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Renal denervation for resistant hypertension (Review)

Coppolino G, Pisano A, Rivoli L, Bolignano D

Coppolino G, Pisano A, Rivoli L, Bolignano D.
Renal denervation for resistant hypertension.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD011499.
DOI: 10.1002/14651858.CD011499.pub2.

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[Intervention Review]

Renal denervation for resistant hypertension

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Editorial group: Cochrane Hypertension Group.
Publication status and date: New, published in Issue 2, 2017.

Citation: Coppolino G, Pisano A, Rivoli L, Bolignano D. Renal denervation for resistant hypertension. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD011499. DOI: 10.1002/14651858.CD011499.pub2.

ABSTRACT

Background

Resistant hypertension is highly prevalent among the general hypertensive population and the clinical management of this condition remains problematic. Different approaches, including a more intensified antihypertensive therapy, lifestyle modifications, or both, have largely failed to improve patients' outcomes and to reduce cardiovascular and renal risk. As renal sympathetic hyperactivity is a major driver of resistant hypertension, renal sympathetic ablation (renal denervation) has been recently proposed as a possible therapeutic alternative to treat this condition.

Objectives

We sought to evaluate the short- and long-term effects of renal denervation in individuals with resistant hypertension on clinical end points, including fatal and non-fatal cardiovascular events, all-cause mortality, hospital admissions, quality of life, blood pressure control, left ventricular hypertrophy, cardiovascular and metabolic profile, and kidney function, as well as the potential adverse events related to the procedure.

Search methods

We searched the following databases to 17 February 2016 using relevant search terms: the Cochrane Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and ClinicalTrials.gov

Selection criteria

We considered randomised controlled trials (RCTs) that compared renal denervation to standard therapy or sham procedure to treat resistant hypertension, without language restriction.

Data collection and analysis

Two authors independently extracted data and assessed study risks of bias. We summarised treatment effects on available clinical outcomes and adverse events using random-effects meta-analyses. We assessed heterogeneity in estimated treatment effects using Chi^2 and I^2 statistics. We calculated summary treatment estimates as a mean difference (MD) or standardised mean difference (SMD) for continuous outcomes, and a risk ratio (RR) for dichotomous outcomes, together with their 95% confidence intervals (CI).

Main results

We found 12 eligible studies (1149 participants). In four studies, renal denervation was compared to sham procedure; one study compared a proximal ablation to a complete renal artery denervation; in the remaining, renal denervation was tested against standard or intensified antihypertensive therapy.

None of the included trials was designed to look at hard clinical end points as primary outcomes.

When compared to control, there was low quality evidence that renal denervation did not reduce the risk of myocardial infarction (4 studies, 742 participants; RR 1.31, 95% CI 0.45 to 3.84), ischaemic stroke (4 studies, 823 participants; RR 1.15, 95% CI 0.36 to 3.72), or unstable angina (2 studies, 201 participants; RR 0.63, 95% CI 0.08 to 5.06), and moderate quality evidence that it had no effect on 24-hour ambulatory blood pressure monitoring (ABPM) systolic BP (5 studies, 797 participants; MD 0.28 mmHg, 95% CI -3.74 to 4.29), diastolic BP (4 studies, 756 participants; MD 0.93 mmHg, 95% CI -4.50 to 6.36), office measured systolic BP (6 studies, 886 participants; MD -4.08 mmHg, 95% CI -15.26 to 7.11), or diastolic BP (5 studies, 845 participants; MD -1.30 mmHg, 95% CI -7.30 to 4.69). Furthermore, low quality evidence suggested that this procedure produced no effect on either serum creatinine (3 studies, 736 participants, MD 0.01 mg/dL; 95% CI -0.12 to 0.14), estimated glomerular filtration rate (eGFR), or creatinine clearance (4 studies, 837 participants; MD -2.09 mL/min, 95% CI -8.12 to 3.95). Based on low-quality evidence, renal denervation significantly increased bradycardia episodes compared to control (3 studies, 220 participants; RR 6.63, 95% CI 1.19 to 36.84), while the risk of other adverse events was comparable or not assessable.

Data were sparse or absent for all cause mortality, hospitalisation, fatal cardiovascular events, quality of life, atrial fibrillation episodes, left ventricular hypertrophy, sleep apnoea severity, need for renal replacement therapy, and metabolic profile.

The quality of the evidence was low for cardiovascular outcomes and adverse events and moderate for lack of effect on blood pressure and renal function.

Authors' conclusions

In patients with resistant hypertension, there is low quality evidence that renal denervation does not change major cardiovascular events, and renal function. There was moderate quality evidence that it does not change blood pressure and and low quality evidence that it caused an increaseof bradycardia episodes. Future trials measuring patient-centred instead of surrogate outcomes, with longer follow-up periods, larger sample size and more standardized procedural methods are necessary to clarify the utility of this procedure in this population.

PLAIN LANGUAGE SUMMARY

Renal denervation for improving outcomes in individuals with resistant hypertension

Review question

What are the benefits and harms of renal denervation in individuals with resistant hypertension, on clinically important outcomes, including cardiovascular morbidity and mortality, blood pressure control, kidney function, and the occurrence of various adverse events.

Background

Resistant hypertension is a condition characterised by persistently high blood pressure levels in spite of multiple blood pressure lowering (antihypertensive) medications, given at maximum doses. The estimated prevalence of this condition ranges from 10% to 20% of the general hypertensive population. Despite therapeutic and lifestyle approaches that have been proposed, the management of individuals with resistant hypertension remains difficult, with a high incidence of poor outcomes and adverse cardiovascular events. Recently, renal sympathetic denervation, a procedure consisting of destroying renal nerves with a radiofrequency catheter inserted through a minimally invasive incision, has emerged as a possible therapeutic alternative to treat this condition.

Study characteristics

Twelve studies of variable quality were identified that included a total of 1149 participants. There was high heterogeneity among studies for design, methods, and blinding of investigators. Most of the studies assessed the impact of renal denervation on surrogate (e.g. blood pressure control), rather than patient-centred outcomes (e.g. mortality or quality of life).

Key results

Overall, there was no evidence of benefits of renal denervation over standard treatment on cardiovascular morbidity and mortality. Similarly, renal denervation had no tangible effects on blood pressure control and renal function. However, it was associated with an increased risk of episodes of bradycardia (very slow heart rate).

Quality of the evidence

The quality of the evidence was low for cardiovascular morbidity and adverse events and moderate for lack of effect on blood pressure and renal function. The evidence is current to 17 February 2016.

Conclusions

Current evidence is inconclusive to support the use of renal denervation to improve cardiovascular and renal risk and blood pressure control in patients with resistant hypertension. Future studies targeting patient-centred outcomes, with longer duration and larger number of participants are needed to identify whether individuals can benefit from this procedure.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Renal denervation versus sham denervation or standard treatment

Patient or population: people with resistant hypertension
Setting: Outpatient
Intervention: renal denervation
Comparison: sham denervation or standard treatment

Outcomes	Illustrative comparative risks* (95% CI)		Effect estimate (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Sham denervation/ Standard treatment	Renal denervation			
myocardial infarction	14 per 1000	18 per 1000 (6 to 54)	RR 1.31 (0.45 to 3.84)	742 (4 studies)	⊕⊕⊝⊝ low[1,2]
ischaemic stroke	12 per 1000	14 per 1000 (4 to 45)	RR 1.15 (0.36 to 3.72)	823 (4 studies)	⊕⊕⊝⊝ low[1,2]
unstable angina	20 per 1000	12 per 1000 (2 to 101)	RR 0.63 (0.08 to 5.06)	201 (2 studies)	⊕⊕⊝⊝ low[1,2]
systolic 24-hour ABPM (mmHg)	-	-	MD 0.28 (-3.74 to 4.29)	797 (5 studies)	⊕⊕⊕⊝ moderate[1]
diastolic 24-hour ABPM (mmHg)	-	-	MD 0.93 (-4.50 to 6.36)	756 (4 studies)	⊕⊕⊕⊝ moderate[1]
systolic office BP (mmHg)	-	-	MD -4.08 (-15.26 to 7.11)	886 (6 studies)	⊕⊕⊕⊝ moderate[1]
diastolic office BP (mmHg)	-	-	MD -1.30 (-7.30 to 4.69)	845 (5 studies)	⊕⊕⊕⊝

					moderate[1]
eGFR or creatinine clearance (mL/min/1.73m^2)	-	-	MD -2.09 (-8.12 to 3.95)	837 (4 studies)	⊕⊕⊕⊖ moderate[1]

*The **assumed risk** is the observed risk in the reference (control) group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Legend
ABPM: ambulatory blood pressure monitoring; BP: blood pressure; CI: Confidence interval; CV: cardiovascular; NA: information not available (data sparse or absent); eGFR: estimated glomerular filtration rate; MD: mean difference; RR: Risk Ratio.
1. Wide confidence intervals.
2. Only reported by less than half of the studies.

BACKGROUND

Description of the condition

Resistant or refractory hypertension is characterised by blood pressure levels persistently above target, in spite of the concurrent use of three antihypertensive agents of different classes at best-tolerated doses, including a diuretic (Calhoun 2008). Data from cross-sectional and hypertension outcome studies suggest that this condition is not infrequent, with an estimated prevalence of 10% to 20% in the general hypertensive population (Myat 2012). Individuals with resistant hypertension are 50% more likely to experience poor outcomes and adverse cardiovascular events than those with controlled hypertension (Judd 2014). The lack of efficacy of multiple interventions in addition to pharmacological therapy, including dietary and lifestyle modifications, emphasises the importance of finding new effective and safe treatments for treating this condition.

Description of the intervention

Renal sympathetic denervation comprises the ablation of renal afferent and efferent nerves by a radiofrequency catheter through a minimally invasive, percutaneous intervention performed via femoral access. The thermal increase generated by the application of low-dose radiofrequency energy is effective in disrupting large portions of nervous fibres located within the adventitia of the renal artery.

How the intervention might work

Sympathetic hyperactivity has long been acknowledged as a major player in the genesis of resistant hypertension (Huan 2013). In studies conducted in the eighties, surgical sympathectomy was effective in some individuals in lowering blood pressure and symptoms associated with severe hypertension. However, this procedure is no longer used because of considerable side effects (Leong 2014). As with sympathectomy, renal denervation might improve blood pressure control by reducing abnormal renal adrenergic nerve activity. Furthermore, since other conditions, such as congestive heart failure, atrial fibrillation, sleep breathing disorders, and diabetes mellitus are all associated with an overactive sympathetic drive, this procedure might result in pleiotropic benefits, including improvements in glycaemic levels, sleep apnoea, arrhythmias, and oxidative stress (Witkowski 2011). Of note, in spontaneously hypertensive rats, renal denervation was able to ameliorate metabolic control and to prevent hypertensive stroke and brain injury, in addition to controlling blood pressure (Nakagawa 2013a; Nakagawa 2013b).

Why it is important to do this review

As shown in a recent meta-analysis, renal denervation reduced mean blood pressure at six months in individuals with persistent hypertension; intra-procedural complications, including renal artery dissection and femoral pseudoaneurysms were rare (Davis 2013). Unfortunately, data were mostly derived from observational, uncontrolled studies with limited follow-up, small sample sizes, and high heterogeneity in blood pressure measurement. Whether the benefits of renal denervation on blood pressure control are maintained in the long term, and particularly, whether this procedure might impact hard outcomes, such as mortality and cardiovascular events, remain unknown at this time. New evidence, based on larger, randomised controlled trials (RCTs), is now accruing, and long-term data on the efficacy of renal denervation on surrogate and hard end points in the long term are becoming available. Therefore, an updated assessment of the efficacy and safety profile of this procedure is mandatory to define whether the benefits of implementing renal denervation in the clinical management of individuals with resistant hypertension outweigh the harms.

OBJECTIVES

To evaluate the short- and long-term effects of renal sympathetic denervation in individuals with resistant hypertension on:

- patient-centred end points, including cardiovascular morbidity and mortality, all-cause mortality, hospital admissions, and quality of life;
- blood pressure control;
- cardiovascular and metabolic profile;
- kidney function;
- adverse events, including but not limited to bradycardia, hypotension episodes, femoral artery pseudoaneurysm, and renal artery dissection.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) of individuals with resistant hypertension undergoing renal sympathetic denervation procedures, without duration or language restrictions.

Types of participants

Adults (older than 18 years), with refractory or resistant hypertension, defined by the presence of a clinic blood pressure above target (higher than 140/90 mmHg, or higher than 130/80 mmHg in individuals with type 2 diabetes mellitus), despite the concomitant use of three or more antihypertensive drugs of different classes, including a diuretic.

Types of interventions

Any transcatheter renal sympathetic denervation procedures performed using contemporary percutaneous catheters and radiofrequency probes compared with standard medical therapy or sham intervention.

Types of outcome measures

Primary outcomes

- Fatal and non-fatal cardiovascular events, including but not limited to myocardial infarction, cerebrovascular accidents, and congestive heart failure
- All-cause mortality
- Any hospitalisation and duration of hospital stay (if long-term data are available)
- Quality of life (assessed using validated scales or any other instrument as reported by authors, such as the Short-Form Health Survey (SF-36))

Secondary outcomes

- Blood pressure control (change in office and clinic systolic, diastolic, and mean blood pressure)
- Left ventricular hypertrophy
- Atrial fibrillation episodes
- Obstructive sleep apnoea severity (apnoea-hypopnoea index)
- Kidney function (change in serum creatinine, glomerular filtration rate (GFR), proteinuria or albuminuria, need for renal replacement therapy)
- Metabolic profile (change in lipid and blood glucose levels and insulin resistance indices)
- Withdrawal due to adverse effects, including but not limited to bradycardia and hypotensive episodes, femoral artery pseudoaneurysm, renal artery dissection, transient dizziness, pitting oedema, flank pain, and anaemia

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist conducted systematic searches in the following databases for randomised controlled trials without language, publication year or publication status restrictions:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 16 February 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) via the Cochrane Register of Studies Online (CRSO) (searched 15 February 2016);
- MEDLINE Ovid (from 1946 onwards), and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 15 February 2016);
- PubMed (searched 16 February 2016);
- Embase Ovid (searched 15 February 2016);
- ClinicalTrials.gov (www.clinicaltrials.gov) searched 15 February 2016);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) searched 15 February 2016).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Box 6.4.b. (Handbook 2011)). Search strategies for major databases are provided in Appendix 1.

Searching other resources

- The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE and Epistemonikos for systematic reviews) to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.
- We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
- Where necessary, we contacted authors of key papers and abstracts to request additional information about their trials.
- We did not perform a separate search for adverse effects of interventions used for the treatment of hypertension. We considered adverse effects described in included studies only.
- We checked the reference lists of cardiology and nephrology textbooks for additional resources.

Data collection and analysis

Selection of studies

Two authors (AP and LR) independently screened titles and abstracts, and retained studies and reviews that might include relevant data or information on trials for review in detail; studies that were not applicable were excluded. The same authors (AP and LR) independently assessed retrieved abstracts, and if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Two authors (AP and LR) independently carried out data extraction using a standard electronic data extraction form. We arranged for translations of studies reported in non-English language journals before assessment. If more than one publication of a study existed, we grouped the reports together and used the publication with the most complete data in the analyses. If relevant outcomes were published only in earlier versions of the study, we used such data.

Assessment of risk of bias in included studies

Two authors (AP and DB) independently assessed the following items using the 'Risk of bias' assessment tool (Higgins 2011).

- Sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding (detection bias)
  - Participants and personnel
  - Outcome assessors;
- Completeness of outcome data (attrition bias);
- Selective outcome reporting (reporting bias);
- Other sources of bias:e.g. funding bias.

Measures of treatment effect

We expressed dichotomous outcome results as risk ratios (RRs) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, we reported results as mean differences (MD) or standardised mean differences (SMD) if different scales were reported, with 95% CI.

Unit of analysis issues

We appraised unit of analysis issues according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Dealing with missing data

We requested additional information from the corresponding author(s) by email. We carefully evaluated important data, such as numbers of screened and randomised participants,

as well as numbers of intention-to-treat, as-treated, and per-protocol populations. We explored attrition in the study, such as drop-outs, losses to follow-up, and withdrawals. We appraised issues of missing data and imputation methods (such as last-observation-carried-forward) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We tested heterogeneity with a Chi^2 test on n - 1 degrees of freedom, using an alpha of 0.05 for statistical significance, and used the I^2 statistic (Higgins 2003). We considered I^2 values of 25%, 50%, and 75% to correspond to low, medium, and high levels of heterogeneity.

Assessment of reporting biases

Where possible, we had planned to construct funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

We analysed data for each outcome using Review Manager 5.3 (RevMan 2014) in an attempt to estimate the overall effect. We used the Mantel-Haenszel method for the fixed-effect model, except when statistical heterogeneity was observed, in which case we applied the random-effects model, to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses to explore possible sources of heterogeneity (e.g. participants, treatments). Heterogeneity among participants could be related to age, the presence of comorbidities (e.g. diabetes, cardiovascular diseases), the presence or severity of renal function impairment, and the duration and severity of hypertension (e.g. number and dosage of antihypertensive drugs used). Heterogeneity in treatments could be related to the type and duration of the renal sympathetic denervation procedure and the type of catheter and radiofrequency probe used. We also planned an exploration of the effect of short- and long-term follow-up as a source of significant heterogeneity between studies.

Sensitivity analysis

If applicable, we had planned sensitivity analyses to explore the influence of the following factors on effect size:

- repeating the analysis excluding any large studies, to establish how much they impact on the results;
- repeating the analysis taking into account the risk of bias;
- repeating the analysis excluding unpublished studies.

