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SPYRAL HTN-ON MED, NCT02439775	Praxisblutdruck $\geq 150$ und $< 180$ mm Hg 24-h ABPM $\geq 140$ und $< 170$ mm Hg unter 1-3 Standard-Antihypertensiva	RF-RD vs. SI (+ ergänzende Medikation)	Mahfoud et al. Lancet 2022 [230], 24 und 36-Monatergebnisse Kandzari et al. Lancet 2018 [231], 6-Monatergebnisse SPYRAL HTN Global Clinical Trial Program (eine der ersten beiden Untersuchungen)
SYMPPLICITY, NCT01534299	Patient*innen mit unkontrollierter Hypertonie (inkl. schweren Hypertonieformen, Praxisblutdruck $\geq 160$ 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 SYMPPLICITY Registry (GSR) Denervation Findings in Real World (DEFINE)
SYMPPLICITY HTN-3, NCT01418261	schwere therapieresistente Hypertonie systolischer Blutdruck $\geq 160$ mm Hg systolischer 24-h ABPM $\geq 135$ 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-Monatergebnisse Bakris et al. J Am Coll Cardiol 2014 [235], ABPM, systolisch, 6-Monatergebnisse Bhatt N Engl J Med 2014 [236], office BP, systolisch, 6-Monatergebnisse
WAVE IV, Phase II, NCT02029885	unkontrollierte, primäre arterielle Hypertonie Praxisblutdruck $\geq 160$ mmHg systolischer ABMP $\geq 135$ mmHg 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], SYMPPLICITY Flex Catheter (Metronic)

ABPM=ambulante Blutdruckmessung, ACE=Angiotensinkonversionsenzymeinhibitor (wie Enalapril, Ramipril), ARB=Angiotensin-II-Rezeptorantagonisten (Sartane), BB=Betablocker, CCB=Kaliumkanalblocker (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	SYMPPLICITY HTN-3
Bakris et al. J Am Coll Cardiol 2015 [234]	unklar	unklar	unklar	unklar	hoch	niedrig	Metronic	SYMPPLICITY HTN-3
Bhatt et al. N Engl J Med 2014 [236]	unklar	unklar	unklar	unklar	hoch	niedrig	Metronic	SYMPPLICITY 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	Performance 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 Zentreffekte (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**

Studiename	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]	<ul style="list-style-type: none"> <li>schwerwiegende unerwünschte Ereignisse:</li> </ul>

Studiename	Primäre(r) Endpunkt(e)	Sicherheit
	<p>2 Monate: n=74 vs. n=72 -8,5 (9,3) vs. -2,2 (10,0) [218]</p>	<p>n=0 nach 30 Tagen, 6 und 12 Monaten für beide Gruppen [216–218]</p> <ul style="list-style-type: none"> <li>Schmerzen nach dem Eingriff, Schmerzdauer &gt; 2 Tage: n=8 (11 %) vs. n=8 (11 %) [218]</li> <li>6 Monate (RD vs. SI): <ul style="list-style-type: none"> <li>hypertensive Krise n=0 vs. n=2 [217]</li> <li>orthostatische Hypotonie: n=2 vs. n=0 [217]</li> <li>Progress und Stenoseinsatz in der Nierenarterie: n=1 vs. n=0 [217]</li> </ul> </li> <li>12 Monate: <ul style="list-style-type: none"> <li>Tod n=0 vs. n=1 [216]</li> <li>zerebrovaskuläres Ereignis n=0 vs. n=1 [216]</li> </ul> </li> </ul>
<p>RADIANCE-HTN TRIO, NCT02649426 [222], 2021, 2-Monate</p>	<p>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]</p> <p>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]</p> <p>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]</p>	<p>Schmerzen nach dem Eingriff, Schmerzdauer &gt; 2 Tage: n=12 (17%) vs. n=10 (15%) [222]</p> <p>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]</p>
<p>RADIOSOUND-HTN, NCT02920034 [224], 2019, 3-Monate</p>	<p>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&gt;0,99 [224] -6,5 (SD 10,3) vs. -8,3 (SD 11,7) mm Hg [224]</p> <p>Differenz zu Baseline innerhalb der Gruppe (n=120), mm Hg (SD) 3 Monate: n=120 systolisch -9,5 (SD 12,3), P&lt;0,001 [224] diastolisch -6,3 (SD 7,8) mm Hg, p&lt;0,001 [224]</p>	<p>schwerwiegende unerwünschte Ereignisse: n=1 Nierenarterienkrampf (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]</p> <p>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]</p>

Studiename	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 $\pm$ SD (95 % KI), vgl. Anhang zur Publikation 8 Wochen, n=32 vs. n=15 143,3 $\pm$ 14,2 (138,3; 148,2) vs. 139,9 $\pm$ 8,4 (135,7; 144,2) 3,3 $\pm$ 12,7 (-4,4; 11,1), p=0,407 83,3 $\pm$ 8,9 (80,2; 86,4) vs. 80,5 $\pm$ 9,1 (75,9; 85,2) 2,8 $\pm$ 9,0 (-2,7; 8,3), p=0,328 6 Monate, n=30 vs. n=15 130,7 $\pm$ 13,4 (125,9; 135,5) vs. 138,1 $\pm$ 10,6 (132,7; 143,4) -74 $\pm$ 12,6, (-15,2; 0,4), p=0,071 76,5 $\pm$ 10,0 (72,9; 80,0) vs. 79,5 $\pm$ 8,7 (75,1; 84,0) -3,1 $\pm$ 9,6 (-9,0; 2,9), p=0,317 12 Monate, n=29 vs. n=12 130,1 $\pm$ 13,9 (125,0; 135,2) vs. 135,0 $\pm$ 8,6 (130,1; 139,9) -4,9 $\pm$ 1,6 (-13,4; 3,6), p=0,266 74,7 $\pm$ 8,5 (71,6; 77,8) vs. 79,1 $\pm$ 9,4 (73,7; 84,4) -4,4 $\pm$ 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 $\pm$ 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 $\pm$ 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 schwerwiegenden 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

