systems **Studientyp:** - subanalysis of a prospective cohort study **Land:** Amerika **Zeitraum:** 18 Monate		
ID 30349 Gosse P. ECG detection of left ventricular hypertrophy: The simpler, the better? J Hypertens 2012; 30(5):990–6. [29] https://www.ncbi.nlm.nih.gov/pubmed/22441347. Kein freier Volltext	2012	**Fragestellung:** we examined the value of these criteria in three circumstances: diagnosis of a LVH with respect to that determined by echocardiography, ability to identify changes in LVM, prediction of the incidences of cardiovascular events (CVE). **Population:** - Office BP > 140/90mmHg on ≥2 occasions before the inclusion consultation - Essential hypertension **Indextest:** - 12-lead ECG - Sokoloff index, Cornell index, Cornell product **Referenztest:** - Echo - LVH was defined [3,4] as an LVMI > 51 g/m2 **ausgewählte Ausschlusskriterien:** - CV complications/ pathology likely to modify prognosis - type-1-diabetes. - Proteinurie, verminderte GFR - sekundäre HTN - duration of QRS exceeded 150 ms **Studientyp:** Kohortenstudie **Land:** Frankreich **Zeitraum:** seit 1984	**ausgewählte Baseline-Charakteristika:** - n= 985 - Alter: 48 ± 13 - prevalence of echocardiographic LVH in this population (LVMI>51 g/m2.7) was 41% **Ergebnisse** **receiver-operating characteristic curves for prediction of LV-hypertrophy** - Cornell (mm): AUC 0.669; SD 0.02; 95%KI 0.633–0.706 - Cornell product (mm ms): AUC: 0.670, SD 0.02; 95%KI 0.633–0.706 - Sokoloff (mm): AUC 0.521, SD 0.02 **Korrelation zwischen LV-Mass index und** - Sokoloff (mm): M±SD 24±7.6; R=0.06 - Cornell (mm): M±SD 15,8±6,2; R=0,378 - Cornell product (mm x ms): M±SD 1411±622; R=0.372 **receiver-operating characteristic curves for prediction of CV events** - Cornell (mm): AUC 0.561; SD 0.027 - Cornell product (mm ms): AUC: 0.586, SD 0.028; 95%KI 0.532–0.640 - Sokoloff (mm): AUC 0.520, SD 0.027	
ID 30344 Calderon A. Detection of left ventricular hypertrophy by different electrocardiographic criteria in clinical practice. Findings from the Sara study. Clin Exp Hypertens 2010; 32(3):145–	2010	**Fragestellung:** compare the validity of different product duration-based ECG- criteria with the classical voltage criteria and to estimate the prevalence of LVH for each criterion **Population:** - mild to moderate newly or treated but uncontrolled essential hypertension - >18 Jahre **Indextest:** - EKG - Cornell and Sokolow-Lyon voltage indexes, Cornell and Sokolow-Lyon products, Cornell and Sokolow-Lyon areas	**ausgewählte Baseline-Charakteristika:** - n= 248 - Alter: 62,3 ± 11,7y - 50% female - prevalence of echocardiographic LVH was 49.6%, being higher in men (53.5 vs. 46.5%). - Angina (in Anamnese): 13,5% **Ergebnisse** **Sensitivität und Spezifität** - nur grafisch dargestellt **AUC** - Cornell area: 0,763 ± 0,035	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
53. [27] https://www.ncbi.nlm.nih.gov/pubmed/20504121. Kein freier Volltext		**Referenztest:** - Echo (keine weitere Angabe) **ausgewählte Ausschlusskriterien:** k.A. **Studientyp:** post-hoc-Analyse der SARA-Studie **Land:** Spanien	- Cornell product: 0,651 ± 0,038 - Sokolow-Lyon criteria: 0,877 ± 0,037	

4.4 Proteinurie/ Albuminurie/ Mikroalbuminurie

Systematische Übersichtsarbeiten

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Kelly DM. Proteinuria as an independent predictor of stroke: Systematic review and meta-analysis. International journal of stroke official journal of the International Stroke Society 2020; 15(1):29–38. [33] https://www.ncbi.nlm.nih.gov/pubmed/31935154. Freier Volltext	2020	critically low	**Fragestellung**: assess the impact of proteinuria on stroke risk and whether any association present remained after more complete adjustment for BP. **Suchzeitraum**: 2013-02/2018 **Einschlusskriterien** - RCTs and cohort studies - proteinuria at baseline (Cut-off siehe Tab 1.) - report risk of incident or recurrent stroke. - Proteinuria: quantified by 24 h urine collection, urine aliquot albumin:creatinine ratio or urine protein:creatinine ratio (UPCR), urine dipstick, or agglutination assay. - studies using equivalent or sex-specific cut-off points were also included. - eGFR: had to be either estimated using a validated formula (Cockcroft–Gault, MDRD, CKD-EPI), measured directly, approximated from urinary creatinine clearance or estimable from serum creatinine. - outcome: symptomatic stroke confirmed by physician examination, hospital record review, or identified from data-linkage of administrative records. **Ausschlusskriterien**: - participants with end stage renal disease (by history of dialysis or an eGFR <15 ml/min/1.73m2),	**Allgemeines**: - 38 studies (n= 1,735,390) - 6 RCTs, 32 Kohortenstudien - 26,405 stroke events: 21,853 not classified by pathological subtype (unspecified), 3730 ischemic and 822 hemorrhagic - follow-up duration: 1 - 324 months - Proteinuria quantified: urine dipstick (14 studies; 36.8%), urine albumin:creatinine ratio (14 studies; 36.8%), multiple methods (4 studies; 10.5%), urine albumin excretion rate (2 studies; 5.3%), 24 h urine collection (2 studies: 5.3%), and UPCR (1 study; 2.6%) *- 36.8% of included studies reported a high prevalence of diabetes (≥30%).* **Ergebnisse**: - unadjusted results showed that incident stroke increased among patients with any level of proteinuria (RR 2.00, 95%CI 1.63–2.46; - multivariate adjusted analysis, this risk association attenuated to an RR of 1.72 (1.51–1.95) - stroke risk was similar for both macroalbuminuria (adjusted RR 1.78, 1.53–2.08), 24 studies (n= 1,709,402) and microalbuminuria (adjusted RR 1.66, 1.28–2.16), 18 studies (n= 1,181,884) **Subgruppenanalysen für Assoziation Proteinurie/Stroke**	Zu AMSTAR-II: 2 kritische Kriterien nicht erfüllt - RoB/ Qualität der Primärstudien nicht in Interpretation einbezogen - keine Dokumentation der VT-Screening ausgeschlossenen PS

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- outcomes measured by self-reports or proxy reports, radiological but clinically silent stroke disease.	*Diabetics* <15%: adjusted RR 1.59 (1.40-1.82), 10 Studien ≥15 to <30%: adjusted RR 1.38 (1.13-1.69), 9 Studien ≥30%: adjusted RR 2.18 (1.60-2.99), 12 Studien *Hypertensives* <25%: adjusted RR 1.80 (1.25-2.58), 4 Studien ≥25 to <50%: adjusted RR 1.41 (1.18-1.67), 5 Studien ≥50 to <75%: adjusted RR 1.63 (1.17-2.26), 6 Studien ≥75%: adjusted RR 1.49 (1.26-1.76), 10 Studien	

Metaanalysen von Individualdaten des CKD-Consortiums

Charakteristika des CKD-Konsortiums

Siehe auch: https://www.ckdpc.org/ oder https://www.jhsph.edu/research/centers-and-institutes/chronic-kidney-disease-prognosis-consortium/index.html

Methodische Anmerkungen

- keine methodische Bewertung gemäß AMSTAR-II möglich

- Identifikation der Kohorten: Recherche in Literaturdatenbanken (2009), dann Sichtung der Referenzlisten und Kontaktieren/ Einladen weiterer Autoren von Kohortenstudien

- transparente Darstellung der ausgewählten Kohorten und der statistischen Verfahren

- Kohorten werden nur für IPD herangezogen, wenn betreuende Wissenschaftler damit einverstanden sind (Bias-Risiko?)

- 3 Populationen relevant: general population, high risk population, CKD-population

Auswertungen, die high risk population einschließen

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
van der Velde M. Lower estimated glomerular filtration rate and higher albuminuria are associated with **all-cause and cardiovascular mortality**. A collaborative meta-analysis of high-	2011	**Ziel/ Hypothese:** - analysis of associations between eGFR and albuminuria with all-cause and cardiovascular mortality in high-risk populations in a collaborative meta-analysis. - A priori we hypothesized that both eGFR and albuminuria would be associated with these outcomes, independent of traditional CV risk factors and independent of each other, and despite inclusion of diverse study populations. **Einschlusskriterien:** - prospective cohort study; - subjects referred for evaluation of CKD risk factors or - subjects with ≥ 1 risk factor defined as a history of CV disease,	**Beschreibung der Kohorten** - 12 cohorts met inclusion criteria. *- investigators of 10 eligible studies were willing to participate in this meta-analysis* - 6 cohorts: data on ACR (n= 117,500) and 4 on dipstick proteinuria (n= 149,475 subjects) - 8706 all-cause deaths and 3171 CV disease deaths during follow-up. - Dipstick-Kohorte: 7303 all-cause deaths and 2485 CV disease deaths during follow-up. - chronic CKD: 36.7% of subjects in pooled study population	>> eine ausführlichere Extraktion der Ergebnisse/ Subgruppenanalysen folgt, wenn AG entscheidet, dass Studie zur Beantwortung der Fragestellung herangezogen werden kann

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
risk population cohorts. Kidney international 2011; 79(12):1341–52. [34] https://www.ncbi.nlm.nih.gov/pubmed/21307840. Freier Volltext		diabetes, hypertension, hypercholesterolemia, or family history of CV disease; - information at baseline on eGFR and albuminuria; - ≥ 1000 subjects/ cohort; - information on mortality - ≥ 50 events for all-cause mortality or CV mortality **Definitionen:** - CV disease history: myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. - Hypertension: SBP ≥140mmHg or DBP ≥90mmHg or use of antihypertensive medication. - Hypercholesterolemia: total cholesterol >5.0 mmol/l in the case of a positive history of CV disease and >6.0 mmol/l in the case of a negative history of CV disease. - Diabetes mellitus: fasting glucose ≥7.0 mmol/l or non-fasting glucose ≥11.1 mmol/l or use of glucose-lowering drugs. - Smoking habit: dichotomised as current vs. not current - albumin-to-creatinine ratio: 4 categories: <10, 10–29, 30–299, and ≥300 mg/g. - When information on ACR was lacking, information on dipstick proteinuria used: 4 dipstick categories: negative, trace, 1+, and ≥2+	> This subgroup accounted for 58.6% of all-cause mortality events and 59.4% of CV mortality events - ACR-Kohorte: weighted mean 49.6% Diabetes - Dipstic-Kohorte: weighted mean 32.4 Diabetes **Ergebnisse** - relationship of ACR to the relative risk of all-cause mortality and CV mortality was monotonic with log hazard ratios increasing linearly with increasing log albumin-to-creatinine ratio, without threshold effects **HR for all-cause mortality** - 5 mg/g with ACR of 10: HR 1.08 (95%KI 1.01–1.16), - 5 mg/g with ACR of 30: HR1.38 (95%KI 1.23–1.56), - 5 mg/g with ACR of 300: HR2.16 (95%KI 1.99–2.35), **HR for CV mortality** - 5 mg/g with ACR of 10: HR 1.13 (95%KI 1.07–1.20), - 5 mg/g with ACR of 30: HR 1.55 (95%KI 1.30–1.86) - 5 mg/g with ACR of 300: HR 2.59 (95%KI 1.95–3.44)	
Mahmoodi BK. Associations of kidney disease measures with **mortality** and end-stage renal disease in **individuals with and without hypertension**: A meta-analysis. Lancet 2012; 380(9854):1649–61. [35] https://www.ncbi.nlm.nih.gov/pubmed/23013600. Freier Volltext	2012	**Fragestellung:** whether hypertensive status modifies the association of decreased eGFR and increased albuminuria with all-cause and cardiovascular mortality and ESRD. **Einschlusskriterien:** - general population or a high-risk cohort (i.e. cohorts selected on the basis of CV disease or CV risk factors) - at least 1000 participants, - with baseline information on eGFR and albuminuria, - information on either mortality or ESRD, with a minimum of 50 events. - eligibility criterion for cohorts enrolling exclusively individuals with CKD was similar, except that studies with fewer than 1000 participants **Exposures, effect modifier and outcome variables definitions** - Albuminuria was ascertained by albumin-to-creatinine ratio (ACR), urine albumin excretion rate, protein-to-creatinine ratio (PCR) or quantitative dipstick. Hypertension: SBP ≥140 mm Hg, DBP ≥90 mm Hg, or use of	**Beschreibung der Kohorten** combined general (25 cohorts) and high-risk populations (7 cohorts): - n= 742,240 without hypertension followed for 6,277,878 person-years - n= 347,256 with hypertension followed 2,970,318 person-years in the CKD cohorts: - n= 21,072 without hypertension followed for 86,970 person-years - n= 17,088 with hypertension followed 72,299 person-years - mean age of participants and prevalence of traditional CV risk factors (diabetes) was higher in hypertensive individuals *- Due to similarity in range of eGFR and albuminuria and risk, general population and high-risk cohorts were combined in the primary meta-analysis.* **Ergebnisse:** Of the general population and high-risk cohorts	Auch hier general und high risk population gemeinsam ausgewertet: Aber: high risk durch CV-Erkrankung und Risikofaktoren charakterisiert

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
		antihypertensive medication in the general and high-risk population cohorts. - In primary analyses of CKD cohorts, hypertension status was categorized only by the aforementioned SBP or DBP values, because antihypertensive medication was used in ≥97% of participants in 4 cohorts and information on antihypertensive medication was not available in 1 cohort. **Endpunkte** all-cause and CV disease (CVD) mortality, defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death. **Definition der Covariaten:** - History of CV disease: previous myocardial infarction, coronary revascularization, heart failure, or stroke. - Diabetes mellitus: fasting glucose concentration ≥7.0 mmol/L (≥126 mg/dL), non-fasting glucose concentration ≥11.1 mmol/L (≥200 mg/dL) or hemoglobin A1c ≥ 6.5%, or use of glucose lowering drugs or self-reported diabetes. - Smoking: dichotomized to current vs. former or never-smokers. - BMI was calculated as body weight in kilograms divided by height in meters squared.	- 30 studies: data on all-cause mortality (27,836 deaths [cumulative incidence, 4.1%] in non-hypertensives vs. 47,335 [15.0%] in hypertensives) - 23 studies: data on CV mortality (6,601 deaths [0.9%] in non-hypertensives vs. 15,634 deaths [6.8%] in hypertensives) - Higher ACR was associated with greater risk of all-cause and cardiovascular mortality among both non-hypertensive and hypertensive individuals - Individuals with hypertension had higher mortality risk compared to those without hypertension at ACR below ~100 mg/g - non-hypertensives had a steeper relative risk gradient in the ACR range >30 mg/g, and their mortality risk was comparable or even higher as compared to hypertensives at ACR values above ~100 mg/g. - Overall interaction for all-cause mortality (average relative HR for 10-fold higher ACR 0.91 [95% CI, 0.83-0.98], - Overall interaction for CV mortality (HR0.87 [0.74-1.03]	
Hallan SI. **Age and association** of kidney measures with **mortality** and end-stage renal disease. JAMA 2012; 308(22):2349–60. [36] https://www.ncbi.nlm.nih.gov/pubmed/23111824. Freier Volltext	2012	**Fragestellung:** To evaluate possible effect modification (interaction) by age of the association of eGFR and albuminuria with clinical risk, examining both relative and absolute risks. **Einschlusskriterien:** - general, high-risk (for vascular risk), and CKD populations - baseline information on eGFR and albuminuria, - =/> 1000 participants (not applied to CKD cohorts) - ≥50 events for any outcome of interest during follow-up **Measurements:** Albuminuria: preferably as ACR, but urine albumin excretion rate, urine protein-tocreatinine ratio (PCR), or dipstick protein also included primary endpoints were all-cause mortality and ESRD. results for cardiovascular mortality (death due to myocardial infarction, heart failure, sudden cardiac death, or stroke) are shown in the Appendix only **statistische Auswertung**: Age categorized as 18–54, 55–64, 65–74, and 75+ years.	**Beschreibung der Kohorten:** - 46 cohorts (20 from North America, 12 from Europe, 10 from Asia, 1 from Australia, and 3 international) - with 2 million adults - mean period of 5.8 years during 1972–2011. - Mean age 49.4 years (range 18–103 with 148,951 (7.3%) subjects above age 75). - prevalences of diabetes were 10.7%, treated hypertension 27.9% and current smoking 21.5 % - In general population and high risk cohorts, older age was associated with lower mean GFR and a higher prevalence of albuminuria (Table 1), history of cardiovascular disease, hypertension, diabetes, and other risk factors (eTable 1). - There were a total of 112,325 deaths **Ergebnisse (high-risk und general population gemeinsam)** - Mortality (112,325 deaths) risks were higher at higher albuminuria in every age category. HRs of all-cause mortality at ACR 300 (vs. 10 mg/g) were	auch hier general population und high risk popualtion gemeinsam ausgewertet aber: high-risk-Population ist durch CV-Erkrankungen charakterisiert

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
		ACR risk associations, with knots at 10, 30, and 300 mg/g (30, 300, and 1000 mg/g in CKD cohorts) and the reference point of 10 mg/g (20 mg/g in CKD cohorts).	- in 18–54 years: 2.53 (95% CI 2.13–3.03) - in 55–64 years: 2.30 (1.84–2.88) - in 65–74 years: 2.10 (1.83–2.44) - in 75+ years: 1.73 (1.45–2.05) differences in absolute risk were higher in older age categories - in 18–54 years 7.5 [95% CI, 4.3-11.9], - in 55–64 years: 12.2 [95% CI, 7.9-17.6], - in 65–74 years: 22.7 [95% CI, 15.3-31.6], - in 75+ years: 34.3 [95% CI, 19.5-52.4] excess deaths per 1000 person-years >> associations were consistent across subgroups detmined by race, sex, and hypertension and diabetes status	

Zurückgestellte IPD

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
Matsushita K. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: A collaborative meta-analysis of individual participant data. The lancet. Diabetes & endocrinology 2015; 3(7):514–25. [37] https://www.ncbi.nlm.nih.gov/pubmed/26028594. Freier Volltext	2015	**Fragestellung:** assess the addition of creatinine-based eGFR and albuminuria to traditional risk factors for prediction of cardiovascular risk with a meta-analytic approach. **Einschlusskriterien:** Zusammensetzung der Kohorte - general population - high risk population = Diabetes mellitus - CKD population	**Allgemeines:** - high risk population durch Diabetes charakterisiert - 637 315 individuals without a history of CV disease from 24 cohorts - median follow-up 4·2-19·0 years **Ergebnisse** *general cohort und high risk cohort gemeinsam ausgewertet* - The addition of eGFR and ACR improved the discrimination of cardiovascular outcomes beyond traditional risk factors in general populations, but the improvement was greater with ACR than with eGFR, **für ACR:** - cardiovascular mortality (C statistic difference 0·0139 [95% CI 0·0105-0·0174] - heart failure (0·0196 [0·0108-0·0284] - coronary disease (0·0048 [0·0029-0·0067] - stroke 0·0105 [0·0058-0·0151] - Dipstick proteinuria showed smaller improvement than ACR. - The discrimination improvement with eGFR or ACR was	wird zunächst zurückgestellt high-risk-Population ist durch Diabets charakterisiert Population nicht HT-spezifisch verschiedene Modelle genutzt HT ja/nein Diab ja/ nein klinische Relevanz mit Autoren besprechen

Zitat	Jahr	Charakteristika	Ergebnisse	Kommentar
			especially evident in individuals with diabetes or hypertension, but remained significant with ACR for CV mortality and heart failure in those without either of these disorders.	

Zusammenfassung der Evidenz

Evidenzbasis und Versorgungsproblem

Die Bestimmung der Mikroalbuminurie in der Basisdiagnostik von Endorganschäden zu empfehlen (siehe Abbildung 1), beruht auf der klinischen Erfahrung der Leitliniengruppe und der in der systematischen Recherche identifizieren Evidenz.

Die Leitliniengruppe stellte sich die Fragen, ob mit der Bestimmung einer Proteinurie oder Mikroalbuminurie Patienten identifiziert werden können, die im Krankheitsverlauf ein höheres Risiko haben, Endorganschäden zu erleiden. In der systematischen Recherche wurden dazu eine systematische Übersichtsarbeit [33] und drei Metaanalysen von Individualdaten (IPD) des „chronic kidney disease prognosis consortium“ identifiziert [34–36].

Evidenzbeschreibung und klinische Erwägungen

Ob die Proteinurie einen Prädiktor für das Auftreten eines Schlaganfalles darstellt, untersuchten Kelly et al. [33] in einer systematischen Übersichtsarbeit, in die sie 6 RCTs und 32 Kohortenstudien einschlossen (n= 1 735 390). Die betrachteten Populationen waren hinsichtlich des Erkrankungsprofils gemischt. 36,8% der eingeschlossenen Studien berichteten eine Prävalenz des Diabetes von ≥ 30%, 31,6 % der Studien hatten eine Prävalenz der Hypertonie von ≥ 75%. In einer für kardiovaskuläre Risikofaktoren adjustierten Analyse war die Proteinurie mit einem erhöhten relativen Risiko für das Auftreten eines Schlaganfalls assoziiert (RR 1,72 (95% KI 1,51; 1,95), I^2= 77,3%, 24 Studien, n= 1 726 550). In einer adjustierten Analyse zu der Ausprägung der Albuminurie ergab sich eine Assoziation zwischen dem Vorhandensein einer Mikroalbuminurie und einem erhöhten relativen Risiko für einen Schlaganfall (RR 1,66 (95% KI 1,28; 2,16), I^2= 94,0%, 18 Studien, n= 1 185 152). Subgruppenanalysen erbrachten Hinweise, dass das relative Risiko für einen Schlaganfall bei Vorhandensein einer Proteinurie unabhängig von der Prävalenz der Hypertonie in der Studienpopulation erhöht war (Prävalenz <25 %: RR 1,80 (95% KI 1,25; 2,58), 4 Studien; Prävalenz ≥ 75%: RR 1,49 (95% KI 1,26; 1,76), 10 Studien). [33]

Die Auswahl der Kohorten für die IPD wurde in einer gesonderten Publikation [38] dargestellt. Neben der Recherche in einer Literaturdatenbank sichteten die Autoren der IPD auch Referenzlisten und kontaktierten weitere Autoren von Kohortenstudien. Das statistische Vorgehen wurde in den einzelnen Publikationen beschrieben. Als limitierend wird angesehen, dass keine Bewertung des Verzerrungsrisikos der eingeschlossenen Kohorten erfolgte. Für die Beantwortung der Fragestellungen der NVL Hypertonie werden nur die Auswertungen der „general“ und „high risk“, nicht jedoch der „chronic kidney disease population“ zitiert.

Die Assoziation zwischen einer erhöhten Albumin-Creatinin-Ratio (ACR) und dem Risiko für kardiovaskuläre oder Gesamtmortalität bei Patient*innen mit (n= 347 256) und ohne Hypertonie (n= 742 240) untersuchten Mahmoodi et al. anhand von 32 Kohorten der gemischten Population (general und high risk) [35]. Die ACR war in der untersuchten Population bei Patient*innen mit und ohne Hypertonie mit einem höheren Risiko für Gesamtmortalität und kardiovaskuläre Mortalität assoziiert. Bei Patient*innen mit einer ACR unter 100 mg/g war das Mortalitätsrisiko derjenigen mit Hypertonie höher als das derer ohne Hypertonie. [35]

Ggf. weitere wichtige Informationen aus Publikation:

- Overall interaction was significant for all-cause mortality (average relative HR for 10-fold higher ACR 0.91 [95% CI, 0.83-0.98]) but did not reach significance for cardiovascular mortality (0.87 [0.74-1.03]).
- majority of studies showed a stronger risk association for ACR in non-hypertensives compared to hypertensives with low heterogeneity

Die Assoziation zwischen einer Albuminurie und dem Risiko für Gesamt- bzw. kardiovaskuläre Mortalität untersuchten van der Velde [34] in einer Hochrisikopopulation anhand von 10 Kohorten. In 6 Kohorten (n= 117 500) erfolgte die Messung mittels ACR in 4 mittels Streifentest (n= 149 475). Hochrisiko war definiert als Vorhandensein von Hypertonie, Diabetes oder kardiovaskulären Erkrankungen. Der gewichtete Mittelwert der Patient*innen mit Hypertonie betrug in der ACR-Kohorte 49,3% und in der Streifentest-Kohorte 58,8%. In den ACR-Kohorten war der mittlere Anteil von Patient*innen mit kardiovaskulären Erkrankungen höher als in den Streifentest-Kohorten (32,7% vs. 15,3%). Je stärker ausgeprägt die Albuminurie war, desto höher war das assoziierte relative Risiko für die kardiovaskuläre oder die Gesamtmortalität. Die aus den Auswertungen der Individualdaten errechneten Informationen zur Gesamtmortalität waren für beide Messverfahren ähnlich. [34]

Ausführliche Informationen:

- As compared with an albumin-to-creatinine ratio of 5 mg/g, hazard ratios for all-cause mortality at albumin-to-creatinine ratios of 10, 30, and 300 mg/g were 1.08 (1.01–1.16), 1.38 (1.23–1.56), and 2.16 (1.99–2.35), respectively, and for cardiovascular mortality 1.13 (1.07–1.20), 1.55 (1.30–1.86), and 2.59 (1.95–3.44), respectively.
- For cohorts with dipstick data, unadjusted incidence rates for all-cause and cardiovascular mortality are shown in Table 4, and pooled hazard ratios for these end points in Table 5. This latter table shows that pooled hazard ratios for all-cause mortality were similarly increased for a higher dipstick category across all eGFR levels and for a lower eGFR across all dipstick categories.
- For all-cause mortality in dipstick cohorts, these patterns were generally similar to those in albumin-to-creatinine ratio cohorts (Table 8, Seite 8/12).
- Only one of the two dipstick cohorts that reported on cardiovascular mortality included subjects X65 years of age. For this reason, no data are shown for risk for cardiovascular mortality according to age group in dipstick cohorts.

Den Einfluss des Alters auf die Assoziation einer Albuminurie zur Mortalität untersuchten Hallan et al. [36]. Eingeschlossen wurden 26 General- und 8 High-Risk-Kohorten. Der mittlere Anteil der Patienten mit einer Hypertonie, mit einem Diabetes oder mit kardiovaskulären Erkrankungen war in allen Altersgruppen jeweils in der High-Risk-Kohorte höher als in der General-Risk-Kohorte. In beiden Kohorten war eine höheres Alter mit einer erhöhten Prävalenz der Albuminurie assoziiert. Das Mortalitätsrisiko war bei einer erhöhten Albuminurie in jeder Alterskategorie erhöht. Das relative Mortalitätsrisiko bei einer erhöhten Albuminausscheidung sank leicht mit zunehmendem Alter (HRs der Gesamtmortalität bei ACR 300 vs. 10 mg/ g: 2.53 (95% CI 2.13–3.03) bei 18–54-Jährigen, 2.30 (1.84–2.88) bei 55–64-Jährigen, 2.10 (1.83–2.44) bei 65–74-Jährigen und 1.73 (1.45–2.05) bei >75-Jährigen. Das absolute Risiko war hingegen in den höheren Altersgruppen erhöht: (Übersterblichkeit/ 1000 Personen-Jahre bei ACR 300 mg/g vs. 10 mg/g nach Altersgruppen: 7.5 [95% CI, 4.; 11.9] bei 18–54-Jährigen, 12.2 [7.9; 17.6] bei 55–64-Jährigen, 22.7 [15.3; 31.6] bei 65–74-Jährigen und 34.3 [19.5;52.4] bei >75-Jährigen). [36]

5 Evidenztabellen Monitoring (Stand: 27.01.2021)

Stand: 27.01.2021 (IV; strukturierte Recherche 2019) + Update (Palmer et al. 2021)

5.1 NICE Evidence Review

ER for monitoring (blood pressure)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [B] Evidence review for monitoring [39] https://www.nice.org.uk/guidance/ng136/evidence/b-monitoring-pdf-6896748207 (frei verfügbar)	2019	low	**Objective** In adults with treated primary hypertension, what is the best method of measuring blood pressure (home, ambulatory or clinic measurement) to assess the response to treatment and prevent cardiovascular events? **Search** up to 10/2018 **Inclusion and exclusion criteria** ▪ randomized controlled trial (RCT) ▪ systematic review (SR) ▪ non-randomised studies in the absence of RCT and SR evidence ▪ adults (> 18 years) ▪ treated primary hypertension **Quality assessment** GRADE **Intervention** Different methods of measuring blood pressure followed by appropriate treatment based on the blood pressure measurement (test plus treatment): ▪ Home blood pressure measurement (HBPM) without telemonitoring ▪ HBPM with telemonitoring ▪ Ambulatory measurement (ABPM)	n=8 studies (Table2 within the review) ▪ n=1 individual patient data meta-analysis (Tucker 2017[135]) ○ reported outcomes for BP and proportion controlled to target ○ authors rated the study as highest quality design (other considered results of the other included studies if they evaluate additional outcomes not found in IPD) ▪ n=7 open label studies comparisons (n=8): ▪ HBPM without telemonitoring vs. ambulatory/clinic monitoring (n=1) ▪ HBPM without telemonitoring vs. clinic monitoring (n=2) ▪ HBPM without telemonitoring vs. HBPM with telemonitoring (n=2) ▪ HBPM with telemonitoring vs. clinical monitoring (n=3) ▪ HBPM with telemonitoring vs. HBPM with telemonitoring and pharmacist care (n=1) ▪ HBPM with telemonitoring and pharmacist care vs. clinical monitoring (n=1) ▪ HBPM (with self-titration) and telemonitoring vs. clinic monitoring (n=1) ▪ pharmacy monitoring vs. clinical monitoring (n=2) **clinical evidence statements** s.a. Appendix E: Forest plots (page 86 ff within the publication) ▪ HBPM without telemonitoring vs. ambulatory and clinic monitoring	(goal: to identify those who might need additional or alternative treatment strategies)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ Clinic/office measurement (CBPM) ▪ Pharmacy measurement **Comparator** against each other **Outcomes** (individual's response to treatment ≥12 months) **critical:** ▪ all-cause mortality ▪ health-related quality of life ▪ stroke (ischaemic or haemorrhagic) ▪ myocardial infarction (MI) **important:** ▪ reduction in clinic BP ▪ proportion of people controlled to a target ▪ average daily dose of antihypertensive medication ▪ average number of visits ▪ intolerance to device, ▪ hypotension (dizziness) ▪ combined CV-disease outcomes in absence of MI and stroke data ▪ coronary heart disease outcome in the absence of MI data	○ showed no clinically important difference between home monitoring compared to ambulatory and clinic monitoring for reduction in systolic and diastolic clinic blood pressure, (low quality evidence) n=1 study, n=145 patients ▪ HBPM vs. clinic monitoring ○ showed a clinically important increase of cardiovascular events for home monitoring compared to clinic monitoring, ▪ RR 1.42 [0.61, 3.33], (very low quality evidence), n=1 study, n=678 patients ○ showed no clinically important difference between home and clinic monitoring for reduction in systolic or diastolic clinic blood pressure, (very low quality evidence), n=2 studies, n=2,610 patients ○ showed no clinically important difference between home monitoring and clinic monitoring for proportion not meeting target, mean number of consultations and overall defined daily dose and dizziness, (low to very low quality evidence), from single studies ranging from 672 to 1,934 patients ▪ HBPM with telemonitoring vs. HBPM without telemonitoring ○ showed a clinically important increase in occurrence of dizziness for home monitoring with telemonitoring compared to without telemonitoring, (very low quality evidence), n=1 study, n=650 patients ○ showed no clinically important difference between home monitoring with or without telemonitoring for cardiovascular events, reduction in systolic and diastolic clinic blood pressure, mean number of consultations or overall defined daily dose (number of participants was 655–658 depending on the outcome), (low to very low quality evidence), n=1 study, n=658 partients ○ showed no clinically important difference for average number of visits, (very low quality evidence), n=1 study, n=100 patients ▪ HBPM with telemonitoring vs. clinic monitoring ○ showed a clinically important benefit for home monitoring with telemonitoring compared to clinic monitoring in terms of proportion controlled to a target, (low quality evidence), n=1 study, n=493 patients	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ showed a greater occurrence of all-cause mortality with home monitoring with telemonitoring compared to clinic monitoring, (very low quality evidence), n=1 study, n=493 patients ○ showed a greater occurrence of cardiovascular events for home monitoring with telemonitoring, (very low quality evidence), n=2 studies, n=1,173 patients ○ showed no clinically important difference between the monitoring methods for reduction in systolic and diastolic clinic blood pressure, (very low quality evidence), n=3 studies, n=2,357 patients ○ showed no clinically important difference between home monitoring with clinic monitoring for quality of life on the emotional, physical and general SF-12 subscale, for proportion not meeting a target, mean number of consultations and overall defined daily dose and dizziness, (low to very low quality evidence), from single studies ranging from 493 to 1,189 patients ■ HBPM with telemonitoring and pharmacist care vs. clinic monitoring ○ showed a clinically important benefit of home monitoring with telemonitoring and pharmacist interaction for change in systolic blood pressure, proportion controlled to a target and quality of life with the physical SF-12 subscale, (low quality evidence), n=1 study, n=484 patients ○ showed a greater occurrence of non-fatal cardiovascular events with home monitoring with telemonitoring and pharmacist interaction compared to clinic monitoring, (very low quality evidence), n=1 study, n=484 patients ○ showed no clinically important difference for all-cause mortality, change in diastolic blood pressure or quality of life measured on the emotional or general subscales of the SF-12 scale, (low to very low quality evidence), n=1 study, n=484 patients ■ HBPM with telemonitoring and pharmacist care vs. HBPM with telemonitoring ○ failed to demonstrate a clinically important difference for occurrence of non-fatal cardiovascular events, change in diastolic blood pressure or quality of life on the emotional and general subscale of the	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				SF-12 scale, (low to very low quality evidence), n=1 study, n=484 patients ○ showed a clinically important benefit of home monitoring with tele-monitoring and pharmacist care compared to home monitoring with telemonitoring (without pharmacist care) for all-cause mortality, change in systolic blood pressure and quality of life on the physical subscale of the SF-12 scale, (low to very low quality evidence), n=1 study, n=483 patients ■ HBPM (with self-titration) and telemonitoring vs. clinic monitoring ○ showed a clinically important benefit of self-monitoring with self-titration for change in systolic blood pressure, (low quality evidence), n=1 study, n=480 patients ○ showed no clinically important difference for change in diastolic blood pressure, quality of life, mean number of consultations and mean number of antihypertensive drugs, (low quality evidence), n=1 study, n=480 patients ■ Pharmacy monitoring versus clinic monitoring ○ showed a clinically important benefit of pharmacy compared to clinic monitoring for all-cause mortality and reduction in systolic blood pressure, but no difference in terms of reduction in diastolic blood pressure, and an increased number of contacts per patient for pharmacy monitoring, (very low quality evidence), n=1 study, n=260 patients **Outcomes** blood pressure (mean difference mmHg), quality of evidence ■ Home monitoring vs. clinic monitoring, 12 months, n=2 trials (McManus 2018, Tucker 2017), n=2,610 patients ○ systolic -2.23 (-3.84, -0.63), very low ○ diastolic -1.31 (-2.19, -0.44), very low ■ Home monitoring without telemonitoring vs. ambulatory and clinic monitoring, 12 months, n=1 trial (Stergiou 2014), n=145 patients ○ systolic -2.10 (-6.80, 2.60), low ○ diastolic -1.40 (-4.30, 1.50), low	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				▪ Home monitoring with telemonitoring versus home monitoring without telemonitoring, 12 months, n=1 trial (McManus 2018), n=655 / 656 patients ○ systolic -1.00 (-3.51, 1.51), low ○ diastolic 0.90 (-0.62, 2.42), low ▪ Home monitoring with telemonitoring versus clinic monitoring, 12 months, n=3 trials (Green, 2008, McManus 2018, Tucker 2017), n=2,357 patients ○ systolic -3.08 (-4.71, -1.44), very low ○ diastolic -0.83 (-1.51, -0.15), very low ▪ Home monitoring with telemonitoring and pharmacist care versus clinic monitoring, 12 months, n=1 trial (Green 2008), n=484 patients ○ systolic -8.90 (-11.43, -6.37), low ○ diastolic -3.50 (-4.91, -2.09), low ▪ Home monitoring with telemonitoring and pharmacist care versus home monitoring with telemonitoring, 12 months, n=1 trial (Green 2008), n=483 patients ○ systolic -6.00 (-8.53, -3.47), low ○ diastolic -2.60 (-4.01, -1.19), low ▪ Home-monitoring (with self-titration) and telemonitoring versus clinic monitoring, 12 months, n=1 trial (McManus 2010), n=480 patients ○ systolic -5.60 (-8.91, -2.29), low ○ diastolic -2.30 (-4.41, -0.19), low ▪ Pharmacy monitoring versus clinic monitoring, 12 months, n=1 trial (Simpson, 2011), n=260 patients ○ systolic -4.90 (-8.75, -1.05), very low ○ diastolic -2.90 (-5.70, -0.10), low **Articles included:** ▪ 49, Green BB, Cook AJ, Ralston JD, Fishman PA, Catz SL, Carlson J et al. Effectiveness of home blood pressure monitoring, Web communication, and pharmacist care on hypertension control: A randomized controlled trial. JAMA. 2008; 299(24):2857-67	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				▪ 73, Logan AG, Irvine MJ, McIsaac WJ, Tisler A, Rossos PG, Easty A et al. Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics. Hypertension. 2012; 60(1):51-57 ▪ 84, McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): A randomised controlled trial. The Lancet. 2010; 376(9736):163-172 ▪ 85, McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. The Lancet. 2018; 391(10124):949-59 ▪ 122, Simpson SH, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, Johnson JA. Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes: A randomized controlled trial. Diabetes Care. 2011; 34(1):20-6 ▪ 131, Stergiou GS, Karpettas N, Destounis A, Tzamouranis D, Nasothimiou E, Kollias A et al. Home blood pressure monitoring alone vs. combined clinic and ambulatory measurements in following treatment-induced changes in blood pressure and organ damage. American Journal of Hypertension. 2014; 27(2):184-192 ▪ 135, Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. PLoS Medicine. 2017; 14(9):e1002389 ▪ 136, Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP et al. Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART): A protocol. BMJ Open. 2015; 5(9):e008532	

Detailaufbereitung: Monitoring

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
Green 2008 RCT	778	Adults without Type 2 diabetes Mean age =59.1y (SD =8.5y)	HBPM with telemonitoring: - device used - BP measurement for ≥2 days/week with a minimum of 2 measurements at a time - duration not specified - HBPM target of 135/85mmHg, - CBPM target of 140/90mmHg. - Readings sent via email. - Number of GP visits or communications not specified. HBPM with telemonitoring and pharmacist care: - assigned to home BP monitoring and Web training plus pharmacist care - same strategy as HBPM with telemonitoring + a pharmacist assisting them to improve their BP through telephone calls. - HBPM target of 135/85mmHg, - CBPM target of 140/90mmHg. - communication every 2 weeks until BP was controlled. - Number of GP visits not specified.	Usual care - told their BP was not in control - encouraged to work with their physician to improve it. - No further details given: number of GP visits and communication.	Downgraded for intervention indirectness as it was comparing with usual care not clearly stating clinic measurement
Logan 2012 RCT	110	Adults with diabetes Mean age =62.9 y (SD=8.4 y)	HBPM with telemonitoring: - Validated Bluetooth-enabled home BP device - Guideline target of <130/80mmHg. - readings automatically transmitted by smartphone to application servers. - Messages: if BP fell outside target range - to take additional BP readings, - were then used to provide advice on urgency to make a follow-up visit with their physician. - No further details: number of measurements, GP visits or how often measurements were taken.	HBPM without telemonitoring: - Subjects issued with an identical appearing home BP device - without built-in Bluetooth capability for use during the study. - No further details: GP visits, communications or how often measurements were taken.	Downgraded for population indirectness, as it did not specify type of diabetes present
McManus 2010 RCT	527	Adults with diabetes (n=35) Mean age =66.4 y (SD=8.8 y)	Home monitoring (HM) with telemonitoring: - 2 self-measurements each morning - 5-min interval, 2nd reading acted upon - validated automated sphygmomanometer - transmit BP readings to research team by means of an automated modem device	Clinic monitoring: - review by their family doctor. - Number of GP visits not stated. - No specific instructions to the clinicians about the content of this visit other than to review medication. - care was at the discretion of the family doctor.	Downgraded for population indirectness, as it did not specify type of diabetes Par-

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
			- connected to sphygmomanometer and plugged into a telephone socket. - If 2 consecutive months of readings above target: make medication changes in accordance with titration schedule without seeing family doctor. - if BP remained above target after 2 changes: returned to family doctor for a further titration schedule - Home targets for people without diabetes: 130/85mmHg - Home targets for people with diabetes: 130/75mmHg - Monthly summaries of each participant's BP readings sent to their family doctor. - Number of GP visits not stated.	- No further details given for communications and targets were not specified.	ticipants receiving more than 2 antihypertensive drugs at baseline were excluded
McManus 2018 RCT	1182	Adults with diabetes (n=108) Mean age =66.93 y (SD=9.43 y)	HBPM with telemonitoring: - readings via a simple free SMS text-based telemonitoring service with web-based data entry back up. - non-dominant arm - twice each morning and evening, - first week of every month using standard recommendations. - make contact with practice if average BP was > target, and presented readings to attending clinicians via a web interface. - clinicians: review readings on a monthly basis. - BP targets at home: <135/85 mmHg < 80 y, <145/85 mmHg ≥80 y, and <135/75 mmHg for those with diabetes. - Clinicians: freedom to adjust antihypertensive and other medication as they sought fit - No further details given on number of GP visits.	Clinic monitoring: - Participants managed with titration of antihypertensive treatment based on CBPM at discretion of attending health-care professional. - clinicians: review participants as often as they wished. - BP targets at home: <135/85 mmHg < 80 y, <145/85 mmHg ≥80y, <135/75 mmHg for those with diabetes. - Clinicians: complete freedom to adjust antihypertensive and other medication as they sought fit - No further details given on number of GP visits or communications.	Downgraded for population indirectness, as it did not specify type of diabetes present
Stergiou 2014 RCT	145	Adults with diabetes (n=145) Mean age=50.75 y (SD=10.3 y)	HBPM without telemonitoring - validated oscillometric devices with automated memory - during 12-month follow-up: Treatment titration based on home BP measurements. - Target of average home BP <135/85 mmHg for low/moderate-risk participants and <125/80 mmHg for high-risk participants. - Treatment titration: at 4-week intervals until pre-set BP goal was reached. - treated 12 months: aim to reach pre-set BP goals. - Controlled hypertension = home BP levels at pre-set goal in 2 visits 4 weeks apart.	Ambulatory and clinic monitoring - ABPM on routine workday at 20-minute interval for 24 h - validated oscillometric devices - during 12-month follow-up: Treatment titration made on CBPM and ABPM - Target: CBP <140/90 mmHg and awake ABP <135/85 mmHg for low/moderate-risk people and <130/80 mmHg and <125/80 mmHg for high-risk people. - Treatment titration: at 4-week intervals until the pre-set BP goal was reached. - treated for 12 months: aim to reach pre-set BP goals.	Downgraded for population indirectness, as it did not specify type of diabetes present

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
			- No details: number of GP visits, communication or number of measurements.	- No details: number of GP visits, communication or number of measurements.	
Tucker 2017 Systematic review und Individual-daten-Metaanalyse	3123	Adults	HBPM with telemonitoring - Self-monitoring without medical professional input (that is, by participant with or without carer support) - validated monitor - with or without other co-interventions - comparator group had organised self- measurement of BP. - Targets ranged from 120/75-140/90 from home and from 130/80- 140/90 for clinic. - Number of readings/session: 1- 3. - Self-monitoring: daily for 1 week every 2 months-daily for 1st week of each month. - No details: number of GP visits or communication.	Usual care - No details about usual care. - Targets ranged 120/75 - 140/90 from home and from 130/80 - 140/90 for clinic. - No details: number of GP visits or communication.	IPD Downgraded for intervention indirectness and for population indirectness, as it was comparing with usual care not clearly stating clinic measurement and did not specify type of diabetes present

5.2 Strukturierte Recherche (Cochrane Reviews)

Palmer et al. 2021 Mobile-phone-based (education, adherence, blood pressure)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Palmer et al. [40] https://pubmed.ncbi.nlm.nih.gov/33769555/	2021		**Objective** effectiveness of interventions delivered by mobile phone to improve adherence to medication prescribed for the primary prevention of cardiovascular disease (CVD) in adults **Search** CENTRAL, MEDLINE, Embase, and two other databases, two clinical trials registers, reference lists (Jan 2020) **Inclusion and exclusion criteria** - randomised controlled trials (parallel-group or cluster-randomized) - minimum of one-year follow-up - patients aged ≥ 18 years	Update of Palmer 2018 [41] https://pubmed.ncbi.nlm.nih.gov/29932455/ n=14 studies were included (n=25,633 patients; range 59 to 9642), 33 references - (n=13 ongoing studies, 19 studies awaiting classification; additional updated search, repeated on 8 January 2021, resulted in a further 18 studies (19 references) awaiting classification) - community-based primary and tertiary care or outpatient clinics - mean age 49 years to 67 years	heterogeneity was reported (intervention, population) blinding (performance bias and detection bias) were rated as high risk of bias in most of the studies

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- with medication for (primary) prevention of CVD - history of prior CVD event[4] - investigating interventions delivered wholly or partly by mobile phones to improve adherence to cardiovascular medications[5] - adherence to lifestyle modifications were also possible **Quality assessment** Risk of Bias; GRADE **Intervention** mobile phone-specific delivery mechanism, including short messaging service (SMS), multimedia messaging (MMS), applications (apps) and Interactive Voice Response **Comperator** usual care or control groups receiving no mobile phone-delivered component of the intervention **Outcomes** primary: - objective measures of adherence to treatment (low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and highdensity ■ lipoprotein cholesterol (HDL-C), for the effect of statins; blood pressure for antihypertensive drugs; heart rate for the effect of atenolol; urinary 11-dehydrothromboxane B2 for the ■ antiplatelet effects of aspirin) - combined CVD events (fatal or non-fatal) - adverse effects including self-reported road traffic accidents secondary:	- interventions included: o general health education (e.g. targeting behaviours (lifestyle modifications, healthy diet, physical activity) o messaging focusing on medication adherence o blood pressure control and the rationale for medical therapy - interventions varied widely: delivered solely through short messaging service (SMS) to involving a combination of modes of delivery, such as SMS in addition to healthcare worker training, face-to-face counselling, electronic pillboxes, written materials, and home blood pressure monitors - n=14 studies reported medication adherence - n=13 reported measured blood pressure ■ (Bobrow 2016; Choudhry 2018; He 2017; Liu 2015; Logan 2012; Márquez Contreras 2019; McManus 2018; Morillo-Verdugo 2018; Párraga-Martínez 2017; Prabhakaran 2019; Peiris 2019; Saleh 2018; Tobe 2019) - n=6 reported measured cholesterol levels - n=3 reported cardiovascular outcomes ■ (McManus 2018; Peiris 2019; Tobe 2019) - n=1 study reported CVD-related deaths ■ (Bobrow 2016) - n=6 reported adverse events - n=9 reported indirect measured adherence	

[4] defined as: a previous myocardial infarction, stroke, revascularisation procedure (coronary artery bypass grafting or percutaneous coronary intervention), people with angina, and people with angiographically-defined CHD
[5] interventions targeting adherence to antihypertensive drugs (thiazide-like diuretic, angiotensin-converting enzyme inhibitor, calcium channel blocker, beta-blocker); lipid-lowering drugs (statins); and antiplatelet drugs (low-dose aspirin, non-aspirin antiplatelet drugs)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- indirect measures of adherence to treatment (self-report, tablet counts, medication event monitoring systems, pharmacy prescription data) - fatal cardiovascular events - non-fatal cardiovascular events (CHD, stroke) - health-related quality of life assessed using validated instruments (e.g. 36-Item Short Form Health Survey (SF-36), EQ-5D) - cognitive outcomes (any measures of: satisfaction with treatment, medication-taking self-efficacy, autonomy related to medication, attitudes (e.g. concerns about medicine adverse effects)) - costs	▪ (e.g. Morisky-Green-scale, self-reported medication adherence, proportion of days covered (PDC), Medication Event Monitoring System (MEMS)) - n=3 reported quality of life (EuroQol 5) ▪ (Bobrow 2016; McManus 2018; Peiris 2019) - n=2 reported cognitive outcomes - n=4 reported process measures - n=2 reported costs - most results were reported qualitatively (due to heterogeneity) - n=2 trials were included in quantitative analyses (Bobrow 2016 and Tobe 2019) o intervention solely through text messages about hypertension and it's medical therapy to target adherence, and recorded blood pressure outcomes (systolic blood pressure, and controlled' blood pressure) **Outcomes** (s.a. page 95 ff within the publication, forest plot) **primary:** adherence to treatment cholesterol (low-density lipoprotein) - n=2 studies found evidence of a small beneficial intervention effect on reducing LDL-C (−9.20 mg/dL, and 5.3 mg/dL), and - n=3 studies found results varying from a small reduction (−7.7 mg/dL) to a small increase in LDL-C (0.77 mg/dL), all of which had wide confidence intervals that included no effect; - n=5 studies, n=5,441 patients (low certainty of evidence) (follow-up: range 1 –2 years) blood pressure - **Systolic BP**: 9 of 13 studies found lower systolic blood pressure with mobile-phone interventions, although	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				only 4 of these reductions in systolic blood pressure had confidence intervals excluding no effect. Across the 13 studies, effect estimates varied greatly, from those showing a large reduction (−12.45 mmHg) to those reporting a small increase (+2.80 mmHg) in systolic blood pressure. - Meta-analysis of 2 trials evaluating an intervention targeting adherence to blood pressure medication delivered solely by SMS messaging provided a pooled ▪ MD of −1.55 mmHg, 95% CI −3.36 to 0.25 - n=13 studies, n=25,166 patients, (low certainty of evidence) (follow-up: range 1 –2 years) ▪ - **Diastolic BP:** 8 of 11 studies found lower diastolic blood pressure with mobile-phone interventions, but in 4 of these the confidence intervals included no effect. Across the 11 studies, effect estimates varied widely from those showing a large reduction (−12.23 mmHg) to those showing a small increase (+1.64 mmHg) in diastolic blood pressure. - n=11 studies, n=19,716 patients, (low certainty of evidence) (follow-up: range 1 –2 years) ▪ - **Controlled BP:** 7 studies reported 'controlled' blood pressure as an outcome, of which six reported increased blood pressure control with mobile phone interventions, although in only one of these studies did the confidence interval exclude no effect. Effect estimates varied from negligible (OR 1.01) to large improvements in blood pressure control (OR 2.41) - Meta-analysis of 2 trials evaluating an intervention targeting adherence to blood-pressure medication delivered solely by SMS messaging indicated a modest beneficial intervention effect: ▪ pooled OR of 1.32, 95% CI 1.06 to 1.65	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- n=7 studies, n=19,185 patients (low certainty of evidence) (follow-up: range 1 –2 years) Combined CVD events - 1 trial reported on deaths due to CVD, and 3 recorded non-fatal CVD events. For 3 studies the effect estimate was in the direction of harm, and for the 4th it was in the direction of intervention benefit. However, the number of events in each trial was low and all effect estimates had wide 95% confidence intervals encompassing no effect. - n=4 studies, n=12,439 patients (very low certainty of evidence) Adverse events - 3 studies reported that there were no adverse events attributable to the intervention. 1 reported that there was no difference between groups in adverse effects of statins, and that no participants reported intervention-related adverse events. 1 study reported that potential side effects were similar between groups. 1 study reported a similar number of deaths in the intervention and control arms, but did not provide further information relating to potential adverse events. - n=6 studies, n=8,285 patients, (moderate certainty of evidence) (follow-up: range 1 –2 years) Cognitive outcome: satisfaction with treatment - 1 study measured satisfaction with treatment, and found no evidence of a difference between intervention and control arms. 1 study reported on perceived quality of care, with little difference observed between the 2 groups. - n=2 studies, n=2,535 patients (low certainty of evidence) **secondary**: indirect measured adherence s. page 99 within the publication	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				s.a. page 18/19 (non-)fatal cardiovascular events, QoL, cognitive outcomes, costs, process measures	

Palmer et al. 2018 Mobile-phone-based (medication adherence) (Update 2021 s.o.)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Palmer MJ. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev 2018; 6(6):CD012675. [41] https://www.ncbi.nlm.nih.gov/pubmed/29932455.	2018	high	Fragestellung To establish the effectiveness of interventions delivered by mobile phone to improve adherence to medication prescribed for the primary prevention of CVD in adults. Suchzeitraum: 14 July 2017 Population: - adults (≥ 18 years) - prescribed medication for primary prevention of CVD. - not had a prior CVD event: previous myocardial infarction, stroke, revascularisation procedure (coronary artery bypass grafting or percutaneous coronary intervention), angina, angiographically defined CHD. - only trials in which at least 75% of participants met the criteria for primary prevention were included. Studientypen: - RCT Intervention: - delivered wholly or partly by mobile phones to improve adherence to CV-medications prescribed for the primary prevention of CVD. - minimum of one-year follow-up in order that outcome measures related to longer-term, sustained medication adherence behaviours and outcomes. Vergleich: - comparators were usual care or control groups receiving no mobile phone-delivered component of the intervention.	Allgemeines: - 2 von 4 eingeschlossenen Primärstudien betrachten Patienten mit Hypertonie - Dauer beider Studien: 1 Jahr Logan 2012 - n= 110 - with diabetes mellitus, with uncontrolled systolic hypertension, defined as a mean daytime SBP of >130 mmHg on ABPM - mean age: 62,9y - primary prevention: 79% - setting: offices or clinics of physicians practicing - both groups: - taught how to measure their BP correctly, - validated home BP monitoring device with appropriate-sized upper arm cuff, - booklet with detailed information on self-measurement of BP, treatment of hypertension and goals of therapy - primary care physician was given outline of study's objectives and BP treatment goal, asked to provide relevant medical information and given a copy of the 24-hour ABPM report. - treatment decisions (medication adjustments and changes in lifestyle) made by participant's primary care physician - Intervention: BP monitoring and feedback messages delivered via smartphone (self-care message) - Vergleich: did not received feedback via smartphone. >> did not report on adverse events >> Blutdruck: - greater reduction in SBP and DBP in intervention group compared with control group at 12 months for: 24-hour BP and daytime ABPM (mean between-group difference in change (SE):	Mobile phone-based interventions Auch „ongoing studies“ berichtet: Franssen 2017, ggf. Jha 2017, Xu 2017

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- 24-hour SBP: -6.8 mmHg (SE 2.4); - 24-hour DBP: -3.6 mmHg (SE 1.3); - daytime SBP: -7.10 mmHg (SE 2.3); - daytime DBP: -3.9 mmHg (SE 1.3)). - weak evidence of a benefit for change in nighttime BP (SBP: -4.7 mmHg (SE 2.8); DBP: -2.3 mmHg (SE 1.6)) (n= 105) >> adherence rate: 65.4% (SD 30) to home blood pressure measurement schedule (≥ 8 readings/ weeks) in intervention group Bobrow 2016 - n= 1372 - mean age: 54,4 y - primary prevention: 78.3% of participants - setting: outpatient chronic disease service in a single, large, public sector clinic - Group 2: 'informational SMS texting: text messages to motivate collecting and taking medicines and to provide education about hypertension and its treatment. - Group 3: 'interactive SMS texting' group: same messages as the information-only group but could also respond to selected messages using free-to-user "please call me" requests. - Vergleich (group 1): written information about hypertension and healthy living and continued to receive care from clinic. only received the texts sent to all trial participants, which were sent no more frequently than 1 text every 4 weeks >> Blutdruck - greater reduction in mean SBP from baseline to 12-month follow-up in intervention group receiving information-only text messages vs. control group (MD -2.2 mmHg, 95% CI -4.4; 0.00), - no difference between intervention group receiving interactive text messaging and control group (MD -1.6 mmHg, 95%CI -3.70; 0.50) - proportion of participants achieving SBP and DBP < 140/90 mmHg: benefit for both - information-only text messaging intervention group (65% with information-only text messaging vs. 58% with control; OR 1.42, 95% CI 1.03; 1.95)	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- interactive text messaging group (65% with interactive text messaging vs. 58% with control; OR 1.41, 95% 1.02; 1.95), compared with control group receiving usual care >> adverse events: - reported no adverse events attributable to the intervention (low quality of evidence) >> Euro-Qol 5-Dimension Index: - no effect of information-only text messages (median Diff. 0.01, quartiles 1-3: -0.01; 0.02) or interactive text messages (median Diff.: 0.003, quartiles 1-3: -0.02; 0.02) compared with control >> Fatal cardiovascular events - 2 participants in the information-only text messaging group died due to ischaemic heart disease, - 2 participants in the interactive text messaging group died due to congestive cardiac failure - no deaths in the control group known to be due to CVD. - lost to follow-up due to reason of 'lost contact': (usual care arm: n= 14; information SMS arm: n=7; interactive SMS arm: n= 7) - possible that differential lost to follow-up due to lost contact could have underestimated deaths, including those due to CVD in usual care arm.	

Posadzki et al. 2016 Automated telephone communication (prevention)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Posadzki P. Automated telephone communication systems for preventive healthcare and management of long-term conditions.	2016	high	Fragestellung: - assess the effects of ATCS for preventing disease and managing long-term conditions on behavioural change, clinical, process, cognitive, patient-centred and adverse outcomes. Suchzeitraum: 1980 and June 2015. Population: - consumers, including carers, who received ATCS for prevention or management of long-term conditions, regardless of age, sex, education, marital status, employment status, or income. - ≥1 concurrent long-term conditions (i.e. multimorbidity).	Allgemeines: 132 Studien zu verschiedenen Krankheitsbildern identifiziert Baseline-Informationen der hypertoniespezifischen Studien: - N= 5 - 1 Honduras/Mexico (Piette 2012), 4 USA (Bove 2013; Dedier 2014; Harrison 2013; Magid 2011). - mean age: 58 years - 66 years - Bove 2013, Magid 2011, Harrison 2013: diabetes mellitus	Automated telephone communication systems Siehe S. 29/469 S. 55/469 S. 96/469

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Cochrane Database Syst Rev 2016; 12(12):CD009921. [42] https://www.ncbi.nlm.nih.gov/pubmed/27960229.			- in all settings. Studientyp: - Randomised, cluster- and quasi-randomised trials, interrupted time series and controlled before-and-after studies - all settings, for all consumers/carers, in any preventive healthcare or long term condition management role Intervention: - ATCS interventions Kontrolle: - with any control or another ATCS type	- Bove 2013 and Magid 2011: complex interventions (ATCS + system with additional communicative (and in the case of Bove 2013, also supplementary) functions vs. usual care. - Bove 2013: sphygmomanometer, weighting scale, pedometer - Magid 2011: patient education, home BP monitoring, clinical pharmacist management of hypertension with physician oversight in addition to usual care. - Piette 2012: ATCS system with communicative functions to primary care and education. - Dedier 2014: IVR system underpinned by social cognitive theory vs. primary care and education, - Harrison 2013: unidirectional ATCS vs. usual care. Interventions: aimed at planning action and setting goals, prompting self-monitoring of behavioural outcome, providing rewards contingent on effort or progress towards behaviour, setting graded tasks and tailoring, prompting self-monitoring of behaviour and providing follow-up prompts or providing feedback on performance. - Call duration: up to 10 min (weekly) (Magid 2011 and Dedier 2014) - Call frequency: biweekly in Bove 2013. Ergebnisse - SBP nach 6 Wochen: 3 trials, found that ATCS probably reduced slightly SBP vs. usual care with or without information (MD -1.89 mmHg, 95%KI -2.12; -1.66; moderate certainty evidence; 3 Studien, I2 = 0%, n= 65256). - DBP nach 14 Wochen: no effect for ATCS vs. usual care, MD 0.02 (95%KI -2.62, 2.66), low certainty evidence, 2 Studien, I^2= 72%, n= 65056 - Health status: ATCS Plus vs. enhanced usual care (+ information): Plus may have slightly improved overall health status (mean (SE) 2.5 (0.09) vs. 2.1 (0.08), where 1 = poor and 5 = excellent) at 6 weeks (low certainty evidence). - No studies reported adverse events.	

Jongh et al. 2012 Mobile phone messaging (self-management)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Jongh T de. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database Syst Rev 2012; 12(12):CD007459. dx.doi.org/10.1002/14651858.CD007459.pub2. [43] https://www.ncbi.nlm.nih.gov/pubmed/23235644.	2012	high	Fragestellung - assess effects of mobile phone messaging applications designed to facilitate self-management of long-term illnesses, in terms of impact on health outcomes and patients' capacity to self-manage their condition. - Secondary objectives: assessment of user evaluation of intervention; health service utilisation and costs; and possible risks and harms associated with intervention. Suchzeitraum bis 06/2009 Population - regardless of age, gender and ethnicity, as well as all types and stages of diseases. - primary care settings (services of primary health care), - outpatient settings (outpatient clinics), - community settings (public health services, anywhere where a person can use a mobile phone) - hospital settings. Studientyp - RCTs, quasi-randomised controlled trials (QRCTs), controlled before-after (CBA) studies, or interrupted time series (ITS) studies with at least 3 time points before and after intervention. Intervention: - studies where it was possible to assess effects of mobile phone messaging independent of other technologies or interventions.	Allgemeines: - 4 RCTs (n= 182) eine hypertoniespezifische Studie: Marquez Contreras 2004 - Population: not well controlled with monotherapy were started a combination of a single-dose angiotensin II antagonist and a diuretic. - aim of the messages: provide information on hypertension; promote compliance, good health and dietary habits; and remind patients to take medication Ergebnisse: - compared SBP and DBP in groups of patients with and without text message support, at baseline, 1, 3, 6 months after initiation of the study. - BP levels at 6 months: comparable in the two groups (SBP MD 1.10, 95% CI -4.37; 6.57); DBP MD 1.84, 95% CI -2.14; 5.82). - Achievement of good BP control (defined by BP < 140/90 mm Hg in patients without diabetes and 130/85 mm Hg in patients with diabetes) at the end of the study: not statistically different between the control and intervention (RR of not achieving BP control 0.73, 95% CI 0.41 to 1.29). - body weight at 6 months: comparable between groups (MD -2.76 (95% CI -8.17; 2.65). - evidence is considered to be of moderate quality - observed effect sizes are likely to be affected by further research - marginally significant increase in rate of compliance of intervention group at six months (MD 8.90, 95% CI 0.18; 17.62)	Mobile phone messaging

Flodgren et al. 2015 Interactive telemedicine (blood pressure, others)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Flodgren G. Interactive telemedicine: Effects on professional practice and	2015	moderate	Fragestellung: To assess the effectiveness, acceptability and costs of interactive TM as an alternative to, or in addition to, usual care (i.e. face-to-face care, or telephone consultation). Suchzeitraum: up to June 2013	Allgemeines: - 4 studies recruited patients (n = 1 073) with hypertension - Monitoring of a chronic condition to detect early signs of deterioration and prompt treatment and advice (N= 3) - Education, advice for self-management, and support (N= 1)	Interactive telemedicine S.22/583 S. 525/583

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
health care outcomes. Cochrane Database Syst Rev 2015(9):CD002098. dx.doi.org/10.1002/14651858.CD002098.pub2. [44] https://www.ncbi.nlm.nih.gov/pubmed/26343551.			Studientyp: RCTs Intervention: - interactive TM that involved direct patient-provider interaction and was delivered in addition to, or substituting for, usual care compared with usual care alone, to participants with any clinical condition. - telephone only interventions and wholly automatic self-management TM interventions excluded Popuation: 1. Patients receiving interactive TM from any qualified healthcare practitioner, compared with those receiving usual care. 2. Healthcare professionals from any discipline providing patient care through interactive TM.	- Remote monitoring with automatic review of data and a system for alerting healthcare professional of out of range values (N= 1) Blood pressure measurement Artinian 2007; n= 387: - greater decrease in mean SBP in TM delivered in addition to usual care, as compared with usual care alone at 12 months - Mean office SBP at 12 months: TM:145.0 (21.0), n=167; UC: 148.1 (22.3), n=169 - Mean office DBP at 12 months: TM: 83.8 (12.1); UC: 83.5 (13.6)) Madsen 2008; n= 236: - no differences in diastolic daytime and night time ABPM between groups at 6 months but did report that a greater proportion of intervention patients achieved a target BP at 6 months. Daytime ABPM at 6 months: - Systolic: TM: 141.1 (11.5), n=113; UC: 142.7 (13.3), MD (95%CI): -2.3 (-6.1; 1.5), - Diastolic: TM: 85.0 (7.1); UC: 85.1 (8.2); MD (95%CI): -0.8 (-3.1; 1.4), Nighttime ABPM at 6 months: - Systolic: TM: 122.6 (14.4); UC: 125.2 (16.0); MD (95%CI): -1.0 (-5.0; 3.0), - Diastolic: TM:71.8 (7.9); UC: 72.6 (8.5), MD (95%CI): -0.7 (-2.9; 1.6) Rogers 2001; n = 121: - greater decrease in 24-hour systolic and diastolic ABPM and a greater change in mean BP in the TM group at 8 weeks, as compared with control. - Mean change in arterial BP at 8 weeks: Mean diff (95% CI):4.1 mmHg (0.91; 7.38) - Mean change in systolic ABPM at 8 weeks: Mean diff. (95%CI): 4.8mmHg (0.10; 9.37), - Mean change in diastolic ABPM at 8 weeks: Mean diff. (95%CI): 4.1mmHg (0.93; 7.13), n= 60 in each group Parati 2009; n = 329: - monitoring study with automated review of data with alerts: greater proportion of TM participants achieving daytime normalisation of arterial BP as compared with control.	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- Percent of patients with daytime arterial BP normalisation 3 at 24 weeks: TM:62%, n= 216; UC: 50%, n= 113 Quality of life Madson 2008: Mean SF-36 domain scores at 12 months: Physical functioning: TM: 88.2 (14. 0); UC: 84.2 (19.2) Role physical: TM: 80.0 (36.4); UC: 77.3 (36.2) Bodily pain: TM: 85.3 (20.2);UC: 78. 3 (26.4), General health:TM: 77.1 (15.4);UC: 73. 5 (17.4), Vitality: TM: 68. 8 (17.6); UC: 67.8 (21.8), Social functioning: TM: 89.5 (18.4); UC: 91.6 (17.8), Role emotional: TM: 83. 8 (32.4); UC: 84.5 (27.8), Mental health: TM: 79.3 (16.4);UC: 81. 5 (15.7), TM: n=105;UC: n= 118 Parati 2009: QOL (Quality Of Life Assessment in Hypertensive Patients questionnaire 4): End of study: UC: 38.3(5.4); TM: 38.4(4.6) End of study – baseline difference: UC: 0.1(3.9); TM: 0.7 (4.3), P End of study – baseline difference (%): UC: 0.5(10.4); TM: 2.6(12.7)	

Devi et al. 2015 Internet-based interventions (prevention)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Devi R. Internet-based interventions for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2015(12):CD009386. dx.doi.org/10.	2015	moderate	Fragestellung - determine effectiveness of Internet-based interventions targeting lifestyle changes and medicines management for secondary prevention of CHD. Suchzeitraum: bis 01/2015 Studientyp: RCTs Intervention: - evaluating Internet-delivered secondary prevention interventions aimed at people with CHD. Population: - Adults (18 years of age or older) - with CHD, including those having experienced a myocardial infarction, a revascularisation procedure (including stent, coronary	Allgemeines: - 18 trials met our inclusion criteria. - 11 studies are complete (1392 participants), 7 are ongoing. - 7 interventions are broad, targeting the lifestyle management of CHD, and four focused on physical activity promotion. - length of the programmes: 6 weeks - 1 year. - comparison group in trials was usual care (n = 6), minimal intervention (n = 3), or traditional cardiac rehabilitation (n = 2). - 1392 people with coronary heart disease were recruited. - average age 54.9 to 66.27 years. - majority of people recruited were men. Ergebnisse:	Internet-based interventions Frage an AG: Population hat bereits CV-Folgeerkrankungen Sind die Ergebnisse für die NVL Hypertonie anwendbar

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
1002/14651858.CD009386.pub2. [45] https://www.ncbi.nlm.nih.gov/pubmed/26691216.			artery bypass grafting, or percutaneous transluminal coronary angioplasty), those with angina, or angiographically defined CHD	- no effects of Internet-based interventions for all-cause mortality (OR 0.27, 95% CI 0.04; 1.63; n = 895; N = 6; low-quality evidence). - one case of CV-mortality in a control group (n = 895; N = 6). - No incidences of non-fatal re-infarction reported across any of the studies. - no effects for revascularisation (OR 0.69, 95% CI 0.37 to 1.27; n = 895; N = 6; low-quality evidence). - 7 studies measured SBP and DBP; did not pool data due to substantial heterogeneity. - SBP: 2 studies showed a reduction with the intervention, but the remaining studies showed no effect. - DBP: 2 studies showed a reduction with the intervention, 1 study showed an increase with the intervention, and the remaining four studies showed no effect. - 5 trials measured HRQOL:. We could draw no conclusions from 1 study due to incomplete reporting; 1 trial reported no effect; 2 studies reported a short- and medium-term effect respectively; and 1 study reported both short- and medium-term effects	

Glynn et al. 2010 Interventions to improve BP control

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Glynn LG. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev 2010(3):CD005182. dx.doi.org/10.1002/14651858.CD005182.	2010	Critically low	**Fragestellung:** 1) Evaluate which models of care are effective in improving “control” of high blood pressure; (2) Evaluate the effectiveness of reminders on improving the follow-up of patients with hypertension. **Suchzeitraum:** bis 02/2008 **Population:** - adult patients (aged 18 years or over) with essential hypertension - treated or not currently treated with blood pressure lowering drugs - in a primary care, outpatient or community setting **Intervention:** (1) self-monitoring (2) educational interventions directed to the patient	72 RCTs eingeschlossen -methodological quality of included studies varied. organized system of regular review allied to vigorous antihypertensive drug therapy - reduced SBP (WMD) - 8.0 mmHg, 95% CI: -8.8 to -7.2 mmHg) and DBP (WMD -4.3 mmHg, 95% CI: -4.7; -3.9 mmHg) for 3 strata of entry BP, - reduced all-cause mortality at 5 years follow-up (6.4% vs. 7.8%, difference 1.4%) in a single large RCT- the Hypertension Detection and Follow-Up study. Self-monitoring (18 RCTs) - associated with moderate net reduction in SBP (WMD -2.5 mmHg, 95% CI: -3.7 to -1.3 mmHg) (12 RCTs) and DBP (WMD -1.8 mmHg, 95% CI: -2.4 to -1.2 mmHg) (14 RCTs). educational interventions directed at patients (20 RCTs)	Glynn LG. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev 2010(3):CD005182. dx.doi.org/10.1002/14651858.CD005182.p

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
pub4. [46] https://www.ncbi.nlm.nih.gov/pubmed/20238338.			(3) educational interventions directed to the health professional (4) health professional (nurse or pharmacist) led care (5) organisational interventions that aimed to improve the delivery of care (6) appointment reminder systems **Vergleich**: - no intervention or usual care Studientyp: RCTs	- heterogeneous but appeared unlikely to be associated with large net reductions in BP by themselves. - a trend towards improved BP control and this was significant (OR 0.83, 95% CI 0.75 to 0.91), (8 RCTs) educational interventions directed at health professionals (10 RCTs) - not associated with a significant decrease in mean SBP (mean difference -0.4 mmHg, 95% CI -1.1 to +0.2 mmHg) or DBP (mean difference -0.4 mmHg, 95% CI -1.1 to +0.3 mmHg) whilst control of BP produced heterogeneous results (OR ranged from 0.8 to 1.0). Nurse or pharmacist led care (12 RCTs) - pooling of results from individual RCTs produced heterogeneous results, so pooled MD may not be valid. - may be a promising way forward, with the majority of RCTs being associated with improved BP control and mean SBP and DBP but these interventions require further evaluation. Appointment reminder systems - require further evaluation due to heterogeneity and small trial numbers - majority of trials increased the proportion of individuals who attended for followup (OR 0.41, 95% CI 0.32 to 0.51) and in 2 small trials also led to improved BP control, OR favouring intervention 0.54 (95% CI 0.41 to 0.73).	ub4. https://www.ncbi.nlm.nih.gov/pubmed/20238338.

5.3 Handsuche / Literaturlistensuche

Mengden and Weisser 2021 Monitoring (arterial hypertension)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Mengden. Monitoring of Treatment for Arterial Hypertension. Dtsch Arztebl Int. 2021 Jul 12;118(27-	2021	not applicable	**Objective** to present current recommendations from Germany and from international guidelines as well as the findings of the main studies on the use of these methods to guide treatment **Search** PubMed was searched up to and including March 2020 **Inclusion and exclusion criteria**	guidelines included from: ■ the American Heart Association (AHA/ACC 2017 [6]), ■ the European Society of Hypertension and the European Society of Cardiology (ESH/ESC 2018 [7]), ■ the UK's National Institute for Health and Care Excellence (NICE 2019 [8]) ■ and the position paper of the German Hypertension Society (DHL, Deutsche Hochdruckliga [9])	Scoping Review (one source) -unterstützend betrachtet

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
28):473-478. doi: 10.3238/arztebl.m2021.0158. [47] https://pubmed.ncbi.nlm.nih.gov/33734987/			▪ prospective follow-up studies with cardiovascular endpoints ▪ reviews, meta-analyses, ▪ blood pressure guidelines, ▪ scientific statements, ▪ and position papers **Quality assessment** **Investigation** monitoring the treatment of arterial hypertension: ▪ office blood pressure (office BP), ▪ home blood pressure (home BP), ▪ or 24 hours ambulatory blood pressure (ABPM) **Outcomes** blood pressure	▪ recommendations for monitoring varied widely (see Table 1 within the publication): ▪ favoured (+++): □ **office BP**: NICE 2019**; ESC/ESH 2018 □ **Home-BP:** AHA 2017*; DHL 2017 □ 24h BP: - * Potentially in conjunction with telemedicine case management ** If “white coat” effect or masked hypertension is suspected or if patient preference than HBPM was prefered ▪ guideline (clinical) arguments: □ greater patient acceptance of blood pressure self-measurement compared to 24-hour ambulatory blood pressure measurement □ home blood pressure monitoring may promote adherence □ circadian variability over 24 hours and variability between blood pressure checks during physician visits □ Office blood pressure measurement, is limited by examiner error, poor reproducibility and white-coat effect ▪ authors arguments for HBPM: □ Best blood pressure measurement reproducibility of all methods □ Revealing adherence issues □ Overcoming “therapeutic inertia“ □ Detection even of small therapeutic effects □ Unlimited repeatability compared to ABPM □ Patient preference. ▪ note: lack of randomized trials on the prognostic significance of different methods of blood pressure measurement (gaps in evidence) ▪ note: patients should be adequately educated in the use of systems which automatically store measurements for treatment monitoring, potentially in conjunction with telemedicine interventions	

6 Evidenztabellen Therapieplanung (Stand: 28.10.2021)

6.1 Allgemein (Therapieziele)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [D] Evidence review for targets [48] https://www.nice.org.uk/guidance/ng136/evidence/d-targets-pdf-6896748209	2019	high	**Fragestellung 2: What is the optimum BP target for adults with treated primary hypertension?** **Suchzeitraum:** bis 10/2018 **Population:** - Adults (over 18 years) with primary hypertension, Stratified by: T2DM (y/n) **Intervention:** - Blood pressure or CV-risk targets - Systolic blood pressure targets: < 120; 120—129, 130–139, 140–159, ≥160 mmHg - Diastolic blood pressure targets: < 80, 80–84, 85–89, 90–94, ≥ 95 mmHg **Vergleich:** - each other **Endpunkte:** *critical:* All-cause mortality, HrQoL, Stroke, Myocardial infarction (MI) *important:* Heart failure needing hospitalisation, Vascular procedures, Angina needing hospitalisation, Discontinuation or dose reduction due to side effects, Resource use *Side effects:* Acute kidney injury, New onset diabetes, Change in creatinine or estimated glomerular filtration rate (eGFR), Hypotension, Combined CVD outcomes in the absence of MI and stroke data, Coronary heart disease outcome in absence of MI data **Studientyp:** RCTs, SR **Fragestellung 1:** Should targets used for antihypertensive therapy be based on BP, CV-risk or a combination of both? **Suchzeitraum:** bis 10/2018 **Population:** - Adults (over 18 years) with primary hypertension, Stratified by: T2DM (y/n) **Intervention:**	**Fragestellung 1:** keine Studien identifiziert **Fragestellung 2:** 3 Studien identifiziert (ACCORD, SPRINT, Cardio SiS) **SPRINT: Systolic BP < 120 mmHg vs. < 140 mmHg (non-diabetic; n= 6,715)** Blutdruckmessung: mean of 3 office BP measurements, seated position with automated measurement device - n = 4,082 alone throughout measurement - n = 2,247 never alone - n = 1,746 alone for the rest period only - n = 570 alone for BP measurement only (these numbers include the CKD population) **Ergebnisse siehe Tabelle** 18 S. 64/74 https://www.nice.org.uk/guidance/ng136/evidence/d-targets-pdf-6896748209 - Fallzahl entspricht nicht der der SPRINT-Studie, da Patienten mit CKD aus Auswertung ausgeschlossen wurden **ACCORD: Systolic BP < 120 mmHg vs. < 140 mmHg (diabetic, n= 3140)** Blutdruckmessung: automated device after 5 min. rest with participant seated in a chair (average of 3 measurements). **Ergebnisse siehe Tabelle** 19 S. 66/74: https://www.nice.org.uk/guidance/ng136/evidence/d-targets-pdf-6896748209 **Cardio-SIS: Systolic BP < 130 mmHg vs. < 140 mmHg (non-diabetic,n= 1111)** Blutdruckmessung: standard mercury sphygmomanometers, after seated for at least 10 min. average of 3 consecutive readings at every visit	- nehmen Bezug auf CR

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- BP targets - CV-risk targets - Combination of BP and CV-risk target **Vergleich:** - each other - BP and CV-risk targets combined compared to either target type alone - No target **Endpunkte:** *critical:* All-cause mortality, HrQoL, Stroke, Myocardial infarction (MI) *important:* Heart failure needing hospitalisation, Vascular procedures, Angina needing hospitalisation, Discontinuation or dose reduction due to side effects, Resource use *Side effects:* Acute kidney injury, New onset diabetes, Change in creatinine or estimated glomerular filtration rate (eGFR), Hypotension, Combined CVD outcomes in the absence of MI and stroke data, Coronary heart disease outcome in absence of MI data **Studientyp:** RCTs, SR	**Ergebnisse siehe Tabelle** 20 S. 66/74: https://www.nice.org.uk/guidance/ng136/evidence/d-targets-pdf-6896748209	
Arguedas JA. Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev 2009(3):CD004349. [49] https://www.ncbi.nlm.nih.gov/pubmed/19588353.	2009	low	**Fragestellung:** determine if there is a reduction in total mortality and morbidity associated with treatment of blood pressure to "lower targets" as compared with "standard targets" in the management of patients with elevated arterial BP. **Suchzeitraum:** bis 06/2008 **Population:** - adults, with elevated BP documented in a standard way on at least 2 occasions - or adults already receiving treatment for elevated BP. - Since any numerical definition of elevated BP is arbitrary, we accepted any trial where patients were randomised to the 2 targets described and did not require that patients at baseline have any specific BP. **Intervention/ Vergleich** - Trials were included if individuals were randomized to a "lower" target systolic/diastolic BP (135/85mmHg) as compared with a "standard" target BP (140-160 /90-100 mmHg).	Extraktion der 3 vor 2000 veröffentlichen Primärstudien, die in NICE-Review nicht betrachtet wurden: - Charakteristika der Primärstudien siehe Cochrane Review ab S. 23/44 - HOT 1999, Toto 1995, MDRD 1994 - verglichen diastolische Blutdruckwerte miteinder BP <135/85 vs. BP <140-160/90-100 **Total mortality** - HOT: 401/12526 vs. 188/6264; RR 1.07 [0.90, 1.27] **Cardiovascular mortality** - HOT: 186/12526 vs. 87/6264; RR 1.07 [0.83, 1.38] **Non-CV mortality** - HOT: 215/12526 vs. 101/6264; RR 1.06 [0.84, 1.35] **Myocardial infarction** - HOT 214/12526 vs. 127/6264 ; RR 0.84 [0.68,	In NICE-Review ausgeschlossen: Arguedas 2009 excluded due to including people with various chronic renal conditions or previous CV-disease, who were excluded from this review protocol Abgleich der Primärstudien (PS) zwischen CR und NICE 2/7 PS in NICE ausgeschlossen (Aa) 3/7 PS vor 2000 veröffentlicht, daher nicht in NICE erwähnt 2/7 PS Komorbidität Nierenerkrankung aus Titel erkennbar, daher wahrscheinlich in TiAb bei NICE ausgeschlossen

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Endpunkte: *Primary:* All-cause mortality + CV and non-CV mortality separately; Total serious adverse events, CV serious adverse events combined and separately: myocardial infarction, stroke, congestive heart failure, end-stage renal failure, All other serious adverse events. *Secondary:* Systolic BP achieved, Diastolic BP achieved, Proportion of patients not achieving the target BP levels,Withdrawals due to AE, Number of antihypertensive drugs needed per patient. **Studientyp**: RCTs, unverblindet	1.05] - incidence of silent myocardial infarctions reported in the HOT trial was not different between the lower (89/ 12526) and the traditional target groups (43/6264): RR1.04, 99% CI (0.64, 1.67) **STROKE** - HOT 200/12526 vs. 94/6264; RR 1.06 [0.83, 1.36] **Congestive heart failure** - HOT 32/12526 vs. 21/6264; RR 0.76 [0.44, 1.32] **Major CV events** - HOT 483/12526 vs. 253/6264; RR 0.95 [0.82, 1.11] **End-stage renal disease** - Toto 7/42 vs. 2/35; RR 2.92 [0.65, 13.15] **Achieved systolic blood** - HOT n=12526; Mean (SD)140.55 (11.7) vs. n= 6264 Mean (SD) 143.7 (11.3); MD -3.15 [-3.50, -2.80] - Toto n= 42 Mean (SD)133 (19.4) vs. n=35 Mean (SD) 138 (11.8); MD -5.00 [-12.05, 2.05] **Achieved diastolic blood** - HOT n=12526 Mean (SD) 82.15 (5.05); n= 6264 Mean (SD) 85.2 (5.1); MD -3.05 [-3.20, -2.90] - Toto n= 42 Mean (SD) 81 (6.48); n= 35 Mean (SD) 87 (5.92); MD -6.00 [-8.77, -3.23] **Bias-Bewertung:** - HOT, MDRD: randomization was done at the study coordinating center. - Blocked randomization in MDRD, HOT - HOT: Randomization was computer generated (method of randomization not described in other trials) - Toto: exclusion of patients not able to achieve the lower target during the prerandomization period is a limitation of the trial as the results are only relevant to “responders” as defined in	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				that study. - None of the trials was blinded to BP-goal because of need to titrate treatment to achieve the specific target. - HOT, 486 patients (2.6%) were lost to follow-up; they were equally distributed between the three target arms. - MDRD: 14 patients (1.6%) lost to follow-up, but their distribution according to target is not provided. - HOT: specifically stated that an independent clinical event committee, masked to the group allocation, evaluated all clinical events.	
Arguedas et al. Blood pressure targets in adults with hypertension. Cochrane Database Syst Rev. 2020 Dec 17;12(12):CD004349. doi: 10.1002/14651858.CD004349.pub3. [50] https://pubmed.ncbi.nlm.nih.gov/33332584/	2020	low	**Objectives** to determine if lower blood pressure targets (any target less than or equal to 135/85 mm Hg) are associated with reduction in mortality and morbidity as compared with standard blood pressure targets (less than or equal to 140/ 90 mm Hg) for the treatment of patients with chronic arterial hypertension. **Search methods** Cochrane Hypertension Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov; also unpublished work was searched (up to May 2019) **Inclusion and exclusion criteria** ■ randomised controlled trials (RCTs) ■ patients allocated to lower or to standard blood pressure targets (see above) **Quality assessment** Cochrane risk of bias tool certainty of the evidence using the GRADE approach **Outcomes** primary ■ total mortality; ■ total serious adverse events;	Update od Arguedas 2009 (s.a.) n=11 trials, n=38,688 patients ■ mean follow-up of 3.7 years ■ mean weighted age 63.1 years (baseline) ■ mean weighted blood pressure 155/91 mm Hg (baseline) **Outcomes** **primary** total mortality ■ (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.86 to 1.05; 11 trials, 38,688 participants; high certainty evidence) ■ total serious adverse events (RR 1.04, 95% CI 0.99 to 1.08; 6 trials, 18,165 participants; moderate certainty evidence) ■ authors argued that the benefits of lower targets do not outweigh the harms as compared to standard blood pressure targets	detailed results see within the publication results of the review are primarily applicable to older people with moderate to high cardiovascular risk they may not be applicable to other populations

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ (myocardial infarction, stroke, congestive heart failure, end stage renal disease, and other serious adverse events) secondary ▪ mean SBP and DBP, ▪ withdrawals due to adverse effects, and ▪ mean number of antihypertensive drugs		

6.2 Komorbiditäten oder ausgewählte Patientengruppen

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Saiz LC. Blood pressure targets for the treatment of people with hypertension and **cardiovascular disease.** Cochrane Database Syst Rev 2018; 7(7):CD010315. [51] https://www.ncbi.nlm.nih.gov/pubmed/30027631.	2018	high	**Fragestellung:** determine if lower BP targets (≤ 135/85 mmHg) are associated with reduction in mortality and morbidity as compared with standard BP targets (≤ 140 to 160/90 - 100 mmHg) in the treatment of people with hypertension and a history of cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular occlusive disease). **Suchzeitraum:** bis 02/2018 **Population:** - ≥ 18 y - hypertension documented in standard way, or receiving treatment for hypertension, with positive CV history of myocardial infarction, stroke (not including TIA), chronic pAVK, or angina pectoris. - not limited by any other factor nor by baseline risk **Intervention:** - lower BP treatment target: ≤ 135/85 mmHg; mean BP ≤ 102 mmHg. - Mean BP (MBP) was accepted as a valid way of measuring interventions, while prespecified targets are taken into account and according to the following equation: MBP = [(2 × diastolic) + systolic]/3.	**Allgemeines:** - 6 Studien eingeschlossen (n= 9484: lower target, n= 5301; standard target, n=4183). - design in all trials: randomized and open with blinded end point - baseline BP required for inclusion varied: - AASK 2002 and HOT 1998 required DBP ≥95 mmHg and DBP 100-115 mmHg, respectively - ACCORD BP 2010 and SPRINT 2015 required SBP 130-180 mmHg, - Past BP 2016 sought SBP 125 mmHg, and SPS3 2013: SBP ≥130 mmHg and/or DBP ≥85 mmHg or history of hypertension with BP lowering medication at randomization. **Primäre EP** **total mortality:** lower 366/5301 vs. higher 285/4182; RR 1.06, 95%CI 0.91;1.23) I²=39%, 6 studies, moderate **Serious AE:** lower 1197/5301 vs. higher 1052/4183 (RR 1.01, 95% CI 0.94; 1.08) I²=0% 6 studies, low **CV events**: lower 562/5301 vs. higher 532/4183; RR 0.89, 95% CI 0.80; 1.00; I²=0%, 6 studies, low **CV mortality:** lower 172/5301 vs. higher 131/4183 (RR 1.03, 95%CI 0.82; 1.29) I²= 23%, 6 studies, moderate **Sekundäre EP:**	CV-Erkrankung

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Vergleich: - standard BP treatment target: ≤ 140-160/90-100 mmHg; mean BP ≤107-120 mmHg. **Endpunkte:** - Primär: Total mortality, Total serious adverse events, Total CV events, CV mortality - Sekundär: withdrawals due to AE, Systolic BP and difference from baseline at 1 year, or both; Diastolic BP and difference from baseline at 1 year, or both; Proportion of participants reaching target BP level; Number of antihypertensive drugs each participant needed at the end of study **Studientyp:** RCTs	Withdrawals due to AE: lower 22/420 vs. higher 2/270, RR 8.16, 95%CI 2.06;32.28;I²= 38,9%, 2 studies, very low	
Saiz LC. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database of Systematic Reviews 2020. Issue9. Art.No.: CD010315 [52]	2020	high	**Fragestellung:** determine if lower BP targets (≤ 135/85 mmHg) are associated with reduction in mortality and morbidity as compared with standard BP targets (≤ 140 to 160/90 - 100 mmHg) in the treatment of people with hypertension and a history of cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular occlusive disease). **Suchzeitraum:** bis 11/2019 **Population:** - ≥ 18 y - hypertension documented in standard way, or receiving treatment for hypertension, with positive CV history of myocardial infarction, stroke (not including TIA), chronic pAVK, or angina pectoris. - not limited by any other factor nor by baseline risk **Intervention:** - lower BP treatment target: ≤ 135/85 mmHg; mean BP ≤ 102 mmHg. - Mean BP (MBP) was accepted as a valid way of measuring interventions, while prespecified targets are taken into account and according to the following equation: MBP = [(2 × diastolic) + systolic]/3. **Vergleich:** - standard BP treatment target: ≤ 140-160/90-100 mmHg; mean BP ≤107-120 mmHg.	**Allgemeines:** - 6 Studien eingeschlossen (n= 9484: lower target, n= 5301; standard target, n=4183). - design in all trials: randomized and open with blinded end point - baseline BP required for inclusion varied: - AASK 2002 and HOT 1998 required DBP ≥95 mmHg and DBP 100-115 mmHg, respectively - ACCORD BP 2010 and SPRINT 2015 required SBP 130-180 mmHg, - Past BP 2016 sought SBP 125 mmHg, and SPS3 2013: SBP ≥130 mmHg and/or DBP ≥85 mmHg or history of hypertension with BP lowering medication at randomization. CV-Erkrankungen: - AASK 2002: IHD, stroke, or PVD - ACCORD BP 2010 und HOT 1998: myocardial infarction, stroke, or angina. - PAST BP 2016: stroke or, less frequently, IHD. - SPRINT 2015: IHD or PVD. - SPS3 2013: some had IHD, all recent lacunar stroke. **Primäre EP** **total mortality:** lower 366/5301 vs. higher 285/4182; RR 1.06, 95%CI 0.91;1.23) I²=39%, 6 studies, moderate **Serious AE:** lower 1197/5301 vs. higher 1052/4183 (RR 1.01, 95% CI 0.94; 1.08) I²=0% 6 studies, low **CV events**: lower 562/5301 vs. higher 532/4183; RR 0.89, 95%	Aktualisiert, um zu evaluieren, ob „ongoing studies“ bereits veröffentlicht sind Keine neuen Studien identifiziert

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Endpunkte: - Primär: Total mortality, Total serious adverse events, Total CV events, CV mortality - Sekundär: withdrawals due to AE, Systolic BP and difference from baseline at 1 year, or both; Diastolic BP and difference from baseline at 1 year, or both; Proportion of participants reaching target BP level; Number of antihypertensive drugs each participant needed at the end of study **Studientyp:** RCTs	CI 0.80; 1.00; I²=0%, 6 studies, low **CV mortality:** lower 172/5301 vs. higher 131/4183 (RR 1.03, 95%CI 0.82; 1.29) I²= 23%, 6 studies, moderate **Sekundäre EP:** Withdrawals due to AE: lower 22/420 vs. higher 2/270, RR 8.16, 95%CI 2.06;32.28;I²= 38,9%, 2 studies, very low	
Garrison SR. Blood pressure targets for hypertension **in older adults**. Cochrane Database Syst Rev 2017; 8(8):CD011575. [53] https://www.ncbi.nlm.nih.gov/pubmed/28787537.	2017	high	**Fragestellung:** assess effects of higher BP target (<150-160 mmHg bzw. < 95-105 mmHg) compared to lower BP target (<140/90 mmHg) in hypertensive adults ≥65 years of age **Suchzeitraum:** bis 02/2017 **Population:** Adults ≥ 65 years of age who are either: 1. already being treated for hypertension; or 2. have elevated BP (≥ 140/90 mmHg) documented in a standard way on ≥ 2 occasions. **Intervention:** A higher systolic or diastolic BP treatment target (ambulatory, home, or office measurements) in range of systolic BP <150-160 mmHg or diastolic BP <95-105 mmHg. **Vergleich:** BP treatment target that is < 140/90 mmHg. **Endpunkte:** 1. All-cause mortality 2. Stroke (fatal and non-fatal, excluding transient ischaemic attack) 3. Institutionalisation (i.e. nursing home admission) 4. CV serious adverse events **Studientyp:** open-label RCTs	**Allgemeines:** 2/3 trials (n= 4418; n= 3079): Japanese outpatients - systolic hypertension irrespective of diastolic BP or isolated systolic hypertension - age: mid 70s, baseline BP: 170/90 and 170/81 - 61% women, 12% diabetes, 16% smoked - systolic BP targets of < 140 mmHg to higher systolic targets of < 150mmHg or < 160 mmHg 1/3 trials (n= 724): Chinese general practice patients - either systolic or diastolic hypertension - baseline BP 160/84 mmHg, 66% men; 23% diabetes and 25% smoked - target of < 140/90 mmHg to < 150/90 mmHg **Primäre Endpunkte (3 Studien, alle EP: low-quality evidence:** **All-cause mortality:** higher target 159/4101 vs. lower target 129/4120 (RR 1.24, 95%CI 0.99; 1.54); I2= 79% **stroke:** higher target 101/4101 vs. lower target 81/4120 (RR 1.25, 95% CI 0.94; 1.67); I2 = 38% **CV serious adverse events**: higher target 205/4101 vs. lower target 173/4120 (RR 1.19, 95% CI 0.98; 1.45); I2 = 59% **Sekundäre Endpunkte:** **CV mortality**: higher target 68/4101 vs. lower target 45/4120 (RR 1.52, 95% CI 1.06; 2.19; I2 = 52%), 2 studies **Non-cardiovascular mortality:** higher target 91/4101 vs. lower target 84/4120 (RR 1.09, 95% CI 0.81; 1.46) I2 = 52%, 3 studies **Unplanned hospitalisation:** higher target 14/1534 vs. lower target 12/1545 (RR 1.18, 95% CI 0.55 to 2.53), 1 study	Patienten ≥ 65J.

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Withdrawals due to adverse effects: higher target 54/3740 vs. lower target 65/3757 RR 0.83 (0.58; 1.19), 2 studies verschiedene Endpunkte in der Kategorie **CV serious adverse events** berichtet: Extraktion nach Bedarf	
Musini VM. Pharmacotherapy for hypertension in **adults 60 years or older**. Cochrane Database Syst Rev 2019; 6(6):CD000028. [54] https://www.ncbi.nlm.nih.gov/pubmed/31167038	2019	low	**Fragestellung/ Ziele:** - quantify the effects of antihypertensive drug treatment as compared with placebo or no treatment on all-cause mortality in people ≥ 60 years with mild to moderate systolic or diastolic hypertension Secondary objectives - quantify the effects of antihypertensive drug treatment as compared with placebo or no treatment on cardiovascular-specific morbidity and mortality in people ≥ 60 years with mild to moderate systolic or diastolic hypertension - quantify the rate of withdrawal due to adverse effects of antihypertensive drug treatment as compared with placebo or no treatment in people ≥ 60 years with mild to moderate systolic or diastolic hypertension **Suchzeitraum**: bis 11/2017 **Population**: - adult patients (≥ 60 years old) - hypertension defined as BP > 140/90 mmHg. **Intervention:** antihypertensive drug therapy **Vergleich:** placebo or no treatment **Studientyp:** RCTs of at least one year's duration comparing and providing morbidity and mortality data for	**Baseline-Informationen:** - 16 trials (N = 26,795) in healthy ambulatory adults 60 years or older (mean age 73.4 years) from western industrialised countries with moderate to severe systolic and/or diastolic hypertension (average 182/95 mmHg) - Most trials evaluated first-line thiazide diuretic therapy for a mean treatment duration of 3.8y Ergebnisse: **all-cause mortality**: (high-certainty evidence; 11% control vs 10.0% treatment; RR 0.91, 95% CI 0.85 to 0.97; 13 RCTs, n= 25932 **CV morbidity and mortality:** (moderate-certainty evidence; 13.6% control vs 9.8% treatment; RR 0.72, 95% CI 0.68 to 0.77; 15 RCTs, n=26747 **cerebrovascular mortality and morbidity** (moderate-certainty evidence; 5.2% control vs 3.4% treatment; RR 0.66, 95% CI 0.59 to 0.74; 13 RCTs, n=26042 **coronary heart disease mortality and morbidity** (moderate-certainty evidence; 4.8% control vs 3.7% treatment; RR 0.78, 95% CI 0.69 to 0.88, 11 RCTs, n= 24559 **Withdrawals due to adverse effects** (low-certainty evidence; 5.4% control vs 15.7% treatment; RR 2.91, 95% CI 2.56 to 3.30, 4 RCTs, n= 11310 **Subgruppenanalyse:** **Mortality:** 60- to 79-year-old patient subgroup (high-certainty evidence; RR 0.86, 95% CI 0.79 to 0.95). **CV mortality an morbidity:** significantly reduced in both subgroups 60 to 79 years old (moderate-certainty evidence; RR 0.71, 95% CI 0.65 to 0.77) and 80 years or older (moderate-certainty evidence; RR 0.75, 95% CI 0.65 to 0.87), the magnitude of absolute risk reduction was probably higher among 60- to 79-year-old patients (3.8% vs 2.9%). - reduction in CV mortality and morbidity was primarily due to a reduction in cerebrovascular mortality and morbidity.	Ursprünglich dem Kapitel medikamentöse Therapie zugeordnet

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Musini VM. Pharmacotherapy for hypertension in **adults aged 18 to 59 years**. Cochrane Database Syst Rev 2017; 8(8):CD008276. [55] https://www.ncbi.nlm.nih.gov/pubmed/28813123.	2017	high	**Fragestellung/ Ziele:** - quantify antihypertensive drug effects on all-cause mortality in adults aged 18 to 59 years with mild to moderate primary hypertension. - quantify effects on CV mortality plus morbidity (including cerebrovascular and coronary heart disease mortality plus morbidity), withdrawal due adverse events and estimate magnitude of SBP and DBP lowering at 1 year. **Suchzeitraum:** bis 01/2017 **Population:** - adults aged 18 to 59 years - mild to moderate primary hypertension defined as SBP ≥140 mmHg or DBP ≥90 mmHg at baseline, or both **Intervention:** antihypertensive pharmacotherapy **Vergleich:** placebo or no treatment **Studientyp:** RCTs s of at least 1 year' duration comparing with a in .	**Baseline-Informationen:** - 7 included studies (17,327 participants) - predominantly healthy adults with mild to moderate primary hypertension. - The Medical Research Council Trial of Mild Hypertension contributed 14,541 (84%) of total randomized participants, with-mean age of 50 years and mean baseline BP of 160/98mmHg and a mean duration of follow-up of 5 years. - Treatments used in this study: bendrofluazide 10 mg daily or propranolol 80 mg to 240 mg daily with addition of methyldopa if required. - risk of bias in the studies was high or unclear for a number of domains and led us to downgrade the quality of evidence for all outcomes. **Ergebnisse (jeweils Intervention vs. Kontrolle):** **- all cause mortality:** (194/8419 vs. 204/8357; RR 0.94, 95% CI 0.77 to 1.13), 5 studies, low quality **- coronary heart disease mortality plus morbidity:** 208/8134 vs. 201/8107 (RR 0.99, 95% CI 0.82 to 1.19), low quality, 4 RCTs **- CV mortality and morbidity:** 277/8672 vs. 351/8606 (RR 0.78, 95% CI 0.67 to 0.91), 6 RCTs, low quality **- cerebrovascular mortality and morbidity** (55/8672 vs. 116/8606) RR 0.46, 95% CI 0.34 to 0.64), 6 RCTs, low quality **- withdrawals due to AE:** 19/626 to 4/597 (RR 4.82, 95% CI 1.67 to 13.92), 3 RCTs, very low quality	Ursprünglich dem Kapitel medikamentöse Therapie zugeordnet
Arguedas JA. Blood pressure targets for hypertension in people **with diabetes mellitus.** Cochrane Database Syst Rev 2013(10):CD008277. [56] https://www.ncbi.nlm.nih.gov/pubmed/24170669	2013	critically low	**Fragestellung:** determine if lower BP targets (<130/85 mmHg) are associated with reduction in mortality and morbidity compared with standard BP targets (<140-160/90-100 mmHg) in people with diabetes. **Suchzeitraum:** bis 10/2013 **Population:** - adults with diabetes mellitus and elevated blood pressure, documented in a standard way on at least two occasions, or already receiving treatment for elevated blood pressure. Since any numerical definition of elevated blood pressure is arbitrary, we included trials if people with diabetes were	**Allgemeines:** - Systolic blood pressure target: 1 trial (ACCORD BP 2010) compared clinical outcomes associated with different systolic blood pressure (SBP) targets within our definitions for 'lower' (<120 mmHg) and 'standard' (<140 mmHG) targets. - Diastolic blood pressure target: 4 trials (ABCD-H 1998, ABCD-N 2002, ABCD-2V 2006, and the subgroup of people with diabetes in HOT 1998) - design: randomized and open label - inclusion criteria and baseline BP varied **Ergebnisse:**	Diabetes AMSTAR: 2 kritische Kriterien nicht erfüllt (Publication bias, Einbezug des RoB in Diskussion)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			randomized to one of the two targets described below, irrespective of their baseline blood pressure. **Intervention/ Vergleich**: randomized to a 'lower' compared with a 'standard' target BP as defined above **Primary outcomes** 1. All-cause mortality + CV and non-CV mortality separately. 2. Total serious adverse events (total serious morbidity and mortality). 3. CV serious adverse events, including myocardial infarction, stroke, congestive heart failure, end-stage renal failure. 4. All other serious adverse events. **Secondary outcomes** 1. Systolic BP achieved. 2. Diastolic BP achieved. 3. Withdrawals due to adverse effects. 4. Number of antihypertensive drugs needed per participant. **Studientyp:** RCTs	1. Systolic blood pressure target (ACCORD BP 2010) lower vs. standard target **- Total mortality:** 150/2363 vs. 144/2371; RR 1.05, 95% CI 0.84 to 1.30 **- CV mortality:** 60/2363 vs. 58/2371; RR 1.04, 95% CI 0.73 to 1.48, **- non-CV mortality:** 90/2363 vs. 86/2371; RR 1.05, 95% CI 0.79 to 1.40 **- Total serious adverse events:** 518/2363 vs. 513/2371; RR 1.01, 95% CI 0.91 to 1.13 **- Stroke:** intensive: 36 (34 non-fatal) vs. in standard 62 (55 non-fatal); RR 0.58, 95% CI 0.39 to 0.88, **- All other serious adverse events** (hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, renal failure): intensive 77/2363 vs. standard 30/2371: RR 2.58, 95% CI 1.70; 3.91 **- mean number of antihypertensive drugs used after first year**: intensive 3.4 vs standard 2.1 >> keine signifikanten Unterschiede im Gruppenvergleich für Myocardial infarction, Congestive heart failure, End-stage renal failure 2. Diastolic blood pressure (DBP) target (4 Studien) **Vorabbemerkung zu Baselinecharakteristika:** - ABCD-Studien combined; established CV or cerebrovascular disease: standard 41,0% vs. lower target 33.5% - 2 ABCD-trials included only normotensive diabetic participants (DBP 80-89 mmHg. - 26 participants (5.4%) with isolated systolic hypertension (SBP > 160mmHg and DBP 80-89 mmHg) were enrolled in ABCD-N 2002 during the first year of recruitment, but none thereafter. - when trials were conducted, diagnostic criteria for diabetes mellitus were different from those currently used: 2 FPG levels, on different days, > 7.7 mmol/L (140 mg/dL), instead of 7.0 mmol/L (126 mg/dL), as currently defined. - **Total mortality:** lower (75/1540) vs. standard target (72/1040): RR 0.73, 95% CI 0.53 to 1.01, 4 Studien, I^2= 3%	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- **CV mortality:** lower 47/1474 vs. standard target 41/977: RR 0.79, 95% CI 0.52 to 1.19, P = 0.26 - **Non-CV mortality**: lower 27/1474 vs. standard target 31/977: RR 0.62, 95% CI 0.36 to 1.06, P = 0.08 **- Total serious adverse events:** were not reported in any of the trials. >> keine signifikanten Unterschiede im Gruppenvergleich für: Myocardial infarction, Stroke, Congestive heart failure	
McGuinness B. Blood pressure lowering in patients **without prior cerebrovascular disease for prevention of cognitive impairment and dementia.** Cochrane Database Syst Rev 2009(4):CD004034. [57] https://www.ncbi.nlm.nih.gov/pubmed/19821318.	2009	critically low	**Fragestellung:** ■ 1.In hypertensive patients with no history of cerebrovascular disease, to assess the effects of BP lowering treatments for the prevention of: (a) dementia, (b) cognitive decline. 2. To assess whether: ■ (a) there is an optimal BP level for prevention of dementia or cognitive decline ■ (b) there is an optimal antihypertensive agent, or class of antihypertensive agent, for the prevention of dementia or cognitive decline ■ (c) there are different effects of treatment according to aspects of baseline risk including sex, age, BP level, pulse pressure, associated CV disease, smoking and diabetes. ■ Suchzeitraum: bis 02/2008 ■ **Population:** - diagnosis of hypertension - BP readings were ≥ 160/90 mmHg - SBP 160-219 mmHg and DBP <90 mmHg in 1 systolic hypertension study. - no clinical history or signs of previous cerebrovascular disease. - examined separately: when cognitively impaired, but not fulfil the accepted criteria for classification of dementia - people with dementia analysed separately.	**Allgemeines:** - 4 trials (n= 15,936) - Average age was 75.4 years. Mean BP at entry: 171/86 mmHg. **Ergebnisse:** **Incidence of dementia:** treatment 236/7767 and placebo 259/7660 (OR 0.89; 95% CI 0.74, 1.07), 4 Studien, I²= 17% **Cognitive change from baseline:** change in MMSE indicate a significant benefit from treatment (WMD = 0.42; 95% CI 0.30, 0.53) n= 10640, 3 Studien **Change in SBP level:** indicated a significant benefit of treatment (WMD = -10.22; 95% CI -10.78, -9.66) 4 Studien, I²=98%, n= 16810 **Change in DBP level:** indicated a significant benefit from treatment (WMD = -4.28; 95% CI -4.58, -3.98) 4 Studien, I²=97%, n= 16810 **AE requiring discontinuation of treatment:** indicated no significant difference between treatment 11138/6080 and placebo 1117/6011 (OR = 1.01; 95% CI 0.92, 1.11) 3 Studien, I²= 98%	Prävention kognitiver Beeinträchtigung (Zahl der Teilnehmer in Abb. 4,5,6 erscheint nicht schlüssig, wenn Gesamtzahl 15936) AMSTAR: 2 kritische Kriterien nicht erfüllt (Publication bias, Einbezug des RoB in Diskussion)

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- no exclusion on the basis of level of BP, age, or prior use of antihypertensive therapy. - diagnosis of dementia: based on DSM, ICD 10, National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, or acceptable equivalents used. - Cognitive function: Mini-Mental State Examination, Global Deterioration Scale, Clinical Dementia Rating scale or acceptable alternative. ▪ **Intervention:** - Pharmaceutical agents (six months or longer), Non-Pharmacological Interventions ▪ Primäre Endpunkte: ▪ - Incidence of dementia, diagnosed according standard diagnostic criteria or those appropriate at time - Cognitive change from baseline **Secondary outcomes** - Blood pressure level - Incidence and severity of adverse effects - Quality of life **Studientyp:** double-blind RCTs in which pharmacological or non-pharmacological interventions to lower BP were administered for > 6 months.		
Giuseppe Forte et al. Effects of Blood Pressure on Cognitive Performance: A Systematic Review. J Clin Med. 2020 Jan; 9(1): 34. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7019226/	2020	Critically low	**Fragestellung:** whether high BP represents a risk factor for the decline of different cognitive domains. Moreover, it points to evaluate whether some cognitive functions, more than others, are negatively affected by high blood pressure **Suchzeitraum:** bis 06/2018 **Population:** - one or more cognitive processes and reported the measurement of blood pressure were selected. - participants with medical conditions that could potentially influence the investigated relationship and those that included participants diagnosed with dementia, psychiatricdisorders, strokes, and head traumas were excluded.	**Baseline-Informationen:** - fifty studies, n= 107,405. - results reported considering different cognitive domains separately: global cognitive functioning, attention, processing speed, executive functions,memory and visuospatial abilities. **Ergebnisse**: - Higher blood pressure appears to influence cognitive performance in different domains in the absence of dementia and severe CV diseases,such as strokes. - relationship seems to be independent of demographic factors (gender andeducation), medical co-morbidity (diabetes), and psychiatric disorders (depression).	Methodische Limitationen des SR: 4x n in kritischen Domänen des AMSTAR-II Instrumentes PICO bleibt größtenteils unklar **nicht in NVL zitiert**

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Studientyp: k.A. identifiziert	- presents different patterns considering ageing: in elderly, a sort of “cardiovascular paradox”is highlighted, which allows considering higher blood pressure as a protective factor for cognitivefunctioning.	