Summary of findings' table

We had planned to construct a summary table via the GRADEpro-GDT(GRADEpro GDT 2015), reporting:

- a summary of findings from all the primary outcomes
- a summary of findings from some secondary outcomes, that have been pre-selected according to their clinical importance. These include blood pressure outcomes (24 h-ABPM and office blood pressure), renal function (serum creatinine and eGFR), bradycardia and hypotensive episodes.
- the quality of the body of evidence supporting each of these outcomes

RESULTS

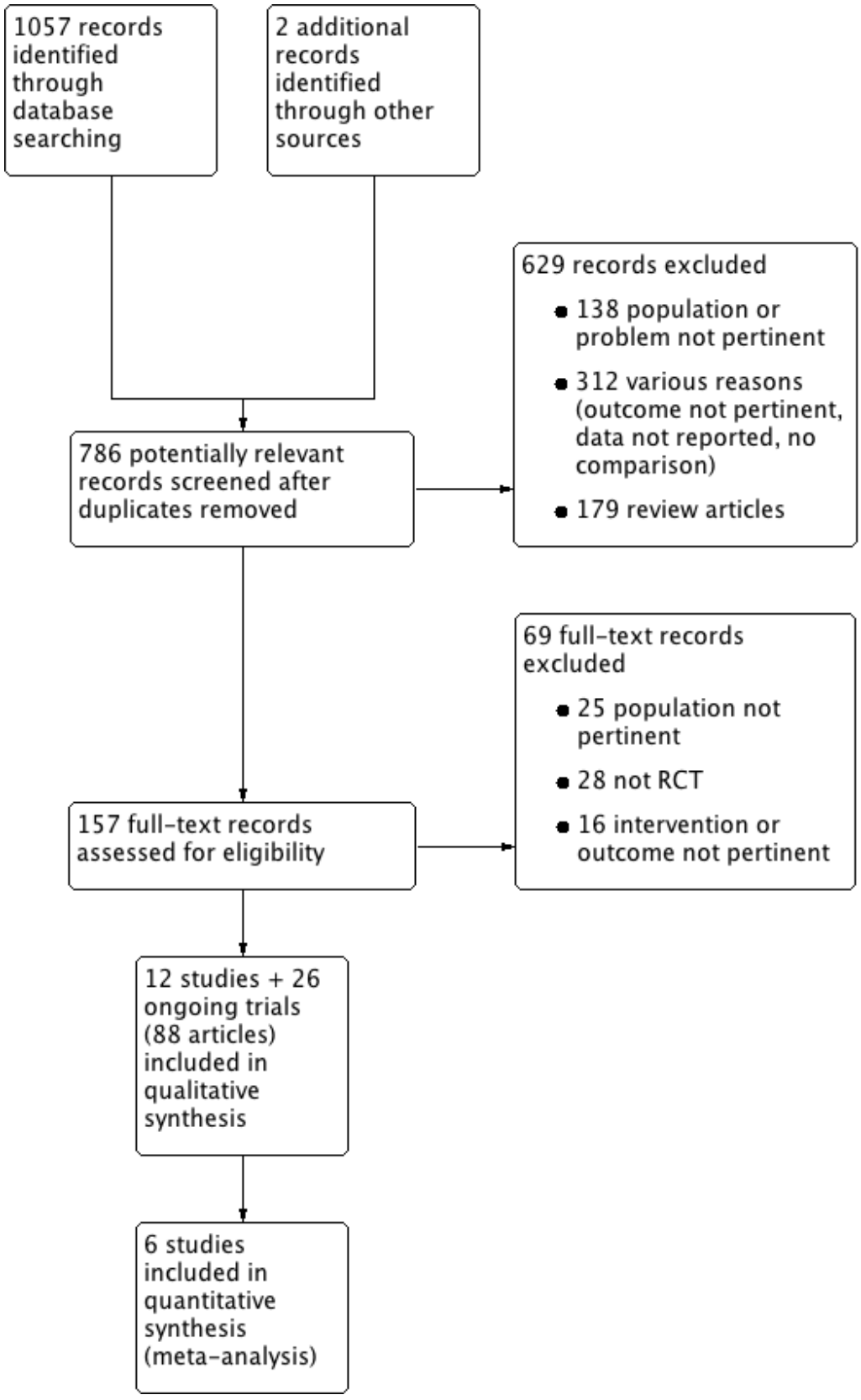
Description of studies

The literature search was current to 17 February 2016.

Results of the search

The search identified 1057 records; we also identified two additional records from personal searches. Full-text assessment of 157 records resulted in the inclusion of twelve eligible studies (58 articles), comprising a total of 1149 participants (DENER-HTN 2015; Desch 2015; Franzen 2012; Oslo RDN 2014; Prague-15 2016; RELIEF 2012; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014; Xiang 2014; HTN-JAPAN 2015; ReSET 2015), and 26 ongoing trials (30 articles; INSPIRED; DEPART; RENO; RSD4CKD; ReSET-2; RENSYMPIS; NCT01848275; RDNP-2012-01; ALLEGRO-HTN; PaCE; EnligHTN IV; RAPID II; NCT01968785; SYMPLICITY HTN-4; KPS; NCT02021019; DENERVHTA; ENSURE; NCT02346045; RSDforAF; SYMPATHY; NCT02444442; NCT02608632; NCT02667912; NCT01918111; NTR3444). We contacted the authors of some of the included studies for additional information about study methods, and unreported data; three investigators responded to our queries (DENER-HTN 2015; Prague-15 2016; SYMPLICITY HTN-2 2010). Figure 1 depicts the flow of study selection.

Figure 1. Study flow diagram.



Included studies

All twelve included studies were parallel RCTs (Characteristics of included studies). All studies were conducted in adults. Study duration ranged from 3 to 12 months. All studies except DENER-HTN 2015, Warchol 2014, and ReSET 2015 excluded patients with estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2. The renal sympathetic denervation procedure was performed with the electrode radiofrequency Symplicity catheter system in nine studies (DENER-HTN 2015; Desch 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014; HTN-JAPAN 2015; ReSET 2015). Ablation was performed with an off-the-shelf saline-irrigated radiofrequency catheter in RELIEF 2012. In Xiang 2014, ablation was made with the IBI-Therapy, St. Jude Medical radiofrequency catheter. In Franzen 2012, details of the denervation procedure were not provided. In seven studies, a series of four to six ablations per renal artery was performed (DENER-HTN 2015; Desch 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Xiang 2014; HTN-JAPAN 2015). In Oslo RDN 2014, an average of eight (range 6 to11) radiofrequency ablations were applied per renal artery. The number of ablations was not reported in four studies (Franzen 2012; RELIEF 2012; Warchol 2014; ReSET 2015). In four studies, renal denervation was compared to sham procedure (Desch 2015; RELIEF 2012; SYMPLICITY HTN-3 2014; ReSET 2015). Xiang 2014 compared a proximal ablation to a complete renal artery denervation. SYMPLICITY HTN-2 2010, Warchol 2014, Franzen 2012, and HTN-JAPAN 2015 compared renal denervation plus antihypertensive medications with antihypertensive medications alone. In three studies, the effects of renal denervation plus standard antihypertensive therapy were tested against an intensified pharmacological regimen (DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016). Outcomes available from studies were: incidence of myocardial infarction (DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-3 2014), ischaemic stroke (DENER-HTN 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014), unstable angina (Prague-15 2016; SYMPLICITY HTN-2 2010), all-cause-mortality and hospitalisations (SYMPLICITY HTN-3 2014), 24-hour ambulatory blood pressure monitoring (ABPM) or blood pressure (BP; DENER-HTN 2015; Desch 2015; Oslo RDN 2014; Prague-15 2016; RELIEF 2012; SYMPLICITY HTN-3 2014; Warchol 2014; ReSET 2015; HTN-JAPAN 2015), office ABPM or BP (DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; RELIEF 2012; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014; Xiang 2014; HTN-JAPAN 2015), home BP (DENER-HTN 2015; HTN-JAPAN 2015), left ventricular hypertrophy (Prague-15 2016), and kidney function (serum creatinine, eGFR; DENER-HTN 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; HTN-JAPAN 2015). In addition, DENER-HTN 2015; Desch 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Xiang 2014, and HTN-JAPAN 2015 looked systematically at the incidence of adverse effects associated to the procedure.

Excluded studies

We excluded 698 records, 629 of which were excluded at title and abstract screening (Figure 1). Sixty-nine records were excluded after full-text evaluation. Reasons for exclusion were: inappropriate population, problem, or both (163 reports); inappropriate intervention, outcome, or both (328 reports); not an RCT (28 reports); editorial, comment or letter without reporting randomised trial data (179 reports). See Characteristics of excluded studies.

Risk of bias in included studies

We have shown summaries of the risks of bias in the included studies in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

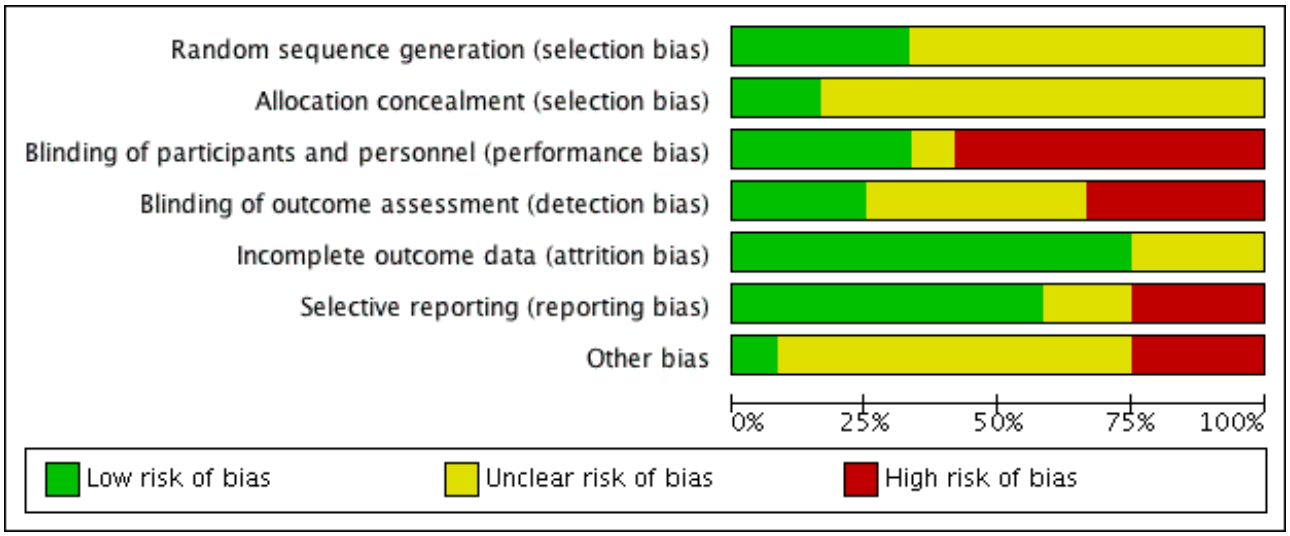
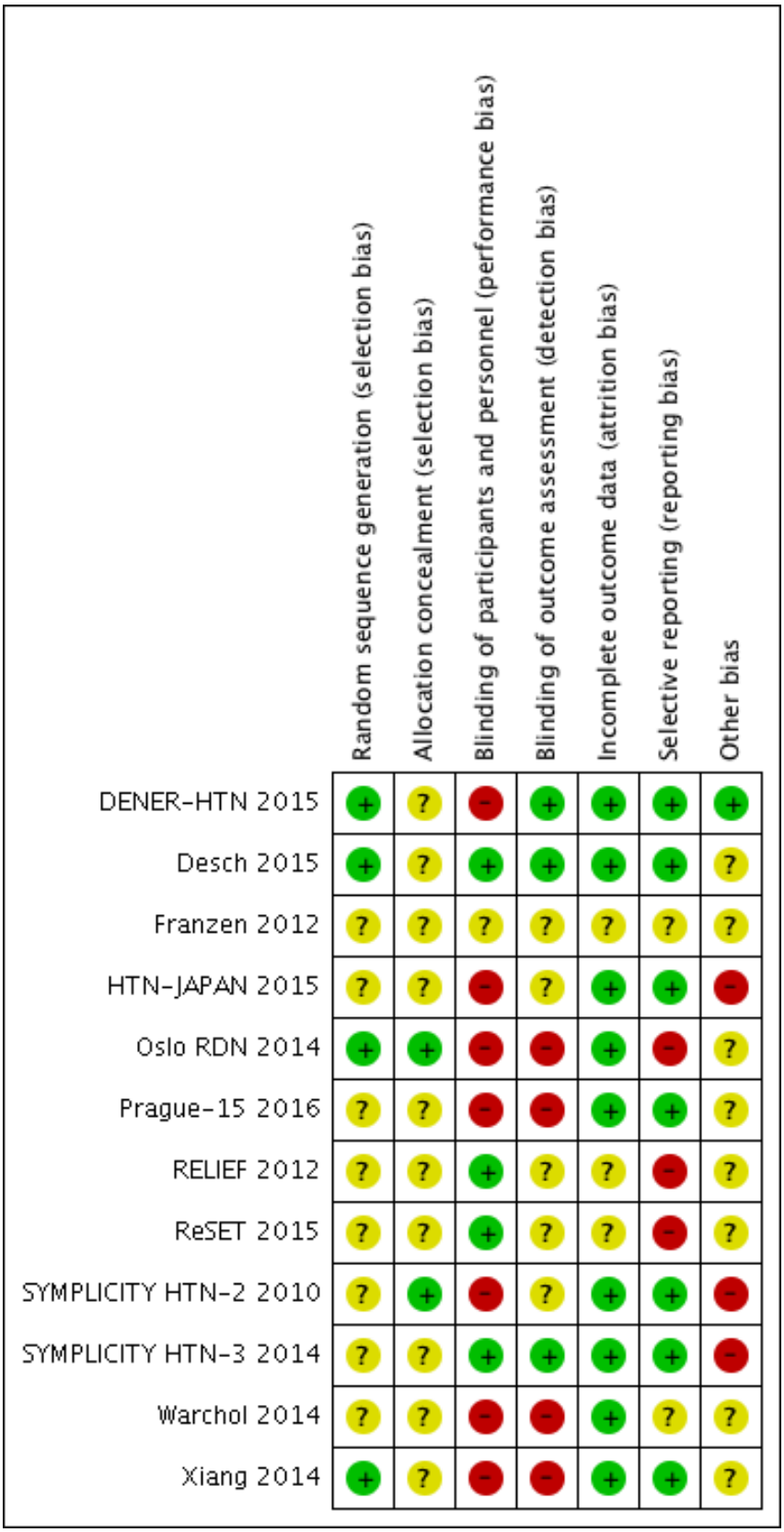


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The overall risk of selection bias was highly variable. Random sequence generation was detailed in four studies with a low risk of bias (DENER-HTN 2015; Desch 2015; Oslo RDN 2014; Xiang 2014), while there were insufficient data to inform assessment in the remainder. Only two of the included studies adequately described the allocation concealment methodologies that were applied (Oslo RDN 2014; SYMPLICITY HTN-2 2010); this information was not stated in the remainder.

Blinding

The risk of performance and detection bias was also variable. Six studies were fully open label, thus allowing a high risk of both biases (Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; Warchol 2014; Xiang 2014; HTN-JAPAN 2015). DENER-HTN 2015 was an open-label trial but outcome assessors were blinded to the procedure. ReSET 2015 was double-blinded; participants and personnel were unaware of treatment arm, while blinding of outcome assessment was not stated. In Desch 2015 and SYMPLICITY HTN-3 2014, participants and outcome assessors were blinded to the treatment. In RELIEF 2012, patients were blinded to renal denervation or sham procedure, while outcome assessor blinding was unclear. In Franzen 2012, no overall information on blinding was specified.

Incomplete outcome data

The overall drop-out rate ranged from 3% to 37% with no differences among groups, with the exception of DENER-HTN 2015 and SYMPLICITY HTN-3 2014, in which drop-outs were more prevalent in the treatment arm, and in Prague-15 2016, in which 31 participants (62%) dropped out from the control group. Four studies reported no drop-outs (Oslo RDN 2014; Warchol 2014; Xiang 2014; HTN-JAPAN 2015). The information provided on attrition bias was insufficient to permit assessment in three studies (Franzen 2012; RELIEF 2012; ReSET 2015). Six studies were analysed on an intention-to-treat basis (DENER-HTN 2015; Oslo RDN 2014; SYMPLICITY HTN-3 2014; Warchol 2014; Xiang 2014; HTN-JAPAN 2015). In SYMPLICITY HTN-2 2010, analyses were performed on a per-protocol basis. In Desch 2015 and Prague-15 2016, results were analysed on both a per-protocol and intention-to-treat basis.

Selective reporting

All the predefined outcomes were reported in seven studies (DENER-HTN 2015; Desch 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Xiang 2014; HTN-JAPAN 2015). Some prespecified outcomes were not reported in RELIEF 2012 (office BP, serum creatinine) or in ReSET 2015 (daytime and night time BP, dipping status, diastolic and systolic ventricular function, left ventricular hypertrophy, renal sodium excretion, pulse wave velocity, a 25% or more decline in eGFR). Possible selective reporting was unclear in the remainder.

Other potential sources of bias

Five studies declared to be funded from industry (DENER-HTN 2015; Oslo RDN 2014; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; HTN-JAPAN 2015). In DENER-HTN 2015, the authors stated that the sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. In Oslo RDN 2014, the involvement of industry was unclear. In SYMPLICITY HTN-2 2010, SYMPLICITY HTN-3 2014, and HTN-JAPAN 2015 the authors declared that data were monitored, collected, and managed by the sponsor. No other sources of apparent bias were noticed in the other studies.

Effects of interventions

See: **Summary of findings for the main comparison**

The main effects of renal denervation on the primary outcomes and on the most important secondary outcomes are summarized in Summary of findings for the main comparison.

Primary outcomes

Non-fatal cardiovascular events

In a meta-analysis of four studies (742 participants), renal denervation was not significantly associated with a lower risk of myocardial infarction than sham or standard treatment (RR 1.31, 95% CI 0.45 to 3.84; Analysis 1.1); there was no heterogeneity (Chi^2 = 0.79; P = 0.85; I^2 = 0%; DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-3 2014). In data pooled from four studies (823 participants), renal denervation was not significantly associated with a lower risk of ischaemic stroke than no treatment (RR 1.15, 95% CI 0.36 to 3.72; Analysis 1.2); there was no heterogeneity (Chi^2 = 1.27; P = 0.74; I^2 = 0%; DENER-HTN 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014). In a meta-analysis of two studies (201 participants), renal denervation was not associated with a lower risk of unstable angina than standard therapy (RR 0.63, 95% CI 0.08 to 5.06; Analysis 1.3); there was no heterogeneity (Chi^2 = 0.29; P = 0.59; I^2 = 0%; Prague-15 2016; SYMPLICITY HTN-2 2010).

