NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous transluminal renal sympathetic denervation for resistant hypertension

High blood pressure (hypertension) can be caused by overactivity of a type of nerve (sympathetic) that helps the kidneys (renal) control blood pressure. Sometimes medicines to treat it do not work well enough (resistant). In this procedure, using a local anaesthetic, sedation and anticoagulation, a device is inserted through the skin (percutaneous) into an artery in the thigh and then into the renal arteries (transluminal). It sends radio or sound waves to destroy the nerves in the renal arteries (sympathetic denervation). The aim is to lower blood pressure.

Contents

Abbreviations

Word or phrase	Abbreviation
Ambulatory blood pressure monitoring	ABPM
Blood pressure	BP
Confidence interval	CI
Estimated glomerular filtration rate	eGFR
Hazard ratio	HR
Interquartile range	IQR
Mean difference	MD
Odds ratio	OR
Randomised controlled trial	RCT
Renal sympathetic denervation	RDN
Radiofrequency ablation of the main renal artery, branches, and accessories	RFB-RDN
Radiofrequency ablation of the main renal artery	RFM-RDN
Risk ratio	RR
Standard deviation	SD
ST-elevation myocardial infarction	STEMI
Ultrasound-based ablation of the main renal artery	USM-RDN

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2022 and updated in October 2022.

Procedure name

- Percutaneous transluminal renal sympathetic denervation for resistant hypertension

Professional societies

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

Description of the procedure

Indications and current treatment

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

NICE's guideline on hypertension in adults describes diagnosing and managing hypertension, including resistant hypertension. Current treatments for hypertension include lifestyle modifications and antihypertensive medications. Blood pressure and treatment are regularly monitored and treatment is adjusted as needed. For resistant hypertension, additional medications and device-based antihypertensive therapies (for example renal denervation and carotid baroreceptor stimulation) can be considered.

What the procedure involves

This procedure is usually done using 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 is connected to a generator which delivers radiofrequency or ultrasound energy (depending on the type of system used) 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. There are

different systems with different technologies in use for renal sympathetic denervation.

Efficacy summary

Ambulatory blood pressure (BP)

Radiofrequency RDN

In a Cochrane review of 15 studies (1,416 patients with resistant hypertension) that compared percutaneous transluminal renal sympathetic denervation (RDN) with antihypertensive therapy or sham procedure (control), there were statistically significantly greater reductions in 24-hour ambulatory systolic BP (mean difference [MD] -5.29 mmHg, 95% CI -10.46 to -0.13, p=0.04; I^2=77%; 9 studies, n=1,045; GRADE, moderate quality) and 24-hour ambulatory diastolic BP (MD -3.75 mmHg, 95% CI -7.10 to -0.39, p=0.03; I^2=73%; 8 studies, n=1,004; GRADE, moderate quality) after RDN compared with control. The high heterogeneity depended on the type of radiofrequency system (multi-electrode compared with single-electrode catheter). For daytime ambulatory BP monitoring, there were less reductions in systolic and diastolic BP after RDN compared with control, but the effects were not statistically significant (systolic BP, MD 3.87 mmHg, 95% CI -5.02 to 12.76, p=0.39, I^2=70%, 5 studies, n=234; diastolic BP, MD 2.93 mmHg, 95% CI -3.22 to 9.08, p=0.35, I^2=76%, 5 studies, n=234). For nighttime ambulatory BP monitoring, there were greater reductions in systolic and diastolic BP after RDN compared with control, but the effects were not statistically significant (systolic BP, MD -1.65 mmHg, 95% CI -12.74 to 9.45, p=0.77, I^2=75%, 5 studies, n=234; diastolic BP, MD -1.08 mmHg, 95% CI -9.25 to 7.08, p=0.79, I^2=87%, 5 studies, n=234; Pisano 2021).

In an RCT of 535 patients with resistant hypertension, the mean change in 24-hour ambulatory systolic BP was –15.6 mmHg in the RDN group of 152 patients and –0.3 mmHg in the sham control group of 119 patients (adjusted treatment difference –16.5 mm Hg, 95% CI –20.5 to –12.5; p≤0·0001) at 36 months (Bhatt 2022).

In a case series of 2,237 patients with uncontrolled hypertension (antihypertensive medication classes, mean 4.5) who had RDN (using the single-electrode denervation system), 24-hour ambulatory systolic BP statistically significantly decreased (mean change, -7.2 mmHg, p<0.0001) at 6-month follow up. Statistically significant decrease in 24-hour ambulatory systolic BP was sustained over 3 years (1 year, -7.2 mmHg; 2 years, -8.2 mmHg; 3 years, -8.0 mmHg; all p<0.0001; Mahfoud 2019).

In a case series of 407 patients with resistant hypertension who had RDN (mainly using the single-electrode denervation system), 24-hour systolic and diastolic BP

reduced at 3 months (mean change in systolic BP, -8 mmHg [SD 19]; mean change diastolic BP, -4 mmHg [SD 13]), 6 months (-8 mmHg [SD 17] and -5 mmHg [SD 11]) and 12 months (-10 mmHg [SD 18] and -6 mmHg [SD 12]). All reductions were statistically significant (all p<0.001). Both systolic and diastolic BP at daytime and nighttime also statistically significantly reduced at 3 months, 6 months and 12 months after the procedure (all p<0.001). At 6 months, the ambulatory BP response rate (24-hour ambulatory BP reduction of 5 mmHg or more) was 55% (120/220). In total, 22% of patients reached the systolic 24-hour BP goal of less than130 mmHg at every follow up. Subgroup analysis showed that 24-hour BP reduction after the procedure was statistically significantly more apparent in group A (patients with a mean 24-hour BP more than145/90 mmHg, equivalent to an office BP of 160/100 mmHg) compared with group B (patients with a mean 24-h BP of 145/90 mmHg or below; p<0.01 at every follow-up; Zweiker 2016).

In a case series of 253 patients with resistant hypertension who had RDN (mainly using the single-electrode denervation system), daytime ambulatory BP statistically significantly reduced from 170 mmHg (SD 22) at baseline to 158 mmHg (SD 25) at 8.5-month follow up for systolic BP (MD, -12 mmHg; p<0.001), and from 98 mmHg (SD 16) to 91 mmHg (SD 17) for diastolic BP (MD, -7 mmHg; p<0.001). For nighttime ambulatory BP, systolic BP decreased from 154 mmHg (SD 26) to 145 mmHg (SD 26) and diastolic BP from 86 mmHg (SD 18) to 83 mmHg (SD 17). According to baseline daytime ambulatory systolic BP from quartiles 1 to 4 (142 mmHg for quartile 1, 162 mmHg for quartile 2, 176 mmHg for quartile 3 and 199 mmHg for quartile 4), at 8.5-month follow up the mean reduction in daytime ambulatory systolic BP was 0.4 mmHg for quartile 1, 6.5 mmHg for quartile 2, 14.5 mmHg for quartile 3, and 22.1 mmHg for quartile 4 (p value for quartile trend <0.001). Overall, 62% of patients who responded to RDN (daytime ambulatory systolic BP reduction of 5 mmHg or more; Sharp 2016).

Ultrasound RDN

In an RCT of 136 patients with resistant hypertension who had RDN or sham procedure, 24-hour ambulatory systolic BP reduced in both groups (RDN, -6.6 mmHg, 95% CI -10.4 to -2.8; sham, -6.5 mmHg, 95% CI -10.3 to -2.7) at 3-month follow up. There were no statistically significant differences in 24-hour ambulatory systolic and diastolic BP reductions between groups (difference in systolic BP, −0.1 mmHg, p=0.971; difference in diastolic BP, -0.4 mmHg, p=0.806; Kario 2022).

In an RCT of 136 patients with resistant hypertension who had RDN or sham procedure, 24-hour ambulatory systolic BP reduced in the RDN group (median difference, -8.5 mmHg, IQR -15.1 to 0.0) and the sham group (median difference, -2.9 mmHg, IQR -12.6 to 2.5) at 2-month follow up. The median between-group difference was -4.2 mmHg (95% CI -8.3 to -0.3, baseline-adjusted p=0.016).

During the same period, 24-hour ambulatory diastolic BP also reduced in both groups (median difference in the RDN group, -5.4 mmHg, IQR -10.4 to 0.0; median difference in the sham group, -2.4 mmHg, IQR -7.8 to 0.5), with a median between-group difference being -2.0 mmHg (95% CI -4.5 to 0.6; baseline-adjusted p=0.12). When considering daytime and nighttime BP separately, there were statistically significantly greater reductions in daytime and nighttime systolic BP after RDN compared with sham (median between-group difference in daytime systolic BP, -4.5 mmHg, 95% CI -8.5 to -0.3, baseline-adjusted p=0.022; median between-group difference in nighttime systolic BP, -3.9 mmHg, 95% CI -8.8 to 1.0, baseline-adjusted p=0.044) but not for diastolic BP (median between-group difference in daytime diastolic BP, -1.8 mmHg; 95% CI -4.5 to 0.8, baseline-adjusted p=0.18; median between-group difference in nighttime diastolic BP, -2.8 mmHg, 95% CI -6.1 to 0.2, baseline-adjusted p=0.053; Azizi 2021). At 6-month follow up (n=129), 24-hour ambulatory systolic BP reduced in the RDN group (mean difference, -11.4 mmHg, SD 14.1) and the sham group (mean difference, -12.1 mmHg, SD 14.5). The mean between-group difference was 0.1 mmHg (95% CI -4.3 to 4.6, baseline-adjusted p=0.85). During the same period, 24-hour ambulatory diastolic BP also reduced in both groups (mean difference in the RDN group, -8.0 mmHg, SD 8.9; mean difference in the sham group, -8.3 mmHg, SD 9.2), with a mean between-group difference being 0.2 mmHg (95% CI –2.8 to 3.1; baseline-adjusted p=0.74). For daytime ambulatory systolic BP, the overall change from baseline to 6 months was −2.5mmHg lower with RDN compared with sham (95% CI -6.7 to 1.7mmHg, p=0.25) in a mixed linear model (Azizi 2022).

Radiofrequency and ultrasound RDN

In a 3-arm randomised trial of 117 patients with resistant hypertension who had radiofrequency ablation of the main renal artery (RFM-RDN using the multi-electrode denervation system), radiofrequency ablation of the main renal artery, branches, and accessories (RFB-RDN using the multi-electrode denervation system) or ultrasound-based ablation of the main renal artery (USM-RDN), there were statistically significant reductions in daytime systolic BP (-9.5 mmHg [SD 12.3]), daytime diastolic BP (-6.3 mmHg [SD 7.8]) and nighttime systolic BP (- 6.1 mmHg [SD 14.2]) in all patients (all p<0.001) at 3 months after treatment. Comparison between groups showed that there was a statistically significantly greater reduction in daytime systolic BP in the USM-RDN group than the RFM-RDN group (MD -6.7 mmHg, 98.3% CI -13.2 to -0.2, adjusted p=0.043) but not between RFM-RDN and RFB-RDN (MD -1.8 mmHg, 98.3% CI –8.5 to 4.9, adjusted p>0.99) and between USM-RDN and RFB-RDN (MD -4.9 mmHg, 98.3% CI -11.5 to 1.7, adjusted p=0.22). The systolic BP response rate (systolic BP reduction of 5 mmHg or more) was observed in 66% of patients who had RFM-RDN compared with 73% in the RFB-RDN group and 67% in the USM-RDN group (p=0.77). Profound BP response was found in 8% of patients who had RFM-RDN, 14% of patients who had RFB-RDN, and 29% of patients who had USM-RDN (p=0.039; Fengler 2019).

In a case series of 296 patients with resistant hypertension who had RDN using radiofrequency or ultrasound, 24-hour ambulatory systolic and diastolic BP statistically significantly reduced by 8.3 mmHg (SD 12.2) and 4.8 mmHg (SD 7.0) at 3 months, by 8.0 mmHg (SD 12.4) and 5.1 mmHg (SD 7.1) at 6 months, and by 8.7 mmHg (SD 14.1) and 5.4 mmHg (SD 7.8) at 12 months (all p<0.001). At 3 months, 61% of patients (180/296) were classified as BP responders (24-hour ambulatory systolic BP reduction of 5 mmHg or more) and 39% (116/296) as non-responders. Systolic BP at 6 months and 12 months remained statistically significantly more reduced in patients who responded to RDN than patients who did not (-12.1 mmHg [SD 2.8] compared with -2.8 mmHg [SD 13.8], and -11.7 mmHg [SD 12.0] compared with -2.0 mmHg [SD 10.7], p<0.001 for both, compared with baseline BP values; Fengler 2021).

Office BP

Radiofrequency RDN

In the Cochrane review of 15 studies, there was a statistically significantly greater reduction in office diastolic BP after RDN compared with control (MD -4.61 mmHg, 95% CI -8.23 to -0.99, p=0.01; I^2=77%; 8 studies, n=1,049; GRADE, moderate quality) but not for systolic BP (MD -5.92 mmHg, 95% CI -12.94 to 1.10, p=0.10; I^2=86%; 9 studies, n=1,090; GRADE, moderate quality). Subgroup analyses showed that benefits on office systolic BP became evident in studies using a multi-electrode radiofrequency catheter (MD -5.10 mmHg, 95% CI -9.14 to -1.06) compared with those using a single-electrode catheter system, also nullifying the heterogeneity among studies (I^2=0%; Pisano 2021).

In the RCT of 535 patients, the mean change in office systolic BP was –26.4 mmHg in the RDN group of 219 patients and –5.7 mmHg in the sham control group of 134 patients (adjusted treatment difference –22.1 mm Hg, 95% CI –27.2 to –17.0, p≤0·0001) at 36 months (Bhatt 2022).

In the case series of 2,237 patients, there was a statistically significant decrease in office systolic BP (mean change, -12.8mmHg, p<0.0001) at 6 months after the procedure. Statistically significant decrease in office systolic BP was sustained over 3 years (1 year, -12.3 mmHg; 2 years, -14.7 mmHg; 3 years, -16.5 mmHg; all p<0.0001; Mahfoud 2019).

In the case series of 407 patients, office systolic and diastolic BP statistically significantly reduced at 3 months (mean change, -16 mmHg [SD 25] and -4 mmHg [SD18]), 6 months (-20 mmHg [SD 26] and -7 mmHg [SD 18]), and 12 months (-20 mmHg [SD 27] and -8 mmHg [SD 18]) after the procedure (all p<0.001). The office BP response rate (office systolic BP decrease of 10 mmHg or more) after 6 months was 69% (128/185). In total, 30% of patients reached the office systolic BP goal of 140 mmHg or less at every follow-up (Zweiker 2016).

In the case series of 253 patients, office BP statistically significantly reduced from 185 mmHg (SD 26) at baseline to 163 mmHg (SD 28) at 11-month follow up for systolic BP (MD -22 mmHg [SD 29]; p<0.001), and from 102 mmHg (SD 19) to 93 mmHg (SD 19) for diastolic BP (MD -9 mmHg [SD 19]; p<0.001). According to baseline daytime ambulatory systolic BP from quartiles 1 to 4 (142 mmHg for quartile 1, 162 mmHg for quartile 2, 176mmHg for quartile 3 and 199 mmHg for quartile 4), at 8.5-month follow up the mean reduction in office systolic BP was 15.2 mmHg for quartile 1, 22.3 mmHg for quartile 2, 22.9 mmHg for quartile 3 and 30.3 mmHg for quartile 4 (p=0.001 for quartile trend). Overall, 65% of patients responded to RDN (office systolic BP reduction of 10 mmHg or more; Sharp 2016).

Ultrasound RDN

In the RCT of 136 patients, office systolic and diastolic BP reduced in the RDN group (-11.0 mmHg and -4.9 mmHg) and the sham group (-9.0 mmHg and -5.0 mmHg) at 3-month follow up. There were no statistically significant differences in office systolic and diastolic BP reductions between groups (difference in systolic BP, −2.0 mmHg, p=0.511; difference in diastolic BP, 0.1 mmHg, p=0.946; Kario 2022).

In the RCT of 136 patients, office systolic BP reduced in the RDN group (median difference, -9.0 mmHg, IQR -19.5 to -1.5) and the sham group (median difference, -4.0 mmHg, IQR -12.0 to 9.0) at 2-month follow up. The median between-group difference was statistically significant (-7.0 mmHg, 95% CI - 13.0 to -0.0, baseline adjusted p=0.037). For office diastolic BP, there were reductions in both groups (RDN, -5.0 mmHg, IQR -13.5 to 2.5; sham, -1.0 mmHg, IQR -7.0 to 6.0) but the median between-group difference was not statistically significant (-4.0 mmHg, 95% CI -9.0 to 0.0, baseline-adjusted p=0.16; Azizi 2021). At 6-month follow up (n=129), office systolic BP reduced in the RDN group (mean difference, -10.4 mmHg, SD 16.8) and the sham group (mean difference, -11.2 mmHg, SD 22.7). The mean between-group difference was 0.7 mmHg (95% CI -5.3 to 6.6, p=0.93). For office diastolic BP, there were reductions in both groups (RDN, -6.6 mmHg, SD 11.5; sham, -7.5 mmHg, SD 13.7). The mean between-group difference was 1.9 mmHg (95% CI -1.9 to 5.7, p=0.32). The overall change from baseline to 6 months was −2.9 mmHg lower with RDN compared with sham (95% CI -7.9 to 2.0 mmHg, p=0.24) in a mixed linear model (Azizi 2022).

Home BP

Radiofrequency RDN

In the Cochrane review of 15 studies, there were greater reductions in home systolic and diastolic BP in the RDN group than the control group, but the effects were not statistically significant (between-group difference in systolic BP, -

5.6 mmHg, 95% CI -14.5 to 3.2, p=0.205; between-group difference in diastolic BP, -4.8 mmHg, 95% CI -9.8 to 0.3, p=0.065) in the HTN-JAPAN 2015 study. In the DENER-HTN 2015 study, home systolic and diastolic BP reduced in the RDN group (MD in systolic BP, -15.4 mmHg, 95% CI -20.4 to -10.4; MD in diastolic BP, -8.7 mmHg, 95% CI -12.1 to -5.4) and the control group (MD in systolic BP, -11.8 mmHg, 95% CI -16.5 to -7.1; MD in diastolic BP, -6.7 mmHg, 95% CI -9.8 to -3.5), and the between-group differences were not statistically significant for both systolic and diastolic BP (Pisano 2021).

Ultrasound RDN

In the RCT of 136 patients, home systolic BP reduced by 8.7 mmHg and diastolic BP by 3.6 mmHg in patients who had RDN, and home systolic BP reduced by 6.9 mmHg and diastolic BP by 3.7 mmHg in patients who had sham procedures at 3-month follow up. There were no statistically significant between-group differences in both home systolic and diastolic BP reductions (between-group difference in systolic BP, −1.8 mmHg, p=0.488; between-group difference in diastolic BP, 0.1 mmHg, p=0.949; Kario 2022).