6.3 Beginn der medikamentösen Therapie

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [C] Evidence review for initiating treatment [58] https://www.nice.org.uk/guidance/ng136/evidence/c-initiating-treatment-pdf-6896748208	2019	moderate	**Fragestellung:** To establish which blood pressure or cardiovascular disease risk threshold antihypertensive drug treatment should be initiated at. **Suchzeitraum:** bis 10/2018 **Population:** Adults (> 18 y) not on current pharmacological treatment for hypertension (wash-out: ≥4 weeks) Stratify by: Presence or absence of type 2 diabetes, CV or BP baseline risk **Intervention:** **Treatment initiation at different thresholds** *Systolic BP targets:* <120, 120–129, 130–139 mmHg, 140–59 mmHg, ≥ 160 mmHg *Diastolic BP targets*: <80 mmHg; 80–84 mmHg; 85–89 mmHg; 90–94 mmHg; ≥ 95 mmHg *CV-risk thresholds:* 5–9%; 10–14%; 15–19%; > 20% **Vergleich:** against each other (comparing different BP and/or CV risk thresholds), also within each other **Endpunkte:** minimum of 12 months *Critical:* All-cause mortality, HrQoL, Stroke (ischaemic or haemorrhagic), Myocardial infarction *Important*: **H**eart failure needing hospitalisation, Vascular procedures (including lower limb, coronary and carotid artery procedures), Angina needing hospitalisation, *Side effects:* Acute kidney injury, New onset diabetes, Treatment related admission, Hypotension (dizziness), [Combined CV disease outcomes in absence of MI and stroke data], [Coronary heart disease outcome in the absence of MI data]	**Allgemeines:** - Umbrella Review: 2 SR, 1 Kohortenstudie und 1 Metaanalyse von Individualdaten eingeschlossen (IPD) - da IPD von NICE für diese Fragestellung als höchste Form der Evidenz gesehen wurde, wurden andere Studientypen nur dann eingeschlossen, wenn sie nach der IPD veröffentlicht wurden **Ergebnisse:** **Siehe Volltext:** https://www.nice.org.uk/guidance/ng136/evidence/c-initiating-treatment-pdf-6896748208 **Basline-Charakteristika der einschlossenen Publikationen:** Tabelle 2 S. 8/91 **tabellarische Übersicht aller Ergbnisse**: ab Tabelle 4, S. 12/91 ff. **GRADE-Tabellen:** ab Tab. 21 S. 76/91 ff.	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Studientyp: RCTs, SR, nicht-randomisierte Studien		

6.4 Adhärenz

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Nieuwlaat R. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014(11):CD000011. [59] https://www.ncbi.nlm.nih.gov/pubmed/25412402.	2014	high	**Objectives** assess the effects of interventions intended to enhance patient adherence to prescribed medications for medical conditions, on both medication adherence and clinical outcomes. **Search:** on 11 January 2013 **Selection criteria** - Patients who were prescribed medication for a medical (including psychiatric) disorder, but not for addictions - Interventions of any sort intended to affect adherence with prescribed, self administered medications - unconfounded RCTs - measuring both medication adherence and clinical outcome - at least 80% follow-up of each group studied and, for long-term treatments, at least 6 months follow-up for studies with positive findings at earlier time points.	**Allgemeines:** - 182 RCTs (109 since previous update in January 2007) - heterogeneous patients, medical problems, treatment regimens, adherence interventions, outcome measurements, - most high risk of bias. - 17 lowest risk of bias for study design features and primary clinical outcome, 11 from present and 6 from previous update. - complex interventions with multiple components: pharmacists, who often delivered intense education, counseling (including motivational interviewing or cognitive behavioral therapy by professionals) or daily treatment support (or both), and sometimes additional support from family or peers. - 5 RCTs reported improvements adherence and clinical outcomes, and no common intervention characteristics were apparent. Even most effective interventions did not lead to large improvements in adherence or clinical outcomes. **Conclusion:** Across the body of evidence, effects were inconsistent from study to study, and only a minority of lowest risk of bias RCTs improved both adherence and clinical outcomes **Hypertension**: - 17 RCTs, 1 mit niedrigem RoB **Morgado 2011** n =197; antihypertensive therapy ≥ 6 months **Intervention:** - counseling from hospital pharmacist at specialized outpatient clinic - interviewed patients, assessed problems with BP control, educated patients, advised physicians on medication changes, provided intervention patients with written educational material. - encouraged to bring all empty blisters and boxes of antihypertensive medication to clinic visits for recycling and to verify compliance with therapy.	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Cotrol: regular care at a traditional hospital clinic without a hospital pharmacist. **Ergebnisse**: - improved primary outcome of proportion of patients with BP controlled to target - reduced proportion of patients with low medication adherence as measured by a 5 item questionnaire. - medical therapy advice from pharmacists to physicians might have contributed to the improved BP control in addition to the improved adherence, although authors report that there were no marked differences compared with control group regarding therapy changes.	
Schroeder K. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. Cochrane Database Syst Rev 2004(2):CD004804. [60] https://www.ncbi.nlm.nih.gov/pubmed/15106262.	2004	moderate	**Fragestellung:** - locate and describe studies evaluating interventions aimed at improving adherence to antihypertensive medication - undertake a critical review of quality of the study methods looking in particular at study design and validity - summarise effectiveness of above interventions - indicate areas for future research **Suchzeitraum:** bis 04/2002 **Population:** - Adults with a diagnostic label of essential hypertension (as defined in individual studies) in a primary care, outpatient or other community setting. **Intervention:** to enhance medication adherence, including the following: 1. Education of caregivers and patients (e.g. counselling, health education) 2. Simplification of dosage regimens 3. Involvement of allied health professionals (e.g. nurses, pharmacists) 4. Special monitoring (e.g. vial caps, blood pressure self-measurement)	**Allgemeines:** - 38 studies (n= 15519) - USA (n = 21), Canada (n = 8), Europe (n = 8), Australia (n = 1) and South Africa (n = 1) - Adherence measurement: self-report, direct questioning, pill counts, medication event monitoring system (MEMS®), which logs time and date of each opening of a medication container - follow- up: 2 to 60 months. - quality of included studies: generally low **Kategorien der Interventionen:** **(i) simplification of dosing regimens:** - improved adherence in 7/9 studies (relative improvement 8-19.6%) - 5 Studien: once-daily instead of twice-daily dosage regimens - 1 study: increase in adherence (90 vs. 82 %) together with a reduction in systolic BP of 6 mmHg systolic **(ii) patient education:** - educational programme via slides, audiotape and booklet, group education, written educational material, education via visual aids, lecture, discussion and knowledge test - seemed largely unsuccessful. - 1 trial (n=110) improved adherence (93 vs. 69 %) with no reported effect on BP. This study used group education in groups of 15 people over 90 minutes and additional postal information leaflets at 1 3 and 5 months. **(iii) patient motivation, support and reminders** - special compliance dispensers, drug reminder charts, self-recording of BP, monthly home visits, teaching on self-determination, counseling,	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			5. Motivation (e.g. financial incentives, reminder packages, reminder aids including diaries or follow-up appointments) **Vergleich:** - Control groups should either have received no intervention or "usual care" and have similar characteristics as the intervention groups. **Endpunkte:** - Adherence to medication (including any definition of adherence and noting how this was defined and measured in each study) - BP change in mmHg or change in BP control according to criteria used in each individual RCT **Studientyp:** RCTs	nurse phone calls, social support, small group training, postal reminders, telephone-linked computer counselling - Motivational strategies: successful in 10/24 study interventions with mostly small increases in adherence up to a maximum of 23% (measuring adherence: pill counts, self-report, direct questioning, prescription refill records, less reliable than electronic monitoring); - Successful interventions included daily drug reminder charts (mean adherence score 82.4 vs. 70.4 %, training on self-determination (4.6/7 weeks adherent vs. 3.3 weeks in control group, reminders and packaging (increase in adherence between 8% for reminders alone and 23 % for reminders and packaging in combination, social support (98% achieved maximum adherence score vs. 93 %), nurse phone calls (96% achieved maximum adherence score vs. 91%), family member support (53 % high adherers vs. 40% low adherers) electronic medication aid cap (mean adherence 95 % vs. 78 %) and telephone-linked computer counseling (18 % adherent vs. 12% in the control group) **(iv) complex health and organizational interventions** **-** increased adherence in 8/18 study interventions, ranging from 5% to a 41%. - Worksite care through trained nurses improved adherence (67% vs. 49%) and led to a net reduction in diastolic BP of 4 mmHg between intervention and control groups - combination of home visits, education and special dosing devices improved adherence in a small trial of 16 patients (92% vs. 71%) - strategy involving educational leaflet, telephone reminder, mailed reminder and educational newsletter was successful in both previously treated hypertensives ('medication possession ratio' 82 % vs. 48 % and those who were newly diagnosed (93% vs 52%) - 2 trials: weak evidence of an effect of a patient-centered pharmaceutical care model in which pharmacists either used a structured, brief questioning protocol to identify patients' medication related problems and their information needs relating to hypertension and its treatment compliance score 0.23 vs. 0.61, or a combination of structured brief questioning protocol with advice, information and referral to the family practitioner (62% adherent vs. 50 %). BP was better controlled (i.e. BP readings of ≤159/89 mmHg) in the intervention group (35.7% became controlled vs. 17.1%)	

6.5 Motivational interviewing: RCTs

Risk of Bias

Referenz	Selection bias 1	Selection bias 2	Performance bias	Detection bias	Attrition bias	Reporting bias	anderen Ursachen für Bias / Kommentare
Ma C. Evaluation of the effect of motivational interviewing counselling on hypertension care. Patient Educ Couns 2014; [61]	niedrig	unklar	hoch	hoch	niedrig	unklar	- k.A. zu Komorbiditäten aber auch kein Hinweis, dass Population ausschließlich HT hatte

Inhalte

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
Ma C. Evaluation of the effect of motivational interviewing counselling on hypertension care. Patient Educ Couns 2014; 95(2):231–7. [61] https://www.ncbi.nlm.nih.gov/pubmed/24530144.	2014	**Ziel:** - test effectiveness of motivational interviewing compared with usual care for Chinese hypertensive patients. **Design:** - RCT - nicht verblindet **Einschlusskriterien:** - patients > 18 years - diagnosed with essential hypertension by a cardiovascular physician - ≥ 1 antihypertensive medication. **Ausschlussktiterien:** - secondary hypertensive patients - Pregnancy **Intervention:** - Schulung der "clinical nurses" Adapted motivational interviewing (8x/ 6 Monate) - build rapport with patients - evaluate patients' confidence and motivation for behaviour changes and selfcffi-ciency: - help patients become aware of and adress ambivalence blocking behaviour to change - help patients find discrepancies between values and current behaviours; - provide strategies of adherence to behaviour changes - summarise pros and cons of proposed behaviour changes - set realistic and specific goals for behaviour modlfication - prompt patients to follow plan	**Baseline-Charakteristika** - n= 120 - average age: 58 years (SD 11,68) - range of medication duration: 6 months - 10 years. **Adhärenz nach 24 Wochen** jeweils Intervention vs. Kontrolle: Mean (SD) - medication: 29,72 (3,46) vs. 25,30 (3,11) - treatment dietary habits: 27.48 (2.69) vs. 25.95 (3.01) - physical activity levels: 6,91 (1,26) vs. 5,73 (1,12) - smoking and alcohol: 14.61(2.27) vs. 12.17 (2.00) - Gewichtskontrolle: 6.19 (1.03) vs. 6.24 (1.18) - relieving stress: 8,85 (2,15) vs. 8,29 (2,11) - Total: 80,94 (8,95) vs. 78,22 (9,14) **Quality of life nach 24 Wochen (sekundärer EP)** - total scores on SF-36 questionnaire of intervention groupwere higher than of control group, difference value was 2.72	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
		for behaviour change - provide an overall summary of MI session and patients' performances **Kontrolle:** - provision of hypertension information incl. recommendations to improve treatment adherence and change unhealthy lifestyles - cardiologists or specialist nurses delivered a lecture on hypertension prevention for these patients every 6 weeks - leaflets concerning hypertension information were freely delivered to patients **Follow-up:** 24 Wochen **Endpunkterhebung**: Treatment Adherence Questionnaire of Patients with Hypertension (4-Point-Likert-Scale), 28 Items in 6 Gruppen		

6.6 Monitoring/ Selbstmanagement

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Glynn LG. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev 2010(3):CD005182. dx.doi.org/10.1002/14651858.CD005182.pub4. [46] https://www.ncbi.nlm.nih.gov/pubmed/20238338.	2010	Critically low	**Fragestellung:** 1) Evaluate which models of care are effective in improving “control” of high blood pressure; (2) Evaluate the effectiveness of reminders on improving the follow-up of patients with hypertension. **Suchzeitraum:** bis 02/2008 **Population:** - adult patients (aged 18 years or over) with essential hypertension - treated or not currently treated with blood pressure lowering drugs - in a primary care, outpatient or community setting **Intervention:** (1) self-monitoring (2) educational interventions directed to the patient	72 RCTs eingeschlossen -methodological quality of included studies varied. organized system of regular review allied to vigorous antihypertensive drug therapy - reduced SBP (WMD) - 8.0 mmHg, 95% CI: -8.8 to -7.2 mmHg) and DBP (WMD -4.3 mmHg, 95% CI: -4.7; -3.9 mmHg) for 3 strata of entry BP, - reduced all-cause mortality at 5 years follow-up (6.4% vs. 7.8%, difference 1.4%) in a single large RCT- the Hypertension Detection and Follow-Up study. Self-monitoring (18 RCTs) - associated with moderate net reduction in SBP (WMD -2.5 mmHg, 95% CI: -3.7 to -1.3 mmHg) (12 RCTs) and DBP (WMD -1.8 mmHg, 95% CI: -2.4 to -1.2 mmHg) (14 RCTs). educational interventions directed at patients (20 RCTs) - heterogeneous but appeared unlikely to be associated with large net reductions in BP by themselves. - a trend towards improved BP control and this was significant (OR 0.83, 95% CI 0.75 to 0.91), (8 RCTs) educational interventions directed at health professionals (10 RCTs) - not associated with a significant decrease in mean SBP (mean difference -0.4 mmHg, 95% CI -1.1 to +0.2 mmHg) or DBP (mean difference -0.4	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			(3) educational interventions directed to the health professional (4) health professional (nurse or pharmacist) led care (5) organisational interventions that aimed to improve the delivery of care (6) appointment reminder systems **Vergleich**: - no intervention or usual care Studientyp: RCTs	mmHg, 95% CI -1.1 to +0.3 mmHg) whilst control of BP produced heterogeneous results (OR ranged from 0.8 to 1.0). Nurse or pharmacist led care (12 RCTs) - pooling of results from individual RCTs produced heterogeneous results, so pooled MD may not be valid. - may be a promising way forward, with the majority of RCTs being associated with improved BP control and mean SBP and DBP but these interventions require further evaluation. Appointment reminder systems - require further evaluation due to heterogeneity and small trial numbers - majority of trials increased the proportion of individuals who attended for followup (OR 0.41, 95% CI 0.32 to 0.51) and in 2 small trials also led to improved BP control, OR favouring intervention 0.54 (95% CI 0.41 to 0.73).	
Hypertension in adults: diagnosis and management [B] Evidence review for monitoring [39] https://www.nice.org.uk/guidance/ng136/evidence/b-monitoring-pdf-6896748207	2019	low	**Fragestellungen:** In adults with treated primary hypertension, what is the best method of measuring blood pressure (home, ambulatory or clinic measurement) to assess the response to treatment and prevent cardiovascular events? **Suchzeitraum**: bis 10/2018 **Population:** Adults (over 18 years) with treated primary hypertension **Intervention:** Different methods of measuring blood pressure followed by appropriate treatment based on the blood pressure measurement (test plus treatment): HBPM without telemonitoring, HBPM with telemonitoring, ABPM, Clinic/office measurement (CBPM), Pharmacy measurement **Vergleich:** against each other **Endpunkte**: ≥ 12 months. Where multiple time points reported within study, longest time point only will be extracted Critical: All-cause mortality, Health-related quality of life, Stroke (ischaemic or haemorrhagic), Myocardial infarction	**Baseline-Informationen:** - 8 Studien eingeschlossen, 7 open label RCTs, 1 IPD - Form der Blutdruckmessung und des Telemonitorings siehe Detailauswertung **Home monitoring versus clinic monitoring** **- CV-events:** 3,7% vs. 2,6%, RR 1.42 (0.61; 3.33), 1 study, n= 678, Very low - **dizziness:** 15,4% vs. 17,5%, RR 0.88 (0.63; 1.24), 1 study, n= ranging from 672, Low-very low - **reduction in systolic and diastolic clinic BP:** 2 studies, n= 2610, Risiko der Kontrollgruppen nicht verfügbar, Very Low **Home monitoring without telemonitoring versus ambulatory and clinic monitoring** **- reduction in systolic and diastolic clinic BP:** 1 study, n= 145, Risiko der Kontrollgruppe nicht verfügbar, Low **Home monitoring with telemonitoring versus home monitoring without telemonitoring** - **CV-events**: 3,3% vs. 3,7%, RR 0.91 (0.41; 2.04), 1 study, n= 658, Low-very low - **dizziness:** 22,1% vs. 15,4%, RR 1.43 (1.03; 1.98), 1 study, n= 650, Very low **Home monitoring with telemonitoring versus clinic monitoring** - **all-cause mortality:** 0,81% vs. 0%, Peto OR 7.45 (0.46; 119.44), 1	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Important: Reduction in clinic BP, Proportion of people controlled to a target, Average daily dose of antihypertensive medication, Average number of visits, Intolerance to device, Hypotension (dizziness), Combined CV-disease outcomes in absence of MI and stroke data, Coronary heart disease outcome in the absence of MI data **Studientypen**: RCT, SR, Non-randomised studies in the absence of RCT and SR evidence	study, n= 493, Very low - **CV-events:** 2,6% vs. 1,69%, RR 1.43 (0.66; 3.08), 2 studies, n= 1173, Very low - **reduction in SBP and DBP:** Risiko der Kontrollgruppe nicht verfügbar, 3 studies, n= 2357, Very low - **quality of life (general scale):** Risiko der Kontrollgruppe nicht verfügbar, 1 Study, n= 294, low - **dizziness:** 22,1% vs. 17,5%; RR 1.26 (0.93 to 1.71), 1 study, n=674, very low. **Home monitoring with telemonitoring and pharmacist care versus clinic monitoring 1 study, n=484:** - **systolic blood pressure:** mean change in SBP in control -5.3 mmHg**,** MD in intervention 8.90 lower (11.43 to 6.37 lower) low - **quality of life** (general subscale, 0-100, high is good): mean in control 66.7; MD in intervention 0.10 lower (3.9 lower to 3.7 higher), low - **non-fatal CV-events** 1,3% vs. 0,81%, RR 1.56 (0.26 to 9.27), Very low - **all-cause mortality:** 0,42% vs. 0%, Peto OR 7.71 (0.15 to 388.76), very low - **diastolic blood pressure:** mean change in DBP in control -3.5 mmHg, MD in intervention 3.50 lower (4.91 to 2.09 lower), low **Home monitoring with telemonitoring and pharmacist care versus home monitoring with telemonitoring 1 study, n=483** - **all-cause mortality:** 0,42 % vs. 0,81%, RR 0.52 (0.05 to 5.69), very low - **non-fatal CV events:** 1,3% vs. 1,6 %, RR 0.78 (0.18 to 3.44), very low - **quality of life** (general subscale, 0-100, high is good): mean in control was 66.6, mean in the intervention 0.00 higher (3.85 lower to 3.85 higher), Low to very low), low - **systolic blood pressure:** mean change in control -8.2mmHg, MD in intervention was 6.00 mmHg lower (8.53 to 3.47 lower), low - **diastolic blood pressure:** mean change in control -4.4mmHg, mean change in intervention 2.60 mmHg lower (4.01 to 1.19 lower), low **Home monitoring (with self-titration) and telemonitoring versus clinic monitoring, 1 study, n= 480:** - **quality of life (EQ-5D):** mean in control 0.838, MD in intervention 0.01 lower (0.06 lower to 0.03 higher), Low - **change in SBP:** mean in control 140.3mmHg, MD in intervention 5.60 lower (8.91 to 2.29 lower), Low	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- **diastolic blood pressure:** mean in control 79.8mmHg, MD in intervention 2.30 lower (4.41 to 0.19 lower), low	

6.7 Therapiebeendigung

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Jongstra S. Antihypertensive withdrawal for the prevention of cognitive decline. Cochrane Database Syst Rev 2016; 11(11):CD011971. [62] https://www.ncbi.nlm.nih.gov/pubmed/27802359.	2016	moderate	**Fragestellung:** - assess effects of complete withdrawal ≥ 1 antihypertensive medication on incidence of dementia, cognitive function, BP and other safety outcomes in cognitively intact and cognitive impaired adults. **Suchzeitraum:** bis 02/2015 **Population:** - aged ≥ 18 years - must have been taking the antihypertensive medications for a ≥ 1 month irrespective of indication. - any healthcare setting - healthy participants or those with all grades of existing dementia or cognitive impairment. **Intervention:** Withdrawal of any medication with blood pressure lowering effects with no restriction to duration of follow-up. **Vergleich:** k.A. **Endpunkte:** - Cognitive impairment or rates of incident dementia in cognitively intact and cognitively impaired adults. - Cognition in the short-term in adults with or without established cognitive impairment. Sekundär: Changes in systolic and diastolic BP, SAE, Adherence to withdrawal of antihypertensive medications, **Studientyp:** RCTs, CCTs	**Allgemeines:** - 2 Studien (n= 2490) - populations were clinically distinct - Bath 2015: participants had to have an acute stroke; Moonen 2015: participants had MCI (= MMSE 21-27) and taking antihypertensive medications - age: 73y; 81 y - comorbidities at baseline reported in both studies; seemed comparable between intervention and control groups **Ergebnisse:** - **Incident dementia:** Neither study evaluated the presence of incident dementia at follow-up. - **Change in cognitive test scores:** **Bath:** cognitive assessment conducted via the telephone. - t-MMSE score was mean of 1.0 point higher in participants who withdrew vs continued them (95% CI 0.35; 1.65; n=1784) TICS-M was a mean of 2.10 points higher (95% CI 0.69 to 3.51; n= 1784) (very low quality) **Moonen 2015:** data for 351/388 cognitive performance using a composite of ≥ 5/6 cognitive tests. - higher score represented a better cognitive performance. - no evidence of mean difference in cognitive performance between participants who withdrew than who continued (MD 0.02 points, 95% CI -0.19; 0.23) n= 351 (low quality) - no evidence of change in cognitive performance in participants who withdrew medications using the MMSE score (MD 0.34 points, 95% CI -0.08 to 0.76; n=356); the 15-Word Verbal Learning Immediate Recall score (MD 0.24 points, 95% CI -0.66 to 1.14; n=356) the Delayed Recall score (MD 0.16 points, 95% CI -0.29 to 0.61; n=356); or the Visual Association	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Test score (MD 0.14 points, 95% CI -0.17 to 0.45; n=356) (low quality) **Mortality:** RR 0.88, 95% CI 0.72 to 1.08, I2 = 0%; n= 2485; 2 studies; moderate quality evidence **Cardiovascular events**: RR 1.29, 95% CI 0.96; 1.72; I2 = 0%; n= 2485; 2 studies; low quality **Falls:** Neither study report data on incidence of falls **Hospitalisations**: RR 0.85, 95% CI 0.36 to 2.06; n= 388; low quality	

6.8 Ausgeschlossene systematische Reviews

Referenz	Jahr	Kapitel	Thema	Charakteristika	Kommentar
Zaugg V. Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication. Cochrane Database Syst Rev 2018; 1(1):CD012042. dx.doi.org/10.1002/14651858.CD012042.pub2. [63] https://www.ncbi.nlm.nih.gov/pubmed/29320600.	2018	Therapieplanung	Adhärenz		- Relevanz für NVL vor ausführlicher Betrachtung mit AG besprechen - nur 1/9 Studien (n= 100) hat ausschließlich HT-Patienten eingeschlossen (Kronisch et al) - Ergebnisse nicht mit KI berichtet
Hróbjartsson A. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2010(1):CD003974. dx.doi.org/10.1002/14651858.CD003974.pub3. [64] https://www.ncbi.nlm.nih.gov/pubmed/20091554.	2010	Therapieplanung	Placebowirkung		nicht NVL-relevant nur ein HT-pezifisches Ergebnis berichtet: S. 453/458 (10 Studien, n= 308)

6.9 Handsuche / Literaturlistensuche

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Stacey D et al. Decision aids for peo-ple facing health treat-	2017	moderate	**Fragestellung**: Welche Effekte haben Entscheidungshilfen **Suchzeitraum**: Update (Stacey 2014),	**Baseline-Charakteristika:** - 10 countries	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
ment or screen-ing de-cisions. In: Cochrane Database Syst Rev 4 (4), CD001431. DOI:10.1002/ 14651858. CD001431.pub 5. [65]			**Population**: people facing health treatment or screening decisions In-terventionen: Entscheidungshilfen vs. Usual Care (usual care, general information, clinical practice guideline, placebo interven-tion or no intervention) **Endpunkte**: International Patient Decision Aids Standards (IPDAS)-Kriterien: Knowledge, Risikowahrnehmung, Beteili-gung an Entscheidungsfindung, Übereinstimmung von Werten und Entscheidung (values-choice congruence) u. a. **Studies**: published, RCT design Ausschluskriterien: detailed deci-sion aids eingeschlossene Studien: Body of Evidence: 105 Studien, 31.043 Teilnehmer Bewertung der strength of evidence mit GRADE	- 105 included studies evaluated decision aids that focused on 50 different decisions. - Most common decisions were prostate cancer screening (14 studies), colon cancer screening (10 studies), medication for diabetes (4 studies), breast cancergenetic testing (4 studies), prenatal screening (4 studies), medicationfor atrial fibrillation (4 studies), and surgery (mastec-tomy for breast cancer, 4 studies; hysterectomy, 3 studies; prostate cancertreatment, 4 studies). **Ergebnisse (als intervention vs. control)** - Attributes of the choice made:Participants`s Knowledge (Score): MD 13,27% (95% CI 11,32; 15,23); 52 studies; N = 13,316; high-quality evidence, - Accuracy of risk perceptions: 565 von 1000 vs. 269 von 1000, Risk ratio (RR) 2,10 (95% CI 1,66; 2,66), 17 studies; N = 5096; moderate-quality evidence - Congruency between informed values and care choices: 289 von 1000 vs. 595 von 1000, RR 2,06 (95% CI 1,46; 2,91), 10 studies; N = 4626; low-quality evidence - Attributes related to the decision-making process: decision aids de-creased: - decisional conflict related to feeling unin-formed MD −9,28/100 (95% CI −12,20; −6,36), 27 studies; N = 5707; high-quality evidence, - indecision about personal values: MD −8,81/100 (95% CI −11,99, −5,63), 23 studies; N = 5068; high-quality evidence, - proportion of people who were passive in decision makingRR 0,68 (95% CI 0,55, 0,83), 16 studies; N = 3180; moderate-quality evidence. The median effect of decision aids on length of consultation was 2,6 minutes longer (24 versus 21; 7,5% increase).	

Zitat
Bieber C, Gschwendtner K, Müller N, et al. Partizipative Entscheidungsfindung (PEF) - Patient und Arzt als Team. Psychother Psychosom Med Psychol 2016; 66(5):195–207. DOI: 10.1055/s-0042-105277. http://www.ncbi.nlm.nih.gov/pubmed/27119359. [66]
Deutsches Netzwerk Evidenzbasierte Medizin (DNEbM). Gute Praxis Gesundheitsinformation. Ein Positionspapier des Deutschen Netzwerks Evidenzbasierte Medizin. Version 2.0. 2015 [cited: 2017-10-17]. http://www.ebm-netzwerk.de/pdf/publikationen/gpgi2.pdf. [67]
Deutsches Netzwerk Evidenzbasierte Medizin (DNEbM). Gute Praxis Gesundheitsinformation. Liste der Unterzeichner. 2016 [cited: 2018-02-07]. http://www.ebm-netzwerk.de/pdf/publikationen/gpgi-unterzeichner.pdf. [68]

7 Evidenztabellen Nichtmedikamentöse Therapie (Stand: 28.10.2021)

7.1 Spezielle Ernährungsformen

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
[A05-21C] Nutzenbewertung nichtmedikamentöser Behandlungsstrategien bei Patienten mit essenzieller Hypertonie: Spezielle Ernährungsformen ohne primär körpergewichts- oder kochsalzreduzierte Intention - Rapid Report [69] https://www.iqwig.de/download/A05-21C_RR_Spezielle_Ernaehrungsformen_bei_Hypertonie.pdf (frei verfügbar)	2011	high	**Fragestellung:** Nutzenbewertung der **„DASH-Diät“** im Vergleich zu keiner entsprechenden speziellen Ernährungsform bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und Kriterien der Blutdruckkontrolle. **Suchzeitraum:** bis 03/2011 **Population:** die erwachsene Patienten mit essenzieller arterieller Hypertonie **Intervention** - Ernährungsumstellung auf die spezielle Ernährungsform „DASH-Diät“. **Vergleich** - war das Fehlen einer entsprechenden speziellen Ernährungsform bei sonst gleicher antihypertensiver Behandlung wie in der Interventionsgruppe. **Studientyp:** RCTs mit einer Mindestdauer von 24 Wochen **Ausschlusskriterium:** RCTs, in denen DASH als alleinige Behandlung mit einer anderen antihypertensiven Behandlung verglichen wurde (z.	**Allgemeines:** - 1 multizentrischer RCT - Personen mit hochnormalem Blutdruck oder Hypertonie der Stufe 1 über 18 Monate - mittleres Alter: 50 Jahre - 2/3 waren Frauen - offenes Studiendesign, drei Behandlungsgruppen - 1. Gruppe: komplexen Verhaltensintervention: die eine Kalorien-, Kochsalz- und Alkoholreduktion sowie eine Steigerung der körperlichen Aktivität zum Ziel hatte. - 2. Gruppe: dieselbe Verhaltensintervention + Beratungen zur DASH-Diät. - 3. Gruppe: allgemeine Lebensstilberatung. >> Bewertung des Nutzens einer DASH-Diät anhand der ersten beiden Gruppen >> für Population der Patienten mit Hypertonie **Endpunkte:** - keine Ergebnisse: Gesamtmortalität, CV-Mortalität bzw. Morbidität, terminale Niereninsuffizienz, gesundheitsbezogene Lebensqualität und alle unerwünschten Ereignisse - Verzerrungspotenzial für „Änderung bezüglich einer antihypertensiven Medikation“ und „Dauer und Ausmaß der Blutdruckänderung“: niedrig - SBP-Unterschied am Studienende: 0,4 mmHg (95% KI -2,6; 3,3); alleinige Verhaltensintervention MD -11,0 (SD 13,0) vs. Gruppe mit zusätzlicher DASH-Diät–Empfehlung MD -11,4 (SD 13,5) - DBP-Unterschied am Studienende: MD -0,1 (95% KI -2,1; 1,9); alleinige	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			B. DASH-Diät vs. Stressreduktion oder eine andere diätetische Maßnahme).	Verhaltensintervention MD -7,4 (SD 8,8) vs. Gruppe mit zusätzlicher DASH-Diät–Empfehlung MD -7,3 (SD 8,4) - Keiner dieser Unterschiede war statistisch signifikant. - „Änderung bezüglich einer antihypertensiven Medikation“ zeigte sich kein statistisch signifikanter Unterschied zwischen den beiden Vergleichsgruppen.	
Rees K. **Mediterranean-style diet** for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2019; 3(3):CD009825. [70] https://www.ncbi.nlm.nih.gov/pubmed/30864165.	2019	moderate	**Fragestellung:** determine effectiveness of Mediterranean-style diet for primary and secondary prevention of CVD. **Suchzeitraum:** bis 09/2018 **Population:** ≥18 years Primärprävention: without established CVD - defined as general population and those at increased risk of CVD - patients with type 2 diabetes excluded Sekundärprävention: with established Established CVD - defined as previous myocardial infarction (MI), stroke, revascularisation procedure (coronary artery bypass grafting (CABG) or PTCA, people with angina, or angiographically defined CHD, cerebrovascular disease (stroke) and peripheral arterial disease. **Intervention:** Mediterranean-style diet or a provision of foods relevant to the Mediterranean diet >> high monounsaturated/saturated fat ratio, intake of plant-based foods Studiendauer: ≥ 3 Monate + post intervention follow-up **Vergleich:** - no intervention or minimal intervention for primary prevention; - another dietary intervention for primary prevention; - usual care for secondary prevention; - another dietary intervention for secondary prevention. **Studientyp:** RCTs	**Allgemeines:** - 1 Studie berichtet hypertoniespezifische Ergebnisse (Lapetra et al 2018) - RCT of parallel-group design **Popultation:** - 180 hypertensive patients - 55-75 y - at high CVD risk but no previous history of CVD (CHD, stroke, HF or AF), - randomised to a Mediterranean diet or low-fat diet; - 92% men **Vergleich**: Low-fat diet according to AHA guidelines **stroke in hypertensive patients (2 years of follow-up):** - Mediterranean diet (1/90) vs. a lowfat diet (3/90); unadjusted RR 0.33 (95% CI 0.04 to 3.14), 1 trial, n= 180	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Clar C. **Low glycaemic index** diets for the prevention of cardiovascular disease. Cochrane Database Syst Rev 2017; 7(7):CD004467. [71] https://www.ncbi.nlm.nih.gov/pubmed/28759107.	2017	low	**Fragestellung:** assess the effect of the dietary GI on total mortality, CV events, and CV risk factors (blood lipids, BP) in healthy people or people who have established cardiovascular disease or related risk factors, using all eligible randomised controlled trials. **Suchzeitraum:** bis 07/2016 **Population:** - adults (age > 18 years) - healthy, had established cardiovascular disease, ≥1 of following risk factors: abnormal blood lipid levels (high and low density lipoprotein (HDL, LDL) cholesterol, triglycerides and total cholesterol), raised BP/hypertension, overweight (BMI > 25 kg/m2), or obesity (BMI > 30 kg/m2). **Intervention/ Vergleich:** - advice on diet or dietary carbohydrate or a prescribed diet. - Diets with a lower GI had to be compared with a diet with a higher GI and the GI of diets had to be reported. - Compared diets had to have similar overall energy levels and levels of carbohydrate, fat, and protein. Studies manipulating any other components of the diet were included if this was similar for the low and high GI groups.	**Allgemeines:** - 21 RCTs were included, - n= 2538 - low GI intervention (n= 1288) or high GI (n= 1250). - 20 RCTs: primary prevention populations (healthy individuals or those at high risk of CVD, with mean age range from 19 to 69 years) - 1 RCT: participants diagnosed with pre-existing CVD (secondary prevention population, with mean age 26.9 years) - Most of the studies did not have an intervention duration of longer than six months. - Difference in GI intake between comparison groups varied widely from 0.6 to 42. **primäre Endpunkte:** - None reported effect on CV mortality and CV events such as fatal and nonfatal myocardial infarction, unstable angina, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, stroke. - unclear risk of bias of most of the included studies makes overall interpretation of the data difficult. **Sicherheit:** - Only 2 of the included studies (n= 38 participants) reported on adverse effects and did not observe any harms (low-quality evidence). **Sekundäre Endpunkte:** Primary Prevention studies - no evidence of a difference between comparison groups in SBP (MD 0.52 mmHg, 95% CI -1.21 to 2.25, P = 0.55, n= 786, 9 studies, 10 comparisons, I2 = 7%. - no evidence of a difference between comparison groups in DBP (MD -0.23 mmHg, 95% CI -1.42 to 0.96, P = 0.71, n= 786, 9 studies, 10 comparisons, I2 = 38%. **Secondary prevention:** - 1 study including participants with CHD: no evidence of any differences seen between groups in SBP (MD -2.00 mmHg, 95% CI -14.97 to 10.97, n= 55 1 study) and DBP (MD -4.00 mmHg, 95% CI -13.41 to 5.41).	

7.2 Körperlich Aktivität

Gesundheitsberichterstattung

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Finger JD, Mensink GBM, Lange C. Arbeitsbezogene körperliche Aktivität bei Erwachsenen in Deutschland. Journal of health monitoring 2017; 2(2):29–36. DOI: 10.17886/RKI-GBE-2017-026. [72]	2017	RKI	- GEDA 2014/2015-EHIS - erstmals erfasst - deutsche validierte Version des European Health Interview Survey – Physical Activity Questionnaires (EHIS-PAQ) [14,15]. - n= 18.026 im erwerbsfähigen Alter (18 - 64 Jahre) - 10.146 Frauen, 7.880 Männer - Berechnungen mit Gewichtungsfaktor für Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung korrigiert **Frage** (>> eine Antwortkategorie möglich): - „Wenn Sie arbeiten, was beschreibt am besten was Sie tun? (a) Vorwiegend sitzen oder stehen, (b) Vorwiegend gehen oder mäßig anstrengende körperliche Tätigkeiten, (c) Vorwiegend schwere körperliche Arbeit oder körperlich beanspruchende Tätigkeiten oder (d) Ich führe keine arbeitsbezogenen Tätigkeiten aus“. Begriff „Arbeit“: bezahlte oder unbezahlte Tätigkeiten (z.B. Studium, Hausarbeit).	während der Arbeit vorwiegend zu sitzen oder zu stehen: - 47,5% (95% KI 46,1–49,0) der Frauen - 47,2% (95% KI 45,6–48,8) der Männer im erwerbstätigen Alter (18 - 64 J). - Frauen: größter Anteil in Altersgruppe 18-29J (55,5%, 95% KI 52,6–58,4). - Männer: größter Anteil in Altersgruppe 30-44J (50,2%, 95% KI 47,6–52,9). - Je höher der Bildungsstand, desto häufiger wird vorwiegend im Sitzen oder Stehen gearbeitet. - Verglichen mit Frauen geben Männer fast fünfmal so häufig an, vorwiegend schwere körperliche Arbeit zu verrichten. **Quellen** 14.Baumeister SE, Ricci C, Kohler S et al. (2016) Physical activity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnai-re (EHIS-PAQ). International Journal of Behavioral Nutrition and Physical Activity 13(1):1-10 15.Finger JD, Tafforeau J, Gisle L et al. (2015) Development of the European Health Interview Survey – Physical Activity Questi-onnaire (EHIS-PAQ) to monitor physical activity in the European Union. BMC Archives of Public Health 73:59
Finger JD, Mensink GBM, Lange C. Gesundheitsfördernde körperliche Aktivität in der Freizeit bei Erwachsenen in Deutschland. Journal of health monitoring 2017; 2(2):37–44. DOI: 10.17886/RKI-GBE-2017-027. [73]	2017	RKI	- GEDA 2014/2015-EHIS) - deutsche validierte Version des European Health Interview Survey – Physical Activity Questionnaires (EHIS-PAQ) erfasst [9, 10]. - Selbstngabe - Zeitdauer/Woche: mäßig anstrengende aerobe körperliche Aktivität in der Freizeit und Radfahren zur Fortbewegung - Anzahl von Tagen/ Woche: Aktivitäten zur Muskelkräftigung - Darstellung der Anteile derer, die - ≥2,5 h/ Woche mindestens mäßig anstrengende Ausdaueraktivitäten ausüben (1. Teil der WHO-Bewegungsempfehlung) bzw.	**WHO-Empfehlung zur Ausdaueraktivität:** - 42,6% (95% KI 41,3–43,9) der Frauen - 48,0% (95% KI 46,6–49,4) der Männer **WHO-Empfehlung zur Muskelkräftigungsaktivität:** - 27,6% (95% KI 26,7–28,6) der Frauen - 31,2% (95% KI 30,2–32,3) der Männer **Beide Empfehlungen zusammen:** - 20,5% (95% KI 19,6–21,4) der Frauen - 24,7% (95% KI 23,6–25,8) der Männer

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			- ≥ 2 /Woche Aktivitäten zur Muskelkräftigung ausüben (2. Teil der WHO-Bewegungsempfehlung) sowie - beide Teile der WHO-Empfehlung erfüllen (2,5 Stunden Ausdauer + 2x Muskelkräftigung/ Woche). - Stratifizierung: nach Geschlecht, Altersgruppen, Bildungsstand, Bundesländern - n= 22.959 ab 18 Jahren - 12.511 Frauen - 10.448 Männer - Gewichtungsfaktor Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung korrigiert.	**Quellen**: 9. Baumeister SE, Ricci C, Kohler S et al. (2016) Physical activity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnai-re (EHIS-PAQ). International Journal of Behavioral Nutrition and Physical Activity 13(1):1-10 10.Finger JD, Tafforeau J, Gisle L et al. (2015) Development of the European Health Interview Survey – Physical Activity Questi-onnaire (EHIS-PAQ) to monitor physical activity in the European Union. BMC Archives of Public Health 73:59

Klinisch relevante Endpunkte

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
"[A05-21D] Steigerung der körperlichen Aktivität bei essenzieller Hypertonie - Rapid Report [74] https://iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21d-steigerung-der-koerperlichen-aktivitaet-bei-essenzieller-hypertonie-rapid-report.1127.html	2010	Low	**Fragestellung:** Nutzenbewertung von Interventionen zur Steigerung der körperlichen Aktivität im Vergleich zu keiner entsprechenden Intervention bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und Kriterien der Blutdruckkontrolle **Suchzeitraum:** bis 09/2009 **Population:** - erwachsenen Patienten - essenzielle Hypertonie **Intervention:** - Mindestdauer von 24 Wochen. - Maßnahme zur Steigerung der körperlichen Aktivität **Vergleich:** - keine Maßnahme zur Steigerung der körperlichen Aktivität **Endpunkte:** **- G**esamtmortalität - CV-Mortalität (koronare, zerebrovaskuläre) - CV Morbidität (koronare, zerebrovaskuläre, periphere arterielle) - terminale NI (Dialysetherapie oder Nierentransplantation)	**Algemeines:** - 8 RCTs (n=838) - randomisierte offene Parallelgruppenstudien - Beobachtungsdauer: in 5 Studien 6 Monate, in 1 Studie 9 Monate und in 2 Studien 1 Jahr - mittlere Alter zwischen 42,0 (Kontrollgruppe bei Sohn 2007) und 71,3 Jahren (Lee 2007). - 6/8 Studien: Patienten mit bestehender Hypertonie; 2 RCTs: Mischpopulation aus Hypertonie und hochnormalem Blutdruck - 4 Studien: Beratung / Empfehlung zu gesteigerter körperlicher Aktivität; 4 Studien: vorgegebenes Ausdauertrainingsprogramm (supervidiert) **Endpunkte** Gesamtmortalität: Daten unzureichend Kardiovaskuläre Mortalität: Daten unzureichend Kardiovaskuläre Morbidität: keine Daten Terminale Niereninsuffizienz: Keine Daten Gesundheitsbezogene Lebensqualität: Daten unzureichend Alle unerwünschten Ereignisse: Keine Daten Dauer / Ausmaß der Änderung des SBD: Anhaltspunkt für einen blutdrucksenkenden Effekt; Kein Nachweis für einen blutdrucksenkenden Effekt - in 5 Studien: mittlere systolische Blutdrucksenkung zwischen -5 und -8 mmHg, - in 2 Studien:Effekte bis zu -15 mmHg gefunden - in 1 Studie: eine geringgradige Blutdrucksteigerung.	

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			Sekundäre: - gesundheitsbezogene Lebensqualität - Dauer und Ausmaß der Blutdruckänderung - alle unerwünschten Ereignisse - Absetzen und / oder Reduktion vorbestehender antihypertensiver Medikation **Studientyp:** SR, RCTs	Dauer / Ausmaß der Änderung des DBD: Kein Anhaltspunkt für einen blutdrucksenkenden Effekt; Kein Nachweis für einen blutdrucksenkenden Effekt - variierten zwischen 0 mmHg und -10 mmHg Änderung antihypertensiver Medikation: Daten unzureichend	
Rossi A. The impact of **physical activity** on mortality in patients with high blood pressure: A systematic review. J Hypertens 2012; 30(7):1277–88. [75] https://www.ncbi.nlm.nih.gov/pubmed/22573122.	2012	low	**Ziel:** to identify and synthesize the literature examining the impact of physical activity on mortality in patients with high blood pressure (BP). **Suchzeitraum:** between 1985 and January 2012 **Stdudientyp:** longitudinal design with ≥ 1-year follow-up; **Einschlusskriteriwn** - hypertensive status of the cohort was indicated and BP, physical activity, and mortality were measured. **Anmerkung:** körperliche Aktivität mittels Selbstauskunft erhoben	**Allgemeines:** - 6 articles evaluating a total of 48,448 men and 47,625 women - cohorts from Northern Europe (Denmark, Sweden, Iceland, Norway, Finland, UK or USA) - follow up: 5-24 Jahre - medication usage only indicated for Losartan Intervention for Endpoint (LIFE) trial - none of other studies reported use of medications, apart from stating that participants using BP-lowering drugs were icluded and classified as hypertensive. - activity classification and parameters, such as frequency, duration, intensity, and volume, as well as BP status, were not consistent across studies (siehe Tabelle 2 in Publikation) - General and leisure time physical activity were main types of activity considered **Ergebnisse:** - CV and/or all-cause mortality were shown to be inversely related to physical activity in all studies. - patients with high BP who participated in any level of physical activity had a reduced risk (by 16-67%) of CV mortality, whereas a greater than 2-fold increase in risk of mortality was noted in nonactive individuals. .	SR aus Kohortenstudien AMSTAR-II - ein kritisches Kriterien nicht erfüllt: Protokoll ausgeschlossenen Studien mit Ausschlussgrund im Fließtext inkl. Quellenangabe berichtet
Hartley L. **Qigong** for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2015; 2015(6):CD010390. [76]	2015	moderate	**Fragestellung**: To determine the effectiveness of qigong for the primary prevention of CVD **Suchzeitraum:** bis 11/2014 **Population**: - Healthy adults 18 years and older from general population - and those at high risk for CVD. **Intervention:**	**Allgemeines:** - 11 RCTs (n= 1369) - 8 studies: hypertensive patients (Kuang 1979; Kuang 1987a; Wang 1991; Kuang 1986; Kuang 1987; Li 1989; Li 1993; Wang 1989) - follow up: 6 month (Li 1993), 1 year (Kuang 1987a; Wang 1989) to 2 years (Li 1989) to 4 years (Kuang 1979). 3 studies reported very long-term follow-up (20 to 30 years), but trials were originally designed for and reported on follow-up between 6 and 12 months (Kuang 1986; Kuang 1987;	**Zurückgestellt** für CV-Endpunkte: examined all-cause mortality and mortality from stroke after 20 to

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https://www.ncbi.nlm.nih.gov/pubmed/26068956.			- Trials investigated any style of qigong (internal or external). **Vergleich:** - no intervention or minimal intervention (e.g. leaflets promoting physical activity, other more general forms of health promotion, but no face-to-face interaction). **Studientyp:** RCTs	Wang 1991). - häufig unklares RoB **Hypertoniespezifische Ergebnisse**: **- all-cause mortality** - RR 0.54, 95% CI 0.33; 0.90, n= 204 (Kuang 1986) - RR 0.56, 95% CI 0.39 to 0.79, n= 306 (Wang 1991)) **- stroke mortality:** - RR 0.50, 95% CI 0.26 to 0.95, n= 204 (Kuang 1986) - RR 0.49, 95% CI 0.31 to 0.78, n= 306 (Wang 1991)). **stroke incidence:** - RR 0.56, 95% CI 0.38 to 0.83) after 25 to 30 years of follow-up, n= 306 **SBP (keine Pooling: Heterogenität)** - 3 of 5 trials showed extremely large effects and statistically significant reductions in SBP with qigong. *Intervention vs. Kontrolle* - Kuang 1987: n=104, M -37.6 (SD 12.7) vs. n= 100, M-19.4 (SD 11.5), MD -18.2 [-21.52,-14.88] - Kuang 1987a: n=23, M -42.1 (SD28.9) vs. n= 23, M -29.9 (SD 41.3), MD -12.2 [-32.78,8.38] - Li 1993: n=25, M -27 (SD 10.1) vs. n=14; M -15.1 (SD 7.3), MD -11.85 [-17.35,-6.35] **BDP (kein Pooling: Heterogenität)** - 2 of 5 trials showed statistically significant reductions in DBP with qigong *Intervention vs. Kontrolle* - Kuang 1979: n=68; M-21.3 (SD9.9) vs n= 67, M= -14.8 (SD 9.1), MD -6.57 [-9.77,-3.37] Kuang 1987a: n=23, M -25.2 (SD 20.3) vs. n=23, M -14.9 (SD 27.2); MD -10.34 [-24.21, 3.53] Li 1993: n=25, M -15.5 (SD6) vs. n=14, M -8.3 (SD4.7), MD -7.2 [-10.59,-3.81 **Adverse events:** None of the included studies provided information on adverse events. **Quality of life:** None of the included studies reported quality of life outcomes.	30 years of follow-up, but these trials were originally designed to look for outcomes at 6 months to 1 year, and it is unclear whether qigong was continued as practised during the 20- to 30- year period, or if randomisation was preserved Aussagen zum Blutdruck können verwendet werden
Hartley L. **Tai chi** for primary prevention of cardiovascular disease. Cochrane Database Syst Rev	2014	high	**Fragestellung:** To determine the e?ectiveness of tai chi for the primary prevention of CVD. **Suchzeitraum**: bis 12/2013 **Population:** - Adults aged 18 years and over from the general population	**Allgemeines:** - 13 RCTs - 1 study: borderline hypertension (Tsai 2003); - 2 studies: essential hypertension (Luo 2006; Wen 2005); - 1 study: hypertension with liver and kidney yin deficiency syndrome (Wang 2010);	- Wen (2005) berichtete keine BD- Ergebnisse

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2014(4):CD010366. [77] https://www.ncbi.nlm.nih.gov/pubmed/24715694.			- adults at high risk of CVD. **Intervention**: - any style of tai chi **Vergleich:** - no intervention - minimal intervention (e.g. leaflets to promote increased physical activity or other more general health education with no face-to-face interaction or reinforcement **Endpunkte:** **Studientyp:** RCTs	- 1 study: hypertension (Sun 2010). - duration of classes: 40 minutes to 2 hours (1- 7x/ week) - 12 weeks - 1 year - RoB häufig unklar **Ergebnisse in der Population der HTN-Patienten:** - We found no trials that reported CV mortality, all-cause mortality or non-fatal endpoints. **SBP** - keine Metaanalyse significant heterogeneity (I2=96%): - MD -22 mmHg, 95% CI -26.3 to -17.7 (Tsai 2003) - MD -12.90 mmHg, 95% CI -17.87 to -7.93 (Luo 2006); - MD -12.97 mmHg, 95% CI -22.71 to -3.23 (Sun 2010); - MD -12.97, 95% CI -21.53 to -4.41 (Wang 2010); **DBP** - keine Metaanalyse significant heterogeneity (I2=96%): - MD -12.2 mmHg, 95% CI -15.8 to -8.7 (Tsai 2003); - MD -7.20 mmHg, 95% CI -12.11 to -2.29 (Sun 2010); - MD -2.69 mmHg, 95% CI -6.30 to 0.92 (Luo 2006)).	
Hartley L. **Yoga** for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2014(5):CD010072. [78] https://www.ncbi.nlm.nih.gov/pubmed/24825181.	2014	moderate	**Fragestellung:** determine the elect of any type of yoga on primary prevention of CVD. **Suchzeitraum:** bis 11/2013 **Population:** - Healthy adults (≥ 18 y), worldwide - general population - those at moderate to high risk of CVD **Intervention:** - any type of yoga (postural exercises, breathing control and meditation) - follow-up periods ≥ 3 months **Vergleich:** - no intervention or minimal intervention **Studientyp:** RCTs	**Allgemeines:** - 11 RCTs (n= 800) - 2 ongoing trials --> 1 study recruited essential hypertensives (Latha 1991) - 6 month follow up, twice weekly - did not state which type of yoga they used - hohes RoB: Randomisierung, Allocation concealment, Blinding, selective reporting **Hypertoniespezifische Ergebnisse:** - Useable data for meta-analysis were not available for one study (Latha 1991), - no data for control group were provided, only changes since baseline for the yoga group. - SBP was reduced by yoga (MD) -5.71 mmHg and DBP was also reduced (MD -3.71 mmHg).	- None of the included studies provided CV or all-cause mortality data. - 1 HTN-spezifische Studie eingeschlossen - hoher RoB in 4 Kategorien - keinen Vergleich zur Kontrollgruppe vorgenommen
Lauche R. Efficacy of **Tai Chi and qigong** for the prevention of stroke and stroke risk factors: A systematic review with meta-	2017	low	**Fragestellung**: examine and summarize the evidence regarding Tai Chi and qigong interventions for the primary prevention of stroke, including the effects of such intervention on populations with selected major stroke risk factors **Suchzeitraum:** bis 01/2016 **Population:**	**Allgemeines:** - 26 Studien eingeschlossen (n= 1604) - 8 Studien: Population HTN - no trial examining effects of Tai Chi/qigong on incidence of stroke or TIA. **Hypertoniespezifische Ergebnisse:** - control groups: no intervention (n=4), exercises or nonexercise related activities (n= 3) (PMR or reading)	**Zurückgestellt** - keine Primärstudien gefunden, die patientenrelevanten Endpunkte untersucht

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analysis. Medicine (Baltimore) 2017; 96(45):e8517. [79] https://www.ncbi.nlm.nih.gov/pubmed/29137055.			- one of stroke risk factors were included irrespective of gender **Intervention:** - Tai Chi or qigong regardless of the form, tradition, frequency, and duration of the intervention **Vergleich:** - no treatment, nonexercise control intervention and *exercise control interventions* **Studientyp:** RCTs	- duration of the interventions: 5 days - 12 months, majority of trials 8 - 24 weeks (median 12 weeks). - frequency of Tai Chi or qigong: 2 days a week to daily (median 4x/week), 3 trials included selfdirected home practice. **SBP** - Tai Chi/ qigong vs. pooled group (no intervention controls, or interventions such as reading or computer training.) - SBP: MD -15.55mm Hg (95% CI -21.16; -9.95; I2=82%) N= 5, n= 468; - DBP MD -10.66mm Hg (95% CI: -14.90, - 6.43; I2=83%). - 1 trial compared qigong with PMR: no group differences for BP - 1 trial that compared qigong with conventional exercise found no group differences for BP, and concluded that both interventions had similar moderate effects.	Unterschied zu anderen SR: schließt auch direkte Vergleiche ein - Sprache: engl. und dt.
Zheng G. **Tai chi** chuan for the primary prevention of stroke in middle-aged and elderly adults: A systematic review. Evid Based Complement Alternat Med 2015; 2015:742152. [80] https://www.ncbi.nlm.nih.gov/pubmed/25784950.	2015	low	**Fragestellung**: conduct a systematic review and meta-analysis of existing studies on TCC exercise as an intervention for primary prevention of stroke in middle-aged and elderly adults **Suchzeitraum:** bis 10/2013 **Population:** - aged 30 or older with or without high risk factors of stroke **Intervention**: - Type of TCC exercise not limited - frequency of at least 30 minutes per time and 3 times per week for 4 weeks **Vergleich:** - no intervention **Studientyp:** RCTs, NRCTs, quasi-RCTs	**Allgemeines** - 36 Studien mit verschiedenen Populationen - 8 Studien, die Pat. mit HTN einschließen, davon nur eine, die CV-Endpunkte untersucht (Dauer 48 Wochen): Han 2009 **keine Ergebnisse berichtet, die nur für Patienten mit HTN gelten** - Studie von Han et al 2009 (n= 60) mit einer weiteren Studie gepoolt, die gesunde Ältere (n= 125) einschloss: - incidence of nonfatal stroke (RR = 0.11, 95% CI 0.01; 0.85) n= 185, I²=0%, zugunsten TCC - incidence of fatal stroke (RR = 0.33, 95% CI 0.05 to 2.05), n= 185, N= 2, I²= 0%	**Zurückgestellt** Ergebnis aus Sicht der AG nicht extrapolierbar Studie von Han et al. nicht identifizierbar Ergebnisse für EP Blutdruck nicht verwendbar, da Studien mit unterschiedlichen Populationen gepoolt

Surrogatendpunkt für priorisierte Interventionen

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
Zhong D. **Tai Chi** for Essential Hyper-	2020	moderate	**Fragestellung:** evaluate the effect of Tai Chi for hypertension and explore whether cumulative data were adequately	**Allgemeines:** - 28 RCTs - n= 2937	**Zurückgestellt**

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tension: A Systematic Review of Randomized Controlled Trials. Curr Hypertens Rep 2020; 22(3):25. [81] https://www.ncbi.nlm.nih.gov/pubmed/32124064.			powered to evaluate outcomes by performing trial sequential analysis (TSA). **Suchzeitraum:** bis 01/2020 **Population:** - ≥ 18 J - Patienten mit Hypertonie **Intervention**: - Tai Chi (no limit on the duration, frequency or style) **Kontrolle:** - antihypertensive drugs (AHD) - other exercises, no treatment (NT), - health education (HE); **Studientyp**: RCTs	**Tai Chi vs. Health Education/No Treatment** - RCTs - SBP: MD = −14.784, 95% CI − 19.587 to − 9.981, I2 = 94%, - DBP: MD = − 7.035, 95% CI − 9.083 to − 4.988, I2 = 74.5%, - No differences were found between subgroups in age, intervention duration, exercise frequency, session duration, and weekly exercise time. **Tai Chi vs. Other Exercises** - 5 RCTs - SBP: MD = − 7.934, 95% CI − 14.221 to − 1.674, I2 = 93.9% - DBP: MD = − 3.856, 95% CI − 6.544 to − 1.168, I2 = 73.2% **Tai Chi vs. AHD** - 15 RCTs - SBP: MD = − 9.070, 95% CI − 14.033 to − 4.108, I2 = 97.2%, - DBP: MD = − 5.625, 95% CI − 8.836 to − 2.414, I2 = 96.2%, **sensitivity analyses** - Tai Chi for hypertension patients < 50 years old showed 3 times the reduction of SBP and DBP than patients ≥ 50 years old. - Intervention of 12– 24 weeks could significantly lower SBP and DBP than intervention of < 12 weeks and intervention of > 24weeks. - Weekly exercise time of < 150 min/week suggested no significant difference.	AG entscheidet sich nach klinischer Sichtung des SR, den Cochrane-Review von Hartley heranzuziehen Der Suchzeitraum ist zwar älter aber die Methodik transparenter Subgruppenanalyse für Studiendauer (> 24 Wochen)
Liu D. The Efficacy of **Tai Chi and Qigong** Exercises on Blood Pressure and Blood Levels of Nitric Oxide and Endothelin-1 in Patients with Essential Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med 2020; 2020:3267971. [82] https://www.ncbi.nlm.nih.gov/pubmed/32802122.	2020	critically low	**Fragestellung:** - primary aim is to evaluate the efficacy of TCQE on lowering the BP of patients with EH. **Suchzeitraum:** bis 01/2020 **Population:** - > 49 years - no severe complication - explicit diagnosis of EH (SBP ≥140 mmHg, and/or DBP ≥90 mmHg, and/or antihypertensive drug use for at least 2 weeks. - Studies that confirmed participants with EH but without providing specific diagnostic criteria for HT were also taken into account **Intervention:** - TCQE alone or plus control regimen as the primary intervention **Kontrolle:** - Any type of control such as no intervention, usual	**Allgemeines:** - 9 RCTs - n= 516 - average age of subjects ranged from 56 to 70 years. **compositive analysis:** **- SBP** in experimental groups lower than in control groups (SMD −1.13; 95% CI: −1.47 to −0.79;I²= 65%, n= 451, 8 Studien - **DBP** in experimental groups lower than in control groups (SMD −1.14; 95% CI: −1.59 to −0.68; I²= 80%, n= 451, 8 Studien **SBP in Abhängigkeit der Kontrollgruppe** - no intervention: (SMD −1.40; 95% CI: −1.76 to −1.05; I²= 0%, N=3, n= 158) - antihypertensive drug (SMD −0.89; 95% CI: −1.47 to −0.31; I²= 74%, N= 4, n= 109) - aerobic exercise (SMD −1.29; 95% CI: −1.76 to −0.81; N=1, n= 84 **DBP in Abhängigkeit der Kontrollgruppe:**	**Zurückgestellt** AG entscheidet sich nach klinischer Sichtung des SR, die beiden Cochrane-Reviews von Hartley heranzuziehen Der Suchzeitraum ist zwar älter aber die Methodik transparenter Subgruppenanalyse für Studiendauer (> 24 Wochen)2 kritische

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			care, and standard antihypertensive therapy and any kind of physical exercises. **Studientyp:** RCTs	- no intervention (SMD −1.56; 95% CI: −2.29 to −0.83, I²= 75%, N= 3, n= 158 - antihypertensive drug (SMD −0.87; 95% CI: −1.59 to −0.15; I²= 84%, N= 4, n= 109) - aerobic exercise (SMD −1.00; 95% CI: −1.46 to −0.55; N=1, n= 84) **Einfluss der Dauer der Intervention (short 1.5 mo, medium 2.5-3 mo, long term 6 mo)** - short-term intervention was not statistically significant in changing BP levels (N=1, n= 54). - SBP: long-term (SMD −1.54; 95% CI: −1.98 to −1.11, I²= 0, N= 2, n= 108) and medium-term (SMD −1.14; 95% CI: −1.47 to −0.81, I²= 40%, N= 4, n= 289). - DBP: long-term (SMD −1.53; 95% CI: −2.75 to −0.31, I²= 86%, N= 2, n= 108) and medium-term (SMD −1.20; 95% CI: −1.65 to −0.74, I²= 68%, N= 4, n= 289). Einfluss der Formen der Intervention untersucht: Extraktion bei Bedarf	Kriterien nicht erfüllt (Protokoll, Liste der exkludierten PS)
Lee L-L. Walking for hypertension. Cochrane Database Syst Rev 2021; 2(2):CD008823. [83] https://www.ncbi.nlm.nih.gov/pubmed/33630309.	2021		**Objectives** To determine the effect of walking as a physical activity intervention on blood pressure and heart rate. **Search** Cochrane Hypertension Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase, CINAHL, PsycINFO, SPORTDiscus, PEDro, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov. (up to March 2020) - also searched: Chinese databases, **Inclusion and exclusion criteria** - randomised controlled trials - hypertensive and normotensive adults - aged 16 years and over **Intervention** walking **Control** non-exercising and non-intervention controls **Outcomes**	n=73 trials (5763 participants)were included - age rage from 16 to 84 years - characteristics of walking interventions: ○ the majority of walking interventions was at home/community (n = 50) but supervised (n = 36 out of 47 reported the information of supervision); ○ the average intervention length was 15 weeks, average walking time per week was 153 minutes and ○ the majority of walking intensity was moderate **primary outcome:** - suggesting that walking reduces: ○ systolic blood pressure (SBP) (MD -4.11 mmHg, 95% CI -5.22 to -3.01; 73 studies, n = 5060) (moderate-certainty evidence) ○ SBP in participants aged 40 years and under (MD -4.41 mmHg, 95% CI -6.17 to -2.65; 14 studies, n = 491), (moderate-certainty evidence)	aus der Update Recherche der strukturierten Recherche 2021 Many studies were at risk of selection bias and performance bias

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
			blood pressure (systolic/diastolic) heart rate **note:** Walking interventions including community, laboratory-based (e.g. treadmill), or non-stair and non-uphill treadmill walking were included. Mixed interventions of walking with other modes of physical activity, such as jogging, or other forms of lifestyle modification, such as dietary salt reduction, were excluded. **note:** primary outcomes Systolic blood pressure (SBP) (continuous): measured by any standard devices, such as electronic or traditional mercury sphygmomanometer, or 24 hours ambulatory blood pressure measurement in millimetres of mercury (mmHg) pressure units.	○ SBP in participants aged 41 to 60 years (MD -3.79 mmHg, 95% CI -5.64 to -1.94, P < 0.001; 35 studies, n =1959), and those aged 60 years of over (MD -4.30 mmHg, 95% CI -6.17 to -2.44, 24 studies, n = 2610) (low-certainty evidence) ○ SBP in both females (MD -5.65 mmHg, 95% CI -7.89 to -3.41; 22 studies, n = 1149) and males (MD -4.64 mmHg, 95% CI -8.69 to -0.59; 6 studies, n = 203) (low certainty-evidence)	
Igarashi Y. **Running** to Lower Resting Blood Pressure: A Systematic Review and Meta-analysis. Sports Med 2020; 50(3):531–41. [84] https://www.ncbi.nlm.nih.gov/pubmed/31677122.	2020	critically low	**Ziel:** - summarize effects of running regularly on RBP and to investigate the most efficacious form of running in reducing RBP for this purpose. **Population:** - involving healthy adults or adults with hypertension, **Intervention:** - regular running **Kontrolle:** - did not exercise, **Studientyp**: RCTs	**Allgemeines:** - 22 trials - n= 736 - mea nage: 21-49y **trials involving subjects with hypertension:** - the WMD in RBP decreased significantly - RSBP: - 5.6 mmHg (95% CI - 9.1 to - 2.1); I(2) = 62.2% - RDBP: - 5.2 mmHg (95% CI - 9.0 to - 1.4) I(2) = 87.7% - meta-regression analysis showed that percentage of maximum heart rate was significantly associated with WMD in RSBP [slope: 0.56 (95% CI 0.21 to 0.92), intercept: - 48.76 (95% CI - 76.30 to - 21.22), R(2) = 0.88] and RDBP [slope: 0.45 (95% CI 0.01 to 0.87), intercept: - 38.06 (95% CI - 72.30 to - 4.08), R(2) = 0.41]. **trials involving subjects with hypertension and a mean age ≥ 40 years:** - a meta-regression analysis showed that total exercise time throughout intervention was significantly associated with WMD in RDBP [slope: 0.82 (95% CI 0.54 to 1.09), intercept: - 22.90 (95% CI - 29.04 to - 16.77), R(2) = 0.99].	2 kritische Kriterien nicht erfüllt - Liste der ausgeschlossenen PS - Einbezug des Biasrisiko in Diskussion

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
Cao L. The effectiveness of **aerobic exercise** for hypertensive population: A systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2019; 21(7):868–76. [85] https://www.ncbi.nlm.nih.gov/pubmed/31169988.	2019	critically low	**Fragestellung:** evaluate the effectiveness of AE in hypertensive patients and analyzed the relationship between changes in blood pressure and the duration of exercise, so as to provide reliable clinical evidence for the treatment of hypertension **Suchzeitraum:** bis 07/2018 **Population:** - 30-85 Jahre - diagnosed with hypertension based on clinical and laboratory studies (SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg) - not accompanied by other metabolic or cardiovascular diseases, no alcohol use and nonsmoking, able to voluntary join exercise; **Intervention:** - regular Aerobic exercise **Vergleich:** - did not receive any type exercise **Studientyp**: RCTs	**Allgemeines:** - 14 Studien - n= 860 - mean age: ranged between 39.67 and 83.4 y - SBP at baseline ranged: 130.3- 170.45 mmHg - DBP at baseline ranged: 67.5 to 95.2 mm Hg - Interventionen in den Baseline-Charakteristika nicht benannt, daher Sichtung der TiAbs der eingeschlossenen Primärstudien [Zitatnummer]: - [40] Wassergymnastik, [26] treadmill, [28] AE (nich näher bezeichtnet, [15] aerobic dance, 12 Ausdauer, 25 brisk walking, 16 treadmill + resistance training, [13] treadmill, [14] arm cycling, [41] treadmill + Zirkeltraining, [42] bicycle ergometer, [27] walking, [43] jogging, [24] AE nicht näher bezeichnet - duration of intervention: 40 minutes - 6 months. **Ergebnisse (Pooling unabhängig der Studiendauer):** **- SBP:** MD −12.26 mmHg (95% CI: −15.17 to −9.34), I²=75%, n= 757, N= 13 **- DBP:** MD − 6.12 mmHg (95% C I: –7.76 to −4.48) **Subgruppenanalyse SBP:** 8-12 weeks: MD −11.74 mmHg (95% CI: −15.94 to −7.54), I²=70%, n= 422, N= 8 >12 weeks: MD − 8.84 mmHg (95% C I: −13.52 to −4.15), I²=70%, n= 72, N= 2 **Subgruppenanalyse DBP:** 8-12 weeks: MD −5,44 mmHg (95% CI: −8,22 to −2,66), I²=68%, n= 420, N= 8 >12 weeks: MD − 7,52 mmHg (95% C I: −12,42 to −2,62), I²=77%, n= 72, N= 2 **Quality of life (**WHOQoL-BREF) je Intervention vs. Kontrolle (N= 1, n= 103) - physical health: +23.33 vs. 15,42 - psychological health: +18.17 vs. 9,72 - social relationships: +14.51 vs. 9.55	1 Studie eingeschlossen, deren Interventionsdauer nur 40 Minuten betrug >> Auswirkungen auf BP jedoch nach Interventionsdauer (<8,>8,>12 Wo) untersucht, daher trotzdem Einschluss möglich - 2 kritische Kriterien bei AMSTAR nicht erfüllt (Protokoll, Exlusionsliste)
Costa EC. Effects of **High-Intensity Interval Training Versus Moderate-Intensity Continuous Training** On	2018	critically low	**Fragestellung:** 1. compare efficacy of HIIT vs. MICT for reducing resting and ambulatory BP in adults with pre- to established hypertension. 2. compared efficacy of HIIT vs. MICT for improv-	**Allgemeines:** - 9 studies - n= 245 **HIIT-Gruppe:** - 60.0% men - age 57.8 ± 8.6 years;	2 kritische Kriterien nicht erfüllt (PB, Liste der excludierten PS)

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
Blood Pressure in Adults with Pre- to Established Hypertension: A Systematic Review and Meta-Analysis of Randomized Trials. Sports Med 2018; 48(9):2127–42. [86] https://www.ncbi.nlm.nih.gov/pubmed/29949110.			ing maximal oxygen uptake (VO2max) and completion rate of intervention, attendance at exercise training sessions, and safety (i.e., reported AE) with HIIT and MICT programs **Population:** - ≥ 18 years - pre- to established hypertension (i.e., baseline resting SBP ≥130 mmHg and/or DBP ≥ 85 mmHg and/or under antihypertensive medication(s). - For ambulatory BP, the mean values of baseline 24-hour SBP ≥130 mmHg and/or DBP ≥80 mmHg - Studies including individuals with additional risk factors (e.g., high cholesterol, overweight, obesity, prediabetes, etc.) or known cardiometabolic diseases (e.g., T2DM, CHD, HF etc.) were eligible for inclusion **Intervention:** - repeated HIIT bouts between 80% and 100% of HRpeak interspersed with recovery periods or light exercise - Studies using percentage of VO2max, oxygen uptake reserve (VO2-reserve), HR-reserve, or rating of perceived exertion (RPE) to define exercise intensity were included when values were equivalent to 80–100% of HRpeak according to American College of Sports Medicine (ACSM) - duration ≥ 4 weeks - regimes that included a combination of HIIT and resistance training or nutritional interventions were not included **Kontrolle:** - MICT: exercise interventions with intensity between 64 and 76% of HRpeak performed continuously. - Studies that prescribed exercise intensity as a percentage of VO2max, VO2-reserve, HRreserve, or RPE equivalent to 64–76% of HRpeak were included as MICT - duration ≥ 4 weeks - regimes that included a combination of MICT and	- BMI: 30.6 ± 2.1 kg/m2) **MICT-Gruppe:** - 49.4% men - age 56.1 ± 11.7 years - BMI 30.4 ± 2.3 kg/m2 **Effects of HIIT Versus MICT on Resting Blood Pressure:** - 7 Studien - resting systolic BP: (MD -0.22 mmHg [CI 95%, -5.36 to 4.92]), I2 = 53%, n= 164 - resting diastolic BP: (MD -0.38 mmHg [CI 95%, -3.31 to 2.54], I2 = 0%, n= 164 **- completion rate of the intervention:** (HIIT: 82.7 ± 12.9%; MICT: 81.8 ± 9.7%) **- attendance at training sessions:** (HIIT: 88.9 ± 4.3%; MICT: 85.2 ± 6.7%) **- adverse events:** - 3 studies did not report this information - 3 studies reported no adverse events in both HIIT and MICT groups - 3 studies reported some adverse events - Cheema et al. [27]: 2 participants from HIIT group had musculoskeletal injuries (elbow epicondylitis, gastrocnemius muscle strain) related to intervention. - Rognmo et al. [31]: 1 dropout in HIIT group due to ankle fracture and 1 dropout in MICT group due to knee injury. - Molmen-Hansen et al. [33]: 3 dropouts in HIIT group because of pain and 1 dropout in MICT group due to a myocardial infarction when participant was at home. - However, in both of these studies [31, 33] the authors did not state clearly if the AE were directly associated with training interventions.	

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
			resistance training or nutritional interventions were not included **Studientyp:** Randomized trials		
Macdonald HV. Dynamic Resistance Training as Stand-Alone Antihypertensive Lifestyle Therapy: A Meta-Analysis. J Am Heart Assoc 2016; 5(10). [87] https://www.ncbi.nlm.nih.gov/pubmed/27680663.	2016	low	**Fragestellung:** provide more precise estimates regarding the efficacy of dynamic RT as stand-alone antihypertensive therapy, and identify potential moderators of this response to provide insight into the optimal dose of dynamic RT to lower BP among adults with high BP **Suchzeitraum:** bis 01/2014 **Population:** - involved adult participants (≥19 years) - with and without CVD-related chronic diseases - only excluded studies that involved populations with disease(s) or health conditions unrelated to CVD (eg, arthritis, cancer, HIV/AIDS **Intervention:** - dynamic RT **Kontrolle:** - non-exercise/non-diet **Studientyp:** - controlled studies (RCTs and non-RCTs)	**Allgemeines:** - 64 controlled studies eingeschlossen - 82% RCTs - 86% non-exercise/ wait-listed control group - 9 studies: a “placebo” control group - “moderate” methodological study quality (63%) - age (47.4 +/- 19.0 years), - overweight (26.7 +/- 3.5 kg/m2) - adults with prehypertension (SBP/DBP: 126.4 +/- 9.4/76.6 +/- 8.4 mm Hg) - Approximately 15% of the total sample was on antihypertensive medication (N=349), - 60% involved adults without CVD-related chronic diseases or health conditions other than their high BP (n=1286). - subset included participants with known CVD-related chronic diseases (3 studies; N=64) **Ergebnisse der multiplen Moderatorenanalyse:** - we included overall methodological study quality or individual quality dimensions (eg, BP-focused study outcome) in our multiple moderator models when feasible **Population mit HTN:** **SBP:** -5,7 mmHG (95% KI -9,0;-2,7), N= 14 indicates the moderator dimensions/levels that conferred the largest SBP reductions and were used to generate the additive SBP model. **DBP:** -5.2 mmHG (95% KI -8.4, -1.9), N= 14 (Indicates the moderator dimensions/levels that conferred the largest DBP reductions and were used to generate the additive DBP model)	
Loaiza-Betancur AF. Is Low-Intensity Isometric Handgrip Exercise an Efficient Alternative in Lifestyle Blood Pressure Management? A Systematic Review. Sports Health	2020	Critically low	**Ziel:** To assess whether low-intensity isometric handgrip exercise (LI-IHE) is an effective strategy to lower blood pressure levels in prehypertensive and hypertensive patients. **Suchzeitraum:** bis 03/2019 **Population**: - pre-HTN - HTN,	**Allgemeines:** - 11 Studien (n= 311) - 10 RCTs - 1 Parallel-Gruppen-Design - 7/10 RCTs berichteten kein random assignment - 7/10 Studien: Pat. mit medikamentöser Therapie (nicht als Teil der Intervention) - keine Beschreibung der Kontrollinterventionen in Baseline-Charakteristika	

Referenz	Jahr	AMSTA-II	Charakteristika	Ergebnisse	Kommentar VT
2020; 12(5):470–7. [88] https://www.ncbi.nlm.nih.gov/pubmed/32776866.			- ≥ 18 y. **Intervention**: - Low-Intensity Isometric Handgrip Exercise, - ≥ 6 Wochen, min 2x/Woche **Kontrolle (Info aus Protokoll entnommen):** - Isometric handgrip exercise with intensities higher than 50% MCVI; - other types of exercise (dynamic aerobic exercise or dynamic strength); - placebo groups **Studientyp:** randomized controlled trials that	- SBP: MD -5.43 mm Hg; (95% CI, -8.47 to -2.39), I^2= 67%, N= 11, n= 332 - DBP: MD -2.41 mm Hg (95% CI, -4.33 to -0.48), I^2= 69%, N= 11, n= 332	

7.3 Schulung

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Nieuwlaat R. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014(11):CD000011. [59] https://www.ncbi.nlm.nih.gov/pubmed/25412402.	2014	high	**Objectives:** assess the effects of interventions intended to enhance patient adherence to prescribed medications for medical conditions, on both medication adherence and clinical outcomes. **Search:** on 11 January 2013 **Selection criteria** - Patients who were prescribed medication for a medical (including psychiatric) disorder, but not for addictions - Interventions of any sort intended to affect adherence with prescribed, self administered medications - unconfounded RCTs - measuring both medication adherence and clinical outcome - at least 80% follow-up of each group studied and, for long-term treatments, at least 6 months follow-up for studies with positive findings at earlier time points.	**Allgemeines:** - 182 RCTs (109 since previous update in January 2007) - heterogeneous patients, medical problems, treatment regimens, adherence interventions, outcome measurements, - most high risk of bias. - 17 lowest risk of bias for study design features and primary clinical outcome, 11 from present and 6 from previous update. - 5 RCTs reported improvements adherence and clinical outcomes, and no common intervention characteristics were apparent. Even most effective interventions did not lead to large improvements in adherence or clinical outcomes. **Hypertension**: - 17 RCTs, 1 mit niedrigem RoB **Morgado 2011** n =197; antihypertensive therapy ≥ 6 months **Intervention:** - counseling from hospital pharmacist at specialized outpatient clinic - interviewed patients, assessed problems with BP control, **educated patients,** advised physicians on medication changes, provided intervention patients with written educational material.	1 hypertonie-spezifische Studie mit komplexer Intervention, die Schulung beinhalten

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- encouraged to bring all empty blisters and boxes of antihypertensive medication to clinic visits for recycling and to verify compliance with therapy. **Cotrol:** regular care at a traditional hospital clinic without a hospital pharmacist. **Ergebnisse**: - improved primary outcome of proportion of patients with BP controlled to target - reduced proportion of patients with low medication adherence as measured by a 5 item questionnaire. - medical therapy advice from pharmacists to physicians might have contributed to the improved BP control in addition to the improved adherence, although authors report that there were no marked differences compared with control group regarding therapy changes.	
Glynn LG. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev 2010(3):CD005182. dx.doi.org/10.1002/14651858.CD005182.pub4. [46] https://www.ncbi.nlm.nih.gov/pubmed/20238338.	2010	Critically low	**Fragestellung:** 1) Evaluate which models of care are effective in improving “control” of high blood pressure; 2) Evaluate the effectiveness of reminders on improving the follow-up of patients with hypertension. **Suchzeitraum:** bis 02/2008 **Population:** - adult patients (aged 18 years or over) with essential hypertension - treated or not currently treated with blood pressure lowering drugs - in a primary care, outpatient or community setting **Intervention:** (1) self-monitoring (2) educational interventions directed to the patient (3) educational interventions directed to the health professional (4) health professional (nurse or pharmacist) led care	72 RCTs eingeschlossen educational interventions directed at patients (20 RCTs) - heterogeneous but appeared unlikely to be associated with large net reductions in BP by themselves. - a trend towards improved BP control and this was significant (OR 0.83, 95% CI 0.75 to 0.91), (7 RCTs), n= 7950) educational interventions directed at health professionals (10 RCTs) - not associated with a significant decrease in mean SBP (mean difference -0.4 mmHg, 95% CI -1.1 to +0.2 mmHg) or DBP (mean difference -0.4 mmHg, 95% CI -1.1 to +0.3 mmHg) whilst control of BP produced heterogeneous results (OR ranged from 0.8 to 1.0).	Nur Inhalte zum Thema Schulung dargestellt AMSTAR: 2 kritische Kriterien nicht erfüllt: Protokoll, Publikation bias

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			(5) organisational interventions that aimed to improve the delivery of care (6) appointment reminder systems **Vergleich**: - no intervention or usual care **Studientyp:** RCTs		
Schroeder K. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. Cochrane Database Syst Rev 2004(2):CD004804. [60] https://www.ncbi.nlm.nih.gov/pubmed/15106262.	2004	moderate	**Fragestellung:** - locate and describe studies evaluating interventions aimed at improving adherence to antihypertensive medication - undertake a critical review of quality of the study methods looking in particular at study design and validity - summarise effectiveness of above interventions - indicate areas for future research **Suchzeitraum:** bis 04/2002 **Population:** - Adults with a diagnostic label of essential hypertension (as defined in individual studies) in a primary care, outpatient or other community setting. **Intervention:** to enhance medication adherence, including the following: 1. Education of caregivers and patients (e.g. counselling, health education) 2. Simplification of dosage regimens 3. Involvement of allied health professionals (e.g. nurses, pharmacists) 4. Special monitoring (e.g. vial caps, blood pressure self-measurement) 5. Motivation (e.g. financial incentives, reminder packages, reminder aids including diaries or follow-up appointments) **Vergleich:** - Control groups should either have received no	**Allgemeines:** - 38 studies (n= 15519) - USA (n = 21), Canada (n = 8), Europe (n = 8), Australia (n = 1) and South Africa (n = 1) - Adherence measurement: self-report, direct questioning, pill counts, medication event monitoring system (MEMS®), which logs time and date of each opening of a medication container - follow- up: 2 to 60 months. - quality of included studies: generally low **Kategorien der Interventionen:** **(ii) patient education:** - **educational programme** via slides, audiotape and booklet, group education, written educational material, **education via visual aids**, lecture, discussion and knowledge test - seemed largely unsuccessful. - 1 trial (n=110) improved adherence (93 vs. 69 %) with no reported effect on BP. This study used group education in groups of 15 people over 90 minutes and additional postal information leaflets at 1, 3 and 5 months. **(iv) complex health and organizational interventions** - **combination of home visits, education and special dosing devices** improved adherence in a small trial of 16 patients (92% vs. 71%) - strategy **involving educational leaflet**, telephone reminder, mailed reminder and educational newsletter was successful in both previously treated hypertensives ('medication possession ratio' 82 % vs. 48 % and those who were newly diagnosed (93% vs 52%)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			intervention or "usual care" and have similar characteristics as the intervention groups. **Endpunkte:** - Adherence to medication (including any definition of adherence and noting how this was defined and measured in each study) - BP change in mmHg or change in BP control according to criteria used in each individual RCT **Studientyp:** RCTs		

7.4 Telemedizin in Diagnostik und Monitoring

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [A] **Evidence review for diagnosis** [26] https://www.nice.org.uk/guidance/ng136/evidence/a-diagnosis-pdf-6896748206 (frei verfügbar)	2019	low	**Fragestellung:** In people with suspected hypertension, which test is most accurate in identifying whether hypertension is present, as indicated by the reference standard, ambulatory blood pressure measurement? **Suchzeitraum**: bis 10/2018 **Population:** Adults (over 18 years) with suspected primary hypertension **Intervention:** Home measurement (HBPM) without telemonitoring, HBPM with telemonitoring, Clinic or office measurement (CBPM), Pharmacy measurement **Reference standard:** ABPM (daytime or 24 hour) **Endpunkte:** Critical: Sensitivity, Specificity, Raw data to calculate 2x2 tables to calculate sensitivity and specificity Important: AUC, Likelihood ratios, Predictive values **Studientypen**: Cross-sectional, diagnostic accuracy observational cohort studies, SRs of observational cohort	**Baseline-Informationen** - 13 Studien identifiziert, 11 für Evidenzsynthese nutzbar - 3 diagnostic tests evaluated **Art der Blutdruckmessung/ des Telemonitorings** - siehe Appendix D (S. 61f/104) o. Detailaufbereitung **Home BP measurement with telemonitoring:** - 3 studies, n=539: specificity 63%, sensitivity of 80% diagn. threshold ≥135/85 mmHg (Very low quality)	
Hypertension in adults: diagnosis and management [B] **Evidence review**	2019	low	**Fragestellung:** In adults with treated primary hypertension, what is the best method of measuring blood pressure (home, ambulatory or clinic measurement) to assess the response to treatment and prevent cardiovascular events? **Suchzeitraum:** bis 10/2018	**Baseline-Informationen:** - 8 Studien eingeschlossen, 7 open label RCTs, 1 IPD - Form der Blutdruckmessung und des Telemonitorings siehe Detailauswertung **Home monitoring with telemonitoring versus home monitoring without telemonitoring** (McManus, 2018)	folgende EP nicht extrahiert: - proportion not meeting target - definded daily dose - number of visits

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
for monitoring [39] https://www.nice.org.uk/guidance/ng136/evidence/b-monitoring-pdf-6896748207 (frei verfügbar)			**Population:** Adults (> 18 y) with treated primary hypertension **Intervention:** Different methods of measuring blood pressure followed by appropriate treatment based on the blood pressure measurement (test plus treatment): HBPM without telemonitoring, HBPM with telemonitoring, ABPM, Clinic/office measurement (CBPM), Pharmacy measurement **Vergleich:** against each other **Endpunkte:** ≥12 months. Where multiple time points reported within study, longest time point only will be extracted *Critical:* All-cause mortality, Health-related quality of life, Stroke (ischaemic or haemorrhagic), Myocardial infarction *Important:* Reduction in clinic BP, Proportion of people controlled to a target, Average daily dose of antihypertensive medication, Average number of visits, Intolerance to device, Hypotension (dizziness), Combined CV-disease outcomes in absence of MI and stroke data, Coronary heart disease outcome in the absence of MI data **Studientypen:** RCT, SR, Non-randomised studies in the absence of RCT and SR evidence	- **CV-events**: 3,3% vs. 3,7%, RR 0.91 (0.41; 2.04), 1 study, n= 658, very low - **dizziness:** 22,1% vs. 15,4%, RR 1.43 (1.03; 1.98), 1 study, n= 650, Very low **Home monitoring with telemonitoring versus clinic monitoring** - **all-cause mortality:** 0,81% vs. 0%, Peto OR 7.45 (0.46; 119.44), 1 study (Green 2008), n= 493, Very low - **CV-events:** 2,6% vs. 1,69%, RR 1.43 (0.66; 3.08), 2 studies (Green 2008, McManus 2018), n= 1173, Very low - **reduction in SBP and DBP:** Risiko der Kontrollgruppe nicht verfügbar, 3 studies, n= 2357, Very low - **quality of life (general scale, 0-100, higher is better):** 66,6 (20,9) vs. 66,7 (20,4); MD -0,1 (95%KI -3,75; 3,55), 1 Study (Green 2008), low - **dizziness:** 22,1% vs. 17,5%; RR 1.26 (0.93 to 1.71), 1 study (McManus), n=674, very low. **Home monitoring with telemonitoring and pharmacist care versus clinic monitoring 1 study, n=484** (Green 2008)**:** - **systolic blood pressure:** mean change in SBP in control -5.3 mmHg**,** MD in intervention 8.90 lower (11.43 to 6.37 lower) low **- quality of life** (general subscale, 0-100, high is good): mean in control 66.7; MD in intervention 0.10 lower (3.9 lower to 3.7 higher), low - **non-fatal CV-events** 1,3% vs. 0,81%, RR 1.56 (0.26 to 9.27), Very low - **all-cause mortality:** 0,42% vs. 0%, Peto OR 7.71 (0.15 to 388.76), very low - **diastolic blood pressure:** mean change in DBP in control -3.5 mmHg, MD in intervention 3.50 lower (4.91 to 2.09 lower), low **Home monitoring with telemonitoring and pharmacist care versus home monitoring with telemonitoring 1 study (Green 2008), n=483** **- all-cause mortality:** 0,42 % vs. 0,81%, RR 0.52 (0.05 to 5.69), very low	- mean number of antihypertensive drugs

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- **non-fatal CV events:** 1,3% vs. 1,6 %, RR 0.78 (0.18 to 3.44), very low - **quality of life** (general subscale, 0-100, high is good): mean in control was 66.6, mean in the intervention 0.00 higher (3.85 lower to 3.85 higher), Low to very low), low - **systolic blood pressure:** mean change in control -8.2mmHg, MD in intervention was 6.00 mmHg lower (8.53 to 3.47 lower), low - **diastolic blood pressure:** mean change in control -4.4mmHg, mean change in intervention 2.60 mmHg lower (4.01 to 1.19 lower), low **Home monitoring (with self-titration) and telemonitoring versus clinic monitoring, 1 study (McManus 2010), n= 480** **- quality of life (EQ-5D):** mean in control 0.838, MD in intervention 0.01 lower (0.06 lower to 0.03 higher), Low - **change in systolic blood pressure:** mean in control 140.3mmHg, MD in intervention 5.60 lower (8.91 to 2.29 lower), Low - **diastolic blood pressure:** mean in control 79.8mmHg, MD in intervention 2.30 lower (4.41 to 0.19 lower), low	

Detailaufbereitung: Diagnostik

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
Gill 2017 Querschnitt-studie	551	Hypertensive people recruited from primary care	**1. Index test: HBPM (with telemonitoring).** - Threshold >135/85 mmHg - Participants fitted with device - Home measurements: 2x/morning and evening for 1 week, - first days readings discarded - mean of remaining readings calculated. - minimum of 12 readings were considered valid if there were ≥ 4 days readings using average except the 1st day's readings.	**Daytime ABPM** - ambulatory monitor - Readings: half-hourly intervals during day (07.00-23.00h); hourly overnight - mean daytime BP calculated. - ABPM readings: valid if there were ≥ 14 daytime (07.00-23.00h) readings/person - Threshold >135 mmHg SBP/85 DBP	Keine weiteren Angaben	Unclear if participants were taking antihypertensive medication
Mansoor 2004 Querschnitt-	48	People referred to health centre	**HBPM (with telemonitoring)** - taught by nurses: measure BP and check devices' accuracy.	**daytime ABPM** - device. - studied on a typical workday	Index Test - trans-telephonic BP device that	Unclear if participants were already diagnosed

Primärstudie	n	Population	Indextest	Referenztest	Telemonitoring	Kommentar
studie		with an office BP >140/09 mmHg	- sit quietly for 5 minutes beforehand - large cuff used for mid-arm circumference >34cm. - 3 readings 07.00-22.00h for 7 days. - device set to allow readings at 1-minute intervals - Threshold SBP >135 mmHg.	- ≥ 75% of readings had to be valid for a participant to be included, with < 3-hour gap without a reading/hour - Participant diaries: check sleep times, calculate nighttime averages. - Threshold >135 mmHg SBP or >85 DBP daytime readings.	transmitted data over analogue telephone lines.	with hypertension
Nunan 2015 Querschnitt-studie	247	SBP between 130–179 mmHg	**HBPM (with telemonitoring):** - 2-7 day; 1-5 day; 2-5 day or 1-5 day measurement - 5minute seated test: identify which arm should be used for HBPM. - non-dominant arm was used (if difference of ≥ 10 mmHg SBP between arms, highest reading used) - 6 sequential measurements separated by a 1-minute rest using same device. - self-monitored BP daily for 28 days - 2 readings morning and 2 evening - 1-3 minute gap between 1st and 2nd and following a 5 minute seated rest - Threshold 135/85 mmHg.	**Daytime hour ABPM** - undertaken after index test - using clinically validated monitor - 07.00-23.00h: readings half-hourly - 23.00-07.00h: readings hourly - Threshold 135/85 mmHg.	Indextest: - automated sphygmomanometer paired to mobile phone via Bluetooth - transmit BP readings securely to a dedicated web database. - Email alerts automatically generated for critically high or low BP values.	Participants already diagnosed with hypertension or receiving antihypertensive treatment were excluded

Detailaufbereitung: Monitoring

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
Green 2008 RCT	778	Adults without Type 2 diabetes Mean age =59.1y (SD =8.5y)	**HBPM with telemonitoring:** - device used - BP measurement for ≥2 days/week with a minimum of 2 measurements at a time - duration not specified - HBPM target of 135/85mmHg, - CBPM target of 140/90mmHg. - Readings sent via email. - Number of GP visits or communications not specified. **HBPM with telemonitoring and pharmacist care:** - assigned to home BP monitoring and Web training plus pharmacist care	**Usual care** - told their BP was not in control - encouraged to work with their physician to improve it. - No further details given: number of GP visits and communication.	Downgraded for intervention indirectness as it was comparing with usual care not clearly stating clinic measurement

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
			- same strategy as HBPM with telemonitoring + a pharmacist assisting them to improve their BP through telephone calls. - HBPM target of 135/85mmHg, - CBPM target of 140/90mmHg. - communication every 2 weeks until BP was controlled. - Number of GP visits not specified.		
Logan 2012 RCT	110	Adults with diabetes Mean age =62.9 y (SD=8.4 y)	**HBPM with telemonitoring:** - Validated Bluetooth-enabled home BP device - Guideline target of <130/80mmHg. - readings automatically transmitted by smartphone to application servers. - Messages: if BP fell outside target range - to take additional BP readings, - were then used to provide advice on urgency to make a follow-up visit with their physician. - No further details: number of measurements, GP visits or how often measurements were taken.	**HBPM without telemonitoring:** - Subjects issued with an identical appearing home BP device - without built-in Bluetooth capability for use during the study. - No further details: GP visits, communications or how often measurements were taken.	Downgraded for population indirectness, as it did not specify type of diabetes present
McManus 2010 RCT	527	Adults with diabetes (n=35) Mean age =66.4 y (SD=8.8 y)	**Home monitoring (HM) with telemonitoring:** - 2 self-measurements each morning - 5-min interval, 2nd reading acted upon - validated automated sphygmomanometer - transmit BP readings to research team by means of an automated modem device - connected to sphygmomanometer and plugged into a telephone socket. - If 2 consecutive months of readings above target: make medication changes in accordance with titration schedule without seeing family doctor. - if BP remained above target after 2 changes: returned to family doctor for a further titration schedule - Home targets for people without diabetes: 130/85mmHg - Home targets for people with diabetes: 130/75mmHg - Monthly summaries of each participant's BP readings sent to their family doctor. - Number of GP visits not stated.	**Clinic monitoring:** - review by their family doctor. - Number of GP visits not stated. - No specific instructions to the clinicians about the content of this visit other than to review medication. - care was at the discretion of the family doctor. - No further details given for communications and targets were not specified.	Downgraded for population indirectness, as it did not specify type of diabetes Participants receiving more than 2 antihypertensive drugs at baseline were excluded

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
McManus 2018 RCT	1182	Adults with diabetes (n=108) Mean age =66.93 y (SD=9.43 y)	**HBPM with telemonitoring:** - readings via a simple free SMS text-based telemonitoring service with web-based data entry back up. - non-dominant arm - twice each morning and evening, - first week of every month using standard recommendations. - make contact with practice if average BP was > target, and presented readings to attending clinicians via a web interface. - clinicians: review readings on a monthly basis. - BP targets at home: <135/85 mmHg < 80 y, <145/85 mmHg ≥80 y, and <135/75 mmHg for those with diabetes. - Clinicians: freedom to adjust antihypertensive and other medication as they sought fit - No further details given on number of GP visits.	**Clinic monitoring:** - Participants managed with titration of antihypertensive treatment based on CBPM at discretion of attending health-care professional. - clinicians: review participants as often as they wished. - BP targets at home: <135/85 mmHg < 80 y, <145/85 mmHg ≥80y, <135/75 mmHg for those with diabetes. - Clinicians: complete freedom to adjust antihypertensive and other medication as they sought fit - No further details given on number of GP visits or communications.	Downgraded for population indirectness, as it did not specify type of diabetes present
Stergiou 2014 RCT	145	Adults with diabetes (n=145) Mean age=50.75 y (SD=10.3 y)	**HBPM without telemonitoring** - validated oscillometric devices with automated memory - during 12-month follow-up: Treatment titration based on home BP measurements. - Target of average home BP <135/85 mmHg for low/moderate-risk participants and <125/80 mmHg for high-risk participants. - Treatment titration: at 4-week intervals until pre-set BP goal was reached. - treated 12 months: aim to reach pre-set BP goals. - Controlled hypertension = home BP levels at pre-set goal in 2 visits 4 weeks apart. - No details: number of GP visits, communication or number of measurements.	**Ambulatory and clinic monitoring** - ABPM on routine workday at 20-minute interval for 24 h - validated oscillometric devices - during 12-month follow-up: Treatment titration made on CBPM and ABPM - Target: CBP <140/90 mmHg and awake ABP <135/85 mmHg for low/moderate-risk people and <130/80 mmHg and <125/80 mmHg for high-risk people. - Treatment titration: at 4-week intervals until the pre-set BP goal was reached. - treated for 12 months: aim to reach pre-set BP goals. - No details: number of GP visits, communication or number of measurements.	Downgraded for population indirectness, as it did not specify type of diabetes present
Tucker 2017 Systematic review und Individual-daten-Metaanalyse	3123	Adults	**HBPM with telemonitoring** - Self-monitoring without medical professional input (that is, by participant with or without carer support) - validated monitor - with or without other co-interventions - comparator group had organised self- measurement of BP. - Targets ranged from 120/75-140/90 from home and from 130/80- 140/90 for clinic. - Number of readings/session: 1- 3.	**Usual care** - No details about usual care. - Targets ranged 120/75 - 140/90 from home and from 130/80 - 140/90 for clinic. - No details: number of GP visits or communication.	IPD Downgraded for intervention indirectness and for population indirectness, as it was comparing with usual care

Primärstudie	n	Population	Intervention	Vergleich	Kommentar
			- Self-monitoring: daily for 1 week every 2 months-daily for 1st week of each month. - No details: number of GP visits or communication.		not clearly stating clinic measurement and did not specify type of diabetes present

7.5 Telemedizin

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Palmer MJ. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev 2018; 6(6):CD012675. [41] https://www.ncbi.nlm.nih.gov/pubmed/29932455.	2018	high	**Fragestellung** To establish the effectiveness of interventions delivered by mobile phone to improve adherence to medication prescribed for the primary prevention of CVD in adults. **Suchzeitraum**: 14 July 2017 **Population**: - adults (≥ 18 years) - prescribed medication for primary prevention of CVD. - not had a prior CVD event: previous myocardial infarction, stroke, revascularisation procedure (coronary artery bypass grafting or percutaneous coronary intervention), angina, angiographically defined CHD. - only trials in which at least 75% of participants met the criteria for primary prevention were included. **Studientypen**: - RCT **Intervention:** - delivered wholly or partly by mobile phones to improve adherence to CV-medications prescribed for the primary prevention of CVD. - minimum of one-year follow-up in order that outcome measures related to longer-term, sustained medication adherence behaviours and outcomes. **Vergleich:** - comparators were usual care or control groups receiving no mobile phone-delivered component of the intervention.	**Allgemeines**: - 2 von 4 eingeschlossenen Primärstudien betrachten Patienten mit Hypertonie - Dauer beider Studien: 1 Jahr **Logan 2012** - n= 110 - with diabetes mellitus, with uncontrolled systolic hypertension, defined as a mean daytime SBP of >130 mmHg on ABPM - mean age: 62,9y - primary prevention: 79% - setting: offices or clinics of physicians practicing - **both groups**: - taught how to measure their BP correctly, - validated home BP monitoring device with appropriate-sized upper arm cuff, - booklet with detailed information on self-measurement of BP, treatment of hypertension and goals of therapy - primary care physician was given outline of study's objectives and BP treatment goal, asked to provide relevant medical information and given a copy of the 24-hour ABPM report. - treatment decisions (medication adjustments and changes in lifestyle) made by participant's primary care physician - **Intervention**: BP monitoring and feedback messages delivered via smartphone (self-care message) - **Vergleich:** did not received feedback via smartphone.	Mobile phone-based interventions Auch „ongoing studies“ berichtet: Fransen 2017, ggf. Jha 2017, Xu 2017

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				>> did not report on adverse events >> **Blutdruck**: - greater reduction in SBP and DBP in intervention group compared with control group at 12 months for: 24-hour BP and daytime ABPM (mean between-group difference in change (SE): - 24-hour SBP: -6.8 mmHg (SE 2.4); - 24-hour DBP: -3.6 mmHg (SE 1.3); - daytime SBP: -7.10 mmHg (SE 2.3); - daytime DBP: -3.9 mmHg (SE 1.3)). - weak evidence of a benefit for change in nighttime BP (SBP: -4.7 mmHg (SE 2.8); DBP: -2.3 mmHg (SE 1.6)) (n= 105) >> adherence rate: 65.4% (SD 30) to home blood pressure measurement schedule (≥ 8 readings/ weeks) in intervention group **Bobrow 2016** - n= 1372 - mean age: 54,4 y - primary prevention: 78.3% of participants - setting: outpatient chronic disease service in a single, large, public sector clinic - **Group 2:** 'informational SMS texting: text messages to motivate collecting and taking medicines and to provide education about hypertension and its treatment. - **Group 3**: 'interactive SMS texting' group: same messages as the information-only group but could also respond to selected messages using free-to-user "please call me" requests. - **Vergleich (group 1):** written information about hypertension and healthy living and continued to receive care from clinic. only received the texts sent to all trial participants, which were sent no more frequently than 1 text every 4 weeks **>> Blutdruck** - greater reduction in mean SBP from baseline to 12-month follow-up in intervention group receiving information-only text messages vs. control group (MD -2.2 mmHg, 95% CI -4.4; 0.00), - no difference between intervention group receiving interactive text messaging and control group (MD -1.6 mmHg, 95%CI -3.70; 0.50)	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- proportion of participants achieving SBP and DBP < 140/90 mmHg: benefit for both - information-only text messaging intervention group (65% with information-only text messaging vs. 58% with control; OR 1.42, 95% CI 1.03; 1.95) - interactive text messaging group (65% with interactive text messaging vs. 58% with control; OR 1.41, 95% 1.02; 1.95), compared with control group receiving usual care **>> adverse events:** - reported no adverse events attributable to the intervention (low quality of evidence) **>> Euro-Qol 5-Dimension Index:** - no effect of information-only text messages (median Diff. 0.01, quartiles 1-3: -0.01; 0.02) or interactive text messages (median Diff.: 0.003, quartiles 1-3: -0.02; 0.02) compared with control **>> Fatal cardiovascular events** - 2 participants in the information-only text messaging group died due to ischaemic heart disease, - 2 participants in the interactive text messaging group died due to congestive cardiac failure - no deaths in the control group known to be due to CVD. - lost to follow-up due to reason of 'lost contact': (usual care arm: n= 14; information SMS arm: n=7; interactive SMS arm: n= 7) - possible that differential lost to follow-up due to lost contact could have underestimated deaths, including those due to CVD in usual care arm.	
Posadzki P. Automated telephone communication systems for preventive healthcare and management of long-term conditions.	2016	high	**Fragestellung:** - assess the effects of ATCS for preventing disease and managing long-term conditions on behavioural change, clinical, process, cognitive, patient-centred and adverse outcomes. **Suchzeitraum:** 1980 and June 2015. **Population:** - consumers, including carers, who received ATCS for prevention or management of long-term conditions, regardless of age, sex, education, marital status, employment status, or income. - ≥1 concurrent long-term conditions (i.e. multimorbidity).	**Allgemeines:** 132 Studien zu verschiedenen Krankheitsbildern identifiziert **Baseline-Informationen der hypertoniespezifischen Studien:** **-** N= 5 - 1 Honduras/Mexico (Piette 2012), 4 USA (Bove 2013; Dedier 2014; Harrison 2013; Magid 2011). - mean age: 58 years - 66 years - Bove 2013, Magid 2011, Harrison 2013: diabetes mellitus	Automated telephone communication systems Siehe S. 29/469 S. 55/469 S. 96/469

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Cochrane Database Syst Rev 2016; 12(12):CD009921. [42] https://www.ncbi.nlm.nih.gov/pubmed/27960229.			- in all settings. **Studientyp:** - Randomised, cluster- and quasi-randomised trials, interrupted time series and controlled before-and-after studies - all settings, for all consumers/carers, in any preventive healthcare or long term condition management role **Intervention:** - ATCS interventions **Kontrolle**: - with any control or another ATCS type	- Bove 2013 and Magid 2011: complex interventions (ATCS + system with additional communicative (and in the case of Bove 2013, also supplementary) functions vs. usual care. - Bove 2013: sphygmomanometer, weighting scale, pedometer - Magid 2011: patient education, home BP monitoring, clinical pharmacist management of hypertension with physician oversight in addition to usual care. - Piette 2012: ATCS system with communicative functions to primary care and education. - Dedier 2014: IVR system underpinned by social cognitive theory vs. primary care and education, - Harrison 2013: unidirectional ATCS vs. usual care. Interventions: aimed at planning action and setting goals, prompting self-monitoring of behavioural outcome, providing rewards contingent on effort or progress towards behaviour, setting graded tasks and tailoring, prompting self-monitoring of behaviour and providing follow-up prompts or providing feedback on performance. - Call duration: up to 10 min (weekly) (Magid 2011 and Dedier 2014) - Call frequency: biweekly in Bove 2013. **Ergebnisse** - **SBP nach 6 Wochen:** 3 trials, found that ATCS probably reduced slightly SBP vs. usual care with or without information (MD -1.89 mmHg, 95%KI -2.12; -1.66; moderate certainty evidence; 3 Studien, I2 = 0%, n= 65256). - **DBP nach 14 Wochen:** no effect for ATCS vs. usual care, MD 0.02 (95%KI -2.62, 2.66), low certainty evidence, 2 Studien, I^2= 72%, n= 65056 - **Health status**: ATCS Plus vs. enhanced usual care (+ information): Plus may have slightly improved overall health status (mean (SE) 2.5 (0.09) vs. 2.1 (0.08), where 1 = poor and 5 = excellent) at 6 weeks (low certainty evidence). - No studies reported **adverse events**.	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Flodgren G. Interactive telemedicine: Effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2015(9):CD002098. dx.doi.org/10.1002/14651858.CD002098.pub2. [44] https://www.ncbi.nlm.nih.gov/pubmed/26343551.	2015	**moderate**	**Fragestellung:** To assess the effectiveness, acceptability and costs of interactive TM as an alternative to, or in addition to, usual care (i.e. face-to-face care, or telephone consultation). **Suchzeitraum:** up to June 2013 **Studientyp:** RCTs **Intervention:** - interactive TM that involved direct patient-provider interaction and was delivered in addition to, or substituting for, usual care compared with usual care alone, to participants with any clinical condition. - telephone only interventions and wholly automatic self-management TM interventions excluded **Popuation:** 1. Patients receiving interactive TM from any qualified healthcare practitioner, compared with those receiving usual care. 2. Healthcare professionals from any discipline providing patient care through interactive TM.	**Allgemeines**: - 4 studies recruited patients (n = 1 073) with hypertension - Monitoring of a chronic condition to detect early signs of deterioration and prompt treatment and advice (N= 3) - Education, advice for self-management, and support (N= 1) - Remote monitoring with automatic review of data and a system for alerting healthcare professional of out of range values (N= 1) **Blood pressure measurement** **Artinian 2007**; n= 387: - greater decrease in mean SBP in TM delivered in addition to usual care, as compared with usual care alone at 12 months - Mean office SBP at 12 months: TM:145.0 (21.0), n=167; UC: 148.1 (22.3), n=169 - Mean office DBP at 12 months: TM: 83.8 (12.1); UC: 83.5 (13.6)) **Madsen 2008;** n= 236: - no differences in diastolic daytime and night time ABPM between groups at 6 months but did report that a greater proportion of intervention patients achieved a target BP at 6 months. Daytime ABPM at 6 months: - Systolic: TM: 141.1 (11.5), n=113; UC: 142.7 (13.3), MD (95%CI): -2.3 (-6.1; 1.5), - Diastolic: TM: 85.0 (7.1); UC: 85.1 (8.2); MD (95%CI): -0.8 (-3.1; 1.4), Nighttime ABPM at 6 months: - Systolic: TM: 122.6 (14.4); UC: 125.2 (16.0); MD (95%CI): -1.0 (-5.0; 3.0), - Diastolic: TM:71.8 (7.9); UC: 72.6 (8.5), MD (95%CI): -0.7 (-2.9; 1.6) **Rogers 2001;** n = 121: - greater decrease in 24-hour systolic and diastolic ABPM and a greater change in mean BP in the TM group at 8 weeks, as compared with control. - Mean change in arterial BP at 8 weeks: Mean diff (95% CI):4.1 mmHg (0.91; 7.38)	Interactive telemedicine S.22/583 S. 525/583

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- Mean change in systolic ABPM at 8 weeks: Mean diff. (95%CI): 4.8mmHg (0.10; 9.37), - Mean change in diastolic ABPM at 8 weeks: Mean diff. (95%CI): 4.1mmHg (0.93; 7.13), n= 60 in each group **Parati 2009;** n = 329: - monitoring study with automated review of data with alerts: greater proportion of TM participants achieving daytime normalisation of arterial BP as compared with control. - Percent of patients with daytime arterial BP normalisation 3 at 24 weeks: TM:62%, n= 216; UC: 50%, n= 113 **Quality of life** **Madson 2008**: Mean SF-36 domain scores at 12 months: Physical functioning: TM: 88.2 (14. 0); UC: 84.2 (19.2) Role physical: TM: 80.0 (36.4); UC: 77.3 (36.2) Bodily pain: TM: 85.3 (20.2);UC: 78. 3 (26.4), General health:TM: 77.1 (15.4);UC: 73. 5 (17.4), Vitality: TM: 68. 8 (17.6); UC: 67.8 (21.8), Social functioning: TM: 89.5 (18.4); UC: 91.6 (17.8), Role emotional: TM: 83. 8 (32.4); UC: 84.5 (27.8), Mental health: TM: 79.3 (16.4);UC: 81. 5 (15.7), TM: n=105;UC: n= 118 **Parati 2009:** QOL (Quality Of Life Assessment in Hypertensive Patients questionnaire 4): End of study: UC: 38.3(5.4); TM: 38.4(4.6) End of study – baseline difference: UC: 0.1(3.9); TM: 0.7 (4.3), P End of study – baseline difference (%): UC: 0.5(10.4); TM: 2.6(12.7)	
Jongh T de. Mobile phone messaging for facilitating self-management of long-term illnesses.	2012	high	**Fragestellung** - assess effects of mobile phone messaging applications designed to facilitate self-management of long-term illnesses, in terms of impact on health outcomes and patients' capacity to self-manage their condition.	**Allgemeines:** - 4 RCTs (n= 182) eine hypertoniespezifische Studie: Marquez Contreras 2004 - Population: not well controlled with monotherapy were started a combination of a single-dose angiotensin II antagonist and a diuretic.	Mobile phone messaging

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Cochrane Database Syst Rev 2012; 12(12):CD007459. dx.doi.org/10.1002/14651858.CD007459.pub2. [43] https://www.ncbi.nlm.nih.gov/pubmed/23235644.			- Secondary objectives: assessment of user evaluation of intervention; health service utilisation and costs; and possible risks and harms associated with intervention. **Suchzeitraum** bis 06/2009 **Population** - regardless of age, gender and ethnicity, as well as all types and stages of diseases. - primary care settings (services of primary health care), - outpatient settings (outpatient clinics), - community settings (public health services, anywhere where a person can use a mobile phone) - hospital settings. **Studientyp** - RCTs, quasi-randomised controlled trials (QRCTs), controlled before-after (CBA) studies, or interrupted time series (ITS) studies with at least 3 time points before and after intervention. **Intervention**: - studies where it was possible to assess effects of mobile phone messaging independent of other technologies or interventions.	- aim of the messages: provide information on hypertension; promote compliance, good health and dietary habits; and remind patients to take medication **Ergebnisse**: - compared SBP and DBP in groups of patients with and without text message support, at baseline, 1, 3, 6 months after initiation of the study. - BP levels at 6 months: comparable in the two groups (SBP MD 1.10, 95% CI -4.37; 6.57); DBP MD 1.84, 95% CI -2.14; 5.82). - Achievement of good BP control (defined by BP < 140/90 mm Hg in patients without diabetes and 130/85 mm Hg in patients with diabetes) at the end of the study: not statistically different between the control and intervention (RR of not achieving BP control 0.73, 95% CI 0.41 to 1.29). - body weight at 6 months: comparable between groups (MD -2.76 (95% CI -8.17; 2.65). - evidence is considered to be of moderate quality - observed effect sizes are likely to be affected by further research - marginally significant increase in rate of compliance of intervention group at six months (MD 8.90, 95% CI 0.18; 17.62)	
Devi R. Internet-based interventions for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2015(12):CD009386. dx.doi.org/10.1002/14651858.CD009386.pub2. [45] https://www.ncbi.nlm.nih.go	2015	moderate	**Fragestellung** - determine effectiveness of Internet-based interventions targeting lifestyle changes and medicines management for secondary prevention of CHD. **Suchzeitraum:** bis 01/2015 **Studientyp:** RCTs **Intervention:** - evaluating Internet-delivered secondary prevention interventions aimed at people with CHD. **Population:** - Adults (18 years of age or older) - with CHD, including those having experienced a myocardial infarction, a revascularisation procedure (including stent, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty), those with angina, or angiographically defined CHD	**Allgemeines**: - 18 trials met our inclusion criteria. - 11 studies are complete (1392 participants), 7 are ongoing. - 7 interventions are broad, targeting the lifestyle management of CHD, and four focused on physical activity promotion. - length of the programmes: 6 weeks - 1 year. - comparison group in trials was usual care (n = 6), minimal intervention (n = 3), or traditional cardiac rehabilitation (n = 2). - 1392 people with coronary heart disease were recruited. - average age 54.9 to 66.27 years. - majority of people recruited were men. **Ergebnisse:** - no effects of Internet-based interventions for all-cause mortality (OR 0.27, 95% CI 0.04; 1.63; n = 895; N = 6; low-quality evidence).	Internet-based interventions **Frage an AG:** Population hat bereits CV-Folgeerkrankungen Sind die Ergebnisse für die NVL Hypertonie anwendbar

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
v/pubmed/26691216.				- one case of CV-mortality in a control group (n = 895; N = 6). - No incidences of non-fatal re-infarction reported across any of the studies. - no effects for revascularisation (OR 0.69, 95% CI 0.37 to 1.27; n = 895; N = 6; low-quality evidence). - 7 studies measured SBP and DBP; did not pool data due to substantial heterogeneity. - SBP: 2 studies showed a reduction with the intervention, but the remaining studies showed no effect. - DBP: 2 studies showed a reduction with the intervention, 1 study showed an increase with the intervention, and the remaining four studies showed no effect. - 5 trials measured HRQOL:. We could draw no conclusions from 1 study due to incomplete reporting; 1 trial reported no effect; 2 studies reported a short- and medium-term effect respectively; and 1 study reported both short- and medium-term effects	

7.6 Gewichtsreduktion

Gesundheitsberichterstattung

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Schienkiewitz A, Mensink GBM, Kuhnert R. Übergewicht und Adipositas bei Erwachsenen in Deutschland. Journal of health monitoring 2017; 2(2):21–8. DOI: 10.17886/RKI-GBE-2017-025. *[89]*	2017	RKI	- „Gesundheit in Deutschland aktuell“ (GEDA-2014/2015-EHIS) - Erhebungsmethode: schriftlich oder online Fragebogen - Grundgesamtheit: Bevölkerung ab 18 Jahren mit ständigem Wohnsitz in Deutschland - Stichprobe: Einwohnermeldeamt – zufällig ausgewählte Personen aus 301 Gemeinden in Dtld. - Untersuchungszeitraum: November 2014 – Juli 2015 - n= 23.791 Personen ab 18 Jahren - 13.006 Frauen, 10.785 Männer - gültige Angabe zu Körpergewicht und -größe. - Gewichtungsfaktor: korrigiert Abweichungen der Stichprobe von Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung **Klassifikationsschema der WHO [1] Erwachsener:**	- 46,7 % (95% KI 45,6 – 47,9) der Frauen und 61,6 % der Männer einen BMI von mehr als 25 kg/m2 auf und sind damit übergewichtig oder adipös. - Prävalenz von Übergewicht einschließlich Adipositas steigt mit zunehmendem Alter **Frauen**: - 45 – 64 Jahre: 50,1% (95% KI 48,4 – 51,9) - ≥ 65 Jahre: 58,9% (95% KI 56,5 – 61,3) **Männer**: - 45 – 64 Jahre: 70,1% (95% KI 68,3 – 71,7) - ≥ 65 Jahre: 71,3% (95% KI 69,2 – 73,2) - Prävalenz von Übergewicht einschließlich Adipositas in den lag 2012 für Frauen bei 45,8 % und für Männer bei

Referenz	Jahr	Quelle	Methodik	Ergebnisse
			- BMI < 18,5 kg/m2 untergewichtig. - BMI 18,5 -< 25 kg/m2 Normalgewicht, - BMI 25 - < 30 kg/m2 Übergewicht - BMI ≥ 30 kg/m2 Adipositas definiert **Limitation:** - Selbstangaben - BMI eher unterschätzt: da Körpergewicht häufig unter-, die Körpergröße eher überschätzt - auf Gruppenebene korreliert BMI gut mit direkten Messungen zur Bestimmung der Körperfettmasse - Vergleich der aktuellen GEDA 2014/2015-EHIS-Zahlen mit GEDA-Befragungen: Änderung der Verfahren der Stichprobenziehung sowie der Befragungsmodus (Selbstausfüllfragebogen, telefonisches Interview)	59,7 % [12]. **Quellen**: 1. World Health Organization (2000) Obesity: preventing and managing the global epidemic. World Health Organization. Technical Report Series 894. Geneva 12. Robert Koch-Institut (2014) Ergebnisse der Studie „Gesundheit in Deutschland aktuell 2012". Beiträge zur Gesundheitsberichterstattung des Bundes. Robert Koch-Institut, Berlin http://edoc.rki.de/documents/rki_fv/recJuHnzacx8A/PDF/28GsWuNtFjVqY.pdf (Stand: 18.04.2017)

Systematische Übersichtsarbeit

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	
Semlitsch T. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev 2016; 3(3):CD008274. [90] https://www.ncbi.nlm.nih.gov/pubmed/26934541. Semlitsch et al. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database	2016 / 2021	moderate	**Fragestellung:** assess long-term effects of weight-reducing diets in people with hypertension on all-cause mortality, CV morbidity and adverse events (including total serious AE, withdrawal due to AE, and total non-serious AE). **Suchzeitraum:** bis 03/2015 **Population:** - men and non-pregnant women - ≥18 years - essential hypertension (= baseline SBP ≥ 140 mm Hg or baseline DBP ≥ 90 mm Hg or people on antihypertensive treatment). **Intervention:** dietary intervention with intention to reduce body weight **Vergleich:** no dietary intervention to reduce body weight	Im Update der systematischen Übersichtsarbeit von Semlitsch et al. 2021 wurden keine neuen Studien ermittelt und die Schlussfolgerungen gegenüber den vorherigen Versionen nicht verändert: **Allgemeines:** - 8 Studien - parallel and open-label design - n= 2100 - mean age: 45-66 years, - baseline SBP: 128-178 mmHg, baseline DBP: 72-107 mmHg. - Mean treatment duration was 6-36 months. - 8 verschiedene Interventionen: > physicians taught by behavioural psychologist; reduce caloric content without radically changing lifestyle > dietary advice for weight reduction by 2 experienced dietitians: importance of weight reduction for BP control > 8 initial weekly group sessions followed by monthly sessions + individual consultation as needed > energy-restriction: 1000-1500 kcal/day, behavioural modification, choice	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	
Syst Rev. 2021 Feb 8;2(2):CD008274. doi: 10.1002/14651858.CD008274.pub4. [91] https://pubmed.ncbi.nlm.nih.gov/33555049/				of food, physical exercise, medical aspects of overweight and weight reduction (total 40 hours); leaflets (reduction of salt and fat, increase of physical activity); lectures by medical experts; nutritionists interview; laboratory tests > individual dietary counselling (+ spouse); low-calorie diet, increase intake of fish products, vegetables, fibre-rich products (complex carbohydrates); reduction of sugar and saturated fat; target weight reduction: 0.5-1 kg monthly and 0.5 to 2 kg, reduce salt intake > weight-reducing diet, no restriction on salt uptake > weight-reducing diet (goal: 10% of baseline or 4.54 kg, whichever was greater); 10 weekly sessions (in 6 months) + individual or group sessions with nutritionist (every 6 weeks), after 12 months dietary: quarterly basis > achieving + maintaining weight loss of ≥4.5 kg; dietary advice in small groups, change eating behaviours, achieve and maintain reductions; increase physical activity (no detailed information) **Ergebnisse:** **Mortality:** None of the included studies was designed to evaluate the effects of weight loss diet versus no diet on mortality. **Cardiovascular morbidity:** - combined endpoint (necessity of reinstating antihypertensive therapy and cardiovascular complications) after 30 months: HR 0.70 (95% CI 0.57 to 0.87), 1 study, n= 294, zugunsten Interventionsgruppe (nur HR, keine Zahlen pro Gruppe berichtet) **Adverse events** - None of the included studies evaluated the endpoint AE as designed in our protocol - 1 Study (n= 176): reported AE as withdrawals due to need to resume antihypertensive medication: 40.5% (intervention group) vs. 64.7% (control group) **Changes in SBP:** MD -4.5 mm Hg (95% KI -7.2; -1.8), I^2= 21%, 5 studies, n= 731, zugunsten Intervention **Changes in DBP:** MD -3.2 mm Hg (95% KI -4.8; -1.5), I^2= 35%, 5 studies, n= 731, zugunsten Intervention **Body weight**: MD -4.0 kg (95% KI -4.8; -3.2); I^2= 34%, 5 studies, n= 880, zugunsten Intervention	

7.7 Alkoholkonsum

Gesundheitsberichterstattung

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Lange C, Manz K, Kuntz B (2017) Alkoholkonsum bei Erwachsenen in Deutschland: Riskante Trinkmengen. Journal of Health Monitoring 2(2): 66 – 73. DOI 10.17886/RKI-GBE-2017-031 [92] https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsJ/FactSheets/JoHM_2017_02_Alkoholkonsum_Erwachsene.pdf?__blob=publicationFile (frei verfügbar)	2017	RKI	Konsum riskanter Alkoholtrinkmengen = erhöht Risiko von schädlichen Konsequenzen für körperliche und psychische Gesundheit Grenzwerte für riskante Alkoholtrinkmenge: > 10-12 g/d für Frauen und 20-24 g/d für Männer Basis: „Gesundheit in Deutschland aktuell“ 2014/2015-EHIS (GEDA 2014/2015-EHIS): Frequenz und Menge des Alkoholkonsums mittels Instrument aus Europäischen Health Interview Survey (E-HIS) Basis: Daten von 23.561 Personen ab 18 Jahren (12.913 Frauen, 10.648 Männer) >> Selbstangaben der Befragten, wobei sowohl das Erinnerungsvermögen, die richtige Einschätzung von Glasgrößen als auch sozial erwünschtes Antwortverhalten die Ergebnisse beeinflussen können	- niemals Alkohol: 16,9 % (95% KI 15,9 – 17,8) der Frauen und 10,3 % (95% KI 9,6 – 11,2) der Männer - mindestens wöchentlicher Konsum riskanter Alkoholtrinkmengen: 13,8 % (95% KI 13,0 – 14,7) der Frauen und 18,2 % (95% KI 17,3 – 19,1) der Männer. >> Männer konsumieren demnach signifikant häufiger Alkohol in riskanten Trinkmengen als Frauen. - höchste Prävalenz bei 45- bis 64-Jährigen: 17,2 % bei Frauen und 21,7 % bei Männern - Frauen der oberen Bildungsgruppe: höhere Prävalenzen des Risikokonsums als aus der unteren Bildungsgruppe (Ausnahme: 30- bis 44-Jährigen) - Bei Männern zeigt sich in der Altersgruppe ab 65 Jahren das gleiche Bild wie bei Frauen mit höheren Anteilen des Konsums riskanter Trinkmengen in der oberen Bildungsgruppe. - In den Altersgruppen 18 bis 64 Jahre gibt es hinsichtlich des Bildungsstatus keine relevanten Unterschiede im Risikokonsum. - Prävalenzen der Länder unterscheiden sich kaum vom Bundesdurchschnitt.