All-cause mortality

Data on all-cause mortality were provided by one study, in which two patients in the renal denervation group and one in the sham procedure group died (SYMPLICITY HTN-3 2014).

Hospitalisation

Data on hospitalisation were only available in SYMPLICITY HTN-3 2014. Five patients in the renal denervation and one patient in the sham group had hospital admissions for atrial fibrillation episodes; nine patients in the renal denervation group and three in the sham group required hospitalisation for a new-onset of heart failure.

Secondary outcomes

24-hour ambulatory blood pressure monitoring (ABPM)

Twenty-four hour ABPM was measured in eight studies (DENER-HTN 2015; Desch 2015; Oslo RDN 2014; Prague-15 2016; RELIEF 2012; SYMPLICITY HTN-3 2014; HTN-JAPAN 2015; ReSET 2015). In a meta-analysis of five studies (797 participants), renal denervation did not produce significant changes in systolic 24-hour ABPM when compared with sham or standard therapy (MD 0.28 mmHg, 95% CI -3.74 to 4.29; Analysis 1.4); there was low heterogeneity (Chi^2 = 7.27; P = 0.12; I^2 = 45%; DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-3 2014; HTN-JAPAN 2015). Similarly, renal denervation was not superior to sham or standard therapy in reducing diastolic 24-hour ABPM (4 studies, 756 participants; MD 0.93 mmHg, 95% CI -4.50 to 6.36; Analysis 1.5). There was high heterogeneity in this latter analysis (Chi^2 = 22.50, P < 0.0001; I^2 = 87%) that could not be further explained due to the paucity

of studies available (DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-3 2014).

In RELIEF 2012, the 24-hour systolic/diastolic BP decreased by -17/-12 mmHg (P = 0.006/P = 0.001) in the bilateral renal denervation group versus -5/-5 mmHg (P = 0.22/P = 0.42) in the sham control group. In ReSET 2015, renal denervation (RD) and sham procedures showed a similar reduction in 24-hour systolic ABPM after six-month follow-up (-6.1 ± 18.9 (RD) versus -4.3 ± 15.1 mmHg (sham)). HTN-JAPAN 2015 recorded no difference between groups in 24-hour diastolic BP (-3.8 mmHg, 95% CI -8.3 to 0.6; P = 0.091). In Desch 2015, the mean change for the 24-hour systolic BP was −7.0 mmHg (95%CI −10.8 to −3.2) for patients undergoing renal denervation and −3.5 mmHg (95%CI −6.7 to −0.2) in the sham group (P = 0.15), as analysed on an intention-to-treat basis. In the per-protocol population, the change in 24-hour systolic BP at six months was −8.3 mmHg (95%CI −11.7 to −5.0) for patients undergoing renal denervation and −3.5 mmHg (95%CI −6.8 to −0.2) in the sham group (P = 0.042). No statistically significant changes in 24-hour diastolic BP were recorded in either the intention-to-treat or per-protocol analysis. All these single-study data were directly retrieved from the correspondent papers.

Office BP

In separate meta-analyses of six studies (886 participants) and five studies (845 participants), renal denervation had no conclusive effects on systolic or diastolic office BP when compared with sham procedure or standard therapy (systolic: MD -4.08 mmHg, 95% CI -15.26 to 7.11; Analysis 1.6; DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; HTN-JAPAN 2015; diastolic: MD -1.30 mmHg, 95% CI -7.30 to 4.69; Analysis 1.7; DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014. There was high heterogeneity in these analyses (Chi^2 = 59.87; P < 0.00001; I^2 = 92% and Chi^2 = 27.44; P < 0.00001; I^2 = 85%, respectively) that could not be further explained due to the low number of studies included.

In Xiang 2014, at six-month follow-up, the average office systolic/diastolic BP decreased significantly from 191.2/98.3 at baseline to 136.3/80.2 mmHg in the group undergoing proximal ablation, and from 181.4/98.5 to 136.5/79.5 mmHg in the group undergoing the whole ablation. HTN-JAPAN 2015 recorded a greater average diastolic office BP reduction in the renal denervation group than in the control group, with a change difference of -6.9 mmHg (95% CI -13.2 to 0.5; P = 0.036). These data were obtained from the correspondent study article.

Home BP

In HTN-JAPAN 2015, no change difference in home systolic and diastolic BP was observed between the renal denervation and control groups (-5.6 mmHg (95% CI -14.5 to 3.2; P = 0.205) and -4.8 mmHg (95% CI -9.8 to 0.3; P = 0.065), respectively). In DENER-HTN 2015, the mean change in home systolic and diastolic BP was -15.4 mmHg (95% CI -20.4 to -10.4) and -8.7 mmHg (95% CI -12.1 to -5.4) in patients undergoing renal denervation and -11.8 mmHg (95% CI -16.5 to -7.1) and -6.7 mmHg (95% CI-9.8 to -3.5) in the control group, with no differences between groups (P = 0.30 and P = 0.37) for systolic and diastolic BP, respectively.

Left ventricular mass (LVH)

Twelve-month follow-up data on left ventricular mass (LVM) and LVM indexed (LVMI) were provided by one study, which reported no significant difference in change between the renal denervation and control groups (10 (95% CI -13 to 33) and 2.3 (95% CI -2.7 to 7.4) for LVM and LVMI, respectively (Prague-15 2016).

Kidney function

In a meta-analysis of three studies (736 participants), renal denervation had no tangible effects over sham or standard treatment on serum creatinine levels (MD 0.01 mg/dL, 95% CI -0.12 to 0.14; Analysis 1.8), with high heterogeneity (Chi^2 = 12.75; P = 0.002; I^2 = 84%), which could not be further explored, as only three studies were included (Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014). Nevertheless, SYMPLICITY HTN-3 2014 reported five cases in the renal denervation group and one case in the sham group, who had an increase in serum creatinine levels greater than 50% from baseline. One case of 50% increase in serum creatinine was also reported in the renal denervation group after six months of follow-up in HTN-JAPAN 2015.

In another meta-analysis of four studies (837 participants), renal function, as estimated by eGFR or creatinine clearance, remained unaffected after renal denervation compared to control (MD -2.09 mL/min, 95% CI -8.12 to 3.95; Analysis 1.9), with moderate heterogeneity (Chi^2 = 7.09, P = 0.07; I^2 = 58%), which could not be further explored (DENER-HTN 2015; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014).

Prague-15 2016 recorded an unspecified decline in renal function in one patient undergoing the standard treatment.

Adverse events

Major adverse events were systematically collected by seven studies (DENER-HTN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Xiang 2014; HTN-JAPAN 2015). HTN-JAPAN 2015 reported no periprocedural complications in either the renal denervation or control arms. No study provided information on the occurrence of transient dizziness or anaemia.

Bradycardia

In a meta-analysis of three studies (220 participants), renal denervation was significantly associated with an almost seven-fold higher risk of bradycardia symptoms than other treatments (RR 6.63, 95% CI 1.19 to 36.84; Analysis 1.10), with no heterogeneity (Chi^2 = 0.63; P = 0.73; I^2 = 0%; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010).

Femoral artery pseudoaneurysm

Pooled data from two studies (201 participants) showed that renal denervation was not statistically associated with a higher risk for femoral artery pseudoaneurysm than standard therapy (RR 3.96, 95% CI 0.44 to 35.22; Analysis 1.11), with no heterogeneity (Chi^2 = 0.04; P = 0.84; I^2 = 0%; Prague-15 2016; SYMPLICITY HTN-2 2010).

Renal artery dissection

In Prague-15 2016, there was one case of renal artery dissection related to the procedure.

Renal artery vasospasm

Four cases of renal artery vasospasm in patients undergoing renal denervation were observed in Prague-15 2016. Xiang 2014 reported two cases of renal artery vasospasm in the whole ablation group versus none in the proximal ablation group.

New renal-artery stenosis

SYMPLICITY HTN-3 2014 reported one case of re-stenosis in the renal denervation group (documented as new renal artery stenosis of more than 70%) within the six-month follow-up.

Flank pain

In a meta-analysis of two studies (199 participants), renal denervation was not significantly associated with a higher risk of flank pain than control (RR 4.30, 95% CI 0.48 to 38.28; Analysis 1.12), with no heterogeneity (Chi^2 = 0.08; P = 0.78; I^2 = 0%; DENER-HTN 2015; SYMPLICITY HTN-2 2010).

Pitting oedema

One case of oedema requiring hospital admission was provided by SYMPLICITY HTN-2 2010.

Hypotensive episodes

In a meta-analysis of two studies (119 participants), the renal denervation procedure was not associated with a higher risk of hypotensive episodes than no treatment (RR 0.67, 95% CI 0.07 to 6.64; Analysis 1.13), with low heterogeneity (Chi^2 = 1.61; P = 0.20; I^2 = 38%; Oslo RDN 2014; SYMPLICITY HTN-2 2010).

Hypertensive crisis

In data pooled from three studies (722 participants), renal denervation was not significantly associated with a higher risk for hypertensive episodes than no treatment (RR 0.71, 95% CI 0.35 to 1.45; Analysis 1.14), with no heterogeneity (Chi^2 = 1.83; P = 0.40; I^2 = 0%; DENER-HTN 2015; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014).

Hyperkalemia

In a meta-analysis of two studies (200 participants), patients in the renal denervation group had no higher risk of hyperkalaemia than those in standard therapy (RR 0.48, 95% CI 0.01 to 21.33; Analysis 1.15). There was moderate heterogeneity in this analysis (Chi^2 = 3.17; P = 0.07; I^2 = 68%), which could not be further explored, as only two studies were included (Prague-15 2016; DENER-HTN 2015).

Syncope

In DENER-HTN 2015, one patient in the control group experienced an episode of syncope.

Embolic event

In SYMPLICITY HTN-3 2014, one case of embolic event resulting in end-organ damage was reported in the renal denervation group.

Withdrawals

Nine studies provided information on withdrawals (DENER-HTN 2015; Desch 2015; HTN-JAPAN 2015; Oslo RDN 2014; Prague-15 2016; SYMPLICITY HTN-2 2010; SYMPLICITY HTN-3 2014; Warchol 2014; Xiang 2014). SYMPLICITY HTN-3 2014 recorded 14 (3.8%) withdrawals from the renal denervation group and two (1.2%) from the control arm. In SYMPLICITY HTN-2 2010, there were three withdrawals from both the intervention and control arms. DENER-HTN 2015 reported five (10%) withdrawals from the renal denervation group. In Desch 2015, six participants (17%) withdrew from the renal denervation and two (5.55%) from the sham group. Prague-15 2016 recorded seven (13.7%) and 31 (62%) withdrawals from the renal denervation and control groups, respectively. Four studies reported no withdrawals (Oslo RDN 2014; Warchol 2014; Xiang 2014; HTN-JAPAN 2015).

Outcomes not stated

No RCT provided data on the following outcomes: fatal cardiovascular events, quality of life, atrial fibrillation episodes, sleep apnoea severity, need for renal replacement therapy, proteinuria, albuminuria, or metabolic profile (blood glucose, insulin resistance).

Sensitivity analyses, investigation of heterogeneity, and publication bias

Although planned, such analyses were not performed due to the small number of studies retrieved and analysed.

DISCUSSION

Summary of main results

In patients with resistant hypertension, a renal denervation procedure did not reduce the risk of major cardiovascular events, including myocardial infarction, ischaemic stroke, and unstable angina, compared with controls. Furthermore, this procedure had no definite effects on 24-hour ABPM, office systolic or diastolic blood pressure, and no apparent benefits on renal function, while it increased the risk of bradycardia episodes. Conversely, renal denervation was not associated with a significantly higher risk of other adverse effects, such as femoral artery pseudo-aneurysm, flank pain, hypotensive or hypertensive episodes, and long-term hyperkalaemia. Data on mortality, hospitalisations, and other adverse effects were limited to single studies.

Overall completeness and applicability of evidence

The evidence on the benefits of this procedure remains inconclusive, and hence, poorly applicable in clinical practice. Many clinically relevant outcomes, such as fatal cardiovascular events, quality of life, sleep apnoea severity, need for renal replacement therapy, and metabolic profile, were not explored in any included RCT. Heterogeneity was high to very high in the majority of analyses carried out, hampering the overall reliability of findings. Although exploration of heterogeneity was not feasible due to the paucity of studies included in each analysis, it can be speculated that differences among individual study designs (e.g. use of sham procedure or standard therapy as control, presence or/ absence of blinding in outcome assessment) may represent one of the main causes underlying this phenomenon. In most trials, both study groups were simultaneously treated with optimal anti-hypertensive therapy to decrease blood pressure to an established target. Administration of these drugs was variable and non-reproducible. Procedural methods were also heterogeneous among studies, particularly in terms of type of catheter employed, number of applications, energy delivered and target portion of renal artery. Sakakura et al. recently observed that nervous fibres are mostly concentrated in the middle and proximal segments of

the renal artery while their number decrease in the distal segment (Sakakura 2014). Recent data evidenced maximum procedural efficacy after ablation in the whole circumference of renal artery and a dose-response dependency directly related to the amount of energy delivered (Kandzari 2015).The lack of standardized methods for renal denervation may hamper the reliability of comparisons among studies and, in some cases, even raise the question as to whether the procedure was truly successful (Esler 2015). For instance, in a corollary analysis of the SYMPLICITY HTN-2 2010 trial the measurement of norepinephrine spillover seemed to indicate that in only 47% of patients renal denervation was truly achieved. Hence, technical bias should be considered in future trials as a potential cause of lack of response in many patients and reliable markers to confirm successful denervation are advocated. In addition, accumulating evidence indicated that the phenomena of re-innervation of renal arteries after denervation may seriously hamper the achievement of long term benefits (Booth 2015).

Quality of the evidence

The GRADE quality of the evidence (Guyatt 2008) was low for cardiovascular morbidity outcomes and adverse effects and moderate for blood pressure and renal function outcomes. The quality of evidence was mostly influenced by the imprecision of results (wide confidence intervals) and/or the low number of studies providing quantitative data on the same outcome.

Potential biases in the review process

Points of strength of this review are represented by a peer-reviewed protocol, a systematic search of electronic databases, and data extraction, analysis, and 'Risk of bias' assessment completed independently by two authors, according to current methodological standards. The main limitation is represented by the data obtainable from the included studies. Studies were mainly focused on small populations and short treatment periods. As a result, most trials were not adequately powered to capture exhaustive information on hard, patient-centred outcomes, such as fatal or non-fatal cardiovascular events. The limited evidence available also prevented more complex analyses, such as sensitivity analyses, interaction tests, and analysis for publication bias.

Agreements and disagreements with other studies or reviews

In a recent systematic review, renal denervation was apparently efficacious in reducing mean blood pressure at six months in individuals with resistant hypertension (Davis 2013). Unfortunately, this review was mostly based on data from observational, uncontrolled studies with limited follow-up, small sample sizes, and high heterogeneity in blood pressure measurement. Findings from our review were in line with observations made by a more recent meta-analysis of the European Network Coordinating Research On Renal Denervation (ENCOReD) Consortium (Fadl Elmula 2015). The authors confirmed the current lack of evidence supporting a widespread use of this procedure in clinical practice, advocating for future clinical trials with a longer observation time, which enrol hypertensive patients with fewer comorbidities.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence accrued so far is insufficient to support the use of renal denervation as a clinically useful procedure for improving cardiovascular risk and blood pressure control in patients with resistant hypertension. In patients with resistant hypertension, there is low quality evidence that renal denervation does not change major cardiovascular events, and renal function. There is moderate quality evidence that renal denervation does not change blood pressure and and low quality evidence that it caused an increase of bradycardia episodes.

Implications for research

Focused trials, powered for patient-centred instead of surrogate outcomes, with longer follow-up periods, larger sample sizes, more standardised procedural methods, and possibly examining particular subgroups of patients with resistant hypertension (e.g. subjects with different cardiovascular or renal risk profile) are needed to clarify the optimal target population for this procedure. Study design providing a sham control procedure and blinded outcome assessors are indispensable for minimising bias and improving reliability of findings.

