Interventional procedure overview of alcohol-mediated perivascular renal sympathetic denervation for resistant hypertension

Contents

Table 1 Abbreviations

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
IQR	Interquartile range
MAE	Major adverse event
MCID	Minimal clinically important difference
MD	Mean difference
MI	Myocardial infarction
RDN	Renal denervation
RDUS	Renal duplex ultrasound
SD	Standard deviation
TIA	Transient ischaemic attack
TIMI	Thrombolysis in myocardial infarction

Indications and current treatment

Hypertension is a major risk factor for cardiovascular and chronic kidney diseases. Hypertension can be primary or secondary. Primary hypertension does not have a single known cause, but secondary hypertension develops because of an underlying medical condition. Hypertension is traditionally considered resistant if it is not controlled after treatment with 3 or more antihypertensive medications from different classes.

NICE's guideline on hypertension in adults (NG136) describes diagnosing and managing hypertension, including resistant hypertension. Current treatments for hypertension include lifestyle modifications and antihypertensive medications. BP and treatment are regularly monitored and treatment is adjusted as needed. For resistant hypertension, treatment options include additional medications and

device-based antihypertensive therapies (such as radiofrequency or ultrasound RDN, and carotid baroreceptor stimulation).

Unmet need

Hypertension remains a major cardiovascular risk factor, affecting approximately one-third of adults worldwide. Prevalence increases with age, rising to over 60% in people aged over 60 years. In the UK, hypertension is common and at least one quarter of adults (and more than half of those older than 60) have high BP. For resistant hypertension, NG136 acknowledges that its estimates vary, but it is generally thought to be about 5% of people with hypertension.

The risk associated with increasing BP is continuous, with each 2 mmHg rise in systolic BP associated with a 7% increased risk of mortality from ischaemic heart disease and 10% increased risk of mortality from stroke. So, lowering systolic and diastolic BP to recommended targets is associated with a substantial reduction in cardiovascular risk. Decrements in office systolic BP of 5 and 10 mmHg are associated with 10% and 20% reductions in cardiovascular disease events, respectively, and independent of other comorbidities.

However, hypertension management is challenging. Current pharmacological treatment regimens often fail to achieve adequate reductions in BP because of non-adherence to prescribed antihypertensive medications and lifestyle interventions. Due to the issue of highly variable adherence to medication, true treatment-resistant hypertension can be difficult to identify in clinical practice. So, hypertension because of lower or non-adherence to recommended medications can also be considered treatment-resistant (pseudo-resistant) and further treatment should be considered (NG136). NICE acknowledges that the concept of resistant hypertension is evolving (IPG754). So, to address the unmet need in

the NHS, this assessment considers people with hypertension regardless of the number of antihypertensive medications prescribed.

What the procedure involves

Before the procedure, renal artery imaging is needed to evaluate renal arterial anatomy.

The procedure is usually done under local anaesthesia, with sedation and anticoagulation. A catheter is introduced through the femoral artery and advanced into each renal artery under fluoroscopic guidance. The catheter has 3 microneedles contained within 3 guide tubes. Once the catheter is positioned within the target site, the 3 tubes are simultaneously deployed against the intimal surface of the renal artery. The 3 microneedles are advanced through the renal artery wall into the adventitia and surrounding perivascular space. Microdoses of neurolytic agent (medical grade dehydrated alcohol) are then infused slowly into the perivascular space from the distal to proximal end of each renal artery. This ablates the renal nerves leading to the kidney, with the aim of disrupting neurogenic reflexes involved in blood pressure control.

After the withdrawal of the catheter, renal artery imaging can be done to identify any adverse vascular events related to the device or the procedure.

Outcome measures

The main outcomes included reduction in BP (ABPM and office BP), use of antihypertensive medications, renal function (such as eGFR and serum creatinine), major or serious adverse events, and device- or procedure-related, nonserious adverse events. The key measures used are detailed in the following paragraphs.

Reduction in BP included ABPM and office BP at follow ups compared with baseline, or between arms. A reduction in mean 24-hour ambulatory systolic BP of at least 5 mmHg relative to baseline was considered a clinically meaningful response to RDN (Mahfoud 2015). A mean decrease in office BP of 10 mmHg for systolic BP compared with baseline was judged to be a clinically meaningful reduction (Persu 2014).

eGFR was used to indicate the overall index of kidney function, with a normal eGFR usually greater than 90 ml/min/1.73m^2 and different stages are detailed as follows:

- 90 or above: possible kidney damage with normal kidney function
- 60 to 89: kidney damage with mild loss of kidney function
- 45 to 59: mild to moderate loss of kidney function
- 30 to 44: moderate to severe loss of kidney function
- 15 to 29: severe loss of kidney function
- less than 15: kidney failure.

eGFR could also be shown as a percentage of normal, ranging from 100% (full function) to 0% (no function). It is noted that eGFR declines with age, even in people without kidney disease.

MAEs included all-cause death, end-stage renal disease, significant embolic event resulting in end-organ damage or needing intervention, major vascular complications, major bleeding events, postprocedural renal artery stenosis (>60% diameter stenosis), hypertensive crisis, and symptomatic hypotension needing medication.

Evidence summary

Population and studies description

This interventional procedure overview is based on 480 people from 2 RCTs (Kandzari 2024; Pathak 2023) and 3 single-arm studies (Mahfoud 2020, 2021; Janas 2020; Fischell 2016). Of these 480 people, 271 people had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 5 studies (6 papers) as the key evidence in table 2 and table 3. Other relevant studies are listed in table 5 in appendix B.

All the studies were done in Europe and the US, and the follow-up duration ranged from 6 months to 24 months. Only Fischell (2016) was a single-centre study, the other 4 studies were done in 2 or more centres. Both RCTs compared RDN with sham controls (diagnostic renal angiography only).

The mean age ranged from 54 to 60 years across studies. The common morbidities were diabetes (type 2), hyperlipidaemia, and cardiovascular disease. In terms of antihypertensive drugs prescribed, the mean number ranged from 3.4 to 5.1 in 3 studies (Fischell 2016; Mahfoud 2020, 2021; Janas 2020). For the other 2 studies, Kandzari (2024) described 77% of people taking 3 or more medications, and Pathak (2023) reported 45% of people taking 2 or more medications, 30% having 1 medication and 25% of people with no medications. Recognising that escalation of medication burden is a considerable predictor of nonadherence, inconsistency of medication adherence was considered one of the confounding factors.

Table 2 presents study details.

Figure 1 Flow chart of study selection

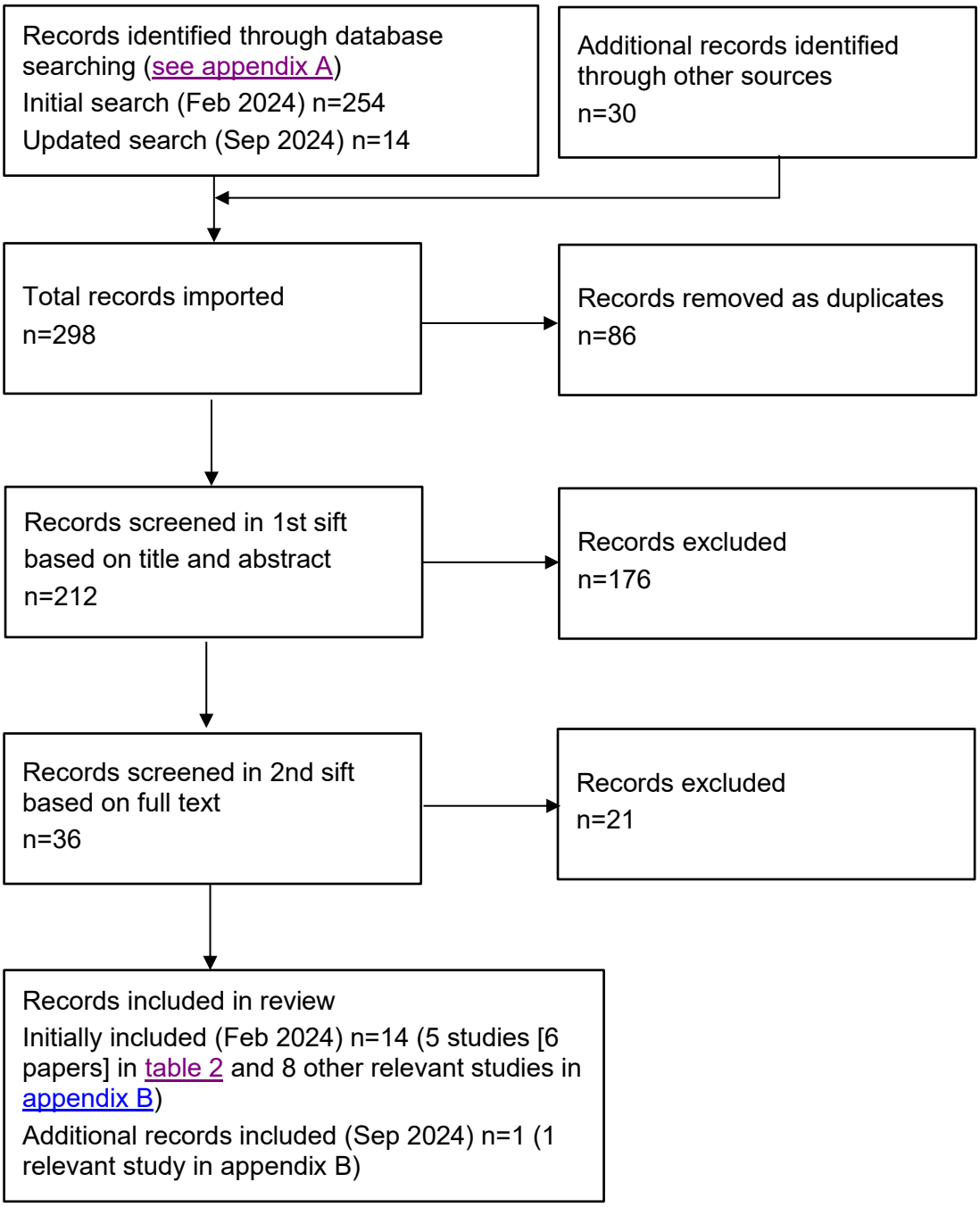

Table 2 Study details

Study no.	First author, date country	Population	Drugs	Study design	Inclusion criteria	Intervention	Follow up
1.	Kandzari (2024) 9 countries (99 centres)	n=301 (224 males, 77 females) • RDN, n=148 • Sham, n=153 Mean 56.1 years	Range 2 to 5 (233 people with 3 or more drugs)	RCT (NCT02910414; TARGET BP I; phase 3)	People (18 to 80 years old) with hypertension (office systolic BP of 150 to 180 mmHg and diastolic BP of 90 mmHg or above), despite prescription of 2 to 5 antihypertensive medications. Approximately 1 week before randomisation, people with a mean 24-hour systolic ABPM of 135 to 170 mmHg and confirmed anatomic eligibility.	Alcohol-mediated perivascular RDN: using a novel 3 needle-based delivery device (Peregrine System Infusion Catheter) with 0.6 ml alcohol infused per treated renal artery with a maximum dose of 2.4 ml per person. In addition to the main renal arteries, eligible renal accessory arteries were also treated. Sham: diagnostic renal angiography only.	6 months (efficacy outcomes limited to 3 months)
2.	Pathak (2023) Europe and US (25 centres)	n=106 (78 males, 28 females) • RDN, n=50 • Sham, n=56 mean 54.1 years	2 or more: • RDN, n=21 • Sham, n=26	RCT (NCT03503773; TARGET BP OFF-MED; phase 2)	People (18 to 80 years old) with hypertension (office systolic BP of 140 to 180 mmHg and diastolic BP of 90 mmHg or above), taking 0 to 2 antihypertensive medications. After a 4-week run-in period, people with 24-hour systolic ABPM of 135 to 170	Alcohol-mediated perivascular RDN: using a novel 3 needle-based delivery device (Peregrine System Infusion Catheter) with 0.6 ml alcohol infused per treated renal artery with a maximum dose of 2.4 ml. In addition to the main renal arteries, 5 renal accessory arteries were treated.	12 months