Studiename	Primäre(r) Endpunkt(e)	Sicherheit
<p>[230], 2022, 24 und 36-Monate</p> <p>[231], 2018, 6-Monate</p>	<p>Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI)</p> <p>6 Monate, n=36 vs. n=36</p> <p>-7,0 (-12,0; -2,1), p=0,0059, adjustiert [231]</p> <p>-9,0 (SD 11,0) vs. -1,6 (10,7) [231]</p> <p>24 Monate, n=33 vs. n=17</p> <p>-11,2 (-18,4; -4,0); p=0,0031, adjustiert [230]</p> <p>-16,0 (SD 11,0) vs. -4,7 (SD 13,9) [230]</p> <p>36 Monate, n=30 vs. n=32</p> <p>-10,0 (-16,6; -3,3); p=0,0039; adjustiert [230]</p> <p>-18,7 (SD 12,4) vs. -8,6 (SD 14,6) [230]</p> <p>Mittlere Differenz zu Baseline zwischen den Gruppen (RD vs. SI), vgl. Abb. 1 aus Mahfoud et al. 2022 [230] + supplement</p> <p>3 Monate -4,0 vs. 0,3; p=0,231; n=35 vs. n=32</p> <p>147,9 (SD 10,9) vs. 150,2 (SD 11,9); p=0,41</p> <p>6 Monate -9,3 vs. -1,6; p=0,553; n=36 vs. n=36</p> <p>142,6 (SD 10,9) vs. 149,5 (SD 11,3); p=0,01</p> <p>12 Monate -9,7 vs. -7,8; p=0,533; n=34 vs. n=38</p> <p>142,0 (SD 12,9) vs. 142,8 (SD 13,0); p=0,81</p> <p>24 Monate -16,0 vs. -4,7; p=0,0031, n=33 vs. n=17</p> <p>135,8 (SD 11,7) vs. 146,8 (SD 14,6); p=0,006</p> <p>36 Monate -18,7 vs. -8,6; p=0,0039, n=30 vs. n=32</p> <p>132,9 (SD 12,2) vs. 142,8 (SD 14,1); p=0,004 (inkl. cross-over)</p> <p>Patient*innenzahlen ohne fehlende Visite bzw. zurückgezogene Einwilligungserklärung</p>	<p>n=1 vs. n=1 kombinierter Sicherheitsendpunkt (z.B. inkl. Gesamtanzahl Todesfälle; terminale Niereninsuffizienz)</p> <p>n=0 vs. n=1 Todesfall</p> <p>n=1 vs. n=0 Schlaganfall</p> <p>n=1 vs. n=0 Hospitalisierung auf Grund eines hypertensiven Notfalls</p>
<p>SYMPPLICITY, NCT01534299</p> <p>[232], 2017, Register, isolierte systolische Hypertonie</p> <p>[233], 2015, Register, 6 Monate, insb. zur Sicherheit</p>	<p>ambulanter systolischer 24h-Blutdruck, mm Hg (SD) „effectiveness“</p> <p>Mittlere Differenz innerhalb der Gruppe (RD), mm Hg (SD)</p> <p>6 Monate, n=998</p> <p>-6,6 (18,0); p&lt;0,001</p> <p>Mittlerer SBP (SD) 144,6 (17,4) mm Hg</p> <p>Charakteristika: Autor*innen dokumentierten: Patient*innen mit isolierter systolischer Hypertonie waren älter, hatten eine geringere eGFR sowie geringere Herzraten</p> <p>Prädiktoren für eine Veränderung des SBP nach 6 Monaten waren:</p> <p>baseline SBP, Puls (PP)</p> <p>Anzahl an Ablationsversuchen</p> <p>baseline Gebrauch von Aldosteronantagonisten</p> <p>fehlende Vasodilatoren baseline</p> <p>kombinierte systolische-diastolische Hypertonie</p>	<p>schwere unerwünschte Ereignisse</p> <p>1 Monat, n=8 (0.8%)</p> <p>n=2 erneute Intervention an der Nierenarterie</p> <p>n=4 Gefäßkomplikationen</p> <p>n=3 Pseudoaneurysma</p> <p>n=1 Hämatom</p> <p>6 Monate</p> <p>n=7 Schlaganfälle</p> <p>n=7 Herzinfarkte</p> <p>n=6 Hospitalisierungen auf Grund von Vorhofflimmern</p> <p>n=5 Hospitalisierungen auf Grund hypertensiver Notfälle</p> <p>n=4 Hospitalisierungen auf Grund von Herzinsuffizienz</p> <p>n=2 terminale Niereninsuffizienz</p> <p>n=1 neue Nierenarterienstenose &gt;70%</p>
<p>SYMPPLICITY HTN-3, NCT01418261</p> <p>[234], 2015, 12-Monate</p> <p>[235], 2014, ABPM, tags-nachts, 6-Monate</p> <p>[236], 2014, office BP, systolisch, 6-Monate</p>	<p>systolischer Praxisblutdruck, mm Hg (SD)</p> <p>Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI)</p> <p>6 Monate</p> <p>-2,39 (95 % KI -6,89; 2,12); p=0,26 [236]</p> <p>-14,13 (23,93) vs. -11,74 (25,94) [236]</p> <p>ambulanter systolischer 24h-Blutdruck, mm Hg (SD)</p> <p>Mittlere Differenz zwischen den Gruppen (RD vs. SI), mm Hg (95 % KI)</p>	<p>schwere unerwünschte Ereignisse (RD vs. SI)</p> <p>6 Monate</p> <p>n=5/361 (1,4 %) vs. n=1/171 (0,6 %) [236]</p> <p>kombinierter Sicherheitsendpunkt</p> <p>n=14/354 (4,0 %) vs. n=10/171 (5,8 %) [236]</p> <p>hypertensiver Notfall</p>

Studiename	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**

Studiename	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
SYMPPLICITY HTN-3 + HTN-Japan	Kairo et al. Hypertension 2015 [248]

**Tabelle 9 Protokolle**

Studiename	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**

Studiename	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 + intensiviertere 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 Antihypertensivtherapie
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
SYMPPLICITY HTN-2	Esler et al. Eur Heart J 2014 [262], RD + Antihypertensivtherapie oder Antihypertensivtherapie allein, 3-Jahresergebnisse
SYMPPLICITY 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]	SYMPPLICITY HTN-3, „reasons for screen failure“
Pocock et al. J Am Coll Cardiol 2016 [275]	“Regression to the Mean“, SYMPPLICITY 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
Kanzari et al. Eur Heart J 2015 [278]	„confounding“, SYMPPLICITY 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
Vözl 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

Entwurfsversion, Stand: 12/2022

## 10.4 Handsuche/Literaturlistensuche

### Bisognano 2011 / baroreflex activation therapy (resistant hypertension, systolic blood pressure)

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
<p>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. <i>J Am Coll Cardiol.</i> 2011 Aug 9;58(7):765-73. doi: 10.1016/j.jacc.2011.06.008. <a href="https://pubmed.ncbi.nlm.nih.gov/21816315/">https://pubmed.ncbi.nlm.nih.gov/21816315/</a></p>	<p><b>Objective</b> to determine the effect of baroreflex activation therapy (BAT) on systolic blood pressure (SBP) in patients with resistant hypertension</p> <p><b>Study design</b> 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</p> <p><b>Inclusion and exclusion criteria</b></p> <ul style="list-style-type: none"> <li>- resistant HTN defined as at least 1 out-patient, in-office, systolic blood pressure (SBP) <math>\geq 160</math> mm Hg with diastolic BP <math>\geq 80</math> mm Hg taken per protocol utilizing a standardized device</li> <li>- at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic</li> <li>- ambulatory SBP <math>\geq 135</math> mm Hg for a 24-h average, obtained via a standardized protocol</li> <li>- core laboratory</li> <li>- absence of clinically significant orthostatic BP changes</li> </ul>	<p>n=265 subjects were randomized 2:1</p> <ul style="list-style-type: none"> <li>- n=181 to Group A (immediate BAT)</li> <li>- n=84 to Group B (BAT deferred until after Month 6)</li> <li>- 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</li> <li>- baseline characteristics                             <ul style="list-style-type: none"> <li>o male: 64% (n=116) vs. 55% (n=46)</li> <li>o mean age 53.7 vs. 52.4 years</li> <li>o mean systolic blood pressure 169 vs. 168 mm Hg</li> <li>o mean diastolic blood pressure 101 vs. 100 mm Hg</li> <li>o comorbidity: between 7 and 35 %</li> <li>o antihypertensive medications: averaged 5.2 +/- 1.7</li> <li>o &gt;90% with a diuretic</li> <li>o average follow-up was 21 +/- 8 months</li> <li>o total of 463 person-years of follow-up</li> </ul> </li> </ul> <p><b>Outcomes</b></p> <ul style="list-style-type: none"> <li>- acute efficacy (response rate): at 6 months                             <ul style="list-style-type: none"> <li>o 54% in Group A and 46% in Group B (p=0.97)</li> </ul> </li> <li>- sustained efficacy: at 6 months                             <ul style="list-style-type: none"> <li>o 88% of responders, maintaining response at 12 months per the protocol definition (p &lt; 0.001)</li> </ul> </li> <li>- secondary: mean change in SBP                             <ul style="list-style-type: none"> <li>o 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)</li> </ul> </li> </ul>	<p>RoB Tool not applicable: parallel-design clinical trial (experimental: on and off)</p> <p>approved under an investigational device exemption</p> <p>high/wide standard deviation</p> <p>limitations related to e.g. placebo effect, excess variability, Hawthorne effect, heterogeneous sample of patients</p>	<p>Literaturlistensuche, enthalten in NICE 2015 Rapid Review (s.o.) [241]</p> <p>when optimized, the majority of subjects (~75%) were programmed to a unilateral pathway</p>