Systematische Übersichtsarbeiten

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Acin MT. Alcohol intake reduction for controlling hypertension. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD010022. [93]	2020	hoch	**Fragestellung:** assess effect of any intervention to reduce alcohol intake in terms of BP decrease in hypertensive people with alcohol consumption compared to a control intervention or no intervention at all. To determine additional effects related to mortality, major CV-events, serious adverse events or quality of life. **Suchzeitraum**: bis June 2020	Nur eine Studie identifiziert (PATHS 1998). Diese wurde bereits im IQWiG-Report [A05-21E] ausführlich betrachtet.	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010022.pub2/full			**Selection criteria** - RCTs ≥ 12 weeks duration - ≥ 50 subjects per group - quantitative measurement of alcohol consumption and/or biological measurement of the outcomes of interest. - adults (16 years of age or older) - SBP > 140 mmHg and DBP > 90 mmHg - participants with diabetes: SBP ≥ 130 or DBP ≥ 80 mmHg in - any intervention implemented to reduce alcohol intake.		
[A05-21E] Reduktion des Alkoholkonsums bei essentieller Hypertonie - Rapid Report [94] https://iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21e-reduktion-des-alkoholkonsums-bei-essentieller-hypertonie-rapid-report.1126.html (frei verfügbar)	2011	high	**Fragestellung:** Nutzenbewertung von Interventionen zur Reduktion des Alkoholkonsums im Vergleich zu keiner entsprechenden Intervention als nichtmedikamentöse Behandlungsstrategien bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und Kriterien der Blutdruckkontrolle. **Suchzeitraum:** bis 03/2011 **Population:** - erwachsenen Patienten (≥ 18 Jahre) - essenzieller (primärer) arterieller Hypertonie **Intervention/ Kontrolle:** - Intervention zur Reduktion des Alkoholkonsums - intendierte Alkoholkonsum in der Interventionsgruppe niedriger war als in der Kontrollgruppe - In diesen Studien musste im Falle einer Kombinationsbehandlung der Prüfintervention mit einer anderen blutdrucksenkenden Behandlung diese zusätzliche, andere blutdrucksenkende Behandlung auch Bestandteil der Vergleichsintervention sein. - mindestens 24 Wochen - Nicht berücksichtigt: Reduktion des Alkoholkonsums mit einer anderen antihypertensiven	**Allgemeines:** - 2 relevante RCTs identifiziert (Frankreich; USA) - Dauer 2 Jahre. - n= 129 bzw. 266 zumeist männliche Patienten mit Hypertonie mit hohem Alkoholkonsum (etwa 6 bis 7 alkoholische Getränke/Tag). - Patienten mit Alkoholabhängigkeit waren ausgeschlossen **Intervention:** - französischen Studie: im Rahmen der betriebsärztlichen Versorgung durchgeführten Programm zur Reduktion des Alkoholkonsums. Ziel: die bei Studieneinschluss erhöhten Leberenzymwerte (Gamma-GT) zu normalisieren. - Studie USA: langfristig angelegtes kognitives Verhaltenstraining mit psychodynamischen und sozialen Komponenten. Ziel: Konsum halbiert werden oder weniger als 28 g/Tag getrunken werden. - beiden Studien: speziell ausgebildetes Personal, völlige Alkoholabstinenz nicht das Ziel **Alkoholkonsum:** - französischen Studie: Alkoholkonsum sank in Interventionsgruppe nicht statistisch signifikant stärker als in der Kontrollgruppe, - amerikanischen Studie: Teilnehmer tranken in Interventionsgruppe zum Studienende etwa 1,4 alkoholische Getränke weniger pro Tag als in Vergleichsgruppe. **Ergebnisse zu berichtsrelevanten Endpunkten:** potenziell hochverzerrt **patientenrelevante Endpunkte:** Gesamtmortalität, kardiovaskuläre Mortalität und Morbidität, terminale Niereninsuffizienz, gesundheitsbezogene	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Behandlung verglichen wurde (z. B. vs. Diät oder vs. medikamentöse Blutdrucksenkung). **Studientyp:** SR, RCTs	Lebensqualität, unerwünschte Ereignisse: keine oder nur unzureichende Daten aus RCTs, Beurteilung des potenziellen Nutzens oder Schadens nicht möglich ist. **Auswirkungen auf den Blutdruck** - amerikanischen Studie: reduzierter Alkoholkonsum ging nicht mit einer statistisch signifikanten Reduktion des SBP oder DBP einher - französischen Studie: keine statistisch signifikante Reduktion des Alkoholkonsums erreicht, aber eine im Vergleich zur Kontrollgruppe statistisch signifikante Senkung des SBP, jedoch nicht des DBP. **Änderung der antihypertensiven Medikation** - beide Studien: keine wesentlichen bzw. statistisch signifikanten Gruppenunterschiede **Hinweis:** Der grundsätzliche, d. h. von der Behandlung der Hypertonie unabhängige, Nutzen der Therapie einer Alkoholabhängigkeit bzw. eines riskanten Alkoholkonsums wird mit dem Ergebnis des vorliegenden Berichtes keineswegs infrage gestellt.	
Tasnim S. Effect of alcohol on blood pressure. Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD012787. [95] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012787.pub2/abstract	2020	hoch	**Primary objective:** determine short-term dose-related effects of alcohol vs. placebo on SBP and DBP in healthy and hypertensive adults over 18 years of age. **Secondary objective:** To determine short-term dose-related effects of alcohol versus placebo on heart rate in healthy and hypertensive adults over 18 years of age. **Suchzeitraum**: up to March 2019: **Selection criteria** - RCTs - comparing effects of a single dose of alcohol versus placebo on BP or heart rate in adults (≥18 years of age).	**Allgemeines:** - 32 RCTs (n= 767) - nost participants were male (N = 642) and healthy - mean age: 33 years, mean body weight: 78 kilograms. **Ergebnisse der Einzelstudien für Population mit Hypertonie:** **Low-dose alcohol (< 14 g):** keine Studien identifiziert **Medium-dose alcohol (14 to 28 g)** Foppa 2002 (n= 13), cross-over - SBP und DBP jeweils nach 6, 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen Kawano 1992 (n= 13), cross-over - SBP und DBP jeweils nach 6, 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen Kawano 2000 (n= 10), cross-over - SBP nach 6h: MD zugunsten Alkohol gesenkt -16.30 [-25.05, -7.55], Datenqualität sehr gering - DBP nach 6h: MD zugunsten Alkohol gesenkt -11.10 [-16.73, -5.47], Datenqualität sehr gering - SBP und DBP jeweils nach 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen	Subgruppenanalyse für Populationen (Hypertonie/ keine Hypertonie) wurde nicht durchgeführt Herzfrequenz als weiterer Endpunkt erhoben

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Kojima 1993 (n= 21), cross over - SBP nach 6h: MD zugunsten Alkohol gesenkt -18.00 [-26.32, -9.68], Datenqualität sehr gering - DBP nach 6h: MD zugunsten Alkohol gesenkt -12.00 [-17.50, -6.50], Datenqualität sehr gering - SBP und DBP jeweils nach 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen **High-dose alcohol (> 30 g)** Hering 2011 (n= 24), cross over SBP und DBP nach 6h: kein Unterschied in der MD zwischen Gruppen **Ergebnisse für gemischte Population:** **Low-dose alcohol (< 14 g)** - within 6 hours (2 RCTs, N = 28) did not affect BP but did increase HR by 5.1 bpm (95% CI 1.9 to 8.2) (moderate-certainty evidence). **Medium-dose alcohol (14 to 28 g)** - within 6 hours (10 RCTs, N = 149) decreased SBP by 5.6 mmHg (95% CI -8.3 to -3.0) and DBP by 4.0 mmHg (95% CI -6.0 to -2.0) and increased HR by 4.6 bpm (95% CI 3.1 to 6.1) (moderate-certainty evidence for all). - within 7 to 12 hours (4 RCTs, N = 54) did not affect BP or HR. - > 13 hours after consumption (4 RCTs, N = 66) did not affect BP or HR. **High-dose alcohol (> 30 g)** - within 6 hours (16 RCTs, N = 418) decreased SBP by 3.5 mmHg (95% CI -6.0 to -1.0), decreased DBP by 1.9 mmHg (95% CI-3.9 to 0.04), and increased HR by 5.8 bpm (95% CI 4.0 to 7.5). >> certainty of evidence was moderate for SBP and HR, and was low for DBP. - within 7 to 12 hours of consumption (3 RCTs, N = 54) decreased SBP by 3.7 mmHg (95% CI -7.0 to -0.5) and DBP by 1.7 mmHg (95% CI –4.6 to 1.8) and increased HR by 6.2 bpm (95% CI 3.0 to 9.3). The certainty of evidence was moderate for SBP and HR, and low for DBP. - ≥ 13 hours after consumption (4 RCTs, N = 154) increased SBP by 3.7 mmHg (95% CI 2.3 to 5.1), DBP by 2.4 mmHg (95% CI 0.2 to 4.5), and HR by 2.7 bpm (95% CI 0.8 to 4.6) (moderate-certainty evidence for all).	

7.8 Tabakkonsum

Gesundheitsberichterstattung

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Zeiher J, Kuntz B, Lange C (2017) Rauchen bei Erwachsenen in Deutschland. Journal of Health Monitoring 2(2):59–65. DOI 10.17886/RKI-GBE-2017-030 [96] https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsJ/FactSheets/JoHM_2017_02_Rauchen_Erwachsene.pdf?__blob=publicationFile (frei verfügbar)	2017	RKI	„Gesundheit in Deutschland aktuell“ 2014/2015-EHIS (GEDA 2014/2015-EHIS) - Erhebung mit der Frage: „Rauchen Sie?“ - Antwortoptionen: „ja, täglich“, „ja, gelegentlich“, „nein, nicht mehr“, „habe noch nie geraucht“ Kategorisierung: - aktuelle Raucher (täglich oder gelegentlich), ehemalige Raucher und Nieraucher. - Rauchstatus in früheren Gesundheitssurveys ähnlich erhoben → zeitliche Entwicklungen und Trends möglich sind - Datenbasis: 23.960 Personen ab 18 Jahren (13.108 Frauen, 10.852 Männer)	Erwachsenenbevölkerung Deutschlands: - Raucher/ gelegentlich Raucher: Frauen: 20,8 % (95% KI 19,9; 21,7); Männer 27,0 % 95% KI (25,9; 28,1) - Nie geraucht: Frauen: 52,6 % (95% KI 51,4 – 53,8), Männer 38,0 % (95%KI 36,9 – 39,1) - Absinken der Rauchquote: bei Männern 45 Jahren, bei Frauen ab 65 Jahren - in höheren Bildungsgruppen deutlich weniger verbreitet als in niedrigen Bildungsgruppen. - Anteil der aktuell Rauchenden in den jüngeren Altersgruppen am höchsten. Regionale Unterschiede: - Rauchquote: Bei Männern in Sachsen-Anhalt am höchsten, in Bayern am niedrigsten. - Rauchquote: Bei Frauen in Sachsen am niedrigsten und in Bremen am höchsten. - Tendenziell liegt die Rauchquote im Norden höher als im Süden, im Osten höher als im Westen und in den Stadtstaaten höher als in den Flächenstaaten - anhand Daten früherer Gesundheitssurveys des RKI lässt sich zeigen, dass der Anteil der Raucherinnen und Raucher in der Erwachsenenbevölkerung seit dem Jahr 2003 um gut 8 %-Punkte bei Frauen bzw. gut 11 Prozentpunkte bei Männern zurückgegangen [14]. Quellen: 14. Robert Koch-Institut (Hrsg) (2014) Daten und Fakten: Ergebnisse der Studie „Gesundheit in Deutschland aktuell 2012“ Beiträge zur Gesundheitsberichterstattung des Bundes. Robert Koch-Institut, Berlin http://edoc.rki.de/documents/rki_fv/recJuHnzacx8A/PDF/28Gs- WuNtFjVqY.pdf (Stand: 23.02.2017)

Systematische Übersichtsarbeiten

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
[A05-21G] Rauchverzicht bei essenzieller Hypertonie - Rapid Report [97] https://iqwig.de/de/projekte-ergeb-	2011	high	**Fragestellung:** Nutzenbewertung von Interventionen mit der Intention eines Rauchverzichtes im Vergleich zu keiner entsprechenden Intervention bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und Kriterien der Blutdruckkontrolle.	Es liegen keine Studien vor, die Daten liefern für eine Nutzenbewertung einer Intervention zum Rauchverzicht bei Patienten mit essenzieller Hypertonie hinsichtlich der patientenrelevanten Endpunkte Gesamtmortalität, kardiovaskuläre Mortalität oder Morbidität, terminale Niereninsuffizienz, gesundheitsbezogene Lebensqualität und unerwünschte Ereignisse. Auch lassen sich Effekte auf die antihypertensive Medikation oder hinsichtlich des Surrogatparameters Blutdruck nicht bewerten.	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
nisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21g-rauchverzicht-bei-essenzieller-hypertonie-rapid-report.1301.html (frei verfügbar)			**Suchzeitraum:** bis 03/2010 **Population:** - erwachsenen Patienten (≥ 18 Jahre) - essenzieller (primärer) arterieller Hypertonie **Intervention:** - Maßnahme zum Rauchverzicht - alleinigen Rauchverzicht - Maßnahmen mit ergänzenden Interventionen, die möglicherweise den Erfolg einer Tabakentwöhnung unterstützen: z. B. psychosoziale Interventionen, Nikotinersatzbehandlungen, medikamentöse Therapien - mindestens 24 Wochen **Kontrolle:** - Fehlen einer spezifischen Intervention zum Rauchverzicht - Placebo - unspezifische Maßnahmen, wie z. B. allgemeine Informationen über mögliche Nachteile durch das Rauchen verstanden **Studientyp:** SR, RCTs **Endpunkte:** patientenrelevant	Der grundsätzliche, d. h. von der Behandlung der Hypertonie unabhängige, Nutzen eines Rauchverzichts wird mit dem Ergebnis des vorliegenden Berichtes keineswegs infrage gestellt.	

Global Burden of Disease-Studie

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019 [98] https://www.thelancet.com/journals/lancet/article/PIIS0140-	2020	Lancet	- GBD 2019 estimated attributable mortality, years of life lost (YLLs), years of life lived with disability (YLDs), disability-adjusted life-years (DALYs) for 87 risk factors and combinations of risk factors, at global level, regionally, and for 204 countries and territories. - hierarchical list of risk factors so that specific risk factors (eg, sodium intake), related aggregates (eg, diet quality), are both evaluated. this method has 6 analytical steps: (1) included 560 risk–outcome pairs that met criteria for convincing or probable evidence on the basis of research studies. 12 risk–outcome pairs included in GBD 2017 no longer met inclusion criteria and 47 risk–outcome pairs for risks already included in GBD 2017 were added based on new evidence.	In 2019, leading **Level 2 risk factor globally for attributable deaths** was: - high SBP, which accounted for 10,8 million (95% uncertainty interval [UI] 9,51–12,1) deaths (19,2% [16,9–21,3] of all deaths in 2019), - followed by tobacco (smoked, second-hand, and chewing), which accounted for 8,71 million (8,12–9,31) deaths (15,4% [14,6–16,2] of all deaths in 2019). % of all **DALYs attributable** to the 5 leading Level 2 risk factors, 2019, in Germany: - Tobacco: 12,5% to <15% - High SBP: 10% to <12,5%

Referenz	Jahr	Quelle	Methodik	Ergebnisse
6736(20)30752-2/fulltext (frei verfügbar)			(2) Relative risks were estimated as a function of exposure based on published systematic reviews, 81 systematic reviews done for GBD 2019, and meta-regression. (3) Levels of exposure in each age-sex-location-year included in the study were estimated based on all available data sources using spatio-temporal Gaussian process regression, DisMod-MR 2.1, a Bayesian meta-regression method, or alternative methods. (4) We determined, from published trials or cohort studies, the level of exposure associated with minimum risk, called the theoretical minimum risk exposure level. (5) Attributable deaths, YLLs, YLDs, and DALYs were computed by multiplying population attributable fractions (PAFs) by the relevant outcome quantity for each agesex-location-year. (6) PAFs and attributable burden for combinations of risk factors were estimated taking into account mediation of different risk factors through other risk factors. - Across all 6 analytical steps, 30 652 distinct data sources used - Uncertainty in each step of analysis was propagated into final estimates of attributable burden. - Exposure levels for dichotomous, polytomous, and continuous risk factors were summarised with use of summary exposure value to facilitate comparisons over time, across location, and across risks. - time series from 1990 to 2019 has been re-estimated with use of consistent data and methods, these results supersede previously published GBD estimates of attributable burden.	%-**change in all-age deaths** from 2010 to 2019 in Germany (siehe App 2A S. 18/1194) - High SBP: 0,174 to 0,223 - Smoking: 0,007 to 0,052 %-change in **all-age DALYs from 2010 to 2019** in Germany. DALYs=disability-adjusted life-years. (siehe App 2A S. 39/1194) - High SBP: 0.073 to 0.120 - Smoking: -0.010 to 0.029

7.9 Entspannungsverfahren

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Hypertension in adults: diagnosis and management [H] Evidence review for relaxation therapies [99]	2019	moderate	**Fragestellung:** What is the clinical and cost-effectiveness of relaxation therapies for the management of primary hypertension in adults? **Suchzeitraum:** **Population:** **Intervention:** designed to promote relaxation (relaxation	**Allgemeines:** - 1 RCT identifiziert - Relaxation therapy (breathing exercises, deep muscle relaxation and simple meditation) (n=49) vs. no treatment (n=54) - 35-64y **Ergebnisse (nach 12 Monaten):** **Intervention vs. Vergleich**	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
https://www.nice.org.uk/guidance/ng136/evidence/h-relaxation-therapies-pdf-6896748213 (frei verfügbar)			therapies): • Biofeedback • Breathing • Meditation • Mindfulness • Muscle relaxation • Relaxation imagery • Yoga **Vergleich:** • No active treatment (usual care or blood pressure [BP] monitoring) • Sham or placebo therapy Endpunkte: - assessed at 12 or more months - patientenrelevant **Studientyp:** RCTs, SR	- stroke: 1/49 vs. 0/54; Peto OR 8.18 (0.16 to 414.3) - Myocardial infarction: 0/49 vs. 1/54; Peto OR 0.15 (0 to 7.52) - Angina: 0/49 vs. 1/54; Peto OR 0.15 (0 to 7.52) >> Qualität der Evidenz: jeweils sehr gering	
[A05-21F] Stressbewältigungsmaßnahmen bei essenzieller Hypertonie - Rapid Report [100] https://iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21f-stressbewaeltigungsmassnahmen-bei-essenzieller-hypertonie-rapid-report.1299.html (frei verfügbar)	2011	low	**Fragestellung:** Nutzenbewertung von Maßnahmen zur Stress-bewältigung im Vergleich zu keiner entsprechenden Intervention bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und Kriterien der Blutdruckkontrolle. **Suchzeitraum:** bis 05/2010 **Population:** - erwachsenen Patienten (≥ 18 Jahre) mit essenzieller (primärer) arterieller Hypertonie **Intervention:** - Maßnahme zur Stressbewältigung: > Kognitive Verhaltenstherapie bzw. kognitives Verhaltenstraining > Meditation, Atemübungen, Entspannungstherapie und Yoga > Biofeedback > Stressmanagement > Ärgerkontrolle **Vergleich:** - Fehlen einer entsprechenden Maßnahme zur Stressbewältigung	**>> Kurzfassung:** im Hinblick auf die untersuchten patientenrelevanten Endpunkte bei unzureichender Datenlage ein Nutzen von Maßnahmen zur Stressbewältigung bei Patienten mit Hypertonie nicht belegt, die vorhandenen Daten lassen jedoch ein Anzeichen für einen diastolisch blutdrucksenkenden Effekt erkennen **Algemeines:** - 14 SR (systematische Reviews) einbezogen - eigene Analyse: in SR eingeschlossenen RCTs + Ergänzungsrecherche nach RCTs (N= 16, n= 1100) **Design:** - randomisierte Parallelgruppenstudien, 1 doppelblind, 15 offenes Design - 9 - 72 Teilnehmern pro Studiengruppe. - 1970er und 1980er publiziert - Studiendauer: 6 - 60 Monate. - Verzerrungspotenzial: für alle berichteten Endpunkte, mit Ausnahme der Gesamtmortalität und kardiovaskulären Mortalität bzw. kardiovaskulären Morbidität in Patel 1988, als hoch bewertet. **Population:** - 2 RCTs: antihypertensive Medikation als Ausschlussgrund; - 3 Studien: antihypertensiven Medikamenten als Einschlusskriterium; - restliche Studien: behandelte und unbehandelte Patienten, in 1 Studie Medikation zu Studienbeginn abgesetzt	Nur ein kritisches AMSTAR-2-Kriterium nicht erfüllt: Publikationsbias nicht erhoben

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Studientypen: - SR, RCTs	- mittlerer BP zu Studienbeginn: SBD 122,7 mmHg-179,1 mmHg; DBD 79,0 mmHg-108,8 mmHg **Interventionen:** - 5 (4 Studien): Biofeedback alleine - 13: PMR, autogenes Training, Imaginationsübungen, Atemübungen, Qi-gong - 7: mehrere Komponenten wie z. B. Entspannungstrainings, Biofeedback, Meditation oder kognitive Verhaltenstherapie **Ergebnisse:** **Gesamtmortalität, kardiovaskuläre Mortalität und Morbidität, terminale Niereninsuffizienz, gesundheitsbezogene Lebensqualität und unerwünschte Ereignisse:** - keine oder unzureichende Daten aus RCTs, Beurteilung des Nutzens oder Schadens für diese Endpunkte nicht möglich **Einschätzung der Blutdruckänderung** - Daten aus 14 Studien - 2 Studien = Reduktions- / Auslassversuch bzgl. der antihypertensiven Medikation hin angelegt und konnten hierfür nicht herangezogen werden. - 14 Studien: Heterogenität bezüglich Interventionen und Umgang mit der antihypertensiven Begleitmedikation während der Studie - Ursache für Heterogenität der Ergebnisse nicht zufriedenstellend erklärt: daher keine gemeinsamen Effektschätzer **mittlere diastolische Blutdrucksenkung:** - Stressbewältigung vs. Kontrolle: zwischen −10 und +1 mmHg, - 13 Studien: Punktschätzer zugunsten der Intervention - 6 Studien: statistisch signifikante diastolische Blutdrucksenkung **mittlere systolische Blutdruckänderung** - Punktschätzer variierten zwischen −12 und +10 mmHg - 5 Studien: statistisch signifikante Blutdrucksenkung, allerdings fielen auch mehrere Punktschätzer zugunsten der Kontrollintervention aus. - keine Studie: statistisch signifikante Erhöhung der beiden Blutdruckparameter im Vergleich zur Kontrollgruppe **Änderung der antihypertensiven Medikation im Laufe der Studie** - 9/16 Studien berichtet - 2 Studien: statistisch signifikanter Effekt der Stressbewältigungsmaßnahme auf den Blutdruck mit einer resultierenden Änderung der antihypertensiven Medikation (zugunsten der Stressbewältigungsmaßnahme) - gleichzeitig keine statistisch signifikante Blutdruckänderung.	

7.10 Reduktion des Salzkonsums

Gesundheitsberichterstattung

Referenz	Jahr	Quelle	Methodik	Ergebnisse
Klenow S, Mensink GBM (2016) Natriumzufuhr in Deutschland. Journal of Health Monitoring 1(2):31–35 DOI 10.17886/RKI-GBE-2016-03 [101] https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsJ/FactSheets/JoHM_2016_02_ernaehrung3.pdf?__blob=publicationFile (frei verfügbar)	2016	RKI	Biomarker für die Natriumzufuhr: im Urin gemessene Natriummenge Studie zur Gesundheit Erwachsener in Deutschland (DEGS 1): - Spontanurinproben gesammelt - Natriumkonzentration wurde mithilfe der Kreatininkonzentration auf die Natrium-Tagesausscheidung umgerechnet **Informationen zu DEGS1** - 2008 - 2011 vom RKI durchgeführt - Befragungen und körperliche Untersuchungen - repräsentativ für gesundheitliche Situation von Männern und Frauen zwischen 18 und 79 Jahren - n ≈ 8.000	Natriumzufuhr in der erwachsenen Bevölkerung in Deutschland pro Tag im Median: - insgesamt 3,7 g (IQR 2,4; 5,3) - Frauen 3,4 g (IQR 2,3; 5,0) - Männer: 4,0 g (IQR 2,7; 5,7) >> Etwa 50 % der erwachsenen Bevölkerung in Deutschland nehmen also täglich mehr als diese Menge zu sich. Mittelwerte der geschätzten täglichen Natriumzufuhr: - Frauen: 3,8 g - Männer: 4,5 g **Weitere ggf. wichtige Aspekte:** - Natriumzufuhr nimmt bei Frauen bis zur Altersgruppe der 40- bis 59-Jährigen zu - Männer der hohen Statusgruppe verzehren etwas weniger Natrium als Männer der mittleren bzw. niedrigen Statusgruppe - Den Orientierungswert der Deutschen Gesellschaft für Ernährung [14] von bis zu 6 g Speisesalz pro Tag (= 2,4 g Natrium) überschreiten 73 % der Frauen und 80 % der Männer in Deutschland. - Die Zufuhrempfehlung der WHO [20] von weniger als 2 g Natrium pro Tag überschreiten sogar 80 % der Frauen und 86 % der Männer in Deutschland *Quellen:* *14. Strohm D, Boeing H, Leschik-Bonnet E et al. (2016) Speisesalzzufuhr in Deutschland, gesundheitliche Folgen und resultierende Handlungsempfehlungen. Ernährungs Umschau 63(3):62-70* *20. World Health Organization (2012) Guideline: Sodium Intake for Adults and Children. WHO, Geneva*

Systematische Übersichtsarbeit mit patientenrelevanten Endpunkten

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Adler AJ. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database Syst Rev 2014(12):CD009217.	2014	moderate	**Fragestellung:** 1. To assess the long-term effects of advice and salt substitution, aimed at reducing dietary salt, on mortality and cardiovascular morbidity. 2. To investigate whether a reduction in blood pressure is an explanatory factor in the effect of	**Allgemeines:** - 3 trials in people with normotension (n = 3518) - 2 in people with hypertension (n = 748) - 3 in a mixed population of people with normo- and hypertension (n = 3018) ***>> mixed: normo- and hypertensive individuals included in analysis with the hypertensive studies***	

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
dx.doi.org/10.1002/14651858.CD009217.pub3. [102] https://www.ncbi.nlm.nih.gov/pubmed/25519688.			such dietary interventions on mortality and cardiovascular outcomes. **Suchzeitraum:** 05/2013 **Population:** - ≥18 years irrespective of gender or ethnicity. - We excluded studies in patients with heart failure, children or pregnant women. **Intervention/ Vergleich:** - Reducing dietary salt intake, either by advice from health professionals or provision of low-sodium salt substitution vs. usual, control or placebo diet, or no intervention. - **Follow up:** at least 6 month **Studientyp**: RCTs	**hypertensive population** - male: 15% - 100% of participants - median age: 60 y. - mean DBP at entry: 71 mmHg - 97 mmHg - mean SBP at entry: 131 mmHg to 162 mmHg - Sodium goals varied from < 80 mmol/day to 70 - 100 mmol/day and unspecified sodium intake **Ergebnisse der *hypertensive* population (Intervention vs. Kontrolle)** **All-cause mortality:** 278/1603 vs. 396/2077; RR 1.00, 95% CI 0.86; 1.15, 565 deaths in total, I^2=0%), 5 Studien **Cardiovascular mortality:** 33/1103 vs. 73/1553; RR 0.67, 95% CI 0.45; 1.01, 106 CV deaths, I^2=0%), 3 Studien **Cardiovascular morbidity:** 74/1474 vs. 120/1923, RR 0.76, 95% CI 0.57; 1.01, 192 events, I^2=0%), 4 Studien SBP: (MD -4.14 mmHg, 95% CI -5.84; -2.43, I^2 = 0%), 3 Studien, n= 1288, zugunsten Intervention DBP: (MD -3.74 mmHg, 95% CI -8.41; 0.93, I^2 = 67%), 2 Studien, n= 675	

Primärstudien aus Adler et al.

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
Morgan T, Adam W, Gillies A, et al. Hypertension treated by salt restriction. Lancet 1978; 1(8058):227–30. DOI: 10.1016/s0140-6736(78)90479-8. [103] http://www.ncbi.nlm.nih.gov/pubmed/74660	1978	**Baseline-Charakteristika** 4-arm trial: - 2 arms were of drug treatments and not considered here. - dietary sodium restriction arm and control arm are used here. - 67 (N = 34 intervention, N = 33 control). **intervention:** SBP mean 160 (SD23), DBP 97 (SD8); **control:** SBP mean 165 (SD 17), DBP mean 97 (SD 8) Case mix: untreated hypertensives **Age**: intervention: mean 57.1 (SD NR); control: mean 58.6 (SD NR) CV diagnoses: borderline hypertensives (DBP 95 to 109 mmHg) and hypertensives (DBP 110+ mmHg) Percentage male: 100%, Percentage white: not reported **Inclusion:** males with borderline hypertension on admission to hospital or outpatient visit **Exclusion:** malignant disease, severe psychiatric disturbances, severe physical incapacity or a disease likely to be fatal in the next 2	**Intervention vs. Kontrolle** All-cause mortality at end of trial: 1/34 vs. 0/33, RR 2.91 [95% KI 0.12, 69.08] All-cause mortality at longest follow-up: 4/35 vs. 5/42, RR 0.96 [95%KI 0.28, 3.30] Cardiovascular mortality at end of trial: 2/33 vs. 3/34, RR 0.69 [95%KI 0.12, 3.85] Cardiovascular events at end of trial: 3/34 vs. 3/33, RR 0.97 [95% KI 0.21, 4.47] Cardiovascular disease events at longest follow-up: 2/35 vs. 2/42 1.20 [95% KI 0.18, 8.09] SBP at end of trial: n=31, mean (SD) -5.5 (22.3) vs. n=31 mean (SD) -4 (22.3), MD -1.50 [95% KI -12.60, 9.60] DBP at end of trial: n=31 mean (SD) -5 (11.1) vs. n=31 mean (SD) 2 (11.1), MD -7.00 [95%KI -12.53, -1.47]	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
		years, serum-creatinine levels > 0.18 mmol/l, abnormal liver function tests, in cardiac failure or on diuretic **Follow up:** BP at 24 months; clinical outcomes at 24 months (end of trial) and at extra follow-up to 70 months **Intervention** Salt reduction/advice component: patients instructed to reduce their sodium chloride intake and given a diet that should have reduced their sodium intake to 70 - 100 mmol/day. advice was repeated at 6 months, No details on who gave advice Other dietary component: at each 6-month review visit, if serum potassium levels < 3.4 mmol/L, potassium supplements were given **Comparator** No treatment, reviewed at 6 months (as intervention) Other: not given any treatment, but reviewed at 6-monthly intervals and if DBP rose above 115 mmHg treatment was started		
Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA 1998; 279(11):839–46. DOI: 10.1001/jama.279.11.839. [104] http://www.ncbi.nlm.nih.gov/pubmed/9515998.	1998	**Baseline-Charakteristika** n= 681 (N = 340 intervention, N = 341 control) - part of a factorial design study SBP 128.0 (9.4), DBP 71.3 (7.3) mmHg Case mix: treated hypertensives **Age**: 65.8 (SD 4.6) CV diagnoses: none Percentage male: 53%, Percentage white: 76% **Inclusion:** - aged 60 to 80 years, - SBP < 145 mmHg and DBP < 85 mmHg while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a non-diuretic agent. - Individuals taking 2 antihypertensive medications were also eligible if they were successfully weaned off one of them during the screening phase. **Exclusion:** - cancer within the last 5 years; - treatment with diuretics, ACE inhibitors, or digitalis for CHF or unknown reason; drug therapy with nitrates, beta-blockers or calcium channel blockers for CHD or reason other than hypertension;	**Intervention vs. Kontrolle** All-cause mortality at longest follow-up: 51/294 vs. 50/291, RR 1.01 [95% KI 0,71; 1,44] Cardiovascular events at end of trial: 36/370 vs. 46/371, RR 0.78 [95% KI 0,52; 1,18] Cardiovascular disease events at longest follow-up: 36/340 vs. 46/341, RR 0.78 [95% KI 0.52, 1.18] SBP at end of trial: n= 317, mean (SD) -4.6 (11.3) vs. N= 296, mean (SD) -0.4 (10.5), MD -4.20 [95% KI -5.93, -2.47] DBP at end of trial: n= 317, mean (SD) -2.2 (8) vs. n=296 mean (SD) -0.2 (7); MD -2.00 [95%KI -3.19, -0.81] Antihypertensive drug stop: 92,6% vs. 86,8%	

Referenz	Jahr	Charakteristika	Ergebnisse	Kommentar
		- MI or stroke within 6months; “active” CHD (e.g. angina pectoris); CHF; atrial fibrillation; second- or third-degree heart block without permanent pacemaker; - drug therapy for ventricular arrhythmias; self report of heart valve replacement; clinically important valvular heart disease; insulin-dependent diabetes mellitus; - severe hypertension; - current or recent (within 6 months) drug therapy for asthma or COPD; corticosteroid therapy for > 1 month; serious mental or physical illness; involuntary weight loss (>= 4.5 kg) during previous year; BMI < 21, or > 33 in men or > 37 in women, weitere Laborparameter (siehe Publikation) **Follow-up:** 30 months **Intervention** - 4-month “intensive” phase, 3-month “extended” phase, maintenance phase (duration unclear) Salt reduction/advice component: individual and group sessions with an interventionist (typically a registered dietician) - information using centrally and locally prepared materials, motivated participants to make and sustain long-term lifestyle changes, and frequently monitored progress of groups and individuals. - Individualised feedback provided. Participants learned about sources of sodium, in particular those foods with a high salt content, and they learned about possible alternatives, how to adapt recommendations for a low-salt diet to their lifestyle. - goal of this intervention for the group: achieve and maintain a 24-h dietary sodium intake of ≤80 mmol (1800 mg) (measured by 24-h urine collection); attempt to withdraw hypertensive therapy began 3 months post-randomisation **Comparator** Dietary: in order to enhance retention of control participants, meetings were held on a regular basis with speakers on subjects unrelated to BP, CVD or nutrition, drug withdrawal began at a comparable time to the intervention group		

Systematische Übersichtsarbeiten mit Surrogatendpunkten

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Graudal NA. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev 2017; 4(4):CD004022. dx.doi.org/10.1002/14651858.CD004022.pub4. [105] https://www.ncbi.nlm.nih.gov/pubmed/28391629. Graudal et al. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev. 2020 Dec 12;12(12):CD004022. doi: 10.1002/14651858.CD004022.pub5. [106] https://pubmed.ncbi.nlm.nih.gov/33314019/	2017 / 2020	low	**Fragestellung:** estimate effects of low sodium intake vs. high sodium intake on SBP and DBP, plasma or serum levels of renin, aldosterone, katecholamines, cholesterol, HDL, LDL and triglycerides **Suchzeitraum:** bis 03/2016 **Population:** - Persons with normal or elevated BP irrespective of race and age - Exclusion: Studies investigating unhealthy patients with other diseases than elevated BP (e.g. diabetes or heart failure) **Intervention/ Vergleich:** - "low" sodium diet v.s "high" sodium diet. - "low" sodium diet: low range (< 100 mmol/day) or usual range (100 mmol to 250 mmol/day) - "high" sodium diet: usual range (100 mmol to 250 mmol/day) or above the usual range (≥ 250 mmol/day). - studies treating persons with a concomitant intervention such as an antihypertensive medication, potassium supplementation or weight reduction were only included if the concomitant intervention was identical during the low and the high-sodium diet. - subgroup sub-analyses of 125 studies with a duration of ≥ 7 days and a salt intake of maximum 14.5 g **Studientyp:** RCTs k.A. zu notwendiger Studiendauer identifiziert	**Note:** Update 2021 **Allgemeines (2017):** - 185 studies (n= 12210) - average sodium intake was reduced from 201 mmol/day to 66 mmol/day - lasting 4 to 1100 days **Effect of sodium reduction on BP was as follows:** White people with hypertension (High-quality evidence): SBP: MD -5.51 mmHg (95% CI: -6.45 to -4.57); 84 studies, n= 5925; DBP: MD -2.88 mmHg (95% CI: -3.44 to -2.32); 85 studies, n= 6001. Black people with hypertension (Moderate-quality evidence): SBP MD -6.64 mmHg (95% CI:-9.00 to -4.2); 8 studies, n= 619; DBP -2.91 mmHg (95% CI:-4.52, -1.30); 8 studies, n= 619. Asian people with hypertension (Moderate-quality evidence): SBP: MD -7.75 mmHg (95% CI:-11,44 to -4.07) 9 studies, n= 501; DBP: MD -2.68 mmHg (95% CI: -4.21 to -1.15). **Update 2021:** - since the first review in 2003 the number of included references increased from n= 96 to n=195 - analyses with stratification of BP by race white participants (effect of sodium reduction (from 203 to 65 mmol/day) on BP): - normal blood pressure: o SBP: mean difference (MD) -1.14 mmHg (95% confidence interval (CI): -1.65 to -0.63), 5982 participants, 95 trials (high-quality evidence) o DBP: MD + 0.01 mmHg (95% CI: -0.37 to 0.39), 6276 participants, 96 trials (high-quality evidence) - hypertension: o SBP: MD -5.71 mmHg (95% CI: -6.67 to -4.74), 3998 participants,88 trials (high-quality evidence)	- keine klinisch kritischen Endpunkte berichtet - 2017 Ergebnisse der Population mit Hypertonie extrahiert

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ DBP: MD -2.87 mmHg (95% CI: -3.41 to -2.32), 4032 participants, 89 trials (high-quality evidence) black participants effect of sodium reduction (from 195 to 66 mmol/day) on BP): - normal blood pressure: ○ SBP: mean difference (MD) -4.02 mmHg (95% CI:-7.37 to -0.68) ○ DBP: MD -2.01 mmHg (95% CI:-4.37, 0.35), 253 participants, 7 trials (low-quality evidence) - hypertension: ○ SBP: MD -6.64 mmHg (95% CI:-9.00, -4.27); ○ DBP: MD -2.91 mmHg (95% CI:-4.52, -1.30), 398 participants, 8 trials (low-quality evidence) asian participants (effect of sodium reduction (from 217 to 103 mmol/day) on BP): - normal blood pressure: ○ SBP: mean difference (MD) -1.50 mmHg (95% CI: -3.09, 0.10); ○ DBP: MD -1.06 mmHg (95% CI:-2.53 to 0.41), 950 participants, 5 trials moderate-low-quality evidence) - hypertension: ○ SBP: MD -7.75 mmHg (95% CI:-11.44, -4.07); ○ DBP: MD -2.68 mmHg (95% CI: -4.21 to -1.15), 254 participants, 8 trials (moderate-low-quality evidence)	
He FJ. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2013(4):CD004937. dx.doi.org/10.1002/14651858.CD004937.pub2. [107]	2013	low	**Fragestellung**: - assess effect of a longer-term modest reduction in salt intake (i.e. of public health relevance) on BP and whether there was a dose-response relationship; - effect on BP by sex and ethnic group; - effect on plasma renin activity, aldosterone, noradrenaline, adrenaline, cholesterol, LDL, HDL and triglycerides	**Allgemeines:** - 30 Studien eingeschlossen - 4 Studien: hyper- und normotensive Patienten eingeschlossen, Ergebnisse in jeweilige Metaanalysen integriert (daher N= 34) - hypertensives (N= 22), normotensives (N= 12) - 16 crossover design, 6 paralleled comparisons. 14 double blind, 7 BP observer blind, 1 blinding procedure not reported **Trials in hypertensive individuals:** - 990 hypertensive individuals - Median age: 50 y (24 to 73 y).	Ergebnisse der Population mit Hypertonie extrahiert

Referenz	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
https://www.ncbi.nlm.nih.gov/pubmed/23633321.			**Suchzeitraum: bis 11/2012** **Population:** - ≥18 years - normal or raised BP, - pregnant women, or patients with other diseases rather than hypertension, such as diabetes, heart failure, were excluded **Intervention/ Vergleich:** - modestly reduced salt intake vs. usual salt intake (i.e. control). - Duration: ≥ 4 weeks - Exclusion: concomitant interventions (i.e. non-pharmacologic interventions, antihypertensive or other medications) **Studientyp:** RCTs	- median duration: 5 weeks (4weeks to 1 year). - median BP on usual salt intake: 148/93 mmHg. - median 24-h urinary sodium on usual salt intake: 162 mmol (9.5 g/d salt), ranging from 125 to 191 mmol (7.3 to 11.2 g/d salt). **pooled estimate of change** - 24-h urinary sodium from usual to reduced salt intake: -75 mmol (-53; -117 mmol), equivalent to reduction in salt intake of 4.4 g/d (3.1; 6.8 g/d). - systolic BP: -5.39 mmHg (95% CI: - 6.62 to -4.15, I2=61%) - diastolic BP: -2.82 mmHg (95% CI: -3.54 to -2.11, I2=52%) >> Meta-regression - dependent variable: change in BP - independent variable: age, ethnic group and the change in 24-h urinary sodium - change in 24-h urinary sodium and ethnic group significantly associated with fall in systolic BP, whereas age not significantly associated with fall in systolic BP. - 100mmol reduction in 24 hour urinary sodium (6 g/day salt) was associated with a fall in systolic BP of 10.8 mmHg (95CI: 3.5 to 18.2) after adjusting for age and ethnic group.	

7.11 Ausgeschlossene oder zurückgestellte Übersichtsarbeiten

Referenz	Jahr	Abstract	Thema	Ausschlussgrund
Dickinson HO. Relaxation therapies for the management of primary hypertension in adults. Cochrane Database Syst Rev 2008(1):CD004935. dx.doi.org/10.1002/14651858.CD004935.pub2. [108] https://www.ncbi.nlm.nih.gov/pubmed/18254065.	2008	OBJECTIVES To evaluate the effects of relaxation therapies on cardiovascular outcomes and blood pressure in people with elevated blood pressure. SEARCH: k.A INCLUSION CRITERIA RCTs of a parallel design comparing relaxation therapies with no active treatment, or sham therapy; follow-up >/=8 weeks; participants over 18 years, with raised systolic blood pressure (SBP) >/=140 mmHg or diastolic blood pressure (DBP) >/=85 mmHg); SBP and DBP reported at end of follow-up. EXCLUSION CRITERIA participants were pregnant; participants received antihypertensive medication which changed during the trial.	Entspannungsverfahren	Zürückgestellt: NICE-Review mit aktuellerem Suchzeitraum vorhanden

Referenz	Jahr	Abstract	Thema	Ausschlussgrund
Hooper L. Advice to reduce dietary salt for prevention of cardiovascular disease. Cochrane Database Syst Rev 2004(1):CD003656. dx.doi.org/10.1002/14651858.CD003656.pub2. [109] https://www.ncbi.nlm.nih.gov/pubmed/14974027.	2004	OBJECTIVES To assess in adults the long term effects (mortality, cardiovascular events, blood pressure, quality of life, weight, urinary sodium excretion, other nutrients and use of anti-hypertensive medications) of advice to restrict dietary sodium using all relevant randomised controlled trials. SEARCH: k.A. SELECTION CRITERIA Inclusion decisions were independently duplicated and based on the following criteria: 1) randomisation was adequate; 2) there was a usual or control diet group; 3) the intervention aimed to reduce sodium intake; 4) the intervention was not multifactorial; 5) the participants were not children, acutely ill, pregnant or institutionalised; 6) follow-up was at least 26 weeks; 7) data on any of the outcomes of interest were available.	Salz	Zurückgestellt: SR mit aktuelleren Suchzeiträumen vorhanden
[A05-21B] Kochsalzreduktion bei essenzieller Hypertonie - Rapid Report [110] IQWiG: https://iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21b-kochsalzreduktion-bei-essenzieller-hypertonie-rapid-report.1129.html (frei verfügbar)	2009	Ziel der Untersuchung: Ziel der vorliegenden Untersuchung ist die Nutzenbewertung von Interventionen zur Reduktion der Kochsalzaufnahme im Vergleich zu keiner speziellen die Kochsalzaufnahme reduzierenden Intervention bei Patienten mit essenzieller Hypertonie hinsichtlich patientenrelevanter Therapieziele und von Kriterien der Blutdruckkontrolle. Suchzeitraum bis: Dezember 2008 Selektionskriterien: Eingeschlossen wurden systematische Übersichten von randomisierten kontrollierten Studien mit erwachsenen Patienten mit essenzieller Hypertonie mit einer Mindestdauer von 4 Wochen. Die zu prüfende Intervention in diesen Studien war eine Maßnahme zur Reduktion der Kochsalzaufnahme und die intendierte Kochsalzaufnahme in der Interventionsgruppe war niedriger als in der Kontrollgruppe. Nicht berücksichtigt wurden systematische Übersichten und HTA-Berichte, in denen die Reduktion der Kochsalzaufnahme als primäre Intervention mit einer anderen antihypertensiven Behandlung als primäre Intervention verglichen wurde (z. B. reduzierte Kochsalzzufuhr versus Diät oder versus medikamentöse Blutdrucksenkung).	Salz	Suchzeitraum weit zurückliegend Umbrella Review klinisch relevante Endpunkte untersucht + hypertoniespezifische Population anhand von in SR eingeschlossenen Primärstudien betrachtet
Foster G. Self-management education programmes by lay leaders for people with chronic conditions. Cochrane Database Syst Rev 2007(4):CD005108. dx.doi.org/10.1002/14651858.CD005108.pub2. [111]	2007	OBJECTIVES To assess systematically the effectiveness of lay-led self-management programmes for people with chronic conditions. SEARCH: July 2006 SELECTION CRITERIA	Selbstmanagement	keine hypertoniespezifische Auswertung

Referenz	Jahr	Abstract	Thema	Ausschlussgrund
https://www.ncbi.nlm.nih.gov/pubmed/17943839.		Randomised controlled trials (RCTs) comparing structured lay-led self-management education programmes for chronic conditions against no intervention or clinician-led programmes.		
Ashworth NL. Home versus center based physical activity programs in older adults. Cochrane Database Syst Rev 2005(1):CD004017. dx.doi.org/10.1002/14651858.CD004017.pub2. [112] https://www.ncbi.nlm.nih.gov/pubmed/15674925.	2005	OBJECTIVES To assess the effectiveness of 'home based' versus 'center based' physical activity programs on the health of older adults. SEARCH: Sept 2002 SELECTION CRITERIA Randomised or quasi-randomised controlled trials of different physical activity interventions in older adults (50 years or older) comparing a 'home based' to a 'center based' exercise program. Study participants had to have either a recognised cardiovascular risk factor, or existing cardiovascular disease, or chronic obstructive airways disease (COPD) or osteoarthritis. Cardiac and post-operative programs within one year of the event were excluded.	Training	keine hypertoniespezifische Auswertung
[A05-21A] Gewichtsreduktion bei essenzieller Hypertonie [113] IQWiG: https://iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2010-oder-frueher/a05-21a-gewichtsreduktion-bei-essenzieller-hypertonie.1131.html (frei verfügbar)	2006	Fragestellungen: 1. Gewichtsreduktion mit medikamentöser Therapie vs. Keine Gewichtsreduktion 2. Gewichtsreduktion mit nicht medikamentöser Therapie vs. Keine Gewichtsreduktion 3. Gewichtsreduktion mit invasiven Maßnahmen vs. Keine Gewichtsreduktion 4. Vergleich medikamentöser und/oder nicht-medikamentöser Maßnahmen (auch in Kombination) Suchzeitraum bis 09/2006 Population: Pat. mit essentieller HT	Gewichtsreduktion	Zurückgestellt: Suchzeitraum weit zurückliegend

7.12 Handsuche / Literaturlistensuche

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
Acin MT. Alcohol intake reduction for controlling hypertension. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD010022. [93]	2020	hoch	Fragestellung: assess effect of any intervention to reduce alcohol intake in terms of BP decrease in hypertensive people with alcohol consumption compared to a control intervention or no intervention at all. To determine additional effects related to mortality, major CV-events, serious adverse events or quality of life. Suchzeitraum: bis June 2020 Selection criteria - RCTs ≥ 12 weeks duration - ≥ 50 subjects per group	Nur eine Studie identifiziert (PATHS 1998). Diese wurde bereits im IQWiG-Report [A05-21E] ausführlich betrachtet.	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
https://www.cochraneli-brary.com/cdsr/doi/10.1002/14651858.CD010022.pub2/full			- quantitative measurement of alcohol consumption and/or biological measurement of the outcomes of interest. - adults (16 years of age or older) - SBP > 140 mmHg and DBP > 90 mmHg - participants with diabetes: SBP ≥ 130 or DBP ≥ 80 mmHg in - any intervention implemented to reduce alcohol intake.		
Finger JD, Mensink GBM, Lange C. Arbeitsbezogene körperliche Aktivität bei Erwachsenen in Deutschland. Journal of health monitoring 2017; 2(2):29–36. DOI: 10.17886/RKI-GBE-2017-026. [72]	RKI	Körperliche Aktivität während der Arbeit	- GEDA 2014/2015-EHIS - erstmals erfasst - deutsche validierte Version des European Health Interview Survey – Physical Activity Questionnaires (E-HIS-PAQ) [14,15]. - n= 18.026 im erwerbsfähigen Alter (18 - 64 Jahre) - 10.146 Frauen, 7.880 Männer - Berechnungen mit Gewichtungsfaktor für Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung korrigiert **Frage** (>> eine Antwortkategorie möglich): - „Wenn Sie arbeiten, was beschreibt am besten was Sie tun? (a) Vorwiegend sitzen oder stehen, (b) Vorwiegend gehen oder mäßig anstrengende körperliche Tätigkeiten, (c) Vorwiegend schwere körperliche Arbeit oder körperlich beanspruchende Tätigkeiten oder (d) Ich führe keine arbeitsbezogenen Tätigkeiten aus“. Begriff „Arbeit“: bezahlte oder unbezahlte Tätigkeiten (z.B. Studium, Hausarbeit).	während der Arbeit vorwiegend zu sitzen oder zu stehen: - 47,5% (95% KI 46,1–49,0) der Frauen - 47,2% (95% KI 45,6–48,8) der Männer im erwerbstätigen Alter (18 - 64 J). - Frauen: größter Anteil in Altersgruppe 18-29J (55,5%, 95% KI 52,6–58,4). - Männer: größter Anteil in Altersgruppe 30-44J (50,2%, 95% KI 47,6–52,9). - Je höher der Bildungsstand, desto häufiger wird vorwiegend im Sitzen oder Stehen gearbeitet. - Verglichen mit Frauen geben Männer fast fünfmal so häufig an, vorwiegend schwere körperliche Arbeit zu verrichten. **Quellen** 14.Baumeister SE, Ricci C, Kohler S et al. (2016) Physical activity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnai-re (EHIS-PAQ). International Journal of Behavioral Nutrition and Physical Activity 13(1):1-10 15.Finger JD, Tafforeau J, Gisle L et al. (2015) Development of the European Health Interview Survey – Physical Activity Questi-onnaire (EHIS-PAQ) to monitor physical activity in the European Union. BMC Archives of Public Health 73:59	
Finger JD, Mensink GBM, Lange C. Ge-	RKI	Körperliche Aktivität in der Freizeit	- GEDA 2014/2015-EHIS)	**WHO-Empfehlung zur Ausdaueraktivität:** - 42,6% (95% KI 41,3–43,9) der Frauen - 48,0% (95% KI 46,6–49,4) der Männer	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
sundheitsför-dernde körperli-che Aktivität in der Freizeit bei Erwachsenen in Deutschland. Journal of health monito-ring 2017; 2(2):37–44. DOI: 10.17886/RKI-GBE-2017-027. [73]			- deutsche validierte Version des European Health Interview Survey – Physical Activity Questionnaires (E-HIS-PAQ) erfasst [9, 10]. - Selbstngabe - Zeitdauer/Woche: mäßig anstrengende aerobe kör-perliche Aktivität in der Freizeit und Radfahren zur Fortbewegung - Anzahl von Tagen/ Woche: Aktivitäten zur Muskel-kräftigung - Darstellung der Anteile derer, die - ≥2,5 h/ Woche mindestens mäßig anstrengende Aus-daueraktivitäten ausüben (1. Teil der WHO-Bewe-gungsempfehlung) bzw. - ≥ 2 /Woche Aktivitäten zur Muskelkräftigung ausüben (2. Teil der WHO-Bewegungsempfehlung) sowie - beide Teile der WHO-Empfehlung erfüllen (2,5 Stun-den Ausdauer + 2x Muskelkräftigung/ Woche). - Stratifizierung: nach Geschlecht, Altersgruppen, Bil-dungsstand, Bundesländern - n= 22.959 ab 18 Jahren - 12.511 Frauen - 10.448 Männer - Gewichtungsfaktor Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung korrigiert.	**WHO-Empfehlung zur Muskelkräftigungsaktivität:** - 27,6% (95% KI 26,7–28,6) der Frauen - 31,2% (95% KI 30,2–32,3) der Männer **Beide Empfehlungen zusammen:** - 20,5% (95% KI 19,6–21,4) der Frauen - 24,7% (95% KI 23,6–25,8) der Männer **Quellen**: 9. Baumeister SE, Ricci C, Kohler S et al. (2016) Physical ac-tivity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnai-re (EHIS-PAQ). International Journal of Behav-ioral Nutrition and Physical Activity 13(1):1-10 10.Finger JD, Tafforeau J, Gisle L et al. (2015) Development of the European Health Interview Survey – Physical Activity Questi-onnaire (EHIS-PAQ) to monitor physical activity in the European Union. BMC Archives of Public Health 73:59	
GBD 2019 Risk Factors Collab-orators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease	Lancet	Rauchen	- GBD 2019 estimated attributable mortality, years of life lost (YLLs), years of life lived with disability (YLDs), disability-adjusted life-years (DALYs) for 87 risk fac-tors and combinations of risk factors, at global level, regionally, and for 204 countries and territories. - hierarchical list of risk factors so that specific risk fac-tors (eg, sodium intake), related aggregates (eg, diet quality), are both evaluated. this method has 6 analytical steps: (1) included 560 risk–outcome pairs that met criteria for convincing or probable evidence on the basis of re-search studies. 12 risk–outcome pairs included in	In 2019, leading **Level 2 risk factor globally for attributable deaths** was: - high SBP, which accounted for 10,8 million (95% uncertainty interval [UI] 9,51–12,1) deaths (19,2% [16,9–21,3] of all deaths in 2019), - followed by tobacco (smoked, second-hand, and chewing), which accounted for 8,71 million (8,12–9,31) deaths (15,4% [14,6–16,2] of all deaths in 2019). % of all **DALYs attributable** to the 5 leading Level 2 risk fac-tors, 2019, in Germany: - Tobacco: 12,5% to <15% - High SBP: 10% to <12,5%	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
Study 2019. Lancet 2020; 396(10258):1223–49. DOI: 10.1016/S0140-6736(20)30752-2. [98] http://www.ncbi.nlm.nih.gov/pubmed/33069327			GBD 2017 no longer met inclusion criteria and 47 risk–outcome pairs for risks already included in GBD 2017 were added based on new evidence. (2) Relative risks were estimated as a function of exposure based on published systematic reviews, 81 systematic reviews done for GBD 2019, and meta-regression. (3) Levels of exposure in each age-sex-location-year included in the study were estimated based on all available data sources using spatiotemporal Gaussian process regression, DisMod-MR 2.1, a Bayesian meta-regression method, or alternative methods. (4) We determined, from published trials or cohort studies, the level of exposure associated with minimum risk, called the theoretical minimum risk exposure level. (5) Attributable deaths, YLLs, YLDs, and DALYs were computed by multiplying population attributable fractions (PAFs) by the relevant outcome quantity for each agesex-location-year. (6) PAFs and attributable burden for combinations of risk factors were estimated taking into account mediation of different risk factors through other risk factors. - Across all 6 analytical steps, 30 652 distinct data sources used - Uncertainty in each step of analysis was propagated into final estimates of attributable burden. - Exposure levels for dichotomous, polytomous, and continuous risk factors were summarised with use of summary exposure value to facilitate comparisons over time, across location, and across risks. - time series from 1990 to 2019 has been re-estimated with use of consistent data and methods, these results supersede previously published GBD estimates of attributable burden.	%-**change in all-age deaths** from 2010 to 2019 in Germany (siehe App 2A S. 18/1194) - High SBP: 0,174 to 0,223 - Smoking: 0,007 to 0,052 %-change in **all-age DALYs from 2010 to 2019** in Germany. DALYs=disability-adjusted life-years. (siehe App 2A S. 39/1194) - High SBP: 0.073 to 0.120 - Smoking: -0.010 to 0.029	
Klenow S, Mensink GBM. Natriumzufuhr in	RKI	Natrium	Biomarker für die Natriumzufuhr: im Urin gemessene Natriummenge	Natriumzufuhr in der erwachsenen Bevölkerung in Deutschland pro Tag im Median: - insgesamt 3,7 g (IQR 2,4; 5,3)	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
Deutschland. Journal of health monitoring 2016; 1(2):31–5. DOI: 10.17886/RKI-GBE-2016-035. *[101]*			Studie zur Gesundheit Erwachsener in Deutschland (DEGS 1): - Spontanurinproben gesammelt - Natriumkonzentration wurde mithilfe der Kreatinin-konzentration auf die Natrium-Tagesausscheidung umgerechnet **Informationen zu DEGS1** - 2008 - 2011 vom RKI durchgeführt - Befragungen und körperliche Untersuchungen - repräsentativ für gesundheitliche Situation von Männern und Frauen zwischen 18 und 79 Jahren - n ≈ 8.000	- Frauen 3,4 g (IQR 2,3; 5,0) - Männer: 4,0 g (IQR 2,7; 5,7) >> Etwa 50 % der erwachsenen Bevölkerung in Deutschland nehmen also täglich mehr als diese Menge zu sich. Mittelwerte der geschätzten täglichen Natriumzufuhr: - Frauen: 3,8 g - Männer: 4,5 g Weitere ggf. wichtige Aspekte: - Natriumzufuhr nimmt bei Frauen bis zur Altersgruppe der 40- bis 59-Jährigen zu - Männer der hohen Statusgruppe verzehren etwas weniger Natrium als Männer der mittleren bzw. niedrigen Statusgruppe - Den Orientierungswert der Deutschen Gesellschaft für Ernährung [14] von bis zu 6 g Speisesalz pro Tag (= 2,4 g Natrium) überschreiten 73 % der Frauen und 80 % der Männer in Deutschland. - Die Zufuhrempfehlung der WHO [20] von weniger als 2 g Natrium pro Tag überschreiten sogar 80 % der Frauen und 86 % der Männer in Deutschland *Quellen:* *14. Strohm D, Boeing H, Leschik-Bonnet E et al. (2016) Speisesalzzufuhr in Deutschland, gesundheitliche Folgen und resultierende Handlungsempfehlungen. Ernährungs Umschau 63(3):62-70* *20. World Health Organization (2012) Guideline: Sodium Intake for Adults and Children. WHO, Geneva*	
Lange C, Manz K, Kuntz RE. Alkoholkonsum bei Erwachsenen in Deutschland: Riskante Trinkmengen. Journal of health monitoring 2017; 2(2):66–73.	RKI	Alkohol	Konsum riskanter Alkoholtrinkmengen = erhöht Risiko von schädlichen Konsequenzen für körperliche und psychische Gesundheit Grenzwerte für riskante Alkoholtrinkmenge: > 10-12 g/d für Frauen und 20-24 g/d für Männer Basis: „Gesundheit in Deutschland aktuell“ 2014/2015-EHIS (GEDA 2014/2015-EHIS): Frequenz und Menge des Alkoholkonsums mittels Instrument aus Europäischen Health Interview Survey (EHIS) Basis: Daten von 23.561 Personen ab 18 Jahren (12.913 Frauen, 10.648 Männer)	- niemals Alkohol: 16,9 % (95% KI 15,9 – 17,8) der Frauen und 10,3 % (95% KI 9,6 – 11,2) der Männer - mindestens wöchentlicher Konsum riskanter Alkoholtrinkmengen: 13,8 % (95% KI 13,0 – 14,7) der Frauen und 18,2 % (95% KI 17,3 – 19,1) der Männer. >> Männer konsumieren demnach signifikant häufiger Alkohol in riskanten Trinkmengen als Frauen. - höchste Prävalenz bei 45- bis 64-Jährigen: 17,2 % bei Frauen und 21,7 % bei Männern	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
DOI: 10.17886/RKI-GBE-2017-031 [92]			>> Selbstangaben der Befragten, wobei sowohl das Erinnerungsvermögen, die richtige Einschätzung von Glasgrößen als auch sozial erwünschtes Antwortverhalten die Ergebnisse beeinflussen können	- Frauen der oberen Bildungsgruppe: höhere Prävalenzen des Risikokonsums als aus der unteren Bildungsgruppe (Ausnahme: 30- bis 44-Jährigen) - Bei Männern zeigt sich in der Altersgruppe ab 65 Jahren das gleiche Bild wie bei Frauen mit höheren Anteilen des Konsums riskanter Trinkmengen in der oberen Bildungsgruppe. - In den Altersgruppen 18 bis 64 Jahre gibt es hinsichtlich des Bildungsstatus keine relevanten Unterschiede im Risikokonsum. - Prävalenzen der Länder unterscheiden sich kaum vom Bundesdurchschnitt.	
Schienkiewitz A, Mensink GBM, Kuhnert R. Übergewicht und Adipositas bei Erwachsenen in Deutschland. Journal of health monitoring 2017; 2(2):21–8. DOI: 10.17886/RKI-GBE-2017-025. *[89]*		Gewicht	- „Gesundheit in Deutschland aktuell“ (GEDA-2014/2015-EHIS) - Erhebungsmethode: schriftlich oder online Fragebogen - Grundgesamtheit: Bevölkerung ab 18 Jahren mit ständigem Wohnsitz in Deutschland - Stichprobe: Einwohnermeldeamt – zufällig ausgewählte Personen aus 301 Gemeinden in Dtld. - Untersuchungszeitraum: November 2014 – Juli 2015 - n= 23.791 Personen ab 18 Jahren - 13.006 Frauen, 10.785 Männer - gültige Angabe zu Körpergewicht und -größe. - Gewichtungsfaktor: korrigiert Abweichungen der Stichprobe von Bevölkerungsstruktur (31.12.2014) hinsichtlich Geschlecht, Alter, Kreistyp und Bildung **Klassifikationsschema der WHO [1] Erwachsener:** - BMI < 18,5 kg/m2 untergewichtig. - BMI 18,5 -< 25 kg/m2 Normalgewicht, - BMI 25 - < 30 kg/m2 Übergewicht - BMI ≥ 30 kg/m2 Adipositas definiert **Limitation:** - Selbstangaben - BMI eher unterschätzt: da Körpergewicht häufig unter-, die Körpergröße eher überschätzt	- 46,7 % (95% KI 45,6 – 47,9) der Frauen und 61,6 % der Männer einen BMI von mehr als 25 kg/m2 auf und sind damit übergewichtig oder adipös. - Prävalenz von Übergewicht einschließlich Adipositas steigt mit zunehmendem Alter **Frauen**: - 45 – 64 Jahre: 50,1% (95% KI 48,4 – 51,9) - ≥ 65 Jahre: 58,9% (95% KI 56,5 – 61,3) **Männer**: - 45 – 64 Jahre: 70,1% (95% KI 68,3 – 71,7) - ≥ 65 Jahre: 71,3% (95% KI 69,2 – 73,2) - Prävalenz von Übergewicht einschließlich Adipositas in den lag 2012 für Frauen bei 45,8 % und für Männer bei 59,7 % [12]. **Quellen**: 1. World Health Organization (2000) Obesity: preventing and managing the global epidemic. World Health Organization. Technical Report Series 894. Geneva 12. Robert Koch-Institut (2014) Ergebnisse der Studie „Gesundheit in Deutschland aktuell 2012“. Beiträge zur Gesundheitsberichterstattung des Bundes. Robert Koch-Institut, Berlin http://edoc.rki.de/documents/rki_fv/recJuHnzacx8A/PDF/28GsWuNtFjVqY.pdf (Stand: 18.04.2017)	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
			- auf Gruppenebene korreliert BMI gut mit direkten Messungen zur Bestimmung der Körperfettmasse - Vergleich der aktuellen GEDA 2014/2015-EHIS-Zahlen mit GEDA-Befragungen: Änderung der Verfahren der Stichprobenziehung sowie der Befragungsmodus (Selbstausfüllfragebogen, telefonisches Interview)		
Tasnim S. Effect of alcohol on blood pressure. Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD012787. [95] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012787.pub2/abstract	2020	hoch	Primary objective: determine short-term dose-related effects of alcohol vs. placebo on SBP and DBP in healthy and hypertensive adults over 18 years of age. Secondary objective: To determine short-term dose-related effects of alcohol versus placebo on heart rate in healthy and hypertensive adults over 18 years of age. Suchzeitraum: up to March 2019: Selection criteria - RCTs - comparing effects of a single dose of alcohol versus placebo on BP or heart rate in adults (≥18 years of age).	Allgemeines: - 32 RCTs (n= 767) - nost participants were male (N = 642) and healthy - mean age: 33 years, mean body weight: 78 kilograms. Ergebnisse der Einzelstudien für Population mit Hypertonie: Low-dose alcohol (< 14 g): keine Studien identifiziert Medium-dose alcohol (14 to 28 g) <u>Foppa 2002 (n= 13), cross-over</u> - SBP und DBP jeweils nach 6, 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen <u>Kawano 1992 (n= 13), cross-over</u> - SBP und DBP jeweils nach 6, 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen <u>Kawano 2000 (n= 10), cross-over</u> - SBP nach 6h: MD zugunsten Alkohol gesenkt -16.30 [-25.05, -7.55], Datenqualität sehr gering - DBP nach 6h: MD zugunsten Alkohol gesenkt -11.10 [-16.73, -5.47], Datenqualität sehr gering - SBP und DBP jeweils nach 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen <u>Kojima 1993 (n= 21), cross over</u> - SBP nach 6h: MD zugunsten Alkohol gesenkt -18.00 [-26.32, -9.68], Datenqualität sehr gering - DBP nach 6h: MD zugunsten Alkohol gesenkt -12.00 [-17.50, -6.50], Datenqualität sehr gering - SBP und DBP jeweils nach 7-12 und 13h: kein Unterschied in der MD zwischen Gruppen High-dose alcohol (> 30 g) Hering 2011 (n= 24), cross over	Subgruppenanalyse für Populationen (Hypertonie/ keine Hypertonie) wurde nicht durchgeführt Herzfrequenz als weiterer Endpunkt erhoben

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
				SBP und DBP nach 6h: kein Unterschied in der MD zwischen Gruppen Ergebnisse für gemischte Population: Low-dose alcohol (< 14 g) - within 6 hours (2 RCTs, N = 28) did not affect BP but did increase HR by 5.1 bpm (95% CI 1.9 to 8.2) (moderate-certainty evidence). Medium-dose alcohol (14 to 28 g) - within 6 hours (10 RCTs, N = 149) decreased SBP by 5.6 mmHg (95% CI -8.3 to -3.0) and DBP by 4.0 mmHg (95% CI -6.0 to -2.0) and increased HR by 4.6 bpm (95% CI 3.1 to 6.1) (moderate-certainty evidence for all). - within 7 to 12 hours (4 RCTs, N = 54) did not affect BP or HR. - > 13 hours after consumption (4 RCTs, N = 66) did not affect BP or HR. High-dose alcohol (> 30 g) - within 6 hours (16 RCTs, N = 418) decreased SBP by 3.5 mmHg (95% CI -6.0 to -1.0), decreased DBP by 1.9 mmHg (95% CI-3.9 to 0.04), and increased HR by 5.8 bpm (95% CI 4.0 to 7.5). >> certainty of evidence was moderate for SBP and HR, and was low for DBP. - within 7 to 12 hours of consumption (3 RCTs, N = 54) decreased SBP by 3.7 mmHg (95% CI -7.0 to -0.5) and DBP by 1.7 mmHg (95% CI –4.6 to 1.8) and increased HR by 6.2 bpm (95% CI 3.0 to 9.3). The certainty of evidence was moderate for SBP and HR, and low for DBP. - ≥ 13 hours after consumption (4 RCTs, N = 154) increased SBP by 3.7 mmHg (95% CI 2.3 to 5.1), DBP by 2.4 mmHg (95% CI 0.2 to 4.5), and HR by 2.7 bpm (95% CI 0.8 to 4.6) (moderate-certainty evidence for all).	
Zeiher J, Kuntz B, Lange C. Rauchen bei Erwachsenen in Deutschland.	RKI	Rauchen	„Gesundheit in Deutschland aktuell“ 2014/2015-EHIS (GEDA 2014/2015- EHIS) - Erhebung mit der Frage: „Rauchen Sie?“	Erwachsenenbevölkerung Deutschlands: - Raucher/ gelegentlich Raucher: Frauen: 20,8 % (95% KI 19,9; 21,7); Männer 27,0 % 95% KI (25,9; 28,1) - Nie geraucht: Frauen: 52,6 % (95% KI 51,4 – 53,8), Männer 38,0 % (95%KI 36,9 – 39,1)	

Zitat	Quelle	Thema	Charakteristika	Ergebnisse	Kommentar
Journal of health monitoring 2017; 2(2):59–65. DOI: 10.17886/RKI-GBE-2017-030. *[96]*			- Antwortoptionen: „ja, täglich“, „ja, gelegentlich“, „nein, nicht mehr“, „habe noch nie geraucht“ Kategorisierung: - aktuelle Raucher (täglich oder gelegentlich), ehemalige Raucher und Nieraucher. - Rauchstatus in früheren Gesundheitssurveys ähnlich erhoben → zeitliche Entwicklungen und Trends möglich sind - Datenbasis: 23.960 Personen ab 18 Jahren (13.108 Frauen, 10.852 Männer)	- Absinken der Rauchquote: bei Männern 45 Jahren, bei Frauen ab 65 Jahren - in höheren Bildungsgruppen deutlich weniger verbreitet als in niedrigen Bildungsgruppen. - Anteil der aktuell Rauchenden in den jüngeren Altersgruppen am höchsten. Regionale Unterschiede: - Rauchquote: Bei Männern in Sachsen-Anhalt am höchsten, in Bayern am niedrigsten. - Rauchquote: Bei Frauen in Sachsen am niedrigsten und in Bremen am höchsten. - Tendenziell liegt die Rauchquote im Norden höher als im Süden, im Osten höher als im Westen und in den Stadtstaaten höher als in den Flächenstaaten - anhand Daten früherer Gesundheitssurveys des RKI lässt sich zeigen, dass der Anteil der Raucherinnen und Raucher in der Erwachsenenbevölkerung seit dem Jahr 2003 um gut 8 %-Punkte bei Frauen bzw. gut 11 Prozentpunkte bei Männern zurückgegangen [14]. Quellen: 14. Robert Koch-Institut (Hrsg) (2014) Daten und Fakten: Ergebnisse der Studie „Gesundheit in Deutschland aktuell 2012“ Beiträge zur Gesundheitsberichterstattung des Bundes. Robert Koch-Institut, Berlin http://edoc.rki.de/documents/rki_fv/recJuHnzacx8A/PDF/28GsWuNtFjVqY.pdf (Stand: 23.02.2017)	

Gibbs 2021 (Physical activity (elevated blood pressure or cholesterol))

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Gibbs et al. Physical activity as a critical component of first line treatment for elevated blood pressure or cholesterol: Who,What,and How. An Am Heart Ass.	2021	not applicable	**Aim**: (1) highlight the mild-moderate–risk patient groups indicated for lifestyle-only treatment for elevated blood pressure or cholesterol; (2) describe recommendations, average effects, and additional considerations when prescribing lifestyle treatment with physical activity;	authors documented information on: - Physical Activity Guidelines - Average Effects of Increasing Physical Activity - Treatment Effect of Physical Activity Among Patients With Baseline Values in the Mild to Moderate Range of Elevated Blood Pressure and Blood Cholesterol	scientific statement from the American Heart Association authors estimated that 21% and

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Scientific statement. Hypertension 2021,;78:e26-e37. https://pubmed.ncbi.nlm.nih.gov/34074137/			(3) provide guidance and resources for clinicians to assess, prescribe, counsel, and refer to support increased physical activity in their patients **Questions asked:** WHO ARE THE INDIVIDUALS WITH ELEVATED BLOOD PRESSURE OR CHOLESTEROL INDICATED FOR FIRST-LINE TREATMENT WITH LIFESTYLE APPROACHES? WHAT PHYSICAL ACTIVITY PRESCRIPTION IS RECOMMENDED FOR THE TREATMENT OF ELEVATED BLOOD PRESSURE OR BLOOD CHOLESTEROL? HOW CAN CLINICIANS HELP THEIR PATIENTS ADOPT AND MAINTAIN A PHYSICALLY ACTIVE LIFESTYLE?	- Dose-Response of Physical Activity on Blood Pressure and Blood Cholesterol - Variable and Adverse Responses to Exercise - Comparison of Physical Activity With Other Lifestyle Treatments - Role of Physical Activity in the Prevention of CVD - Helping Patients Become More Physically Active - Ideas and Resources for Increasing Physical Activity (e.g. Table 4 **Tips and Resources for Supporting Physical Activity in Patients**) Auszug (!copyright beachten!): *Simple ideas to increase daily physical activity* - Using public transportation? Try walking to a further stop before you get on or get off 1 stop early. - Always busy at work? Have a walking meeting with a colleague, get your coffee at a shop that is a little farther than the usual one, or go for a walk on your lunch break. - At work, home, or shopping? Take the stairs instead of the elevator/escalator every time you have the choice to do so. - Have a pet? Find a new route that is a little longer for the dog's walk. - Making plans with family or friends? Rather than a movie, choose walking through a museum, bowling, or mini golf. - In your free time? Garden, volunteer, or take on a home improvement project, rather than using social media, online shopping, or watching TV. *Talking points for increasing planned exercise* - Never been an athlete or do not like gyms? Walking is a great place to start. Start slow and build up to 30 minutes or more per day of brisk walking. Recording steps or time spent walking with a paper diary, pedometer, or activity tracker can help you monitor progress! - Bad weather or no access to an exercise facility? At-home exercise options like yoga, cardio-dance, and circuit training are available online or from your cable provider, often do not require any extra equipment, and many are free! Look for content from a trusted provider, such as the YMCA. - No time or too tired to exercise?	28% to 37% of US adults, respectively, have mild-moderate–risk blood pressure and cholesterol note: Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at https://www.heart.org/permissions. A link to the "Copyright Permissions Request Form" appears in the second paragraph (https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form).

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Every minute of exercise counts toward weekly goals, and a little is better than none. If you cannot get 30 minutes on one day, adding a few minutes of dancing to your favorite song, playing tag with kids, or marching/jogging in place during commercials can improve your health and increase your energy. - Like to exercise with others? Join a softball, ultimate Frisbee, or tennis league, find an accountability buddy like a family member or friend, create a walking group at work or home, or sign up for an exercise class at your local community center, workplace, or place of worship. authors opinion: - guidelines published by the American Heart Association and the American College of Cardiology broadly recommend lifestyle approaches to prevent and treat elevated blood pressure and cholesterol - for patients with mildly or moderately elevated blood pressure and blood cholesterol, lifestyle-only approaches are the first line of therapy - of the recommended lifestyle changes, increasing physical activity has extensive benefits, including improving both blood pressure and blood cholesterol, that are comparable, superior, or complementary to other healthy lifestyle changes - physical activity assessment and prescription are an excellent lifestyle behavior treatment option for all patients, including for the large population of mild-moderate–risk patients with elevated blood pressure and blood cholesterol	

Neal 2021 (Salt substitution (adults - history of stroke))

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
Neal et al. Effect of Salt Substitution on Cardiovascular Events and Death. N Engl J Med. 2021 Sep 16;385(12):1067-1077. doi: 10.1056/NEJMoa2105675. Epub 2021 Aug	2021	Cochrane Risk of Bias Tool not applicable	**Objective** Salt Substitute and Stroke Study (SSaSS), China to define the overall balance of benefits and risks of salt substitute as compared with regular salt on stroke, cardiovascular events, death, and clinical hyperkalemia. **Design** open-label, cluster-randomized trial (600 villages) *note*: villages were randomly assigned in a 1:1 ratio	n=20,995 participants - mean age 65.4 years - 49.5% female - 72.6% had a history of stroke - 88.4% a history of hypertension - mean duration of follow-up: 4.74 years - final follow-up: o n=13,130 participants face-to-face o n=1,357 by contact o n=317 through record linkage o n=19 in-person follow-up visit	cluster randomization note: General health advice about stroke prevention, which included a recommendation to reduce salt intake, was provided at

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
29. https://pubmed.ncbi.nlm.nih.gov/34459569/			follow-up 5 years (at 6-month intervals) ClinicalTrials.gov number, NCT02092090 **Inclusion and exclusion criteria** - participants: adult men and women - history of stroke or aged 60 years or older - poorly controlled blood pressure ○ (systolic blood pressure ≥140 mm Hg if receiving blood-pressure–lowering medication or ≥160 mm Hg if not) - provide personal identifiers - could be contacted - excluded if they had a potential contraindication to the salt substitute; e.g. use of a potassium-sparing diuretic, potassium supplement, known serious kidney disease **Intervention** salt substitute (75% sodium chloride and 25% potassium chloride by mass) free-of-charge[6] **Control** continued to use regular salt (100% sodium chloride) **Outcomes** primary: stroke[7] secondary: - major adverse cardiovascular events[8] and death from any cause - safety outcome: clinical hyperkalemia	- mean blood pressure: 154.0/89.2 mm Hg ○ 79.3% using at least one blood-pressure–lowering medication: ▪ 41.8% calcium antagonist, ▪ 22.8% angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, ▪ 11.5% diuretic, ▪ 5.7% beta-blocker, ▪ 0.9% alpha-blocker - mean 24-hour urinary sodium excretion: 4.3 g (187 mmol) - mean 24-hour urinary potassium excretion: 1.4 g (36 mmol) **results:** **primary:** **rate of fatal or nonfatal stroke** salt-substitute group vs. regular-salt group • 29.14 events vs. 33.65 events per 1000 person-years • rate ratio 0.86 (95% CI 0.77 to 0.96); P = 0.006 **secondary:** **major adverse cardiovascular events** salt-substitute group vs. regular-salt group • 49.1 events vs. 56.3 events per 1000 person-years • rate ratio 0.87 (95% CI, 0.80 to 0.94); P<0.001 **death from any causes** salt-substitute group vs. regular-salt group - n=4,172 died - 39.3 events vs. 44.6 events per 1000 person-years - rate ratio 0.88 (95% CI, 0.82 to 0.95); P<0.001) **safety (clinical hyperkalemia)** salt-substitute group vs. regular-salt group - definite or probable hyperkalemia: n=2 vs. n=1 - possible hyperkalemia: n=313 (including 302 who died and 11 who had a nonfatal event) - 3.35 events vs. 3.30 events per 1000 person-years	trial commencement to all villages but was not reinforced thereafter. Use of other medical therapy was permitted according to local guidelines. potassium was not measured serially p-values should be interpreted with caution (number of participants)

[6] Sufficient salt substitute was provided to cover all household cooking and food preservation requirements at an average of approximately 20 g per person per day.
[7] Defined as: acute disturbance of focal neurologic function resulting in death or symptoms lasting more than 24 hours
[8] (a composite of nonfatal stroke, nonfatal acute coronary syndrome, or death from vascular causes)

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
				- rate ratio, 1.04 (95% CI, 0.80 to 1.37); P = 0.76 authors concluded that: - among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt	

Pescatello 2019 (Physical activity (hypertension))

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Pescatello et al., Physical activity to prevent and treat hypertension: A systematic review. Med.Science Sports Exerc 2019,51:1314-1323. https://pubmed.ncbi.nlm.nih.gov/31095088/	2019	not applicable	**Objective** (systematic umbrella review) examines and updates the evidence on the relationship between physical activity (PA) and blood pressure (BP) presented in the 2008 Physical Activity Guidelines Advisory Committee Scientific Report **Sources** - PubMed®, Cumulative Index to Nursing and Allied Health Literature, and Cochrane - supplemented by the authors who were experts in the area to provide additional articles **Inclusion and exclusion criteria** - systematic reviews and meta-analyses - published from 2006 to February 2018 - included adults with normal BP, prehypertension, and hypertension[9] - studies of non-ambulatory adults, hospitalized patients, or animals were excluded **Quality assessment** grading of evidence rubric can be found in the 2018 PAGAC Report assessment of methodological study quality: AMSTARExBP **Research question:**	n=1 systematic review of - n=2 longitudinal prospective cohort studies (influence of general and leisure-time habitual physical activity on CVD mortality; 31,32) n=17 meta-analyses of RCT - n=15 of the meta-analyses included RCT that examined the BP response to an exercise training intervention among adults with normal BP (k = 7) (14,15,17–19,21), prehypertension (k = 5) (17–20,24), or hypertension (k = 15) (14–21,24–30) compared with a control condition among similar adults who were physically inactive at baseline - n=2 of the meta-analyses examined prospective cohort studies of adults initially free of hypertension for the influence of general and leisure-time habitual physical activity on the risk of the development of hypertension (22,23) (n=594,129 adults ≥18 y, range 216 to 330,222) (body mass index (BMI) ranged from normal weight to obese) **results** - relationship between physical activity and BP, assessed as - indicators of the risk of incident hypertension: ○ a) BP response to an exercise training intervention ranging from low to vigorous intensity ○ b) association between habitual leisure-time physical activity and the risk of developing hypertension	umbrella review of systematic reviews and meta-analyses; search from 2006 until February 2018 overall methodological study quality of the qualifying reports was moderate, with 83.3% of the included trials scoring poor to moderate and 16.7% high methodological study quality

[9] The JNC 7 BP definitions are as follows: Hypertension, resting SBP of ≥140 mm Hg and/or a resting DBP of ≥90 mm Hg, or taking antihypertensive medication, regardless of the resting BP level; Prehypertension, resting SBP from 120 to 139 mm Hg and/or DBP from 80 to 89 mm Hg; and Normal BP, a resting SBP <120 mm Hg and DBP <80 mm Hg.

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- relationship between all types and intensities of physical activity and BP among healthy adults ≥18 y with normal BP, prehypertension, and hypertension	**authors conclusion**: strong evidence: 1) an inverse dose–response relationship between PA and incident hypertension among adults with normal BP; 2) physical activity reduces the risk of cardiovascular disease (CVD) progression among adults with hypertension; 3) PA reduces BP among adults with normal BP, prehypertension, and hypertension; 4) the magnitude of the BP response to PA varies by resting BP, with greater benefits among adults with prehypertension than normal BP moderate evidence: - indicates the relationship between resting BP and the magnitude of benefit does not vary by type of physical activity among adults with normal BP, prehypertension, and hypertension limited evidence suggests the magnitude of the BP response to PA varies by resting BP among adults with hypertension insufficient evidence is available to determine if factors such as sex, age, race/ethnicity, socioeconomic status, and weight status or the frequency, intensity, time, and duration of PA influence the associations between PA and BP	

Posadzki 2014 (Yoga ((pre-) hypertension))

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Posadzki et al. Yoga for hypertension: a systematic review of randomized clinical trials. Complement Ther Med. 2014 Jun;22(3):511-22. doi:10.1016/j.ctim.2014.03.009. Epub 2014 Mar 31.	2014	low	**Objective** to evaluate the effectiveness of yoga as a treatment of hypertension **Sources** 17 databases (up to January 2014), AMED (EBSCO), CINAHL (EBSCO), EMBASE (OVID), MEDLINE (OVID),PsycINFO, The Cochrane Library, ISI Web of Knowledge, two Indian databases (Indian Council of Medical Research and INDMED), one Chinese database (China National Knowledge Infrastructure), three Japanese databases (J stage,	n=17 randomized controlled trials (n=1310 patients) - authors noted that patients were treated with yoga combined with concomitant medication in 8 trials - n=15 trials used parallel design; n=2 trials used cross-over design - details of yoga regimen were reported - over-all quality of the RCT was rated as poor - all RCT had methodological limitations - authors reported n=2 RCTs with acceptable methodological quality **Outcome** - for n=3 of 13 trials data were not reported	systematic review, no metaanalysis excluded studies not reportetd im Hintergrundtext der Leitlinie ist Yoga beispielhaft aufgeführt, wobei ein

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

https://pubmed.ncbi.nlm.nih.gov/24906591/			Journal archive, and Science Links Japan), and four Korean databases (DBpia, Korea National Assembly Library, Research Information Sharing Service and Oriental Medicine Advanced Searching Integrated System)
			Quality assessment
			Risk of bias (Cochrane criteria)
			Inclusion and exclusion criteria
			- randomized clinical trials (RCTs)
			- adult patients [≥18 of age]
			- with pre-hypertension[120—139/80—89 mm Hg]
			- or hypertension [≥140/90 mm Hg] (as defined by AHA)
			- with or without existing co-morbidities
			Intervention
			- yoga[10]
			Control
			- any type of control
			Outcome
			- post-treatment differences in SBP and DBP (assessed descriptively using measures of treatment effects)
				- n=10 trials: calculated effect sizes ranged from −0.018 (small) to −1.952 (large) (differences scores, Cohen's d), x= 0.58 (medium) (Table 1 documented effect size (differences) for systolic and/or diastolic blood pressure)
				- (subgroup analyses (authors summary):
				  ○ in all RCTs investigating patients with co-morbidities; yoga reduced SBP and DBP
				  ○ n=9 RCTs investigating patients without co-morbidities; n=6 yoga reduced SBP; n=5 reduced DBP
				- authors abstract summary :
				  ○ n=11 RCT suggested that yoga leads to a (significantly) greater reduction in systolic blood pressure (SBP) compared to various forms of pharmacotherapy, breath awareness or reading, health education, no treatment (NT), or usual care (UC)
				  ○ n=8 RCT suggested that yoga leads to a (significantly) greater reduction in diastolic blood pressure (DBP) or night-time DBP compared to pharmacotherapy, NT, or UC
				  ○ n=5 RCT indicated that yoga had no effect on SBP compared to dietary modification (DIM), enhanced UC, passive relaxation (PR), or physical exercises (PE)
				  ○ n=8 RCT indicated that yoga had no effect on DBP compared to DIM, enhanced UC, pharmacotherapy, NT, PE, PR, or breath awareness or reading. One RCT did not report between-group comparisons
				authors recommendation for practice (GRADE):
				- a weak recommendation for the use of yoga in high BP
					Cochrane-Review (2014) herangezogen wurde [78], eine Primärstudie entsprach den Einschlusskriterien und ergab Hinweise auf eine Blutdrucksenkung

[10] practice that was based on traditional yoga philosophy or yoga practice and that ''can consist of one or more of the following: specific postures, breathing exercises, body cleansing, mindfulness meditation, and lifestyle modifications'' was considered as yoga and therefore eligible for inclusion

8 Evidenztabellen Medikamentöse Therapie (Stand: 26.10.2021)

8.1 Medikationskatalog 2021

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Medikationskatalog 2021 – Hypertonie [114] https://www.kbv.de/html/medikationskatalog.php	2021	-	**Ziel** Hilfe zur evidenz-basierten, sicheren und wirtschaftlichen Verordnungsentscheidung Ermittlung von Standard- oder Reservewirkstoffen und nachrangig zu verordnenden Wirkstoffen[11] (Als „Standard“ sind im Medikationskatalog diejenigen Wirkstoffe definiert, die für den überwiegenden Anteil der Patient*innen zur Behandlung der Erkrankung zur Verfügung stehen.) (Die zweite Kategorie „Reservewirkstoff“ bezieht sich auf den Einsatz bei relevanten Patient*innengruppen, für die die Standardwirkstoffe nicht in Frage kommen.) **Suche** Leitlinien[12], AkdÄ, GBA, DMP, IQWIG, Cochrane Library; weitere Quellen wie PRISCUS Liste und Rote-Hand-Briefe	**Evidenzübersicht**: ▪ die eingeschlossenen, gültigen und anerkannten Leitlinien beinhalten allgemeine Regeln zur pharmakotherapeutischen Behandlung der Hypertonie wie auch Empfehlungen zum Einsatz einzelner und kombinierter Wirkstoffe ▪ auf Seite 29 f werden unter den Pubkten 1 bis 13 die Grundzüge der Pharmakotherapie als Algorithmus aus den LL zusammengefasst (für Details s. Medikationskatalog 2021) ▫ 1. ACE-Hemmer, Sartane, Betablocker, Calciumkanalblocker und Diuretika (Thiazide und Thiazid-artige) zeigen effektive Senkung des Blutdrucks und kardiovaskulärer Ereignisse in RCTs → Basis antihypertensiver Therapie ▫ 2. für die meisten hypertensiven Patient*innen initial eine Kombinationstherapie (bevorzugt ACE-Hemmer oder Sartan und Calciumkanalblocker oder Diuretikum) ▫ 3. Betablocker in bestimmten klinischen Situationen, z.B. Angina pectoris, Postmyokardinfarkt, Herzinsuffizienz oder Herzfrequenz-Kontrolle (z.B. Vorhofflimmern) oder bei jungen Frauen mit Kinderwunsch/Schwangeren	Nutzungsbedingungen: Bitte beachten Sie: Dieses ist kein allgemein zugängliches Dokument. Mit der Nutzung erkennen Sie die unter: https://www.kbv.de/html/nutzungsbedingungen.php hinterlegten Bedingungen an. Eine Bewertung mit dem AMSTAR II Tool ist auf Grund der vertraulichen Dokumentation der Methodik nicht möglich

[11] Hinweis: „Bei einigen Fixkombinationen orientieren sich die Einstufungen an der übergeordneten Bedeutung der Arzneimittel-Richtlinie in § 9 und § 16 (2) 5 (Wirtschaftlichkeitsgebot), so dass in diesen Fällen nicht die Einstufungen ihrer Einzelwirkstoffe übernommen werden können.“ sowie „(…) werden in dem Medikationskatalog nur Wirkstoffe und Wirkstoffkombinationen bewertet, für die zugelassene Fertigpräparate existieren“ (vgl. Medikationskatalog 2021 S. 5)

[12] ESC/ESH Guidelines for the management of arterial hyperten-sion (2018), herausgegeben von der European Society of Cardiology (ESC) und der Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH); „Leitlinien für das Management der arteriellen Hypertonie“, die von der Deutschen Gesellschaft für Kardiologie und der Deutschen Hochdruckliga neben den oben genannten europäischen Gesellschaften als ESC Pocket Guidelines;
Clinical guideline 136 Hypertension in adults: diagnosis and management. National Institute for Healthand Care Excellence (NICE) (2019) → Aufgrund der Fokussierung des Medikationskatalogs auf den deutschen Versorgungskontext nicht weiter berücksichtigt; Clinical Practice Guidelines for the Management of Hypertension in the Community (2014). American Society of Hypertension and International Society of Hypertension → Aufgrund der Fokussierung des Medikationskatalogs auf den deutschen Versorgungskontext nicht weiter berücksichtigt; Evidence-Based Guideline for the Management of High Blood Pressure in Adults (2014). Report from the panel members appointed to the eighth Joint National Committee → Aufgrund der Fokussierung des Medikationskatalogs auf den deutschen Versorgungskontext nicht weiter berücksichtigt; AWMF-Leitlinie (S2k) Pädiatrische Kardiologie, Pädiatrische Nephrologie und Pädiatrie: Arterielle Hypertonie im Kindes- und Jugendalter (2015). Deutsche Gesellschaft für Pädiatrische Kardiologie. → Die Angaben von Norm- und Schwellenwerten für Kinder und Heranwachsende sowie von Arzneimittelzulassungen im pädiatrischen Bereich werden im Medikationskatalog nicht näher dargestellt; ACC/AHA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults (2017). American College of Cardiology,

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				◻ 4. antihypertensive Behandlung mit Zweifachkombination einleiten, Ausnahmen: gebrechliche ältere Patient*innen und solche mit niedrigem Risiko und Grad-1-Hypertonie ◻ 5. bei unzureichender Blutdruckeinstellung: Dreifachkombination (üblicherweise ACE-Hemmer oder Sartan + Calciumkanalblocker + Thiazid oder Thiazid-artiges Diuretikum ◻ 6. bei resistenter Hypertonie: Therapietreue kontrollieren; Therapie erweitern (Hinzugabe Spironolacton, oder anderen Diuretika wie Amilorid oder Betablocker oder Alphablocker) ◻ 7. Kombination von 2 Blockern des Renin-Angiotensin-Systems (z.B. ACE-Hemmer + Sartan) wird nicht empfohlen ◻ 8. skizzierte stufenweise Behandlung (unter Einschluss der Betablocker) eignet sich außer für die unkomplizierte Hypertonie auch für die meisten Patienten mit Hypertonie-bedingten Organschäden, ze-rebrovaskulärer Erkrankung, Diabetes oder peripherer arterieller Erkrankung ◻ 9. bei Komorbidität KHK initial Zweifachkombination (ACE-Hemmer oder Sartan + Betablocker oder Calciumkanalblocker oder Calciumkanalblocker + Betablocker oder Diuretikum oder Betablocker + Diuretikum; in nächster Stufe Kombination mit dritter Substanz aus genannten Gruppen ◻ 10. bei Komorbidität chronische Niereninsuffizienz initial Calciumkanalblocker + RAS-Inhibitor (ACE-Hemmer oder Sartan) oder Diuretikum (u.U. Schleifendiuretikum) + RAS-Inhibitor; in nächster Stufe Dreierkombination aus RAS-Inhibitor + Calciumkanalblocker + (Schleifen-)Diuretikum ◻ 11. bei Komorbidität Herzinsuffizienz mit reduzierter Ejektionsfraktion initial Dreifachkombination (RAS-Inhibitor + (Schleifen-)Diuretikum + Betablocker); in nächster Stufe als vierte Komponente Aldosteron-Antagonist (Spironolacton oder Eplerenon) hinzu; Calciumkanalblocker vom Typ Verapamil oder Diltiazem sollen nicht eingesetzt werden	

American Heart Association → Die Empfehlungen zur medikamentösen Therapie wurden mit den ESC/ESH-Guidelines verglichen. Von einigen Besonderheiten abgesehen stimmen die amerikanischen und die europäischen Guidelines im Wesentlichen überein. Innerhalb der Wirkstoffgruppen sind keine einzelnen Wirkstoffe bewertet. In der Leitlinie wird auf besondere Indikationen eingegangen, die im Sinne der Komorbidität für die Hypertonie oder deren Behandlung bedeutsam sind, z. B. die Herzinsuffizienz. Im Medikationskatalog wird auf Abweichungen bzw. auf länderspezifisch und historisch bedingte Bevorzugungen einzelner Wirkstoffe nicht weiter eingegangen; Hypertension Canada's Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children (2018). Nerenberg KA, Zarnke KB, Leung AA et al. → Aufgrund der Fokussierung des Medikationskatalogs auf den deutschen Versorgungskontext nicht weiter berücksichtigt.