Study no.	First author, date country	Population	Drugs	Study design	Inclusion criteria	Intervention	Follow up
					mmHg and confirmed anatomic eligibility.	Sham: diagnostic renal angiography only.	
3.	Mahfoud (2020) Europe (9 centres in Poland, Czech Republic, Belgium, and Germany)	n=45 with 94 treated arteries (28 men,17 women; 1 withdrew consent at 6-month follow up) mean 55 years	Mean 5.1 (SD 1.5)	Single-arm study	People with uncontrolled hypertension, despite taking at least 3 antihypertensive medications of different classes for at least 4 consecutive weeks; the renal artery diameter between 4 and 7 mm, with a renal artery length of 5mm or more	Bilateral RDN using the Peregrine Catheter with 0.6 ml alcohol infused per renal artery: • Bilateral RDN: n=44 • 2 procedures for unilateral RDN: n=2 (1 person) 4 people had an accessory artery treated in addition to the 2 main renal arteries.	6 months
	Mahfoud (2021)	n=41 completed the trial (as 4 losses to follow up) age same as above	Same as above	Same as above	Same as above	Same as above	12 months
4.	Janas (2020)	n=10 (5 males, 5	Mean 4.8 (SD 1.3)	Single-arm study	People with resistant hypertension (office	Alcohol-mediated RDN, using a novel 3 needle-	24 months

Study no.	First author, date country	Population	Drugs	Study design	Inclusion criteria	Intervention	Follow up
	Czechia (single centre) and Poland (2 centres)	females) with 20 treated arteries mean 60 years			systolic BP >160 mm Hg or >150 mm Hg if people with type 2 diabetes), despite taking at least 3 antihypertensive medications including a diuretic agent for at least 4 weeks; mean 24-hour systolic pressure of 135 mmHg or higher based upon ABPM	based delivery device (Peregrine System Infusion Catheter) with 0.3 ml alcohol infused per renal artery: • Bilateral RDN: n=5 • Unilateral RDN: n=10	(1 person was lost to follow up at 24 months)
5.	Fischell (2016) US (single centre)	n=18 (9 males,9 females) with 37 treated arteries mean 53.5 years	Mean 3.4 (SD 0.7)	Single-arm study	People with resistant hypertension (office systolic BP >160 mm Hg or >150 mm Hg if people with type 2 diabetes), despite taking at least 3 antihypertensive medications, including a diuretic agent	Alcohol-mediated RDN, using a novel 3 needle-based delivery device (Peregrine System Infusion Catheter) with 0.3 ml alcohol infused per renal artery: • Bilateral RDN per session: n=13 • Unilateral RDN per session: n=10	6 months (1 person died and 1 lost to follow up)
The risk of bias (RoB) was assessed using the Cochrane RoB Tool for RCTs and adapted RWE framework tool for single-arm studies. The RoB for RCTs was graded as “low” for low risk, “high” for high risk, and “some concerns”. For single-arm studies, each domain of the RoB was rated as “low”, “moderate”, “serious”, or “critical” for RoB. The overall RoB was determined according to the judgment for each domain.							

Study no.	First author, date country	Population	Drugs	Study design	Inclusion criteria	Intervention	Follow up
For the 2 RCTs (Kandzari 2024; Pathak 2023), some concerns were raised for 1 domain (bias due to missing outcome data) and a low level of concerns was rated for other domains. So, the overall risk of bias was judged as some concerns. For the 3 single-arm studies, Mahfoud (2020, 2021) was rated as low for all RoB domains, so the overall risk of bias was low. For the other 2 single-arm studies, Janas (2020) was rated moderate for 1 domain (bias due to measurement of outcomes) and as low for all other domains whereas Fischell (2016) was judged as moderate for 2 domains (bias due to measurement of outcomes and reporting bias) and as low for all other domains. So, the overall risk of bias was considered moderate.							

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Kandzari (2024)	**Total sample:** n=301 (RDN, n=148; sham, n=153) Both ITT and per-protocol analyses were carried out. Per-protocol analysis included 100 people with RDN and 115 people with a sham procedure. Reasons for lost to follow up were unclear. **Procedure success**: RDN, 95.3%; sham, 92.6% **Mean change in 24-hour systolic ABPM** at 3 months from baseline, mmHg: • RDN: -10.0±14.2 • Sham: -6.8±12.1 • Difference between groups: -3.2; 95% CI, -6.3 to 0.0; p=0.0487	Two people randomised to the sham group inadvertently had RDN so they were included in the safety analysis. **MAEs at 30 days**: • RDN (n=149): 4.7% (n=7), including 1 major vascular complication, 1 hypertensive emergency and 6 hypotension needing intervention or medication change. • Sham (n=150): 0% • between groups: p=0.007 **MAEs at 6 months**:

First author, date	Efficacy outcomes	Safety outcomes
	Subgroup analysis of the primary endpoint revealed no significant interaction across the predefined subgroups (grouped according to the median age, gender, region, ethnicity), suggesting a consistent effect of RDN. However, numerically greater reductions in both ambulatory and office systolic BP was observed relative to region, with a greater treatment effect of RDN compared with sham control in the US compared with non-US sites (between group difference for ambulatory systolic BP -5.0 (95% CI, -10.0 to 0.1; p=0.048) versus -1.6 mmHg (95% CI, -5.5 to 2.3; p=0.512); p=0.222 for interaction. **Mean change in 24-hour diastolic ABPM** at 3 months from baseline, mmHg: • RDN: -5.4±7.7 • Sham: -4.1±6.1 • Difference between groups: -1.4; 95% CI, -3.1 to 0.3; p=0.1146) **Mean change in office systolic BP** at 3 months from baseline, mmHg: • RDN: -12.7±18.3 • Sham: -9.7±17.3 • Difference between groups: -3.0; 95% CI, -7.0 to 1.0; p=0.173 no significant difference was observed in office diastolic BP between the RDN and sham control groups. **Antihypertensive medications**: Between groups, no significant differences in prescribed medication changes from baseline to 3 months, and no notable differences in dose titration score, DDD, or medication index at 3 months.	• RDN (n=145): 5.3% (n=11), including 1 death (unrelated to the procedure, device or drug), 1 myocardial infarction, 1 major vascular complication, 2 hypertensive emergencies, and 7 hypotension needing intervention or medication change. • Sham (n=146): 4% (n=6), including 1 myocardial infarction, 2 hypertensive emergencies, and 3 hypotension needing intervention or medication change. • Between groups: p=0.223 **Renal function** - eGFR: • RDN: -1.2 ± 9.9 mL/min/1.73m^2 • Sham: -0.9 ± 9.0 mL/min/1.73m^2 • Between groups: p=0.728

First author, date	Efficacy outcomes	Safety outcomes
	Adherence testing: • Full adherence: baseline, 43% versus 41%, p=0.712; 3 months, 51% versus 49%, p=0.765 • Partial and complete non-adherence: similar between groups at all time points and did not statistically vary	
Pathak (2023)	**Total sample**: n=106 (RDN, n=50; sham, n=56) **Procedure success**: 96% (48/50). In 2 patients, challenging anatomies, due to vessel angulation/tortuosity, permitted only unilateral RDN. **Mean change in 24-hour systolic ABPM** from baseline, mmHg (RDN, 147.6±8.6; sham, 148.8±9.6) – ITT population: • 8 weeks: RDN, -2.9±7.4 (p=0.0089); sham, -1.4±8.6 (p=0.25); between-group difference, -1.5 (95% CI, -4.8 to 1.7), p=0.2682 • 6 months: RDN, -13.9±11.6 (p<0.0001); sham, -13.4±12.9 (p<0.0001); between-group difference, -0.55 (95% CI -5.7 to 4.6), p=0.6964 • 12 months: RDN, -10.6±11.5 (p<0.0001); sham, -15.9±13.1 (p<0.0001); between-group difference, 5.3 (95% CI -0.1 to 10.7), p=0.0775 **Mean change in 24-hour diastolic ABPM** from baseline, mmHg (RDN, 92.2±7.6; sham, 91.0±6.8) – ITT population: • 8 weeks: RDN, -2.0±5.1 (p=0.0086); sham, -1.1±6.6 (p=0.2443); between-group difference, -0.9 (95% CI, -3.3 to 1.4), p=0.4734	**Complications up to 30 days after procedure**: • MAE: RDN, 2.0%; sham, 1.8% • Hypertensive crisis: n=1 after RDN • Vascular complication (the person developed a small subcutaneous haematoma; pseudoaneurysm was subsequently diagnosed): n=1 after sham No evidence of renal artery stenosis was identified at 6 months after the procedure via any of the imaging modalities. eGFR remained stable in the RDN group (mean change, -2.1±8.9 ml/min/1.73m^2) but decreased in the sham group up to 12 months (mean change, -6.4±10.0 ml/min/1.73m^2) after the procedure. The difference between groups was statistically significant (p=0.0224) although baseline values were comparable between groups.