Referenz	Charakteristika / Methodik	Ergebnisse	methodische Qualität/Sonstiges	Kommentar
	<p>- patients with presence of carotid stenosis were excluded, as well as subject being an inappropriate surgical candidate as assessed by the vascular surgeon investigator</p> <p><b>Intervention</b> Device: Rheos® Baroreflex Hypertension System*</p> <p><b>Outcome</b> 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)</p> <p>interim statistical analyses were performed at 6-month intervals</p>	<p>- safety: n=265 participants</p> <ul style="list-style-type: none"> <li>o n=7 deaths</li> <li>o most common adverse events (AE)                             <ul style="list-style-type: none"> <li>▪ procedural (surgical complication, nerve injury)</li> <li>▪ BAT (hypertensive crisis 5% (n=9) vs. 8.3% (n=7))</li> <li>▪ device (hypertension related stroke)</li> </ul> </li> <li>o procedure event-free rate 30 days: 74.8% vs. 70.5% p=1.00</li> <li>o BAT event-free rate 6 months 91.7% vs. 89.3%, (noninferiority) 2.4 vs. 4.1 p &lt; 0.001</li> <li>o device event-free rate 12 months: 87.2% vs. 83.8% p &lt; 0.001</li> </ul>		

\* 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.































Referenz	Charakteristika , Methodik	Ergebnisse	methodische Qualität	Kommentar
	<p>usual care</p> <p><b>Quality assessment:</b> certainty of the evidence (GRADE approach)</p> <p><b>Outcomes:</b> 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</p>	<ul style="list-style-type: none"> <li>- 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)</li> <li>- studies probably showed little or no difference in hospital admissions, service utilisation and patient health behaviours (with evidence of moderate certainty)</li> </ul> <p>Authors' conclusions:</p> <ul style="list-style-type: none"> <li>- suggests that shared care improves depression outcomes</li> <li>- limitations: methodological shortcomings, particularly inadequate length of follow-up</li> <li>- growing evidence base for shared care in the management of depression</li> <li>- shared care interventions for other conditions should be developed within research settings</li> </ul>		

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	<p><b>Objectives:</b> To assess clinical, patient-reported, and resource use outcomes of non-medical prescribing* for managing acute and chronic</p>	<p><b>Main results:</b> n=46 studies (37,337 participants);</p> <ul style="list-style-type: none"> <li>- non-medical prescribing                             <ul style="list-style-type: none"> <li>o by nurses (n=26 studies; n=28,621 participants), Colombia, South Africa,</li> </ul> </li> </ul>	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





























154. Hermida RC. Sleep-time ambulatory blood pressure as a prognostic marker of vascular and other risks and therapeutic target for prevention by hypertension chronotherapy: Rationale and design of the Hygia Project. *Chronobiol Int* 2016; 33(7):906–36. DOI: 10.1080/07420528.2016.1181078. <http://www.ncbi.nlm.nih.gov/pubmed/27221952>.
155. Hermida RC, Ríos MT, Crespo JJ, et al. Treatment-time regimen of hypertension medications significantly affects ambulatory blood pressure and clinical characteristics of patients with resistant hypertension. *Chronobiol Int* 2013; 30(1-2):192–206. DOI: 10.3109/07420528.2012.701460. <http://www.ncbi.nlm.nih.gov/pubmed/23098160>.
156. Hermida RC, Ayala DE, Mojón A, et al. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. *J Am Soc Nephrol* 2011; 22(12):2313–21. DOI: 10.1681/ASN.2011040361. <http://www.ncbi.nlm.nih.gov/pubmed/22025630>.
157. Hermida RC, Ayala DE, Mojón A, et al. Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk. *J Am Coll Cardiol* 2011; 58(11):1165–73. DOI: 10.1016/j.jacc.2011.04.043. <http://www.ncbi.nlm.nih.gov/pubmed/21884956>.
158. Hermida RC, Ayala DE, Mojón A, et al. Influence of circadian time of hypertension treatment on cardiovascular risk: Results of the MAPEC study. *Chronobiol Int* 2010; 27(8):1629–51. DOI: 10.3109/07420528.2010.510230. <http://www.ncbi.nlm.nih.gov/pubmed/20854139>.
159. Si S, Ofori-Asenso R, Briffa T, et al. Long-term persistence and adherence to blood pressure lowering agents among older Australians. *Pharmacoepidemiol Drug Saf* 2019; 28(6):788–95. DOI: 10.1002/pds.4742. <http://www.ncbi.nlm.nih.gov/pubmed/30784140>.
160. Verma AA, Khuu W, Tadrous M, et al. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study. *PLoS Med* 2018; 15(6):e1002584. DOI: 10.1371/journal.pmed.1002584. <http://www.ncbi.nlm.nih.gov/pubmed/29889841>.
161. Schulz M, Krueger K, Schuessel K, et al. Medication adherence and persistence according to different antihypertensive drug classes: A retrospective cohort study of 255,500 patients. *Int J Cardiol* 2016; 220:668–76. DOI: 10.1016/j.ijcard.2016.06.263. <http://www.ncbi.nlm.nih.gov/pubmed/27393848>.
162. Breitscheidel L, Ehlik B, Kostev K, et al. Real-life treatment patterns, compliance, persistence, and medication costs in patients with hypertension in Germany. *J Med Econ* 2012; 15(1):155–65. DOI: 10.3111/13696998.2011.635229. <http://www.ncbi.nlm.nih.gov/pubmed/22035215>.
163. Ah Y-M, Shin J, Lee J-Y. The association of angiotensin receptor blocker-based combination therapy with persistence and adherence in newly treated, uncomplicated hypertensive patients. *Patient Prefer Adherence* 2019; 13:241–8. DOI: 10.2147/PPA.S195423. <http://www.ncbi.nlm.nih.gov/pubmed/30774320>.
164. Hsu C-I, Hsiao F-Y, Wu F-LL, et al. Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: A population-based cohort study. *Int J Clin Pract* 2015; 69(7):729–37. DOI: 10.1111/ijcp.12591. <http://www.ncbi.nlm.nih.gov/pubmed/25395349>.
165. Machnicki G, Ong SH, Chen W, et al. Comparison of amlodipine/valsartan/hydrochlorothiazide single pill combination and free combination: Adherence, persistence, healthcare utilization and costs. *Curr Med Res Opin* 2015; 31(12):2287–96. DOI: 10.1185/03007995.2015.1098598. <http://www.ncbi.nlm.nih.gov/pubmed/26397178>.
166. Ho C-T, Tung Y-C, Chou S-H, et al. Clinical outcomes in hypertensive patients treated with a single-pill fixed-dose combination of renin-angiotensin system inhibitor and thiazide diuretic. *J Clin Hypertens (Greenwich)* 2018; 20(12):1731–8. DOI: 10.1111/jch.13413. <http://www.ncbi.nlm.nih.gov/pubmed/30375168>.
167. Dineva S, Uzunova K, Pavlova V, et al. Network meta-analysis of efficacy and safety of chlorthalidone and hydrochlorothiazide in hypertensive patients. *Blood Press Monit* 2021; 26(2):160–8. DOI: 10.1097/MBP.0000000000000486. <http://www.ncbi.nlm.nih.gov/pubmed/32909966>.
168. Roush GC, Messerli FH. Chlorthalidone versus hydrochlorothiazide: Major cardiovascular events, blood pressure, left ventricular mass, and adverse effects. *J Hypertens* 2021; 39(6):1254–60. DOI: 10.1097/HJH.0000000000002771. <http://www.ncbi.nlm.nih.gov/pubmed/33470735>.
169. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: Systematic review and network meta-analyses. *Hypertension* 2012; 59(6):1110–7. DOI: 10.1161/HYPERTENSIONAHA.112.191106. <http://www.ncbi.nlm.nih.gov/pubmed/22526259>.
170. Roush GC, Abdelfattah R, Song S, et al. Hydrochlorothiazide vs chlorthalidone, indapamide, and potassium-sparing/hydrochlorothiazide diuretics for reducing left ventricular hypertrophy: A systematic review and meta-analysis. *J Clin Hypertens (Greenwich)* 2018; 20(10):1507–15. DOI: 10.1111/jch.13386. <http://www.ncbi.nlm.nih.gov/pubmed/30251403>.
171. Arroll B, Wallace H. Should we switch from bendrofluazide to chlorthalidone as the initial treatment for hypertension? A review of the available medication. *J Prim Health Care* 2017; 9(2):105–13. DOI: 10.1071/HC16038. <http://www.ncbi.nlm.nih.gov/pubmed/29530222>.
172. Chen P, Chaugai S, Zhao F, et al. Cardioprotective Effect of Thiazide-Like Diuretics: A Meta-Analysis. *Am J Hypertens* 2015; 28(12):1453–63. DOI: 10.1093/ajh/hpv050. <http://www.ncbi.nlm.nih.gov/pubmed/25926533>.
173. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs—overview and meta-analyses. *J Hypertens* 2015; 33(2):195–211. DOI: 10.1097/HJH.0000000000000447. <http://www.ncbi.nlm.nih.gov/pubmed/25485720>.
174. Ernst ME, Carter BL, Zheng S, et al. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: Effects on systolic blood pressure and potassium. *Am J Hypertens* 2010; 23(4):440–6. DOI: 10.1038/ajh.2010.1. <http://www.ncbi.nlm.nih.gov/pubmed/20111008>.

