HTA Austria
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Renal denervation (RDN) in patients with treatment resistant hypertension

2. Update 2024
Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

List of figures

List of tables

List of abbreviations

24h.....24-hour
95% CI .....95% confidence interval
ABP .....ambulatory blood pressure
AWMF .....German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BAT.....baroreceptor activation therapy
BGD .....between group difference
CE.....Conformité Européenne
CoR .....Certainty of Recommendation
CVS .....cardiovascular
DGfN .....Deutsche Gesellschaft für Nephrologie e.V.
DGK.....Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V.
DHL.....Deutsche Gesellschaft für Hypertonie und Prävention – Deutsche Hochdruckliga e.V.
eGFR.....estimated glomerular filtration rate
ESC .....European Society of Cardiology
ESH.....European Society of Hypertension
EUnetHTA .....European Network for Health technology Assessment
EVBA .....endovascular baroreflex amplification
FU .....follow-up
GMDN .....Global Medical Device Nomenclature
GRADE.....Grading of Recommendations, Assessment, Development and Evaluations
INAHTA.....International Network of Agencies for Health technology Assessment
IQR.....interquartile range
LKF.....Leistungsorientierte Krankenanstaltenfinanzierung
LoE.....Level of Evidence
MDHT .....multi-disciplinary hypertension team
NICE.....National Institute of Care Excellence
NR.....not reported
OMT.....optimal medical treatment
OSA .....obstructive sleep apnea
PRISMA.....preferred reporting items for systematic reviews and meta-analysis
PROM .....patient-reported outcome measurements
QoL .....quality of life
RCT.....randomized controlled trial
RDN.....renal denervation
RF-RDN .....radiofrequency renal denervation
RoB.....risk of bias
SADE .....serious adverse device effect
SAE .....(serious) adverse events
SD.....standard deviation
SE .....standard error
SNS .....sympathetic nervous system
SR.....systematic review
TRH .....treatment-resistant hypertension
U-RDN .....ultrasound renal denervation
US.....United States

Executive Summary

Introduction

This report is the second update of the systematic review on percutaneous renal denervation initially prepared in 2011 by the Ludwig-Boltzmann Institute for Health Technology Assessment (LBI-HTA) and updated in 2012.

2nd update 2024

Health Problem

Treatment-resistant hypertension (TRH) is diagnosed when blood pressure remains above 140/90 mmHg systolic/diastolic despite having implemented lifestyle changes and despite the use of at least three or more antihypertensive agents at maximum tolerated doses, including a diuretic.

definition of treatment-resistant hypertension (TRH)

Multiple factors can cause poor BP control and need to be excluded before the diagnosis of TRH can be made. Patients might be pseudo-resistant due to common causes like the "white-coat effect", medication non-adherence or insufficient dosing, interference with concurrent medication or simply due to inadequate measuring techniques or failure to apply guideline-directed lifestyle changes. TRH could also be masked by secondary hypertension, representing a large group of patients suffering from hormonal alterations, vascular pathologies (renal artery stenosis), or secondary conditions like obstructive sleep apnea. Once a diagnosis of TRH has been confirmed, patients are treated with a multimodal approach consisting of antihypertensive medication and non-pharmacological interventions such as lifestyle changes to reduce cardiovascular sequelae and preserve kidney function.

differential diagnosis of TRH

multimodal treatment

According to the current 2023 ESH guidelines for the diagnosis and management of hypertension, after the exclusion of other causative factors, the prevalence of „true resistant hypertension" is estimated at around 5%.

prevalence of TRH: approx. 5% of all hypertensive patients

Description of Technology

RDN is a minimally invasive intervention that reduces the sympathetic nerve activity along the renal arteries through ultrasound or radiofrequency ablation, consequently lowering BP. Currently, two products exist with CE- and FDA-certification: the Paradise® ultrasound RDN System and the radiofrequency-based Symplicity Spyral™ Catheter System.

renal denervation (RDN): Ablation of the sympathetic nerve fibres along the renal arteries to reduce activity

Methods

This update report synthesizes the evidence on the efficacy and safety of RDN in patients with TRH. We changed the research question, inclusion criteria, and search strategies slightly compared to the original assessments by including only sham-controlled randomised studies. A systematic search was conducted in four databases. Two researchers independently performed study selection, data extraction and quality-assessment of included studies. The quality of evidence was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Scheme.

systematic search in 4 databases, quality appraisal of literature

GRADE

Domain effectiveness

The following efficacy outcomes were considered critical to derive a recommendation: All-cause mortality, cardiovascular mortality, cardiovascular events, and 24-hour (24h) systolic/diastolic ambulatory blood pressure (ABP).

efficacy outcomes: mortality, cardiovascular events and 24-hour (24h) ambulatory blood pressure (ABP)

Domain safety

Serious adverse events and adverse events were considered critical for decision-making.

safety outcomes: (serious) adverse events (S)AE

Results

Ten randomised sham-controlled trials (RCT) (in 18 publications) were eligible for inclusion in this update report, none of which were included in previous LBI-HTA reports. The overall risk of bias was considered low for nine of ten trials. All studies compared renal denervation with a sham procedure. In total, 2,043 patients with uncontrolled blood pressure and treated with varying numbers of antihypertensive medication prior to enrolment were included.

10 sham-controlled randomised control trials (RCTs)

The certainty of evidence was evaluated as low for the endpoints mortality and cardiovascular events due to insufficient statistical power. For blood pressure changes up to six months of follow-up, the certainty of evidence was considered moderate due to heterogenous inclusion criteria and wide confidence intervals. The certainty of evidence was graded low for blood pressure changes beyond six months of follow-up due to lack of continued blinding.

certainty of evidence low to moderate for efficacy endpoints

The certainty of evidence for safety outcomes was considered moderate due to imprecision concerns.

certainty of evidence moderate for safety endpoints

Ultrasound renal denervation

Four studies with a total of 649 included patients evaluated U-RDN. All studies defined BP changes as the primary efficacy endpoint, and one also defined a composite safety endpoint as a primary safety endpoint. Significance testing was only performed for the primary endpoints.

4 studies on U-RDN

All-cause mortality ranged from 0 to 1% in the intervention and control groups, respectively. None of the patients suffered a **cardiovascular death** and up to 3% of patients in the intervention group and 4% of patients in the control group suffered a cardiovascular event.

mortality: 0-1% vs 0-1% cardiovascular events: 0-3% vs 0-4%

Three of the four studies detected a statistically significant difference in favour of the intervention for **systolic 24h ABP**, and one study for **diastolic 24h ABP** after **three months of follow-up**. Across all studies, between-group differences in BP reductions ranged from -6.3 to -0.1 mmHg and from -4.1 to -0.4 mmHg, respectively. Neither of the two studies that reported further 6-month follow-up data found significant between-group differences, nor did the one that reported 12-month follow-up data.

24h systolic ABP changes favour intervention in 3/4 RCTs after 3 months

Serious adverse events occurred in 0 to 4% of the intervention group and 0 to 1% of the control group up to the six-month follow-up. They included vasospastic angina, puncture site haemorrhage, doubling of serum creatinine and postural dizziness. **Adverse events** occurred in 0 to 17% and 0 to 15%, respectively. The most frequently reported adverse event was procedure-related pain lasting longer than two days. The primary safety endpoint was met in the study that had prespecified this in their analysis.

SAE: 0-1% vs 0-4%

most frequent AE: pain ≥ 2 days

Radiofrequency renal denervation

6 studies on RF-RDN

Six studies, including a total of 1,394 patients, evaluated RF-RDN. The primary efficacy endpoint set by all was a reduction in BP. Two studies additionally defined a composite safety endpoint as a primary safety endpoint. Significance testing was only performed for primary endpoints.

mortality: 0-4% vs 0-11%
cardiovascular events: 0-10% vs 0-12%

The overall rate of **all-cause mortality** ranged from 0 to 4% and 0 to 11% in intervention and control groups, respectively, and no **cardiovascular deaths** were recorded. **Cardiovascular events** occurred in up to 10% and 12% of patients, respectively, after six months of follow-up.

24h systolic/diastolic ABP: Changes in favour of intervention in 1/6 RCTs after 6 months

long-term follow-up results significant but unblinded

Only one of six studies found a significant difference in **systolic and diastolic 24h ABP** up until the **6-month** follow-up. The mean between-group difference of BP reductions ranged from -7.4 to -1.9 mmHg and -3.1 to -0.8 mmHg, respectively. Two studies reported 12-month follow-up results. Only one of the two studies found a significant between-group difference favouring the intervention and reported a mean higher reduction in systolic/diastolic 24h ABP of -8.5/-5.6 mmHg compared to the control group. Two studies also reported unblinded outcomes at 36 months, with both reporting statistically significant group differences in BP reductions in favour of the intervention group at a range of -16.5 to -11.2 mmHg for systolic and -11.2 to -5.7 mmHg for diastolic 24h ABP.

SAE: 0-1% vs 0-1%

Serious adverse events occurred in 0 to 1% of the intervention and control groups, respectively. The primary safety endpoint was met in two studies that had pre-defined performance goals. **Adverse events** were reported by one study only and included atypical chest pain, muscle spasms, headaches, and tiredness.

Ongoing studies

10 sham-controlled studies in progress

Ten sham-controlled RCTs are currently ongoing, of which seven already reached completion, and the others are estimated to reach their completion date between 2024 and 2028.

Discussion

limitations:

heterogenous inclusion criteria

long-term effect of RDN on blood pressure is unknown

Although the internal validity of the included sham-RCTs on BP control was adequate, there are notable applicability concerns and evidence gaps that relate to uncertainties regarding long-term effectiveness, effect on patient-centred outcomes (PRO) and a potential reduction of cardiovascular events, the magnitude of benefit for specific indications and, subsequently, uncertainties surrounded by the specific role of RDN in clinical practice. Despite current data from sham-controlled trials suggesting an effect on blood pressure and a favourable safety profile, the lack of an indicator of technical ablation success remains a burden of the technology. Due to the design of the currently available trials as well as the lack of a validated threshold value for the perceptibility of the antihypertensive effect (Minimal Important Difference/ MCID), the impact of RDN on mortality and cardiovascular outcome can only be extrapolated from the impact of the well documented BP reduction on long-term cardiovascular outcomes. Therefore, RDN should be performed within clinical trials or registries and the current level of evidence should be critically evaluated continuously.

Conclusion

Moderate certainty evidence indicates that renal denervation improves blood pressure control up to six months follow-up in patients with TRH and that the technology is relatively safe. Evidence is insufficient to assess the effect on other outcome measures, such as health-related quality of life (HRQoL) or cardiovascular events. Uncertainty remains on the exact patient population, who would benefit the most from RDN and the magnitude of its effect.

moderate certainty evidence for reduction of BP in TRH ≤6 months of follow-up

A re-evaluation is recommended for 2026 after the publication of the results of currently ongoing sham-controlled studies.

re-evaluation recommended in 2026

Zusammenfassung

Einleitung

2tes Update 2024

Dieser Bericht ist das zweite Update des systematischen Reviews „Perkutane renale Denervation bei therapieresistenter Hypertonie“, der erstmals 2011 vom Ludwig-Boltzmann-Institut für Health Technology Assessment (LBI-HTA) erstellt wurde und im Jahr 2012 aktualisiert wurde.

Indikation und therapeutisches Ziel

Definition therapieresistente Hypertonie (TRH)

Unter therapieresistenter Hypertonie (TRH) versteht man einen Blutdruck (BD), welcher über einem Blutdruckzielwert von 140/90 mmHg bleibt, trotz Änderungen des Lebensstils und der Einnahme einer maximal tolerierten Dosis von mindestens drei Antihypertensiva mit komplementärem Wirkmechanismus, darunter ein Diuretikum.

Risikofaktoren für TRH u. a. Alter, physische Inaktivität oder Diabetes

Risikofaktoren für TRH sind unter anderem das Alter, physische Inaktivität oder Diabetes mellitus und häufige sekundäre Faktoren für TRH sind Schlafapnoe, primärer Hyperaldosteronismus oder Nierenarterienstenose. Bluthochdruck kann oftmals jahrelang asymptotisch und somit unbemerkt bleiben. Dieser hat jedoch eine hohe Auswirkung auf das kardiovaskuläre Risikoprofil der Patient*innen und geht mit Folgeerkrankungen wie der peripheren arteriellen Verschlusskrankheit oder terminalen Niereninsuffizienz, sowie laut neueren Ergebnissen auch mit kognitivem Verfall, einher. Charakteristisch für Patient*innen mit TRH spezifisch sind außerdem eine höhere Prävalenz von Endorganschäden sowie eine schlechtere Langzeitprognose.

Prävalenz TRH: ca. 5 % der Patient*innen mit Hypertonie

Die Prävalenz von Hypertonie in Österreich lag 2015 bei 17 % der Frauen und 25 % der Männer. Aufgrund der Uneinigkeit über die genaue Definition von TRH, war es bisher schwierig, die tatsächliche Prävalenz zu bestimmen. Laut den ESH (European Society of Hypertension)-Leitlinien 2023 wird die Prävalenz der pseudoresistenten Hypertonie auf 10 % bis 20 % der Patient*innen mit Hypertonie geschätzt, während die Prävalenz der echten TRH bei 5 % der Patient*innen mit Hypertonie liegt.

Diagnose von TRH und anschließende, multimodale Behandlung

Um TRH zu diagnostizieren, müssen daher zunächst andere klinische wie auch pathophysiologische Faktoren (wie unter anderem der „Weißkitteleffekt“, d. h., ein erhöhter BD während dem Arztbesuch, medikamentöse Nonadhärenz oder die Beeinflussung durch andere Medikamente) ausgeschlossen werden. Erst nach Ausschluss dieser Faktoren und somit dem Verdacht auf tatsächliche TRH, kann die Behandlung von TRH mithilfe eines multimodalen Ansatzes, erfolgen. Dieser kann unter anderem aus nicht-medikamentösen Maßnahmen, wie z. B. Lebensstiländerungen, oder auch aus weiterer medikamentöser Behandlung bestehen. Das therapeutische Ziel bei der Behandlung von TRH ist es, den BD zu senken, um die Nierenfunktion langfristig zu erhalten und insgesamt kardiovaskuläre Folgeerkrankungen zu reduzieren.

renale Denervierung (RDN) als zusätzliche Behandlungsoption bei Patient*innen mit TRH

Bei Patient*innen, bei denen die medikamentöse Behandlung nicht anspringt, oder die die medikamentöse Behandlung nicht vertragen, erwähnen verschiedene Leitlinien, unter anderem die der European Society of Hypertension (ESH), der American College of Cardiology (ACC) und der deutschen Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaft (AWMF), die sogenannte renale Denervierung (RDN), als eine zusätzliche Behandlungsoption.

Beschreibung der Technologie

RDN: Verödung der überaktiven Nerven entlang der Nierenarterien

RDN ist ein minimalinvasives Verfahren, bei dem ein flexibler Katheter über die Leistenarterie bis zur Nierenarterie geführt wird. Über Elektroden an der Katheterspitze werden dann die sympathischen Nerven entlang der Nierenarterie beidseitig verödet, wodurch die blutdrucksteigernde Wirkung dieser unterbunden wird. Dieses Verfahren stellt für medikamentös nicht einstellbare Bluthochdruckpatient*innen eine neue Therapieoption dar.

zwei RDN-Produkte mit CE- und FDA-Zulassung:

Aktuell verfügen zwei RDN-Produkte, sowohl über eine CE- als auch über eine FDA-Zertifizierung: das Paradise® Ultraschall RDN System und das radiofrequenzbasierte Symplicity Spyral™ Katheter System.

Paradise® Ultraschall RDN System

Das Paradise® Ultraschall RDN System besteht aus einem Katheter mit einem Ultraschallwandler, welche eine Rundum-Ablation ermöglicht. Es können die Hauptnierenarterien sowie zentrale Abzweigungen mit einem Durchmesser zwischen 3 und 8 mm behandelt werden. Pro Arterien werden zwei bis drei Ablationen, für je sieben Sekunden, durchgeführt.

Symplicity Spyral™ Katheter System

Das Symplicity Spyral™ Katheter System besteht aus einer adjustierbaren Einwegspirale mit vier Radiofrequenz-Elektroden entlang dessen Umfang. Alle zugänglichen Arterien mit einem Umfang zwischen 3 und 8 mm können behandelt werden. Die Ablation erfolgt maximal für 60 Sekunden.

Methoden

Fragestellung, systematische Suche und Studienselektion

Ziel der vorliegenden Arbeit war es, die Evidenz zur klinischen Wirksamkeit und Sicherheit der renalen Denervierung bei Patient*innen mit TRH zu überprüfen. Die Fragestellung, die Einschlusskriterien und die Suchstrategie des Berichts wurden im Vergleich zu den beiden früheren Assessments minimal verändert: Es wurden nur randomisierte, Sham-kontrollierte Studien in die Evidenzsynthese eingeschlossen.

Datenextraktion und GRADE-Bewertung

Es wurde eine systematische Literatursuche in vier medizinischen Datenbanken durchgeführt (Medline, Embase, the Cochrane Library und INAHTA). Die Studienselektion, Datenextraktion sowie Qualitätsbewertung erfolgten jeweils durch zwei Personen unabhängig voneinander. Die Vertrauenswürdigkeit der Evidenz wurde nach dem GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema bewertet.

Klinische Wirksamkeit

Wirksamkeitsendpunkte: Mortalität, kardiovaskuläre Ereignisse und Reduktion 24-Stunden (Std.) Blutdruckts (BD)

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert:

- Mortalität/kardiovaskuläre Mortalität
- Kardiovaskuläre Ereignisse
- 24-Std. Blutdruck

Sicherheit

Sicherheitsendpunkte: (schwere) unerwünschte Ereignisse (SUE/UE)

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert:

- Schwere unerwünschte Ereignisse (SUE)
- Unerwünschte Ereignisse (UE)

Ergebnisse

Verfügbare Evidenz

insgesamt 10 RCTs mit Sham-Kontrolle RoB: niedrig in 9/10 RCTs

Für das Update 2024 konnten im Rahmen der Literaturrecherche zehn neue randomisiert Sham-kontrollierte Studien, mit insgesamt 18 Publikationen, identifiziert werden. Keine dieser Studien war in den früheren LBI-HTA-Berichten enthalten. Das Verzerrungspotenzial wurde in neun von zehn der RCTs als niedrig bewertet. Acht der zehn Studien waren multi-zentristisch und wurden vom jeweiligen Hersteller finanziert. Zusätzlich wurden in allen Studien sowohl die Patient*innen, als auch das datenerhebende Personal der Gruppeneinteilung gegenüber verblindet.

insgesamt 2.043 Patient*innen,

4 ultraschallbasierte RDN (U-RDN) und 6 radiofrequenzbasierte RDN (RF-RDN) Studien

Alle Studien verglichen RDN mit der Scheintherapie mittels Nierenangiogramm. Vier Studien untersuchten die Wirksamkeit und Sicherheit von U-RDN, während sechs Studien RF-RDN untersuchten. Insgesamt wurden 2.043 Patient*innen eingeschlossen (U-RDN=649; RF-RDN=1.394). Während das Blutdruckziel in allen Studien bei einem 24-Std. BD von unter 140/90 mmHg lag, waren die Einschlusskriterien zwischen den Studien sehr heterogen. Darunter gab es ebenfalls vier Studien, in denen die Patient*innen vor der RDN ihre Medikamente absetzen mussten (zwei U-RDN und zwei RF-RDN Studien). Häufig auftretende Komorbiditäten waren Schlafapnoe und Typ 2-Diabetes. Die primäre Nachbeobachtungszeit betrug zwischen zwei und sechs Monaten. Einige Studien berichteten außerdem noch Langzeitdaten nach der primären Analyse der Resultate.

Vertrauenswürdigkeit der Evidenz

Vertrauenswürdigkeit der Evidenz für Wirksamkeitsendpunkte: niedrig bis moderat

Die Vertrauenswürdigkeit der Evidenz wurde bei den Endpunkten Mortalität und kardiovaskuläre Mortalität aufgrund von statistischer Ungenauigkeit als niedrig bewertet. Für die Blutdrucksenkung wurde die Vertrauenswürdigkeit der Evidenz nach sechs Monaten als moderat (vor allem wegen uneinheitlichen Einschlusskriterien der verschiedenen Studien) und nach über sechs Monaten vor dem Hintergrund fehlender Verblindung als niedrig eingestuft.

Vertrauenswürdigkeit der Evidenz für Sicherheitsendpunkte: moderat

Die Vertrauenswürdigkeit der Evidenz bezogen auf die Sicherheit von RDN war moderat. Der Grund für diese Einschätzung war, dass die optimale Informationsgröße bei diesem Endpunkt nicht erreicht wurde.

Ultraschall-basierte renale Denervierung (U-RDN)

4 U-RDN Studien mit 649 Patient*innen

Vier Studien mit insgesamt 649 Teilnehmer*innen (Range: 143-146) mit unkontrolliertem Blutdruck und variierender Anzahl an vorheriger antihypertensiver Medikation untersuchten die ultraschallbasierte renale Denervierung (U-RDN). Alle Studien definierten die Blutdrucksenkung als primären Wirksamkeitsendpunkt.

Klinische Wirksamkeit

Mortalität: 0-1 % vs. 0-1 %

kardiovaskuläre Ereignisse: 0-3 % vs. 0-4 %

Die Endpunkte **Gesamtmortalität/kardiovaskuläre Mortalität** und **kardiovaskuläre Ereignisse** wurden in allen vier U-RDN Studien als sekundäre Endpunkte erfasst, jedoch wurde hier in den meisten Studien aufgrund fehlender statistischer Genauigkeit auf Signifikanztests verzichtet. Die Mortalitätsrate schwankte sowohl in der Interventions-, als auch der Kontrollgruppe, zwischen 0 % und 1 %. Kardiovaskuläre Mortalität trat in keiner der Studien auf. Kardiovaskuläre Ereignisse schwankten zwischen 0 % und 3 % in der Interventions- und zwischen 0 % und 4 % in der Kontrollgruppe.

Alle vier Studien erfassten den **systolischen/diastolischen 24-Std. BD,** wobei die Studien entweder den Median oder den Mittelwert des Gruppenunterschiedes angaben. Nach einer Nachbeobachtungszeit von bis zu **drei Monaten** lag der Gruppenunterschied des systolischen 24-Std. BDs zwischen -6.3 und -0.1 mmHg, wobei der Unterschied in drei Studien signifikant war (Range: -6.3 bis -4.1 mmHg). Der Gruppenunterschied der diastolischen 24-Std. BDs-Senkung lag zwischen -4.1 und -0.4 mmHg und war nur in einer Studie signifikant. Zwei Studien berichteten zusätzlich eine **sechs-monatige Nachbeobachtungszeit**, ohne signifikante Gruppenunterschiede beim systolischen (jeweils -2.0 und 0.1 mmHg) oder diastolischen (jeweils -1.0 und 0.2 mmHg) 24-Std. BD.

24-Std. BD Werte stat. signifikant zugunsten der U-RDN in 3/4 Studien nach 3 Monaten,

keine Unterschiede nach 6 Monaten in 2 RCTs

In einer Studie (n=146) mit einer Nachbeobachtungszeit von **zwölf Monaten**, war der Gruppenunterschied zwischen der Interventions- und der Kontrollgruppe beim **systolischen** (-0.8 mmHg) und **diastolischen** (-0.2 mmHg) **24-Std. BD** statistisch nicht signifikant.

keine Unterschiede nach 12 Monaten in 1 RCT

Sicherheit

Schwere unerwünschte Ereignisse (**SUE**) variierten in den vier Studien zwischen 0 % und 4 % der Interventionsgruppe und 0 % und 1 % in der Kontrollgruppe. Unerwünschte Ereignisse (**UE**) traten hingegen bei 0 bis 17 % der Interventionsgruppe und bei 0 bis 15 % der Kontrollgruppe auf. Am häufigsten wurde von interventionsbedingten Schmerzen, die länger als zwei Tage anhielten, berichtet (Interventionsgruppe: 8-17 %; Kontrollgruppe: 8-15 %). Zusätzlich wurden von einer Studie Vasospasmen (6 % vs. 3 %) und Komplikationen an der Einstichstelle (6 % vs. 4 %) berichtet. Eine Studie erfasste außerdem einen kombinierten Sicherheitsendpunkt als primären Endpunkt, welcher erreicht wurde.

SUE: 0-4 % vs. 0-1 %

UE: 0-17 % vs. 0-15 %, v. a. interventionsbedingte Schmerzen >2 Tage

Radiofrequenz-basierte renale Denervierung (RF-RDN)

Sechs Studien mit insgesamt 1.394 Teilnehmer*innen (Range: 51-535) mit unkontrolliertem Blutdruck und unterschiedlicher Anzahl an vorheriger antihypertensiver Medikation untersuchten die RF-RDN. Alle Studien definierten eine Blutdrucksenkung als primären Wirksamkeitsendpunkt und zwei Studien definierten zusätzlich einen Sicherheitscomposite als primären Sicherheitsendpunkt.

6 RF-RDN Studien mit 1.394 Patient*innen

Klinische Wirksamkeit

Auch in den RF-RDN RCTs berichteten alle sechs Studien **Gesamtmortalität**, **kardiovaskuläre Mortalität** und die Rate an **kardiovaskulären Ereignissen** als sekundäre Endpunkte, ohne bei diesen auf Signifikanz zu testen. Nach sechs Monaten variierte die Gesamtmortalität in den Interventionsgruppen zwischen 0 % und 4 % und in den Kontrollgruppen zwischen 0 % und 11 %. Es trat keine kardiovaskuläre Mortalität auf. In der Nachbeobachtungszeit von bis zu sechs Monaten erlitten jeweils zwischen 0 % und 10 % der Patient*innen der Interventionsgruppe und zwischen 0 % und 12 % der Patient*innen in der Kontrollgruppe kardiovaskuläre Ereignisse. Die hypertensive Krise war nach einem Beobachtungszeitraum von bis zu 36 Monaten das am häufigsten berichtete kardiovaskuläre Ereignis (Interventionsgruppe: 1-11 %; Kontrollgruppe 0-11 %).

Mortalität: 0-4 % vs. 0-11 %

kardiovaskuläre Ereignisse: 0-10 % vs. 0-12 %

In allen Studien wurde der systolische/diastolische 24-Std. BD berichtet. Nach einer Nachbeobachtungszeit von bis zu **sechs Monaten** lag der Gruppenunterschied des **systolischen 24-Std. BD** zwischen -7.4 und -1.9 mmHg und war in einer (n=331) der sechs Studien zugunsten von RF-RDN signifikant. Der Gruppenunterschied des **diastolischen 24-Std. BD** war ebenfalls in einer (n=331) der sechs Studien signifikant und variierte zwischen -3.1 und -0.8 mmHg.