First author, date	Efficacy outcomes	Safety outcomes
	• 6 months: RDN, -9.3±6.9 (p<0.0001); sham, -8.0±8.5 (p<0.0001); between-group difference, -1.3 (95% CI -4.5 to 1.9), p=0.5386 • 12 months: -7.3±7.5 (p<0.0001); sham, -9.8±8.3 (p<0.0001); between-group difference, 2.5 (95% CI -0.9 to 6.0), p=0.0341 **Mean change in office systolic BP** from baseline, mmHg (RDN, 159.4±10.9; sham, 160.1±11.0) – ITT population: • 8 weeks: RDN, -4.0±12.6 (p=0.029); sham, 0.63±13.24 (p=0.73); between-group difference, -4.6 (95% CI, -9.7 to 0.4), p=0.0605 • 6 months: RDN, -12.9±15.6 (p<0.0001); sham, -14.7±15.7 (p<0.0001); between-group difference, 1.8 (95% CI -4.5 to 8.2), p=0.724 • 12 months: -11.0±15.3 (p<0.0001); sham, -13.2±16.6 (p<0.0001); between-group difference, 2.2 (95% CI -4.5 to 8.9), p=0.6823 **Mean change in office diastolic BP** from baseline, mmHg (RDN, 100.4±7.0; sham, 98.3±6.1) – ITT population: • 8 weeks: RDN, -3.5±7.6 (p=0.0022); sham, -1.1±8.8 (p=0.3578); between-group difference, -2.3 (95% CI, -5.6 to 0.9), p=0.1843 • 6 months: RDN, -10.0±9.0 (p<0.0001); sham, -8.4±9.5 (p<0.0001); between-group difference, -2.5 (95% CI -6.1 to 1.2), p=0.3575 • 12 months: -9.4±9.4 (p<0.0001); sham, -9.6±11.0 (p<0.0001); between-group difference, -1.6 (95% CI -5.4 to 2.1), p=0.6375	

First author, date	Efficacy outcomes	Safety outcomes
	A primary endpoint analysis using the per-protocol population was consistent with observations in the ITT population. For **daytime and night-time systolic ABPM**, the changes from baseline to 8 weeks in the RDN group were –3.2±9.5 mmHg compared with –1.7±9.9 mmHg in the sham group with a mean between-group difference of –1.5 mmHg (95% CI: –5.4 to 2.4; p=0.2660) and –3.3±9.4 mmHg in the RDN group versus –0.6±12.2 mmHg in the sham group with a mean between-group difference of –2.8 mmHg (95% CI: –7.1 to 1.6; p=0.1908), respectively. Post hoc analysis showed treatment of all renal accessory arteries (n=5) was associated with a larger decrease in 24-hour systolic BP compared with people with untreated renal accessory arteries (n=8) (change from baseline: –6.6 mmHg versus –0.7 mmHg; p=0.0127). Following primary endpoint collection at 8 weeks, antihypertensive medication was uptitrated to achieve a target office systolic BP ≤140 mmHg. Mean number of **antihypertensive medications**, RDN versus sham: • 8 weeks: 0.06 versus 0.089 • 3 months: 0.62 versus 0.89, p=0.092 • 6 months: 0.96 versus 1.40, p=0.035 • 12 months: 1.10 versus 1.60, p=0.0081 Proportion of people on 2 or more antihypertensive medications, RDN versus sham: • 8 weeks: 0% versus 0% • 3 months: 12% versus 30%, p=0.033	

First author, date	Efficacy outcomes	Safety outcomes
	• 6 months: 26% versus 52%, p=0.009 • 12 months: 29% versus 57%, p=0.005 Antihypertensive medication defined daily dose, RDN versus sham: • 8 weeks: 0.08 versus 0.12 • 3 months: 0.81 versus 1.30, p=0.07 • 6 months: 1.20 versus 2.00, p=0.012 • 12 months: 1.50 versus 2.30, p=0.0168 Antihypertensive medication index, RDN versus sham: • 8 weeks: 0.039 versus 0.038 • 3 months: 0.40 versus 0.84, p=0.1683 • 6 months: 0.58 versus 52, p=0.057 • 12 months: 0.71 versus 0.95, p=0.1137	
Mahfoud (2020)	**Total sample** included in the analysis: n=44 (94 treated renal arteries) **Mean change in 24-hour ABPM at 3 months** from baseline (n=36): • Systolic: -10±12 mmHg (95% CI, -14 to -6), p<0.001 • Diastolic: -6±8mmHg (95% CI, -9 to -4), p<0.001 **Mean change in 24-hour ABPM at 6 months** from baseline (n=42): • Systolic: -11±14 mmHg (95% CI, -15 to -7), p<0.001 • Diastolic: -7±9 mmHg (95% CI, -9 to -4), p<0.001 Decreases of ≥5 and ≥10 mmHg in 24-hour systolic ABPM at 6 months were recorded in 71% (30/42) and 52% (22/42) of people,	**Primary safety endpoint** (absence of any periprocedural major vascular complications or major bleeding, acute kidney injury, or death within 1 months of the procedure) reached: 96% (43/45; 95% CI, 85% to 99%). **Primary safety endpoint events** within 1 month of the procedure: 4% (2/45, unrelated to the Peregrine Catheter) • Periprocedural major vascular complication (vascular access pseudoaneurysm): 4% (2/45) • Major bleeding (TIMI classification): 2% (1/45) No acute kidney injury or periprocedural death. **Secondary safety endpoints**:

First author, date	Efficacy outcomes	Safety outcomes

	respectively. For 24-hour mean ABPM, 21% (9/42) of people were controlled to <130/80 mmHg at 6 months.
	Mean change in office BP at 3 months from baseline (n=43):
	• Systolic: -18±22 mmHg (95% CI, -24 to -11), p<0.001
	• Diastolic: -8±12 mmHg (95% CI, -12 to -5), p<0.001
	Mean change in office BP at 6 months from baseline (n=44):
	• Systolic: -18±21 mmHg (95% CI, -25 to -12), p<0.001
	• Diastolic: -10±11 mmHg (95% CI, -13 to -6), p<0.001
	Decreases of ≥5 and ≥10 mmHg in office systolic BP at 6 months were recorded in 70% (31/44) and 61% (27/44) of people, respectively. For office BP, 30% (13/44) of people were controlled to <140/90 mmHg at 6 months.
	People-reported **antihypertensive medications** at 6 months:
	• Reduction: 23% (10/44)
	• Increase: 5% (2/44)
	Urine toxicological analyses revealed that adherence to the antihypertensive regimen remained relatively consistent over time: 74.6% (n=42), 81.9% (n=43), and 77.9% (n=41) after 1, 3, and 6 months of follow-up. This was also reflected in the proportion of people who were fully adherent (100%) with their antihypertensive regimens, with 52.4%, 60.5%, and 58.5% at 1, 3, and 6 months of follow up, respectively.
		• Stroke or TIA within 1 month of the procedure: 0%
		• MI within 1 month of the procedure: 0%
		• MAEs through 6 months post procedure: 7% (3/44)
		  ○ Major vascular complication: 5% (2/44)
		  ○ Severe hypotension or syncope: 2% (1/44)
		No death, end stage renal failure, hypertensive crisis, significant embolic event or significant new renal artery stenosis (>60% diameter stenosis)
		Renal function:
		• Serum creatinine level: baseline, 0.92±0.19 mg/dl (n=45); 6 months, 0.94±0.17 mg/dl (n=44); p=0.55
		No clinically significant serum creatinine level change
		• Change in eGFR: -2.7±12.1 ml/min/1.73m^2, p=0.15
		• Cystatin C: baseline, 0.98±0.19 mg/l; 6 months, 1.04±0.52 mg/l; p=0.39
		• Spot urine albumin level: baseline, 20±75 mg/dl; 6 months, 20±58 mg/dl
		• eGFR >25% decrease at 6 months from baseline: 5% (2/44)

First author, date	Efficacy outcomes	Safety outcomes
		Device- or procedure-related AEs: procedural pain (n=1) and minor vessel dissection (n=2) Transient microleaks: 42% and 49% of the left and right main renal arteries **Device deficiencies**: n=5
Mahfoud (2021)	**Total sample** included in the analysis: n=41 **Mean change in 24-hour ABPM** at 12 months from baseline (n=38): • Systolic: -10±17 mmHg (95% CI -16 to -5), p<0.001 • Diastolic: -7±11 mmHg (95% CI -10 to -3), p<0.001 Decreases of ≥5 and ≥10 mmHg in 24-hour systolic ABPM at 12 months were recorded in 61% (23/38) and 47% (18/38) of people, respectively. **Mean change in ABPM** at 12 months from baseline: • Daytime systolic BP: -12 mmHg (95% CI, -17 to -6) • Daytime diastolic BP: -8 mmHg (95% CI, -12 to -4) • Nighttime systolic BP: -8 mmHg (95% CI, -15 to -2) • Nighttime diastolic BP: -5 mmHg (95% CI, -9 to -2) **Mean change in office BP** at 12 months from baseline (n=41): • Systolic: -20±23 mmHg (95% CI, -27 to -13), p<0.001 • Diastolic: -10±12 mmHg (95% CI, -14 to -6), p<0.001 Decreases of ≥5 and ≥10 mmHg in office systolic BP at 12 months were recorded in 76% (31/41) and 71% (29/41) of people, respectively. For office BP, 32% (13/41) of people were controlled to <140/90 mmHg at 12 months.	Long-term follow-up imaging by RDUS at 12 months after procedure showed no evidence of new renal artery stenosis or other anatomic abnormalities. **Renal function**: • Mean serum creatinine level: baseline, 0.92±0.19 mg/dl; 12 months, 0.96±0.19 mg/dl; p=0.06 • Mean urea levels: baseline, 33.84±10.33 mg/dl; 12 months, 36.71±14.44 mg/dl; p=0.34 • Mean cystatin C level: baseline, 0.98±0.19 mg/l; 12 months, 0.98±0.21 mg/l; p=0.67 • Mean eGFR: baseline, 85±16 mL/minute per 1.73 m^2; 12 months, 80±17 mL/minute per 1.73 m^2; mean difference, -3.9±10.3 mL/minute per 1.73 m^2; 95 CI, -7.1 to -0.75; p=0.02 • Mean spot urine albumin level: baseline, 20±75 mg/dl; 12 months, 12±32 mg/dl; p=0.25

First author, date	Efficacy outcomes	Safety outcomes
	Mean change in antihypertensive medications at 12 months from baseline: -0.1±1.4 (95% CI -0.5 to 0.4)	
Janas (2020)	**Total sample** included in the analysis: n=10 (20 treated renal arteries), 1 person was lost to follow up at 24 months Mean hospital stay: 2 days **Mean change in 24-hour ABPM** from baseline (146±12 mmHg): • systolic BP: 3 months, -7±10 mmHg; 6 months (outside window), -3±10 mmHg; 12 months, -6±5 mmHg; 24 months, -1±6 mmHg; p<0.05 at 3 and 12 months but not 6 and 24 months • diastolic BP: 3 months, -2 mmHg; 6 months (outside window), 2 mmHg; 12 months, -3 mmHg; 24 months, -1 mmHg **Mean change in office BP** from baseline (168±8 mmHg): • systolic BP: 3 months, -37±14 mmHg; 6 months, -28±14 mmHg; 12 months, -21±13 mmHg; 24 months, -25±7 mmHg; all p<0.001 • diastolic BP: 3 months, -7 mmHg; 6 months, -7 mmHg; 12 months, -2 mmHg; 24 months, -6 mmHg. Over the follow-up period, 60% of people had a reduction in office systolic BP by more than 10% in comparison to the baseline. **Antihypertensive medications** at 24 months: • no changes: n=6 • increase in medications: n=2 • decrease in medications: n=1	**Serious adverse events**: n=3 (2 people) • Inflammation of the duodenum mucosae membrane at 6 months: n=1 • Upper respiratory tract infections: n=1 • Diabetes intensification: n=1 The last 2 events happened in the same person. All serious adverse events were resolved without sequelae and were determined by an independent medical reviewer as not related to the device and procedures. **Pain**: during 2 procedures, people felt lower back pain during and just after alcohol injection described as 2 points on a 10-point scale. Both people received, intravenously, 500 mg of paracetamol, which relieved the discomfort. **Renal function** – no renal deterioration during the follow up (up to 12 months, n=10; 24 months, n=8): • Mean blood urea nitrogen: baseline, 17.4±5.3 mg/dl; 6 months, 17.4±4.5 mg/dl; 12 months, 18.3±4.0 mg/dl; 24 months, 16.2±4.1 mg/dl • Mean serum creatinine: baseline, 0.96±0.37 mg/dl; 6 months, 0.91±0.30 mg/dl; 12 months, 0.94±0.29 mg/dl; 24 months, 0.85±0.22 mg/dl