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				◻ 12. bei Komorbidität Vorhofflimmern initial Zweifachkombination (RAS-Inhibitor + Betablocker oder Verapamil- bzw. Diltiazem-artiger Calciumkanalblocker oder Betablocker + Calciumkanalblocker (CAVE: Routinemäßige Kombination aus Betablocker + Verapamil-/ Diltiazem-artigem Calciumkanalblocker wird wegen möglicher zu starker Senkung der Herzfrequenz nicht empfohlen)) ◻ 13. Hypertonie während der Schwangerschaft: Methyldopa, Metoprolol und Calciumkanalblocker; ! ACE-Hemmer, Sartane oder direkte Renininhibitoren werden ausdrücklich nicht empfohlen; in der Stillzeit: bevorzugt Nifedipin ◻ Hinweis: Hautkrebs-Risiko bei HCT-Therapie → kein Absetzen blutdrucksenkender Präparate; begrenzte Aussagefähigkeit der Registerstudie ◻ Reservemedikation: Nebivolol oder Lercanidepin (aus Kommentar zur LL) ▪ Therapiempfehlungen der AkdÄ: ◻ Mono- oder Kombinationstherapie unter Abwägung des kardiovaskulären Risikos und des Ausgangsblutdrucks ◻ Monotherapie: Diuretikum, ACE-Hemmer oder Sartan (z.B. bei Reizhusten), Ca-Kanal-Blocker oder Betablocker ◻ Zweifachkombination: Diuretikum oder langwirksamer Ca-Kanal-Blocker ◻ Diuretika Basistherapeutika (v.a. bei Älteren) ◻ Betablocker erste Wahl bei Komorbidität KHK und Herzinsuffizienz (Senkung der kardiovaskulären Morbidität und Mortalität) → bevorzugt Beta1-selektive; Kombination nur mit Ca-Kanal-Blockern vom Dihydropyridintyp ◻ Calciumkanal-Blocker in Monotherapie bei Älteren oder ausgeprägten Krankheitsmanifestationen in Kombination ◻ Alpha-Blocker werden im bei einer Mono- oder Zweifachkombination nicht mehr empfohlen (Beschränkung der Anwendung auf schwere Hypertonieformen) ◻ Antisympathotonika (Moxonidin, Clonidin, Methyldopa) sind Reservemedikamente, ebenso Vasodilatatoren für besondere Situationen (Dihydralazin und Minoxidil) ◻ Methyldopa bevorzugt bei Schwangerschaftshypertonie ◻ Clonidin bei hypertensiven Notfällen	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				▫ Reserpin und Reserpin-Kombinationen zur Behandlung der essenziellen Hypertonie sind nicht mehr in Verkehr ▫ ür Renininhibitor Aliskiren liegen Langzeitstudien mit harten Endpunkten nicht vor; Stellenwert der Substanz ist unklar ▫ Sicherheitsaspekte zu HCT (Rote-Hand-Brief) → regelmäßige Hautinspektionen; generelle Therapieumstellung nicht erforderlich und sollte individuell geprüft werden (Chlortalidon oder Indapamid mögliche Alternativen), Vorsichtsmaßnahmen prüfen ■ IQWIG-Abschlussbericht: ▫ Vergleiche mit Diuretika › Diuretika vs. Betablocker: kein Unterschied › Diuretika vs. ACE-Hemmer: geringe, signifikant stärkere blutdrucksenkende Wirkung von Diuretika › Diuretika vs. Ca-Kanal-Blocker: keine Studien vorhanden ▫ Vergleiche mit Betablockern › Betablocker vs. ACE-Hemmer: keine Aussage möglich wegen heterogener Ergebnisse › Betablocker vs. Ca-Kanal-Blocker: kein Unterschied › Betablocker vs. Sartane: Kein Vorteil für Sartane. Diabetes-Patienten: Hinweis auf einen Zusatznutzen der Sartane hinsichtlich der Zielgrößen „Mortalität“ und „Herzinsuffizienz“ ▫ Vergleiche mit ACE-Hemmern › ACE-Hemmer vs. Ca-Kanal-Blocker: Für Ca-Kanal-Blocker kann eine stärkere Blutdrucksenkung angenommen werden › Betablocker vs. Ca-Kanal-Blocker: Es liegt keine vergleichende Untersuchung vor. ▫ Vergleiche mit Ca-Kanal-Blockern › Ca-Kanal-Blocker vs. Sartane: Stärkere Blutdrucksenkung unter Ca-Kanal-Blockern ■ Therapiehinweise des GBA: ▫ Aliskiren: weder Reduktion der Mortalität noch der kardiovaskulären Morbidität wurden nachgewiesen ▫ blutdrucksenkende Effekt ist mit derjenigen Wirkung vergleichbar, die mit anderen Klassen von Antihypertensiva, einschließlich ACE-Hemmern und Sartanen, erreicht wird	

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				◻ mögliche Therapieoption, wenn eine Kombinationstherapie etablierter Antihypertensiva unter Berücksichtigung der jeweiligen Nebenwirkungen und Kontraindikationen ausgeschöpft ist (Langzeitdaten fehlen) ◻ keine Empfehlung für Aliskiren/Amlodipin als Standardwirkstoff- oder Reservewirkstoffkombination ■ ein Disease-Management-Programm (DMP) liegt aktuell nicht vor ■ Cochrane Reviews seit 2012: ◻ n=13 zu antihypertensiven Wirkstoffen, davon n=2 Updates früherer Arbeiten ◻ die Studienlage erlaubt außer der Aussage nur geringer Wirkunterschiede keine Erkenntnisse zum klinischen Nutzen der Alphablocker ◻ Heran BS, Galm BP, Wright JM: Blood pressure lowering efficacy of alpha blockers for primary hypertension (2012): • Blutdrucksenkung gering • Unterschied zwischen Alphablockern nicht erkennbar • Studienlage erlaubt keine verlässlichen Aussagen zum Nutzen der Alphablocker ◻ Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH: Betablockers for hypertension (2012) / Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH: Betablockers for hypertension (2017): • Wirksamkeit und Sicherheit einer Therapie mit Betablockern als First-line-Therapie bei Erwachsenen mit Bluthochdruck (vs. Placebo, Diuretika, Calciumkanalblockern oder ACE-Hemmer) • n=13 RCTs mit mindestens 1 Jahr Beobachtungsdauer; im Update keine weitere Studie • Fazit: Atenolol anderen Antihypertensiva hinsichtlich der Mortalität und kardiovaskulären Morbidität unterlegen; Limitation: Verzerrungen in den Studien • Gesamtmortalität: kein Unterschied zwischen Betablockern und Diuretika, RAS-Hemmern oder Placebo, jedoch eine höhere Mortalität im Vergleich zu Ca-Kanal-Blockern ◻ Musini VM, Nazer M, Bassett K, Wright JM: Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension (2014): • dosisabhängige Wirksamkeit von Thiaziden im Vergleich zu Placebo (Bluddrucksenkung, unerwünschte Wirkungen) • n=60 RCT, durchschnittliche Studiendauer 8 Wochen	

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				• HCT mit dosisabhängiger Blutdrucksenkung, andere Thiazide bei höherer Dosis keine stärkere Senkung des Blutdrucks • Wirkung der Thiazide auf den systolischen Blutdruck stärker als bei ACE-Hemmern, Sartanen oder anderen Renininhibitoren □ Musini VM, Rezapour P, Wright JM, Bassett K, Jauca CD: Blood pressure-lowering efficacy of loop diuretics for primary hypertension (2015): • dosisabhängige Wirksamkeit von Schleifendiuretika im Vergleich zu Placebo zur Reduktion des systolischen und diastolischen Blutdrucks sowie unerwünschte Wirkungen • n=9 Studien, deren Studienqualität als gering bewertet wurde, so dass nach Aussage der Autoren aus den Ergebnissen keine belastbaren Schlussfolgerungen gezogen werden können □ Wong GWK, Laugerotte A, Wright JM: Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension (2015): • dosisabhängige Wirksamkeit von verschiedenen sowohl Alpha- als auch Betablocker • n=8 Studien • Carvedilol verringerte den systolischen Blutdruck um durchschnittlich 4 mmHG und diastolisch 3 mm HG; mit hohen Dosierungen konnte der Blutdruck nicht weiter gesenkt werden, es traten jedoch vermehrt Bradykardien auf • Blutdrucksenkung durch duale Blocker ist schwächer ausgeprägt als bei allen anderen Betablockern, Thiazid-Diuretika, ACE-Hemmern und Sartanen • Autoren bewerten die Studienqualität als gering □ Wong GWK, Boyda HN, Wright JM: Blood pressure lowering efficacy of partial agonist beta blocker monotherapy for primary hypertension (2014): • dosisabhängige Wirksamkeit von selektiven Betablockern auf systolischen und diastolischen Blutdruck sowie Puls im Vergleich zu Placebo • n=13 RCT • untersuchte Betablocker reduzierten den Blutdruck und den Puls • keine Belege, ob höhere Dosen mit stärkerer Blutdrucksenkung einhergehen • nicht ableitbar, ob die selektiven Betablocker zu mehr Nebenwirkungen als Placebo führen	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				• Qualität der Evidenz wird aufgrund kleiner Fallzahlen oder vorhandenem Bias als sehr gering eingeschätzt □ Wong GWK, Wright JM: Blood pressure lowering efficacy of nonselective beta blockers for primary hypertension (2014): • dosisabhängige Wirksamkeit nicht selektiver Betablockern auf systolischen und diastolischen Blutdruck im Vergleich zu Placebo • n=25 RCT (sieben Betablocker, meist Propranolol und Penbutol) • nichtselektive Betablocker reduzieren den systolischen und diastolischen Blutdruck um -10/-7mmHg und den Puls um 12 Schläge pro Minute im Vergleich zu Placebo • Blutdrucksenkung bei höherer Dosierung nicht deutlich stärker • Dosisabhängigkeit zeigt sich bei der Reduktion des Pulses (höhere Dosen – mehr Nebenwirkungen wie Bradykardie) • Qualität der Evidenz gering, da die Studien extreme Ausreißer aufwiesen und einem hohen Risiko für Verzerrung unterliegen □ Xue H, Lu Z, Tang WL, et al. First-line drug inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension (2015): • Nutzen und Schaden einer Behandlung mit RAS-Inhibitoren im Vergleich zu anderen Antihypertensiva erster Wahl • n=42 RCT • Gesamtmortalität, Hospitalisierung aufgrund von Schlaganfall (jeweils fatal/nichtfatal), Herzinfarkt, Herzinsuffizienz, kardiovaskulären Ereignisse (insgesamt) und terminaler Niereninsuffizienz • moderater Qualität der Evidenz • Gesamtmortalität: vergleichbar zwischen Behandlung mit RAS-Inhibitoren und anderen first-line Antihypertensiva • first-line-Thiazide verursachen weniger Herzinsuffizienz und Schlaganfälle • im Vergleich zu Calciumkanalblockern tritt unter RAS seltener Herzinsuffizienz jedoch häufiger Schlaganfall auf, wobei das Ausmaß der Risikosenkung bei Herzinsuffizienz größer ist als die Zunahme des Risikos für Schlaganfall • Schlussfolgerungen zum Vergleich mit Betablocker sind weniger belastbar □ Li ECK, Heran BS, Wright JM: Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension (2014):	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				• vergleichende Wirkung von ACE-Hemmern und Sartanen • Gesamtmortalität und kardiovaskuläre Ereignisse sowie Abbruchraten aufgrund von unerwünschten Ereignisse • n=9 RCT (Head-to-head-Studien) • Studienqualität: moderat bis gut • kein Unterschied zwischen ACE-Hemmern und Sartanen in Bezug auf die Gesamtmortalität und die kardiovaskulären Ereignisse • Hinweis: dies bedeutet nicht, dass Sartane eine den ACE-Hemmern vergleichbare Wirkung aufweisen, wenn man sie mit Placebo vergleichen würde □ Wong GKW, Boyda HN, Wright JM: Blood pressure lowering efficacy of beta-1-selective beta blockers for primary hypertension (2016): • Vergleich der blutdrucksenkenden Wirkung verschiedener Dosen beta-1-seletiver Betablocker versus Placebo • n= 56 RCTs mit n=7812 Patienten; • 26 RCTs wiesen ein Parallelgruppendesign auf, 30 ein Cross-over-Design • bei mildem bis moderatoren Hochdruck wurde die Blutdruckwerte im Mittel um -10/-8 mm Hg gesenkt; ebenfalls reduzierte sich die Herzschlagrate • stärksten Effekt auf die Blutdrucksenkung hatte eine doppelte Startdosis • im Rahmen der Dosierempfehlungen zeigte sich keine dosisabhängige Wirkung bei der Blutdrucksenkung, jedoch auf die Herzschlagrate • Beta-1-selektive Betablocker waren wirksamer als Betablocker mit dualer Funktion • die Effekte auf den systolischen Blutdruckwert waren vergleichbar, die auf den diastolischen Wert stärker ausgeprägt als bei Diuretika, ACE-Hemmern und Sartanen □ Musini VM, Lawrence KAK, Fortin PM, Bassett K, Wright JM: Blood pressure lowering efficacy of renin inhibitors for primary hypertension (2017): • dosisabhängige Wirksamkeit von Renin-Inhibitoren im Vergleich zu Placebo auf die Reduktion des systolischen und diastolischen Blutdrucks • n=12 Studien mit einer durchschnittlichen Dauer von acht Wochen, n=7.439 Patienten	

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				• Renin-Inhibitor: Aliskiren • Aliskiren senkte im Vergleich zu Placebo dosisabhängig den Blutdruck • Ausmaß der Blutdrucksenkung ist vergleichbar mit dem von ACE-Hemmern und Sartanen • für eine aussagekräftige Bewertung von Nebenwirkungen ist die Studiendauer zu kurz □ Tam TSC, Wu MHY, Masson SC, Tsang MP, Stabler SN, Kinkade A, Tung A, Tejani AM: Eplerenone for hypertension (2017): • Wirkung von Eplerenon versus Placebo auf Blutdrucksenkung (systolisch/diastolisch), Gesamt-mortalität, fataler und nicht-fataler Herzinfarkt, fataler und nichtfataler Schlaganfall, unerwünschte Wirkungen und Therapieabbruch aufgrund von UAW • n= fünf RCTs, n=1.437 Patienten (acht bis 16 Wochen Studiendauer) • Eplerenon-Dosis von 25 bis 400 mg täglich • 50 mg bis 200 mg Eplerenon senken im Vergleich zu Placebo den Blutdruck • Datenlage und Studienqualität reichen nicht aus, um Dosis-Wirkungen und patientenrelevante Outcomes belastbar zu untersuchen □ Musini VM, Gueyffier F, Puil L, Salzwedel DM, Wright JM: Pharmacotherapy for hypertension in adults aged 18 to 59 years (2017): • Effekte medikamentöser antihypertensiver Behandlung bei Erwachsenen (18 bis 59 Jahre) auf Gesamtmortalität, kardiovaskulärer Mortalität und Morbidität, Ausmaß an systolischer und diastolischer Blutdrucksenkung sowie Abbruchraten auf-grund unerwünschter Wirkungen • n=7 RCTs (mindestens 1 Jahr Dauer), n=17.327 Patienten (Durchschnittsalter 50 Jahre) • Bendrofluazid (= Bendroflumethiazid) oder Propranolol (gegebenenfalls mit Methyldopa) • Gesamtmortalität im Vergleich zu Placebo oder keiner Therapie zeigte nur wenig oder keine Effekte • Wirkung auf eine kardiovaskuläre Erkrankung konnte mangels Studienqualität in n=4 Studien nicht abgeschätzt werden	

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				□ Chen YJ, Li LJ, Tang WL et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension (2018): • Update des Reviews von 2015 • Nutzen und Schaden einer Behandlung mit RAS-Inhibitoren im Vergleich zu anderen Antihypertensiva erster Wahl • gegenüber 2015 konnten drei weitere RCT in die Analyse einbezogen werden (insgesamt 45 RCTs mit 66.625 Teilnehmern, Durchschnittsalter 66 Jahre) • Outcomes: Gesamtmortalität, Hospitalisierung (jeweils fatal/nicht-fatal) aufgrund von Schlaganfall, Herzinfarkt, Herzinsuffizienz, kardiovaskulären Ereignisse (insgesamt) und terminaler Niereninsuffizienz • nach Absicht der Autoren ist Gesamtmortalität der RAS-Inhibitoren als first-line Therapie vergleichbar mit first-line eingesetzten Ca-Kanal-Blockern, Thiaziden und Betablockern • Unterschiede bestehen hinsichtlich der Auswirkungen auf die Morbidität: ▪ unter RAS-Inhibitoren mehr Herzinsuffizienz und Schlaganfälle im Vergleich zu Thiaziden ▪ im Vergleich zu Ca-Kanal-Blockern verhinderten RAS Inhibitoren häufiger das Auftreten einer Herzinsuffizienz, waren jedoch in Bezug auf die Verhinderung von Schlaganfällen unterlegen ▪ im Vergleich zu first-line Betablocker reduzierten RAS-Inhibitoren kardiovaskuläre Ereignisse und Schlaganfall ▪ wie schon 2015 wird die Evidenzlage für einen Vergleich zwischen RAS-Inhibitoren und Betablockern als gering eingeschätzt □ Wright JM, Musil VM, Gill R. First-line drugs for hypertension (2018): • Update eines Reviews von 2009 • Auswirkungen einer first-line Therapie mit Thiaziden, Betablockern, Ca-Kanal-Blockern, ACE-Hemmern, Sartanen und Alphablockern im Vergleich zu Placebo oder keiner Behandlung • Mortalität und Morbidität (Schlaganfall, KHK, kardiovaskuläre Ereignisse)	

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				• Effekt auf die Blutdrucksenkung und Absetzen auf Grund von Nebenwirkungen • es konnten keine neuen RCTs identifiziert werden (Original-Review: n=24 Studien mitn= 58.040 Patienten (Durchschnittsalter 56 Jahre) • niedrig dosierte Thiazide reduzieren die Mortalität und die untersuchte Morbidität bei Erwachsenen mit moderater bis schwere primärer Hypertonie • ACE-Hemmer und Ca-Kanal-Blockern sind möglicherweise vergleichbar wirksam, jedoch ist die Evidenzlage unsicherer • hochdosierte Thiazide und Betablocker als fist-line Behandlung bei fehlenden kardiovaskulären Begleiterkrankungen sind first line niedrig dosierten Thiaziden unterlegen □ Musini VM, Tejani AM, Bassett K, Puil L, Wright JM (2019): Pharmacotherapy for hypertension in adults 60 years or older: • 2. Update eines Reviews von 2009 • Quantifizierung des Effektes einer antihypertensiven Behandlung bei sonst gesunden 60-Jährigen und Älteren mit mildem bis moderatem Bluthochdruck (systolisch oder diastolisch) auf die Gesamtmortilität im Vergleich zu Placobo oder keiner Behandlung • kardiovaskulären Mortalität sowie ein Vergleich in Bezug auf Therapieabbrüche • n=1 zusätzliche RCT (Dauer mindestens 1 Jahr); insgesamt: n=16 Studien mit 26.795 Teilnehmern; zumeist Thiazid-Diuretika als Erstlinie • Gesamtmortalität als auch kardiovaskuläre Mortalität mit signifikanter Risikoreduktion • insbesondere Risikoreduktion in der Altersgruppe der 60- bis 79-Jährigen • Risiko für ein Absetzen aufgrund unerwünschte Wirkungen war in der Behandlungsgruppe deutlich erhöht PRISCUS-Liste: - einige Medikamente für antihypertensiven Therapie älterer Patienten eher ungeeignet/erhöhte Vorsicht geboten - für das Indikationsgebiet Hypertonie aufgeführt: Alphablocker › Doxazosin, Prazosin, Terazosin	

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				Ca-Kanal-Blocker › Nifedipin (in der nicht retardierten Form) weitere Arzneimittel › Clonidin, Methyldopa, Reserpin ■ Bei Anwendung Kontrollen der Herz-Kreislauf-Funktion, von ZNS-Wirkungen und von anderen unerwünschten Arzneimittelwirkungen ■ Reserpin sowie eine Reserpin-Clopamid-Kombination sind inzwischen nicht mehr verfügbar Rote-Hand-Briefe zu: ■ Hydrochlorothiazid (17.10.2018) – zum Risiko von nicht melanozytärem Hautkrebs ■ ACE-Hemmer und Sartane (30.04.2019 (Drug Safety Mail)) - erhöhtes Risiko für Lungenkrebs unter Therapie mit ACE-Hemmern verglichen mit Sartanen (Registerstudie); nach Überprüfung durch die Europäische Arzneimittel-Agentur (EMA) weder ausreichende Evidenz für einen kausalen Zusammenhang noch einen regulatorischen Handlungsbedarf) **Ergebniszusammenfassung Medikationskatalog 2021**: ■ in einer Übersicht ab Seite 7 bis Seite 23 des Medikationskatalogs sind die dargelegten Wirkstoffe nach den untersuchten Kategorien sowie mit ergänzenden Hinweisen (z.B. Rote-Hand-Brief) tabellarisch aufgeführt ■ auf Seite 24 findet sich eine Abbildung zur Übersicht über Monotherapie, Zweifach- und ggf. Dreifachkombination mit dem entsprechenden Quellenhinweis (Entscheidungsbaum) ■ als Standard- und Reservewirkstoffe benennt der Medikationskatalog 2021 (Details sind dem Katalog zu entnehmen): **Standardwirkstoffe:** ○ › Amlodipin ○ › Bisoprolol ○ › Bisoprolol + Amlodipin ○ › Bisoprolol + Hydrochlorothiazid	

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				○ › Chlortalidon ○ › Enalapril ○ › Enalapril + Hydrochlorothiazid ○ › Hydrochlorothiazid3 ○ › Lisinopril ○ › Lisinopril + Hydrochlorothiazid ○ › Metoprolol ○ › Metoprolol + Chlortalidon ○ › Metoprolol + Hydrochlorothiazid ○ › Nitrendipin ○ › Ramipril ○ › Ramipril + Amlodipin ○ › Ramipril + Hydrochlorothiazid ○ › Ramipril + Amlodipin + Hydrochlorothiazid **Reservewirkstoffe:** ○ › Candesartan ○ › Candesartan + Amlodipin ○ › Candesartan + Hydrochlorothiazid ○ › Enalapril + Lercanidipin ○ › Furosemid ○ › Lercanidipin ○ › Losartan ○ › Losartan + Amlodipin ○ › Losartan + Hydrochlorothiazid ○ › Methyldopa (linksdrehend) ○ › Nebivolol ○ › Torasemid ○ › Valsartan ○ › Valsartan + Hydrochlorothiazid	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ › Verapamil ○ › Verapamil + Hydrochlorothiazid **Fazit des Medikationskatalogs**: ■ Ziel pharmakologische Therapie: symptomatische Blutdrucksenkung ○ dafür grundsätzlich fünf unterschiedlichen Wirkstoffgruppen und ihre Kombinationen verfügbar (sowohl für initiale als auch dauerhafte Therapie): ▪ Thiazid- oder thiazidähnliche Diuretika ▪ Betablocker ▪ Calciumkanalblocker ▪ ACE-Hemmer ▪ Sartane ○ Mortalität und kardiovaskuläre Ereignisse bei der initialen Therapie vergleichbar ○ in Bezug auf einzelne Outcomes zeigen sich Unterschiede zwischen den Wirkstoffklassen (s.a. Cochrane) ○ Hinweise auf Unterschiede in Bezug auf Persistenz und Therapieabbruchraten ○ antihypertensive Therapie mit Zweifach-Fixkombination als Basistherapie (bessere Therapietreue) ○ Ausnahmen: Patient*innen mit Grad-1-Hypertonie (v. a. < 150 mm Hg sys) und niedrigem Risiko sowie Patient*innen ab 80 Jahren oder gebrechliche Patient*innen → hier Monotherapie ○ bei unzureichender Blutdruckeinstellung: initiale Therapie später zu (wenn möglich fixen) Dreifach- (oder Vierfach-) Kombination erweitern ○ weitere zugelassene Antihypertensiva (wie zentral wirkende Wirkstoffe oder Alphablocker) nachrangig zu betrachten (dann relevant, wenn die Basis-/Kombinationstherapie nicht wirkungsvoll genug) → resistente Hypertonie ○ ESC/ESH LL-Update 2018 empfielt niedrig dosiertes Spironolacton (off label) oder weitere Diuretika bzw. wenn nicht vertragen:	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Eplerenon (off label), Amilorid, hochdosierte Thiazide oder verwandte Substanzen, Schleifendiuretika oder zusätzlich Bisoprolol oder Doxazosin ■ Auswahl geeigneter therapeutischer Maßnahmen bei der Hypertonie in starkem Maße von den individuellen Gegebenheiten, besonders auch den kardiovaskulären Komorbiditäten, mitbestimmt ■ individuell unterschiedlich akzentuierte Therapieziele unter Berücksichtigung von Kontraindikationen und potentiellen Wechselwirkungen mit anderen erforderlichen Arzneimitteln sowie der Präferenzen der Patient*innen (Adhärenz) ■ Medikationskatalog beschränkt sich auf eine schematische Kategorisierung der für die Indikation zugelassenen Arzneimittel; ärztliche Betreuung für bestgeeignetstes therapeutisches Vorgehen wichtig ■ Kombinationen: in Studien weniger gut untersucht; Kombinationen mit fixen Anteilen an Wirkstoffen können hinsichtlich möglicher Nebenwirkungen oder pharmakodynamischer Interaktionen Vor- oder Nachteile aufweisen ■ Sonderstatus: Betablocker gehören zur medikamentösen Basisstrategie; können auf jeder Therapiestufe eingesetzt werden; Einsatz sollte sich nach bestimmten Bedingungen richten (spezifische Indikationen, häufig vorkommende Komorbiditäten); keine Herabstufung im Vergleich zu anderen Wirkstoffgruppen ■ besonderer Hinweis: 2018/2019 Bewertung von Hydrochlorothiazid (HCT) in Bezug auf das Risiko von Basalzell- und kutanen Plattenepithelkarzinomen (Rote-Hand-Brief 2018) → aktuell keine Wirkstoffalternativen, daher weiter empfohlen, unter Berücksichtigung der Sicherheitshinweise ■ Kontraindikation: ○ Thiazide und Thiazid-artige: Gicht; (relative KI) metabolisches Syndrom, Glucoseintoleranz, Schwangerschaft, Hyperkaliziämie, Hyperkaliämie ○ Schleifendiuretika: Hypovolämie, Überempfindlichkeit gegenüber Sulfonamiden, Nierenversagen mit Anurie, Coma he-paticum, Hypokaliämie, Hyponatriämie, Dehydratation	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ Betablocker: Asthma, jeder hochgradige sinoatriale oder AV-Block, Bradykardie (Herzfrequenz < 60 Schläge/Min.); (relative KI) metabolisches Syndrom, Glukoseintoleranz, athletischer Habitus, sportliche Aktivität ○ Dihydropyridin-Ca-Kanal-Blocker: (relative KI) Tachyarrhythmie, Herzinsuffizienz mit reduzierter Ejektionsfraktion, Klasse III oder IV, vorbestehendes schweres Beinödem ○ andere Ca-Kanalblocker (Verapamil/Diltiazem) jeder hochgradige sinoatriale oder AV-Block, schwere linksventrikuläre Dysfunktion (linksventrikuläre Auswurffraktion < 40 %), Bradykardie (< 60 Herzschläge pro Minute); (relative KI) Verstopfung ○ ACE-Hemmer: Schwangerschaft, angioneurotisches Ödem, Hyperkaliämie (Kalium > 5,5 mmol/l), bilaterale Nierenarterienstenose; (relative KI) Frauen im gebärfähigen Alter ohne zuverlässige Kontrazeption ○ Sartane: Schwangerschaft, Hyperkaliämie (Kalium > 5,5 mmol/l), bilaterale Nieren-arterienstenose; (relative KI) Frauen im gebärfähigen Alter ohne zuverlässige Kontrazeption	

8.2 NICE Evidence Reviews

ER for initiating treatment

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Initiating treatment [58]: https://www.nice.org.uk/guidance/ng136/evidence/c-initiating-treatment-pdf-6896748208		Moderate	**Objective** To establish which blood pressure or cardiovascular disease risk threshold antihypertensive drug treatment should be initiated at. **Search** Medline, Embase, the Cochrane Library **Inclusion and exclusion criteria** ▪ Systematic reviews (SR), randomised control trials (RCT), Non-randomised study (NRS) ▪ Adults aged > 18 years **Quality assessment** Risk of Bias; GRADE **Intervention** Treatment initiation at different thresholds **Comperator** Compared against each other (comparing different blood pressure and/or cardiovascular risk thresholds); also within each other **Outcomes** Assessed at 12 months or more (final endpoint) **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • Heart failure needing hospitalisation • Vascular procedures (coronary / carotid artery) • Angina needing hospitalisation • Side effect 1: Acute kidney injury	▪ n=1 individual patient data (IPD) meta-analysis (Sundstrom 2015) ▪ n=1 longitudinal cohort study (Sheppard 2018) ▪ n=2 systematic reviews (Brunström 2018, Law 2009) **Clinical evidence statements** (forest plots see page 71ff) Treatment vs. no treatment as systolic blood pressure thresholds (with and without type 2 diabetes) below 140 mmHg threshold - no clinically important difference between starting treatment at below 140 mmHg and not starting treatment for all-cause mortality or coronary heart disease at 4 years (n=1 study, n=62,617–68,816 participants, low quality evidence) - no clinically important difference for stroke or heart failure at 4 years (n=1 study, n=60,879 participants, very low quality evidence) 140–159 mmHg threshold - a clinically important benefit of starting treatment at 140–159 mmHg for all-cause mortality risk ratio (RR) 0.87 (95% confidence interval (CI) 0.75-1.01), stroke RR 0.70 (95 % CI 0.66-0.76), coronary heart disease RR 0.86 (95% CI 0.76-0.97) and heart failure RR 0.87 (95% CI 0.73-1.04) at 4 years (n=1 study, n=35,254–42,543 participants, very low quality evidence) 160 mmHg or above threshold - a clinically important benefit of starting treatment at 160 mmHg or above for all-cause mortality RR 0.93 (95% CI 0.87-0.99) and stroke RR 0.63 (95% CI 0.54-0.72) at 4 years (n=1 study, n=79,900 participants, low quality evidence) - a clinically important benefit of starting treatment at this threshold for reducing occurrence of coronary heart disease RR 0.86 (95% CI 0.78-0.95) at 4 years (n=1 study, n=78,617 participants, very low quality evidence)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			• Side effect 2: New onset diabetes • Side effect 3: Changes in estimated Glomerular filtration rate (eGFR) or creatinine • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]	- a clinically important benefit of starting treatment in terms of reducing occurrence of heart failure RR 0.53 (95% CI 0.42-0.67) at 4 years (n=1 study, n=23,395 participants, low quality evidence) Treatment vs. no treatment as diastolic blood pressure thresholds (with and without type 2 diabetes) below 80 mmHg threshold - a clinically important benefit of starting treatment at a diastolic blood pressure of below 80 mmHg in terms of stroke occurrence RR 0.74 (95% CI 0.68-0.82) at 4 years (n=1 study, n=42,599 participants, very low quality evidence) 80–84 mmHg threshold - a clinically important benefit of starting treatment at a diastolic blood pressure of 80–84 mmHg in terms of stroke occurrence RR 0.76 (95% CI 0.67-0.87) at 4 years (n=1 study, n=37,516 participants, very low quality evidence) 85–89 mmHg threshold - a clinically important benefit of starting treatment at a diastolic blood pressure of 85–89 mmHg in terms of stroke occurrence RR 0.68 (95% CI 0.62-0.75) at 4 years (n=1 study, n=39,731 participants, low quality evidence) 90–94 mmHg threshold - a clinically important benefit of starting treatment at a diastolic blood pressure of 90–94 mmHg in terms of stroke occurrence RR 0.63 (95% CI 0.56, 0.71) at 4 years (n=1 study, n=38,646 participants, low quality evidence) 95 mmHg or above threshold - a clinically important benefit of starting treatment at a diastolic blood pressure of 95 mmHg or above in terms of stroke occurrence RR 0.51 (95% CI 0.41-0.63) at 4 years (n=1 study, n=6,195 participants, low quality evidence) **Intervention / comparison** **population** **outcomes** **comments** Brunström 2018 (systematic review of RCTs)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse				Kommentar
				Systolic blood pressure: <140 (n=68,966) 140–159 (n=43,889) ≥160 mmHg (n=79,940) Treatment versus no treatment	Adults with hypertension, with and without diabetes (n=192,795)	At 4 y: All-cause mortality Stroke Coronary heart disease Heart failure	Study downgraded for very serious indirectness as the population included coronary artery disease (CAD), mixed CVD and post-stroke. Also, the review included studies that pooled low intensity treatment and no treatment arms (16% of study population).	
				Law 2009 (systematic review of RCTs and non-randomised studies)				
				Diastolic blood pressure: >80 (n=42,599) 80–84 (n=37,516) 85–89 (n=39,731) 90–94 (n=38,646) >95 (n=6,195) Treatment vs. no treatment.	Adults with hypertension, with and without diabetes (n=464,000; multiple comparisons, participants included within the diastolic thresholds analysis: n=164,687)	At 4 y: Stroke Coronary heart disease	Study downgraded for very serious indirectness as the population included CAD, mixed CVD and post-stroke. Also, review included studies that pooled low intensity treatment and no treatment arms.	
				Sheppard 2018 (cohort study)				
				Systolic blood pressure threshold of 140–159 mmHg with a low cardiovascular risk (mean cardiovascular risk threshold of 8%; QRISK2) Treatment versus no treatment	Adults with hypertension, without diabetes (n=38,286)	At 5.8 y: Mortality Stroke Heart failure MI Non-MI acute coronary syndrome Hypotension Acute Kidney Injury	Participants with previous cardiovascular events were excluded from the trial; 7,720 participants (20.2%) included in the main analysis had a previous risk score recorded, and an additional 9,096 (23.8%) had available risk factor information to calculate a QRISK2 score. For the remaining 21,050 (56%), cardiovascular risk	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse				Kommentar
				Sundstrom 2015 (IPD)				
				Systolic blood pressure threshold of 140–159 mmHg Treatment versus no treatment	Adults with hypertension and type 2 diabetes (n=6361)	At 4.4 y: All-cause mortality Stroke Heart failure	RCTs where at least 80% of participants had grade 1 hypertension and had no previous cardiovascular disease were included. To note that risk of bias for individual studies included within the review was not available. (ROBIS checklist was used)	

ER for step 1 treatment (initiating with mono- or combination therapy)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Therapie der Stufe 1 [115]: https://www.nice.org.uk/guidance/ng136/evidence/e-step-1-treatment-pdf-6896748210	2019	Moderate	**Objective:** To establish whether monotherapy or combination therapy is most clinically and cost effective as a step 1 treatment for primary hypertension **Search** Medline, Embase, the Cochrane Library **Inclusion and exclusion criteria** ▪ Systematic reviews (SR), randomised control trials (RCT) ▪ Adults aged > 18 years ▪ not on current pharmacological treatment for hypertension (minimum wash-out 4 weeks) ▪ Minimum follow up time: 1 year **Quality assessment** Risk of Bias; GRADE	▪ n=3 studies were included in the review **Clinical evidence statements** (forest plots see page 57ff) Monotherapy versus combination (adults with hypertension and type 2 diabetes strata) ▪ a clinically important benefit of combination therapy compared to monotherapy for serious cardiovascular events RR 0.39 (95% CI 0.15-0.98) in people with type 2 diabetes (n=1 study, n=481 participants, very low quality evidence) ▪ no clinically important difference for change in creatinine clearance, discontinuation due to adverse events and dizziness (n=1 study, n=481 participants, very low to low quality evidence) ▪ no clinically important difference for discontinuation due to adverse events (n=1 study, n=538 participants, very low quality evidence) Monotherapy versus combination (adults with hypertension and without type 2 diabetes strata) ▪ no clinically important difference between monotherapy or combination therapy for change in creatinine (n=1 study, n=457 participants, high quality evidence)	lack of data for described outcomes or rather limited evidence available

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Intervention
Combination antihypertensive therapy – adjunct or non-adjunct (definition: 2 antihypertensive medications prescribed simultaneously – may be in 1 pill or 2). Examples include:

- Angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker (CCB)
- Angiotensin-II receptor blocker (ARB) and CCB
- ACE inhibitor and diuretic (thiazide like or conventional)
- ARB and diuretic (thiazide like or conventional)
- ACE inhibitor and CCB (Trandolapril and verapamil; TARKA)
- Beta blocker and CCB (atenolol and nifedipine)
- Beta blocker and thiazides (atenolol and chlortalidone,chlortalidone; timolol and bendroflumethiazide)
- Non-thiazide and thiazide diuretic (amiloride and hydrochlorothiazide)

Comperator
Antihypertensive Monotherapy. Examples include: • ACE inhibitor or low-cost ARB)

- Thiazide-like diuretic (such as chlortalidone chlortalidoneor indapamide)
- Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide)
- CCB • Beta-blockers
- Aliskiren (direct renin inhibitors)
- Doxazosin, prazosin, terazosin, (alpha blockers)
- Clonidine, moxonidine, methyldopa (centrally acting anti-HTN)

Outcomes

- no clinically important difference for discontinuation due to adverse events (n=1 study, n=418 participants, very low quality evidence)

Intervention / comparison	Population	Outcomes	Comments
Asmar 2003 (REASON trial)			
Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=235) Monotherapy: Atenolol 50 mg (n=234)	Hypertension (Systolic BP 160-210; Diastolic BP 95-110 mmHg) without type 2 diabetes (n=471)	At 12 months: • Discontinuation due to adverse events • Change in creatinine	Mixed population; 65% had received previous medication
Dahlof 2005 (PIXCEL trial)			
Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=341) Monotherapy: Enalapril 10 mg (n=338)	Hypertension with or without type 2 diabetes (n=679)	At 12 months: • Discontinuation due to adverse events	Number of participants with type 2 diabetes not specified
Mogensen 2003 (PREMIER trial)			
Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=237) Monotherapy: Enalapril 10 mg (n=244)	Hypertension with type 2 diabetes (n=481)	At 12 months • Serious cardiovascular events • Change in creatinine clearance • Discontinuation due to adverse events • Hypotension	

Included studies:
Asmar RG, London GM, O'Rourke ME et al. Amelioration of arterial properties with a perindopril-indapamide very-low-dose combination. Journal of Hypertension Supplement. 2001; 19(4):S15-20

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Assessed 12 months or more (using final endpoint) **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • Heart failure needing hospitalisation • Vascular procedures (including both coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Changes in eGFR or creatinine • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]	Asmar RG, London GM, O'Rourke ME, Safar ME, Reason Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: A comparison with atenolol. Hypertension. 2001; 38(4):922-6 Dahlof B, Gosse P, Gueret P et al. Perindopril/indapamide combination more effective than enalapril in reducing blood pressure and left ventricular mass: The PICXEL study. Journal of Hypertension. 2005; 23(11):2063-70 de Luca N, Asmar RG, London GM et al. Reason Project Investigators. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. Journal of Hypertension. 2004; 22(8):1623-30 London GM, Asmar RG, O'Rourke MF, Safar ME, Reason Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: Comparison with atenolol. Journal of the American College of Cardiology. 2004; 43(1):92-9 Mallion JM, Chamontin B, Asmar R et al. Twenty-four-hour ambulatory blood pressure monitoring efficacy of perindopril/indapamide first-line combination in hypertensive patients: The REASON study. American Journal of Hypertension. 2004; 17(3):245-51 Mogensen CE, Viberti G, Halimi et al. Effect of low-dose perindopril/indapamide on albuminuria in diabetes - Preterax in albuminuria regression: Premier. Hypertension. 2003; 41(5):1063-1071	

ER for step 2 and step 3 treatment (sequence of pharmacological treatment)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Therapie der Stufe 2 und 3 [116]: https://www.nice.org.uk/guidance/ng136/evidence/f-step-2-and-step-3-treatment-pdf-6896748211	2019	Moderate	**Objective:** To identify the most clinically and cost-effective sequence of pharmacological treatment for adults with hypertension **Search** Medline, Embase, the Cochrane Library **Inclusion and exclusion criteria** ▪ Systematic reviews (SR), randomised control trials (RCT)	▪ no relevant clinical studies for step 2 or step 3 antihypertensive pharmacological therapy received for a minimum of 1 year were identified ▪ n=2 Cochrane reviews relevant to this review question were identified. Chen 2010 and Garjon 2017 were both excluded due to having less than the minimum duration of follow up defined in the protocol for this review; participants were on therapy for 3 to 12 weeks **Clinical evidence statements** No relevant published evidence was identified.	no study was included

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ Adults aged > 18 years ▪ have previously received medication for hypertension ▪ have had an inadequate response ▪ Minimum follow up time: 1 year **Quality assessment** Risk of Bias; GRADE **Intervention** Step 2 or step 3 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: • Angiotensin-converting enzyme (ACE) inhibitor • Angiotensin-II receptor blocker (ARB) • Thiazide-like diuretic (such as chlortalidone or indapamide) • Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide) • Calcium channel blockers (CCB) • Beta-blockers • Aliskiren (direct renin inhibitors) • Alpha blockers (doxazosin, prazosin, terazosin) • Centrally acting antihypertensives (clonidine, moxonidine, methyldopa) • Combinations including 2 or 3 antihypertensive medications (including where a medication is added to the previous medication[s]) **Comperator** Compared against each other (class comparisons) **Outcomes**	- The committee agreed that given the lack of evidence to inform choice of step 2 or step 3 treatments, it would not recommend a rigid pathway, but instead it recommended a more individualised approach to choice of treatment. - It was agreed that the choice of drug should be discussed and agreed with the person according to the risks and benefits and the step 1 treatment that had been used. - In order to help inform this discussion, it was agreed that a patient decision aid should be developed to accompany the recommendation to enable healthcare professionals to discuss with the person with hypertension informing that person's choice. This could be used during consultations to enhance knowledge on the risks and benefits of each drug. This would also likely aid adherence, which is a significant issue for asymptomatic long-term conditions such as hypertension.	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]		

ER for step 4 treatment

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Therapie der Stufe 4 [117]: https://www.nice.org.uk/guidance/ng136/evidence/g-step-4-treatment-pdf-6896748212	2019	Moderate	**Objective:** To establish which step 4 treatment is most clinically and cost effective in adults with hypertension that remains uncontrolled following step 3 treatment. **Search** Medline, Embase, the Cochrane Library Key papers: PATHWAY-2 trial (2015) http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00257-3/abstract **Inclusion and exclusion criteria** ▪ Systematic reviews (SR), randomised control trials (RCT) ▪ Adults aged > 18 years ▪ taking the maximally tolerated doses of at least 3 drugs (including a diuretic) ▪ blood pressure is still not controlled ▪ Minimum follow up time: 1 year **Quality assessment** Risk of Bias; GRADE **Intervention** Step 4 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: • Alpha-blockers • Beta-blockers • Other or further diuretics such as amiloride and spironolactone • Aliskiren (direct renin inhibitors) • Clonidine, minoxidil, methyldopa, moxonidine (centrally acting antihypertensive) **Comperator**	▪ no relevant clinical study comparing step 4 antihypertensive pharmacological treatment received for a minimum of 1 year was identified ▪ n=1 Cochrane review relevant to this review question was identified (Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD008169. DOI: https://dx.doi.org/10.1002/14651858.CD008169.pub2). ▪ This was excluded because it included crossover studies without the minimum washout period of 4 weeks as required for inclusion within this review. The references were checked for any relevant studies. **Clinical evidence statements** No relevant published evidence was identified. ▪ The committee discussed the use of different step 4 antihypertensive treatments. It agreed that there was very little evidence within this area, so the committee formed consensus recommendations based on their clinical experience. ▪ They were aware of a trial (PATHWAY-2) that assessed the step 4 treatment in resistant hypertension. Afterdiscussing the findings of the PATHWAY-2 trial, they agreed that this study did not meet the inclusion criteria for this review due to having a short follow-up and no outcomes relevant to the agreed protocol. ▪ Nevertheless, it suggested that adding spironolactone could be effective at reducing blood pressure as a step 4 treatment. It was noted that higher doses of spironolactone were used (25 mg–50 mg), and the 50 mg dose was noted to lower blood pressure more. However, it was unclear what proportion of people were receiving the 50 mg dose. ▪ The study also suggested that amiloride could be as effective as spironolactone in lowering blood pressure. However, the committee noted that amiloride is more expensive, and it is taken twice a day, whereas spironolactone is taken only once daily making it a more convenient option for people who are already taking multiple medications.	no study was included the PATHWAY-2 trial was discussed and recommendations were given based on their clinical experience (Williams et al. Lancet 2015 s.a. 0)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Compared against each other (class comparisons) Compared to placebo (class compared to placebo) **Outcomes** All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]	▪ The committee agreed that changes in blood pressure alone, without information on cardiovascular events was not very informative to patient important outcomes, however they agreed that there was no evidence to suggest a better treatment option was available than spironolactone, which was now part of common clinical practice, and so it should still be recommended as step 4 treatment for those who had an inadequate response to 3 previous treatments. ▪ It was discussed that the previous spironolactone dose recommendation of 25 mg once daily was too specific given the limited evidence base; instead, the committee decided to leave this more open as a 'low-dose' if the potassium level was 4.5 mmol/l or lower. ▪ The committee suggested that they were aware of recent evidence, outside of the remit for this review, which suggested a smaller dose of 12.5 mg could be effective as a step 4 treatment. ▪ The committee also agreed that there was no evidence with hard outcomes data to warrant recommending a higher dose thiazide in people with higher potassium levels, and it was agreed that in this case alpha- or beta-blockers should be considered instead, as higher dose thiazide diuretics are not more effective than lower dose thiazide diuretics. ▪ The need for further research to inform choice of step 4 treatment was discussed; however, the committee considered this would be unlikely to be funded, as the PATHWAY-2 trial had addressed this question previously, despite not including the hard cardiovascular outcomes this committee considered necessary to make a strong recommendation on the topic.	

8.3 SR Basistherapie

Wright et al. 2018 First-line drugs

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wright et al Cochrane [118]	2018	moderate	**Objective**	n=24 trials (28 active treatment arms), n=58,040 patients	limitations of the studies (sample

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
https://www.ncbi.nlm.nih.gov/pubmed/29667175			mortality and morbidity effects from anti-hypertensive drug classes **Search** Cochrane Library; MEDLINE; Embase, WHO Trial Registry (to 24 November 2017) **Inclusion and exclusion criteria** ■ randomized controlled trials (RCT) ■ at least one year duration ■ baseline blood pressure ≥140 mmHg systolic or diastolic ≥ 90 mmHg **Quality assessment** Risk of Bias; GRADE **Intervention** ACE inhibitors; angiotensin II receptor blockers; alpha-blockers; beta-blockers, calcium channel blockers, thiazides **Comperator** placebo or no treatment **Outcomes** **primary:** mortality (death) and morbidity (stroke, coronary heart disease, cardiovascular events) **secondary:** ■ blood pressure lowering effect of antihypertensive treatment when different drug classes are used as the first-line drug ■ rate of withdrawal due to adverse drug effects	■ updated search (2017) failed to identify any new trials ■ four drug classes as first-line drugs: ○ ACE inhibitors (three trials in 6002 patients) ○ beta-blockers (five trials in 19,313 patients) ○ calcium channel blockers (one trial in 4695 patients) ○ thiazides (19 trials in 39,713 patients)[13] ■ no RCTs for ARBs or alpha-blockers ■ adult patients with moderate to severe primary hypertension (results are mostly applicable) ■ mean age of participants was 56 years ■ mean follow-up: three to five years **Outcomes:** mortality ■ ACE inhibitors (13.6% with control versus 11.3% with treatment; RR 0.83, 95% CI 0.72 to 0.95; moderate-quality evidence) ■ beta-blockers (6.2% with control versus 6.0% with treatment; RR 0.96, 95% CI 0.86 to 1.07; moderate-quality evidence) ■ calcium channel blockers (6.0% with control versus 5.1% with treatment; RR 0.86, 95% CI 0.68 to 1.09; low-quality evidence) ■ low-dose thiazides (11.0% with control versus 9.8% with treatment; RR 0.89, 95% CI 0.82 to 0.97; high-quality evidence) ■ high-dose thiazides (3.1% with control versus 2.8% with treatment; RR 0.90, 95% CI 0.76 to 1.05; moderate-quality evidence) cardiovascular events ■ ACE inhibitors (20.1% with control versus 15.3% with treatment; RR 0.76, 95% CI 0.67 to 0.85; moderate-quality evidence)	size, study design)

[13] classified groups according to the starting dose in the trial:
High-dose thiazide group: starting dose (• hydrochlorothiazide ≥ 50 mg per day • chlorothiazide ≥ 500 mg per day • chlorthalidone ≥ 50 mg per day • bendrofluazide ≥ 5 mg per day • methylclothiazide ≥ 5 mg per day • trichlormethiazide ≥ 2 mg per day • indapamide ≥ 5 mg per day)
Low-dose thiazide group: starting dose (• hydrochlorothiazide < 50 mg per day • chlorthiazide < 500 mg per day • chlorthalidone < 50 mg per day • bendrofluazide < 5 mg per day • methylclothiazide < 5 mg per day • trichlormethiazide < 2 mg per day • indapamide < 5 mg per day)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				▪ beta-blockers (7.6% with control versus 6.8% with treatment; RR 0.89, 95% CI 0.81 to 0.98; low quality evidence) ▪ calcium channel blockers (8.0% with control versus 5.7% with treatment; RR 0.71, 95% CI 0.57 to 0.87; low-quality evidence) ▪ low-dose thiazides (12.9% with control versus 9.0% with treatment; RR 0.70, 95% CI 0.64 to 0.76; high-quality evidence) ▪ high-dose thiazides (5.1% with control versus 3.7% with treatment; RR 0.72, 95% CI 0.63 to 0.82; moderate-quality evidence) stroke ▪ ACE inhibitors (6.0% with control versus 3.9% with treatment; RR 0.65, 95% CI 0.52 to 0.82; low-quality evidence) ▪ beta-blockers (3.4% with control versus 2.8% with treatment; RR 0.83, 95% CI 0.72 to 0.97; low-quality evidence) ▪ calcium channel blockers (3.4% with control versus 1.9% with treatment; RR 0.58, 95% CI 0.41 to 0.84; low-quality evidence) ▪ low-dose thiazides (6.2% with control versus 4.2% with treatment; RR 0.68, 95% CI 0.60 to 0.77; high-quality evidence) ▪ high-dose thiazides (1.9% with control versus 0.9% with treatment; RR 0.47, 95% CI 0.37 to 0.61; moderate-quality evidence) coronary heart disease ▪ ACE inhibitors (13.5% with control versus 11.0% with treatment; RR 0.81, 95% CI 0.70 to 0.94; moderate-quality evidence) ▪ beta-blockers (4.4% with control versus 3.9% with treatment; RR 0.90, 95% CI 0.78 to 1.03; low-quality evidence) ▪ calcium channel blockers (3.1% with control versus 2.4% with treatment; RR 0.77, 95% CI 0.55 to 1.09; low-quality evidence) ▪ low-dose thiazides (3.9% with control versus 2.8% with treatment; RR 0.72, 95% CI 0.61 to 0.84; high-quality evidence) ▪ high-dose thiazides (2.7% with control versus 2.7% with treatment; RR 1.01, 95% CI 0.85 to 1.20; low-quality evidence) Withdrawal due to adverse effects	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				(outcome was not reported in most of the trials; high heterogeneity between trials, high risk of bias) drug therapy vs. placebo or no treatment: ■ beta-blockers RR 4.59, 95%CI 4.11 to 5.13; N= 18,565; RCTs = 4; I^2 = 96%) ■ low-dose thiazides RR 2.38, 95% CI 2.06 to 2.75; N = 8870; RCTs = 3; I^2 = 96%) ■ high-dose thiazides RR 4.48, 95%CI 3.83 to 5.24; N = 15,170; RCTs = 7; I^2 = 31%) blood pressure (for each class of drugs, the blood pressure datawere heterogeneous, low to very low quality of evidence) ■ ACE Inhibitors vs. placebo or no treatment (systolic blood pressure (MD-21.14, 99%CI -23.13 to -19.15; N = 1071; RCTs = 2; I^2 = 98%), and diastolic blood pressure (MD -9.64, 99% CI -10.70 to -8.58; N = 1071; RCTs = 2; I^2 = 98%) ■ beta-blockers vs. placebo or no treatment (systolic blood pressure (MD -9.51, 99% CI -10.16 to -8.85; N= 18,833; RCTs = 5; I^2 = 92%), and diastolic blood pressure (MD -5.64, 99% CI -6.06 to -5.22; N = 18,833; RCTs = 5; I^2 = 89%) ■ calcium-channel blockers vs. placebo or no treatment (systolic blood pressure (MD -8.90, 99% CI -10.14 to -7.66; N = 4695; RCT = 1), and diastolic blood pressure (MD -4.50, 99% CI -5.10 to -3.90; N = 4695; RCT = 1) ■ low-dose thiazides vs. placebo or no treatment (systolic blood pressure (mean difference (MD) -12.56, 99% CI -13.22 to -11.91; N = 18,685; RCTs = 8; I^2 = 98%), and diastolic blood pressure (MD -4.73, 99% CI -5.12 to -4.34; N = 18,685; RCTs = 8; I^2 = 98%) ■ high-dose thiazides vs. placebo or no treatment (systolic blood pressure (MD -13.66, 99% CI -14.40 to -12.91; N = 14,906; RCTs = 6; I^2 = 98%), and diastolic blood pressure (MD -6.82, 99% CI -7.24 to -6.41; N = 19,347; RCTs = 10; I^2 = 97%)	

8.4 SR Wirkstoffgruppenvergleiche

Chen et al. 2010 CCB vs. other antihypertensives

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Chen et al. Cochrane [119] https://pubmed.ncbi.nlm.nih.gov/20687074/	2010	low	**Objective** to determine whether calcium-channel-blockers (CCB) used as first-line therapy for hypertension are different from other first-line drug classes in reducing the incidence of major adverse cardiovascular events **Search** Cochrane Central Register of Controlled Trials, MEDLINE, EMBASEand the WHO-ISH Collaboration Register (up to May 2009) **Inclusion and exclusion criteria** ▪ randomized controlled trial (RCT) ▪ baseline BP of at least 140 mm Hg systolic ▪ or 90 mm Hg diastolic ▪ comparing first-line CCBs with other antihypertensive classes ▪ a follow-up of at least two years ▪ at least 100 randomized hypertensive participants **Quality assessment** Cochrane 'Risk of bias' tool **Intervention** first-line calcium-channel-blockers (CCB) **Comperator** other first-line antihypertensive classes note: supplemental drugs other than CCBs from other drug classes were allowed as stepped therapy **Outcomes**	n=18 studies included, n=141,807 patients ▪ 14 dihydropyridines, 4 non-dihydropyridines ▪ all RCTs recruited participants of both sex, but requirements for age differed among trials: o > 40 years (MIDAS) > 50 years (INVEST; VALUE) > 55 years (ALLHAT; CONVINCE) or > 60 years (NICS-EH; SHELL), 18-70 years (AASK), 30-70 years (IDNT), 40-65 years (VHAS), 40-74 years (ABCD), 40-79 years (ASCOT-BPLA), 45-69 years (TOMHS), 45-75 years (ELSA), 50-74 years (NORDIL), 55-80 years (INSIGHT), or 70-84 years (STOP-Hypertension-2) ▪ definition of hypertensive patients varied between studies: o 140/90 mm Hg or more (FACET; INVEST); o more than 160/95 mm Hg (VHAS); o more than 135/85 mm Hg for patients with diabetes mellitus ▪ (IDNT); o 140-179 mm Hg systolic and/or 90-109 mm Hg diastolic ▪ (ALLHAT); o 150-210 mm Hg systolic and 95-115 mm Hg diastolic (ELSA); o systolic BP ≥180 mm Hg and/or diastolic BP ≥105 mm Hg (STOP-Hypertension-2); o diastolic BP of 100 mm Hg or more (NORDIL) or of 90-99 mm Hg (TOMHS); o treated hypertension with a upper limit of 175/100 mm Hg or untreated hypertension of 140-190 mm Hg systolic or 90-110 mm Hg diastolic (CONVINCE); o BP ≥160/100 mmHg for subjects with untreated hypertension or BP ≥140/90mmHg for subjects on antihypertensive	publication bias was discussed but not assessed most of included trials were large and multicenter trials with standardized protocols supplemental antihypertensive agents other than study drugs were allowed (MI) significant statistical heterogeneity was shown between trials comparing CCBs to diuretics and beta-blockers (I2=72%, p = 0.03) and CCBs to ACE inhibitors (I2=72%, p = 0.006). The possible reason might be that the CCB studied was of

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			primary: 1. all cause mortality 2. myocardial infarction (MI) (non-fatal and fatal MI plus sudden or rapid death) 3. stroke (non-fatal and fatal stroke) 4. congestive heart failure 5. cardiovascular mortality 6. major cardiovascular events (MI, congestive heart failure, stroke and cardiovascular mortality) 7. systolic and diastolic BP	▪ treatment (ASCOT-BPLA); ▪ systolic BP ≥150 mm Hg and diastolic BP ≥95 mm Hg, or only systolic BP ≥160 mm Hg (INSIGHT); only diastolic BP ≥95 mm Hg (AASK) or of 90-115 mm Hg (MIDAS); ○ 160-210/220 mm Hg systolic and less than 115 mm Hg diastolic (VALUE/NICS-EH); ○ ≥160 mmHg systolic, and ≥95 mmHg diastolic (SHELL) ○ one trial (ABCD) did not limit patients to elevated BP (diastolic BP ≥80 mm Hg), but it separately reported outcomes on patients with elevated BP (diastolic BP ≥90 mm Hg), so data of hypertensive patients could be extracted ▪ ▪ most trials followed a goal BP in their protocols, mostly less than 140/90 mm Hg (ALLHAT;ASCOT-BPLA; CONVINCE; FACET INVEST; INSIGHT; VALUE), or less than 130/85 mm Hg for patients with diabetes or renal impairment (ASCOTBPLA; INVEST) ▪ ▪ of CCBs for hypertension, dihydropyridines (DHPs) were the most commonly studied, especially amlodipine ▪ also studied nifedipine (INSIGHT), felodipine (STOP-Hypertension-2), nisoldipine (ABCD), nicardipine (NICS-EH), lacidipine (ELSA; SHELL), and isradipine (MIDAS) ▪ non-DHPs, such as an aralkylamine derivative verapamil (CONVINCE; INVEST; VHAS), and a benzothiazepine derivative diltiazem (NORDIL) ▪ compared to other antihypertensive drugs: ○ diuretic (ALLHAT; INSIGHT;MIDAS;NICS-EH; SHELL; TOMHS; VHAS), ○ beta-blocker (AASK;ASCOT-BPLA; ELSA; INVEST;TOMHS) ○ diuretic or beta-blocker or both (CONVINCE;NORDIL; STOP-Hypertension-2),	different kind in each trial. (stroke) significant statistical heterogeneity between trials comparing CCBs to diuretics and beta-blockers (I2=55%, p = 0.11) might be related to the type of CCBs, similar to what was explained in the MI results

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ 1-antagonist (TOMHS), ○ ACE inhibitor (AASK; ABCD; ALLHAT; FACET; STOP-Hypertension-2; TOMHS), ○ angiotensin receptor blocker (ARB) (IDNT; VALUE) **Outcomes** ▪ differed among studies - not every trial supplied data to each meta-analysis ▪ results of cardiovascular events and BP changes were reported in most trials ▪ fatal MI, stroke and heart failure were sometimes contained in death events, and components of cardiovascular events were not separately reported in some trials 1. all cause mortality ▪ effect of CCBs was not significantly different from that of any other evaluated agents: ○ diuretics (5 trials with 35,057 participants: RR 0.98, 95% CI [0.92, 1.04], I2=0%), ○ beta-blockers (4 trials with 44,825 participants: RR 0.94, 95% CI [0.88, 1.00], I2=0%), ○ diuretics and beta-blockers (3 trials with 31,892 participants: RR 1.03, 95%CI [0.94, 1.12], I2=0%), ○ ACE inhibitors (5 trials with 24,006 participants: RR 0.96, 95% CI [0.91, 1.03], I2=0%), ○ ARBs (2 trials with 16,391 participants: RR 0.98, 95% CI [0.90, 1.07], I2=0%) 2. myocardial infarction (MI) (non-fatal and fatal MI plus sudden or rapid death): ▪ effect of CCBs was not significantly different from that of ○ diuretics (5 trials with 34,072 participants: RR 1.00, 95% CI [0.92, 1.08], I2=0%), ○ beta-blockers (3 trials with 22,249 participants: RR 0.90, 95% CI [0.79, 1.02], I2=0%),	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ diuretics and beta-blockers (3 trials with 31,892 participants: RR 1.05, 95% CI [0.93, 1.19], I2=72%), ○ ACE inhibitors (5 trials with 24,006 participants: RR 1.06, 95% CI [0.98, 1.15], I2=72%) - incidence of MI was statistically significantly lower (p = 0.009) for CCBs compare to: ○ ARBs (2 trials with 16,391 participants: RR 0.83, 95% CI [0.72, 0.96], I2=35%), with a risk difference (RD) of -0.01 3. stroke (non-fatal and fatal stroke) - incidence of stroke was not significantly different between CCB and: ○ diuretic groups (5 trials with 34,072 participants: RR 0.94, 95% CI [0.84, 1.05], I2=0%), ○ diuretic and beta-blocker group (3 trials with 31,892 participants: RR 0.92, 95% CI [0.81, 1.03], I2=55%) - significantly lower risk of developing a stroke for CCB than for: ○ beta-blocker (3 trials with 22,249 participants: RD-0.01; RR 0.77, 95% CI [0.67, 0.88], I2=0%) ○ ACE inhibitor (5 trials with 24,006 participants: RD -0.01; RR 0.89, 95% CI [0.80, 0.98], I2=40%) ○ ARB (2 trials with 16,391 participants: RD -0.01; RR 0.85, 95% CI [0.73, 0.99], I2=53%) - insignificantly higher stroke incidence in verapamil compared to: ○ diuretics and beta-blockers (RR 1.14, 95% CI [0.89, 1.46]); - with insignificantly lower stroke incidence in diltiazem (RR 0.82, 95% CI [0.67, 1.01]) and felodipine (RR 0.88, 95% CI [0.74, 1.05]) 4. congestive heart failure - no significantly difference in development of congestive heart failure between patients on CCB and ○ beta-blocker (2 trials with 19,915 participants: RR 0.83, 95%CI [0.67, 1.04], I2=0%), ○ diuretic and beta-blocker (3 trials with 31,892 participants: RR 1.15, 95% CI [0.99, 1.33], I2=0%)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				- risk of developing congestive heart failure was markedly higher in patients on CCBs than those on o diuretics (5 trials with 34,072 participants: RD 0.02; RR 1.37, 95%CI [1.25, 1.51], I2=17%), o ACE inhibitors (4 trials with 23,626 participants: RD 0.01; RR 1.16, 95% CI [1.06, 1.27], I2=0%), o ARBs (2 trials with 16,391 participants: RD 0.01; RR1.20, 95% CI [1.06, 1.36], I2=73%) 5. cardiovascular mortality - significant lower cardiovascular mortality in CCB than in: o beta-blocker (4 trials with 44,825 participants: RR 0.90, 95%CI [0.81, 0.99], I2=62%, RD -0.003 - other comparisons for this outcome were not different 6. major cardiovascular events (MI, congestive heart failure, stroke and cardiovascular mortality) - CCBs significantly reduced major cardiovascular events o compared to beta-blocker (3 trials with 22,249 participants: RD-0.01; RR 0.84, 95% CI [0.77, 0.92], I2=0%) - CCBs significantly increased major cardiovascular events o compared to diuretics (4 trials with 33,642 participants: RD 0.01; RR 1.05 , 95% CI [1.00, 1.09], I2=0% p = 0.03) - no significant difference comparing CCB o to diuretics or beta-blockers (2 trials with 21,011 participants: RR 1.02, 95% CI [0.95, 1.10], I2=0%), o to ACE inhibitors (4 trials with 23,536 participants: RR 0.98, 95%CI [0.94, 1.02], I2=56%) - major cardiovascular events could not be extracted from the trials involving ARBs 7. systolic and diastolic BP - weighted mean-difference betwenn CCB and comperator o systolic BP:	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				▪ diuretic 0.81 mmHg, 95% CI [0.56, 1.06], I2=0%, n=3 trials, n=24,963 patients ▪ beta-blockers 0.25 mmHg, 95% CI [-0.31; 0.81], I2=42%, n=3 trials, n=23,474 patients ▪ diuretic or beta-blocker 3.00 mmHg, 95% CI [2.59, 3.41] , I2=not applicable, n=1 trial, n=10,881 patients ▪ ACE inhibitor -1.11 [-1.40; -0.82], I2=85%, n=4 trials, n=19,368 patients ▪ ARB, -2.10 mmHg, 95% CI [-2.46, -1.74], I2=not applicable, n=1 trial, n=15,245 patients ▪ Alpha1-antagonist -1.40 mmHg, 95% CI [-3.89, 1.09], I2=not applicable, n=1 trial, n=235 patients ○ diastolic BP: ▪ diuretic -0.68 mmHg, 95% CI [-0.84, -0.52], I2=28%, n=3 trials, n=24,963 patients ▪ beta-blocker 0.15 mmHg, 95% CI [-0.16, 0.45], I2=21%, n=3 trials, n=23,474 patients ▪ diuretic or beta-blocker 0.10 mmHg, 95% CI [-0.07, 0.27], I2=not applicable, n=1 trial, n=10,881 patients ▪ ACE inhibitors -0.63 mmHg, 95% CI [-0.81, -0.44], I2=0%, n=4 trials, n=19,368 patients ▪ ARB -1.70 mmHG, 95% CI [-1.91, -1.49], I2=not applicable, n=1 trial, n=15,245 patients ▪ Alpha1-antagonist -1.20 mmHg, 95% CI [-2.39, -0.01], I2=not applicable, n=1 trial, n=235 patients	

Chen et al. 2018 RAS-inhibitors vs. other antihypertensives

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Chen et al. Cochrane [120] https://www.ncbi.nlm.nih.gov/pubmed/30480768	2018	moderate	**Objective**
			benefits and harms of first-line renin angiotensin system inhibitors (RAS inhibitors) vs. other first-line antihypertensive drugs
			Search
			Cochrane Hypertension Specialised Register, Cochrane CENTRAL, MEDLINE, Embase, World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov (up to November 2017)
			Inclusion and exclusion criteria
			▪ randomized controlled trials (RCT)
			▪ double-blinded
			▪ at least six months follow-up
			▪ elevated blood pressure (≥ 130/85 mmHg)
			▪ compared first-line RAS inhibitors with other first-line antihypertensive drug classes
			▪ reported morbidity and mortality or blood pressure outcomes
			▪ people with proven secondary hypertension were excluded
			Quality assessment
			Cochrane 'Risk of bias' tool; GRADE
			Intervention
			first- line RAS inhibitors (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or renin inhibitors)[14]
				▪ update of a previous published version[15]
				▪ n=45 trials (n=87 citations) (total), n=3 trials (update), n=66,625 participants (mean age 66 years)
				▪ mean duration of therapy: 1.9 years (range 0.5 to 5.6 years)
				▪ participants who received
				  ○ RAS inhibitors: n=25,421,
				  ○ Beta-blockers: n=5,525
				  ○ CCBs: n=19,040
				  ○ Thiazides: n=16,316
				  ○ alpha-blockers: n=240
				  ○ CNS active drugs: n=83
				primary:
				all-cause death (RAS-inhibitors vs. control)
				▪ Betablockers: risk ratio (RR) 0.89 (95% CI 0.78-1.01), n=1 study, n=9193 participants, low quality of evidence
				▪ CCB: RR 1.03 (95% confidence interval (CI) 0.98-1.09), n=5 studies, n=35,226 participants, moderate quality of evidence
				▪ Thiazides: RR 1.00 (95% CI 0.94-1.07), n=1 study, n=24,309 participants, moderate quality of evidence
				fatal and non-fatal stroke (RAS-inhibitors vs. control)
				▪ Betablockers: RR 0.75 (95% CI 0.63-0.88), n=1 study, n=9193 participants, low quality of evidence
				▪ CCB: RR 1.19 (95% CI 1.08-1.32), n=4 studies, n=34,673 participants, moderate quality of evidence
					small number of large RCT at low risk for most sources of bias
					
					(n=37 studies with unclear risk of bias for allocation)
					
					authors downgraded the quality of evidence because of imbalance in the added secondline antihypertensive drugs

[14] 1. ACE inhibitors include: alacepril, altiopril, benazepril, captopril, ceronapril, cilazapril, delapril, derapril, enalapril, enalaprilat, fosinopril, idapril, imidapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, and zofenopril / 2. ARBs include: candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan, and KT3-671 / 3. Renin inhibitors include: aliskiren, remikiren

[15] Xue H, Lu Z, Tang WL, Pang LW,Wang GM,Wong GWK, Wright JM. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database of Systematic Reviews 2015, Issue 1. DOI: 10.1002/14651858.CD008170.pub2

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Comperator other antihypertensive drug class (thiazides, betablockers, calcium channel blockers (CCB), alpha-blockers, or central nervous system (CNS) active drugs) **Outcomes** **primary:** ▪ all-cause death ▪ all-cause serious morbidity (non-fatal serious adverse events) ▪ total cardiovascular events (fatal and non-fatal stroke, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal congestive heart failure (CHF) requiring hospitalizations, end-stage renal failure (ESRF)) **secondary:** change in or end-point systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR)	▪ Thiazides: RR 1.14 (95% CI 1.02-1.28), n=1 stuy, n=24,309 participants, moderate quality of evidence fatal and non-fatal myocardial infarction (MI) (RAS-inhibitors vs. control) ▪ Betablockers: RR 1.05 (95% CI 0.86-1.27), n=2 studies, n=9239 participants, low quality of evidence ▪ CCB: RR 1.01 (95% CI 0.93-1.09), n=5 studies, n=35,043 participants, moderate quality of evidence ▪ Thiazides: RR 0.93 (95% CI 0.86-1.01), n= 2 studies, n=24,379 participants, moderate quality of evidence fatal and non-fatal congestive heart failure (CHF) requiring hospitalizations (RAS-inhibitors vs. control) ▪ Betablockers: RR 0.95 (95% CI 0.76-1.18), n=1 study, n=9193 participants, low quality of evidence ▪ CCB: RR 0.83 (95% CI 0.77-0.90), n=4 studies, n=35,143 participants, moderate quality of evidence ▪ Thiazides: RR 1.19 (95% CI 1.07-1.31), n=1 study, n=24,309 participants, moderate quality of evidence total cardiovascular (CV) events (fatal and non-fatal stroke, fatal and non-fatal MI and fatal and non-fatal CHF requiring hospitalization) (RAS-inhibitors vs. control) ▪ Betablockers: RR 0.88 (95% CI 0.80-0.98), n=2 studies, n=9239 participants, low quality of evidence ▪ CCB: RR 0.98 (95% CI 0.93-1.02), n=6 studies, n=35,223 participants, moderate quality of evidence ▪ Thiazides: RR 1.05 (95% CI 1.00-1.11), n=2 studies, n=24,379 participants, moderate quality of evidence end-stage renal failure (ESRF) (RAS-inhibitors vs. control) ▪ CCB: RR 0.88 (95% CI 0.74-1.05), n=4 studies, n=19,551 participants, low quality of evidence ▪ Thiazides: RR 1.10 (95% CI 0.88-1.37), n=1 study, n=24,309 participants, low quality of evidence	

Li et al. 2014 ACEI vs. ARB

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Li et al. Cochrane [121] https://www.ncbi.nlm.nih.gov/pubmed/25148386	2014	low	**Objective** angiotensin converting enzyme (ACE) inhibitors vs. angiotensin receptor blockers for primary hypertension **Search** Cochrane Hypertension Group Specialized Register, CENTRAL, MEDLINE, EMBASE, the World Health Organization (WHO) International Clinical Trials Registry Platform, ISI Web of Science (up to July 2014) **Inclusion and exclusion criteria** - randomized controlled trials - primary hypertension (un-, controlled) ○ systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg - duration at least one year **Quality assesment** Cochrane Risk of Bias Tool **Intervention** angiotensin receptor blockers (ARB) **Comparator** ACE inhibitor (ACEI) **Outcomes** **primary**: - all-cause mortality - cardiovascular mortality - cardiovascular events (myocardial infarction, ■ coronary heart disease mortality, stroke, congestive heart failure, hospitalization for congestive heart failure)	■ n=9 trials, n=11,007 patients - n=8 studies, n=10,963 patients were selected for meta-analysis ■ ■ **primary:** (note: limitations, authors included selected patients from non-inferiority analysis; most data came from one study) ■ ■ mortality: n=5 trials (ARB vs. ACEI) - 578 / 5219 vs. 583 / 5029 - risk ratio (RR) 0.98; 95% confidence interval (CI) 0.88 to 1.10 ■ cardiovascular mortality, n=4 trial - 339 / 4885 vs. 345 / 4862 - RR 0.98; 95% CI 0.85 to 1.13 ■ cardiovascular events: n=3 trials - 526 / 2750 vs. 492 / 2749 - RR 1.07; 95% CI 0.96 to 1.19 ■ secondary: ■ withdrawals due to adverse effects, n=8 trials - 530 / 5577 vs. 610 / 5386 - RR 0.83; 95% CI 0.74 to 0.93	included studies were rated as good to moderate quality quality of evidence was limited due to possible publication bias, incomplete data note: publication bias was not assessed, but discussed note: risk of bias tool shows unclear classification in some domains (e.g. allocation concealment, attrition bias (incomplete data for lost to follow-up)) note: authors excluded one trial (n=44 patients) from meta-analyses due to lack of events

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			secondary: - withdrawals due to adverse effects		

Wang et al. 2020 Renininhibitors vs. ACEI

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wang et al. Cochrane [122] https://www.ncbi.nlm.nih.gov/pubmed/33089502	2020	high	**Objective** efficacy and safety of renin inhibitors compared to ACE inhibitors **Search** Cochrane Hypertension Specialized Register, Cochrane CENTRAL, MEDLINE, Embase, World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov (searched 5 August 2020) **Inclusion and exclusion criteria** - randomized controlled trials - double-blinded - follow-up at least four weeks - primary hypertension - patients with secondary hypertension were excluded **Quality assesment** Cochrane Risk of Bias Tool **Intervention** renin inhibitors[16] **Comperator** angiotensin converting enzyme (ACE) inhibitors[17]	n=11 trials, n=13,627 patients (aged 51.5-74.2 years) - follow-up four weeks to 36.6 months - cardiovascular events (myocardial infarction, stroke, (hospitalization caused by) congestive heart failure): → only myocardial infarction could be analysed - end-stage renal disease (ESRD) could not be analyzed **primary:** (renin inhibitors vs. ACE inhibitors) - all-cause mortality: risk ratio (RR) 1.05, 95% confidence interval (CI) ▪ 0.93 to 1.18; I^2=0%; n=5 studies, n=5,962 patients; low quality of evidence - myocardial infarction: RR 0.86, 95% CI 0.22 to 3.39; I^2=36%, n=2 studies, n=957 patients; very low quality od evidence - withdrawal due to adverse events: RR 0.85, 95% CI 0.68 to 1.06, I^2=0%, n=10 studies, n=6,008; low quality of evidence - serious adverse events: RR 1.21, 95% CI 0.89 to 1.64, I^2=0%, n=10 studies, n=6,007; low quality of evidence - adverse events: RR 0.98, 95% CI 0.93 to 1.03, n=10 studies, n=6,007 patients; moderate quality of evidence	note: inclusion criteria: follow-up vs. defined outcomes (e.g. mortality) note: only soubgroups of patients were included note: limitations, authors included selected patients from superirity analyses; most data came from one study (s.a. confidence interval) hetergogenity could be discussed

[16] aliskiren, ciprokiren, ditekiren, enalkiren, remikiren, rasilez, tekturna, terlakiren and zankiren
[17] alacepril, altiopril, benazepril, captopril, ceranapril, ceronapril, cilazapril, deacetylalacepril, delapril, derapril, enalapril, enalaprilat, epicaptopril, fasidotril, fosinopril, foroxymithine, gemopatrilat, idapril, imidapril, indolapril, libenzapril, lisinopril, moexipril, moveltipril, omapatrilat, pentopril, perindopril, pivopril, quinapril, ramipril, rentiapril, s-nitrosocaptopril, spirapril, temocapril, teprotide, trandolapril, utibapril, zabicipril, and zofenopril

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			Outcomes **primary**: - all-cause mortality - cardiovascular events (myocardial infarction, stroke, (hospitalization caused by) congestive heart failure - end-stage renal disease (ESRD) - withdrawal due to adverse events - serious adverse events - adverse events **secondary:** - individual cardiovascular events - change in systolic and diastolic BP - change in heart rate	**secondary:** - blood pressure, n=9 trials, n=5,001 patients: o systolic (SBP) mean difference (MD) −1.72, 95% CI −2.47 to −0.97; I^2=34% o diastolic (DBP) MD −1.18, 95% CI −1.65 to −0.72; I^2=36% o low quality of evidence	allocation concealment was rated as unclear for some studies

8.5 SR Wirkstoffgruppen

Aldosteronantagonisten: Batterink 2010 (spironolactone vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Batterink et al. Cochrane [123] https://www.ncbi.nlm.nih.gov/pubmed/20687095	2010	low	**Objective** effect of spironolactone monotherapy **Search** Cochrane Central Register of Controlled Trials (3rd Quarter 2009), MEDLINE (2005 - Sept. 2009), and EMBASE (2007 - Sept. 2009) **Inclusion and exclusion criteria** ▪ randomized, controlled trials (RCT) ▪ patients with primary hypertension ▪ aged > 18 years ▪ systolic blood pressure (BP) > 140 mm Hg or diastolic BP > 90 mm Hg or both	n=6 trials ▪ n=5 with cross-over design and n=137 patients, duration between 4 to 6 weeks; ▪ n=1 parallel group design and n=50 patients, duration 8 weeks (excluded from the meta-analysis) ▪ spironolactone daily dose 25-500 mg **primary:** none of the included studies reported results for: ▪ all cause mortality, ▪ cardiovascular mortality, ▪ non-cardiovascular mortality, ▪ serious adverse events,	publication bias was not assesed allocation sequence generation was rated as unclear or as high risk of bias in all studies blinding was poorly described in most of the studies for three studies incomplete outcome data were decribed

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			■ studies with secondary or gestational hypertension were excluded ■ studies with multiple antihypertensives were excluded **Quality assessment** Cochrane risk of bias tool **Intervention** spironolactone **Comperator** placebo **Outcomes** **primary:** ■ all cause mortality ■ cardiovascular mortality ■ non-cardiovascular mortality ■ number of patients experiencing at least one serious adverse event ■ fatal and non-fatal stroke ■ fatal and non-fatal myocardial infarction **secondary:** ■ patients who withdrew due to adverse effects ■ patients with at least one adverse event ■ mean change in systolic blood pressure ■ mean change in diastolic blood pressure	■ fatal and non-fatal myocardial infarction, ■ fatal and non-fatal stroke **secondary:** blood pressure (mean difference, 95 % confidence interval (CI)) systolic blood pressure (SBP) (spironolactone vs. placebo): ■ -20.09 mmHg (95%CI -23.06 to -16.58), p<0.00001, I^2=9%, n=5 studies, n=137 patients diastolic blood pressure (DBP) (spironolactone vs. placebo): ■ -6.75 mmHg (95%CI -8.69 to -4.80), p<0.00001, I^2=0%, n=5 studies, n=137 patients	lack of an adequate washout period was identified in five trials power calculation?, estimated study population

Aldosteronantagonisten: Tam 2017 (eplerenone vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Tam et al. Cochrane [124] https://www.ncbi.nlm.nih.gov/pubmed/28245343	2017	low	**Objective** effect of eplerenone monotherapy **Search** Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE, Embase, and two trial registers (up to 3 March 2016)	n=5 studies, n=1437 patients, treatment duration of 8 to 16 weeks, mean age of 54 years ■ eplerenone daily dose 25-400 mg **primary:** none of the included studies reported results for:	publication bias was not assessed unclear risk of bias in most domains

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Inclusion and exclusion criteria ▪ randomized placebo-controlled trials ▪ adult patients (> 18 years) ▪ primary hypertension ▪ systolic blood pressure (SBP) > 140 mmHg, ▪ diastolic blood pressure (DBP) > 90 mmHg, or both ▪ studies with secondary or gestational hypertension were excluded ▪ studies with patients receiving multiple antihypertensives were excluded **Quality assessment** Cochrane risk of bias tool **Intervention** eplerenone **Comperator** placebo **Outcomes** **primary:** ▪ all cause mortality ▪ cardiovascular mortality ▪ non-cardiovascular mortality ▪ number of patients experiencing at least one serious adverse event ▪ fatal and non-fatal stroke ▪ fatal and non-fatal myocardial infarction **secondary:** ▪ patients with at least one adverse event ▪ patients who withdrew due to adverse events ▪ change blood pressure □ change in systolic blood pressure □ change in diastolic blood pressure	▪ all cause mortality, ▪ cardiovascular mortality, ▪ non-cardiovascular mortality, ▪ serious adverse events, ▪ fatal and non-fatal myocardial infarction, ▪ fatal and non-fatal stroke **secondary:** ▪ any adverse events (eplerenone vs. placebo): Odds Ratio (OR) 1.07 (95% CI 0.82-1.41), I^2 0%, n=3 trials ▪ change in blood pressure (eplerenone vs. placebo): □ systolic blood pressure: - 9.21 mmHg (95% CI −11.08 to −7.34; I^2 = 58%) (moderate quality evidence), n=5 studies, n=1437 patients □ diastolic blood pressure: - 4.18 mmHg (95% CI −5.03 to −3.33; I^2 = 0%) (moderate quality evidence), n=5 studies, n=1437 patients	the domain other bias was rated as high risk because of the industrial funding

Alpha-Adrenozeptorantagonisten: Heran 2012 (alphablockers vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Heran et al. Cochrane [125] https://www.ncbi.nlm.nih.gov/pubmed/22895943	2012	low	**Objective** dose-related systolic and/or diastolic blood pressure (BP) lowering efficacy of alpha blockers **Search** CENTRAL, MEDLINE, EMBASE (to May 2012) **Inclusion and exclusion criteria** ■ randomized, controlled trial ■ double-blind ■ BP lowering efficacy of fixed-dose monotherapy with an alpha blocker vs. placebo ■ duration of 3 to 12 weeks ■ patients with primary hypertension **Quality assessment** Cochrane risk of bias tool **Intervention** ■ alpha blockers[18] **Comperator** ■ placebo **Outcomes** **primary:** dose-related systolic (SBP) and/or diastolic (DBP) blood pressure lowering efficacy **secondary:** ■ variability of blood pressure ■ effects on pulse pressure ■ dose-related effect on heart rate ■ dose-related effect on withdrawals due to adverse events	n=10 studies, n=1175 participants, mean age 57.4 years, mean duration 5.9 weeks ■ bunazosin, n=1 trial, n=16 patients, imbalenced baseline characteristics ■ doxazosin, n=3 trials ■ prazosin, n=1 trial ■ terazosin, n=4 trials ■ because of a lack of data, an estimate of the lowest dose with near maximal blood pressure lowering efficacy and an estimate of the near maximal blood pressure lowering efficacy could not be determined for any of the individual alpha blocker drugs **primary:** dose-related BP lowering (placebo effect): ■ weighted mean (SBP and DBP, respectively): ■ -1.7 (95%CI -7.0, 3.5; range -5.5 to 5.5) mmHg and ■ -3.9 (95%CI -7.3, -0.5; range -5.6 to 3.5) mmHg dose-related BP lowering (SBP/DBP) (alpha blockers vs. placebo): ■ -8/-5 mmHg (baseline BP of 155/101 mmHg) Table: blood pressure lowering efficacy of alpha blockers **bunazosin** / **doxazosin** / **prazosin** / **terazosin** **Lowest effective dose (mg/day)**: not estimated / 4 / 10 / 5 **Lowest dose with near maximal BP lowering (mg/day)**: not estimated / not estimated / not estimated / not estimated **Near maximal SBP lowering**: not estimated / not estimated / not estimated / not estimated **Near maximal DBP lowering**: not estimated / not estimated / not estimated / not estimated **SBP lowering (mm Hg), 95% CI**: not estimated / -6.42 (-10.12, -2.80) / -10.38 (-16.21, -4.56) / -6.59 (-10.22, -2.96)	publication bias was not assessed n=9 studies did not report details of allocation concealment patient selection bias was reported an assumed publication bias was reported

[18] including alfuzosin, bunazosin, doxazosin, prazosin, tamsulosin, terazosin, trimazosin and indoramin

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse					Kommentar
				DBP lowering (mm Hg), 95% CI	not estimated	-3.53 (-4.99, -2.07)	-6.90 (-9.79, -4.01)	-4.40 (-5.95, -2.84)	

Angiotensin-Konversionsenzym-Hemmer: Heran 2008 (ACEI vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Heran et al. Cochrane [126] https://pubmed.ncbi.nlm.nih.gov/18843651/	2008	moderate	**Objective** dose-related systolic and diastolic BP with ACE inhibitors in the treatment of primary hypertension **Search** CENTRAL, MEDLINE, EMBASE (up to February 2007) **Inclusion and exclusion criteria** ■ randomized, controlled trials ■ follow-up ≥ 3 weeks ■ baseline blood pressure ≥140 mmHg systolic or diastolic ≥ 90 mmH **Quality assessment** Risk of Bias (Allocation); Jaded Scale **Intervention** - fixed-dose monotherapy with an ACE inhibitor **Comperator** - placebo **Outcomes** **primary: c**hange in systolic and diastolic blood pressure **secondary:** change in blood pressure (standard deviation); change in blood pressure (standard deviation); change in pulse pressure; change in heart rate compared; number of patient withdrawals due to adverse effects	n=92 studies, n=12954 patients (n=14 different ACE-inhibitors), mean age 54.4 years, mean treatment duration 6.2 weeks ■ n=76 (82%) with fixed dose monotherapy (randomized, double-blind) ■ n=8 (9%) with forced-titrated therapy ■ n=8 (9%) with titration to blood pressure response ■ published between 1983 and 2002 **Outcomes:** primary: authors documented a lowered systolic and diastolic blood pressure (detailed results were presented in the appendix oft he review)	94.6% of the studies did not report allocation concealment authors documented a risk of publication bias limitations of the studies (sample size, study design)

Angiotensin-II-Rezeptorblocker (ARB): Heran 2008 (ARB vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Heran et al. Cochrane [127] https://pubmed.ncbi.nlm.nih.gov/18843650/	2008	high	**Objective** to quantify the dose-related systolic and/or diastolic BP lowering efficacy of ARBs versus placebo in the treatment of primary hypertension **Search** CENTRAL (The Cochrane Library 2007, Issue 1), MEDLINE (1966 to February 2007), EMBASE (1988 to February 2007) and reference lists of articles **Inclusion and exclusion criteria** ▪ randomized, controlled trial ▪ double-blind ▪ evaluating the blood pressure (BP) ▪ fixed-dose monotherapy with an ARB compared with placebo ▪ duration of 3 to 12 weeks ▪ patients with primary hypertension ▪ baseline blood pressure at least 140 mm Hg systolic and/or 90 mm Hg diastolic **Quality assessment** Cochrane approach (allocation concealment: Adequate, Unclear, Inadequate, not used) Jadad 1996 Scale **Intervention** angiotensin receptor blocker (ARB)[19] **Comperator** placebo **primary:** ▪ change from baseline in systolic and diastolic blood pressure (BP) at 3 to 12 weeks **secondary:**	n=46 trials were included (n=13,451 patients, n=9 ARBs) ▪ mean age 55.0 years ▪ baseline BP 156/101 mm Hg ▪ mean duration 7.4 weeks ▪ daily doses ranging from 10 to 150 mg daily ▪ most studies had multiple treatment arms ▪ Jaded Scale (n=39 trials were of good quality=2 trials of excellent quality, n=5 trials of poor quality) ▪ n=2 trials were forced-titration studies and n=10 trials were titration to BP response at pre-specified intervals ▪ only the pre-titration BP data were used in the analysis (n=10 studies) ▪ there was an increase in the number of published studies through the 1990 ▪ authors argued that the data do not suggest that any one ARB is better or worse at lowering BP ▪ there were insufficient data to evaluate the dose-related effect of the individual ARBs on withdrawals due to adverse effects **Outcome (blood pressure):** weighted mean placebo effect across all trials -2.3 (95% CI -2.8, -1.8; range -13.4 to 3.2) mm Hg and -3.3 (95% CI -3.6 - 3.0; range -7.7 to -0.4) mm Hg for SBP and DBP, respectively weighted mean difference from placebo (maximal BP lowering efficacy of 9 ARB range from -6/-3 mm Hg to -10/-7 mm Hg) ARB (lowest effective dose (mg/day)) near maximal trough SBP lowering (mm Hg), 95% CI; near maximal trough DBP lowering (mm Hg), 95% CI Table 2 within the publication (p 153) candesartan (4) -8.93 (-11.37, -6.50); -4.92 (-6.47, -3.36)	six duplicate publications of 3 included trials were identified n=44 studies not report allocation concealment quality of the blood pressure results in the included trials appeared to be independent of the quality of reporting of the methodology due to evidence of publication bias, the largest trials provide the best estimate of the trough BP lowering efficacy

[19] candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan, and KT3-671

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ standard deviation of the change in BP ▪ change in standard deviation of BP ▪ change in pulse pressure ▪ change in heart rate ▪ number of patient withdrawals due to adverse effects	eprosartan (600) -6.79 (-9.35, -4.22); -5.43 (-6.47, -4.40) irbesartan (75) -5.58 (-7.84, -3.32); -3.50 (-4.40, -2.60) losartan (50) -8.66 (-10.48, -6.84); -4.80 (-5.81, -3.79) olmesartan (20) -10.39 (-13.36, -7.42); -7.31 (-8.92, -4.40) tasosartan (25) -9.30 (-14.83, -3.78); -5.76 (-9.44, -2.07) telmisartan (20) -8.00 (-10.14, -5.85); -4.76 (-5.92, -3.60) valsartan (20) -8.45 (-11.99, -4.91); -4.38 (-6.29, -2.46) KT3-671 (Not estimable) -7.09 (-9.56, -4.61); -5.02 (-6.22, -3.82) class:best estimate of the near maximal blood pressure lowering for ARB: SBP: -9.31 (95%CI -10.25, -8.37) mm Hg DBP: -6.22 (95% CI -6.82, -5.62) mm Hg	

Betablocker: Wiysonge 2017 (betablockers vs. placebo or other antihypertensives)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wiysonge et al. Cochrane [128] https://pubmed.ncbi.nlm.nih.gov/28107561/	2017	moderate	**Objective** effects of beta-blockers on morbidity and mortality in adults with hypertension **Search** from 19 January 2015 up to 14 June 2016; Cochrane CENTRAL, MEDLINE, Embase; ClinicalTrials[20] **Inclusion and exclusion criteria** - randomised controlled trials (RCTs) - duration ≥ 1 year - men and non-pregnant women - aged ≥18 years - with hypertension **Quality assessment**	n=13 trials, n=91,561 patients n=4 beta-blocker vs. placebo n=2 trials beta-blocker vs. angiotensin-converting-enzyme-inhibitor n=1 trials beta-blocker vs. angiotensin receptor blockers n=4 trials beta-blocker vs. calcium-channel-blocker n=5 trials beta-blocker vs. diuretic **Outcomes:** mortality: beta-blocker vs. placebo: RR 0.99, 95% CI 0.88 to 1.11; I2 = 0%; moderate certainty evidenc; n=4 trials, n=23,613 participants beta-blocker vs. rening-angiotensin-system (RAS) inhibitor RR 1.10, 95% CI 0.98 to 1.24, I2 = 54%; moderate certainty evidence; 3 trials, 10,828 participants beta-blockers vs. calcium-channel blockers (RR 1.07, 95% CI 1.00 to 1.14, I2 = 2%; moderate certainty evidence; 4 trials; 44,825 participants	Attrition bias (unclear) – lost to follow up varied between 0-25%; one study did not report lost to follow up; Other bias (unclear) – all studies added other antihypertensive drugs to first-line therapy adverse events: heterogenity; incomplet data (not all studies

[20] search for previous version: June 2006, May 2011, December 2011, and November 2012 (Bradley 2006; Wiysonge 2007b; Wiysonge 2012; Wiysonge 2013)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Cochrane Risk of Bias Tool **Intervention** beta-blocker as mono- or as first-line therapy in a stepped-care approach **Comperator** placebo, no treatment, or another antihypertensive drug (including a different beta-blocker or the same beta-blocker at a different dose) **Outcomes** **primary:** mortality **secondary:** fatal and non-fatal stroke; coronary heart disease (CHD: myocardial infarction, sudden death); total cardiovascular disease (CVD: i.e. fatal and non-fatal CHD, stroke, congestive heart failure, and transient ischaemic attacks); adverse events leading to discontinuation of treatment; degree of reduction in systolic and diastolic blood pressure achieved by beta-blocker therapy	beta-blocker vs. diuretic: RR 1.04, 95% CI 0.91 to 1.19, I2 = 0%; moderate certainty evidence; 5 trials, 18,241 participants	were included); withdrawal, depression, fatigue, and sexual dysfunction were analysed

Betablocker: Wong 2016 (selective betablockers vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wong et al. Cochrane [129] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6486283/	2016	moderate	**Objective** dose-related effects of various doses and types of beta-1 selective adrenergic receptor blockers on systolic and diastolic blood pressure versus placebo in people with primary hypertension **Search** Cochrane CENTRAL, MEDLINE, EMBASE (to 15 October 2015); DARE, CINHAL, other sources[21] **Inclusion and exclusion criteria**	n=56 studies (n=8 beta-blocker-nebivolol, atenolol, metoprolol, betaxolol, bisoprol, bevantolol, pafenolol, practolol); n=7812 patients - n=26 RCT; n=30 studies with cross-over design **Outcomes:** **primary**: authors documented a lowered systolic and diastolic blood pressure (summary of findings table), single data were presented qualitative	no metaanalysis could be performed; funnel plot shows asymmetry heterogenity was reported

[21] same study inclusion criteria were used for the other three beta blocker reviews (Wong 2014a; Wong 2014b;Wong 2015).

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ placebo-controlled (cross-over design was allowed) ▪ follow-up ≥ 3 weeks ▪ baseline blood pressure ≥140 mmHg systolic or diastolic ≥ 90 mmH **Quality assesment** Cochrane Risk of Bias Tool **Intervention** beta blocker monotherapy (atenolol, betaxolol, bevantolol, bisoprolol, esmolol, metoprolol and nebivolol, pafenolol, practolol) **Comperator** placebo **Outcomes** **primary:** change in systolic and diastolic blood pressure **secondary:** change in standard deviation change in pulse pressure change in heart rate number of participants who withdrew due to adverse events		data from trials in which titration to a higher dose was based on blood pressure response were not excluded allocation (randomsequence generation and allocation concealment were poorly reported) withdrawal due to adverse events was reported within 2 trials (follow-up)

Betablocker: Wong 2014 (non-selective betablockers vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wong et al. Cochrane [130] https://pubmed.ncbi.nlm.nih.gov/24585007/	2014	moderate	**Objective** dose-related effects of nonselective betaadrenergic receptor blockers (beta-blockers) on systolic blood pressure (SBP) and diastolic blood pressure (DBP) **Search** Cochrane, MEDLINE, EMBASE, ClinicalTrial, DARE (to 11 October 2013) **Inclusion and exclusion criteria**	n=26 publications (n=25 trials), n= 1279 participants ▪ n=4 with parallel group design and n=21 with cross-over design **Outcomes**: ▪ **primary**: estimatd systolic blood pressure -10 mmHg (95% CI -11 ▪ to -8) and diastolic -7 mmHg (95% CI -8 to -6) (low-quality evidence); (combining the 1x and 2x starting dose subgroup)	details of the statistical analyses were presented separately handling with missing data is unclear

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ placebo-controlled trials (cross-over design was allowed) ▪ follow-up ≥ 3 weeks ▪ baseline blood pressure ≥140 mmHg systolic or diastolic ≥ 90 mmH **Quality assesment** Cochrane Risk of Bias Tool **Intervention** - monotherapy with any non-selective beta-blocker **Comperator** placebo **Outcomes** **primary:** change in systolic and diastolic blood pressure **secondary: c**hange in standard deviation; change in pulse presssure; change in heart rate; number of participants who withdraw due to adverse effects		follow-up was reported with 4 weeks fort he majority of trials (3-12 weeks)

Betablocker: Chen 2010 (beta-blockers as second-line therapy)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Chen et al. Cochrane [131] https://pubmed.ncbi.nlm.nih.gov/20091622/	2010	low	**Objective** to quantify the reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of beta-blocker as secondline therapy in patients with primary hypertension **Search** Cochrane CENTRAL, MEDLINE, EMBASE (to 2009), reference lists of all papers and relevant reviews identified **Inclusion and exclusion criteria** ▪ randomized controlled trials (RCTs) ▪ double-blind (parallel design)	n=20 trials (n=3,744 patients) were included ○ n=2,465 patients treated with combination therapy ○ n=1,279 patients treated with monotherapy ▪ mean baseline BP: 158/102 mmHg ▪ sitting, standing and supine BP measurements were extracted in 7, 8 and 5 trials, respectively ▪ mean age: 53 years ▪ mean duration: 7 weeks ▪ most of the trials included multiple comparison treatment arms ▪ beta-blocker analyzed:	publication bias was not assessed in most trials the risk of bias was judged to be low limitations: - different starting-doses and dosing intervals

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ washout period at least 2 weeks prior to randomization ▪ minimum duration of 3 to 12 weeks ▪ men and non-pregnant women ▪ at least 18 years old ▪ office baseline blood pressure: □ systolic (SBP) ≥140 mmHg and/or diastolic (DBP) ≥90 mmHg ▪ participants with significant renal failure or creatinine level greater than 1.5 times the normal value were excluded **Quality assessment** Cochrane Risk of Bias Tool **Intervention** combination therapy with a beta-blocker plus an antihypertensive drug of another class[22] **Comperator** the other drug alone (without betablocker) **Outcomes** **primary** blood pressure: (SBP/DBP) change from baseline (following washout, at 3 to 12 weeks, combination vs. monotherapy) **secondary** ▪ change in pulse rate (combination therapy vs. monotherapy) ▪ standard deviation of BP (combination vs. monotherapy) ▪ change in heart rate (combination vs. monotherapy)	○ Atenolol, Bisoprolol, Metorprolol, Nebivolol, Oxprenolol, Pindolol, Propranolol, Timolol ▪ beta-blocker were added to: ○ thiazide diuretic or a thiazide diuretic/potassium sparing diuretic combination (n=15 studies) ○ dihydropyridine calcium-channel blocker (n=5 studies) ▪ no study was found that evaluated beta-blocker second line to: ○ angiotensin-receptor blocker (ARB), ○ angiotensin-converting enzyme inhibitor (ACEI), ○ renin inhibitor or centrally acting antihypertensive drug ▪ the doses (beta-blocker) were categorized according to the proportions of the starting dose (0.25x, 0.5x, 1x, 2x, 4x and 8x) ▪ authors concluded: ○ that only the comparison between adding a beta-blocker to a thiazide diuretic or to a calcium-channel-blocker (CCB) could be assessed ○ that they do not have enough data with CCBs to be confident that the effect is the same when added to a CCB (n=5 trials) as to a thiazide (n=15 trials) **outcomes:** ▪ addition of a beta-blocker at one-quarter the starting dose (0.25x) ○ n=4 trials (doses 0.2x and 0.25x the manufacturer's recommended starting dose) ○ reduction in systolic BP -2.9 (95% CI -4.6, -1.2) mmHg and diastolic BP -1.4 (95% CI -2.5, -0.4) mmHg ▪ addition of a beta-blocker at half the starting dose (0.5x) ○ n=5 trials	of beta-blockers were assessed (lower as well as higher doses as recommended by professional product information) - timing of blood pressure measurement was not reported for all trials

[22] The other drug classes included the following: thiazide or loop diuretic; angiotensin-converting enzyme inhibitor (ACEI); calcium channel blocker (CCB); angiotensin receptor blocker (ARB); renin inhibitor (RI); and centrally-acting drugs (CAD) (but limited to guanabenz, rilmenidine, clonidine, moxonidine, methyldopa and guanfacine).

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ incidence of withdrawals due to adverse effects (combination vs. monotherapy)	○ reduction in systolic BP -5.2 (95% CI -6.9, -3.4) mmHg and diastolic BP -2.7 (95% CI -3.8, -1.6) mmHg ▪ addition of a beta-blocker at the starting dose (1x) ○ n=13 trials ○ reduction in systolic BP -5.9 (95% CI -7.3, -4.4) mmHg and diastolic BP -4.3 (95% CI -5.1, -3.4) mmHg ○ indirect comparisons were reported ▪ addition of a beta-blocker at twice the starting dose (2x) ○ n=8 trials (adding a beta-blocker at 2x (range 1.5x to 2.6x) the starting dose) ○ reduction in systolic BP -8.0 (95% CI -9.5, -6.4) mmHg and diastolic BP by -6.3 (95% CI, -7.2, -5.3) mmHg ▪ addition of a beta-blocker at doses four times the starting dose (4x) ○ n=1 trial showed that adding a beta-blocker at 4x the starting ○ reduction in systolic BP -7.4 (95% CI -9.0, -5.8) mmHg and diastolic BP by -5.4 (95% CI -7.1, -13.8) mmHg ▪ addition of a beta-blocker at doses eight times the starting dose (8x) ○ n=1 trial ○ reduction in systolic BP -10.2 (95% CI -15.1, -5.3) mmHg and diastolic BP by -8.8 (95% CI -1.8, -5.8) mmHg	

Diuretika: Chen 2009 (diuretics as second-line therapy)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Chen et al. Cochrane [132] https://pubmed.ncbi.nlm.nih.gov/19821398/	2009	moderate	**Objective** To quantify the additional reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of diuretics as second-line therapy in patients with primary hypertension. **Search**	n=56 trials included (n)=53 published in English, n=1 in German, n=1 in French, n=1 in Spanish) n=53 trials (n=15,129 patients) assessed thiazides ▪ n=49 (92%) hydrochlorothiazid), ▪ n=2 indapamide, ▪ n=1 clopamide, and ▪ n=1 chlorthalidone	unclear risk of bias was reported for allocation concealment and blinding due to a lack of detailed description

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Cochrane CENTRAL, MEDLINE, EMBASE (to July 2008) and bibliographic citations of articles and reviews **Inclusion and exclusion criteria** ▪ double-blind, randomized, controlled trials ▪ washout period of at least 2 weeks prior to randomization ▪ patients with primary hypertension ▪ men and non-pregnant women ▪ ≥ 18 years old ▪ office blood pressure baseline ○ systolic (SBP) ≥ 140 mmHg ○ diastolic (DBP) ≥ 90 mmHg ▪ duration of 3 to 12 weeks ▪ patients with significant renal failure or creatinine level greater than 1.5 times the normal value were excluded ▪ dose-titration studies based on BP response were excluded ▪ forced titration trials were included **Quality assesment** **Intervention** diuretic[23] in combination therapy with another class of anti-hypertensive drugs[24] (second-line therapy) note: all dosages and combinations of these drugs were considered **Comperator** respective monotherapy (without a diuretic) **Outcomes** **primary**	▪ n=9483 patients treated with combination therapy and n=5646 treated with monotherapy ▪ baseline BP of 156/101 mmHg ▪ mean age 54 years ▪ mean duration 6-week double-blind treatment period n=3 studies assessed loop diuretics ▪ n=2 piretanide and ▪ n=1 furosemide no studies assessed the effect of a diuretic as a third-line drug n=7 studies assessing thiazide and a potassium-sparing diuretic combination as second-line therapy were excluded ▪ different treatment arms were described **outcome:** differences in blood pressure (combination vs. monotherapy) were reported ▪ authors documented that patients who received combination therapy (with a thiazide) experienced greater reductions in both systolic and diastolic BP than participants receiving monotherapy (without thiazide) ▪ blood pressure was reported for different doses ▪ authors documented a decrease in SBP/DBP ranged from an additional 4/2 mmHg for lower dose thiazides to 14/6 mmHg for higher dose thiazides ▪ authors documented that the BP lowering effect was dose related ▪ authors noted that the population probably not generalizable to all patients with hypertension (selective study population) ▪ for loop diuretics as a second drug limited data were available	selection bias could not be assessed authors documented imputation of missing variance data analyses were performed separately for thiazide diuretics and loop diuretics dose of hydrochlorithiazid varied widely (5 mg/d to 45 mg/d) with a majority of 12,5 and 25 mg/d

[23] The diuretics that were included in this review were loop diuretics and thiazide or thiazide-like drugs. Potassium-sparing diuretics and aldosterone antagonists were not included in this review.
[24] included pharmacological agents in the following drug classes: Angiotensin-converting enzyme inhibitor (ACEI); calcium channel blocker (CCB); beta-blocker (BB); angiotensin receptor blocker (ARB); renin inhibitor (RI); and centrally-acting drugs (CAD) (but limited to guanabenz, rilmenidine, clonidine, moxonidine, methyldopa and guanfacine).

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			blood pressure (systolic/diastolic) **secondary** • change in standard deviation • incidence of withdrawals due to adverse effects • change in heart rate with • change in pulse rate	(n=3 trials reported data for analyses) ▪ for recommended doses of loop diuretics additional reduction in systolic BP of -6.5 (95%CI -9.0, -4.0) mmHg and reduction in diastolic BP -3.1 (95% CI -4.5, -1.7) mmHg were reported ▪ a small study with only 16 patients in the combination group, adding loop diuretic 2x showed an additional reduction of -13.0 (95%CI -33.0, -7.0) mmHg in SBP and -8.0 (95%CI -19.0, +3.0) mmHg in DBP ▪ Due to a paucity of data at each dose, a dose-response relationship could not be determined. Unfortunately, due to the wide confidence intervals, it is not possible to assess how loop diuretics compare with thiazides.	