175. Peterzan MA, Hardy R, Chaturvedi N, et al. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012; 59(6):1104–9. DOI: 10.1161/HYPERTENSIONAHA.111.190637. <http://www.ncbi.nlm.nih.gov/pubmed/22547443>.
176. van Blijderveen JC, Straus SM, Rodenburg EM, et al. Risk of hyponatremia with diuretics: Chlorthalidone versus hydrochlorothiazide. *Am J Med* 2014; 127(8):763–71. DOI: 10.1016/j.amjmed.2014.04.014. <http://www.ncbi.nlm.nih.gov/pubmed/24811554>.
177. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension* 2018; 72(5):e53–e90. DOI: 10.1161/HYP.000000000000084. <http://www.ncbi.nlm.nih.gov/pubmed/30354828>.
178. Roush GC, Abdelfattah R, Song S, et al. Hydrochlorothiazide and alternative diuretics versus renin-angiotensin system inhibitors for the regression of left ventricular hypertrophy: A head-to-head meta-analysis. *J Hypertens* 2018; 36(6):1247–55. DOI: 10.1097/HJH.0000000000001691. <http://www.ncbi.nlm.nih.gov/pubmed/29465713>.
179. Roush GC, Sica DA. Diuretics for Hypertension: A Review and Update. *Am J Hypertens* 2016; 29(10):1130–7. DOI: 10.1093/ajh/hpw030. <http://www.ncbi.nlm.nih.gov/pubmed/27048970>.
180. DiNicolantonio JJ, Bhutani J, Lavie CJ, et al. Evidence-based diuretics: Focus on chlorthalidone and indapamide. *Future Cardiol* 2015; 11(2):203–17. DOI: 10.2217/fca.14.83. <http://www.ncbi.nlm.nih.gov/pubmed/25760879>.
181. Roush GC, Ernst ME, Kostis JB, et al. Not just chlorthalidone: Evidence-based, single tablet, diuretic alternatives to hydrochlorothiazide for hypertension. *Curr Hypertens Rep* 2015; 17(4):540. DOI: 10.1007/s11906-015-0540-6. <http://www.ncbi.nlm.nih.gov/pubmed/25821163>.
182. Barrios V, Escobar C. Which thiazide to choose as add-on therapy for hypertension? *Integr Blood Press Control* 2014; 7:35–47. DOI: 10.2147/IBPC.S40248. <http://www.ncbi.nlm.nih.gov/pubmed/25161365>.
183. Roush GC, Kaur R, Ernst ME. Diuretics: A review and update. *J Cardiovasc Pharmacol Ther* 2014; 19(1):5–13. DOI: 10.1177/1074248413497257. <http://www.ncbi.nlm.nih.gov/pubmed/24243991>.
184. Mukete BN, Rosendorff C. Effects of low-dose thiazide diuretics on fasting plasma glucose and serum potassium—a meta-analysis. *J Am Soc Hypertens* 2013; 7(6):454–66. DOI: 10.1016/j.jash.2013.05.004. <http://www.ncbi.nlm.nih.gov/pubmed/23800570>.
185. Roush GC, Buddharaju V, Ernst ME. Is chlorthalidone better than hydrochlorothiazide in reducing cardiovascular events in hypertensives? *Curr Opin Cardiol* 2013; 28(4):426–32. DOI: 10.1097/HCO.0b013e3283622075. <http://www.ncbi.nlm.nih.gov/pubmed/23736816>.
186. Chan CY, Peterson EJ, Ng TM. Thiazide diuretics as chronic antihypertensive therapy in patients with severe renal disease—is there a role in the absence of diuresis? *Ann Pharmacother* 2012; 46(11):1554–8. DOI: 10.1345/aph.1R212. <http://www.ncbi.nlm.nih.gov/pubmed/23136355>.
187. Viera AJ. Resistant hypertension. *J Am Board Fam Med* 2012; 25(4):487–95. DOI: 10.3122/jabfm.2012.04.110275. <http://www.ncbi.nlm.nih.gov/pubmed/22773717>.
188. Reilly RF, Peixoto AJ, Desir GV. The evidence-based use of thiazide diuretics in hypertension and nephrolithiasis. *Clin J Am Soc Nephrol* 2010; 5(10):1893–903. DOI: 10.2215/CJN.04670510. <http://www.ncbi.nlm.nih.gov/pubmed/20798254>.
189. Baguet JP, Legallier B, Auquier P, et al. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. *Clin Drug Investig* 2007; 27(11):735–53. DOI: 10.2165/00044011-200727110-00001. <http://www.ncbi.nlm.nih.gov/pubmed/17914893>.
190. Baguet J-P, Robitail S, Boyer L, et al. A meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. *Am J Cardiovasc Drugs* 2005; 5(2):131–40. DOI: 10.2165/00129784-200505020-00007. <http://www.ncbi.nlm.nih.gov/pubmed/15725044>.
191. Calhoun DA. Low-dose aldosterone blockade as a new treatment paradigm for controlling resistant hypertension. *J Clin Hypertens (Greenwich)* 2007; 9(1 Suppl 1):19–24. DOI: 10.1111/j.1524-6175.2007.06334.x. <http://www.ncbi.nlm.nih.gov/pubmed/17215651>.
192. Ames R. Hyperlipidemia of diuretic therapy. *Arch Mal Coeur Vaiss* 1998; 91 Suppl(SUPPL):23–7. <http://www.ncbi.nlm.nih.gov/pubmed/9805566>.
193. Ames RP. A comparison of blood lipid and blood pressure responses during the treatment of systemic hypertension with indapamide and with thiazides. *Am J Cardiol* 1996; 77(6):12b–16b. DOI: 10.1016/s0002-9149(97)89233-8. <http://www.ncbi.nlm.nih.gov/pubmed/8848987>.
194. Ernst ME, Lund BC. Renewed interest in chlorthalidone: Evidence from the Veterans Health Administration. *J Clin Hypertens (Greenwich)* 2010; 12(12):927–34. DOI: 10.1111/j.1751-7176.2010.00373.x. <http://www.ncbi.nlm.nih.gov/pubmed/21122058>.
195. Hwang AY, Dave C, Smith SM. Trends in Antihypertensive Medication Use Among US Patients With Resistant Hypertension, 2008 to 2014. *Hypertension* 2016; 68(6):1349–54. DOI: 10.1161/HYPERTENSIONAHA.116.08128. <http://www.ncbi.nlm.nih.gov/pubmed/27777360>.
196. Lund BC, Ernst ME. The comparative effectiveness of hydrochlorothiazide and chlorthalidone in an observational cohort of veterans. *J Clin Hypertens (Greenwich)* 2012; 14(9):623–9. DOI: 10.1111/j.1751-7176.2012.00679.x. <http://www.ncbi.nlm.nih.gov/pubmed/22947361>.