First author, date	Efficacy outcomes	Safety outcomes
		• Mean eGFR: baseline, 78±21 ml/min/1.73m^2; 6 months, 80±20 ml/min/1.73m^2; 12 months, 77±20 ml/min/1.73m^2; 24 months, 85±14 ml/min/1.73m^2 • ≥25% reduction in eGFR: 12 months, 10%; 24 months, 0%

Fischell (2016)	**Total sample**: n=18 (37 treated renal arteries), 16 people (32 treated arteries) completed the study.
	Device and procedural success: 100% (n=18 with 37 arteries)
	Mean changes in office BP at 6 months from baseline (n=16):
	• Systolic BP: -24±22 mmHg
	• Diastolic BP: -12±9 mmHg
	Antihypertensive medications (n=12 with available medication data): baseline, 3.4±0.7 medications; 6 months, 2.0±0.9 medications
	• No changes: n=3
	• Reduction in medications: n=9
	• Increase in medications: n=0
	• **Mean changes in office BP** at 6 months from baseline (n=12):
	  ○ Systolic BP: -24±16 mmHg
	  ○ Diastolic BP: -12±9 mmHg
		Pain during infusion of the alcohol: no or minimal pain.
		In people who noted some **discomfort**, this resolved within 1 to 2 min without any intervention.
		No perforation, dissection, or significant spasm (>20% diameter stenosis) by visual assessment and no device or intervention-related complications or adverse events.
		Death at 9 weeks: n=1 unrelated to the device or the procedure.
		No renal artery stenosis or any other angiographic abnormalities, and no adverse nephrotoxic or systemic effects seen up to 6 months by laboratory testing.
		Mean eGFR (n=16): baseline, 66±16 ml/min/1.73 m^2; 6 months, 75±13 ml/min/1.73m^2; p=0.15
		Serum creatinine, blood urea nitrogen, and electrolytes remained stable over the study period.

Procedure technique

All the studies described the procedure technique and device used. Under fluoroscopic guidance, a 3-needle-based endovascular delivery device (Peregrine System Infusion Catheter, Ablative Solutions, Inc.,) was used to deliver microdoses of dehydrated alcohol, as a neurolytic agent, locally into the perivascular space of the renal artery to achieve ablation of the afferent and efferent sympathetic nerves. The amount of alcohol infused per renal artery ranged from 0.3 ml (Janas 2020; Fischell 2016) to 0.6 ml (Mahfoud 2020, 2021; Pathak 2023; Kandzari 2024). Most procedures were bilateral RDNs.

When reported, the mean treatment time (from the advancement of the device or infusion catheter insertion to time of retraction) ranged from 7 minutes (Mahfoud 2020) to 10 minutes (Fischell 2016) per artery, and the mean procedure time (from femoral artery access to sheath removal) was between 49 minutes (Mahfoud 2020) and 62 minutes (Pathak 2023). The mean total volume of contrast used was 100 mL (Pathak 2023).

Procedure success (device success with freedom from periprocedural MAE) was reported in 3 studies, ranging from 95% to 100% (Kandzari 2024; Pathak 2023; Fischell 2016).

Efficacy

Reduction in BP

Reduction in BP covered both 24-hour ABPM and office BP. A meta-analysis was done, with the pooled results of 24-hour systolic ABPM and office systolic BP shown in appendix C.

ABPM

24-hour ABPM was assessed and reported in 4 of the 5 studies. After RDN, systolic BP reduced statistically significantly across studies and a MCID of 5 mmHg was met at final follow-up time points in most studies. When comparing RDN with sham procedure, the 2 RCTs showed statistically significant difference in BP reductions at 3 months but not at 12 months when reported in 1 RCT. Considerable BP reductions in the sham controls mitigated the between-group differences.

In an RCT of 301 people who had RDN (n=148) or a sham procedure (n=153), Kandzari (2024) reported that the mean change at 3 months from baseline in 24-hour systolic ABPM was greater in the RDN group compared with the sham group (-10.0 mmHg compared with -6.8 mmHg), with a statistically significant between-group difference, favouring RDN (-3.2 mmHg; 95% CI -6.3 to 0.0; p=0.0487). But there was no statistically significant difference in 24-hour diastolic ABPM reduction between RDN and sham control (-5.4 mmHg compared with -4.1 mmHg; treatment difference, -1.4 mmHg; 95% CI -3.1 to 0.3; p=0.1146).

In an RCT of 106 people who had RDN (n=50) or a sham procedure (n=56), Pathak (2023) found statistically significant reductions in 24-hour systolic ABPM at 6 months and 12 months after the procedure in both groups (RDN: -13.9 mmHg and -10.6 mmHg at 6 and 12 months, respectively; all p<0.0001; sham: -13.4 mmHg and -15.9 mmHg at 6 and 12 months, respectively; all p<0.0001). But the authors did not see a statistically significant difference in BP reduction between groups at both time points (-0.55 mmHg and 5.3 mmHg at 6 and 12 months, respectively; all p>0.05). For 24-hour diastolic ABPM, the authors observed statistically significant reductions at 6 and 12 months in both groups, and reported a statistically significant difference in BP reduction between groups at 12 months, favouring sham procedure (2.5 mmHg, p=0.0341), but not at 6-month follow up.

Mahfoud (2020, 2021) reported that, of the 45 people who had RDN, 24-hour systolic and diastolic ABPM statistically significantly reduced at 6 months (mean change in systolic BP, -11 mmHg; mean change in diastolic BP, -7 mmHg; both p<0.001), and at 12 months from baseline (mean change in systolic BP, -10 mmHg; mean change in diastolic BP, -7 mmHg; both p<0.001).

Janas (2020) found that, of the 10 people who had RDN, 24-hour systolic ABPM statistically significantly reduced at 12 months from baseline (mean change, -6 mmHg; p<0.05) but not at 6 months (mean change, -3 mmHg) and 24 months (mean change, -1 mmHg). For 24-hour diastolic ABPM, the mean change was 2 mmHg at 6 months, -3 mmHg at 12 months and -1 mmHg at 24 months.

Office BP

Office BP was evaluated in all 5 studies. After RDN, both statistically and clinically (a MCID of 10 mmHg) significant reductions in systolic BP were shown across all studies. When comparing RDN with the sham procedure, the 2 RCTs reported statistically significant difference in BP reductions at 3 months but not at 12 months when reported in 1 RCT. Notable BP reductions in the sham controls lessened the between-group differences.

Kandzari (2024) reported that the mean reduction in office systolic BP at 3 months was -12.7 mmHg (SD 18.3) for the RDN group compared with -9.7 mmHg (SD 17.3) for the sham control group. The difference between groups was not statistically significant (-3.0 mmHg; 95% CI -7.0 to 1.0; p=0.173). Similarly, there was no statistically significant difference observed in office diastolic BP reduction between groups.

Pathak (2023) found that the mean changes in office systolic BP at 6 and 12 months were -12.9 mmHg (SD 15.6; p<0.0001) and -11.0 mmHg (SD 15.3; p<0.0001) in the RDN group and -14.7 mmHg (SD 15.7; p<0.0001) and -13.2

mmHg (SD 16.6; p<0.0001) in the sham group. Between-group comparison did not show any statistically significant differences in mean changes at both time points (6 months, 1.8 mmHg [95% CI -4.5 to 8.2], p=0.724; 12 months, 2.2 mmHg [95% CI -4.5 to 8.9], p=0.6823). For office diastolic BP, the mean changes at 6 and 12 months were -10.0 mmHg (SD 9.0; p<0.0001) and -9.4 mmHg (SD 9.4; p<0.0001) in the RDN group and -8.4 mmHg (SD 9.5; p<0.0001) and -9.6 mmHg (SD 11.0; p<0.0001) in the sham group. No statistically significant difference in mean changes between groups at both follow-up durations (6 months, -2.5 mmHg [95% CI -6.1 to 1.2], p=0.3575; 12 months, -1.6 mmHg [95% CI -5.4 to 2.1], p=0.6375).

Mahfoud (2020, 2021) reported statistically significant reductions in office systolic and diastolic BP at 6 months (mean change in systolic BP -18 mmHg; mean change in diastolic BP -10 mmHg; both p<0.001), and at 12 months from baseline (mean change in systolic BP -20 mmHg; mean change in diastolic BP -10 mmHg; both p<0.001).

Janas (2020) found that office systolic BP statistically significantly reduced at 6, 12 and 24 months from baseline (mean change, -28 mmHg, -21 mmHg and -25 mmHg, respectively; all p<0.001). For office diastolic BP, the authors reported that the reduction was 7 mmHg, 2 mmHg and 6 mmHg at 6, 12 and 24 months, respectively.

Fischell (2016) described that, of the 18 people who had RDN, office systolic and diastolic BP reduced at 6 months (mean change in systolic BP, -24 mmHg; mean change in diastolic BP, -12 mmHg). The authors also reported similar BP outcomes in the 12 people with accurate medication data (mean change in systolic BP, -24 mmHg; mean change in diastolic BP, -12 mmHg).

Use of antihypertensive medications

Data on antihypertensive medications was described in all 5 studies. But medication adherence was evaluated and reported in 2 studies only, with the rate of full adherence between 50% and 60% over time (Kandzari 2024; Mahfoud 2020).

Kandzari (2024) described that there were no statistically significant differences between groups in prescribed medication changes from baseline to 3 months, and no notable differences between groups in dose titration score, defined daily does, or medication index at 3 months. Adherence testing revealed that 43% and 41% of people in the RDN and sham groups, respectively, were fully adherent to their prescribed medications at baseline (p=0.712). At 3 months, the adherence rates increased to 51% and 49%, respectively (p=0.765). The rates of partial and complete non-adherence were similar between groups at all time points and did not statistically significantly vary.

Pathak (2023) reported that the medication burden was statistically significantly lower in the RDN group than the sham group at 12 months (mean daily defined dose: 1.5 compared with 2.3; p=0.017). The authors also described that following primary endpoint collection at 8 weeks, antihypertensive medication was uptitrated to achieve a target office systolic BP of 140 mmHg or less, and that the medication burden increased from 8 weeks in both groups (RDN, 0.08; sham, 0.12).

Mahfoud (2020) described that urine toxicological analyses revealed that adherence to the antihypertensive regimen remained relatively consistent over time (75%, 82%, and 78% after 1, 3, and 6 months of follow up). This was also reflected in the proportion of people who were fully adherent with their antihypertensive regimens, with 52%, 61%, and 59% at 1, 3, and 6 months of

follow up, respectively. At 12 months, Mahfoud (2021) reported that the number of antihypertensive medications reduced from baseline (-0.1; 95% CI -0.5 to 0.4).

Janas (2020) found that antihypertensive medications increased in 2 people, reduced in 1 person and remained the same in 6 people at 24 months after RDN.

Fischell (2016) reported that the number of antihypertensive medications reduced to 2 at 6 months from 3.4 at baseline in the 12 people with accurate medication data.

Renal function

Renal function was reported in all 5 studies. There were no statistically significant changes in renal function after RDN except for Mahfoud (2021) who found a statistically significant reduction in eGFR at 12 months.

Kandzari (2024) described that renal function remained unchanged from baseline through 3 and 6 months in both the RDN and sham groups (mean change in eGFR through 6 months: -1.2 and -0.9 mL/min/1.73m^2 for the RDN and sham control groups, respectively; p=0.728)

Pathak (2023) reported that eGFR remained stable in the RDN group (mean change, -2.1 ml/min/1.73m^2) but decreased in the sham group up to 12-month follow up (mean change, -6.4 ml/min/1.73m^2). The difference between groups was statistically significant (p=0.0224) although baseline values were comparable between groups.