Diuretika: Heran 2012 (potassium-sparing add-on vs. HCT or chlorthalidone alone)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Heran et al. Cochrane [133] https://pubmed.ncbi.nlm.nih.gov/23152254/	2012	moderate	**Objective** dose-related effects of potassium-sparing diuretics on blood pressure **Search** ▪ CENTRAL (The Cochrane Library 2012), MEDLINE (1950 to August 2012), EMBASE (1980 to August 2012) **Inclusion and exclusion criteria** ▪ placebo-controlled trials (washout period) ▪ double-blind ▪ follow-up at least 3 weeks ▪ primary hypertension ▪ baseline systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg **Quality assesment** Cochrane Risk of Bias Tool **Intervention** fixed dose monotherapy potassium-sparing diuretics (amiloride and triamterene) or	Update of: Heran et al. Blood pressure lowering efficacy of potassium-sparing diuretics (that block the epithelial sodium channel) for primary hypertension. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD008167. doi: 10.1002/14651858.CD008167.pub2. PMID: 20091662 n=0 trial evaluating monotherapy with amiloride or triamterene could be identified n=6 trials were included (secondline in addition to hydrochlorothiazide (HCT) or chlorthalidone), n=496 patients ▪ n=4 trials amilorid ▪ n=2 trials triamteren **primary**: changed blood pressure (mean difference, 95% confidence interval): ▪ amilorid secondline added to HCT vs. HCT alone, n=4 trials, n=224 patients, mean difference in SBP: -1.56 (-5.97, 2.84), I^2 =14%; DBP: -0.67 (-3.53, 2.19), I^2 =0.0% ▪ triamterene secondline added to chlorthalidone vs. chlorthalidone alone, n=2 trials, n=211 patients, mean differnence in SBP: -0.01 (-3.63, 3.61), I^2 =0.0%, DBP: 0.20 (-2.01, 2.41), I^2 =0.0%	authors documented that allocation concealment was unclear for all studies potential selective reporting bias for heart rate

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			or scondline as combinationtherapy with other antihypertensive drugs **Comperator** placebo or monotherapy **Outcomes** **primary**: ■ changed blood pressure (from baseline – 3 to 12 weeks) **secondary:** ■ variability of blood pressure (systolic SBP, diastolic DBP) ■ pulse ■ heart rate ■ withdrawals due to adverse effects		

Diuretika: Musini 2015 (loop diuretics vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Musini et al. Cochrane [134] https://pubmed.ncbi.nlm.nih.gov/26000442/	2015	moderate	**Objective** dose-related decrease in systolic or diastolic blood pressure **Search** ■ Cochrane, MEDLINE, EMBASE, ClinicalTrials, DARE, other sources (October 2014) **Inclusion and exclusion criteria** ■ placebo-controlled trials (washout phase) ■ follow-up ≥ 3 weeks ■ baseline systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg **Quality assesment** Cochrane Risk of Bias Tool	n=9 studies, n=460 patients (until 2009) – no new study was identified **Outcomes:** **primary** ■ estimated mean systolic blood pressure-difference: -7.9, 95% CI -10.4 to -5.4) mmHg for a mean duration of 8.8 weeks (single data were presented descriptively) ■ estimated mean diastolic blood pressure difference: -4.4, 95% CI -5.9 to -2.8) mmHg for a mean duration of 8.8 weeks (single data were presented descriptively)	Selection bias (unclear) – n=1 study reported random sequence generation and allocation concealment; reporting bias – n=2 studies reported all outcome data

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Intervention loop diuretics **Comperator** placebo **Outcomes** **primary**: change in systolic and diastolic blood pressure **secondary**: number of patients withdrawals due to adverse events; change in levels of serum potassium, uric acid, creatinine, glucose, and lipids		

Diuretika: Musini 2014 (thiazide diuretics vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Musini et al. Cochrane [135] https://pubmed.ncbi.nlm.nih.gov/24869750/	2014	moderate	**Objective** dose-related systolic and diastolic blood pressure due to thiazide diuretics in the treatment of patients with primary hypertension **Search** Cochrane CENTRAL, MEDLINE, EMBASE, ClinicalTrials (up to February 2014) **Inclusion and exclusion criteria** ■ placebo-controlled trial, randomization ■ follow-up ≥ 3 weeks ■ cross-over-design was not allowed ■ baseline systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg **Quality assesment** Cochrane Risk of Bias Tool **Intervention** monotherapy thiazide diuretics **Comperator** placebo	n=60 studies; n=11282 patients, mean duration ranged between 6 and 12 weeks **Outcomes**: primary: systolic blood pressure -9.1 (-9.7 to -8.5) n=7733 patients, n=47 studies, high quality of evidenz diastolic blood pressure -3.6 (-4.0 to -3.3) n=8064 patients, n=51 studies, quality of evidence high	trials in which thiazides were titrated to a higher dose were excluded selection bias (unclear) – n=9 (15%) studies reported details of the randomization process, selective reporting (high risk for secondary outcomes)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Outcomes **primary**: change in systolic and diastolic blood pressure **secondary**: withdrawals due to adverse effects; change in the concentration of serum potassium, uric acid, creatinine, glucose and lipids		

Duale Alpha- und Betarezeptorenblocker: Wong 2015 (carvedilol or labetalol vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Wong et al. Cochrane [136] https://pubmed.ncbi.nlm.nih.gov/26306578/	2015		**Objective** dose-related effects of various types of dual alpha and beta adrenergic receptor blockers **Search** Cochrane Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and ClinicalTrials.gov (up to October 2014), WHO International Clinical Trials Registry Platform (ICTRP) **Inclusion and exclusion criteria** ▪ randomized controlled trial, double blinded ▪ parallel group design or cross-over design ▪ primary hypertension ▪ duration at least 3 ▪ baseline blood pressure: systolic: ≥ 140 mm Hg systolic, diastolic: ≥ 90 mm Hg, or both **Quality assesment** Cochrane Risk of Bias Tool **Intervention** monotherapy dual alpha and beta adrenergic receptor blockers (beta blockers are carvedilol, dilevalol and labetalol)	n=8 trials, n=1493, duration 3 to 12 weeks ▪ n=5 trials with parallel group design ▪ n=3 trials with cross-over design ▪ n=4 trials carvedilol, n=4 trials labetalol **primary:** blood pressure, dual alpha and beta adrenic receptor blockers vs. placebo, adjusted (different dosing regimen) ▪ systolic: -5.59 mm Hg (95% CI -7.47 to -3.70), n=1007 patients, I^2=37.18%, low quality of evidence ▪ diastolic: -3.88 mm Hg (95% CI -4.95 to -2.82), n=1007 patients, I^2=48.3%, low quality of evidence	allocation concealment was rated as unclear for most of the studies (reanzodization process not described) detection bias was rated as high (blinding of outcome measurement was not possible) note: unpublished data/results for carvedilol were considered (obtained from industrial sources) – data were incomplete

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Comperator placebo **Outcomes** **primary**: blood pressure (systolic and diastolic blood pressure) **secondary:** ■ - variability of blood pressure ■ - pulse ■ - heart rate ■ - withdrawals due to adverse effects		for labetalol publication bias was reported

Kalziumkanalblocker: Ghamami 2014 (CCB vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Ghamami et al. Cochrane [137] https://pubmed.ncbi.nlm.nih.gov/25173808/	2014	moderate	**Objective** systolic or diastolic blood pressure **Search** Cochrane CENTRAL, MEDLINE, EMBASE, ClinicalTrials (to February 2014) **Inclusion and exclusion criteria** ■ controlled trials, randomized ■ follow-up ≥ 3 weeks ■ baseline systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg ■ blood pressure measurement over 24-hours **Quality assesment** Cochrane Risk of Bias Tool **Intervention** calcium channel blocker **Comperator** placebo **Outcomes**	n=16 studies (n=21 publications), n=2768 patients (studies had washout periods), trials were excluded if they combine study intervention with other antihypertensive drugs **Outcomes:** **Primary:** systolic blood pressure: (estimated mean differences per hour ranged between 9.45 mmHg and 13.2 mmHg) diastolic blood pressure: (estimated mean differences per hour ranged between 5.85 mmHg and 8.5 mmHg)	most of the studies were classified as unclear risk within the domain of allocation (randomization unclear) limitations of the studies (sample size, study design)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			primary: systolic/diastolic blood pressure (24 h)		

Kalziumkanalblocker: Zhu 2022

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Zhu et al. Calcium channel blockers versus other classes of drugs for hypertension. Cochrane Database Syst Rev. 2022 Jan 9;1(1):CD003654. doi: 10.1002/14651858.CD003654.pub6. [138]	Update of Chen et al. 2010 [119] Objective: to determine whether calcium channel blockers (CCB) used as first-line therapy for hypertension are dilerent from other classes of antihypertensive drugs in reducing the incidence of major adverse cardiovascular events Search:	n=23 RCT (n= 153,849 patients[27]) were included (AASK; ABCD; ALLHAT; ASCOT-BPLA; CASEJ; CONVINCE; ELSA; FACET; HOMED-BP; IDNT; INSIGHT; INVEST; J-MIC(B); MIDAS; NAGOYA; NICS-EH; NORDIL; SHELL; STOP-Hypertension-2; TOMHS; VALUE; VART; VHAS) n=5 of 23 trials were new in this update (CASE-J; HOMED-BP; J-MIC(B); NAGOYA; VART) 18 dihydropyridines, 4 non-dihydropyridines, 1 not specified)	AMSTAR II high	definition of blood pressure and inclusion criteria varied (e.g. included risk factor(s) like coronary hear disease, diabetes mellitus (type 2), nephropathy or hypertensive kidney disease

[27] note: hypertensive participants were defined differently, as follows:
- 140/90 mmHg or more (FACET; INVEST; NAGOYA; VART);
- 150/90 mmHg or more (JMIC(B));
- more than 160/95 mmHg (VHAS);
- more than 135/85 mmHg for participants with diabetes mellitus (IDNT);
- 140 to 179 mmHg systolic and/or 90 to 109 mmHg diastolic (ALLHAT);
- 150 to 210 mmHg systolic and 95 to 115 mmHg diastolic (ELSA);
- systolic BP U 180 mmHg and/or diastolic BP U 105 mmHg (STOP-Hypertension-2);
- diastolic BP of 100 mmHg or more, NORDIL, or of 90 to 99 mmHg (TOMHS);
- treated hypertension with an upper limit of 175/100 mmHg or untreated hypertension of 140 to 190 mmHg systolic or 90 to 110 mmHg diastolic (CONVINCE);
- BP U 160/100 mmHg for participants with untreated hypertension or BP U 140/90 mmHg for participants on antihypertensive treatment (ASCOT-BPLA);
- systolic BP U 150 mmHg and diastolic BP U 95 mmHg, or only systolic BP U 160 mmHg (INSIGHT);
- only diastolic BP U 95 mmHg, AASK, or 90 to 115 mmHg (MIDAS);
- 160 to 210/220 mmHg systolic and less than 115 mmHg diastolic (NICS-EH; VALUE);
- U 160 mmHg systolic and V 95 mmHg diastolic (SHELL);
- systolic BP U 140 mmHg or diastolic BP U 90 mmHg in participants < 70 years old, or systolic BP U 160 mmHg or diastolic BP U 90 mmHg in participants U 70 years old (CASE-J);
- mild-to-moderate hypertension (HOMED-BP)
- Only one trial did not limit participants to elevated BP (diastolic BP U 80 mmHg) (ABCD), but it reported outcomes on participants with elevated BP (diastolic BP U 90 mmHg) separately, so data for hypertensive participants could be extracted.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

	the Cochrane Hypertension Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 1), Ovid MEDLINE, Ovid Embase, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov (up to 1 September 2020)[25]
	Quality assessment:
	Cochrane Risk of Bias tool (RCT), GRADE
	Inclusion and exclusion criteria:
	population:
	participants with baseline blood pressure (BP) of at least 140 mmHg systolic or 90 mmHg diastolic
	or participants with
	diabetes mellitus with a BP of more than 135/85 mmHg
	intervention:
	first-line CCB[26]
	comparison:
	other first-line antihypertensive classes
	study design:
	randomized controlled trial (RCT)
	randomised 100 or more participants
	follow-up at least two years
		mean duration of follow-up ranged from 2 to 5.3 years
		
		n=1 trial stated no lost to follow-up (STOP-Hypertension-2), for n=22 trials loss to follow-up and withdrawal were reported
		
		Outcomes:
		primary
		All-cause mortality: (CCB vs.) – not statistically different
		diuretics (5 trials with 35,057 participants: risk ratio (RR) 0.98, 95% confidence interval (CI) 0.92 to 1.04, I2 = 0%; moderate-certainty evidence);
		beta-blockers (4 trials with 44,825 participants: RR 0.94, 95% CI 0.88 to 1.00, P = 0.54, I2 = 0%; moderate-certainty evidence);
		diuretics and beta-blockers (3 trials with 31,892 participants: RR 1.03, 95% CI 0.94 to 1.12, I2 = 0%; moderate-certainty evidence);
		ACE inhibitors (7 trials with 27,999 participants: RR 0.97, 95% CI 0.91 to 1.03, I2 = 0%; low-certainty evidence);
		ARBs (6 trials with 25,611 participants: RR 1.00, 95% CI 0.92 to 1.08, I2 = 0%; moderate-certainty evidence)
		Myocardial infarction: (CCB vs.)
		diuretics (5 trials with 34,072 participants: RR 1.00, 95% CI 0.92 to 1.08, I2 = 0%; moderate-certainty evidence);
		beta-blockers (3 trials with 22,249 participants: RR 0.90, 95% CI 0.79 to 1.02, I2 = 0%; moderate-certainty evidence);
				trials with small sample size were excluded
				
				most domains of the risk of bias tool were rated as low risk of bias

[25] note: search strategies were adapted
[26] note: The majority (> 70%) of participants in all study groups must be taking the assigned drug class after one year. Supplemental drugs from drug classes other than CCBs were allowed as stepped therapy.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	Outcome: primary: 1. All-cause mortality 2. Myocardial infarction (non-fatal and fatal MI plus sudden or rapid death) 3. Stroke (non-fatal and fatal stroke) 4. Congestive heart failure 5. Cardiovascular mortality 6. Major cardiovascular events (MI, congestive heart failure, stroke, and cardiovascular mortality) secondary: 1. Reduction in systolic and diastolic blood pressure	diuretics and beta-blockers (3 trials with 31,892 participants: RR 1.05, 95% CI 0.93 to 1.19, I2 = 72%; moderate-certainty evidence); ACE inhibitors (7 trials with 27,999 participants: RR 1.05, 95% CI 0.97 to 1.14], I2 = 66%; low-certainty evidence) ARBs (6 trials with 25,611 participants: RR 0.82, 95% CI 0.72 to 0.94, I2 = 0%; moderate-certainty evidence) Stroke (CCB vs.) diuretic groups (5 trials with 34,072 participants: RR 0.94, 95% CI 0.84 to 1.05, I2 = 0%; moderate-certainty evidence) diuretic and beta-blocker groups (3 trials with 31,892 participants: RR 0.92, 95% CI 0.81 to 1.03, I2 = 55%; moderate certainty evidence) beta-blocker (3 trials with 22,249 participants: RR 0.77, 95% CI 0.67 to 0.88, I2 = 0%; moderate-certainty evidence) ACE inhibitor (7 trials with 27,999 participants: RR 0.90, 95% CI 0.81 to 0.99, I2 = 28%; low-certainty evidence) ARB groups (6 trials with 25611 participants: RR 0.87, 95% CI 0.76 to 1.00, p = 0.05, I2 = 15%; moderate-certainty evidence) Congestive heart failure (CCS vs.) beta-blocker groups (2 trials with 19,915 participants: RR 0.83, 95% CI 0.67 to 1.04, I2 = 0%; low certainty evidence) diuretic and betablocker groups (3 trials with 31,892 participants: RR 1.15, 95% CI 0.99 to 1.33, I2 = 0%; low-certainty evidence) diuretics (5 trials with 34,072 participants: RR 1.37, 95% CI 1.25 to 1.51, I2 = 17%; moderate-certainty evidence) ACE inhibitors (5 trials with 25,276 participants: RR 1.16, 95% CI 1.06 to 1.28, I2 = 0%; low-certainty evidence) ARBs (5 trials with 23,265 participants: RR 1.20, 95% CI 1.06 to 1.36, I2 = 66%; low-certainty evidence) cardiovascular mortality (CCB vs.)		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		(death caused by cardiovascular disease was added as a supplemental outcome) beta-blocker group (n=4 trials; n=44,825 participants: RR 0.90, 95% CI 0.81 to 0.99, I2 = 62%; low certainty evidence) diuretics (n=4 trials n=32721 participants: RR 1.02, 95% CI 0.93 to 1.12, I2 = 0%; moderate certainty evidence) diuretics and beta-blockers (n=3 trials, n=31892 participants: RR 1.04, 95% CI 0.92 to 1.18, I2 = 0%) ACE inhibitors (n=6 trials n=27619 participants: RR 0.98, 95% CI 0.89 to 1.07, I2 = 0%; moderate-certainty evidence) ARBs (n=3 trials, n=4642 participants: RR 0.79, 95% CI 0.54 to 1.15, I2 = 0%; moderate certainty evidence) major cardiovascular events ((MI, congestive heart failure, stroke, and cardiovascular mortality) (CCB vs.) beta-blockers (n=3 trials, n=22,249 participants: RR 0.84, 95% CI 0.77 to 0.92, I2 = 0%) diuretics (n=4 trials, n=33,643 participants: RR 1.05, 95% CI 1.00 to 1.09, I2 = 0%, P = 0.03) diuretics or beta-blockers (n=2 trials, n=21,011 participants: RR 1.02, 95% CI 0.95 to 1.10, I2 = 0%) ACE inhibitors (n=5 trials, n=25,186 participants: RR 0.98, 95% CI 0.94 to 1.02, I2 = 45%) ARBs (n=3 trials, n=6874 participants: RR 0.97, 95% CI 0.78 to 1.22, I2 = 32%) poor methodological quality and heterogeneity amongst the five trials comparing CCBs with ACE inhibitors were described (sensitivity analysis with unchanged results (n=4 trials, n=24,806 participants: RR 0.98, 95% CI 0.94 to 1.02, I2 = 0%) systolic and diastolic BP reduction weighted mean difference (fixed-effect model) CCB group was 0.81 mmHg (95% CI 0.56 to 1.06) less than that of the diuretic-based regimen group,		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		and 3.00 mmHg (95% CI 2.59 to 3.41) less than the diuretic-and-beta-blocker-based regimen group systolic BP reduction was -1.11 mmHg (95% CI −1.40 to −0.82) more with CCBs than with ACE inhibitors, and -2.10 mmHg (95% CI −2.46 to −1.74]) more than with ARBs was no significant dilerence between the CCB group and beta-blocker group (P = 0.38), or between the CCB group and alpha-1-antagonist group (P = 0.27) diastolic BP, the mean reduction of the CCB group was −0.68 mmHg (95% CI −0.84 to −0.52) more than the diuretic group; −0.63 mmHg (95% CI −0.81 to −0.44) more than the ACE inhibitor group; −1.70 mmHg (95% CI −1.91 to −1.49) more than the ARB group; mean diastolic changes between the CCB and beta-blocker groups were not significantly different		

Methyldopa: Mah 2009 (methyldopa vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Mah et al. Cochrane [139] https://www.ncbi.nlm.nih.gov/pubmed/19821316	2009	low	**Objective** effect of methyldopa as monotherapy vs. placebo **Search** Cochrane databases, MEDLINE, EMBASE (up to June 2009) **Inclusion and exclusion criteria** ▪ randomized controlled trials ▪ cross-over design was allowed ▪ primary hypertension ◻ blood pressure: systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg	n=12 studies, n=595 (intervention: n=296 patients, control: n=299 patients) (n=4 studies with cross-over design) ▪ duration three to 52 weeks ▪ data on mortality, morbidity and withraw due to adverse events were not reported **secondary:** ▪ blood pressure:	publication bias was not assessed sequence generation and allocation concealment were rated as unclear lost to follow up and incomplete outcome data were reported

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ studies of patients with secondary hypertension or gestational hypertension were excluded **Quality assesment** Cochrane Risk of Bias Tool **Intervention** methyldopa **Comperator** placebo **Outcomes** **primary**: ▪ all cause mortality ▪ cardiovascular mortality ▪ non-cardiovascular mortality ▪ at least one serious adverse event ▪ stroke ▪ myocardial infarction **secondary:** ▪ withraw due to adverse events ▪ at least one adverse event ▪ changed blood pressure	methyldopa vs. placebo, mean difference, n=7 trials, n=231 patients □ systolic -21.88 (95% CI -41.14; -2.63), I^2=97% □ diastolic -8.53 (95% CI -12.21; -4.84), I^2=73%	significant heterogeneity was reported

Renin-Inhibitoren: Musini 2017 (aliskiren vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Musini et al. Cochrane [140] https://www.ncbi.nlm.nih.gov/pubmed/28379619	2017	High	**Objective** effects on blood pressure of renin inhibitors **Search** Cochrane Hypertension Specialized Register, CENTRAL, MEDLINE, Embase, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov, EMA, the Novartis Clinical Study Results Database (up to Feb 2017) **Inclusion and exclusion criteria**	update of Musini et al. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD007066. doi: 10.1002/14651858.CD007066.pub2 - n=12 studies, n=7439 patients (n=4 additional studies, n=2 studies (published data), n=2 data of unpublished studies → Novartis Clinical Trial Results Database) - Aliskiren (renin inhibitor) - mean duration of eight weeks, mean age 54 years - n=6 studies with cross-over design	studies or study arms with dose titration were excluded authors rated attrition bias as high risk of bias due to incomplete outcome

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

			- randomized controlled trial
			- published and unpublished data
			- double-blind
			- minimum duration of three to 12 weeks
			- adults
			- primary hypertension
			  ○ blood pressure systolic ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg
			- washout periode was allowed
			Quality assesment
			Cochrane Risk of Bias Tool, GRADE
			Intervention
			fixed-dose monotherapy with renin inhibitor
			Comperator
			placebo
			Outcomes
			primary:
			- change of blood pressure from baseline
			secondary:
			- blood pressure variability
			- pulse
			- heart rate
			- adverse events
				○ different arms:
				  ▪ of aliskiren, combination therapy with valsartan, hydrochlorothiazide (HCTZ), and the respective monotherapies
				primary:
				- blood pressure, systolic, change from baseline
				  ○ aliskiren 75 mg vs. comperator
				■ mean difference (MD) -2.97, 95% confidence interval (CI) -4.76 to -1.18; patients = 1100; studies = 5; I2 = 0%
				  ○ aliskiren 150 mg vs. comperator
				■ MD -5.95, 95% CI -6.85 to -5.06; patients = 3786; studies = 12; I2 =17%
				  ○ aliskiren 300 mg vs. comperator
				■ MD -7.88, 95% CI -8.94 to -6.82; patients = 3009; studies = 10; I2 = 22%
				  ○ aliskiren 600 mg vs. comperator
				■ MD -11.35, 95% CI -14.43 to -8.27; patients = 393; studies = 2; I2 = 0%
				  ○ authors rated quality of evidence as moderate for 75 mg, 150 mg and 300 mg dose and as low for 600 mg dose
				- blood pressure, diastolic, change from baseline
				  ○ aliskiren 75 mg vs. comperator
				■ MD -2.05, 95% CI -3.13 to -0.96; patients = 1100; studies = 5; I2 = 0%
				  ○ aliskiren 150 mg vs. comperator
				■ MD -3.16, 95% CI -3.74 to -2.58; patients = 3783; studies = 12; I2 = 47%
				  ○ aliskiren 300 mg vs. comperator
				■ MD -4.49, 95%CI -5.17 to -3.82; patients = 3001; studies =
				■ 10; I2 = 17%
					data --> difference of patients withdrew/withdrawal from allocated study group were reported

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ aliskiren 600 mg vs. comperator ■ MD -5.86, 95% CI -7.73 to -3.99; participants = 393; studies = 2; I2 = 0% ○ Quality of evidence was graded as moderate for 75 mg, 150 mg and 300 mg dose, and as low for 600 mg dose	

Reserpin: Shamon 2016 (rauwolfia serpentine vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Shamon et al. Cochrane [141] https://www.ncbi.nlm.nih.gov/pubmed/27997978	2016	Low	**Objective** dose-related effects of reserpine **Search** Cochrane Hypertension Group Specialised Register, CENTRAL, MEDLINE, Embase, ClinicalTrials.gov (up to October 2016) **Inclusion and exclusion criteria** - randomised controlled trials - primary hypertension ○ blood pressure, systolic > 140 mmHg and/or diastolic > 90 mmHg **Quality assesment** Cochrane Risk of Bias Tool **Intervention** reserpine[28] (monotherapy; any dose) **Comperator** placebo or no treatment **Outcomes**	update: n=0 studies total: n=4 trials, n=237 patients (published between 1957-1975) - cross-over design was allowed **primary:** - change in blood pressure (reserpine vs. placebo): ○ systolic: weighted mean difference (WMD) -7.92, 95% confidence interval (CI) -14.05 to -1.78, I^2=0% ○ diastolic: WMD -4.15; 95% CI -9.19, 0.90, I^2=0% ○ significant heterogeneity was reported	limitation (study design) heterogeneity could be discussed publication bias was discussed but not analyzed

[28] whole root extract and other alkaloid extracts of Rauwolfia serpentina

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			primary: change in blood pressure (systolic/diastolic) from baseline (three- to 12-week interval) **secondary:** - changes in mean arterial blood pressure - heart rate - withdrawal due to adverse events		

Vasodilatatoren: Kandler 2011 (hydralazine vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Kandler et al. Cochrane [142]	2011	moderate	**Objective** To determine the effect of hydralazine as monotherapy compared to placebo in adults (of varying age and race) with essential hypertension (with and without co-morbidities). **Search** Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched (SR) and Cochrane Central Register of Controlled Trials (Issue 3, 2011), bibliographic databases (MEDLINE, EMBASE) and International Pharmaceutical Abstracts (1970 - June 2009) **Inclusion and exclusion criteria** - randomized controlled trials - cross-over design was allowed - primary (essential) hypertension (blood pressure: systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg or both) - patients aged ≥18 years - secondary hypertension was excluded **Quality assesment**	no studies were found that would meet the inclusion criteria - n=41 retrieved full text articles were excluded o n=6 studies were duplicate publications o n=17 studies did not randomize patients o n=2 studies did not evaluate patients with primary hypertension o n=7 studies evaluated hydralazine as an "add-on" drug to other antihypertensives o n=8 studies were not randomized controlled trials o n=1 study did not publish results of patients who received only oral hydralazine versus patients who received only oral placebo an updated search in 2011 did not identify any randomized controlled trials which compared oral hydralazine to oral placebo or any randomized cross-over trials ▪ n=6 cross-over trials were excluded, compared hydralazine monotherapy with placebo (Abraham 1986, Junor 1979, O'Malley 1975, Persson 1976, Saavedra 1975, Siitonen 1980) ▪ trials reported blood pressure during a placebo period compared to blood pressure during a hydralazine period ▪ studies had small sample sizes (4 to 30 patients)	n=0 studies were included; some domains of the AMSTAR-II Tool could not be assessed Cochrane Hypertension Group was involved

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			overall methodological quality of each study was assessed (e.g. randomization, allocation concealment, selective reporting) **Intervention** oral hydralazine monotherapy **Comperator** oral placebo **Outcomes** **primary** o All cause mortality o Cardiovascular mortality o Non-cardiovascular mortality o Number of patients experiencing at least one serious adverse event o Fatal and non-fatal stroke o Fatal and non-fatal myocardial infarction **secondary** o Number of patients who withdrew due to adverse effects o Number of patients with at least one adverse effect o Change in systolic blood pressure o Change in diastolic blood pressure	▪ reduction in systolic blood pressure: range 5-20 mmHg ▪ reduction in diastolic blood pressure: range 5-15 mmHg, after 3 to 6 weeks of hydralazine ■ ▪ Hydralazine has been used since the 1950's ▪ was used commonly in the 1970's and 1980's ▪ its use has largely been replaced by newer antihypertensive drugs with more acceptable tolerability profiles ▪ it is still widely used in developing countries due to its lower cost, and in specific circumstances, such as pregnancy or heart failure ■ ▪ important to note: adverse effects of hydralazine are not uncommon and can be serious: o include reflex tachycardia, o immune mediated haemolytic anemia, o vasculitis, o glomerulonephritis, o and a lupus-like syndrome (up to 10% after 3 years of treatment) o (Brunton 2006, Cameron 1984) authors conclusion: - lack of evidence comparing hydralazine vs. placebo for primary (essential) hypertension - hydralazine should not be recommended as monotherapy ■ - blood pressure reduction (based on non-randomized cross-over trials) ■ - treatment-emergent adverse effects → weigh up the risks of potential serious side effects (see above) against the potential benefits of blood	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				pressure reduction with no proven beneficial effect on adverse cardiovascular outcomes	

8.6 SR Kombinationstherapie – s.a. 8.2 NICE

Garjón et al. 2020 combination (at least 2 antihypertensives) vs. monotherapy

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Garjón at al. Cochrane [143] https://pubmed.ncbi.nlm.nih.gov/32026465/	2020	moderate	**Objective**
			differences in clinical outcomes between mono- and combination therapy as initial treatment
			Search
			Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov (up to April 2019)
			Inclusion and exclusion criteria
			- randomised contolled trials
			- double-blinded
			- primary hypertension
			  ○ systolic/diastolic ≥ 140/90 mmHg
			  ○ systolic/diastolic ≥130/80 mmHg for patients with diabetes
			- at least 50 patients per arm
			- aged ≥ 18 years
			- at least 12 months' follow-up
			- initial treatment
			- studies investigating patients with confirmed secondary hypertension were excluded
			Quality assesment
			Cochrane Risk of Bias Tool, GRADE
				Update of: Garjón et al. First-line combination therapy versus first-line monotherapy for primary hypertension. Cochrane Database Syst Rev. 2017 Jan 13;1(1):CD010316. doi: 10.1002/14651858.CD010316.pub2.
				
				n=4 studies (n=1 new trial),
				
				n=3 trials, 568 patients (30% of the whole population - monotherapy: n=335 patients; combination: n=233 patients)
				- follow-up 12 to 36 months
				- ACEI/thiazide-type diuretic vs. ACEI
				- ACEI/thiazidetype diuretic vs. beta-blocker
				- ACEI or CCB (non-dihydropyridine) vs. ACEI/CCB (non-dihydropyridine)
				primary:
				combination therapy vs. monotherapy, n=3 trials, n=568 patients
				- all-cause mortality (RR 1.35, 95% CI 0.08 to 21.72),
				- serious adverse events (RR 0.77, 95% CI 0.31 to 1.92),
				- cardiovascular events (RR 0.98, 95% CI 0.22 to 4.41),
				- cardiovascular mortality (zero events reported)
				secondary:
				combination therapy vs. monotherapy, n=3 trials, n=568 patients
				- withdrawals due to adverse events (RR 0.85, 95% CI 0.53 to 1.35)
				- change of systolic blood pressure (mean difference -2.06, 95% CI -5.39, 1.27) 568 patients, n=3 trials
					authors described changed study protocol for one study
					
					authors analyzed subgroups of patients of included trials (population differed from inclusion criteria of the Cochrane review)
					
					quality of evidence was rated as very low for all investigated outcomes (e.g. heterogeneity, soubgroup-analyzes, wide confidence interval)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Intervention combination of at least two first-line antihypertensive drugs[29] **Comperator** monotherapy with antihypertensives **Outcomes** **primary**: - all-cause mortality - serious adverse events - cardiovascular events (myocardial infarction, stroke, sudden death, hospitalisation or death from congestive heart failure, vascular events) - cardiovascular mortality **secondary:** - withdrawals due to adverse events - reaching blood pressure control - change in systolic/diastolic blood pressure from baseline	- change in diastolic blood pressure (mean difference -0.12, 95% CI -1.21, 0.96) 443 participants; n=2 trials ■ n=1 trial, n=200 patients - potassium-sparing diuretic monotherapy (n=84) vs. combination therapy (n=116 patients) - follow-up of 18 months **primary:** combination therapy vs. monotherapy, n=1 trial, n=200 patients - all-cause mortality (RR 0.24, 95% CI 0.01 to 5.87), - serious adverse events (RR 0.72, 95% CI 0.10 to 5.04), - cardiovascular events (RR 1.45, 95% CI 0.13 to 15.71), - cardiovascular mortality (n=0) **secondary:** combination therapy vs. monotherapy, n=1 trial, n=200 patients - withdrawals due to adverse events (n=0) - reaching blood pressure control (RR 1.15, 95% CI 0.93 to 1.42)	

8.7 SR Akutmedikation

Perez et al. 2008 antihypertensives vs. placebo or other antihypertensives

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Perez et al. Cochrane [144] https://www.ncbi.nlm.nih.gov/pubmed/18254026	2008	critically low	**Objective** pharmacological interventions for antihypertensive emergency care **Search**	n=15 trials, n=869 patients, n=1 double blind, n=14 open-label - patients with elevated blood pressure in the presence of acute end organ damage (e.g. acute pulmonary edema, hypertensive encephalopathy), (blood pressure entry criteria differed among trials)	limitations e.g. due to small study size (largest trial con-

[29] thiazide-type diuretics, loop diuretics, beta-blockers, calcium-channel-blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), renin inhibitors, or alpha-adrenergic blockers

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			MEDLINE, EMBASE, Cochrane clinical trial register (August 2007) **Inclusion and exclusion criteria** ■ randomized controlled trials ■ patients with hypertensive emergency □ any clinical setting where patients present with "marked elevation"[30] of blood pressure in the presence of acute end organ damage □ e.g.: myocardial infarction, unstable angina, acute left ventricular failure with pulmonary oedema, acute aortic dissection, encephalopathy, stroke, and life-threatening bleeding (intracerebral haemorrhage, subarachnoid haemorrhage) ■ note: pregnancy-related hypertensive emergencies are excluded from this review **Quality assesment** only allocation concealment was avaluated **Intervention** 1. anti-hypertensive drug therapy or 2. first-line antihypertensives[31] **Comperator** 1. placebo or no treatment 2. other antihypertensives **Outcomes** **primary**: mortality (all cause), morbidity (cardiovascular events), serious adverse events **secondary:**	- n=2 trial with placebo-arm - seven drug classes were observed: ○ ACE-inhibitors (n=7 trials), ○ alpha-1 adrenergic antagonists (n=4 trials), ○ calcium channel blockers (n=6 trials), ○ direct vasodilators (n=2 trials), ○ diuretics (n=3 trials), ○ dopamine agonists (n=1 trial), ○ nitrates (n=9 trials) **primary:** - mortality was reported in seven trials (totalled 6 deaths in 3 RCTs, n=4 trials mortality was reported as nil); no meta-analysis was conducted) - cardiovascular events were reported in five trials, no meta-analysis was conducted ■ myocardial infarction: □ ACE-inhibitors vs. placebo, n=1 trial, RR 0.72 (95%CI 0.31-1.72) □ nitrates vs. alfa-adrenergic antagonist, n=1 trial, RR 0.55 (95%CI 0.09-3.17) □ nitrates vs. diuretics, n=1 trial, RR 1.30 (95%CI 0.40-4.19) □ diazoxide vs. dihydralazine, n=1 trial, RR 0.86 (95%CI 0.06-12.98) ■ pulmonary edema: □ captopril vs. placebo, n=1 trial, RR 0.40 (95%CI 0.09 -1.86) □ nitrates vs. alfa-adrenergic antagonist, n=1 trial, RR 4.12 (95%CI 0.20-84.24) □ nitrates vs. ACE-Inhibitor, n=1 trial, RR 0.33 (95%CI 0.01-7.78)	sisted of 133 patients [Schreiber 1998]) or duration (longest trial [Elliott 1990] lasted 10 days) (No trial was designed for or had the power to detect differences in clinical outcomes.)

[30] e.g. patients with acute myocardial infarction SBP ≥ 180 and/or DBP ≥110 mm Hg; patients with acute aortic dissection or with left ventricular failure and pulmonary oedema SBP ≥120 mm Hg and/or DBP ≥ 70 mm Hg; patients with intracranial haemorrhage or subarachnoid haemorrhage SBP ≥ 160 mm Hg; patients with any other acute end organ damage setting SBP ≥ 180 and/or DBP ≥ 110 mmHg; without definition: **baseline BP in patients with end-organ damage was used: SBP ≥ 180 and/or DBP ≥ 110 mmHg**
[31] First-line anti-hypertensive drug classes included: nitrates, beta blockers, ACE-inhibitors, diuretics, calcium channel blockers, dopamine agonists, alpha-adrenergic antagonists, and direct vasodilators (diazoxide, hydralazine)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			■ change in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) ■ withdrawals due to adverse events	■ serious adverse events were not reported **secondary:** ■ change in blood pressure: □ calcium channel blockers, angiotensin converting enzyme inhibitors, or alpha-1 adrenergic antagonists vs. placebo or no treatment, n=1 trial, ○ systolic (weighted mean difference: -13.14 (95%CI -19.48,-6.80) ○ diastolic (weighted mean difference: -8.03 (95%CI -12.61,-3.45) □ nitrates (nitroglycerine or isosorbide) vs. diuretics (furosemide), n=3 trials ○ authors documented no statistically significant difference in blood pressure between between nitrates and diuretics □ nitrates (nitroprusside or nitroglycerine) vs. alpha-1 antagonist (Urapidil), n=2 trials ○ authors only present single data for described drug classes and described significant heterogeneity □ nitrates vs. dopamine agonist, n=1 trial ○ systolic blood pressure (weighted mean difference: -14.00 (95%CI -27.72, -0.28) ○ authors documented no difference in diastolic blood pressure □ nitrates vs. ACE-inhibitors, n=1 trial ○ authors documented no difference in blood pressure □ nitrates vs. calcium channel blockers, n=2 trials ○ authors documented no difference in blood pressure □ nitrates vs. direct vasodilator, n=1 trial	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				○ authors documented no difference in blood pressure □ ACE inhibitors vs. calcium channel blockers, n=4 trials ○ authors documented no difference in systolic blood pressure ○ diastolic (weighted mean difference: 7.86 (95% CI 4.92, 10.81) □ ACE inhibitors (captopril) vs. alpha-1 adrenergic antagonist (prazosin, ketanserin), n=2 trials ○ systolic: weighted mean difference: -20 (95% CI -22.85,-17.39) ○ diastolic: weighted mean difference: -3.70 (95% CI -7.08,-0.31) □ diazoxide vs. hydralazine, n=1 trial ○ authors documented no differences in blood pressure ■ withdrawal due to adverse events: □ alpha-blocker vs. nitroglycerine, n=1 trial, 5% vs 2.7%; RR 3.38 (95%CI 0.17-68.84)	

8.8 SR Therapiekonzepte – (De-) Eskalation, Absetzen

Reeve et al. 2020 withdrawal/tapering/dose-reduction vs. continuation

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Reeve et al. Cochrane [145] https://www.ncbi.nlm.nih.gov/pubmed/32519776	2020	low	**Objective** feasibility and effect of withdrawal of antihypertensive medications in older people **Search** Cochrane Hypertension Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov (up to April 2019) **Inclusion and exclusion criteria**	■ n=6 studies, n=1073 patients - range of duration 4 weeks to 56 weeks - n=4 studies diuretics - n=2 antihypertensive drugs **primary**:	quality of evidence was rated as low (study size and duration, power calculation - primary outcome)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ randomised controlled trials ▪ hypertension or primary prevention of cardiovascular disease ▪ older adults (defined as 50 years and over) **Quality assesment** Cochrane Risk of Bias Tool, GRADE **Intervention** withdrawal/tapering/dose reduction of antihypertensive drugs[32] **Comperator** continuation of antihypertensive drugs **Outcomes** **primary**: ▪ mortality (all-cause, cardiovascular mortality) ▪ myocardial infarction (fatal and non-fatal) ▪ adverse drug reactions ▪ adverse drug withdrawal reactions **secondary:** ▪ blood pressure (BP, systolic and diastolic) ▪ hospitalisation (all-cause, cardiovascular hospitalisation, heart failure hospitalisation) ▪ stroke (fatal and non-fatal, ischaemic and haemorrhagic, transient ischaemic attack) - success (rate) of withdrawal from antihypertensive drugs (12 months) - quality of life (QoL) - falls	- mortality, n=4 studies, n=640 patients, duration 12 to 16 weeks o all-cause (intervention vs. control) ▪ odds ratio (OR) 2.08 (95% confidence interval (CI) 0.79-5.46, I^2 = 0%), low quality of evidence o cardiovascular mortality, follow-up 12 months ▪ death: n=2 patients of 38 vs. n=1 patients of 39, very low quality of evidence - myocardial infarction, n=2 studies, 12 to 16 months follow-up o OR 1.86, 95% CI = 0.19-17.98, I2 = 0%, very low quality of evidence - adverse events: variations within an between the studies were reported (definition, measurement, reporting) ▪ secondary: - blood pressure (BP), n=5 studies (n = 767) (intervention vs. control) o mean difference systolic BP: 9.75 mmHg (95% CI = 7.33-12.18), I^2=67%	

[32] ACE-inhibitors, angiotensin II receptor antagonists, betablockers, calcium-channel-blockers, diuretics, renin-inhibitors

8.9 SR (Einnahmezeitpunkte)

Zhao et al. 2021 / SR / chronotherapy (angiotensin-II-receptorblockers - sartan)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Zhao et al. Am J Med Sci [146] https://pubmed.ncbi.nlm.nih.gov/32948291/	2021	low	**Objective**
			chronotherapy of angiotensin-II-receptorblockers (ARB)
			Search
			PubMed, Web of Science, Cochrane databases (up to June 2019)
			Inclusion and exclusion criteria
			- randomized controlled trials
			- patients with mild to moderate hypertension
			  ○ systolic between 140 and 179 mmHg and/or diastolic between 90 and 109 mmHg
			- follow-up ≥ 6 weeks
			Quality assesment
			JADED scale
			Intervention
			angiotensin-II-receptorblockers (ARB) (bedtime dosing)
			Comperator
			angiotensin-II-receptorblockers (ARB) (awakening dosing)
			Outcomes
			blood pressure (systolic and diastolic) (change from baseline)
			adverse event
			seriouse asverse events (withdrawal due to)
				n=8 studies, n=805 patients
				- follow-up 12 ± 3 weeks (range 6-16 weeks)
				- opel-label
				- ibesartan, olmesartan, telmisartan, valsartan were observed
				
				Outcomes:
				blood pressure (BP):
				- sleep-time BP (bedtime vs. awake): weighted mean difference (WMD)
				  ○ systolic WMD -5.23 (95% confidence interval (CI) -7.27; -3.20) mmHg, p<0.001, I^2 66%
				  ○ diastolic WMD -2.94 (95% CI -4.52; -1.36) mmHg, p<0.001, I^2=87%
				- day-time BP (bedtime vs. awake):
				  ○ systolic WMD 0.98 (95% CI -0.20; 2.17) mmHg, p=0.10, I^2=0%
				  ○ diastolic WMD 0.11 (95% CI -0.50; 0.89) mmHg, p=0.79, I^2=14%
				- 24h BP (bedtime vs. awake):
				  ○ systolic WMD -0.75 (95% CI -1.93; 0.42) mmHg, p=0.21, I^2=0%
				  ○ diastolic WMD -0.77 (95% CI -1.55; 0.01) mmHg, p=0.05, I^2=42%
				
				Articles included:
				13 Hermida et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension 2003 https://pubmed.ncbi.nlm.nih.gov/12874091/
				14 Hermida et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. Chronobiol Int. 2005 https://pubmed.ncbi.nlm.nih.gov/16147905/
					studies with small sample sizes were included and meta-analyzed
					
					reasons for excluding studies were described qualitatively
					
					n=5 studies from one network were included (Hermida et al. 2003 - 2009) → the MAPEC study (s.a. Hermida et al. 2010-2020 Hygia)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				15 Hermida et al. Treatment of non-dipper hypertension with bedtime administration of valsartan. J Hypertens 2005 https://pubmed.ncbi.nlm.nih.gov/16148616/ 16 Hermida et al. Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. Hypertension 2007 https://pubmed.ncbi.nlm.nih.gov/17635851/ 17 Hermida et al. Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients. Chronobiol Int. 2009 https://pubmed.ncbi.nlm.nih.gov/19142758/ 18 Pechère-Bertschi et al. Renal response to the angiotensin II receptor subtype 1 antagonist irbesartan versus enalapril in hypertensive patients. J Hypertens. 1998 https://pubmed.ncbi.nlm.nih.gov/9557932/ 19 Povedano et al. 24-hour and nighttime blood pressures in type 2 diabetic hypertensive patients following morning or evening administration of olmesartan. J Clin Hypertens (Greenwich). 2009 https://pubmed.ncbi.nlm.nih.gov/19695030/ 20 Ushijimaet al. Different chronotherapeutic effects of valsartan and olmesartan in non-dipper hypertensive patients during valsartan treatment at morning. J Pharmacol Sci. 2015 https://pubmed.ncbi.nlm.nih.gov/25704020/	

Zhang et al. 2020 / SR / time course (beta-blockers)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Zhang et al. Cochrane [147] https://www.ncbi.nlm.nih.gov/pubmed/32888198	2020	high	**Objective** degree of variation in hourly blood pressure (BP) lowering efficacy of beta-blockers with partial agonist activity (BBPAA) over a 24-hour period **Search** Cochrane Hypertension Specialised Register; CENTRAL; MEDLINE; Embase; World Health Organization International Clinical Trials Registry Platform; ClinicalTrials.gov (up to June 2020) **Inclusion and exclusion criteria** - randomised and non-randomised trials	n=14 non-randomised controlled trials - n=7 studies, n=121 patients (with pindolol and bopindolol) reported data for the primary end-point and were included in meta-analysis **primary**: beta-blockers with partial agonist activity vs. no treatment (n=7 studies, n=121 patients, very low certainty of evidence) - variation in the decrease in 24-hour ambulatory hourly SBP (at 3 to 12 weeks): SBP lowering at each hour ranged from -3.68 mmHg to ▪ -17.74 mmHg over the 24-hour period - SBP-lowering effects were lower at night than during the day and evening across three 8-hourly time intervals (day, evening, night):	most of studies were judged as high or unclear risk of bias for selection bias, attrition bias, and reporting bias overall certainty of the evidence was judged as very low for all outcomes

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- ambulatory monitoring - patients with essential hypertension - baseline systolic blood pressure (SBP) of at least 140 mmHg, or diastolic blood pressure (DBP) of at least 90 mmHg, or bot - aged > 18 years - a minimum follow-up of three weeks - appropriate washout period - blinding was not required **Quality assesment** according to the Cochrane Risk of Bias Tool, GRADE **Intervention** beta-blocker with partial agonist activity (BBPAA)[33] **Comperator** placebo or no intervention **Outcomes** **primary**: - end-point hourly systolic and diastolic blood pressure (SBP and DBP) **secondary:** - heart rate (HR) (measured using a 24-hour ambulatory BP monitoring (ABPM) device)	o day (MD -12.04 mmHg, 95% CI -13.12 to -11.07); o evening (MD -12.17 mmHg, 95% CI -13.43 to -10.90); o night (MD -6.65 mmHg, 95% CI -7.90 to -5.36) ▪ - variation in the decrease in 24-hour ambulatory hourly DBP (at 3 to 12 weeks): DBP lowering at each hour ranged from -2.27 mmHg to -9.34 mmHg over the 24-hour period - DBP-lowering effects were lower at night than during the day and evening across three 8-hourly time intervals (day, evening, night): o day (MD -7.87 mmHg, 95% CI -8.33 to -7.41), o evening (MD -7.53, 95% CI -8.13 to -6.93), o night (MD -5.16 mmHg, 95% CI -5.60 to -4.73) ▪ **secondary:** - variation in the decrease in 24-hour ambulatory hourly HR (at 3 to 12 weeks): HR lowering at each hour ranged from -0.29 beats/min to ▪ -10.29 beats/min over the 24-hour period - HR-lowering effects were lower at night than during the day and evening across three 8-hourly time intervals (day, evening, night): o day (MD -6.76 beats/min, 95% CI -7.49 to -6.00), o evening (MD -5.28 beats/min, 95% CI -6.03 to -4.52), o night (MD -3.30 beats/min, 95% CI -4.00 to -2.61)	note: authors included baseline controlled trials because there is negligible, or no placebo effect, with 24-hour ambulatory BP measurement sample size was small in all included studies (11-77 patients)

[33] acebutolol, celiprolol, oxprenolol, pindolol, alprenolol, and bopindolol

Luo et al. 2019 / SR / evening vs. morning (calcium-chanel-blockers - amlodipine)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Luo et al. Rev Cardiovasc Med [148] https://pubmed.ncbi.nlm.nih.gov/31345001/	2019	critically low	**Objective**
			compare the effects of amlodipine in morning and evening dosingregimen
			Search
			Pubmed, Embase, Web of Science and Chinese Academic Journal from CNKI, VIP, and Wanfang (up December 2018)
			Inclusion and exclusion criteria
			▪ randomized controled trials (RCTs)
			▪ patients with hypertension
			▪ patients with cardiac failure or cerebral infarctions were excluded
			Quality assesment
			modified Jadad scale
			Intervention
			amlodipine (morning)
			Comperator
			amlodipine (evening)
			Outcomes
			▪ daytime / nighttime blood pressure,
			▪ 24 h mean blood pressure,
			▪ heart rate (HR)
			▪ non-dipper alteration
				n=25 studies/publications included in qualitative analysis (n=1,481 patients)
				▪ n=19 studies included in meta-analysis (n= 1,215 patients, range 6-160 patients)
				
				outcome
				blood pressure (amlodipine - morning vs. evening):
				▪ office: mean difference (MD) = -0.03 (95% confidence interval (CI) -0.93-0.88), P = 0.96, I^2=0%
				  ▫ systolic, MD 0.05 (-1.15; 1.25), I^2=0%, n=9 studies
				  ▫ diastolic, MD -0.12 (-1.50; 1.25), I^2=0%, n=6 studies
				▪ daytime: MD = -0.30 (-1.05-0.46), P = 0.44, I^2=0%
				  ▫ systolic, MD -0.57 (-1.57; 0.43), I^2=0%, n=10 studies
				  ▫ diastolic, MD 0.05 (-1.08; 1.20), I^2=0%, n=9 studies
				▪ nighttime: MD = 2.04 (1.27-2.81), P < 0.00001, I^2=41%
				  ▫ systolic, MD 2.47 (1.39; 3.54), I^2=46% n=13 studies
				  ▫ diastolic, MD 1.50 (0.50; 2.69), I^2=35%, n=11 studies
				▪ 24 h mean: MD = 1.15 (-0.39-2.70), P = 0.14, I^2=81%
				  ▫ systolic, MD 1.62 (-0.63; 3.88), I^2=83%, n=16 studies
				  ▫ diastolic, MD 0.57 (-1.50; 2.64), I^2=75%, n=13 studies
				▪ heart rate: MD = 0.11 (-1.22-1.45), P = 0.87, I^2=0%
				  ▫ 24h MD -0.06 (-2.33; 2.20), I^2=0%, n=4 studies
				  ▫ daytime MD 0.91 (-1.65; 3.46), I^2=0%, n=4 studies
				  ▫ nighttime MD -0.30 (-2.47; 1.86), I^2=0%, n=4 studies
				▪ non-dipper alteration: risk ratio (RR) = 0.51 (0.41-0.63), P < 0.00001, I^2=23%, n=7 studies
					the definition of observed outcomes was unclear (PIC**O**)
					
					sample size of included studies was small
					
					authors combined results (MD) of systolic and diastolic blood pressure

Xie et al. 2021 / SR / chronotherapy (antihypertensive drugs)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Xie et al. BMC Cardiovasc Disord [149] https://pubmed.ncbi.nlm.nih.gov/34088274/	2021	critically low	**Objective** effects of chronotherapy **Search**	n=10 studies (n=8 studies parallel-designed, n=2 cross-over design), n=1724 patients (range 31 to 639 patients), mean age 61 years - mean follow-up 2 to 48 weeks	authors documented that the risk of bias assemsment was

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			MEDLINE, EMBASE, CENTRAL, the Chinese Biomedical literature database (up to April 2020), hand-searched **Inclusion and exclusion criteria** ▪ randomized controlled trials (cross-over design was allowed) ▪ adults (aged > 18 years) ▪ primary hypertension □ blood pressure systolic and/or diastolic > 140/90 mmHg ▪ secondary hypertension, alternating shift workers, and severe cardiac insufficiency ▪ (NYHA III-IV) were exclusion criteria **Quality assesment** Based on Cochrane risk of bias tool **Intervention** antihypertensive drugs[34] (bedtime: 18-24:00) **Comperator** antihypertensive drugs (awakening: 6-12:00) **Outcomes** **primary**: ▪ change in MBPS (morning blood pressure surge) from baseline to the end of treatment ▪ or the value of MBPS at the end of treatment if the baseline is comparable ▪ or the ratio of patients whose MBPS exceeded the settled threshold after treatment ▪ **secondary:** ▪ night blood pressure dipping ▪ 24-h mean systolic blood pressure (SBP) and diastolic blood pressure (DBP)	**outcomes** **primary:** - change in MBPS (morning blood pressure surge) from baseline to the end of treatment (calcium channel blockers; renin-angiotensin system inhibitors; β-blockers, angiotensin II receptor blockers) ○ mean difference (evening vs. morning administration): -5.30 (95% CI -8.80; -1.80) mmHg, I^2=98% - adverse effects (evening vs. morning) ○ overall: RR 0.65 (95% CI 0.30 to 1.41), I^2 = 69% ○ discontinuation due to adverse effects: RR 0.95 (95% CI 0.53 to 1.71), I^2 = 0%) ○ adverse effects (most common): headache, as well as nausea observed in the morning regimen **Articles included:** 18 Acelajado MC, Pisoni R, Dudenbostel T, Oparil S, Calhoun DA, Glasser SP. Both morning and evening dosing of nebivolol reduces trough mean blood pressure surge in hypertensive patients. J Am Soc Hypertens. 2012;6(1):66–72. 19 Zappe DH, Crikelair N, Kandra A, Palatini P. Time of administration important? Morning versus evening dosing of valsartan. J Hypertens. 2015;33(2):385–92. (ClinicalTrials.gov Identifier: NCT00241124) 20 Zhang Z, Zhang Z, Liu M, Che M, Cao F, Wang R, et al. Influence of different time treatment regimen of antihypertensive medication on morning blood pressure surge and blood pressure variability in hypertension patients. Med J West China. 2014;26(2):221-3 + 6. 21 Zhao L, Liu S, Gan B. Effect of different time of taking medicine on blood pressure of elderly patients with non-dipper hypertension. Occup Health. 2015;31(13):1794-7 + 801.	difficult due to lack of information

[34] diuretics, adrenergic beta-antagonists (β-blockers), alpha-antagonists, calcium channel blockers (CCB),vasodilator agents and renin-angiotensin system inhibitors (RASI, including angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			▪ daytime mean SBP and DBP ▪ night-time SBP and DBP ▪ safety outcomes □ overall adverse effects □ withdrawals due to adverse effects during treatment □ withdrawals due to adverse effects are reported as events leading to permanent trial discontinuation	22 Qiao Z, Zhuang R, Li Y. Effect of candesartan taken before going to bed on morning blood pressure surge and mALB in hypertensive patients. Chin J Geriatric Heart Brain Vessel Dis. 2015;17(5):492–4. 23 Li H, Wang D. Intervention effect of enalapril folic acid tablets on H-type hypertensive patients with morning peak blood pressure. Pract J Cardiac Cereb Pneumal Vasc Dis. 2016;24(S1):21–3. 24 Lai J. The clinical effect of chronotherapeutics on morning blood pressure surge in patients with hypertension. J Trop Med. 2015;15(11):1495–8. 25 Peng G, Wang Y, Xiao Y, Chen J, Yang Y, Ye Y, et al. Blood pressure lowering efficacy of telmisartan and amlodipine taking on the morning or at bedtime: ABPM results. Chin J Cardiol. 2013;41(6):484–7. 26 Hermida RC, Ayala DE, Mojon A, Alonso I, Fernandez JR. Reduction o morning blood pressure surge after treatment with nifedipine GITS at bedtime, but not upon awakening, in essential hypertension. Blood Pres Monit. 2009;14(4):152–9. Dion 2015 (ciation not available) Hoshino 2010 (citation not available)	

Sun et al. 2016 / SR / evening (antihypertensive drug therapy)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Sun et al. [150] https://pubmed.ncbi.nlm.nih.gov/27296158/	2016	critically low	**Objective** effects of bedtime administration of blood pressure lowering agents on ambulatory BP monitoring (ABPM) results **Search** ISI Web of Science, Embase, Cochrane, and Pubmed (up to October 2015) **Inclusion and exclusion criteria** - clinical trials (randomized and non-randomized) - follow-up/treatment-duration at least 8 weeks - adult patients with hypertension (essential and secondary hypertension)	n= 6 studies, n=1,566 patients (range 41-661) - n=5 parallel group design, n=1 cross-over design - follow-up 8 weeks to 5.4 years **outcomes** blood pressure (bedtime vs. morning (awaking) administration), mean difference (MD) (95% confidence interval (CI)) - diurnal, n=6 studies ○ SBP MD -1.67 mm Hg (-5.23-1.89, p = 0.36) ○ DBP MD -1.13 mm Hg (-4.28-2.03, p = 0.48) - nocturnal, n=6 studies ○ SBP MD -6.32 mm Hg (-12.01 to -0.62, p = 0.03)	outcomes were not described in detail within the methods section authors documented significant heterogeneity (population (e.g. comorbidities) and antihypertensive drugs were different between the included studies

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			○ blood pressure: systolic (SBP) ≥ 140 mm Hg or diastolic (DBP) ≥ 90 mm Hg **Quality assesment** - **Intervention** one or more antihypertensive drugs[35] (bedtime administration, 5 p.m.-12:00 midnight) **Comperator** antihypertensive drugs (morning administration, 6 a.m – 12:00 noon) **Outcomes** **primary**: blood pressure	○ DBP MD -3.17 mm Hg (- 5.49 to -0.85, p = 0.007) - 24-h, n=5 studies ○ SBP MD -2.78 mm Hg (-6.02-0.47, p = 0.09) ○ DBP MD -0.36 mm Hg (-1.80-1.08, p = 0.62) - absolute BP reduction from baseline between two groups, n=3 studies, n=763 patients ○ diaurnal SBP MD 0.09 mm Hg (-2.29-2.47, P=0.94) ○ diaurnal DBP MD 0.20 mm Hg (-1.84-2.24, P=0.85) ○ nocturnal SBP MD 4.72 mm Hg (1.13-8.32, P=0.01) ○ norctural DBP MD 3.57 mm Hg (0.02-7.12, P=0.05) **Authors included** 8 Farah R, Makhoul N, Arraf Z, Khamisy-Farah R. Switching therapy to bedtime for uncontrolled hypertension with a nondipping pattern: A prospective randomized-controlled study. Blood Press Monit, 2013; 18: 227–231. doi: 10.1097/MBP.0b013e3283624aed 11 Hermida RC, Ayala DE, Fontao MJ, Mojon A, Alonso I, Fernandez JR. Administration-time-dependent effects of spirapril on ambulatory blood pressure in uncomplicated essential hypertension. Chronobiol Int, 2010; 27: 560–574. doi: 10.3109/07420528.2010.485411 12 Rossen NB, Knudsen ST, Fleischer J et al. Targeting nocturnal hypertension in type 2 diabetes mellitus. Hypertension, 2014; 64: 1080–1087. doi: 10.1161/HYPERTENSIONAHA.114.03958 13 Hermida RC, Ayala DE, Mojon A, Fernandez JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. J Am Soc Nephrol, 2011; 22: 2313–2321. doi: 10.1681/ASN.2011040361 14 Kario K, Hoshide S, Shimizu M et al. Effect of dosing time of angiotensin II receptor blockade titrated by self-measured blood pressure recordings on cardiorenal protection in hypertensives: The Japan Morning Surge-Target Organ Protection (J-TOP) study. J Hypertens, 2010; 28: 1574–1583. doi: 10.1097/HJH.0b013e3283395267	participants of Hermida et al. 2005, 2010, 2011 were included in BP analysis (n=3 of n=6) participants of Hermida et al. 2005 and 2010 were included in absolute BP analysis

[35] angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, diuretics, angiotensin receptor blockers, and alpha-blockers

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				15 Hermida RC, Calvo C, Ayala DE et al. Treatment of non-dipper hypertension with bedtime administration of valsartan. J Hypertens, 2005; 23: 1913–1922.	

Zhao et al. 2011 / SR / evening vs. morning (antihypertensive drug therapy)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Zhao et al. Cochrane [151] https://pubmed.ncbi.nlm.nih.gov/21975743/	2011	moderate	**Objective**
			evaluate the administration-time-related-effects of antihypertensive drugs administered as once daily monotherapy in the evening versus morning administration regimen
			Search
			Cochrane CENTRAL on Ovid (4th Quarter 2009), Ovid MEDLINE (1950 to October 2009), EMBASE (1974 to October 2009), the Chinese Biomedical literature database (1978 to 2009)
			Inclusion and exclusion criteria
			▪ randomized controlled trials
			▪ patients with primary hypertension
			▪ systolic and/or diastolic blood pressure levels were 140/90 mmHg or greater
			▪ patients with known secondary hypertension, shift workers or white coat hypertension were excluded
			▪ at least 3 weeks treatment duration
			Quality assesment
			Cochrane Risk of Bias Tool
			Intervention
			monotherapy with an antihypertensive drug[36] (once daily in the evening)
				n=21 trials, n=1,993 patients (range 10-259)
				▪ n=13 with parallel group design
				▪ n=8 with crossover design
				▪ angiotensin-converting-enzyme inhibitors - ACEI (5 trials), calcium-channel blockers - CCB (7 trials), angiotensin II receptor blockers - ARB (6 trials), diuretics (2 trials), alpha-blockers (1 tri beta-blockers (1 trial)
				no RCT reported on all cause mortality, cardiovascular mortality, cardiovascular morbidity and serious adverse events
				
				adverse events (evening vs. morning):
				▪ overall RR=0.78 (95%CI 0.37-1.65)
				▪ withdrawals due to adverse events RR=0.53 (95%CI 0.26-1.07)
				morning BP (evening vs. morning):
				▪ SBP (-1.62 mm Hg, 95% CI -4.19 to 0.95), I^2=59%
				▪ DBP (-1.21 mm Hg, 95% CI -3.28 to 0.86), I^2=66%
				24-hour BP (evening vs. morning):
				▪ in general:
				  ▫ SBP (-1.71 mm Hg, 95% CI -2.78 to -0.65), I^2= 85%
				  ▫ DBP (-1.38 mm Hg, 95% CI -2.13 to -0.62), I^2=85%
				▪ ACEI:
				  ▫ SBP (-0.93 mm Hg, 95%CI -3.11 to 1.24)
				  ▫ DBP (-1.56 mm Hg (95%CI -3.18 to 0.06)
				▪ alpha-blocker:
					significant heterogeneity was reported
					
					lack on information on allocation concealment and selective reporting lead to downgraded quality

[36] angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta-blockers (BBs), diuretics, angiotensin II receptor blockers (ARBs) and alpha-blockers

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Comperator monotherapy with an antihypertensive drug (once daily in the morning) **Outcomes** **primary**: ■ all cause mortality, ■ cardiovascular mortality, ■ cardiovascular morbidity (stroke, myocardial infarction, congestive heart failure, aortic aneurysm), ■ reduction of blood pressure **secondary:** ■ serious/overall adverse events ■ withdrawals due to adverse effects ■ change from baseline in 24-hour mean SBP and DBP by ambulatory BP monitoring ■ change from baseline in morning SBP and DBP (assessed by ambulatory BP monitoring during the periods from 6 a.m. to 12 noon)	□ SBP (-5.10 mm Hg, 95%CI -8.43 to -1.77) □ DBP (-2.70 mm Hg, 95%CI -5.17 to -0.23) ■ ARB: □ SBP (-0.87 mm Hg, 95%CI -2.12 to 0.38) □ DBP (-0.72 mm Hg, 95%CI -1.86 to 0.43) ■ beta-blocker: □ SBP (-1.40 mm Hg, 95%CI -3.60 to 6.40) □ DBP (-1.10 mm Hg, 95%CI -2.27 to 4.47) ■ diuretics: □ SBP (-6.22 mm Hg, 95%CI -9.34 to -3.10) □ DBP (-5.60 mm Hg, 95%CI -6.82 to -4.38) ■ CCB: □ SBP (-1.64 mm Hg, 95%CI -3.39 to 0.12) □ DBP (-0.61 mm Hg (95%CI -1.58 to 0.35)	

Kaur et al. 2016 / SR + recommendations / Timing of Administration (Australia)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Kaur et al.Pharmaceutics [152] https://pubmed.ncbi.nlm.nih.gov/27092523/	2016	critically low	**Objective** ■ to investigate the “time of administration” recommendations on chronotherapy[37] for commonly-prescribed medicines in Australia	n=27 research studies (for 12 of the 30 most commonly-prescribed medicines) (study design: randomised controlled trials, comparative trials (drug administration done at more than one time point), combination trials (more than one drug combination))	Hinweis: nach strengen Ein- und Ausschlusskriterien wäre diese

[37] chronotherapy (administration of medication in coordination with the body’s circadian rhythms to maximise therapeutic effectiveness and minimise/avoid adverse effects);
authors note: gives rise to rhythmic variations in the physiological status of the body’s systems and even influences the susceptibility of human beings to morbid and mortality events: e.g the incidence of myocardial infarction (vgl. page 2 of the publication)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			▪ explore the quality of information on the timing of administration presented in drug information sources (e.g. consumer medicine information (CMI) and approved product information (PI)) **Study design** systematic review and analysis of Consumer Medicine Information and Australian Approved Product Information (authors compared recommendations) **Search** Embase and Medline **Inclusion and exclusion criteria** ▪ original research studies ▪ reporting on the impact of "time of administration" of the 30 most commonly-prescribed medicines in Australia for 2014 ▪ human subjects (patients) **Outcomes** chronotherapy recommendations[38]	▪ "Time of administration" studies have been reported for 40% (n = 12) of the 30 most commonly-prescribed medicines (e.g for perindopril, ramipril, irbesartan, telmisartan, candesartan, amlodipine, atenolol) ▪ Results were presended descriptively **outcomes** ▪ 56% (n = 15 of n=27 studies) indicated that the therapeutic effect of the medicine varied with the time of administration of medication, i.e., supported chronotherapy (including e.g. antihypertensives) ▪ n=9 of n=15 studies demonstrated different effects on blood pressure control depending on the time of administration [citation 58–66 within the publication] s.a. Table 3 on page 7ff ▪ drug information sources (CMI and PI): administration time was only available for perindopril (CMIs and PIs approved "morning" administration for perindopril, whereas the literature evidence suggests bedtime administration) ▪ authors note as supporting evidence (vgl. page 5) : "Studies have demonstrated that in hypertensive patients, a reduced blood pressure (BP) drop during sleep is associated with increased cardiac events" [47] - Boggia, J.; Li, Y.; Thijs, L.; Hansen, T.W.; Kikuya, M.; Björklund-Bodegård, K.; Richart, T.; Ohkubo, T.; Kuznetsova, T.; Torp-Pedersen, C.; et al. Prognostic accuracy of day versus night ambulatory blood pressure: A cohort study. Lancet 2007, 370, 1219–1229. ▪ and "Hence, antihypertensives were assessed based on their ability to control nocturnal BP. Based on the findings of these morning-evening administration time studies, morning administration is suggested for amlodipine, evening/bedtime administration for ramipril, candesartan, telmisartan, amlodipine/hydrochlorothiazide, amlodipine/olmesartan and amlodipine/valsartan, night-time administration for perindopril and evening administration for atorvastatin, simvastatin, amlodipine/valsartan and rabeprazole. For the remaining 44% (n = 12) of the studies, the therapeutic effect of the medicine did not vary with the time of medicine administration."	Arbeit in der Recherche ausgeschlossen worden die Autoren berichten ihre Methodik, weisen allerdings nicht auf ein Protokoll hin es erfolgte keine Qualitätsbewertung der Studien

[38] e.g. "Is there a specific circadian 'time or time range' of medication administration that can result in better effect for the given medicine?"

Hermida et al. 2010-2016 / Prospektiv / Treatment-time regimen (Hygia)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar

Hermida et al. Eur Heart J 2020 [153] https://pubmed.ncbi.nlm.nih.gov/31641769/
 	
Hermida et al. Chronobiol Int 2016 [154] https://pubmed.ncbi.nlm.nih.gov/27221952/ (protokol)
 	
Hermida et al. Hypertens Res 2016 https://pubmed.ncbi.nlm.nih.gov/26657008/
 	
Hermida et al. Chronobiol Int 2013 [155] https://pubmed.ncbi.nlm.nih.gov/23098160/
 	
Hermida et al. J Am Soc Nephrol 2011 [156] https://pubmed.ncbi.nlm.nih.gov/22025630/
 	
Hermida et al. J Am Coll Cardiol 2011 [157] https://pubmed.ncbi.nlm.nih.gov/21884956/
 	
Hermida et al. Chronobiol Int 2010 [158]
	2010-2020	-	Ambulatory blood pressure monitoring (ABPM)-based Hygia Projekt (research network of 40 primary care centres), Northern Spain
			Objective
			ABPM-measurement for diagnosis, monitoring treatment respons and assessment of cardiovascular (and other) risks
			Study design
			prospective trial, controlled, multicentre
			different analyses; participants were included between 2008 and 2018
			Inclusion and exclusion criteria
			▪ Spanish men and women
			▪ aged ≥ 18 years
			▪ normotensive to sustained hypertension (by 48 h ABPM)
			▪ e.g. pregnant participants and and patients with drug/alcohol abuse, night/shift work employement, AIDS, secondary hypertension, cardiovascular diseases were excluded
			▪ minimum targeted median follow-up 5 years
			▪ required ≥ 1-year minimal follow-up per participant
			Investigation
			bedtime ≥ 1 antihypertensive drug(s) (ARB, ACEI, CCB, betablockers and/or diuretics)
			Comperator
			awaking hypertension therapy (all drugs)
			Outcomes
			death, myocardial infarction, stroke, cardiovascular diseases, diabetes (definitions see page 921 of Hermida et al. Chronobiol Int 2016 [154])
			▪ total events (composite)
			▪ events (different combinations of events)
			prognostic value of:
			▪ cardiovascular morbidity and mortality
				Hermida et al. Eur Heart J 2020 [153]: Hygia Chronotherapy Trial
				n=19,084 patients (10 614 men/8470 women, 60.5 ± 13.7 years of age)
				▪ bedtime ≥ 1 drug (n=9552), awakening (all drugs) (n=9532 patients)
				▪ median follow-up 6.3 years (inter-quartile range (IQR) 4.1–8.3 years)
				▪ most frequently prescribed monotherapies:
				  ▫ ARBs (mainly valsartan or telmisartan) or ACEIs (mostly enalapril or ramipril; 69% of participants)
				  ▫ CCBs (mainly amlodipine; 13% of patients)
				▪ most commonly prescribed dual combination therapies:
				  ▫ ARB/ACEI with diuretic—mostly hydrochlorothiazide in doses up to 25 mg/day—(43%) or CCB (26%)
				▪ most used triple therapy:
				  ▫ ARB/ACEI–diuretic–CCB (69%)
				
				Outcomes
				▪ total events: n=3246 participants
				▪ cardiovascular (CV) events:
				  ▫ myocardial infarction: n=274
				  ▫ coronary revascularization: n=302
				  ▫ heart failure: n=521
				  ▫ stroke: n=345
				  ▫ CVD death: n=310
				▪ adjusted hazard ratio (HR, 95% confidence interval (CI)): bedtime vs. awaking
					documention of the study design was not based on one standard
					
					sample size calculation for hypotheses testing was based on event-rates of the MAPEC study

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
https://pubmed.ncbi.nlm.nih.gov/20854139/			■ blood pressure (systolic SBP, diastolic DBP), heart rate, pulse ■ change in blood pressure factors that influenced investigated outcomes	□ total events HR 0.58 (0.54-0.62), P< 0.001, n=3246 □ CV events HR 0.55 (0.50–0.61), P<0.001, n=1752 □ stroke HR 0.51 (0.41–0.63), P<0.001, n=345 □ death HR 0.55 (0.48-0.63), P<0.001, n=957 □ CVD death HR 0.44 (0.34–0.56), P<0.001, n=310 □ ischemic stroke HR 0.54 (0.42-0.69), P<0.001, n=274 □ haemorrhagic stroke HR 0.39 (0.23–0.65), P<0.001, n=71 □ myocardial infarction HR 0.66 (0.52–0.84), P<0.001, n=274 □ coronary revascularization HR 0.60 (0.47–0.75), P<0.001, n=302 □ heart failure HR 0.58 (0.49–0.70), P<0.001, n=521 □ transient ischemic attack HR 0.73 (0.51-1.04), P=0.078, n=127 □ angina pectoris HR 0.65 (0.51-0.83), P<0.001, n=279 □ peripheral artery disease HR 0.52 (0.41–0.67), P<0.001, n=296 ■ treatment-time differences in the prevalence of patients reporting adverse effects at any visit: 6.7% vs. 6.0% for the awakening and bedtime-treatment regimen, respectively; P = 0.061	

8.10 SR (Fixkombination mit Diuretika vs. freie Kombination)

Si 2019 / antihypertensive combination (adherence, elderly, Australia)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Si et al. Pharmacoepidemiol Drug Saf [159] https://pubmed.ncbi.nlm.nih.gov/30784140/	2019		**Objective** long-term adherence, persistence, and re-initiation of BPL agents **Study design/source** - cohort study (retrospective) - national dispensing claims data from Australian Pharmaceutical Benefits Scheme (PBS) - data extracted from 2006-2016 **Inclusion and exclusion criteria** - patients aged ≥65 years - "long-term concession" individuals - had no blood pressure lowering (BPL) dispensing for at least two consecutive years from 2006 to 2016 (wash-out period) (newly initiated therapy) - had at least two dispensing records of any BPL agent following the 2-year wash-out period from 2008 to 2016 **Investigation** World Health Organisation Anatomical Therapeutic Chemical (ATC) classification codes: - C02 (other antihypertensives) - C03 (diuretics) - C07 (betablockers (BB)) - C08 (calcium-channel-blockers (CCB)) - C09A (angiotensin-converting-enzyme-inhibitors (ACEI) - C09C (angiotensin-II-receptor-blockers (ARB)) - C09B/C09D (fixed dose combinations [FDC] that contained either ACEI or ARB) **Outcomes**	n=31,088 older Australians were included (≥2 BLP dispensing records) - mean age 75.4 years; 56% females - mean follow-up 3.8 years (standard deviation (SD) 2.5 years) - 40% to 70% of included patients discontinued a BPL agent - median time to discontinuation: range 159-373 days - death n=4.982 (16%) patients received: - ACEI n=9,619 (30.9%) - ARB n=6,735 (21.7%) - BB n=4,830 (15.5%) - CCB n=2,768 (8.9%) - diuretics n=4,743 (15.3%) - other antihypertensives n=1,312 (4.2%) - FDC n=1,078 (3.5%) **Outcomes:** persistence at 6, 12 and 36 months (% of patients): - FDC: 68%, 58%, and 41% - ACEI: 62%, 51%, and 34% - ARB: 69%, 58%, and 40% - BB: 67%, 54%, and 36% - CCB: 57%, 47%, and 31% - diuretics: 59%, 41%, and 23% - other anti-hypertensives: 52%, 37%, and 18% (30%-50% of those who discontinued, re-initiated therapy) hazard ratio (HR) of discontinuation (ACEI (reference category), adjusted	study population was limited patients aged ≥65 years (randomly selected) source limitations: information on indications for prescribing was not available the prescribing dosage of BPL agents was not avalable from the PBS data, because these are not recorded (validated 75th percentile was used to determine duration)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- persistence (discontinuation was defined as ≥90 days without BPL coverage) - adherence (proportion of days covered (PDC) at 6-month intervals) note: Cox regression was used (with ACEI reference category)	- FDC: aHR, 0.78; 95% CI, 0.75-0.81 - ARB: aHR, 0.80; 95% CI, 0.77-0.83 - BB: aHR, 0.86; 95% CI, 0.83-0.89 - CCBs: aHR,1.09; 95% CI, 1.05-1.14 - diuretics: aHR, 1.10; 95% CI, 1.07-1.14 - other anti-hypertensives: aHR, 1.29; 95% CI, 1.22-1.37 ■ “good” adherence (PDC ≥ 0.8) to BPL therapy at 6, 12 and 36 months: - 50%-60%, 34%-51%, and 21%-42% of the study population	

Verma 2018 / antihypertensive combination (adherence, clinical outcomes)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar

Verma et al. PLoS Med [160] https://pubmed.ncbi.nlm.nih.gov/29889841/	2018		**Objective**
			adherence and clinical outcomes of fixed-dose combination or separate drug combinations
			Study design/source
			- cohort study (retrospective)
			- Ontario Drug Benefit claims database
			- Canadian Institute for Health Information Discharge Abstract Database
			- National Ambulatory Care Reporting System
			- Registered Persons Database
			- Institute for Clinical Evaluative Sciences (ICES) Physicians Database
			- Ontario Health Insurance Plan claims database
			Inclusion and exclusion criteria
			- residents of Ontario, Canada
				n=31,508 partients were included before matching
				- n=13,350 patients were matched: n=6,675 patients in both groups
				- median follow-up time: 1,826 days
				- median age 71 years (IQR 68±77)
				- dose of medication:
				  ○ low-dose: 42.7%
				  ○ intermediate: 43.0%
				  ○ high: 14.3%
				- fixed dose combinations more often included ARB (65.1% vs. 23.3%) and hydrochlorothiazide (HCT, 88.2% vs. 82.9%) compared with the multipill group
				Outcomes:
				- non-persistence (break in therapy), FDC vs. multipill:
				  ○ 83.1% vs. 88.7% HR 0.80, 95% CI 0.77±0.83, P < 0.01
				- adherence, multipill vs. FDC:
					new users over the age of 66 years were included
					possibility of residual confounding remains
					a limitation

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- aged ≥66 years - initiation of combination therapy between April 2004 and December 2014 (new users) - follow-up 5 years or until March 2015 **Investigation** single-pill fixed-dose combinations (FDC): - one angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II-receptor blocker (ARB) plus one thiazide diuretic **Comperator** separate drugs in multipill combination **Outcomes** persistence and adherence (proportion of days covered) all-cause death and hospitalization for acute myocardial infarction (AMI), heart failure, or stroke note: propensity score matching and cox regression were used	○ PDC: 0.42 (0.11-0.91) vs. 0.70 (0.19-0.98), P < 0.01 - composit (death and hospitalisation) - on-treatment analysis (censored when first discontinuation occurs) ○ event rate: ▪ FDC: 2.4 events per 100 person-years (198 events/ 8,227 years of follow-up) ▪ multipill: 2.4 events per 100 person-years (149 events/ 6,306 years of follow-up) ▪ HR 1.06, 95% CI 0.86±1.31, P = 0.60 ▪ (s.a. page 10 Table 4 within the publication) - intention-to treat analysis ○ event rate: ▪ FDC: 3.4 per 100 person-years (1,008 events/ 25,967 years of follow-up) ▪ multipill: 3.9 per 100 person-years (904 events/ 26,226 years of follow-up) ▪ HR 0.89, 95% CI 0.81±0.97, P < 0.01 ▪ (s.a. page 11 Table 5 within the publication)	

Schulz 2016 / antihypertensive combination (adherence, Germany)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Schulz et al. [161] https://pubmed.ncbi.nlm.nih.gov/27393848/	2016		**Objective** determine and compare medication adherence and persistence to different antihypertensive drug classes **Study design/source** - cohort study (retrospective)	n=255,501 patients patients received: - ACEi 31.9%, n = 81,512 - ARB 10.9%, n=27,830 - BB 42.5%, n = 108,590 - CCB 9.0%, n=23,094	switching the index substance/fixed combination during the observation period was not allowed

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- claims data for prescriptions in the German statutory health insurance scheme (2004-2007) - database of the German Institute for Drug Use Evaluation (DAPI) **Inclusion and exclusion criteria** - first prescription of an antihypertensive (2005) - follow-up 24 months - ≥2 prescriptions of the same antihypertensive **Investigation** monotherapy of (anatomical therapeutic chemical (ATC) code): - angiotensin II receptor blockers (ARB; C09CA) - angiotensin-converting enzyme inhibitors (ACEi; C09AA) - calcium channel blockers (CCBs; C08C, C08D, C08E) - beta-blockers (BBs; C07AA, C07AB, C07AG) - thiazide and sulfonamide diuretics (C03AA and C03BA) and fixed-dose combinations of ARBs, ACEi, CCBs, and BBs with a diuretic (C09DA, C09BA, C08G, C07BB, C07BA, C07CB, C07CA, C03EA) **Outcomes** - non-persistence (determined on gaps exceeded 0.5 times the number of days supplied with medication in continuous dispensation) - adherence (medication possession ratio (MPR)) note: Cox-regression (persistence) and logistic regression (adherence; MPR <0.8 vs. MPR ≥0.8) were used	- Diuretics 5.7%, n = 14,475 - fixed-dose combinations of ARB and diuretics were prescribed as frequent as monotherapies of these drug classes - fixed-dose combinations of CCB and diuretics were prescribed for 127 patients; this group was excluded from further evaluations - other drug classes were more frequently prescribed as monotherapies - CCB and diuretics were predominantly prescribed for retired patients - younger patients received particularly BB - ~75% of patients received up to six additional drug classes **Outcomes:** ***non-persistence (gap 0.5 times of days supplied) of incident users:*** - monotherapy: 79.3% (n=159,159) patients - combination therapy with diuretic: 76.2% (n=41,713) patients hazard ratio (HR) for non-persistence (combination- vs. monotherapy), adjusted, 99.9% confidence interval (CI) - HR 0.916, (0.863–0.973), p< 0.001 (s.a. Table 4 page 674 and Figure 3 within the publication) ***non-adherence (MPR < 0.8) of incident users:*** - monotherapy: 56.3% (n=113,136) patients - combination with diuretics: 50.0% (n=27,587) patients odds ratio (OR) for non-adherence (combination- vs. monotherapy), adjusted, 99.9% confidence interval (CI) - OR 0.802 (0.715-0.900), p<0.001 (s.a. Table 4 page 674 and Figure 5 within the publication)	claims for different brand products/generics of the index substance were counted source limitations: information on indications for prescribing was not available

Breitscheidel 2012 / antihypertensive combination (compliance, Germany)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Breitscheidel et al. [162] https://pubmed.ncbi.nlm.nih.gov/22035215/	2012		**Objective** describe current treatment patterns of patients in Germany with hypertension **Study design/ source** - retrospective study - prescription data collected by general practitioners (GPs), using a longitudinal database, the German IMS Disease Analyzer (DA) **Inclusion and exclusion criteria** - diagnosis hypertension (ICD-10 code I10) - treatment data for period 09/2009 to 08/2010 - prescriptions of angiotensin receptor blockers (ARB), as single agents or in combination (fixed-dose or unfixed) with other anti-hypertensive drugs (e.g., diuretics, calcium-channel-blockers (CCB), beta-blockers (BB), angiotensin-converting-enzyme-inhibitors (ACEI) - period 09/2008 to 08/2009 (12 months follow-up) **Investigation** fixed-dose combination of angiotensin receptor blocker (ARB), amlodipine (AML), and hydrochlorothiazide (HCT) **Comperator** unfixed combinations **Outcomes** compliance (medication possession ratio (MPR)), persistence, and medication costs	n=406,888 patients were identified - n=347,619 patients had at least one prescription of anti-hypertensives (between Sep 2009 ans Aug 2010) o ACEI 56.7% o ARB: 27.3% o BB: 55.1% o CCB: 27.6% o diuretics: 28.0% - averaged age 64.9 years (SD 14.3) - authors described differences regarding sociodemographics between patients receiving fixed-dose and unfixed dose combinations of ARB, amlodipine and hydrochlorothiazide (HCT): e.g. higher number of patients with comorbidities (fixed vs. unfixed combinations) ■ (s.a. page 159 Tabel 4) **Outcomes:** mean compliance value at 12 months (%): - non-fixed- or fixed-dose combinations of ARB (n=17,310 patients): o ARB + other antihypertensives: 74.2, P=not applicable ■ o ARB + HCT (unfixed): 71.5, P < 0.0001 o ARB + HCT (fixed): 78.1 ■ o ARB + HCT + other antihypertensives (unfixed): 72.0, P < 0.0001 o ARB + HCT + other antihypertensives (fixed): 79.4 ■ o ARB + Amlodipine (unfixed): 75.5, P=0.1964 o ARB + Amlodipine (fixed): 72.8 ■	the true extent of treatment duration or dosing frequency could be under- or over-estimated because of indirect measurement of compliance based on prescription information not for all included patients a follow-up of 12 months was available authors described that no missing data imputation was performed (they assumed that data in the database were missing at random)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
				○ ARB + Amlodipine + other antihypertensives (unfixed): 76.2, P= 0.1158 ○ ARB + Amlodipine + other antihypertensives (fixed): 78.1 ■ ○ ARB + Amlodipine + HCT (unfixed): 75.4, P=not applicable ○ ARB + Amlodipine + HCT (fixed): compliance assessment not done due to very small patient numbers ■ ○ (s.a. Table 5 page 161 within the publication)	

Ah 2019 / ARB combination (adherence, Korea)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Ah et al. Patient Prefer Adherence [163] https://pubmed.ncbi.nlm.nih.gov/30774320/	2019		**Objective** to compare medication adherence and persistence between angiotensin receptor blocker (ARB) fixed combination (SPC) and free equivalent combination (FEC) as initial treatment and between SPC of an ARB with thiazide diuretic (TD) and an ARB with calcium channel blocker (CCB) **Study design/ source** - retrospective cohort study - Korean national claims database (HIRA) **Inclusion and exclusion criteria** - adult patients (≥18 years old) - uncomplicated hypertensive patients (ICD-10 code I10, I11, I12, I13, or I15) - newly treated with combination therapy of ARB and either a TD or CCB in 2012 **Investigation** - ARB fixed combination (SPC) - ARB-TD-SPC	n=20,175 patients per cohort (ARB-SPC and ARB-FEC) were matched n=45,253 patients per cohort (ARB+TD-SPC and ARB+CCB-SPC) were matched - mean age 56.1 years - the ARB-SPC cohort had a higher prevalence of ARB + TD use than the ARB-FEC cohort (56.3% vs 15.2%; P 0.01) **Outcomes (adjusted):** ARB-SPC vs. ARB-FEC / ARB+CCB-SPC vs. ARB+TD-SPC persistence (1 year): HR 1.33 (1.28, 1.39) / HR 1.02 (0.99, 1.04) persistence (initial): HR 1.61 (1.56, 1.64) / HR 1.12 (1.10, 1.14) adherence (1 year): OR 1.31 (1.25, 1.37) / OR 1.03 (1.00, 1.06) HR=hazard ratio (95% confidence interval (CI)), OR=odds ratio (95% CI), ARB=angiotensin-receptor-antagonist, CCB=calcium-channel-blocker, TC=thiazide diuretic, FEC=free equivalent combination, SPC=fixed combination (s.a. page 245 Table 2 within the publication) **persistence (ARB-SPC vs. ARB-FEC):**	authors documented risk of selection/channelling bias clinical outcomes could not be investigated due to the relatively short-term follow-up and the unavailability of clinical data (prescription claims data were used)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			Comperator - ARB free equivalent combination (FEC) - ARB-CCB-SPC **Outcomes** - persistence (a gap of no more than 60 days between medication supplies) - adherence (medication possession ratio (MPR) over 1 year* note: propensity score matching, logistic regression and cox regression were used * MPR was truncated MPR to 1.0 and categorized as fully adherent (MPR ≥0.8), intermediate (MPR 0.4–0.79), or low (MPR ,0.4)	- SPC cohort had significantly higher rates of overall persistence (66.4% vs 59.2%; P,0.01), and initial treatment persistence (41.9% vs 34.4%; P,0.01), compared with FEC cohort **persistence (ARB+TD-SPC vs. ARB+CCB-SPC):** - overall rate of persistence did not differ significantly between the ARB + TD and ARB + CCB cohorts - initial persistence of the ARB + CCB cohort was significantly higher compared with the ARB + TD cohort (HR 1.12, 95% CI 1.10–1.14) **adherence (ARB-SPC vs. ARB-FEC):** - about two-thirds of the entire population were fully adherent - SPC cohort had a significantly higher proportion of patients with full or intermediate adherence, compared with FEC cohort - SPC cohort had significantly higher rates of medication adherence (0.8±0.3 vs 0.7±0.3; P,0.01), compared with FEC cohort **adherence (ARB+TD-SPC vs. ARB+CCB-SPC):** - rate of medication adherence did not differ significantly between the ARB + TD and ARB + CCB cohorts	

Hsu 2015 / ARB combination (drug utilisation and adherence, Taiwan)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Hsu et al. Int J Clin Pract [164] https://pubmed.ncbi.nlm.nih.gov/25395349/	2015		**Objective** to compare adherence and persistence in patients using fixed-dose (FDC) and free combinations (FC) of angiotensin receptor blocker (ARB)/thiazide diuretic **Study design/ source** - cohort study - National Health Insurance Research Database, Taiwan, 2000-2011 **Inclusion and exclusion criteria**	n=7.348 patients were identified - FDC: n=5.725 patients - FC: n=1.623 patients - patients receive ≥ 3 different categories of antihypertensive medications 1 year prior the cohort entry date: FDC 21.3% vs. FC 41.4%, p < 0.0001 **Outcomes:** **persistence (FDC vs. FC):**	switchers between FDC and FC during the follow-up period were excluded age differed between FDC and FC group (patients ≥ 65 years: 23.6% vs. 26.2%, p=0.0328)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- newly diagnosed hypertensive patients (ICD-9-CM codes 401.xx- 405.xx) during 2005–2008 - aged ≥ 20 years - newly initiated combination therapy of ARB and thiazide diuretics[39] - follow-up 2 years **Investigation** fixed-dose combinations (FDC) of angiotensin receptor blocker (ARB) and thiazide diuretic (TD) **Comparator** free combinations (FC) of ARB and TD **Outcomes** - persistence (time from day of initiation to treatment discontinuation) - adherence (medication possession ratio (MPR)) note: linear regression and Kalan Meier analyses were used; high adherence was classified as MPR ≥ 80%	- a higher proportion of patients initiated FDC therapy were persistent throughout the followup period: o 26.1% still on the therapy after 2 years vs. 19.5% (overall log rank p < 0.0001) - adjusted hazard ratio (HR) for discontinuation 0.79 (95% confidence interval (CI) 0.74–0.85), P < 0.0001 **adherence (FDC vs. FC):** - overall, MPR decreased with the increased follow-up time - adjusted MPR were significantly higher among patients initiated FDC therapy compared with patients initiated FC therapy: - adjusted MPR: o 6 months: 66.55% vs. 63.86%, P=0.0012 o 1 year: 52.58% vs. 46.73%, P < 0.0001 o 1.5 year: 46.30% vs. 38.07%, P < 0.0001 o 2 year: 42.06% vs. 32.45%, P < 0.0001 - MPR ≥ 80%: adjusted odds ratio (OR) 1.37 (95% CI = 1.22–1.55), P < 0.0001	

Machnicki 2015 / ARB and CCB combination (adherence, USA)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Machnicki et al. Curr Med Res Opin [165] https://pubmed.ncbi.nlm.nih.gov/26397178/	2015		**Objective** determine persistence, adherence, utilization and costs with amlodipine/valsartan/hydrochlorothiazide fixed dose combination copared to corresponding free combination **Study design/ source**	n=10,800 patients for FDC and n= 3.794 patients for FC were identified (median age 57 years vs. 65 years) - FDC: n=1.884 patients (mean age 66.4 years) and - FC: n=1.884 patients (mean age 66.8 years) were matched	risk of residual confounding was reported

[39] Anatomical Therapeutic Chemical (ATC) codes: losartan and diuretics [C09DA01], valsartan and diuretics [C09DA03], irbesartan and diuretics [C09DA04], candesartan and diuretics [C09DA06], telmisartan and diuretics [C09DA07], and olmesartan medoxomil and diuretics [C09DA08] and FC (prescribed at the same date) of ARB (losartan [C09CA01], valsartan [C09CA03], irbesartan [C09CA04], candesartan [C09CA06], telmisartan [C09CA07], olmesartan [C09CA08]) and thiazide diuretic (hydrochlorothiazide [C03AA03], trichlorothiazide [C03AA06], benzylhydrochlorothiazide [C03AA91], indapamide [C03BA11], and metolazone [C03BA08]) after the index diagnosis date

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar

			- retrospective cohort study
			- commercial and Medicare Supplemental insurance in the Truven MarketScan database
			- study period 2008-2012, USA
			Inclusion and exclusion criteria
			- patients with hypertension (ICD-9 diagnosis between 2009 and 2011)
			- adults aged ≥ 18 years
			- follow-up 12 months
			Investigation
			amlodipine/valsartan/hydrochlorothiazide fixed dose combination (FDC)
			Comperator
			amlodipine/valsartan/hydrochlorothiazide free combination (FC)
			Outcomes
			primary:
			- adherence (proportion of days covered (PDC) and medication possession ratio (MPR))
			- non-persistence (treatment gap >30 days)
			secondary: healthcare utilization and costs at 12 months
			note: propensity score matching and logistic regression were used
				Outcomes:
				adherence adjusted (FDC vs. FC):
				- mean PDC 73.8% vs. 60.6%, P < 0.0001
				- mean MPR 85.7% vs. 77.0%, P < 0.0001
				■
				- PDC ≥80% 55.2% vs. 33.4%; P < 0.0001
				  ○ Odds Ratio (OR) 2.88 (95% confidence interval (CI) 2.55-3.26)
				- MPR≥80% 72.9% vs. 57.5%; P < 0.0001
				  ○ OR 2.72 (95% CI 2.40-3.08)
				Persistence adjustiert (FDC vs. FC):
				- gap ≤ 30 days: 46.8% vs. 23.6%, P < 0.0001
				  ○ OR 3.51 (95% CI 3.08-4.02)	

Ho 2018 / RAS-inhibitor + HCT combination (clinical outcomes, adherence)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Ho et al. J Clin Hypertens [166] https://pubmed.ncbi.nlm.nih.gov/30375168/	2018		**Objective** to compare the clinical outcomes of fixed-dose combinations (FDC) vs free combinations of renin-angiotensin system (RAS) inhibitor and thiazide diuretic in real-world hypertension management **Study design/ source**	- FDC (n = 13 176), mean follow-up 887.89 days - free combinations (n = 4392), mean follow-up 830.22 days - mean age 58 years **Outcomes:**	author documented risk of bias due to residual confounding (e.g. lack of laboratory

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- retrospective cohort study - claims database analysis - National Health Insurance Research Database (NHIRD) of Taiwan **Inclusion and exclusion criteria** - patients with hypertension (ICD-9-CM: 401.x) - newly diagnosed between July 1st, 2008 and December 31st, 2011 - aged ≥18 years - follow-up 1 year - patients with concurrent prescription of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) or switch between these two classes of drugs during the study period were excluded **Investigation** fixed-dose combinations (FDC) of renin-angiotensin system (RAS) inhibitor and thiazide diuretic **Comperator** free combinations **Outcomes** **primary:** major adverse cardiovascular events (MACE): all-cause mortality, myocardial infarction (410-410.9), stroke (430-437), and coronary revascularization (PCI: 36.0-36.03 and 36.05-36.09; CABG: 36.1-36.99 and V45.81) **secondary**: hospitalization of heart failure, new diagnosis of chronic kidney disease, and the initiation of dialysis medication adherence (proportion of days covered (PDC)) note: patients were matched in 3:1 ratio using the propensity score method	**MACE** (FDC vs. free combination): - n=785//34,495,321 person-years vs. n=293/10,941,830 person-years - hazard ratio [HR]: 0.85 (95% confidence interval [CI]: 0.74-0.97), P = 0.017 hospitalization for heart failure - HR 0.76 (95% CI 0.6-0.95), P = 0.015 diagnosis of CKD - HR 0.91 (95% CI 0.81-1.01), P = 0.087 initiation of dialysis - HR 0.69 (95% CI 0.53-0.89) P = 0.005 **medication adherence** (FDC vs. free combination): - mean PDC 58.01% vs 46.96%; P < 0.001 - in patients with PDC≥80%, the clinical outcomes did not differ significantly between the two groups - among the patients with PDC <80%, FDC was associated with better survival free from MACE and all the secondary end points	data) and channelling bias (preferences of patients or physicians may lead to selection bias) RAS inhibitors were not defined or rather reported (e.g. as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or/and renin inhibitors)

8.11 SR (thiazidartige vs. Thiaziddiuretika)[40]

Dineva 2019 / SR / CTDN vs. HCTZ (Blutdruck (BP), Na/K)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Dineva et al. [4] https://pubmed.ncbi.nlm.nih.gov/31595024/	2019	low	**Objective**
			to compare the the influence of Hydrochlorothiazide (HCTZ) and Chlorthalidone (CTLD) on systolic and diastolic BP and on the levels of serum sodium and serum potassium in patient with mild to moderate essential hypertension
			Search
			PubMed, MEDLINE, Scopus, PsyInfo, eLIBRARY.ru, registries for data of clinical trials (1975–2017/Dec)
			Inclusion and exclusion criteria
			- randomized controlled studies and observational studies
			- investigating different doses of CTLD and HCTZ;
			- CTLD and HCTZ alone or in combination with other antihypertensive regimen;
			- determination of changes in systolic and/or diastolic BP and/or determination of changes in the serum levels of Na+ and/or K+;
			- patients with mild to moderate essential hypertension
			Quality assessment
			- Effective Public Health Practice Project (tool)[41]
				n=9 trials directly compared HCTZ and CTLD and were included (n=2 observational studies and n=7 randomized controlled or rather matched)
				- n=51,789 patients (mono- or combination therapy, with hypertension or with coronary heart disease)
				- duration: between 4 and 364 weeks
				- HCTZ: range of 12.5–100 mg/day
				- CTLD: range 6.25–100 mg mg/day
				- n=4 studies were rated with weak quality
				- n=2 studies were excluded from meta-analysis (Dhalla 2013 – propensity score matched cohort study and van Blijderveen 2014 – case-control study)
				- n=7 studies were included within meta-analyses
				  ○ n=2 of these studies were classified as weak quality (retrospective observational cohort analysis [7], retrospective analysis [26] (randomization and blinding)
				results (weighed mean difference (WMD, mmHg) with a 95% confidence interval (CI)) CTLD vs. HCTZ
				- SBP -3.26 (-4.58; -1.07) mmHg, I2=23%, n=7 studies
				  ○ n=3 studies with combination therapy (Kwon BJ et al. 2013 (candesartan), Bakris GL et al. 2012 (azilsartan), Pareek A et al. 2009 (losartan))
				- DBP -2.41 (-3.87; -0.95) mmHg, I2=43%, n=4 studies
				  ○ only n=4 studies included data about measurement of DBP
					sensitivity analyses were performed in order to evaluate the degree of significance of each study
					
					authors chose to analyze the data for most commonly used 12.5–25 mg doses due to great variety
					
					asymmetry in funnel plots may indicate publication bias

[40] Chlorthalidon, Indapamid (oder Xipamide) vs. Hydrochlorothiazid, Bendroflumethazid oder Bemetizid bzw. Chlorthalidon vs. Indapamid (oder Xipamid)
[41] Effective Public Health Practice Project was utilized to assess study quality. This tool includes assessment of different characteristics like selection bias, study design, blinding, data collection method, confounders, and dropouts in order to help raters form an opinion of quality based upon information contained in the study. Mixed methods studies can be quality assessed using this tool with the quantitative component of the study.

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			Intervention Hydrochlorothiazide (HCTZ) **Comperator** Chlorthalidone (CTLD) **Outcomes** systolic blood pressure (SBP), diastolic blood pressur (DBP) levels of of serum sodium, and levels of serum potassium	- serum K+ -0.22 (-0.32; -0.11) mEq/L, I2=18%, n=3 studies - serum Na+ n=1 study (Pareek et al. 2009 “conclude that there are no significant changes in serum electrolytes, blood sugar, and other laboratory parameters in patients treated with CTLD and HCTZ.”) **Articles included:** 6. Dhalla IA et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a **population-based cohort study**. Ann Intern Med. 2013;158:447–55. https://doi.org/10.7326/0003-4819-158-6-201303190-00004. (**propensity-score matched**) 7. Dorsch MP et al. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: **a retrospective cohort analysis**. Hypertension. 2011;57:689–94. https://doi.org/10.1161/HYPERTENSIONAHA.110.161505. 14. Ernst ME et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension. 2006;47:352–8. (**randomized single blinded**) 21. Kwon BJ et al. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naïve patients of hypertension. Hypertens Res. 2013;36:79–84. https://doi.org/10.1038/hr.2012.143. (**open-label, randomized, cross-over design**) 26. Saseen JJ et al. Comparing clinical effectiveness and drug toxicity with hydrochlorothiazide and chlorthalidone using two potency ratios in a managed care population. J Clin Hypertens. 2015;17:134–40. https://doi.org/10.1111/jch.12453. (**retrospective analysis**) 27. Bakris GL et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. Am J Med. 2012;125:1229.e1–1229.e10. https://doi.org/10.1016/j.amjmed.2012.05.023. (**randomized, double-blind**) 28. Pareek A et al.. A randomized, comparative study evaluating the efficacy and tolerability of losartan-low dose chlorthalidone (6.25 mg) combination with losartan-hydrochlorothiazide (12.5 mg) combination in Indian patients with mild-to-moderate essential hypertension. Expert Opin Pharmacother. 2009;10:1529–36. https://doi.org/10.1517/14656560902991514 (**randomized, open-label, parallel group design**) 29. Pareek AK et al. Efficacy of low-dose chlorthalidone and hydrochlorothiazide as assessed by 24-h ambulatory blood pressure monitoring. J Am	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				Coll Cardiol. 2016;67:379–89. https://doi.org/10.1016/j.jacc.2015.10.083. (**randomized, double-blind, parallel group design)** 30. van Blijderveen JC et al. Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. Am J Med. 2014;127:763–71. https://doi.org/10.1016/j.amjmed.2014.04.014. (**observational case-control study**)	

Liang 2017 / SR / CTDN-INDAP vs. HCTZ (BP, Na/K, cholesterol, Glc)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Liang et al. [5] https://pubmed.ncbi.nlm.nih.gov/28631393/	2017	critically low	**Objective** to examine whether thiazide-like diuretics were superior over the thiazide-type diuretics in lowering blood pressure without affecting the biochemical properties, we undertook a meta-analysis of clinical trials with either HCTZ versus chlorthalidone or HCTZ versus indapamide as the independent comparative arms. **Search** PubMed (1948–2017/Jan) and Embase (1980–2017/Jan), Google Scholar, the ScienceDirect, the metaRegister of Controlled Trials and the Cochrane Central Register of Controlled Trials **Inclusion and exclusion criteria** - randomized clinical trial or double-blind controlled trial - thiazide-like or thiazide-type therapy - people with hypertension (SBP ≥ 140 mmHg ▪ or DBP ≥ 90 mmHg) - patients were allocated to 2 monotherapy thiazide or combined with other kind of antihypertensive drugs in fixed-dose arms - duration of follow-up ≥4 weeks - baseline washout and run-in phase of medication ≥1 week	n=12 studies (n=1,580 patients), n=5 indapamide vs. hydrochlorothiazide, n=7 chlorthalidone vs. hydrochlorothiazide - in the thiazide-like diuretics group, authors integrated the indapamide and chlorthalidone together - there was lack of the head-to-head comparison trials between chlorthalidone and HCTZ, authors found only three eligible trials used them in the monotherapy arm, while the remaining four trials compared the chlorthalidone and HCTZ both combined with another drug (e.g. with beta-blocker, ACEI or calcium channel blocker) **results:** blood pressure (pooled effect size (mean difference) (95% confidence interval CI)) thiazide-like vs. thiazide-diuretics (HCTZ) - SBP, -5.59 (-5.69; -5.49), I^2 = 10%, n=10 studies, n=1,307 patients, P < 0.001 - DBP, -1.98 (-3.29, -0.66), I^2 = 85%, n=11 studies, n=1,347 patients, P=0.003 ▪ incidence of (pooled effect size (95% confidence interval CI)) thiazide-like vs. thiazide-diuretics (HCTZ) - hypokalemia, odds ratio (OR) 1.58 (0.80, 3.12), I^2 = 27%, n=4 studies, n=1,050 patients, P = 0.16 - hyponatremia, mean difference (MD) -0.14 (-0.57, 0.30), I^2 = 0%, n=2 studies, P = 0.54	There were not yet enough trials including thiazide-like or thiazide-type diuretics for meta-analysis with the exception of hydrochlorothiazide, chlorthalidone and indapamide, so only trials including the comparison between hydrochlorothiazide and chlorthalidone or hydrochlorothiazide and indapamide were included. heterogeneity was reported for DBP analysis

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- measurements of ≥1 of the following, systolic BP, diastolic BP, serum potassium, uric acid, serum cholesterol, glucose or heart rate **Quality assessment** Jadad Scale **Intervention** hydrochlorothiazide (HCTZ) **Comperator** chlorthalidone or indapamide **Outcomes** systolic and/or diastolic blood pressure (SBP, DBP) incidence of hypokalemia, hyponatremia and change of serum total cholesterol and glucose	- change of serum total cholesterol, MD 0.11 (-0.02, 0.24), I^2 = 0%, n=4 studies, n=550 patients, P=0.11 - change of glucose, MD 0.13 (-0.16, 0.41), I^2 = 69%, n=7 studies, n=804 patients, P=0.39 **Articles included:** 11. Bakris GL, Sica D, White WB, et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. Am J Med. 2012; 125: 1229.e1-.e10. 12. Pareek A, Basavanagowdappa H, Zawar S, et al. A randomized, comparative study evaluating the efficacy and tolerability of losartan-low dose chlorthalidone (6.25 mg) combination with losartan-hydrochlorothiazide (12.5 mg) combination in Indian patients with mild-to-moderate essential hypertension. Expert Opin Pharmacother. 2009; 10: 1529–36. 13. Pareek A, Zawar SD, Salagre SB, et al. Antihypertensive efficacy of metoprolol XL/low dose chlorthalidone (6.25 mg) combination: a randomized, comparative study in indian patients with mild-to-moderate essential hypertension. Eur J Med Res. 2009; 14:297–303. 14. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension (Dallas, Tex: 1979). 2006; 47: 352–8. 15. Emeriau JP, Knauf H, Pujadas JO, et al. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens. 2001; 19: 343–50. 16. Spence JD, Huff M, Barnett PA. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000; 7: 32–7. 17. Siegel D, Hulley SB, Black DM, et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA. 1992; 267: 1083–9. 18. Plante GE, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. Curr Med Res Opin. 1983; 8(Suppl 3): 59–66. 19. Senior R, Imbs JL, Bory M, et al. Indapamide reduces hypertensive left ventricular hypertrophy: an international multicentre study. J Cardiovasc Pharmacol. 1993; 22 (Suppl 6): S106–10.	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				20. Radevski IV, Valtchanova ZP, Candy GP, et al. Comparison of indapamide and lowdose hydrochlorothiazide monotherapy in black patients with mild to moderate hypertension. S Afr Med J. 2002; 92: 532–6. 21. Kwon BJ, Jang SW, Choi KY, et al. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naive patients of hypertension. Hypertens Res. 2013; 36: 79–84. 22. Pareek AK, Messerli FH, Chandurkar NB, et al. Efficacy of low-dose chlorthalidone and hydrochlorothiazide as assessed by 24-h ambulatory blood pressure monitoring. J Am Coll Cardiol. 2016; 67: 379–89.	

Roush 2015 / SR / INDAP-CTDN vs. HCTZ (BP, K, keine Ergebnisse zu kardiovaskulären Ergebnissen)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Roush et al. [6] https://pubmed.ncbi.nlm.nih.gov/25733245/	2015	critically low	**Objective** hydrochlorothiazide (HCTZ) compares with another thiazide-like medication, indapamide (INDAP) or chlorthalidone (CTDN) **Search** PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (period?) **Inclusion and exclusion criteria** - randomized trials - hypertensives - reported in English - with systolic blood pressure (SBP), metabolic parameters, or cardiovascular events as outcomes - contrasting 2 or 3 of the diuretics (HCTZ, CTDN, and INDAP) with one another - limitations: for trials limited to antihypertensive and metabolic effects as outcomes, exclusion criteria were BP limited to standing BP only, drug dose titrated to effect on the outcome; follow-up <2	n=14 trials - n=10 with HCTZ-INDAP comparison (SBP) - n=3 with HCTZ-CTDN comparisons (SBP) - n=9 with HCTZ-INDAP comparisons (metabolic parameters) - no trials compared CTDN with INDAP - all trials lacked cardiovascular events as outcomes - contrasting CTDN with HCTZ on metabolic effects was lacking - follow-up 4 to 26 weeks **results:** - systolic blood pressure (SBP), difference in mean: INDAP vs. HCTZ - 5.1 mm Hg (95% CI, −8.7 to −1.6), P=0.004, n=10 trials - systolic blood bressure (SBP), difference in mean: CTDN vs. HCTZ - 3.6 mmHg (95% CI, −7.3 to 0.03), P=0.052, n=3 trials - serum potassium, difference in mean: INDAP vs. HCTZ -0.054 mEq/L (95% CI -0.296 to 0.188), P=0.661, n=9 trials - metabolic effects (Relative differences in other metabolic effects are shown in Table 2 within the publication) **Articles included:**	Trials were limited to diuretics at commonly prescribed doses (online-only Data Supplement). doses (mg): HCTZ: 12.5, 25, and 50; CTDN: 6.25, 12.5, and 25; INDAP immediate-release: 1.25, 2.5, and 5; INDAP sustained release: 1.5, 2.0, and 2.5. publication bias was assessed and risk of bias discussed (sensitivity analyses were conducted), but

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			weeks; and follow-up >6 months (because such trials are likely to be focused on other outcomes and therefore might measure blood pressure less rigorously). **Quality assessment** - not documented **Intervention** hydrochlorothiazide (HCTZ) **Comperator** indapamide (INDAP) or chlorthalidone (CTDN) **Outcomes** systolic blood pressure (SBP), metabolic parameters, or cardiovascular events	9. Bhigjee AI, Seedat YK, Hoosen S, Neerahoo RM, Naidoo K. Biochemical changes in black and Indian hypertensive patients on diuretic therapy. S Afr Med J. 1983;64:969–972. 10. Elliott WJ, Weber RR, Murphy MB. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. J Clin Pharmacol. 1991;31:751–757. 11. Emeriau JP, Knauf H, Pujadas JO, Calvo-Gomez C, Abate G, Leonetti G, Chastang C; European Study Investigators. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens. 2001;19:343–350. 12. Kreeft JH, Langlois S, Ogilvie RI. Comparative trial of indapamide and hydrochlorothiazide in essential hypertension, with forearm plethysmography. J Cardiovasc Pharmacol. 1984;6:622–626. 13. Krum H, Skiba M, Gilbert RE. Comparative metabolic effects of hydrochlorothiazide and indapamide in hypertensive diabetic patients receiving ACE inhibitor therapy. Diabet Med. 2003;20:708–712. 14. Madkour H, Gadallah M, Riveline B, Plante GE, Massry SG. Comparison between the effects of indapamide and hydrochlorothiazide on creatinine clearance in patients with impaired renal function and hypertension. Am J Nephrol. 1995;15:251–255. 15. Malini PL, Strocchi EN, Ricci CM, Ambrosinioni E. Indapamide or hydrochlorothiazide in hypertensive patients resistant to treatment with an angiotensin-converting enzyme inhibitor. Curr Therap Res. 1994;55:932–937. 16. Plante GE, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. Curr Med Res Opinion. 1983;8:59–66. 17. Plante GE, Dessurault DL. Hypertension in elderly patients. A comparative study between indapamide and hydrochlorothiazide. Am J Med. 1988;84(1B):98–103. 18. Radevski IV, Valtchanova ZP, Candy GP, Wald AM, Ngcezula T, Sareli P. Comparison of indapamide and low-dose hydrochlorothiazide monotherapy in black patients with mild to moderate hypertension. S Afr Med J. 2002;92:532–536. 19. Spence JD, Huff M, Barnett PA. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000;7:32–37.	the assessment of the risk of bias was not reported (Table S2 within the supplement shows blinding, loss to follow-up, drop out and ITT-analyses)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				20. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension. 2006;47:352–358. doi: 10.1161/01.HYP.0000203309.07140.d3. 21. Kwon BJ, Jang SW, Choi KY, Kim DB, Cho EJ, Ihm SH, Youn HJ, Kim JH. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naive patients of hypertension. Hypertens Res. 2013;36:79–84.doi: 10.1038/hr.2012.143. 22. Pareek A, Basavanagowdappa H, Zawar S, Kumar A, Chandurkar N. A randomized, comparative study evaluating the efficacy and tolerability of losartan-low dose chlorthalidone (6.25 mg) combination with losartan-hydrochlorothiazide (12.5 mg) combination in Indian patients with mild-to-moderate essential hypertension. Expert Opin Pharmacother. 2009;10:1529–1536. doi: 10.1517/14656560902991514.	

Hripcsak 2020 / Kohorte / CTDN vs. HCTZ (Tod, kardiovaskuläre Ereignisse)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Hripcsak et al. [9] https://pubmed.ncbi.nlm.nih.gov/32065600/	2020		**Objective** to compare the effectiveness and safety of chlorthalidone and hydrochlorothiazide as first-line therapies for hypertension in real-world practice **Study design/ source** - Retrospective, controlled cohort study - part of the Observational Health Data Sciences and Informatics (OHDSI) Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND) for Hypertension initiative, USA - 3 OHDSI databases (2 administrative claims databases and 1 collection of electronic health records) analysis began June 2018 **Inclusion and exclusion criteria**	n=730 225 individuals - mean age, 51.5 [standard deviation (SD) 13.3] years - n=450 100 women [61.6%] - n=36 918 were dispensed or prescribed chlorthalidone and had 149 composite outcome events, - n=693 337 were dispensed or prescribed hydrochlorothiazide and had 3089 composite outcome events **results:** primary: (s.a. supplemental material) stratified on-treatment calibrated hazard ratio (cHR) (95 % confidence interval (CI)), CTDN vs. HTCZ: - all-cause mortality cHR 0.93 (0.61-1.42) - cardiovascular mortality cHR 1.24 (0.62-2.51) ■	Two time-at-risk periods were used: • On-treatment. Starting one day after the index event and stopping at the termination of the drug or on the addition of a second anti-hypertensive agent. A maximum gap of 30 days was allowed between prescriptions, and the treatment is considered to end after the last prescription runs out.