ACKNOWLEDGEMENTS

We thank Dr Murray Esler, Dr Michel Azizi, and Dr Jan Rosa for providing additional trial data. We would also like to thank the Cochrane Hypertension Group, particularly Mr Ciprian Jauca and Mr Douglas Salzwedel, for their valuable support, and the referees for their feedback and advice during the preparation of the review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

DENER-HTN 2015

Methods	• Study type: parallel, RCT • Country: France • Setting: University

Participants	• Number of patients randomised/analysed: 106/101
	• Age: range 18 to 75 years, mean 55.2
	• Males (%): ˜62.2
	• Office Blood Pressure (BP; mmHg): ˜158/93
	• Diabetes mellitus (%): ˜21.7
	• Hyperlipidaemia (%): ˜46.2
	• Prior cardiovascular event (%): ˜25.5
	• Prior stroke (%): ˜10.4
	• Obstructive sleep apnoea (%): ˜27.4
	• eGFR (mL/min/1.73 m^2): ˜89
	• Antihypertensive treatment
	  • Diuretics (%): 100
	  • ACEIs (%): 84
	  • ARBs (%): 16
	  • CCBs (%): 94.3
	
	Exclusion criteria: secondary hypertension, eGFR < 40 mL/min/1.73 m^2, history of severe cardiovascular disease or stroke in the previous three months, history of contraindication or intolerance to the study drugs, type 1 diabetes mellitus, brachial circumference > 42 cm, atrial fibrillation, unsuitable renal artery anatomy (accessory renal arteries > 3 mm in diameter, main renal artery < 4 mm in diameter or < 20 mm in length, renal artery stenosis > 30%, prior renal artery intervention or kidney length <

DENER-HTN 2015 *(Continued)*

	90 mm) ruled out by computed tomography angiogram, magnetic resonance angiogram or renal angiogram
Interventions	• Treatment group: N = 48, renal denervation plus standardised stepped-care antihypertensive treatment (SSAHT) • Control group: N = 53, standardised stepped-care antihypertensive treatment (SSAHT) alone • Renal denervation procedure: Ablation done with the single electrode radiofrequency Symplicity catheter. A series of four to six ablations per renal artery were performed. • SSAHT: Initial standardised triple therapy (indapamide 1.5 mg, ramipril 10 mg or irbesartan 300 mg, and amlodipine 10 mg daily) + spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day • Follow-up: up to 6 months
Outcomes	• Day-time ambulatory blood pressure monitoring (ABPM) • 24-hour ABPM • Office and home ABPM • Proportion of patients with controlled blood pressure • estimated Glomerular Filtration Rate (eGFR) • Adverse events
Notes	Modified intention-to-treat and per-protocol analyses performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	quote: "The randomisation sequence was generated by computer and stratified by centres using randomised blocks of small size and permutation of treatments within each block"
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/48 (10%) drop-outs in treatment group (three lost to follow-up and two with missing ABPM). A modified intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	all the pre-specified outcomes have been reported
Other bias	Low risk	The funder of the study (French Ministry of Health) had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Desch 2015

Methods	• Study type: parallel, RCT

Desch 2015 *(Continued)*

- Country: Germany
- Setting: University

Participants	• Number of patients randomised/analysed (intention-to-treat, per-protocol): 71/(67,63)
	• Age: ˜60 years
	• Males (%): ˜73
	• Day-time ABPM (mmHg): ˜144/82
	• Smokers (%): 14
	• History of stroke/transient ischaemic attack (%): 7
	• Coronary artery disease (%): ˜53
	• Peripheral arterial disease (%): ˜9
	• Diabetes mellitus (%): ˜45
	• eGFR (mL/min/1.73 m^2): ˜82
	• Antihypertensive drugs (n): ˜4.4
	• ≥ 5 antihypertensive drugs (%): ˜40
	• Antihypertensive treatment
	  • Diuretics (%): ˜96
	  • ACEIs (%): ˜54
	  • ARBs (%): ˜47
	  • CCBs (%): ˜67
	  • Direct renin inhibitors (%): ˜6
	  • β-blockers (%): ˜93
	  • α-blockers (%): ˜18
	  • Aldosterone antagonists (%): ˜5
	
	Exclusion criteria: mean day-time systolic BP on 24-hour ABPM < 135 and > 149 mmHg or mean day-time diastolic BP < 90 and > 94 mmHg, unsuitable anatomy for renal denervation, severe renal artery stenosis, eGFR < 45 mL/min/1.73 m^2, change in BP medication in the 4 weeks preceding randomisation, unwillingness to adhere to unchanging BP medication during the study period of 6 months, unstable angina pectoris, myocardial infarction within 6 months prior to randomisation, planned surgery or cardiovascular intervention within 6 months after randomisation, severe heart valve disease, pregnancy, and severe comorbidities with limited life expectancy

Interventions	• Treatment group: N = 35, renal denervation • Control group: N = 36, sham procedure • Renal denervation procedure: Ablation done with the Symplicity Flex catheter. Four to 6 ablation runs of 2 minutes for each renal artery were delivered circumferentially to the renal artery wall from distal to proximal • Sham procedure: Angiography of the renal arteries and a simulated renal denervation procedure with 4 to 6 sham runs for each renal artery guided by 2-minute acoustic signals similar to those of the Symplicity generator • Follow-up: up to 6 months
Outcomes	• 24-hour BP in the intention-to-treat population • 24-hour BP in the per-protocol population • Adverse events • All-cause death
Notes	Intention-to-treat and per-protocol analyses performed

Risk of bias

Bias	Authors' judgement	Support for judgement

Desch 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	quote: "Patients were assigned to the treatment groups by simple randomisation, in a 1:1 ratio, via an internet-based system using a computer-generated list of random numbers"
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	single blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	all investigators (including personnel responsible for BP assessment) were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/71 (11%) drop-outs (6 in RD and 2 in sham procedure); intention-to-treat and per-protocol analyses performed
Selective reporting (reporting bias)	Low risk	all the pre-specified outcomes have been reported
Other bias	Unclear risk	no apparent other sources of bias

Franzen 2012

Methods	• Study type: parallel, RCT • Country: Germany • Setting: Hospital
Participants	• Number of patients randomised/analysed: 27/27 • Age: range 18 to 82 years, mean 63 • Systolic BP (mmHg): > 150 • Antihypertensive drugs (n): ˜4.7
Interventions	• Treatment group: N = 21 • Control group: N = 6 • Follow-up: up to 6 months
Outcomes	• Peripheral systolic BP • Central systolic BP • Pulse wave velocity (PWV) • Aortic stiffness parameters
Notes	study in abstract version only. Unclear if patients were truly randomised (quote: "21 patients were randomised to PRD. 6 patients served as controls")

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified

Franzen 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not specified
Selective reporting (reporting bias)	Unclear risk	not specified
Other bias	Unclear risk	not specified

HTN-JAPAN 2015

Methods	• Study type: parallel, RCT • Country: Japan • Setting: University and Hospital

Participants	• Number of patients randomised/analysed: 41/41
	• Age: range 20 to 80 years, mean: ˜58
	• Males (%): ˜76
	• Office systolic BP (mmHg): ˜180
	• 24-h mean systolic ABPM (mmHg): ˜164
	• type 2 diabetes mellitus (%): ˜50
	• Hypercholesterolemia (%): ˜32
	• Prior stroke (%): ˜17
	• Obstructive sleep apnoea (%): ˜10
	• eGFR (mL/min/1.73 m^2): ≥45
	• Antihypertensive drugs (n): ˜4.9
	• Antihypertensive treatment
	  • Diuretics (%): 100
	  • ACEIs (%): ˜12
	  • ARBs (%): ˜98
	  • CCBs (%): ˜95
	  • Direct renin inhibitors (%): 0
	  • β-blockers (%): ˜75
	  • α-blockers (%): ˜33
	  • Aldosterone antagonist (%): ˜41
	
	Exclusion criteria: Main renal arteries < 4 mm in diameter or < 20 mm treatable length, multiple renal arteries, renal artery stenosis > 50% or renal artery aneurysm in either renal artery, history of prior renal artery intervention including balloon angioplasty or stenting and unilateral (functional or morphological) kidney, > 1 inpatient hospitalisation for hypertensive crisis not related to non-adherence to

HTN-JAPAN 2015 *(Continued)*

	medication within the previous year, type 1 diabetes mellitus and ≥ 1 episodes of orthostatic hypotension not related to medication changes, secondary hypertension
Interventions	• Treatment group: N = 22, Renal denervation plus antihypertensive medications • Control group: N = 19, antihypertensive medications alone • Renal denervation procedure: Ablation done with the Symplicity™ RDN system (Medtronic, Santa Rosa, CA, USA). Four to 6 ablation runs of 120 sec for each renal artery were delivered circumferentially to the renal artery wall from distal to proximal • Follow-up: up to 6 months
Outcomes	• Change in office BP • Change in 24-hour ABPM and home BP • Incidence of major adverse events (composite of 1-month all-cause mortality, end stage renal disease, significant embolic event resulting in end-organ damage, renal artery dissection or perforation requiring intervention, vascular complications, hospitalisation for hypertensive crisis or new renal artery stenosis > 70% confirmed on angiography within 6 months after randomisation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs. Intention-to-treat analysis performed
Selective reporting (reporting bias)	Low risk	all the pre-specified outcomes have been reported
Other bias	High risk	Honoraria from Medtronic. Involvement of Medtronic in data collection and statistical analyses

Oslo RDN 2014

Methods	• Study type: parallel, RCT • Country: Norway • Setting: University
Participants	• Number of patients randomised/analysed: 19/19

Oslo RDN 2014 *(Continued)*

- Age: range 37 to 70 years, mean ˜60
- Males (%): ˜89
- Office BP (mmHg): ˜158/90
- Diabetes mellitus (%): ˜26
- Coronary artery disease (%): ˜35
- Left ventricular hypertrophy (%): ˜58
- Peripheral arteriosclerosis (%): ˜5
- Previous stroke (%): ˜10
- Hypercholesterolaemia (%): ˜31
- Microalbuminuria (%): ˜37
- Cystatin C (mg/L): ˜1.0
- Antihypertensive drugs (n): ˜5.1
- Antihypertensive treatment
  - Diuretics (%): 100
  - ACEIs/ARBs (%): 100
  - CCBs (%): ˜80
  - Direct renin inhibitors (%): ˜10
  - β-blockers (%): ˜73
  - α-blockers (%): ˜37
  - Aldosterone antagonist (%): ˜47

Exclusion criteria: secondary and spurious hypertension, known primary hyperaldosteronism not adequately treated, eGFR < 45 mL/min/1.73 m^2, urine albumin/creatinine ratio > 50 mg/mmol, type 1 diabetes mellitus, stenotic valvular heart disease, myocardial infarction, unstable angina, or CVA in the prior 6 months, haemodynamically or anatomically significant renal artery abnormalities or stenosis > 50% or prior renal artery intervention, known primary pulmonary hypertension, known pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism

Interventions

- Treatment group: N = 9, renal denervation plus baseline antihypertensive treatment
- Control group: N = 10, drug-adjusted treatment
- Renal denervation procedure: renal denervation performed using a 6 French guide Symplicity catheter system. On average 8 (range 6 to 11) radiofrequency ablations were applied per renal artery
- Follow-up: up to 6 months

Outcomes

- 24-hour ABPM
- Office BP
- Day-time ABPM
- Normalization of haemodynamics: cardiac index, heart rate, stroke systemic vascular resistance index, pulse wave velocity (PWV), and central blood pressure
- Adverse events

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	quote: "randomisation performed using a permuted block randomisation list"
Allocation concealment (selection bias)	Low risk	quote: "A hospital employee opened a sealed envelope arranged in a fixed order"

Oslo RDN 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	no drop-outs
Selective reporting (reporting bias)	High risk	some pre-specified outcomes were not reported
Other bias	Unclear risk	Honoraria from Medtronic and Hemo Sapiens. Involvement of industry in data collection and analyses not specified

Prague-15 2016

Methods	• Study type: parallel, RCT • Country: Czech Republic • Setting: University

Participants	• Number of patients randomised/analysed: 101/101
	• Age: ˜58 years
	• Males (%): ˜70
	• Office BP (mmHg): ˜157/91
	• 24-hour ABPM (mmHg): ˜148/85
	• Duration of hypertension (yrs): ˜17
	• Diabetes mellitus (%): ˜20
	• Coronary heart disease (%): ˜6
	• Smokers (%): 15
	• Statin users (%): ˜53
	• Creatinine (µmol/L): ˜86
	• Creatinine clearance (mL/s/1.73 m^2): ˜1.6
	• Antihypertensive drugs (n): ˜5.3
	• Antihypertensive treatment
	  • Diuretics (%): 100
	  • ACEIs/ARBs (%): 100
	  • CCBs (%): 89
	  • β-blockers (%): ˜67
	  • α-blockers (%): ˜50
	
	Exclusion criteria: secondary hypertension, non-compliance with medical treatment, presence of any chronic renal disease (serum creatinine > 200 µmol/L), pregnancy, history of myocardial infarction or stroke in the previous 6 months, presence of severe valvular stenotic disease, anatomical abnormality or a variant structure of either renal artery, including aneurysm, stenosis, a reference diameter < 4 mm and a length < 20 mm, an increased bleeding risk (thrombocytopenia < 50.000 platelets/µL and an INR > 1.5)

Interventions	• Treatment group: N = 51, renal denervation plus baseline medical therapy

Prague-15 2016 *(Continued)*

	• Control group: N = 50, intensified pharmacological treatment including spironolactone (PHAR) • Renal denervation procedure: ablation involved ≥ 4 to 6 applications of low-power (8 W) radiofrequency energy to each renal artery using the Symplicity renal denervation system • Follow-up: up to 12 months
Outcomes	• 24-hour ABPM • Office BP • Average number of antihypertensive drugs used after 6 months • Renal function (serum creatinine, creatinine clearance)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	38/101 (37%) drop-outs (7 in RD and 31 in PHAR group); intention-to-treat and per-protocol analyses performed
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes have been reported
Other bias	Unclear risk	No apparent other sources of bias

RELIEF 2012

Methods	• Study type: parallel, RCT • Country: Czech Republic • Setting: Hospital
Participants	• Number of patients randomised/analysed: 23/23 • Age: range 18 to 85 years • Office BP (mmHg): ≥ 140 • Exclusion criteria: secondary hypertension, eGFR < 45 mL/min/1.73 m^2, type 1 diabetes mellitus, renovascular abnormalities (renal artery stenosis, previous renal artery stenting or angioplasty), life expectancy < 1 year for any medical condition
Interventions	• Treatment group: N = 11, bilateral RD with a saline-irrigated catheter

RELIEF 2012 *(Continued)*

	• Control group: N = 12, sham procedure • Renal denervation procedure: ablation performed with an off-the-shelf saline-irrigated radiofrequency ablation catheter • Sham procedure: angiography of the renal arteries (manipulation of catheter within the renal arteries without the delivery of any energy) • Follow-up: up to 3 months
Outcomes	• 24-hour ABPM • Office BP • Serum creatinine
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	High risk	Some pre-specified outcomes were not reported
Other bias	Unclear risk	No apparent other sources of bias

ReSET 2015

Methods	• Study type: parallel, RCT • Country: Denmark • Setting: University and Hospital
Participants	• Number of patients randomised/analysed: 69/69 • Age: range 30 to 70 years, mean: 56 ± 9 • 24-h systolic ABPM (mmHg): ˜159 • eGFR (mL/min/1.73 m^2): ≥ 30 Exclusion criteria: pregnancy, no compliance, heart failure (NYHA 3 to 4), left ventricular ejection fraction < 50%. Unstable coronary heart disease, coronary intervention within 6 months, myocardial infarction within 6 months. Claudication. Orthostatic syncope within 6 months, secondary hypertension, per-

ReSET 2015 *(Continued)*

	manent atrial fibrillation. significant heart valve disease. Clinically significant abnormal electrolytes, haemoglobin, liver enzymes and TSH. Second and third degree heart block, macroscopic haematuria, proximal significant coronary stenosis, renal artery anatomy not suitable for renal artery ablation (stenosis, diameter < 4 mm, length < 20 mm, multiple renal arteries, severe calcifications)
Interventions	• Treatment group: N = 36, renal denervation • Control group: N = 33, sham procedure • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the Ardian Medtronic Simplicity catheter. • Follow-up: up to 6 months
Outcomes	• 24-hour systolic ABPM after 3-month follow-up • Daytime and night time BP, dipping status, morning BP surge and BP variation • Coronary flow reserve (LAD), diastolic and systolic ventricular function. Left ventricular hypertrophy. • Biomarkers of renal sodium excretion • Pulse wave velocity, augmentation index, central BP estimates • Decline in eGFR ≥ 25% • Forearm minimum vascular resistance
Notes	study in abstract version only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not specified
Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not specified
Selective reporting (reporting bias)	High risk	Some pre-specified outcomes were not reported
Other bias	Unclear risk	not specified

SYMPLICITY HTN-2 2010

Methods	• Study type: parallel, RCT • Country: Multicentre • Setting: Hospital, University

SYMPLICITY HTN-2 2010 *(Continued)*

Participants	• Number of patients randomised/analysed: 106/100
	• Age: 58 years
	• Males (%): ˜57
	• BP (mmHg): ˜178/98
	• Race (white) (%): ˜97
	• Diabetes mellitus (%): ˜97
	• Coronary artery disease (%): ˜13
	• Hypercholesterolaemia (%): ˜52
	• eGFR (mL/min/1.73 m^2): ˜82
	• Serum creatinine (µmol/L): ˜85
	• Urine albumin-to-creatinine ratio (mg/g): ˜118
	• Cystatin C (mg/L): ˜0.9
	• Antihypertensive drugs (n): ˜5.3
	• Antihypertensive treatment
	  • Diuretics (%): ˜90
	  • ACEIs/ARBs (%): ˜95
	  • CCBs (%): ˜81
	  • Direct renin inhibitors (%): ˜17
	  • β-blockers (%): ˜76
	  • α-blockers (%): ˜26
	  • Aldosterone antagonists (%): ˜17
	  • Vasodilators (%): ˜16
	
	Exclusion criteria: eGFR < 45 mL/min/1.73 m^2, type 1 diabetes mellitus, contraindications to MRI, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study, history of myocardial infarction, unstable angina or cerebrovascular accident in the previous 6 months, haemodynamically significant renal artery stenosis, previous renal artery intervention or renal artery anatomy ineligible for treatment (< 4 mm diameter, < 20 mm length or more than one main renal arteries)

Interventions	• Treatment group: N = 52, bilateral renal denervation plus baseline antihypertensive medications • Control group: N = 54, baseline antihypertensive medications • Renal denervation procedure: renal denervation with Symplicity catheter system. Four to six discrete, low-power radio frequency treatments were applied along the length of both main renal arteries • Follow-up: up to 6 months
Outcomes	• Office BP • Short and long-term safety profile: reduction of eGFR > 25% or new stenosis > 60%, composite cardiovascular end point (myocardial infarction, sudden cardiac death, new onset heart failure, death from progressive heart failure, stroke, aortic or lower limb revascularization procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to non-adherence or non-persistence with drugs and hospital admission for atrial fibrillation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	quote: "Randomisation was done with sealed envelopes"

SYMPLICITY HTN-2 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data analysers were not masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/100 (6%) drop-outs (3 in RD and 3 in control group); quote: "all analyses were done with data for all patients at randomisation minus those lost to follow-up"
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes have been reported
Other bias	High risk	Data were monitored, collected, and managed by the sponsor (Ardian)

SYMPLICITY HTN-3 2014

Methods	• Study type: parallel, RCT • Country: US • Setting: Hospital, University

Participants	• Number of patients randomised/analysed: 535/535
	• Age: ˜57 years
	• Males (%): ˜62
	• Race
	  • Black (%): ˜27
	  • White (%): ˜70
	  • Asian (%): ˜0.3
	  • Other (%): ˜1.5
	• 24-hour ABPM (mmHg): ˜160/90
	• eGFR < 60 mL/min/1.73 m^2 (%): ˜9.5
	• Renal artery stenosis (%): ˜1.8
	• Obstructive sleep apnoea (%): ˜29
	• Stroke (%): ˜10
	• Transient ischaemic attack (%): ˜4
	• Peripheral artery disease (%): ˜4
	• Coronary artery disease (%): ˜26
	• Myocardial infarction (%): ˜8
	• Diabetes mellitus (%): ˜44
	• Hyperlipidemia (%): ˜67
	• Smokers (%): ˜11
	• Hospitalisation for hypertensive crisis (%): ˜23
	• Hospitalisation for hypotension (%): ˜2
	• Antihypertensive drugs (n): ˜5.2
	• Antihypertensive treatment
	  • Diuretics (%): ˜100
	  • ACEIs (%): ˜45
	  • ARBs (%): ˜52
	  • CCBs (%): ˜72