24 Std. BD: stat. signifikanter Gruppenunterschied in 1/6 Studien nach 6 Monaten

Zwei Studien berichteten Daten über eine **zwölf-monatige Nachbeobachtungszeit**. Der Gruppenunterschied lag hier jeweils bei -8.5 und -4.9 mmHg für den **systolischen 24-Std. BD** und bei -5.6 und -4.4 mmHg für den **diastolischen 24-Std. BD**. Wobei der jeweils größere Gruppenunterschied statistisch signifikant war. Zusätzlich wurden von einer Studie und der Pilotphase einer zweiten Studie Daten nach **24 und/oder 36 Monaten** berichtet. Dabei waren die jeweiligen Gruppenunterschiede des **systolischen 24-Std. BD** (zwischen -16.5 bis -11.2 mmHg) und des **diastolischen 24-Std. BD** (zwischen -11.2 bis -5.7 mmHg) statistisch signifikant. Alle Daten aus der langfristigen Nachbeobachtungszeit waren jedoch unverblindet.

langfristige Daten in 2/6 Studien: z. T. statistisch signifikant, aber unverblindet

Sicherheit

Schwere unerwünschte Ereignisse (**SUE**) wurden von allen sechs Studien erfasst und traten nach sechs Monaten Nachbeobachtungszeit bei jeweils 0 % bis 1 % der Interventions- und Kontrollgruppe auf. Zwei Studien erreichten außerdem einen kombinierten primären Endpunkt. Unerwünschte Ereignisse (**UE**), darunter Kopfschmerzen, untypische Brustschmerzen, Muskelkrämpfe und Müdigkeit, wurden von einer Studie berichtet. Diese traten bei 14 % der RDN-Gruppe und bei 18 % der Sham-Gruppe auf.

niedrige Rate an SUE,

UE in einer Studie bei 14 % vs. 18 % der Patient*innen

Laufende Studien

Es wurden zehn laufende Sham-kontrollierte RCTs identifiziert, wovon acht einen Abschluss zwischen 2020 und 2023 und die restlichen zwei einen Abschluss für 2024 bzw. 2028 angeben. Acht der Studien untersuchen die Wirksamkeit von RDN in Patient*innen mit Hypertonie. Zusätzlich untersucht jeweils eine Studie den Effekt von RDN in Patient*innen mit Nierenversagen und gleichzeitiger Hypertonie und Patient*innen mit Herzversagen und gleichzeitiger Hypertonie. Während vier Studien die Wirksamkeit von RF-RDN anhand anderer Produkte untersuchen (Netrod® System, DENEX System and SyMapCath™), wird in zwei Studien das Paradise™ Ultraschall System und in zwei weiteren Studien das Peregrine System untersucht. Bei Letzterem wird Alkohol mithilfe von Mikro-Nadeln in den perivaskulären Raum der Nierenarterie eingeführt.

10 laufende Sham-kontrollierte RCTs

neue Produkte, wie auch Technologien für RDN

Diskussion

Obwohl die interne Validität der Primärstudien als hoch eingestuft werden kann, bestehen folgende Limitationen, die vor allem die externe Validität der Evidenz betreffen: **Erstens** betrug die primäre Nachbeobachtungszeit der Studien zwei bis maximal sechs Monate. Es besteht daher noch Unsicherheit über die Nachhaltigkeit des blutdrucksenkenden Effekts. Die vorliegenden Langzeitdaten deuten zwar auf einen signifikanten Effekt hin, jedoch sind diese Ergebnisse vor allem aufgrund fehlender Verblindung und Cross-over in den Sham-Gruppen wenig vertrauenswürdig. **Zweitens** besteht Unklarheit darüber, welche Patient*innen am meisten von der renalen Denervierung profitieren. Die Einschlusskriterien der Studien sind als heterogen einzustufen

Limitationen der Evidenz:

Langzeitwirkung der Blutdrucksenkung unbekannt

Einschlusskriterien über Studien hinweg heterogen, nicht alle Patient*innen mit TRH

und umfassten nicht nur Patient*innen mit TRH. Die Übertragbarkeit der Evidenz ist daher eingeschränkt. Zudem wurden patient*innenzentrierte Endpunkte (sog. Patient-Reported Outcomes/PRO) wie die Lebensqualität nicht gemessen und der direkte Vergleich der Wirksamkeit verschiedener RDN ist unklar.

Fokus der Studien auf BD-Senkung verständlich

Schlussendlich muss noch erwähnt werden, dass die Differenz zwischen normalen und abnormale Blutdruck aufgrund von Mortalitätsdaten großer longitudinaler Studien „künstlich" geschaffen wurde. Da die Auswirkungen eines hohen Blutdrucks auf die Sterblichkeit als erwiesen gilt, ist auch die zunehmend strenger werdende Abgrenzung zwischen normalem und erhöhtem Blutdruck als Triebkraft für eine nachhaltige Senkung des BD akzeptiert. Gleichzeitig mangelt es konkret für TRH aber an einem eindeutigen Schwellenwert für die klinische Relevanz des blutdrucksenkenden Effekts (sogenannter Minimal Important Difference/MCID). Jedoch hat jegliche Blutdrucksenkung möglicherweise eine langfristige Auswirkung auf klinische Endpunkte, sowie auf den Erhalt der Nierenfunktion.

Schlussfolgerung

Evidenz deutet auf Zusatznutzen bei Patient*innen mit TRH hin

Evidenz von moderater Vertrauenswürdigkeit deutet darauf hin, dass die renale Denervierung eine blutdrucksenkende Wirkung bis zu sechs Monate nach der Intervention erzielt und dabei relativ sicher ist. Die Evidenz ist unzureichend, um einen etwaigen Effekt auf andere Endpunkte, wie etwa kardiovaskuläre Ereignisse oder die Lebensqualität, einschätzen zu können.

Unsicherheiten hinsichtlich Ausmaß und Nachhaltigkeit des Effekts

Die vorliegende Evidenz deutet insgesamt auf einen Zusatznutzen der renalen Denervierung bei Patient*innen mit therapieresistenter Hypertonie hin. Es besteht jedoch noch Unsicherheit über die Patient*innenpopulation (welche am meisten von der renalen Denervierung profitieren) und über das Ausmaß und die Nachhaltigkeit des blutdrucksenkenden Effekts.

Re-Evaluierung in 2026, nach Veröffentlichung neuer Ergebnisse

Eine Re-Evaluation wird für 2026, nach Veröffentlichung der Ergebnisse der laufenden randomisiert Sham-kontrollierten Studien, empfohlen.

Summary of previous assessments 2012

1. Update 2012

This chapter summarizes the initial assessment results published in 2011 [1] and the update report 2012 [2]. The section "Health problem and characteristics of technology" was added.

Health problem and characteristics of the technology

Overview of the disease, health condition and target population

resistente Hypertonie (TRH): keine Blutdrucksenkung trotz optimaler Medikation

The health condition in the scope of this assessment is treatment-resistant hypertension (TRH). Patients with TRH represent a high-risk subgroup of hypertensive patients, although identification/diagnosis of those patients remains challenging within current definitions of (suspected) TRH [3, 4]. The European Society of Cardiology/European Society of Hypertension (ESH) and the American Heart Association define TRH as a systolic/diastolic blood pressure (BP) of ≥140/90 mmHg or ≥130/80 mmHg, respectively, despite implementing lifestyle changes and using optimal medical treatment (OMT) consisting of ≥3 antihypertensive agents including a diuretic [5, 6].[1]

weitere Definition von TRH

The Joint National committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines (JNC7) similarly defined it as BP measurements that exceed 140/90 mmHg or 130/80 mmHg despite the regular use of three or more hypertensive drugs of different classes including one diuretic at the maximum dose unchanged for at least one month without interruption [7].

Differentialdiagnostik für TRH notwendig

As only a small percentage of patients fulfilling the diagnostic criteria for (suspected) TRH are truly resistant to treatment, adequate patient selection has been highlighted as a crucial step before considering any further treatment options as accentuated by the current ESC 2019 and ESH 2023 guidelines [6, 8]. This includes following the established diagnostic steps to exclude BP pseudo-resistance, white-coat hypertension, as well as secondary causes for hypertension [4, 9].

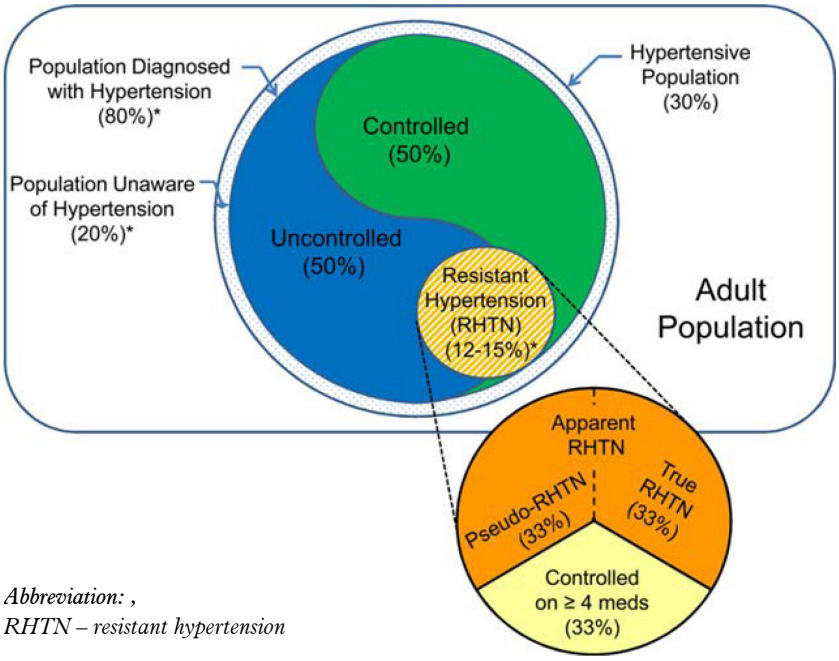
Figure 1 illustrates the complexity of and need for differential diagnosis within the context of the target population in the scope of this assessment (see also section Current clinical practice).[2]

refraktäre Hypertonie unterschiedlich definiert, z. B. TRH mit min. 5 Antihypertensiva

While the term refractory hypertension is sometimes used synonymously with TRH to distinguish hypertension that is difficult to treat, the term refractory has also been applied to define those patients whose BP remains uncontrolled with maximal antihypertensive treatment [10]. The definition is less well-defined, with attempts to operationalise the maximum OMT as ≥5 classes of antihypertensive agents [10].

[1] **A0001** – For which health conditions, and for what purposes is the technology used?

[2] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?



Abbreviation: ,
RHTN – resistant hypertension

Figure 1: Categorisation of the hypertensive population (Source: [4])

Despite semantic differences in definitions, we broadly defined the population of interest in our assessment as patients whose BP remained uncontrolled despite standard care consisting of, among other things, lifestyle changes or OMT or those patients who are intolerant to further antihypertensive treatment. Newly diagnosed uncontrolled hypertensive patients were beyond the scope of the target population within this assessment.

betrachtete Population: keine Senkung des Blutdrucks, trotz Standardtherapie

Burden of Disease

Risk factors for hypertension, as well as TRH, range from genetic influences, age, and lifestyle factors such as physical inactivity, tobacco use, alcohol and high salt consumption to stress and obesity and other health conditions such as diabetes and chronic kidney disease [11].[3] Certain medications can also interfere with BP control, including nonsteroidal anti-inflammatory agents (NSAID), oral contraceptives, hormone replacement therapy, immunosuppressants, VEGF-inhibitors and erythropoietin [12]. Common secondary causes of TRH are obstructive sleep apnoea (OSA), primary hyperaldosteronism and renal artery stenosis [13].

Risikofaktoren für TRH, z. B. Alter, physische Inaktivität, Diabetes, etc.

erhöhter Blutdruck erhöht Risiko für kardiovaskuläre Folgeerkrankungen

Hypertension is a chronic health problem which can go unnoticed by patients for a long time as it can be asymptomatic in its early stage. Typically, hypertension only becomes symptomatic through secondary organ damage, including diastolic dysfunction and heart failure. However, elevated BP, particularly when uncontrolled, is a significant factor contributing to the overall cardiovascular (CVS) risk profile of patients and has been shown to account for around 70% of the global mortality and disability burden due to ischaemic heart disease and haemorrhagic and ischaemic stroke. Other sequelae associated with continually elevated BP are peripheral artery disease and end-stage renal disease, and evidence is emerging for an increased risk of atrial

hoher Blutdruck im klinischen Kontext von peripherer aterieller Verschlusskrankheit und chronischer Niereninsuffizenz

[3] **A0003** – What are the known risk factors for the disease or health condition?

fibrillation and cognitive decline [11]. Patients with TRH are characterised by an increased prevalence of target organ-damage and an even poorer long-term prognosis [14].[4]

Epidemiology

Prävalenz von Hypertonie in Ö bei 17 % von Frauen und 25 % von Männern

Global age-standardised prevalence of raised BP was 24.1% (95% CI 21.4-27.1) in men and 20.1% (95% CI 17.8-22.5) in women in 2015 [15]. In Austria, around 16.8% of women and 25.2% of men suffer from elevated BP. CVS events are the leading cause of death in Austria (37% of female and 31% of male deaths), with total direct and indirect healthcare costs estimated at 8.5 million per year. In 2021, costs attributed to CVS disease in the European Union were estimated at 282 billion euros [16].

Prävalenz von resistenter Hypertonie kontrovers diskutiert ca. 5-10 %

The prevalence of true TRH is not fully known and the subject of ongoing scientific debate. There is a variance in the estimated prevalence of TRH due to the developing consensus on a most practical clinical definition. A recent meta-analysis of 91 studies reports a global prevalence of true TRH of 10.3% in the general population [17], while the 2023 ESH guidelines for the diagnosis and management of hypertension, state that while "apparent" resistant hypertension is found in 10-20% of hypertensive patients and after exclusion of other causative factors the prevalence of "true resistant hypertension" is much lower with estimates around 5% [8].

Current clinical practice

Differentialdiagnostik bei Verdacht auf TRH

A dedicated clinical workup following a standardized protocol to assess the patients' history and exclude secondary factors for poor BP control is critical for adequate treatment of hypertension and for the identification of TRH [5, 14].[5] After the diagnosis of hypertension and the indication for medical treatment have been established, treatment resistance is confirmed by BP measurements despite OMT. Secondly, pseudo-resistance must be ruled out, e.g., by using 24-hour (24h) ambulatory blood pressure (ABP) and assessing potential non-adherence to OMT. Thirdly, further lifestyle factors contributing to high BP, such as obesity or physical inactivity, may be identified and attempted to be changed. Fourthly, potentially interfering substances such as NSAIDs, oral contraceptives, hormone replacement therapy or stimulants need to be discontinued or substituted. Fifthly, secondary hypertension may be ruled out by screening for, among other things, endocrinological alterations, OSA or renal artery stenosis. Finally, further pharmacological treatment, such as maximising diuretic therapy, may be indicated before a patient is referred to a specialist [5].[6]

multimodaler Behandlungspfad bei TRH

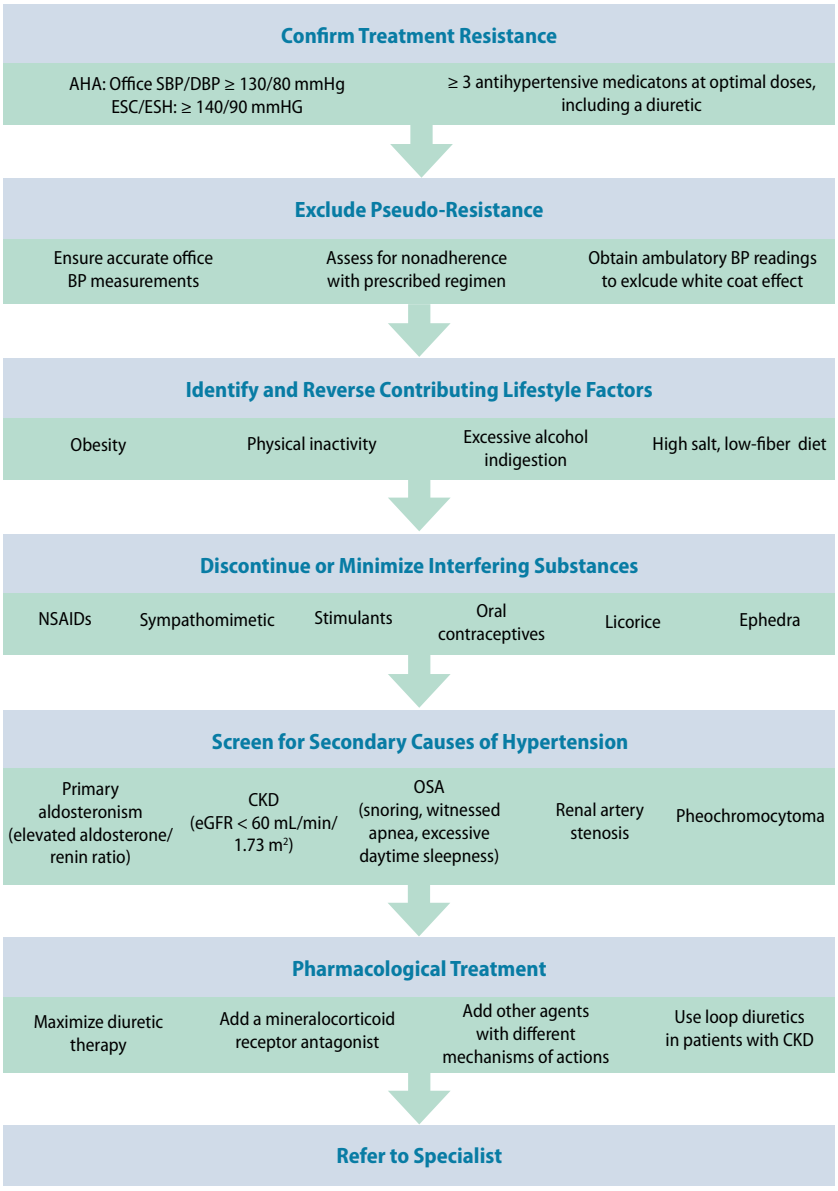
For (suspected) TRH, a multimodal treatment approach may be used that can consist of further non-pharmacological (such as lifestyle changes) and phar-

[4] **A0004** – What is the natural course of the disease or health condition?
A0005 – What is the burden of disease for the patients with the disease or health condition?

[5] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?

[6] **A0024** – How is TRH currently diagnosed according to published guidelines and in practice?

macological treatment. In Figure 2, a treatment pathway for suspected TRH is described. Device-based therapies are discussed within guidelines as potential additional therapeutic options for TRH.[7] These include renal denervation (RDN) and other device-based therapies such as baroreceptor stimulation (BAT) [8].



Abbreviations:
SBP – systolic blood pressure;
DBP – diastolic blood pressure;
ESC – European Society of Cardiology; ESH – European Society of Hypertension;
BP – blood pressure;
NSAID – non-steroidal anti-inflammatory drug;
CKD – chronic kidney disease;
OSA – obstructive sleep apnea

Figure 2: Diagnostic and therapeutic pathway when TRH is suspected (Source: slightly adapted from [5], including target BP from ESC/ESH [6])

[7] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

Empfehlungen der ESH:

The ESH has issued evidence-based recommendations within the context of RDN [8]:[8]

RDN bei unkontrolliertem Blutdruck trotz medikamentöser Therapie und …

- RDN can be considered as a treatment option in patients with a glomerular filtration rate (eGFR) >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy or if drug treatment elicits serious side effects and poor quality of life (QoL) (CoR: II, LoE: B[9])

… bei TRH als zusätzliche Behandlungsoption, aber: Shared-Decision-Making und spezialisierte Zentren erforderlich

- RDN can be considered as an additional treatment option in patients with true TRH, if eGFR is >40 ml/min/1.73m 2 (CoR: II, LoE: B)
- Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient information (CoR: I, LoE: C)
- RDN should only be performed in experienced specialized centres to guarantee the appropriate selection of eligible patients and completeness of the denervation procedure (CoR: I, LoE: C)

Empfehlungen der ACC & ESC zur RDN:

Similarly, and according to a consensus paper by the American College of Cardiology (ACC) and the European Society of Cardiology (ESC), the following preliminary recommendations were formulated in the context of RDN in 2023 [18]:

RDN bei unkontrollierter TRH und bei Intoleranz der Medikamente

- RDN may be used in adult patients with uncontrolled TRH (office BP)[10] ≥140/≥90 mmHg confirmed by 24h systolic ABP ≥130 mmHg or daytime systolic BP ≥135 mmHg) treated with ≥3 antihypertensive drugs and an eGFR ≥40 ml/min/1.73 m^2.
- RDN may be a possible treatment option for patients unable to tolerate antihypertensive drugs in the long term or patients who express a preference to undergo RDN in a tailored shared decision-making process.

CV-Risiken müssen evaluiert werden

- The patient's global CVS risk should be evaluated, accounting for hypertension-mediated organ damage and CVS complications. High CVS risk favours the use of RDN.

Empfehlungen der AWMF zur RDN:

The German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) has published the following recommendations in the context of RDN in its 2023 national care guidelines on hypertension treatment [19]:

RDN in einem zertifizierten Zentrum bei Patient*innen die Behandlungsziel nicht erreichen

- If patients with hypertension do not achieve their individual treatment goal despite exhausting therapy (medication and lifestyle), renal denervation can be offered (open recommendation, grade of recommendation: 0)
- RDN should be performed in a centre certified for this purpose (positive recommendation, grade of recommendation: B)

Empfehlung NICE zu RDN

A recent National Institute of Care Excellence (NICE) update recommends that RDN should only be used when special arrangements for clinical governance, consent, and audit or research are in place [20].

[8] Due to insufficient evidence, no recommendations were formulated for all other devices, such as baroreceptor stimulation [8].

[9] Certainty of Recommendation (CoR), Level of Evidence (LoE)

[10] BP measured at an office or screening centre setting by a sphygmamometer

Features of the intervention

renale Denervierung: Verödung der Nervenbahnen um die Nierenarterien zur Reduktion der Sympathikusaktivität

The sympathetic nervous system (SNS) and its bidirectional connection between SNS centers in the brain stem and the kidneys as effectors is one of the most crucial determinants of blood pressure in health and disease. In patients with arterial hypertension, overactivity of the SNS precedes the onset of overt high blood pressure by many years. Renal nerves following the abdominal aorta and branching off around the renal arteries are the anatomic correlate of the connection between central SNS and kidneys. RDN is an interventional minimally invasive procedure in which a catheter is delivered into the renal artery via the femoral artery under fluoroscopic guidance to target the sympathetic nerves (Figure 3). The nerves are severed bilaterally by applying energy, such as ultrasound or radiofrequency, interrupting their activity and consequently lowering BP [8, 21].[11]

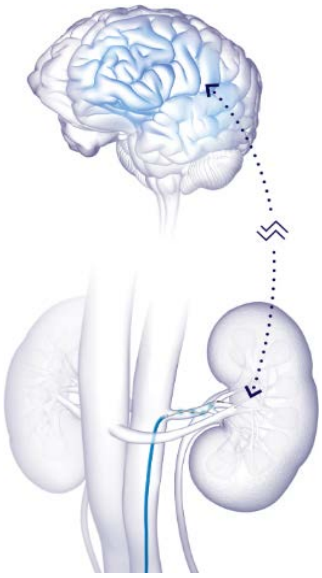


Figure 3:
Function of renal denervation (Source: [22]).

Symplicity Spyral™ & Paradise® System derzeit zugelassen

Two second-generation RDN devices hold CE marks: The Paradise® ultrasound RDN System from ReCor Medical and the Symplicity Spyral™ catheter from Medtronic. Although a multitude of interventional devices were developed and tested in proof-of-concept trials in cohorts of TRH patients of varying sizes since 2012, most products have been discontinued due to the impact of the Simplicity-HTN-3 trial [23] with substantial concerns within the scientific hypertension community as to its therapeutic efficacy.

Paradise® System mit CE (2011) und FDA-Zulassung (2023), Nutzung von Ultraschall

The Paradise® ultrasound RDN System received a CE certification in 2011 and FDA approval in November 2023. It is intended to be used for the treatment of hypertension patients, in whom BP could not be controlled through lifestyle interventions and antihypertensive medications.[12] The system includes a catheter with an ultrasound transducer that delivers circumferential energy (Figure 4), an energy generator, a cartridge and a connection cable.[13] Treatment can be performed on the main renal arteries and its central branch-

[11] **B0001** – What is renal denervation?

[12] **A0020** – For which indications has the technology received marketing authorisation or CE marking?

[13] **B0009** – What supplies are needed to use the technology and the comparator(s)?

es with a diameter between 3 to 8 mm. Two to three ablations are delivered per artery, lasting seven seconds each. During the ablations, sterile water circulates through a balloon surrounding the transducer, providing a cooling effect to protect the arterial wall [18, 24].

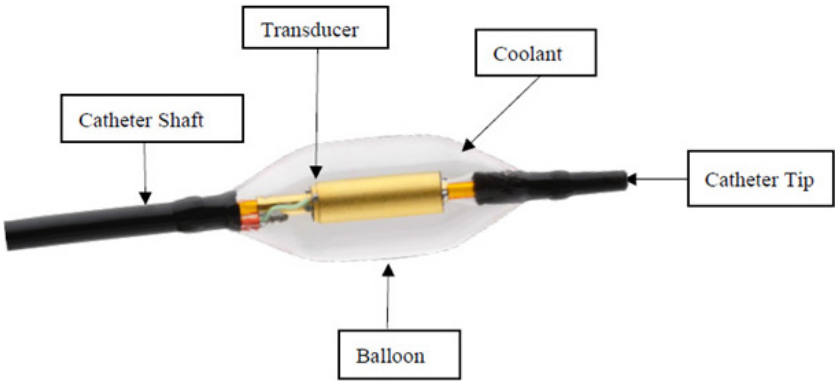


Figure 4: Structure of the Paradise® ultrasound RDN System (Source: [24])

Symplicity Spyral™ mit CE (2013) und FDA-Zulassung (2023), Nutzung von Radiofrequenz

The Symplicity Spyral™ Multi-Electrode Catheter and the Symplicity G3™ Generator received CE certification in 2013 and are intended to be used for the treatment of uncontrolled hypertension [25].[14] In addition, the system has received MDR approval and FDA approval in 2023. The Symplicity Spyral™ catheter consists of a single-use adjustable spiral with four radiofrequency electrodes along its circumference and an attached cable at the handle, which connects to the radiofrequency generator.[15] All accessible arteries with a diameter of 3 to 8 mm can be treated. Ablation at the arterial wall is delivered simultaneously at four unipolar electrodes (Figure 5) for at least 45 seconds, and ideally for 60 seconds [26]. An overview of both devices with further details is available in Table 1.