In the RCT of 136 patients, home systolic and diastolic BP reduced in the RDN group (median difference in systolic BP, -6.0 mmHg, IQR -17.0 to 1.5; median difference in diastolic BP, -4.0 mmHg, IQR -9.0 to 2.0) and in the sham group (median difference in systolic BP, -2.0 mmHg, IQR -9.5 to 2.0; median difference in diastolic BP, -1.0 mmHg, IQR -5.0 to 4.0) at 2-month follow up. The median between-group differences were not statistically significant for both systolic BP (- 4.0 mmHg, 95% CI -8.0 to 0.0, baseline-adjusted p=0.052) and diastolic BP reductions (-3.0 mmHg, 95% CI -6.0 to 0.0, baseline-adjusted p=0.053; Azizi 2021). At 6-month follow up (n=129), home systolic BP reduced in the RDN group (mean difference, -11.5 mmHg, SD 15.9) and the sham group (mean difference, -8.9 mmHg, SD 13.0). The mean between-group difference was -2.9 mmHg (95% CI -8.0 to 2.2, p=0.26). For home diastolic BP, there were reductions in both groups (RDN, -6.9 mmHg, SD 10.4; sham, -5.0 mmHg, SD 8.5). The mean between-group difference was -1.9 mmHg (95% CI -5.2 to 1.5, p=0.28). The overall change from baseline to 6 months was −4.3 mmHg lower with RDN compared with sham (95% CI -8.1 to -0.5 mmHg, p=0.03) in a mixed linear model (Azizi 2022).

Medication load

Radiofrequency RDN

In the RCT of 535 patients, the mean change in the number of prescribed medications classes was -0.3 (SD 1.4) in the RDN group and -0.2 (SD 0.9) in the sham group at 36 months (p=0.22; Bhatt 2022).

In the case series of 2,237 patients, patients were prescribed 4.5 (SD 1.4) antihypertensive medication classes at baseline and 4.4 (SD 1.5) at 3 years ($p<0.001$), reflecting a statistically significant decrease in angiotensin-converting enzyme inhibitor and centrally acting sympatholytic use with a concomitant increase in aldosterone antagonist use (Mahfoud 2019).

In the case series of 407 patients, the median number of antihypertensive drugs used was 4 (IQR 4 to 5) at baseline and 4 (IQR 3 to 5) at 12 months after the procedure (difference, 0; IQR -1 to 0, $p<0.05$; Zweiker 2016).

In the case series of 253 patients, the median number of antihypertensive drugs was 5.0 before the procedure. After the procedure, the mean number of drugs added per patient was 0.36 and the mean number of drugs withdrawn was 0.91. The mean dose changes were 0.21 doses up-titrated per patient and 0.17 doses decreased per patient (Sharp 2016).

Ultrasound RDN

In the RCT of 136 patients, there was no statistically significant difference in the reduction in antihypertensive medication load between the RDN and sham groups (RDN, 4.2 [SD 1.7] at baseline, 4.3 [SD 1.7] at 3 months; sham, 3.9 [SD 1.2] at baseline, 3.9 [SD 1.1] at 3 months; Kario 2022).

In the RCT of 136 patients, 93% (64/69) of patients in the RDN group and 85% (57/67) of patients in the sham group had no change in their antihypertensive treatment ($p=0.15$) at 2-month follow up. The proportion of patients who had additional antihypertensive medication was 4% (3/69) in the RDN group and 12% (8/67) in the sham group ($p=0.10$). The proportion of patients who reduced their antihypertensive medications was 3% for each group ($p=1.0$). The proportion of patients who fully adhered to antihypertensive medications with urine samples was 83% (49/59) at baseline and 82% (42/51) at 2 months in the RDN group, and 76% (44/58) at baseline and 82% (47/57) at 2 months in the sham group (Azizi 2021). At 6-month follow up (n=129), the mean change in number of medications was 0.7 (SD 1.0) in the RDN group and 1.1 (SD 1.1) in the sham group ($p<0.05$). The most frequently added antihypertensive medication was an aldosterone antagonist (predominantly spironolactone). However, an aldosterone antagonist was less frequently added at each monthly visit in the RDN group compared with the sham group through 6 months (RDN, 40% (26/65); sham, 61% (39/64); $p=0.02$; overall OR, 0.4; 95% CI, 0.2 to 0.7; $p<0.001$; Azizi 2022).

Radiofrequency and ultrasound RDN

In the 3-arm randomised trial of 117 patients, 9% (11/117) of patients changed their medications at 3-month follow up. Of these patients, 3 patients who increased medication dose or number were in the RFM-RDN group, 7 patients (2 decreased, 5 increased) in the RFB-RDN group, and 1 patient who decreased the number of drugs in the USM-RDN group (Fengler 2019).

Quality of life

In the Cochrane review of 15 studies, the self-reported health status according to the visual analogue scale (ranging from 0 [worst imaginable health] to 100 [best imaginable health]) improved in the RDN group (baseline, 64.2 [SD 21.5]; 6 months, 75.0 [SD 14.1]) but not in the control group (baseline, 53.9 [SD 28.5]; 6 months, 53.8 [SD 22.3]). The baseline-adjusted between-group difference was not statistically significant (13.6, 95% CI -7.4 to 34.6, p=0.28; INSPIRED) at 6-month follow up (Pisano 2021).

Safety summary

Mortality

Radiofrequency RDN

The mortality rate was less than 1% (10/2,237) at 6 months, 1% (28/2,112) at 1 year, 3% (54/1,917) at 2 years, and 4% (59/1,345) at 3 years after the procedure in the case series of 2,237 patients. The cardiovascular death rate was 0.3% at 6 months, 0.8% at 1 year, 1.5% at 2 years and 2.0% at 3 years, and the non-cardiovascular death rate was 0.1% at 6 months, 0.3% at 1 year, 1.0% at 2 years and 1.6% at 3 years (Mahfoud 2019).

All-cause mortality was reported in 2 patients who had RDN and 1 patient who had a sham procedure (SYMPLICITY HTN-3 2014) in the Cochrane review of 15 studies (Pisano 2021).

Death because of acute aortic dissection was reported in 1 patient at 2 months after the procedure in the RFM-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019).

The rate of the composite safety endpoint to 48 months (including all-cause death, new-onset end stage renal disease, significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, or hypertensive emergency) was 15% (54/352) in the RDN group, 14% (13/96) in the crossover group, and 14% (10/69) in the non-crossover group in the RCT of 535 patients (Bhatt 2022).

Ultrasound RDN

All-cause mortality was described in 1 patient in the RDN group in the RCT of 136 patients (Azizi 2021, 2022).

Radiofrequency and ultrasound RDN

Death was reported in 10% (29/296) of patients during a median follow up of 48 months in the case series of 296 patients. Cardiovascular death was described in 5% (16/296) of patients. When considering response status, death was reported in 11% (19/180) of patients who responded to RDN and 9% (10/116) of patients who did not (hazard ratio [HR] 1.22, 95% CI 0.58 to 2.57, p=0.69; Fengler 2021).

Major adverse cardiovascular or ischaemic events

Radiofrequency and ultrasound RDN

Major adverse cardiovascular events (cardiovascular death, ischaemic stroke or intracranial bleeding, acute myocardial infarction, critical limb ischaemia and acute renal failure) were reported in 15% (45/296) of patients during a median follow up of 48 months in the case series of 296 patients. When considering response status, major adverse cardiovascular events occurred less frequently in patients who responded to RDN than patients who did not, and the effect was statistically significant (12% [22/180] compared with 20% [23/116], HR 0.53, 95% CI 0.28 to 0.97, p=0.041). This statistically significant effect remained after adjustment for relevant covariates (p=0.041) and a propensity matched analysis (p=0.043). A proportional relationship was found between BP reduction after 3 months and frequency of major adverse cardiovascular events (HR 0.75 [95% CI 0.58 to 0.97] per 10 mmHg 24-hour systolic ambulatory BP reduction, p=0.031; Fengler 2021).

Ischaemic events (ischaemic stroke, acute myocardial infarction, peripheral artery disease needing intervention, and critical limb ischaemia) were reported in 11% (34/296) of patients during a median follow up of 48 months in the case series of 296 patients. When considering response status, ischaemic events happened less frequently in patients who responded to RDN than patients who did not, and the effect was statistically significant (8% [15/180] compared with 16% [19/116], HR 0.44, 95% CI 0.22 to 0.89, p=0.022). This statistically significant effect remained after a propensity matched analysis (p=0.08; Fengler 2021).

Myocardial infarction

Radiofrequency RDN

RDN was associated with a higher risk of myocardial infarction compared with control, but the effect was not statistically significant (RR 1.31, 95% CI 0.45 to 3.84, p=0.62; I^2=0%; 4 studies, n=742; GRADE, low quality) in the Cochrane review of 15 studies (Pisano 2021).

The rate of myocardial infarction was less than 1% (16/2,237) at 6 months, 1% (23/2,112) at 1 year, 2% (31/1,917) at 2 years, and 2% (33/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Ultrasound RDN

Acute myocardial infarction (STEMI or non-STEMI) was reported in 1 patient in the RDN group and 1 patient in the sham group in the RCT of 136 patients within 6 months (Azizi 2022).

Heart failure

Radiofrequency RDN

Hospital admission for new onset heart failure was described in 9 patients in the RDN group and 3 patients in the sham group (SYMPLICITY HTN-3 2014) in the Cochrane review of 15 studies (Pisano 2021).

The rate of hospitalisation for new onset heart failure was less than 1% (16/2,237) at 6 months, 1% (24/2,112) at 1 year, 2% (38/1,917) at 2 years and 3% (46/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Hospitalisation for acute decompensated heart failure was reported in 1 patient in the RFB-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019).

Radiofrequency and ultrasound RDN

Heart failure hospitalisation was reported in 7% (20/296) of patients during a median follow up of 48 months in the case series of 296 patients. When considering response status, heart failure hospitalisation was described in 7% (13/180) of patients who responded to RDN and 6% (7/116) of patients who did not (HR 1.27, 95% CI 0.52 to 3.11, p=0.59; Fengler 2021).

Stroke

Radiofrequency RDN

RDN might have little or no effect on the risk of ischaemic stroke compared with control (RR 0.98, 95% CI 0.33 to 2.95, p=0.97; I^2 =0%; 5 studies, n=892; GRADE, low quality) in the Cochrane review of 15 studies (Pisano 2021).

The rate of stroke was less than 1% (15/2,237) at 6 months, 1% (27/2,112) at 1 year, 2% (41/1,917) at 2 years, and 3% (47/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Angina

Radiofrequency RDN

RDN had a lower risk of unstable angina compared with control, but the effect was not statistically significant (RR 0.51, 95% CI 0.09 to 2.89, p=0.45; I^2 =0%; 3 studies, n=270; GRADE, low quality) in the Cochrane review of 15 studies (Pisano 2021).

Ultrasound RDN

Vasospastic angina was reported in 1 patient during the RDN procedure in the RCT of 136 patients (Kario 2022).

Atrial fibrillation

Radiofrequency RDN

The rate of hospitalisation for atrial fibrillation was less than 1% (15/2,237) at 6 months, 2% (32/2,112) at 1 year, 2% (46/1,917) at 2 years, and 3% (45/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Hospitalisation for atrial fibrillation episodes was reported in 5 patients in the RDN group and 1 patient in the sham group (SYMPLICITY HTN-3 2014) in the Cochrane review of 15 studies (Pisano 2021).

Renal function reduction

Radiofrequency RDN

There were no statistically significant differences in the changes in serum creatinine levels (MD 0.03 mg/dL, 95% CI -0.06 to 0.13, p=0.50; I^2=68%; 5 studies, n=721; GRADE, moderate quality) and in eGFR or creatinine clearance (MD -2.56 mL/min/1.73m^2, 95% CI -7.53 to 2.42, p=0.31; I^2=50%; 6 studies, n=822; GRADE, moderate quality) between RDN and control in the Cochrane review of 15 studies (Pisano 2021).

The rate of new onset end-stage renal disease was 0.2% (4/2,237) at 6 months, 0.4% (9/2,112) at 1 year, 1.0% (19/1,917) at 2 years, and 1.6% (23/1,345) at 3 years after the procedure in the case series of 2,237 patients. The rates of serum creatinine elevation of more than 50% mg/dL were 0.4% (9/2,237) at 6 months, 0.9% (1.9/2,112) at 1 year, 1.2% (24/1,917) at 2 years and 1.5% (24/1,345) at 3 years (Mahfoud 2019).

There was a statistically significant decrease in renal function at 12 months (-2 mL/min/1.73 m^2; p<0.05) in the case series of 407 patients (Zweiker 2016).

Ultrasound RDN

Doubling of plasma creatinine was reported in 1 patient in the RDN group in the RCT of 136 patients (Azizi 2021). At 6-month follow up, the mean difference was 2.0 mL/min/1.73 m^2 (95% CI -2.6 to 6.6; baseline adjusted p value, p=0.39) in eGFR and -0.0 mg/dl (95% CI -0.1 to 0.0; baseline adjusted p value, p=0.67) between the RDN and sham groups (Azizi 2022).

Hypotensive episode

Radiofrequency RDN

RDN was associated with a higher risk of hypotensive episodes compared with control, but the effect was not statistically significant (RR 1.60, 95% CI 0.20 to 12.63, p=0.66; I^2=58%; 3 studies, n=143) in the Cochrane review of 15 studies (Pisano 2021).

Symptomatic hypotension was reported in 2 patients in the RFB-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019).

Therapy-resistant hypotension was reported in 1 patient in the case series of 407 patients (Zweiker 2016).

Ultrasound RDN

Decreased BP was described in 1 patient within 3 months after RDN in the RCT of 136 patients (Kario 2022).

Hypertensive crisis or episode

Radiofrequency RDN

RDN was associated with a lower risk of hypertensive crisis compared with control, but the effect was not statistically significant (RR 0.71, 95% CI 0.35 to 1.45, p=0.34; I^2=0%; 3 studies, n=722) in the Cochrane review of 15 studies (Pisano 2021).

Symptomatic hypertension needing medical treatment was described in 1 patient in the RFM-RDN group and 2 patients in the RFB-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019).

The rate of hospitalisation for hypertensive crisis or emergency was less than 1% (17/2,237) at 6 months, 1% (24/2,112) at 1 year, 2% (36/1,917) at 2 years, and

3% (40/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Ultrasound RDN

Increased BP was reported in 1 patient within 3 months after RDN in the RCT of 136 patients (Kario 2022).

Procedural safety events

Renal artery dissection or stenosis

Radiofrequency RDN

Renal artery damage after RDN (using the single-electrode denervation system) was reported in 0.45% (26/5,769) of patients (stenosis [more than 50% diameter stenosis], n=19, 0.33%; dissection, n=7, 0.12%) within a median follow up of 6 months (range 1 to 36 months) in a meta-analysis of 50 studies (5,769 patients). Of the 26 patients with renal artery damage, 24 patients needed stent implantation. Time to reported stenting ranged from 0 to 33 months with most events occurring within 6 months after the procedure. An annual incidence rate of renal artery stenting following RDN was 0.20% per year (95% CI 0.12 to 0.29%, I^2=0%; Townsend 2020).

Renal artery dissection was reported in 1 patient who had RDN (Prague-15 2016) in the Cochrane review of 15 studies (Pisano 2021). Renal arterial dissection was reported in 1 patient in the case series of 407 patients and this patient needed stent implantation (Zweiker 2016).

The rate of new artery stenosis (more than 70% diameter stenosis) was 0.05% (1/2,237) at 6 months, 0.1% (3/2,112) at 1 year, 0.2% (4/1,917) at 2 years and 0.3% (4/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019). Re-stenosis (new renal artery stenosis more than 70%) was reported in 1 patient within the 6-month follow up (SYMPLICITY HTN-3 2014) in the Cochrane review of 15 studies (Pisano 2021). Renal artery stenosis was reported in 2 patients at 72 days and 452 days after the procedure in the case series of 407 patients, and both patients needed percutaneous transluminal renal angioplasty (Zweiker 2016).

Renal artery spasm

Radiofrequency RDN

Renal artery vasospasm was reported in 4 patients who had RDN (Prague-15) and transient renal artery spasm in 1 patient after radiofrequency application (Warchol 2014) in the Cochrane review of 15 studies (Pisano 2021).

Renal artery spasm was described in 1 patient in the case series of 407 patients (Zweiker 2016).

Ultrasound RDN

Transient renal artery spasm was reported in 1 patient in the USM-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019).

Vasospasm of renal artery was observed in 6% (4/72) of patients who had RDN within 30 days in the RCT of 136 patients. All events resolved quickly during the procedure with intra-arterial injection of nitrates (Kario 2022).

Renal artery reintervention

Radiofrequency RDN

The rate of renal artery reintervention was 0.2% (5/2,237) at 6 months, 0.4% (8/2,112) at 1 year, 0.4% (9/1,917) at 2 years and 0.6% (10/1,345) at 3 years after the procedure in the case series of 2,237 patients (Mahfoud 2019).

Pain

Radiofrequency RDN

RDN increased the risk of flank pain compared with control, but the effect was not statistically significant (RR 4.30, 95% CI 0.48 to 38.28, p=0.19; I^2=0%; 2 studies, n=199) in the Cochrane review of 15 studies (Pisano 2021).

Ultrasound RDN

Procedure-related pain lasting for more than 2 days was reported in 8% of patients in each group (RDN, 6/72; sham, 6/71) in the RCT of 136 patients (Kario 2022).

Procedure-related pain lasting for more than 2 days was reported in 17% (12/69) of patients in the RDN group and 15% (10/67) of patients in the sham group in the RCT of 136 patients. In the RDN group, 7 patients had pain at the femoral access site, 4 patients had back pain, and 1 patient had extremity pain. In the sham group, 8 patients had pain at the femoral access site and 2 patients had back pain (Azizi 2021, 2022).

Procedure access site complications

Radiofrequency RDN

The rate of procedure access site complications was 1% (82/5,769) in the meta-analysis of 50 studies (Townsend 2020).

RDN increased the risk of femoral artery pseudoaneurysm compared with control, but the effect was not statistically significant (RR 3.96, 95% CI 0.44 to 35.22, p=0.22; I^2 =0%; 2 studies) in the Cochrane review of 15 studies (Pisano 2021). Femoral artery pseudoaneurysm was reported in 2 patients in the case series of 407 patients (Zweiker 2016).

Symptomatic groin haematoma was reported in 1 patient in the RFB-RDN group in the 3-arm randomised trial of 117 patients. This event did not need any further medical intervention (Fengler 2019). Inguinal haematoma was reported in 1 patient in the case series of 407 patients and this event was managed successfully in the catheter room (Zweiker 2016). Postprocedural intracapsular and retroperitoneal haematoma was reported in 1 patient in the RFM-RDN group in the 3-arm randomised trial of 117 patients and this event resolved spontaneously (Fengler 2019).

Ultrasound RDN

Complications at femoral puncture site were reported in 6% (4/72) of patients in the RDN group and 4% (3/71) in the sham control group within 30 days after treatment in the RCT of 136 patients. These complications included pain (n=4), skin injury (n=1) and haematoma (n=2; Kario 2022).

Pseudoaneurysm was developed in 1 patient in the USM-RDN group in the 3-arm randomised trial of 117 patients (Fengler 2019). Femoral access site pseudoaneurysm was reported in 1 patient after the procedure and this event was treated with thrombin injection (Azizi 2021).

Others

Radiofrequency RDN

RDN statistically significantly increased the risk of bradycardia symptoms compared with control (RR 6.63, 95% CI 1.19 to 36.84, p=0.03; I^2 =0%; 3 studies, n=220) in the Cochrane review of 15 studies (Pisano 2021).

RDN was associated with a lower risk of hyperkalaemia compared with control, but the effect was not statistically significant (RR 0.43, 95% CI 0.05 to 3.89, p=0.45; I^2=37%; 3 studies, n=224) in the Cochrane review of 15 studies (Pisano 2021).

Dissection of the abdominal aorta was reported in 1 patient in the case series of 407 patients (Zweiker 2016).