SYMPLICITY HTN-3 2014 *(Continued)*

	• Direct renin inhibitors (%): ˜7 • β-blockers (%): ˜86 • α-blockers (%): ˜12 • Aldosterone antagonists (%): ˜25 Exclusion criteria: secondary causes of hypertension or more than one hospitalisation for hypertensive emergency in the previous year, primary pulmonary hypertension, 24-h ABPM average SBP < 135 mmHg, eGFR < 45 mL/min/1.73 m^2, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnoea, renal artery stenosis > 50%, renal artery aneurysm, prior renal artery intervention, multiple renal arteries, renal artery diameter < 4 mm or treatable segment < 20 mm in length, myocardial infarction, unstable angina pectoris, syncope or a cerebrovascular accident within 6 months of the screening period, history of pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism or hyperparathyroidism, pregnancy, nursing or planning to be pregnant
Interventions	• Treatment group: N = 364, bilateral renal denervation plus baseline antihypertensive medications • Control group: N = 171, sham procedure plus baseline antihypertensive medications • Renal denervation procedure: Four to six ablations of up to 120 seconds delivered to the renal artery wall beginning at the distal end of the artery • Sham procedure: angiography of the renal arteries • Follow-up: up to 6 months
Outcomes	• 24-hour ABPM • Office systolic BP • Day-time and night-time BP • Incidence of major adverse events (composite of: all-cause mortality, end-stage renal disease, significant embolic event resulting in end-organ damage, renal artery perforation or dissection requiring intervention, vascular complications, hospitalisation for hypertensive crisis not related to non-adherence with medications or new renal artery stenosis > 70%)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	quote: "Randomization (2:1 ratio) is performed using an interactive voice response system"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	quote: "Outcome's assessors were blinded to the treatment. Blood pressure assessments were done by blinded, trained personnel".
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/535 (3%) drop-outs (14 in RD and 2 in sham procedure); ITT analysis performed
Selective reporting (reporting bias)	Low risk	All the pre-specified outcomes have been reported

SYMPLICITY HTN-3 2014 *(Continued)*

Other bias	High risk	quote: "Data were collected and analysed by the sponsor (Medtronic, Minneapolis, Minnesota) and independently validated by Harvard Clinical Research Institute (Boston, Massachusetts)"

Warchol 2014

Methods	• Study type: parallel, RCT • Country: Poland • Setting: Institute of Cardiology
Participants	• Number of patients randomised/analysed: 35/35 • Age: range 32 to 69 years, mean 55.4 ± 7.9 • Males (%): 77 • Office BP (mmHg): ≥140/90 • Obstructive sleep apnoea (apnea/hypopnoea index, AHI): ≥ 15 events/hour • Exclusion criteria: renal artery abnormalities, eGFR < 60mL/min, previous TIA, stroke, heart failure, type 1 diabetes mellitus, implantable cardioverter defibrillator or pacemaker
Interventions	• Treatment group: N = 19, renal denervation plus antihypertensive medications • Control group: N = 16, antihypertensive medications alone • Renal denervation procedure: ablation done using a catheterbased procedure (Symplicity) • Follow-up: 3 months
Outcomes	• Office BP • 24-hour, day-time and night-time ABPM • Responses to renal denervation (sleep apnoea course, metabolic assessment, cardiac changes)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs

Warchol 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Unclear risk	No apparent other sources of bias

Xiang 2014

Methods	• Study type: parallel, RCT • Country: China • Setting: University

Participants	• Number of patients randomised/analysed: 16/16
	• Age: range 18 to 85 years, mean 67.5
	• Males (%): 100
	• BP (mmHg): ˜186/98
	• Diabetes mellitus (%): 31.2
	• Coronary artery disease (%): 12.5
	• Hypercholesterolaemia (%): 12.5
	• Atrial fibrillation (%): 6.25
	• Heart failure (%): 12.5
	• eGFR (mL/min/1.73 m^2): ˜76
	• Antihypertensive treatment
	  • Diuretics (%): 100
	  • ACEIs/ARBs (%): 100
	  • CCBs (%): 100
	  • Direct renin inhibitors (%): 6.25
	  • β-blockers (%): 100
	  • α-blockers (%): 6.25
	
	Exclusion criteria: eGFR < 45 mL/min/1.73 m^2, type 1 diabetes mellitus, stenotic valvular heart disease and pregnancy. Renal artery anatomy ineligible for treatment (main renal arteries < 4 mm in diameter or < 20 mm in length, abnormality or stenosis in either renal artery, prior renal artery angioplasty or stenting or multiple main renal arteries)

Interventions	• Treatment group: N = 8, proximal ablation • Control group: N = 8, whole ablation • Renal denervation procedure: ablation made through a radiofrequency catheter (5 French, IBI-Therapy, St. Jude Medical). Six ablations were performed for the whole ablation group, whereas three ablations at the proximal segment for the proximal ablation group. • Follow-up: up to 6 months
Outcomes	• Office BP • Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	quote: "All the patients were randomly divided using a computer algorithm into two groups"

Xiang 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	no drop-outs
Selective reporting (reporting bias)	Low risk	all the pre-specified outcomes have been reported
Other bias	Unclear risk	no apparent other sources of bias

Legend
ABPM: ambulatory blood pressure monitoring; ACEi: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; BP: blood pressure; CCBs: calcium channel blockers; CVA: cardiovascular; eGFR: estimated glomerular filtration rate; ITT: intention-to-treat; RCT: randomized controlled trial; RD: renal denervation; SBP: systolic blood pressure.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmed 2012b	not RCT
Ahmed 2013	wrong population
Brandt 2012	not RCT
Brandt 2012a	not RCT
ChiCTR-ONC-12002901	not RCT
ChiCTR-ONC-13003231	wrong intervention
ChiCTR-TNC-12002900	not RCT
EnligHTN III	not RCT
Esler 2013	wrong population
Ewen 2014	not RCT
Fadl Elmula 2013	not RCT
Grassi 2015	not RCT
Hering 2013	not RCT

Study	Reason for exclusion
Kandzari 2016	wrong population
Karbasi-Afshar 2013	not RCT
Katholi 2014	wrong population
Kjeldsen 2014	not RCT
Krum 2014	not RCT
Mahfoud 2011	wrong population
Mahfoud 2011a	wrong population
Mahfoud 2012	not RCT
Mahfoud 2014	not RCT
NCT01117025	wrong intervention
NCT01465724	not RCT
NCT01583881	wrong population
NCT01631370	not RCT
NCT01635998	wrong population
NCT01687725	not RCT
NCT01733901	wrong population
NCT01814111	wrong population
NCT01848314	not RCT
NCT01873352	wrong population
NCT01888315	not RCT
NCT01897545	wrong intervention
NCT01901549	wrong population
NCT01907828	wrong population
NCT01932450	wrong population
NCT02016573	wrong population
NCT02057224	not RCT
NCT02115100	wrong population
NCT02115230	wrong population

Study	Reason for exclusion
NCT02155790	not RCT
NCT02164435	not RCT
NCT02272920	wrong population
NCT02559882	wrong intervention
Pokushalov 2012	wrong intervention
Pokushalov 2012a	wrong intervention
Pokushalov 2012b	wrong intervention
Pokushalov 2014	wrong intervention
Pokushalov 2014a	not RCT
Pokushalov 2014b	wrong intervention
RADIANCE-HTN	wrong population
RAPID	not RCT
ReD	not RCT
REDUCE HTN:REINFORCE	wrong population
RNS-NTR 4384	not RCT
RSDAH	wrong population
Shipman 2014	not RCT
SPYRAL HTN-OFF MED	wrong population
SPYRAL HTN-ON MED	wrong population
SYMPLICITY 2011	not RCT
SYMPLICITY AF	wrong population
UMIN000012020	not RCT
Wage 2015	wrong outcome
WAVE IV	wrong intervention
Wave VI	wrong intervention
Witkowski 2011	not RCT
Yin 2013	wrong population
Zhang 2014	not RCT

Characteristics of ongoing studies *[ordered by study ID]*

ALLEGRO-HTN

Trial name or title	Renal denervation by Allegro System in patients with resistant hypertension
Methods	• Study type: parallel, RCT • Country: China • Setting: Hospital
Participants	• Estimated number of patients: 160 • Age: range 18 to 65 years • Office BP (mmHg): ≥ 160/100 (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • ABPM (mmHg): ≥ 140/90 • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, secondary hypertension. ICD or pacemaker, myocardial infarction, unstable angina, syncope, cerebrovascular accident in the previous 6 months. Intravascular thrombosis or unstable atherosclerotic plaques, significant valvular heart disease. Renal artery stenosis (≥ 50%) or renal artery aneurysm in either renal artery, history of prior renal artery intervention including balloon angioplasty or stenting. Multiple renal arteries where the main renal artery is estimated to supply < 75% of the kidney. Main renal arteries with < 4 mm diameter or with < 20 mm treatable length (by visual estimation), renal artery abnormalities
Interventions	• Treatment group: renal angiography followed by renal sympathetic denervation • Control group: renal angiography alone • Renal denervation procedure: Allegro Renal Denervation System (AngioCare) • Follow-up: up to 48 months
Outcomes	• Change in office SBP from baseline to 6 months • Change in average 24-hour SBP by ABPM from baseline to 6 months • Incidence of major adverse events (MAE) at 1 month post-randomisation • Office SBP and DBP at 1, 3, 6 months post-randomisation • Patient-recorded home systolic blood pressure at 1, 3, 6 months post-randomisation • MAE at 6-month post-randomisation, including new renal artery stenosis > 60%
Starting date	May 2013
Contact information	Xiongjing Jiang: jxj103@hotmail.com
Notes	

DENERVHTA

Trial name or title	Sympathetic renal denervation versus increment of pharmacological treatment in resistant arterial hypertension
Methods	• Study type: parallel, RCT • Country: Spain • Setting: Hospital
Participants	• Estimated number of patients: 50 • Age: range 18 to 80 years

DENERVHTA *(Continued)*

	• Office BP (mmHg): ≥ 140/90 (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, secondary hypertension, unsuitable anatomy of renal arteries (diameter < 4 mm and length < 20 mm) including significant (≥ 50%) renal arterial stenosis, renal artery stent, single functional kidney, previous nephrectomy, contrast agent allergy, hyperthyroidia, Treatment with an aldosterone receptor blocker (spironolactone, eplerenone), pre-randomization serum potassium (K^+) level ≥ 5.5 mmol/L, significant renal vascular anomalies, significant valvular heart disease, major vascular event (myocardial infarction, unstable angina or cerebrovascular disease) < 6 months prior to study enrolment
Interventions	• Treatment group: sympathetic renal denervation • Control group: treatment with aldactone • Renal denervation procedure: radiofrequency catheter-based therapy for renal denervation. Four-to-six low-power radio frequency treatments along the length of both main renal arteries. • Follow-up: up to 36 months
Outcomes	• 24-hour SBP
Starting date	September 2012
Contact information	Anna OLiveras, PhD 0034932483162 87052 @parcdesalutmar.cat
Notes	

DEPART

Trial name or title	Study of catheter-based renal denervation therapy in hypertension (DEPART)
Methods	• Study type: parallel, RCT • Country: Belgium • Setting: Hospital
Participants	• Estimated number of patients: 240 • Age: range 18 to 85 years • Office BP (mmHg): ≥ 135/85 • eGFR (mL/min/1.73 m^2): ≥ 30 Exclusion criteria: unsuitable anatomy of renal arteries (diameter < 4 mm and length < 20 mm) including significant (≥ 50%) renal arterial stenosis, renal artery stent or single functional kidney. Secondary hypertension, previous nephrectomy, contrast agent allergy, Hyperthyroidia
Interventions	• Treatment group: renal angiography followed by renal sympathetic denervation • Control group: renal angiography alone • Renal denervation procedure: radiofrequency catheter-based therapy for renal denervation. Four-to-six low-power radio frequency treatments along the length of both main renal arteries. • Follow-up: up to 48 months
Outcomes	• 24-hour SBP • Change in GFR and 24h urine sample measure • Baroreflex sensitivity • Biological markers of acute kidney injury

DEPART *(Continued)*

Starting date	January 2012
Contact information	Contact: ARGACHA Jean Francois, MD Jean.Francois.Argacha@erasme.ulb.ac.be
Notes	

EnligHTN IV

Trial name or title	Multi-center, randomized, single-blind, sham controlled clinical investigation of renal denervation for uncontrolled hypertension (EnligHTN IV)
Methods	• Study type: parallel, RCT • Country: US • Setting: University and Hospital
Participants	• Estimated number of patients: 590 • Age: range 18 to 80 years • Office BP (mmHg): ≥ 160 • Systolic ABPM ≥ 140 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension. Previous renal denervation, secondary hypertension, significant renovascular abnormalities. Myocardial infarction, unstable angina pectoris, or cerebrovascular accident < 180 days prior to enrolment. Blood clotting abnormalities, life expectancy < 12 months. Renal arteries < 4 mm in diameter or < 20 mm in length or multiple renal arteries where the main renal arteries supply < 75% of the kidney, abdominal aortic aneurysm (AAA), pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism and hyperparathyroidism
Interventions	• Treatment group: renal denervation • Control group: sham procedure • Renal denervation procedure: renal artery ablation with the EnligHTN™ Renal Denervation System • Follow-up: up to 36 months
Outcomes	• Proportion of subjects who experience any major adverse event (MAE) • Reduction of office systolic BP at 6 months • Procedure-related adverse events • Incidence of achieving ≥ 10 mmHg, ≥ 15 mmHg, and ≥ 20 mmHg reductions in office BP • Reduction in ABPM
Starting date	October 2013
Contact information	NA
Notes	

ENSURE

Trial name or title	Effect of renal denervation on arterial stiffness and haemodynamics in patients with uncontrolled hypertension (ENSURE)
Methods	• Study type: parallel, RCT • Country: China • Setting: Hospital
Participants	• Estimated number of patients: 400 • Age: range 18 to 80 years • Office BP (mmHg): ≥ 160/100 (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • ABPM (mmHg): ≥ 140/90 • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension, ABPM 24 hour average SBP < 135 mmHg
Interventions	• Treatment group: Renal denervation • Control group: Baseline anti-hypertensive medications • Renal denervation procedure: MDT-2211 Renal Denervation System • Follow-up: up to 36 months
Outcomes	• Change in 24-hour ambulatory aortic and brachial blood pressure and blood pressure variability • Incidence of major adverse events through 1 month post-randomisation • Change in asymptomatic organ damages (including electrocardiographically or echocardiographically diagnosed left ventricular hypertrophy, carotid intima-media thickness or plaque, microalbuminuria, pulse wave velocity).
Starting date	September 2014
Contact information	Yawei Xu; yizshcn@gmail.com
Notes	

INSPIRED

Trial name or title	Investigatorsteered project on intravascular renal denervation for management of drugresistant hypertension (INSPiRED)
Methods	• Study type: parallel, RCT • Country: Belgium • Setting: University
Participants	• Estimated number of patients: 240 • Age: range 20 to 69 years • Office BP (mmHg): ≥ 140/90 • eGFR (mL/min/1.73 m^2): ≥ 60 Exclusion criteria: pregnancy, secondary hypertension, unsuitable anatomy of renal arteries (diameter < 4 mm and length < 20 mm) including significant (≥ 50%) renal arterial stenosis, renal artery stent or single functional kidney, isolated systolic or isolated diastolic hypertension, body mass index ≥ 40 kg/m^2, unstable diabetes mellitus, major cardiovascular events within 6 months prior to

INSPIRED *(Continued)*

	enrolment, any serious medical condition, alcohol or substance abuse or psychiatric illnesses, patients on the waiting list of elective surgery
Interventions	• Treatment group: renal denervation plus usual medical treatment • Control group: usual medical treatment alone • Renal denervation procedure: ablation done using the EnligHTN™ multi-electrode denervation system performing four ablations simultaneously delivered at the mid/distal segment of the renal artery • Follow-up: up to 36 months
Outcomes	• 24-hour SBP • Change in eGFR • proportion of patients reaching and maintaining blood pressure control • acute and chronic procedural safety • new renal artery stenosis of over 60% • decline in eGFR ≥ 25% • cardiovascular outcomes
Starting date	April 2014
Contact information	Jan A. Staessen, MD, PhD; jan.staessen@med.kuleuven.be
Notes	

KPS

Trial name or title	Renal protection using sympathetic denervation in patients with chronic kidney disease (KPS)
Methods	• Study type: parallel, RCT • Country: Czech Republic • Setting: University/Hospital
Participants	• Estimated number of patients: 40 • Age: range 18 to 80 years • Office SBP (mmHg): ≥ 140 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • eGFR (mL/min/1.73 m^2): ≤ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, significant valvular disease, renovascular abnormalities, secondary hypertension, white coat hypertension
Interventions	• Treatment group: renal denervation and optimal medical therapy • Control group: optimal medical therapy alone • Follow-up: up to 60 months
Outcomes	• Changes of eGFR • Changes in proteinuria (microalbuminuria) • Changes in Cystatin C values • Time to the development of end-stage renal disease (ESRD)/Hemodialysis • Combined renal end point • All-cause mortality • Cardiovascular mortality • Changes of systolic and diastolic blood pressure at 6 months

KPS *(Continued)*	• Changes in concentration of blood urea nitrogen (BUN), creatinine in 6 months • Changes in cardiac structure and function • Changes in renal resistive index
Starting date	November 2013
Contact information	Jean Claude Lubanda, Ass.Prof. MD; Jean-Claude.Lubanda@vfn.cz
Notes	