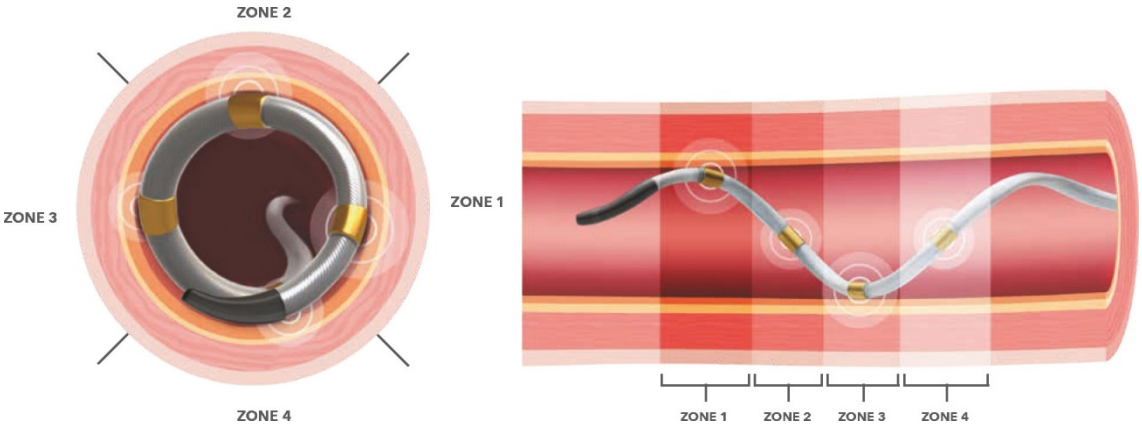


Figure 5: Placement of the Symplicity Spyral™ Multi-Electrode Catheter in the renal artery (Source: [22])

[14] **A0020** – For which indications has the technology received marketing authorisation or CE marking?

[15] **B0009** – What supplies are needed to use the technology and the comparator(s)?

Table 1: Current RDN devices

Device name/ manufacturer	Design	CE Mark/ indication	US FDA approval/ indication	Class/ GMDN code
Ultrasound device(s)				
Paradise® ultrasound RDN System ReCor Medical	Transducer delivering circumferential energy with a distal balloon pressurised via coolant fluid Necessary components: ■ Paradise™ Catheter ■ Paradise™ Generator ■ Paradise™ Cartridge ■ Paradise™ Connection Cable	Yes (2011)	PMA Yes (2023) Adjunctive treatment option to lower BP in hypertensive patients	Class III/ Code: 65657
Radiofrequency device(s)				
Symplicity Spyral™ Medtronic	Spiral catheter delivering electrical radiofrequency energy at four unipolar electrodes Necessary components: ■ Symplicity Spyral multi-electrode RDN catheter ■ Symplicity G3™ RDN RF generator	Yes (2013)	PMA Yes (2023) Adjunctive treatment option to lower BP in hypertensive patients	Class III/ Code: 58893

Abbreviations: CE – Conformité Européenne; FDA – U.S. Food and Drug Administration; GMDN – Global Medical Device Nomenclature; PMA – Premarket Approval; RDN – renal denervation; US – United States

Administration, investments, personnel and tools required to use the technology

RDN im Spital: spezialisiertes, multidisziplinäres Hypertonieteam …

According to the ESC [18], a multidisciplinary hypertension team (MDHT) is required to provide/confirm the indication for and facilitate RDN. Clinical cardiologists, angiologists and/or nephrologists with expertise in hypertension and/or percutaneous CVS interventions should be involved in such MDHTs. These specialised centres with MDHTs should be equipped with [18]:

- a hypertension outpatient clinic,
- an inpatient ward,
- a radiology division,
- a clinical/hormonal laboratory,
- a catheterisation laboratory and
- a coronary (or intensive) care unit with access to an emergency surgery facility.[16]

… und extensives Training zur Etablierung eines RDN-Zentrums notwendig

Extensive training is required to establish a dedicated RDN centre. It should include guidance in the management of the access site, haemostasis and analgesia, knowledge of radiation protection measures, interventional angiography and techniques to limit contrast use. Training should also include knowledge about the renal artery anatomy and current concepts of SNS nerve distribution along its main branches. Additionally, basic interventional techniques with handling of guidewires and catheters, as well as BP management during the procedure, are basic requirements. Interventionalists should receive hands-on training on a bench model (demo or simulator) and perform at least five proctored RDN interventions with the device intended to be used at the particular site before treating patients on their own. Further, an under-

[16] **B0004** – Who administers the technology and the comparators and in what context and level of care are they provided?

B0009 – What supplies are needed to use the technology and the comparator(s)?

standing of the organisational structure of the RDN procedure (e.g., patient preparation and follow-up) should be acquired through the attendance of an already active RDN centre [18].[17]

formulierte Mindestanforderungen an ein RDN-Zentrum aus Deutschland

In Germany, minimal requirements were developed together by the German Cardiac Society (DGK), the German Society for Hypertension and Prevention (DHL) and the German Society for Nephrology (DGfN) to be able to perform RDN, spanning personnel and procedural, room, equipment, patient selection and diagnostic requirements, as well as therapeutic strategies, follow-up examinations and needed cooperation [27].

Regulatory and reimbursement status

5-30 Prozeduren pro Jahr in Ö

According to the submitting hospital, the expected number of RDN interventions in Austria ranges from five to 30 treatments per year.[18]

seit 2015 nicht mehr im Leistungskatalog abgebildet

At present, RDN is not a fully reimbursable service in the Austrian healthcare system as it is not included in the LKF (Leistungsorientierte Krankenanstaltenfinanzierung). In 2011, the technology received an LKF-Code as a new examination and treatment method (XN06 – Catheter ablation of the renal sympathetic nerve plexus) for the purpose of documentation. However, this code was subsequently deleted in 2015.[19]

Potential comparator devices

andere potentielle Technologien für TRH zurzeit in Untersuchung

Currently, from a multitude of about 20 devices for RDN, no other device-based treatments are recommended for TRH, although subsequent clinical data from ongoing trials in TRH patients are expected from numerous competitors. One of these treatment options targeting the opposite functional pathway by activating the parasympathetic nervous system via carotid BP receptors is baroreceptor activation therapy (BAT), which activates baroreceptors in the carotid artery bifurcation through electrical stimulation via a subcutaneous pacemaker-like device. After the first-generation device failed to receive FDA approval, a second-generation device with a smaller housing and a smaller single unipolar electrode was developed but has not been investigated in an RCT for TRH, yet. Another therapy targeting baroreceptor activation is endovascular baroreflex amplification (EVBA), with several ongoing RCTs investigating this option. The goal is to passively increase wall stretch with a stent implantation. Finally, the Moderato system reduces BP by shortening the atrioventricular coupling interval via an implantable pulse generator. The system showed promising six-month results in an RCT, although long-term efficacy and safety still need to be investigated [8].

[17] **B0008** – What kind of special premises are needed to use the technology and the comparator(s)?

[18] **A0011** – How much are the technologies utilised?

[19] **A0021** – What is the reimbursement status of the RDN?

Results

The initial report in 2011 included one randomised controlled trial (RCT) and one before-after study [1]. Overall, the evidence indicated that RDN may have a BP-lowering effect. The lack of blinding and short follow-up were mentioned as limitations of the evidence. The authors of the LBI-HTA report 2011 concluded that there is a paucity of evidence on RDN in patients with essential hypertension.

2011: 1 RCT, 1 Vorher-Nacher-Vergleich → niedrige Beweislage mit Limitationen

In 2012, the initial assessment was updated [28]. Based on the same RCT and two before-after studies, the update report found a two-year BP-lowering effect. The RCT was not sham-controlled and measured office BP. The authors critiqued the lack of information on mortality, long-term efficacy and QoL.

Update 2012: 1 RCT, 2 Vorher-Nacher-Vergleiche → RCT ohne Sham-Kontrolle

Recommendation

The inclusion into the Austrian hospital services catalogue was, therefore, not recommended.

Empfehlung 2012: keine Aufnahme in den Leistungskatalog

UPDATE 2024

1 Objectives and Scope

1.1 PICO question

PIKO-Frage 2024

Is RDN plus standard therapy in patients with treatment-resistant and refractory hypertension as safe as standard therapy and more effective concerning BP control, CVS morbidity, mortality, hospitalisation, and other patient-relevant outcomes (e.g., QoL)?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Individuals older than 18 years with uncontrolled TRH defined as ■ presence of clinic BP above target (higher than 140/90 mmHg, or higher than 130/80 mmHg in individuals with type 2 diabetes mellitus) despite ■ standard therapy (i.e. concomitant antihypertensive drug treatment[20] and lifestyle changes) MeSH Terms: Hypertension (C14.907.489) Rationale: Informed by information from relevant guidelines [5, 6, 18] and a Cochrane report 2021 [29]
Intervention	Percutanous renal denervation (RDN) using a catheter system and standard therapy ■ Ultrasound RDN (U-RDN) ■ Radiofrequency RDN (RF-RDN) Product names: Symplicity Spyral RDN catheter system (Medtronic) Paradise ultrasound catheter system (ReCor) MeSH Terms: Denervation (E04.525.210),
Control	Standard therapy alone
Outcomes	
Efficacy	■ All-cause mortality and CVS mortality ■ Major CVS events including but not limited to myocardial infarction, heart failure and stroke ■ BP control, i.e. change of systolic/diastolic BP (24h and 48h ABP) ■ Hospitalisation ■ Health-related Quality of Life (HRQoL) measured with a validated instrument Rationale: Informed by information from relevant guidelines [5, 6, 18] and a Cochrane report 2021 [29]
Safety	Adverse events, including but not limited to hypotension, bradicardia episodes and perioperative issues – hemorragias, hematomas
Study design	Randomised sham-controlled trials[21]

Abbreviations: ABP – ambulatory blood pressure; BP – blood pressure; CVS – cardiovascular; h – hour(s); TRH – treatment-resistant hypertension.

[20] In light of slightly different definitions on what constitutes resistant or refractory uncontrolled hypertension, we did not exclude studies with less than 3 or 4 antihypertensive agents.

[21] Long-term follow-up post-hoc analyses of total (randomised) population patients were included. All other post-hoc analyses such as (exploratory) subgroup analyses were excluded.

2 Methods

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customized to the specific objectives of this assessment [30].

EUnetHTA Core Model® Version 4.2. für SR herangezogen

2.1 Systematic literature search

Prior to the systematic search, we conducted a focused search on PubMed to identify high-quality and up-to-date systematic reviews (SRs) from which primary studies were identified and then selected based on the specific inclusion criteria of our report. We found five SRs and one HTA report of high quality [29, 31-33] with no notable concerns regarding the study selection process as assessed with the ROBIS tool [34]. The ROBIS assessment is provided in the appendix (Table A-5).

Suche nach SRs in PubMed

The systematic literature search was conducted on the 6th and 7th of December 2023 in the following four databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

systematische Literatursuche in 4 Datenbanken

The systematic search was limited to September 2021 to December 2023, and in Medline and Embase to only randomised controlled trials (RCTs) and to articles published in English or German. The specific search strategy employed can be found in the Appendix.

Suchzeitraum: September 2021 bis Dezember 2023

Manufacturers from the two commercially available products (Paradise® System and Symplicity Spyral™) submitted 75 (Recor Medical: 19; Medtronic: 66) publications of which 5 new citations were screened on their full text basis.

keine neuen Referenzen von Herstellern identifiziert

No additional sources were found by hand-search, which resulted in a total of 429 hits, and 277 hits after deduplication.

insgesamt 429 Publikationen identifiziert

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on 02.01.2024, resulting in 76 potentially relevant hits.

Suche nach laufenden Studien (76 Treffer)

2.2 Flow chart of study selection

Literaturauswahl: 10 RCTs eingeschlossen

Overall, 429 hits were identified. The references were screened by two independent researchers (DG and GG), and in case of disagreement, a third researcher (JK) was involved in solving the differences. Ten RCTs were included in this qualitative synthesis. The selection process is displayed in Figure 2-1.

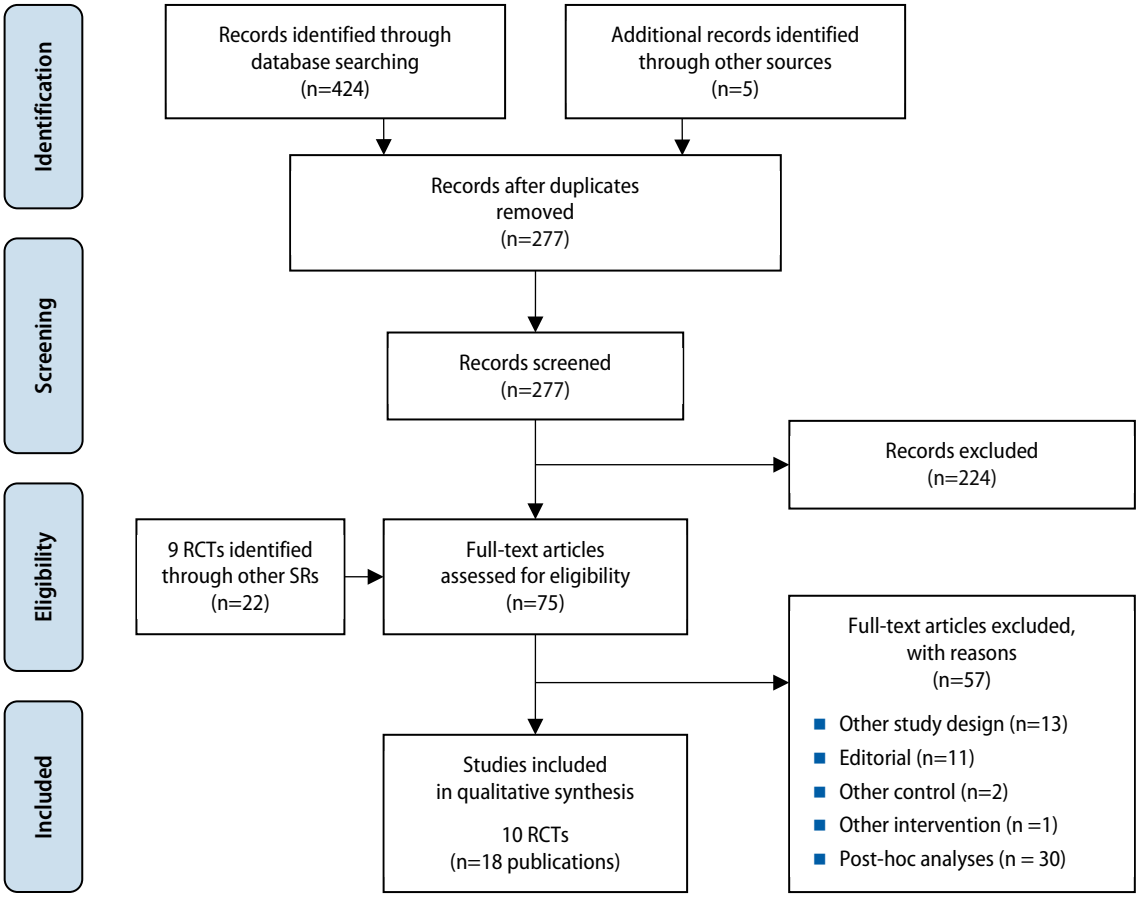


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)[22]

[22] Only primary, incorporated pilot analyses, and long-term follow-up studies counted in the final number of included publications.

2.3 Analysis

Datenextraktion & Bewertung der Studienqualität durch jeweils 2 Wissenschafter*innen

Relevant data from eligible studies were extracted into piloted data-extraction tables. The internal validity of included studies and the certainty of evidence was assessed using the Cochrane Risk of Bias (RoB) tool v.2 [35] and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) scheme [36], respectively. Each working step was performed by one reviewer and validated by another (GG, DG, or JK). Any disagreements were resolved by consensus.

2.4 Synthesis

qualitative Synthese der Evidenz

A narrative synthesis of the evidence was performed. The questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

In addition, the GRADE scheme was used to summarise the identified evidence [36]. GRADE evidence profiles and summary of findings tables are available in the appendix (Table A-6, Table A-7, Table A-8).

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

kritische Endpunkte: Mortalität, kardiovaskuläre Ereignisse und Senkung des Blutdrucks (mittels 24 Stunden Messung)

The following outcomes were defined as *critical* to derive a recommendation:

- All-cause mortality and CVS mortality.
- Major CVS events including but not limited to myocardial infarction, heart failure, and stroke.
- Reduction in 24h systolic or diastolic ABP. To measure ABP, an automated device that measures BP at predetermined intervals throughout a day is used. The patient is required to keep a diary of their activity throughout the day. The device software can additionally provide mean 24h, daytime, and nighttime BP measurements. Generally, ABP measurements show better reproducibility than office BP measurements and are better predictors for different outcomes, such as mortality [8].

weitere wichtige Endpunkte: Hospitalisierung und Lebensqualität

The following endpoints were defined to be important, but not critical, for decision-making:

- Hospitalisation.
- Health-related Quality of Life (HRQoL is a patient-reported outcome and can be measured with established instruments [37, 38] such as the Short-Form 36-item health survey (SF-36) or EuroQol 5-dimension questionnaire Scale (EQ-5D).

andere Blutdruckmessungen extrahiert, aber nicht beschrieben

Although BP control can be measured differently, we focused on the most reliable measurement (i.e. ABP), since its recommendation as the gold-standard for BP assessment by all major hypertension guidelines. Other measurements were extracted but considered to not be critical to derive a recommendation (e.g., office BP, daytime ABP) and therefore not described.

keine validierte MCID für Blutdruck

To the author's best knowledge, no validated minimally clinically important difference (MCID) exists for BP changes. The Core Outcomes Measures in Effectiveness Trial (COMET) Initiative was searched to define the MCID that would need to be reached or exceeded to conclude that a difference between groups was clinically significant [39].

3.1.2 Outcomes safety

entscheidungsrelevante Sicherheitsendpunkte

The following outcomes were defined as *critical* to derive a recommendation:

- Serious adverse events (SAE)
- Adverse events (AE)

The following definition was used for (serious) adverse events based on the European Commission guidelines [40] for medical devices on SAE reporting:

unerwünsche Ereignisse (UE)

AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational

medical device. This includes events related to the investigational device or related to the procedures involved (any procedure in the clinical investigation plan).

SAE is an adverse event that led i) to death, ii) to a serious deterioration in the health of the subject that either resulted in a life-threatening illness or injury, iii) a permanent impairment of a body structure or a body function, iv) in-patient hospitalisation or prolongation of existing hospitalisation, v) medical or surgical intervention to prevent a life-threatening illness or injury.

schwerwiegende unerwünschte Ereignisse (SUE)

3.2 Included studies

3.2.1 Included studies effectiveness and safety

In total, ten sham-controlled RCTs (in 18 publications) met our pre-defined inclusion criteria (Primary analyses: [23, 41-48]). Nine of these studies were identified through their inclusion in previous SRs [29, 31-33, 49]. We additionally identified one new RCT [42] and several follow-up analyses of existing RCTs [50-55]. Two studies incorporated pilot phases testing primarily the proof of concept of RDN and also provided long-term follow-up data of these patients (see Table 3-1) [53, 56, 57].

10 Sham-kontrollierte RCTs mit insgesamt 18 Publikationen inkludiert

Table 3-1: Overview of included studies and their follow-up

RCT		Product	2/3m FU	6m FU	12m FU	24m FU	36m FU
U-RDN							
RADIANCE HTN SOLO		*Paradise™ System ReCor Medical*	[43]	[52]	[50]	-	-
RADIANCE HTN TRIO			[41]	[51]	-	-	-
RADIANCE II			[42]	-	-	-	-
REQUIRE			[44]	-	-	-	-
RF-RDN							
REDUCE HTN		*Vessix™ system, Boston scientific*	[45]	[45]	[45]	-	-
RESET		*Unipolar Flex Catheter Medtronic*	[46]	[46]	-	-	-
SPYRAL HTN-OFF MED Pivotal	**Pilot**	*Symplicity™ System Medtronic*	[56]	-	-	-	-
	PA		[47]	-	-	-	-
SPYRAL HTN-ON MED Expansion	**Pilot**	*Symplicity™ System Medtronic*	-	[57]	-	[53]	[53]
	PA		-	[48]	-	-	-
SYMPLICITY FLEX		*Symplicity™ System Medtronic*	-	[58]	-	-	-
SYMPLICITY HTN-3		*Unipolar Flex Catheter Medtronic*	-	[23]	[54]	-	[55]

Abbreviations: m – month; FU – follow-up; PA – primary analysis

Study characteristics

8 RCTs mit niedrigem Verzerrungspotenzial

Eight studies were multicentre and two single-centre RCTs, located in Denmark [46] and Germany [58], respectively. Two multicentre RCTs were conducted in the USA [23, 45]; three recruited patients from European centres and the USA [41-43], one study recruited patients from centres in Japan and South Korea [44], and two studies recruited patients from Australia, Europe, Japan and North America [44]. All but two studies had a 1:1 randomisation, with the other two randomising patients in a 2:1 ratio [47, 48]. All eight multicentre RCTs were commercially sponsored, while the Danish single-centre RCT was sponsored by the Danish Heart Foundation [46], and the German single-centre RCT was sponsored by the conducting hospital [58]. In all studies, patients and outcome assessors were blinded to allocation for at least the primary analysis period [23, 48].

in 4 RCTs wurden Medikamente vor RDN abgesetzt

U-RDN in 4 Studien, RF-RDN in 6 Studien untersucht

In all of the included studies, the intervention group received RDN, and the control group received a sham procedure (only a renal angiogram was performed). Additionally, in four studies, patients were required to discontinue their antihypertensive medication prior to randomisation [42, 43, 45, 47], while in the other six studies, patients continued their medication treatment [23, 41, 44, 46, 48, 58]. Four studies investigated the effectiveness and safety of U-RDN, all evaluating the Paradise™ System [41-44]. Six further studies evaluated RF-RDN, of which one study evaluated the Vessix System [45], two the unipolar flex catheter [23, 46] and three the Symplicity System [47, 48, 58].

bayesianische Statistik von zwei RCTs verwendet

Most trials used classic frequentists statistics, while two trials used a Bayesian approach for their data analysis [47, 48].

Patient characteristics, follow-up and outcomes

insgesamt 2.043 Patient*innen eingeschlossen

Blutdruckziel bei allen < 140/90 mmHg

Einschlusskriterien der Studien heterogen

In total, 2,043 patients with uncontrolled BP despite the use or prescription of OMT were analysed across the ten studies. Target BP control was set to be < 140/90 mmHg in all included studies. The specific inclusion criteria were somewhat heterogenous across trials. Five studies recruited patients with TRH on three or more antihypertensive medications [23, 41, 44, 46, 58]. In comparison, four studies recruited patients with uncontrolled hypertension with differing numbers of medications participants took at baseline: 0 to 2 medications [42], 1 to 3 medications [48], or patients who were required to discontinue medication prior to treatment [45, 47]. One further study [43] recruited patients with essential controlled hypertension on 1 to 2 medications, as well as uncontrolled hypertension on 0 to 2 medications. None of the studies distinguished between pseudo-resistant and true TRH within their patient population.

häufige Komorbiditäten: Schlafapnoea und Diabetes Typ 2

Common comorbidities were OSA (8 to 28% in the intervention groups and 7 to 32% in the control groups) and type 2 diabetes (3 to 54% in the intervention groups and 5 to 41% in the control groups).

primäre Endpunkte: BD-Werte

None of the studies used mortality, CVS-mortality, and CVS events as a primary efficacy outcome. Instead, the primary efficacy outcome in the majority of studies was systolic ABP, with five studies selecting their primary endpoint to be 24h systolic ABP [44, 45, 47, 48, 58]. Further four studies primarily concentrated on daytime systolic ABP [41-43, 46]. Only SYMPLICITY HTN-3 [23] had office systolic BP as the primary endpoint. Hospitalisation and HRQoL endpoints were not recorded by any studies. Further, three studies had a composite of major adverse events as a primary safety endpoint [23, 42, 48], whilst all others reported safety only as a secondary outcome.

A total number of 649 patients were included in the U-RDN trials, with sample sizes ranging between 136 and 224 patients per trial. Mean age ranged between 51 and 56 years, with around ~70% male participants. The follow-up length was two months in the RADIANCE trials [41-43] and three months in the REQUIRE trial [44]. In two of the four studies, patients had to discontinue medication before randomisation and during the primary analysis follow-up period [42, 43]. Loss to follow-up was relatively low in both intervention and control group, with 12 (3%) and five (2%) loss to follow-up cases, respectively.

649 Patient*innen in 4 U-RDN RCTs

Ø Alter 51-56

FU 2-3 Monate

A total number of 1,394 patients were included in the RF-RDN RCTs, samples ranging between 51 to 535 participants, with the lowest sample coming from one study [50], where further recruitment was ceased after a pre-defined interim analysis showed no possibility of achieving a significant BP change with further recruitment. Mean age ranged between 53 and 65 years, with around ~70% male participants. The follow-up length of primary analyses ranged from three to twelve months, with long-term follow-up available from one RCT of up to 36 months [23, 55]. For the SPYRAL HTN-ON MED trial, 36-month follow-up data was only available from the pilot analysis [48, 53, 57]. In both cases, patients were unblinded after the primary analysis follow-up period ended. In two of the six trials, patients had to discontinue medication before randomisation and during the follow-up period [45, 47]. Depending on the outcome, loss to follow-up rates ranged between 0 to 12% in the intervention groups and 0 to 18% in the control groups.

1.394 Patient*innen in 6 RF-RDN RCTs

Ø Alter 53-65

FU der primären Analysen zwischen 3 und 12 Monaten

in 2 RCTs 36 Monate FU-Daten verfügbar

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

3.3 Results: Clinical effectiveness and safety

3.3.1 Clinical effectiveness outcomes

Mortality[23]

All-cause mortality

All of the included studies reported mortality as a secondary endpoint [23, 41-48, 50-59]. The studies were not adequately powered and usually did not formally test for a potential statistical difference due to low event rates. Across all studies, mortality ranged from 0 to 4% in the RDN groups as opposed to 0 to 11% in patients receiving a sham intervention up to 36 months follow-up.

Mortalität:
IG: 0-4 %
KG: 0-11 %

In the studies evaluating **U-RDN (n=649)**, *two deaths* occurred across four included RCTs [41-44, 50-52]. In RADIANCE HTN SOLO, one patient (1%) died in the control group after 12 months follow-up, while one patient (1%) died in the intervention group in RADIANCE HTN TRIO [43] after 30 days. The death was a sudden death classified as not in relation to the study procedure.

je 1 Todesfall pro Gruppe in 4 U-RDN RCTs (n=649)

In the trials evaluating **RF-RDN (n=1,394)** [23, 45-48, 53-58], *three patients died* during the 6-month follow-up, two in the intervention group and one in the control group of SYMPLICITY HTN-3 [23] and one further patient in the control group of SPYRAL HTN-ON MED during the 36-month follow-up period [53]. SYMPLICITY HTN-3 [23] also reports 12-month and 36-month mortality with 2% compared to 4% and 4% compared to 11% of patients having died in the intervention and control group, respectively.