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- patients initiating antihypertensive treatment with chlorthalidone or hydrochlorothiazide - patients with a prior or concurrent diagnosis of hypertension - patients initiating another hypertension treatment within 7 days after starting were excluded - continuous observation in the database for at least 365 days before treatment initiation **Investigation** chlorthalidone (CTDN) and hydrochlorothiazide (HCTZ) **Outcomes** **primary** - hospitalization for acute myocardial infarction, ■ heart failure, ischemic or hemorrhagic stroke, - and a composite cardiovascular disease outcome including the first 3 outcomes and sudden cardiac death Fifty-one safety outcomes were measured propensity score stratification, cox proportional hazards model, Kaplan-Meier survival plots, Bonferroni correction	- acute myocardial infarction cHR 0.92 (0.64-1.31) - heart failure cHR 1.01 (0.73-1.40) - hospitalization with heart failure cHR 1.05 (0.82-1.34) - hemorrhagic stroke cHR 0.92 (0.39-2.18) - ischemic stroke cHR 1.09 (0.84-1.42) - stroke cHR 1.10 (0.86-1.41) - transient ischemic attack cHR 1.23 (0.93-1.64) - composite cardiovascular disease cHR 1.00 (0.85-1.17); n(CTDN)=149 events of n(CTDN)=36 628 patients vs. n(HCTZ)=3089 events of n(HCTZ)=687 106 patients ■ stratified intention to treat calibrated hazard ratio (cHR) (95 % confidence interval (CI)), CTDN vs. HTCZ: - all-cause mortality cHR 1.07 (0.95-1.21) - cardiovascular mortality cHR 1.01 (0.80-1.27) ■ - acute myocardial infarction cHR 1.04 (0.91-1.18) - heart failure cHR 1.05 (0.95-1.16) - hospitalization with heart failure cHR 1.05 (0.95-1.17) - hemorrhagic stroke cHR 0.95 (0.72-1.25) - ischemic stroke cHR 1.10 (0.97-1.25) - stroke cHR 1.09 (0.97-1.23) - transient ischemic attack cHR 1.07 (0.88-1.30) - composite cardiovascular disease cHR 1.04 (0.96-1.13); n(CTDN)= 892 events of n(CTDN)=36 654 patients vs. n(HCTZ)=20 824 events of n(HCTZ)=688 446 patients ■ safety: stratified on-treatment calibrated hazard ratio (cHR) (95 % confidence interval (CI)), CTDN vs. HTCZ:	• Intent-to-treat (ITT): Starting one day after the index event and stopping at the end of observation in the database. limitation: possibility of residual confounding, including confounding by indication, differences in physician characteristics that may be associated with drug choice

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
				- hyperkalemia cHR 1.34 (1.03-1.74) - hypokalemia cHR 2.72 (2.38-3.12) - hyponatremia cHR 1.31 (1.16-1.47) stratified intention to treat calibrated hazard ratio (cHR) (95 % confidence interval (CI)), CTDN vs. HTCZ: - hyperkalemia cHR 1.16 (1.02-1.33) - hypokalemia cHR 2.23 (1.92-2.59) - hyponatremia cHR 1.18 (1.03-1.35)	

Dhalla 2013 / Kohorte / CTDN vs. HCTZ (Tod oder Hospitalisierung, Na/K)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Dhalla et al. [10] https://pubmed.ncbi.nlm.nih.gov/23552325/	2013		**Objective** to compare the effectiveness and safety of chlorthalidone and hydrochlorothiazide in older adults **Study design/ source** - retrospective cohort study - Ontario Drug Benefit database - Registered Persons Database - Canadian Institute for Health Informations Discharge Abstract Database - National Ambulatory Care Reparing System - Institute for Clinical Evaluative Sciences Physicians Database - Ontario Health Insurance Plan Database follow-up up to 5 years, Canada **Inclusion and exclusion criteria** - residents of Ontario, Canada - aged 66 years or older	n=1 123 418 patients were identified, - after matching n=10 384 patients treated with chlorthalidone and n=19 489 patients treated with hydrochlorothiazide werde included - median follow-up: o chlorthalidone 255 days (interquartile range 100-873 days) o hydrochlorothiazide 398 days (IQR 123-1307 days) - before matching chlorthalidone recipients were younger, had fewer hospitalizations in the 3 years before, were more likely to be prescribed ß-blocker and less likely to be prescribed ACE-inhibitors or angiotensin-II-receptorblockers **primary:** death or hospitalization: - chlorthalidone n=510 (3.2 events per 100 person-years of follow-up) - hydrochlorothiazide n=1265 (3.4 events per 100 person-years) - adjusted hazard ratio (HR) 0.93 (95 % CI 0.81-1.06) safety: patients with hypokalemia hospitalized:	potential for unmeasured confounding was reported

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- initiated chlorthalidone or hydrochlorothiazide between Jan 1993 and March 2010 **Investigation** newly treated with chlorthalidone or hydrochloro-thiazide **Outcomes** - composite of death or hospitalization for heart failure, stroke, or myocardial infarction - safety: hospitalization with hypokalaemia or hyponatriemia propensity score-matched patients were censored if they switched study medication, discontinued treatment	- chlorthalidone: n=109 (0.69 events per 100 person-years of follow-up) - hydrochlorothiazide: n=102 (0.27 events per 100 person-years) - adjusted HR 3.06 (95% CI 2.04-4.58) patients with hyponatremia hospitalized: - chlorthalidone: n=109 (0.69 events per 100 person-years) - hydrochlorothiazide: n=184 (0.49 events per 100 person-years) - adjusted HR 1.68 (95% CI 1.24-2.28) note: dose-related HR were also reported within Table 4 within the publica-tion	

Dorsch 2011 / Kohorte / CTDN vs. HCTZ (komplexe Intervention (MRFIT), kardiovaskuläre Ereignisse, BP, Na/K, weitere)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Dorsch et al. [11] https://pub-med.ncbi.nlm.nih.gov/21383313/	2011		**Objective** to evaluate the effects of chlorthalidone (CTD) compared with hydrochlorothiazide (HCTZ) on car-diovascular event (CVE) rates **Study design/ source** - retrospective cohort study Multiple Risk Factor Intervention Trial (MRFIT) data set from the National Heart, Lung, and Blood Institute (cardiovascular primary prevention trial in 12 866 men, 35 to 57 years of age, who were enrolled and followed beginning in 1973, complexe inter-vention) **Inclusion and exclusion criteria** - patients upper 15% of risk for death from cor-onary heart disease (CHD) based on risk fac-tors of elevated cholesterol, elevated diastolic	n=12 866 patients in the MRFIT - n=6441 patients were initially prescribed either CTD (n=2392) or HCTZ (n=4049) - median follow-up of 6 years - 57% of the initial HCTZ patients and 76% of the initial CTD patients crossed over into either the other drug group or the drugstopped group - of the initial HCTZ patients, 29% crossed over into the CTD group, whereas 37% of the initial CTD patients crossed over into the HCTZ group sometime during follow-up - overall, 46% of the time patients were in the HCTZ group, 32% in the CTD group, and 23% in the stopped-drug group, accounting for 33 614 years of exposure among the 6441 patients **cardiovascular events (CVE)**	authors docu-mented potential unmeasured con-founding, selection bias, and information bias

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			blood pressure, and cigarette smoking from the Framingham Heart Study - patients also could not have had preexisting, definite clinical CHD before entering the study **Investigation** chlorthalidone or hydrochlorothiazide as first line therapy **Outcomes** **primary:** cardiovascular events (CVE) **secondary:** change in systolic blood pressure (SBP), total cholesterol (TC), lowdensity lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, potassium, glucose, and uric acid Cox regression was used	n=1244 cardiovascular events were documented over the 7 years of follow-up - compared with those on neither drug o chlorthalidone (CTD) (adjusted hazard ratio (HR): 0.51 [95% CI: 0.43 to 0.61]; P<0.0001) o hydrochlorothiazide (HCTZ) (adjusted hazard ratio (HR): 0.65 [95% CI: 0.55 to 0.75]; P<0.0001) ■ - CTD vs. HCTZ aHR: 0.79 [95% CI: 0.68 to 0.92]; P=0.0016	

Saseen 2015 / Kohorte / CTDN vs. HCTZ (BP, K)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Saseen et al. [12] https://pubmed.ncbi.nlm.nih.gov/25496048/	2015		**Objective** to compare the clinical effectiveness and drug toxicity of chlorthalidone and hydrochlorothiazide **Study design/ source** - retrospective cohort study electronic health records and claims data were used (health plan's electronic health record (EHR) database), USA extract data from January 1, 2005, to December 31, 2012 **Inclusion and exclusion criteria** - patients diagnosed with hypertension (ICD-9-CM) - age 18 to 89 years	n=3793 patients met the inclusion criteria (n=214 with chlorthalidone and n=3216 with hydrochlorothiazide) - n=214 patients prescribed CTDN 25 mg matched with n= 428 patients prescribed HCTZ 25 mg (1:1 potency ratio) and n=214 patients prescribed HCTZ 50 mg (1:2 potency ratio) - first prescription could have been as a single-pill or fixed-dose combination formulation - patients prescribed CTDN were more likely to be prescribed combination antihypertensive therapy **results:** mean systolic blood pressure (SBP)/diastolic blood pressure (DBP): (values at least 30 days after initial prescription) - Chlorthalidone 25 mg (n=180)	authors documentet that accuracy of BP measurements that are documented in the EHR cannot be assured and that they may have lacked the power to see differences in some of the study endpoints (e.g. urate concentration)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- patients initially prescribed CTDN or HCTZ - a minimum of 13 months of continuous enrollment in the health plan after the index date; - high adherence with HCTZ or CTDN; - a minimum of 6 months of continuous enrollment before the index date without any prescription for CTDN or HCTZ - patients were excluded if they switch the diuretic or continued with fixed dose combination or change in prescribed dose - patients with heart failure were also excluded **Investigation** chlorthalidone (CTDN) and hydrochlorothiazide (HCTZ) **Outcomes** systolic blood pressure (SBP)/diastolic blood pressure (DBP) serum potassium concentrations, serum glucose concentrations, and serum urate concentrations propensity score matching and adjusted regression analyzes were used	○ SBP 132.2 mm Hg ○ DBP 74.0 mm Hg - Hydrochlorothiazide 25 mg (n=355) ○ SBP 137.0 mm Hg; P<0.01 vs. CTDN 25 mg; MD -3.16 (- 5.25 to -1.07) mm Hg ○ DBP 77.5 mm Hg; P<0.01 vs. CTDN 25 mg; MD -2.59 (- 3.84 to -1.3) mm Hg - Hydrochlorothiazide 50 mg (n=177) ○ SBP 138.6 mm Hg; P<0.01 vs. CTDN 25 mg; MD -4.6 (-7.4 to -1.8) mm Hg ○ DBP 78.5 mm Hg; P<0.01 vs. CTDN 25 mg; MD -3.68 (-5.41 to -1.95) mm Hg patients at SBP*/DBP** goal: - Chlorthalidone 25 mg (n=180) ○ SBP 45.0% ○ DBP 78.3% ○ both 40.6% - Hydrochlorothiazide 25 mg (n=355) ○ SBP 32.1%; P<0.01 vs. CTDN 25 mg ○ DBP 63.9%; P<0.01 vs. CTDN 25 mg ○ both 27.0; P<0.01 vs. CTDN 25 mg; OR 1.38 (0.98-1.94) - Hydrochlorothiazide 50 mg (n=177) ○ SBP 32.8%; P<0.05 vs. CTDN 25 mg ○ DBP 68.9%; P<0.05 vs. CTDN 25 mg ○ both 28.8%; P<0.05 vs. CTDN 25 mg, OR 1.81 (1.12-2.94) ■ *SBP goal defined as <140 mm Hg, except <130 mm Hg if diabetes. **DBP goal defined as <90 mm Hg, except <80 mm Hg if diabetes MD=Mean difference; OR=Odds Ratio (95 % confidence interval CI)) ■	combination antihypertensive drug therapy was prescribed commonly, especially with CTDN

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
				mean serum potassium: - CTDN 25 mg: 3.94 mEq/L, n=143 - HCTZ 25 mg: 4.13 mEq/L, n=299; P<.01 vs CTDN - HCTZ 50 mg: 3.96 mEq/L, n=152	

Ernst 2011 / Kohorte / CTDN vs. HCTZ (komplexe Intervention, MRFIT, BP, EKG)

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
Ernst et al. [13] https://pubmed.ncbi.nlm.nih.gov/22025372/	2011		**Objective** examining change in continuous measures of electrocardiographic left ventricular hypertrophy using both an ecological analysis by previously reported C- or H-clinic groupings** and an individual participant analysis where use of CTD or HCTZ by special intervention participants was considered and updated annually **Study design/ source** - cohort study based on: Multiple Risk Factor Intervention Trial (MRFIT)*** (n=8012 patients at risk were randomized to special intervention or usual care) risk score included e.g. diastolic blood pressure n=8012 (62%) men were classified as hypertensive at baseline, defined as average diastolic blood pressure level of ≥90 mm Hg or those who had been receiving antihypertensive drugs on entry **Inclusion and exclusion criteria** - n=8012 men of the MRFIT - initial antihypertensive medication: diuretic, ■ either CTD or HCTZ, at a dose of 50 or 100 mg daily (the standard doses used at the time MRFIT was carried out)	n=8012 hypertensive men, mean age 46.7 years (SD 5.9) - n=2112 (n=1046 special intervention and n=1066 usual care) were randomly assigned by 6 clinics predominantly used CTD (C-clinics) - n=3399 (n=1725 special intervention and n=1674 usual care) were randomly assigned by 9 clinics predominantly used HCTZ (H-clinics) - n=2501 (n=1248 special intervention and n=1253 usual care) were randomly assigned by 7 clinics predominantly used CTD and then switched to HCTZ (switching clinics) - approximately 31% were taking antihypertensive medications at entry - special intervention group: use of CTD declined during the first 4 years, from ~33.4% at 12 months to 26.6% at 48 months, whereas use of HCTZ increased from 27.4% at 12 months to a high of 42.5% at 48 months - after the protocol change, which occurred after all of the participants had completed the 48-month visit, use of CTD increased (to 50.8% by 84 months), whereas use of HCTZ declined to 14.7% by 84 months - at 48 months, of special intervention hypertensive participants, 80% in C-clinics, 75% in H-clinics, and 76% in switching clinics were prescribed antihypertensive medication blood pressure through 48 months: - mean difference (SI-UC) for C-clinics compared with H-clinics (SE) o change in SBP: -10.4 (0.4) vs. -8.6 (0.3) mm Hg; P=0.001 o change in DBP: -6.5 (0.3) vs. -5.1 (0.2) mm Hg; P<0.001	diuretic assignment in MRFIT was not randomized (heterogeneity betwenn C- and H-clinics) within many clinics there was a tendency to use predominantly one diuretic or the other (C-clinic: CTD; H-clinic: HCTZ) higher doses of both CTD and HCTZ were used in MRFIT than what are currently used addition of other drugs was possible to achieve blood pressure goal

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			- followed by stepwise addition of other drugs to achieve and maintain a diastolic blood pressure goal of 80 to 89 mm Hg - 4 years follow-up **Investigation** special intervention (SI) could use chlorthalidone (CTD) or hydrochlorothiazide (HCTZ) initially - the choice of diuretic was left to the discretion of the individual physician **Outcomes** clinic blood pressure (sphygmomanometer) electrocardiographic left ventricular hypertrophy (LVH) - standard 12-lead resting electrocardiograms were recorded - association stratified as C- / H- and switching clinics - second individual participant analysis with CTD, HCTZ or other antihypertensives longitudinal regression models were used (2 models, one with covariates and one included propensity score) ** “previous analyses have grouped clinics by their main diuretic used (C-clinics: CTD; H-clinics: HCTZ). After 48 months, SI participants receiving HCTZ were recommended to switch to CTD, in part because higher mortality was observed for SI compared with usual care participants in H-clinics, whereas the opposite was found in C-clinics.”[42]	- mean difference (95% CI) at 48 months; adjusted for propensity score (SI-UC; stratified by C-clinics-H-clinics) at 48 months: o change in SBP: -1.7 (-2.3, -1.2) mm Hg; P< 0.001 o change in DBP: -0.7 (-1.1, -0.4) mm Hg; P< 0.001 potassium (mmol/L) through 48 months: - mean difference (SI-UC) for C-clinics compared with H-clinics (SE): o -0.33 (0.02) mmol/L vs. -0.23 (0.01) mmmol/L; P<0.001 - mean difference (95% CI) at 48 months; adjusted for propensity score (SI-UC; stratified by C-clinics-H-clinics) at 48 months: o -0.23 (-0.25, -0.21) mmol/L; P<0.001 criteria for electrographic left ventricular hypertrophy through 48 months: - mean difference (SI-UC) for C-clinics compared with H-clinics (SE) o Sokolow-Lyon: -93.9 (15.1) µV versus -54.9 (12.1) µV, P=0.049 o Cornell voltage: -68.1 (9.6) µV versus -35.9 (8.0) µV, P=0.019 o Cornell voltage product: -4.6 (0.9) µV/ms versus -2.2 (0.8) µV/ms, P=0.071 o left ventricular mass: -4.4 (0.4) g versus -2.8 (0.3) g, P=0.002 - mean difference (95% CI) at 48 months; adjusted for propensity score (SI-UC; stratified by C-clinics-H-clinics) at 48 months: o Sokolow-Lyon: -38.8 (-57.9, -19.7) µV P<0.001 o Cornell voltage: 3.7 (-8.8, 16.3) µVP=0.56 o Cornell voltage product: 1.7 (0.5, 3.0) µV/ms P=0.008	sensitivity analyses were performed authors documented that LVH is strongly influenced by blood pressure and is an established risk factor for coronary heart disease

[42] Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA. 1982;248:1465–1477.
Multiple Risk Factor Intervention Trial Research Group. Mortality after 10 ½ years for hypertensive participants in the Multiple Risk Factor Intervention Trial. Circulation. 1990;82:1616 –1628.
Bartsch G, Broste S, Grandits G, Grimm RH, Neaton JD, Svendsen KH. Hydrochlorothiazide, chlorthalidone and mortality in the Multiple Risk Factor Intervention Trial [abstract]. Circulation. 1984;70(suppl II):1438.

Zitat	Jahr		Charakteristika	Ergebnisse	Kommentar
			MRFIT: randomized primary prevention trial designed to determine effects on coronary heart disease mortality of a multifaceted intervention targeting smoking cessation, reduction in serum cholesterol, and stepped-care treatment of hypertension.	○ left ventricular mass: -0.6 (-1.0, -0.1) gm P=0.02 s.a. Table 2 within the publication and Table S2 within the supplement	

Evidenzzusammenfassung (Arbeitsversion)

Systematische Recherche Low-Ceiling-Diuretika (Hydrochlorothiazid, Bendroflumethazid oder Bemetizid vs. Chlorthalidon, Indapamid (oder Xipamid) bzw. Chlorthalidon vs. Indapamid) Stand: 06. August 2021

Systematischen Literaturrecherche

Für die NVL Hypertonie wurde eine systematische Recherche zur Schlüsselfrage der Vergleiche bestimmter Low-Ceiling-Diuretika (Thiaziddiuretika (Hydrochlorothiazid, Bendroflumethazid oder Bemetizid) vs. thiazidartige Diuretika (Chlorthalidon, Indapamid (oder Xipamide) bzw. Chlorthalidone vs. Indapamid) durchgeführt. Die Recherche erfolgte in Medline via PubMed, den Cochrane Datenbanken sowie Epistemonikos bis zum 22. Juli 2021 in einem zweistufigen Verfahren, wobei systematische Übersichtsarbeiten, randomisierte kontrollierte Studien und vergleichende Kohortenstudien gesucht wurden (s. *Recherchedokumentation*). Die Ergebnisse der RCT wurden in Bezug auf die Recherchezeiträume der ermittelten systematischen Übersichtsarbeiten eingeschränkt (Screening der Publikationen im Zeitraum von 2011-2021).

Aus 503 Treffern wurden drei systematische Übersichtsarbeiten eingeschlossen [4–6] – Chlorthalidon vs. Hydrochlorothiazid (2019, Blutdruck) [4], thiazidähnliche vs. Thiazid-Diuretika (2017, Blutdruck) [5], Hydrochlorothiazid vs. Indapamid und Chlorthalidon (2015, Blutdruck, kardiovaskuläre Ereignisse konnten nicht analysiert werden) [6] – zwei randomisierte kontrollierte Studien (Chlorthalidon vs. Hydrochlorothiazid, Blutdruck, 2015, 2016) [7,8] sowie fünf Kohortenstudien (Chlorthalidon vs. Hydrochlorothiazid, u.a. kardiovaskuläre Ereignisse, Tod und Hospitalisierung, Blutdruck) [9–13] – wobei Saseen et al. 2015 [12] primär Blutdruck und Kaliumspiegel über 12 Monate betrachteten und Dorsch et al. 2011 [11] sowie Ernst et a. 2011 [13] eine komplexe Intervention (Datengrundlage: MRFIT) untersuchten, bei der die behandelnden Ärzt*innen das Diuretikum individuell auswählten (s.u. bzw. *begleitende Evidenztabellen*).

Ergänzend wurden vier Netzwerkmetaanalysen (NMA) beziehungsweise Übersichtsarbeiten, die auch NMA analysierten, ermittelt [167–170] und auf Grund des Studientyps nicht eingeschlossen. Eine Übersicht dieser Arbeiten findet sich in Tabelle 4.

Unter den systematischen Übersichtsarbeiten fanden sich zudem Arrol et al. 2017 [171], Chen et al. 2015 [172], Musini et al. 2014 [135] und Thomopoulos et al. 2015 [173], die Placebovergleiche gegenüber den Diuretika analysierten und Ernst et al. 2010 [174] sowie Peterzan et al. 2012 [175], die Dosis-Wirkungs-Beziehung untersuchten.

Ergänzende systematische Übersichtsarbeiten, die **Kombinationstherapien mit Diuretika** im Vergleich untersuchten – Circelli et al. 2012 (Delapril/Indapamid vs. ACE-Hemmer/Hydrochlorothiazid) [14], Filipova et al. 2020 (Angiotensin-II-Rezeptorblocker und Chlorthalidon oder Hydrochlorothiazid) [15]. Unter den RCT im Recherchezeitraum 2011 bis 2021 fanden sich zudem acht Studien, die Kombinationen von Chlorthalidon oder Hydrochlorothiazid mit Sartanen (Azilsartan, Candesartan, Losartan, Olmesartan) [16–23] oder Indapamid oder Hydrochlorothiazid mit ACE Hemmer (Quinapril) verglichen [19] .

Zusammenfassung der Ergebnisse der systematischen Recherche

Im Rahmen der Bewertung mit dem AMSTAR II Tool erhielten eine systematische Übersichtsarbeit die Klassifikation als „low“ [4] – u.a. auf Grund der fehlenden Präsentation der Liste ausgeschlossener Volltexte – wobei anzumerken ist, dass auch Studien in die Metaanalyse eingeschlossen wurden, die Kombinationen von Hydrochlorothiazid oder Chlorthalidon mit Sartanen untersuchten [4], sowie zwei Arbeiten als „critically low“ [5,6], u.a. auf Grund der unzureichend beschriebenen Methodik [5], der fehlenden Präsentation der ausgeschlossenen Volltexte [5,6], der nicht ausreichend beschriebenen Analyse des Risk of Bias und damit einer unzureichenden Berücksichtigung bei der Analyse und Ergebnisinterpretation [6] sowie der fehlenden Analyse eines Publication Bias [5] (kritische Domänen). Roush et al. 2015 [6] diskutierten das Risk of Bias, dokumentieren im Supplement Parameter des Risk of Bias Tools und führten Sensitivitätsanalysen durch, die Bewertung wurde aber nicht ausreichend methodisch beschrieben, mit Ausnahme des Publication Bias – eine klinische Bewertung könnte herangezogen worden sein.

Die ermittelten systematischen Übersichtsarbeiten sowie Kohortenstudien sind nachfolgend zusammengefasst; die Ergebnisse finden sich in Tabelle 1 und Tabelle 3. Die eingeschlossenen Studien aus den systematischen Recherchen wurden in Tabelle 2 dargestellt. Es ist anzumerken, dass bei Liang et al. 2017 [5] in den Tabelle und Abbildungen der Publikation nicht alle eingeschlossenen Studien als Zitat eindeutig nachvollziehbar sind.

Die beiden ergänzenden randomisierten kontrollierte Studien (RCT, 2015, 2016) im Recherchezeitraum (2011-2021) untersuchten ebenfalls Chlorthalidon vs. Hydrochlorothiazid und betrachteten den Blutdruck [7,8]. Sie wurden

nicht separat aufbereitet. Eine Arbeit [7] wurde in den Analysen von Dineva et al. 2019 und Liang et al. 2017 bereits berücksichtigt [4,5]. Zum Vergleich zwischen Chlorthalidon und Indapamid fand sich keine RCT im Recherchezeitraum.

Tabelle 1 Ergebnisse der ermittelten systematischen Übersichtsarbeiten

	Dineva et al. 2019 [4]	Liang et al. 2017 [5]	Roush et al. 2015 [6]
Mortalität, CVE	-	-	-
SBP, mmHg	(CTLD vs. HCTZ) WMD -3,26 (95 % KI -4,58; -1,07) I^2=23 %, n=7 Studien*	(CTLD oder INDAP vs. HCTZ) MD -5,59 (95 % KI -5,69; -5,49) I^2 = 10 %, n=10 Studien, n=1.307 Patient*innen, P < 0,001	(INDAP vs. HCTZ) MD -5,1 (95 % KI −8,7; −1,6), n=10 Studien, P=0,004 (CTDN vs. HCTZ) MD -3,6 (95 % KI −7,3; 0,03), n=3 Studien, P=0,052
DBP, mmHg	(CTLD vs. HCTZ) WMD -2,41 (95 % KI -3,87; -0,95) I^2=43 %, n=4 Studien	(CTLD oder INDAP vs. HCTZ) MD -1,98 (95 % KI -3,29; -0,66), I^2 = 85 %, n=11 Studien, n=1.347 Patient*innen, P=0,003	-
Serum-Na/K, mEq/L	(CTLD vs. HCTZ) K WMD -0,22 (95 % KI -0,32; - 0,11), I^2=18 %, n=3 Studien Na, n=1 Studie (Pareek et al. 2009 “conclude that there are no significant changes in serum electrolytes, blood sugar, and other laboratory parameters in patients treated with CTLD and HCTZ.”).	(CTLD oder INDAP vs. HCTZ) Incidenz von: - Hypokaliämie, OR 1,58 (95 % KI 0,80; 3,12), I^2=27 %, n=4 Studien, n=1.050 Patient*innen, P=0,16 - Hyponatriämie, MD -0,14 (- ,57; 0,30), I^2=0%, n=2 Studien, P=0,54	(INDAP vs. HCTZ) K MD -0,054 (95 % KI -0,296; 0,188), n=9 Studien, P=0,661
weitere	-	(CTLD oder INDAP vs. HCTZ) Veränderung: - Serumcholesterol, MD 0,11 (- 0,02; 0,24), I^2=0%, n=4 Studien, n=550 Patient*innen, P=0,11 - Serumglucose, MD 0,13 (- 0,16; 0,41), I^2=69 %, n=7 Studien, n=804 Patient*innen, P=0,39	-

CTLD=Chlorthalidon, CVE=kardiovaskuläre Ereignisse, DBP=diastolischer Blutdruck, HCTZ=Hydrochlorothiazid, INDAP=Indapamid, KI=Konfidenzintervall, MD=mittlere Differenz, OR=Odds Ratio, SBP=systolischer Blutdruck, WMD=gewichtete, mittlere Differenz

* n=3 Studien mit Kombinations-therapie (Kwon BJ et al. 2013 (Candesartan), Bakris GL et al. 2012 (Azilsartan), Pareek A et al. 2009 (Losartan))

Dineva et al. 2019 verglichen Hydrochlorothiazid (HCTZ) mit Chlorthalidon (CTLD) in Bezug auf den Blutdruck und die Serum-Kalium- sowie Natriumspiegel und schlossen neun Studien (n=51.789 Patient*innen, Dauer 4 bis 364 Wochen) mit direkten Vergleichen ein (Recherche bis Dezember 2019, randomisierte kontrollierte oder Beobachtungsstudien, Diuretika allein oder in Kombination, milde oder moderate, essentielle Hypertonie – es wurden auch Studien berücksichtigt, die Patient*innen mit Koronarer Herzkrankheit einschlossen) [4]. Die Autor*innen berücksichtigten für Ihre Analyse Daten zu Patient*innen mit am häufigsten genutzten Dosierungen der Diuretika, wobei 12,5-25 mg angegeben wurden und über eine Variation der Dosen für HCTZ von 12,5–100 mg/Tag sowie für CTLD von 6,25–100 mg mg/Tag berichtet wurde [4]. Zur Qualitätsbewertung der eingeschlossenen Studien verwendeten die Autor*innen ein Tool des Effective Public Health Practice Projects, wobei vier der Studien mit geringer Qualität bewertet wurden; zwei dieser Studien wurden aus den Metaanalysen ausgeschlossen [4]. Zudem berichteten die Autor*innen von einem möglichen Publikationsbias auf Grund eines asymmetrischen Funnelplots [4].

Liang et al. 2017 verglichen thiazidartige gegenüber Thiaziddiuretika in Bezug auf den Blutdruck und Serumkonzentrationen von Kalium, Natrium, Cholesterol sowie Glucose und schlossen 12 Studien ein (n=1.580 Patient*innen) [5]. Auf Grund weniger Studien zum Vergleich dieser Diuretika allgemein wurden in der Auswertung Chlorthalidon (n=7 Studien) oder Indapamid (n=5 Studien) zusammengefasst gegenüber Hydrochlorothiazid (HCTZ) betrachtet (Recherche bis Januar 2019, randomisierte kontrollierte Studien oder doppelt verblindete kontrollierte Studien, Patient*innen mit Bluthochdruck (SBP≥140 mmHg oder DBP ≥ 90 mmHg), Mono- oder Kombinationstherapie waren zulässig) [5]. Zur Qualitätsbewertung der eingeschlossenen Studien verwendeten die Autor*innen die Jaded Scale [5].

Roush et al. 2015 verglichen untereinander Hydrochlorothiazid (HCTZ) und Chlorthalidon (CTDN) sowie Indapamid (INDAP) (Recherchezeitraum leider nicht angegeben), wobei sie 14 randomisierte Studien fanden (n=10 mit HCTZ-INDAP Vergleich sowie n=3 mit HCTZ-CTDN Vergleich zum systolischen Blutdruck (SBP) und n=9 mit HCTZ-INPAD Vergleich zu metabolischen Parametern; Nachbeobachtungszeit 4 bis 26 Wochen) [6]. Die Autor*innen fanden keine randomisierte kontrollierte Studie (RCT), die CTDN mit INDAP verglich und insgesamt keine RCT, die kardiovaskuläre Endpunkte im Vergleich der Diuretika berichtete [6]. Die Autor*innen diskutierten das Risiko für Fehler und führten Sensitivitätsanalysen durch, berichteten aber kein Tool für die Bewertung der Qualität der eingeschlossenen Studien.

Tabelle 2 Eingeschlossene Studien (Recherchezeiträume in Klammern)

Studien	Dineva et al. 2019 [4]	Liang et al. 2017 [5]	Roush et al. 2015 [6]	Systematische Recherche (SR) NVL[43]
	n=9 Studien	n=12 Studien	n=14 Studien	n = 10 Studien SR n = 3 [4–6]** RCT* n = 2 [7,8]** Kohorten n= 5 [9–13]
randomisiert kontrolliert	(bis 2017)	(bis 2017)	-	(2011-2021)
Bakris GL et al. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. Am J Med. 2012;125:1229.e1–1229.e10. https://doi.org/10.1016/j.amjmed.2012.05.023. (randomized, double-blind)	[17]	[17]	-	[17] ** Kombinationen Chlorthalidon oder Hydrochlorothiazid mit Sartanen
Bhigjee AI, Seedat YK, Hoosen S, Neerahoo RM, Naidoo K. Biochemical changes in black and Indian hypertensive patients on diuretic therapy. S Afr Med J. 1983;64:969–972.	-	-	Bhigjee et al. S Afr Med J. 1983	vor dem SR-Recherchezeitraum Population, Endpunkte, Phase I/II ?
Elliott WJ, Weber RR, Murphy MB. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. J Clin Pharmacol. 1991;31:751–757.	-	-	Elliott et al. J Clin Pharmacol 1991	vor dem SR-Recherchezeitraum ? Population, Endpunkte, Phase I
Emeriau JP, Knauf H, Pujadas JO, et al. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens. 2001; 19: 343–50.	-	Emeirau et al. Hypertens 2001	Emeirau et al. Hypertens 2001	vor dem SR-Recherchezeitraum
Ernst ME et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension. 2006;47:352–8. (randomized single blinded)	Ernst et al. Hypertension. 2006	Ernst et al. Hypertension. 2006	Ernst et al. Hypertension. 2006	vor dem SR-Recherchezeitraum

[43] *Hinweis: RCT Screening für die letzten 10 Jahre, da Fragestellung in Übersichtsarbeiten teilweise beantwortet
**Hinweis: zudem wurden 2 SR [14,15] und 8 RCT [16–23] ermittelt, die Kombinationen von Chlorthalidon oder Hydrochlorothiazid mit Sartanen bzw. Indapamid oder Hydrochlorothiazid mit ACE Hemmern verglichen

Studien	Dineva et al. 2019 [4]	Liang et al. 2017 [5]	Roush et al. 2015 [6]	Systematische Recherche (SR) NVL[43]
Kreeft JH, Langlois S, Ogilvie RI. Comparative trial of indapamide and hydrochlorothiazide in essential hypertension, with forearm plethysmography. J Cardiovasc Pharmacol. 1984;6:622–626.	-	-	Kreeft et al. J Cardiovas-Pharmacol 1984	vor dem SR-Recherchezeitraum Population, Phase I/II ?
Krum H, Skiba M, Gilbert RE. Comparative metabolic effects of hydrochlorothiazide and indapamide in hypertensive diabetic patients receiving ACE inhibitor therapy. Diabet Med. 2003;20:708–712.	-	-	Krum et al. Diabet Med. 2003	vor dem SR-Recherchezeitraum Kombinationen mit ACE-Hemmer, Diabetes Mellitus, Endpunkte
Kumar B, Kaur S, Manzoor S, et al. First among equals: A comparative study of the effect of hydrochlorothiazide and chlorthalidone on recently diagnosed hypertensives. Asian journal of pharmaceutical and clinical research 2015; 8(6):195–8. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01126131/full.	-	-	-	[8]
Kwon BJ et al. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naïve patients of hypertension. Hypertens Res. 2013;36:79–84. https://doi.org/10.1038/hr.2012.143. (open-label, randomized, cross-over design)	[18]	[18]	[18]	[18] ** Kombinationen Chlorthalidon oder Hydrochlorothiazid mit Sartanen
Madkour H, Gadallah M, Riveline B, Plante GE, Massry SG. Comparison between the effects of indapamide and hydrochlorothiazide on creatinine clearance in patients with impaired renal function and hypertension. Am J Nephrol. 1995;15:251–255.	-	-	Madkour et al. Am J Nephrol. 1995	vor dem SR-Recherchezeitraum eingeschränkte Nierenfunktion, Endpunkte
Malini PL, Strocchi EN, Ricci CM, Ambrosinioni E. Indapamide or hydrochlorothiazide in hypertensive patients resistant to treatment with an angiotensin-converting enzyme inhibitor. Curr Therap Res. 1994;55:932–937.	-	-	Malini et al. Curr Therap Res. 1994	vor dem SR-Recherchezeitraum eingeschränkte Folgetherapie
Pareek A et al.. A randomized, comparative study evaluating the efficacy and tolerability of losartan-low dose chlorthalidone (6.25 mg) combination with losartan-hydrochlorothiazide (12.5 mg) combination in Indian patients with mild-to-moderate essential hypertension. Expert Opin Pharmacother. 2009;10:1529–36. https://doi.org/10.1517/14656560902991514 (randomized, open-label, parallel group design)	Pareek et al. Expert Opin Pharmacother. 2009	Pareek et al. Expert Opin Pharmacother. 2009	Pareek et al. Expert Opin Pharmacother. 2009	vor dem SR-Recherchezeitraum, Kombinationen Chlorthalidon oder Hydrochlorothiazid mit Sartanen
Pareek A, Zawar SD, Salagre SB, et al. Antihypertensive efficacy of metoprolol XL/low dose chlorthalidone (6.25 mg) combination: a randomized, comparative study in indian patients with mild-to-moderate essential hypertension. Eur J Med Res. 2009; 14:297–303.	-	Pareek et al. Eur J Med Res. 2009	-	vor dem SR-Recherchezeitraum Kombinationen Chlorthalidon oder Hydrochlorothiazid mit Sartanen
Pareek AK et al. Efficacy of low-dose chlorthalidone and hydrochlorothiazide as assessed by 24-h ambulatory blood pressure monitoring. J Am Coll Cardiol. 2016;67:379–89. https://doi.org/10.1016/j.jacc.2015.10.083. (randomized, double-blind, parallel group design)	[7]	[7]	-	[7]

Studien	Dineva et al. 2019 [4]	Liang et al. 2017 [5]	Roush et al. 2015 [6]	Systematische Recherche (SR) NVL[43]
Plante GE, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. Curr Med Res Opin. 1983; 8(Suppl 3): 59–66.	-	Plante et al. Curr Med Res Opin 1983	Plante et al. Curr Med Res Opin 1983	vor dem SR-Recherchezeitraum, Fallzahl, Phase I ?
Plante GE, Dessurault DL. Hypertension in elderly patients. A comparative study between indapamide and hydrochlorothiazide. Am J Med. 1988;84(1B):98–103.	-	-	Plante et al. Am J Med. 1998	vor dem SR-Recherchezeitraum, Phase II ?
Radevski IV, Valtchanova ZP, Candy GP, et al. Comparison of indapamide and lowdose hydrochlorothiazide monotherapy in black patients with mild to moderate hypertension. S Afr Med J. 2002; 92: 532–6.	-	Radevski et al. S Afr Me J 2002	Radevski et al. S Afr Me J 2002	vor dem SR-Recherchezeitraum, Population, Phase I/II ?
Senior R, Imbs JL, Bory M, et al. Indapamide reduces hypertensive left ventricular hypertrophy: an international multicentre study. J Cardiovasc Pharmacol. 1993; 22 (Suppl 6): S106–10.	-	Senior et al. J Cardiovasc Pharmacol. 1993	-	vor dem SR-Recherchezeitraum, Methodik ?
Siegel D, Hulley SB, Black DM, et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA. 1992; 267: 1083–9.	-	Siegel et al. JAMA 1992		vor dem SR-Recherchezeitraum, Endpunkte
Spence JD, Huff M, Barnett PA. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000; 7: 32–7.	-	Spence et al. Can J Clin Pharmacol 2000	Spence et al. Can J Clin Pharmacol 2000	vor dem SR-Recherchezeitraum, Endpunkte
vergleichende Kohorten	**(bis 2017)**	**-**	**-**	**(bis 2021)**
Dhalla IA et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. Ann Intern Med. 2013;158:447–55. https://doi.org/10.7326/0003-4819-158-6-201303190-00004. (propensity-score)	[10]	-	-	[10]
Dorsch MP et al. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. Hypertension. 2011;57:689–94. https://doi.org/10.1161/HYPERTENSIONAHA.110.161505	[11]	-	-	[11]
Ernst ME, Neaton JD, Grimm RH, et al. Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. Hypertension (Dallas, Tex. 1979) 2011; 58(6):1001–7. DOI: 10.1161/HYPERTENSIONAHA.111.181248. http://www.ncbi.nlm.nih.gov/pubmed/22025372.	-	-	-	[13]
Hripcsak G, Suchard MA, Shea S, et al. Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension. JAMA internal medicine 2020; 180(4):542–51. DOI: 10.1001/jamainternmed.2019.7454. http://www.ncbi.nlm.nih.gov/pubmed/32065600.	-	-	-	[9]
Saseen JJ et al. Comparing clinical effectiveness and drug toxicity with hydrochlorothiazide and chlorthalidone using two potency ratios in a managed care population. J Clin Hypertens. 2015;17:134–40. https://doi.org/10.1111/jch.12453. (retrospective analysis)	[12]	-	-	[12]

Studien	Dineva et al. 2019 [4]	Liang et al. 2017 [5]	Roush et al. 2015 [6]	Systematische Recherche (SR) NVL[43]
van Blijderveen JC et al. Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. Am J Med.2014;127:763–71. https://doi.org/10.1016/j.amjmed.2014.04.014. (observational case-control study)	[176]	-	-	ausgeschlossen aus der systematischen Recherche (s.u. interessante Treffer)

Tabelle 3: Ergebnisse der ermittelten Kohortenstudien

	Mortalität	kardiovaskuläre Ereignisse	Blutdruck systolisch	diastolisch	Kalium/Natrium	Weitere
Hripcsak 2020 [9]	CTDN vs. HTCZ: HR stratifiziert, kalibriert **on-treatment** Gesamtmortalität 0,93 (0,61-1,42) kardiovaskuläre Mortalität 1,24 (0,62-2,51) **intention to treat** Gesamtmortalität 1,07 (0,95-1,21) kardiovaskuläre Mortalität 1,01 (0,80-1,27)	CTDN vs. HTCZ: HR stratifiziert, kalibriert **on-treatment** Herzinfarkt 0,92 (0,64-1,31) Herzinsuffizienz 1,01 (0,73-1,40) Hospitalisierung auf Grund von Herzinsuffizienz 1,05 (0,82-1,34) kardiovaskuläre Erkrankungen 1,00 (0,85-1,17) **intention to treat** Herzinfarkt 1,04 (0,91-1,18) Herzinsuffizienz 1,05 (0,95-1,16) Hospitalisierung auf Grund von Herzinsuffizienz 1,05 (0,95-1,17) kardiovaskuläre Erkrankungen 1,04 (0,96-1,13)	-	-	CTDN vs. HTCZ: HR stratifiziert, kalibriert **on-treatment** Hyperkaliämie 1,34 (1,03-1,74) Hypokaliämie 2,72 (2,38-3,12) Hyponatriämie 1,31 (1,16-1,47) **intention to treat** Hyperkaliämie 1,16 (1,02-1,33) Hypokaliämie 2,23 (1,92-2,59) Hyponatriämie 1,18 (1,03-1,35)	CTDN vs. HTCZ: HR stratifiziert, kalibriert **on-treatment** hämorrhagischer Schlaganfall 0,92 (0,39-2,18) Ischämischer Schlaganfall 1,09 (0,84-1,42) Schlaganfall 1,10 (0,86-1,41) TIA 1,23 (0,93-1,64) **intention to treat** hämorrhagischer Schlaganfall 0,95 (0,72-1,25) ischämischer Schlaganfall 1,10 (0,97-1,25) Schlaganfall 1,09 (0,97-1,23) TIA 1,07 (0,88-1,30)
Dhalla 2013 [10]	s. weitere	s. weitere	-	-	Hospitalisierung mit Hypokaliämie: CTDN: n=109 (0,69 Fälle pro 100 Personenjahre)	Tod oder Hospitalisierung (Composit-Endpunkt): CTDN: n=510 (3,2 Fälle pro 100 Personenjahre)

	Mortalität	kardiovaskuläre Ereignisse	Blutdruck systolisch	diastolisch	Kalium/Natrium	Weitere
					HCTZ: n=102 (0,27 Fälle pro 100 Personenjahre) adjustierte HR 3,06 (2.04-4.58) Hyponatriämie: CTDN: n=109 (0,69 Fälle pro 100 Personenjahre) HCTZ: n=184 (0,49 Fälle pro 100 Personenjahre) adjustierte HR 1,68 (1.24-2.28)	HCTZ: n=1.265 (3,4 Fälle pro 100 Personenjahre) adjustierte HR 0,93 (0,81-1,06)
Dorsch 2011 [11]	-	n=1.244 über 7 Jahre adjustierte HR gegenüber keiner Arznei-mitteltherapie: CTDN 0,51 (0,43-0,61); P<0,0001 HCTZ 0,65 (0,55-0,75); P<0,0001 CTD vs. HCTZ: 0,79 (0,68-0,92); P=0,0016	sekundär	-	sekundär	sekundär
Saseen 2015 [12]	-	-	mindestens 30 Tage nach Erstverordnung adjustierte Regression nach Propensity Score Matching mittlerer SBP mm Hg CTDN (25 mg), n=180 132,2	mindestens 30 Tage nach Erstverordnung adjustierte Regression nach Propensity Score Matching mittlerer DBP mm Hg CTDN (25 mg), n=180 74,0	mittlerer K-Spiegel: CTDN (25 mg): 3,94 mEq/L, n=143 HCTZ (25 mg): 4,13 mEq/L, n=299; P<0,01 vs. CTDN HCTZ (50 mg): 3,96 mEq/L, n=152	Patient*innen mit erreich-ten SBP*/DBP** Zielen: CTDN (25 mg), n=180 SBP 45,0 % DBP 78,3 % Beide 40,6 % HCTZ (25 mg), n=355

	Mortalität	kardiovaskuläre Ereignisse	Blutdruck systolisch	diastolisch	Kalium/Natrium	Weitere
			HCTZ (25 mg), n=355 137,0; P<0,01 vs. CTDN HCTZ (50 mg), n=177 138,6; P<0,01 vs. CTDN MD (95% KI) mm Hg CTDN vs. HCTZ (25) - 3,16 (- 5,25 bis -1,07) CTDN vs. HCTZ (50) - 4,6 (-7,4 bis -1,8)	HCTZ (25 mg), n=355 77,5; P<0,01 vs. CTDN HCTZ (50 mg), n=177 78,5; P<0,01 vs. CTDN MD (95% KI) mm Hg CTDN vs. HCTZ (25) - 2,59 (- 3,84 bis -1,3) CTDN vs. HCTZ (50) - 3,68 (-5,41 bis -1,95)		SBP 32,1 %; P<0,01 DBP 63.9 %; P<0,01 Beide 27,0; P<0,01; OR 1,38 (0,98-1,94) HCTZ (50 mg), n=177 SBP 32,8 %; P<0,05 DBP 68,9 %; P<0,05 Beide 28,8 %; P<0,05, OR 1,81 (1,12-2,94)
Ernst 2011 [13]	-	**Kriterien LVH:** nach 48 Monaten stratifizierte Regression mit Kovariaten MD (SE) SI-UC C-Clinics vs. H-Clinics Sokolow-Lyon µV: -93,9 (15,1) vs. -54,9 (12,1), P=0,049 Cornell voltage µV: -68,1 (9,6) vs. -35,9 (8,0), P=0,019 Cornell voltage product µV/ms: -4,6 (0,9) vs. - 2,2 (0,8), P=0,071 left ventricular mass g: -4,4 (0,4) vs. -2,8 (0,3), P=0,002	nach 48 Monaten stratifizierte Regression mit Kovariaten MD (SE) mm Hg SI-UC C-Clinics vs. H-Clinics -10,4 (0,4) vs. -8,6 (0,3); P=0,001 adjustierte Regression mit Propensity Score MD (95 % KI) mm Hg SI-UC; C-Clinics-H-Clinics -1,7 (-2,3, -1,2); P< 0,001	nach 48 Monaten stratifizierte Regression mit Kovariaten MD (SE) mm Hg SI-UC C-Clinics vs. H-Clinics -6,5 (0,3) vs. -5,1 (0,2); P<0,001 adjustierte Regression mit Propensity Score MD (95 % KI) mm Hg SI-UC; C-Clinics-H-Clinics -0,7 (-1,1, -0,4); P< 0,001	**Kaliumserumspiegel** nach 48 Monaten stratifizierte Regression mit Kovariaten MD (SE) mmol/L SI-UC C-Clinics vs. H-Clinics -0,33 (0,02) vs. -0,23 (0,01); P<0,001 adjustierte Regression mit Propensity Score MD (95 % KI) mmol/L SI-UC; C-Clinics-H-Clinics -0,23 (-0,25, -0,21); P<0,001	-

	Mortalität	kardiovaskuläre Ereignisse	Blutdruck systolisch	diastolisch	Kalium/Natrium	Weitere
		adjustierte Regression mit Propensity Score MD (95 % KI) SI-UC; C-Clinics, H-Clinics Sokolow-Lyon µV: -38,8 (-57,9, -19,7) P<0,001 Cornell voltage µV: 3,7 (-8,8, 16,3) P=0,56 Cornell voltage product µV/ms: 1,7 (0,5; 3,0) P=0,008 left ventricular mass g: - 0,6 (-1,0, -0,1) P=0,02				

C-Clinics=Kliniken, die vorranging Chlorthalidon verordneten; CTDN=Chlorthalidon; DBP=diastolischer Blutdruck; H-Clinics=Kliniken, die vorrangig Hydrochlorothiazid verordneten; HCTZ=Hydrochlorothiazid; HR=Hazard Ratio (95 % KI); KI=Konfidenzintervall; LVH=linksventrikuläre Hypertrophie; MD=mittlere Differenz; OR=Odds Ratio (95% KI); SBP=systolischer Blutdruck; SE=Standardfehler; SI-UC=spezielle Intervention vs. Standardversorgung; TIA= transitorische ischämische Attacken

*SBP Ziel <140 mm Hg, oder <130 mm Hg bei Diabetes mellitus.

**DBP Ziel <90 mm Hg, oder <80 mm Hg bei Diabetes Mellitus

Hripcsak et al. 2020 verglichen Chlorthalidon (CTDN) und Hydrochlorothiazid (HCTZ) als Erstlinientherapie bei Hypertonie in der Versorgung (retrospektive Kohorte, 1 Jahr Nachbeobachtung, Observational Health Data Sciences and Informatics (OHDSI) Datenbanken, USA, n=730.225 Patient*innen, mittleres Alter 51,5 Jahre) [9]. Als primäre Endpunkte wurden Hospitalisierung (auf Grund von Herzinfarkt, Herzinsuffizienz, ischämischer oder hämorrhagischer Schlaganfall) sowie ein kombinierter Endpunkt aus diesen drei Endpunkten und Tod untersucht [9]. Ergänzend wurden 51 Endpunkte in Bezug auf die Sicherheit betrachtet, u.a. Hyper- und Hypokaliämie sowie Hyponatriämie [9]. Die Analysen erfolgten unter Stratifizierung mittels Propensity Score und Bonferroni Korrektur auf zwei Arten („on-treatment“ und „intention-to-treat“) [9]. Die Autor*innen berichteten u.a. Residual Confounding (z.B. „Confounding by Indication“) als Limitation [9]. Für die Patient*innen unter CTDN wurden insgesamt 149 kombinierte Endpunkte/36.628 Patient*innen (on-treatment) bzw. 892 kombinierte Endpunkte/36.654 Patient*innen (intention-to-treat) berichtet; für die Patient*innen unter HCTZ insgesamt 3.089 kombinierte Endpunkte/687.106 Patient*innen (on-treatment) bzw. 20.824 kombinierte Endpunkte/688.446 Patient*innen (intention-to-treat) [9]. Die Ergebnisse der Auswertungen sind in Tabelle 3 aufgeführt [9].

Dhalla et al. 2013 verglichen Patient*innen in einem Alter von 66 Jahren oder älter in Bezug auf einen kombinierten Endpunkt (Tod oder Hospitalisierung auf Grund von Herzinsuffizienz, Schlaganfall oder Herzinfarkt, Tabelle 3), die eine Therapie mit Chlorthalidon oder Hydrochlorothiazid zwischen 1993 und 2010 begannen (retrospektive Datenbankanalyse, Propensity-Score-Matching, Kanada) [10]. Die Patient*innen wurden in der Analyse zensiert, wenn sie die Studienmedikation wechselten (Switch) oder die Therapie beendeten [10]. Vor dem Matching waren Patient*innen, die CTDN erhielten jünger als Patient*innen mit HCTZ und hatten in den drei Jahren vor der Betrachtung weniger Krankenhausaufenthalte [10]. Zudem erhielten Patient*innen mit CTDN häufiger Betablocker und weniger häufig ACE-Hemmer oder Angiotensin-II-Rezeptorblocker im Vergleich zu HCTZ [10]. Unmeasured Confounding wurde als eine Limitation dokumentiert [10]. Nach dem Matching wurden 10.384 Patient*innen mit CTD (mediane Nachbeobachtung 255 Tage) und 19.489 Patient*innen mit HCTZ (mediane Nachbeobachtung 398 Tage) analysiert [10]. In der Publikation (Tabelle 4) wurden zudem Dosis-bezogene Hazard Ratios berichtet [10].

Dorsch et al. 2011 verglichen in einer retrospektiven Kohortenstudie die kardiovaskulären Ereignisraten (Tabelle 3) bei Patient*innen unter Risiko (>15 %; erhöhter systolischer Blutdruck als ein Risikofaktor) für Tod auf Grund von koronarer Herzkrankheit (KHK) behandelt mit Chlorthalidon (CTDN) oder Hydrochlorothiazid (HCTZ) als Erstlinientherapie (Basis: Multiple Risk Factor Intervention Trial data set from the National Heart, Lung, and Blood Institute (MRFIT)) [11]. Ergänzend betrachtet wurden der Blutdruck sowie verschiedenen Laborparameter (wie Kalium) [11]. Berichtet wurde über 6.441 Patient*innen, die initial eins der beide Diuretika erhielten (CTDN n= 2.392 und HCTZ n=4.049) und die median über sechs Jahre nachbeobachtet wurden [11]. 57 % der Patient*innen unter HCTZ sowie 76 % der Patient*innen unter CTDN wechselten die Therapie (cross-over) oder beendeted die Therapie mit HCTZ oder CTDN [11]. Die Autor*innen berichteten über ein potentielles „Unmeasured Confounding“ sowie das Risiko für einen Selection oder Information Bias [11].

Saseen et al. 2015 untersuchten in einer retrospektiven Kohortenstudie u.a. den Blutdruck vergleichend zwischen Chlorthalidon (25 mg/Tag, n=214 Patient*innen) gegenüber Hydrochlorothiazid (25 mg/Tag, n=428 Patient*innen sowie 50 mg/Tag, n=214 Patient*innen) bei Hypertonie (ICD-9-CM), wobei Fixkombinationen oder freie Kombinationen eingeschlossen wurden (health plan’s electronic health record (EHR) database), USA) [12]. Es wurde von einer häufigen Verordnung im Rahmen einer Kombinationstherapie mit weiteren Antihypertensiva berichtet, insbesondere bei Patient*innen mit Chlorthalidon [12]. Die adjustierten Regressionsanalysen wurden nach Propensity-Score-Matching umgesetzt [12]. Für einige präspezifizierte Endpunkte berichteten die Autor*innen zu geringe Fallzahlen bzw. dokumentierte Ergebnisse, weshalb möglicherweise keine signifikanten Unterschiede ermittelt werden konnten (z.B. Harnsäure-Konzentration) [12]. Die Ergebnisse zum Zeitpunkt von mindestens 30 Tagen Nachbeobachtung sind in Tabelle 3 aufgeführt [12].

Ernst et al. 2011 führten mit einer Kohorte von Männern mit Bluthochdruck (n=8012, mittleres Alter 46,7 Jahre) aus einer randomisierten Interventionsstudie mit komplexer Intervention bei koronarer Herzkrankheit (Multiple Risk Factor Intervention Trial (MRFIT), USA, *s. Evidenztabellen*) zwei Analysen u.a. zu Blutdruckveränderungen sowie Kriterien für eine elektrografisch bestimmte ventrikuläre Hypertrophie durch [13]. Die Intervention enthielt dabei auch eine antihypertensive Therapie mit Chlorthalidon (CTD) oder Hydrochlorothiazid (HCTZ), wobei diese Zuteilung nicht randomisiert erfolgte (Auswahl durch die behandelnden Ärzt*innen) [13]. Daher wurden vergleichende Regressionsanalysen stratifizierte nach Kovariaten sowie basierend auf dem Propensity Score durchgeführt [13]. Die Autor*innen führten an, dass in der zugrundeliegenden Studie höhere Dosen von CTD und HCTZ eingesetzt wurden (50 oder 100 mg pro Tag), als später üblicherweise genutzt wurden [13]. Zudem waren zusätzliche Wirkstoffe zum Erreichen der Blutdruckzielwerte sowie Wechsel in der Therapie zulässig [13]. Vorrangig CTD wurde

von sechs Kliniken randomisiert gegenüber der Standardversorgung verordnet (n(gesamt)=2.112; C-Clinics); vorrangig HCTZ von neun Kliniken (n(gesamt)=3.399; H-Clinics) [13]. Die Autori*innen berichteten eine Veränderung im Protokoll der zugrundeliegenden Studie, nach einer Nachbeobachtung von 48 Monaten, die zu einer gesteigerten Verordnung von Chlorthalidon führte [13]. Die Ergebnisse zum Zeitpunkt der 48-monatigen Nachbeobachtung sind in Tabelle 3 aufgeführt [13].

Ergänzende Hinweise:

Im Rahmen der systematischen Recherche wurden zudem die nachfolgenden Arbeiten und Zufallsfunde ermittelt, die nicht die Einschlusskriterien erfüllten, aber eventuell dennoch von Interesse für weitere Diskussionen sein könnten. Diese Arbeiten wurden an dieser Stelle nicht bewertet und nicht aufbereitet.

– Carey et al. 2018 (resistente Hypertonie, Überblicksartikel) [177], Roush et al. 2018 (Diuretika vs. RAAS-Inhibitoren) [178], Roush and Sica 2016 (Diuretika bei Bluthochdruck, Überblicksartikel) [179], DiNicolantonio et al. 2015 (Diuretika mit einem Fokus auf Chlorthalidon und Indapamid, Überblicksartikel) [180], Roush et al. 2015 (Diuretika-Alternativen zu Hydrochlorothiazid, Überblicksartikel) [181], Barrios und Escobar 2014 (Thiazide als add-on-Therapie, Überblicksartikel) [182], Roush et al. 2014 (Diuretika, Überblicksartikel) [183], Mukete und Rosendorff 2013 (Thiazide, gering dosiert, Effekte auf Plasmaglucose- und Kaliumspiegel) [184], Roush et al. 2013 (Vergleich Chlorthalidon vs. Hydrochlorithiazid, Überblicksartikel) [185], Chan et al. 2012 (Thiazide in der antihypertensiven Therapie bei renalen Erkrankungen) [186], Viera et al. 2012 (resistente Hypertonie, Überblicksartikel) [187], Reilly et al. 2010 (Thiazide bei Hypertonie und Nephrolithiasis) [188], Baguet et al. 2005 und 2007 (antihypertensive Therapieansätze, häufig genutzt in Frankreich) [189,190], Calhoun 2007 (resistente Hypertonie, Aldosteronantagonisten in geringer Dosierung) [191], Ames 1998 (Hyperlipidämie bei Diuretika-Therapie) [192], Ames 1996 (Effekte von Indapamid und Thiaziden, Überblicksarbeit) [193].

- Ergänzend Ernst et al. 2010 (Trend in der Anwendung antihypertensiver Arzneimittel, USA, therapieresistente Hypertonie, epidemiologische Analyse) [194], Hawang et al. 2016 (Trends in der Anwendung antihypertensiver Arzneimittel, USA, resistente Hypertonie, epidemiologische Analyse) [195], Lund et al. 2012 (Persistenz und Abwesenheit einer ergänzenden medikamentösen Therapie innerhalb eines Jahres (Chlorthalidon vs. Hydrochlorothiazid, vergleichende Kohortenstudie) [196], Wilson et al. 2014 (Chlorthalidon vs. Hydrochlorothiazid, Vergleich unerwünschter Wirkungen (Gicht, „new-onset gout“), retrospektive Kohortenstudie) [197].

- Zudem Chrysant et al. 2021 [198], Düsing et al. 2011 [199], Licht et al. 1983 [200], Messerli et al. 2017 [201], National Institute of Diabetes and Digestive and Kidney Disease 2012 [202], Ravioli et al. 2021 [203], van Blijderveen et al. 2014 [176].

Tabelle 4 Netzwerkmetaanalysen (NMA), bzw. Übersichtsarbeiten, die auch NMA einschlossen, aus der systematischen Recherche (22. Juli 2021)

Nr.	Link	Year	Title	Study type	Source	Population	Comparison	Included studies		Outcome	Comment
[167]	https://pubmed.ncbi.nlm.nih.gov/32909966	2021	Network meta-analysis of efficacy and safety of chlorthalidone and hydrochlorothiazide in hypertensive patients	systematic review and (network-) meta-analysis	PubMed, Medline, Scopus, PsycInfo, eLIBRARY.ru, registries of clinical trials	adult hypertensive patients	chlorthalidone vs. hydrochlorothiazide (different doses, combinations, (in-) direct comparison, placebo)	n=37 (n=28 indirect, n=9 direct)	randomized controlled studies (n=33) and observational studies (n=4)	SBP, DBP, changes in serum potassium levels	Quality assessment: Jadad Scale
[168]	https://pubmed.ncbi.nlm.nih.gov/33470735	2021	Chlorthalidone versus hydrochlorothiazide: major cardiovascular events, blood pressure, left ventricular mass, and adverse effects	systematic review and (network-) meta-analysis	PubMed, Cochrane Register	-	chlorthalidone vs. hydrochlorothiazide (different doses)	n=14 (n=8 observational, n=37 trials, n=9 direct RCT in NMA)	randomized controlled trials, observational studies (n=8) and network meta-analysis (NMA, n=2)	MACE, left ventricular mass	based on Roush et al. 2012 [169], and 2018 [170] included 7 and 28 trials of NMA; incomplete methods section
[170]	https://pubmed.ncbi.nlm.nih.gov/30251403/	2018	Hydrochlorothiazide vs chlorthalidone, indapamide, and potassium-sparing/hydrochlorothiazide diuretics for reducing left ventricular hypertrophy: A systematic review and meta-analysis	systematic review and (network-) meta-analysis	PubMed, Cochrane, Scopus, clinicaltrials, prior meta-analysis	patients with hypertension	hydrochlorothiazide vs. chlorthalidone, indapamide, and potassium-sparing/ hydrochlorothiazide diuretics	n=27 articles, representing n=38 RCT	randomized controlled trials	left ventricular hypertrophy; systolic and diastolic blood pressure (SBP and DBP)	strength of evidence was evaluated by GRADE criteria
[169]	https://pubmed.ncbi.nlm.nih.gov/22526259/	2012	Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses	systematic review and (network-) meta-analysis	PubMed (Ovid)	-	chlorthalidone vs. hydrochlorothiazide (HCT) (mono- or combination therapy)	n=9 comparisons (n=3 arms on HCT and n=6 arms on chlorothiazid)	randomized controlled trials	all cause mortality or ≥1 CVE (#)	

CVE (myocardial infarction, new diagnosis of coronary heart disease, stroke, or congestive heart failure); CVE = cardiovascular events, DBP = diastolic blood pressure, MACE = major cardiovascular events, SBP = systolic blood pressure

* eingeschlossene Quellen:

Dineva et al. 2021 [167]

indirect:

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cohort: Dhalla et al. Ann Intern Med 2013 (cohort), Hripcsak et al. JAMA Int Med 2020 (cohort), Dorsch et al. Hypertension 2011 (cohort), van Blijderveen et al. Am J Med 2014 (cohort)
trial: Ernst et al. Hypertension 2011, Bowlus et al. Clin Pharm Ther 1964, Finnerty et al. Angiology 1976, Licht et al. Arch Intern Med 1983, Pareek et al. Expert Opin Pharmacother 2009, Kumar et al. Asian J Pharmaceutical Clin Res 2015, Pareek et al. J Am Coll Cardiol 2016

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8.12 Handsuche/Literaturlistensuche

Engberink 2015 / SR / thiazide-type and thiazide-like diuretics vs. placebo (kardiovaskuläre Ergebnisse)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Engberink et al. [204] https://pubmed.ncbi.nlm.nih.gov/25733241/	2015	critically low	**Objective** to compare the effect of thiazide-type (TT) and thiazide-like diuretics (TL) on CVE, coronary events, heart failure, cerebrovascular events, and all-cause mortality in adult hypertensive (BP >140/90 mm Hg) patients **Search** Medline, Embase, and Cochrane library (until July 2014) **Inclusion and exclusion criteria** - randomized, controlled studies - thiazide diuretics as first-line antihypertensive treatment - effect of either TT or TL diuretics - hypertensive patients aged ≥18 years - mean systolic/diastolic BP ≥140 / ≥90 mm Hg	n=21 studies with 25 comparisons were included - n=17 studies for TT (n=8 studies TT vs. placebo, n=9 studies TT vs. other antihypertensives) - n=8 studies for TL (n=3 studies TL vs. placebo, n=5 studies TL vs. other antihypertensives) - weighted average value of mean ages across studies was lower in studies investigating TT diuretics (60 versus 68 years) when compared with studies involving TL diuretics - mean follow-up time: o TT diuretics (4.3 years; SD, 0.9) o TL diuretics (4.2 years; SD, 1.0) - n=17 studies reported adverse events o TL diuretics vs. placebo n=2 studies; authors do not estimate the risk of adverse events for the comparison of TL diuretics and placebo	wurde in Recherche nicht gefunden, da die Suche nach Abstimmung auf bestimmte Wirkstoffe begrenzt wurde und nicht übergeordnet gesucht werden sollte; Vergleiche vs. Plazebo oder andere Anttihypertensiva - unterstützend betrachtet

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			- follow-up period ≥ 1 year **Quality assessment** according to the Cochrane Handbook Guidelines (risk of bias tool) **Intervention** thiazide diuretics (first-line treatment) **Comperator** placebo or other antihypertensive therapy **Outcomes** cardiovascular events (CVE)*	○ TT diuretics vs. other antihypertensives ■ RR, 0.92 [0.74–1.15] ○ TL diuretics vs. other antihypertensives ■ RR, 0.84 [0.68–1.03] **Outcomes: (Forest plot S2 s. supplement page 34)** number of CVE: - TT diuretics vs. placebo RR, 0.67 [0.56–0.81]; I2=37% - TL diuretics vs. placebo RR, 0.67 [0.60–0.75]; I2=0% - TT diuretics vs. other antihypertensives RR, 0.96 [0.84-1.09]; I2=59% - TL diuretics vs. other antihypertensives RR, 0.86 [0.72–1.04]; I2=88% *corrected for BP changes* - TT diuretics vs. placebo (corrected) RRc, 1.00 [0.91–1.09] - TL diuretics vs. placebo (corrected) RRc, 0.88 [0.79–0.98] cerebrovascular events - TT diuretics vs. placebo RR, 0.52 [0.38–0.69]; I2=25% - TL diuretics vs. placebo RR, 0.68 [0.57–0.80]; I2=0% - TT diuretics vs. other antihypertensives RR, 0.94 [0.76-1.16]; I2=56% - TL diuretics vs. other antihypertensives RR, 0.93 [0.86–1.01]; I2=0% coronary events - TT diuretics vs. placebo RR 0.81 [0.63-1.05]; I2=38% - TL diuretics vs. placebo RR, 0.76 [0.61–0.96]; I2=0% - TT diuretics vs. other antihypertensives RR, 1.01 [0.83-1.24]; I2=62% - TL diuretics vs. other antihypertensives RR, 1.01 [0.95–1.07]; I2=0%	publication bias was not assessed diuretics as first-line therapy with a standardized protocol for dose titration or add-on BP-lowering therapy

* aggregate of cerebrovascular events, coronary events, and heart failure (cerebrovascular events were defined as a composite of stroke and transient ischemic attack, whereas coronary events included myocardial infarction and sudden death. We did not include cardiac angina, peripheral artery disease, coronary artery bypass grafting, coronary revascularization, other cardiovascular procedures, and accelerated hypertension because of differences in definitions and event reporting, or because they were only reported in few studies. Adverse events were defined as discontinuation of the drug because of side effects or serious adverse events.

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
				all-cause mortality - TT diuretics vs. placebo RR 0.86 [0.75-1.00]; I2=12% - TL diuretics vs. placebo RR, 0.84 [0.74–0.96]; I2=0% - TT diuretics vs. other antihypertensives RR, 1.03 (0.94-1.12); I2=0% - TL diuretics vs. other antihypertensives RR, 1.00 [0.95–1.05]; I2=0% heart failure - TT diuretics vs. placebo RR, 0.36 [0.16–0.84]; I2=14% - TL diuretics vs. placebo RR, 0.47 [0.36–0.61]; I2=0% - TT diuretics vs. other antihypertensives RR, 0.87 [0.61-1.23]; I2=53% - TL diuretics vs. other antihypertensives RR, 0.71 [0.53–0.95]; I2=91% *corrected for BP changes* - TT diuretics vs. placebo (corrected) RR, 0.90 [0.68–1.21] - TL diuretics vs. placebo (corrected) RR, 0.71 [0.57–0.89] **Articles included** vs. Placebo: - IND HYVET 2008; - CTDN 12,5/25 mg/d SHEP 1991; CTDN 25 mg/d SHEP pilot 1989; - thiazide (HCT) n=8 RCT; combination therapy was allowed 15. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA. 2000;283:1967–1975. 16. The Australian therapeutic trial in mild hypertension: Report by the Management Committee. Lancet. 1980;1:1261–1267. doi: 10.1016/S0140-6736(80)91730-4. 17. Amery A, Brixko P, Clement D et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet. 1985;1:1349–1354. 18. Kuramoto K, Matsushita S, Kuwajima I, Murakami M. Prospective study on the treatment of mild hypertension in the aged. Jpn Heart J. 1981;22:75–85.	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
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Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
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Ishani et al. N Engl J Med. 2022 Chlorthalidone vs. Hydrochlorothiazide (cohort, pragmatic trial)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Ishani et al. Chlorthalidone vs. Hydrochlorothiazide for Hypertension-Cardiovascular Events. N Engl J	**Background** whether chlorthalidone is superior to hydrochlorothiazide for preventing major adverse cardiovascular events in patients with hypertension is unclear	- from June 2016 through October 2021, a total of 72 VA health care systems (which encompassed 537 locations) were enlisted in the trial	selection bias: low (subgroup analysis of the primary outcome showed a qualitative interaction between	als Handsuche aus der Konsultationsphase;

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Med. 2022 Dec 29;387(26):2401-2410. doi: 10.1056/NEJMoa2212270 . Epub 2022 Dec 14. https://pubmed.ncbi.nlm.nih.gov/36516076/ [205]	**Design** - pragmatic trial - point-of-care approach - randomly assignement - open label - intention-to-treat analysis* - planned interim analysis of the primary hypothesis was performed after 500 primary-outcome events - adjusted secondary analyses were also performed - ClinicalTrials.gov number, NCT02185417 **Inclusion and exclusion criteria** - adults ≥65 years of age - had hypertension: ○ a systolic blood pressure of at least 120 mm Hg at their most recent clinical visit - were patients in the Department of Veterans Affairs health system - receiving hydrochlorothiazide at a daily dose of 25 or 50 mg **Intervention** switch to chlorthalidone at a daily dose of 12.5 or 25 mg **Control** continue therapy with hydrochlorothiazide **Outcome**	- n=13,523 underwent randomization ○ n=6756 assigned to the chlorthalidone group and n= 6767 to the hydrochlorothiazide group ○ n=12 patients withrew informed consent in the chlorthalidone group and n=7 patients in the hydrochlorothiazide group ○ n=1039 patients (15.4%) assigned to chlorthalidone were switched back to ▪ hydrochlorothiazide; n=260 patients (3.8%) assigned to continue treatment ▪ with hydrochlorothiazide were switched to chlorthalidone - mean age of the patients was 72 years - 97%, n=13,092 were men - 15%, n=2027 were Black - 10.8%, n=1455 had a history of stroke or myocardial infarction - 45%, n=6122 resided in rural areas - at baseline, n=12,781 patients (94.5%) received a prescription for hydrochlorothiazide at a daily ▪ dose of 25 mg - mean number of medications that patients were receiving for blood-pressure control was 2.6 - at baseline at baseline mean systolic blood pressure was 139 mm Hg **Results** (Table 2 within the publication) primary - median follow-up of 2.4 years: primary composite outcome event had occurred in 1377 patients: n=702 (10.4%) chlorthalidone	treatment assignment and a history at baseline of myocardial infarction or stroke) performance bias: high (open-label design) detection bias: high attrition bias: low reporting bias: low anderen Ursachen für Bias / Kommentare - the trial was stopped, because the target number of total events occurred before 3 years had elapsed; thus, only a subset of follow-up data were available at the time of publication - funded by the Veterans Affairs Cooperative Studies Program (pragmatic trial was carried out within the framework of the VA point-of-care program; the score on the basis of eight PRECIS-2 (Pragmatic–Explanatory Continuum Indicator Summary) criteria (with each criterion scored on a scale from 1 to 5, with higher scores indicating greater pragmatism) was 37 out of 40 (Fig. S3 (*S2?*)).[16] supplement Figure S2. DCP PRECIS-2 Figure and Scoring Domain Score Rationale **Eligibility**	nach Diskussion in der Leitliniengruppe redaktionelle Ergänzung im Hintergrundtext: kurze Textergänzung; ergänzende Literatur; im HGT als Handsuche auf S. 56 3. Absatz mit aufnehmen (Extraktion + Bewertung in ET); Begründung: Aktualität, große Kohorte (mit der Einschränkung des Alters, ≥65 Jahre) - in Tabelle 13 "Thiazidartige Diuretika oder Thiazide" empfohlen; https://pubmed.ncbi.nlm.nih.gov/36516076/ Zusatzinformation aus der Publikation: “In 2020, Part D Medicare expenditures showed that approximately 1.5 million persons received prescriptions for chlorthalidone as compared with 11.5 million who received prescriptions for hydrochlorothiazide, despite

* authors calculated that 1055 primary-outcome events would provide the trial with 90% power to detect a 17.5% lower hazard for the primary outcome in the chlorthalidone group at a two-sided alpha level of 0.049, assuming a 3% annual incidence of the primary outcome in the hydrochlorothiazide group

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	primary: - first occurrence of a composite outcome consisting of a nonfatal ▪ cardiovascular disease event* or non–cancer-related death (time-to-event analysis) - safety secondary: - individual components of the primary outcome	group vs. n=675 (10.0%) hydrochlorothiazide group o hazard ratio, 1.04; 95% confidence interval [CI], 0.94 to 1.16; P = 0.45 secondary hazard ratio for - myocardial infarction 1.01 (95% CI, 0.80; 1.28); - stroke, 1.00 (95% CI, 0.74; 1.36); - hospitalization for heart failure, 1.04 (95% CI, 0.87; 1.25); - revascularization for unstable angina, 1.54 (95% CI, 0.77; 3.10); - non–cancerrelated death, 1.01 (95% CI, 0.88; 1.17) - n=446 patients (6.6%) in the chlorthalidone group and n=448 (6.6%) in the hydrochlorothiazide group died from any cause o hazard ratio, 1.00; 95% CI, 0.87; 1.13) - there was no difference between the groups in the adjusted analysis - the incidence of hypokalemia was higher in the chlorthalidone group than in the hydrochlorothiazide group (6.0% vs. 4.4%, P<0.001) authors conclusions - study with thiazide diuretics at doses commonly used in clinical practice - patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non-cancer-related deaths than patients who received hydrochlorothiazide	5 Only exclusion criteria are related to drug of interest and disease being studied **Recruitment** 4 Not recruited through normal appointments, but don't have additional appointments to consent and randomize; phone and mail process **Setting** 5 Done in typical primary care environment **Organization** 4 Study nurses must check eligibility and assign drug, but PCPs sign the drug order, and the drug is delivered by the normal pharmacy; not research med **Flexibility: delivery** 5 Drug delivered through normal pharmacy mechanism and physicians can modify per usual care **Follow-up** 5 No protocolized follow-up; any labs, visits or tests are per PCP usual care routine **Primary outcome** 4 Reduction in serious cardiovascular events is relatable to patients, though the small, expected effect size may not resonate **Primary analysis** 5 All randomized are included; ITT practices followed **TOTAL 37**)	guidelines that recommended chlorthalidone as the preferred agent." aim of the Diuretic Comparison Project was developed to provide a real-world assessment of the effectiveness of chlorthalidone as compared with hydrochlorothiazide in routine clinical care

* nonfatal cardiovascular disease events were nonfatal myocardial infarction, stroke, hospitalization for heart failure, or urgent coronary revascularization for unstable angina

Webster 2018 (Low-dose triple therapy (hypertension))

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar

Webster et al. Fixed Low-Dose Triple Combination Antihypertensive Medication vs Usual Care for Blood Pressure Control in Patients With Mild to Moderate Hypertension in Sri Lanka: A Randomized Clinical Trial. JAMA. 2018 Aug 14;320(6):566-579. doi: 10.1001/jama.2018.10359. https://pubmed.ncbi.nlm.nih.gov/30120478/
 	
Protocol (2014): https://pubmed.ncbi.nlm.nih.gov/24439972/
Amendment (2017): https://pubmed.ncbi.nlm.nih.gov/28888276/
	2018	selection bias: low;
		performance bias: high (open-label design);
		detection bias: high;
		attrition bias: high (incomplete follow-up, missing data);
		reporting bias low
			Objective
			to assess whether a low-dose triple combination antihypertensive medication would achieve better blood pressure (BP) control vs usual care
			Design
			randomized, open-label trial
			enrolled from February 2016 to May 2017;
			follow-up ended in October 2017
			11 urban hospital clinics in Sri Lanka
			(Triple Pill vs. Usual Care Management for Patients
			With Mild-to-Moderate Hypertension (TRIUMPH) pragmatic trial)
			ACTRN12612001120864
			note: medical management of all patients occurred at hypertension clinics
			Inclusion and exclusion criteria
			- adults with hypertension (≥18 years)
			  ○ systolic BP >140mmHg and/or diastolic BP >90mmHg
			  ○ or in patients with diabetes or chronic kidney disease: >130mmHg and/or >80mmHg
			- requiring initiation (untreated patients) or escalation (patients receiving monotherapy) of antihypertensive therapy
			- patients were excluded e.g. with:
			  - current use of 2 or more blood pressure–lowering drugs
			  - severe or uncontrolled blood pressure (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg)
			Intervention
				n=700 patients randomized: n(I)=349; n(C)=351
				- mean age 56 years
				- 58% women
				- 29% had diabetes
				- mean baseline systolic/diastolic BP, 154/90mmHg
				- n=675 (96%) completed the trial
				
				results:
				primary proportion achieving target systolic/ diastolic BP at 6 months
				triple combination pill vs. usual care
				- 70% vs 55%
				- risk difference 12.7% (95%CI 3.2%-22.0%); P < .001
				
				secondary
				- mean systolic/diastolic BP difference
				- mean systolic/diastolic BP at 6 months:
				  ○ 125/76mmHg for the triple combination pill vs. 134/81mmHg for usual care
				- adjusted difference:
				  ○ systolic BP, −9.8 [95%CI, −7.9 to −11.6]mmHg
				  ○ diastolic BP, −5.0 [95%CI, −3.9 to−6.1] mmHg; P < .001 for both comparisons
				- withdrawal of BP medications due to adverse events
				- n=419 adverse events reported in n=255 patients
				  ○ 38.1% for triple combination pill vs 34.8% for usual care
				  ○ most common musculoskeletal pain (6.0%and 8.0%, respectively) and dizziness, presyncope, or syncope (5.2%and 2.8%)
				  ○ no significant between-group differences in the proportion of patient withdrawal from BP-lowering therapy due to adverse events (6.6% for triple combination pill vs 6.8%for usual care)
					limitation of open label designs relates to the potential for differences in study related procedures
					
					intervention varied (footnote)
					
					during follow-up, there were increases in the prescription of antiplatelet drugs and statins in both groups
					
					medications in this study for both groups were provided free of charge
					
					exclusion criteria were primarily left to the judgment of investigators, which may have led to the underrepresentation of certain patient subgroups such as those with chronic kidney disease

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
			low-dose triple blood pressure (BP) therapy* (once daily)† **Control** usual care **Outcome** **primary** proportion achieving target systolic/ diastolic BP (<140/90mmHg or <130/80mmHg in patients with diabetes or chronic kidney disease) at 6 months‡ **secondary** - mean systolic/diastolic BP difference - withdrawal of BP medications due to adverse events		

Wilke 2022 / single pill combination vs. multi pill therapy (hypertension, dyslipidemia, secondary cardiovascular prevention)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
Wilke et al. Effects of Single Pill Combinations Compared to Identical Multi Pill Therapy on Outcomes in Hypertension, Dyslipidemia and Secondary Cardiovascular Prevention: The START§-Study. Integr Blood Press Control. 2022 Feb 27;15:11-21. doi: 10.2147/IBPC.S336324. eCollection 2022.	**Objective** to assess whether the single pill combination (SPC) concept is clinically superior to multi pill combination (MPC) with identical drugs **Study design/source** explorative study, observational longitudinal design (retrospective) (anonymized claims data sets)	- after propensity score matching, data from n=59,336 patients were analysed o n=29.668 per group - combination: o bisoprolol/amlodipine n=317 per group after matching o valsartan/amlodipine n=10,801 per group o candesartan/amlodipine n=1,026 per group o valsartan/amlodipine/hydrochlorothiazide n=1,823 per group o ramipril/amlodipine n=15,349 per group	new user design (combination) propensity score matching possibility of residual confounding remains a limitation, as well as channelling bias and unmeasured confounding (e.g. adherence)	information on indications for prescribing was not available; at least a diagnosis of hypertension (BIS/AMLO, VAL/AMLO, CAR/AMLO, VAL/AMLO/HCTZ, RAMI/AMLO) and at least one event as MI or HF or TIA or stroke or embolism or peripheral artery

* Low Dose: Telmisartan 20mg, Amlodipine 2.5mg, Chlorthalidone 12.5mg; High Dose: Telmisartan 40mg, Amlodipine 5mg, Chlorthalidone 25mg
† During follow-up, the triple combination pill therapy could be discontinued, maintained, or uptitrated at the discretion of the treating physician. A higher-dose version of the triple combination pill therapy, which contained a standard dose of telmisartan (40 mg), amlodipine (5 mg), and chlorthalidone (25mg), was available for titration.
In addition, another blood pressure–lowering therapy could be prescribed in combination with either dose of the triple combination pill.
‡ usual blood pressure management provided by the responsible clinician according to current guidelines for a total period of 6 months
§ effect of SPCs on Treatment Adherence and persistence as well as on clinical and pharmacoeconomic outcomes in the Real-world Treatment of hypertension, CHD, hyperlipidemia and in secondary prevention of CV events - START

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
https://pubmed.ncbi.nlm.nih.gov/35250308/	(insured by the German AOK PLUS statutory health fund covering 01/07/2012-30/06/2018)* hypothesis: superiority or equality **Inclusion and exclusion criteria** - patients suffering from CV disease (ICD for hypertension, CHD, hyperlipidemia, myocardial infarction (MI), HF, stroke, transient ischemic attack (TIA), CHD or peripheral artery disease) - continuously insured (07/2012–06/2018) - aged ≥18 years - at least one inpatient or two outpatient claims (in two different quarters) - treated with a combination as SPC or identical MPC† - follow-up to one year - patient groups who started identical drug combinations **Investigation** patients received either a SPC or MPC with identical drugs	○ ezetimibe/atorvastatin n=141 per group ○ ASA/atorvastatin/ramipril n=211 ■ *note*: number of patients before matching was lower in SPC compared with MPC (overall: n(SPC)=52,517 vs. n(MPC)=142,720), overall ramipril/amlodipine; bisoprolol/amlodipine and valsartan/amlodipine were the most common combinations followed by valsartan/amlodipine/hydrochlorothiazide - mean age (after PSM): 64-71 years - female (after PSM): 29-58% - mean Charlson Comorbidities Index (CCI) (after PSM): 2-4 - mean CHA2-DS2-VASc score: 3-4 - mean number prescribed agents: 4-7 **Main results for combination with diuretics:** VAL/AMLO/HCTZ - n=1,823 per group (SPC vs. MPC) MI IRR (95%-CI) p-value 0.739 (0.395–1.428) p=0.322 Coronary Artery Disease IRR (95%-CI) p-value 0.314 (0.183–0.532) p≤0.001 HF IRR (95%-CI) p-value 0.432 (0.322–0.579) p≤0.001 Stroke IRR (95%-CI) p-value 0.538 (0.338–0.862) p=0.007	to address issue of confounding, two additional analyses were conducted: an analysis of number of events in a Poisson regression and a multivariable Cox regression analysis both based on the unmatched SPC/MPC samples within above cohorts they only had access to claims-based proxies to identify the outcomes of interest (outcomes not assessed within clinical study design) – ICD – to address weaknesses, multiple outcomes were observed funding: APONTIS PHARMA GmbH & Co. KG	disease (ASA/ATOR/RAMI) or dyslipidemia (EZE/ATOR) were required for patient inclusion in sub-cohorts confirmed by ICD introduction: non-adherence to medical therapy was noted for multiple combinations – authors noted, follow-up periods were significantly different between SPC and MPC regimens **mainly due to the higher persistence of SPC patients with their treatment** limitation: only specific combination therapies were addressed

* data set: information on socio-demographic characteristics of patients, inpatient and outpatient care as well as all documented diagnoses, prescriptions of medications, and other data such as prescriptions of outpatient aids and devices
† sub-cohorts according to specific drug treatment profile: bisoprolol/amlodipine (BIS/AMLO), valsartan/amlodipine (VAL/AMLO), candesartan/amlodipine (CAR/AMLO), valsartan/amlodipine/hydrochlorothiazide (VAL/AMLO/HCTZ), ramipril/amlodipine (RAMI/AMLO), ezetimibe/atorvastatin (EZE/ATOR), acetylsalicylic acid / atorvastatin/ramipril (ASA/ATOR/RAMI) – multiple assignments of patients to groups were possible

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
	one to one propensity score matching (PSM)* **Outcomes** cardiovascular (CV) outcomes mortality - incidence rate ratio (IRR), based on number of events per observed 100 patient years - unadjusted hazard ratio (HR) – unadjusted Cox regression - percentage of event-free patients – Kaplan-Meier (log rank test)	Transient Ischemic Attack IRR (95%-CI) p-value 0.179 (0.057–0.497) p≤0.001 All Cause Mortality IRR (95%-CI) p-value 0.515 (0.375–0.709) p≤0.001 CV Hospitalization IRR (95%-CI) p-value 0.450 (0.328–0.620) p≤0.001 All Cause Hospitalization (per 100 patient years, IRR) n=157,406 per 100 patient years vs. 83,006 per 100 patient years IRR 0.527 (0.494-0.563) p<0.001 HR for the composite outcome of all-cause death and all-cause hospitalizations (SPC vs. MPC) HR=0.68 (95% CI: 0.61–0.74, p ≤ 0.001) authors concluded that SPC regimens are associated with a lower incidence of cardiovascular events and lower all-cause mortality in clinical practice (prognosis)		

Williams 2015 / RCT / spironolactone vs. placebo (PATHWAY-2) s.a. 0 NICE

Zitat	Jahr	RoB	Charakteristika	Ergebnisse	Kommentar
Williams et al. [206] https://pubmed.ncbi.nlm.nih.gov/26414968/	2015	selection bias **low** performance bias **low**	**Objective** to determine optimal treatment for drug-resistant hypertension (fourth-line treatment added to standard triple drug therapy*) **Design**	- between May 2009 and July 2014 n=335 patients were randomized - mean age 61.4 years - baseline blood pressure (systolic/diastolic) home 147.6/84.2 mm Hg; clinic 157.0/90.0 mm Hg - baseline eGFR=estimated glomerular filtration rate 91.1 mL/min	Diskussionsgrundlage in NICE [117] - unterstützend betrachtet

* PSM analysis: separately matched, propensity scores were calculated using logistic regression (group affiliation as dependent variable) including age, gender, and Charlson Comorbidity Index (CCI) without age factor as fixed independent variables (29 different variables, plausible as predictors of CV outcomes) were included as independent variables (supplement Table 1 (Word)) - backward elimination approach – PSM quality was assessed

Zitat	Jahr	RoB	Charakteristika	Ergebnisse	Kommentar
protocol https://bmjopen.bmj.com/content/bmjopen/5/8/e008951.full.pdf		detection bias **low** attrition bias **low** reporting bias **low** other bias -	double-blind, placebo-controlled, crossover trial, (PATHWAY-2); initiated May 2009; NCT02369081 **Population** patients from 12 secondary care and 2 primary care sites in the UK **Inclusion/exclusion criteria** - patients with hypertension (not controlled to target) - seated clinic systolic blood pressure ≥140 mm Hg (or ≥135 mm Hg for patients with diabetes) and home systolic blood pressure (18 readings over 4 days) ≥ 130 mm Hg - aged 18–79 years - despite treatment for at least 3 months with maximally tolerated doses of three drugs* - additional drugs were possible - patients e.g. with secondary or accelerated hypertension were excluded, as well as patients with eGFR<45 mls/min **Investigation** - 4 weeks single-blind placebo run-in, - thereafter patients rotated through four cycles† of once daily oral treatment with: ▪ (1) spironolactone 25–50 mg, ▪ (2) doxazosin modified release 4–8 mg, ▪ (3) bisoprolol 5–10 mg, and ▪ (4) placebo. - the treatment cycles were initiated for 6 weeks at the lower dose, followed by forced titration to twice this dose for a further 6 weeks (total of 12 weeks) - no washout period - duration 12 months	- n=21 patients had no follow-up for any drug (and were excluded from ITT) - n=314 patients were analysed as ITT with complete follow-up o n=282 doxazosin, o n=285 bisoprolol, o n=285 spironolacton, o n=274 placebo - 230 patients completed all treatment cycles **Outcomes** hierarchical primary endpoints: home systolic blood pressure throughout the treatment cycle (Table 2 within the publication) - (1) with spironolactone vs. placebo: ▪ –8.70 mm Hg [95% CI –9.72 to –7.69]; p<0.0001 - (2) with doxazosin and bisoprolol: ▪ –4.26 [–5.13 to 3.38]; p<0.0001 - (3) with doxazosin: ▪ –4.03 [–5.04 to 3.02]; p<0.0001 - with bisoprolol: ▪ –4.48 [–5.50 to –3.46]; p<0.0001 secondary objectives - (1) clinic blood pressure responses to randomised treatments Table S5 supplement: mean differences o spironolactone vs. placebo: ▪ -9.92 (-11.3,-8.59), p<0.001 o spironolactone vs. mean bisoprolol/doxazosin	(note: “A pill count will be made at the end of the 4 week run-in period and those with adherence <70% will be excluded from randomisation”)

* ACE inhibitor or ARB, CCB, and diuretic
† 12-week treatment cycles with add-on α-blocker (doxazosin), β-blocker (bisoprolol), spironolactone and placebo

Zitat	Jahr	RoB	Charakteristika	Ergebnisse	Kommentar
			Outcomes hierarchical primary endpoints: (1) difference in the home systolic blood pressure between spironolactone and placebo - ok, sign. (2) difference in home systolic blood pressure between spironolactone and the average of the other two active drugs, (doxazosin and bisoprolol) - ok, sign. (3) difference in home systolic blood pressure between spironolactone and each of the other two active drugs - ok, sign. secondary objectives (1) clinic blood pressure responses to randomised treatments (2) blood pressure control rates—ie, home systolic blood pressure less than 135 mm Hg (3) whether plasma renin concentrations and other baseline characteristics could help personalise treatment by predicting the best drug treatment (4) adverse event rates during each treatment cycle	▪ -4.44 (-5.59,-3.28), p<0.001 o spironolactone vs. doxazosin ▪ -4.42 (-5.75,-3.09), p<0.001 o spironolactone vs. bisoprolol ▪ -4.45 (-5.80,-3.11), p<0·001 - (2) blood pressure control rates ▪ n= 219 (68.9% [95% CI 63.6–73.8]) of n=314 patients achieved target home systolic blood pressure of less than 135 mm Hg - (3) whether plasma renin concentrations and other baseline characteristics could help personalise treatment by predicting the best drug treatment (Figure 3 within the publication) o "There was a clear inverse relation between the home systolic blood pressure fall with spironolactone and plasma renin, not seen with bisoprolol or doxazosin." - (4) adverse events (that occurred in at least 5% of patients) Table S8 supplement: ▪ most common: o doxazosin: muscle spasm (n=20, 6.6%), dizziness (n=36, 6.0%) o bisoprolol: dizziness (n=72, 12.2%), fatigue (n=18, 6.1%) o spironolactone: fatigue (n=22, 7.4%), bradycardia (n=19, 6.4%), dizziness (n=36, 6.1%) o placebo: dizziness (n=26, 4.5%), fatigue (n=9, 3.1%)	

9 Evidenztabellen Medikamentöse Therapie - Kinderwunsch

9.1 S2k Leitlinie Hypertensive Schwangerschaftserkrankungen (2019)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Hypertensive Schwanger-	2019	Methodik nach der Stufenklassifikation des AWMF-Regelwerks (Version 1.0)	**2019:** - hypertensive Erkrankungen in der Schwangerschaft: 6 – 8 % aller Schwangerschaften	Stand: 01.05.2019; gültig bis gültig bis 30.04.2022	entfällt

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
schaftserkrankungen: Diagnostik und Therapie (015 – 018) https://www.awmf.org/leitlinien/detail/ll/015-018.html [207]		die Leitlinie entspricht der Stufe: S2k (konsensbasiert)	- tragen zu 20 – 25 % der perinatalen Mortalität bei - in Europa an führender Stelle der mütterlichen Todesursachen - Präeklampsie von besonderer Bedeutung - das Management dieser Schwangerschaftspathologie sollte so weit als möglich evidenzbasiert, interdisziplinär und in einer Klinik der richtigen Versorgungsstufe erfolgen Medikamentöse Therapie - moderater Blutdruckanstieg allein scheint einen geringen Effekt für den Ausgang der Schwangerschaft zu haben - hohe Blutdruckwerte sind jedoch oft mit maternalen Komplikationen und ungünstigem fetalem	(in Überarbeitung*, geplante Fertigstellung 31.12.2022 https://www.awmf.org/leitlinien/detail/anmeldung/1/ll/015-018.html) Thema in der NVL Hypertonie: Frauen mit Hypertonie und Kinderwunsch; Verweismöglichkeiten auf weiterführende Quellen	

* Überarbeitung der bisherigen: Definition, Diagnostik und Entscheidungshilfe im klinischen Management; Verbesserung der Diagnostik und der Therapie der hypertensiven Schwangerschaftserkrankungen; Verbesserung der Nachsorge / Nachbetreuung (interdisziplinär)
Anmelder bei der AWMF (Person): Prof. Dr. med. M.W. Beckmann, DGGG-Leitlinienbeauftragter
Anmeldende Fachgesellschaft(en):
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG)
Beteiligung weiterer AWMF-Gesellschaften:
Deutsche Gesellschaft für Perinatale Medizin e.V. (DGPM)
Deutsche Gesellschaft für Ultraschall in der Medizin e.V. (DEGUM)
Deutsche Gesellschaft für Hypertonie und Prävention - Deutsche Hochdruckliga e.V. (DHL)
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V. (DGAI)
Gesellschaft für Neonatologie und pädiatrische Intensivmedizin e.V. (GNPI)
Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V. (DGKL)
Deutsche Gesellschaft für Nephrologie e.V. (DGfN)
Beteiligung weiterer Fachgesellschaften/Organisationen:
Arbeitsgemeinschaft Geburtshilfe und Pränatalmedizin – Sektion Hypertensive Schwangerschaftserkrankungen und fetale Wachstumsrestriktion
Berufsverband der Frauenärzte e.V. (BVF)
Deutsche Gesellschaft für Pränatal- und Geburtsmedizin e.V. (DGPGM)
Deutscher Hebammenverband (DHV)
Österreichische Gesellschaft für Gynäkologie und Geburtshilfe e. V. (OEGGG)
Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG)
Österreichische Gesellschaft für Anästhesiologie, Reanimaion und Intensivmedizin (ÖGARI)
Schweizerische Gesellschaft für Anästhesiologie und Perioperative Medizin (SSAPM)
European Foundation for the Care of Newborn Infants (EFCNI)
Leitliniensekretariat: DGGG-Leitliniensekretariat, Frauenklinik Universitätsklinikum Erlangen, Universitätsstr. 21-23, 91054 Erlangen, Tel.: 09131 85 44063 oder 44060
Koordination: PD Dr. med. Dietmar Schlembach, Vivantes Klinikum Neukölln, Klinik für Geburtsmedizin, Rudower Strasse 48, 12351 Berlin, Prof. Dr. med. Ulrich Pecks, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Klinik für Gynäkologie und Geburtshilfe, Arnold-Heller-Straße 3 (Haus C), 24105 Kiel

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			Outcome assoziiert - antihypertensive Behandlung dient bei schwerer Hypertonie der Prävention maternaler zerebro- / kardiovaskulärer Komplikationen - Vermeidung zerebraler Blutungen steht im Vordergrund - zur wirksamen Eklampsie-Prophylaxe ist zusätzliche Gabe von Magnesium i.v. erforderlich - Nutzen für die fetale Entwicklung und somit eine Verbesserung der kindlichen Prognose durch eine medikamentöse Blutdrucksenkung konnte bisher nicht nachgewiesen werden **Milde bis moderate Hypertonie (Blutdruck 140 -159/90-109 mm Hg)** - Unterscheidung in der Geburtshilfe zwischen milder / moderater Hypertonie (Blutdruckwerte 140-159/90-109 mm Hg) und schwerer Hypertonie (≥160/110 mm Hg) - derzeit weltweit kein Konsens, ob Schwangere mit milder bis moderater Hypertonie antihypertensiv behandelt werden soll - meist nur geringe Risiken für kardiovaskuläre Komplikationen - durch eine antihypertensive Therapie werden Episoden von schweren Hypertonien reduziert - medizinische Evidenz für eine antihypertensive Therapie bei milder bis moderater Hypertonie als unzureichend bewertet Empfehlungen für die medikamentöse Therapie: - Blutdruckwerte von ≥ 150-160/100-110 mm Hg sollen medikamentös therapiert werden - Ziel: Reduktion der maternalen Komplikationen, für die der systolische Blutdruck als bester Prädiktor gilt - bei Blutdruckwerten ≥160/110 mm Hg Therapie unter stationären Bedingungen - diastolischer Blutdruck von 80 mm Hg sollte nicht unterschritten werden - Zielblutdruckwerte zwischen 130-150 mm Hg systolisch und 80-100 mm Hg diastolisch - „Frauen mit Kinderwunsch und chronischer Hypertonie sollen mit Medikamenten behandelt		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			werden, die mit einer Schwangerschaft vereinbar sind.“ - **geeignet:** o Alpha-Methyldopa 250 – 500 mg oral (2 - 4x/d) / max. 2 g/d Mittel der 1. Wahl o Labetalol (Österreich, Schweiz) Startdosis 3x200 mg/d max. 4x300 mg/d o Nifedipin retard 20 – 60 mg ret. oral max. 120 mg/d - eingeschränkt geeignet: o selektive ß-1-Rezeptor-blocker (Metoprolol Mittel der Wahl) Dosis 25 - 100 mg (2x tgl.) - nicht geeignet: o Diuretika o ACE-Hemmer o Angiotensin AT1-Antagonisten o Alle anderen Antihypertensiva - zur initialen Behandlung der **schweren Hypertonie in der Schwangerschaft** stehen in Deutschland Urapidil, Nifedipin und Dihydralazin zur Verfügung.[146,158] In Österreich und der Schweiz steht Labetalol i.v. als Akutmedikation zusätzlich zu Verfügung.		

9.2 NICE Evidence Reviews

ER interventions for chronic hypertension in pregnancy (2019)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Hypertension in pregnancy [A] Evidence review for interventions for chronic hypertension NICE guideline NG133 June 2019 https://www.nice.	2019	**Review question** What interventions for chronic hypertension are effective at improving outcomes for women and infants? **Sources** Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase **Inclusion and exclusion criteria**	n=18 articles from 15 randomised controlled trials (RCTs) and 2 individual participant data (IPD) meta-analyses (n=5377) (Askie 2007, Atallah 1996, Butters 1990, Cockburn 1982, Hamed 2014, Kasawara 2013, Magee 2015, Moore 1982, Moore 2015, Parazzini 1993, Poon 2017, Redman 1976, Sibai 1990, van Vliet 2017, Vigil-de Gracia 2014, Viinikka 1993, Webster 2017, Weitz 1987)	note: [209–212] Quality standard www.nice.org.uk/guidance/qs3 Last updated: 23 July 2019 NICE guideline Published: 25 June 2019 www.nice.org.uk/guidance/ng133 /	AMSTAR-II Rating: moderate

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität

org.uk/guidance/ng133/evidence/a-interventions-for-chronic-hypertension-pdf-6836186126 [208]		- published full text papers in English language
		- Systematic reviews of RCTs
		- RCTs
		- comparative cohort studies (only if RCTs unavailable or limited data to inform decision making)
		- pregnant women with chronic hypertension. (essential (primary) hypertension, secondary hypertension e.g. secondary to chronic kidney disease, diabetes)
		Quality assessment
		GRADE
		Intervention
		- centrally acting α2-Adrenoceptor Agonists
		- Beta blockers/mixed alpha beta blockers
		- Calcium (Ca2+) channel blockers
		- Diuretics
		- ACE inhibitors
		- Acetylsalicylic acid (aspirin)
		- Elective (planned) delivery versus expectant management
		- Tight management (e.g. target = 85mmHg)
		- Less tight management (e.g. target = 100 mmHg)
		- Automated monitoring of blood pressure (BP)
		- Ambulatory/self-monitoring of blood pressure
		- Exercise
		- Dietary interventions
		- Dietary salt reduction
		Control
		- No intervention
		- Placebo
		- Each other of the interventions outlined above
		- Combinations of the interventions outlined above
		Outcomes
		Outcomes for babies:
			committee's discussion of the evidence
			outcomes that matter most
			- aims of treatment: to control the mother's blood pressure without leading to any adverse effects on the baby
			- 3 critical outcomes were identified:
			  ○ control of blood pressure (outcome for women)
			  ○ perinatal mortality (including stillbirth and neonatal death)
			  ○ small for gestational age (both outcomes for babies)
			- additionally, 7 important outcomes for babies were classified to provide further information on the potential harms to babies
			  ○ birth weight, gestational age at birth, preterm birth (< 28 weeks, <34 weeks, <37 weeks), admission to a neonatal unit, cerebral palsy, neurodevelopmental delay, and neurosensory impairment
			- 6 further important outcomes for women with chronic hypertension were identified:
			  ○ superimposed pre-eclampsia, HELLP, placental abruption, onset of labour, mode of birth, and maternal death
			quality of the evidence
			n=18 articles were included
			- quality of the evidence:
			- Cochrane Risk of Bias tool (ranged from moderate to very low)
			- main sources of potential bias:
			  ○ lack of information on the randomisation method used,
			  ○ unreported or unclear concealment of allocation,
			  ○ lack of blinding of participants and investigators
			- the committee determined that there was sufficient evidence to allow them to make some recommendations relating to treatment initiation thresholds and treatment targets, but not
				https://pathways.nice.org.uk/pathways/hypertension-in-pregnancy	

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
		Critical outcomes: - Perinatal mortality o Stillbirth (include if reported as part of perinatal mortality) o Neonatal death up to 7 days (include if reported as part of perinatal mortality) - Small-for-gestational-age (BW<10th centile) Important outcomes: - Birth weight - Gestational age at delivery - Preterm birth (<28 weeks, <34 weeks, <37 weeks) - Admission to neonatal unit - Neurodevelopmental outcome o Cerebral palsy (dichotomous outcome, reported as present/absent, not severity of condition) o Neurodevelopmental delay (dichotomous outcome, not continuous outcomes such as mean change in score): - Severe (score of >2SD below normal on validated assessment scales, or Bayley's assessment scale of mental development index [MDI] or psychomotor developmental index [PDI] <70, or complete inability to assign score due to CP or severe cognitive delay) - Moderate (Score of 1-2 SD below normal on validated assessment scales, or Bayley's assessment scale MDI or PDI 70-84) o Neurosensory impairment (dichotomous outcome, present or absent, not severity of condition) - Severe hearing impairment (e.g. deaf) - Severe visual impairment	enough evidence to discriminate between different pharmacologic treatments (research recommendation) - there was also concern (based on the committee's clinical knowledge and expertise) over the potential neonatal adverse outcomes with the use of beta-blockers in women with hypertension (research recommendation) ***benefits and harms*** - the committee agreed that the principles of treatment and advice (suchas exercise and healthy diet) are similar for adults with hypertension and pregnant women with hypertension - the treatment threshold had been a diastolic blood pressure of ≥90mmHg (CHIPS study, Magee 2015), - treatment thereshold for systolic blood pressure of ≥140mmHg (NICE: hypertension in adults) - target blood pressure of ≤85mmHg diastolic (CHIPS) and of ≤135mmHg systolic (NICE hypertension in adults) - clinicians continuing existing treatment or initiating treatments should inform women of these risks and benefits - there was evidence for beneficial effects on the mother's blood pressure with tight blood pressure control - some evidence for a reduction in stillbirths and increased gestational age at birth with some of the pharmacologic interventions - some evidence for harm with interventions – a possible increase in small-for-gestational age babies with tight blood pressure control and atenolol – based on their clinical expertise as		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
		(e.g. blind) Outcomes for women: Critical outcome: - Blood pressure control o Severe hypertension Important outcomes: - Superimposed pre-eclampsia o including eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets) o Placental abruption o Onset of labour o Mode of birth o Maternal death NICE reviewed in 2019 the evidence in the following areas and made recommendations (labelled [2019]): A. Interventions for chronic hypertension B. Monitoring gestational hypertension C. Prediction of complications in pre-eclampsia D. Interventions for pre-eclampsia E. Postnatal management of hypertension F. Advice at discharge G. Assessment of proteinuria	well, agreed that treatment with antihypertensive medication should be continued or initiated in pregnant women with chronic hypertension, in order to reduce the risk of serious complications such as severe hypertension, placental abruption or preterm birth - available evidence not sufficient to recommend one antihypertensive medicine over another (labetalol, nifedipine and methyldopa) - committee discussed the fact that labetalol was specifically licensed in pregnancy (after the 1st trimester) whereas other treatments are not, but that all three medicines had been used in pregnant women for many years with no reports of major adverse effects - recommend labetaolol as the first-line choice due to its licensed status, with nifedipine or methylodopa as alternative treatment options - recently updated Cochrane systematic review and meta-analysis on antihypertensive treatment in pregnancy, which indicated that beta-blockers and calcium channel blockers were more effective than methyldopa at preventing severe hypertension - **→ it would be appropriate to recommend methyldopa as the third-line option, after labetalol and nifedipine, based on the findings of the Cochrane review and their experience of the side-effect profile of methyldopa**		

9.3 AHRQ Evidence Report

ER chronic hypertension during pregnancy (2000)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Management of	2000	**Review question**	**main results**	(August 2000; Suche	AMSTAR-II Rating: low (note:

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
chronic Hypertension During Pregnancy: https://archive.ahrq.gov/clinic/tp/pregtp.htm		- evidence report addresses several questions related to management of chronic hypertension - e.g. risks and benefits of antihypertensive agents before and during pregnancy **Sources** 16 electronic databases, references of pertinent articles and reviews (from 1947 or from their inception to February 1999) **Inclusion and exclusion criteria** - English and non-English research literature - Four general search strategies: (1) efficacy, (2) harms, (3) blood pressure risks, and (4) monitoring techniques - for the question regarding harm associated with antihypertensive therapy, we selected case reports, case-control and cohort studies, randomized trials, and surveillance studies that reported adverse maternal and/or fetal outcomes - to estimate the magnitude of risk associated with chronic hypertension, we examined case-control and cohort studies that compared maternal and fetal outcomes in women with chronic hypertension compared with those in either a general obstetrical population or pregnant women without chronic hypertension note: because of concerns about heterogeneity in study populations and interventions, quantitative methods were not used to combine trial results.	Benefits of treating chronic hypertension before conception: - There was no evidence that addressed the effect of blood pressure control before conception on fetal outcomes. - With regard to maternal outcomes, evidence from randomized trials involving nonpregnant women 30 to 54 years of age showed that approximately 250 (95 percent confidence interval 158 to 1,606) such women with mild to moderate hypertension need to be treated for 5 years to prevent one cardiovascular event such as stroke or myocardial infarction. Much larger numbers of women younger than age 30 (approximately 8,000) would need to be treated for 1 year to prevent a cardiovascular event. Benefit of treating chronic hypertension during pregnancy: - There was insufficient evidence to prove or disprove moderate to large clinical effects of antihypertensive agents on perinatal outcomes. Adverse effects of antihypertensive drugs. - The quality of evidence addressing this question was poor. - The best-established adverse effect of antihypertensive agents in pregnancy was renal failure associated with use of the angiotensin-converting enzyme inhibitors. There was evidence suggesting that atenolol used early in pregnancy may be associated with small-for-gestational-age fetuses. **Authors conclusions:** - despite the burden of illness and costs imposed by chronic hypertension in pregnancy, evidence to date remains scant and provides little direction for clinicians - epidemiological data demonstrate increased risks of perinatal morbidity and mortality in pregnant women with mild to moderate chronic hypertension	bis Feb 1999)	no meta-analysis)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			- treatment with antihypertensive agents has not been proven to lower those risks, though the evidence base is too small to rule out moderate to large effects on perinatal mortality, preeclampsia, and intrauterine growth retardation - data on adverse effects of drug treatment is scant; the data on angiotensin-converting enzyme inhibitors suggest that their adverse effects are substantially greater than for other drugs		

9.4 Embryotox

https://www.embryotox.de/erkrankungen/details/ansicht/erkrankung/hypertonie/ (z.g. 09.03.2022)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Embryotox (Online-Portal Hypertonie)	z.g. 09.03.2022	Hypertonie (Synonym bzw. assoziierte Erkrankungen: Bluthochdruck)	**Grundsätzliches:** - arterielle Hypertonie bei etwa jeder 10. Schwangeren - Hochdruckerkrankungen in der Schwangerschaft: ○ **Chronische Hypertonie (mit oder ohne Proteinurie), vor, während oder nach der Schwangerschaft diagnostiziert (ca. 3% aller Schwangerschaften)** ○ Präeklampsie, Eklampsie: Proteinurie (>300 mg/24h) und neu aufgetretene Hypertonie (fakultativ: Ödeme), (etwa 5-8% aller Schwangerschaften) ○ Pfropfgestose: Präeklampsie bei Schwangeren mit chronischer Hypertonie (bei etwa 20-25% der Schwangeren mit chronischer Hypertonie) ○ Schwangerschaftshochdruck: eine nach 20 Schwangerschaftswochen entstehende Hypertonie ohne Proteinurie, die sich spätestens 12 Wo-	Thema in der NVL Hypertonie: Frauen mit Hypertonie und Kinderwunsch; Verweismöglichkeiten auf weiterführende Quellen bzw. Beratungsangeboten	entfällt

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			chen nach der Entbindung zurückbildet (bei ca. 6% aller Schwangerschaften; bei 15%-45% zur Präeklampsie) Besonderheiten einer Therapie in der Schwangerschaft: - keine einheitlichen Empfehlungen für die Behandlung schwangerer Frauen mit Bluthochdruck o ab welchem Blutdruckwert soll therapiert werden o welche Medikation soll gewählt werden o insbesondere für die Behandlung einer Schwangeren mit vorbestehender Hypertonie - unbestritten: die Auswahl antihypertensiver Arzneimittel unterscheidet sich von einer Behandlung außerhalb der Schwangerschaft o Ursache u.a.: o Vermeidung potentieller Schädigung der Feten (bspw. durch ACE-Hemmstoffe und Sartane) o vs. Vermeidung von Komplikationen bei der Mutter durch eine antihypertensive Therapie für eine ungestörte fetale Entwicklung o zumeist sind randomisierte kontrollierte Studien mit großer Fallzahl und Exposition im 1. Trimenon nicht vorhanden/möglich - wichtig: o physiologische Blutdruckabfall in der ersten Schwangerschaftshälfte ist bei vorbestehender Hypertonie zu berücksichtigen o zu Beginn jeder parenteralen, aber auch oralen antihypertensiven Medikation kann eine abrupte Blutdrucksenkung auftreten - Blutdruckwert 140/90 mmHg gilt als Grenzwert für eine Hypertonie in der Schwangerschaft ■		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität

			- niedriges Risiko:
			  o Werte noch im Grenzbereich
			  o keine Auffälligkeiten in der körperlichen Untersuchung
			  o EKG und Echokardiogramm normal
			  o keine Proteinurie
			- ab einer Hypertonie von 150/100 mm Hg soll die Schwangere in der Klinik vorgestellt werden
			
			- größte Risiken für Mutter und Kind bei einer schweren Hypertonie und einer Präeklampsie (Hinweis: **nicht Bestandteil der NVL Hypertonie; Verweis möglich**)
			
			Therapiehinweise:
			- ACE-Hemmer und Angiotensin-II-Rezeptorantagonisten in der Schwangerschaft, insbesondere jedoch im 2. und 3. Trimenon kontraindiziert bzw. schweren nicht anders zu behandelnden Erkrankungen vorbenthalten
			- falls möglich sollten Diuretika ersetzt werden
			- Mittel der Wahl:
			  o Alpha-Methyldopa (ältestes Antihypertensivum mit Erfahrungen in der Schwangerschaft; gut verträglich; kaum Studien nach Exposition im 1. Trimenon)
			  o Metoprolol hinsichtlich der Anwendung im 1. Trimenon breiter untersucht, allerdings Diskussion eines erhöhten Risikos für fetale Wachstumsrestriktion)
			  o Nifedipin kann als Mittel der zweiten Wahl auch im 1. Trimenon eingesetzt werden
			  o zu Dihydralazin gibt es kaum dokumentierte Erfahrungen nach Anwendung im 1. Trimenon; in der späteren Schwangerschaft wird es nur noch sehr zurückhaltend eingesetzt
			  o bei Präeklampsie-bedingten Hochdruckformen haben sich Nifedipin und Urapidil bewährt		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			○ Dihydralazin zur antihypertensiven Therapie in der Schwangerschaft zugelassen, aber - insbesondere nach intravenöser Applikation - erheblichen Nebenwirkungen bei der Mutter und Kind möglich ○ auch ß-Rezeptorenblocker können eingesetzt werden (Labetalol am besten untersucht) – Hinweis Embryotox: in Deutschland nicht verfügbar		

9.5 Cochrane Reviews: Strukturierte Recherche

www.cochranelibrary.com/cdsr/reviews/topics (pregnancy and childbird)

Abalos et al. 2018 drug therapy (mild to moderate hypertension)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Abalos E. et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev	2018	**Objective** to assess the effects of antihypertensive drug treatments for women with mild to moderate* hypertension during pregnancy ‡ **Search** Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (up to	Update of Abalos et al. 2014 (first published in 2001, updated in 2007 and 2014) - n=63 trials were included (data from 58 trials, 5909 women included in meta-analysis) - moderate to high risk of bias overall - GRADE assessments for the main 'antihypertensive drug versus placebo/no antihypertensive drug' comparison only - note: for many outcomes, trials contributing	overall, the quality of included studies was rated as moderate to poor (blinding was rated as high rik of bias in most of the studies; unclear risk of bias was given in some domains) evidence was graded from	AMSTAR-II rating high (15/16)

* **moderate hypertension** is defined as systolic blood pressure of **140 mmHg or more, and/or** diastolic blood pressure **of 90 mmHg or above** on two consecutive occasions at least four hours apart; Severe hypertension is defined as systolic blood pressure of 160 mmHg or 170 mmHg and/or diastolic blood pressure of 110 mmHg or more two consecutive occasions up to 15 minutes apart (ACOG Task Force 2013; Canadian HDP Working Group 2014; NHBPEP 2000); note: For this review authors accepted broad and pragmatic criteria for identifying women with mild to moderate hypertension during pregnancy. This reflects clinical practice, and is justifiable in the context of randomised trials as within each study the same criteria will have been used for women in both groups.