197. Wilson L, Nair KV, Saseen JJ. Comparison of new-onset gout in adults prescribed chlorthalidone vs. hydrochlorothiazide for hypertension. *J Clin Hypertens (Greenwich)* 2014; 16(12):864–8. DOI: 10.1111/jch.12413. <http://www.ncbi.nlm.nih.gov/pubmed/25258088>.
198. Chrysant SG, Chrysant GS. Superior antihypertensive and cardioprotective effects of chlorthalidone compared with hydrochlorothiazide. *Drugs Today (Barc)* 2021; 57(4):291–301. DOI: 10.1358/dot.2021.57.4.3266245. <http://www.ncbi.nlm.nih.gov/pubmed/33851692>.
199. Düsing R. Therapie der Hypertonie mit Diuretika. Wirksamkeit, Sicherheit und Verträglichkeit. *Internist (Berl)* 2011; 52(12):1484–91. DOI: 10.1007/s00108-011-2915-3. <http://www.ncbi.nlm.nih.gov/pubmed/21833757>.
200. Licht JH, Haley RJ, Pugh B, et al. Diuretic regimens in essential hypertension. A comparison of hypokalemic effects, BP control, and cost. *Arch Intern Med* 1983; 143(9):1694–9. DOI: 10.1001/archinte.143.9.1694. <http://www.ncbi.nlm.nih.gov/pubmed/6412642>.
201. Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. *JACC Heart Fail* 2017; 5(8):543–51. DOI: 10.1016/j.jchf.2017.04.012. <http://www.ncbi.nlm.nih.gov/pubmed/28711447>.
202. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury: Diuretics. 2012 [cited: 2021-07-27]. <https://www.ncbi.nlm.nih.gov/books/NBK548808>.
203. Ravioli S, Bahmad S, Funk G-C, et al. Risk of Electrolyte Disorders, Syncope, and Falls in Patients Taking Thiazide Diuretics: Results of a Cross-Sectional Study. *Am J Med* 2021. DOI: 10.1016/j.amjmed.2021.04.007. <http://www.ncbi.nlm.nih.gov/pubmed/33974908>.
204. Olde Engberink RH, Frenkel WJ, van den Bogaard B, et al. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: Systematic review and meta-analysis. *Hypertension* 2015; 65(5):1033–40. DOI: 10.1161/HYPERTENSIONAHA.114.05122. <http://www.ncbi.nlm.nih.gov/pubmed/25733241>.
205. Ishani A, Cushman WC, Leatherman SM, et al. Chlorthalidone vs. Hydrochlorothiazide for Hypertension-Cardiovascular Events. *N Engl J Med* 2022; 387(26):2401–10. DOI: 10.1056/NEJMoa2212270. <http://www.ncbi.nlm.nih.gov/pubmed/36516076>.
206. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 2015; 386(10008):2059–68. DOI: 10.1016/S0140-6736(15)00257-3. <http://www.ncbi.nlm.nih.gov/pubmed/26414968>.
207. Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG), Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG). S2k-Leitlinie Hypertensive Schwangerschaftserkrankungen: Diagnostik und Therapie: Registernummer 015-018, Version 2019-07. 2019 [cited: 2019-08-08]. <https://www.awmf.org/leitlinien/detail/II/015-018.html>.
208. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: Evidence review for interventions for chronic hypertension. London; 2019 (NICE Guideline; 133). <https://www.nice.org.uk/guidance/ng133/evidence/a-interventions-for-chronic-hypertension-pdf-6836186126>.
209. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: Diagnosis and management. London; 2019 (NICE Guideline; 133). <https://www.nice.org.uk/guidance/ng133>.
210. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: Quality standard. London; 2013. <https://www.nice.org.uk/guidance/qs35>.
211. National Institute for Health and Care Excellence (NICE). NICE Pathway: Chronic hypertension in pregnancy. 2021 [cited: 2022-03-03]. <https://pathways.nice.org.uk/pathways/hypertension-in-pregnancy#content=view-index&path=view%3A/pathways/hypertension-in-pregnancy/chronic-hypertension-in-pregnancy.xml>.
212. National Institute for Health and Care Excellence (NICE). NICE Pathway: Hypertension in pregnancy overview. 2021 [cited: 2022-03-03]. <http://pathways.nice.org.uk/pathways/hypertension-in-pregnancy>.
213. Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2018; 10(10):CD002252. DOI: 10.1002/14651858.CD002252.pub4. <http://www.ncbi.nlm.nih.gov/pubmed/30277556>.
214. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2013(7):CD001449. DOI: 10.1002/14651858.CD001449.pub3. <http://www.ncbi.nlm.nih.gov/pubmed/23900968>.
215. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2003; B2(3):CD002863. DOI: 10.1002/14651858.CD002863. <http://www.ncbi.nlm.nih.gov/pubmed/12917933>.
216. 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 Cardiovasc Interv* 2020; 13(24):2922–33. DOI: 10.1016/j.jcin.2020.09.054. <http://www.ncbi.nlm.nih.gov/pubmed/33357531>.
217. 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:[Epub ahead of print]. DOI: 10.1161/CIRCULATIONAHA.119.040451. <http://www.ncbi.nlm.nih.gov/pubmed/30880441>.
218. 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(10137):2335–45. DOI: 10.1016/S0140-6736(18)31082-1. <http://www.ncbi.nlm.nih.gov/pubmed/29803590>.