3 Todesfälle innerhalb von 6 Monaten (n=1.394) in 6 in RF-RDNs

Cardiovascular mortality

CVS mortality was also reported but not statistically analysed in all trials [23, 41-43, 45-48, 50-59], with SYMPLICITY HTN-3 only reporting CVS mortality at 12 and 36 months [54, 55]. *No CVS deaths* occurred.

kein kardiovaskulärer Todesfall

Morbidity[24]

All included studies [23, 41-43, 45-48, 50-57, 59] reported on *CVS events* as a secondary outcome. None of the studies was able to quantify a potential effect of RDN on CVS events. Patients suffering a CVS event ranged between 0 to 11% in the intervention groups and 0 to 12% in the patients receiving the sham procedure up to 36-month follow-up.

Mortalität:
IG: 0-11 %
KG: 0-12 %

In the studies evaluating **U-RDN (n=649)** [41-44, 50-52], CVS events occurred in 0 to 3% of patients in the intervention cohort as opposed to 0 to 4% in the sham groups up until the 6-month follow-up period. *Hypertensive crisis* was reported in two trials [51, 52] and occurred in none of the patients receiving U-RDN but in 3% of patients in the control group. *Myocardial infarction* occurred in 0 to 1% of the intervention and sham cohorts in one study, respectively [41, 51]. *Stroke* occurred in 1% of patients in the intervention

kein Unterschied bei kardiovaskulären Ereignissen in U-RDN RCTs

Hypertensive Krise, Herzinfarkt, Schlaganfall und Koronararterienbypass

[23] **D0001** – What is the expected beneficial effect of RDN on mortality in comparison to sham procedure.

[24] **D0005** – How does RDN affect cardiovascular sequelae of Hypertension?
D0006 – How does RDN affect the occurrence of CVS events?

group but in no patients from the sham group in the two trials [51, 52] that reported this outcome and the need for *coronary revascularisation* occurred in up to 3% of patients in the intervention group compared to 1% in the control group in the trial that reported this outcome [41, 51]. No further events occurred in the study that reported 12-month follow-up data [50].

auch kein Unterschied bei kardiovaskulären Ereignissen in RF-RDN RCTs

In the studies evaluating **RF-RDN (n=1,394)** [23, 45-48, 53-58], occurrence of CVS events ranged between 0 to 10% vs 0 to 12% up until the 6-month follow-up and between 3 to 11% and 0 to 11% in the two studies that reported 36-month follow-up data [53, 55].

am häufigsten aufgetreten: Hypertensive Krise

Overall, CVS events occurred at a similar frequency in patients receiving RDN and those receiving sham procedures up until six months of follow-up. The most frequent CVS event was a *hypertensive crisis*, which was reported in three trials [23, 47, 53-57] at a frequency ranging from 1 to 11% in the patients receiving RDN as opposed to 0 to 11% in the patients receiving a sham procedure. *Myocardial infarction* was reported in one trial in 2% of patients in each group, respectively. *Stroke* was reported in four trials at 0 to 1% compared to 0 to 3% of patients [23, 54, 55]. Hospitalisation for *new-onset heart failure* was reported in one trial at 3% and 2%, respectively. *Atrial fibrillation* was reported in one trial [23, 54, 55] at 1% in both groups. The need for *percutaneous coronary intervention* in one trial [46] occurred in 0% of the intervention group compared to 3% of the control group. The majority of events recorded occurred in one study, with 33 compared to 18 patients suffering a CVS event [55, 60].

24h ambulatory BP changes[25]

statistisch signifikanter Unterschied zugunsten der RDN in 4/10 Studien zu 24-Std. BD

24h ABP changes were reported as the primary endpoint by all included studies [23, 41-43, 45-48, 50-57, 59]. Overall, four out of ten trials [41-43, 47, 50-53, 56, 57, 59] found a statistically significant difference in favour of the intervention for 24h ABP at the primary analysis timepoint which varied between two to six months.

24h ambulatory BP ≤ 6 months follow-up

U-RDN: stat. signifikanter Unterschied zugunsten von RDN von systolischem 24-Std. BD in 3/4 Studien und diastolischem 24-Std BD in 1/2 Studien

In the **U-RDN (n=649)** studies [41-44, 50-52], at *three months follow-up*, three out of four studies found a statistically significant difference favouring the intervention for 24h systolic ABP reductions [41-43, 59]. The mean between-group difference ranged from –0.1 mmHg (SD: 2.7) to -6.3 mmHg (95% CI –9.2 to –3.4) [41-43]. One in four trials found a statistically significant difference favouring the intervention for 24h diastolic ABP reductions [42]. The mean between-group difference ranged from –0.4 (SD: 1.4) to –4.1 (95% CI –5.7 to 2.4).

6 Monate FU: kein signifikanter Gruppenunterschied von 24-Std. BD in 2/2 U-RDN RCTs

At *six months follow-up*, neither of the two studies analysing data at this timepoint reported a statistical difference in favour of the intervention. The mean between-group difference in 24h systolic ABP reduction ranged from 0.1 mmHg (95% CI –4.3 to 4.6) to –2 mmHg (95% CI –6.1 to 1.1), and in diastolic ABP reduction from –1.0 (95% CI –3.3 to 1.3) to 0.2 mmHg (95% CI -2.8 to 3.1).

[25] **D0005** – How does RDN affect BP values?

In the studies on **RF-RDN (n=1,394)** [23, 45-48, 53-58], only SPYRAL HTN-ON MED found a statistical difference in favour of the intervention for systolic and diastolic ABP up until *6 months of follow-up*. [47, 56, 57]. The mean between-group difference in 24h systolic ABP reductions post-intervention ranged from -1.9 mmHg (95% CI -4.4 to 0.5) to -7.4 mmHg (95% CI -15.2 to 0.4), and the mean between-group difference in 24h diastolic ABP reductions ranged from -0.8 mmHg (95% CI -2.4 to 0.9) to -3.1 mmHg (95% CI -9.0 to 2.9).

RF-RDN: nach 6 Monaten stat. signifikanter Unterschied zugunsten RDN in 1/6 RCTs vom 24-Std. systolischem und diastolischen BD

24h ambulatory BP ≤ 12 months follow-up

One study [47] on **U-RDN (n=649)** reported (unblinded) follow-up data *at 12 months* and did not find a statistically significant between-group difference. The difference in reduction of 24h systolic and diastolic ABP between the patients in the intervention and control groups in RADIANCE HTN SOLO was -0.8 mmHg (95% CI -4.5 to 2.9) and -0.2 mmHg (95% CI -2.7 to 2.3), respectively.

nach 12 Monaten FU: kein stat. signifikanter Unterschied in U-RDN Studien

Of the studies on **RF-RDN (n=1,394)** [23, 45-48, 53-58], two reported outcomes *at 12-month follow-up* [45, 54]. SYMPLICITY HTN-3 reported a statistically significant difference in favour of the intervention for 24h systolic and diastolic ABP reductions, respectively [54]. The mean between-group difference was -8.5 mmHg (95% CI -11.9 to -5.1) for systolic ABP and -5.6 mmHg (95% CI -7.7 to -3.6) for diastolic ABP reduction. It is of note that in REDUCE HTN [45], blinding was maintained until this point, while for SIMPLICITY HTN-3 [54], these outcomes were unblinded.

nach 12 Monaten FU: in 1/2 RF-RDN RCTs stat. signifikanter Unterschied zugunsten RDN von 24-Std. ambulantem systolisch/ diastolischem BD

24h ambulatory BP≥ 12 months follow-up

No studies on **U-RDN** reported outcomes beyond a 12-month follow-up.

In the studies on **RF-RDN (n=1,394)** [23, 45-48, 53-58], two reported unblinded [23, 45-48, 53-58] *24-month and/or 36-month follow-up* results [53, 55]. SPYRAL HTN-ON MED and SYMPLICITY HTN-3 found statistically significant differences favouring RF-RDN for 24h systolic ABP and diastolic ABP at both timepoints. The mean between-group differences in reductions ranged from -11.2 mmHg (95% CI -18.4 to -4.0) to -16.5 mmHg (95% CI -20.5 to -12.5) for 24h systolic ABP and -5.7 mmHg (95% CI -10.6 to -0.7) to -11.2 mmHg (95% CI -13.6 to -8.7) for 24h diastolic ABP. The 36-month data for SPRYAL HTN-ON MED [53] comes from the pilot trial, as no data beyond the 6-month follow-up was available for the primary analysis.

24-36 Monate FU: 2/2 RF-RDN RCTs mit stat. signifikanter Gruppendifferenz von 24-Std. ambulantem systolisch/diastolischem BD

48h ambulatory BP

No studies reported 48-hour systolic or diastolic ABP as an endpoint.

48 Std. BD in keinem RCT berichtet

Hospitalisation[26]

No studies reported on the endpoint hospitalisation.

kein RCT berichtete Hospitalisierung oder Lebensqualität

Quality of life[27]

None of the included studies reported on the endpoint HRQoL.

[26] How does RDN affect hospitalization rates?

[27] **D0012** – How does RDN affect patient's quality of life?

*Table 3-2: Ambulatory **systolic** blood pressure lowering Effect of RDN: Between group differences of sham-controlled randomised controlled trials*

RCT		Between group differences of systolic ambulatory blood pressure (RDN versus Sham)				
Follow-up, in months		≤3	6	12	24	36
Certainty of Evidence		MODERATE[a]	MODERATE[a]	LOW[b]	LOW[b]	LOW[b]
U-RDN						
RADIANCE HTN SOLO (n=146)		-4.1 (-7.1 to -1.2), ***p=0.006*** [43]	-2 (-6.0 to 1.1), *p=0.178* [52]	-0.8 (-4.5 to 2.9), *p=0.656* [50]	-	-
RADIANCE HTN TRIO (n=136)		-4.2 (-8.3 to -0.3)*, ***p=0.016*** [41]	0.1 (-4.3 to 4.6)*, *p=0.85* [51]	-	-	-
RADIANCE II (n=224)		-6.3 (-9.2 to −3.4), ***p<.001*** [42]	-	-	-	-
REQUIRE (n=143)		-0.1 (2.7)**, *p=0.971* [44]	-	-	-	-
RF-RDN						
REDUCE HTN (n=51)		3.3 (-4.4 to 11.1), *p=0.407* [45]	-7.4 (-15.2 to 0.4), *p=0.071* [45]	-4.9 (-13.4 to 3.6), *p=0.266* [45]	-	-
RESET (n=69)		ND, *p=0.88**** [46]	ND, *p=0.76****[46]	-	-	-
SPYRAL HTN OFF MED	**Pilot (n=80)**	-5.0 (-9.9 to -0.2), ***p=0.041*** [56]	-	-	-	-
	Primary analysis (n=331)	-3.6 (-5.9 to -1.4), ***p=0.002*** [47]	-	-	-	-
SPYRAL HTN-ON MED	**Pilot (n=80)**	-	-7.4 (-12.5 to -2.3), ***p=0.0051*** [57]	-	-11.2 (-18.4 to -4.0), ***p=0.0031*** [53]	-10.0 (-16.6 to -3.3), ***p=0.0039*** [53]
	Primary analysis (n=337)	-	-1.9 (-4.4 to 0.5), *p=0.12* [48]	-	-	-
SYMPLICITY FLEX (n=71)		-	ND, *p=0.15**** [58]	-	-	-
SYMPLICITY HTN-3 (n=535)		-	-1.96 (-4.97 to 1.1), *p=0.98* [23]	-8.5 (-11.9 to -5.1), ***p≤.0001*** [54]	-	-16.5 (-20.5 to -12.5), ***p≤.0001*** [55]

Abbreviations: ABP – ambulatory blood pressure, IQR – interquartile range, LSM – least square mean, ND – no statistically significant group difference, SD – standard deviation, SE – standard error

BGD values in mean (±SD) or mean (95% CI) unless marked otherwise.

Median (IQR), ** LSM(SE). * Between-group difference was tested within the respective study, without reporting on specific values.*

Notes:

[a] *The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.*

[b] *All but one long-term follow-up results (at 12 m FU) were collected under unblinded conditions, hence certainty of evidence was further downgraded to low.*

*Table 3-3: Ambulatory **diastolic** blood pressure lowering Effect of RDN: Between group differences of sham-controlled randomised controlled trials*

RCT		Between group differences of diastolic ambulatory blood pressure (RDN versus Sham)				
Certainty of evidence		MODERATE[a]	MODERATE[a]	LOW[b]		
Follow-up, in months		≤3	6	12	24	36
U-RDN						
RADIANCE HTN SOLO (n=146)		-1.8 (-3.7 to 0.2), *p=0.07* [43]	-1.0 (-3.3 to 1.3), *p=0.383* [52]	-0.2 (-2.7 to 2.3), *p=0.875* [50]	-	-
RADIANCE HTN TRIO (n=146)		-2.0 (-4.5 to 0.6), *p=0.12* [41]	0.2 (-2.8 to 3.1)*, *p=0.74* [51]	-	-	-
RADIANCE II (n=224)		−4.1 (−5.7 to −2.4), ***p<.001*** [42]	-	-	-	-
REQUIRE (n=143)		-0.4 (1.4)**, *p=0.806* [44]	-	-	-	-
RF-RDN						
REDUCE HTN (n=51)		2.8 (-2.7 to 8.3), *p=0.328* [45]	-3.1 (-9.0 to 2.9), *p=0.317* [45]	-4.4 (-10.2 to 1.5), *p=0.154* [45]	-	-
RESET (n=69)		Effect estimate: NR, *p=0.47* [46]	Effect estimate: NR, *p=0.64* [46]	-	-	-
SPYRAL HTN-OFF MED	**Pilot (n=80)**	-4.4 (-7.2 to -1.6), ***p=0.002*** [56]	-	-	-	-
	Primary Analysis (n=331)	-2.9 (-4.4 to -1.5), ***p<.001*** [47]	-	-	-	-
SPYRAL HTN ON MED	**Pilot (n=80)**	-	-4.1 (-7.8 to -0.4), ***p=0.0292*** [57]	-	-5.7 (-10.6 vs -0.7), ***p=0.025*** [53]	-5.9 (-10.1 to -1.8), ***p=0.0055*** [53]
	Primary Analysis (n=337)	-	-0.8 (-2.4 to 0.9), *p=0.37* [48]	-	-	-
SYMPLICITY FLEX (n=71)		-	Effect estimate: NR, *p=0.57* [58]	-	-	-
SYMPLICITY HTN-3 (n=535)		-	Effect estimate: NR, *p=0.28* [23]	-5.6 (-7.7 to -3.6), ***p≤.0001***[54]	-	-11.2 (-13.6 to -8.7), ***p≤.0001*** [55]

Abbreviations: ABP – ambulatory blood pressure; IQR – interquartile range; LSM – least square mean; ND – no statistically significant group difference; SD – standard deviation, SE – standard error

*BGD values in mean (±SD) and mean (95% CI) unless marked otherwise. *Median (IQR), ** LSE (SD)*

Notes:

[a] *The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.*

[b] *All but one long-term follow-up results (at 12 m FU) were collected under unblinded conditions, hence certainty of evidence was further downgraded to low.*

3.3.2 Safety

Sicherheit als primärer Endpunkt in 3 RCTs

Three studies reported *safety outcomes* [23, 42, 54, 55, 57] as primary endpoints, and all others described safety as a secondary endpoint. Most studies did not report on an aggregated number of patients suffering from adverse events, and overall occurrence was low in patients in the intervention and control groups. We report all serious adverse events and specific adverse events with a frequency of more than 5%. Data extraction Table A-1 and Table A-2 in the appendix can be referred to for further details on safety events.

kein signifikanter Gruppenunterschied in SUE und UE

None of the studies were able to detect a statistically significant difference in SAEs or AEs between the patients receiving RDN and those receiving sham procedures. No procedure-related death occurred in any trial.

SUE U-RDN: 0-4 % vs 0-1 %

In the studies on **U-RDN (n=649)** [41-44, 50-52], the rate of *serious adverse events* ranged from 0 to 4% in the intervention groups and from 0 to 1% in the control groups, up to the 6-month follow-up. These included, among others, vasospastic angina, puncture site haemorrhage, and postural dizziness. RADIANCE II [42] reported that composite safety endpoint was met as no patients in either group suffered from any of the pre-defined events included in the composite safety[28] endpoint compared to the performance goal (9.8%) and no major adverse event occurred in patients receiving U-RDN or patients receiving a sham device.

häufigstes UE: verfahrensbedingte Schmerzen >2 Tage 8-17 % vs. 8-15 %

Adverse events ranged from 0 to 17% in the intervention groups and from 0 to 15% in the control groups. Procedure-related pain lasting longer than two days was the most frequently occurring adverse event in three studies [41, 43, 44]. In REQUIRE [40], Vasospasm was reported in 6% of patients in the intervention group but in no patients of the control group and puncture site complications occurred in 6% and 4%, respectively.

SUE RF-RDN: 0-1 % je Gruppe

2 RCTs mit kombinierten Sicherheitsendpunkt: kein Unterschied

geringfügige UE in 1 RCT 14 % vs. 18 %

In the **RF-RDN** trials **(n=1,394)** [23, 45-48, 53-58], the rate of serious adverse events ranged from 0 to 1% in both the intervention groups and control groups up to the 6-month primary analysis point. Two studies [23, 48, 54, 55] reported a composite safety endpoint (defined as above) as the primary safety endpoint. In SYMPLICITY HTN-3 [23, 54, 55], 4% of patients receiving RDN compared to 6% of patients receiving sham procedures suffered an adverse event specified in the composite safety endpoint up to 6-month follow-up, and in 7% of both groups, respectively, at the 12-month follow-up. The safety endpoint was met as event rates remained below the pre-specified performance goal of 9.8%. The SPYRAL HTN-ON MED [48] reported no patients suffering an event included in the composite endpoint, compared to the performance goal of 7.1% or less. A 36-month follow-up analysis from this study's pilot trial reported that only 1% of patients in the intervention and control groups suffered a prespecified event [53]. Minor adverse events such as headache, atypical chest pain, muscle convulsion, and fatigue were reported by REDUCE HTN [42] in 14% and 18% of each group, respectively. Procedure-related pain was either not reported or did not occur in the studies on RF-RDN.

It is of note that the majority of adverse events reported stem from SYMPLICITY HTN-3 [23].

[28] The composite safety endpoint was defined as all-cause mortality, end-stage renal disease, significant embolic event resulting in end-organ damage, renal artery perforation or dissection requiring surgical repair, interventional procedure, thrombin injection or blood transfusion, hospitalization for hypertensive crisis or new renal artery stenosis of ≥70%.

4 Certainty of evidence

Verzerrungspotential mit Cochrane RoB V2 bewertet: niedrig in 9 RCTs, moderat in 2 Endpunkten in 1 RCT

The risk of bias (RoB) of the individual outcomes in the primary analysis of RCTs was assessed with the Cochrane RoB tool v.2 and is presented in Table A-3 for the U-RDN trials and Table A-4 for the RF-RDN trials in the Appendix. Generally, the RoB of all outcomes was considered low in nine studies. Only blood pressure and mortality outcomes of the SPYRAL HTN-ON MED study [48] showed some concerns in the domain "bias arising from the randomisation process", as baseline imbalances were found especially with respect to sleep apnoea (Sham-group: 24%; RDN-group: 5%)

Vertrauenswürdigkeit der der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [36] for each endpoint individually. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [36].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low** = We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

RF- und U-RDN: niedrige bis moderate Vertrauenswürdigkeit der Evidenz zur Wirksamkeit, moderate Vertrauenswürdigkeit der Evidenz zur Sicherheit

The certainty of evidence for the efficacy of RDN compared to sham control was rated as low for all-cause mortality, CVS mortality and CVS events and moderate to low for BP changes depending on the follow-up time. The certainty of evidence for safety was rated moderate.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-6.

Table 4-1: Summary of findings table of ultrasound renal denervation (U-RDN) in patients with TRH

Outcome	Anticipated effects (U-RDN vs Sham)		N of participants (studies)	Certainty	Comments
	U-RDN	Sham			
Efficacy					
All-cause mortality (up to 12 months FU)	0-1%	0-1%	649 (4 RCTs)	⨁⨁◯◯[a] low	No formal testing for statistical difference due to low event rates. No apparent difference between groups in any study.
CVS mortality	-	-	649 (4 RCTs)	⨁⨁◯◯[a] low	No patients died of CVS events in any study.
CVS events	0-3%	0-4%	649 (4 RCTs)	⨁⨁◯◯[a] low	
24h systolic ABP (up to 6 months FU)	Three studies were able to detect a statistically significant difference in favour of the intervention at 3m FU Range of mean improvement BGD: -0.1 (2.7) to -6.3 (-9.2 to -3.4) mmHg but statistical significance was not reported at the 6m follow-up reported in two studies.		649 (4 RCTs)	⨁⨁⨁◯[b] moderate	
24h diastolic ABP (up to 6 months FU)	One study was able to detect a statistically significant difference in favour of the intervention at 3m FU Range of mean improvement BGD: -0.4 (1.4) to -4.1 (-5.7 to 2.4) mmHg No further statistical significance at the 6m follow-up reported in two studies.		649 (4 RCTs)	⨁⨁⨁◯[b] moderate	
24h systolic ABP (up to 12 months FU)	No statistically significant difference in improvement was detected		282 (1 RCT)	⨁⨁◯◯[c] low	
24h diastolic ABP (up to 12 months FU)	No statistically significant difference in improvement was detected		282 (1 RCT)	⨁⨁◯◯[c] low	
HRQoL	NR	NR	NR	NR	HRQoL outcomes were not recorded by any of the studies
Hospitalisation	NR	NR	NR	NR	Hospitalisation rates were not recorded by any of the studies
Safety					
Adverse Events*	No procedure-related deaths Range of patients suffering SAE: 0-4%[9] Range of patients suffering AE: 0-17% Pain was most frequently reported: 8-17% Vasospasm: 6% Puncture site complications: 6% 1 study reported safety composite as primary endpoint: 0 %	No procedure-related deaths Range of patients suffering SAE: 0-1% Range of patients suffering AE: 0-15% Pain was most frequently reported: 8-15% Vasospasm: 0% Puncture site complications: 4% 1 study reported safety composite as primary endpoint: 0 %	649 (4 RCTs)	⨁⨁⨁◯[d] moderate	No apparent difference between groups in any study. No formal testing of statistical difference.

Abbreviations: 24h – 24-hour; ABP – ambulatory blood pressure; BGD – between-group difference; CVS – cardiovascular; FU – follow-up; HRQoL – Health-related Quality of Life; m – month(s); NR – not reported; RCT – randomised control trial; SAE – (serious) adverse event; TRH – treatment resistant hypertension; U-RDN – ultrasound renal denervation.

*Comments: * We reported specific adverse events if they occurred at a frequency of ≥5%.*

*** For reasons of practicality, we combined endpoints of different time points that reached the same overall GRADE rating.*

Notes: [a] Optimal information size was not reached. The studies were not powered for this outcome.

[b] The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.

[c] Unblinded, wide confidence intervals. [d] Optimal information size was not reached.

Table 4-2: Summary of findings table of radiofrequency renal denervation (RF-RDN) in patients with TRH

Outcome	Anticipated effects (RF-RDN vs Sham)		N of participants (studies)	Certainty	Comments
	RF-RDN	Sham			
All-cause mortality (up to 36 months FU)	Range of any deaths 0-4%	Range of any death 0-11%	1,394 (6 RCTs)	⨁⨁◯◯[a] low	No apparent difference between groups in any study
CVS mortality (up to 36 months FU)	-	-	1,394 (6 RCTs)	⨁⨁◯◯[a] low	No patients died of CVS events in any study
CVS events	Up to 6m: 0-10% Up to 36m: 3-11% Hypertensive crisis most frequently reported: 1-11%	Up to 6m: 0-12% Up to 36m: 0-11% Hypertensive crisis most frequently reported: 0-11%	1,394 (6 RCTs)	⨁⨁◯◯[a] low	No apparent difference between groups
24h systolic ABP (up to 6 months FU)	One study was able to detect a statistically significant difference in favour of the intervention Range of mean improvement BGD: -1.9 (-4.4 to 0.5) to –7.4 (-15.2 to 0.4) mmHg		1,394 (6 RCTs)	⨁⨁⨁◯[b] moderate	
24h diastolic ABP (up to 6 months FU)	One study was able to detect a statistically significant difference in favour of the intervention Range of mean improvement BGD: -0.8 (-2.4 to 0.9) to –3.1 (-9.0 to 2.9) mmHg		1394 (6 RCTs)	⨁⨁⨁◯[b] moderate	
24h systolic ABP (up to 12 months FU)	One study was able to detect a statistically significant difference in favour of the intervention BGD: -8.5 (-11.9 to –5.1) mmHg, p≤0.0001		586 (2 RCTs)	⨁⨁◯◯[c] low	
24h diastolic ABP ≤12m (up to 12 months FU)	One study was able to detect a statistically significant difference in favour of the intervention BGD: -5.6 (-7.7 to –3.6) mmHg, p≤0.0001		586 (2 RCTs)	⨁⨁◯◯[c] low	
24h systolic ABP (up to 36 months FU)	Two studies were able to detect a statistically significant difference in favour of the intervention Range of mean improvement BGD: -11.2 (-18.4 to –4.0),p=0.0031 and -16.5 (-20.5 to -12.5) mmHg , p≤0.0001		615 (2 RCTs)	⨁⨁◯◯[c] low	
24h diastolic ABP (up to 36 months FU)	Two studies were able to detect a statistically significant difference in favour of the intervention Range of mean improvement BGD:-5.7 (-10.6 to – 0.7), p=0.025 and -11.2 (-13.6 to -8.7) mmHg, , p≤0.0001		615 (2 RCTs)	⨁⨁◯◯[c] low	
HRQoL	NR	NR	NR	NR	HRQoL outcomes were not recorded by any of the studies
Hospitalisation	NR	NR	NR	NR	Hospitalisation rates were not recorded by any of the studies
Adverse Events*	Range of patients suffering SAE: 0-1% (vascular complications) 2 studies reported safety composite as primary endpoint. At 6m: 4% At 36m: 2-4%	Range of patients suffering SAE: 0-1% (vascular complications) 2 studies reported safety composite as primary endpoint. At 6m: 6% At 36m: 6-7%	1,394 (6 RCTs)	⨁⨁⨁◯[c] moderate	No apparent difference between groups in any study

Abbreviations: 24h – 24-hour; ABP – ambulatory blood pressure; BGD – between-group difference; CVS – cardiovascular; FU – follow-up; HRQoL – Health-related Quality of Life; m – month(s); NR – not reported; RCT – randomised control trial; RF-RDN – radiofrequency renal denervation; SAE – (serious) adverse event; TRH – treatment-resistant hypertension.