Embolic event resulting in end-organ damage was reported in 1 patient and pitting oedema needing hospital admission in 1 patient who had RDN (SYMPLICITY HTN-3 2014) in the Cochrane review of 15 studies (Pisano 2021).

Ultrasound RDN

Cellulitis was described in 1 patient and postural dizziness in 1 patient in the RDN group in the RCT of 136 patients (Kario 2022).

Transient non-invasive ventilation was needed in 1 patient in the USM-RDN group after conscious sedation in the RCT of 117 patients (Fengler 2019).

Coronary revascularisation was reported in 2 patients in the RDN group and 1 patient in the sham group in the RCT of 136 patients (Azizi 2022).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts did not list any additional anecdotal adverse events but considered that the following were additional theoretical adverse events: renal arterial perforation, femoral artery complication, sedation related complications, renovascular disorder, and contrast induced acute kidney injury in those with chronic kidney disease.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous transluminal renal sympathetic denervation for resistant hypertension. The following databases were searched, covering the period from their start to 10 October 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with resistant hypertension.
Intervention/test	Percutaneous transluminal renal sympathetic denervation using radiofrequency or ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 8,624 patients from 1 Cochrane review (Pisano 2021), 1 meta-analysis (Townsend 2020), 3 RCTs (Kario 2022; Azizi 2021, 2022; Bhatt 2022), 1 3-arm randomised trial (Fengler 2019), and 4 case series (registries; Mahfoud 2019; Zweiker 2016; Sharp 2016; Fengler 2021). Additional documentation in confidence provided by a company was also considered by the committee.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on percutaneous transluminal renal sympathetic denervation for resistant hypertension

Study 1 Pisano A (2021)

Study details

Study type	Cochrane review
Country	Belgium (n=1), Czech Republic (n=2), Denmark (n=1), France (n=1), Germany (n=2), Japan (n=1), Norway (n=1), Poland (n=1), Romania (n=1), Spain (n=1), US (n=1), the Netherlands (n=1), Multicentres (n=1)
Recruitment period	Search: up to 2020
Study population and number	n=15 RCTs (1,416) Patients with refractory or resistant hypertension
Age and sex	Mean range 48 to 63 years; 36% to 89% male, when reported
Study selection criteria	Inclusion criteria: RCTs that compared RDN with standard therapy or sham procedure to treat resistant hypertension, without language restriction.
Technique	Any transcatheter renal sympathetic denervation procedures done using contemporary percutaneous catheters compared with standard medical therapy or sham intervention.
Follow up	3 months (1 study), 6 months (12 studies), 24 months (1 study), 84 months (1 study)
Conflict of interest/source of funding	Funding: no internal or external sources of support Conflict of interest: DB declared conflict of interest and 5 authors were unknown.

Analysis

Follow-up issues: Twelve studies provided information on withdrawals. SYMPLICITY HTN-3 2014 recorded 14 (3.8%) withdrawals from the RDN group and 2 (1.2%) from the control arm. In SYMPLICITY HTN-2 2010, there were 3 withdrawals from both the intervention and control arms. DENER-HTN 2015 reported 5 (10%) withdrawals from the RDN group. In Desch 2015, 6 patients (17%) withdrew from the RDN and 2 (5.55%) from the sham group. Prague-15 recorded 7 (13.7%) and 31 (62%) withdrawals from the RDN and control groups, respectively. Three studies reported no withdrawals. SYMPATHY recorded 8 withdrawals (5.8%) (5 in the RDN and 3 in the usual care group).

Study design issues: This study evaluated the short- and long-term effects of RDN in individuals with resistant hypertension on clinical end points, including fatal and non-fatal cardiovascular events, all-cause mortality, hospital admissions, quality of life, BP control, left ventricular hypertrophy, cardiovascular and metabolic profile and kidney function, as well as the potential adverse events related to the procedure.

Primary outcomes included i) fatal and non-fatal cardiovascular events, including but not limited to myocardial infarction, cerebrovascular accidents, and congestive heart failure; 2) all-cause mortality; 3) any hospitalisation and duration of hospital stay (if long-term data are available); 4) quality of life (assessed using validated scales or any other instrument as reported by authors).

Refractory or resistant hypertension was defined by the presence of a clinic BP 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 3 or more antihypertensive drugs of different classes, including a diuretic.

Two authors independently screened and selected eligible studies, carried out data extraction, assessed the quality of each study using the 'risk of bias' assessment tool.

Study population issues: This review included 15 eligible studies and 25 ongoing trials (115 articles). Of these 15 studies, 12 studies were included in quantitative synthesis (meta-analysis). In 4 studies, RDN was compared with sham procedure; in the remaining studies, RDN was tested against standard or intensified antihypertensive therapy. Most studies had unclear or high risk of bias for allocation concealment and blinding.

Of the 15 studies, RDN was done with the electrode radiofrequency Symplicity catheter system in 11 studies. Ablation was done with an off-the-shelf saline-irrigated radiofrequency catheter in 1 study (RELIEF 2012). In 2 studies (INSPIRED and SYMPATHY), ablation was made with the EnligHTN™ multi-electrode denervation system. In 1 study (Franzen 2012), details of the denervation procedure were not provided.

Other issues: The main limitation was represented by the data obtainable from the included studies. Studies were mainly focussed 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. More studies that look at factors important to patients such as quality of life are needed. Studies that last longer and have more participants are needed to find out if denervation can lower BP. Moreover, use of multiple catheter systems could potentially contribute to the heterogeneity observed in the analysis.

Key efficacy findings

Number of patients analysed: 1,149 (12 studies)

Quality of life:

- Self-reported health status after 6 months: RDN, 75.0±14.1; control, 53.8±22.3; baseline-adjusted between-group difference: 13.6; 95% CI -7.4 TO 34.6; p=0.28 (INSPIRED)

24-hour ambulatory BP monitoring:

- Systolic BP: MD -5.29 mmHg, 95% CI -10.46 to -0.13, p=0.04; I^2=77%; 9 studies (n=1,045) comparing RDN with control (GRADE: moderate quality). The high heterogeneity was fully dependent on the type of radiofrequency system, multi-electrode instead of a single electrode catheter (I^2=6%).

- Diastolic BP: MD -3.75 mmHg, 95% CI -7.10 to -0.39, p=0.03; I^2=73%; 8 studies (n=1,004) comparing RDN with control (GRADE: moderate quality). The high heterogeneity was reduced by selecting studies using different radiofrequency system (I^2=59%).

Daytime ambulatory BP monitoring:

- Systolic BP: MD 3.87 mmHg, 95% CI -5.02 to 12.76, p=0.39; I^2=70%; 5 studies (n=234) comparing RDN with control
- Diastolic BP: MD 2.93 mmHg, 95% CI -3.22 to 9.08, p=0.35; I^2=76%; 5 studies (n=234) comparing RDN with control

Nighttime ambulatory BP monitoring:

- Systolic BP: MD -1.65 mmHg, 95% CI -12.74 to 9.45, p=0.77; I^2=75%; 5 studies (n=234) comparing RDN with control
- Diastolic BP: MD -1.08 mmHg, 95% CI -9.25 to 7.08, p=0.79; I^2=87%; 5 studies (n=234) comparing RDN with control

Office BP:

- Systolic BP: MD -5.92 mmHg, 95% CI -12.94 to 1.10, p=0.10; I^2=86%; 9 studies (n=1,090) comparing RDN with control (GRADE: moderate quality). Subgroup analyses showed that benefits on systolic office BP became evident in studies using a multi-electrode radiofrequency catheter (MD -5.10 mmHg, 95% CI -9.14 to -1.06) compared with in those using a single-electrode catheter system, also nullifying the heterogeneity among studies (I^2=0%).

- Diastolic BP: MD -4.61 mmHg, 95% CI -8.23 to -0.99, p=0.01; I^2=77%; 8 studies (n=1,049) comparing RDN with control (GRADE: moderate quality). The high heterogeneity was completely nullified after excluding studies performing ablations with a single-electrode catheter system (I^2=0%).

Home BP:

- In HTN-JAPAN 2015: no change deference in home systolic and diastolic BP was observed between the renal denervation (-5.6 mmHg, 95% CI -14.5 to 3.2; p=0.205) and control groups (-4.8 mmHg, 95% CI -9.8 to 0.3; p=0.065).
- 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 having 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 deference between groups (p=0.30 and p=0.37) for systolic and diastolic BP, respectively.

Renal function:

- Serum creatinine: MD 0.03 mg/dL, 95% CI -0.06 to 0.13, p=0.50; I^2=68%; 5 studies (n=721) comparing RDN with control (GRADE: moderate quality)

  SYMPLICITY HTN-3 2014 reported 5 cases in the renal denervation group and 1 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 RDN group after 6 months of follow up in HTN-JAPAN 2015.

- eGFR or creatinine clearance: MD -2.56 mL/min/1.73m^2, 95% -7.53 to 2.42, p=0.31; I^2=50%; 6 studies (n=822) comparing RDN with control (GRADE: moderate quality)

Left ventricular mass index (LVMI): MD -2.34 g/m^2, 95% CI -12.93 to 8.25; p=0.67; I^2=0%; 2 studies

Key safety findings

Non-fatal cardiovascular events:

- Myocardial infarction: RR 1.31, 95% CI 0.45 to 3.84, p=0.62; I^2 =0%; 4 studies (n=742) comparing RDN with control (GRADE: low quality)

- Ischaemic stroke: RR 0.98, 95% CI 0.33 to 2.95, p=0.97; I^2 =0%; 5 studies (n=892) comparing RDN with control (GRADE: low quality)

- Unstable angina: RR 0.51, 95% CI 0.09 to 2.89, p=0.45; I^2 =0%; 3 studies (n=270) comparing RDN with control (GRADE: low quality)

All-cause mortality (2 studies):

- SYMPLICITY HTN-3: RDN, n=2; sham, n=1
- Prague-15: no deaths during the 24-month follow up.

Hospitalisation: RR 1.24, 95% CI 0.50 to 3.11, p=0.64; I^2=0%; 3 studies (n=743; GRADE: low quality)

SYMPLICITY HTN-3 2014 recorded hospital admissions for atrial fibrillation episodes (n=12; 9 patients in the RDN group and 3 patients in the sham group) and for new-onset of heart failure (n=6: 5 patients in the RDN group and 1 patient in the sham group); otherwise, in ReSET 2015 and SYMPATHY, patients needed hospitalisation to adjust antihypertensive medication.

Adverse events:

Bradycardia: RR 6.63, 95% CI 1.19 to 36.84, p=0.03; I^2 =0%; 3 studies (n=220) comparing RDN with control

Femoral artery pseudoaneurysm: RR 3.96, 95% CI 0.44 to 35.22, p=0.22; I^2 =0%; 2 studies (n=201) comparing RDN with control

Renal artery dissection: n=1 (Prague-15 2016)

Renal artery vasospasm: n=4 (Prague-15)

Transient renal artery spasm: n=1 (Warchol 2014)

New renal-artery stenosis: n=1 re-stenosis (new renal artery stenosis of more than 70%) (SYMPLICITY HTN-3 2014)

Flank pain: RR 4.30, 95% CI 0.48 to 38.28, p=0.19; I^2=0%; 2 studies (n=199) comparing RDN with control

Pitting oedema needing hospital admission: n=1 (SYMPLICITY HTN-2 2010)

Hypotensive episodes: RR 1.60, 95% CI 0.20 to 12.63, p=0.66; I^2=58%; 3 studies (n=143) comparing RDN with control

Hypertensive crisis: RR 0.71, 95% CI 0.35 to 1.45, p=0.34; I^2=0%; 3 studies (n=722) comparing RDN with control

Hyperkalaemia: RR 0.43, 95% CI 0.05 to 3.89, p=0.45; I^2=37%; 3 studies (n=224) comparing RDN with control

Embolic event: n=1 in the RDN group (SYMPLICITY HTN-3 2014)

Study 2 Townsend RR (2020)

Study details

Study type	Meta-analysis
Country	Not reported for individual study
Recruitment period	2009 to 2019
Study population and number	n=50 studies (5,769) patients with uncontrolled hypertension
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: both randomised and non-randomised trials and registries that used either the Symplicity Flex™ and/or the Symplicity Spyral™ RF denervation systems (Medtronic, Santa Rosa, CA); updated reviews of the SYMPLICITY HTN-3 trial and the Global SYMPLICITY Registry. Exclusion criteria: other radiofrequency devices or devices using other sources; reports that did not specifically address safety, including the presence or absence of renal artery events, and secondary analyses of previously reported studies; a case series (n=51) of RDN with the Symplicity Flex device employed via non-standard brachial access.
Technique	Percutaneous transluminal renal sympathetic denervation using radiofrequency: Symplicity Flex or Spyral systems
Follow up	Median 6 months (range 1 to 36)
Conflict of interest/source of funding	None

Analysis

Study design issues: This study estimated the occurrence of renal artery adverse events following denervation with common radiofrequency systems to determine whether radiofrequency ablation increases the risk of renal artery stenosis in the uncontrolled hypertensive population.

Other issues: Clinical trials and registries did not always mandate renal artery imaging of asymptomatic patients and therefore renal artery abnormalities after the radiofrequency RDN procedure might be missed. Subclinical weakening of the renal artery wall might not become clinically manifest for several months or years, so the current estimated rates could change as trials with longer follow up are reported. However, authors conducted a separate meta-analysis only including trials with ≥12 months of follow-up that resulted in a similar result. Authors also gained consistent results across methodological sensitivity analyses.

Key efficacy findings

Number of patients analysed: 5,769 (50 studies)

Key safety findings

Renal artery damage: n=26 (0.45%), including stenoses (n=19, 0.33%) and dissections (n=7, 0.12%)

- Renal artery damage needing stent implant: n=24 (0.42%), including 1 case with 2 stents
- Renal stenting: 0.20% per year (95% CI 0.12 to 0.29%, I^2=0%; 50 studies)

The subanalysis limited to trials with greater than one-year follow up showed 0.19% (95% CI 0.10 to 0.28%, I^2=0%).

Postprocedural renal artery events:

Renal artery stenosis: n=11 (11 case reports) at a median follow up of 5 months (range 3 to 28)

- Renal artery stenosis needing stent implant: n=10

Combining case reports and clinical studies, renal artery damage following denervation with the Symplicity Flex catheter: n=37

- Renal artery damage needing stent implant: n=34, the median time to renal artery stenting being 5.5 months (range 0 to 33)

High-resolution renal artery imaging after RDN: significant stenosis, n=1 (0.2%; 14 studies of 511 patients) after a median follow up of 11 months (range 1 to 36)

Procedural events:

- Stent implantation during the RDN procedure: 36% (9/34), including 7 cases of acute renal artery dissection.
- Procedure access site complications: 1.4% (82/5,769; 50 studies)

No cases of stenosis or dissection were reported involving the second-generation multi-electrode Symplicity Spyral system among 15 studies (706 patients).

Ten studies (396 patients) reported on radiofrequency RDN therapy beyond the main bifurcation with no renal reinterventions reported.

Study 3 Fengler K (2019)

Study details

Study type	3-arm randomised trial (RADIOSOUND-HTN; NCT02920034)
Country	Germany (single centre)
Recruitment period	2015 to 2018
Study population and number	n=117 (radiofrequency ablation of the main renal artery [RFM-RDN], n=38; radiofrequency ablation of the main artery, branches and accessories [RFB-RDN], n=37; ultrasound-based ablation of the main renal artery [USM-RDN], n=42) patients with resistant hypertension (antihypertensive drugs, mean 5.0±1.4)
Age and sex	Mean 64 years; 68% male; BMI, mean 31.6 kg/m^2
Patient selection criteria	Inclusion criteria: resistant hypertension with systolic daytime BP >135 mmHg on ABPM and renal artery diameter of at least 1 main renal artery ≥5.5 mm. Exclusion criteria: age <18 or >75 years, pregnancy, life expectancy <6 months, evidence for secondary hypertension, participation in any other randomised clinical trial, known renal artery stenosis or anatomy unsuitable for interventional RDN, and any main renal artery diameter <4.0 mm (including renal artery stenosis).
Technique	Percutaneous transluminal renal sympathetic denervation using radiofrequency: multipolar Symplicity Spyral catheter (Medtronic) was used. In the RFM-RDN group, multiple ablation runs of 1 minute were delivered to the main renal artery from distal to proximal. In the RFB-RDN group, the main renal arteries, any side branch >3.0 mm, and all accessory renal arteries >3.0 mm, as well, were treated, with lesion distribution from distal to proximal. Percutaneous transluminal renal sympathetic denervation using ultrasound: Paradise catheter (ReCor Medical), a balloon-cooled device was used to able the main renal artery only, as described for the RFM-RDN group. A transfemoral access route was used in all patients.
Follow up	3 months
Conflict of interest/source of funding	Costs related to conduct of the trial were covered by the Leipzig Heart Institute. One author received speaker fees and worked as a consultant to ReCor Medical and Medtronic. The other authors declared that they had no competing interests.

Analysis

Follow-up issues: One patient in the RFM-RDN and 2 patients in the RFB-RDN group did not attend follow up. In total, 117 patients were available for analysis.

Study design issues: This single-blind, 3-arm randomised trial investigated the effects of ultrasound-based or additional side branch ablation in patients with large renal arteries and compared them with radiofrequency ablation of the main renal artery. The primary end point was change in systolic daytime BP on ABPM at 3 months. Key secondary end points were rate of responders, change in 24-hour systolic ABPM and diastolic BP changes.

Patients were randomly assigned in a 1:1:1 ratio using a time-based nonrestricted computer algorithm. Patients were blinded to the assigned treatment. Authors assumed a change of 12 mmHg in systolic daytime

BP on ABPM after 3 months in the USM-RDN and RFB-RDN groups and 6 mmHg in the RFM-RDN group, and a SD of 11 mmHg, as well. To achieve a power of 80% at a 2-sided α-level of 0.05, a sample size of 114 patients was required. To compensate for a potential loss to follow-up, enrollment of 120 patients was planned for the entire cohort. Per protocol analysis was used.

All procedures were done by experienced interventional cardiologists with experience in RDN using all 3 treatment strategies.

Study population issues: Clinical baseline characteristics and medication were well balanced between the groups, except for a numerically different prescription rate of α-blockers and centrally acting sympathicolytics that did not reach statistical significance.

Other issues: The total number of patients was limited, especially considering a 3-arm approach, and the results warrant confirmation in a larger, multicentre trial. Nevertheless, according to power analysis and observed outcomes, the study was adequately powered to assess the primary end point. This trial was carried out in a single-centre and the follow-up period was short (3 months). This trial included patients with larger renal arteries only, based on the assumption that sympathetic fibres are a greater distance from the lumen than in smaller arteries, and so RFB-RDN or higher penetration depth would be more relevant. Therefore, results might have differed in patients with smaller renal artery diameters.