Mahfoud (2020, 2021) found that eGFR statistically significantly reduced at 12 months from baseline (mean change, -3.9±10.3 ml/min/1.73m^2; p=0.02) but not at 6 months (mean change, -2.7±12.1 ml/min/1.73m^2; p=0.15). The authors did not observe any statistically significant changes in serum creatinine, cystatin C and spot urine albumin at both 6 and 12 months.

Janas (2020) reported that there was no deterioration in renal function (including blood urea nitrogen, serum creatinine and eGFR) during the 24-month follow up and no significant divergences between the follow-up time points. The authors noted that 25% or more reduction in eGFR was observed in 1 person at 12 months.

Fischell (2016) described that eGFR increased from 66 ml/min/1.73m^2 at baseline to 75 ml/min/1.73m^2 at 6 months, but this change was not statistically significant (p=0.15). The authors also found that serum creatinine, blood urea nitrogen, and electrolytes remained stable over the study period.

Safety

Major or serious adverse events

Major or serious adverse events were reported in all 5 studies and the observation period ranged from 1 to 6 months. The rate of MAEs was up to 7% in 3 studies (Kandzari 2024; Pathak 2023; Mahfoud 2020) and the rate of serious adverse events was 20% in Janas (2020). Although death was reported in the Fischell (2016) study, it was unrelated to the device or procedure.

Kandzari (2024) found that at 30 days, the proportion of people with MAEs was 5% (n=7) for the RDN group and zero for the sham control group, with a statistically significant difference between groups (p=0.007). In the RDN group, MAEs included 1 major vascular complication, 1 hypertensive emergency and 6 hypotension needing intervention or medication change. By 6 months, cumulative occurrence of MAEs was similar between groups (RDN, 5% [n=11]; sham, 4% [n=6], p=0.224). In the RDN group, the 11 events included 1 death (unrelated to the procedure, device or drug), 1 myocardial infarction, 1 major vascular complication, 2 hypertensive emergencies, and 7 hypotension needing intervention or medication change. In the sham group, the 6 events consisted of

1 myocardial infarction, 2 hypertensive emergencies, and 3 hypotension needing intervention or medication change.

Pathak (2023) reported that the rate of MAEs up to 30 days after treatment was 2% in the RDN group and less than 2% in the sham group. The authors described that 1 person experienced a hypertensive crisis up to 30 days after RDN and 1 person had a vascular complication after the sham procedure (the person developed a small subcutaneous haematoma, subsequently diagnosed as aneurysm spurium).

Mahfoud (2020) reported that the proportion of people with primary safety endpoint events (any periprocedural major vascular complications or major bleeding, acute kidney injury, or death within 1 month of the procedure) within 1 month after RDN was 4% (n=2), including periprocedural major vascular complications/vascular access pseudoaneurysm (n=2) and major bleeding (TIMI classification, n=1). Within 6 months postprocedure, the proportion of people with MAEs was 7% (n=3), including major vascular complications (n=2) and severe hypotension or syncope (n=1).

Janas (2020) found that there were 3 serious adverse events in 2 people, including inflammation of the duodenum mucosae membrane at 6 months (n=1), upper respiratory tract infections (n=1) and diabetes intensification (n=1). The last 2 events happened to the same person.

Fischell (2016) reported death in 1 person at 9 weeks after RDN but this was unrelated to the device or procedure.

Device- or procedure-related, nonserious adverse events

Device- or procedure-related, nonserious adverse events were reported in 3 studies, including minimal pain, minor vessel dissection, transient microleaks and device deficiency.

Mahfoud (2020) reported procedural pain in 1 person, minor vessel dissection in 2 people, and device deficiency in 5 people. The authors also noted transient microleaks in 42% and 49% of the left and right main renal arteries, respectively. Janas (2020) reported procedural pain in 2 people, with a score of 2 on a 10-point scale. Fischell (2016) also observed minimal pain or some discomfort in some people during the procedure (exact data was not reported).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal and theoretical adverse events: angiography related complications (such as rupture of arteries and cholesterol emboli) and specific complications (such as loss of a kidney).

Eight professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

The key evidence includes 2 RCTs and 3 single-arm studies. Most studies had a follow up of 6 to 12 months and only Janas (2020) reported the data for 24 months. All studies were done in Europe and the US.

In addition to the RoB assessment detailed in table 2, 1 RCT (Kandzari 2024) was adequately powered for 24-hour systolic ABPM (a between-group difference

of 6 mmHg). But the other RCT (Pathak 2023) was a phase 2 trial and underpowered for statistical comparisons of efficacy or safety events. The sample sizes for the 3 single-arm studies were small, so there was no statistically powered endpoint in these studies. Also, all 5 studies were sponsored by Ablative Solutions, Inc., and had more than 1 author with conflicts of interest reported.

Across studies, there was variation in the population groups and procedure techniques; this might affect the efficacy and safety outcomes. For the population groups, 3 studies (Mahfoud 2020, 2021; Janas 2020; Fischell 2016) included people with resistant hypertension, 1 study (Kandzari 2024) recruited people with moderate uncontrolled hypertension and resistant hypertension, and 1 study (Pathak 2023) selected people with mild to moderate uncontrolled hypertension.

In terms of the procedure techniques, there were different doses of alcohol infused per renal artery. A low dose of 0.3 ml was used in 2 studies (Janas 2020; Fischell 2016) but a high dose of 0.6 ml was applied in 3 studies (Kandzari 2024; Pathak 2023; Mahfoud 2020, 2021). In addition, it is acknowledged that complete renal artery treatment is important for BP reduction; in particular treating accessory arteries, which has been shown to contribute to the sympathetic innervation of the renal parenchyma. But there was no measure of effective or complete ablation of renal sympathetic nerves (Kandzari 2024; Pathak 2023).

Taken together, the evidence suggested statistically and clinically significant reductions in 24-hour systolic ABPM and office systolic BP after RDN from baseline. But this pre- and post-RDN effect should be interpretated with caution and might be vulnerable to Hawthorne effect such as improvement in adherence to antihypertensive medications and change in lifestyles.

When comparing RDN with the sham procedure, the effect of RDN on BP lowering was only found at 3 months (not beyond this time point). But its

magnitude was small, given unexpected large BP reductions observed in the sham controls. This indicated a potential placebo effect on BP lowering after sham procedures. Also, Pathak (2023) argued that most people in their trial were recruited during the COVID-19 pandemic, which might contribute to the increase in systolic BP and potentially introduce additional confounding factors. To support this point, the authors found larger and clinically meaningful BP changes in people who were enrolled before the start of the COVID-19 pandemic. Pathak (2023) also claimed that there was a possibility that the confounding effect of the COVID-19 pandemic was not evenly distributed between people and treatment groups (RDN and sham).

Data on antihypertensive medications was reported across studies, and the changes were generally small. Pathak (2023) found that antihypertensive medication use was lower in the RDN group at 3, 6, and 12 months postprocedure. But antihypertensive medication utilisation increased from 8 weeks to 12 months in both groups. This was because people stopped their antihypertensive medications 4 weeks before randomisation and, after primary endpoint collection at 8 weeks, antihypertensive medication was uptitrated to achieve a target office systolic BP. Notably, across all the studies, medication adherence was only measured in 2 studies and the rate of full adherence was between 50% and 60%. This highlighted the potential for confounding factors relating to inconsistency of medication adherence and indicated medication adherence being an ongoing challenge in hypertension management. With regard to renal function, evidence generally suggested that it remained stable after RDN.

For the safety outcomes, the rates of MAEs were up to 7% in 3 studies and the rate of serious adverse event was 20% (2/10) in the Janas (2020) study. Device- or procedure-related, nonserious adverse events included transient microleaks at needle puncture sites after needle retraction, minimal pain, minor vessel

dissection and device deficiency; these events did not raise significant safety concerns.

In summary, the evidence suggested that absolute reductions in both 24-hour systolic ABPM and office systolic BP achieved within the RDN groups were statistically significant and clinically relevant. But the relative differences between RDN and sham controls were of uncertain clinical significance and in particular the duration of effect was unclear. The effect of RDN on BP reductions could be affected by various factors. So, adequately powered RCTs and other well-designed studies with larger samples and longer follow ups are warranted to conclusively determine the BP-lowering effect of alcohol-mediated RDN in the management of hypertension and to provide greater assurance of procedural safety.

It is noted that the Kandzari (2024) study (NCT02910414), included in the key evidence, is still ongoing to continue examining whether the theoretical advantages of alcohol-mediated denervation with the Peregrine System Kit translate into clinical benefits. At the time of preparing this overview, the estimated completion date is December 2025. No other ongoing trials have been identified.

Related NICE guidance

Interventional procedures

- Percutaneous transluminal renal sympathetic denervation for resistant hypertension (2023) NICE interventional procedures guidance (IPG754) (Recommendation: special arrangements).

NICE guidelines

- Hypertension in adults: diagnosis and management (2023) NICE guideline (NG136).

Professional societies

- British and Irish Hypertension Society
- British Cardiovascular Society
- British Cardiovascular Intervention Society
- British Society of Interventional Radiology
- The UK Kidney Association

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures technical team and any relevant points have been taken into consideration when preparing this overview.

References

1. Kandzari DE, Weber MA, Pathak A et al. (2024) Effect of alcohol-mediated renal denervation on blood pressure in the presence of antihypertensive medications: primary results from the TARGET BP I randomized clinical trial. Circulation.
2. Pathak A, Rudolph UM, Saxena M et al. (2023) Alcohol-mediated renal denervation in patients with hypertension in the absence of antihypertensive medications. DOI: 10.4244/EIJ-D-23-00088
3. Mahfoud F, Renkin J, Sievert H et al. (2020) Alcohol-mediated renal denervation using the peregrine system infusion catheter for treatment of hypertension. JACC. Cardiovascular interventions 13(4): 471-84
4. Mahfoud F, Sievert H, Bertog S et al. (2021) Long-term results up to 12 months after catheter-based alcohol-mediated renal denervation for

treatment of resistant hypertension. Circulation: Cardiovascular Interventions: 918-26

5. Janas A, Krol M, Hochul M et al. (2020) Evaluation of transcatheter alcohol-mediated perivascular renal denervation to treat resistant hypertension. Journal of Clinical Medicine 9(6): 1-12

6. Fischell TA, Ebner A, Gallo S et al. (2016) Transcatheter alcohol-mediated perivascular renal denervation with the peregrine system: first-in-human experience. JACC. Cardiovascular interventions 9(6): 589-98

Appendix A: methods and literature search strategy

NICE has identified studies and reviews relevant to alcohol-mediated perivascular renal denervation for resistant hypertension from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 03/05/2023 and updated them on 22/02/2024 and 19/09/2024. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual

deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The search was not limited by date or language.