*Comments: * We reported specific adverse events if they occurred at a frequency of ≥5%*

*** For reasons of practicality, we combined endpoints of different time points that reached the same overall GRADE rating.*

Notes: [a] Optimal information size was not reached. The studies were not powered for this outcome.

[b] The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.

[c] Unblinded, wide confidence intervals in some studies.

5 Discussion

Renal denervation (RDN) is an add-on intervention that aims to lower blood pressure (BP), potentially leading to improved patient-relevant outcomes such as lower risk for cardiovascular (CVS) events and reduced risk of mortality in patients with uncontrolled hypertension who are resistant to antihypertensive medication. This second update report aimed at synthesising the currently best available evidence regarding the comparative effectiveness and safety of RDN. In total, this systematic review captures evidence from ten sham-controlled randomised controlled trials (RCTs) ([23, 41-48, 50-58], of which none were included in the previous LBI-HTA reports [1, 2].

2. Update-Report: 10 Sham-kontrollierte RCTs eingeschlossen

5.1 Summary of findings

Overall, this systematic review (SR) found moderate certainty evidence from ten RCTs that RDN reduces BP short- to mid-term in patients with uncontrolled hypertension. The magnitude of benefit of all sham-controlled trials appears to be modest. Some long-term follow-up data were available, although these were considered insufficient to draw any conclusion regarding a potential BP lowering effect, as blinding of these post-hoc analyses was often not upheld. Evidence was insufficient to determine the impact of RDN on CVS outcomes and mortality and no evidence was available for quality of life or hospitalisation.

moderate Vertrauenswürdigkeit der Evidenz für Senkung des Blutdrucks (<6 Monate)

Ultrasound renal denervation (U-RDN)

Four studies with a total of 649 participants with uncontrolled hypertension with varying numbers of previous medications investigated the add-on benefit of using RDN in terms of lowering BP. The risk of bias (RoB) was assessed with the Cochrane Risk of Bias tool v.2 [35]. All studies evaluating U-RDN were considered to be at low RoB.

Verzerrungsrisiko in U-RDN Studien als niedrig eingestuft

Efficacy

None of the studies were able to detect a statistically significant difference in patient-relevant outcomes such as mortality or major CVS events. However, three out of four trials found statistically significant differences favouring RDN in terms of 24-hour (24h) systolic ambulatory blood pressure (ABP) at two months follow-up. The between-group difference of improvement ranged from -0.1 mmHg (SD: 2.7) to -6.3 mmHg (95% CI -9.2 to 3.4). One out of four trials found statistically significant differences favouring RDN regarding 24h diastolic ABP at two months follow-up. The between-group difference of improvement ranged from -0.4 mmHg (SD: 1.4) to -4.1 mmHg (95% CI -5.7 to 2.4) mmHg. Two trials reported 6-month follow-up data,and one reported 12-month-follow-up none of which showed further statistically significant differences in 24h systolic and diastolic ABP in the patients receiving RDN treatment.

keine Unterschiede bei Mortalität & kardiovaskulären Ereignissen, stat. signifikanter Unterschied zugunsten RDN von systolischem 24-Std. BD in 3/4 RCTs und von diastolischem 24-Std. BD in 1/4 RCTs

Safety

No statistically significant difference in severe adverse events and adverse events was detected between patients receiving U-RDN and patients undergoing a renal angiogram as sham procedure. The primary safety endpoint was met in the study that had prespecified this in their analysis. Although numerous studies did not report on an aggregated number of patients suffering from serious adverse events, the event rate of specific serious adverse events was low, ranging from none to 4%. These included, among others, vasospastic angina, puncture site haemorrhage, and postural dizziness. Further, procedure-related pain lasting more than two days appeared to be frequent, with these adverse events occurring in 8 to 17% and 8 to 15% in U-RDN and sham groups across studies, respectively. Less frequently occurring adverse events were vasospasm in 6% in one intervention group compared to none in the control group and puncture site complications in 6% and 4%, respectively.

kein Unterschied in SUE und UE

häufigste Nebenwirkung in beiden Gruppen: verfahrensbedingte Schmerzen

Radiofrequency renal denervation (RF-RDN)

Six studies with a total of 1,394 participants with uncontrolled hypertension and with varying numbers of previous medications investigated the add-on benefit of using RDN in terms of lowering BP. The RoB was assessed with the Cochrane Risk of Bias tool v.2 [35] and considered low in five studies and moderate in one due to concerns regarding randomisation as the proportion of patients with sleep apnoea was not evenly distributed between the groups which could have skewed results in favour of the RDN group.

Verzerrungsrisiko in RF-RDN Studien niedrig in 5 Studien und moderat in 1 Studie

Efficacy

None of the studies detected a statistically significant difference in patient-relevant outcomes such as mortality or major CVS events. However, one out of six trials found statistically significant differences favouring RDN in terms of 24h systolic and diastolic ABP until the 6-month follow-up. The between-group difference of improvement ranged from -1.9 mmHg (95% CI -4.4 to 0.5) to -7.4 mmHg (95% CI -15.2 to 0.2I) for systolic ABP and -0.8 mmHg (95% CI -2.4 to 0.9) to -3.1 mmHg (95% CI -9.0 to 2.9) for diastolic ABP. At 12-month follow-up, one out of two trials reported statistically significant differences favouring RDN in terms of 24h systolic and diastolic ABP under unblinded conditions, and the between-group difference of improvement ranged from -8.5 mmHg (95% CI -11.9 to -5.1) and -5.6 mmHg (95% CI -7.7 to -3.6), respectively. Two studies also reported unblinded data up to 36-month follow-up, with both detecting a statistically significant difference in favour of the intervention. The between-group difference of improvement ranged from -11.2 mmHg (95% CI -18.4 to -4.0) to -16.6 mmHg (95% CI -20.5 to -12.5) for systolic ABP and -5.7 mmHg (95% CI -10.6 to -0.7) to -11.2 mmHg (95% CI -13.6 to -8.7) for diastolic ABP.

keine Unterschiede bei Mortalität & kardiovaskulären Ereignissen

nur in 1/6 RCTs signifikanter Unterschied zugunsten RDN bezüglich 24-Std. BD nach 6 Monaten

Langzeitergebnisse stat. signifikant aber unverblindet

Safety

There was no statistically significant difference detected in severe adverse events and adverse events between patients receiving RF-RDN and patients undergoing a renal angiogram as sham procedure. Although most studies did not report on an aggregated number of patients suffering from serious adverse events, the event rate of specific serious adverse events was low, ranging from none to 1% in the studies reporting safety as a secondary endpoint. One study reported specific details on vascular complications. In the studies reporting safety as a primary outcome, the primary safety endpoint was met.

kein Unterschied in SUE und UE

Our SR complements other available SRs insofar as the latest RCT and long-term follow-up data of existing RCTs were identified and systematically synthesised using the GRADE approach [36]. Additionally, we present findings separately for each technology.

in diesem Bericht: 1 neuer RCT und neue Langzeitdaten

One SR was conducted in 2023, including nearly all but one of our identified studies [31]. In this review, BP control was used as the only outcome of interest, and a meta-analysis and meta-regression were conducted based on the included trials. RDN was equally found to statistically lower systolic BP and diastolic BP over a mean follow-up period of 4.2 months. The authors concluded that the effect measure was within the expected bound of BP-lowering drugs.

SR von 2023 mit 9 RCTs: nur Blutdruck als Outcome, RDN senkt stat. signifikant den Blutdruck

A Cochrane review [29] which was conducted in 2021, reported on a wider range of trials including non-sham-controlled studies as well. In total, 15 RCTs (1,416 participants) were identified, of which four met our inclusion criteria and were included in this SR as well. The authors found that there is low certainty evidence that RDN effects CVS endpoints and renal function. Moderate certainty evidence was found that RDN may improve 24h ABP. The authors of the Cochrane report [29] concluded that there is a need for larger trials that focus on patient-centred endpoints and longer follow-up periods.

Conclusio Cochrane Review 2021 mit 15 RCTs: größere Studien mit Fokus auf Patienten-relevante Endpunkte nötig

5.2 Internal validity, external validity and evidence gaps

The internal validity of sham-controlled trials was assessed with the Cochrane Risk of Bias tool v.2 [35]. Generally, the RoB of all outcomes was considered low in nine studies. Only the BP outcome and mortality outcome of the SPYRAL HTN-ON MED study [48] showed some concerns in the domain "bias arising from the randomisation process", as the proportion of patients with sleep apnoea in the sham group was higher than in the RDN group (24% vs 5%), which could have skewed results in favour of the RDN group. Generally, however, the internal validity of the included trials was considered to be robust.

Verzerrungsrisiko niedrig in 9 Studien, nur Blutdruck und Mortalität in einem RCT mit moderatem Verzerrungsrisiko

Further evidence gaps were identified that primarily, but not exclusively, address concerns regarding the external validity of identified results:

Evidence Gaps:

- *Lack of proof of long-term effectiveness*: Most of the identified evidence focused on short- and mid-term benefit of RDN (2-12 months). Although some post-hoc long-term follow-up data indicate a substantial BP lowering effect, these results are prone to bias as blinding was not upheld, and cross-over typically occurred. Hence, there is high uncertainty with regard to the sustainability of BP control – also in light of potential regrowth of the renal efferent nerves [61].

Fokus derzeit v. a. auf kurz- und mittelfristige Wirksamkeit, Langzeitdaten unverblindent und mit Cross-over

- *Patient-reported outcome measurements (PROM)*: None of the studies measured PROMs, hindering both the knowledge of a potential effect of RDN on, inter alia, quality of life and the incorporation of the patient perspective more broadly within the evaluation of RDN.

keine patientenzentrierten Endpunkte berichtet

- *Lack of adequate knowledge on patient populations [62]*: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) treatment-resistant hypertension (TRH) [4]. TRH and patients who do not tolerate antihypertensive treatment were the target population of our assessment. The inclusion criteria in the different studies may not only include pseudo-resistant TRH per definition, but also those patients who would eventually benefit from further antihypertensive treatment (see Applicability Table A-8 in the appendix). This represents a significant applicability concern. Based on theoretical considerations, patients with true TRH would be in high need of a technology that enables a BP lowering effect as both morbidity and mortality may be substantial [62]. In this context, an individual participant data meta-analysis [63] may help to evaluate RDN in specific indications, e.g., those truly resistant to antihypertensive medications.

Patient*innenpopulation derzeit sehr heterogen

Anwendbarkeit aufgrund dessen beschränkt

- *Comparative effectiveness between different technologies*: Although we clustered the evidence according to features of the intervention, the head-to-head comparison and effectiveness between radiofrequency and ultrasound RDN are unknown. Furthermore, the search for ongoing studies revealed that newer approaches are using alcohol-mediated RDN, whose comparative effectiveness is also unknown. Other neurotoxic agents and cryoablation have also been investigated as possibilities for RDN but these technologies are not currently CE certified [64, 65].

derzeit kein direkter Vergleich der Wirksamkeit verschiedener RDN-Produkte

- *Comparator and role of RDN:* The available evidence and current practice are restricted to using the device as an adjunct treatment in patients who do not respond to or do not tolerate antihypertensive medication. Some proponents of RDN also see a role of the technology to be potentially used instead of complex antihypertensive regiments that may include frequent dosing schedules [61]. Although some of our included studies (e.g., [42]) included patient populations with a potential indication for a further line of antihypertensive medication, it is important to stress that an antihypertensive medication would need to be set as a comparator in future trials to fully assess the comparative effectiveness of RDN in comparison to antihypertensive medication. Evidence requirements would arguably also shift in this context.

zukünftiger Vergleich zw. RDN und Antihypertensiva nicht auszuschließen

5.2.1 Ongoing studies

The search for ongoing studies revealed that ten sham-controlled RCTs are currently ongoing, of which seven have already reached their primary completion date between 2020 and 2023. Two other ongoing studies are estimated to reach their primary completion date in 2024, and the third will be completed in 2028. Eight of the ongoing studies evaluate patients with different degrees of hypertension (80-300 enrolled patients), although the specified indications remain heterogeneous. The other two ongoing studies evaluate RDN in hypertensive patients with chronic kidney disease (44 actual enrolled patients) and hypertensive patients with heart failure with preserved ejection fraction (68 planned patients), respectively.

10 laufende shamkontrolliere RCTs identifiziert, 8 davon mit primärem Abschluss zwischen 2020 und 2023

keine Verwendung patientenberichteter Endpunkte

None of the ongoing studies use direct patient-relevant endpoints, such as a reduction in CVS events. Instead, BP was used as a primary endpoint in all ongoing studies, with six of the ongoing studies defining 24h systolic ABP as their primary outcome measure, and two further studies defining office systolic BP.

andere RDN Technolgien (Alkohol) und neue RDN-Produkte

Four of the ongoing trials investigate RF-RDN, although, in three of the studies, new devices are used (Netrod® System, DENEX System and SyMapCath I™). Two ongoing studies are evaluating the Paradise™ ultrasound System. In addition, two studies investigate RDN with the Peregrine System, in which a neurolytic agent (alcohol) is delivered into the perivascular space surrounding the renal artery via micro-needles. In two other trials the exact type of RDN technology used is not clear.

5.3 Limitations

keine quantitative Analyse aufgrund klinischer Heterogenität

keine MCID identifiziert

post-hoc Analysen und Registerdaten wurden ausgeschlossen

Our SR should be viewed in light of its limitations. Firstly, we did not pool study results quantitatively given clinical heterogeneity and differences in in- and exclusion criteria. An individual participant data meta-analysis [63] could help to analyse and pool data across studies using harmonised inclusion criteria (e.g., those patients with a true TRH), although access to trial data would be needed in this context. Second, we did not identify an established minimally important clinical different (MCID) for BP reductions. Hence, the interpretation of the magnitude of identified short-term benefit is limited. Third, we excluded publications on post-hoc analyses of randomised trials (unless these addressed long-term follow-up results of the total randomised patient population) and registry data. Most of the identified excluded post-hoc analyses appeared to be either exploratory or investigating on surrogate endpoints, minimising the risk that these publications would have changed our interpretation of the evidence. Registry data could reveal more insights on rare adverse events, which demonstrates a limitation of exclusively looking at RCTs.

Registerdaten bestätigen seltenes Auftreten von schwerwiegenden unerwünschten Ereignissen

Although we excluded single-arm evidence on safety, it appears that available registry data confirm the safety profile of RCT data. The currently available Global Simplicity registry [66] is a prospective registry of roughly 200 active sites. In 2019, data from 2,237 patients for over a three-year follow-up period found no long-term safety concerns regarding the RDN procedure. For U-RDN, the Global Paradise System registry [67] plans to enrol up to 3,000 patients, which will provide further safety data from a large population.

aus klinischer Perspektive Verwendung der BD-Werte am aussagekräftigsten

From a clinical perspective, arterial hypertension constitutes a major global burden of disease and there is interest from scientists and clinicians to alleviate patient suffering and to prevent serious cardiovascular events. Since the entire definition of arterial hypertension as an “artificial” clinical entity [68] is founded on outcome data in large longitudinal trials, and since its impact on mortality is the most widely accepted driver for the progressively stricter delineation between normal and elevated BP [69, 70], it is only consistent to expect outcome data as the key assessment variable for the clinical value of RDN in patients with TRH. Such data are also available for other forms of antihypertensive therapy, e.g. various drug classes. At the same time, a clear and unambiguous threshold value for the perceptibility of the antihyperten-

sive effect (so-called Minimal Important Difference/MCID) has not been established specifically for TRH. Conclusions about a potential effect of RDN on cardiovascular endpoints can only be indirectly inferred by the documented effect which any BP reduction has on long-term clinical endpoints and long-term preservation of kidney function [71].

5.4 Conclusion

Schlussfolgerung: Verbesserung des Blutdrucks bei TRH bis zu 6 Monaten

The available evidence indicates that RDN improves BP control up to six months of follow-up in patients with uncontrolled TRH. Due to limited follow-up intervals and the fact that statistically major adverse events often occur after many years of clinically overt hypertension, the currently available trial results do not provide robust data on long-term outcomes after RDN in TRH patients. Uncertainty remains about the exact patient population who would benefit from RDN as well as the extent of the additional benefit.

Unzureichende Evidenz zu Lebensqualität und kardiovaskulären Ereignissen

None of the RCTs assessed quality of life of patients and the evidence was insufficient to assess a potential effect on mortality or cardiovascular events as these results were affected by high statistical imprecision. Future trials should emphasise on more direct outcome measures using longer follow-up periods.

6 Evidence-based conclusion

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: Evidence based recommendations

	Strong evidence for added benefit in routine use
	Evidence indicates added benefit only in specific indications
X	**Less robust evidence indicating an added benefit in routine use or in specific indications**
	No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest
	Strong evidence indicates that intervention is ineffective and or harmful

Reasoning:

The current evidence indicates that renal denervation yields an added benefit in terms of lowering blood pressure when used as an adjunct treatment in patient who are treatment resistant or do not tolerate antihypertensive medication. However, uncertainties exist regarding exact patient populations who would benefit most from renal denervation and the magnitude of benefit.

Evidenz deutet auf Zusatznutzen bei Patient*innen mit TRH hin

The re-evaluation is recommended in 2026 if new randomised controlled trials are likely to change the available evidence.

Re-Evaluierung 2026, bei Vorliegen neuer Ergebnisse

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Ultrasound renal denervation: Results from randomised controlled trials

Study name	RADIANCE HTN SOLO	RADIANCE HTN TRIO	RADIANCE II	REQUIRE
Publications; first author, year	**Azizi, 2018 [43]; Azizi, 2019 (6m FU) [52]; Azizi, 2020 (12m FU) [50]**	**Azizi, 2021 [41]; Azizi, 2022 (6m FU) [51]**	**Azizi, 2023 [42]**	**Kario, 2022 [44]**
NCT	**NCT02649426**	**NCT02649426**	**NCT03614260**	**NCT02918305**
Country	USA, Europe	USA, Europe	USA, Europe	Japan, South Korea
Sponsor	ReCor Medical	ReCor Medical	ReCor Medical	JIMRO, Korea Otsuka Pharmaceuticals
Intervention/Product	U-RDN (Paradise™ system, ReCor Medical)	U-RDN (Paradise™ system, ReCor Medical)	U-RDN (Paradise™ system, ReCor Medical)	U-RDN (Paradise™ system, ReCor Medical)
Comparator	Sham procedure	Sham procedure	Sham procedure	Sham procedure
Study design	Multi-centre RCT	Multi-centre RCT	Multi-centre RCT	Multi-centre RCT
Study duration	03/2016 – 12/2017	03/2016 – 03/2020	01/2019 – 03/2022	01/2017 – 03/2020
Blinding	Patients, outcome assessors	Patients, outcome assessors	Patients, outcome assessors	Patients, outcome assessors
Primary endpoints	EFF: Mean change in daytime systolic ABP at 2 months.	EFF: Change in daytime systolic ABP at 2 months	EFF: Mean change in daytime systolic ABP at 2 months SAF: Composite endpoint of major adverse events	EFF: Change in 24h systolic ABP at 3 months
Number of pts	146 (74 vs 72)	136 (69 vs 67)	224 (150 vs 74)	143 (72 vs 71)
Loss to FU, n (%)	2m: 0 (0) vs 0 (0) Post hoc FU: 6m[29]: 5 (7) vs 1 (1) 12m: 9 (12) vs 5 (7)	2m: 6 (9)[30] vs 0 (0) Post hoc FU: 6m: 4 (6) vs 3 (4)[29]	5 (2) vs 1 (1)	1 (1) vs 4 (6)

[29] Continued blinding

[30] Baseline ABP values were imputed at 2-month follow-up.

Study name	RADIANCE HTN SOLO	RADIANCE HTN TRIO	RADIANCE II	REQUIRE
Publications; first author, year	**Azizi, 2018 [43]; Azizi, 2019 (6m FU) [52]; Azizi, 2020 (12m FU) [50]**	**Azizi, 2021 [41]; Azizi, 2022 (6m FU) [51]**	**Azizi, 2023 [42]**	**Kario, 2022 [44]**
NCT	**NCT02649426**	**NCT02649426**	**NCT03614260**	**NCT02918305**
Inclusion criteria	■ Men or women aged 18-75 years with combined systolic – diastolic hypertension ■ For patient with controlled hypertension on 1-2 antihypertensive medications: average seated office BP <140/90 mmHg ■ For patients with uncontrolled hypertension on 0-2 medications: average seated office SBP/DBP of ≥140/90 mmHg, but <180/110 mmHg ■ After 4 week medication washout, daytime systolic/diastolic ABP ≥135/85 mmHg and ≤170/105 mmHg ■ eGFR of greater than or equal to 40 mL/min per 1.73 m^2 (based on the Modification of Diet in Renal Disease formula) and no history of cardiovascular or cerebrovascular events.	■ Men or women aged 18-75 years ■ TRH on min 3 medication despite three or more antihypertensive medications including a diuretic ■ Office BP ≥140/90 mmHg	■ Average office BP ≥140/90 mmHg and <180/120 mmHg while stable for at least 4 weeks on 0-2 classes of anti-hypertensive medication ■ Documented daytime ABP ≥135/85 mmHg and <170/105 mmHg after 4-week washout/run-in period ■ Previously or currently prescribed anti-hypertensive therapy	■ resistant hypertension defined as: ■ Average office BP ≥150/90 mm Hg and ■ 24h systolic ABP ≥140 mmHg despite 3 antihypertensiva including a diuretic with suitable renal artery anatomy
Age of patients, yrs (SD)	54.4 (10.2) vs 53.8 (10.0)	52.3 (7.5) vs 52.8 (9.1)	55.1 (9.9) vs 54.9 (7.9)	50.7 (11.4) vs 55.6 (12.1)
Male, n (%)	46 (62) vs 39 (54)	56 (81) vs 53 (79)	103 (69) vs 57 (77)	48 (70) vs 53 (79)
Antihypertensive Medication (at time of procedure) Yes/No	No[31]	Yes	No	Yes
Antihypertensive medication during FU	Use of medication post procedure was only assessed by patient/physician reports	Adherence to medication was assessed by urinalysis All patients on same 3in1 up until 2m, then stepped care antihypertensive treatment initiated if BP >135/85 mmHg Number of patients adhering to medication at FU: 41 (82%) vs 47 (82%)	Adherence to remain off medication was assessed by urinalysis but samples only availabe in 13/47 (9%) and 4/50 (8%) patients at FU	Patients to continue same medication regime No objective assessment of adherence
Antihypertensive medications, n (%)	0: 12 (16) vs 16 (22) 1: 33 (45) vs 28 (39) 2: 28 (38) vs 27 (38) 3: 1 (1) vs 1 (1)	Baseline, mean (SD): 4.0 (1.0) vs 3.9 (1.1) 3: 27 (39) vs 28 (42) 4: 22 (32) vs 24 (36) ≥5: 20 (29) vs 15 (22)	1: 52 (35) vs 25 (34) 2: 44 (29) vs 25 (34) >2: 0 (0) vs 1 (1)	Baseline, mean (SD): 4.1 (1.6) vs 3.9 (1.1) 3: 32 (46) vs 29 (43) 4: 20 (29) vs 23 (34) ≥5: 17 (25) vs 15 (22)
Comorbidities, n (%)	Abdominal obesity: 41 (56) vs 44 (61) T2D: 2 (3) vs 5 (7) Obstructive sleep apnoea: 6 (8) vs 8 (11)	T2D: 21 (30) vs 17 (25) Obstructive sleep apnoea: 19 (28) vs 11 (16)	Obstructive sleep apnoea: 21 (14) vs 13 (18)	Diabetes: 18 (26) vs 20 (30) Obstructive sleep apnoea: 11 (16) vs 8 (12)
Follow-up (months)	2 Post hoc long-term FU: 6, 12[32]	2	2	3

[31] Patients could be reintroduced to drugs after 2-month follow-up period of the primary analysis.

Study name	RADIANCE HTN SOLO		RADIANCE HTN TRIO		RADIANCE II	REQUIRE
Publications; first author, year	Azizi, 2018 [43]; Azizi, 2019 (6m FU) [52]; Azizi, 2020 (12m FU) [50]		Azizi, 2021 [41]; Azizi, 2022 (6m FU) [51]		Azizi, 2023 [42]	Kario, 2022 [44]
NCT	NCT02649426		NCT02649426		NCT03614260	NCT02918305
Outcomes						
Efficacy						
	Primary analysis	**Long-term FU**	**Primary analysis**	**6m FU**	**Primary analysis**	**Primary analysis**
All cause mortality, n (%)	0 (0) vs 0 (0)	**6m:** 0 (0) vs 0 (0) **12m:** 0 (0) vs 1 (1)	30 days: 1 (1) vs 0 (0)[33]	> 30 days: 0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
CVS mortality, n (%)	0 (0) vs 0 (0)	**6m:** 0 (0) vs 0 (0) **12m:** 0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
Major CVS events, n (%)	0 (0) vs 0 (0)	**At 6m:** Hypertensive crisis: 0 (0) vs 2 (3) Stroke 0 (0) vs 1 (1) No new events at 12m	**At 2m:** Acute myocardial infarction (STEMI or non-STEMI): 1 (1) vs 0 (0) Any coronary revascularisation: 0 (0) vs 1 (1)	Hypertensive crisis: 0 (0) vs 1 (1) Stroke, transient ischemic attack, cerebrovascular accident: 0 (0) vs 1 (1) AMI: 1 (1) vs 1 (1) Any coronary revascularization: 2 (3) vs 1 (1)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
BLOOD PRESSURE control, changes in mmHg	Mean (SD or 95% CI)		Mean (SD) or Median (IQR)		Mean (SR or 95% CI)	LSM (SE)
Changes in office systolic BP	-10.8 (13.6) vs -3.9 (17.4) BGD: -6.5 (-11.3 to -1.8), **p=0.007**	**6m:** -18.2 (14.2) vs -15.9 (17.2) BGD: -1.6 (-6.1 to 2.8) p=0.471 **12m:** -18.1 (14.9) vs -13.6 (17.2) BGD: -4.3 (-9.2 to 0.7), p=0.091	-9.0 (-19.5 to -1.5) vs -4.0 (-12.0 to 9.0) BGD: -7.0 (-13.0 to 0.0), **p=0.037**	6m: -10.4 ± 16.8 vs. -11.2 ± 22.7 BGD: 0.7 (-5.3, 6.6), p=0.93	-11.0 (13.5) vs -5.5 (12.9) BGD: -5.5 (-9.2 to -1.8), **p=0.004**	-11.0 (2.1) vs -9.0 (2.1) BGD: -2.0 (3.0), p=0.511
Changes in office diastolic BP	-5.5 (8.4) vs -1.2 (10.0) BGD: -4.1 (-7.0 to -1.3), **p=0.005**	**6m:** -10.1 (9.6) vs -9.5 (10.1) BGD: -0.3 (-3.2 to 2.6), p=0.847 **12m:** -9.7 (9.8) vs -8.4 (11.5) BGD: -1.1 (-4.4 to 2.2), p=0.527	-5.0 (-13.5 to 2.5) vs -1.0 (-7.0 to 6.0) BGD: -4.0 (-9.0 to 0.0), p=0.16	-6.6 ± 11.5 vs -7.5 ± 13.7 BGD: 1.9 (-1.9, 5.7), p= 0.32	-5.9 (9.4) vs -3.3 (9.2) BGD: -2.4 (-5.1 to 0.2), p=0 .07	-4.9 (1.5) vs -5.0 (1.5) BGD: 0.1 (2.1), p=0.946

[32] Patients remained blinded until 6 months.