Key efficacy findings

Number of patients analysed: 117 (RFM-RDN, n=38; RFB-RDN, n=37; USM-RDN, n=42)

Procedural characteristics

Characteristics	All (n=120)	RFM-RDN (n=39)	RFB-RDN (n=39)	USM-RDN (n=42)	P value
Ablation points right renal artery	10.0±7.4	9.1±3.0	18.3±6.1	3.2±0.8	<0.001
Ablation points left renal artery	9.2±6.7	8.1±2.2	16.8±6.0	3.2±0.9	<0.001
Right renal arteries treated	1.8±1.2	1.1±0.4	3.3±0.9	1.0±0.0	<0.001
Left renal arteries treated	1.7±1.2	1.1±0.2	3.2±1.0	1.0±0.2	<0.001
Contrast agent used, mL	110.6±62.2	90.8±54.8	143.1±66.6	98.7±52.9	<0.001
Cincefluoroscopy time, minutes	11.2±7.8	8.9±5.6	16.8±8.0	8.1±6.5	<0.001

BP at 3 months:

- Daytime BP in all patients n=117
    - Change in daytime systolic BP: -9.5±12.3 mmHg, p<0.001
    - Change in daytime diastolic BP: -6.3±7.8 mmHg, p<0.001
- Each group: daytime systolic and diastolic BP statistically significantly reduced within each group (all p<0.001)

Change in systolic daytime APBM: statistically significant difference between group (global p=0.038)

Change in daytime systolic BP:

- USM-RDN: -13.2±13.7 mmHg
- RFM-RDN: -6.5±10.3 mmHg
- RFB-RDN: -8.3±11.7 mmHg
- mean difference between USM-RDN and RFM-RDN: -6.7 mmHg, 98.3% CI -13.2 to -0.2, adjusted p=0.043
- mean difference between RFM-RDN and RFB-RDN: -1.8 mmHg, 98.3% CI –8.5 to 4.9, adjusted p>0.99
- mean difference between USM-RDN and RFB-RDN: -4.9 mmHg, 98.3% CI -11.5 to 1.7, adjusted p=0.22

Systolic daytime BPs were comparable after adjustment for baseline BP values: global p=0.048

Daytime diastolic, and systolic and diastolic 24-hour ambulatory BP changes differed significantly between USM-RDN and RFM-RDN but not between the RFM-RDN and RFB-RDN groups (global p<0.05 and adjusted p<0.05 for all)

Systolic BP response of ≥5 mmHg: RFM-RDN, 66%; RFB-RDN, 73%; USM-RDN, 67%; p=0.77

Profound BP response: RFM-RDN, 8%; RFB-RDN, 14%; USM-RDN, 29%; p=0.039

Baseline systolic nighttime blood pressure was lower in the RFM-RDN group than in the USM-RDN group (p=0.043 by ANOVA, adjusted p=0.040), but was not different from the RFB-RDN group (adjusted p>0.99).

Changes in systolic nighttime BP:

- All patients: -6.1±14.2 mmHg in the overall cohort, p<0.001
- USM-RDN: -10.2±13.9 mmHg, p<0.001
- RFB-RDN; -5.1±16.0 mmHg, p=0.041
- RFM-RDN: –2.1±13.3 mmHg, p=0.34
- Unadjusted comparison of these changes between the groups: global p=0.043
- Comparison of these changes between the groups after adjustment for systolic nighttime BP at baseline: global p=0.32

Change in medication: 9% (n=11, including 3 in the RFM-RDN group [increased medication doses or number of drugs in all patients], 7 in the RFB-RDN group [decreased, 5 increased], and 1 in the USM-RDN group [decreased number of drugs, global p=0.039 by ANOVA])

When analysing patients on stable medication only, results for between-group comparison of systolic and diastolic 24-hour and daytime ABPM were consistent with those for the entire cohort (global p<0.05 for all between-group comparisons, adjusted p<0.05 for pairwise comparison of RFM-RDN compared with USM-RDN).

Key safety findings

Procedural safety:

- Transient renal artery spasm: n=1 in the USM-RDN group
- Transient non-invasive ventilation needed after conscious sedation: n=1 in the USM-RDN group
- Symptomatic groin hematoma: n=1 in the RFB-RDN group
- Pseudoaneurysm: n=1 in the USM-RDN group
- Postprocedural intracapsular and retroperitoneal haematoma: n=1 in the RFM-RDN group

All events resolved without sequelae.

Adverse events at follow up:

- Symptomatic hypotension: n=2 in the RFB-RDN group
- Symptomatic hypertension needing medical treatment: n=1 in the RFM-RDN group; n=2 in the RFB-RDRN group
- Hospitalisation for acute decompensated heart failure: n=1 in the RFB-RDN group
- Death because of acute aortic dissection at 2 months after the procedure: n=1 in the RFM-RDN group

Study 4 Kario K (2022)

Study details

Study type	RCT (REQUIRE; NCT02918305)
Country	Japan and South Korea (72 centres)
Recruitment period	2017 to 2020
Study population and number	n=136 (RDN, n=69; sham, n=67) patients with resistant hypertension
Age and sex	RDN: mean 50.7 years; 69% (47/69) male; BMI, mean 29.5 kg/m^2 Sham: mean 55.6 years; 79% (53/67) male: BMI, mean 28.4 kg/m^2
Patient selection criteria	Inclusion criteria: patients aged 20 to 75 years and had resistant hypertension (average seated office BP ≥ 150/90 mmHg) despite treatment with a stable regimen including maximum tolerated dosages of at least 3 antihypertensive medications from different classes (including a diuretic) and 24-hour ambulatory systolic BP of ≥140 mmHg during a screening period of 4 to 8 weeks prior to the procedure. Renal artery anatomy eligibility was determined using computed tomography or magnetic resonance angiogram at the end of the screening period, then confirmed by renal artery angiography at the time of procedure. Exclusion criteria: patients with unsuitable renal artery anatomy, chronic kidney disease (estimated glomerular filtration rate <40 mL/min/1.73 m^2), secondary hypertension (although patients with sleep apnoea were eligible), inadequately controlled diabetes mellitus, inflammatory bowel disease, history of severe cardiovascular event, or other chronic conditions.
Technique	Percutaneous transluminal renal sympathetic denervation using ultrasound: The catheter-based Paradise^{TM} RDN was used to thermally ablate the renal sympathetic nerves by delivering circumferential ultrasound energy. Patients had renal denervation using minimum of two 7-second ultrasound sonications delivered bilaterally to the main renal artery; at least 1 sonication was delivered within accessory arteries of ≥4mm and ≤8 mm in diameter. Sham control: patients had a renal angiogram without denervation and stayed in the catheterisation laboratory with the sheath inserted for ≥20 min.
Follow up	3 months
Conflict of interest/source of funding	Funding: The REQUIRE trial was funded by JIMRO Co., Ltd. And Korea Otsuka Pharmaceutical Co., Ltd. Conflict of interest: K.K., Y.Y., K.O., H.U., K.S., M.N., K.T., H.Y., H.J.K., Y.S., K.S., H.T., Y.M., and S.N. declared conflict of interests. Other authors declared no competing interest.

Analysis

Follow-up issues: Of the 143 patients (72 in the RDN group and 71 in the sham control group), all but 1 patient completed the 3-month follow up (1 patient in the sham control group withdrew from the study). Patients were assessed at day 7 after the procedure and then months 1, 2 and 3. Valid ambulatory BP monitoring data at 3 months were available for 69 patients in the renal denervation group and 67 patients in the sham control group.

Study design issues: The sham-controlled REnal denervation on Quality of 24-hr BP control by Ultrasound In Resistant hypertension (REQUIRE) trial assessed the BP lowering efficacy of renal denervation in treated patients with resistant hypertension.

The primary endpoint was the between-group difference in change in 24-hour ambulatory systolic BP from baseline at 3 months. Secondary endpoints were change in daytime and nighttime ambulatory SBP from baseline at 3 months, change in 24-hour, daytime and nighttime ambulatory diastolic BP from baseline at 3 months, and change in seated office SBP and DBP from baseline at 3 months.

Patients were randomised in a 1:1 ratio to have renal denervation using the Paradise™ Renal Denervation System (ReCor Medical Inc., Palo Alto, CA, USA) or to a sham procedure (renal angiogram only). Randomisation was done using a web-based randomisation tool and was stratified by country (South Korea or Japan), study site, and baseline 24-hour ambulatory SBP (140 to <160 mmHg or ≥160 mmHg). Subjects remained blinded to treatment allocation until 6 months after the procedure. All physicians and study coordinators, including those who interacted with patients, were aware of treatment allocation, but BP assessments were done by study personnel who were unaware of treatment allocation.

Sample size calculation was done based on the assumption that the reduction in 24-hour ambulatory SBP would be 6 mmHg greater in the RDN group than in the sham control group (SD 12 mmHg), it was calculated that the number of patients required to detect a difference between the renal denervation and the sham control groups with 80% power and a 2-sided significance level of 5% was 128 (64 per group). Allowing for a 10% dropout rate over the first 3 months after the procedure, the target sample size was 140 (70 per group).

Study population issues: Demographic and clinical characteristics of the 136 patients at baseline are detailed, below:

	Renal denervation (n=69)	**Sham control (n=67)**
eGFR, mL/min per 1.73m^2	74.2±16.2	69.6±17.1
Office systolic blood pressure, mmHg	157.6±19.5	160.4±14.9
Office diastolic blood pressure, mmHg	97.7±16.6	95.3±14.2
Home systolic blood pressure, mmHg	163.5±18.7	163.3±15.4
Home diastolic blood pressure, mmHg	98.0±13.7	93.4±13.9
24-hour ambulatory systolic BP, mmHg	161.9±13.4	161.5±13.1
24-hour ambulatory diastolic BP, mmHg	94.9±9.3	92.7±9.4
Daytime ambulatory systolic BP, mmHg	166.7±13.1	167.3±13.8
Daytime ambulatory diastolic BP, mmHg	97.9±9.7	96.2±9.6
Nighttime ambulatory systolic BP, mmHg	149.9±18.9	150.1±18.1
Nighttime ambulatory diastolic BP, mmHg	86.7±11.0	85.5±11.2
Number of antihypertensive drugs, n	4.1±1.6	3.9±1.1
Comorbidities, n (%)		
Cardiovascular disease	9 (13.0%)	9 (13.4%)
Diabetes mellitus	18 (26.1%)	20 (29.9%)
Dyslipidaemia	39 (56.5%)	40 (59.7%)
Peripheral arterial disease	1 (1.4%)	2 (3.0%)
Cerebrovascular disease	0 (0%)	5 (7.5%)
Sleep apnoea syndrome	11 (15.9%)	8 (11.9%)

	Renal denervation (n=69)	Sham control (n=67)
Aortic dissection	1 (1.4%)	0 (0%)

Other issues: There were several limitations. There was no standardisation of antihypertensive medications or objective measurement of medication adherence using blood or urine. The nature of the intervention meant that it was not possible to conduct a double-blind study where medical personnel were unaware of treatment group allocation and authors did not prohibit unblinded physicians from participating in follow-up care. There was also no assessment of blinding conducted to determine whether or not the blinding was maintained. There were significant seasonal variation of the temperature and BPs in Japan - morning BP increased in the winter, while the nighttime BP increase in the summer. There was unexpected BP reduction in the sham control group, highlighting study design issues.

Key efficacy findings

Number of patients analysed: 136

Procedural success rate: 98.6%

Procedure time: RDN, 86.7 minutes; sham, 40.6 minutes

X-ray fluoroscopy time: RDN, 23.6 minutes; sham, 5.2 minutes

Contrast volume: RDN, 147.8 mL; sham, 54.1 mL

Proportion of patients with at least 2 sonications in each renal artery: RDN, 98.6% (n=71).

24-hour ambulatory systolic BP:

- Difference in reduction at 3 months between RDN and sham groups: −0.1, 95% CI −5.5 to 5.3; p=0.971
- Change at 3 months from baseline: RDN, -6.6 mmHg (95% CI -10.4 to -2.8); sham, -6.5 mmHg (95% CI -10.3 to -2.7)
- Proportion of patients with a ≥5 mmHg decrease: RDN, 53.6%; sham, 49.3%

There was no statistically significant difference between groups in 24-hour ambulatory systolic BP across patient subgroups based on age, sex, country, and baseline values of 24-hour ambulatory, office, and home systolic BP.

About half of patients in both groups showed a decrease in 24-hour ambulatory systolic BP at 3 months after the procedure.

24-hour ambulatory BP profiles were similar before and after the procedure in both groups.

Change from baseline in blood pressure between the renal denervation and sham control groups at 3 months

Variables	RDN (mmHg)		Sham (mmHg)		Between-group difference (mmHg)	
	N	Least squares (LS) mean ± standard error (SE)	N	LS mean ± SE	LS mean ± SE	P value
Office systolic BP	69	-11.0±2.1	66	-9.0±2.1	-2.0±3.0	0.511
Office diastolic BP	69	-4.9±1.5	66	-5.0±1.5	0.1±2.1	0.946
24-hour ambulatory systolic BP	69	-6.6±1.9	67	-6.5±1.9	-0.1±2.7	0.971
24-hour ambulatory diastolic BP	69	-3.6±1.0	67	-3.3±1.0	-0.4±1.4	0.806
Daytime ambulatory systolic BP	61	-8.4±2.0	66	-7.2±1.9	-1.2±2.8	0.672
Daytime ambulatory diastolic BP	61	-4.8±1.1	66	-4.0±1.0	-0.8±1.5	0.585
Nighttime ambulatory systolic BP	68	-4.2±2.4	67	-4.7±2.4	0.5±3.3	0.883
Nighttime ambulatory diastolic BP	68	-1.4±1.3	67	-2.0±1.3	0.6±1.9	0.770
Home systolic BP	60	-8.7±1.8	59	-6.9±1.8	-1.8±2.6	0.488
Home diastolic BP	60	-3.6±1.1	59	-3.7±1.1	0.1±1.6	0.949
Morning home systolic BP	60	-9.1±1.8	59	-6.6±1.8	-2.5±2.5	0.319
Morning home diastolic BP	60	-3.7±1.2	59	-3.1±1.2	-0.7±1.7	0.684

Medication changes

Period	RDN		Sham	
	Number of antihypertensive medications, mean±SD (no. of patients)	Antihypertensive load index, mean±SD (no. of patients)	Number of antihypertensive medications, mean±SD (no. of patients)	Antihypertensive load index, mean±SD (no. of patients)
Informed consent	4.2±1.6 (69)	-	4.0±1.1 (67)	-
Baseline	4.2±1.7 (62)	2.6±1.7 (69)	3.9±1.2 (62)	2.4±1.2 (67)
1 month	4.1±1.6 (59)	-	3.9±1.2 (57)	-
2 months	4.2±1.6 (60)	-	3.9±1.1 (60)	-
3 months	4.3±1.7 (60)	2.5±1.7 (69)	3.9±1.1 (59)	2.4±1.2 (67)

Change from baseline in blood pressure between the renal denervation and sham control groups at 3 months in patients without any change of antihypertensive drugs

Variables	RDN (mmHg)		Sham (mmHg)		Between-group difference (mmHg)	
	N	LS±SE	N	LS±SE	LS±SE	P value
Office systolic BP	60	-10.5±2.1	60	-7.8±2.1	-2.7±2.9	0.370
Office diastolic BP	60	-4.3±1.5	60	-3.8±1.5	-0.5±2.1	0.795
24-hour ambulatory systolic BP	60	-6.2±1.9	61	-5.7±1.9	-0.5±2.7	0.844
24-hour ambulatory diastolic BP	60	-3.2±1.0	61	-2.6±1.0	-0.6±1.5	0.699
Daytime ambulatory systolic BP	53	-7.8±2.0	60	-6.6±1.9	-1.2±2.7	0.667
Daytime ambulatory diastolic BP	53	-4.4±1.1	60	-3.5±1.0	-0.9±1.5	0.537
Nighttime ambulatory systolic BP	59	-3.3±2.5	61	-3.5±2.5	0.2±3.6	0.952
Nighttime ambulatory diastolic BP	59	-0.8±1.4	61	-1.2±1.4	0.4±2.0	0.852
Home systolic BP	53	-8.3±1.8	55	-5.9±1.8	-2.4±2.5	0.347
Home diastolic BP	53	-3.6±1.1	55	-3.3±1.1	-0.4±1.6	0.816
Morning home systolic BP	53	-8.5±1.8	55	-5.8±1.7	-2.8±2.5	0.268
Morning home diastolic BP	53	-3.8±1.2	55	-2.7±1.2	-1.1±1.7	0.518

At both 1 and 2 months postprocedure, patients without any change in antihypertensive drugs showed a statistically significantly greater reduction from baseline in home systolic BP after RDN compared with sham procedure (between-group difference of −7.3 mmHg [p=0.004] and −4.4 mmHg [p=0.050], respectively).

Post-hoc analysis excluding 44 patients with hyperaldosteronism:

- Reduction in 24-hour ambulatory systolic BP from baseline to 3 months: RDN, −7.6 mmHg; sham, −4.2 mmHg; between-group difference, −3.3 mmHg (p>0.05)
- Reduction in home SBP from baseline to 1 month: RDN, −12.1 mmHg; sham, −3.6 mmHg; between-group difference, −8.5 mmHg (p=0.012)

Key safety findings

Specific clinical events within 30 days postprocedure

	Renal denervation (n=72)	Sham control (n=71)
Vasospasm of renal artery treated with medication	4 (5.6%)	0
Complication at femoral puncture site*	4 (5.6%)	3 (4.2%)
Procedure-related pain lasting for >2 days	6 (8.3%)	6 (8.5%)

*pain (n=4), skin injury (n=1), haematoma (n=2); 1 haematoma in the RDN group needed a balloon catheter.

Serious procedure-/device-related adverse events within 3 months

	Renal denervation (n=72)	Sham control (n=71)
Vasospastic angina (Prinzmetal angina)	1 (1.4%)	0
Puncture site haemorrhage	1 (1.4%)	0
Pyrexia	0	1 (1.4%)
Cellulitis	1 (1.4%)	0
Blood pressure decrease	1 (1.4)	0
Blood pressure increased	1 (1.4%)	0
Postural dizziness	1 (1.4%)	0

The procedure- or device-related major adverse events was not seen.

Study 5 Azizi M (2021, 2022)

Study details

Study type	RCT (RADIANCE-HTN TRIO; NCT02649426)
Country	US (28 centres) and Europe (25 centres in France, the UK, Germany, Poland, Belgium, and the Netherlands)
Recruitment period	2016 to 2020
Study population and number	n=136 (RDN, n=69; sham, n=67) Patients with resistant hypertension
Age and sex	RDN: mean 52.3 years; 81% (56/69) male; BMI, mean 32.8 kg/m^2 Sham: mean 52.8 years; 79% (53/67) male; BMI, mean 32.6 kg/m^2
Patient selection criteria	Inclusion criteria: aged 18 to 75 years with resistant hypertension and an estimated glomerular filtration rate of at least 40 mL/min per 1.73 m².
Technique	The Paradise System (ReCor Medical, Palo Alto, CA, USA) was used for ultrasound renal denervation.
Follow up	6 months
Conflict of interest/source of funding	Funding: ReCor Medical. Conflict of interest: MA, KS, M Sax, PG, LCR, APe, JB, MJB, JD, MDL, FM, RES, ASPS, MAW, APa, DH, SB, JW, NCG, HR-S, LC, CKM, AJK declared completing interests. All other authors declared no competing interests

Analysis

Follow-up issues: Patients completed a masking questionnaire at discharge and at the 2-month follow up. At 6 months, of the 136 patients, 3 patients in the RDN group and 3 patients in the sham group were excluded (1 died and 5 lost to follow up). A total of 65 of 69 patients (94.2%) in the ultrasound RDN group and 64 of 67 patients (95.5%) in the sham group had ambulatory BP measurements at 6 months.

Study design issues: This adequately powered, sham-controlled, randomised trial reported the primary efficacy and safety results of ultrasound renal denervation in the TRIO cohort of patients with more severe hypertension resistant to 3 or more antihypertensive medications (of patients with combined systolic–diastolic hypertension resistant to a fixed-dose, single-pill, triple combination antihypertensive therapy).