NCT01848275

Trial name or title	Full length versus proximal renal arteries ablation
Methods	• Study type: parallel, RCT • Country: China • Setting: University
Participants	• Estimated number of patients: 40 • Age: > 18 • Office SBP (mmHg): ≥ 160 • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, significant valvular disease, ICD, renovascular abnormalities, secondary hypertension, white coat hypertension
Interventions	• Treatment group: full length renal denervation by the Thermocool®R catheter • Control group: proximity renal denervation by the Thermocool®R catheter • Follow-up: up to 36 months
Outcomes	• Office BP • ABPM • Ablation-related complications
Starting date	March 2011
Contact information	Yuehui Yin, MD; yinyh63@163.com
Notes	

NCT01918111

Trial name or title	Effects of renal denervation for resistant hypertension on exercise diastolic function and regression of atherosclerosis and the evaluation of new methods predicting a successful renal sympathetic denervation (RENEWAL-EXERCISE, -REGRESS, and -PREDICT Trial From RENEWAL RDN Registry)
Methods	• Study type: cross-over, RCT • Country: Republic of Korea • Setting: University
Participants	• Estimated number of patients: 52 • Age: range 20 to 85 years

NCT01918111 *(Continued)*

	• BP ≥ 140/90 mmHg or ≥ 130/80 mmHg for patients with diabetes (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • Exclusion criteria: Hemodynamically or anatomically significant renal artery abnormalities, main renal arteries < 4 mm in diameter or < 20 mm in length or prior renal artery intervention, eGFR < 30 mL/min/1.73m^2, using the MDRD formula. Valvular heart disease, history of congestive heart failure with left ventricular ejection fraction < 35%, ST-segment elevation MI within 48 hours, scheduled or planned surgery or cardiovascular intervention in the 6 months after procedure. Chronic diseases with life expectancy < 1 year, hormone replace treatment and/or oral contraceptives, pregnant, nursing or planning to be pregnant, chronic liver cirrhosis
Interventions	• Treatment group: renal denervation • Control group: adenosine infusion treatment • Renal denervation procedure: catheter-based renal denervation performed via common femoral artery with standard endovascular technique and Simplicity catheter • Follow-up: up to 24 months
Outcomes	• Change in BP at 6 and 12 months post procedure
Starting date	September 2013
Contact information	Yangsoo Jang, MD 82-2-2228-8460, jangys1212@yuhs.ac
Notes	

NCT01968785

Trial name or title	Renal denervation in patients with uncontrolled blood pressure
Methods	• Study type: parallel, RCT • Country: US • Setting: University
Participants	• Estimated number of patients: 20 • Age: range 18 to 85 years • Office SBP (mmHg): ≥ 160 (≥ 150 mmHg for type 2 diabetics) (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: pregnancy, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension, previous renal denervation. Secondary hypertension, significant renovascular abnormalities, myocardial infarction, unstable angina pectoris, or cerebrovascular accident < 180 days prior to enrolment. Blood clotting abnormalities, life expectancy < 12 months, renal arteries < 4 mm in diameter or < 20 mm in length or multiple renal arteries where the main renal arteries supply < 75% of the kidney, abdominal aortic aneurysm (AAA). Pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism, hyperparathyroidism
Interventions	• Treatment group: beta radiation dosage of 50 Gy during renal denervation procedure • Control group: beta radiation dosage of 25 Gy during renal denervation procedure • Follow-up: up to 24 months
Outcomes	• Safety (need for intervention to treat renal artery injury induced by the procedure within 6 months) • Decrease in SBP and DBP ≥ 10 mmHg at six months following the procedure • Effects on Blood Pressure

NCT01968785 *(Continued)*

	• Acute procedural safety; renal artery dissection or perforation requiring intervention and serious groin complications specifically • eGFR drop > 25% or new renal artery stenosis > 60% confirmed by angiogram at six months following renal artery brachytherapy procedure • Medication changes • Serious Adverse Events
Starting date	August 2013
Contact information	Ron Waksman, MD
Notes	

NCT02021019

Trial name or title	Renal denervation to improve outcomes in patients with end-stage renal disease
Methods	• Study type: parallel, RCT • Country: Australia • Setting: University
Participants	• Estimated number of patients: 100 • Age: range 18 to 85 years • Office SBP (mmHg): ≥ 140/90 • End stage renal disease Exclusion criteria: myocardial infarction, unstable angina, cerebrovascular accident within 3 months of the screening visit
Interventions	• Treatment group: renal denervation • Control group: usual care • Renal denervation procedure: ablation done using catheter-based (Symplicity) radiofrequency approach • Follow-up: up to 24 months
Outcomes	• Office SBP change 6 months after the procedure
Starting date	January 2014
Contact information	Markus P Schlaich, MD Baker IDI Heart and Diabetes Institute
Notes	

NCT02346045

Trial name or title	Effect of renal denervation in end staged renal disease with resistant hypertension
Methods	• Study type: parallel, RCT • Country: South Korea • Setting: Hospital
Participants	• Estimated number of patients: 40

NCT02346045 *(Continued)*

	• Age: range 18 to 90 years • Office BP (mmHg): ≥ 160 (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • Haemodialysis patients Exclusion criteria: pregnancy, type 1 diabetes mellitus, secondary hypertension. ICD or pacemaker, myocardial infarction, unstable angina pectoris, syncope, cerebrovascular accident in the previous 6 months. Intravascular thrombosis or unstable atherosclerotic plaques, significant valvular heart disease, renal artery stenosis (≥ 50%) or renal artery aneurysm in either renal artery, history of prior renal artery intervention including balloon angioplasty or stenting, multiple renal arteries where the main renal artery is estimated to supply < 75% of the kidney. Main renal arteries with < 4 mm diameter or with < 20 mm treatable length (by visual estimation). Renal artery abnormalities.
Interventions	• Treatment group: renal sympathetic denervation + medical therapy • Control group: sham procedure + medical therapy • Renal denervation procedure: renal denervation from distal to proximal portion by a Symplicity radiofrequency ablation catheter. Four to five ablations per each renal artery • Follow-up: up to 24 months
Outcomes	• Change in office SBP • Change in office DBP • Change in ABPM • Change in plasma norepinephrine • Change in pulse wave velocity
Starting date	September 2014
Contact information	Kiyuk Chang, MD, PhD; kiyuk@40catholic.ac.kr
Notes	

NCT02444442

Trial name or title	The Australian SHAM controlled clinical trial of renal denervation in patients with resistant hypertension
Methods	• Study type: parallel, RCT • Country: Australia • Setting: Hospital
Participants	• Estimated number of patients: 105 • Age: range 18 to 85 years • Systolic BP ≥ 140 mmHg and ambulatory day time average ≥ 130mmHg despite concurrent treatment with ≥ 3 anti-hypertensive drugs Exclusion criteria: renal artery anatomy ineligible for treatment, eGFR < 15mL/min/1.73m^2 (using MDRD calculation), myocardial infarction, unstable angina or cerebrovascular accident within 3 months of screening visit, life expectancy < 12 months, pregnancy
Interventions	• Treatment group: renal denervation • Control group: sham procedure • Renal denervation procedure: radiofrequency catheter-based therapy for renal denervation • Follow-up: up to 36 months

NCT02444442 *(Continued)*

Outcomes	• Change in ambulatory SBP from baseline to 6 months • Change in mean 24-hour SBP from baseline to 6 months • Change in mean office SBP from baseline to 6 months • Change in left ventricular function 6 months post procedure • Change in serum biochemistry (Plasma Renin Activity, aldosterone levels, estimated Glomerular Filtration Rate (eGFR), inflammatory markers, fasting glucose, fasting insulin, C-peptide, Homeostasis Model Assessment (HOMA) index, Lipid profile) 6 months post procedure • Change in urine biochemistry (Urinary albumin creatinine ratio (UACR), 24 hour urinary creatinine clearance, sodium) 6 months post procedure • Change in quality of life
Starting date	June 2015
Contact information	Markus P Schlaich, Professor +61 3 85321502, Markus.Schlaich@bakeridi.edu.au Murray Esler, Professor +61 3 85321338, Murray.Esler@bakeridi.edu.au
Notes	

NCT02608632

Trial name or title	High frequency guided renal artery denervation for improving outcome of renal ablation procedure
Methods	• Study type: parallel, RCT • Country: Russia • Setting: Research Institute/Hospital
Participants	• Estimated number of patients: 170 • Age: range 18 to 80 years • Office BP (mmHg): ≥ 140/90 mm Hg and < 160/100 mm Hg (moderate resistant hypertension) or ≥160/100 mm Hg (severe resistant hypertension), despite treatment with 3 antihypertensive drugs (including a diuretic) • eGFR (mL/$\mathtt{min/1.73}$ m^2): ≥ 45 (MDRD formula) Exclusion criteria: secondary hypertension, severe renal artery stenosis or dual renal arteries, congestive heart failure, left ventricular ejection fraction < 35%, previous renal artery stenting or angioplasty, type 1 diabetes mellitus
Interventions	• Treatment group: renal denervation guided by HFS • Control group: renal denervation as standard procedure • Renal denervation guided by HFS: high-frequency stimulation (HFS) used before the initial and after each radiofrequency (RF) delivery within the renal artery. Ablations of 8 to 12 watts applied from the first distal main renal artery bifurcation all the way back to the ostium and performed both longitudinally and rotationally within each renal artery. • Renal denervation as standard procedure: ablations of 8 to 12 watts applied from the first distal main renal artery bifurcation all the way back to the ostium and performed both longitudinally and rotationally within each renal artery • Follow-up: 12 months
Outcomes	• Number of responders to RD procedure up to 12 months • Incidence of adverse events through 12 months after procedure
Starting date	February 2013

NCT02608632 *(Continued)*

Contact information	NA
Notes	

NCT02667912

Trial name or title	Distal renal denervation
Methods	• Study type: parallel, RCT • Country: Russia • Setting: Research Institute
Participants	• Estimated number of patients: 45 • Age: range 18 to 80 years • Office BP (mmHg): ≥ 160/100 mmHg, with full doses of at least 3 antihypertensive drugs including a diuretic Exclusion criteria: secondary hypertension, 24-h mean systolic BP < 135 mmHg, eGFR < 30 mL/min/1.73 m^2, disease of renal artery, any clinically important disorders/comorbidities significantly increasing risk of endovascular intervention
Interventions	• Treatment group: distal renal denervation • Control group: conventional renal denervation • Distal renal denervation procedure: catheter-based renal denervation applied to inner surface of segmental branches renal artery in a number of points equally distributed along the length and circumference of the vessels • Conventional renal denervation procedure: catheter-based renal denervation applied to inner surface of the main trunk of renal artery in a number of points equally distributed along its length and circumference • Follow-up: up to 12 months
Outcomes	• Between-group difference in change of 24-hour mean systolic and diastolic BP assessed by ambulatory blood pressure monitoring (ABPM) at 6 and 12 months of follow-up • Between-group difference in change of office systolic and diastolic BP at 6 and 12 months of follow-up • Between-group difference in change of daytime/nighttime systolic and diastolic BP at 6 and 12 months of follow-up • Between-group difference in renal function (serum creatine and eGFR) at 6 and 12 months of follow-up • Between-group difference in the incidence of adverse events
Starting date	January 2013
Contact information	Stanislav Pekarskiy, MD, PhD
Notes	

NTR3444

Trial name or title	Comparison of renal sympathetic denervation with spironolactone in patients with still a high blood pressure despite the use of 3 different antihypertensive agents

NTR3444 *(Continued)*

Methods	• Study type: parallel, RCT • Country: The Netherlands • Setting: Hospital
Participants	• Estimated number of patients: not provided • Age: range 18 to 75 years • Treatment-resistent hypertension Exclusion criteria: secondary hypertension, renal arteries inaccessible for endovascular denervation, suboptimal dosing of BP lowering medication, non compliant to treatment, white coat hypertension, pregnancy, eGFR < 45 mL/min/1.73 m^2, use of vitamin K antagonist that can not be discontinued for a short period, spironolactone intolerance, myocardial infarction or cerebrovascular accident 3 months prior to randomisation, life expectancy < 2 years
Interventions	• Treatment group: renal denervation • Control group: antihypertensive treatment + spironolactone • Renal denervation procedure: catheter-based renal denervation • Follow-up: up to 6 months
Outcomes	• Between groups difference in 24-hour ambulatory BP after 6 months of follow-up • Between groups difference in quality of life score
Starting date	June 2012
Contact information	A van den Meiracker, MD, PhD +31-10-4639222, a.vandenmeiracker@erasmusmc.nl
Notes	

PaCE

Trial name or title	A study of renal denervation in patients with treatment resistant hypertension (PaCE)
Methods	• Study type: parallel, RCT • Country: Canada • Setting: Hospital
Participants	• Estimated number of patients: 100 • Age: range 18 to 85 years • eGFR (mL/min/1.73m^2): ≥ 45 • Office SBP ≥ 160 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • Baseline average systolic ABPM ≥ 135 mmHg Exclusion criteria: pregnancy, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension, previous renal denervation, secondary hypertension, significant renovascular abnormalities. Myocardial infarction, unstable angina pectoris or cerebrovascular accident < 180 days prior to enrolment. Blood clotting abnormalities, life expectancy < 12 months, renal arteries < 4 mm in diameter or < 20 mm in length or multiple renal arteries where the main renal arteries supply < 75% of the kidney. Pheochromocytoma, Cushing's disease, coarctation of the aorta
Interventions	• Treatment group: early renal denervation • Control group: delayed renal denervation (6 months after patient's randomisation)

PaCE *(Continued)*

	• Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the Ardian Medtronic Simplicity catheter • Follow-up: up to 24 months
Outcomes	• Average systolic ABPM • Proportion of patients achieving target SBP • Average daytime and night-time systolic ambulatory BP • Variability of 24-hour ambulatory systolic BP • Average office BP using an approved, automated office BP device • Hypertensive medication complexity index (MRCI) • Number of hypertensive medications • Periprocedural mean cost per patient in Canadian dollars • Generic quality of life (EQ-5D) • Body mass index (BMI) • 24-hour urine sodium • Acute periprocedural renal injury • Creatinine clearance measured on 24-hour urine • Vascular complications • Evidence of renal artery stenosis compared to pre-procedure (determined by renal imaging, CT or MRA) for early intervention group • Composite cardiovascular end points • Microalbumin to creatinine ratio (MACR) from random urine sample
Starting date	October 2013
Contact information	Harindra C. Wijeysundera, MD
Notes	

RAPID II

Trial name or title	Rapid renal sympathetic denervation for resistant hypertension II (RAPID II)
Methods	• Study type: parallel, RCT • Country: Italy • Setting: Hospital/University
Participants	• Estimated number of patients: not provided • Age: range 18 to 75 years • SBP (mmHg): ≥ 160 (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) Exclusion criteria: pregnancy,type 1 diabetes mellitus, renal anatomy unsuitable for treatment, significant valvular heart disease, scheduled or planned surgery within 6 months of study entry
Interventions	• Treatment group: bilateral renal ablation plus antihypertensive medications • Control group: optimal medical therapy • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the OneShot system • Follow-up: up to 60 months
Outcomes	• Major adverse event (MAE) rate through 30 days post randomisation • Change in office SBP from baseline to 6 months

RAPID II *(Continued)*

	• Acute procedural safety • Chronic procedural safety • Reduction in SBP > 10 mmHg at 6 months • Changes in office SBP and DBP from baseline to follow-up visits
Starting date	September 2013
Contact information	Dierk Scheinert, MD Guiseppe Mancia, MD Universita Milano-Bicocca, Ospedale San Gerardo di Monza
Notes	

RDNP-2012-01

Trial name or title	Renal denervation for resistant hypertension (RDNP-2012-01)
Methods	• Study type: parallel, RCT • Country: Australia • Setting: Hospital
Participants	• Estimated number of patients: 100 • Age: range 18 to 85 years • SBP ≥ 140 mmHg or ≥ 130 mmHg for patients with diabetes (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • eGFR (mL/min/1.73 m^2): ≥ 15 Exclusion criteria: pregnancy, unsuitable anatomy of renal arteries (diameter < 4 mm and length < 20 mm)
Interventions	• Treatment group: renal denervation • Control group: usual care • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the Ardian Medtronic Symplicity catheter • Follow-up: up to 24 months
Outcomes	• Percentage of patients achieving BP target (BP < 140/90 mmHg, or < 130/80 mmHg in diabetic patients) at 6 months post procedure • Time to achieve BP target • Change in markers of sympathetic nerve activity • Change in left ventricular structure and function • Change in quality of life • Serum and urine biochemistry • Change in markers of arterial stiffness
Starting date	February 2012
Contact information	Markus Schlaich, MD Baker IDI Heart & Diabetes Institute
Notes	

RENO

Trial name or title	Effect of renal denervation on no-mediated sodium excretion and plasma levels of vasoactive hormones (RENO)
Methods	• Study type: parallel, RCT • Country: Denmark • Setting: Hospital
Participants	• Estimated number of patients: 30 • Age: range 30 to 70 years • Office BP (mmHg): ≥ 145/75 • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: non-compliance, pregnancy, radiocontrast allergy, malignancy, congestive heart failure, unstable angina pectoris, previous myocardial infarction or PCI (< 6 mdr), secondary hypertension, renal artery stenosis or multiple renal arteries on CT, claudication
Interventions	• Treatment group: renal denervation plus L-NMMA treatment • Control group: sham procedure plus L-NMMA treatment • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the Ardian Medtronic Simplicity catheter • Follow-up: up to 24 months
Outcomes	• Fractional excretion of sodium after acute L-NMMA treatment • Glomerular filtration rate (GFR) before and after L-NMMA treatment
Starting date	March 2012
Contact information	Esper N Bech, MD, Ph.D; jnbech@dadlnet.dk
Notes	

RENSYMPIS

Trial name or title	Renal sympathetic denervation and insulin sensitivity (RENSYMPIS Study)
Methods	• Study type: parallel, RCT • Country: Finland • Setting: University
Participants	• Estimated number of patients: 60 • Age: range 30 to 69 years • Office systolic BP (mmHg): ≥ 160 • eGFR (mL/min/1.73 m^2): ≥ 45 Exclusion criteria: secondary hypertension, pseudohypertension, pregnancy, significant stenotic valvular disease, oral anticoagulation, CCS III-IV symptoms or CABG/PCI in the previous 6 months, prior stroke, contrast agent allergy, inappropriate renal artery anatomy (< 4mm diameter, < 20mm length)
Interventions	• Treatment group: renal artery denervation • Control group: optimisation of medical therapy • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the Ardian Medtronic Simplicity catheter