[33] "Sudden death unrelated to the device or procedure 21 days post-procedure"[41]

Study name	RADIANCE HTN SOLO		RADIANCE HTN TRIO		RADIANCE II	REQUIRE
Publications; first author, year	Azizi, 2018 [43]; Azizi, 2019 (6m FU) [52]; Azizi, 2020 (12m FU) [50]		Azizi, 2021 [41]; Azizi, 2022 (6m FU) [51]		Azizi, 2023 [42]	Kario, 2022 [44]
NCT	NCT02649426		NCT02649426		NCT03614260	NCT02918305
Changes in home systolic BP	-8.1 (9.7) vs -1.1 (10.6) BGD: -7.1 (-10.4 to -3.8), **p<0.0001**	**6m:** -16.5 (12.3) vs -13.5 (12.2) BGD: -3.0 (-6.5 to 0.4), p= 0.086 **12m:** -14.7 (10.5) vs -14.1 (13.6) BGD: -0.8 (-4.6 to 3.0), p=0.683	-6.0 (-17.0 to 1.5) vs -2.0 (-9.5 to 2.0) BGD: -4.0 (-8.0 to 0.0), p=0.052	-11.5 ± 15.9 vs -8.9 ± 13.0 BGD: -2.9 (-8.0, 2.2), p=0.26	-9.0 (9.5) vs -0.9 (7.9) BGD: -7.8 (-10.4 to -5.1), **p<.001**	-8.7 (1.8) vs -6.9 (1.8) BGD: -1.8 (2.6), p=0.488
Changes in home diastolic BP	-4.9 (6.7) vs -1.3 (6.2) BGD: -3.6 (-5.6 to -1.5), **p=0.0009**	**6m:** -9.8 (7.8) vs -9.1 (7.1) BGD: -0.5 (-2.7 to 1.6), p=0.613 **12m:** -8.8 (7.4) vs -9.1 (8.3) BGD: 0.2 (-2.4 to 2.9), p=0.858	-4.0 (-9.0 to 2.0) vs -1.0 (-5.0 to 4.0) BGD: -3.0 (-6.0 to 0.0), p=0.053	-6.9 ± 10.4 vs -5.0 ± 8.5 BGD: -1.9 (-5.2, 1.5), p= 0.28	-5.1 (6.0) vs -0.3 (4.5) BGD: -4.4 (-6.0 to -2.9), **p<0.001**	-3.6 (1.1) vs -3.7 (1.1) BGD: 0.1 (1.6), p=0.949
Changes in 24h systolic ABP	-7.0 (8.6) vs -3.1 (9.7) BGD: -4.1 (-7.1 to -1.2), **p=0.006**	**6m:** -16.5 (11.8) vs -14.9 (12.8) BGD: -2 (-6.0 to 1.1), p=0.178 **12m:** -15.1 (12.4) vs -15.3 (12.4) BGD: -0.8 (-4.5 to 2.9), p=0.656	-8.5 (-15.1 to 0.0) vs -2.9 (-12.6 to 2.5) BGD: -4.2 (-8.3 to -0.3), **p=0.016**	-11.4 ± 14.1 vs -12.1 ± 14.5 BGD: 0.1 (-4.3, 4.6), p= 0.85	-7.7 (10.7) vs -1.7 (9.3) BGD: -6.3 (-9.2 to -3.4), **p<.001**	-6.6 (1.9) vs -6.5 (1.9) BGD: -0.1 (2.7), p=0.971
Changes in 24h diastolic ABP	-4.4 (5.8) vs -3.0 (6.1) BGD: -1.8 (-3.7 to 0.2), p=0.07	**6m:** -9.7 (7.3) vs -9.4 (7.8) BGD: -1.0 (-3.3 to 1.3), p=0.383 **12m:** -9.2 (7.8) vs -9.5 (7.5) BGD: -0.2 (-2.7 to 2.3), p=0.875	-5.4 (-10.4 to 0.0) vs -2.4 (-7.8 to 0.5) BGD: -2.0 (-4.5 to 0.6), p=0.12	-8.0 ± 8.9 vs -8.3 ± 9.2 BGD: 0.2 (-2.8, 3.1), p= 0.74	-5.3 (6.4) vs -1.2 (5.4) BGD: -4.1 (-5.7 to -2.4), **p<.001**	-3.6 (1.0) vs -3.3 (1.0) BGD: -0.4 (1.4), p=0.806
Changes in daytime systolic ABP	-8.5 (9.3) vs -2.2 (10.0) BGD: -6.3 (-9.4 to -3.1), **p=0.0001**	**6m:** -18.1 (12.2) vs -15.6 (13.2) BGD: -2.3 (-6.0 to 1.5), p=0.242 **12m: -**16 (12.9) vs -15.8 (13.1) BGD: -0.4 (-4.3 to 3.4), p=0.836	-8.0 (-16.4 to 0.0) vs -3.0 (-10.3 to 1.8) BGD: -4.5 (-8.5 to -0.3), **p=0.022**	-11.8 ± 14.2 vs -12.3 ± 14.2 BGD: -0.0 (-4.6, 4.5), p= 0.65	-7.9 (11.6) vs -1.8 (9.5) BGD: -6.3 (-9.4 to -3.2), **p<.001**	-8.4 (2.0) vs -7.2 (1.9) BGD: -1.2 (2.8), p=0.672
Changes in daytime diastolic ABP	-5.1 (5.9) vs -2.6 (6.5) BGD: -2.6 (-4.6 to -0.6), **p=0.01**	**6m:** -10.7 (7.8) vs -9.7 (8.1) BGD: -1.3 (-3.7 to 1.2), p=0.321 **12m:** -9.8 (8.3) vs -9.6 (7.9) BGD: -0.4 (-3.0 to 2.3), p=0.770	-4.9 (-10.4 to 0.0) vs -2.0 (-7.8 to 1.0) BGD: -1.8 (-4.5 to 0.8), p=0.18	-7.9 ± 9.1 vs -8.4 ± 9.7 BGD: 0.3 (-2.8, 3.4), p= 0.79	-5.4 (6.5) vs -1.3 (5.7) BGD: -3.9 (-5.6 to -2.2), **p<.001**	-4.8 (1.1) vs -4.0 (1.0) BGD: -0.8 (1.5), p=0.585
Changes in nightime systolic ABP	-4.8 (11.7) vs -3.1 (11.5) BGD: -2.5 (-6.0 to 0.9), p=0.15	**6m:** -13.9 (13.6) vs -12.8 (13.5) BGD: -2.7 (-6.4 to 1.0), p=0.157 **12m:** -12.9 (15.0) vs -13.6 (14.5) BGD: -1.1 (-5.5 to 3.2), p=0.607	-8.3 (-15.7 to 0.0) vs -1.8 (-16.2 to 5.0) BGD: -3.9 (-8.8 to 1.0), **p=0.044**	-10.3 ± 17.2 vs -11.6 ± 18.3 BGD: 0.3 (-4.8, 5.5), p= 0.81	-6.6 (12.8) vs -1.3 (11.3) BGD:- 5.9 (-9.1 to -2.6), **p<.001**	-4.2 (2.4) vs -4.7 (2.4) BGD: 0.5 (3.3), p=0.883
Changes in nighttime diastolic ABP	-3.3 (8.5) vs -2.7 (7.3) BGD: -1.4 (-3.8 to 1.0), p=0.25	**6m:** -7.9 (9.1) vs -8.3 (8.7) BGD: -0.8 (-3.3 to 1.7), p=0.534 **12m:** -8.0 (9.7) vs -8.9 (9.7) BGD: -0.2 (-3.2 to 2.8), p=0.888	-5.1 (-12.7 to 0.0) vs -2.0 (-9.5 to 4.1) BGD: -2.8 (-6.1 to 0.2), p=0.053	-7.9 ± 10.0 vs -7.4 ± 11.1 BGD: -0.3 (-3.7, 3.0), p= 0.85	-4.7 (8.2) vs -0.5 (6.7) BGD: -4.3 (-6.3 to -2.2), **p<.001**	-1.4 (1.3) vs -2.0 (1.3) BGD: 0.6 (1.9), p=0.770
Changes in 48h ABP	NR	NR	NR	NR	NR	NR
Quality of life	NR	NR	NR	NR	NR	NR
Hospitalisations, days	NR	NR	NR	NR	NR	NR

Study name	RADIANCE HTN SOLO		RADIANCE HTN TRIO		RADIANCE II	REQUIRE
Publications; first author, year	Azizi, 2018 [43]; Azizi, 2019 (6m FU) [52]; Azizi, 2020 (12m FU) [50]		Azizi, 2021 [41]; Azizi, 2022 (6m FU) [51]		Azizi, 2023 [42]	Kario, 2022 [44]
NCT	NCT02649426		NCT02649426		NCT03614260	NCT02918305
Safety						
(Serious) adverse events, n (%)	**SAE:** 0 (0) vs 0 (0) **At 2m:** Procedure-related pain lasting longer than 2 days: 8 (11) vs 8 (11)	**At 6m:** Stroke, transient ischemic attack, cerebrovascular accident: 0 (0) vs 1 (1) Need for renal artery angioplasty or stenting: 1 (1) vs 0 (0) New orthostatic hypotension (transient): 2 (3) vs 0 (0) No new events at 12m	Major adverse events: Procedure related: Major access site complications requiring intervention: 1(1) vs 0 (0) Further AEs: Procedure-related pain lasting for >2 days: 12 (17) vs 10 (15) **At 2m:** Doubling of plasma creatinine: 1 (1) vs 0 (0)	Major adverse events: 3 (4) vs 0 (0)[34] Vascular complication requiring intervention within 30 days: 1 (1) vs 0 (0) Doubling of serum creatinine within 30 days 1 (1) vs 0 (0) Further AEs: Procedure-related pain lasting for > 2 days 12 (17) vs 10 (15) Doubling of serum creatinine (>30 days) 1 (1) vs 0 (0)	**SAE:** **Composite outcome of major AE**[35]: 0 (0) vs 0 (0) **AE:** NR	**AE** (within 30 days): Vasospasm: 4 (6) vs 0 (0) Complications at femoral puncture site: 4 (6) vs 3 (4) Procedure-related pain lasting >2 days: 6 (8) vs 6 (9) **Procedural SAE** (3m): Vasospastic angina (Prinzmetal angina): 1 (1) vs 0 (0) Puncture site hemorrhage: 1 (1) vs 0 (0) Pyrexia: 0 (0) vs 1 (1) Cellulitis: 1 (1) vs 0 (0) Blood pressure decreased: 1 (1) vs 0 (0) Blood pressure increased: 1 (1) vs 0 (0) Postural dizziness: 1 (1) vs 0 (0) Procedure related major AEs: 0 (0) vs 0 (0)
Procedure-related mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)

Abbreviations: ABP – ambulatory blood pressure; AMI – acute myocardial infarction; BGD – between group difference; BP – blood pressure; CVS – cardiovascular; DBP – diastolic blood pressure; EFF – efficacy endpoint; FU – follow-up; h – hour(s); m – month(s); n – number; NR – not reported; pts – patients; RCT – randomised controlled trial; (S)AE – (serious) adverse event; SAF – safety endpoint; SBP – systolic blood pressure; SD – standard deviation; STEMI – ST-elevation myocardial infarction; T2D – type two diabetes; TRH – treatment-resistant hypertension; U-RDN – ultrasound renal denervation; USA – United States of America; yrs – years.

[34] Data on mortality and CVS events extracted above.

[35] Composite endpoint included "death, kidney failure, and major embolic, vascular, CVS, cerebrovascular, and hypertensive events at 30 days and renal artery stenosis greater than 70% detected at 6 months." [42]

Table A-2: Radiofrequency renal denervation: Results from randomised controlled trials (part 1)

Study name	REDUCE HTN	RESET	SPYRAL HTN-OFF MED Pivotal	
Publications; first author, year	Weber, 2020 [45]	Mathiassen, 2016 [46]	Pilot: Townsend, 2017 [56]	Primary analysis: Böhm, 2020 [47]
NCT	NCT02392351	NCT01459900	NCT02439749	
Country	USA	Denmark	Australia, Europe, Japan, North America	
Sponsor	Boston Scientific	Supported by a grant from the Danish Heart Foundation	Medtronic	
Intervention/Product	RF-RDN (Vessix™ system, Boston Scientific)	RF-RDN (Unipolar Flex catheter, Medtronic)	RF-RDN (Symplicity™ system, Medtronic)	
Comparator	Sham procedure	Sham procedure	Sham procedure	
Study design	Multi-centre RCT	Single-centre RCT	Multi-center RCT	
Study duration	04/2015 – 10/2017	09/2011 – 02/2015	06/2015 – 01/2017	06/2015 – 10/2019
Blinding	Patients, outcome assessors	Patients, outcome assessors	Patients, outcome assessors	
Primary endpoints	EFF: Comparison of mean reduction in average 24h systolic ABP after 8 weeks	EFF: Mean change in daytime systolic ABP from baseline at 3 months	EFF: Baseline adjusted change in 24h systolic ABP at 3 months	
Number of pts	51[36] (34 vs 17)	69 (36 vs 33)	80 (38 vs 42)	331 (166 vs 165)[37]
Loss to FU, n (%)	2m: 1 (3) vs 0 (0) 6m: 1 (3) vs 0 (0) 12m: 0 (0) vs 2 (12)	0 (0) vs 0 (0)	Escape pts: 2 (5) vs 4 (10) 24h BP loss to FU: 3 (8) vs 8 (19) Office BP loss to FU: 2 (5) vs 4 (10)	Clinical loss to FU: 4 (2) vs 1 (1) 24h BP loss to FU: 20 (12) vs 30 (18) Office BP loss to FU: 6 (4) vs 14 (8)
Inclusion criteria	■ 18-75 years old ■ With uncontrolled hypertension on medication ■ Office SBP≥150 mmHg and ≤180 mmHg ■ After 4-week medication washout, average 24h SBP of ≥135 mmHg and ≤170 mmHg	■ 30-70 years old ■ Daytime systolic ABP ≥145 mmHg (preceded by 14 days of scheduled drug intake showing at least 85% adherence) ■ One month of stable antihypertensive treatment with at least three antihypertensive agents including a diuretic (or in case of diuretics intolerance a minimum of three nondiuretic antihypertensive drugs)	■ 20-80 years old ■ Mean 24h systolic ABP ≥140 mmHg and <170 mmHg ■ Office SBP ≥150 mmHg and <180 mmHg ■ Office DBP ≥90 mmHg ■ Willingness to discontinue current antihypertensive medication at screening	
Age of patients, mean yrs (SD)	58.5 (10.1) vs 58.2 (9.8)	54.3 (7.8) vs 57.1 (9.6)	55.8 (10.1) vs 52.8 (11.5)	52.4 (10.9) vs 52.6 (10.4)
Male, n (%)	18 (53) vs 13 (77)	27 (75) vs 24 (73)	26 (68) vs 31 (74)	107 (64) vs 113 (68)

[36] During the "*trial, a pilot analysis indicated no possibility of achieving a significant treatment effect on BP by the 8-week primary endpoint according to pre-defined statistical decision rules, so recruitment to the trial was terminated*". [Weber, 2020]

[37] 80 from pilot, 251 from pivotal

Study name	REDUCE HTN	RESET	SPYRAL HTN-OFF MED Pivotal	
Publications; first author, year	**Weber, 2020 [45]**	**Mathiassen, 2016 [46]**	**Pilot: Townsend, 2017 [56]**	**Primary analysis: Böhm, 2020 [47]**
NCT	**NCT02392351**	**NCT01459900**	**NCT02439749**	
Antihypertensive Medication (at time of procedure) Yes/No	No	Yes	No[38]	
Antihypertensive Medication during FU	Patients to remain off medication for 8 weeks but not information on how or whether adherence was assessed	Patients continued on same medication unless change was required for medical reason and to adjust for confounding in the analysis, they assumed a change of 5 mmHg per added/removed medication but adherence was not officially assessed	Patients had to remain off medication for 3 months and compliance was assessed with urine and plasma sampling at baseline and 3 month FU.	
Antihypertensive medications, n (%)	NA	Baseline, mean (±SD): 4.1 (1.2) vs 4.2 (1.1)	NA	NA
Comorbidities, n (%)	Obstructive sleep apnoea: 7 (21) vs 1 (6)	Obstructive sleep apnoea: 3 (8) vs 4 (12) Potentially: History of coronary heart disease: 2 (6) vs 5 (15)	Current smoker: 4 (11) vs 10 (24) T2D: 1 (3) vs 3 (7) Obstructive sleep apnoea: 3 (8) vs 3 (7)	T2D: 6 (4) vs 9 (5) Obstructive sleep apnea: 14 (8) vs 12 (7)
Follow-up (months)	**2**, 6, 12	1, **3**, 6	3	
Outcomes				
Efficacy				
	Primary analysis	**Primary analysis**	**Pilot**	**Primary analysis**
All cause mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
CVS mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
Major CVS events, n (%)	0 (0) vs 0 (0)	Total: 1 (3) vs 4 (12) Stroke: 0 (0) vs 1 (3) Percutanous coronary intervention: 0 (0) vs 1 (3) Hospitalisation due to increasing BPs: 1 (3) vs 2 (6)	0 (0) vs 0 (0)	Total: 1 (1) vs 1 (1) Hypertensive crisis/emergency: 1 (1) vs 0 (0) Stroke: 0 (0) vs 1 (1)
BLOOD PRESSURE control, changes in mmHg	Mean (95% CI)	Mean (±SD)	Mean (95% CI)	Mean (95% CI)

[38] Required to discontinue before randomisation.

Study name	REDUCE HTN	RESET	SPYRAL HTN-OFF MED Pivotal	
Publications; first author, year	Weber, 2020 [45]	Mathiassen, 2016 [46]	Pilot: Townsend, 2017 [56]	Primary analysis: Böhm, 2020 [47]
NCT	NCT02392351	NCT01459900	NCT02439749	
Changes in office systolic BP	**2m:** -5.2 (0.4 to -10.8)[39] vs -7.1 (2.2 to -16.5) BGD: 1.7 (-8 to 11.8), p=0.749 **6m:** -26.2 (-21.7 to -30.6) vs -14.8 (-8.3 to -21.3) BGD: -11.0 (-18.9 to -3.1), **p=0.009** **12m:** -25.4 (-18.2 to -32.3) vs -15.3 (-7.0 to -23.8) BGD: -10.5 (-21.01 to 0.1), p=0.06	NR	-10.0 (-15.1 to -4.9) vs -2.3 (-6.1 to 1.6) BGD: -7.7 (-14 to -1.5), **p=0.016**	-10.9 (12.9) vs -4.1 (11.8)[40] BGD: -6.6 (-9.4 to -3.8), **p<.001**
Changes in office diastolic BP	**2m:** -2.5 (0.1 to -5.5) vs -4.8 (0.1 to -10.1) BGD: 2.2 (-5.7 to 10.2), p=0.583 **6m:** -12.9 (-10 to -16.1) vs -7.5 (-4.1 to -11.1) BGD: -5.1 (-11.9 to 1.7), p=15 **12m:** -13.0 (-8.6 to -17.7) vs -8.1 (-3.3 to -13.3) BGD: -3.3 (-10.9 to 4.2), p=393	NR	-5.3 (-7.8 to -2.7) vs -0.3 (-2.9 to 2.2) BGD: -4.9 (-8.5 to -1.4), **p=0.008**	-5.6 (7.9) vs -1.8 (7.9) BGD: -4.0 (-5.8 to -2.3), **p<.001**
Changes in home systolic BP	NR	NR	NR	NR
Changes in home diastolic BP	NR	NR	NR	NR
Changes in 24h systolic ABP	**2m:** -5.3 (-1.8 to -8.8) vs -8.5 (-3.9 to -13.4) BGD: 3.3 (-4.4 to 11.1), p=0.407 **6m:** -16.7 (-11.8 to -21.7) vs -9.5 (3.7 to -15.2) BGD: -7.4 (-15.2 to 0.4), p=0.071 **12m:** -18.2 (-13.1 to -23.6) vs -14.3 (-9.5 to -19.1) BGD: -4.9 (-13.4 to 3.6), p=0.266	**1m:** -4.5 (11.2) vs 0.6 (12.8) BGD: p=0.10 **3m:** -3.9±17.0 vs -4.4±12.0 BGD: p=0.88 **6m:** -3.7±16.4 vs -2.6±12.8 BGD: p=0.76	-5.5 (-9.1 to -2.0) vs -0.5 (-3.9 to 2.9) BGD: -5.0 (-9.9 t0 -0.2), **p=0.041**	-4.6 (10.4) vs -0.8 (8.6) BGD: -3.6 (-5.9 to -1.4), **p=0.002**
Changes in 24h diastolic ABP	**2m:** -2.6 (-0.3 to -4.9) vs -4.6 (-2.4 to -6.8) BGD: 2.8 (-2.7 to 8.3), p=0.328 **6m:** -9.1 (-6.1 to -12.1) vs -5.5 (-1.3 to -9.6) BGD: -3.1 (-9.0 to 2.9), p=0.317 **12m:** -11.0 (-7.5 to -14.6) vs -9.0 (-5.8 to -12.2) BGD: -4.4 (-10.2 to 1.5), p=0.154	**1m:** -2.6 (6.3) vs 0.0 (6.6) BGD: p=0.12 **3m:** -1.3 (9.7) vs -2.7 (5.6) BGD: p=0.47 **6m:** -1.7 (8.6) vs -2.6 (7.5) BGD: p=0.64	-4.8 (-7.0 to -2.6) vs -0.4 (-2.2 to 1.4) BGD: -4.4 (-7.2 to -1.6), **p=0.002**	-3.7 (6.6) vs -1.0 (5.3) BGD: -2.9 (-4.4 to -1.5), **p<.001**
Changes in daytime systolic ABP	**2m:** BGD: 4.9 (-3.2 to 12.9), p=0.241 **6m:** BGD: -9.4 (-17.5 to -1.2), **p=0.029**	**1m:** -6.0 (11.0) vs 0.0 (15) BGD: p=0.08 **3m:** -6.2 (18.8) vs -6.0 (13.5) BGD: p=0.95	NR	NR

[39] Confidence-intervals for within group differences were estimated via the tool WebPlotDigitizer https://apps.automeris.io/wpd/.

[40] The authors primarily report results from a Bayesian analysis. The also reported frequentist ANCOVA-adjusted analyses results were extracted for BP values and BGD differences.

Study name	REDUCE HTN	RESET	SPYRAL HTN-OFF MED Pivotal	
Publications; first author, year	Weber, 2020 [45]	Mathiassen, 2016 [46]	Pilot: Townsend, 2017 [56]	Primary analysis: Böhm, 2020 [47]
NCT	NCT02392351	NCT01459900	NCT02439749	
Changes in daytime systolic ABP *(continuation)*	**12m:** BGD: -4.6 (-12.7 zo 3.6), p=0.277	**6m:** -6.1 (18.9) vs -4.3 (15.1) BGD: p=0.66		
Changes in daytime diastolic ABP	**2m:** BGD: 4.5 (-1.0, 10.0), p=0.116 **6m:** BGD: -3.7 (-10.3 to 2.9), p=0.278 **12m:** BGD: -4.6 (-10.8 to 1.7), p=0.16	**1m:** -4.2 (6.6) vs 0.2 (8.4) BGD: **p<.05** **3m:** -2.4 (10.3) vs -3.2 (6.2) BGD: p=0.71 **6m:** -3.2 (10.8) vs -3.6 (8.3) BGD: p=0.87	NR	NR
Changes in nightime systolic ABP	**2m:** BGD: 0.1 (-9.7 to 9.9), p=0.986 **6m:** BGD: -5.0 (-14.3 to 4.3), p=0.297 **12m:** BGD: -5.9 (-16.3 to 4.5), p=0.272	**1m:** -2.8 (17.2) vs 0.7 (15.0) BGD: p=0.39 **3m:** -0.4 (20.5) vs -4.7 (16.6) BGD: p=0.35 **6m:** -1.4±18.2 vs -1.1±14.4 BGD: p=0.95	NR	NR
Changes in nighttime diastolic ABP	**2m:** BGD: 0.1 (-6.9 to 7.2), p= 0.971 **6m:** BGD: -1.7 (-8.0 to 4.6), p=0.597 **12m:** BGD: -4.6 (-11.2 to 2.1), p=0.186	**1m:** -1.7 (10.5) vs 0.4 (7.7) BGD: p=0.39 **3m:** 0.8 (13.4) vs -2.6 (8.9) BGD: p=0.23 **6m:** -0.6 (10.1) vs -0.7 (8.8) BGD: p=0.97	NR	NR
Changes in 48h ABP	NR	NR	NR	NR
Quality of life	NR	NR	NR	NR
Hospitalisations, days	NR	NR	NR	NR
Safety				
AE, n (%)	0 (0) vs 0 (0)	Minor symptoms such as tiredness, headache, atypical chest pain, muscle convulsions and fatigue: 5 (14) vs 6 (18)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
Procedure-related mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)

Abbreviations: ABP – ambulatory blood pressure; AE – adverse event; BP – blood pressure; BGD – between group difference; CI – confidence interval; CVS – cardiovascular; DBP – diastolic blood pressure; EFF – efficacy endpoint; eGFR – estimated glomerular filtration rate; FU – follow-up; h – hour(s); m – month(s); n – number of people; NR – not reported; pts – patients; RCT – randomised control trial; RF-RDN – radiofrequency renal denervation; SBP – systolic blood pressure; SD – standard deviation; T2D – type 2 diabetes; yrs – years.