Intention-to-treat analysis was used for 2-month outcomes. The primary efficacy endpoint was the change in daytime ambulatory systolic blood pressure from baseline to 2 months. Secondary efficacy endpoints specified for hierarchical testing at 2 months were change in 24-hour ambulatory systolic and diastolic blood pressures, nighttime ambulatory systolic and diastolic BP, and daytime ambulatory diastolic BP. Prespecified major adverse events were all-cause mortality, renal failure, an embolic event, renal artery or vascular complications needing intervention, or hypertensive crisis within 30 days of the study procedure, and new onset renal artery stenosis greater than 70% within 6 months of the study procedure. For 6-month outcomes, the main results included 6-month change in medications, change in daytime ambulatory systolic BP, change in home systolic BP adjusted for baseline BP and medications, and safety.

Resistant hypertension was defined as seated office BP of at least 140 mmHg systolic and 90 mm Hg diastolic despite a stable regimen of three or more antihypertensive medications including a diuretic.

Sample size calculation showed that a sample of 128 participants would yield 80% power to detect a 6-mmHg difference in change in daytime ambulatory systolic BP at 2 months between the RDN and sham groups (common standard deviation 12 mmHg, 2-sided type I error rate of 5%). To account for up to 10% missing observations, authors initially planned to randomly assign 146 participants. However, the decision was made to stop enrolment on May 8, 2020, after random assignment of 134 patients with evaluable follow up at 2 months because of the COVID-19 pandemic constraining further recruitment. The decision was consistent with guidance from the US Food and Drug Administration.

Eligible participants were randomly assigned (1:1) to receive ultrasound renal denervation or a sham procedure. The randomisation sequence was generated by computer and stratified by centre using randomised blocks of 4 or 6 and permutation of treatments within each block. Authors randomly assigned patients with resistant hypertension confirmed by ambulatory BP after adjusting their antihypertensive treatment to a single-pill, fixed-dose, triple combination consistent with current guidelines. By reducing pill burden, a high adherence to the standardised treatment was achieved at baseline in both groups. To maintain masking, participants were sedated and wore headphones and eye covers. Patients and clinicians involved in follow-up care were masked to treatment allocation for 6 months after random assignment.

The procedure assignment was masked for 6 months after randomisation for both patients and the clinical staff responsible for follow up. Patients were to remain undergoing the initial antihypertensive treatment until 2 months, unless specified BP criteria were exceeded. From the second to the fifth month after randomisation, a guideline-recommended, standardised, stepped-care antihypertensive treatment (SSAHT) was recommended in both groups if the mean BP at home was 135 mmHg or higher (systolic) or 85 mmHg or higher (diastolic). The SSAHT included guideline-recommended sequential addition of (1) an aldosterone antagonist (preferentially spironolactone, 25 mg/day), (2) a β1-blocker (preferentially bisoprolol, 10mg/day), (3) a central α2-receptor agonist (clonidine,0.1 to 0.2 mg/day; rilmenidine, 1 to 2 mg/day; or moxonidine, 0.2 to 0.4 mg/day), and (4) an α1-receptor blocker (prazosin, 5 to 10 mg/day or doxazosin, 4 to 8mg/day).

Of the 53 study centres, 35 centres with 40 different interventionalists had patients assigned to the renal denervation group; each interventionalist did a mean of two (range 1 to 6) renal denervation procedures. Circumferential renal denervation treatment was planned based on the pre-procedural imaging.

Study population issues: Baseline characteristics were similar across both groups and did not differ from those of the intention-to-treat population.

	Renal denervation (n=69)	**Sham control (n=67)**
eGFR, mL/min per 1.73m^2	86.0±25.2	82.2±19.2
Type 2 diabetes	30% (n=21)	25% (n=17)
Sleep apnoea syndrome	28% (n=19)	16% (n=11)
Previous admission to hospital for hypertensive crisis	22% (n=15)	16% (n=11)
Previous cardiovascular or cerebrovascular event	12% (n=8)	13% (n=9)
History of heart failure	1% (n=1)	4% (n=3)
Office BP and heart rate at screening		
Systolic BP, mmHg	161.9±15.5	163.6±16.8
Diastolic BP, mmHg	105.1±11.6	103.3±12.7
Heart rate, beats per minute	74.5±11.0	77.6±12.9
Number of antihypertensive medications at screening	4.0±1.0	3.9±1.1
3 medications	39% (n=27)	42% (n=28)

4 medications	32% (n=22)	36% (n=24)
≥5 medications	29% (n=20)	22% (n=15)

Other issues: One limitation was the short duration of follow up to assess longer-term durability of the BP lowering effect of ultrasound RDN and its safety in patients with resistant hypertension, although extended follow up in unblinded conditions after 6 months has been planned. In addition, there was large between-patient variation in the BP response to ultrasound RDN plus SSAHT as well as to the SSAHT alone, some of which might be attributed to variable renal nerve ablation, medication adherence, prevailing state of sympathetic hyperactivity or other factors.

Key efficacy findings

Number of patients analysed: 136 at 2 months

Successful bilateral renal nerve ablations with mean 5.8 (SD 1.2) ultrasound emissions: 97% (67/69)

RDN for accessory renal artery ablation: 25% (17/69)

The number of ultrasound emissions, the presence of non-ablated accessory renal arteries, and the number of RDN procedures per interventionalist did not influence the BP response to RDN (data not shown).

Primary and secondary efficacy endpoints in the intention-to-treat population

	RDN (n=69)			**Sham (n=67)**			**Unadjusted median between-group difference**	**Baseline-adjusted**
	At random assignment	**2 months**	**Difference (median [IQR])**	**At random assignment**	**2 months**	**Difference (median [IQR])**	**Difference (95% CI)**	**P value**
Systolic BP parameters								
Daytime ambulatory BP	150.0 (11.9)	141.0 (16.1)	-8.0 (-16.4 to 0.0)	151.1 (12.6)	146.3 (18.8)	-3.0 (-10.3 to 1.8)	-4.5 (-8.5 to -0.3)	0.022
24-h ambulatory BP	143.9 (13.4)	135.2 (16.0)	-8.5 (-15.1 to 0.0)	145.4 (14.0)	140.5 (18.7)	-2.9 (-12.6 to 2.5)	-4.2 (-8.3 to -0.3)	0.016
Nighttime ambulatory BP	134.4 (18.0)	126.3 (18.4)	-8.3 (-15.7 to 0.0)	136.4 (18.6)	131.9 (20.9)	-1.8 (-16.2 to 5.0)	-3.9 (-8.8 to 1.0)	0.044

	RDN (n=69)			Sham (n=67)			Unadjusted median between-group difference	Baseline-adjusted
	At random assignment	2 months	Difference (median [IQR])	At random assignment	2 months	Difference (median [IQR])	Difference (95% CI)	P value
Office BP	155.6 (16.7)	147.1 (20.3)	-9.0 (-19.5 to -1.5)	154.9 (16.8)	152.1 (22.0)	-4.0 (-12.0 to 9.0)	-7.0 (-13.0 to 0.0)	0.037
Home BP*	152.0 (16.2)	144.6 (18.2)	-6.0 (-17.0 to 1.5)	153.1 (17.0)	149.9 (18.9)	-2.0 (-9.5 to 2.0)	-4.0 (-8.0 to 0.0)	0.052
Diastolic BP parameters								
Daytime ambulatory BP	93.8 (7.7)	88.5 (11.6)	-4.9 (-10.4 to 0.0)	94.6 (9.1)	90.7 (12.2)	-2.0 (-7.8 to 1.0)	-1.8 (-4.5 to 0.8)	0.18
24-h ambulatory BP	88.9 (8.2)	83.6 (10.9)	-5.4 (-10.4 to 0.0)	89.5 (9.5)	85.8 (12.0)	-2.4 (-7.8 to 0.5)	-2.0 (-4.5 to 0.6)	0.12
Nighttime ambulatory BP	81.3 (10.7)	76.2 (12.2)	-5.1 (-12.7 to 0.0)	81.3 (12.1)	78.4 (13.2)	-2.0 (-9.5 to 4.1)	-2.8 (-6.1 to 0.2)	0.053
Office BP	101.4 (11.6)	96.6 (13.9)	-5.0 (-13.5 to 2.5)	99.4 (10.9)	98.7 (13.8)	-1.0 (-7.0 to 6.0)	-4.0 (-9.0 to 0.0)	0.16
Home BP*	96.5 (11.2)	93.2 (14.7)	-4.0 (-9.0 to 2.0)	96.7 (11.4)	96.0 (12.8)	-1.0 (-5.0 to 4.0)	-3.0 (-6.0 to 0.0)	0.053

Data are mean (SD) or median (IQR) unless otherwise stated.
*There were 60 patients in the RDN group and 64 patients in the sham group with home BP measurements included in the intension-to-treat population.

Antihypertensive medications – RDN compared with sham:

- No change: 93% (64/69) compared with 85% (57/67), p=0.15
- Additional antihypertensive medication: 4% (3/69) compared with 12% (8/67), p=0.10
- Reduction in antihypertensive medications: 3% (2/69) compared with 3% (2/67), p=1.0
- Down-titration of the amlodipine done from 10 mg to 5 mg: 6% (4/69) compared with 1% (1/67)
- Full adherence to the combination medications in patients with urine samples:
    - baseline: 83% (49/59) compared with 76% (44/58)

- 2 months: 82% (42/51) compared with 82% (47/57), p=0.99

Heart rate: There was no between-group difference in heart rate at 2 months.

In the intention-to-treat population, 24 (35%) of 69 patients in the renal denervation group had controlled daytime ambulatory blood pressure at 2 months compared with 14 (21%) of 67 patients in the sham procedure group.

The median between-group difference in daytime ambulatory systolic blood pressure in the per-protocol population was -5.4 mm Hg (95% CI -9.5 to -1.3; adjusted p=0.011) and was -5.8 mm Hg (-9.7 to -1.6; adjusted p=0.0051) among patients with complete ambulatory blood pressure data.

Number of patients analysed: 129 (RDN, n=65; sham, n=64) at 6 months

Mean number of medications at 6 months: RDN, 3.8±1.0; sham, 4.1±1.1; p=0.08

Mean change in number of medications between 6 months and baseline: RDN, 0.7±1.0; sham, 1.1±1.1; p<0.05

The most frequently added antihypertensive medication was an aldosterone antagonist (predominantly spironolactone). However, an aldosterone antagonist was less frequently added at each monthly visit in the ultrasound RDN group compared with the sham group through 6 months (RDN, 40% (26/65); sham, 60.9% (39/64); p=0.02; overall OR, 0.4; 95% CI, 0.2 to 0.7; p<0.001).

Full adherence to medications at 6 months: RDN, 71.4% (40/56); sham, 78.2% (43/55); p=0.41

The mean (SD) daytime ambulatory systolic BP at 6 months decreased by 11.8 (14.2) mmHg from baseline reaching 138.3 (15.1) mmHg in the ultrasound RDN group (−2.4 [16.6] mmHg from month 2) and decreased by 12.3 (14.2) mmHg from baseline in the sham group, reaching 139.0 (14.3) mmHg (−7.0 [16.7] mmHg from month 2).

Mean difference in BP (mmHg) between 6 months and baseline

	RDN: mean difference	Sham: mean difference	Mean between-group difference adjusted for baseline BP (95% CI)	P value
Daytime ambulatory systolic BP	-11.8±14.2	-12.3±14.2	-0.0 (-4.6 to 4.5)	0.65
Daytime ambulatory diastolic BP	-7.9±9.1	-8.4±9.7	0.3 (-2.8 to 3.4)	0.79
24-hour ambulatory systolic BP	-11.4±14.1	-12.1±14.5	0.1 (-4.3 to 4.6)	0.85
24-hour ambulatory diastolic BP	-8.0±8.9	-8.3±9.2	0.2 (-2.8 to 3.1)	0.74
Nighttime ambulatory systolic BP	-10.3±17.2	-11.6±18.3	0.3 (-4.8 to 5.5)	0.81
Nighttime ambulatory diastolic BP	-7.9±10.0	-7.4±11.1	-0.3 (-3.7 to 3.0)	0.85
Home systolic BP	-11.5±15.9	-8.9±13.0	-2.9 (-8.0 to 2.2)	0.26
Home diastolic BP	-6.9±10.4	-5.0±8.5	-1.9 (-5.2 to 1.5)	0.28
Office systolic BP	-10.4±16.8	-11.2±22.7	0.7 (-5.3 to 6.6)	0.93

Office diastolic BP	-6.6±11.5	-7.5±13.7	1.9 (-1.9 to 5.7)	0.32

Linear mixed models for repeated measures from baseline through 6 months for BP in the ultrasound RDN group and the sham group in the analysis population

Outcome	Mean (95% CI)	P value
Daytime ambulatory systolic BP (mmHg)		
Treatment difference: model excluding interaction term	-2.7 (-6.9 to 1.6)	0.22
Treatment difference: model including visit by group interaction term	-2.5 (-6.7 to 1.7)	0.25
Home systolic BP (mmHg)		
Treatment difference: model excluding interaction term	-4.4 (-8.3 to -0.6)	0.02
Treatment difference: model including visit by group interaction term	-4.3 (-8.1 to -0.5)	0.03
Office systolic BP (mmHg)		
Treatment difference: model excluding interaction term	-3.1 (-8.1 to 1.9)	0.22
Treatment difference: model including visit by group interaction term	-2.9 (-7.9 to 2.0)	0.24

Daytime ambulatory systolic BP: months 2 and 6 included in analysis.
Treatment difference - model excluding interaction term: estimates from a linear regression model (with compound symmetry covariance structure) including treatment group, baseline BP value, and number of medications at visit as fixed effects.
Treatment difference - model including visit by group interaction term: estimates from a linear regression model (with compound symmetry covariance structure) including treatment group, visit, interaction between treatment group and visit, baseline BP value, and number of medications at visit as fixed effects.
Home and office systolic BP: months 1, 2, 3, 4, 5 and 6 included in analysis.

In the mixed linear model, out-of-office BP control (home and daytime ambulatory) was achieved more frequently with RDN compared with sham (OR, 10.0; 95%CI, 2.7 to 37.2; p=0.03 and OR, 1.8; 95% CI, 0.9 to 3.6; p=0.07, respectively). There was a larger mean (SD) decrease in daytime ambulatory heart rate in the sham group (−7.3 [9.6] beats/minute) than in the RDN group (−1.9 [8.8] beats/minute; p=0.04) perhaps reflecting the more frequent use of β-blockers.

Key safety findings

Incidence of safety events from baseline to 2 months

	RDN (n=69)	Sham (n=67)
Procedural safety events		
Major access site complications needing intervention	1% (n=1)	0%
Procedure-related pain lasting for >2 days	17% (n=12)	15% (n=10)
Other safety events from baseline to 2 months		
All-cause mortality	1% (n=1)	0%
Acute myocardial infarction (STEMI or non-STEMI)	1% (n=1)	0
Any coronary revascularisation	0%	1% (n=1)
Doubling of plasma creatinine	1% (n=1)	0%

Major access site complications needing intervention: 1 femoral access site pseudoaneurysm postprocedure treated with thrombin injection met the definition of a major adverse event.

Procedure-related pain lasting for more than 2 days: In the RDN group, 7 patients had pain at the femoral access site, 4 patients had back pain, and 1 patient had extremity pain. In the sham group, 8 patients had pain at the femoral access site and 2 patients had back pain.

Safety events from baseline to 6 months

	RDN (n=69)	Sham (n=67)
Major adverse events		
Death within 30 days	1% (n=1)	0
Vascular complication needing intervention within 30 days	1% (n=1)	0
Doubling of serum creatinine within 30 days	1% (n=1)	0
Other prespecified safety events through 6 months		
Procedure-related pain lasting for > 2 days	17% (n=12)	15% (n=10)
Any coronary revascularization	3% (n=2)	1% (n=1)
Acute myocardial infarction (STEMI/non-STEMI)	1% (n=1)	1% (n=1)
Doubling of serum creatinine (>30 days)	1% (n=1)	0
Hypertensive crisis (>30 days)	0	1% (n=1)
Stroke, transient ischemic attack, cerebrovascular accident	0	1% (n=1)

Death within 30 days (n=1): sudden death unrelated to device or procedure 21 days after RDN.

No new kidney artery stenosis of 50% or greater was detected on non-invasive imaging in either group at 6 months.

Estimated eGFR and serum creatinine – mean difference at baseline and 6 months

- eGFR:
  - RDN (n=63): -2.8±14.1 mL/min/1.73m^2
  - Sham (n=62): -4.1±11.5 mL/min/1.73m^2
  - Mean between-group difference adjusted for baseline value: 2.0 mL/min/1.73m^2 (95% CI -2.6 to 6.6)
  - Baseline adjusted p=0.39

- Serum creatinine
  - RDN (n=63): 0.0±0.2 mg/dL
  - Sham (n=62): 0.0±0.1 mg/dL
  - Mean between-group difference adjusted for baseline value: -0.0 mg/dL (95% CI -0.1 to 0.0)
  - Baseline adjusted p=0.67

Study 6 Bhatt DL (2022)

Study details

Study type	RCT (SYMPLICITY HTN-3; NCT01418261)
Country	US (88 centres)
Recruitment period	2011 to 2013
Study population and number	n=535 (RDN, n=364; sham, n=171 [crossover, n=101; non-crossover, n=70]) Patients with resistant hypertension (mean antihypertensive classes: RDN, 4.9 (SD 1.2); sham, 5.0 (SD 1.2)
Age and sex	Mean 57.9 years; 61% (325/535) male
Patient selection criteria	Inclusion criteria: adults aged 18 to 80 years with treatment-resistant hypertension on stable, maximally tolerated doses of 3 or more drugs including a diuretic, were eligible for screening. Patients were recruited if their seated office systolic BP (averaged over 3 measurements) was 160 mmHg or more at screening and their 24-hour ambulatory systolic BP was 135 mmHg or more at random assignment. Exclusion criteria were secondary causes of hypertension, recurrent hospitalisations for hypertensive emergency in the year preceding study recruitment, and anatomical features (renal artery stenosis of >50%, renal artery aneurysm, previous renal artery intervention, multiple renal arteries, a renal artery of <4 mm in diameter, or a treatable segment of <20 mm in length).
Technique	RDN: radiofrequency ablation within the main renal arteries using the simplicity renal artery denervation system (first-generation Symplicity Flex catheter). Sham: renal angiography alone.
Follow up	Efficacy: 36 months Safety: 48 months
Conflict of interest/source of funding	Funding: Medtronic. In collaboration with the funder, the executive committee designed the protocol and identified clinical sites. The funder was responsible for collection, monitoring, and analysis of the data. The funder assisted in figure and table generation, copy editing, and formatting. Authors declared conflict of interests.

Analysis

Follow-up issues: All patients who had RDN were followed up twice a year for 36 months, whereas annual follow up was for the non-crossover group. 36-month follow-up data were available for 219 patients (original RDN group), 63 patients (crossover group), and 33 patients (non-crossover group).

Study design issues: SYMPLICITY HTN-3 was a single-blind, multicentre, sham-controlled, randomised clinical trial, evaluating the efficacy and safety of catheter-based renal artery denervation. This final report of SYMPLICITY HTN-3 aimed to describe the efficacy and safety of renal artery denervation at 36-month follow up. The main outcome for this study was the comparison of changes in BP between the RDN group and the sham control group at 36 months.