219. Coppolino G, Pisano A, Rivoli L, et al. Renal denervation for resistant hypertension. *Cochrane Database Syst Rev* 2017; 2(2):CD011499. DOI: 10.1002/14651858.CD011499.pub2. <http://www.ncbi.nlm.nih.gov/pubmed/28220472>.
220. Pisano A, Iannone LF, Leo 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>.
221. 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* 2017; 390(10108):2160–70. DOI: 10.1016/S0140-6736(17)32281-X. <http://www.ncbi.nlm.nih.gov/pubmed/28859944>.
222. 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* 2021; 397(10293):2476–86. DOI: 10.1016/S0140-6736(21)00788-1. <http://www.ncbi.nlm.nih.gov/pubmed/34010611>.
223. Ahmad Y, Kane C, Arnold AD, et al. Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: A meta-analysis. *Cardiovasc Revasc Med* 2021; 34:112–118. DOI: 10.1016/j.carrev.2021.01.031. <http://www.ncbi.nlm.nih.gov/pubmed/33551282>.
224. 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>.
225. 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 Cardiovasc Interv* 2020; 13(4):461–70. DOI: 10.1016/j.jcin.2019.10.061. <http://www.ncbi.nlm.nih.gov/pubmed/32081240>.
226. Kario K, Yokoi Y, Okamura K, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: The randomized, controlled REQUIRE trial. *Hypertens Res* 2022; 45(2):221–31. DOI: 10.1038/s41440-021-00754-7. <http://www.ncbi.nlm.nih.gov/pubmed/34654905>.
227. 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 Press* 2017; 26(6):366–80. DOI: 10.1080/08037051.2017.1368368. <http://www.ncbi.nlm.nih.gov/pubmed/28830251>.
228. 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. *J Hypertens* 2016; 34(8):1639–47. DOI: 10.1097/HJH.0000000000000977. <http://www.ncbi.nlm.nih.gov/pubmed/27228432>.
229. 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* 2020; 395(10234):1444–51. DOI: 10.1016/S0140-6736(20)30554-7. <http://www.ncbi.nlm.nih.gov/pubmed/32234534>.
230. 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* 2022; 399(10333):1401–10. DOI: 10.1016/S0140-6736(22)00455-X. <http://www.ncbi.nlm.nih.gov/pubmed/35390320>.
231. 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* 2018; 391(10137):2346–55. DOI: 10.1016/S0140-6736(18)30951-6. <http://www.ncbi.nlm.nih.gov/pubmed/29803589>.
232. 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. *Eur Heart J* 2017; 38(2):93–100. DOI: 10.1093/eurheartj/ehw325. <http://www.ncbi.nlm.nih.gov/pubmed/28158510>.
233. 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* 2015; 65(4):766–74. DOI: 10.1161/HYPERTENSIONAHA.114.05010. <http://www.ncbi.nlm.nih.gov/pubmed/25691618>.
234. 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. *J Am Coll Cardiol* 2015; 65(13):1314–21. DOI: 10.1016/j.jacc.2015.01.037. <http://www.ncbi.nlm.nih.gov/pubmed/25835443>.
235. Bakris GL, Townsend RR, Liu M, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: Results from SYMPLICITY HTN-3. *J Am Coll Cardiol* 2014; 64(11):1071–8. DOI: 10.1016/j.jacc.2014.05.012. <http://www.ncbi.nlm.nih.gov/pubmed/24858423>.
236. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370(15):1393–401. DOI: 10.1056/NEJMoa1402670. <http://www.ncbi.nlm.nih.gov/pubmed/24678939>.
237. Schmieder RE, Ott C, Toennes SW, et al. Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. *J Hypertens* 2018; 36(3):680–9. DOI: 10.1097/HJH.0000000000001584. <http://www.ncbi.nlm.nih.gov/pubmed/29035942>.
238. Desch S, Okon T, Heinemann D, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015; 65(6):1202–8. DOI: 10.1161/HYPERTENSIONAHA.115.05283. <http://www.ncbi.nlm.nih.gov/pubmed/25824248>.
239. Shafi T, Chacko M, Berger Z, Wilson LM, Gayleard J, Bass EB, Sozio SM. Renal Denervation in the Medicare Population. Technology Assessment Program Project ID: RENT1115. 2016 [cited: 2020-01-14]. <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id102TA.pdf>.

240. National Institute for Health and Care Excellence (NICE). Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. 2012 (Interventional procedures guidance; 418) [cited: 2020-01-14]. <https://www.nice.org.uk/guidance/ipg418/resources/percutaneous-transluminal-radiofrequency-sympathetic-denervation-of-the-renal-artery-for-resistant-hypertension-pdf-1899869575330501>.
241. National Institute for Health and Care Excellence (NICE). Implanting a baroreceptor stimulation device for resistant hypertension. 2015 (Interventional procedures guidance; 533) [cited: 2020-01-14]. <https://www.nice.org.uk/guidance/ipg533/resources/implanting-a-baroreceptor-stimulation-device-for-resistant-hypertension-pdf-1899871864647109>.
242. Fisher ND, Kirtane AJ, Daemen J, et al. Plasma renin and aldosterone concentrations related to endovascular ultrasound renal denervation in the RADIANCE-HTN SOLO trial. *J Hypertens* 2022; 40(2):221–8. DOI: 10.1097/HJH.0000000000002994. <http://www.ncbi.nlm.nih.gov/pubmed/34433763>.
243. Sanghvi K, Wang Y, Daemen J, et al. Renal artery variations in patients with mild-to-moderate hypertension from the RADIANCE-HTN SOLO trial. *Cardiovasc Revasc Med* 2021; 39:58–65. DOI: 10.1016/j.carrev.2021.09.008. <http://www.ncbi.nlm.nih.gov/pubmed/34620570>.
244. Mahfoud F, Bloch MJ, Azizi M, et al. Changes in blood pressure after crossover to ultrasound renal denervation in patients initially treated with sham in the RADIANCE-HTN SOLO trial. *EuroIntervention* 2021; 17(12):e1024-e1032. DOI: 10.4244/EIJ-D-21-00295. <http://www.ncbi.nlm.nih.gov/pubmed/34236037>.
245. Fengler K, Rommel K-P, Lapusca R, et al. Renal Denervation in Isolated Systolic Hypertension Using Different Catheter Techniques and Technologies. *Hypertension* 2019; 74(2):341–8. DOI: 10.1161/HYPERTENSIONAHA.119.13019. <http://www.ncbi.nlm.nih.gov/pubmed/31203726>.
246. Engholm M, Bertelsen JB, Mathiassen ON, et al. Effects of renal denervation on coronary flow reserve and forearm dilation capacity in patients with treatment-resistant hypertension. A randomized, double-blinded, sham-controlled clinical trial. *Int J Cardiol* 2018; 250:29–34. DOI: 10.1016/j.ijcard.2017.09.200. <http://www.ncbi.nlm.nih.gov/pubmed/29042091>.
247. Böhm M, Mahfoud F, Townsend RR, et al. Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: Data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial. *Eur Heart J* 2019; 40(9):743–51. DOI: 10.1093/eurheartj/ehy871. <http://www.ncbi.nlm.nih.gov/pubmed/30608521>.
248. Kario K, Bhatt DL, Brar S, et al. Effect of Catheter-Based Renal Denervation on Morning and Nocturnal Blood Pressure: Insights From SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan. *Hypertension* 2015; 66(6):1130–7. DOI: 10.1161/HYPERTENSIONAHA.115.06260. <http://www.ncbi.nlm.nih.gov/pubmed/26558819>.
249. Böhm M, Townsend RR, Kario K, et al. Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal) and presence (SPYRAL HTN-ON MED Expansion) of antihypertensive medications: A novel approach using Bayesian design. *Clin Res Cardiol* 2020; 109(3):289–302. DOI: 10.1007/s00392-020-01595-z. <http://www.ncbi.nlm.nih.gov/pubmed/32034481>.
250. Vink EE, Beus E de, Jager RL de, et al. The effect of renal denervation added to standard pharmacologic treatment versus standard pharmacologic treatment alone in patients with resistant hypertension: Rationale and design of the SYMPATHY trial. *Am Heart J* 2014; 167(3):308–314.e3. DOI: 10.1016/j.ahj.2013.11.010. <http://www.ncbi.nlm.nih.gov/pubmed/24576513>.
251. Mahfoud F, Weber M, Schmieder RE, et al. Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: Design of two sham-controlled, randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications. *Am Heart J* 2021; 239:90–9. DOI: 10.1016/j.ahj.2021.05.015. <http://www.ncbi.nlm.nih.gov/pubmed/34052211>.
252. Gosse P, Cremer A, Pereira H, et al. Twenty-Four-Hour Blood Pressure Monitoring to Predict and Assess Impact of Renal Denervation: The DENERHTN Study (Renal Denervation for Hypertension). *Hypertension* 2017; 69(3):494–500. DOI: 10.1161/HYPERTENSIONAHA.116.08448. <http://www.ncbi.nlm.nih.gov/pubmed/28115517>.
253. Azizi M, Pereira H, Hamdidouche I, et al. Adherence to Antihypertensive Treatment and the Blood Pressure-Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial. *Circulation* 2016; 134(12):847–57. DOI: 10.1161/CIRCULATIONAHA.116.022922. <http://www.ncbi.nlm.nih.gov/pubmed/27576780>.
254. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): A multicentre, open-label, randomised controlled trial. *Lancet* 2015; 385(9981):1957–65. DOI: 10.1016/S0140-6736(14)61942-5. <http://www.ncbi.nlm.nih.gov/pubmed/25631070>.
255. La Sierra A de, Pareja J, Armario P, et al. Renal Denervation vs. Spironolactone in Resistant Hypertension: Effects on Circadian Patterns and Blood Pressure Variability. *Am J Hypertens* 2017; 30(1):37–41. DOI: 10.1093/ajh/hpw085. <http://www.ncbi.nlm.nih.gov/pubmed/27650995>.
256. Oliveras A, Armario P, Clarà A, et al. Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: Results from the DENERVHTA study - a randomized controlled trial. *J Hypertens* 2016; 34(9):1863–71. DOI: 10.1097/HJH.0000000000001025. <http://www.ncbi.nlm.nih.gov/pubmed/27327441>.
257. Bergland OU, Søråas CL, Larstorp AC, et al. The randomised Oslo study of renal denervation vs. Antihypertensive drug adjustments: Efficacy and safety through 7 years of follow-up. *Blood Press* 2021; 30(1):41–50. DOI: 10.1080/08037051.2020.1828818. <http://www.ncbi.nlm.nih.gov/pubmed/33030064>.
258. Fadl Elmula FE, Hoffmann P, Larstorp AC, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014; 63(5):991–9. DOI: 10.1161/HYPERTENSIONAHA.114.03246. <http://www.ncbi.nlm.nih.gov/pubmed/24591332>.