‡ classification of hypertensive disorders during pregnancy (NHBPEP 2000): four broad categories: (a) gestational hypertension or pregnancy-induced hypertension, which is hypertension newly diagnosed after 20 weeks of gestation without proteinuria; (b) pre-eclampsia, which is hypertension developed after 20 weeks of gestation with proteinuria; **(c) chronic hypertension, or essential hypertension, which is pre-existing hypertension;** and (d) chronic hypertension with superimposed pre-eclampsia. Recently, the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy extended the diagnosis of pre-eclampsia to those cases in which hypertension, in the absence of significant proteinuria, is associated with other systemic findings such as thrombocytopenia, worsening liver or renal function, pulmonary oedema or new-onset cerebral or visual disturbances (ACOG Task Force 2013).

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität

2018 Oct 1;10(10):CD002252. doi: 10.1002/14651858.CD002252.pub4https://pubmed.ncbi.nlm.nih.gov/30277556/ [213]		13 September 2017)
		reference lists of retrieved studies were also checked
		Quality assesement
		Cochrane Risk of Bias Tool, GRADE assessments
		Inclusion and exclusion criteria
		- randomised trials
		- women with mild to moderate hypertension during pregnancy
		  ○ systolic blood pressure 140 to 169 mmHg and/or
		  ○ diastolic blood pressure 90 to 109 mmHg
		- evaluating antihypertensive drug treatment
		- treatment was planned to continue for at least seven days
		- women who had given birth before trial entry were excluded, as were women with severe hypertension
		Intervention
		one or more antihypertensive drug(s)*
			data evaluated different hypertensive drugs; while we did not downgrade for this indirectness, results should be interpreted with caution
			- antihypertensive drugs used:
			  ○ alpha agonists (methyldopa),
			  ○ beta blockers (acebutolol, atenolol, labetalol, mepindolol, metoprolol, pindolol, oxprenolol and propranolol),
			  ○ calcium channel blockers (amlodipine, isradipine, nicardipine, nifedipine, nimodipine and verapamil),
			  ○ vasodilators (hydralazine and prazozin),
			  ○ ketanserin,
			  ○ glyceryl trinitrate (GTN),
			  ○ furosemide and sildenafil
			  ○ all drugs were given orally, except glyceryl trinitrate, which was given transdermally
			  ○ the dose for several agents varied
			- n=31 trials (n=3280 women) antihypertensive drug vs. placebo or no antihypertensive drug
			- n=30 trilas (n=3093 women) antihypertensive
				very low to moderate certainty, with downgrading mainly due to design limitations and imprecision
				
				all included trials were small (largest n=314)
				
				authors noted levels of attrition and planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis in future updates with more eligible studies
				
				authors noted that hypertension during pregnancy is common (n=1 of n=10 women will have high BP at some time;	

* **Alpha agonists**: inhibit vasoconstriction via a centrally mediated effect (Ingenito 1970); Methyldopa most widely used, available in 1963; Clonidine has the disadvantage that sudden withdrawal may cause a hypertensive crisis (Isaac 1980); common side-effects of methyldopa: dizziness, lightheadedness, drowsiness, headache, stuffy nose, and weakness, especially when starting this medication and when dosage is increased; other side-effects: swelling, muscle pain, dry mouth, swollen or "black" tongue, gastrointestinal symptoms and depression (depressed mood, unusual thoughts, and nightmares)
Beta blockers: block adrenoceptors in the heart, peripheral blood vessels, airways, pancreas and liver (Frishman 1979); Labetalol has additional arteriolar vasodilating action that lowers peripheral resistance; side-effects: oedema, postural hypotension, bradycardia, cold or cyanotic extremities, rashes, masking of the normal response to hypoglycaemia (sweating and tachycardia), nausea, dyspepsia, vomiting, difficulty in micturition (including acute urinary bladder retention, dizziness, headache, taste distortion, vertigo, paraesthesia
Calcium channel blockers: (amlodipine, isradipine, nifedipine, nicardipine, nimodipine and verapamil) inhibit influx of calcium ions to vascular smooth muscle resulting in arterial vasodilatation (Robinson 1980); common side-effects: dizziness, giddiness, lightheadedness, headaches, heat sensation, weakness, flushing, palpitations, transient hypotension, heartburn, nausea, dyspnoea, nasal congestion, and muscle cramps
Peripheral vasodilators: hydralazine is a vasodilator with a direct relaxing effect on smooth muscle in the blood vessels, predominantly in the arterioles (Stunkard 1954); most frequently reported side-effects: palpitations and tachycardia; other side-effects: flushing, hypotension, nausea, vomiting, diarrhoea, gastrointestinal disturbances, headache, arthralgia, joint swelling, myalgia, and anorexia
Serotonin receptor antagonists: ketanserin is a selective serotonin receptor antagonist with weak adrenergic receptor blocking properties (Frishman 1995); effective in lowering blood pressure in essential hypertension; also inhibits platelet aggregation; side-effects: dizziness, headache, drowsiness, fatigue, dry mouth, sedation, lightheadedness, lack of concentration, gastrointestinal disturbances; rare but serious side-effects: ventricular tachycardia
Nitric-oxid donors: glyceryl trinitrate is a nitric oxide donor with vasodilator effect in perivascular smooth-muscle cells (Seligman 1994); side-effects: chest pain, hypoxaemia, difficulty breathing, cyanosis, tachycardia, throbbing headache, spinning sensation, postural hypotension, dizziness, drowsiness, and weakness

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
		Comperator placebo, no antihypertensive drug, or another antihypertensive drug **Outcome** **primary** - severe hypertension (systolic blood pressure (BP) ≥ 170 mmHg, or diastolic BP ≥ 110 mmHg - proteinuria/pre-eclampsia (new proteinuria (1+ or more or 300 mg/24 hours) - total reported fetal or neonatal death (including miscarriage) - small-for-gestational age - preterm birth: all births before 37 completed - weeks **secondary**: for the women - maternal death - severe pre-eclampsia - eclampsia - HELLP syndrome (haemolysis, elevated liver enzymes and lowered platelets) - severe maternal morbidity (e.g. liver or renal failure) - need additional antihypertensive drug - miscarriage - elective delivery - caesarean section - antenatal hospital admission - placental abruption - side-effects - change/stopped drug due to side effects note:	drugs against another - n=8 trials recruited during the first and second trimester **outcomes:** - antihypertensive drug vs. placebo/no antihypertensive drug (n=31 trials, n=3485 women) **primary:** - risk of developing severe hypertension: - risk ratio (RR) 0.49; 95% confidence interval (CI) 0.40 to 0.60; n=20 trials, n=2558 women (moderate-certainty evidence) - risk of proteinuria/pre-eclampsia: - average risk ratio (aRR) 0.92; 95% CI 0.75 to 1.14; n=23 trials, n=2851 women (low-certainty evidence) - fetal or neonatal death (including miscarriage): - aRR 0.72; 95% CI 0.50 to 1.04; n=29 trials, n=3365 women (moderate-certainty evidence) - small-for-gestational-age babies: - aRR 0.96; 95% CI 0.78 to 1.18; n=21 trials, n=2686 babies (moderate-certainty evidence) - preterm birth less than 37 weeks: - aRR 0.96; 95% CI 0.83 to 1.12; n=15 trials, n=2141 women (moderate-certainty evidence) (for secondary outcome authors documented that they were uncertain of the effect of antihypertensive drug(s) on the risk of maternal death (aRR 1.11; 95% CI 0.18 to 7.02; 5 trials, 525 women; Analysis 1.9), severe pre-eclampsia (aRR 0.56; 95% CI 0.15	preeclampsia complicates between 2% to 8% of all pregnancies worldwide) authors added that the clinical importance of the reduction in risk (for developing severe hypertension) depends on factors such as duration and severity of the hypertension, and the impact on the consequences of severe hypertension, such as antenatal hospital admission or stroke	

Phosphodiesterase inhibitors: sildenafil (usually associated with treatment of erectile dysfunction in men) has been attracting the attention of clinicians and researchers; phosphodiesterase type 5 inhibitor that increases intracellular cyclic guanosine monophosphate (cGMP) in the vascular smooth muscle, resulting in vasodilatation (Wareing 2004); most common adverse reactions reported in clinical trials: headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, ddizziness, and rash

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
		- other types of interventions for women with mild to moderate hypertension during pregnancy were not considered in this review (e.g. salt restriction (*Duley 1999*), antiplatelet agents (*Duley 2007*), abdominal decompression (*Hofmeyr 2012*), and bed rest, with or without hospitalisation (*Meher 2005a*) - role of diuretics for women with hypertension during pregnancy is covered by a separate Cochrane review (*Churchill 2007*), as is prevention and treatment of postpartum hypertension (*Magee 2013*) - for women with severe hypertension, usually defined as 170 mmHg or more systolic blood pressure or 110 mmHg or more diastolic blood pressure, there is a risk of direct arterial damage and so antihypertensive drugs are used to lower blood pressure (*Gifford 1990; Redman 1993*). The question of which drug is best in this situation is considered in another Cochrane review and not discussed further here (*Duley 2013*) A separate review assessing the effect of alternative oral beta blocker regimens in mild to moderate hypertension during pregnancy is underway. Beta blockers are included in this review as part of all the spectrum of antihypertensive drugs.	to 2.02; 3 trials, 416 women; Analysis 1.10), eclampsia (aRR 0.52; 95% CI 0.13 to 2.06; 7 trials, 713 women; Analysis 1.11), because the certainty of the evidence was very low) **fetal/neonatal/infant** admission to neonatal or intensive care nursery: - aRR 1.01; 95% CI 0.83 to 1.22; Heterogeneity: TauW = 0.03; ChiW = 13.48, df = 9 (P = 0.14); IW = 33%, n=10 trials (n=1570 babies) (low-certainty evidence risk of developing respiratory distress syndrome: - aRR 0.53; 95% CI 0.29 to 0.99; n=6 trials (n=925 babies) - this effect is seen in the subgroup of beta blocker vs. no antihypertensive drugs/placebo (3 trials, 412 babies; aRR 0.32; 95% CI 0.13 to 0.83), with no evidence of an overall difference in the other subgroups of drugs: (Test for subgroup differences: ChiW = 4.11, df = 3 (P = 0.25), IW = 27.0%) neonatal hypoglycaemia: - aRR 0.77; 95% CI 0.51 to 1.15; 6 trials, 962 babies) neonatal bradycardia: - aRR 1.28; 95% CI 0.31 to 5.24; 3 trials, 418 babies) neonatal jaundice: - aRR 0.78, 95% CI 0.53 to 1.15; 3 trials, 529 babies) uncertain effect of antihypertensive drug(s) on the risk of impaired long-term growth and development in infancy and childhood – one trial (110 infants) reported on the risk of cerebral palsy at one-year follow-up (aRR 0.33; 95% CI 0.01 to 8.01) - one antihypertensive drug vs. another antihypertensive drug (n=29 trials, n=2774 women) **primary:** - risk of developing severe hypertension:		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			- beta blockers and calcium channel blockers together (meta-analysis) vs. methyldopa: - RR 0.70; 95% CI 0.56 to 0.88; n=11 trials, n=638 women) - other antihypertensive drugs vs. calcium channel blockers - RR 1.86; 95% CI 1.09 to 3.15; n=5 trials, n=223 women) - methyldopa and calcium channel blockers together vs. beta blockers - RR1.18, 95% CI 0.95 to 1.48; n=10 trials, n=692 women) - risk of proteinuria/pre-eclampsia - alternative drugs vs. methyldopa - aRR 0.78; 95% CI 0.58 to 1.06; n=11 trials, n=997 women) - alternative drugs vs. calcium channel blockers - aRR: 1.24, 95% CI 0.70 to 2.19; n=5 trials, n=375 women) - alternative drugs vs. beta blockers - aRR 1.21, 95% CI 0.88 to 1.67; n=12 trials, n=1107 women) **risk of total reported fetal or neonatal death (including miscarriage)** - other antihypertensive drugs vs. methyldopa o aRR 0.77, 95% CI 0.52 to 1.14; n=22 trials, n=1791 babies) - other antihypertensive drugs vs. calcium channel blockers o aRR 0.90, 95% CI 0.52 to 1.57; n=9 trials, n=700 babies) - other antihypertensives vs. beta blockers o aRR: 1.23, 95% CI 0.81 to 1.88; n=19 trials, n=1652 babies) risk for small-for-gestational age - other antihypertensives vs. methyldopa o aRR 0.79, 95% CI 0.52 to 1.20; n=7		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
			trials, n=597 babies) - other antihypertensives vs. calcium channel blockers o aRR 1.05, 95% CI 0.64 to 1.73; n=4 trials, n=200 babies), - other antihypertensives vs. beta blockers o average RR 1.13, 95% CI 0.80 to 1.60; n=7 trials, n=680 babies No evidence of an overall difference among groups in the risk of preterm birth (less than 37 weeks) was found in the comparison with methyldopa (aRR: 0.91; 95% CI 0.68 to 1.22; 11 trials, 835 women), with calcium channel blockers (aRR 0.85, 95% CI 0.59 to 1.23; six trials, 330 women), or with beta blockers (aRR 1.22, 95% CI 0.90 to 1.66; 9 trials, 806 women) (secondary outcomes: no cases of maternal death and eclampsia was reported. There is no evidence of a difference in the risk of severe pre-eclampsia, changed/stopped drug due to maternal side-effects, elective delivery, admission to neonatal or intensive care nursery when other antihypertensive drugs are compared with methyldopa, calcium channel blockers or beta blockers. Impaired long-term growth and development in infancy and childhood was not reported for these comparisons.)		

Duley et al. 2013 drug treatment (very high BP)

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität
Duley L. et al. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013 Jul 31;2013(7):CD0	2013	**Objective** to compare different antihypertensive drugs for very high blood pressure during pregnancy **Search** Cochrane Pregnancy and Childbirth Group Trials Register (up to 9 January 2013) **Inclusion and exclusion criteria** - randomised trials - women with severe hypertension during	- n=35 trials (n=3573 women) included - n=15 comparisons - antihypertensive drugs evaluated: o hydralazine (most common comparator), o calcium channel blockers (nifedipine, nimodipine, nicardipine and isradipine), o labetalol, atenolol, o methyldopa, o diazoxide, o prostacyclin,	overall quality was rated as low to moderate (several trils were rated as unclear risk of bias in some domains; e.g. loss to follow-up was not clearly described) all trials were small	AMSTAR-II rating high (15/16)

<table>
<tr><th>Zitat</th><th>Jahr</th><th>Studiencharakteristika</th><th>Studienergebnisse</th><th>Kommentar</th><th>Methodische Qualität</th></tr>
<tr>
<td>01449.doi: 10.1002/14651858.CD001449.pub3 https://pubmed.ncbi.nlm.nih.gov/23900968/
[214]</td>
<td></td>
<td>
pregnancy, requiring immediate treatment
○ diastolic 105 mmHg or more and/or systolic 160 mmHg or more
- antihypertensive drug* therapy at hospital
- studies with quasi-random or cross-over design were excluded
- women postpartum at trial entry were excluded
Quality assesement
Cochrane Risk of Bias Tool
Intervention
one antihypertensive drug
Comperator
another antihypertensive drug
(regardless of dose, route of administration or duration of therapy)
Outcomes
- substantive maternal morbidity
- morbidity and mortality for the baby
- side-effects for the woman
primary:
for the woman
- death
- eclampsia
- stroke
- persistent high blood pressure (need for an antihypertensive drug other than the allocated treatment)
for the child
- death
secondary:
for the woman
- any serious morbidity
</td>
<td>
○ ketanserin,
○ urapidil,
○ (magnesium sulphate),
○ prazosin
○ isosorbide
- most drugs were given either intravenously (IV) or intramuscularly (IM)
- one trial was ongoing (Diemunsch 2008); and one trial (Mesquita 1995) was awaiting assessment

outcomes
primary (RR=risk ratio, CI=confidence interv)
<table>
<tr><th>RR (95% CI) n (trials; women)</th><th>death (women / child)</th><th>eclampsia</th><th>stroke</th><th>persistent high BP</th></tr>
<tr><td>labetalol vs hydralazine</td><td>maternal 0.0 (0.0, 0.0) n=1; n=200 (0 vs. 0) fetal or neonatal 0.75, (0.17 to 3.21), n=4; n=274</td><td>0.0 (0.0, 0.0) n=2; n=220 (0 vs. 0)</td><td>-</td><td>1.57 (0.66 to 3.74) n=2; n=220</td></tr>
<tr><td>CCB (nifedi-</td><td>fetal or neonatal</td><td>-</td><td>-</td><td>0.37 (0.21 to 0.66)</td></tr>
</table>
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<td>
(n=5 studies recruited ≥ 100 women), apart from one large study (n=1750 women) comparing nimodipine with magnesium sulphate (Nimodipine SG2003)

authors documented: that during normal pregnancy there are considerable changes in blood pressure; within the first weeks the woman’s blood pressure falls, largely due to a general relaxation of muscles within the blood vessels (de Swiet 2002).

from around the middle of pregnancy blood pressure slowly rises again until, at term, blood pressure is close to the level it was before pregnancy

blood pressure during pregnancy can be influenced by many other factors including, time
</td>
<td></td>
</tr>
</table>

* most commonly recommended drugs include **hydralazine, labetalol and nifedipine** (Lindheimer 2008; Lowe 2009; Magee 2008; NICE 2010; WHO 2011) and there is most experience with these. / All drugs used to treat hypertension in pregnancy cross the placenta, and somay affect the fetus directly by means of their action within the fetal circulation, or indirectly by their effect on uteroplacental perfusion.

Zitat	Jahr	Studiencharakteristika	Studienergebnisse					Kommentar	Methodische Qualität
		- kidney failure - liver failure - HELLP syndrome - disseminated intravascular coagulation - pulmonary oedema (fluid in the lungs) - hypotension (low blood pressure) - side-effects of the drug - abruption of the placenta or antepartum haemorrhage - need for magnesium sulphate - elective delivery - caesarean section - postpartum haemorrhage - use of hospital resources - postnatal depression - breastfeeding - womens experiences and views of the interventions for the child - preterm birth - death before discharge - respiratory distress syndrome - infection - necrotising enterocolitis - retinopathy of prematurity - intraventricular haemorrhage - apgar score at five minutes - side-effects associated with the drug - special care nursery for more than seven days - use of hospital resources - long-term growth and development note: very high BP needs additional therapy (e.g. prophylactic anticonvulsant drugs (Duley 2010), plasma volume expansion (Duley 1999), and steroids for HELLP (haemolysis, elevated liver enzymes and lowered platelets) syndrome (Woudstra 2010))	pine, isradipine) vs hydralazine	1.36 (0.42, 4.41), n=4; n=161			n=6; n=313	of day, physical activity, position and anxiety pre-eclampsia occurs between two to eight per cent of pregnancies (WHO 1988)	
			prostacyclin vs hydralazine	neonathal 1.14 (0.08, 17.11) n=1; n=47	-	-	0.23 (0.01, 4.47) n=1; n=47		
			ketanserin vs hydralazine	maternal 0.32 (0.03, 2.96) n=2; n=124 perinatal 0.27 (0.05, 1.64) n=2; n=116	0.6 (0.08, 4.24) n=2; n=64	-	4.79, (1.95 to 11.73) n=3; n=180		
			urapidil vs hydralazine	neonatal 0.54 (0.10, 3.03) n=3; n=101	0.0 (0.0, 0.0) n=1; n=26	-	0.69 (0.08, 5.66) n=3; n=101		
			labetalol vs CCB (nicardodipine, nifedipine)	-	0.72 (0.05, 10.26) n=2; n=70	-	1.14 (0.62, 2.09) n=2; n=110		
			labetalol vs methyldopa	fetal or neonatal Subtotals	-	-	1.19 (0.74, 1.94) n=1;		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse					Kommentar	Methodische Qualität
				only			n=72		
			labetalol vs diazoxide	perinatal 0.14 (0.01, 2.69)	-	-	0.5 (0.13, 1.88) n=1; n=90		
			nitrates vs magnesium sulphate	-	0.0 (0.0, 0.0) n=1; n=36	-	0.14 (0.01 to 2.58) n=1; n=36		
			nimodipine vs magnesium sulphate	-	1.03 (0.07 to 16.03) n=2; n=1683	0.0 (0.0, 0.0) n=1; n=1650	0.84, (0.76 to 0.93) n=2; n=1650		
			nifedipine vs prazosin	maternal 0.32 (0.01, 7.73) n=1; n=145	(0.0, 0.0) n=1; n=145	-	-		
			nifedipine vs chlorpromazine	-	2.52 (0.11, 59.18) n=1; n=55	-	0.09 (0.01, 1.57) n=1; n=60		
			hydralazine vs. diazoxide	perinatal 7.42 (0.39, 140.06) neonatal 0.35 (0.01, 8.47) n=1; n=101	-	-	-		
			methyldopa vs	neonatal 1.0	-	-	-		

Zitat	Jahr	Studiencharakteristika	Studienergebnisse	Kommentar	Methodische Qualität

atenolol	(0.07, 15.26) n=1; n=60			
urapidil vs calcium channel blockers	-	-	-	-

CCB=calcium-chanel-blockers

side-effects

- few trials provided data on the specific side-effects, included:
  - for hydralazine: headache, flushing, light head, nausea and palpitations;
  - for labetalol: flushing, light head, palpitations and scalp tingling;
  - for nifedipine: flushing, nausea, vomiting;
  - for urapidil: nausea and tinnitus;
  - for magnesium sulphate: flushing;
  - for methyldopa: somnolence

authors note:

- no clear evidence that one antihypertensive is preferable to the others for improving outcome for women with very high blood pressure during pregnancy, and their babies
- until better evidence is available, the best choice of drug for an individual woman probably depends on the experience and familiarity of her clinician with a particular drug, and on what is known about adverse maternal and fetal side-effects

SR Wirkstoffgruppen

Betablocker: Magee et al. 2003 (betablocker (BB) vs. placebo/no BB)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Magee et al.	2003		**Objectives**	n=29 trials (approximately 2500 women)	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
Cochrane Database Syst Rev. 2003 https://pubmed.ncbi.nlm.nih.gov/12917933/ [215]			to assess whether oral beta-blockers are better than placebo, or no beta-blocker, and have advantages over other antihypertensives, for women with mild to moderate pregnancy hypertension **Sources** Cochrane Pregnancy and Childbirth Group trials register (January 2004) and bibliographies of retrieved papers and personal files (updated search on 4 July 2012) **Selection criteria** - randomized controlled trials - women with mild to moderate pregnancy - comparing beta-blockers with placebo or no therapy, or other antihypertensives **hypertension.** **Intervention** beta-blockers **Control** placebo or no therapy, or other antihypertensives **Outcomes** For the women: - measures that evaluated the effectiveness and safety of antihypertensive therapy - (including stroke, maternal mortality, severe hypertension, proteinuria at delivery (as a surrogate marker for pre-eclampsia), eclampsia, the need for additional antihypertensive therapy, admission to hospital before delivery, placental abruption, caesarean section, and the need to change therapy due to maternal side effects) For the baby: - perinatal mortality, small-for-gesta-	n=13 trilas (1480 women) compared beta-blockers with placebo/ no beta blocker - oral beta-blockers o decrease the risk of severe hypertension ▪ relative risk (RR) 0.37, 95% confidence interval (CI) 0.26 to 0.53; 11 trials, N = 1128 women) o and the need for additional antihypertensives (RR 0.44, 95% CI 0.31 to 0.62; 7 trials, N = 856 women) o There are insufficient data for conclusions about the effect on perinatal mortality or preterm birth. - beta-blockers o seem to be associated with an increase in small-for-gestational-age (SGA) infants ▪ RR 1.36, 95% CI 1.02 to 1.82; 12 trials; N = 1346 women o maternal hospital admission may be decreased, o neonatal bradycardia increased o respiratory distress syndrome decreased o these outcomes are reported in only a small proportion of trials n=13 trials (854 women), beta-blockers were compared with methyldopa - beta-blockers appear to be no more effective and probably equally as safe single small trials have compared beta-blockers with hydralazine, nicardipine or isradipine it is unusual for women to change drugs due to side effects	

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			tional-age infants (SGA; defined as either less than the third, fifth or 10th percentiles when birth weightwas corrected for gestational age), pretermbirth (less than 37 completed weeks' gestation), admission to a special care baby unit (SCBU) or a neonatal intensive care unit (NICU), neonatal morbidity (such as bradycardia, hypotension, hypothermia, and hypoglycaemia), low Apgar scores (less than seven at five minutes), respiratory distress syndrome (RDS), and measures of long-term health and development such as cerebral palsy, and IQ less than one standard deviation below themean. - pretermdelivery and SGA infants are reported for all fetuses, whereas neonatal and pediatric health problems are reported for all live births		

Methyldopa: Mah 2009 (methyldopa vs. placebo)

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar

Mah et al. Cochrane [139] https://www.ncbi.nlm.nih.gov/pubmed/19821316	2009	low	**Objective**
			effect of methyldopa as monotherapy vs. placebo
			Search
			Cochrane databases, MEDLINE, EMBASE (up to June 2009)
			Inclusion and exclusion criteria
			- randomized controlled trials
			- cross-over design was allowed
			- primary hypertension
			  ○ blood pressure: systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg
			- studies of patients with secondary hypertension or gestational hypertension were excluded
			Quality assesment
			Cochrane Risk of Bias Tool
			Intervention
				n=12 studies, n=595 (intervention: n=296 patients, control: n=299 patients) (n=4 studies with cross-over design)
				- duration three to 52 weeks
				- data on mortality, morbidity and withraw due to adverse events were not reported
				
				secondary:
				- blood pressure:
				■ methyldopa vs. placebo, mean difference, n=7 trials, n=231 patients
				  ○ systolic -21.88 (95% CI -41.14; -2.63), I^2=97%
				  ○ diastolic -8.53 (95% CI -12.21; -4.84), I^2=73%
					publication bias was not assessed
					
					sequence generation and allocation concealment were rated as unclear
					
					lost to follow up and incomplete outcome data were reported
					
					significant heterogeneity was reported

Zitat	Jahr	AMSTAR-II	Charakteristika	Ergebnisse	Kommentar
			methyldopa **Comparator** placebo **Outcomes** **primary**: - all cause mortality - cardiovascular mortality - non-cardiovascular mortality - at least one serious adverse event - stroke - myocardial infarction **secondary:** - withraw due to adverse events - at least one adverse event - changed blood pressure		

9.6 Handsuche / Literaturlistensuche

Tita NEJM 2022 (mild chronic hypertension)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

Tita et al. Treatment for Mild Chronic Hypertension during Pregnancy. N Engl J Med. 2022 Apr 2. doi: 10.1056/NEJMoa2201295. Online ahead of print.
 	
investigator-initiated Chronic Hypertension and Pregnancy (CHAP) project, US, ClinicalTrials.gov number, NCT02299414, Phase 4
	Hypothesis:
	strategy of treating mild chronic hypertension during pregnancy with a bloodpressure goal of less than 140/90 mm Hg would result in a lower incidence of adverse maternal and perinatal outcomes than a strategy of withholding treatment until the blood pressure was 160/105 mm Hg or higher (a more conservative cutoff)
	
	Design
	multicenter, pragmatic, open-label, randomized, controlled trial
	
	Inclusion and exclusion criteria
	- pregnant women
		- enrollment between Sep 2015 through Mar 2021
		- n=2,408 women included (n=1,208 intervention, n=1,200 control)
		  ○ n=2,419 were randomized
		  ○ n=10 patients were withdrawn immediately after randomization
		  ○ n=1 withdrew consent
		  ○ n=83 were lost to follow-up (38 in the intervention group and 45 in the control group)
		- mean age: 32.3 (+/- 5.6) years
		- labetalol and nifedipine were the most frequently used antihypertensive drugs before randomization (also documented Amlodipine, Methyldopa, Hydrochlorothiazide, Lisinopril, Metoprolol)
		- non-hispanic black women made up 48% of the patient population
		
		- **adherence**:
		  ○ at 86% of these visits, the patients reported
			Selection bias
			randomization:
			low
			concealment and unpredictability:
			low
			Performance bias
			blinding of participants and staff:
			high
			Detection bias
			blinding of evaluation:
			high
			Attrition bias
			lost to follow-up:
			high
			ITT-analysis:
			low
				note: randomly assigned to a blood-pressure goal of less than 140/90 mm Hg (active treatment) or to standard (control) treatment, in which antihypertensive therapy was withheld or stopped at randomization unless severe hypertension

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

	- known or new diagnosis of chronic hypertension:*
	  ○ systolic blood pressure ≥ 140 mm Hg,
	  ○ diastolic blood pressure ≥ 90 mm Hg,
	  ○ or both
	- a viable singleton fetus before 23 weeks' gestation†
	- severe hypertension or a blood-pressure level warranting antihypertensive treatment with more than one medication, secondary hypertension, multiple foetuses, high-risk co-existing illnesses were excluded
	Intervention‡
	- first-line antihypertensive drug for pregnancy (labetalol or extended-release nifedipine) or other medication (e.g. amlodipine, methyldopa) – patient preference
	Control
	- similar antihypertensive medications only if severe hypertension developed (systolic pressure, ≥160 mm Hg; or diastolic pressure, ≥105 mm Hg)
	Outcomes
		taking their assigned medications (intervention group)
		  ○ at the last antenatal visit: intervention group vs. control group 88.9% vs. 24.4% reported taking medications
		  ▪
		- **mean blood-pressure level**:
		  ○ during the period between randomization and delivery: intervention group vs. control group
		  ▪ systolic pressure, 129.5 mm Hg vs. 132.6 mm Hg for a difference of −3.1; and
		  ▪ diastolic pressure, 79.1 mm Hg vs. 81.5 mm Hg, for a difference of −2.3 mm Hg
		primary outcome (intervention vs. control)
		- complete-case analysis:
		  ○ n=353 of 1170 patients (30.2%) vs. n=427 of 1155 patients (37.0%)
		  ○ risk ratio 0.82, 95% CI 0.73-0.92, p<0.001
		  ○ authors used multiple imputation methods§
		  ○ number needed to treat to prevent one primary-outcome event was 14.7 (95% CI, 9.4-33.7)
		- preeclampsia with severe features:
		  ○ n=272 (23.3%) vs. 336 (29.1%)
		  ○ adjusted risk ratio as calculated by imputation 0.80 (95% CI, 0.70 to 0.92)
		- medically indicated preterm birth before 35 weeks' gestation:
		  ○ n=143 patients (12.2%) vs. n=193 (16.7%)
			(note: used multiple imputation methods)
			Reporting bias
			selective result presentation: low
			Other bias none
			Supported by the National Heart, Lung, and Blood Institute.	

* Blood pressure was measured with an automated device (Omron HEM-907).
† Gestational age was determined according to the criteria of the American College of Obstetricians and Gynecologists (ACOG).
‡ patients were asked about their adherence to their blood-pressure regimen before any dose adjustments; pill counts were performed at the time of each refill
§ BMJ 2009; 338 doi: https://doi.org/10.1136/bmj.b2393 (multiple imputation has potential to improve the validity of medical research, validity of results from multiple imputation depends on such modelling being done carefully and appropriately, first stage: create multiple copies of the dataset, with the missing values replaced by imputed values (sampled from their predictive distribution based on the observed data (bayesian approach), second stage: use standard statistical methods to fit the model of interest to each of the imputed datasets, estimated associations in each of the imputed datasets will differ, standard errors are calculated using Rubin's rules (account for variability in results between the imputed datasets)) – e.g. development of the QRISK tool for cardiovascular risk prediction (other BMJ article), based on a large general practice research database → researchers correctly identified a difficulty with missing data in their database and used multiple imputation to handle the missing data

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	patients were followed until 6 weeks after birth primary - composite of pre-eclampsia with severe features occurring up to 2 weeks after birth, medically indicated preterm birth before 35 weeks' gestation (i.e., because of maternal or fetal illness, not spontaneous labor or membrane rupture), placental abruption, or fetal or neonatal death primary safety outcome: - poor fetal growth, which was defined as a birth weight measuring less than the 10th percentile for gestational age and infant sex according to the Duryea population standard - a small-for-gestational-age birth weight measuring less than the 5th percentile secondary - composite of maternal death or serious complications (heart failure, stroke, or encephalopathy; myocardial infarction or angina; pulmonary edema; admission to an intensive care unit [ICU] or intubation; or renal failure), any preterm birth (<37 weeks' gestation), and a composite of serious neonatal complications (bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, or intraventricular hemorrhage of grade 3 or 4) - preeclampsia and worsening chronic hypertension (severe hypertension without	○ aRRi 0.73 (95% CI, 0.60 to 0.89) **primary safety outcome** (intervention vs. control) - newborns with a birth weight that was under the 10th percentile for their gestational age: ○ n=128 of 1146 infants (11.2%) vs. n=117 of 1124 (10.4%) ○ RR 1.07; 95% CI, 0.85-1.36; P = 0.56 ○ aRRi 1.04; 95% CI, 0.82-1.31; P = 0.76 - newborns with a birth weight that was under the 5th percentile for their gestational age: ○ 5.1% vs. 5.5% ○ RR 0.92; 95% CI, 0.65 to 1.30; P = 0.63 **Secondary Maternal and Neonatal Outcomes** (intervention vs. control) - incidence of the maternal composite outcome was low and did not differ substantially between the two treatment groups - severe maternal hypertension: ○ n=436 of 1208 patients (36.1%) vs. n=531 of 1200 patients (44.2%) - preeclampsia, with or without severe features ○ n=295 (24.4%) vs. n=373 (31.1%) ■ **neonatal outcomes (intervention vs. control)** - preterm birth before 37 weeks' gestation: ○ n=332 of 1208 infants (27.5%) vs. n=377 of 1200 (31.4%) - low birth weight (<2500 g): ○ n= 232 (19.2%) vs. 277 (23.1%) - the frequencies of outcomes of severe neonatal complications and NICU admission did not appear to differ substantially between the two groups authors concluded that active treatment with a blood-pressure target of less than 140/90 mm Hg was associated with better pregnancy outcomes than a control strategy of no antihypertensive treatment unless the systolic blood pressure was 160 mm Hg or higher or the diastolic pressure was 105 mm Hg or higher		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	preeclampsia), mean clinic blood-pressure levels, cesarean delivery, and blood transfusion - newborn outcomes included neonatal ICU (NICU) admission, length of hospital stay, birth weight of less than 2500 g, hypoglycemia, bradycardia, hypotension, ponderal index, head circumference, and placental weight			

10 Evidenztabellen Invasive Therapie

10.1 Systematische Recherche Primärstudien

Kapitel Invasive Therapie (01.03.2014 – 17.05.2022)

RADIANCE-HTN SOLO, NCT02649426

Azizi et al. JACC Cardiovasc Interv 2020, 12-Monatsergebnisse

Azizi et al. Circulation 2019, 6-Monatsergebnisse

Azizi et al. Lancet 2018, 2-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Azizi M, Daemen J, Lobo MD, et al. 12-Month Results From the Unblinded Phase of the RADIANCE-HTN SOLO Trial of Ultrasound Renal Denervation. JACC. Cardiovascular interventions 2020; 13(24):2922–33. DOI: 10.1016/j.jcin.2020.09.054. http://www.ncbi.nlm.nih.gov/pubmed/33357531. [216]	**Objective** whether an alternative technology using endovascular ultrasound renal denervation reduces ambulatory blood pressure in patients with hypertension in the absence of antihypertensive medications **Design** single-blind, randomised, sham-controlled trial, n=21 hospitals (USA),	n=146 were randomised to undergo renal denervation - n=74 RD vs. n=72 sham (ITT) - mean age: 54.1 years (SD 10.1) - females: n= 61 (42%) - office systolic/diastolic blood pressure before antihypertensive medication washout (mm Hg): 142.6 (SD 14.7) vs. 144.6 (SD 15.9)/ 92.3 (SD 10.1) 93·6 (SD 8.3)	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low **Attrition bias**	note: RADIANCE-HTN was designed to compare the BP lowering efficacy of endovascular ultrasound RD with a sham procedure in two separate cohorts: - patients with mild-to-moderate hypertension, who underwent

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
Azizi M, Schmieder RE, Mahfoud F, et al. Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control Following Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial. Circulation 2019. DOI: 10.1161/CIRCULATIONAHA.119.040451. http://www.ncbi.nlm.nih.gov/pubmed/30880441. [217] Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): A multicentre, international, single-blind, randomised, sham-controlled trial. Lancet (London, England) 2018; 391(10137):2335–45. DOI: 10.1016/S0140-6736(18)31082-1. http://www.ncbi.nlm.nih.gov/pubmed/29803590. [218]	n=18 (Europe), randomization between March 2016 and Dec 2017 ClinicalTrials.gov, NCT02649426 *design*: Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J 2018; 195: 115–29. **Inclusion and exclusion criteria:** - patients with combined systolic–diastolic hypertension - aged 18–75 years - ambulatory blood pressure* ≥ 135/85 mm Hg and < 170/105 mm Hg after 4-week discontinuation of up to two antihypertensive medications - suitable renal artery anatomy (CTA or MRA) - estimated glomerular filtration rate (eGFR) ≥ 40 mL/min per 1·73 m² - no history of cardiovascular or cerebrovascular events **Intervention** - renal denervation with the Paradise system (ReCor Medical, Palo Alto, CA,	- most prescribed antihypertensives at screening: ACEI, CCB, ARB and diuretics§, (also patients drug naïve or drug intolerant were included) - total procedure time: RD 72 min vs. sham 38 min - Sedation o Conscious Sedation (e.g. midazolam, fentanyl, and/or morphine) ~75 % o Monitored Anaesthesia Care (e.g. propofol) ~ 15% o General Anaesthesia (e.g. inhaled anaesthetics, muscle relaxants or neuromuscular blocking agents, intubation, and/or ketamine) ~ 8 (8·1%) - no patients were lost to follow-up at 2 months [218] n=69 vs. n=71 patients completed 6 months follow-up [217] o n=45 (65.2%) vs. n=60 (84.5%) were treated with SSAT o average number of antihypertensive medications and defined daily dose: RD vs. SI 0.9±0.9 vs. 1.3±0.9, P=0.010 and 1.4±1.5 vs. 2.0±1.8, P=0.018; respectively n=65 vs. n=67 patients completed 12 months follow-up [216] o patients on ≥2 medications: 27.7% vs. 44.8%; p=0.041 o number of medications: 1.0 vs. 1.4; p=0.015 o defined daily dose: 1.4 vs. 2.2; p=0.007 o overall proportion of patients receiving any antihypertensive medications and those on 2 or more antihypertensive medications increased in both groups **Outcome:**	lost to follow-up: low ITT-analysis: low (sensitivity analysis) **Reporting bias** selective result presentation: low **Other bias** Funding ReCor Medical.	randomisation while off antihypertensive medications (SOLO cohort), - and patients with uncontrolled hypertension despite receiving three antihypertensive medications (TRIO cohort, s.b.) each cohort was independently powered note: authors assessed PubMed up to April 2018 to cover evidence before the study (n=11 MA with RCT and non-RCT) – for Coppolino et al. Cochrane Database Syst Rev 2017 [219] https://pubmed.ncbi.nlm.nih.gov/28220472/ authors described that they did not include trials assessing the effect of renal denervation in patients with hypertension in the absence of antihypertensive medications; Update of this review

* average seated office systolic and diastolic blood pressure of ≥140/90 mm Hg, but <180/110 mm Hg
§ ACEI=Angiotensin converting enzyme inhibitor, ARB=Angiotensin receptor blocker, CCB=Calcium channel blocker

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	USA) – endovascular ultrasound nerve ablation* - after 2 months addition of a recommended standardized stepped-care antihypertensive treatment (SSAT)† under continued blinding to initial treatment if monthly measured home BP was ≥135/85 mm Hg - after 6-months anthypertensive medications could be modified at physician's discretion after unblinding **Control** sham procedure (renal angiography only) note: patients were to remain off antihypertensive medications throughout the 2 months of follow-up unless specified blood pressure criteria were exceeded, monthly outpatient visits, addition of medication after 2 months **Outcomes** **primary** (2-months and 6 months follow-up-adjusted for medication): - change in <u>daytime</u> ambulatory systolic blood pressure at 2 months (ITT)	**primary:** daytime ambulatory systolic blood pressure (mm Hg (SD)) at 2 months (RD vs. SI) n=74 RD vs. n=72 sham (ITT) [218] - mean between-group difference (adjusted): -6.3 (95 % CI -9.4; -3.1), p=0.0001 - difference -8.5 (9.3) vs. -2.2 (10.0) - mean BP 141.9 (11.9) vs. 147.9 (13.3) at 6 months (RD+SSAT vs. SI+SSAT) n=69 vs. n=71 [217] - mean between-group difference (adjusted): −2.3 mm Hg (95% CI, −6.0; 1.5), p=0.242 (adjusted for baseline value) −4.3 mm Hg (95% CI −7.9; −0.6), p=0.024 (adjusted for baseline values and number of medication) - difference −18.1 (12.2) vs. −15.6 (13.2) at 12 months (RD+SSAT vs. SI +SSAT) n=65 vs. n=67 [216] - mean between-group difference (adjusted) -2.3 mm Hg (95% CI -5.9; 1.3) mm Hg; p=0.201 - difference -16.5 (12.9) vs. -15.8 (13.1) major adverse events: - at 30 days [218], 6 months [217] and 12 months [216]: no major adverse events in either group - at 6 months: n=2 hypertensive crisis were reported for sham control and n=2 new orthostatic hypotension (transient) for RD [217] - at 12 months: n=1 patients was death in the sham control group and n=1 with cerebrovascular event [216] - at 2 months: no new renal artery stenosis > 50% was detected in either group [216],		published in 2021: [220] (s.b.) they added an analysis of SPYRAL HTN-OFF MED for RF-RD (3-Months outcomes) Townsend Lancet 2017 [221] (s.b.) to prevent unmasking, patients were sedated and wore headphones and eye covers + questionnaire to assess the effectiveness of masking at discharge and 2-month follow-up

* minimum of two sonications of 7 s each were delivered in the main branch of the right and left renal artery, separated longitudinally by 5 mm, according to individual treatment plans developed on the basis of the pre-randomisation CT or MR angiography
† sequential addition of preferentially amlodipine (5 mg/d, mid-dose of a long-lasting dihydropyridine calcium channel blocker), a standard dose of an angiotensin-converting enzyme inhibitor (preferentially lisinopril 20–40 mg/d or ramipril 10–20 mg/d)/angiotensin receptor blocker (preferentially valsartan 160–320 mg/d or olmesartan 20–40 mg/d), and thiazide diuretic (e.g. hydrochlorothiazide (12.5 mg/d)), followed by the sequential uptitration of hydrochlorothiazide (25 mg/d) and amlodipine (10 mg/d).

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität / Sonstiges	Kommentar
	- major adverse (incl. all-cause mortality, renal failure, an embolic event with end-organ damage, renal artery or other major vascular complications requiring intervention, or admission to hospital for hypertensive crisis within 30 days and new renal artery stenosis within 6 months) **secondary:** - change in average 24-h ambulatory systolic blood pressure, - average 24-h ambulatory diastolic blood pressure, - average night-time ambulatory systolic blood pressure, - average night-time ambulatory diastolic blood pressure at 2 months, in this order - office and home systolic and diastolic blood pressures, - ambulatory and office heart rates, - proportion of patients with controlled blood pressure (<135/85 mm Hg for daytime ambulatory, - <130/80 mm Hg for 24-h ambulatory, or - <140/90 mm Hg for office blood pressure	- at 6 and 12 months: no new renal artery stenosis >70% was detected [217] [216], n=1 patient had a mild progression of a preexisting ostial renal artery stenosis (RD) and underwent renal artery stent placement [217] - procedure-related pain lasting longer than 2 days n=8 (11%) vs. n=8 (11%) [218] patients achieving controlled blood pressure by population and treatment group (ITT) at 2 months [218] - RD n=74 vs. SI n=72 patients - daytime ABPM <135/85 mm Hg: n=17 (23%) vs. n=8 (11%) p-value 0.06 - 24-h ABPM <130/80 mm Hg: n=20 (27%) vs. n=6 (8%) p-value 0.003 - office BP <140/90 mm Hg: n=19 (26%) vs. n=10 (14%) p-value 0.07		

RADIANCE-HTN TRIO, NCT02649426

Azizi et al. Lancet 2021, 2-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): A randomised, multicentre, single-blind, sham-controlled trial. Lancet (London, England) 2021; 397(10293):2476–86. DOI: 10.1016/S0140-6736(21)00788-1. http://www.ncbi.nlm.nih.gov/pubmed/34010611. [222]	**Objective**
	to assess the efficacy and safety of endovascular ultrasound renal denervation in patients with hypertension resistant to three or more antihypertensive medications
	
	Design
	randomised, single-blind, sham-controlled trial, enrolment between March 2016 and March 2020; ClinicalTrials.gov, NCT02649426
	
	design: Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J 2018; 195: 115–29.
	
	procedure: Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 2018; 391: 2335–45.
	
	Inclusion and exclusion criteria:
	- patients aged 18–75 years
	- resistant hypertension: defined as seated office blood pressure ≥ 140/90 mm Hg despite stable regimen of three or more antihypertensive medications including a diuretic
	- estimated glomerular filtration rate of at least 40 mL/min per 1·73 m²
		n=136 randomized
		- renal denervation (n=69) vs.
		- sham procedure (n=67)
		- mean age (SD) 52.3 (7.5) vs. 52.8 (9.1) years
		- female n=13 (19%) vs. n=14 (21%)
		- adherence to the combination medications at 2 months (urine samples) n=42 (82%) of vs. 47 (82%) of 57; p=0·99)
		- mean office blood pressure: 163/104 mm Hg
		- mean of 4·0 (SD 1·0) antihypertensive drugs at screening
		- most prescribed antihypertensives at screening: RAS-blockers n=67 (97%) vs. n=63 (94%), diuretics, CCB, BB, aldosteronantagonists (n=25 (35%) vs. n=21 (31%)
		- additional antihypertensive medications: RD n=3 (4%) patients vs. sham n=8 (12%) patients
		  ○ spironolactone: n=2 (3%) vs. n=7 (10%)
		  ○ amlodipine (dose down-titration 10 mg to 5 mg) n=4 (6%) vs. n=1 (1%) patient in the
		- successful bilateral renal nerve ablations with mean 5·8 (SD 1·2) ultrasound emissions:
		  ○ n=67 (97%) of 69 patients
		  ○ n=17 (25%) patients had accessory renal artery ablations
		- mean procedure time: RD 83.0 vs. sham 41.0 min
		- Sedation
		  ○ Conscious Sedation (e.g. midazolam, fentanyl, and/or morphine) ~ 65%
		  ○ Monitored Anaesthesia Care (e.g. propofol) ~ 25%
		  ○ General Anaesthesia (e.g. inhaled anaesthetics, muscle relaxants or neuromuscular blocking agents, intubation, and/or ketamine) ~ 15 %
		
		Outcomes
		primary
			Selection bias
			randomization:
			low
			concealment and unpredictability:
			low
			Performance bias
			blinding of participants and staff:
			low
			Detection bias
			blinding of evaluation:
			low
			Attrition bias
			lost to follow-up:
			low
			ITT-analysis:
			low
			(imputed values)
			Reporting bias
			selective result presentation:
			low
			Other bias
			Funding ReCor Medical.
				note: n=361 of n=989 enrolled patients with resistant hypertension did not meet ambulatory blood pressure criteria (354 too low)
				
				note: authors assessed PubMed from Jan 2017 to march 2021 to cover evidence before the study (n=11 MA, n=6 sham controlled) –
				
				authors documented one MA from 2021 [223] with n=6 eligible sham-controlled trials (first and second generation devices) + additional MA
				
				the added RADIANCE-HTN TRIO as designed to overcome the limitation of previous studies in patients with resistant hypertension
				
				to maintain masking, participants were sedated and wore headphones and eye covers + masking questionnaire

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- suitable renal artery anatomy (CTA or MRA) - patients switched to a once daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic* *No other antihypertensive medications were allowed except β blockers for chronic coronary syndrome or heart failure* **Intervention** ultrasound renal denervation Paradise System (ReCor Medical, Palo Alto, CA, USA) **Control** sham procedure note: after 4 weeks of standardised therapy, patients with daytime ambulatory blood pressure of ≥135/85 mm Hg were randomized addition of antihypertensive medications was allowed (e.g. BB as well as escape antihypertensive treatment (mainly spironolactone 25 mg)) **Outcomes** **primary** change in daytime ambulatory systolic blood pressure at 2 months	change in daytime ambulatory systolic blood pressure at 2 months (RD n=69 vs. SI n=67) mm Hg (Interquartilrange (IQR) - median between-group difference: –4·5 mm Hg (95% CI –8·5; –0·3); baselineadjusted, p=0·022 - median difference –8·0 (IQR –16·4; 0·0) vs –3·0 (IQR –10·3 to 1·8) - mean BP 141.0 (16.1) vs. 146.3 (18.8) safety - procedure-related pain lasting for >2 days: - n=12 (17%) vs. n=10 (15%) at 2 months: - death: n=1 (1%) vs. n=0 - acute myocardial infarction: n=1 (1%) vs. n=0 - coronary revascularisation: n=0 vs. n=1 (1%)		

* single-pill, fixed-dose, daily combination of amlodipine 10 mg (or 5 mg in the event of severe leg oedema), valsartan 160 mg (or olmesartan 40 mg depending upon medication availability in each country), and hydrochlorothiazide 25 mg

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	safety* **secondary** - change in 24-h ambulatory systolic and diastolic blood pressures - nighttime ambulatory systolic and diastolic blood pressures - daytime ambulatory diastolic blood pressure - change in all other office and home blood pressure …			

RADIOSOUND-HTN, NCT02920034

Fengler et al. Circulation 2019, 3-armig, 3-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

Fengler K, Rommel K-P, Blazek S, et al. A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension (RADIOSOUND-HTN). Circulation 2019; 139(5):590–600. DOI: 10.1161/CIRCULATIONAHA.118.037654. http://www.ncbi.nlm.nih.gov/pubmed/30586691. [224]	**Objective**
	to investigate the effects of ultrasound-based or additional side branch ablation in patients with large renal arteries and compare them with radiofrequency ablation of the main renal artery as a reference standard in a prospective randomized clinical trial
	
	Design
	single-blind, single-center, 3-arm randomized clinical trial; enrolment between June 2015 and Jube 2018, clinicaltrials.gov (NCT02920034)
	
	Inclusion and exclusion criteria:
	- screening of patients with resistant hypertension (office BP
		n=120 patients included
		- n=39 RFM-RDN, n=39 RFB-RDN, n=42 USM-RDN
		- mean age 63.5 (SD 9.4)
		- female n=37 (31%)
		- mean number of antihypertensive drug classes baseline: n=5.0 (SD 1.4)
		- ≥5 drug classes: n=69 (58%)
		- most prescribed antihypertensives at baseline:
		  ○ diuretics n=117 (98%), BB n=104 (87%), CCB n=91 (76%), ARB n=85 (71%) …
		- ablation points right renal artery: 10.0 (SD 7.4), n=120
		  ○ n=39 RFM-RDN, n=39 RFB-RDN, n=42 USM-RDN
		  ○ 9.1 (3.0) vs. 18.3 (6.1) vs. 3.2 (0.8)
		- ablation points left renal artery
		- lost-to follow up: n=1 vs. n=2 vs. n=0
		- n=117 patients were analysed
			Selection bias
			randomization:
			low
			concealment and unpredictability:
			unclear
			Performance bias
			blinding of participants and staff:
			low
			Detection bias
			blinding of evaluation:
			unclear
			Attrition bias
			lost to follow-up:
			unclear
			ITT-analysis:
			high (PP)
			Reporting bias
			selective result presentation:
				patient's general practitioners were contacted and asked if participation was possible and if the patient was considered adherent to medication; patients without sufficient medication adherence according to their treating physician's view were excluded
				
				definitions:
				- BP response:
				reduction of ≥5 mm Hg in systolic daytime BP on ABPM at 3 months

* major adverse events: all-cause mortality, renal failure, an embolic event, renal artery or vascular complications requiring intervention, or hypertensive crisis within 30 days of the study procedure, and new onset renal artery stenosis greater than 70% within 6 months of the study procedure

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	>160 mm Hg systolic or >90 mm Hg diastolic) despite treatment with ≥3 different classes of antihypertensive drugs on at least 50% of maximum dosage for hypertension, including at least 1 diuretic unless intolerant to diuretics) - stable antihypertensive medication for at least 4 weeks - white-coat hypertension was excluded - included were patients with resistant hypertension and systolic daytime BP >135 mm Hg on ABPM and renal artery diameter of at least 1 main renal artery ≥5.5 mm (MRI, i.a. duplex ultrasound) - aged ≥18 and ≤75 years **Comparison** radiofrequency ablation* of the main renal artery (RFM-RDN) vs. radiofrequency ablation of the main renal artery, branches, and accessories (RFB-RDN) vs. ultrasound-based ablation† of the main renal artery (USMRDN) **Outcomes** **primary** - daytime blood pressure change (3 months after Intervention) ABPM **secondary**	**Outcomes** **primary** daytime blood pressure change (3 months after Intervention) ABPM: ○ ultrasound ablation group vs. radiofrequency ablation group of the main renal artery –13.2±13.7 vs. –6.5±10.3 mm Hg mean difference –6.7 [98.3% CI, –13.2 to –0.2], adjusted P=0.043 ○ between the ultrasound and the side branch ablation groups mean difference –4.9 mm Hg [98.3% CI, –11.5 to 1.7], adjusted P=0.22 ○ between the radiofrequency ablation groups –8.3±11.7 mm Hg for additional side branch ablation, mean difference –1.8 mm Hg [98.3% CI, –8.5 to 4.9], adjusted P>0.99 - n=120, systolic/diastolic BP difference from baseline: ○ -9.5 (SD 12.3) mm Hg, P<0.001 / -6.3 (SD 7.8) mm Hg, P<0.001 **safety** n=1 transient renal artery spasm (USM-RDN group) n=1 transient noninvasive ventilation (USM-RDN group) n=1 symptomatic groin hematoma (RFB-RDN group) n=1 pseudoaneurysm (USM-RDN group) n=1 postprocedural intracapsular and retroperitoneal hematoma (RFM-RDN group) adverse events at follow-up n=2 symptomatic hypotension (RFB-RDN group) n=1 symptomatic hypertension requiring medical treatment (RFM-RDN) and n=2 (RFB-RDN group)	unclear (no publication of protocol available) **Other bias** single-center design costs were covered by the Leipzig Heart Institute.	- profound BP response: reduction of ≥20 mm Hg in systolic daytime BP on ABPM at 3 months - isolated systolic hypertension: daytime BP >135 mm Hg systolic and <85 mm Hg diastolic

* multipolar Symplicity Spyral catheter was used (Medtronic), catheter type administers ≤4 ablations simultaneously in a spiral pattern by creating heat using high-frequency electric energy
† Paradise catheter (ReCor Medical), a balloon-cooled device that creates a fully circumferential thermal ablation pattern using acoustic energy

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- rate of responders, change in 24-hour systolic ABPM, and diastolic BP changes	n=1 hospitalized for acute decompensated heart failure (RFB-RDN group) n=1 death (RFM-RDN group)		

REDUCE HTN: REINFORCE, NCT02392351

Weber et al. JACC Cardiovasc Interv 2020, 8-Wochenergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

Weber MA, Kirtane AJ, Weir MR, et al. The REDUCE HTN: REINFORCE: Randomized, Sham-Controlled Trial of Bipolar Radiofrequency Renal Denervation for the Treatment of Hypertension. JACC. Cardiovascular interventions 2020; 13(4):461–70. DOI: 10.1016/j.jcin.2019.10.061. http://www.ncbi.nlm.nih.gov/pubmed/32081240. [225]	**Objective**
	to investigate bipolar radiofrequency renal denervation in patients with hypertension not receiving medications at baseline
	
	Design
	prospective, randomized, blinded investigation; enrolment Apr 2015 to Oct 2017, NCT02392351
	
	Inclusion and exclusion criteria:
	- patients with office systolic blood pressure (SBP) ≥150 and ≤180 mm Hg and average 24-h ambulatory SBP ≥135 and ≤170 mm Hg after medication washout
	- naive to antihypertensive medication or had washed out their medication
	- aged 18 to 75 years
	- suitable renal artery anatomy
	- estimated glomerular filtration rate <40 ml/min/1.73m2
	
	Intervention
		enrollment was terminated for apparent futility before a sufficient sample for powered efficacy comparisons was enrolled
		- all reported BP measurements for both treatment groups are considered exploratory
		
		n=51 patients were included
		n=34 vs. n=17 patients were included
		- n=33 vs. n=1 at 8-week and 6 months follow-up
		- n=33 vs. n=15 at 12 months follow-up
		- one in both groups withdrew
		- mean age 58.5 (SD 10.1) vs. 58.2 (SD 9.8)
		- female n=16 (47%) vs. n=4 (24%)
		- n=8 patients initiated rescue antihypertensive medication prior to 8 week (n=6 RD vs. n=2 SI)
		- number of antihypertensives at 8 weeks 2.5 vs. 2.0
		- baseline 24-h blood pressure:
		  ○ RD: 148.3 (SD 10.9) / 85.7 (SD 9.1) mm Hg (n=34)
		  ○ sham: 149.1 (SD 7.2) / 86.4 (SD 9.8) mm Hg
		
		Outcomes
		mean 24h ambulatory systolic/diastolic blood pressure (RD vs. SI), mm Hg ±SD (95% CI)
		Baseline
		- 148.3±10.9 (144.6, 151.9) vs. 149.1±7.2 (145.7, 152.6)
		- difference -0.9±9.8 (-6.6, 4.9), p=0.771
			Selection bias
			randomization:
			low
			concealment and unpredictability:
			unclear
			Performance bias
			blinding of participants and staff:
			low
			Detection bias
			blinding of evaluation:
			low
			Attrition bias
			lost to follow-up:
			low
			ITT-analysis:
			low
			Reporting bias
			selective result presentation:
			low
			Other bias
			lack of statistical power
				note: intraprocedural anticoagulation therapy

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	bipolar radiofrequency renal denervation (Vessix Renal Denervation System) **Control** sham-control (renal angiography alone) note: antihypertensive medications were not to be used through the 8-week assessment unless rescue criteria were met; stepped medications were introduced per protocol (not considered "rescue") after the 8-week if a patient's office SBP was ≥140 mm Hg* **Outcomes** **primary** 8-week change in 24-h ambulatory SBP safety: all-cause death, renal failure, severe hypotension or sycope, hypertensive crisis, and renal artery stenosis	- 85.7±9.1 (82.6, 88.8) vs. 86.4±9.8 (81.7, 91.0) - difference -0.6±9.3 (-6.1, 4.8), p=0.817 - n=34 vs. n=17 8 weeks - 143.3±14.2 (138.3, 148.2) vs. 139.9±8.4 (135.7, 144.2) - difference 3.3±12.7 (-4.4, 11.1), p=0.407 - 83.3±8.9 (80.2, 86.4) vs. 80.5±9.1 (75.9, 85.2) - difference 2.8±9.0 (-2.7, 8.3), p=0.328 - n=32 vs. n=15 6 months - 130.7±13.4 (125.9, 135.5) vs. 138.1±10.6 (132.7, 143.4) - difference -7.4±12.6 (-15.2, 0.4), p=0.071 - 76.5±10.0 (72.9, 80.0) vs. 79.5±8.7 (75.1, 84.0) - difference -3.1±9.6 (-9.0, 2.9), p=0.317 - n=30 vs. n=15 12 months - 130.1±13.9 (125.0, 135.2) vs. 135.0±8.6 (130.1, 139.9) - difference -4.9±12.6 (-13.4, 3.6), p=0.266 - 74.7±8.5 (71.6, 77.8) vs. 79.1±9.4 (73.7, 84.4) - difference -4.4±8.7 (-10.2, 1.5), p=0.154 - n=29 vs. n=12 percentage of patients at target blood pressure (office BP < 140 mm Hg) o 8 weeks: n=8 (24%) vs. n=4 (24%), p >0.99 o 6 months: n=17 (52%) vs. n=2 (12%), p<0.01 o 12 months: n=14 (42%) vs. n=2 (13%), p=0.048 safety at 12 months: hypertensive urgency: n=1 patient (RD group) progression of renal artery stenosis: n=1 (RD group)		

* 1) amlodipine 5 mg; 2) angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at maximum dose; 3) hydrochlorothiazide 12.5 mg; and 4) a thiazide diuretic agent 25 mg and amlodipine 10 mg.

REQUIRE, NCT02918305

Kario et al. Hypertens Res 2022, Japan und Südkorea, 3-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Kario K, Yokoi Y, Okamura K, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: The randomized, controlled REQUIRE trial. Hypertension research official journal of the Japanese Society of Hypertension 2022; 45(2):221–31. DOI: 10.1038/s41440-021-00754-7. http://www.ncbi.nlm.nih.gov/pubmed/34654905. [226]	**Objective** to assess the BPlowering efficacy of renal denervation in treated patients with resistant hypertension from Japan and South Korea (hypothesis) **Design** randomized, single-blind, sham-controlled trial; enrolment between January 12, 2017 and March 31, 2020; NCT02918305 (http://www.clinicaltrials.gov) *design*: Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. Am Heart J 2018; 195: 115–29. **Inclusion and exclusion criteria:** - resistant hypertension (defined as averaged seated office blood pressure ≥150/90 mmHg and 24-hour ambulatory systolic blood pressure ≥140 mmHg during a screening period of ~4–8 weeks prior to the procedure) despite treatment with stable regimen incl. max. tolerated dosages of at least 3 antihypertensives (including diuretic) - Asian patients (Japan and South Korea)	n=143 patients were included - n=72 RD vs. n=71 sham control - n=1 patient did not complete the 3-months follow-up (withdrew from study) - n=69 vs. n=67 patients were analyzed (valid data for primary outcome) - mean age 50.7 (SD 11.4) vs. 55.6 (SD 12.1) - female n=21 (30%) vs. n=14 (21%) - office BP systolic 157.6 (SD 19.5) (n=69) vs. 160.4 (SD 14.9) (n = 66) - number of antihypertensives (n=3) n=32 (46.4%) vs. n=29 (43.3%) patients - most prescribed antihypertensives: RAS blocker, CCB, diuretics - procedure time (86.7 vs 40.6 min), x-ray fluoroscopy time (23.6 vs 5.2 min) **Outcomes**: **primary** between-group difference in change in 24-hour ambulatory SBP from baseline at 3 months (RD vs. SI), n=69 vs. n=67 - −6.6 mmHg vs. −6.5 mmHg - difference: −0.1, 95% CI −5.5, 5.3; p = 0.971 safety: - procedural success rate 98.6% - procedure-/device-related major adverse events were not seen - within 30 days post-procedure: - n=6 vs. n=6 patients (with most common specific clinical event) procedure related pain lasting for >2 days (e.g., back pain, puncture site pain, etc.) - n=4 vs. n=0 vasospasm of renal artery - n=4 vs. n=3 complication at femoral puncture site	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low **Attrition bias** lost to follow-up: unclear ITT-analysis: unclear **Reporting bias** selective result presentation: low **Other bias** baseline characteristica of analyzed patients differed between groups (e.g age, BP, number of antihypertensives), JIMRO Co., Ltd. And Korea Otsuka Pharmaceutical Co., Ltd.	authors added that SYMPLICITY HTN-JAPAN was stopped early after results of SYMPLICITY HTN-3 were reported and that they therefore want to add information on patients in Asia authors documented no standardization of antihypertensive medications and no objective measurement of medication adherence (introduction notes that there are a number of potential factors that contribute to the suboptimal control of hypertension, including medication non-adherence and prescribing inertia) authors discussed that Global committees of experts recommended a number of important trial design changes including: (1) standardization of the renal denervation procedure; (2) measurement of ambulatory BP as a

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- aged 20–75 years - suitable renal artery anatomy (CTA or MRA) - patients e.g. with chronic kidney diseases, secondary hypertension, inadequately controlled diabetes were excluded **Intervention** ultrasound renal denervation, Paradise TM Renal Denervation System (ReCor Medical Inc., Palo Alto, CA, USA), bilaterally to the main renal artery **Control** sham procedure (renal angiogram only) - stayed in the catheterization laboratory with the sheath inserted for ≥20 min *note:* standard-of-care antihypertensive medication was to remain unchanged up to the 3-month follow-up data collection **Outcomes** **primary** between-group difference in change in 24-hour ambulatory SBP from baseline at 3 months safety **secondary** - change in daytime and nighttime ambulatory SBP from baseline at 3 months,			primary outcome; (3) standardization of medications; and (4) measurement of medication adherence significant seasonal variation of the temperature and BPs in Japan were reported(limitation)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- change in 24-hour, daytime and nighttime ambulatory diastolic BP (DBP) from baseline at 3 months, - change in seated office SBP and DBP from baseline at 3 months			

ReSET, NCT01459900 (auch Pisano et al. Cochrane 2021)

Peters et al. Blood pressure 2017, 6-Monatsergebnisse

Mathiassen et al. J Hypertens 2016, 24 h ABMP

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar

Peters CD, Mathiassen ON, Vase H, et al. The effect of renal denervation on arterial stiffness, central blood pressure and heart rate variability in treatment resistant essential hypertension: A substudy of a randomized sham-controlled double-blinded trial (the ReSET trial). Blood pressure 2017; 26(6):366–80. DOI: 10.1080/08037051.2017.1368368. http://www.ncbi.nlm.nih.gov/pubmed/28830251. [227]
 	
Mathiassen ON, Vase H, Bech JN, et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. Journal of hypertension 2016; 34(8):1639–47. DOI: 10.1097/HJH.0000000000000977.
	Objective
	to address the effect of RDN on BP measured by ABPM
	
	Design
	double-blind, randomized,controlled, single-center trial,
	Denmark, n=7 dedicated hypertension outpatient clinics and a single invasive cardiovascular center*
	NCT01459900, conducted between September 2011 and February 2015
	
	Inclusion and exclusion criteria:
	- therapy-resistant essential hypertension (defined as a sustained BP level above target despite concurrent use of at least three different antihypertensive drugs including a diuretic)
		n=69 patients randomized
		- n=36 RD vs. n=33 SI
		- no patients were lost to follow-up, and no patients were unblended prematurely
		- mean age 54.6 (SD 7.8) vs. 57.1 (SD 9.6) years
		- men 75% vs. 73%
		- mean office blood pressure 160 vs. 166 mmHg
		- mean number of antihypertensive drugs 4.1 vs. 4.2
		- most common at baseline: diuretics 86% vs. 85%, BB 81% vs. 76%, ARB 61% vs. 61%, ACEI 53% vs. 45%, CCB 53% vs. **85%**
		- half of the patients had changes in antihypertensive medication at 3 and 6 months follow-up
		- mean procedure time RD 42+/-11 min
		
		substudy: Peters et al. 2017
		- n=53 patients (77%) were analysed
		  ○ n=26 RD vs. n=27 SI
		  ○ 65% vs. 78% males
		  ○ mean age 54 ± 8 years vs. 59 ± 9
		  ○ mean antihypertensive drugd n=4.4 vs. n=4.2
			Selection bias
			randomization:
			unclear
			concealment and unpredictability:
			unclear
			Performance bias
			blinding of participants and staff:
			low
			Detection bias
			blinding of evaluation:
			low
			Attrition bias
			lost to follow-up:
			low / unclear for Peters et al. 2017 (only n=53 patients were included in this substudy; because phygmoCor measurements were not performed)
			ITT-analysis:
			unclear
			Reporting bias
			selective result presentation:	

* performed by one single experienced invasive cardiologist who, in addition, was both proctored and further qualified by 10 pretrial technically successful RDN procedures

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
http://www.ncbi.nlm.nih.gov/pubmed/27228432. [228] ReSET=Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Controlled Randomized Trial	- aged between 30 and 70 years - systolic daytime ABPM ≥145 mmHg - during the run in of at least 1 month, medication was kept unaltered - single pill medication - e.g. secondary hypertension and chronic renal failure were excluded changes in antihypertensive medication only allowed if requested by the patient or if potentially harmful changes in e.g. BP **Intervention** catheter-based renal denervation (RDN) - catheter-based lowenergy radiofrequency ablation in the renal arteries (Medtronic unipolar Symplicity FlexTM catheter) **Control** SHAM procedure (after unblinding open-label RDN) **Outcomes***	○ systolic brachial BP 154 ± 17 mm Hg vs. 158 ± 18 mm Hg ○ systolic 24-hour ambulatory BP 151 ± 13 mm Hg vs. 153 ± 14 mm Hg ○ PWW 10.1 (SD 2.2) m/s vs. 10.7 (SD 2.1) m/s **Outcomes:** **primary** Changes in systolic 24-h ambulatory blood pressure monitoring parameter from baseline (mmHg), paired data (RD vs. SI), not adjusted for changes in antihypertensives 1-months, n=31 vs. n=31 - -6.0 (SD 11.0) vs. 0.0 (SD 15), p=0.08 3-months, n=35 vs. n=32 - -6.2 (SD 18.8) vs. -6.0 (SD 13.5), p=0.95 6-months, n=35 vs. n=33 - -6.1 (SD 18.9) vs. -4.3 (SD 15.1), p=0.66 safety: no procedural complications were reported apart from two cases of self-limiting femoral hematoma a few patients reported adverse reactions during follow-up n=1 vs. n=2 patients were hospitalized due to increasing BP n=0 vs. n=1 stroke	unclear (no published protocol available, additional outcomes on clinicaltrials.gov) **Other bias** single-center trial, high-risk population, short term outcomes (1 months)	

* Eintrag ClinicalTrials.gov:
Primary Outcome Measures:
daytime systolic blood pressure assessed by 24 hours ambulatory BP measurement [Time Frame: 3 months follow up] Changes in mean daytime systolic BP after 3 months is compared between groups. Also the proportion of responders versus nonresponders after 3 months is compared between groups, responders being defined as A) a minimum decrease in daytime systolic BP of 10 mmHg analysis together with and unchanged/increased number of antihypertensive drugs, or B) a decrease in daytime systolic BP of 0-10 mmHg together with a reduced number of antihypertensive drugs.

Secondary Outcome Measures:
- ambulatory 24 hours BP measurements [Time Frame: 1, 3 and 6 months]
  Systolic, diastolic and mean Blood Pressures at different time points. Daytime and night time BP, dipping status, morning BP surge and BP variation.
- Echocardiography [Time Frame: 6 months]

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	primary mean change in daytime systolic ABPM from baseline to 3 months (between groups) safety **secondary** vasoactive hormones analysis (Angiotensin II and arginine–vasopressin, Aldosterone, plasma renin) central aortic BP (C-BP), carotid-femoral pulse wave velocity (PWV), and heart rate variability (HRV) in Peters et al. 2017 two-sided unpaired and paired t tests; noted level of significance: 0.05 - pulse wave analysis (PWA) and PWV measurements were performed by trained investigators in a quiet room after at least 5 minutes of supine rest using applanation tonometry applied on the carotid artery (CA), femoral artery (FA), and radial artery with the SphygmoCor (version	n=0 vs. n=1 percutaneous coronary intervention due to unstable angina **substudy**: changes in PWV after 6 months - 0.1 ± 1.9 (SHAM) vs. -0.6± 1.3 (RDN) m/s - systolic C-BP -2 ± 17 (SHAM) vs. -8 ± 16 (RDN) mmHg) - diastolic C-BP -2 ± 9 (SHAM) vs. -5 ± 9 (RDN) mmHg - augmentation index 0.7 ± 7.0 (SHAM) vs. 1.0± 7.4 (RDN) %		

Coronary flow reserve (LAD), Diastolic and Systolic ventricular function. LV hypertrophy.
- Biomarkers [Time Frame: 1 months]
  Biomarkers concerning renal sodium excretion
- Applanation tonometry [Time Frame: 6 months]
  Pulse wave velocity, augmentation index, central BP estimates
- forearm plethysmography [Time Frame: 6 months]
  Forearm minimum vascular resistance

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	8.2, Atcor Medical, Sydney, Australia) system			

SPYRAL HTN-OFF MED Pivotal, NCT02439749

Böhm et al. Lancet 2020, 3-Monatsergebnisse (Bayesian design)

Townsend Lancet 2017, 3-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): A multicentre, randomised, sham-controlled trial. Lancet (London, England) 2020; 395(10234):1444–51. DOI: 10.1016/S0140-6736(20)30554-7. http://www.ncbi.nlm.nih.gov/pubmed/32234534. [229] Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): A randomised, sham-controlled, proof-of-concept trial. Lancet (London, England) 2017; 390(10108):2160–70. DOI: 10.1016/S0140-6736(17)32281-X. http://www.ncbi.nlm.nih.gov/pubmed/28859944. [221] SPYRAL HTN Global Clinical Trial Program (eine der ersten beiden Untersuchungen)	**Objective** to assess the efficacy of catheter-based renal denervation in the absence of antihypertensive medications **Design** prospective, single-blind, randomised, controlled trial; from June 25, 2015, to Oct 15, 2019 Bayesian study design (combination of pilot and pivotal); proof-of-concept trial (pilot, SPYRAL HTN-OFF MED, interim analysis), efficacy trial (SPYRAL Pivotal) **Inclusion and exclusion criteria:** - aged 20–80 years - office systolic blood pressure from 150 mm Hg to < 180 mm Hg - office diastolic blood pressure ≥ 90 mm Hg - mean 24h ABPM systolic ≥140 mm Hg but < 170 mm Hg - eligible renal artery anatomy - drug-naiive or wash-out phase	n=331 randomized (pilot: n=80; pivotal n=251) - supplement - ITT: n=166 RD vs. n=165 sham - mean age 52.4 (SD 10.9) vs. 52.6 (SD 10.4) years - at 3 months n=162 vs. n=164 (n=3 vs. n=1 misses visit; n=1 vs. n=0 withdrew consent) - at 3 months 24h-BP n=142 vs. n=134 (without escape and outside analysis window) - at 3 months office BP n=156 vs. n=150 (without escape) - mean procedure time: RD 99·6 min (SD 37·3) vs. sham 52·9 min (16·6) - abstain from all antihypertensive medications was assessed baseline and at 3 months **Outcomes**: **primary**: change in mean 24-h systolic blood pressure from baseline to 3 months (RD vs. SI), ITT - treatment difference: mm Hg (Bayesian 95 % credible interval (BCI)) –3·9 (–6·2; –1·6), p=0.0005 - posterior probability of superiority > 0·999 24-h systolic blood pressure – treatment difference (95% CI), p value Pilot* (n=70) –4·9 (–9·6 to –0·3), 0·037 Pivotal (n=204) –3·6 (–6·2 to –1·0), 0·0064 Overall (n=274) –4·0 (–6·2 to –1·8), 0·0005, ANCOVA-adjusted frequentist analysis, as treated population*	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low **Attrition bias** lost to follow-up: low ITT-analysis: low **Reporting bias** selective result presentation: low **Other bias** Metronic. Townsend et al. 2017 proof-of-concept	authors searched PubMed from Nov 2012 to Jan 2020 and documented SYMPLICITY HTN-3, two pilot studies; they added SPYRAL Pivotal trial as powered to show efficacy first publication: proof-of-concept: authors documented no powered endpoints in the trial; for a properly powered randomised trial assuming a 5 mm Hg SBP reduction with a standard deviation of 12, 246 patients would be required second publication: specified interim analyses: power 94% as well as 83 % prespecified ANCOVA-adjusted frequentist analysis

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- patients with e.g. stable or unstable angina or myocardial infarction, heart failure, AF were excluded **Intervention** renal denervation - Symplicity Spyral multielectrode renal denervation catheter (Medtronic; Galway, Ireland) and the Symplicity G3 radiofrequency generator **Control** sham control (only renal angiography) - patients were required to remain on the table for at least 20 min after renal angiography to help prevent unmasking **Outcomes** **primary** change in mean 24-h systolic blood pressure from baseline to 3 months safety at 3 months **secondary** - change in mean office systolic blood pressure from baseline to 3 months - changes in systolic and diastolic blood pressure from baseline at 3, 6, 12, 24, and 36 months - changes in office systolic and diastolic blood pressure from baseline and incidence of achieving target systolic blood	- -4.7 (-6.4; -2.9) vs. -0.6 (-2.1; 0.9), - n=140 vs. n=134 * all randomized patients, analyzed according to the actual treatment received (randomized to RDN who do not get treated will be analyzed in the control arm) Escape subjects analyzed with last carried forwards to 3 months note: ITT n=1 withdrew consent unclear (data analysis possible?) n=166 vs. n=165 or n=165 vs. n=165 safety: - at 1 months: no major safety events reported, n=166 vs. n=165 - at 3 months: n=1 vs. n=1 major safety event o RD n=1 admission to hospital for hypertensive crisis or emergency o sham n=1 new stroke		Böhm et al. 2020 used a Bayesian design that allows for prespecified interim analyses with predetermined stopping rules for efficacy or futility of the primary and secondary efficacy endpoints enrolment will only stop at an interim analysis if both endpoints meet prespecified stopping criteria the primary and secondary efficacy endpoints were met if the posterior probabilities of superiority were more than 0·975

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	pressure (<140 mm Hg) at 1, 3, 6, 12, 24, and 36 months intention-to-treat (ITT) population was used for the primary efficacy analysis and consists of all randomly assigned patients in this trial and the previous randomised pilot trial, analysed according to their assigned treatment (Bayesian) modified ITT and PP analyses* were also used as sensitivity analysis (prespecified ANCOVA)			

SPYRAL HTN-ON MED, NCT02439775

Mahfoud et al. Lancet 2022, 24/36-Monatsergebnisse

Kandzari et al. Lancet 2018, 6-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): A randomised, sham-controlled trial. Lancet (London, England) 2022; 399(10333):1401–10. DOI: 10.1016/S0140-6736(22)00455-X. http://www.ncbi.nlm.nih.gov/pubmed/35390320. [230]	**Objective** to assess changes in blood pressure, antihypertensive drug use, and safety up to 36 months in renal denervation vs. sham control group **Design** single-blind, controlled, randomised trial; proof-of-concept trial,enrolement between July 2015 and Jun 2017, NCT02439775	n=80 patients randomized - ITT: n=38 RD vs. n=42 SI - mean age 53.9 (SD 8.7) vs. 53.0 (SD 10.7) years - male 87% vs. 81% - mean number of antihypertensives o baseline 2·13 vs. 1·98 o 3 months 1·84 vs. 2·05 o 6 months 2·13 vs. 2·21 o 12 months 2·53 vs. 2·81 o 24 months 2·97 vs. 2·95 o 36 months 3·03 vs. 3·05	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low	authors documented uncertainty regarding the future role of RD for management of hypertension after SYMPLICITY HTN-3; proceed with two smaller proof-of-concept trials that would minimise exposure of patients but have the potential to establish

* "A modified intention-to-treat cohort excluded patients who met escape criteria (SBP ≥180 mm Hg). For patients meeting escape criteria, the last observation was carried forward for the 3-month blood pressure assessment. A per-protocol analysis was also done, which excluded patients meeting escape criteria, who had antihypertensive medications measured in urine or serum, and who had at least one non-standardised blood pressure assessment. To adjust for baseline blood pressure measurements, ANCOVA was used as an additional analysis of changes in blood pressure." (vgl. Townsend et al. Lancet 2017 [221], p 2163)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet (London, England) 2018; 391(10137):2346–55. DOI: 10.1016/S0140-6736(18)30951-6. http://www.ncbi.nlm.nih.gov/pubmed/29803589. [231] SPYRAL HTN Global Clinical Trial Program (eine der ersten beiden Untersuchungen)	- prospectively, additional 260 patients randomly assigned as part of the SPYRAL HTN-ON MED Expansion trial **Inclusion and exclusion criteria:** - aged 20–80 years - office systolic blood pressure ≥ 150 mm Hg but < 180 mm Hg, office diastolic blood pressure ≥ 90 mm Hg, - mean 24-h systolic blood pressure ≥ 140 mm Hg but < 170 mm Hg, - taking one to three standard antihypertensive medications - individuals had undergone prior RD or had renal failure, diabetes mellitus, pulmonary hypertension were excluded **Intervention** radiofrequence renal denervation - Symplicity Spyral multielectrode renal denervation catheter (Medtronic, Galway, Ireland) and the Symplicity G3 renal denervation RF generator (Medtronic, Minneapolis, MN, USA) **Control** sham control **Outcomes** **primary**	- most common: ACEI/ARB (82 vs. 83 %), CCB, diuretic - denervation time 60.8 (SD 25.3) min, n=38 - at 3 months 24-h BP n=35 vs. n=32 - at 6 months 24-h BP n=36 vs. n=36 - at 12 months 24-h BP n=34 vs. n=38 - at 24 months 24-h BP n=33 vs. n=17 - at 36 months 24-h BP n=30 vs. n=19 + 13 cross-overs - in RD n=3 withdrew, and n=3 missed visits - in SI n=2 withdrew, n=10 missed visits and n=1 death **Outcomes** **primary** treatment difference in mean 24-h systolic blood pressure, mm Hg (SD) at 3 months - -4.8 (9.8) vs. -0.2 (13.1), p=0.10 - suppl. Table S5 2018 - mean (SD) 147.9 (10.9), n=35 vs. 150.2 (11.9), n=32, p=0.41 – suppl. Table S4 2022 at 6 months - -7.4 (-12.5; -2.3), p=0.0051, n=36 vs. n=36, unadjusted, unpaired t-test - -7.0 (-12.0; -2.1), p=0.0059, n=36 vs. n=36, ANCOVA analysis adjusted for baseline BP - -9.0 (11.0), n=36 vs. -1.6 (10.7), n=36 - mean (SD) 142.6 (10.9), n=36 vs. 149.5 (11.9), n=36, p=0.01 - -6.9 (95% CI -11.7; -2.0), p=0.0066, n=34 vs. n=35, modified ITT, paired t-test - suppl. Table S7 2018 - -6.8 (-11.5; -2.1), p=0·0055, modified ITT, ANCOVA analysis adjusting for baseline BP, - suppl. Table S7 2018 - -9.4 (11.0), n=34 vs. -2.5 (9.3), n=35 modified ITT - suppl. Table S7 2018 at 12 months	**Attrition bias** lost to follow-up: low ITT-analysis: low **Reporting bias** selective result presentation: low **Other bias** Medtronic. Proof-of-concept trial	sufficient evidence to justify moving to a larger, powered trial they searched PubMed from Jan 2018 to Jan 2022 and reported 39 clinical trial reports ans 24 review papers (11 MA) they added especially long term safety outcomes authors noted that they did not evaluate changes in patients' exercise, diet, or smoking habits, which could have influenced blood pressure measurements; as well as it was unclear whether COVID-19 affected patients' blood pressure and behaviour authors noted that future clinical studies should prioritise equitable enrolment of women *masking*: during the procedures they used of conscious sedation, blindfolding, music, and patients' lack of familiarity with the procedures; the staff was

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	treatment difference in mean 24-h systolic blood pressure at (3), 6 , (12), 24 and 36 months safety **secondary** change in office BP incidence of achieving target office systolic BP before monitoring started, study personnel documented pill identity and observed the patient swallowing their antihypertensive medication (directly observed treatment); at follow-up visits urine and blood analysis were performed (TDM ?) no antihypertensive drug changes were allowed through 6 months unless escape criteria, protocol allowed changes after 6 months at the discretion of the treating physician interim analyses were planned analyses were done based on the intention-to-treat principle modified intention-to-treat (excluding patients with escape criteria) and per-protocol analysis (escape criteria and non-adherence, non-standardized BP assessment) were also performed	- mean (SD) 142.0 (12.9), n=34 vs. 142.8 (13.0), n=38, p=0.81 – suppl. Table S4 2022 at 24 months - -11.2 (95% CI -18.4; -4.0), p=0.003, (without imputation) – suppl. Table S3 - -16.0 (11.0), n=33 vs. -4.7 (13.9), n=17, (without imputation) – suppl. Table S3 - mean (SD) 135.8 (11.7), n=33 vs. 146.8 (14.6), n=17, p=0.006 – suppl. Table S4 - -11·2 mm Hg (95% CI –18·4 to –4·0); p=0·0031, adjusted treatment difference - -16.0, n=33 vs. -4.7, n=17 at 36 months - -6.1 (95% CI -13.6; 1.4), p=0.11; (without imputation) – suppl. Table S3 - -18.7 (12.4), n=30 vs. -12.4 (15.4), n=19; (without imputation) – suppl. Table S3 - mean (SD) 132.9 (12.2), n=30 vs. 142.8 (14.1), n=32, p=0.004 – suppl. Table S4 - –10·0 (95% CI –16·6; –3·3), p=0·0039; adjusted treatment difference - –18·7 (12·4), n=30 vs. –8·6 (14·6), n=32 **safety** during 36 months n=1 vs. n=1 compodite safety endpoint (e.g. all-cause mortality, end-stage renaldisease, others) n=0 vs. n=1 death n=1 vs. n=0 new stroke n=1 vs. n=0 hospitalisation for hypertensive crisis or emergency changes in 24h systolic BP from Mahfoud et al. 2022 Fig1, adjusted treatment difference (?) - 3 months -4.0 vs. 0.3, p=0.231, n=35 vs. n=32 - 6 months -9.3 vs. -1.6, p=0.553, n=36 vs. n=36 - 12 months -9.7 vs. -7.8, p=0.533, n=34 vs. n=38		also blinded at all follow-up visits

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		- 24 months -4.7 vs. -16.0 p=0.0031, n=33 vs. n=17 - 36 months -18.7 vs. -8.6, p=0.0039, n=30 vs. n=32 (cross-over included)		

SYMPLICITY, NCT01534299

Mahfoud et al. Eur Heart J 2017, Registerdaten, isolierte systolische Hypertonie

Böhm et al. Hypertension 2015, Registerdaten, 6 Monate, insb. zur Sicherheit

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Mahfoud F, Bakris G, Bhatt DL, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: Data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. European heart journal 2017; 38(2):93–100. DOI: 10.1093/eurheartj/ehw325. http://www.ncbi.nlm.nih.gov/pubmed/28158510. [232] Böhm M, Mahfoud F, Ukena C, et al. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension (Dallas, Tex. 1979) 2015; 65(4):766–74. DOI: 10.1161/HYPERTENSIONAHA.114.05010. http://www.ncbi.nlm.nih.gov/pubmed/25691618. [233] pooled data from Global SYMPLICITY registry (NCT01534299) and SYMPLICITY HTN-3 (NCT01418261)	**Objective** to assess the safety and effectiveness of renal denervation using the Symplicity system in realworld patients with uncontrolled hypertension **Design** prospective, open-label, multicenter registry (NCT01534299), RDN between Feb 1, 2012 and Sep 9, 2013 - electronic case reports Global SYMPLICITY Registry (goal: ≤5000 patients, aged ≥ 18 years, eligibility for RD via Symplicity RDN system (Metronic), recommended follow-up 5 years) Protocol: Böhm M, Mahfoud F, Ukena C, et al. Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. EuroIntervention. 2013;9:484–492. doi: 10.4244/EIJV9I4A78 **Inclusion and exclusion criteria:** - uncontrolled hypertension	n=998 patients (registry) - n=323 with severe hypertension - mean age: 61 (SD 11.9) years - men 60% - current smoking: 10.0% - mean baseline office systolic BP mm Hg: all patients: 163.5±24.0 patients with severe hypertension: 179.3±16.5 - mean baseline systolic 24-h BP: all patients: 151.5±17.0 patients with severe hypertension: 159.0±15.6 - high proportion of comorbidities, e.g. o diabetes mellitus (41.4%) o chronic kidney disease (22.3%) o atrial fibrillation (12.8%) o heart failure (10.7%) - number of ablations 13.8 (SD 4.1) - number of antihypertensive drug classes 4.5 (SD 1.3) - most common: diuretics (80.1%), CCB (79.2%), BB (76.9%), ACE/ARB (33.8-67.4%) SYMPLICITY HTN-3 (Mahfoud et al. 2017) n=125 ISH (n=48 sham) vs. n=225 CH (n=121 sham) - ISH were older - ISH had lower eGFR - ISH had lower heart rates	nicht anwendbar – Register limitations: - selected patients - lack of defined enrollment criteria fort he registry (real world population) - registry cannot standardize follow-up procedures worldwide - possible under-reporting of adverse events	authors noted that the Global SYMPLICITY registry (GSR)19 will provide data on periprocedural and renal safety as well as effectiveness Mahfoud et al. 2017 compared patients with isolated systolic hypertension (ISH - defined as baseline office SBP ≥140 and office DBP 90 mmHg) and patients with combined systolic–diastolic hypertension (CH – baseline office SBP ≥140 and office DBP ≥90 mmHg) from two study populations from SYMPLICITY HTN-3 and Global SYMPLICITY registry (n=1103)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- as well as severe hypertension (defined as office systolic pressure, ≥160 mm Hg; 24-hour systolic pressure, ≥135 mm Hg; and ≥3 antihypertensive medication classes) **Intervention** renal denervation performed with Symplicity RDN system note: instructions of use were not specified in the registry protocol **Data foundation registry** - diagnosis - confirmed hypertension medication intake (questioning) - medication changes - office and 24-hour ambulatory BP recommended - angiography, MRI, computed tomography, or duplex ultrasounds to detect renal artery abnormalities and to determine anatomic eligibility before the denervation (no mandatory renal artery imaging follow-up) **Outcomes** **primary** office and 24-hour ambulatory blood pressures at 6 months safety	SYMPLICITY registry (Mahfoud et al. 2017) n=288 ISH vs. n=373 CH - ISH patients were older (66 vs. 56 years) - ISH patients had lower eGFR (74.2+25.5 vs. 81.5+24.5 mL/min/1.73 m2) - ISH had lower heart rates (66 vs. 73 bpm) ➢ multivariate predictors of 6-months change in office SBP: o baseline office SBP, o baseline pulse pressure (PP), o total number of ablation attempts, o baseline aldosterone antagonists use, o lack of vasodilator use at baseline, o presence of CH **Outcomes**: changes in (office and 24-hour) systolic BPs, mm Hg (SD) At 6 months: o all patients, n=998: o office −11.6±25.3 P<0.001 mean (SD) 151.9±21.9 o 24-h −6.6±18.0 P<0.001 mean (SD) 144.6±17.4 o patients with severe hypertension, n=323: o office −20.3±22.8 o 24-h −8.9±16.9 P<0.001 major adverse events at 1 months o n=8 (0.8%) o n=2 postprocedural renal artery reintervention o n=4 postprocedural vascular complication o n=3 pseudoaneurysms o n=1 hematoma safety through 6 months o n=7 stroke o n=7 (spontaneous) myocardial failure o n=6 hospitalization for artrial fibrillation o n=5 hospitalization for hypertensive crisis/emergency o n=4 hospitalization for heart failure o n=2 end-stage renal disease		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	independent clinical events committee adjudicated all safety events note: Mahfoud et a. 2017 used multiple linear regression to determine predictors of SBP change	○ n=1 new renal artery stenosis >70%		

SYMPLICITY HTN-3, NCT01418261 (auch Pisano et.al. Cochrane 2021)

Bakris et al. J Am Coll Cardiol 2015, 12-Monatsergebnisse

Bakris et al. J Am Coll Cardiol 2014, ABPM, systolisch

Bhatt N Engl J Med 2014, Praxisblutdruckmessung, systolisch, 6-Monatsergebnisse

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Bakris GL, Townsend RR, Flack JM, et al. 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension: The SYMPLICITY HTN-3 trial. Journal of the American College of Cardiology 2015; 65(13):1314–21. DOI: 10.1016/j.jacc.2015.01.037. http://www.ncbi.nlm.nih.gov/pubmed/25835443. [234] Bakris GL, Townsend RR, Liu M, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: Results from SYMPLICITY HTN-3. Journal of the American College of Cardiology 2014; 64(11):1071–8. DOI: 10.1016/j.jacc.2014.05.012. http://www.ncbi.nlm.nih.gov/pubmed/24858423. [235] Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension.	**Objective** **Design** prospective, single-blind, randomized, controlled trial; NCT01418261, enrolment between oct 2011 and May 2013 Protocoll: Kandzari DE, Bhatt DL, Sobotka PA, et al. Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPLICITY HTN-3 Trial. Clin Cardiol 2012;35:528-35. **Inclusion and exclusion criteria:** - patients with severe resistant hypertension - systolic blood pressure ≥ 160 mm Hg - systolic 24-hour ambulatory blood-pressure ≥ 135 mm Hg - aged 18 to 80 years	n= 535 patients underwent randomization - n=364 vs. n=171 - n=101/171 of sham control crossed-over after unblinding - mean age 57.9 (SD 10.4) vs. 56.2 (SD 11.2) years - male 59.1 % vs. 64.3 % - receiving an average of five antihypertensive medications (the majority received hydrochchlorothiazide) **Outcomes** primary change in office systolic blood pressure at 6 months (RD vs. SI) - −2.39 mm Hg (95% CI, −6.89 to 2.12; P = 0.26 with a superiority margin of 5 mm Hg - −14.13±23.93 mm Hg vs. −11.74±25.94 mm Hg at 12 months - -15.5 (SD 24.1), n=319 RD at 6 months - -18.9 (SD 25.4), n=319 RD at 12 months - -17.7 (SD), n=92 cross-over at 6 months - there were no significant differences between 6- and 12-month ABPM changes	**Selection bias** randomization: unclear concealment and unpredictability: unclear **Performance bias** blinding of participants and staff: unclear **Detection bias** blinding of evaluation: unclear **Attrition bias** lost to follow-up: high ITT-analysis: high n=364 vs. n=171 patients randomized; n=353 vs. n=171 analyzed for primary analysis **Reporting bias** selective result presentation: low **Other bias** Metronic.	Blinding was done by a combination of conscious sedation, sensory isolation (e.g., blindfold and music), and lack of familiarity with procedural details and expected duration

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The New England journal of medicine 2014; 370(15):1393–401. DOI: 10.1056/NEJMoa1402670. http://www.ncbi.nlm.nih.gov/pubmed/24678939. [236]	- stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic **Intervention** - renal denervation **Control** - sham procedure (renal angiography only) changes in antihypertensive medication were not allowed during the 6-month follow-up period unless they were considered to be clinically necessary **Outcomes** **primary** - change in office systolic blood pressure at 6 months safety: composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months and 12 months **secondary** - change in mean 24-hour ambulatory systolic blood pressure	secondary change in ambulatory blood pressure at 6 months (RD vs. SI) - −1.96 mm Hg (95% CI, −4.97 to 1.06); P = 0.98 with a superiority margin of 2 mm Hg - −6.75±15.11 mm Hg vs. −4.79±17.25 mm Hg - additional day- and nighttime ambulatory BP were reported in Bakris et al. 2014 [235] safety: at 6 months major adverse event n=5/361 (1.4%) vs. n=1/171 (0.6%) composit safety end point at 6 months: n=14/354 (4.0%) vs. n=10/171 (5.8%) [236] note: reference values differed between [236] and [234] death: n=2 vs. n=1 hypertensive crisis or emergency: n=9 (2.6%) vs. n=9 (5.3%) at 12 months composite safety 24/355 (RD) vs. 5/95 (cross-over) vs. 5/69 (non-cross-over) death 1.8% vs. n.a. vs. 3.6%	medication adherence was not assessed	

WAVE IV, NCT02029885

Schmieder et al. J Hypertens 2018

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Schmieder RE, Ott C, Toennes SW, et al. Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. Journal of hypertension 2018; 36(3):680–9. DOI: 10.1097/HJH.0000000000001584. http://www.ncbi.nlm.nih.gov/pubmed/29035942. [237]	**Objective** to verify the blood pressure (BP)-lowering efficacy of externally delivered focused ultrasound for renal denervation (RDN) **Design** randomized, controlled, double-blind study, NCT02029885, enrolment from Nov 2014, stopped after an interim analysis (19 July 2016) – note: no safety concern **Inclusion and exclusion criteria:** - aged between 18 and 80 years - uncontrolled primary arterial hypertension - defined as office SBP ≥ 160mmHg while taking three or more antihypertensive medications at the maximally tolerated doses, with one required to be a diuretic - 24-h ABPM average SBP of ≥ 135mmHg - no medication changes within the month prior to baseline - secondary cause of hypertension was excluded **Intervention** renal denervation (Surround Sound System), bilateral ultrasound energy **Control** sham control (Surround Sound System)	n=81 randomized, n=42 vs. n=39 - mean age 60.3 (SD 11.2) vs. 62.0 (11.1) years - baseline office SBP (mmHg) 181.1 (SD 19.7) vs. 184.8 (SD 18.2) - baseline 24-h SBP (mmHg) 155.7 (SD 14.3) vs. 155.5 (SD 12.0) - number of antihypertensives baseline 4.3 vs. 5.0 - most common: diuretics, CCB, ACEI, BB after 12 weeks: n=42 vs. n=38 (ITT) and n=39 vs. n=34 (PP) after 24 weeks: n=29 vs. n=26 (ITT) and n=27 vs. n=22 (PP) **Outcomes** change in systolic office blood pressure (RD vs. SI) after 12 weeks - -13.2 (SD 20) vs. -18.9 (SD 14), P=0.181 at 24 weeks - -12.8 (SD 26) vs. -23 (SD 20), P=0.133 change in systolic ambulatory blood pressure (RD vs. SI) at 24 weeks - -7.11 (SD 13) vs. -5.90 (SD 15), P=0.770 safety serious adverse events: none microscopic haematuria: n=4 RD vs. n=2 SI hypertensive crisis: n=4 RD vs. n=2 SI AE (any grade): n=30/42 (71.4%) vs. n=26/39 (66.6%) most common: back pain (n=12/42 RD vs. n=9/39 SI) - at the 24-week visit, when the stable medication phase ended, antihypertensive medication was altered in 49% of all patients to achieve target BP	**Selection bias** randomization: unclear concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low **Attrition bias** lost to follow-up: high ITT-analysis: high (lost to follow-up, missing data) **Reporting bias** selective result presentation: low **Other bias** -	proof-of-concept study (phase II)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	Outcomes **primary** difference in office SBP between baseline and 24 weeks posttreatment **secondary** hange in 24-h ambulatory SBP between baseline and 24 weeks posttreatment planned to be assessed at 3, 6, 12, 24 and 52 weeks posttreatment			

Desch et al. 2015, NCT01656096 (auch Pisano et.al. Cochrane 2021)

Desch et al. 2015, SYMPLICITY Flex Catheter (Metronic)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Desch S, Okon T, Heinemann D, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension (Dallas, Tex. 1979) 2015; 65(6):1202–8. DOI: 10.1161/HYPERTENSIONAHA.115.05283. http://www.ncbi.nlm.nih.gov/pubmed/25824248. [238]	**Objective** to study a possible blood-pressure lowering effect of renal sympathetic denervation in patients with resistant hypertension and mildly elevated blood pressure (BP) (hypothesis that RSD is superior to a sham intervention) **Design** randomized controlled tria; enrolment completed in Jan 2014 **Inclusion and exclusion criteria** - between 18 and 75 years of age - resistant hypertension - mildly elevated BP - under stable antihypertensive drug therapy of ≥3	n=71 randomized (n=35 RD vs. n=36 SI) - mean age: 64.5 (SD 7.6) years vs. 57.4 (SD 8.6), p>0.001 - average of 4.3 antihypertensive agents - including in the vast majority diuretics (96%) - and renin angiotensin aldosterone system inhibitors (97%) **Outcome:** mean change of 24-hour systolic BP at 6 months, RD vs. SI mm Hg (95 % CI) ITT: −7.0 (−10.8; −3.2) vs. −3.5 (−6.7; −0.2) (P=0.15) PP: −8.3 (−11.7; −5.0) vs. −3.5 (−6.8; −0.2) (P=0.042) safety n=0 deaths n=0 serious adverse events n=0 vascular complications	**Selection bias** randomization: low concealment and unpredictability: low **Performance bias** blinding of participants and staff: low **Detection bias** blinding of evaluation: low **Attrition bias** lost to follow-up: unclear ITT-analysis: unclear n=71 randomized, n=35 vs. n=36; n=32 vs. n=35 analyzed as ITT, n=29 vs. n=34 analyzed as PP **Reporting bias**	

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	agents of different classes, including a diuretic (except when not tolerated/contraindicated) at optimal dosage - mean daytime systolic BP on 24-hour ambulatory BP measurement (ABPM) between 135 and 149 mm Hg or mean day-time diastolic BP between 90 and 94 mm Hg - excluded were patients with ABPM values below or above the ranges **Intervention** renal denervation (Symplicity Flex Catheter (Medtronic)) **Control** invasive sham control (room setup was prepared as in regular RSD procedures; patients received saline infusion to simulate administration of intravenous pain medication and underwent invasive examination (including angiography)) overall procedure time was kept similar **Outcomes** **primary** change in 24-hour systolic BP at 6 months between groups safety **secondary**		selective result presentation: low **Other bias** funding: University of Leipzig, Heart Center. sample size (power)	

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	change in diastolic and mean BP at 6 months and the change in 24-hour mean systolic BP in the per-protocol population			

10.2 Strukturierte Recherche

(August 2021 + allgemein 26.03.2021 - 14.02.2022)

AHRQ Renale Denervation (Medicare) 2016

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Renal Denervation in the Medicare Population https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id102TA.pdf [239]	**Objective:** to evaluate the effectiveness of renal denervation for resistant hypertension*, and determine its applicability to the Medicare population **Search**: PubMed and input from Key Informants and the experts; search limited to the last 10 years (until 2010, updated in March 2016) **Quality assessment:** Cochrane Risk of Bias tool (RCT), for comparative observational studies (selective items from the Downs and Black tool)† **Inclusion and exclusion criteria:** population: - adults with resistant hypertension (on at least	83 studies (published in 98 articles) - 7,660 patients n=9 RCT, n=8 comparative cohorts, and n=66 non-comparative cohorts - number of patients ranged from 18 to 998 - in all but 13 studies, the majority of included subjects were male - mean age: < 65 years (the general age of Medicare eligibility) in all types of studies - chronic kidney disease, which is highly prevalent among the Medicare population, was only partially represented among these studies - most of the studies reported a short duration of follow-up ▪ note: study populations were only partially comparable to the Medicare-eligible population	Not applicable - methodology following rapid reviews	authors documented that data on effectiveness were conflicting results were highly variable; the studies were not designed to determine improvement in clinical outcomes the completeness of renal denervation cannot be confirmed at the time of the procedure (tests are not available for use at point-of-

* definition: (cited: consensus statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research)
resistant hypertension=blood pressure that remains above goal in spite of the concurrent use of three antihypertensive medications of different classes
(ideally, one diuretic, and prescription in ways that take advantage of synergistic effects of different classes of agents and promote adherence to therapy)
(prevalence of treatment resistant hypertension was reported as higher in community-based cohorts of patients with a history of stroke or transient ischemic attacks)
† Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998 Jun;52(6):377-84. PMID: 9764259

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	three medications and blood pressure > 140/90 mm Hg) intervention: - non-surgical renal denervation device comparison: - either anti-hypertensive drugs or lifestyle change study design: - randomized controlled trial (RCT), - comparative cohort with at least 10 patients in each arm, - or non-comparative cohort with at least 25 patients **Outcome:** **primary**: between-group differences in 24-hour ambulatory systolic blood pressure documented outcome (if possible) - office or ambulatory systolic blood pressure - number of blood pressure medications - mortality, CVD mortality, stroke, myocardial infarction, congestive heart failure, hospitalization - adverse events	- most studies selectively included individuals with favorable renal anatomy which reduces the risk of complications - most of the published studies used the Medtronic Symplicity® catheter for renal denervation (about 8 watts of radiofrequency energy for ablation) - other catheter designs include ultrasound energy (ReCor Medical PARADISE® catheter), - peri-vascular chemical injury (Ablative Solutions Peregrine System™ catheter), - multi-electrode design (St. Jude Medical's EnligHTN™, Boston Scientific Vessix™, Medtronic SPYRAL) to allow simultaneous delivery of radio-frequency energy to multiple ablation points within a renal artery - no studies with head-to-head comparison of these devices were reported authors documented: - reduced ambulatory systolic blood pressure for renal denervation in patients with resistant hypertension who continue to receive antihypertensive medications o mean absolute change (between-group difference) was small (range: -8.0 mm Hg to +2.1 mm Hg) (results from RCT) o within-group differences in office systolic blood pressure were higher than the between-group differences for renal denervation: o (-42.0 mm Hg to -8 mm Hg) (results from RCT and comparative cohorts) o (range -58.2 mm Hg to 12 mm Hg) (in non-comparative cohorts) o overestimating the effect of renal denervation due to white coat effect, observation bias, and placebo effect - page 22: Figure 2. Mean between-group difference in the change in ambulatory and office systolic blood pressure* between renal denervation		care) most of the studies did not report the training, certification of the interventionalist, or the quality control changes in the number of antihypertensive medications after renal denervation were neither consistently nor systematically reported adherence to diet and medications was not routinely assessed

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		and control in randomized controlled trials of patients with resistant hypertension - data were scant on clinical endpoints, such as stroke, myocardial infarction, kidney events, hospitalization, or death (not reported as efficacy or effectiveness outcome) - adverse effects were uncommon but potentially serious, and included hematomas, pseudoaneurysms, and renal artery interventions		

NICE Percutaneous transluminal radiofrequency sympathetic denervation (resistant hypertension) (2012)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
IPG418. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. 23 January 2012. [240] https://www.nice.org.uk/guidance/ipg418/ https://www.nice.org.uk/guidance/ipg418/evidence/overview-pdf-438572845/	Rapid Review **Source** MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases (prepared in March 2011, updated in September 2011) **Inclusion and exclusion criteria** - clinical studies (good quality) - conference abstracts were excluded - investigated patients with resistant hypertension **Intervention** percutaneous transluminal radiofrequency sympathetic denervation of the renal artery **Outcome** - Safety and/or efficacy	- approximately 309 patients from: n=1 randomized controlled trial n=2 case series ("it is likely that there is some overlap inpatients reported in these studies") authors reported excluded studies (s. appendix within the publication) **Results:** **Efficacy** A randomised controlled trial (RCT) reported that office-based measurements of blood pressure decreased by 32/12 mm Hg in the 49 patients treated with renal denervation compared with an increase of 1/0 mm Hg for the 51 patients in the control group, from baseline to 6 months ($p < 0.0001$ for both systolic and diastolic blood pressure in treatment group compared with $p = 0.77$ and $p = 0.83$ for diastolic and systolic blood pressure in the control)1.	Not applicable - Rapid review*	

* NICE prepared interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy based on a rapid review of the medical literature and specialist opinion

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		The RCT recorded 24-hour ambulatory blood pressure from baseline to 6 months in 20 patients treated with renal denervation and 25 in the control group based on an average of measurements taken every 15 minutes during the day and every 30 minutes in the evening. The decrease in blood pressure in the renal denervation group was 11/7 mm Hg (p = 0.006 for systolic blood pressure and p = 0.014 for diastolic blood pressure). This compares with a decrease of 3/1 mm Hg for the control group (p = 0.51 for systolic blood pressure and p = 0.75 for diastolic blood pressure)1. A case series of 153 patients treated with the procedure reported a reduction in blood pressure from 176/98 mm Hg at baseline by 25/11 mm Hg at 6 months (n = 86), by 23/11 mm Hg at 12 months (n = 64), by 26/14 mm Hg at 18 months (n = 36) and by 32/14 mm Hg at 24 months (n = 18) (within-patient changes in both systolic and diastolic blood pressure from baseline to each time point were p < 0.0001 for all changes except at 24 months where it was p = 0.002). A case series of 50 patients including 45 patients treated with the procedure, reported a significant reduction in blood pressure by –14/–10 mm Hg at 1 month (n = 41), –22/–11 mmHg at 6 months (n = 26), and –27/–17 mm Hg (n = 9) at 12 months (p < 0.001 for both systolic and diastolic at each time point, except for diastolic blood pressure at 12 months where p = 0.02)3. **Safety** The case series of 153 patients reported renal artery dissection in 1 patient before the delivery of radiofrequency energy. Renal denervation was stopped and the patient was successfully treated with a renal artery stent with no further sequelae2. The same study reported periprocedural pseudoaneurysm or haematoma at the femoral access site in 3 patients which was treated successfully2.		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		The RCT reported transient ischaemic attack in 2% (1/52) of patients treated with renal denervation compared with 4% (2/54) in the control group and angina requiring a coronary stent in 1 patient in each treatment group (timing of events not reported)1. The same study reported the following additional events (requiring hospitalisation) in the treatment group in 1 patient each: nausea and oedema, hypertensive crisis after clonidine was abruptly stopped, and a hypotensive episode resulting in a reduction in antihypertensive medication (timing not reported)1. The same study reported the following periprocedural events which were considered minor in 1 patient each: femoral artery pseudoaneurysm treated with manual compression, postprocedural drop in blood pressure requiring drop in antihypertensive drugs, urinary tract infection, extended hospital admission for assessment of paraesthesias, back pain treated with analgesia and resolving after 1 month, transient intraprocedural bradycardia requiring atropine with no sequelae, and possible progression of underlying atherosclerotic lesion (this was not located near location where radiofrequency energy was delivered)1. The case series of 153 patients reported that 6 patients had transient dizziness for the entirety of the study period (but none had lost consciousness) and that 3 patients had pitting oedema considered to be related to medication adjustment (treated with conservative care, use of diuretics and/or reduction in minoxidil dose)2. The same study reported that 1 patient had idiopathic bilateral flank pain which was successful controlled with ibuprofen over a number of months when it resolved completely. An additional 3 patients had intermittent or transient flank or kidney pain which resolved with or without analgesic intervention2. **Articles**:		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		1Symplicity HTN-2 Investigators. (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 376:1903–9. 2Symplicity HTN-1 Investigators. (2011) Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension: Epub ahead of print March 14, 2011. 3Krum HK, Schlaich M, Whitbourn R et al. (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373:1275–81		

NICE Baroreceptor stimulation device (resistant hypertension) (2015)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
IPG533 Implanting a baroreceptor stimulation device for resistant hypertension Interventional procedures guidance [241] https://www.nice.org.uk/guidance/ipg533/resources/implanting-a-baroreceptor-stimulation-device-for-resistant-hypertension-pdf-1899871864647109 https://www.nice.org.uk/guidance/ipg533/documents/implanting-a-baroreceptor-stimulation-device-for-resistant-hypertension-overview2	**Search** MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases (prepared in October 2014) **Inclusion and exclusion criteria** - clinical studies (good quality studies) - patients with resistant hypertension* **Intervention** - implanting a baroreceptor stimulation device† - Baroreflex activation therapy	n=1 RCT, n=1 cohort study (open label follow up of the RCT), n=4 case series; n=432 patients **Efficacy** **Blood pressure reduction** A randomised controlled trial of 265 patients treated by implantation of a baroreceptor stimulation device that was either turned on 1 month after implantation (immediate stimulation) or turned on after 6 months (deferred stimulation) was carried out. Response rates at 6 months (defined as 10 mmHg or greater decrease in systolic blood pressure at month 6 compared with blood pressure obtained 1 month after implant) of 54% and 46%, respectively (p=0.97)1. Of those patients who responded to active therapy at 6 months, 88% maintained a response at 12 months (p<0.001).	Not applicable - Rapid review	

* NICE defines resistant hypertension as blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor blocker (ARB) plus a calcium-channel blocker (CCB) plus a diuretic
† procedure is usually done with the patient under general anaesthesia or conscious sedation. The exact technique varies according to the type of device being implanted.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	Outcomes safety and/or efficacy	The mean decreases in systolic blood pressure at 6 months were 16±29 mmHg and 9±29 mmHg respectively (p=0.08). The proportion of patients with systolic blood pressure of 140 mmHg or less at 6 months was 42% for immediate stimulation and 24% for deferred stimulation (p=0.005)1. A cohort study of 322 patients, which was an open-label follow-up trial of the randomised controlled trial described above (including all patients who had a device implanted regardless of whether they were subsequently randomised), reported that the mean blood pressure drop was 35/16 mmHg compared with pre-implant; this was after a mean follow-up of 28 months2. Among the 244 patients who had a response, 55% reached goal pressures (less than 140 mmHg or less than 130 mmHg in patients with diabetes or kidney disease) throughout follow-up. A case series of 45 patients reported that mean blood pressure decreased by 21/12 mmHg in 37 evaluable patients after 3 months of baroreceptor stimulation (p=0.001)3. The mean reduction after 2 years follow-up was 33/22 mmHg (n=17, p=0.001 for systolic blood pressure and p=0.002 for diastolic blood pressure). A case series of 30 patients reported a mean reduction in systolic blood pressure from the pre-implant baseline of 26.1±3.3 mmHg at 3 months follow-up (p<0.001)4.The mean reduction was 26.0±4.4 mmHg at 6 months follow-up (p<0.001). The proportion of patients with systolic blood pressure of 140 mmHg or less was 43% at 6 months follow-up. A case series of 25 patients reported that the mean blood pressure decreased from 160/83 mmHg at baseline to 143/74 mmHg at 6 months follow-up (p<0.01). The peripheral mean arterial blood pressure reduced from 109.9 mmHg to 97.3 mmHg (p<0.01)5. **Antihypertensive medications**		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		The cohort study of 322 patients reported that the mean number of prescribed medications fell significantly between pre-implantation and month 12 in those patients who had a response (n=244). These reduced from 5.3±1.9 to 4.7±2.1 and remained lower after a mean follow-up of 28 months (p<0.05)2. The case series of 45 patients reported that the median number of antihypertensive medications per patient was unchanged after 2 years follow-up3. The case series of 30 patients reported that the mean number of medications per patient decreased 0.3±0.3 after 6 months follow-up (p=not significant)4. The case series of 25 patients reported that 60% (15/25) of patients had reduced their use of antihypertensive medication at 6 months follow-up (either withdrawal of an antihypertensive or dose reduction)5. **Safety** **Nerve injury** Nerve injury with residual deficit was reported in 5% (13/265) of patients and transient nerve injury in 5% (12/265) of patients in the randomised controlled trial of 265 patients (no further details given)1. Tongue paresis, most likely due to intraoperative injury to the hypoglossal nerve, was reported in 1 patient in the case series of 45 patients3. **Respiratory complication** Respiratory complication (not otherwise described) after device implantation was reported in 3% (7/265) of patients in the randomised controlled trial of 265 patients1. **Wound complication/infection** Device removal before activation because of infection was reported in 7% (3/42) of patients in the case series of 45 patients. In 1 of these patients, the leads were left in and a new device was implanted 12 months later3. Infection needing device removal was reported in 1 patient in the		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		case series of 10 patients; the infection occurred after the 4-month follow-up visit6. Device pocket haematoma 3 days after device implantation was reported in 1 patient in the case series of 30 patients; the patient recovered with no residual effects4. Wound complication (not otherwise described) after device implantation was reported in 3% (7/265) of patients in the randomised controlled trial of 265 patients1. A self-inflicted wound complication was reported in 1 patient in the case series of 30 patients; the patient recovered with no residual effects4. **Hypertensive crisis** Hypertensive crisis was reported in 5% (9/181) of patients treated by immediate baroreceptor stimulation and 8% (7/84) of patients treated by deferred stimulation in the randomised controlled trial of 265 patients1. **Stroke** Hypertension-related stroke was reported in 2% (6/265) of patients in the randomised controlled trial of 265 patients (timing and study group not reported)1. Perioperative stroke with minimal residual effects was reported in 1 patient in the case series of 45 patients3. **Movement of pulse generator** Movement of the implantable pulse generator, needing further surgery to reposition it, was reported in 1 patient in the case series of 45 patients3. **Pain** Intermittent pain lateral to the device system was reported within 30 days of device implantation in 1 patient in the case series of 30 patients; the patient recovered with no residual effects4. Intermittent pain near the device system more than 30 days after device implantation was reported in 1 patient in the same study; the patient recovered with no residual effects.		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		Other Angioneurotic oedema that caused a patient's death was reported 6 days after implant before device activation, in the case series of 45 patients. The cause could not be determined definitively, but a drug reaction was suspected3. Moderate pulmonary oedema within 30 days of the implant was reported in 1 patient in the same study; this resolved within 6 days. **Authors concluded:** Currently there is a lack of clinical and cost-effectiveness evidence to support the use of the baroreflex stimulation to reduce hypertension. Therefore, this procedure should only be used in the context of research.		