Eligible participants were randomly assigned (2:1) to receive RDN or sham control. Patients were masked to the procedure with background music, blindfolding, and conscious sedation. Randomisation was done centrally

using an independent contract research organisation and was done using block sizes of 3 and 6. Assessors of BP were masked to the randomisation scheme.

Patients were masked for 6 months and then unmasked after the primary endpoint assessment at 6 months, at which point eligible patients in the sham control group could cross over to receive RDN if their office BP was 160 mmHg or more, their 24-hour ambulatory systolic BP was 135 mmHg or more, and they were prescribed 3 or more antihypertensive medications (crossover group).

BP changes from before random assignment to final follow-up at 36 months were reported for the original RDN group and for the non-crossover group. BP changes from before RDN (at 6 months after random assignment) to 30 months after RDN were reported for the crossover group.

For patients in the crossover group, their most recent BP measurement before crossover, medication burden, and laboratory values were used to impute subsequent follow-up values up to 36 months as part of the sham control group. Data from patients in the crossover group were not pooled with the data of patients originally randomly assigned to the RDN group in any analysis.

Study population issues: The 6-month outcomes were included in Pisano (2021).

Before crossover, office systolic BP and 24-hour ambulatory systolic BP was higher in the crossover group than in the non-crossover group. Therefore, 12-month to 36-month values for the crossover group were imputed as part of the control group.

Other issues: This study had a long-term follow up after unmasking and crossover.
It included a smaller number of patients in the sham control group throughout long-term follow up because many patients continued to have suboptimal BP and crossed over. Although analyses with and without imputation for missing data due to crossovers were generally consistent for BP changes, results were not statistically different at all timepoints. Despite being the largest trial of RDN to date, this analysis was not powered for cardiovascular events. The trial did not include testing of antihypertensive medication levels.

Key efficacy findings

Number of patients analysed: 535

Reduction in mean office systolic and 24-hour ambulatory systolic BP, mmHg

Office systolic BP	**RDN, change from baseline (no. of patients)**	**Sham, change from baseline (no. of patients)**	**Adjusted treatment difference between RDN and Sham**	**Adjusted P value**
12 months	-18.9 (n=320)	-6.3 (n=149)	-13.4 (95% CI -17.8 to -9.0)	≤0.0001
24 months	-24.1 (n=266)	-4.3 (n=137)	-20.7 (95% CI -24.7 to -15.7)	≤0.0001
36 months	-26.4 (n=219)	-5.7 (n=134)	-22.1 (95% CI -27.2 to -17.0)	≤0.0001
24-hour ASBP	**RDN, change from baseline (no. of patients)**	**Sham, change from baseline (no. of patients)**	**Adjusted treatment difference between RDN and Sham**	**Adjusted P value**
12 months	-7.5 (n=256)	-0.1 (n=116)	-8.5 (95% CI -11.9 to -5.1)	≤0.0001

24 months	-11.9 (n=188)	0.2 (n=124)	-12.6 (-16.1 to -9.1)	≤0.0001
36 months	-15.6 (n=152)	-0.3 (n=119)	-16.5 (-20.5 to -12.5)	≤0.0001

BP values for the sham control group included last observation carried forward imputed for patients in the crossover group from when they were masked to intervention.

Change in the number of prescribed medications classes at 36 months:

- RDN (n=311): -0.3 (SD 1.4)
- Sham (n=149): -0.2 (SD 0.9)
- Between-group comparison: p=0.22

Post-hoc sensitivity analysis (in which all missing measures for both the RDN and sham control groups, including those lost to follow-up, were imputed up to 36 months):

- Change in office systolic BP at 36 months:
  - RDN (n=364): -22.1 mmHg (SD 26.5)
  - Sham (n=171): -8.5 mmHg (SD 25.0)
  - Adjusted treatment difference: -13.9 mmHg (95% CI -18.3 to -9.5), p≤0.001

- Change in 24-hour ambulatory systolic BP at 36 months:
  - RDN (n=360): -10.6 mmHg (SD 18.7)
  - Sham (n=169): -3.3 mmHg (SD 15.8)
  - Adjusted treatment difference: -7.5 mmHg (95% CI -10.6 to -4.4), p≤0.001

Office systolic BP between the crossover and non-crossover groups without any imputations: BP of patients in the non-crossover group increased after unmasking, whereas patients in the crossover group had continuous BP reductions after RDN.

Time in therapeutic blood pressure range (office systolic BP of 140 mmHg or less and 24-hour ambulatory systolic BP of 130 mmHg or less) up to 36 months:

- RDN (n=357): mean 18% (SD 25) of time in therapeutic BP range (189 days)
- Sham (n=171): mean 9% (SD 19) of time in therapeutic BP range (94 days)
- Between-group comparison: p≤0.001

Key safety findings

The rate of the composite safety endpoint to 48 months (including all-cause death, new-onset end stage renal disease, significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, or hypertensive emergency) was 15% (54 of 352 patients) in the RDN group, 14% (13 of 96 patients) in the crossover group, and 14% (10 of 69 patients) in the non-crossover group.

No treatment associated deaths were reported.

Study 7 Mahfoud F (2019)

Study details

Study type	Case series (Global SYMPLICITY Registry; NCT01534299)
Country	Canada, Western Europe, Latin America, Eastern Europe, South Africa, Middle East, Asia, Australia, and New Zealand (196 centres in 45 countries)
Recruitment period	Not reported
Study population and number	n=2,237 Patients with uncontrolled hypertension (antihypertensive drugs, mean 4.5)
Age and sex	Mean 61 years; 58% male; BMI mean 31 kg/m^2
Patient selection criteria	Inclusion criteria: age of at least 18 years and eligibility for RDN as defined by local regulations.
Technique	Percutaneous transluminal renal sympathetic denervation using the SYMPLICITY^{TM} renal denervation systems - the first-generation, single-electrode SYMPLICITY Flex RDN catheter system (Medtronic, Santa Rosa, CA, USA)
Follow up	Up to 3 years
Conflict of interest/source of funding	The Global SYMPLICITY Registry is funded by Medtronic. F.M., M.B., R.E.S., K.N., L.R., M.S., B.W., M.F. and G.M. declared conflict of interest.

Analysis

Follow-up issues: Patients were followed up at 6 months, 1 year, 2 years and 3 years. Of the 2,237 enrolled patients who had the procedure, 1,742 patients were eligible for follow up at 3 years. Of the enrolled population, 1,734 patients had office BP measurements available at 6 months, 1,654 at 1 year, 1,258 at 2 years, and 872 at 3 years.

Study design issues: This prospective, open-label, single-arm, observational registry assessed the long-term effectiveness, safety, and effects on renal function in the Global SYMPLICITY Registry up to 3 years after RDN. The primary objective was to assess procedural and long-term safety of RDN in a real-world setting.

Severe treatment-resistant hypertension was defined as office SBP ≥160 mmHg and 24-hour ambulatory BP ≥135 mmHg, despite prescription of ≥3 antihypertensive medications, while less severe hypertension was defined as office SBP and diastolic BP 150 to 180mmHg and ≥90mmHg, respectively, and 24-hour ambulatory SBP 140 to 170 mmHg.

Study population issues: Of the 2,237 patients, 21% had a history of CKD (eGFR <60mL/min/1.73 m2), 38% had Type 2 diabetes mellitus, and nearly half had a history of cardiac disease. At baseline, patients were prescribed 4.5±1.4 antihypertensive medication classes, which in most patients included an angiotensin receptor blocker or ACE inhibitor, a calcium channel blocker, a diuretic, and a beta-blocker.

Other issues: The Global SYMPLICITY Registry is a single-arm registry and as such did not involve control groups to compare outcomes. There was no way to rule out a Hawthorne/placebo effect, which could be caused by participation and care during the study. Comparison of eGFR measurements between patients with and without medication changes was limited since reported medication changes were not verified with medication adherence testing. The device (first-generation, single-electrode SYMPLICITY Flex RDN catheter

system) might have made it more difficult to achieve a pattern of 4-quadrant ablations than the current SYMPLICITY Spyral catheter technology, especially within the Global SYMPLICITY Registry study design that did not encourage more treatment ablations or allow for treatment in the renal artery side branches or accessories.

Key efficacy findings

Number of patients analysed: 2,237

Mean RDN time: 49±21 minutes

Total contrasts used per RDN: 129±78 mL

During the RDN procedure, 13.4±4.1 ablation treatments were applied in 2.1±0.4 renal arteries per patient.

Change in BP between 6 months and baseline:

- Office systolic BP: -12.8± 26.2 mmHg (n=1691, p<0.0001)
    - Office systolic BP in patients with severe treatment-resistant hypertension -21.7±24.0 mmHg (n=228, p<0.0001)
    - Office systolic BP in patients with less severe hypertension -15.3±19.5 mmHg (n=55, p<0.0001)
- 24 hr. ambulatory systolic BP: -7.2± 17.8 mmHg (n=966, p<0.0001)
    - 24 hr. ambulatory systolic BP in patients with severe treatment-resistant hypertension -8.1 mmHg (n=92, p<0.0001)
    - 24 hr. ambulatory systolic BP in patients with less severe hypertension -13.6 mmHg (n=28, p<0.0001)

Change in office BP between 1 year and baseline:

- Office systolic BP: -12.3 mmHg (n=1,254, p<0.0001)
    - Office systolic BP in patients with severe treatment-resistant hypertension -23.5 mmHg (n=228, p<0.0001)
    - Office systolic BP in patients with less severe hypertension -15.1 mmHg (n=55, p<0.0001)
- 24-hour ambulatory systolic BP: -7.2 mmHg (n=680, p<0.0001)
    - 24-hour ambulatory systolic BP in patients with severe treatment-resistant hypertension -10.1 mmHg (n=92, p<0.0001)
    - 24-hour ambulatory systolic BP in patients with less severe hypertension -13.3 mmHg (n=28, p<0.0001)

Change in BP between 2 years and baseline:

- Office systolic BP: -14.7 mmHg (n=980, p<0.0001)
    - Office systolic BP in patients with severe treatment-resistant hypertension -23.9 mmHg (n=228, p<0.0001)
    - Office systolic BP in patients with less severe hypertension -16.4 mmHg (n=55, p<0.0001)
- 24-hour ambulatory systolic BP: -8.2 mmHg (n=462, p<0.0001)

- 24-hour. ambulatory systolic BP in patients with severe treatment-resistant hypertension -12.0 mmHg (n=92, p<0.0001)
- 24-hour ambulatory systolic BP in patients with less severe hypertension -14.8 mmHg (n=28, p<0.0001)

Change in BP between 3 years and baseline:

- Office systolic BP: -16.5 mmHg (n=849, p<0.0001)
  - Office systolic BP in patients with severe treatment-resistant hypertension -26.7 mmHg (n=228, p<0.0001)
  - Office systolic BP in patients with less severe hypertension -17.7 mmHg (n=55, p<0.0001)
- 24-hour ambulatory systolic BP: -8.0 mmHg (n=353, p<0.0001)
  - 24-hour ambulatory systolic BP in patients with severe treatment-resistant hypertension -12.4 mmHg (n=92, p<0.0001)
  - 24-hour ambulatory systolic BP in patients with less severe hypertension -15.0 mmHg (n=28, p<0.0001)

Antihypertensive medications in patients eligible for 3-year follow up

	Baseline (n=1,721)	**1 year (n=1,729)**	**2 years (n=1,729)**	**3 years (n=1,730)**	**P value***
Antihypertensive medication classes	4.5±1.4	4.4±1.4	4.4±1.5	4.4±1.5	<0.001
Beta-blockers	77.4%	75.8%	74.7%	74.0%	<0.001
ACE inhibitors	34.2%	30.5%	29.5%	29.2%	<0.001
Angiotensin receptor blockers	66.5%	65.9%	65.7%	65.3%	0.018
Calcium channel blockers	77.6%	76.4%	76.5%	76.2%	0.071
Diuretics	79.3%	77.8%	76.9%	76.0%	<0.001
Aldosterone antagonists	24.8%	27.6%	28.9%	29.2%	<0.001
Alpha-adrenergic blockers	35.1%	33.1%	32.4%	32.4%	0.006
Direct-acting vasodilators	14.1%	13.7%	13.7%	13.8%	0.939
Centrally-acting sympatholytics	38.8%	35.6%	35.0%	34.3%	<0.001
Direct renin inhibitors	6.2%	4.9%	4.7%	4.4%	<0.001

*3 years compared with baseline using the McNemar's test for categorical variable and the paired t-test for number of anti-hypertensive medications.

The only baseline variable associated with a greater reduction in office (and 24-hour) systolic BP at all 3 time points (12, 24, and 36 months) was higher baseline office (and 24 h) systolic BP.

Use of alpha-adrenergic blockers and direct-acting vasodilators was associated with an increase in office systolic BP at 12, 24, and 36 months and current smokers were associated with an increase in 36-month 24-hour systolic BP.

Renal function: eGFR following RDN – baseline compared with 3 years:

- patients without CKD: 87±17 mL/min/1.73 m^2 compared with 80±20 mL/min/1.73 m^2, Δ=-7.1±16.7 mL/min/1.73 m^2, n=289, p<0.0001

- patients with CKD: 47± 11 mL/min/1.73 m^2 compared with 43±19 mL/min/1.73 m^2, Δ=-3.7±16.2 mL/min/1.73 m^2; n=93, p=0.03

Patients with stage 4 severe CKD at baseline (n=37): 2 patients who progressed to stage 5 at 6 months, 4 additional patients at 12 months and 2 additional patients at 24 months

Patients with stage 3 moderate CKD at baseline (n=124): 16 patients who progressed to stage 4 at 6 months.

eGFR measurements at 36 months between patients with and without changes in antihypertensive medication changes: 70± 25 mL/min/1.73 m^2 compared with 69± 25 mL/min/1.73 m^2, p=0.41

change in eGFR in patients with diabetes mellitus compared with those without diabetes mellitus:

- 6 months: -4.1± 12.6 mL/min/1.73 m^2 (n=157) compared with -2.6±13.4 mL/min/1.73 m^2 (n=224), p=0.090

- 3 years: -7.7± 18.1mL/min/1.73 m^2 (n=157) vs. -5.2± 15.5mL/min/1.73 m^2 (n=224), p=0.053

Changes in 24-hour systolic BP for patients with baseline eGFR <60mL/min/1.73 m^2 were not significantly different than for patients with baseline eGFR ≥60mL/min/1.73m^2 at all measured timepoints.

- Change in 24-hour systolic BP:
  - change at 6 months: -6.6 mmHg
  - change at 1 year: -7.2 mmHg
  - change at 2 years: -8.2 mmHg
  - change at 3 years: -8.0 mmHg
- changes in office systolic BP:
  - change at 6 months: -11.7 mmHg
  - change at 1 year: -12.3 mmHg
  - change at 2 years: -14.7 mmHg
  - change at 3 years: -16.5 mmHg

Key safety findings

Safety result using Kaplan-Meier time-to-event analysis

	6 months (number at risk: 2,237)	**1 year (number at risk: 2,112)**	**2 years (number at risk: 1,917)**	**3 years (number at risk: 1,345)**
Death	0.5% (n=10)	1.3% (n=28)	2.8% (n=54)	4.1% (n=59)
Cardiovascular events				
Cardiovascular death	0.3% (n=6)	0.8% (n=16)	1.5% (n=28)	2.0% (n=29)

Stroke	0.7% (n=15)	1.3% (n=27)	2.1% (n=41)	3.2% (n=47)
Hospitalisation for new onset heart failure	0.7% (n=16)	1.1% (n=24)	2.0% (n=38)	3.2% (n=46)
Hospitalisation for atrial fibrillation	0.7% (n=15)	1.5% (n=32)	2.4% (n=46)	3.0% (n=45)
Hospitalisation for hypertensive crisis/hypertensive emergency	0.8% (n=17)	1.1% (n=24)	1.8% (n=36)	2.6% (n=40)
Myocardial infarction	0.7% (n=16)	1.1% (n=23)	1.6% (n=31)	2.2% (n=33)
Renal events				
New onset end-stage renal disease	0.2% (n=4)	0.4% (n=9)	1.0% (n=19)	1.6% (n=23)
Serum creatinine elevation >50% mg/dL	0.4% (n=9)	0.9% (n=19)	1.2% (n=24)	1.5% (n=24)
New artery stenosis (>70% diameter stenosis)	0.05% (n=1)	0.1% (n=3)	0.2% (n=4)	0.3% (n=4)
Postprocedural events				
Non-cardiovascular death	0.1% (n=2)	0.3% (n=7)	1.0% (n=19)	1.6% (n=22)
Renal artery reintervention	0.2% (n=5)	0.4% (n=8)	0.4% (n=9)	0.6% (n=10)

Study 8 Zweiker D (2016)

Study details

Study type	Case series (Austrian TREND registry)
Country	Austria (14 centres)
Recruitment period	2011 to 2014
Study population and number	n=407 (group A, n=245; group B, n=162) Patients with resistant hypertension (antihypertensive drugs: median 4 [IQR 4 to 5])
Age and sex	Median 63 (range 54 to 69); 58% male; BMI, median 30 kg/m^2
Patient selection criteria	Inclusion criteria: patients who retained a 24-hour BP above 145/90 mmHg were eligible for the RDN procedure. Exclusion criteria: (1) a reduced kidney function (estimated glomerular filtration rate ≤45 mL/min) and (2) incompatible anatomy of the renal artery.
Technique	RDN was done using radiofrequency - Symplicity™ RDN (Medtronic Inc., Minneapolis, MN; n=380, 95%), Symplicity Spyral™ RDN (Medtronic Inc., Minneapolis, MN; n=11, 3%) or EnligHTN™ system (St. Jude Medical Inc., St. Paul, MN, n=8, 2%),
Follow up	Median 12 months (range 205 to 383 days)
Conflict of interest/source of funding	Funding: The Austrian Society of Hypertension funded this registry. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Competing Interests: The authors declared that no competing interests exist.

Analysis

Follow-up issues: Follow up was recommended at 2 to 6 weeks, 3 months, 6 months, and on a yearly basis thereafter. Suggested follow-up documentation included office BP, ambulatory BP, renal function, antihypertensive treatment, and long-term safety. To ensure adherence to drug therapy, patients were encouraged to keep a diary.

Study design issues: The Austrian Society of Hypertension created the Austrian Transcatheter RENal Denervation (TREND) Registry in 2011, with an emphasis on ambulatory BP monitoring to monitor safety and efficacy of all RDN procedures performed in Austria. This was the first analysis of the data gathered by the Austrian TREND Registry, reporting efficacy and safety of RDN with respect to office and ambulatory BP in a real-life setting.

Authors did not document quality of ambulatory BP measurements in the registry. Patient management, choice of drug therapy, device selection for RDN as well as vascular access site remained at the discretion of each individual centre.

The Austrian Society of Hypertension suggested RDN for patients on multiple drug treatment, with a mean 24-hour BP >145/90 mmHg, equivalent to an office BP of 160/100 mmHg. Based on this threshold, patients were divided into 2 groups: group A consisted of all patients with a mean baseline 24-hour BP >145/90 mmHg, and all remaining patients were summarised in group B. Responders were defined as follows: office BP responders had a reduction of at least 10 mmHg of office systolic BP after 6 months. Ambulatory BP responders had a 24-h ambulatory BP reduction of at least 5 mmHg after 6 months.