259. Rosa J, Widimský P, Waldauf P, et al. Renal denervation in comparison with intensified pharmacotherapy in true resistant hypertension: 2-year outcomes of randomized PRAGUE-15 study. *J Hypertens* 2017; 35(5):1093–9. DOI: 10.1097/HJH.0000000000001257. <http://www.ncbi.nlm.nih.gov/pubmed/28118281>.
260. Rosa J, Widimský P, Waldauf P, et al. Role of Adding Spironolactone and Renal Denervation in True Resistant Hypertension: One-Year Outcomes of Randomized PRAGUE-15 Study. *Hypertension* 2016; 67(2):397–403. DOI: 10.1161/HYPERTENSIONAHA.115.06526. <http://www.ncbi.nlm.nih.gov/pubmed/26693818>.
261. Rosa J, Widimský P, Toušek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: Six-month results from the Prague-15 study. *Hypertension* 2015; 65(2):407–13. DOI: 10.1161/HYPERTENSIONAHA.114.04019. <http://www.ncbi.nlm.nih.gov/pubmed/25421981>.
262. Esler MD, Böhm M, Sievert H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. *Eur Heart J* 2014; 35(26):1752–9. DOI: 10.1093/eurheartj/ehu209. <http://www.ncbi.nlm.nih.gov/pubmed/24898552>.
263. Kario K, Yamamoto E, Tomita H, et al. Sufficient and Persistent Blood Pressure Reduction in the Final Long-Term Results From SYMPLICITY HTN-Japan - Safety and Efficacy of Renal Denervation at 3 Years. *Circ J* 2019; 83(3):622–9. DOI: 10.1253/circj.CJ-18-1018. <http://www.ncbi.nlm.nih.gov/pubmed/30760655>.
264. Kario K, Ogawa H, Okumura K, et al. SYMPLICITY HTN-Japan - First Randomized Controlled Trial of Catheter-Based Renal Denervation in Asian Patients -. *Circ J* 2015; 79(6):1222–9. DOI: 10.1253/circj.CJ-15-0150. <http://www.ncbi.nlm.nih.gov/pubmed/25912693>.
265. Chen W, Ling Z, Du H, et al. The effect of two different renal denervation strategies on blood pressure in resistant hypertension: Comparison of full-length versus proximal renal artery ablation. *Cathet Cardiovasc Interv* 2016; 88(5):786–95. DOI: 10.1002/ccd.26594. <http://www.ncbi.nlm.nih.gov/pubmed/27219520>.
266. Fengler K, Heinemann D, Okon T, et al. Renal denervation improves exercise blood pressure: Insights from a randomized, sham-controlled trial. *Clin Res Cardiol* 2016; 105(7):592–600. DOI: 10.1007/s00392-015-0955-8. <http://www.ncbi.nlm.nih.gov/pubmed/26728060>.
267. Liu Z, Shen L, Huang W, et al. Efficacy and safety of renal denervation for Chinese patients with resistant hypertension using a microirrigated catheter: Study design and protocol for a prospective multicentre randomised controlled trial. *BMJ Open* 2017; 7(9):e015672. DOI: 10.1136/bmjopen-2016-015672. <http://www.ncbi.nlm.nih.gov/pubmed/28864691>.
268. Pekarskiy SE, Baev AE, Mordovin VF, et al. Denervation of the distal renal arterial branches vs. conventional main renal artery treatment: A randomized controlled trial for treatment of resistant hypertension. *J Hypertens* 2017; 35(2):369–75. DOI: 10.1097/HJH.0000000000001160. <http://www.ncbi.nlm.nih.gov/pubmed/28005705>.
269. Böhm M, Tsioufis K, Kandzari DE, et al. Effect of Heart Rate on the Outcome of Renal Denervation in Patients With Uncontrolled Hypertension. *J Am Coll Cardiol* 2021; 78(10):1028–38. DOI: 10.1016/j.jacc.2021.06.044. <http://www.ncbi.nlm.nih.gov/pubmed/34474735>.
270. Böhm M, Fahy M, Hickey GL, et al. A re-examination of the SPYRAL HTN-OFF MED Pivotal trial with respect to the underlying model assumptions. *Contemp Clin Trials Commun* 2021; 23:100818. DOI: 10.1016/j.conctc.2021.100818. <http://www.ncbi.nlm.nih.gov/pubmed/34258470>.
271. Kandzari DE, Hickey GL, Pocock SJ, et al. Prioritised endpoints for device-based hypertension trials: The win ratio methodology. *EuroIntervention* 2021; 16(18):e1496–e1502. DOI: 10.4244/EIJ-D-20-01090. <http://www.ncbi.nlm.nih.gov/pubmed/33226002>.
272. Hamdidouche I, Gosse P, Cremer A, et al. Clinic Versus Ambulatory Blood Pressure in Resistant Hypertension: Impact of Antihypertensive Medication Nonadherence: A Post Hoc Analysis the DENERHTN Study. *Hypertension* 2019; 74(5):1096–103. DOI: 10.1161/HYPERTENSIONAHA.119.13520. <http://www.ncbi.nlm.nih.gov/pubmed/31995406>.
273. Jacobs L, Persu A, Huang Q-F, et al. Results of a randomized controlled pilot trial of intravascular renal denervation for management of treatment-resistant hypertension. *Blood Press* 2017; 26(6):321–31. DOI: 10.1080/08037051.2017.1320939. <http://www.ncbi.nlm.nih.gov/pubmed/28489464>.
274. Waksman R, Bakris GL, Steinvil A, et al. High screen failure rate in patients with resistant hypertension: Findings from SYMPLICITY HTN-3. *Am Heart J* 2017; 192:76–84. DOI: 10.1016/j.ahj.2017.06.011. <http://www.ncbi.nlm.nih.gov/pubmed/28938966>.
275. Pocock SJ, Bakris G, Bhatt DL, et al. Regression to the Mean in SYMPLICITY HTN-3: Implications for Design and Reporting of Future Trials. *J Am Coll Cardiol* 2016; 68(18):2016–25. DOI: 10.1016/j.jacc.2016.07.775. <http://www.ncbi.nlm.nih.gov/pubmed/27788856>.
276. Rieke J, Seidensticker M, Becker S, et al. Renal Sympathetic Denervation by CT-Guided Ethanol Injection: A Phase II Pilot Trial of a Novel Technique. *Cardiovasc Intervent Radiol* 2016; 39(2):251–60. DOI: 10.1007/s00270-015-1261-6. <http://www.ncbi.nlm.nih.gov/pubmed/26634740>.
277. Schönherr E, Rehwald R, Nasser P, et al. Retrospective morphometric study of the suitability of renal arteries for renal denervation according to the Symplicity HTN2 trial criteria. *BMJ Open* 2016; 6(1):e009351. DOI: 10.1136/bmjopen-2015-009351. <http://www.ncbi.nlm.nih.gov/pubmed/26729385>.
278. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015; 36(4):219–27. DOI: 10.1093/eurheartj/ehu441. <http://www.ncbi.nlm.nih.gov/pubmed/25400162>.
279. Mahfoud F, Mancía G, Schmieder R, et al. Renal Denervation in High-Risk Patients With Hypertension. *J Am Coll Cardiol* 2020; 75(23):2879–88. DOI: 10.1016/j.jacc.2020.04.036. <http://www.ncbi.nlm.nih.gov/pubmed/32527396>.

280. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-Mediated Renal Denervation Using the Peregrine System Infusion Catheter for Treatment of Hypertension. *JACC Cardiovasc Interv* 2020; 13(4):471–84. DOI: 10.1016/j.jcin.2019.10.048. <http://www.ncbi.nlm.nih.gov/pubmed/32081241>.
281. Naduvathumuriyil T, Held U, Steigmiller K, et al. Clinical benefits and safety of renal denervation in severe arterial hypertension: A long-term follow-up study. *J Clin Hypertens (Greenwich. )* 2020; 22(10):1854–64. DOI: 10.1111/jch.14005. <http://www.ncbi.nlm.nih.gov/pubmed/32882101>.
282. Rodriguez-Leor O, Segura J, García Donaire JA, et al. Renal denervation for the treatment of resistant hypertension in Spain. The Flex-Spyral Registry. *Rev Esp Cardiol (Engl Ed)* 2020; 73(8):615–22. DOI: 10.1016/j.rec.2019.08.001. <http://www.ncbi.nlm.nih.gov/pubmed/31561981>.
283. Daemen J, Mahfoud F, Kuck K-H, et al. Safety and efficacy of endovascular ultrasound renal denervation in resistant hypertension: 12-month results from the ACHIEVE study. *J Hypertens* 2019; 37(9):1906–12. DOI: 10.1097/HJH.0000000000002120. <http://www.ncbi.nlm.nih.gov/pubmed/31045964>.
284. Völz S, Spaak J, Elf J, et al. Renal sympathetic denervation in Sweden: A report from the Swedish registry for renal denervation. *J Hypertens* 2018; 36(1):151–8. DOI: 10.1097/HJH.0000000000001517. <http://www.ncbi.nlm.nih.gov/pubmed/29210862>.
285. Fischell TA, Ebner A, Gallo S, et al. Transcatheter Alcohol-Mediated Perivascular Renal Denervation With the Peregrine System: First-in-Human Experience. *JACC Cardiovasc Interv* 2016; 9(6):589–98. DOI: 10.1016/j.jcin.2015.11.041. <http://www.ncbi.nlm.nih.gov/pubmed/27013159>.
286. Judd E, Calhoun DA. Apparent and true resistant hypertension: Definition, prevalence and outcomes. *J Hum Hypertens* 2014; 28(8):463–8. DOI: 10.1038/jhh.2013.140. <http://www.ncbi.nlm.nih.gov/pubmed/24430707>.
287. Kaiser L, Beister T, Wiese A, et al. Results of the ALSTER BP real-world registry on renal denervation employing the Symplicity system. *EuroIntervention* 2014; 10(1):157–65. DOI: 10.4244/EIJV10I1A24. <http://www.ncbi.nlm.nih.gov/pubmed/24472799>.
288. National Institute for Health and Care Excellence (NICE). Hypertension in adults: diagnosis and management [I] Evidence review for same-day specialist review. 2019 (NICE Clinical Guideline; 136) [cited: 2020-01-14]. <https://www.nice.org.uk/guidance/ng136/evidence/i-sameday-specialist-review-pdf-248282935380>.
289. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev* 2021; 1(1):CD006560. DOI: 10.1002/14651858.CD006560.pub4. <http://www.ncbi.nlm.nih.gov/pubmed/33448337>.
290. Steed L, Sohanpal R, Todd A, 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. <http://www.ncbi.nlm.nih.gov/pubmed/31808563>.
291. Laurant M, van der Biezen M, Wijers N, et al. Nurses as substitutes for doctors in primary care. *Cochrane Database Syst Rev* 2018; 7(7):CD001271. DOI: 10.1002/14651858.CD001271.pub3. <http://www.ncbi.nlm.nih.gov/pubmed/30011347>.
292. Barra M de, Scott CL, Scott NW, et al. Pharmacist services for non-hospitalised patients. *Cochrane Database Syst Rev* 2018; 9(9):CD013102. DOI: 10.1002/14651858.CD013102. <http://www.ncbi.nlm.nih.gov/pubmed/30178872>.
293. Smith SM, Cousins G, Clyne B, et al. Shared care across the interface between primary and specialty care in management of long term conditions. *Cochrane Database Syst Rev* 2017; 2(2):CD004910. DOI: 10.1002/14651858.CD004910.pub3. <http://www.ncbi.nlm.nih.gov/pubmed/28230899>.
294. Weeks G, George J, Maclure K, et al. Non-medical prescribing versus medical prescribing for acute and chronic disease management in primary and secondary care. *Cochrane Database Syst Rev* 2016; 11(11):CD011227. DOI: 10.1002/14651858.CD011227.pub2. <http://www.ncbi.nlm.nih.gov/pubmed/27873322>.
295. Nkansah N, Mostovetsky O, Yu C, et al. Effect of outpatient pharmacists' non-dispensing roles on patient outcomes and prescribing patterns. *Cochrane Database Syst Rev* 2010(7):CD000336. DOI: 10.1002/14651858.CD000336.pub2. <http://www.ncbi.nlm.nih.gov/pubmed/20614422>.