RENSYMPIS *(Continued)*

	• Follow-up: up to 36 months
Outcomes	• Office BP • Ambulatory BP • Insulin resistance • Endothelial function
Starting date	January 2013
Contact information	Tuomas Paana, M.D; tuomas.paana@satshp.fi
Notes	

ReSET-2

Trial name or title	Renal denervation in treatment resistant hypertension (ReSET-2)
Methods	• Study type: parallel, RCT • Country: Denmark • Setting: University
Participants	• Estimated number of patients: 70 • Age: range 30 to 70 years • Systolic daytime (24-hour ambulatory blood pressure measurement) > 135 mmHg and < 145 mmHg • eGFR (mL/min/1.73 m^2): > 30 Exclusion criteria: pregnancy, non compliance, heart failure (NYHA 3-4), Left ventricular ejection fraction < 50%, unstable coronary heart disease, coronary intervention within 6 months, myocardial infarction within 6 months, claudication, orthostatic syncope within 6 months, secondary hypertension, permanent atrial fibrillation, significant heart valve disease. Clinically significant abnormal electrolytes, haemoglobin, liver enzymes and TSH. Second and third degree heart block, macroscopic haematuria, proximal significant coronary stenosis, renal artery anatomy not suitable for renal ablation (stenosis, diameter < 4 mm, length < 20 mm, multiple renal arteries, severe calcifications). Moderate/severe obstructive sleep apnoea (AHI > 15) if on CPAP treatment
Interventions	• Treatment group: renal denervation • Control group: sham procedure • Renal denervation procedure: catheter-based renal denervation by applying low power radiofrequency to the renal artery using the EnligHTN catheter • Follow-up: up to 36 months
Outcomes	• Change from baseline in daytime SBP • Change from baseline in ABPM • Change from baseline in central BP, augmentation index and pulse wave velocity • Change from baseline in cold pressor response • Change from baseline in intensity of medical antihypertensive therapy • BP (clinic measurement) • Renal function (eGFR and electrolytes)
Starting date	January 2013
Contact information	Henrik Vase, MD, PhD henvas@rm.dk

ReSET-2 *(Continued)*

	Ole Mathiassen, MD, PhD onm@farm.au.dk
Notes	

RSD4CKD

Trial name or title	Renal sympathetic denervation in patients with chronic kidney disease and resistant hypertension (RSD4CKD)
Methods	• Study type: parallel, RCT • Country: Japan • Setting: University
Participants	• Estimated number of patients: 100 • Age: range 18 to 75 years • eGFR (mL/min/1.73 m^2): > 20 and < 70 • Serum creatinine (mg/dL): 1.5-5.0 • Persistent proteinuria • Resistant hypertension • Nondiabetic renal disease Exclusion criteria: treatment with corticosteroids, nonsteroidal antiinflammatory or immunosuppressive drugs, connective-tissue disease, obstructive uropathy, congestive heart failure (NYHA class III or IV), significant renovascular abnormalities (history of prior renal artery intervention, including balloon angioplasty or stenting; double renal artery on one side, distortion, and extension), measured by abdominal ultrasound or renal angiograms. History of myocardial infarction, unstable angina, cerebrovascular accident or alimentary tract haemorrhage in the previous 3 months, sick sinus syndrome, history of allergy to contrast media, psychiatric disorders, drug or alcohol abuse and pregnancy
Interventions	• Treatment group: renal denervation + standard therapy • Control group: standard therapy • Renal denervation procedure: six to nine ablations at 10 W for 1 min each in both renal arteries • Follow-up: up to 36 months
Outcomes	• All-cause mortality • Doubling of serum creatinine or end-stage renal disease • Urinary protein excretion and renal function • Blood pressure • Blood glucose • Cardiac function and structure • Arrhythmia • Pulse wave velocity • Quality of life • Rehospitalisation rate • Dialysis proportion
Starting date	November 2012
Contact information	Shan Qi jun; qjshan@njmu.edu.cn
Notes	

RSDforAF

Trial name or title	Renal sympathetic denervation in patients with drug-resistant hypertension and symptomatic atrial fibrillation (RSDforAF)
Methods	• Study type: parallel, RCT • Country: China • Setting: Hospital
Participants	• Estimated number of patients: 200 • Age: range 18 to 75 years • Office SPB ≥ 160 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • Baseline average systolic AMBP ≥ 135 mmHg • eGFR (mL/min/1.73 m^2): ≥ 45 • Paroxysmal and persistent AF Exclusion Criteria: pregnancy, type 1 diabetes mellitus, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension, white-coat hypertension, previous renal denervation, secondary hypertension, significant renovascular abnormalities, myocardial infarction, unstable angina pectoris or cerebrovascular accident < 180 days prior to enrolment. Blood clotting abnormalities, life expectancy < 12 months, renal arteries < 4 mm in diameter or < 20 mm in length or multiple renal arteries where the main renal arteries supply < 75% of the kidney. Pheochromocytoma, Cushing's disease, coarctation of the aorta, severely enlarged left atria ≥ 55 mm, sick sinus syndrome, reversible causes of AF
Interventions	• Treatment group: renal denervation + drugs + cardioversion • Control group: drugs • Renal denervation procedure: four to eight ablations at 10 W for 60 seconds each in both renal arteries. In patients with persistent AF, direct-current cardioversion performed immediately after renal sympathetic denervation • Follow-up: up to 36 months
Outcomes	• Change in atrial fibrillation burden • Rate controlling in persistent AF patients • Office SBP • Changes in cardiac structure and function • Fasting blood glucose • Glycated haemoglobin • Blood lipids • Apnea-hypopnea index • Pulse wave velocity • Quality of life
Starting date	July 2012
Contact information	Qijun Shan; qjshan@40njmu.edu.cn
Notes	

SYMPATHY

Trial name or title	Renal sympathetic denervation as a new treatment for therapy resistant hypertension (SYMPATHY)

SYMPATHY *(Continued)*

Methods	• Study type: parallel, RCT • Country: The Netherlands • Setting: Hospital
Participants	• Estimated number of patients: 300 • Age: ≥ 18 years • Average systolic ABPM ≥ 135 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) Exclusion Criteria: Pregnancy, type 1 diabetes mellitus, eGFR (mL/min/1.73 m^2) < 20, chronic oxygen support or mechanical ventilation, primary pulmonary hypertension, white-coat hypertension, previous renal denervation, secondary hypertension, significant renovascular abnormalities. Myocardial infarction, unstable angina pectoris or cerebrovascular accident < 180 days prior to enrolment. Blood clotting abnormalities, life expectancy < 12 months, renal arteries < 4 mm in diameter or < 20 mm in length or multiple renal arteries where the main renal arteries supply < 75% of the kidney. Pheochromocytoma, Cushing's disease, coarctation of the aorta
Interventions	• Treatment group: renal denervation plus usual medical treatment • Control group: usual medical treatment alone • Renal denervation procedure: ablation done using the EnligHTN™ multi-electrode denervation system performing four ablations simultaneously. One 60-s ablation delivered at the mid/distal segment of the renal artery • Follow-up: up to 12 months
Outcomes	• Change in ABPM • Change in the amount of antihypertensive medication • Change in BP in eGFR strata • Change in office BP • Impact on quality of life • Cost-effectiveness
Starting date	May 2013
Contact information	Peter J Blankestijn, MD, PhD; P.J.Blankestijn@40umcutrecht.nl
Notes	

SYMPLICITY HTN-4

Trial name or title	Renal denervation in patients with uncontrolled hypertension (SYMPLICITY HTN-4)
Methods	• Study type: parallel, RCT • Country: USA • Setting: University
Participants	• Estimated number of patients: 44 • Age: range 18 to 80 years • eGFR (mL/min/1.73 m^2): > 30 • Office SBP > 140 mmHg and < 160 mmHg (despite stable medication regimen including 3 or more antihypertensive medications of different classes, including a diuretic) • ABPM average SBP > 135 mmHg

SYMPLICITY HTN-4 *(Continued)*	
	Exclusion Criteria: pregnancy, inappropriate renal artery anatomy, type 1 diabetes mellitus, one or more episodes of orthostatic hypotension, chronic oxygen other than nocturnal respiratory support for sleep apnoea, primary pulmonary hypertension, previous organ transplant
Interventions	• Treatment group: renal denervation • Control group: sham procedure • Renal denervation procedure: ablations done with the SYMPLICITY system • Follow-up: up to 24 months
Outcomes	• Reaching BP goal • Incidence of major adverse events through 1 month post-procedure • Renal artery stenosis measured at 6 months
Starting date	October 2013
Contact information	David Kandzari, MD Piedmont Heart Institute
Notes	

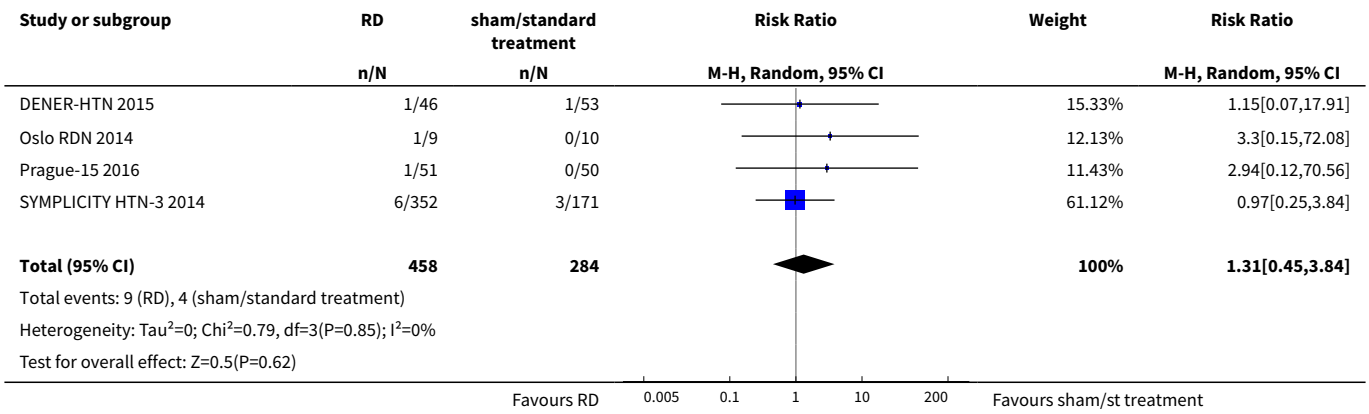
DATA AND ANALYSES

Comparison 1. Renal denervation vs. sham/standard therapy

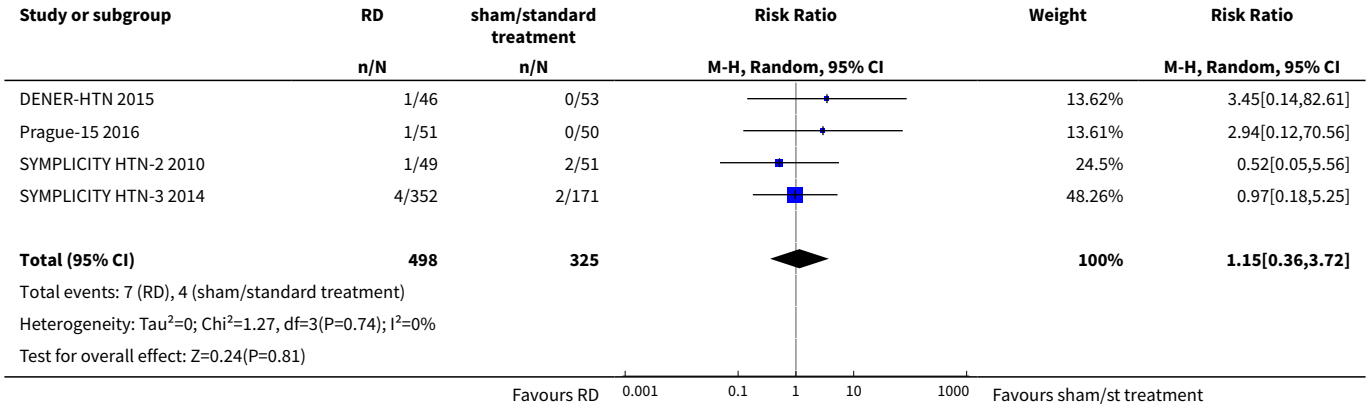
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction	4	742	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.45, 3.84]
2 ischaemic stroke	4	823	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.36, 3.72]
3 unstable angina	2	201	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.08, 5.06]
4 systolic 24-hour ABPM	5	797	Mean Difference (IV, Random, 95% CI)	0.28 [-3.74, 4.29]
5 diastolic 24-hour ABPM	4	756	Mean Difference (IV, Random, 95% CI)	0.93 [-4.50, 6.36]
6 systolic office BP	6	886	Mean Difference (IV, Random, 95% CI)	-4.08 [-15.26, 7.11]
7 diastolic office BP	5	845	Mean Difference (IV, Random, 95% CI)	-1.30 [-7.30, 4.69]
8 serum creatinine	3	736	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.14]
9 eGFR/creatinine clearance	4	837	Mean Difference (IV, Random, 95% CI)	-2.09 [-8.12, 3.95]
10 bradycardia	3	220	Risk Ratio (M-H, Random, 95% CI)	6.63 [1.19, 36.84]
11 femoral artery pseudoaneurysm	2	201	Risk Ratio (M-H, Random, 95% CI)	3.96 [0.44, 35.22]
12 flank pain	2	199	Risk Ratio (M-H, Random, 95% CI)	4.30 [0.48, 38.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 hypotensive episodes	2	119	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.07, 6.64]
14 hypertensive crisis	3	722	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.45]
15 hyperkalemia	2	200	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.01, 21.33]

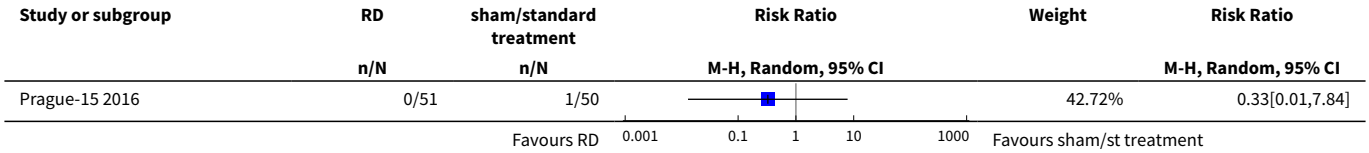
Analysis 1.1. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 1 Myocardial infarction.

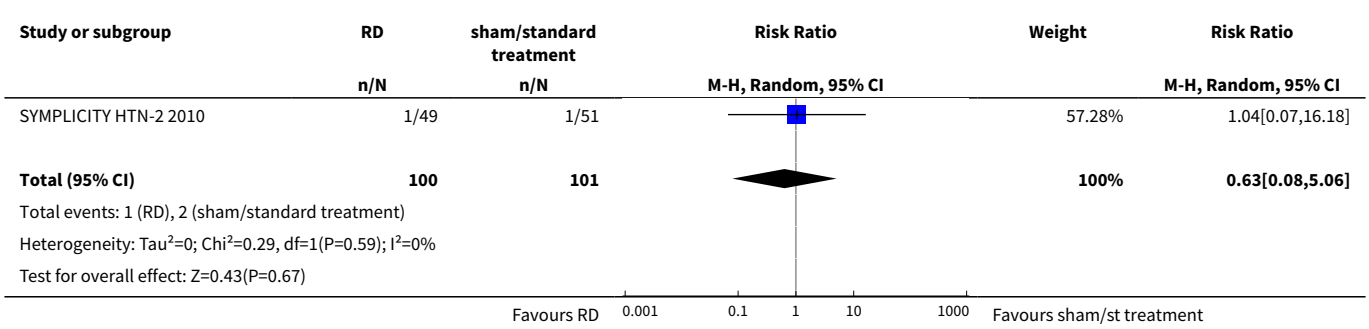


Analysis 1.2. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 2 ischaemic stroke.

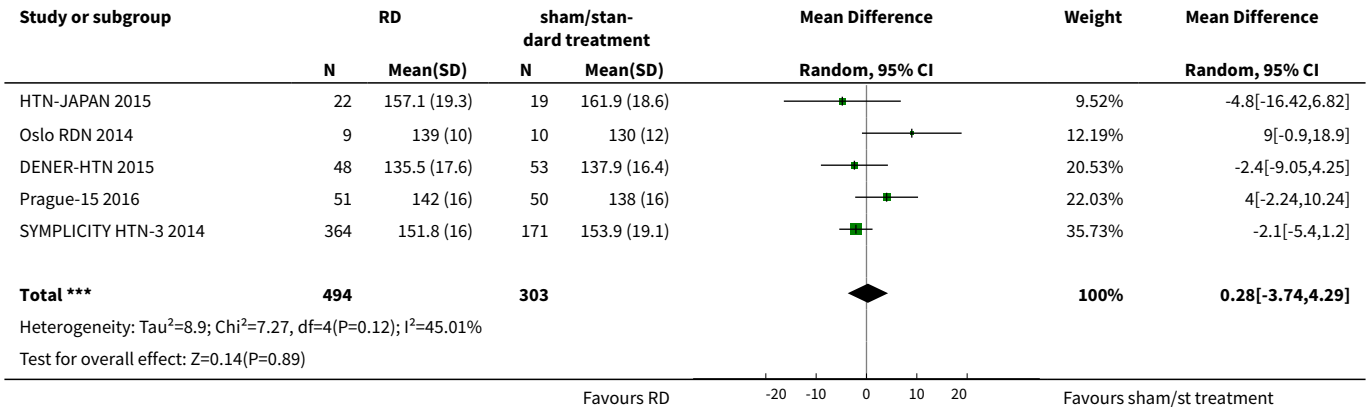


Analysis 1.3. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 3 unstable angina.