Study population issues: At baseline, patients were on antihypertensive treatment for a median of 10 years (IQR 7 to 15; n=128). Average office BP was 170±16/94±14 mmHg; average 24-hour ambulatory BP was 151±18/89±14 mmHg (n=359). In total, 98% of patients had a systolic office BP >140 mmHg and 91% a systolic 24-h ABP >130 mmHg, respectively. Most prevalent comorbidities were coronary artery disease (37%), diabetes mellitus (36%) and cerebrovascular disease (12%).

Patients in group A were statistically significantly younger, had a higher BMI, and received more antihypertensive medications than patients in group B. Mean 24-hour BP in group A was 159/95 mmHg compared with 132/77 mmHg in group B. This difference was statistically significant (p<0.001). Furthermore, the average office BP in group A was statistically significantly higher, but the difference was smaller (173/96 mmHg compared with 166/90 mmHg). There were no statistically significant differences in comorbidities. Procedural details were available for 279 patients (69%). Procedural details were available for 279 patients (69%). Antihypertensive therapy was paused during the procedure in 44% of cases.

Other issues: 6-month ABPM data was availability in 59% of patients, data needs be interpreted with some caution as selection bias might have occurred. Since regression to the mean phenomenon and the regression of the white coat effect may lower BP readings at subsequent follow-up visits, the data might over-estimate especially office BP reductions. Drug prescriptions and changes of medications were documented in the registry, however, urine analysis or pill count for proving accurate drug intake was not available.

Key efficacy findings

Number of patients analysed: 407

In subgroups A and B, a median sum of 11 (IQR 9 to 12) and 10 (IQR 9 to 12) points in both renal arteries were ablated (p=0.412)

Responses to RDN after the procedure

	2 to 6 weeks		**3 months**		**6 months**		**12 months**	
BP, mmHg	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Office BP, n	n=212		n=206		n=188		n=134	
Absolute	158±24	89±13	153±22	89±13	151±22	87±15	153±23	88±16
Change to baseline	-12±27[b]	-5±16[b]	-16±25[b]	-4±8[b]	-20±26[b]	-7±18[b]	-20±27[b]	-8±18[b]
Mean 24-hour BP, n	n=130		n=253		n=239		n=208	
Absolute	142±15	84±11	140±18	83±13	139±16	83±12	137±17	82±13
Change to baseline	-11±18[b]	-6±11[b]	-8±19[b]	-4±13[b]	-8±17[b]	-5±11[b]	-10±18[b]	-6±12[b]
Mean daytime BP, n	n=111		n=241		n=225		n=198	
Absolute	144±15	87±11	141±18	85±14	141±16	85±13	139±18	84±13
Change to baseline	-10±19[b]	-4±11[b]	-8±20[b]	-4±12[b]	-7±18[b]	-4±10[b]	-10±19[b]	-5±12[b]
Mean nighttime BP, n	n=110		n=237		n=221		n=192	
Absolute	137±17	79±14	132±19	77±13	133±19	77±13	131±19	76±13

Change to baseline	-10±18[b]	-5±12[b]	-8±21[b]	-4±13[b]	-7±21[b]	-4±12[b]	-9±21[b]	-5±12[b]

All values are presented as mean±SD
[a]p<0.05
[b]p<0.001

Responses to RDN after the procedure

	2 to 6 weeks	3 months	6 months	12 months
Medication				
Number of antihypertensive medications	n=136	n=142	n=134	n=267
Absolute	5 (4 to 6)	4 (4 to 5)	5 (4 to 6)	4 (3 to 5)
Change to baseline	0 (0 to 0)	0 (-1 to 0)[a]	0 (0 to 0)	0 (-1 to 0)[a]
Renal function				
eGFR, ml min^{-1} per $1.73m^2$	n=174	n=182	n=127	n=112
Absolute	80 (64 to 93)	75 (62 to 90)	74 (63 to 86)	74 (59 to 84)
Change to baseline	-0.5 (-7 to 5)	-0.7 (-9 to 4)[a]	-2 (-11 to 7)	-2 (-11 to 5)[a]

All values are presented as mean±SD
[a]p<0.05

BP responder rate after 6 months:

- Office BP responder rate: 69% (128/185)
- Ambulatory BP responder rate: 55% (120/220)
- Both office and ambulatory BP responder rate: 44% (67/154)

At every follow up:

- Systolic office BP ≤140 mmHg: 30%
- Systolic 24-h BP ≤130 mmHg: 22%

No significant differences between patients treated with different devices in the 24-hour and office BP responders (based on BP changes after 6 months). However, ambulatory daytime and nighttime systolic BP changes were more pronounced in Symplicity Spyral group after 1 month (p≤0.001 for both). There was no follow-up ABPM data available for the EngligHTN group.

Correlation between systolic mean 24-hour and office BP changes at baseline and 6 months after the procedure (n=154): Pearson correlation 0.303, p<0.001

Predictors of 24-hour mean systolic BP reduction ≥5 mmHg after 6 months

Parameter	OR	95% CI	P value
Mean 24-hour systolic BP, per 10 mmHg	3.261	2.175 to 4.888	<0.001
Office systolic BP, per 10 mmHg	0.676	0.515 to 0.888	0.005
Mean nighttime diastolic BP, per 10 mmHg	0.626	0.429 to 0.913	0.015

The resulting model could predict ambulatory BP responders with a sensitivity of 81% and a specificity of 74%.

In group A, 24-hour BP reductions after the procedure were significantly more apparent compared with group B ($p< 0.01$ at every follow-up). Furthermore, with a mean 24-h BP change of -13.7 ±16.8 mmHg for systolic BP and -8.2±11.6 mmHg for diastolic BP after 6 months (n=137), ambulatory BP responder rate was significantly higher (group A 70% compared with group B 29%, $p<0.001$). Office responder rate did not differ between subgroups (68% compared with 69%, p=0.621).

Key safety findings

Periprocedural complication rate: 2.5% (n=7) with no significant difference between subgroups (p=0.712).

- inguinal haematoma needing intervention: n=1
- renal arterial dissection requiring stenting: n=1
- pseudoaneurysm of the femoral artery: n=2
- dissection of the abdominal aorta (treated conservatively): n=1
- spasm of the renal artery: n=1
- therapy-resistant hypotension: n=1

All complications were managed successfully in the catheter room.

Periprocedural mortality: 0%

Renal artery stenosis: n=2. Both patients required percutaneous transluminal renal angioplasty for renal artery stenosis 72 and 452 days after the intervention.

Study 9 Sharp ASP (2016)

Study details

Study type	Case series (UK registry)
Country	UK (18 centres)
Recruitment period	Not reported
Study population and number	n=253 Patients with resistant hypertension (antihypertensive drugs, median 5.0)
Age and sex	Mean 57 years; 47% (120/253) male; BMI, mean 32 kg/m^2
Patient selection criteria	Inclusion criteria: patients who had RDN for treatment-resistant hypertension. Patient selection was typically in accordance with the Joint UK Societies Consensus statement on RDN, which recommended strict criteria for patient selection. Exclusion criteria: patients who had RDN for other indications as part of ongoing clinical trials (e.g. heart failure; sleep apnoea; acknowledged non-compliance with medications)
Technique	Percutaneous transluminal renal sympathetic denervation was done using radiofrequency - Symplicity Flex (n=204); Symplicity Spyral (n=10); Boston Vessix (n=3); St Jude EnligHTN (n=26) and Covidien Oneshot (n=10).
Follow up	Mean 11 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Clinical follow-up was available in 90% of patients, with a mean duration of office BP follow up of 11 months.

Study design issues: This study reported the UK experience with RDN for treatment-resistant hypertension. It examined the nature of the BP response seen on ambulatory monitoring and the impact of drug changes post denervation on the results. Finally, this study examined the interaction of RDN with the use of aldosterone antagonists.

'Responders' to RDN were defined as a reduction in office systolic BP of ≥10 mmHg and reduction in daytime ambulatory systolic BP fall of ≥5 mmHg from baseline to follow up. Absence of normal nocturnal dipping profile on pre-procedural ambulatory BP was defined as a fall in nighttime systolic ambulatory BP of <10%.

Study population issues: Of the 253 patients, 88% were Caucasian and 26.5% had diabetes. Eighty-six percent of patients were seen in a dedicated hypertension clinic with each patient being reviewed by an average of 1.6 hypertension specialists. These included cardiologists, nephrologists, clinical pharmacologists and endocrinologists.

Fifty-eight percent of the cohort had loss of normal nocturnal dipping on ambulatory BP. The median number of antihypertensive drugs prescribed before RDN was 5.0 including 96 % ACEi/ARB; 86 % thiazide or a loop

diuretic and 55 % aldosterone antagonist prescription at the time of denervation. The mean number of cases performed per centre within this registry was 15 (SD 6.7).

Other issues: This study was limited by the design (an open-label retrospective registry). However, authors stated that data quality appeared good, as supported by the relatively high frequency of reporting of ambulatory BP results and the close correlation between office BP and ambulatory BP results. Results also appeared consistent across 18 sites. This study did not mandate measures of adherence to prescribed medications and therefore variable levels of compliance pre- and post-procedure could have had a confounding impact on results.

Key efficacy findings

Number of patients analysed: 253

Blood pressure at baseline and follow up (mean 11 months)

	Before procedure	After procedure	Mean fall	P value
Office BP	n=253	n=228 at a mean follow up of 11 months		
Systolic BP, mmHg	185±26	163±28	22±29	<0.001
Diastolic BP, mmHg	102±19	93±19	9±19	<0.001
Ambulatory BP	n=186	n=177 at a mean follow up of 8.5 months		
Daytime systolic BP, mmHg	170±22	158±25	12	<0.001
Daytime diastolic BP, mmHg	98±16	91±17	7	<0.001
Nighttime systolic BP, mmHg	154±26	145±26		
Nighttime diastolic BP, mmHg	86±18	83±17		

Drug changes:

- Average number of antihypertensive drugs added since procedure (per patient): 0.36
- Average number of antihypertensive drugs stopped since procedure (per patient): 0.91
- Average number of drug doses up-titrated per patient: 0.21
- Average number of drug doses decreased per patient: 0.17
- Patients with no changes in drug numbers or drug doses: n=80
- Patients with changes in either drug numbers of drugs doses: n=128
- Dur dose changes not available: n=45

Change in BP (BP response to RDN) according to quartile of baseline daytime ambulatory systolic BP

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Baseline daytime ambulatory systolic BP, mmHg	142	162	176	199
Daytime ambulatory systolic BP change at follow up*, mmHg	-0.4	-6.5	-14.5	-22.1
Daytime ambulatory diastolic BP change at follow up, mmHg	-1.8	-3.8	-6.4	-13.3
Office systolic BP change at follow up**, mmHg	-15.2	-22.3	-22.9	-30.3
Office diastolic BP change at follow up, mmHg	-5.3	-10.9	-9.0	-12.4

Number of antihypertensive drugs per quartile did not significantly differ (p>0.2).
*p value for quartile trend <0.001
**p=0.001 for quartile trend, but in the lowest quartile, this was not matched by a statistically significant ambulatory systolic BP response.

Responders:

- 65% of patients with a ≥10 mmHg fall in office systolic BP
- 62% of patients with a ≥5 mmHg fall in daytime ambulatory systolic BP

Use of aldosterone antagonist at the time of RDN did not predict the degree of BP response (p>0.2 as univariate predictor). This remained the case after adjustment for the following potential confounders: age, gender, diabetes, estimated glomerular filtration rate (eGFR), number of drugs taken and starting office BP (p>0.2). There remained no association when ambulatory systolic BP was substituted for office systolic BP within the model. The only baseline characteristic that predicted subsequent fall in BP after RDN was BP, as measured by office or ambulatory BP.

Key safety findings

Not reported.

Study 10 Fengler K (2021)

Study details

Study type	Case series (single-centre registry)
Country	Germany (single centre)
Recruitment period	2011 to 2019
Study population and number	n=296 patients with resistant hypertension (antihypertensive drugs, mean 5.2)
Age and sex	Mean 63 years; 70% (208/296) male; BMI, mean 32 kg/m^2
Patient selection criteria	Inclusion criteria: patients with therapy resistant hypertension who had RDN were included into the analysis if baseline and 3 months ABPM results were available.
Technique	Percutaneous transluminal renal sympathetic denervation was done using radiofrequency (main renal artery with Symplicity Flex, n=117; main renal artery with Symplicity Spyral, n=49; main renal artery and side branches with Symplicity Spyral, n=38) or ultrasound (a balloon-irrigated ultrasound-based denervation system, Paradise, n=92).
Follow up	Median 48 months
Conflict of interest/source of funding	Funding: This work was supported by the Leipzig Heart Institute (Leipzig, Germany). Conflict of interest: KF, PL and MB declared conflict of interests. The remaining authors had no disclosures to report.

Analysis

Follow-up issues: Of the 311 patients who had RDN, 14 patients (4.5%) were lost to follow up or had missing 3 months BP values and 1 patient (0.3%) died before reaching the 3-month follow up. In total, 296 patients (95.2%) were available for analysis.

Study design issues: This retrospective single-centre registry study investigated the effect of BP reduction after RDN on long-term cardiovascular outcome in patients with resistant hypertension. Clinical events were assessed in patients from previous RDN trials and clinical routine at the study centre, some patients (exact number was unknown) were included in Fengler (2021) and Pisano (2021).

Clinical outcome was assessed using a standardised questionnaire by a single investigator, who was masked to BP outcome. If contacting patients was unsuccessful, or if necessary to complete clinical event assessment, patient's last treating general practitioners were contacted. In addition, hospital database was searched for clinical events for every individual patient. In all patients, antihypertensive drug treatment was kept stable until the 6-month follow up was reached unless indicated otherwise.

BP response was defined as reduction of ≥5 mmHg in 24-hour average systolic BP on ABPM between baseline and 3 months.

Major adverse cardiovascular event was defined as a composite of cardiovascular death, ischemic stroke or intracranial bleeding, acute myocardial infarction, critical limb ischemia as well as acute renal failure. The ischemic events end point was defined as a composite of ischemic stroke, acute myocardial infarction, peripheral artery disease requiring intervention and critical limb ischemia.

To assess the effect of BP reduction, clinical events were compared between BP responders and non-responders. In a second step, a postulated proportional relationship between BP reduction and clinical events was tested.

Study population issues: At baseline, responders had higher systolic and diastolic ABPM values as well as a lower rate of isolated systolic hypertension. Baseline medication and number of antihypertensive drug classes were balanced between responders and non-responders.

Other issues: There were several limitations. First, this retrospective single-centre registry had its limitations such as selection bias, and an underreporting of clinical events during the long-term follow up. Second, drug adherence testing for the patients enrolled was not provided. Therefore, part of the observed effects might also be attributed to alterations in antihypertensive drug intake during follow up, even though this was unlikely. Third, because of the study design and the lack of a control group, it was impossible to separately analyse effects of RDN from effects by BP reduction in general, but the proportional association of BP reduction within the immediate timeframe of RDN on long-term outcomes suggested an at least partial effect. Fourth, the composite end point (major adverse cardiovascular events) herein differed from other, larger-scaled cardiovascular outcome trials as it was a concession to the smaller sample size available. Effects of RDN on hard clinical end points should be tested in larger-scaled analyses in the future. Lastly, the relatively small number of events and patients included gave this study only a hypothesis generating character and all findings warrant confirmation in larger, prospectively designed trials.

Key efficacy findings

Number of patients analysed: 296

24-hour ambulatory BP at 3 months (n=296):

- Change in systolic BP: -8.3±12.2 mmHg, p<0.001
- Change in diastolic BP: -4.8±7.0 mmHg, p<0.001
- Responders, n=180 (61%); non-responders, n=116 (39%)

24-hour ambulatory BP at 6 months (n=253):

- Change in systolic BP: -8.0±12.4 mmHg, p<0.001
- Change in diastolic BP: -5.1±7.1 mmHg, p<0.001

24-hour ambulatory BP at 12 months (n=183):

- Change in systolic BP: -8.7±14.1 mmHg, p<0.001
- Change in diastolic BP: -5.4±7.8 mmHg, p<0.001

Systolic BP at 6 and 12 months remained significantly more reduced in 3-month responders than in 3-month non-responders (12.1±2.8 compared with 2.8±13.8 mmHg, and 11.7±12.0 compared with 2.0±10.7 mmHg, p<0.001 for both, compared with baseline BP values).

Key safety findings

Clinical events during follow up

	All (n=296)	Responders (n=180)	Non-responders (n=116)	Hazard ratio	95% CI	P value (log-rank)
Death	10% (n=29)	11% (n=19)	9% (n=10)	1.22	0.58 to 2.57	0.69
Cardiovascular death	5% (n=16)	5% (n=9)	6% (n=7)	0.82	0.30 to 2.23	0.69
Stroke	3% (n=9)	2% (n=3)	5% (n=6)	0.31	0.08 to 1.17	0.08
Intracranial haemorrhage	1% (n=4)	2% (n=3)	1% (n=1)	1.82	0.24 to 13.54	0.55
NSTE-ACS	6% (n=12)	3% (n=6)	5% (n=6)	0.62	0.19 to 1.99	0.43
STEMI	1% (n=2)	1% (n=1)	1% (n=1)	0.62	0.04 to 10.64	0.74
Peripheral artery disease needing intervention	4% (n=13)	3% (n=6)	6% (n=7)	0.53	0.17 to 1.61	0.26
Critical limb ischaemia	1% (n=3)	1% (n=1)	2% (n=2)	0.33	0.03 to 3.29	0.34
Acute renal failure	3% (n=11)	2% (n=4)	6% (n=7)	0.36	0.11 to 1.21	0.10
Heart failure hospitalisation	7% (n=20)	7% (n=13)	6% (n=7)	1.27	0.52 to 3.11	0.59
Major adverse cardiovascular events	15% (n=45)	12% (n=22)	20% (n=23)	0.53	0.28 to 0.97	0.041
Ischaemic events	11% (n=34)	8% (n=15)	16% (n=19)	0.44	0.22 to 0.89	0.022

NSTE-ACS, non–ST-segment–elevation acute coronary syndrome
STEMI, ST-segment–elevation myocardial infarction

After adjustment for age, sex, baseline systolic and baseline diastolic ABPM before RDN as well as presence of isolated systolic hypertension and a history of stroke using Cox regression analysis and a stepwise forward approach, besides baseline systolic BP, isolated systolic hypertension, and previous stroke-only responder status reached statistically significant level (p=0.041). Baseline diastolic BP, age, and sex did not reach statistical significance for inclusion into the model.

A proportional relationship was found between BP reduction after 3 months and frequency of major adverse cardiovascular events (HR 0.75 [95% CI 0.58 to 0.97] per 10 mmHg 24-hour systolic ambulatory BP reduction, p=0.031).

Baseline BP corrected event rates by blood pressure reduction quartiles (quartile 1: <1 mm Hg, quartile 2: 1 to 7 mmHg, quartile 3: 7 to 15 mmHg and quartile 4: >15 mmHg 24-hour ABPM reduction after 3 months) using

Cox regression also suggested a proportional relation of blood pressure reduction but did not reach significance level between the different quartiles.