Table A-2: Radiofrequency renal denervation: Results from randomised controlled trials (part 2)

Study name	**SPYRAL HTN-ON MED Expansion**		**SYMPLICITY FLEX**
Publications; first author, year	**Pilot: Kandzari, 2018 [57]; Mahfoud 2022 (36m FU) [53]**	**Primary analysis: Kandzari, 2023 [48]**	**Desch, 2015 [58]**
NCT	**NCT02439775**		**NCT01656096**
Country	Australia, Europe, Japan, North America		Germany
Sponsor	Medtronic		Heart Center of University of Leipzig
Intervention/Product	RF-RDN (Symplicity™ system, Medtronic)		RF-RDN (Symplicity™ system, Medtronic)
Comparator	Sham procedure		Sham procedure
Study design	Multi-centre RCT		RCT
Study duration	07/2014 – 07/2017	07/2015 – 08/2022	NR
Blinding	Patients, outcome assessors		Patients, outcome assessors, other investigators
Primary endpoints	EFF: Change in ABP at 6 months	EFF: ANCOVA-adjusted change in 24 h systolic ABP SAF: Composite of major adverse events in first consecutive 253 patients within 1 month post procedure	EFF: Change in 24h systolic ABP at 6 months
Number of pts	80 (38 vs 42)	337[41] (206 vs 131)	71 (35 vs 36)
Loss to FU, n (%)	**Pilot (6m):** 0 (0) vs 0 (0) **Long term FU:** **24m:** 24h BP loss to FU: 5 (13) vs 25 (60) Office BP loss to FU: 4 (11) vs 25 (60) **36m[42]:** 24h BP loss to FU: 8 (21) vs 23 (55) Office BP loss to FU: 5 (13) vs 21 (50)	24h BP loss to FU: 14 (7) vs 15 (11) Office BP loss to FU: 7 (3) vs 5 (4)	3 (9) vs 1 (3)
Inclusion criteria	■ Mean 24h systolic ABP between 140-170 mmHg ■ Office SBP 150-180 mmHg ■ Office DBP≥90 mmHg ■ 1-3 antiypertensiva at ≥50% of max reccomended dosage. In Japan for thiazide diuretics doses of less than 50% were allowed ■ Drug adherence confirmed by independend laboratory ■ Suitable anatomy confirmed by renal angiogram		■ 18-75 years old ■ Mean daytime SBP on 24h ABP 135-149 mmHg or mean daytime DBP 90-94 mmHg ■ Stable antihypertensive drug regimen of ≥3 agents of different classess, including a diuretic (except when not tolerated/contraindicated) at optimal dosage without change in the 4 weeks preceding randomization

[41] Includes 80 patients from the pilot trial

[42] 13 further patients crossed over and had RDN performed. Their BP measurements prior to the cross over were imputed into the 36-month analysis.

Study name	SPYRAL HTN-ON MED Expansion			SYMPLICITY FLEX
Publications; first author, year	Pilot: Kandzari, 2018 [57]; Mahfoud 2022 (36m FU) [53]		Primary analysis: Kandzari, 2023 [48]	Desch, 2015 [58]
NCT	NCT02439775			NCT01656096
Age of patients, yrs (SD)	53.9 (8.7) vs 53.0 (10.7)		55.2 (9.0) vs 54.6 (9.4)	64.5 (7.6) vs 57.4 (8.6), **p<.001**
Male, n (%)	33 (87) vs 34 (81)		167 (81) vs 103 (79)	27 (77) vs 25 (69)
Antihypertensive Medication (at time of procedure) Yes/No	Yes		Yes	Yes
Antihypertensive medication during FU	Patients continued on their same prescribed drug regime unless escape criteria were met and at FU visits urine and blood analysis was performed to assess adherence as well as witnessing patients taking the BP medication prior to 24h ABP measuring was initiated. 36m: 3.03±1.2 vs 3.05±1.43; p=0.76			Patients had to remain on same medication profile 2 weeks prior procedure and during FU. Prior to the procedure adherence was assessed by patients prospectively recording it, during the FU period this was only assessed by asking patients, no formal urinalysis etc.
Antihypertensive medications, n (%)	Baseline, mean (SD): 2.2 (0.9) vs 2.3 (0.8)		Baseline, mean (SD): 1.9 (0.9) vs 1.9 (0.8) 1: 80 (39) vs 47 (36) 2: 67 (33) vs 47 (36) 3: 59 (29) vs 37 (28)	Baseline, mean (SD): 4.4 (1.3) vs 4.3 (1.3) N Patients with ≥5 hypertensive agents: 14 (40) vs 14 (39)
Comorbidities, n (%)	Obstructive sleep apnea: 2 (5) vs 10 (24)		Currently using CPAP/BiPAP: 16 (8) vs 21 (16), **p<0.05** Obstructive sleep apnea: 23 (11) vs 23 (18)	Diabetes: 19 (54) vs 13 (36)
Follow-up (months)	6 Post hoc long term FU: 24, 36		6	6
Outcomes				
Efficacy				
	Primary interim analysis	**Long term FU**	**Primary analysis**	**Primary analysis**
All cause mortality, n (%)	0 (0) vs 0 (0)	**At 36m:** 0 (0) vs 1 (2)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
CVD mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)
Major CVD events, n (%)	0 (0) vs 0 (0)	Hypertensive crisis and stroke[43]: 1 (3) vs 0 (0)	Stroke: 0 (0) vs 1 (1)	0 (0) vs 0 (0)
BLOOD PRESSURE control, changes in mmHg	Mean (SD or 95% CI)	Mean (SD or 95% CI)	Mean (SD or 95% CI)	Mean (95% CI)

[43] Both in one patient.

Study name	SPYRAL HTN-ON MED Expansion			SYMPLICITY FLEX
Publications; first author, year	Pilot: Kandzari, 2018 [57]; Mahfoud 2022 (36m FU) [53]		Primary analysis: Kandzari, 2023 [48]	Desch, 2015 [58]
NCT	NCT02439775			NCT01656096
Changes in office systolic BP	-9.4 (12.5) vs -2.6 (12.9) BGD: -6.8 (-12.5 to -1.1), p=0.0250	**24m:** -19.3 vs -7.8[44] BGD: -11.1 (-21.6 to -0.5), **p=0.041** **36m:** -20.9 vs -12.5 BGD: -8.2 (-17.1 to 0.8), p=0.073	-9.9 (13.9) vs -5.1 (13.2) BGD: -4.9 (-7.9 to -1.0), p=0.0015[45]	NR
Changes in office diastolic BP	-5.2 (7.6) vs -1.7 (7.9) BGD: -3.5 (-7.0 to 0.0), p=0.0478	**24m:** -10.7 vs -2.7 BGD: -8.5 (-15.0 to -2.1), **p=0.01** **36m:** -10.4 vs -7.2 BGD: -9.8 (-9.8 to1.9), p=0.186	-5.2 (8.8) vs -3.3 (8.2) BGD: -2.0 (-3.9 to -0.1), **p=0.041**	NR
Changes in home systolic BP	NR	NR	NR	NR
Changes in home diastolic BP	NR	NR	NR	NR
Changes in 24h systolic ABP	-9.0 (11.0) vs -1.6 (10.7) BGD: -7.4 (-12.5 to -2.3), **p=0.0051**	**24m:** -16.0 vs -4.7 BGD: -11.2 (-18.4 to -4.0), **p=0.0031** **36m:** -18.7 (12.4) vs -8.6 (14.6) BGD: -10.0 (-16.6 to -3.3), **p=0.0039**	-6.5 (10.7) vs -4 (10.3) BGD: -1.9 (-4.4 to 0.5), p=0.12	-7.0 (-10.8 to -3.2) vs -3.5 (-6.7 to -0.2) BGD[46]: p=0.15
Changes in 24h diastolic ABP	-6.0 (7.4) vs -1.9 (8.2) BGD: -4.1 (-7.8 to -0.4), **p=0.0292**	**24m:** -10.5 vs -5.0 BGD: -5.7 (-10.6 vs -0.7), **p=0.025** **36m:** -11.9 vs -6.0 BGD: -5.9 (-10.1 to -1.8), **p=0.0055**	-4.4 (7.3) vs -3.4 (7.6) BGD: -0.8 (-2.4 to 0.9), p=0.37	-2.8 (-4.8 to -0.99 vs -2.1 (-3.9 to -0.2) BDG: p=0.57
Changes in daytime systolic ABP	-8.8 (11.3) vs -3.2 (11.4) BGD: -5.7 (-11.0 to -0.3), **p=0.039**	**24m:** -15.4 to -6.2 BGD: -10.2 (-18.0 to -2.3), **p=0.013** **36m:** -18.3 vs -10.5 BGD: -8.9 (-16.5 to -1.2), **p=0.024**	NR	-8.5 (-12.3 to -4.6) vs -3.7 (-7.0 to -0.3) BGD: p=0.06
Changes in daytime diastolic ABP	-6.3 (7.9) vs -2.8 (8.3) BGD: -3.5 (-7.3 to 0.3), p=0.0691	**24m:** -10.0 vs -6.7 BGD: -4.2 (-9.7 to 1.3), p=0.134 **36m:**-11.7 vs -7.8 BGD: -4.3 (-8.7 to 0.1), p=0.057	NR	-3.5 (-5.5 to -1.5) vs -1.9 (-3.9 to 0) BGD: p=0.26

[44] Confidence intervals/ SDs for within group BP values not reported.

[45] p-values for BP BGD were ANCOVA adjusted for BP variance.

[46] BGD values and confidence intervals not reported.

Study name	SPYRAL HTN-ON MED Expansion			SYMPLICITY FLEX
Publications; first author, year	Pilot: Kandzari, 2018 [57]; Mahfoud 2022 (36m FU) [53]		Primary analysis: Kandzari, 2023 [48]	Desch, 2015 [58]
NCT	NCT02439775			NCT01656096
Changes in nightime systolic ABP	-9.8 (13.9) vs 2.1 (13.5) BGD: -11.9 (-18.2 to -5.6), **p=0.0003**	**24m:** -16.5 vs -0.7 BGD: -12.9 (-21.1 to -4.7), **p=0.0026** **36m:** -19.3 vs -6.6 BGD: -11.8 (-19.0 to -4.7), **p=0.0017**	NR	-1.9 (-6.9 to 3.0) vs -3.8 (-8.1 to 0.5) BGD: p=0.56
Changes in nighttime diastolic ABP	-5.9 (9.7) vs -0.3 (10.2) BGD: -5.6 (-10.2 to -1.1), **p=0.0167**	**24m:** -11.2 vs -3.1 BGD: -7.1 (-12.8 to -1.4), **p=0.016** **36m:** -13.1 vs -5.1 BGD: -7.5 (-12.8 to -2.2), p=0.006	NR	-0.3 (-2.9 to 2.4) vs -2.4 (-4.8 to 0) BGD: p=0.23
Changes in 48h ABP	NR	NR	NR	NR
Quality of life	NR	NR	NR	NR
Hospitalisations, days	NR	NR	NR	NR
(S)AE, n (%)	0 (0) vs 0 (0)	**36m:** Composite SAE[47]: 1 (2) vs 1 (7)	Vascular complications (requiring surgical repair, intervention procedure thrombin, or blood transfusion): 2 (1) vs 1 (1)	0 (0) vs 0 (0)
Procedure-related mortality, n (%)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)	0 (0) vs 0 (0)

Abbreviations: ABP – ambulatory blood pressure; BGD – between group difference; BiPAP – bilevel positive airway pressure; BP – blood pressure; CI – confidence interval; CPAP – continuous positive airway pressure; DBP – diastolic blood pressure; EFF – efficacy endpoint; FU – follow-up; h – hour(s); n – number; NR – not reported; pts – patients; RCT – randomised control trial; RF-RDN – radiofrequency renal denervation; (S)AE – (serious) adverse event; SAF – safety endpoint; SBP – systolic blood pressure; SD – standard deviation; yrs – years.

[47] "*Defined as a composite of all-cause mortality, end-stage renal disease, embolic event resulting in end-organ damage, renal artery perforation requiring reintervention, renal artery dissection requiring reintervention, vascular complications, hospitalisation for hypertensive crisis or emergency, or new renal artery stenosis >70%.*"

Table A-2: Radiofrequency renal denervation: Results from randomised controlled trials (part 3)

Study name	**SYMPLICITY HTN-3**	
Publications; first author, year	**Bhatt, 2014 [23]; Bakris, 2015 (12m FU) [54]; Bhatt, 2022 (36m FU) [55]**	
NCT	**NCT01418261**	
Country	USA	
Sponsor	Medtronic	
Intervention/Product	RF-RDN (Unipolar Flex catheter, Medtronic)	
Comparator	Sham procedure	
Study design	Multi-centre RCT	
Study duration	10/2011 – 05/2013	
Blinding	Patients, outcome assesors	
Primary endpoints	EFF: Comparison change in office SBP at 6 months SAF: Composite of major adverse events	
Number of pts	535 (364 vs 171)[48] After 6m: 361 vs 101 vs 70[49]	
Loss to FU, n (%)	(6m): 14 (4) vs 2 (1) **Long term FU:** 12m: 39 (11) vs 123 (72)[50] 36m: 50 (14) vs 123 (72)	
Inclusion criteria	■ 18 – 80 years ■ Resistant hypertension ■ Seated office systolic BP ≥160 mmHg and 24h systolic ABP ≥135 mmHg ■ Stable, maximally tolerated doses of ≥3 drugs, including 1 diuretic	
Age of patients, yrs (SD)	57.9 (10.4) vs 56.2 (11.2)	
Male, n (%)	215 (59) vs 110 (64)	
Antihypertensive Medication (at time of procedure) Yes/No	Yes	
Antihypertensive medication during FU	Medication use was documented over a period of 2 weeks in diaries before baseline and before the 6-month follow-up visit. We found no evidence of a significant difference in medication adherence between the groups.	
Antihypertensive medications, n (%)	Baseline, mean (SD): 5.1 (1.4) vs 5.2 (1.4)	
Comorbidities, n (%)	T2D: 171 (47) vs 70 (41) Obstructive sleep apnoea: 94 (26) vs 54 (32)	
Follow-up (months)	6 Post hoc long term FU: 12, 36[51]	
Outcomes		
Efficacy		
	Primary analysis	**Long term FU[52]**
All cause mortality, n (%)	2 (1) vs 1 (1)	**12m:** 7/355 (2) vs 2/69 (4) **36m:** 12/290 (4) vs 5/46 (11)[53]
CVD mortality, n (%)	NR	**12m:** 0 (0) vs 0 (0) **36m:** 0 (0) vs 0 (0)

[48] Randomised into a 2:1 ratio.

[49] RDN vs Crossover vs non-crossover.

[50] 101 patients in the initial sham control group received RDN after 6 months. Their last available outcome measures were imputed for the follow-up analyses.

[51] Patients were unblinded after 6 months and were able to receive RDN if they still met the inclusion criteria.

[52] Only results of RDN and non-cross over reported.

[53] The numbers from 12 months are also counted.

Study name	SYMPLICITY HTN-3	
Publications; first author, year	Bhatt, 2014 [23]; Bakris, 2015 (12m FU) [54]; Bhatt, 2022 (36m FU) [55]	
NCT	NCT01418261	
Major CVD events, n (%)	Myocardial infarction: 6 (2) vs 3 (2) Stroke: 4 (1) vs 2 (1) Hospitalisation for new-onset heart failure: 9 (3) vs 3 (2) Hypertensive crisis or emergency: 9 (3) vs 9 (5) Hospitalization for atrial fibrillation: 5 (1) vs 1 (1) Increase in serum creatinine of >50% from baseline: 5 (1) vs 1 (1)	**12m:** Hypertension crisis/emergency: 17/355 (5) vs 4/69 (6) **36m:** Hypertension crisis/emergency: 31/290 (11) vs 5/46 (11)
BLOOD PRESSURE control, changes in mmHg	Mean (95% CI)	Mean (95% CI)
Changes in office systolic BP	−14.13 (23.93) vs −11.74 (25.94) BGD: −2.39 (4.5), p=.26	**12m:** −18.9 vs −6.3 BGD: −13.4 (−17.8 to −9.0), **p≤.0001** **36m:** −26.4 vs −5.7 BGD: −22.1 (−27.2 to −17.0), **p≤.0001**
Changes in office diastolic BP	−6.6 (11.9) vs −4.6 (13.6) BGD[54]: p=0.12	**12m:** −7.8 vs −2.3 BGD: −6.2 (−8.6 to −3.9), **p≤.0001** **36m:** −12.2 vs −2.0 BGD: −12.0 (−14.6 to −9.3), **p≤.0001**
Changes in home systolic BP	−7.4 (16.9) vs −6.1 (17.5) BGD: −1.3 (−4.5 to 1.9), p=0.41	NR
Changes in home diastolic BP	−2.9 (9.1) vs −2.8 (8.2) BGD: p=.94	NR
Changes in 24h systolic ABP	−6.8 (15.1) vs −4.8 (17.3) BGD: −1.96 (−4.97 to 1.1), p=0.98	**12m:** −7.5 vs −0.1 BGD: −8.5 (−11.9 to −5.1), **p≤.0001** **36m:** −15.6 vs −0.3 BGD: −16.5 (−20.5 to −12.5), **p≤.0001**
Changes in 24h diastolic ABP	−4.1 (9.2) vs −3.1 (10.1) BGD: p=0.28	**12m:** −4.6 vs −0.4 BGD: −5.6 (−7.7 to −3.6), **p≤.0001** **36m:** −9.9 vs −0.5 BGD: −11.2 (−13.6 to −8.7), **p≤.0001**
Changes in daytime systolic ABP	NR	**12m:** −8.7 vs −1.1 BGD: −9.0 (−12.6 to −5.5), **p≤.0001** **36m:** −17.2 vs −1.4 BGD: −17.3 (−21.4 to −13.2), **p≤.0001**
Changes in daytime diastolic ABP	NR	**12m:** −5.4 vs −0.5 BGD: −6.5 (−8.6 to −4.3), **p≤.0001** **36m:** −10.7 vs −0.6 BGD: −12.0 (−14.6 to −9.4), **p≤.0001**
Changes in nightime systolic ABP	NR	**12m:** −6.0 vs 2.3 BGD: −8.5 (−12.45 to −4.5), **p≤.0001** **36m:** −14.5 vs 2.0 BGD: −15.9 (−20.4 to −11.5), **p≤.0001**
Changes in nighttime diastolic ABP	NR	**12m:** −3.5 vs 0.9 BGD: −5.8 (−8.2 to −3.5), **p≤.0001** **36m:** −9.4 vs 0.8 BGD: −11.2 (−14.0 to −8.4), **p≤.0001**
Changes in 48h ABP	NR	NR
Quality of life	NR	NR
Hospitalisations, days	1.0 (0.3) vs 1.0 (0.4)	NA

[54] Between group differences and confidence intervals not reported for DBP values.

Study name	SYMPLICITY HTN-3	
Publications; first author, year	Bhatt, 2014 [23]; Bakris, 2015 (12m FU) [54]; Bhatt, 2022 (36m FU) [55]	
NCT	NCT01418261	
Safety		
AE, n (%)	**MAE**[55]: 5 (1) vs 1 (1) BGD: 0.8 (–0.9 to 2.5), p=0.67 **Compsite safety end point** (6m)[56]: 14 (4) vs 10 (6) **Specific event within 6 months:** Embolic event resulting in end-organ damage: 1 (0) vs 0 (0) New renal-artery stenosis of >70%: 1 (0) vs 0 (0) Vascular complication requiring treatment: 1 (0) vs 0 (0)	**12m:** Composite SAE: 24/355 (7) vs 5/69 (7) New-onset end-stage renal disease: 1/355 (0) vs 0/69 (0) Significant embolic event resulting in end-organ damage: 1/355 (0) vs 0/69 (0) Vascular complication: 1/355 (0) vs 0/69 (0) Renal artery reintervention: 2/355 (1) vs 0/69 (0) **36m**[57]**:** New-onset end-stage renal disease: 10/290 (3) vs 0 (0) Renal artery reintervention: 3/290 (1) vs 0/46 (0)
Procedure-related mortality, n (%)	0 (0) vs 0 (0)	NR

Abbreviations: ABP – ambulatory blood pressure; BGD – between group difference; BP – blood pressure; CI – confidence interval; DBP – diastolic blood pressure; EFF – efficacy endpoint; FU – follow-up; h – hour(s); m – month(s); MAE – major adverse event; n – number; NA – not applicable; NR – not reported; NR – not reported; pts – patients; RCT – randomised control trial; RF-RDN – radiofrequency renal denervation; (S)AE – (serious) adverse event; SAF – safety endpoint; SBP – systolic blood pressure; SD – standard deviation; T2D – type two diabetes; USA – United States of America; yrs – years.

[55] "*… composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months*".

[56] "*… composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis of more than 70% within 6 months*".

[57] Numbers from 12 months are included in the total.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-3: Risk of bias of U-RDN trials – study level (randomised studies), see [35]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
RADIANCE HTN SOLO [43]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
RADIANCE HTN TRIO [41]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
RADIANCE II [42]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
REQUIRE [44]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low

Abbreviations: BP – blood pressure, SAF – Safety

Table A-4: Risk of bias of RF-RDN trials – study level (randomised studies), see [35]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
REDUCE HTN [45]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
RESET [46]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
SPYRAL HTN-OFF MED Pivotal [47]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
SPYRAL HTN-ON MED [48]	BP	Some concern[a]	Low	Low	Low	Low	Some concerns[a]
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Some concern[a]	Low	Low	Low	Low	Some concerns[a]
SYMPLICITY FLEX [58]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low
SYMPLICITY HTN-3 [23]	BP	Low	Low	Low	Low	Low	Low
	SAF	Low	Low	Low	Low	Low	Low
	Mortality	Low	Low	Low	Low	Low	Low

For all RoB assessments, primary analysis of results were used. We clustered the endpoints for practical reasons to BP (including all BP endpoints), SAF (including all safety-related endpoints) and mortality (including all-cause mortality, CVS mortality, and major CVS events).

Abbreviations: BP – blood pressure, SAF – Safety

Notes:

[a] *More patients in the sham group had obstructive sleep apnoea (I: 2 (5%) vs C: 10 (24%)). Obstructive sleep apnoea is a well-established heavy risk factor for TRH. More untreated patients had this condition making them more likely to have high blood pressure and skewing results of the control group [72].*

Table A-5: Risk of Bias of identified systematic review using the ROBIS tool [34]

Study reference/ID	D1: STUDY ELIGIBILITY CRITERIA	D2: IDENTIFICATION AND SELECTION OF STUDIES	D3: DATA COLLECTION AND STUDY APPRAISAL	D4: SYNTHESIS AND FINDINGS	RoB in the Review
Ahmed, 2023 [31]	Low[58]	Low	Low	Low	Low
Ahmad, 2021 [32]	Low	Low	Low	Low	Low
Ogoyama, 2022 [33]	Low	Low	Low	Low	Low
Pisano, 2021 [29]	Low	Low	Low	Low	Low
Wales HTA, 2023 [49]	Low	Low	Low[59]	Low	Low

Abbreviations: Rob – Risk of Bias

[58] We found some concern with regard to the applicability of the review's eligibility criteria and our eligibility criteria. That is, the SR focused exclusively on the effect of renal denervation on blood pressure, whilst our review selected numerous further patient-centred endpoints. This concern did not affect the overall quality of the review, as the link between blood pressure and more patient-relevant outcomes was addressed within the discussion section.

[59] This review was based on recent Cochrane report by Pisano et al. And the authors did not perform separate additional risk of bias assessment newly identified studies included in their update. This is only a small limitation to the study quality as the Cochrane report performed an extensive ROB assessment and authors did include some comments on limitations of the two additional studies identified for the update.

Table A-6: Evidence profile: efficacy and safety of ultrasound renal denervation in patients with TRH based on sham-controlled randomised trials

Certainty assessment							Summary of Findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of patients randomised		Effect	Certainty
							RDN	Sham		
EFFICACY										
Mortality[60]										
4	RCT	not serious	not serious	not serious	very serious[61]	none	356	284	Range of all-cause mortality up to 12m: 0-1% vs 0-1% Range of CVS mortality up to 12m: 0% vs 0%	⨁⨁◯◯ low
Major cardiovascular events										
4	RCT	not serious	not serious	not serious	very serious[61]	none	356	284	Range: 0-3% vs 0-4% Specific events: Hypertensive crisis (2/4): 0% vs 0-3% MI (1/4): 0-1% vs 0-1% Stroke (2/4): 0-1% vs 0% Coronary revascularisation (2/4): 0-3% vs 0-1%	⨁⨁◯◯ low
24h systolic ABP ≤ 6m										
4	RCT	not serious	not serious	serious[62]	not serious	none	356	284	**Up to 3m:** Stat. significant difference favouring RDN in 3/4 trials. Range of mean BGD across studies: -0.1 (2.7) to -6.3 (-9.2 to -3.4) **Up to 6 m:** No stat. difference detected in 2/2 trials. Range of mean BGD: 0.1 (-4.3 to 4.6) to -2 (-6.0 to 1.1)	⨁⨁⨁◯ Moderate
24h systolic ABP ≤12m										
1	RCT	serious[63]	not serious	not serious	serious[64]	none	143	139	No statistical difference detected BGD: -0.8 (-4.5 to 2.9)	⨁⨁◯◯ low
24h diastolic ABP ≤6m										

[60] Outcomes reported stem from 2 and 3 months follow-up and additionally, 6m FU data was available for RADIANCE SOLO and TRIO.

[61] Optimal information size was not reached. The studies were not adequately powered for this outcome.

[62] The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.

[63] unblinded

[64] Wide confidence interval

Certainty assessment							Summary of Findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of patients randomised		Effect	Certainty
							RDN	Sham		
4	RCT	not serious	not serious	serious[62]	not serious	none	356	284	**Up to 3m:** Stat. significant difference favouring RDN in 1/4 trials. Range of mean BGD across studies: -0.4 (1.4) to -4.1 (-5.7 to 2.4) **Up to 6m:** No stat. difference in 2/2 trials. Range of mean BGD: 0.2 (2.8 to 3.1) to -1.0 (3.3 to 1.3)	⊕⊕⊕◯ moderate
24h diastolic ABP ≤12m										
1	RCT	serious[65]	not serious	not serious	serious[66]	none	143	139	No statistical difference detected BGD: -0.2 (-2.7 to 2.3)	⊕⊕◯◯ low
SAFETY										
(Serious) adverse events67										
4	RCT	not serious	not serious	not serious	serious[68]	none	356	284	No procedure related death occurred. None of the studies were able to detect a stat. significant difference in SAEs or AE. Range of SAE: 0-4% vs 0-1% Vascular complications requiring intervention, vasospastic angina, postural dizziness, doubling of serum creatinine amongst others. Range of AE: 0-17% vs 0-15% Most frequently reported AE: procedure related pain lasting longer than 2 days (3/4): 8-17% vs 8-15% Vasospams (1/4): 6% vs 0% Puncture site complications (1/4): 6% vs 4%	⊕⊕⊕◯ moderate

Abbreviations: ABP – ambulatory blood pressure; BGD – between group difference; BP – blood pressure; CVS – cardiovascular; h – hour(s); m – month(s); MI – myocardial infarction; N – number; RCT – randomised controlled trial; RDN – renal denervation; (S)AE – (serious) adverse event.