The CENTRAL database search removed trial registry records and conference material.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	03/05/2023	Wiley	Issue 5 of 12, May 2023	1
Cochrane Database of Systematic Reviews (CDSR)	03/05/2023	Wiley	Issue 5 of 12, May 2023	1
Embase	03/05/2023	Ovid	1974 to 2023 May 02	177
INAHTA International HTA Database	03/05/2023	https://database.inahta.org/	-	0
MEDLINE	03/05/2023	Ovid	1946 to May 02, 2023	59

MEDLINE In Process	03/05/2023	Ovid	1946 to May 02, 2023	0
MEDLINE Epub ahead of print	03/05/2023	Ovid	May 02, 2023	0

Update search

Table 4b Update search results 1

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	22/02/2024	Wiley	Issue 2 of 12, February 2024	1
Cochrane Database of Systematic Reviews (CDSR)	22/02/2024	Wiley	Issue 2 of 12, February 2024	0
Embase	22/02/2024	Ovid	1974 to February 21, 2024	10
INAHTA International HTA Database	22/02/2024	https://database.inahta.org/	-	0
MEDLINE ALL	22/02/2024	Ovid	1946 to February 21, 2024	5

Table 4c Update search results 2

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	19/092024	Wiley	Issue 8 of 12, August 2024	3

Cochrane Database of Systematic Reviews (CDSR)	19/09/2024	Wiley	Issue 9 of 12, September 2024	0
Embase	19/09/2024	Ovid	1974 to September 18, 2024	7
INAHTA International HTA Database	19/09/2024	https://database.inahta.org/	-	0
MEDLINE ALL	19/09/2024	Ovid	1946 to September 18, 1974	4

Search strategy history

For the updated searches there was no change to the strategy apart from the date limit from 3 May 2023 to 22 February 2024 (update search results 1) and 22 February 2024 to 19 September 2024 (update search results 2) and a change from searching individual MEDLINE segments to searching MEDLINE ALL. So, the rerun strategies have not been included.

MEDLINE search strategy

1 exp Hypertension/ 315,613

2 hypertens*.tw. 444,642

3 ((high* or raise* or elevat* or increase*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*).tw. 86,302

4 (HPB or SBP or DBP or HTN).tw. 34,667

5 ((resistant* or refract* or uncontrolled*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*).tw. 1,349

6 or/1-5 575,763

7 exp Sympathectomy/ 12,008

8 Sympathetic Nervous System/ 39,773

9 denervation/ 15,063

10 catheter ablation/ 38,744

11 or/7-10 101,351

12 Kidney/ 291,936

13 Renal Artery/ 18,607

14 (Kidney or Renal).tw. 863,037

15 or/12-14 947,613

16 11 and 15 8,837

17 ((kidney* or renal) adj4 (denervat* or sympathe* or catheter* or ablat* or neurectom* or neurotom* or perivascul*)).tw. 9,229

18 (RSD or RDN).tw. 16,881

19 or/16-18 28,958

20 6 and 19 5,124

21 Ethanol/ 95,258

22 (ethyl* or ethan* or alcohol*or chemical*).tw. 299,355

23 Phenol*.tw. 92,619

24 Phenol/ 6,626

25 neurolytic agent/ 0

26 (neurolytic* adj 4 agent*).tw. 0

27 or/21-26 418,688

28 20 and 27 95

29 (Peregrine adj4 (system* or cathet*)).tw. 13

30 28 or 29 105

31 Animals/ not Humans/ 5,083,921

32 30 not 31 59

EMBASE search strategy

1 exp Hypertension/ 910,007

2 hypertens*.tw. 773,768

3 ((high* or raise* or elevat* or increase*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*).tw. 133,486

4 (HPB or SBP or DBP or HTN).tw. 79,054

5 ((resistant* or refract* or uncontrolled*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*).tw. 2,630

6 or/1-5 1,248,483

7 sympathectomy/ 6,465

8 adrenergic system/ 34,704

9 denervation/ 16,054

10 catheter ablation/ 40,925

11 or/7-10 96,465

12 kidney/ 268,649

13 renal artery/ 12,783

14 (Kidney or Renal).tw. 1,345,913

15 or/12-14 1,424,339

16 11 and 15 6,295

17 ((kidney* or renal) adj4 (denervat* or sympathe* or catheter* or ablat* or neurectom* or neurotom* or perivascul*)).tw. 14,827

18 (RSD or RDN).tw. 28,078

19 or/16-18 44,478

20 6 and 19 8,606

21 alcohol/ 297,575

22 (ethyl* or ethan* or alcohol*or chemical*).tw. 451,102

23 phenol/ 32,633

24 Phenol*.tw. 142,231

25 neurolysis/ 3,833

26 (neurolytic* adj4 agent*).tw. 181

27 or/21-26 751,982

28 20 and 27 223

29 (Peregrine adj4 (system* or cathet*)).tw,dv,dm. 52

30 28 or 29 250

31 Nonhuman/ not Human/ 5,301,123

32 30 not 31 177

33 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5,531,997

34 32 not 33 110

35 32 and 33 67

Cochrane search strategy

#1 MeSH descriptor: [Hypertension] explode all trees 26388

#2 hypertens* 79537

#3 ((high* or raise* or elevat* or increase*) near/4 (arterial* or blood or diastolic* or systolic*) near/4 pressure*) 15124

#4 (HPB or SBP or DBP or HTN) 44407

#5 ((resistant* or refract* or uncontrolled*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*) 53

#6 #1 or #2 or #3 or #4 or #5 101820

#7 MeSH descriptor: [Sympathectomy] this term only 220

#8 MeSH descriptor: [Sympathetic Nervous System] this term only 1185

#9 MeSH descriptor: [Denervation] this term only 247

#10 MeSH descriptor: [Catheter Ablation] this term only 2068

#11 #7 OR #8 OR #9 OR #10 3604

#12 MeSH descriptor: [Kidney] this term only 4697

#13 MeSH descriptor: [Renal Artery] this term only 380

#14 (Kidney or Renal) 103570

#15 #12 OR #13 OR #14 103570

#16 #11 AND #15 292

#17 ((kidney* or renal) near/4 (denervat* or sympathe* or catheter* or ablat* or neurectom* or neurotom* or perivascul*)) 1244

#18 (RSD or RDN) 556

#19 #16 OR #17 OR #18 1556

#20 #6 AND #19 744

#21 MeSH descriptor: [Ethanol] this term only 3862

#22 (ethyl* or ethan* or alcohol*or chemical*) 12044

#23 MeSH descriptor: [Phenol] this term only 715

#24 Phenol* 2320

#25 (neurolytic* near/4 agent*) 19

#26 #21 OR #22 OR #23 OR #24 OR #25 14219

#27 #20 AND #26 8

#28 (Peregrine adj4 (system* or cathet*)) 0

#29 #27 OR #28 8

#30 "conference":pt or (clinicaltrials or trialsearch):so 678650

#31 #29 NOT #30 2

INAHTA search strategy

1 "Hypertension"[mhe] 245

2 hypertens* 258

3 ((high* or raise* or elevat* or increase*) AND (arterial* or blood or diastolic* or systolic*) AND pressure*) 144

4 (HPB or SBP or DBP or HTN) 4

5 ((resistant* or refract* or uncontrolled*) AND (arterial* or blood or diastolic* or systolic*) AND pressure*) 18

6 #5 OR #4 OR #3 OR #2 OR #1 444

7 "Sympathectomy"[mh] 11

8 "Sympathetic Nervous System"[mh] 2

9 "Denervation"[mh] 18

10 "Catheter Ablation"[mh] 148

11 #10 OR #9 OR #8 OR #7 167

12 "Kidney"[mh] 273

13 "Renal Artery"[mh] 15

14 (Kidney or Renal) 503

15 #14 OR #13 OR #12 539

16 #15 AND #11 14

17 ((kidney* or renal) AND (denervat* or sympathe* or catheter* or ablat* or neurectom* or neurotom* or perivascul*)) 35

18	(RSD or RDN)	5
19	#18 OR #17 OR #16	39
20	#19 AND #6	17
21	"Ethanol"[mh]	11
22	(ethyl* or ethan* or alcohol*or chemical*)	247
23	"Phenol"[mh]	3
24	Phenol*	0
25	(neurolytic* and agent*)	0
26	#25 OR #24 OR #23 OR #22 OR #21	251
27	#26 AND #20	0
28	(Peregrine and (system* or cathet*))	0
29	#27 OR #28	0

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes (safety). Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with (resistant) hypertension.
- Intervention or test: Alcohol-mediated perivascular renal sympathetic denervation.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in appendix B.

Find out more about how NICE selects the evidence for the committee.

Appendix B: other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Table 5 additional studies identified

Article	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Azeez GA, Thirunagari M, Fatima N et al. (2024) The efficacy of renal denervation in treating resistant hypertension: a systematic review. Cureus 16(8): e67007. DOI 10.7759/cureus.67007	Systematic review	Renal denervation (RDN) has significantly lowered systolic blood pressure compared to sham control, and this reduction is maintained for multiple years. This effect is observed whether the renal denervation is applied via radiofrequency, ultrasonically, or chemically. It is especially efficacious in patients who have a higher baseline blood pressure. In addition, the renal denervation procedure demonstrates a safety profile, and any noted complications were directly related to vascular access. Future considerations should examine the efficacy of one renal denervation modality against another, such as ultrasound RDN against radiofrequency RDN, and compare renal denervation to other procedural strategies such as carotid baroreceptor stimulation.	Only 1 case report (Luo 2021) is relevant to the procedure and is included in the appendix of the overview.
Fischell TA, Fischell DR, Ghazarossian	Case series	Perivascular RDN using micro-doses of alcohol is a	More recent studies with

VE, et al. (2015) Next generation renal denervation: chemical “perivascular” renal denervation with alcohol using a novel drug infusion catheter. Cardiovascular Revascularization Medicine 16: 221-7.	N=18 Follow up: 6 months	promising alternative to energy-based systems to achieve dose-dependent, predictable, safe and essentially painless renal denervation. Further clinical evaluation is warranted.	larger samples or better design were included in the main evidence.
Gunes-Altan M, Schmid A, Ott C et al. (2024) Blood pressure reduction after renal degermation in patients with or without chronic kidney disease. Clinical Kidney Journal, 17: 1-11	Non-randomised comparative study N=174 (47 people with CKD and 124 people without CKD) Follow up: 12 months	Authors observed a similar reduction in 24-hour, day and night-time ambulatory BP as well as in-office BP in people with and without CKD at any time point up to 12 months. Authors conclude that RDN is an effective and safe treatment option for patients with hypertension and CKD.	Intervention included radiofrequency-, ultrasound- or alcohol-infusion-based RDN, the outcomes for alcohol-mediated RDN not reported separately
Hearon CMJ, Howden EJ, Fu Q et al. (2021) Evidence of reduced efferent renal sympathetic innervation after chemical renal denervation in humans. American journal of hypertension 34(7): 744-52	Pilot study n=7	These results are the first to show efferent sympathetic denervation of the renal cortex following RDN in humans. Further studies of mechanisms underlying variable blood pressure lowering in the setting of documented RDN may provide insights into inconsistencies in clinical trial outcomes.	Small sample with limited efficacy data reported.
Luo G, Zhu JJ, Yao M et al. (2021) Computed tomography-guided chemical renal sympathetic nerve modulation in the treatment of resistant hypertension: A case	Case report n=1 Follow up: 1 year	Computed tomography-guided chemical renal sympathetic modulation may be a feasible method for the treatment of resistant hypertension.	Small sample