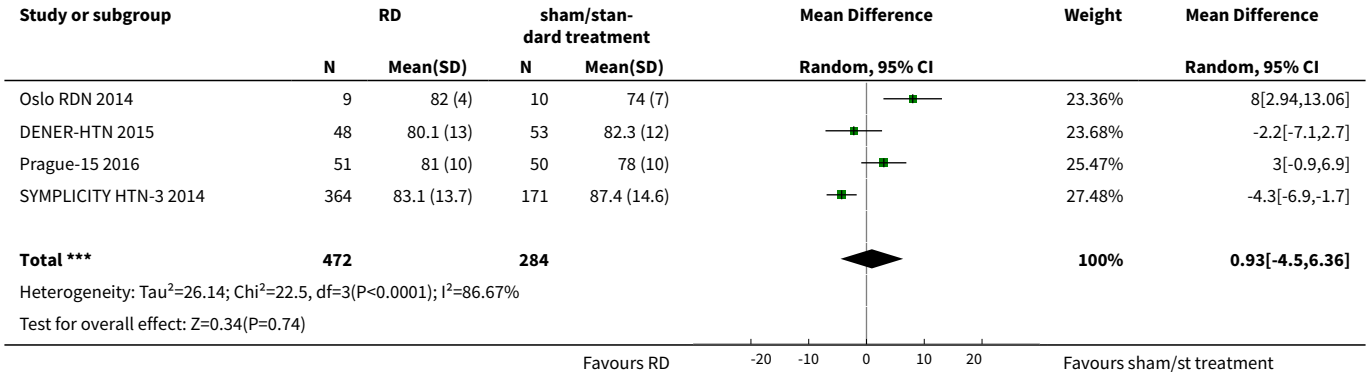




Analysis 1.4. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 4 systolic 24-hour ABPM.



Analysis 1.5. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 5 diastolic 24-hour ABPM.

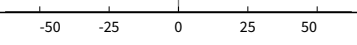


Analysis 1.6. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 6 systolic office BP.

Study or subgroup	RD N	RD Mean(SD)	sham/standard treatment N	sham/standard treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
HTN-JAPAN 2015	22	165.7 (26.1)	19	170.8 (19.5)		14.43%	-5.1[-19.09,8.89]
SYMPLICITY HTN-2 2010	49	146.7 (23.3)	51	179.1 (26.5)		16.32%	-32.4[-42.17,-22.63]
DENER-HTN 2015	48	143.5 (20.4)	53	147.3 (24.1)		16.76%	-3.8[-12.48,4.88]
Oslo RDN 2014	9	148 (7)	10	132 (10)		17.13%	16[8.3,23.7]
Prague-15 2016	51	146 (18)	50	144 (18)		17.37%	2[-5.02,9.02]
SYMPLICITY HTN-3 2014	353	165.6 (23.7)	171	168.4 (28.6)		17.99%	-2.8[-7.75,2.15]
Total ***	**532**		**354**			**100%**	**-4.08[-15.26,7.11]**

Heterogeneity: Tau²=174.65; Chi²=59.87, df=5(P<0.0001); I²=91.65%

Test for overall effect: Z=0.71(P=0.47)

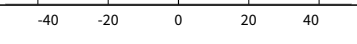


Analysis 1.7. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 7 diastolic office BP.

Study or subgroup	RD N	RD Mean(SD)	sham/standard treatment N	sham/standard treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Oslo RDN 2014	9	89 (8)	10	77 (8)		17.85%	12[4.8,19.2]
SYMPLICITY HTN-2 2010	49	84.4 (17)	51	96.4 (16.5)		18.66%	-12[-18.57,-5.43]
DENER-HTN 2015	48	83.8 (15.5)	53	85.7 (12.3)		20%	-1.9[-7.39,3.59]
Prague-15 2016	51	84 (12)	50	83 (12)		20.97%	1[-3.68,5.68]
SYMPLICITY HTN-3 2014	353	89.5 (16.9)	171	94.1 (17.7)		22.52%	-4.6[-7.79,-1.41]
Total ***	**510**		**335**			**100%**	**-1.3[-7.3,4.69]**

Heterogeneity: Tau²=38.88; Chi²=27.44, df=4(P<0.0001); I²=85.42%

Test for overall effect: Z=0.43(P=0.67)



Analysis 1.8. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 8 serum creatinine.

Study or subgroup	RD N	RD Mean(SD)	sham/standard treatment N	sham/standard treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Prague-15 2016	51	1 (0.2)	50	1.1 (0.4)		30.91%	-0.11[-0.22,0]
SYMPLICITY HTN-2 2010	49	1 (0.3)	51	0.9 (0.2)		31.7%	0.16[0.05,0.27]
SYMPLICITY HTN-3 2014	364	1.1 (0.3)	171	1.1 (0.3)		37.39%	-0.01[-0.06,0.04]
Total ***	**464**		**272**			**100%**	**0.01[-0.12,0.14]**

Heterogeneity: Tau²=0.01; Chi²=12.75, df=2(P=0); I²=84.31%

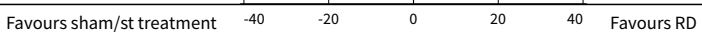
Test for overall effect: Z=0.2(P=0.84)

Analysis 1.9. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 9 eGFR/creatinine clearance.

Study or subgroup	RD N	RD Mean(SD)	sham/standard treatment N	sham/standard treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
DENER-HTN 2015	48	83.4 (27.2)	53	84.2 (22.4)		20.92%	-0.83[-10.61,8.95]
Prague-15 2016	51	108 (36)	50	96 (42)		11.69%	12[-3.27,27.27]
SYMPLICITY HTN-2 2010	49	77.1 (18.8)	51	86.7 (19.9)		26.79%	-9.6[-17.19,-2.01]
SYMPLICITY HTN-3 2014	364	70.6 (17.4)	171	72.4 (19)		40.6%	-1.83[-5.19,1.53]
Total ***	**512**		**325**			**100%**	**-2.09[-8.12,3.95]**

Heterogeneity: Tau²=20.41; Chi²=7.09, df=3(P=0.07); I²=57.67%

Test for overall effect: Z=0.68(P=0.5)



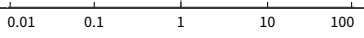
Analysis 1.10. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 10 bradycardia.

Study or subgroup	RD n/N	sham/standard treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Oslo RDN 2014	1/9	0/10		30.95%	3.3[0.15,72.08]
Prague-15 2016	2/51	0/50		32.45%	4.9[0.24,99.66]
SYMPLICITY HTN-2 2010	7/49	0/51		36.59%	15.6[0.91,266.01]
Total (95% CI)	**109**	**111**		**100%**	**6.63[1.19,36.84]**

Total events: 10 (RD), 0 (sham/standard treatment)

Heterogeneity: Tau²=0; Chi²=0.63, df=2(P=0.73); I²=0%

Test for overall effect: Z=2.16(P=0.03)



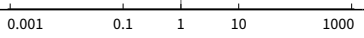
Analysis 1.11. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 11 femoral artery pseudoaneurysm.

Study or subgroup	RD n/N	sham/standard treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Prague-15 2016	2/51	0/50		52.67%	4.9[0.24,99.66]
SYMPLICITY HTN-2 2010	1/49	0/51		47.33%	3.12[0.13,74.8]
Total (95% CI)	**100**	**101**		**100%**	**3.96[0.44,35.22]**

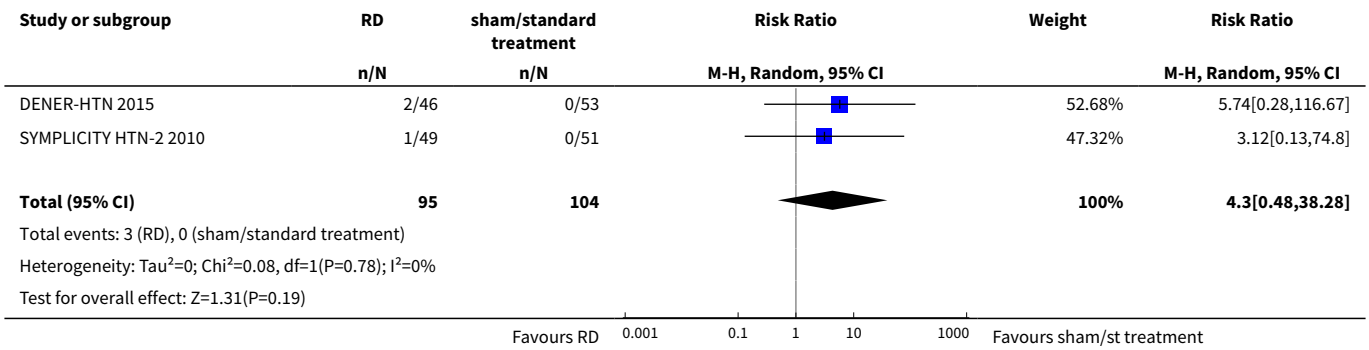
Total events: 3 (RD), 0 (sham/standard treatment)

Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%

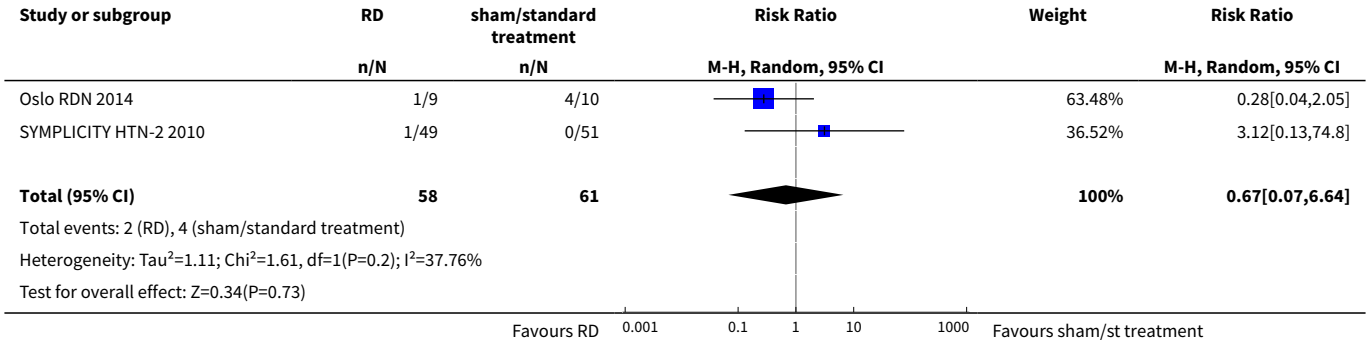
Test for overall effect: Z=1.23(P=0.22)



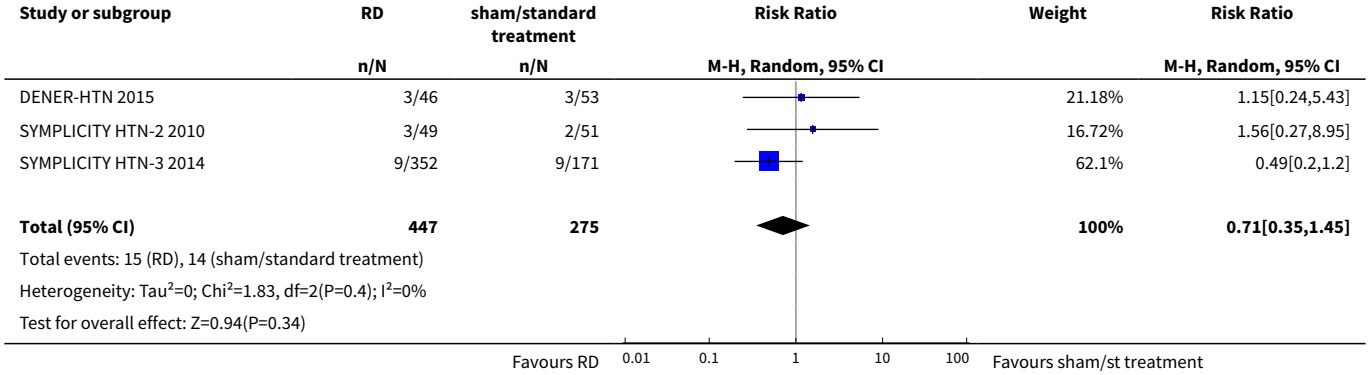
Analysis 1.12. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 12 flank pain.



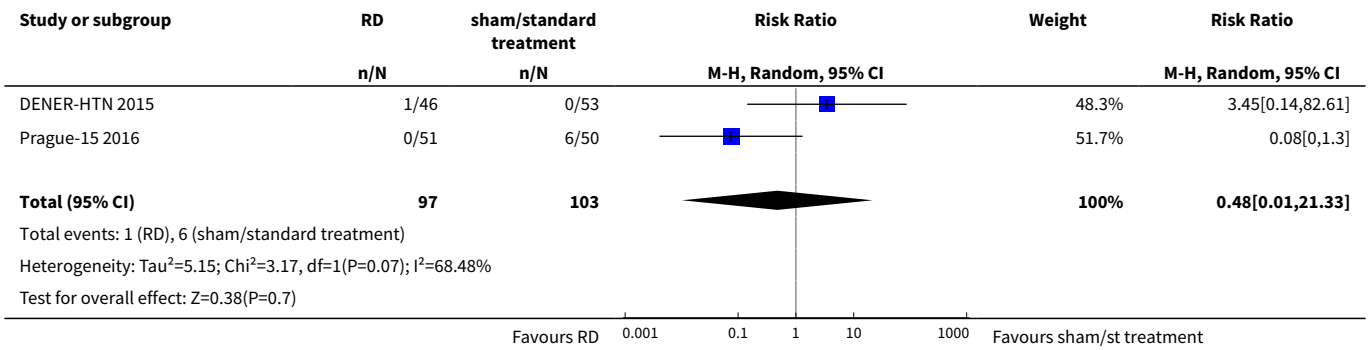
Analysis 1.13. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 13 hypotensive episodes.



Analysis 1.14. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 14 hypertensive crisis.



Analysis 1.15. Comparison 1 Renal denervation vs. sham/standard therapy, Outcome 15 hyperkalemia.



APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 15 February 2016

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1 denervation/ (13728)

2 ((kidney? or renal or transcatheter) adj8 (denervat$ or sympathectom$)).mp. (2344)

3 (RDN or RSDN).tw. (184)

4 or/1-3 (15195)

5 hypertension/ (206622)

6 hypertens$.tw. (322078)

7 exp blood pressure/ (260289)

8 blood pressure.mp. (366575)

9 or/5-8 (619538)

10 randomized controlled trial.pt. (406217)

11 controlled clinical trial.pt. (90055)

12 randomized.ab. (303442)

13 placebo.ab. (155007)

14 drug therapy.fs. (1819658)

15 randomly.ab. (214885)

16 trial.ab. (312775)

17 groups.ab. (1360639)

18 or/10-17 (3449945)

19 animals/ not (humans/ and animals/) (4154861)

20 18 not 19 (2937902)

21 4 and 9 and 20 (275)

22 remove duplicates from 21 (274)

****

Database: Cochrane Central Register of Controlled Trials <2016, Issue 2> via Cochrane Register of Studies Online
Search Date: 15 February 2016

#1 denerv* 501

#2 sympathectom* 208

#3 #1 OR #2 658

#4 hypertens* 37999

#5 #3 AND #4 176

****

Database: Embase <1980 to 2016 February 12>
Search Date: 15 February 2016
---
1 renal denervation/ (2687)

2 ((kidney? or renal or transcatheter) adj8 (denervat$ or sympathectom$)).mp. (4141)

3 or/1-2 (4141)

4 exp hypertension/ (542358)

5 hypertens$.tw. (473931)

6 exp blood pressure/ (432181)

7 (blood pressure or bloodpressure).mp. (471761)

8 or/4-7 (1019811)

9 randomized controlled trial/ (392471)

10 controlled clinical trial/ (391924)

11 crossover procedure/ (46039)

12 double-blind procedure/ (126084)

13 (randomi?ed or randomly).tw. (841320)

14 (crossover$ or cross-over$).tw. (77898)

15 placebo.ab. (218800)

16 (doubl$ adj blind$).tw. (158837)

17 assign$.ab. (270222)

18 allocat$.ab. (96961)

19 or/9-18 (1369620)

20 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5431415)

21 19 not 20 (1206052)

22 3 and 8 and 21 (347)

23 remove duplicates from 22 (331)

****

Database: Hypertension Group Specialised Register
Search Date: 16 February 2016

#1 denerva*

#2 sympathectom*

#3 #1 OR #2

#4 (CCT OR RCT):DE

#5 (Review OR Meta-Analysis):MISC2

#6 #4 OR #5

#7 #3 AND #6

****

Database: ClinicalTrials.gov
Search Date: 15 February 2016

Study type: Interventional Studies
Conditions: hypertension
Interventions: denervation
Outcome Measures: blood pressure
First received: From 03/01/2015 to 02/15/2016 (12)

****

Database: WHO International Clinical Trials Registry Platform
Search Date: 15 February 2016
---
hypertension AND denervation (139)

****

Database: PubMed
Search Date: 16 February 2016

((denervation OR sympathectom* OR RDN or RSDN) AND (hypertens* OR high blood pressure) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]) NOT MEDLINE[sb]) (67)

CONTRIBUTIONS OF AUTHORS

1. Drafting the protocol: GC, DB, LR
2. Study selection: AP, LR

3. Extracting data from studies: AP, LR
4. Entering data into Review Manager: AP, LR
5. Carrying out the analysis: DB, AP
6. Interpreting the analysis: DB, AP, GC
7. Drafting the final review: DB, GC, AP, LR
8. Resolution of disagreements: DB
9. Updating the review: DB, LR, AP, GC

DECLARATIONS OF INTEREST

DB: in 2012, received an Honorary Fellowship from the Cochrane Renal Group as Fellow of the European Renal Best Practice (ERBP) group.

AP: None known.

GC: None known.

LR: None known.

SOURCES OF SUPPORT

Internal sources

- Department of Medical and Surgical Sciences, Nephrology and Dialysis Unit, University 'Magna Graecia', Catanzaro, Italy.
- Institute of Clinical Physiology, CNR - Italian National Council of Research, Reggio Calabria, Italy.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Authors order and contribution was updated after finalizing the last revision of the review to best reflect individual contributions to this new version.

INDEX TERMS

Medical Subject Headings (MeSH)

Angina, Unstable [etiology]; Antihypertensive Agents [therapeutic use]; Blood Pressure Determination; Drug Resistance; Hypertension [*therapy]; Kidney [*innervation]; Myocardial Infarction [etiology]; Stroke [etiology]; Sympathectomy [adverse effects] [*methods]

MeSH check words

Humans