Nomenclature for GRADE table:
Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency
Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty
Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[65] Unblinded.

[66] Wide confidence intervals.

[67] Here we refer to AE with a frequency of ≥5%, for further details on less frequent AE please refer to the extraction table.

[68] Optimal information size was not reached in all trials.

Table A-7: Evidence profile: efficacy and safety of radiofrequency renal denervation in patients with TRH based on sham-controlled randomised trials

Quality assessment							Summary of Findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of patients randomised		Effect	Certainty
EFFICACY										
Mortality										
6	RCT	not serious	not serious	not serious	very serious[69]	none	841	553	Range of all-cause mortality: **Up to 6m:** 0-1% vs 0-1% (6/6) **Up to 36m:** 0-4% vs 0-11% (3/6) Range of CVS mortality: 0% vs 0%	⊕⊕◯◯ low
Major cardiovascular events										
6	RCT	not serious	not serious	not serious	very serious[69]	none	841	553	Range of CVS events: **Up to 6m:** 0-10% vs 0-12% (6/6) **Up to 36m:** 3-11% vs 0-11% (3/6) Hypertensive crisis was most frequently reported CVS Specific events: MI (1/6): 2% vs 2% Stroke (4/6): 0-1% vs 0-3% Hospitalisation for new onset heart failure (1/6): 3% vs 2% Hospitalisation for atrial fibrillation (1/6): 1% vs 1% Hypertensive crisis (3/6): 1-11% vs 0-11% Need for percutaneous coronary intervention (1/6): 0% vs 3%	⊕⊕◯◯ low
24h systolic ABP ≤6m FU										
6	RCT	not serious	not serious	serious[70]	not serious	none	841	553	Stat. significant difference favouring RDN in 1/6 trials[71] Range of mean BGD across studies: -1.9 (-4.4 to 0.5) to –7.4 (-15.2 to 0.4)	⊕⊕⊕◯ moderate
24h systolic ABP ≤12m										
2	RCT	serious[72]	not serious	not serious	serious[73]	none	398	188	Stat. Significant difference favouring RDN in1/2 trials: REDUCE trial: BGD –4.9 (-13.4 to 3.6), p ≤0.266) Simplicity HTN-3: -8.5 (-11.9 to –5.1), p≤0.0001	⊕⊕◯◯ low

[69] Optimal information size not reached. Studies were not adequately powered for this outcome.

[70] The most significant concern affecting the certainty of evidence was indirectness: Most studies used different in- and exclusion criteria, with numerous enrolled patients not fulfilling the narrow and imperfect definition of (true) TRH, representing the target population of this assessment.

[71] Pilot phases of both SPYRAL MED HTN OFF and SPYRAL MED HTN OFF, BGD were also statistically significant. -5, p=0.0041 and -7.4, p=0.0051.

[72] unblinding after 6m/crossover/imputed data in 1/2 studies

[73] Wide confidence intervals in some studies

Quality assessment							Summary of Findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of patients randomised		Effect	Certainty
24h systolic ABP >12m FU										
2	RCT	serious[74]	not serious	not serious	serious[75]	none	402[76]	213	Stat. significant differences favouring RDN in 2/2 trials[77] at 12m and 36m FU mean BGD: -11.2 (-18.4 to –4.0) and -16.5 (-20.5 to -12.5)	⨁⨁◯◯ low
24h diastolic ABP ≤6m FU										
6	RCT	not serious	not serious	serious[70]	not serious	none	841	553	Stat. significant difference favouring RDN in 1/6 trials[78] Range of mean BGD across studies: -0.8 (-2.4 to 0.9) to –3.1 (-9.0 to 2.9)	⨁⨁⨁◯ moderate
24h diastolic ABP ≤12m FU										
2	RCT	serious[79]	not serious	not serious	serious[80]	none	398	188	Stat. Significant difference favouring RDN in 1/2 trials. REDUCE BGD: -4.4 (-10.2 to 1.5) p=0.154 Simplicity HTN-3 BGD: -5.6 (-7.7 to –3.6), p≤0.0001	⨁⨁◯◯ low
24h diastolic ABP >12m FU										
2	RCT	serious[81]	not serious	not serious	serious[82]	none	402[83]	213	Stat. significant differences favouring RDN in 2/2 trials[84] mean BGD: -5.7 (-10.6 to – 0.7) and -11.2 (-13.6 to -8.7)	⨁⨁◯◯ low

[74] All patients and assessors were unblinded after 12m FU.

[75] Wide confidence intervals in some studies

[76] 70 crossover patients

[77] Includes findings from SPYRAL HTN-ON MED pilot analysis because primary analysis did not report longer-term outcomes beyond 6m.

[78] Interim Analyses from SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED also showed statistical significant BGD: -4.4 (p=0.002) and -4.1 (p=0.292)

[79] Downgraded because unblinding/crossover/imputed data in ½ studies.

[80] Wide confidence intervals in some studies

[81] All patients were unblinded during long term FU.

[82] Wide confidence intervals in some studies.

[83] Including 70 crossover patients.

[84] Includes findings from SPYRAL HTN MED ON pilot analysis because primary analysis did not report longer-term outcomes beyond 6m.

Quality assessment							Summary of Findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	N of patients randomised		Effect	Certainty
SAFETY										
Adverse Events*[85]										
6	RCT	not serious	not serious	not serious	serious[86]	none	841	553	No procedure-related deaths reported. None of the studies was able to detect a stat. significant difference in SAEs or AE **Up to 6m:** Range of SAE events: 0-1 % vs 0-1% Composite endpoint (1/6) [87]: 0-4% vs 0-6% minor AE symptoms (1/6)[88]: 14% vs 18% **Up to 36m:** Composite endpoint (2/6): 2-4% vs 6-7%	⨁⨁⨁◯ moderate

* *We reported specific adverse events if the occurred at a frequency of ≥5%.*

Abbreviations: ABP – ambulatory blood pressure; BGD – between group difference; BP – blood pressure; CVS – cardiovascular; FU – follow-up; h – hour(s); m – month(s); MI – myocardial infarction; N – number; RCT – randomised controlled trial; RDN – renal denervation (S)AE – serious adverse event.

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[85] CVS adverse events are reported in CVS events above.

[86] Optimal information size was not reached.

[87] Defined as a composite of all-cause mortality, end stage renal disease, embolic event resulting in end-organ damage, renal artery perforation requiring intervention, renal artery dissection requiring intervention, vascular complications, hospitalization for hypertensive crisis or new renal artery stenosis of > 70%.

[88] Headache, atypical chest pain, muscle convulsion and fatigue.

Applicability table

Table A-8: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Most of the studies assessed or aimed to assess patients with treatment-resistant hypertension (TRH), although TRH is difficult to diagnose due to, among others, the presence of pseudo-resistant TRH falling within some of the definitions of TRH. Our target population was based on guidelines that define the use case for RDN to those TRH patients or do not tolerate OMT. We found applicability concerns with regard to the population included in clinical trials to our target population: According to study protocols, not all studies included a patient population with TRH in its classic definition of "blood pressure that remains above goal despite concurrent use of three or more antihypertensive agents of different classes taken at maximally tolerated doses and at appropriate dosing frequency, one of which should be a diuretic". Some studies included patients with uncontrolled hypertension on a varying number of blood pressure (BP) medications, one even expanded its inclusion criteria to patients with controlled hypertension on one to two antihypertensive drugs. Furthermore, to diagnose true TRH, secondary causes such as hyperaldosteronism, obesity, or sleep apnoea, need to be excluded as well as causes for pseudo-resistance such as white coat syndrome or suboptimal medication adherence. The majority of studies did not clearly report on methods to ensure exclusion of such patients; thus it is possible that some patients were not explicitly reflective of the intended population. There was heterogeneity in the study designs with some requiring patients to continue their medications, and others requiring a 4-week medication washout and in several trials, changes or addition of medication was permitted in after a defined observation period or for patients with BP escalations. The variation in concurrent BP medication makes comparability between trials a concern and limits applicability to the intended population. No information on prior lifestyle interventions was available for any of the trial participants.
Intervention	Two types of catheter-based systems were used in the trials, ultrasound-based or radiofrequency- based technology. Four studies evaluated treatment with the ultrasound-based Paradise™ system, six studies evaluated treatment with the radiofrequency-based Symplicity™ system. Device generations used varied between the studies, with three radiofrequency devices no longer in operation.
Comparators	In all studies the comparator was a sham procedure (renal angiogram).
Outcomes	The critical endpoints of highest relevance are arguably mortality and a potential reduction of cardiovascular events. None of the studies measured these endpoints as primary endpoints. All trials reported further critical efficacy endpoints of 24-hour systolic and diastolic ambulatory blood pressure (ABP). BP changes were defined as the primary outcome in all studies. Four studies focused on daytime systolic ABP, five on 24-hour systolic ABP and one on office systolic BP. No studies reported 48-hour ABP changes. Follow-up (FU) times ranged from 2 months to 6 months with only 3 studies reporting on long-term FU beyond 12 months under unblinded conditions. This reduces the applicability of the evidence on the outcome with regards to the long-term efficacy horizon. The two other predefined critical outcomes, health related quality of life and hospitalisation, were not reported by any studies.
Setting	The majority of randomised controlled trials were conducted as multi-centre studies in different geographical regions (Australia, Japan, Europe, USA) Thus, it is not expected that the applicability of the results is limited by geographic settings.

List of ongoing randomised controlled trials

Table A-9: List of ongoing randomised sham-controlled trials of renal denervation

Identifier/ Trial name	Patient population	Inclusion criteria	Intervention	Comparison	Primary Outcome	N of pts (planned)	Primary completion date	Sponsor
NCT02444442/ AUSHAM-RDN-01	Patients with **resistant** hypertension	Office SBP ≥140 mmHg and ambulatory day time average ≥135 mmHg despite concurrent treatment with ≥3 anti-hypertensive drugs	RF-RDN	Sham procedure	Difference in mean systolic daytime ABP between RDN group and sham-control group at 6 month follow-up.	105	04/2020	Baker Heart and Diabetes Institute
NCT02761811/ SMART	Patients with **essential** hypertension for at least 6 months	Essential hypertension; Office SBP ≥150 mmHg and ≤180 mmHg; and resting heart rate ≥70 bpm without taking beta blocker (Resting heart rate does not taken into account if beta blocker is taken); Average 24h systolic ABP ≥130 mmHg, or systolic ABP during daytime ≥135 mmHg, or systolic ABP during nighttime ≥120 mmHg; History of hypertension is longer than 6 months and poor BP control after 6 months of antihypertensive drug therapy	RF-RDN SyMapCath I™ catheter + SYMPIONEER S1™ Generator	Sham procedure	Control rate of office SBP (<140 mmHg) at 6 months after the treatment; Change in the composite index of antihypertensive drugs to reach control of office SBP (<140 mmHg) at 6 months after the treatment	220 (actual)	08/2022	SyMap Medical (Suzhou), Ltd.
NCT03261375	Patients with **uncontrolled essential** hypertension	Subject with essential hypertension who has an office BP of ≥150/90 mmHg and <180/110 mmHg (both SBP and DBP meet the criteria), and an average SBP of ≥135 mmHg measured by 24h ABP, after taking ≥2 antihypertensive medications for ≥4 weeks; Subject with the resting heart rate ≥70 bpm, if not taking beta-blockers (this criterion does not apply to those taking beta-blockers); Subject with confirmed diagnosis of essential hypertension	RF-RDN Netrod® System	Sham procedure	Office SBP change from baseline at 6 months post procedure	205 (actual)	12/2022	Shanghai Golden Leaf MedTec Co. Ltd
NCT04535050	Patients with hypertension with **no medication**	Subject who is drug-naïve or willing to discontinue current antihypertensive treatment (not on antihypertensive medications for at least 4 weeks prior to Screening Visit 1) at Screening Visit 1 through the 3-month post-procedure visit. Drug-naïve is defined as those with no previous exposure to antihypertensive medications; Subject who meets all of the following BP measurements: Office SBP <180 mmHg at Screening Visit 1; Office SBP ≥150 mmHg and <180 mmHg, and office DBP ≥90 mmHg at Screening Visit 2; 24h systolic ABP ≥140 mmHg and <170 mmHg at Screening Visit 2	RF-RDN DENEX System	Sham procedure	Change in 24h systolic ABP from baseline to 3 months post-procedure; Incidence of MAE within 3 months post-procedure	100	12/2023	Kalos Medical

Identifier/ Trial name	Patient population	Inclusion criteria	Intervention	Comparison	Primary Outcome	N of pts (planned)	Primary completion date	Sponsor
NCT02910414/ TARGET BP I	Patients with hypertentsion	Has 3 office BP measurements with a mean office SBPof ≥150 mmHg and ≤180 mmHg, AND a mean office DBP of ≥90 mmHg when receiving 2 to 5 antihypertensive medications; Has a mean 24h systolic ABP of ≥135 mmHg and ≤170 mmHg with ≥70% valid readings	ethanol RDN Peregrine System	Sham procedure	Change in mean 24h systolic ABP from baseline to 3 months post-procedure	300 (actual)	12/2023	Ablative Solutions, Inc.
NCT03503773/ TARGET BP OFF-MED	Patients with hypertension	Has 3 office BP measurements with a mean office SBP of ≥140 mmHg and ≤180 mmHg, AND a mean office DBP of ≥90 mmHg; Subject is willing to discontinue any current antihypertensive medications during the run-in period and the post-treatment period; Has a mean 24h systolic ABP of ≥135 mmHg and ≤170 mmHg with ≥70% valid readings	ethanol RDN Peregrine System	Sham procedure	Change in mean 24h systolic ABP from baseline to 8 weeks post-treatment	90	12/2023	Ablative Solutions, Inc.
NCT05326230/ RADIANCE-HTN DUO	Hypertensive patients receiving **two antihypertensive drugs** at the time of consent, and treated with a duo combination antihypertensive pill	Patients who have received antihypertensive treatment with two antihypertensive drugs (ARB/ACE inhibitor and Ca channel antagonist, either as a single agent or as a combination) for at least 4 weeks prior to obtaining consent, with no change in the type or dosage; Patients with a mean seated office SBP of between 140 and 180 mmHg and between 90 and 110 mmHg DBP at screening visit; Patients with a mean 24h ABP of between 130 and 170 mmHg systolic and between 80 and 105 mmHg diastolic at baseline visit	U-RDN Paradise™ System	Sham procedure	Mean change in 24h systolic ABP from baseline to 3 months post-procedure	154	12/2024	Otsuka Medical Devices Co., Ltd. Japan
NCT05563337/ WHY-RDN	Women with **essential hypertension**, treated or untreated, who are planning a short term pregnancy.	Not pregnant but planning to be pregnant in the near future (<2 years); Patient using effective contraception, preferably micro-progestational, during the screening phase and the two-month post-procedure follow-up; Essential hypertension confirmed and documented by a previous complete search; Hypertension treated by 0-2 antihypertensive treatment(s) in a stable manner for at least 4 weeks and whose clinical BP measured in the sitting position during consultation is ≤180/110 mmHg at the selection visit	RDN	Sham procedure	Percentage of patients cured of their hypertension (cure defined as 24h BP<130/80 mmHg at Day 100 without treatment)	80	11/2028	University Hospital, Bordeaux

Identifier/ Trial name	Patient population	Inclusion criteria	Intervention	Comparison	Primary Outcome	N of pts (planned)	Primary completion date	Sponsor
Other indications								
NCT04264403/ RDN-CKD	Patients with CKD stages 3a or 3b and **uncontrolled hypertension**	CKD stage 3 (eGFR 30-59 ml/min/1.73m^2 [according to the currently used estimation formulas: MDRD, CKD-EPI]) with diabetic or non-diabetic nephropathy; Uncontrolled hypertension with 1-5 drug classes (renin angiotensin system [RAS] blockade is mandatory, unless intolerance to RAS blockers has been documented) and office (attended) SBP ≥140 mmHg confirmed by 24h systolic ABP ≥130 mmHg; Patient is adhering to a stable drug regimen including RAS blockade without changes for a minimum of 4 weeks	U-RDN Paradise™ System	Sham procedure	Change in 24h systolic ABP at 6 months post-procedure	44 (actual)	12/2023	University of Erlangen-Nürnberg Medical School
NCT05030987/ UNLOAD-HFpEF	Patients with HFpEF and **uncontrolled hypertension**	confirmed arterial hypertension (1-5 antihypertensive drugs without any dosage change in the preceding 4 weeks) and average SBP between >125 and ≤170 mmHg and DBP ≤110 mmHg in 24h ABP measurement; HFpEF (defined by clinical signs and/or symptoms of heart failure, objective structural cardiac abnormalities according to the ESC criteria, elevated NT-proBNP ≥125 pg/mL and left-ventricular ejection fraction ≥55%); NYHA-Class II or III; Confirmation of an elevated cardiac filling pressures (either LVEDP ≥16 mmHg or PCWP ≥15 mmHg at rest or ≥25 mmHg during exercise) by catheterization	RDN	Sham procedure	Exercise PCPW at 20 W workload at 6 months after randomisation	68	03/2024	University of Leipzig

Abbreviations: ABP – ambulatory blood pressure; BP – blood pressure; bpm – beats per minute; CKD – chronic kidney disease; DBP – diastolic blood pressure; h – hour; HFpEF – Heart Failure with preserved Ejection Fraction; MAE – major adverse events; MDRD – modification of diet in renal disease; PCPW – Pulmonary Capillary Wedge Pressure; RDN – renal denervation; RF-RDN – radiofrequency renal denervation; SBP – systolic blood pressure.

Research questions

Table A-10: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0011	How much are the technologies utilised?

Table A-11: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-12: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0012	What is the effect of the technology on generic health-related quality of life?

Literature search strategies

Search strategy for Cochrane

Search Name: Renal Denervation in Hypertension	
Search date: 07.12.2023	
ID	Search
#1	MeSH descriptor: [Hypertension] explode all trees
#2	(hypertensi*) (Word variations have been searched)
#3	(((raised OR high* OR elevated OR increased) NEAR ((blood OR arter* OR systol* OR diastol*) NEAR pressure*))) (Word variations have been searched)
#4	raised OR high* OR elevated OR increased
#5	MeSH descriptor: [Blood Pressure] explode all trees
#6	#4 AND #5
#7	#1 OR #2 OR #3 OR #6
#8	((kidney* OR renal) NEAR denerv*) (Word variations have been searched)
#9	MeSH descriptor: [Kidney] explode all trees
#10	MeSH descriptor: [Renal Artery] explode all trees
#11	#9 OR #10
#12	MeSH descriptor: [Denervation] explode all trees
#13	MeSH descriptor: [Radiofrequency Ablation] explode all trees
#14	#12 OR #13
#15	#11 AND #14
#16	(kidney* OR renal OR sympathetic*) (Word variations have been searched)
#17	#13 AND #16
#18	(RDN):ti,ab,kw
#19	sympathetic* denerv* (Word variations have been searched)
#20	MeSH descriptor: [Sympathectomy] explode all trees
#21	sympathectom* (Word variations have been searched)
#22	((renal OR kidney* OR sympathetic*) NEAR ((catheter* OR trans*catheter* OR trans-catheter* OR radio*frequen* OR radio-frequen*) NEAR (ablat* OR denerv*))) (Word variations have been searched)
#23	#8 OR #15 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	#7 AND #23
#25	#7 AND #23 in Trials
#26	#7 AND #23 with Cochrane Library publication date Between Sep 2021 and Dec 2023, in Trials
#27	(conference proceeding):pt
#28	(abstract):so
#29	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#30	#27 OR #28 OR #29
#31	#26 NOT #30
Total hits: 54	

Search strategy for Embase

Search Name: Renal Denervation in Hypertension		
Search date: 06.12.2023		
No.	Query Results	Results
#1.	'hypertension'/exp	1,031,081
#2.	hypertensi*	1,290,702
#3.	'elevated blood pressure'/exp	1,036,165
#4.	((raised OR high* OR elevated) NEAR/5 (blood OR arter* OR systol* OR diastol*) NEAR/3 pressure*):ab,kw,lnk,de,ti	97,627
#5	#1 OR #2 OR #3 OR #4	1,449,449
#6.	'kidney denervation'/exp	5,190
#7.	(kidney* OR renal) NEAR/5 denerv*	6,821
#8.	'renal artery denervation'/exp	16
#9.	rdn:ti,ab	2,037
#10.	'sympathetic denervation'/exp	108
#11.	'sympathetic* denerv*'	3,797
#12.	'sympathectomy'/exp	10,840
#13.	sympathectom*	13,733
#14.	'radiofrequency ablation'	52,476
#15.	(renal OR kidney*) NEAR/5 (catheter* OR trans?catheter* OR 'trans catheter*' OR radio?frequen* OR 'radio frequen*') NEAR/5 (ablat* OR denerv*)	1,258
#16.	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	74,308
#17.	#5 AND #16	8,875
#18.	#5 AND #16 AND [randomized controlled trial]/lim	349
#19.	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,289,536
#20.	#17 AND #19	1,239
#21.	#18 OR #20	1,268
#22.	(#18 OR #20) AND [01-09-2021]/sd NOT [07-12-2023]/sd	249
#23.	(#18 OR #20) AND [01-09-2021]/sd NOT [07-12-2023]/sd AND ([english]/lim OR [german]/lim)	240
#24.	#23 AND 'Conference Abstract'/it	63
#25.	#23 NOT #24	177
Total hits: 177		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) ALL <1946 to December 05, 2023>	
Search date: 06.12.2023	
ID	Search
#1	exp Hypertension/
#2	hypertensi*.mp.
#3	((raised or high* or elevated) adj5 ((blood or arter* or systol* or diastol*) adj3 pressure*)).mp.
#4	(raised or high* or elevated).mp.
#5	exp Blood Pressure/
#6	4 and 5
#7	1 or 2 or 3 or 6
#8	((kidney* or renal) adj5 denerv*).mp.
#9	exp Kidney/
#10	exp Renal Artery/
#11	9 or 10
#12	exp Denervation/
#13	11 and 12
#14	RDN.ti,ab.
#15	sympathetic* denerv*.mp.
#16	exp Sympathectomy/
#17	sympathectom*.mp.
#18	exp Radiofrequency Ablation/
#19	((kidney* or renal) adj5 ((catheter* or trans?catheter* or trans-catheter* or radio?frequen* or radio-frequen*) adj5 (ablat* or denerv*))).mp.
#20	8 or 13 or 14 or 15 or 16 or 17 or 18 or 19
#21	7 and 20
#22	limit 21 to randomized controlled trial
#23	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
#24	21 and 23
#25	22 or 24
#26	limit 25 to dt=20210901-20231206
#27	limit 25 to ed=20210901-20231206
#28	26 or 27
#29	limit 28 to (english or german)
#30	remove duplicates from 29
Total hits: 193	

Search strategy for HTA-INATHTA

Search Name: Renal Denervation in Hypertension	
Search date: 07.12.2023	
ID	Search
#1	"Hypertension"[mhe],"262","2023-12-07T10:10:05.000000Z"
#2	hypertensi*,"266","2023-12-07T10:10:45.000000Z"
#3	(raised OR high* OR elevated OR increased) AND ("Blood Pressure"),"111","2023-12-07T10:14:18.000000Z"
#4	"Kidney"[mhe],"389","2023-12-07T10:15:09.000000Z"
#5	"Renal Artery"[mhe],"15","2023-12-07T10:15:35.000000Z"
#6	("Renal Artery"[mhe]) OR ("Kidney"[mhe]),"391","2023-12-07T10:15:44.000000Z"
#7	"Denervation"[mhe],"56","2023-12-07T10:16:14.000000Z"
#8	("Denervation"[mhe]) AND (("Renal Artery"[mhe]) OR ("Kidney"[mhe])),"8","2023-12-07T10:16:24.000000Z"
#9	(kidney* OR renal OR sympathetic*) AND (denerv* OR ablat*),"29","2023-12-07T10:20:14.000000Z"
#10	RDN,"3","2023-12-07T10:20:54.000000Z"
#11	"Sympathectomy"[mhe],"12","2023-12-07T10:21:36.000000Z"
#12	sympathectom*,"9","2023-12-07T10:22:28.000000Z"
#13	"Radiofrequency Ablation"[mhe],"188","2023-12-07T10:23:15.000000Z"
#14	kidney* OR renal OR sympathetic*,"546","2023-12-07T10:23:56.000000Z"
#15	(kidney* OR renal OR sympathetic*) AND ("Radiofrequency Ablation"[mhe]),"10","2023-12-07T10:24:03.000000Z"
#16	((raised OR high* OR elevated OR increased) AND ("Blood Pressure")) OR (hypertensi*) OR ("Hypertension"[mhe]),"430","2023-12-07T10:25:05.000000Z"
#17	((kidney* OR renal OR sympathetic*) AND ("Radiofrequency Ablation"[mhe])) OR (sympathectom*) OR ("Sympathectomy"[mhe]) OR (RDN) OR ((kidney* OR renal OR sympathetic*) AND (denerv* OR ablat*)) OR (("Denervation"[mhe]) AND (("Renal Artery"[mhe]) OR ("Kidney"[mhe]))),"40","2023-12-07T10:25:42.000000Z"
#18	(((kidney* OR renal OR sympathetic*) AND ("Radiofrequency Ablation"[mhe])) OR (sympathectom*) OR ("Sympathectomy"[mhe]) OR (RDN) OR ((kidney* OR renal OR sympathetic*) AND (denerv* OR ablat*)) OR (("Denervation"[mhe]) AND (("Renal Artery"[mhe]) OR ("Kidney"[mhe])))) AND (((raised OR high* OR elevated OR increased) AND ("Blood Pressure")) OR (hypertensi*) OR ("Hypertension"[mhe])),"14","2023-12-07T10:26:13.000000Z"
#19	((((kidney* OR renal OR sympathetic*) AND ("Radiofrequency Ablation"[mhe])) OR (sympathectom*) OR ("Sympathectomy"[mhe]) OR (RDN) OR ((kidney* OR renal OR sympathetic*) AND (denerv* OR ablat*)) OR (("Denervation"[mhe]) AND (("Renal Artery"[mhe]) OR ("Kidney"[mhe])))) AND (((raised OR high* OR elevated OR increased) AND ("Blood Pressure")) OR (hypertensi*) OR ("Hypertension"[mhe]))) FROM 2021 TO 2023,"0","2023-12-07T10:27:11.000000Z"
Total hits: 0	

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