report. World Journal of Clinical Cases 9(32): 9970-6			
Mahfoud F, Bertog S, Lauder L et al. (2021) Blood pressure lowering with alcohol-mediated renal denervation using the Peregrine infusion Catheter is independent of injection site location. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 98(6): e832-38	Post-hoc analysis of a feasibility study (Mahfoud 2020) n=45 Follow up: 6 months	In this post-hoc analysis, the location of alcohol infusion within the main renal artery using the Peregrine system, with alcohol as the neurolytic agent for chemical RDN, did not affect the magnitude of BP changes at 6 months.	Mahfoud (2020) is included in the main evidence.
Persu A, Maes F, Toennes SW et al. (2022) Impact of drug adherence on blood pressure response to alcohol-mediated renal denervation. Blood Pressure 31(1): 109-17	Sub-analysis of drug adherence of a feasibility study (Mahfoud 2020, 2021) n=45 Follow up: 12 months	About 40% of patients with apparently treatment-resistant hypertension were not fully adherent at baseline, and adherence decreased further in 30%. Nevertheless, mean blood pressure changes after renal denervation were similar irrespective of drug adherence. The results suggest that such patients may benefit from alcohol-mediated renal denervation, irrespective of drug adherence. These findings are hypothesis-generating and need to be confirmed in ongoing sham-controlled trials.	The feasibility study is included in the main evidence.
Ricke J, Seidensticker M, Becker S et al. (2016) Renal sympathetic denervation by CT-	Case series N=11	CT-guided sympathetic denervation proved to be safe and applicable under various anatomical conditions with more renal	More recent studies with larger samples or better design were included

guided ethanol injection: a phase ii pilot trial of a novel technique. Cardiovascular and interventional radiology 39(2): 251-60	Follow up: 6 months	arteries and such of small diameter.	in the main evidence.
Streitparth F, Gebauer B, Nickel P et al. (2014) Percutaneous computer tomography-guided ethanol sympathicolysis for the treatment of resistant arterial hypertension. Cardiovascular and interventional radiology 37(2): 513-8	Case report n=1 Follow up: 1 month	Image-guided periarterial ethanol injection for renal sympathetic denervation in a patient with drug-resistant hypertension is feasible. Authors provide a detailed description of this new interventional procedure and discuss its potential advantages compared with catheter-based radiofrequency ablation.	Small sample

Appendix C: meta-analysis

The 5 studies in the key evidence (tables 2 and 3) were included in the meta-analysis.

Data analysis

The effects of RDN on 24-hour systolic ABPM and office systolic BP were examined using weighted mean differences, with 95% CI. The random-effects generic inverse variance model was used. The treatment effects consisted of BP reductions between RDN and sham controls (using data at a similar follow-up timepoint), and after RDN from baseline within the RDN groups (using data at the longest follow-up timepoints due to data availability and to reduce potential heterogeneity). Sensitivity analyses were conducted to explore the influence of different doses used (0.3 ml or 0.6 ml alcohol infused per treated renal artery) and hypertension stages (indicated by the numbers of antihypertensive medications taken) on the effect sizes and to investigate heterogeneity where appropriate.

Heterogeneity was assessed using Chi^2 and I^2 statistics. Forest plots were used to display the meta-analysis results. All analyses were performed using Reference Manager V5.

Results

24-hour systolic ABPM

Of the 5 studies, there were only 2 RCTs (Kandzari 2024; Pathak 2023) that compared RDN with sham controls and reported 24-hour systolic ABPM at 2 to 3 months postprocedure. The pooled mean difference from the 2 RCTs (n=407) showed a statistically significant difference in 24-hour systolic ABPM reduction, favouring RDN (-2.37 mmHg; 95% CI, -4.61 to -0.13; p=0.04), with no detectable

heterogeneity (I^2=0%; figure 1). However, the effect of RDN on BP lowering decreased at 6 months (-0.55 mmHg, p=0.6964) and was potentially inferior to that of the sham procedure at 12 months (5.3 mmHg, p=0.0775) in Pathak (2023) whereas Kandzari (2024) is still ongoing.

In terms of BP reduction after RDN from baseline within the RDN groups, 4 studies assessed and reported 24-hour systolic ABPM at the follow-up durations of 3 to 24 months. The pooled mean difference after RDN from baseline was -7.92 mmHg (95% CI, -12.25 to -3.59; n=253; figure 2a). The effect on BP reduction was statistically significant (p=0.0003), and reached the MCID of -5 mmHg. But there was significant heterogeneity (I^2=84%).

The amount of alcohol infused per treated renal artery differed across studies (0.3 versus 0.6 ml per artery). Only Janas (2020) used 0.3 ml per artery whereas other studies applied 0.6 ml per artery. A sensitivity analysis of different doses was carried out. The results showed a statistically significant reduction in 24-hour systolic ABPM in the high dose subgroup (-10.18 mmHg; 95% CI, -11.94 to -8.42; I^2=0%; p<0.00001) but not in the low dose subgroup (-1.00 mmHg; 95% CI, -4.72 to 2.72; p=0.60). There was a statistically significant difference between subgroups (I^2=95%, p<0.0001) as illustrated in figure 2b.

For hypertension stages, 2 studies focused on resistant hypertension, 1 study included both uncontrolled and resistant hypertension, and 1 study emphasised uncontrolled hypertension. A sensitivity analysis demonstrated a statistically significant reduction in 24-hour systolic ABPM across 3 subgroups (high medication load: -5.29 mmHg [95% CI, -14.10 to 3.52]; medium medication load: -10.00 mmHg [95% CI, -12.29 to -7.71]; low medication load: -10.60 mmHg [95% CI, -13.79 to -7.41]). This effect was also clinically relevant. There was no detectable subgroup difference (I^2=0%, p=0.54) as shown in figure 2c.

Although 24-hour systolic ABPM reductions after RDN from baseline within the RDN groups were statistically significant and reached the MCID, the effect of RDN compared with sham controls was uncertain and its duration of effect was unclear. In addition, different factors might influence the effect sizes, such as the amount of alcohol infused per renal artery and hypertension stage. Furthermore, follow-up durations were relatively short. So, careful interpretation of the outcomes is needed.

Office systolic BP

The 2 RCTs also assessed and reported the office systolic BP between RDN and sham procedure. The pooled mean difference was -3.62 mmHg (95 CI, -6.74 to -0.51; I^2=0%; p=0.02; figure 3) at 2 to 3 months, in favour of RDN. However, the effect of RDN on BP reduction was potentially inferior to that of the sham procedure at 6 months (1.8 mmHg) and 12 months (2.2 mmHg), although the differences were not statistically significant (both p>0.05; Pathak 2023).

For pre-post treatment effect, all the 5 studies measured and reported the office systolic BP at the follow-up periods ranging from 3 to 24 months. The pooled mean difference after RDN from baseline was -17.09 mmHg (95% CI, -22.14 to -12.03; n=271; figure 4a). This reduction was statistically significant (p<0.00001) and met the MCID of -10 mmHg, but with significant heterogeneity (I^2=71%). It is noted that this direction of effect on office systolic BP reduction is consistent across all individual studies as illustrated in figure 4a.

A sensitivity analysis of different amounts of alcohol infused per renal artery demonstrated statistically and clinically significant reductions in office systolic BP for both subgroups (studies with higher dose: -13.85 mmHg [95% CI, -18.04 to -9.65], I^2=57%, p<0.00001; studies with lower dose: -24.52 [95% CI -22.14 to -12.03], I^2=0%, p<0.00001). There was a significant subgroup difference (I^2=85%, p=0.01; figure 4b).

For hypertension stages, a sensitivity analysis illustrated a statistically significant reduction across 3 subgroups (high medication load: -22.19 mmHg [95% CI -27.07 to -17.30]; medium medication load: -12.70 mmHg [95% CI, -15.64 to -9.76]; low medication load: -11.00 [95% CI, -22.14 to -12.03]). The effect also reached the MCID of 10 mmHg in all subgroups. The difference between subgroups was statistically significant (I^2=84%, p=0.002; figure 4c).

The effect of RDN on office systolic BP after RDN from baseline within the RDN groups reached both statistically and clinically significant endpoints. However, this effect diminished and was even potentially inferior when comparing with the sham procedure. So, the effect of RDN on BP control was uncertain and its duration of effect was unclear. Similar to 24-hour systolic ABPM, the effect of RDN on office systolic BP might be affected by different doses of alcohol used and varying hypertension stages.

Summary

When comparing RDN with the sham procedure, there were considerable BP reductions in the sham controls that mitigated the between group differences. Thus, the relative differences between treatments were of uncertain clinical significance and in particular the duration of effect was unclear. The large BP reductions in the sham controls indicated a placebo effect on BP lowering.

The placebo effect on BP lowering might also contribute to pre-post treatment effects within the RDN groups, even though BP reductions after RDN were statistically significant and reached the MCIDs. The pre-post treatment effects might also be affected by a Hawthorne effect, such as improvement in adherence to antihypertensive medications and change in lifestyles. Moreover, the values on baseline and post-RDN were not independent of each other, but the value for the correlation was not available and so not reflected in the results. Hence, the pre-post treatment effects were indicative only and should be treated carefully.

Across all the studies, most people were on 2 or more antihypertensive medications, and medication adherence was only measured in 2 studies with the rate of full adherence between 50% and 60% over time. Indeed, evidence suggests that a larger number of prescribed drugs is associated with a high rate of nonadherence (Azizi 2016). Due to the issue of highly variable adherence to medication across studies, usage of antihypertensive medication was not included as an endpoint and relevant data was not pooled. In addition, the variation in the amounts of alcohol infused per renal artery and medication loads relevant to hypertension stages might influence the effects of RDN. Therefore, the effects of RND on BP lowering were inconclusive and should be interpretated with caution.