GBA Methodenbewertung (§ 135 SGB V)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Methodenbewertung gemäß § 135 Absatz 1 des Fünften Buches Sozialgesetzbuch zur katheterbasierten sympathischen renalen Denervation zur Behandlung der schweren resistenten Hypertonie https://www.g-ba.de/beschluesse/2315/ https://www.g-ba.de/bewertungsverfahren/methodenbewertung/54/	-	Vom 20. August 2015 „Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 20. August 2015 folgenden Beschluss gefasst: Die Beratungen zur Methodenbewertung gemäß § 135 Absatz 1 des Fünften Buches Sozialgesetzbuch (SGB V) für die katheterbasierte sympathische renale Denervation zur Behandlung der schweren resistenten Hypertonie werden eingestellt." Die Tragenden Gründe: Pressemitteilung das Unternehmens Medtronic (Hersteller des Kathetersystems Symplicity Flex) Anfang des Jahres 2014. „In dieser wurde mitgeteilt, dass in der randomisiert-kontrollierten Studie Symplicity HTN-3, in der die katheterbasierte renale Denervation mit einer Sham-Behandlung ver-	-	-

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		glichen worden ist, der primäre Wirksamkeitsendpunkt (relevante Senkung des arteriellen Blutdrucks durch die Prozedur) nicht erreicht worden ist. Diese Studie wurde im März 2014 im New England Journal of Medicine (NEJM) veröffentlicht.“ Antrag auf Bewertung wurde daraufhin 2015 zurückgenommen. Literaturrecherche zeigte, dass die Ergebnisse der großen, randomisierten sham-kontrollierten Symplicity HTN-3- Studie aufgrund ihrer Stärken im Design maßgeblich sind und bisher nicht durch Ergebnisse anderer Studien widerlegt werden können. Ferner konnten laufende Studien identifiziert werden, die die qualitativ hochwertige Methodik der Symplicity-HTN-3 anwenden und noch höhere Qualitäts-Anforderungen an die Durchführung der Intervention und die Qualifikation der Durchführenden stellen und deren Ergebnisse noch ausstehen. Methodenbewertung wurde eingestellt.		

Cochrane Pisano et al. 2021 Renal denervation (resistant hypertension)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Pisano A et al. Renal denervation for resistant hypertension. Cochrane Database Syst Rev 2021; 11:CD011499. DOI: 10.1002/14651858.CD011499.pub3. http://www.ncbi.nlm.nih.gov/pubmed/34806762/ [220] Coppolino et al. Cochrane Database Syst Rev 2017 [219]	**Objective**[*] to evaluate the short- and long-term effects of renal denervation in individuals with resistant hypertension on clinical end points **Search** - updated review: Cochrane Hypertension’s Specialised Register, CENTRAL (2020, Issue 11), Ovid MEDLINE, and Ovid Embase (up to 3 November 2020), The World Health Organization International	note: resistant or refractory hypertension (RH) was defined as: “blood pressure levels persistently above target, in spite of the concurrent use of three antihypertensive agents of different classes at best tolerated doses, including a diuretic (Calhoun 2008)” (estimated prevalence 10% to 20% in the general hypertensive population (Myat 2012)) n=15 trials (n=88 articles; n=1416 participants)	AMSTAR II high (15/16)	most of the studies had unclear or high risk of bias for allocation concealment and blinding GRADE quality of the evidence was low for cardiovascular morbidity outcomes and adverse effects

[*] Author noted that: resistant hypertension is highly prevalent among the general hypertensive population and the clinical management of this condition remains problematic. Different approaches, including a more intensified antihypertensive therapy, lifestyle modifications or both, have largely failed to improve patients' outcomes and to reduce cardiovascular and renal risk. As renal sympathetic hyperactivity is a major driver of resistant hypertension, in the last decade renal sympathetic ablation (renal denervation) has been proposed as a possible therapeutic alternative to treat this condition.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
https://pubmed.ncbi.nlm.nih.gov/28220472/	Clinical Trials Registry Platform (via CENTRAL) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (ongoing trials); authors were also contacted for relevant papers regarding further published and unpublished work (Information Specialist modelled subject strategies) **Quality assessment** Cochrane Risk of Bias tool, GRADEproGDT **Inclusion and exclusion criteria** - randomised controlled trials (RCT) and quasi-RCT - adults (older than 18 years) - patients with refractory or resistant hypertension - clinic blood pressure above target (higher than 140/90 mmHg, or higher than 130/80 mmHg in individuals with type 2 diabetes mellitus) - despite the concomitant use of three or more antihypertensive drugs of different classes, including a diuretic **Intervention** transcatheter renal sympathetic denervation procedures **Comperator** standard medical therapy or sham procedure **Outcomes** **primary** - Fatal and non-fatal cardiovascular events, including but not	(DENER-HTN 2015; DENERVHTA; Desch 2015; Franzen 2012; HTN-JAPAN 2015; INSPIRED; Moiseeva 2020-B; Oslo RDN 2014; Prague-15; RELIEF 2012; ReSET 2015; SYMPATHY; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014) n=4 studies (renal denervation vs. sham procedure) remaining studies (renal denervation vs. standard or intensified antihypertensive therapy) - n=1 study (renal denervation plus antihypertensive medications vs. antihypertensive medications alone) - n=5 studies (renal denervation plus standard antihypertensive therapy vs. an intensified pharmacological regimen - n=1 trial randomly divided subjects into three equal groups according to the supplementation to the previously administered medication (M-group, B-group, D-group) - study duration three to 24 months - n=11 studies with electrode radiofrequency Symplicity catheter system - n=1 study off-the-shelf saline-irrigated radiofrequency catheter - n=2 studies EnligHTN™ multi-electrode denervation system - n=1 study did not provide details for denervation procedure (Franzen 2012) - n=12 studies included in meta-analysis - and 25 ongoing trials (27 articles; ALLEGRO-HTN; DEPART; EnligHTN IV; ENSURE; KPS; NCT01848275; NCT01918111; NCT01968785; NCT02021019; NCT02346045; NCT02444442; NCT02608632; NCT02900729; NTR3444; PaCE; RADIANCE-HTN; RAPID II; RDNP-2012-01; RENO; RENSYMPIS; ReSET-2; RSD4CKD; RSDARH; RSDforAF; SYMPLICITY HTN-4). - see also list of excluded studies		moderate for blood pressure and renal function outcomes low to very low for the remaining outcomes - quality of evidence was mostly influenced by the imprecision (wide confidence intervals) or the low number of studies providing quantitative data sensitivity analyses, investigation of heterogeneity, and publication bias were not performed due to the small number of studies retrieved all studies except ReSET 2015, SYMPATHY, and Warchol 2014 excluded patients with estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 mM four to six ablations per renal artery and up to 11 radiofrequency ablations were reported

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	limited to myocardial infarction, cerebrovascular accidents, and congestive heart failure - All-cause mortality - Any hospitalisation and duration of hospital stay (if long-term data are available) - Quality of life (assessed using validated scales or any other instrument as reported by authors, such as the Short-Form Health Survey (SF-36) **secondary** - Blood pressure control (change in ABPM and clinic systolic, diastolic, and mean blood pressure) - Left ventricular hypertrophy - Atrial fibrillation episodes - Obstructive sleep apnoea severity (apnoea-hypopnoea index) - Kidney function (change in serum creatinine, glomerular filtration rate (GFR), proteinuria or albuminuria, need for renal replacement therapy) - Metabolic profile (change in lipid and blood glucose levels and insulin resistance indices) - Withdrawal due to adverse effects, including but not limited to bradycardia and hypotensive episodes, femoral artery, pseudoaneurysm, renal artery dissection, transient dizziness, pitting oedema, flank pain, and anaemia	available outcomes: - incidence of myocardial infarction (DENER-HTN 2015; Oslo RDN 2014; Prague-15; SYMPLICITY HTN-3 2014) - ischaemic stroke (DENER-HTN 2015; Prague-15; ReSET 2015; SYMPLICITY HTN-2 ReSET 2015; SYMPLICITY HTN-2 2010) - all-cause-mortality and hospitalisations (Prague-15; ReSET 2015; SYMPATHY; SYMPLICITY HTN-3 2014)) - quality of life (self-reported health status) (INSPIRED) no RCT provided data on the following outcomes: fatal cardiovascular events, need for renal replacement therapy and proteinuria secondary (e.g): - 24-hour ambulatory blood pressure monitoring (ABPM) ▪ (DENERHTN 2015; DENERVHTA; Desch 2015; HTN-JAPAN 2015; INSPIRED; Moiseeva 2020-B; Moiseeva 2020-M; Oslo RDN 2014; Prague-15; RELIEF 2012; ReSET 2015; SYMPATHY; SYMPLICITY HTN-3 2014; Warchol 2014), - daytime and/or night-time ABPM (DENERVHTA; INSPIRED; Oslo RDN 2014; ReSET 2015; SYMPATHY; SYMPLICITY HTN-3 2014; Warchol 2014) - office BP (DENER-HTN 2015; DENERVHTA; HTN-JAPAN 2015; INSPIRED; Moiseeva 2020-B; Moiseeva 2020-M; Oslo RDN 2014; Prague-15; RELIEF 2012; SYMPATHY; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014), home BP (DENER-HTN 2015; HTN-JAPAN 2015) **Outcomes:** renal denervation (RD) vs. control: all cause mortality: - n=2 studies		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		○ SYMPLICITY HTN-3 2014: n(RD)=2 patients vs. n(sham group)=1 patient died ○ Prague-15: no deaths were reported during the 24-month follow-up non-fatal cardiovascular events: (low-certainty evidence) - risk of myocardial infarction RR 1.31, 95% CI 0.45 to 3.84) (4 studies, 742 participants), RD vs. sham or standard treatment - ischaemic stroke RR 0.98, 95% CI 0.33 to 2.95 (5 studies, 892 participants), RD vs. no treatment - unstable angina RR 0.51, 95% CI 0.09 to 2.89 (3 studies, 270 participants), RD vs. sham or standard therapy hospitalisation (low-certainty evidence) - RR 1.24, 95% CI 0.50 to 3.11 (3 studies, 743 participants) quality of life - only reported in one study (INSPIRED) - self-reported health status after six-month: ○ control: 53.8 ± 22.3 ○ and 75.0 ± 14.1 ○ baseline-adjusted between-group difference: 13.6 ;95% CI -7.4 to 34.6; P = 0.28 24-hour ambulatory blood pressure monitoring (ABPM) (moderate-certainty evidence) ○ systolic BP MD -5.29 mmHg, 95% CI -10.46 to -0.13 (9 studies, 1045 participants), RD vs. sham or standard therapy ○ diastolic BP MD -3.75 mmHg, 95% CI -7.10 to -0.39 (8 studies, 1004 participants), RD vs. sham or standard therapy		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		- RELIEF 2012: o -17/-12 mmHg (P = 0.006/P = 0.001) in the bilateral renal denervation group vs. -5/-5 mmHg (P = 0.22/P = 0.42) in the sham control group - Prague-15: o control: -12.9/-7.1 (RD) vs. (RD) -13.9/-7.0 mmHg (control) renal denervation (RD) and spironolactone addition (15 participants in both arms) after 24-month follow-up - DENERVHTA: o 24-hour SBP after six months: ▪ spironolactone -23.6 mmHg (-31.9 to -15.3) vs. RD -5.7 mmHg (-14.8 to 3.4) o 24-hour DBP after six months: ▪ spironolactone -10.2 (-14.4 to -6.1) vs. RD -3.7 (-8.2 to 0.9) - HTN-JAPAN 2015: o 24-hour diastolic BP ▪ -3.8 mmHg, 95% CI -8.3 to 0.6; P = 0.091) - Desch 2015: o mean change for the 24-hour BP ▪ systolic BP (RD) −7.0 mmHg (95% CI −10.8 to −3.2) vs. (sham control) −3.5 mmHg (95% CI −6.7 to −0.2) (P = 0.15) All these single-study data were directly retrieved from the correspondent papers. ▪ - office BP: (moderate-certainty evidence) o diastolic BP MD -4.61 mmHg, 95% CI -8.23 to -0.99 (8 studies, 1049 participants) o systolic BP MD -5.92 mmHg, 95% CI -12.94 to 1.10 (nine studies, 10 subgroups, 1090 participants), RD vs. sham procedure or standard therapy)		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		- additional data were presented (s.a. within the publication) (moderate certainty evidence) - serum creatinine MD 0.03 mg/dL, 95% CI -0.06 to 0.13 (5 studies, 721 participants), RD vs. sham or standard treatment - estimated glomerular filtration rate (eGFR) or creatinine clearance MD -2.56 mL/min, 95% CI -7.53 to 2.42 (6 studies, 822 participants), RD vs. control - additional data were presented (s.a. within the publication) authors summarised that: - in patients with resistant hypertension, a renal denervation procedure may have little or no effect on the risk of major cardiovascular events, including myocardial infarction, ischaemic stroke, and unstable angina, as well as hospital admission, compared with controls. - the procedure may decrease 24-hour ABPM and office diastolic blood pressure - little or no effect was observed on renal function, while it likely increases the risk of bradycardia episodes - data on mortality and other adverse effects were limited to single studies		

10.3 Evidenzzusammenfassung Renale Denervation

Recherche-Stand: 17. Mai 2022

Systematische Recherche (Primärstudien)

Die Arbeitsgruppe entschied auf Basis der Ergebnisse der strukturierten Recherche (in 2022; insbesondere betrachtet Studien aus: Pisano et al. 2021 (AMSTAR-II-Bewertung „high“, n=15 Studien aus n=88 Publikationen, n=1.416 Patient*innen, Studiendauer zwischen drei und 24 Monaten) [220], s.a. Anhang) eine ergänzende systematische Primärstudienrecherche durchzuführen (Suche am 17.05.2022). Grund hierfür war die unzureichende Aktualität der Recherche der bislang identifizierten systematischen Übersichtsarbeiten sowie noch nicht publizierte bzw. ausgeschlossene, für die Schlüsselfrage bzw. Diskussion als relevant bewertete, Primärstudien.

Die Fragestellung bezog sich auf die Wirksamkeit und Sicherheit der renalen Denervation bei Betroffenen mit therapieresistenter arterieller Hypertonie gegenüber einer Scheinintervention bzw. gegeneinander, wenn ein etabliertes Standardverfahren bereits untersucht wurde. Für die renale Denervation wurden dabei als relevante Verfahren die Radiofrequenzablation, die Ultraschallablation sowie eine chemische Denervation mittels Ethanol angegeben. Als primär relevant betrachtet wurden Blutdruck und Sicherheitsparameter. Gegebenenfalls sollten der Tod sowie kardiovaskuläre Morbiditätsendpunkte (Myokardinfarkt, Schlaganfall, Herzinsuffizienz, Herzrhythmusstörungen) im Rahmen von vergleichenden Kohortenstudien ergänzend betrachtet werden.

Dieses zweistufige Vorgehen richtete sich an einen Recherchezeitraum ab dem März 2014 (01.03.2014 – 17.05.2022), dem Publikationsdatum der SYMPLICITY HTN-3 Studie, 2014 (s.a. [220]).

Eingeschlossen wurden dabei 20 Publikationen zu 11 randomisierten kontrollierten Studien, wobei eine nicht-vergleichende Betrachtung aus Registerdaten hier zusätzlich eingeschlossen wurde (n=2 der 20 Publikationen), u.a. auf Grund von ergänzenden Sicherheitsparametern zu bestehenden Studienpopulationen der Einschlüsse (siehe Tabelle 5) [216–218,221,222,224–238]. Eine Einschätzung zur Qualität findet sich unter 0 Methodische Qualität.

Anzumerken ist, dass strenge Einschlusskriterien ausschließlich Vergleiche, ohne ergänzende antihypertensive Arzneimitteltherapie, zulassen würden (wash-out Phase). Die Arbeitsgruppe bewertete eine ergänzte Pharmakotherapie nach der angestrebten Beobachtungsdauer als zulässig. Eine fixe Kombination von Antihypertensiva in beiden Vergleichsgruppen, ohne Veränderung während der angestrebten Beobachtungsdauer, war ebenfalls zulässig. Ergänzend berichtet wurden drei publizierte Protokolle (Tabelle 9).

Ausgeschlossen im Volltextscreening wurden 28 Publikationen auf Grund nicht den Einschlusskriterien entsprechenden Vergleiche (Intervention und/oder Kontrolle) sowie 15 Publikationen auf Grund anderer betrachteter Endpunkte oder methodischer Betrachtungen. Diese interessanten Zusatzinformationen finden sich nachfolgend als Quellenangabe (Tabelle 8, Tabelle 10, Tabelle 11, Tabelle 12).

Die eingeschlossenen Studien finden sich aufbereitet in den begleitenden Evidenztabellen der NVL Hypertonie. Eine Zusammenfassung wurde nachfolgend eingefügt (unter 0 Methodische Qualität sowie Tabelle 7). Unter den Kohortenstudien fanden sich keine Berichte zu vergleichenden Betrachtungen, welche über die priorisierten Endpunkte berichteten.

Tabelle 5 Eingeschlossenen Studien - Übersicht

Studienname	Population	Vergleiche	Publikationen innerhalb des Recherchezeitraums*
RADIANCE-HTN SOLO, NCT02649426	kombinierte systolische/ diastolische Hypertonie ABPM ≥ 135/85 mm Hg und < 170/105 mm Hg bzw. Praxisblutdruckmessung ≥ 140/90 mm Hg und <180/110 mm Hg	US-RD vs. SI (zw. 2-5 Monaten + Amlodipin, ACE/ARB, HCT stepped-doses) + zw. 6-12 Monaten Anpassung möglich, unverblinded	Azizi et al. JACC Cardiovasc Interv 2020 [216], 12-Monatsergebnisse Azizi et al. Circulation 2019 [217], 6-Monatsergebnisse Azizi et al. Lancet 2018 [218], 2-Monatsergebnisse

* Recherchezeitraum der systematischen Recherche (01.03.2014 – 17.05.2022)

Studienname	Population	Vergleiche	Publikationen innerhalb des Recherchezeitraums*
	nach 4-wöchentlicher wash-out Phase von bis zu 2 Antihypertensiva*		
RADIANCE-HTN TRIO, NCT02649426	therapieresistente Hypertonie Praxisblutdruck ≥ 140/90 mm Hg unter einer stabilen Kombination von mind 3 Antihypertensiva inkl. Diuretikum	US-RD vs. SI (+ fixe Kombination CCB, ARB, Thiaziddiuretikun), + weitere Medikation zulässig (z.B. BB, Spironolacton)	Azizi et al. Lancet 2021 [222], 2-Monatsergebnisse
RADIOSOUND-HTN, NCT02920034	therapieresistente Hypertonie Praxisblutdruck > 160/90 mm Hg unter antihypertensiver Therapie mit mind. 3 Wirkstoffklassen inkl. Diuretikum vor stabiler antihypertensiver Therapie über 4 Wochen dann systolischer ABPM (Tag) > 135 mm Hg	RF-RD vs. RF-RD vs- US-RD (+ stabile Medikation über mind. 4 Wochen)	Fengler et al. Circulation 2019 [224], 3-armig, 3-Monatsergebnisse
REDUCE HTN: REINFORCE, NCT02392351	Praxisblutdruck systolisch ≥150 mm Hg und ≤180 mm Hg + mittlerer 24h ABPM systolisch ≥135 mm Hg und ≤170 mm Hg nach einer wash-out Phase bzw. bei Wirkstoff-naiven Patient*innen*	RF-RD vs. SI (wash-out Phase), nach 8-wöchiger Beobachtunsdauer ergänzende Medikation möglich	Weber et al. JACC Cardiovasc Interv 2020 [225], 8-Wochenergebnisse
REQUIRE, NCT02918305	therapieresistente Hypertonie Praxisblutdruck ≥ 150/90 mmHg und ambulanter 24h Blutdruck systolisch ≥ 140 mmHg unter stabiler Medikation mit mind. 3 Antihypertensiva (inkl. Diuretikum und max. tolerierter Dosis)	US-RD vs. SI (stabile-Medikation), Einschränkung der Autoren: keine standardisierte, antihypertensive Medikation	Kairo et al. Hypertens Res 2022 [226], Japan und Südkorea, 3-Monatsergebnisse
ReSET, NCT01459900	therapieresistente essentielle Hypertonie systolischer Tages-ABPM ≥ 145 mm Hg Blutdruckzielwerte nicht erreicht unter der medikamentösen Therapie mit mind. 3 Antihypertensiva (inkl. Diuretikum)	RF-RD vs. SI (fixe Standard-medikation)	Peters et al. Blood pressure 2017 [227], 6-Monatsergebnisse Mathiassen et al. J Hypertens 2016 [228], 24 h ABMP
SPYRAL HTN-OFF MED Pivotal, NCT02439749	Praxisblutdruck ≥ 150 und < 180 mm Hg 24-h ABPM ≥ 140 und < 170 mm Hg nach einer wash-out Phase oder ohne antihypertensive Vortherapie†	RF-RD vs. SI (Antihypertensiva wash-out Phase) Medikation mögl., Sicherheitsaspekte	Böhm et al. Lancet 2020 [229], 3-Monatsergebnisse (Bayesian design), (Pilot, Pivotal) Townsend Lancet 2017 [221], 3-Monatsergebnisse (Pilot, interim analysis) SPYRAL HTN Global Clinical Trial Program (eine der ersten beiden Untersuchungen)

* Hinweis: Indirektheit: Studienpopulation entspricht nicht der NVL Definition von therapieresistenter Hypertonie

† Hinweis: Indirektheit: Studienpopulation entspricht nicht der NVL Definition von therapieresistenter Hypertonie

Studienname	Population	Vergleiche	Publikationen innerhalb des Recherchezeitraums*
SPYRAL HTN-ON MED, NCT02439775	Praxisblutdruck ≥ 150 und < 180 mm Hg 24-h ABPM ≥ 140 und < 170 mm Hg unter 1-3 Standard-Antihypertensiva	RF-RD vs. SI (+ ergänzende Medikation)	Mahfoud et al. Lancet 2022 [230], 24 und 36-Monatsergebnisse Kandzari et al. Lancet 2018 [231], 6-Monatsergebnisse SPYRAL HTN Global Clinical Trial Program (eine der ersten beiden Untersuchungen)
SYMPLICITY, NCT01534299	Patient*innen mit unkontrollierter Hypertonie (inkl. schweren Hypertonie-formen, Praxisblutdruck ≥160 mm Hg) unter mindestens 3 antihypertensiven Wirkstoffklassen	RF-RD – Nachbeobachtung (1-5 Jahre), Behandlung nach Klinikstandards	Mahfoud et al. Eur Heart J 2017 [232], Register, isolierte systolische Hypertonie Böhm et al. Hypertension 2015 [233], Registerdaten, 6 Monate, insb. zur Sicherheit Global SYMPLICITY Registry (GSR) Denervation Findings in Real World (DEFINE)
SYMPLICITY HTN-3, NCT01418261	schwere therapieresistente Hypertonie systolischer Blutdruck ≥ 160 mm Hg systolischer 24-h ABPM ≥ 135 mm Hg unter stabiler antihypertensiver medikamentöser Therapie mit mind. 3 Antihypertensiva, inkl. Diuretikum	RF-RD vs. SI (+ antihypertensive Medikation ohne Wechsel), cross-over nach 6 Monaten mögl.	Bakris et al. J Am Coll Cardiol 2015 [234], 12-Monatsergebnisse Bakris et al. J Am Coll Cardiol 2014 [235], ABPM, systolisch, 6-Monatsergebnisse Bhatt N Engl J Med 2014 [236], office BP, systolisch, 6-Monatsergebnisse
WAVE IV, Phase II, NCT02029885	unkontrollierte, primäre arterielle Hypertonie Praxisblutdruck ≥ 160mmHg systolischer ABMP ≥ 135mmHg unter Therapie mit mind. 3 Antihypertensiva in der max. tolerierten Dosis, inkl. 1 Diuretikum	US-RD vs. SI (standardisierte Medikation wurde überwacht), Anpassung nach 2 Monaten möglich	Schmieder et al. J Hypertens 2018 [237]
NCT01656096	therapieresistente Hypertonie mittlerer 24-h Tages-ABPM zwischen systolisch 135 und 149 mm Hg bzw. diastolisch 90 und 94 mm Hg unter stabiler Medikation mit mindestens 3 Antihypertensiva, inkl. 1 Diuretikum	RF-RD vs. SI (+antihypertensive Medikation ohne Wechsel)	Desch et al. 2015 [238], SYMPLICITY Flex Catheter (Metronic)

ABPM=ambulante Blutdruckmessung, ACE=Angiotensinkonversionsenzyhemmer (wie Enalapril, Ramipril), ARB=Angiotensin-II-Rezeptorantagonisten (Sartane), BB=Betablocker, CCB=Kalciumkanalblocker (wie Amlodipin), HCT=Hydrochlorothiazid, RD=renale Denervation, RF=Radiofrequenzablation, SI=Scheinintervention, US=Ultraschall

Hinweis: es gibt hier aufgeführte Studien, die strengen Einschlusskriterien nicht entsprechen würden, aber entweder Zusatzinformationen zu eingeschlossenen Studien liefern (Sicherheitsparameter, Mortalität) oder den von der Arbeitsgruppe formulierten Interventions-Kriterien - einer zulässigen fixe Kombination von Antihypertensiva in beiden Vergleichsgruppen, ohne Veränderung während der angestrebten Beobachtungsdauer bzw. nur Anpassung der antihypertensiven Medikation nach der angestrebten Beobachtungsdauer – entsprechen (ergänzende renale Denervation) - *ergänzende Informationen finden sich in den beiden Spalten zur Population und den Vergleichen*

Methodische Qualität

Tabelle 6 Risk of Bias Bewertung

Referenz	Selection bias 1	Selection bias 2	Performance bias	Detection bias	Attrition bias	Reporting bias	Sponsor	Kommentar
Azizi et al. Circulation 2019 [217]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	ReCor Medical	RADIANCE-HTN SOLO
Azizi et al. JACC Cardiovasc Interv 2020 [216]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	ReCor Medical	RADIANCE-HTN SOLO
Azizi et al. Lancet 2018 [218]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	ReCor Medical	RADIANCE-HTN SOLO
Azizi et al. Lancet 2021 [222]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	ReCor Medical	RADIANCE-HTN TRIO
Fengler et al. Circulation 2019 [224]	niedrig	unklar	niedrig	unklar	unklar	unklar	Leipzig Heart Institute	RADIOSOUND-HTN
Weber et al. JACC Cardiovasc Interv 2020 [225]	niedrig	unklar	niedrig	niedrig	niedrig	niedrig	k.A.	REDUCE HTN: REINFORCE
Kario et al. Hypertens Res 2022 [226]	niedrig	niedrig	niedrig	niedrig	unklar	niedrig	JIMRO Co., Ltd. And Korea Otsuka Pharmaceutical Co., Ltd.	REQUIRE
Mathiassen et al. J Hypertens 2016 [228]	unklar	unklar	niedrig	niedrig	niedrig	unklar	The Danish Heart Foundation	ReSET
Peters et al. Blood pressure 2017 [227]	unklar	unklar	niedrig	niedrig	unklar	unklar	The Danish Heart Foundation	ReSET
Böhm et al. Lancet 2020 [229]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	Medtronic	SPYRAL HTN-OFF MED Pivotal
Townsend et al. Lancet 2017 [221]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	Medtronic	SPYRAL HTN-OFF MED Pivotal
Kandzari et al. Lancet 2018 [231]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	Medtronic	SPYRAL HTN-ON MED
Mahfoud et al. Lancet 2022 [230]	niedrig	niedrig	niedrig	niedrig	niedrig	niedrig	Medtronic	SPYRAL HTN-ON MED
Bakris et al. J Am Coll Cardiol 2014 [235]	unklar	unklar	unklar	unklar	hoch	niedrig	Metronic	SYMPLICITY HTN-3
Bakris et al. J Am Coll Cardiol 2015 [234]	unklar	unklar	unklar	unklar	hoch	niedrig	Metronic	SYMPLICITY HTN-3
Bhatt et al. N Engl J Med 2014 [236]	unklar	unklar	unklar	unklar	hoch	niedrig	Metronic	SYMPLICITY HTN-3
Schmieder et al. J Hypertens 2018 [237]	unklar	niedrig	niedrig	niedrig	hoch	niedrig	k.A.	WAVE IV

Referenz	Selection bias 1	Selection bias 2	Perfor-mance bias	Detection bias	Attrition bias	Reporting bias	Sponsor	Kommentar
Desch et al. Hypertension 2015 [238]	niedrig	niedrig	niedrig	niedrig	unklar	niedrig	University of Leipzig, Heart Center	NCT02029885

Einschätzung in Anlehnung an GRADE-Kriterien für die Zusammenfassung

Die Risk-of-Bias Bewertung der eingeschlossenen Studien ist in **Tabelle 6** zusammenfassend dargestellt. Hervorzuheben sind mögliche Effekte durch Einflussfaktoren (Confounding) bei der Langzeitbeobachtung, wie Wechsel in der Therapiegruppe nach der vordefinierten Beobachtungszeit (cross-over), zusätzliche Therapien (medikamentös und nicht-medikamentös), Therapieanpassungen (Switch, Wechsel, Dosisanpassung) sowie eingeschränkte Möglichkeiten der Nachbeobachtung. Eine Berücksichtigung bei der Diskussion der Ergebnisse kann zum Verständnis von Variationen beitragen.

Zudem gibt es potentielle (auch internationale) Variationen in den Messmethoden (Diagnostik und Monitoring) und den komplexen Interventions-Verfahren bzw. Prozessen (bspw. Begleitmedikation wie Antikoagulation, Sedation und Maßnahmen), die in den eingeschlossenen Studien weitestgehend standardisiert wurden. Eingeschränkte Verblindungsmöglichkeiten, die Messung bzw. Berücksichtigung der Adhärenz sowie Variationen in den statistischen Verfahren (z.B. Umgang mit fehlenden Daten) sind ergänzend zu nennen. Weitestgehend sind Details zu den Verfahren in den Publikationen dokumentiert.

Für die Beurteilung der Genauigkeit und Konsistenz sind die Inzidenz der Erkrankung (therapieresistente Hypertonie unter bestimmten Bedingungen) sowie die zu erwartenden Effekte zu berücksichtigen und damit die möglichen Studiengrößen. Die vorliegenden Studien basieren auf Machbarkeitsstudien bzw. Phase-II-Studien, die in größere randomisierte kontrollierte Studien übergehen. Von Relevanz sind die Langzeitbetrachtungen sowie patientenrelevante Endpunkte, insbesondere im Versorgungsalltag.

Zudem können Zentreneffekte (auch im internationalen Bezug) Einfluss auf die Studienpopulation sowie die Therapieeffekte haben (bspw. in Bezug auf das Alter oder Geschlecht der Patient*innen sowie die angewandten Verfahren/Prozesse). Dies ist in Bezug auf die Beurteilung einer direkten oder indirekten Anwendung der Ergebnisse zu beachten (Übertragbarkeit).

Ergebniszusammenfassung

Tabelle 7 Zusammenfassung der primären Ergebnisse der eingeschlossenen Studien

Studienname	Primäre(r) Endpunkt(e)	Sicherheit
RADIANCE-HTN SOLO, NCT02649426 [216], 2020, 12-Monate [217], 2019, 6-Monate [218], 2018, 2-Monate	ambulanter systolischer Blutdruck (Tag), mm Hg (SD) Mittlerer Blutdruck, mm Hg (SD) 2 Monate: n=74 vs. n=72 (ITT) 141,9 (11,9) vs. 147,9 (13,3) [218] Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI), adjustiert 12 Monate (+SSAT): n=65 vs. n=67 -2,3 (-5,9; 1,3); p=0,201 [216] 6 Monate (+SSAT): n=69 vs. n=71 -2,3 (−6,0; 1,5); p=0,242 [217], adjustiert für Baselinecharakteristika -4,3 (−7,9; −0,6), p=0,024 [217], adjustiert für Baselinecharakteristika und Medikation 2 Monate: n=74 vs. n=72 -6,3 (-9,4; -3,1), p=0,0001 [218] Differenz zu Baseline innerhalb der Gruppen (RD vs. SI), mm Hg (SD) 12 Monate (+SSAT): n=65 vs. n=67 -16,5 (12,9) vs. -15,8 (13,1) [216] 6 Monate (+SSAT): n=69 vs. n=71 -18,1 (12,2) vs. -15,6 (13,2) [217]	• schwerwiegende unerwünschte Ereignisse:

Studienname	Primäre(r) Endpunkt(e)	Sicherheit
	2 Monate: n=74 vs. n=72 -8,5 (9,3) vs. -2,2 (10,0) [218]	n=0 nach 30 Tagen, 6 und 12 Monaten für beide Gruppen [216–218] • Schmerzen nach dem Eingriff, Schmerzdauer > 2 Tage: n=8 (11 %) vs. n=8 (11 %) [218] • • 6 Monate (RD vs. SI): • hypertensive Krise n=0 vs. n=2 [217] • orthostatische Hypotonie: n=2 vs. n=0 [217] • Progress und Stenteinsatz in der Nierenarterie: n=1 vs. n=0 [217] • • 12 Monate: • Tod n=0 vs. n=1 [216] • zerebrovaskuläres Ereignis n=0 vs. n=1 [216]
RADIANCE-HTN TRIO, NCT02649426 [222], 2021, 2-Monate	ambulanter systolischer Blutdruck (Tag), mm Hg (SD) Mittlerer Blutdruck, mm Hg (SD) 2 Monate: n=68 vs. n=67 (ITT) 141,0 (16,1) vs. 146,3 (18,8) [222] Mediane Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI), adjustiert 2 Monate: n=68 vs. n=67 -4,5 (-8,5; -0,3), p=0,022 [222] Mediane Differenz zu Baseline innerhalb der Gruppen (RD vs. SI), mm Hg (IQR) 2 Monate: n=68 vs. n=67 [222] -8,0 (-16·4; 0,0) vs. -3,0 (-10,3; 1,8) [222]	Schmerzen nach dem Eingriff, Schmerzdauer > 2 Tage: n=12 (17%) vs. n=10 (15%) [222] 2 Monate (RD vs. SI): Tod: n=1 (1%) vs. n=0 [222] Herzinfarkt: n=1 (1%) vs. n=0 [222] koronare Revaskularisation: n=0 vs. n=1 (1%) [222]
RADIOSOUND-HTN, NCT02920034 [224], 2019, 3-Monate	ambulanter systolischer Blutdruck (Tag), mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RFM-RD vs. RFB-RD vs. USM-RD), mm Hg (98,3 % KI), adjustiert 3 Monate, n=39 vs. n=39 vs. n=42 USM-RD vs. RFM-RD -6,7 (-13,2; -0,2), p=0,043 [224] -13,2 (SD 13,7) vs. -6,5 (SD 10,3) mm Hg [224] USM-RD vs. RFB-RD -4,9 (-11,5; 1,7), p=0,22 [224] -13,2 (SD 13,7) vs. -8,3 (SD 11,7) mm Hg [224] RFM-RD vs. RFB-RD -1,8 (-8,5; 4,9), p>0,99 [224] -6,5 (SD 10,3) vs. -8,3 (SD 11,7) mm Hg [224] Differenz zu Baseline innerhalb der Gruppe (n=120), mm Hg (SD) 3 Monate: n=120 systolisch -9,5 (SD 12,3), P<0,001 [224] diastolisch -6,3 (SD 7,8) mm Hg, p<0,001 [224]	schwerwiegende unerwünschte Ereignisse: n=1 Nierenarterienspasmus (transient) (USM-RD) [224] n=1 benötigte nichtinvasive Beatmung (USM-RD) [224] n=1 symptomatisches Hämatom in der Leistengegend (RFB-RD) [224] n=1 Pseudoaneurysma (USM-RD) [224] n=1 prozedurbedingtes Hämatom (“intracapsular” + “retroperitoneal”) (RFM-RD) [224] 3-Monate: n=1 Todesfall (RFM-RDN) [224] n=2 Hypotonie (RFB-RDN) [224] n=1 (RFM-RD) und n=2 (RFB-RD) Hypertonie, die eine zusätzliche Medikation benötigte (RFM-RDN) [224]

Studienname	Primäre(r) Endpunkt(e)	Sicherheit
		n=1 Hospitalisierung auf Grund dekompensierter (akuter) Herzinsuffizienz (RFB-RD) [224]
REDUCE HTN: REINFORCE, NCT02392351 [225], 2020, 8-Wochen + explorative Nachbeobachtung	ambulanter systolischer/diastolischer Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg ±SD (95 % KI), vgl. Anhang zur Publikation 8 Wochen, n=32 vs. n=15 143,3±14,2 (138,3; 148,2) vs. 139,9±8,4 (135,7; 144,2) 3,3±12,7 (-4,4; 11,1), p=0,407 83,3±8,9 (80,2; 86,4) vs. 80,5±9,1 (75,9; 85,2) 2,8±9,0 (-2,7; 8,3), p=0,328 6 Monate, n=30 vs. n=15 130,7±13,4 (125,9; 135,5) vs. 138,1±10,6 (132,7; 143,4) -74±12.6, (-15,2; 0,4), p=0,071 76,5±10,0 (72,9; 80,0) vs. 79,5±8,7 (75,1; 84,0) -3,1±9,6 (-9,0; 2,9), p=0,317 12 Monate, n=29 vs. n=12 130,1±13,9 (125,0; 135,2) vs. 135,0±8,6 (130,1; 139,9) -4,9±1,6 (-13,4; 3,6), p=0,266 74,7±8,5 (71,6; 77,8) vs. 79,1±9,4 (73,7; 84,4) -4,4±8,7 (-10,2; 1,5), p=0,154	12 Monate n=1 Hypertensiver Notfall (RD) [225]
REQUIRE, NCT02918305 [226], 2022, Japan und Südkorea, 3-Monate	ambulanter systolischer Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg ±SD (95 % KI) 3 Monate, n=69 vs. n=67 −0,1 (95 % KI −5,5; 5,3); p = 0,971 −6,6 mm Hg vs. −6,5 mm Hg	Angabe der Autoren: keine prozedurbezogenen unerwünschten Ereignisse innerhalb 30 Tage nach dem Eingriff berichtet: n=6 vs. n=6 prozedurbezogene Schmerzen > 2 Tage n=4 vs. n=0 Vasospasmen der Nierenarterie n=4 vs. n=3 Komplikationen an der Seite der femoralen Punktur
ReSET, NCT01459900 [227], 2017, 6-Monate [228], 2016, 3-Monate	ambulanter systolischer Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg ±SD (95 % KI), nicht adjustiert 1 Monat, n=31 vs. n=31 -6,0 (SD 11,0) vs. 0,0 (SD 15), p=0,08 3 Monate, n=35 vs. n=32 -6,2 (SD 18,8) vs. -6,0 (SD 13,5), p=0,95 6 Monate, n=35 vs. n=33 -6,1 (SD 18,9) vs. -4,3 (SD 15,1), p=0,66	mit der Ausnahme von n=2 Fällen eines femoralen Hämatoms wurden keine Komplikationen während des Eingriffs berichtet für wenige Patient*innen wurden unerwünschte Ereignisse in der Nachbeobachtungszeit berichtet n=1 vs. n=2 Hospitalisierungen auf Grund eines starken Blutdruckanstiegs n=0 vs. n=1 Schlaganfall n=0 vs. n=1 perkutane koronare Intervention (akute Angina pectoris)
SPYRAL HTN-OFF MED Pivotal, NCT02439749 [229], 2020, Pilot+Pilot, 3-Monate, Bayesian [221], 2017, Pilot, 3-Monate, interim analysis	ambulanter systolischer 24h-Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % Bayesian KI) 3 Monate, ITT (n=166/165 vs. n=165), n=1 (RD) hat die Einwilligung zurückgezogen –3,9 (–6,2; –1,6), p=0,0005 geschätzte Überlegenheitswahrscheinlichkeit > 0,999	1-Monat keine schwerwiegen Sicherheitsereignisse 3-Monate n=1 vs. n=0 Hospitalisierung auf Grund eines hypertensiven Notfalls n=0 vs. n=1 Schlaganfall
SPYRAL HTN-ON MED, NCT02439775	ambulanter systolischer 24h-Blutdruck, mm Hg (SD)	36 Monate

Studienname	Primäre(r) Endpunkt(e)	Sicherheit
[230], 2022, 24 und 36-Monate [231], 2018, 6-Monate	Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI) 6 Monate, n=36 vs. n=36 -7,0 (-12,0; -2,1), p=0,0059, adjustiert [231] -9,0 (SD 11,0) vs. -1,6 (10,7) [231] 24 Monate, n=33 vs. n=17 -11,2 (–18,4; –4,0); p=0,0031, adjustiert [230] -16,0 (SD 11,0) vs. -4,7 (SD 13,9) [230] 36 Monate, n=30 vs. n=32 –10,0 (–16,6; –3,3); p=0,0039; adjustiert [230] –18,7 (SD 12,4) vs. –8,6 (SD 14,6) [230] Mittlere Differenz zu Baseline zwischen den Gruppen (RD vs. SI), vgl. Abb. 1 aus Mahfoud et al. 2022 [230] + supplement 3 Monate -4,0 vs. 0,3; p=0,231; n=35 vs. n=32 147,9 (SD 10,9) vs. 150,2 (SD 11,9); p=0,41 6 Monate -9,3 vs. -1,6; p=0,553; n=36 vs. n=36 142,6 (SD 10,9) vs. 149,5 (SD 11,3); p=0,01 12 Monate -9,7 vs. -7,8; p=0,533; n=34 vs. n=38 142,0 (SD 12,9) vs. 142,8 (SD 13,0); p=0,81 24 Monate -16,0 vs. -4,7; p=0,0031, n=33 vs. n=17 135,8 (SD 11,7) vs. 146,8 (SD 14,6); p=0,006 36 Monate -18,7 vs. -8,6; p=0,0039, n=30 vs. n=32 132,9 (SD 12,2) vs. 142,8 (SD 14,1); p=0,004 (inkl. crossover) Patient*innenzahlen ohne fehlende Visite bzw. zurückgezogene Einwilligungserklärung	n=1 vs. n=1 kombinierter Sicherheitsendpunkt (z.B. inkl. Gesamtanzahl Todesfälle; terminale Niereninsuffizienz) n=0 vs. n=1 Todesfall n=1 vs. n=0 Schlaganfall n=1 vs. n=0 Hospitalisierung auf Grund eines hypertensiven Notfalls
SYMPLICITY, NCT01534299 [232], 2017, Register, isolierte systolische Hypertonie [233], 2015, Register, 6 Monate, insb. zur Sicherheit	ambulanter systolischer 24h-Blutdruck, mm Hg (SD) „effectiveness“ Mittlere Differenz innerhalb der Gruppe (RD), mm Hg (SD) 6 Monate, n=998 −6,6 (18,0); p<0,001 Mittlerer SBP (SD) 144,6 (17,4) mm Hg Charakteristika: Autor*innen dokumentierten: Patient*innen mit isolierter systolischer Hypertonie waren älter, hatten eine geringere eGFR sowie geringere Herzraten Prädiktoren für eine Veränderung des SBP nach 6 Monaten waren: baseline SBP, Puls (PP) Anzahl an Ablationsversuchen baseline Gebrauch von Aldosteronanatagonisten fehlende Vasodilatatoren baseline kombinierte systolische-diastolische Hypertonie	schwere unerwünschte Ereignisse 1 Monat, n=8 (0.8%) n=2 erneute Intervention an der Nierenarterie n=4 Gefäßkomplikationen n=3 Pseudoaneurysma n=1 Hämatom 6 Monate n=7 Schlaganfälle n=7 Herzinfarkte n=6 Hospitalisierungen auf Grund von Vorhofflimmern n=5 Hospitalisierungen auf Grund hypertensiver Notfälle n=4 Hospitalisierungen auf Grund von Herzinsuffizienz n=2 terminale Niereninsuffizienz n=1 neue Nierenarterienstenose >70%
SYMPLICITY HTN-3, NCT01418261 [234], 2015, 12-Monate [235], 2014, ABPM, tags-nachts, 6-Monate [236], 2014, office BP, systolisch, 6-Monate	systolischer Praxisblutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI) 6 Monate −2,39 (95 % KI −6,89; 2,12); p=0,26 [236] −14,13 (23,93) vs. −11,74 (25,94) [236] ambulanter systolischer 24h-Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI)	schwere unerwünschte Ereignisse (RD vs. SI) 6 Monate n=5/361 (1,4 %) vs. n=1/171 (0,6 %) [236] kombinierter Sicherheitsendpunkt n=14/354 (4.0 %) vs. n=10/171 (5.8 %) [236] hypertensiver Notfall

Studienname	Primäre(r) Endpunkt(e)	Sicherheit
	6 Monate −1,96 (95% KI −4,97; 1,06); p=0,98 [236] −6,75 (15,11) vs. −4,79 (17,25) [236]	n=9 (2,6 %) vs. n=9 (5,3 %) [236] 12 Monate kombinierter Sicherheitsendpunkt n=24/355 (RD) vs. n=5/95 (cross-over) vs. n=5/69 (SI) Tod: 1,8 % vs. 3,6 %
WAVE IV, Phase II, NCT02029885 [237], 2018, 24 Wochen	systolischer Praxisblutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (SD) nach 12 Wochen -13,2 (SD 20) vs. -18,9 (SD 14), p=0,181 nach 24 Wochen -12,8 (SD 26) vs. -23 (SD 20), p=0,133 ambulanter systolischer 24h-Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (SD) nach 24 Wochen -7,11 (SD 13) vs. -5,90 (SD 15), p=0,770	schwerwiegende unerwünschte Ereignisse: n=0, RD vs. SI n=4 vs. n=2 mikroskopische Hämaturie n=4 vs. n=2 Hypertensiver Notfall n=30/42 (71.4%) vs. n=26/39 (66.6%) unerwünschte Ereignisse (jeder Grad) am häufigsten dokumentiert: Rückenschmerz n=12/24 RD vs. n=9/39 SI
NCT01656096, [238], 2015	ambulanter systolischer 24h-Blutdruck, mm Hg (SD) Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (SD), n=35 vs. n=36 nach 6 Monaten ITT −7,0 (−10,8; −3,2) vs. −3,5 (−6,7; −0,2), (P=0,15)	es wurden keine schwerwiegenden unerwünschten Ereignisse berichtet

IQR=Interquartilsabstand, KI=Konfidenzintervall, RD=renale Denervation, RFB-RD=" radiofrequency ablation of the main renal artery, branches, and accessories", RFM-RD="radiofrequency ablation of the main renal artery", SD=Standardabweichung, SI=Scheinintervention, SSAT="standardized stepped-care antihypertensive treatment", US=Ultraschall, USMRD="ultrasound-based ablation of the main renal artery"

Zusatzinformationen

Ergänzend ermittelt im Rahmen der systematischen Recherche wurden die folgenden Studien bzw. Publikationen, die nicht den Einschlusskriterien entsprachen, aber ggf. dennoch von Interesse sein könnten (siehe Tabelle 8, Tabelle 9, Tabelle 10, Tabelle 11 und Tabelle 12). Diese Studien wurden nicht bewertet und aufbereitet, sondern nur als Zitationen zur Information zur Verfügung gestellt. Teilweise sind die Publikationen nicht frei zugänglich.

Tabelle 8 Sekundärpublikationen der eingeschlossenen Studien

Studienname	Publikation aus der systematischen Recherche ab März 2014 – 17.05.2022
RADIANCE-HTN Solo	Fisher et al. J Hypertens 2022 [242], Renin und Aldosteron-Konzentration Sanghvi et al. Cardiovasc Revasc Med 2021 [243], anatomische und pathologische Unterschiede der Nierenarterie (CTA, MRA) Mahfoud et al. EuroIntervention 2021 [244], cross-over Betrachtung
RADIOSOUND-HTN	Fengler et al. Hypertension 2019 [245], Datenanalyse – 3-armig – isolierte systolische Hypertonie – Einfluss der Methoden RF 2 Varianten sowie Ultraschallablation
ReSET	Engholm et al. Int J Cardiol 2018 [246], koronare Flussreserve (CFR) und Gefäßwiderstand (C-Rmin and F-Rmin)
SPYRAL HTN-OFF MED	Böhm et al. Eur Heart J 2019 [247], 3-Monatsdaten, Blutdruck, Herzrate
SYMPLICITY HTN-3 + HTN-Japan	Kairo et al. Hypertension 2015 [248]

Tabelle 9 Protokolle

Studienname	Publikation aus der systematischen Recherche ab März 2014 – 17.05.2022
SPYRAL HTN-OFF MED Pivotal + SPYRAL HTN-ON MED Expansion	Böhm et al. Clin Res Cardiol 2020 [249], Bayesian design
SYMPATHY	Vink et al. Am Heart J 2014 [250]
TARGET BP OFF-MED and TARGET BP I	Mahfoud et al. Am Heart J 2021[251]

Tabelle 10 Publikationen zu anderen Vergleichsinterventionen, Populationen oder Endpunkten

Studienname	Publikation aus der systematischen Recherche ab März 2014 – 17.05.2022
DENERHTN	Gosse Hypertension 2017 [252], stepped-care Medikation + RD, 24h-Blutdruckmonitoring, Einflussfaktor Azizi et al. Circulation 2016 [253], standardisierte medikamentöse Therapie + RD, Einfluss der Adhärenz Azizi et al. Lancet 2015 [254], RD + intensivierte Pharmakotherapie (IP) vs. IP allein (stepped care)
DENERVHTA	La Sierra et al. Am J Hypertens 2017 [255], Spironolacton vs. renale Denervation Oliveras et al. J Hypertens 2016 [256], Spironolacton vs. RD
Oslo RDN	Bergland et al. Blood pressure 2021 [257], 7-Jahresdaten Fadl Elmula Hypertension 2014 [258], RD vs. angepasste Antihypertensivatherapie
PRAGUE-15	Rosa et al. J Hypertens 2017 [259], Spironolacton-Ergänzung vs. renale Denervation Rosa et al. Hypertension 2016 [260], Spironolacton-ergänzt vs. renale Denervation Rosa et al. Hypertension 2015 [261], 6-Monatsergebnisse
SYMPLICITY HTN-2	Esler et al. Eur Heart J 2014 [262], RD + Antihypertensivatherapie oder Antihypertensivatherapie allein, 3-Jahresergebnisse
SYMPLICITY HTN-Japan	Kairo et al. Circ J 2019 [263], 3-Jahresdaten Kairo et al. Circ J 2015 [264], 6-Monatsdaten, RD vs. beibehaltene antihypertensive Therapie (keine Scheinintervention)
-	Chen et al. Catheter Cardiovasc Interv 2016 [265], “full-length versus proximal renal artery ablation”
-	Fengler et al. Clin Res Cardiol 2016 [266], Betroffene mit therapieresistenter, milder Hypertonie, RFA-RD vs. Scheinintervention, cardiopulmonary exercise testing differences
NCT02900729	Liu et al. BMJ Open 2017 [267], renale Denervation (RFA) + Antihypertensiva vs. Antihypertensiva - Protokoll
NCT02667912	Pekarskiy et al. J Hypertens 2017 [268], “distale renal arterial branches vs. conventional main renal artery treatment“

Tabelle 11 Methodische Publikationen bzw. Confounderanalysen

Publikation März 2014 – 17.05.2022	Themen
Böhm et al. J Am Coll Cardiol 2021 [269]	SPYRAL HTN-OFF Med, Assoziationsbetrachtung
Böhm et al. Contemp Clin Trials Commun 2021 [270]	SPYRAL HTN-OFF MED, ANCOVA - Bayesian method, Validitätsbetrachtung, Robustheit
Kandzari et al. EuroIntervention 2021 [271]	„win ratio analysis“
Hamdidouche et al. Hypertension 2019 [272]	DENERHTN, non-adherence
Jacobs et al. Blood pressure 2017 [273]	INSPiRED, Pilot; usual medical care + RDN vs. usual medical care alone (optimiert durch die Studienärzt*innen)
Waksman et al. Am Heart J 2017 [274]	SYMPLICITY HTN-3, „reasons for screen failure“
Pocock et al. J Am Coll Cardiol 2016 [275]	“Regression to the Mean”, SYMPLICITY HTN-3

Publikation März 2014 – 17.05.2022	Themen
Ricke et al. Cardiovasc Intervent Radiol 2016 [276]	CT-gestützte renale Denervation mittels Ethanol Injektion, Pilot
Schönherr et al. BMJ Open 2016 [277]	morphologische Untersuchung; retrospektiv
Kandzari et al. Eur Heart J 2015 [278]	„confounding“, SYMPLICYTY HTN-3

Tabelle 12 Sonstiges

Publikation März 2014 – 17.05.2022	Themen
Mahfoud et al. J AM Coll Cardiol 2020 [279]	Einfluss des kardiovaskulären Risikos auf die Therapieeffekte
Mahfoud et al. JACC Cardiovasc Interv 2020 [280]	alkoholbasierte renale Denervation, open-label
Naduvathumuriyil J Clin Hypertens 2020 [281]	retrospektiv, Langzeitnachbeobachtung, Schweiz
Rodriguez-Leor et al. Rev Esp Cardiol 2020 [282]	Register, Spanien
Daemen et al. J Hypertens 2019 [283]	ACHIEVE, Paradise System, single-arm study
Völz et al. J Hypertens 2018 [284]	Flex-SPYRAL-Register, Schweden
Fischell et al. JACC Cardiovasc Interv 2016 [285]	transcatheter alcohol-mediated perivascular renale denervation
Judd et al. J Hum Hypertens 2014 [286]	Definition, Prävalenz resistenter Hypertonie
Kaiser et al. EuroIntervention 2014 [287]	ALSTER BP real-world registry

10.4 Handsuche/Literaturlistensuche

Bisognano 2011 / baroreflex activation therapy (resistant hypertension, systolic blood pressure)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar

Bisognano et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol. 2011 Aug 9;58(7):765-73. doi: 10.1016/j.jacc.2011.06.008. https://pubmed.ncbi.nlm.nih.gov/21816315/	**Objective**
	to determine the effect of baroreflex activation therapy (BAT) on systolic blood pressure (SBP) in patients with resistant hypertension
	
	Study design
	randomized, double-blind, parallel-design clinical trial designed to assess the efficacy and safety (screening between March 2007 and November 2009)
	ClinicalTrials.gov Identifier: NCT00442286
	
	Inclusion and exclusion criteria
	- resistant HTN defined as at least 1 out-patient, in-office, systolic blood pressure (SBP) ≥160 mm Hg with diastolic BP ≥80 mm Hg taken per protocol utilizing a standardized device
	- at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic
	- ambulatory SBP ≥135 mm Hg for a 24-h average, obtained via a standardized protocol
	- core laboratory
	- absence of clinically significant orthostatic BP changes
		n=265 subjects were randomized 2:1
		- n=181 to Group A (immediate BAT)
		- n=84 to Group B (BAT deferred until after Month 6)
		- n=3 subjects (2 in Group A, 1 in Group B) met the emergency unblinding criteria of hypertensive emergency with confirmed diastolic BP of 120 mm Hg or greater with evidence of accelerated symptoms of end-organ damage
		- baseline characteristics
		  ○ male: 64% (n=116) vs. 55% (n=46)
		  ○ mean age 53.7 vs. 52.4 years
		  ○ mean systolic blood pressure 169 vs. 168 mm Hg
		  ○ mean diastolic blood pressure 101 vs. 100 mm Hg
		  ○ comorbidity: between 7 and 35 %
		  ○ antihypertensive medications: averaged 5.2 +/- 1.7
		  ○ >90% with a diuretic
		  ○ average follow-up was 21 +/- 8 months
		  ○ total of 463 person-years of follow-up
		
		Outcomes
		- acute efficacy (response rate): at 6 months
		  ○ 54% in Group A and 46% in Group B (p=0.97)
		- sustained efficacy: at 6 months
		  ○ 88% of responders, maintaining response at 12 months per the protocol definition (p < 0.001)
		
		- secondary: mean change in SBP
		  ○ mean decrease in SBP at 6 months from Month 0: 16 +/- 29 mm Hg for Group A vs. 9 +/- 29 mm Hg for Group B (p = 0.08)
			RoB Tool not applicable: parallel-design clinical trial (experimental: on and off)
			
			approved under an investigational device exemption
			
			high/wide standard deviation
			
			limitations related to e.g. placebo effect, excess variability, Hawthorne effect, heterogeneous sample of patients
				Literaturlistensuche, enthalten in NICE 2015 Rapid Review (s.o.) [241]
				
				when optimized, the majority of subjects (~75%) were programmed to a unilateral pathway

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
	- patients with presence of carotid stenosis were excluded, as well as subject being an inappropriate surgical candidate as assessed by the vascular surgeon investigator **Intervention** Device: Rheos® Baroreflex Hypertension System* **Outcome** 1) acute efficacy (proportion of subjects that achieve at least a 10 mm Hg drop in SBP at Month 6 compared with Month 0, with a superiority margin of 20%); 2) sustained efficacy (required the reduction from Month 0 to Month 12 to be at least 10 mm Hg and to remain at least 50% of that seen at Month 6.); 3) procedural safety (occurring within 30 days); 4) BAT safety (between 30 days post-implant and the Month 6), noninferiority margin was 15%; 5) device safety (between 30 days post-implant and the Month 12) interim statistical analyses were performed at 6-month intervals	- safety: n=265 participants o n=7 deaths o most common adverse events (AE) ▪ procedural (surgical complication, nerve injury) ▪ BAT (hypertensive crisis 5% (n=9) vs. 8.3% (n=7)) ▪ device (hypertension related stroke) o procedure event-free rate 30 days: 74.8% vs. 70.5% p=1.00 o BAT event-free rate 6 months 91.7% vs. 89.3%, (noninferiority) 2.4 vs. 4.1 p < 0.001 o device event-free rate 12 months: 87.2% vs. 83.8% p < 0.001		

* Experimental: On / Subject will be randomized to a 2:1 allocation to the Rheos ON or OFF arms at the time of Rheos System activation (time point 0). After the six month follow up evaluation, all subjects will have therapy activated, though subjects and treating physicians will not be informed of randomized treatment assignment.
Experimental: Off / Subject will be randomized to a 2:1 allocation to the Rheos ON or OFF arms at the time of Rheos System activation (time point 0). After the six month follow up evaluation, all subjects will have therapy activated, though subjects and treating physicians will not be informed of randomized treatment assignment.

11 Evidenztabellen Versorgungskoordination

11.1 NICE evidence review August 2019

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Hypertension in adults: diagnosis and management [I] Evidence review for same-day specialist review. NICE guideline NG136 https://www.nice.org.uk/guidance/ng136/evidence/i-sameday-specialistreview-pdf-248282935380 [288]	**Review question**: What factors indicate the need for same-day specialist review (including the possible presence of malignant or accelerated hypertension)? - prognostic review **Sources**: - Medline, Embase, the Cochrane Library **PICO characteristics** Population: - adults (aged > 18 years) - with suspected malignant hypertension Prognostic variables under consideration:people referred for same-day specialist review based on the following symptoms: - diastolic blood pressure (BP) >120 mmHg, - systolic blood pressure of >180 mmHg - or mean arterial pressure (MAP) >140 mmHg in isolation or in combination with 1 or more of the following: o grade 3 or 4 hypertensive retinopathy o signs of acute organ damage: kidney, heart, eye or brain (confusion) o visual disturbance o headaches o chest pain o seizures	No relevant clinical studies relevant to the review protocol were identified. See also the study selection flow chart in appendix C. No relevant health economic studies were identified. The committee's discussion of the evidence - committee considered mortality, stroke, diagnosis of accelerated hypertension, hospitalisation and renal dialysis to be critical outcomes for decision-making. benefits and harms: - some observational studies were identified (not applicable to the review question) - consensus recommendations for this topic based on its clinical expertise - issues: o the difficulty in differentiating between those that have accelerated hypertension and those that have severe primary hypertension o the balance of sensitivity and specificity in identifying everyone that has accelerated hypertension and agreed that a broader referral criteria would result in a large number of inappropriate referrals, which would be associated with a large resource impact but could identify more people with accelerated hypertension o more specific referral criteria may be more likely to identify only those who have accelerated hypertension with the risk of missing some people who could be at serious risks of target organ damage and death, as it was	AMSTAR II: high (n=6 domaines were not applicable due to n=0 included studies)	-

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	Confounding factors: - Pre-existing secondary hypertension *Studies will be included but downgraded if they do not adjust for pre-existing secondary hypertension.* *Studies adjusting for other confounding factors will also be considered for inclusion.* exclusion criteria: - Univariate analysis - People on renal replacement therapy (RRT) - Pregnant women - Children and young people (aged < 18 years) **Outcomes** Critical - Mortality - Stroke - Diagnosis of malignant or accelerated hypertension - Hospitalisation - Renal dialysis **Study design** - Cohort studies - Case-control studies in the absence of any other evidence - Systematic reviews of the above **Quality assessment**: GRADEpro	noted that untreated accelerated hypertension has around a 95% mortality rate within 1 year - conclusion: o some amendments to clarify the symptoms that healthcare professionals should look for o important symptoms should be added to the recommendation including the presence of emergency features such as chest pain or confusion, to ensure those who appear well but actually have accelerated hypertension are identified o terms used in the previous recommendations such as headache were nonspecific and the amendment to the recommendation should help to clarify further and specify symptoms to be aware of, resulting in the successful identification of people with accelerated hypertension o note: healthcare professionals often already ask about the emergency symptoms listed o it was important for 'new onset' symptoms to be recognised as many of the symptoms listed could pre-exist unrelated to accelerated hypertension, particularly in older people o the recognition of 'new onset' ensures a focus on new symptoms that have rapidly developed and so meeting the specification for accelerated hypertension o importance of considering retinal problems as a part of the diagnostic criteria for accelerated hypertension o a specialist referral might be required to identify these symptoms although looking into people's eyes is also a part of identifying target organ damage o there was a need to have a recommendation regarding action for those who had raised blood pressure but none of the listed symptoms o in this group of people, it was appropriate to recommend an expedited investigation for		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		target organ damage, and only if present, giving treatment ○ note: The previous recommendation advised giving treatment based on severe blood pressure alone; however, the committee considered this could result in some people being treated unnecessarily for example, those with stiff arteries or who are anxious or sick, resulting in temporarily raised blood pressure. ○ the committee added a new recommendation to repeat blood pressure measurement within 7 days if there is severe raised blood pressure with no adverse features or target organ damage, ensuring these people would be followed up. This would further ensure this population are accurately managed and started on treatment pathways as appropriate.		

11.2 Cochrane

Smith 2021 (multimorbidity)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Smith et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev. 2021 Jan 15;1(1):CD006560. doi:10.1002/14651858.CD006560.pub4. https://pubmed.ncbi.nlm.nih.gov/33448337/ [289] (Update, drei Vorversionen aus 2016, 2012 und 2007)	**Objectives:** To determine the effectiveness of health-service or patient-oriented interventions designed to improve outcomes in people with multimorbidity in primary care and community settings. **Search methods:** We searched MEDLINE, EMBASE, CINAHL and seven other databases to 28 September 2015. We also searched grey literature and consulted experts in the field for completed or ongoing studies.	**Main results:** n= 17 RCTs (complex interventions for people with multimorbidity) - n=9 focused on defined comorbid conditions (depression, diabetes and cardiovascular disease) - remaining studies focused on multimorbidity, generally in older people - n=11 studies, the predominant intervention element was a change to the organisation of care delivery, usually through case management or enhanced multidisciplinary team work - n=6 studies, the interventions were predominantly patient-oriented, for example, educational or self-management support-type interventions delivered directly to participants	AMSTAR II: high	

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	Selection criteria: - randomised controlled trials (RCTs), - non-randomised clinical trials (NRCTs), - controlled before-after studies (CBAs), - interrupted time series analyses (ITS) - evaluating interventions to improve outcomes for people with multimorbidity in primary care and community settings. - **Multimorbidity was defined as two or more chronic conditions in the same individual.** This includes studies where participants can have combinations of any condition or have combinations of prespecified common conditions (comorbidity), for example, hypertension and cardiovascular disease. - The comparison was usual care as delivered in that setting. **Data collection and analysis:** study quality, and judgement of the certainty of the evidence using the GRADE approach meta-analysis of the results where possible and carried out a narrative synthesis for the remainder of the results	▪ - overall our confidence in the results: (effectiveness) ranged from low to high certainty ▪ - little or no difference in clinical outcomes (based on moderate certainty evidence) ▪ - mental health outcomes improved (based on high certainty evidence) and there were modest reductions in mean depression scores for the comorbidity studies that targeted participants with depression (standardized mean difference (SMD) -0.41, 95% confidence interval (CI) -0.63 to -0.2) ▪ - there was probably a small improvement in patient-reported outcomes (moderate certainty evidence) ▪ - the intervention may make little or no difference to health service use (low certainty evidence), ▪ - may slightly improve medication adherence (low certainty evidence), ▪ - probably slightly improves patient-related health behaviours (moderate certainty evidence), ▪ - and probably improves provider behaviour in terms of prescribing behaviour and quality of care (moderate certainty evidence) ▪ - Cost data were limited **Authors' conclusions:** - evidence to support policy for the management of people with multimorbidity and common comorbidities in primary care and community settings - uncertainties about the effectiveness of interventions for people with multimorbidity in general due to the relatively small number of RCTs conducted in this area to date, with mixed findings overall - findings may change with the inclusion of large ongoing well-organised trials in future updates		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		- results suggest an improvement in health outcomes if interventions can be targeted at risk factors such as depression in people with co-morbidity		

Steed 2019 (community pharmacy)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Steed et al.. Community pharmacy interventions for health promotion: Effects on professional practice and health outcomes. Cochrane Database Syst Rev 2019; 12(12):CD011207. doi:10.1002/14651858.CD011207.pub2. https://www.ncbi.nlm.nih.gov/pubmed/31808563/ [290] (Update, eine Vorversion aus 2014)*	**Objectives**: To assess the effectiveness and safety of health-promotion interventions† to change community pharmacy workers' professional practice and improve outcomes for users of community pharmacies‡. **Search methods**: MEDLINE, Embase, CENTRAL, six other databases and two trials registers to 6 February 2018 (reference checking, citation searches and contacted study authors to identify any additional studies; e.g. Open Grey (www.opengrey.eu)) **Selection criteria**:§ - randomised trials	**Main results:** n=57 studies (reported in 83 papers) included in qualitative synthesis (n=16,220 participants) n=25 studies included in quantitative synthesis (MA) - five further studies as ongoing (Davis 2016; Ekers 2017; Michiels 2017; Porteous 2013; Spadaro 2010) - n=49 studies conducted in high-income countries, - n=8 studies in (low-high)-middle-income countries - n=0 studies conducted in low-income countries - n=27 cluster randomized trials - n=47 were directed towards secondary prevention (e.g. n=1 cardiovascular disease, Bond 2007; n=4 hypertension, Okada 2018, Park 1996, Skowron 2011, Svarstad 2013) - n=6 focused on prevention of e.g. cardiovascular risk factors (n=4) - most interventions were educational, or incorporated skills training (typically consisted of group workshops supported by written materials for self-directed learning. Training ranged from a single session to sessions	AMSTAR II high	authors imputed missing standard deviations for changes from baseline using other available information (e.g. correlation coefficients) (Higgins 2011b); if it was not possible to impute data, they did not include the study in the analysis and noted its absence an important potential bias in the included studies was the possibility of contamination between intervention and control

* Previous Cochrane Reviews have examined non-dispensing services in pharmacies (De Barra 2018; Nkansah 2010; Pande 2013), however, these have still had a strong focus on medications, including medication reviews or stopping medications, and did not focus solely on community pharmacy. To avoid overlap with this previous work, we have excluded any purely medication-related interventions in this review, including those focused primarily at promoting medication adherence.

† The World Health Organization (WHO) defines health promotion as "the process of enabling people to increase control over, and to improve, their health". The idea of health promotion has expanded beyond a focus on individual behaviour towards a wide range of social and environmental interventions (WHO 2009). Interventions that target a specific aspect of lifestyle - such as smoking - or that address wider aspects of clinical management - such as obesity or type 2 diabetes mellitus - therefore fall within this definition.

‡ Participants in the review were pharmacy workers and users of community pharmacies (defined as regulated pharmacy outlets outside secondary healthcare), under the direction of a pharmacist.
§ In line with Cochrane Effective Practice and Organisation of Care Group (EPOC) recommendations.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- cluster-randomised trials (with at least two intervention sites and two control sites) - excluded interventions where there was no interaction between pharmacy workers and pharmacy users, and those that focused on medication use only - abstracts were excluded - excluded studies where participants were seen in a hospital or non-communitybased pharmacy, e.g. an outpatient clinic **Quality assessment:** Cochrane's 'Risk of bias' assessment tool following the EPOC suggested risk of bias criteria for EPOC reviews GRADE **Intervention:** - health-promotion interventions in community pharmacies - targeted at, or delivered by, pharmacy workers that aimed to improve the health-related behaviour of people attending the pharmacy **Comperator:** - no treatment, or usual treatment received in the community pharmacy **Primary outcomes:** - professional practice outcomes were primarily behavioural and included: o uptake of intervention by pharmacy worker, adherence to the intervention	held over several weeks); in a number of instances the training involved interactive exercises, such as role-play, which are important for the development of skills (e.g. Bond 2007) o directed at pharmacy workers (n = 8), pharmacy users (n = 13), or both (n = 36) o clinical areas most frequently studied: diabetes, hypertension, asthma, and modification of cardiovascular risk o duration of follow-up of interventions was often unclear - narrative analysis for pharmacy worker behaviour due to high heterogeneity in the results - Health-promotion interventions probably improve pharmacy workers' behaviour (2944 participants; 9 studies; moderate-certainty evidence) when compared to no intervention. - These studies typically assessed behaviour using a simulated patient (mystery shopper) methodology. - Pharmacy user outcomes Health-promotion interventions probably lead to a slight improvement in health-related behaviours of pharmacy users when compared to usual treatment (SMD 0.43, 95% CI 0.14 to 0.72; I2 = 89%; 10 trials; 2138 participants; moderate-certainty evidence). - These interventions probably also lead to a slight improvement in intermediate clinical outcomes, such as levels of cholesterol or glycated haemoglobin, for pharmacy users (SMD -0.43, 95% CI -0.65 to -0.21; I2 = 90%; 20 trials; 3971 participants; moderate-certainty evidence). - We identified no studies that evaluated the impact of health-promotion interventions on event-based clinical outcomes, such as stroke or myocardial infarction, or the psychological well-being of pharmacy users.		groups (high risk of other bias); and inadequate blinding certainty of evidence for all outcomes was judged as moderate (downgraded the certainty because of the heterogeneity across studies and evidence of potential publication bias) note: number of included studies differed (qualitative analysis Fig 1 n=58/84 and abstract n=57/83) studies directed towards secondary prevention also on asthma (n=13), type 2 diabetes (n=10), dyslipidaemia (n=4) etc. or prevention of e.g. smoking (n=4) The majority of studies (34 of 57) were funded by grants from national funding bodies, charities, or institutional funds. Five studies were funded by industry and a further five by a combination of public and industry

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	(e.g. number of pharmacy users asked about smoking status); ○ pharmacy worker behaviour (e.g. correct demonstration of inhaler technique) - pharmacy user outcomes included assessment of: ○ health-related behaviour (e.g. smoking, exercise, inhaler technique); ○ health status including: ○ intermediate clinical outcomes (e.g. cholesterol, glycated haemoglobin); ○ event-based clinical outcomes (e.g. stroke, myocardial infarction); ○ psychological well-being (e.g. anxiety and depression); ○ quality of life - Adverse events included any effect defined as adverse by the included studies, either at the professional or user level.	- Health-promotion interventions probably lead to a slight improvement in quality of life for pharmacy users (SMD 0.29, 95% CI 0.08 to 0.50; I2= 82%; 10 trials, 2687 participants; moderate-certainty evidence). - Adverse events No studies reported adverse events for either pharmacy workers or pharmacy users. Authors' conclusions: Health-promotion interventions in the community pharmacy context probably improve pharmacy workers' behaviour and probably have a slight beneficial effect on health-related behaviour, intermediate clinical outcomes, and quality of life for pharmacy users. Such interventions are likely to be cost-effective and the effects are seen across a range of clinical conditions and health-related behaviours. Nevertheless the magnitude of the effects varies between conditions, and more effective interventions might be developed if greater consideration were given to the theoretical basis of the intervention and mechanisms for effecting behaviour change.		funding. Eight studies did not report their funding source.

Laurant 2018 (nurses as substitutes)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Laurant et al. Nurses as substitutes for doctors in primary care. Cochrane Database Syst Rev	**Objectives:**	**Main results:** n=18 randomised trials *	AMSTAR II high	Authors included controlled before-after studies and non-

* Role of the nurse: nurse-doctor substitution in primary care for provision of first contact care (including urgent care), ongoing care for all presenting physical complaints, and follow-up of patients with a particular chronic condition. Nurse-doctor substitution for preventive services and health education in primary care has been less well studied.
- n=5 studies, responsibility for first contact and ongoing care for all presenting patients (Chambers 1978; Hemani 1999; Iglesias 2013; Mundinger 2000; Spitzer 1973).
- n=5 studies, responsibility for first contact care for patients wanting (urgent) consultations during routine practice hours - Campbell 2014; Dierick-van Daele 2009; Shum 2000; Venning 2000 - or out-of-hours - Lattimer 1998.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
2018; 7(7):CD001271. dx.doi.org/10.1002/14651858.CD001271.pub3. https://www.ncbi.nlm.nih.gov/pubmed/30011347/ [291] (Update, zwei Vorversionen aus 2005 und 1998)	to investigate the impact of nurses working as substitutes for primary care doctors* on: - patient outcomes; - processes of care; and - utilisation, including volume and cost. **Search methods:** Cochrane Central Register of Controlled Trials (CENTRAL), part of the Cochrane Library (www.cochranelibrary.com), as well as MEDLINE, Ovid, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EbscoHost (searched 20.01.2015) - (grey literature in the Grey Literature Report and OpenGrey (21.02.2017)) - (International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov trial registries (21.02.2017)) - a cited reference search for relevant studies (searched 27.01 2015) and checked reference lists of all included studies **Selection criteria:** - randomised trials	- n=9 new RCT ((Campbell 2014; Chan 2009; Dierick-van Daele 2009; Houweling 2011; Iglesias 2013; Larsson 2014; Ndosi 2013; Sanne 2010; Voogdt-Pruis 2010)) - n=4 were cluster-randomized (randomized by practice (Campbell 2014; Moher 2001) or by family (Chambers 1978; Spitzer 1973)) - interventions were carried out in: o general practices/family practices (Campbell 2014; Chambers 1978; Dierick-van Daele 2009; Houweling 2011; Iglesias 2013; Lattimer 1998; Moher 2001; Mundinger 2000; Sanne 2010; Shum 2000; Spitzer 1973; Venning 2000; Voogdt-Pruis 2010), o (out-patient) nurse clinics (Chan 2009; Lewis 1967; Larsson 2014; Ndosi 2013), o and specialised practices (Hemani 1999). - study period ranged from 2 weeks to 48 months with a mean of 14 months (standard deviation (SD) 12 months) - n=1 study was conducted in a middle-income country, all other studies in high-income countries - nurses involved in o first contact care (including urgent care), o ongoing care for physical complaints,		randomised trials in the previous version (Laurant 2005). The number of available randomised trials has increased; therefore, controlled before-after studies (n = 3) and non-randomised trials (n = 3) were excluded from this update. (+ authors justified the selection of RCT) authors performed sensitivity analyses, e.g. by excluding trials assessed as having high risk of bias (overall), cluster-randomised trials, trials presenting per-protocol (PP) rather than intention-to-treat (ITT) data when follow-up was < 80%, trials from low-income countries **limitations:**

- n=7 studies, responsibility for ongoing treatment or follow-up of patients with a particular chronic disease (Chan 2009; Houweling 2011; Larsson 2014; Lewis 1967; Moher 2001; Ndosi 2013; Sanne 2010).
- n=1 study, the nurse provided mainly health education or preventive services to a specific group of patients (Voogdt-Pruis 2010).

* Definition: „The current review focusses on tasks in which nurses substitute for doctors, meaning that they provide the same services as doctors (Laurant 2009; Rashidian 2013), and is limited to care delivery for patients presenting with a physical complaint. These tasks may include diagnostics, treatment, referral to other services, health promotion, management of chronic diseases, or management of acute problems needing same-day consultations. Contact with patients may take place in a primary health facility or in the home of the patient.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- doctors working in a primary care setting - qualified registered nurses working as substitutes for doctors in primary care - authors excluded accident and emergency departments in hospitals - excluded full-text articles because they investigated the role of nurses working as supplements to primarycare doctors **Quality assessment:** risk of bias of each included study using the criteria suggested by EPOC; assessing the certainty of evidence (interpreting study results), GRADE **Intervention:** - limited to primary healthcare services that provide first contact and ongoing care for patients **Primary outcomes** Patient outcomes - Mortality - Health status (clinical outcomes and self-reported outcomes) - Satisfaction - Quality of life - Other (compliance, knowledge, preference for doctor or nurse) **Secondary outcomes** Process of care outcomes - Practitioner adherence to clinical guidelines	○ follow-up of patients with a particular chronic conditions such as diabetes - in many of the studies, nurses could get additional support or advice from a doctor - nurse-doctor substitution for preventive services and health education in primary care has been less well studied **Primary outcomes** Patient outcomes - Mortality: ○ n=8 trials ○ doctor-led care, 6 per 1000 people died ○ nurse-led care, 4 and 6 people per 1000 died ○ RR 0.77, 95% CI 0.57 to 1.03, low certainty evidence (wide confidence interval that includes no effect (imprecision) and clinical heterogeneity) ○ I2 = 0%, 95% CI 0 to 68 ○ authors conclusion: Nurse-led primary care may lead to slightly fewer deaths among certain groups of patients, compared to doctor-led care. - Health status ○ clinical outcomes (e.g. blood pressure, cholesterol, glycated haemoglobin (HbA1c)) ▪ n=3 trials (patients with cardiovascular disease or diabetes) ▪ blood pressure (nurse-led primary care vs. doctor-led care) ▪ systolic (MD -3.73, 95% CI -6.02 to -1.44, moderate-certainty evidence) and ▪ diastolic blood pressure (MD -2.54, 95% CI -4.57 to -0.52, moderate-certainty evidence)		found a large variation in outcome measures differences, for example, nurses had protocols or were offered a computerised decision tool, and doctors were not or nurse-led care included a longer time slot for consultations authors documented that over the ten years since our previous review was published, primary care services have changed considerably in many settings clinical heterogeneity was described and wide confidence intervals

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	- Practitioner healthcare activity (examinations, provision of advice) Utilisation outcomes Volume - Frequency and length of consultations - Number of return visits - Number of prescriptions - Numbers of tests and investigations - Number of referrals to or frequency of use of other services Costs - Direct health service costs related to volume - Indirect (societal) costs	▪ (systolic: I2 = 0%, 95% CI 0 to 90; diastolic: I2 = 0%) ▪ ▪ HbA1c for patients with heart failure or diabetes (nurse-led primary care vs. doctor-led care) (HbA1c levels: MD 0.08, 95% CI -0.25 to 0.41, moderate-certainty evidence) ▪ cholesterol for patients with heart failure or diabetes (nurse-led primary care vs. doctor-led care) (total cholesterol: MD -0.15, 95% CI -0.32 to 0.02, high-certainty evidence) ▪ (cholesterol: I2 = 0%, 95% CI 0 to 90; HbA1c: I2 = 0%) ▪ ○ self-reported outcomes (physical functioning (e.g. pain, Disease Activity Score (DAS)) and lifestyle factors (e.g. smoking, alcohol consumption, exercise)) ▪ n=12 trials self-reports of health status ▪ n=2 patients with rheumatological diseases (disease activity and pain) ▪ nurse-led primary care vs. doctor-led care (DAS: MD 0.04, 95% CI -0.17 to 0.24, moderate-certainty evidence; pain: MD 0.76, 95% CI -3.85 to 5.38, moderate-certainty evidence), indirectness, population ▪ (DAS: I2=1%; pain: I2=0%) ▪ ▪ n=3 three studies (physical		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		▪ functioning) nurse-led primary care vs. doctor-led care (RR 1.03, 95% CI 0.98 to 1.09, low-certainty evidence), inconsistency and high risk of bias ▪ (I2 = 62%, 95% CI 0 to 87, P = 0.07) ▪ ▪ studies measured a large number of other outcomes related to health status and lifestyle; it was not possible to pool these results because of the wide range of outcomes assessed - Satisfaction o n=10 trials (note: outcome was assessed in many different ways), therefore only n=7 were included o nurse-led primary care vs. doctor-led primary care (SMD 0.08, 95% CI 0.01 to 0.15, moderate-certainty evidence) o (I2 = 56%, 95% CI 23 to 74) - Quality of life o n=6 trials (nurse-led primary care vs. doctor-led primary care) o SMD 0.16, 95% CI 0.00 to 0.31, low-certainty evidence) o (I2 = 85%, 95% CI 69 to 93), to imprecision, as the confidence interval touches on the null - Other (compliance, knowledge, preference for doctor or nurse) o It was not possible to pool these results. - authors conclusion: study findings suggest that care delivered by nurses, compared to care delivered by doctors, probably generates similar or better health outcomes for a broad range of patient conditions (low- or moderate-certainty evidence)		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		- Consultations are probably longer in nurse-led primary care (moderate-certainty evidence), and numbers of attended return visits are slightly higher for nurses than for doctors (high-certainty evidence). Authors' conclusions: This review shows that for some ongoing and urgent physical complaints and for chronic conditions, trained nurses, such as nurse practitioners, practice nurses, and registered nurses, probably provide equal or possibly even better quality of care compared to primary care doctors, and probably achieve equal or better health outcomes for patients. Nurses probably achieve higher levels of patient satisfaction, compared to primary care doctors. Furthermore, consultation length is probably longer when nurses deliver care and the frequency of attended return visits is probably slightly higher for nurses, compared to doctors. Other utilisation outcomes are probably the same. The effects of nurse-led care on process of care and the costs of care are uncertain, and we also cannot ascertain what level of nursing education leads to the best outcomes when nurses are substituted for doctors.		

Barra 2018 (pharmacists)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Barra et al. Pharmacist services for non-hospitalised patients. Cochrane Database Syst Rev 2018; 9(9):CD013102. dx.doi.org/10.1002/14651858.CD013102. https://www.ncbi.nlm.nih.gov/pubmed/30178872/ [292] (update)	**Objectives**: To examine the effect of pharmacists' non-dispensing services on non-hospitalised patient outcomes. **Search methods**: CENTRAL, MEDLINE, Embase, two other databases and two trial registers (in March 2015, ran top-up searches in January 2018), reference checking and contact with study authors to identify additional	**Main results**: n=116 trials (n=41,851 patients; range 21 to 6000 (median = 198)) - n=111 trials (39,729 participants) pharmacist interventions vs. usual care - n=5 trials (2122 participants) pharmacist services vs. services from other healthcare professionals - n=76 included in meta-analyses - (n=40 remaining trials reported unique outcome measures which could not be combined)	AMSTAR II high	most trials had a low risk of reporting bias and about 25%-30% were at high risk of bias for performance, detection, and attrition; selection bias was unclear for about half of the included studies

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	studies; (+ ongoing or unpublished trials) **Selection criteria**: - randomised trials - cluster randomized trials - services from outpatient pharmacists - multidisciplinary interventions were allowed **Intervention**: - pharmacist service **Comperator**: - delivery of usual care or equivalent/similar services with the same objective delivered by other health professionals **Quality assessment**: Cochrane 'Risk of bias' tool, certainty of evidence (GRADE) **Outcomes**: - percentage outside blood pressure range - percentage outside glycated haemoglobin (HbA1c) range - hospital attendance/admission - adverse drug effects - SF-36 physical functioning - mortality	- n=27 hypertension, n=20 diabetes, n=14 asthma/COPD, n=7 depression, n=5 cardiovascular disease, n=5 heart failure, n=4 cholesterol/lipid management - some studies targeted specific patient populations, e.g. with multiple conditions (n=9), general medicines management (n=10), older participants (n=4) - few studies included pain management (2), epilepsy (2) or metabolic syndrome (2), and single studies targeted HIV, cancer, arthritis, bipolar disease and osteoporosis - intervention vs. usual care (comparison 1; analyses for 15 outcomes): - percentage outside blood pressure range, intervention vs. control o n=18 trials (4107 participants) o blood pressure outside the target range (OR 0.40, 95% CI 0.29 to 0.55, low-certainty evidence; I2 = 81%) - percentage outside glycated haemoglobin range o patients outside the glycated haemoglobin target range (5 trials, N = 558, OR 0.29, 95% CI 0.04 to 2.22, very low-certainty evidence, I2 = 92%) - hospital attendance/admission o (14 trials, N = 3631, OR 0.85, 95% CI o 0.65 to 1.11, moderate-certainty evidence, I2 = 44%) ▪ - Adverse drug effcts o (3 trials, N = 590, OR 1.65, 95% CI 0.84 to 3.24, low-certainty evidence, I2 = 52%) - SF-36 physical functioning		potential of publication bias was described authors imputed standard deviations using the average standard deviation of the other trials within the review certainty of the evidence is very low or low for most of the outcomes (heterogeneity in study populations, types of interventions delivered and reported outcomes)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		○ (measured by the SF-36) (7 trials, N = 1329, MD 5.84, 95% CI 1.21 to 10.48, low-certainty evidence, I2 = 84%) - Mortality ○ (9 trials, N = 1980, OR 0.79, 95% CI 0.56 to 1.12, low-certaintly of evidence, I2 = 13%) other: Continuous measures of blood pressure Thirty-one trials (N = 5939) and 32 trials (N = 6003) were included in the meta-analyses of diastolic and systolic blood pressure, respectively. On average, there was evidence that pharmacist interventions reduced diastolic blood pressure by −3.50 points (95% CI −5.44 to −1.56) and systolic blood pressure by −5.96 points (95% CI −7.35 to −4.57) compared with usual care (Analysis 1.9; Analysis 1.10). In both analyses, there was evidence of statistical heterogeneity (I2 = 94% and 74%, respectively). Authors' conclusions: The results demonstrate that pharmacist services have varying effects on patient outcomes compared with usual care. We found no studies comparing services delivered by pharmacists with other healthcare professionals that evaluated the impact of the intervention on the six main outcome measures. The results need to be interpreted cautiously because there was major heterogeneity in study populations, types of interventions delivered and reported outcomes.There was considerable heterogeneity within many of the meta-analyses, as well as considerable variation in the risks of bias.		

Smith 2017 (shared care)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Smith SM. Shared care across the interface between primary and specialty care in management of long term conditions. Cochrane	**Objectives**: To determine the effectiveness of shared care health service interventions designed to improve the	**Main results**: n=42 studies from n=49 papers (shared care interventions for chronic disease management (n = 18,859 patients) n=39 RCT, n=2 CBAs, n=1 NRCT	AMSTAR II high	confidence in results regarding the effectiveness of interventions ranged from

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Database Syst Rev 2017; 2(2):CD004910.dx.doi.org/10.1002/14651858.CD004910.pub3. https://www.ncbi.nlm.nih.gov/pubmed/28230899/ [293] (Update, zwei Vorversionen aus 2007 und 2004)	management of chronic disease across the primary/specialty care interface. Secondary questions include the following:1. Which shared care interventions or portions of shared care interventions are most effective? 2. What do the most effective systems have in common? **Search methods**: MEDLINE, Embase, Cochrane Library to 12 October 2015; as well as ongoing studies **Selection criteria**: - randomised controlled trials (RCTs), - non-randomised controlled trials (NRCTs), - controlled before-after studies (CBAs) with at least two control sites and at least two intervention sites,and - interrupted time series analyses (ITS) - people with chronic conditions in primary care and community setting **Intervention**: shared care interventions (all types of structured interventions)* **Comperator**:	- n=22 were included in meta-analyses - n=1 for hypertension (McGhee 1994) – with limited or no difference in SBP between intervention and control n=16 studies (15 RCTs and one CBA) evaluated effects on physical health outcomes (patients with diabetes, hypertension, asthma and COPD, vascular conditions, musculoskeletal conditions or combinations of different conditions including cancer) - beneficial but modest effects on blood pressure (BP), few or no differences in clinical outcomes - blood pressure management in the small number of studies on shared care for hypertension, chronic kidney disease and stroke (mean difference (MD) 3.47, 95% confidence interval (CI) 1.68 to 5.25)(based on moderate-certainty evidence) - Mental health outcomes in response to depression treatment (risk ratio (RR) 1.40, 95% confidence interval (CI) 1.22 to 1.62; six studies, N = 1708) and - recovery from depression (RR 2.59, 95% CI 1.57 to 4.26; 10 studies, N = 4482) in studies examining the 'stepped care' design of shared care interventions (based on high-certainty evidence) - modest effects on mean depression scores (standardised mean difference (SMD) -0.29, 95% CI -0.37 to -0.20; six studies, N = 3250)		moderate to high certainty

* Authors included shared care systems that reflect models 3, 4 and 5 in the taxonomy of shared care described above (Hickman 1994), that is: 1. liaison meetings between specialists and primary care team members for discussion and planning of ongoing management of prespecified chronic disease; 2. shared care record cards (usually patient-held); and 3. computer-assisted shared care and electronic mail whereby an agreed data set was collected in both primary and specialty care settings and circulated between sectors. This system could include centrally co-ordinated computerised registration and recall of patients.

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	usual care **Quality assessment**: certainty of the evidence (GRADE approach) **Outcomes**: 1. clinical outcomes, including physical health outcomes such as blood pressure and mental health outcomes such as depression scores; 2. patient-reported outcome measures (PROMs); 3. hospital admissions; 4. process of care, including visits, prescribing and management of risk factors; 5. participation and default rates; 6. treatment satisfaction if this was reported by validated measures in a study that also reported patient outcomes or provider behaviours; 7. patient health behaviours; or 8. cost outcomes including simple cost and economic analyses of cost-effectiveness	- differences in patient-reported outcome measures (PROMs), processes of care and participation and default rates in shared care services were probably limited (based on moderate-certainty evidence) - studies probably showed little or no difference in hospital admissions, service utilisation and patient health behaviours (with evidence of moderate certainty) Authors' conclusions: - suggests that shared care improves depression outcomes - limitations: methodological shortcomings, particularly inadequate length of follow-up - growing evidence base for shared care in the management of depression - shared care interventions for other conditions should be developed within research settings		

Weeks 2016 (prescribing)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Weeks G. Non-medical prescribing versus medical prescribing for acute and chronic disease management in primary and secondary care. Cochrane Database Syst	**Objectives**: To assess clinical, patient-reported, and resource use outcomes of non-medical prescribing* for managing acute and chronic	**Main results**: n=46 studies (37,337 participants); - non-medical prescribing o by nurses (n=26 studies; n=28,621 participants), Colombia, South Africa,	AMSTAR II high	blinding was rated as high risk of bias in all included studies

* non-medical prescribing was used to cover prescribing of medicines by a broad range of healthcare providers other than medical doctors, prescribing in primary or secondary care; non-medical prescribing is done in collaboration or partnership with doctors, and within this practice there are different models of prescribing practice

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Rev 2016; 11(11):CD011227. dx.doi.org/10.1002/14651858.CD011227.pub2. https://www.ncbi.nlm.nih.gov/pubmed/27873322/ [294] (Update, eine Vorversion aus 2014)	health conditions in primary and secondary care settings compared with medical prescribing (usual care). **Search methods**: CENTRAL, CDSR, DARE, MEDLINE, Embase, PsycINFO, CINHAL, and other databases (on 19 July 2016), grey literature and handsearched bibliographies of relevant papers and publications; AHRQ, registries **Selection criteria**: - randomised controlled trials (RCTs), - cluster-RCTs, - controlled before-and-after (CBA) studies (with at least two intervention and two control sites) - interrupted time series analysis (with at least three observations before and after the intervention) **Quality assessment**: risk of bias (Cochrane EPOC Group nine-point criteria for RCTs, non-RCTs, and CBA studies (Cochrane EPOC Group 2015)); GRADE **Intervention vs. Control**: 1. non-medical prescribing vs. medical prescribing in acute care; 2. non-medical prescribing vs. medical prescribing in chronic care;	Uganda, Thailand, Australia, Canada, Ireland, Netherland, UK, USA o pharmacists (n=20 studies, n=8716 participants), Australia, Canada, Ireland, Netherland, UK, USA - management of one or more chronic diseases (heart failure, hypertension, diabetes, dyslipidaemias) - n=45 studies compared non-medical prescribing with usual care - no studies were found with non-medical prescribing being undertaken by other health professionals - education requirement for non-medical prescribing varied with country and location surrogate markers of chronic disease (systolic blood pressure, glycated haemoglobin, and low-density lipoprotein): - intervention vs. control: o blood pressure at 12 months: mean difference (MD) -5.31 mmHg, 95% confidence interval (CI) -6.46 to -4.16; 12 studies, 4229 participants) (moderate-certainty of evidence) o low-density lipoprotein: MD -0.21, 95% CI -0.29 to -0.14; 7 studies, 1469 participants) (moderate-certainty of evidence) o downgraded due to considerations of serious inconsistency (considerable heterogeneity), multifaceted interventions, and variable prescribing autonomy o glycated haemoglobin management at 12 months (MD -0.62, 95% CI -0.85 to -0.38; 6 studies, 775 participants), (high-certainty of evidence) o little difference in medication adherence across studies (MD 0.15, 95% CI		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	3. non-medical prescribing vs. medical prescribing in secondary care; 4 non-medical prescribing vs. medical prescribing in primary care; 5. comparisons between different non-medical prescriber groups; 6. non-medical healthcare providers with formal prescribing training vs. those without formal prescribing training **Outcomes** (objective measures of patient clinical outcomes) - non-inferiority - standard outcome measures covering health and well-beinging (systolic blood pressure, glycated haemoglobin, and low-density lipoprotein) 1. Proportion of prescribers, medical and non-medical, appropriately adhering to practice guidelines 2. Proportion of patients demonstrating medication adherence 3. Proportion of patients and items appropriately prescribed or deprescribed 4. Patient satisfaction, where measured by a validated tool as part of an effectiveness study 5. Non-medical prescriber versus medical prescriber waiting time to care 6. Non-medical prescribers adversely affecting the health outcomes of patients through medication errors, prescribing errors, adverse events, wrong diagnoses or	0.00 to 0.30; 4 studies, 700 participants), downgraded the certainty of evidence for adherence to moderate due to the serious risk of performance bias ○ little difference in patient-related adverse events, downgraded certainty of evidence to low due to indirectness, as the range of adverse events may not be related to the intervention and selective reporting failed to adequately report adverse events in many studies ○ patients were generally satisfied with non-medical prescriber care (14 studies, 7514 participants), downgraded the certainty of evidence from high to moderate due to indirectness, in that satisfaction with the prescribing component of care was only addressed in one study, and there was variability of satisfaction measures with little use of validated tools ○ health-related quality of life scores (SF-12 and SF-36) for the physical component score (MD 1.17, 95% CI 0.16 to 2.17), ○ for the mental component score (MD 0.58, 95% CI -0.40 to 1.55), certainty of evidence to moderate due to indirectness of the measure of effect ○ little difference between groups for hospitalisations, emergency department visits, and outpatient visits ○ in the majority of studies reporting medication use, non-medical prescribers prescribed more drugs, intensified drug doses, and used a greater variety		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	treatment, increased hospitalisations, or representations for medical care	of drugs compared to usual care medical prescribers.The risk of bias across studies was generally low for selection bias (random sequence generation), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). There was an unclear risk of selection bias (allocation concealment) and for other biases. A high risk of performance bias (blinding of participants and personnel) existed. Authors' conclusions: The findings suggest that non-medical prescribers, practising with varying but high levels of prescribing autonomy, in a range of settings, were as effective as usual care medical prescribers. Non-medical prescribers can deliver comparable outcomes for systolic blood pressure, glycated haemoglobin, low-density lipoprotein, medication adherence, patient satisfaction, and health-related quality of life. It was difficult to determine the impact of non-medical prescribing compared to medical prescribing for adverse events and resource use outcomes due to the inconsistency and variability in reporting across studies. Future efforts should be directed towards more rigorous studies that can clearly identify the clinical, patient-reported, resource use, and economic outcomes of non-medical prescribing, in both high-income and low-income countries.		

Nkansah 2010 (pharmacists)

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
Nkansah N. Effect of outpatient pharmacists' non-dispensing roles on patient outcomes and prescribing patterns. Cochrane Database Syst Rev 2010(7):CD000336. dx.doi.org/10.1002/14651858.CD000336.pub2.	**Objectives**: To examine the effect of outpatient pharmacists' non-dispensing roles on patient and health professional outcomes. **Search strategy**:	**Main results**: n=43 studies were included; - n=36 studies (pharmacist interventions targeting patients) - n=7 studies (pharmacist interventions targeting health professionals) comparison 1:	AMSTAR II high	

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
https://www.ncbi.nlm.nih.gov/pubmed/20614422/ [295] (Update, eine Vorversion aus 2000)	Phase I, Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register (January 1966 through March 2007) Phase II, MEDLINE/EMBASE (January 1966 through March 2008) (Phase I reported in this review; Phase II will be summarized in the next update) **Selection criteria**: - randomized controlled trial (RCT), - controlled clinical trial (CCT), - controlled before and after study (CBA) and - interrupted time series (ITS) **Quality assessment**: risk of bias (EPOC Data Extraction Checklist) **Intervention vs. control**: 1. Pharmacist services targeted at patients vs. services delivered by other health professionals; 2. Pharmacist services targeted at patients vs. the delivery of no comparable service; 3. Pharmacist services targeted at health professionals vs. services delivered by other health professionals; 4. Pharmacist services targeted at health professionals vs. the delivery of no comparable service	- the only included study showed a significant improvement in systolic blood pressure for patients receiving medication management from a pharmacist compared to usual care from a physician. comparison 2: - n=5 studies evaluating process of care outcomes, pharmacist services reduced the incidence of therapeutic duplication and decreased the total number of medications prescribed. - n=29 of 36 studies reported clinical and humanistic outcomes. Pharmacist interventions resulted in improvement in most clinical outcomes, although these improvements were not always statistically significant. - n=8 studies reported patient quality of life outcomes; three studies showed improvement in at least three subdomains comparison 3: - no studies were identified meeting the inclusion criteria comparison 4: - two of seven studies demonstrated a clear statistically significant improvement in prescribing patterns Authors' conclusions: Only one included study compared pharmacist services with other health professional services, hence we are unable to draw conclusions regarding comparisons 1 and 3. Most included studies supported the role of pharmacists in medication/therapeutic management, patient counseling, and providing health professional education with the goal of improving patient process of care and clinical outcomes, and of educational outreach visits on physician prescribing patterns. There was great heterogeneity in the types of outcomes measured across all studies. Therefore a standardized approach to measure and report clinical, humanistic, and		

Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
		process outcomes for future randomized controlled studies evaluating the impact of outpatient pharmacists is needed. Heterogeneity in study comparison groups, outcomes, and measures makes it challenging to make generalised statements regarding the impact of pharmacists in specific settings, disease states, and patient populations.		

11.3 Handsuche/Literaturlistensuche

Köberlein-Neu 2016 (Medikationsmanagement, Multimorbidität)

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar

Köberlein-Neu et al. Interprofessional Medication Management in Patients With Multiple Morbidities. https://pubmed.ncbi.nlm.nih.gov/27890050/
 	
controlled trials register ISRCTN41595373
	2016	Cochrane Risk of Bias Tool not applicable	**Objective**
			to study the efficacy of interprofessional medication management for multimorbid patients that takes their medical conditions, but also their general living situation into account
			
			Design
			- cluster-randomized controlled trial
			- stepped wedge design
			  ○ usual parallel group structure
			  ○ design allows for each cluster to start in the control group
			  ○ and the intervention is introduced into the clusters at intervals (in steps)
			  ○ general practices (clusters)
			
			- evaluation over a period of 15 months
			  ○ intervention phase of six to 12 months, with a sub - sequent follow-up period of 3 months
			
			Inclusion criteria
			- age ≥ 65 years
				n=162 patients
				n=142 included in the intention-to-treat analysis
				(n=59 started intervention after end of recruitment period, n=40 started intervention after 3 months and n=43 started intervention after 6 months)
				- 53.3% women, mean age 76.8 ± 6.3 years
				
				Results:
				primary:
				- mean total MAI score: control phase: 29.21 (95% CI [26.09; 32.33]) to the intervention phase (22.27 [19.00; 25.54]), p ≤ 0.001
				  ○ cohort 1: reduced from 30.15±24.14 to 14.09±14.80 points after 15 months
				  ○ cohort 2: reduced from 43.27±30.39 to 24.47±16.17 points
				  ○ cohort 3: reduced from 26.07±17.33 to 18.44±14.67 points
				- effect strength (Cohen's d) of –0.24 [–0.36; –0.13]
				
				secondary:
				- number of drug-related problems declined:
				  ○ –0.45 [–0.81;–0.09]; P=0.014; d= –0.13, [–0.23;–0.03]
				  ○ second medication review showed no additional reduction
				  ○ mean number of drug-related problems at baseline: 7.3±3.4 per patient (most common cause: choice of substance (49.8%))
					cluster randomization
					
					medication management to improve the quality of therapy and medication safety (based on methods of pharmaceutical care)

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
			- minimum of three chronic disorders (affecting two different organ systems, at least one cardiovascular disease) - at least one visit to the PCP in each of the preceding three-month intervals - five or more long-term drug treatments (>3 months) with systemic effects - ability to complete questionnaires, with assistance if required **Exclusion criteria** - life expectancy of less than 12 months (assessed by the treating primary care physician) - participation in another clinical study **Intervention** - comprehensive medication management (involved the collection of information on the drugs each patient took, the way they were stored, the patient's drug intake and handling, and any problems that arose with pharmacotherapy) - home care based intervention in elderly multimorbid patients, interdisciplinary (primary care physicians, pharmacists, home-care specialists, Pflege- und Wohnberatung) **Outcomes** primary endpoint: - quality of pharmacotherapy (Medication Appropriateness Index (MAI) - standardized evaluation of the overall therapy, 10 criteria) – medication safety - mixed model secondary endpoint: - number of drug related problems (DRPs),	o mean observed number of interaction effects per patient: 5.5±3.9 (26.8% categorized as clinically relevant and 32.7% as partially clinically relevant) o depending on the category of cause, up to 60% of drug-related problems were solved	

Zitat	Jahr	Risk of Bias	Charakteristika	Ergebnisse	Kommentar
			- potentially inadequate medication (PIM), - patients' quality of life, - everyday life skills/competencies, - gait stability/risk of falling		

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