Figure 1 pooled mean difference in 24-hour systolic ABPM reduction between RDN and sham

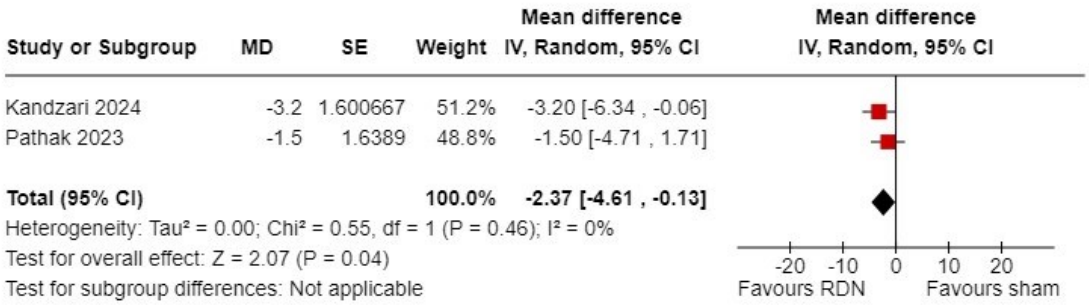

Figure 2a pooled mean reduction in 24-hour systolic ABPM after RDN from baseline

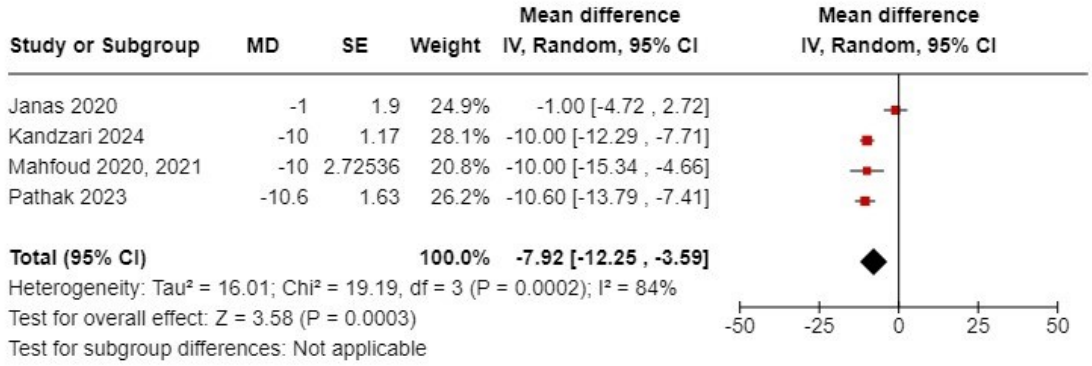

Figure 2b Sensitivity analysis of mean reduction in 24-hour systolic ABPM after RDN for different doses of alcohol infusion

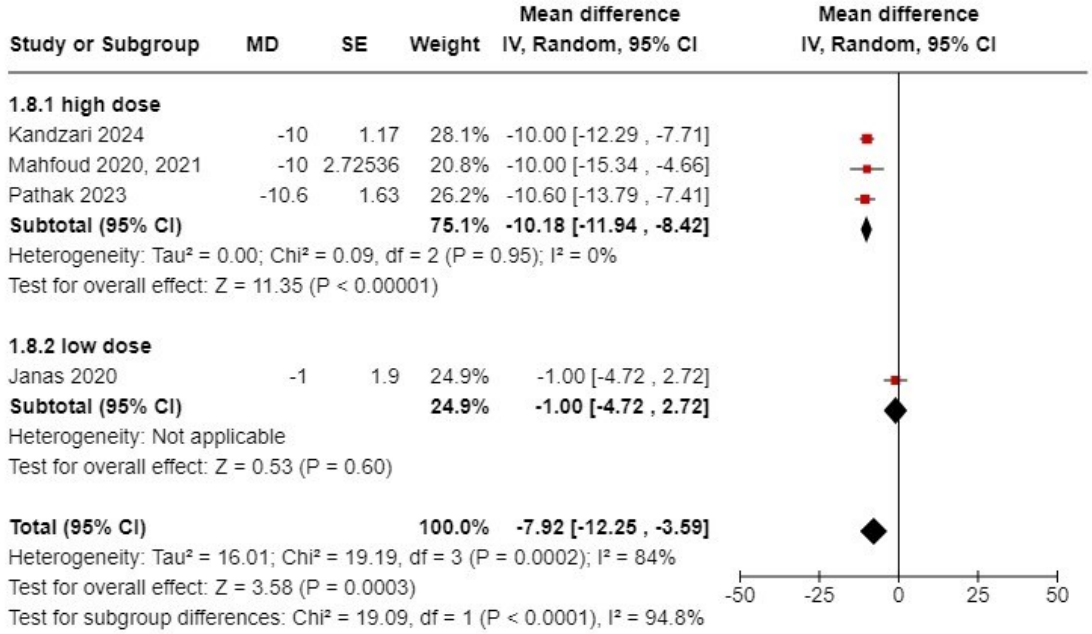

Figure 2c Sensitivity analysis of mean reduction in 24-hour systolic ABPM after RDN for different hypertension stages

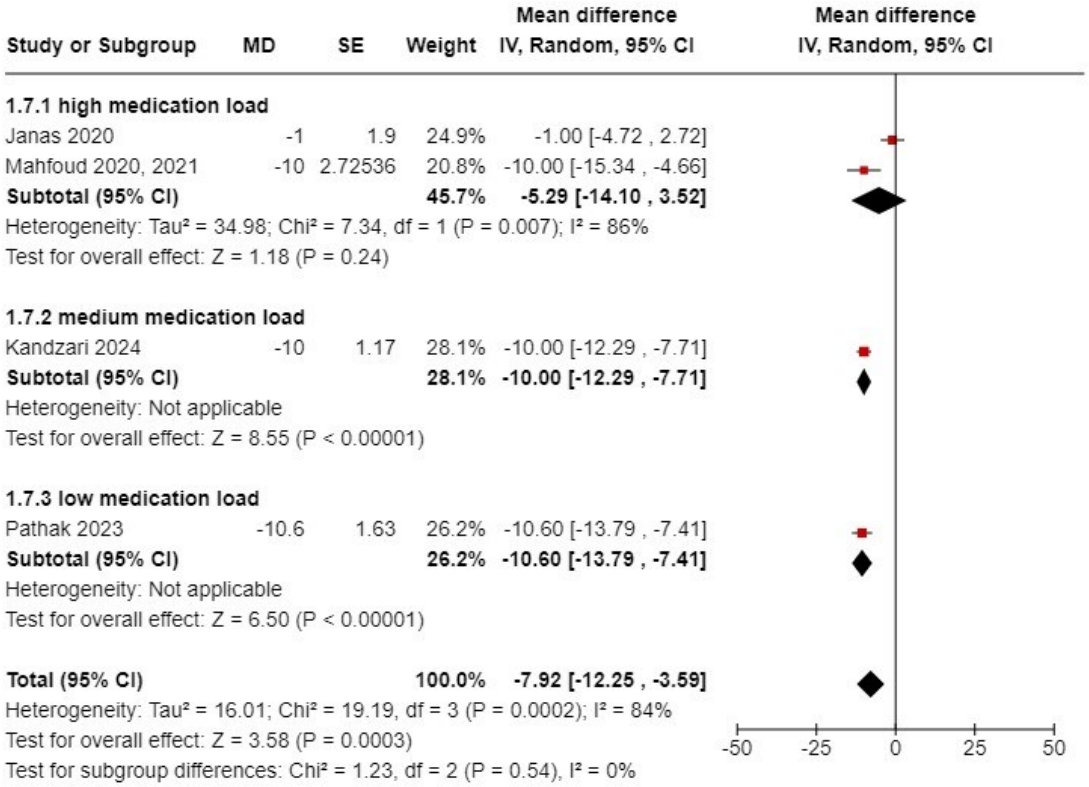

Figure 3 Pooled mean difference in office systolic BP reduction between RDN and sham

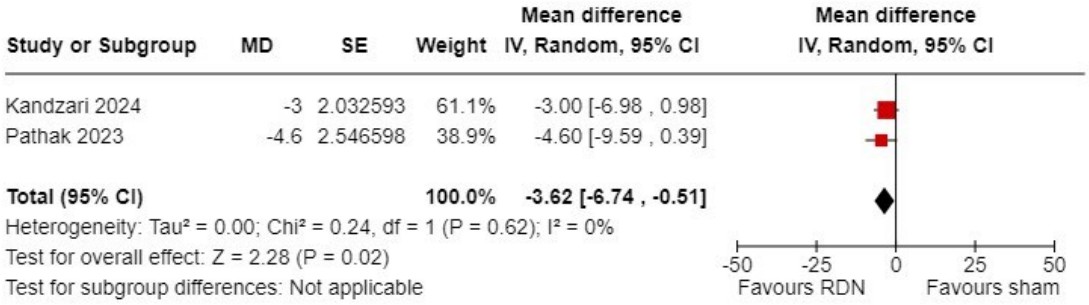

Figure 4a Pooled mean reduction in office systolic BP after RDN from baseline

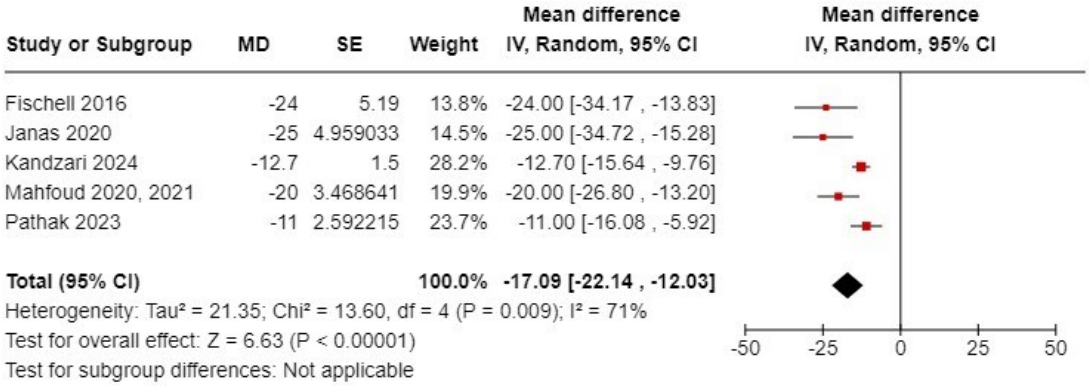

Figure 4b Sensitivity analysis of mean reduction in office systolic BP after RDN for different doses of alcohol infusion

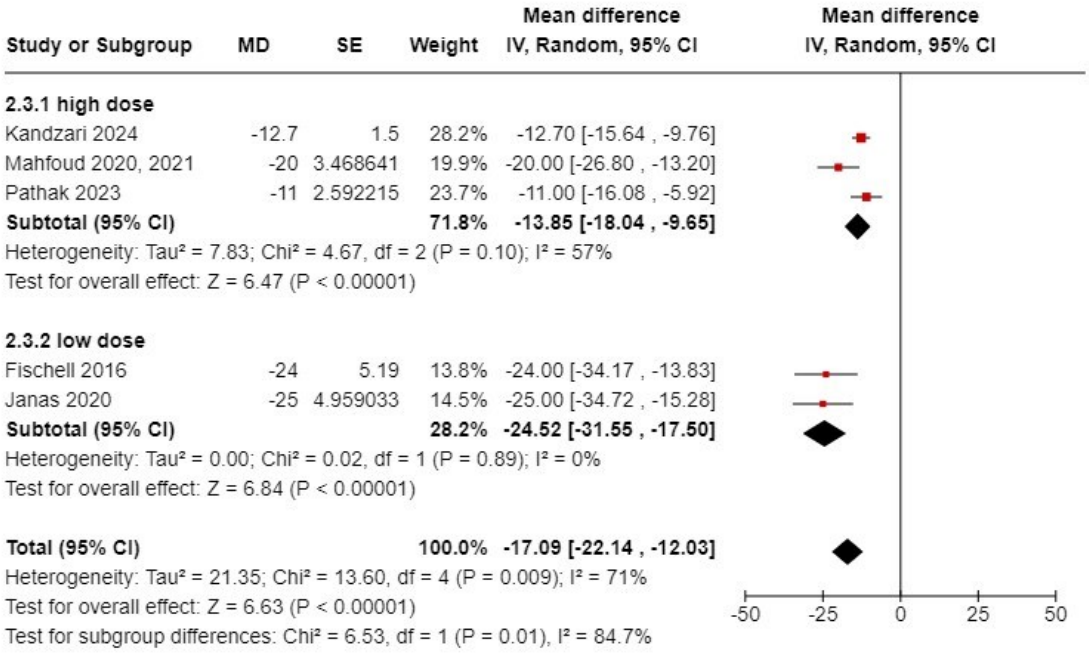

Figure 4c Sensitivity analysis of mean reduction in office systolic BP after RDN for different medication loads