Clinical events in the propensity-score matched cohort

	All (n=196)	Responders (n=98)	Non-responders (n=98)	Hazard ratio	95% CI	P value (log-rank)
Death	8% (n=15)	6% (n=6)	9% (n=9)	0.71	0.26 to 1.95	0.48
Cardiovascular death	5% (n=10)	4% (n=4)	6% (n=6)	0.71	0.21 to 2.45	0.59
Stroke	4% (n=8)	2% (n=2)	6% (n=6)	0.38	0.09 to 1.50	0.16
Intracranial haemorrhage	1% (n=2)	1% (n=1)	1% (n=1)	1.03	0.06 to 16.50	0.99
NSTE-ACS	5% (n=10)	4% (n=4)	6% (n=6)	0.67	0.19 to 2.32	0.51
STEMI	1% (n=2)	1% (n=1)	1% (n=1)	1.02	0.06 to 16.41	0.99
Peripheral artery disease needing intervention	5% (n=10)	3% (n=3)	7% (n=7)	0.55	0.17 to 1.80	0.19
Critical limb ischaemia	1% (n=2)	0% (n=0)	2% (n=2)	-	-	0.16
Acute renal failure	4% (n=7)	1% (n=1)	6% (n=6)	0.25	0.06 to 1.12	0.07
Heart failure hospitalisation	6% (n=12)	6% (n=6)	6% (n=6)	1.18	0.38 to 3.67	0.81
Major adverse cardiovascular events	16% (n=32)	11% (n=11)	21% (n=21)	0.49	0.24 to 0.98	0.043
Ischaemic events	15% (n=30)	11% (n=11)	19% (n=19)	0.53	0.26 to 1.08	0.08

Validity and generalisability of the studies

- Of the 10 papers, 6 papers focused on radiofrequency RDN (Pisano 2021; Townsend 2020; Bhatt 2022; Mahfoud 2019; Zweiker 2016; Sharp 2016), 2 studies emphasised ultrasound RDN (Kario 2022; Azizi 2021, 2022), and 2 studies included both energy sources (Fengler 2019, 2021).
- Studies were conducted in various countries and some data were collected in the UK including a UK registry.
- Most studies had 3- or 6-month follow ups. The longest follow up was 84 months (I study included in Pisano 2021), followed by 4 years (Fengler 2021), 3.5 years (Bhatt 2022) and 3 years (Mahfoud 2019).
- Of the 8 primary studies, there were 4 adequately powered, randomised trials. One RCT compared RDN using radiofrequency with sham procedure (Bhatt 2022). This study had a follow up of 36 months after unmasking and crossover. Two RCTs compared RDN using ultrasound with sham procedure (Kario 2022; Azizi 2021), and 1 randomised trial was a 3-arm trial comparing different techniques (USM-RDN, RFM-RDN and RFB-RDN; Fengler 2019). In terms of population, 3 randomised trials recruited patients from the US and Europe (Azizi 2021; Fengler 2019; Bhatt 2022), and 1 trial included patients from Japan and South Korea (Kario 2022).
- For the 2 RCTs that compared RDN using ultrasound with sham procedure, between-group differences in office and 24-hour ambulatory systolic BP were found to be statistically significant in Azizi (2021) but not in Kario (2022). This was because of the unexpected, large BP reduction in the sham group in Kario (2022), highlighting study design issues (possibly caused by a significant number of unstable patients with uncontrolled hypertension and poor drug adherence enrolled in the study).
- Outcomes might be affected by many factors, such as patient-specific characteristics, effects of comedication and adherence, surgeon’s experience, and the technical aspects of the procedure.

- RDN has evolved over the years and different renal denervation systems have been used. For radiofrequency RDN, the systems used include Symplicity Flex (single-electrode system), Symplicity Spyral (multi-electrode system), EnligHTN (multi-electrode basket), Vessix (balloon with bipolar radiofrequency electrodes), OneShot (balloon with spiral radiofrequency electrode). For ultrasound RDN, the system used is the Paradise system (ultrasound created heat/water-cooled balloon).
- For radiofrequency RDN using different systems, Pisano (2021) found a greater decrease in office and 24-hour ambulatory BP in patients who had RDN using the multi-electrode catheter denervation system, having 4 ablations simultaneously delivered at the mid/distal segment of the renal artery, compared with the first-generation procedures (radiofrequency ablation via single-electrode catheter), with analysis factoring in the device type also reducing the heterogeneity among studies.
- There was a lack of objective measure of medication adherence using blood or urine in most studies.
- There might be a placebo effect on BP lowering after sham procedures or antihypertensive medications. The placebo effect might be greater with sham treatment than with medications.
- Although Townsend (2020) included patients with uncontrolled hypertension, this meta-analysis of 50 trials explicitly reported renal artery damage after RDN. In this study, in addition to the 50 trials in the meta-analysis, authors also reviewed 11 individual cases of renal artery stenosis reported in 11 case reports. Combining case reports and clinical studies, renal artery damage after denervation with the Symplicity Flex catheter was reported in 37 patients, including 34 patients having stent implantation. Most events occurred within 1 year after the procedure. No cases of stenosis or dissection were reported involving the second-generation multi-electrode Symplicity Spyral system.
- Data on efficacy and safety came from 1 Cochrane review, 1 meta-analysis and clinical trials, supplemented by observational studies (registries).

- Studies that measure BP control and end-organ damage, with longer follow ups (possibly 5 to 10 years) and larger sample sizes, are needed.

Existing assessments of this procedure

In 2019, the Joint UK Societies (JUKS) published the consensus statement on RDN (Lobo 2019). JUKS concluded that "*there are insufficient data at present to suggest that RDN should be considered routine standard of care in the management of hypertension in adults and that additional clinical trials data are required"*.

In 2021, the European Society of Hypertension (ESH) published a position paper on RDN (Schmieder 2021). ESH gave the following position statements:

- *On the basis of consistent results of several sham-controlled clinical trials, renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and blood pressure lowering drugs.*
- *Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, that is to effectively reduce an elevated blood pressure and achieve blood pressure targets.*
- *Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available up to 3 years.*
- *Renal denervation is an alternative or additive, not a competitive treatment strategy.*
- *A structured pathway for clinical use of RDN in daily practice is recommended.*
- *Patients' perspective and preference as well as patients' stage of hypertensive disease including comorbidities should lead to an individualized treatment strategy in a shared decision-making process, that carefully includes the various options of treatment, including renal denervation.*

In 2018, the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) published the ESC/ESH guidelines for the management of arterial hypertension (Williams 2018). The Task Force recommended that *"use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available"* (Grade III recommendation). This recommendation differs from the 2013 guidelines, in

which it was recommended that *"in case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered"* (Grade IIa recommendation).

In 2016, the French Society of Hypertension, an affiliate of the French Society of Cardiology, published the expert consensus statement in the management of resistant hypertension (Denolle 2016). They recommended that *"because renal denervation is still undergoing assessment for the treatment of hypertension, it is suggested this technique should only be proposed by a multidisciplinary team in a specialist hypertension clinic."* (Class 1, Level C, Grade +++).

The Task Force of the Hypertension Committee and the Guideline Committee of the Taiwan Society of Cardiology and the Taiwan Hypertension Society published the guidelines for the management of hypertension in 2022. They recommended that *"renal denervation can be considered as a BP-lowering strategy in hypertensive patients with high CV risk, such as resistant or masked uncontrolled hypertension, established ASCVD, intolerant or nonadherent to antihypertensive drugs, or features indicative of neurogenic hypertension after careful clinical and imaging evaluation (COR IIa, LOE B)."* This recommendation differs from the 2015/2017 guidelines, in which it was recommended that *"use of device-based therapies is not recommended for the routine treatment of hypertension."*

In 2022, the Malaysian working group published the consensus statement on renal denervation for arterial hypertension. The working group recommended that "*RDN can be considered for the following patients. Particular emphasis is made with regard to patient selection which is a key determinant of RDN suitability and success.*

- *Treatment resistant hypertension: Treatment resistant hypertension is able to achieve long-term reduction in BP with good safety.*
- *Non-adherence to multiple medications: Persistent BP-lowering effect of RDN would thus theoretically reduce the negative consequences of partial and even full non-adherence on clinical outcomes in hypertensive patients.*
- *Patient on polypharmacy for multiple comorbidities.*
- *Hypertensive patients with hyperactive renal sympathetic component.*"

In 2022, the Spanish Society of Hypertension-Spanish League for Combating High Blood Pressure (SEH-LELHA), and the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) published a joint position statement.

For resistant hypertension, they stated that *"If the BP lowering effect and the safety of RSD are maintained in the long term, RSD might be an alternative to the addition of more antihypertensive medications in patients with R-HTN."*

For uncontrolled hypertension, they mentioned that *"the concept of uncontrolled HTN includes a high percentage of hypertensive patients (maybe even > 60%) with highly heterogenous clinical characteristics and cardiovascular risk. Given the invasive nature of the RSD procedure, and until more information becomes available on the reduction of cardiovascular events in more specific subgroups of patients, there are some high-risk situations in which BP control is essential to reduce the risk of cardiovascular events:*

a) Patients with frequent hypertensive crises.

b) Patients with low compliance to pharmacological treatment.

c) Patients with hypertension-mediated organ damage.

d) Patients at high cardiovascular risk."

They also recommended that *"[RDN] procedures should be performed at centres with proven experience only and that, in centres that lack this experience, the possibility of monitoring should be available including assistance during the patient selection process and supervision of the procedure until enough experience is gained to ensure optimal results."*

The Italian Society of Arterial Hypertension (SIIA) published a position paper in 2022. The authors of this paper recommended that based on a patient-centred principle, *"the concept of difficult-to-treat hypertension is abandoned in favour of the concept of the difficult-to-treat patient. In carefully selected patients undergoing this kind of diagnostic-therapeutic process at specialist hypertension centres, RDN may be offered as a treatment option."* The authors fully agreed with ESC/ESH guidelines on the fact that, given the current uncertainties, the selection process for RDN should be performed only at highly specialised hypertension centres, which should meet a set of minimum requirements.

In 2022, the position of renal denervation in treatment of hypertension: an expert consensus statement was published. Authors concluded that *"established treatment indications are available for which RDN could improve routine clinical practice".* Authors believed that *"RDN could be a valid adjunct treatment option in patients with primary hypertension who do not meet guideline-advised OBP and ABP criteria despite the use of 3 or more antihypertensive drugs (including a diuretic), or in those with a documented intolerance to at least 3 different antihypertensive drug classes. Careful preprocedural workup including multimodal diagnostic testing as well as postprocedural follow-up visits are strongly recommended."*

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

NICE guidelines

- Hypertension in adults: Diagnosis and management of hypertension in adults in primary care. NICE guideline 136 (2019). Available from https://www.nice.org.uk/guidance/ng136

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

Four professional expert questionnaires for percutaneous transluminal renal sympathetic denervation for resistant hypertension were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- Global SYMPLICITY Registry (GSR) Denervation Findings in Real World (DEFINE; NCT01534299). International. Observational (case-only). Estimated enrollment, n=5,000. Estimated study completion date, October 2027.
- SPYRAL HTN-ON MED Study (NCT02439775). International. RCT. Actual enrollment, n=337. Estimated study completion date, July 2026.
- SPYRAL AFFIRM Global Study of RDN With the Symplicity Spyral RDN System in Subjects with Uncontrolled HTN (NCT05198674). US and Germany. Clinical trial (single group assignment). Estimated enrollment, n=1,200. Estimated study completion date, June 2027.

References

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5. Azizi M, Sanghvi K, Saxena M et al. (2021) Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet (London, England) 397(10293): 2476-86
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7. Bhatt DL, Vaduganathan M, Kandzari DE et al. (2022) Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. Lancet (London, England)
8. Mahfoud F, Bohm M, Schmieder R et al. (2019) Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. European Heart Journal 40(42): 3474-82
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10. Sharp ASP, Davies JE, Lobo MD et al. (2016) Renal artery sympathetic denervation: observations from the UK experience. Clinical research in cardiology: official journal of the German Cardiac Society 105(6): 544-52
11. Fengler K, Reimann P, Rommel KP et al. (2021) Comparison of long-term outcomes for responders versus non-responders following renal denervation in resistant hypertension. Journal of the American Heart Association 10(21): e022429

12. Lobo MD, Sharp ASP, Kapil V et al. (2019) Joint UK societies' 2019 consensus statement on renal denervation. Heart 105: 1456-63

13. Schmieder RE, Mahfoud F, Mancia G et al. (2021) European Society of Hypertension position paper on renal denervation 2021. Journal of Hypertension, 39(9), 1733-41.

14. Williams B, Mancia G, Spiering W et al. (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 39: 3021-104

15. Denolle T, Chamontin B, Doll G et al. (2016) Management of resistant hypertension: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. Journal of Human Hypertension 30: 657-663

16. Wang TD, Chiang CE, Chao TH et al. (2022) 2022 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension. Acta Cardiologica Sinica 38(3): 225-325

17. Chia YC, Wan Ahmad WA, Fong AYY et al. (2022) 2022 Malaysian working group consensus statement on renal denervation for management of arterial hypertension. Hypertension research: official journal of the Japanese Society of Hypertension 45(7): 1111-22

18. Rodríguez-Leor O, Jaén-Águila F, Segura J et al. (2022) Renal Denervation for the Management of Hypertension. Joint Position Statement from the SHE-LELHA and the ACI-SEC'. REC: Interventional Cardiology (English Edition), February, 6990. https://doi.org/10.24875/RECICE.M21000235

19. Bruno RM, Taddei S, Borghi C et al. (2020) Italian Society of Arterial Hypertension (SIIA) position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient. High Blood Pressure & Cardiovascular Prevention: The Official Journal of the Italian Society of Hypertension 27 (2): 109–17

20. Zeijen VJM, Kroon AA, van den Born BH et al. (2022a) The position of renal denervation in treatment of hypertension: an expert consensus statement. Netherlands Heart Journal: Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, August.

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	12/10/2022	1946 to October 11, 2022
MEDLINE In-Process (Ovid)	12/10/2022	1946 to October 11, 2022
MEDLINE Epubs ahead of print (Ovid)	12/10/2022	1946 to October 11, 2022
EMBASE (Ovid)	12/10/2022	1974 to 2022 October 11
EMBASE Conference (Ovid)	12/10/2022	1974 to 2022 October 11
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/10/2022	Issue 10 of 12, October 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/10/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	14/10/2022	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

1 exp Hypertension/
2 hypertens*.tw.
3 ((high* or raise* or elevat* or increase*) adj4 (arterial* or blood or diastolic* or systolic*) adj4 pressure*).tw.
4 (HPB or SBP or DBP).tw.
5 or/1-4
6 exp Sympathectomy/
7 Sympathetic Nervous System/
8 denervation/
9 catheter ablation/
10 or/6-9
11 Kidney/
12 Renal Artery/
13 (Kidney or Renal).tw.
14 or/11-13
15 10 and 14
16 ((kidney* or renal) adj4 (denervat* or sympathe* or catheter* or ablat* or neurectom* or neurotom*)).tw.
17 (RSD or RDN).tw.
18 (catheter* adj4 (renal or kidney) adj4 (denervat* or ablation*)).tw. 404
19 symplicit*.tw.
20 or/16-19
21 5 and 20
22 Spyral.tw.

23 21 or 22
24 animals/ not humans/
25 23 not 24
26 limit 25 to english language
27 limit 26 to ed= 20200901-20221031

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. Because of the size of the evidence base, the following studies are not listed in the appendix: review articles, observational studies with less than 50 patients and 3-year follow up, and studies in which RDN combined with other treatments other than antihypertensive medications. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Agasthi P, Shipman J, Arsanjani R et al. (2019) Renal denervation for resistant hypertension in the contemporary era: a systematic review and meta-analysis. Scientific reports 9(1): 6200	Systematic review and meta-analysis n=15 studies (1,473 patients) follow up: 6 months	Based on the current evidence, patients with resistant hypertension and no identifiable secondary cause (renovascular or renal parenchymal disease, etc.), maximised on lifestyle interventions and medical therapy by a hypertension specialist may benefit from renal denervation with an experienced operator.	All relevant studies of percutaneous transluminal RDN for resistant hypertension included in this systematic review were included in Pisano (2021).
Ahmad Y, Francis DP, Bhatt DL et al. (2021) Renal denervation for hypertension: a systematic review and meta-analysis of randomized, blinded, placebo-controlled trials. JACC: Cardiovascular	Systematic review and meta-analysis n=7 studies (1,368 patients)	The randomised placebo-controlled trials show consistently that renal denervation provides significant reduction in ambulatory and office blood pressure. Although the magnitude of benefit, about 4/2 mmHg, is modest, it	All studies in this study were included in Pisano (2021) and the outcomes for resistant hypertension were not reported separately.

Interventions 14(23): 2614-24		is similar between patients on background antihypertensive medications and those who are not. Denervation could therefore be a useful strategy at various points for patients who are not willing to add antihypertensive agents. Whether the effect changes with time is currently unknown.	
Ahmad Y, Kane C, Arnold AD et al. (2022) Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: a meta-analysis. Cardiovascular Revascularization Medicine 34: 112-8	Meta-analysis n=6 studies follow up: 6 months	The totality of blinded, randomized placebo-controlled data shows that renal denervation is safe and provides genuine reduction in blood pressure for at least 6 months post-procedure. If this effect continues in the long term, renal denervation might provide a life-long 10% relative risk reduction in major adverse cardiac events and 7.5% relative risk reduction in all-cause mortality.	All relevant studies of percutaneous transluminal RDN for resistant hypertension in this meta-analysis were included in Pisano (2021) and the outcomes for resistant hypertension were not reported separately.
Ahmed M, Nudy M, Bussa R et al. (2022) A systematic review, meta-analysis, and meta regression of the sham controlled renal denervation randomized controlled trials. Trends in	Systematic review and meta-analysis n=1,544 (10 RCTs)	Compared to a sham procedure, RD was associated with statistically significant reductions in most measures of SBP and DBP that were within bounds of what would be expected from standard blood pressure lowering medications.	Five studies specifically for resistant hypertension are included in the key evidence (Pisano 2021; Azizi 2021; Kario 2022), 1 study (SPYRAL HTN-ON MED pilot) for uncontrolled hypertension in

Cardiovascular Medicine			the appendix, and 4 studies do not meet the inclusion criteria due to indication or procedure.
Aripov M, Mussayev A, Alimbayev S et al. (2017) Individualised renal artery denervation improves blood pressure control in Kazakhstani patients with resistant hypertension. Kardiologia polska 75(2): 101-7	Case series (Kazakhstani Registry) n=63 follow up: 12 months	In this population renal artery denervation resulted in statistically and clinically significant blood pressure reduction at 12 months with minimal adverse events.	Studies with larger samples and better designs are included in the key evidence.
Azizi M, Pereira H, Hamdidouche I et al. (2016) Adherence to antihypertensive treatment and the blood pressure-lowering effects of renal denervation in the renal denervation for hypertension (DENERHTN) trial. Circulation 134(12): 847-57	RCT n=106 (RDN, n=53; control, n=53) follow up: 6 months	In the DENERHTN trial, the prevalence of nonadherence to antihypertensive drugs at 6 months was high (≈50%) but not different in the renal denervation and control groups. Regardless of adherence to treatment, renal denervation plus standardised stepped-care antihypertensive treatment resulted in a greater decrease in blood pressure than standardised stepped-care antihypertensive treatment alone.	DENERHTN was included in Pisano (2021).
Azizi M, Sapoval M, Gosse P et al. (2015) Optimum and stepped care standardised antihypertensive	RCT n=106 (RDN, n=53; control, n=53)	In patients with well-defined resistant hypertension, renal denervation plus a standardised stepped-care	This study was included in Pisano (2021).

treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet (London, England) 385(9981): 1957-65	follow up: 6 months	antihypertensive treatment (SSAHT) decreases ambulatory blood pressure more than the same SSAHT alone at 6 months. This additional blood pressure lowering effect may contribute to a reduction in cardiovascular morbidity if maintained in the long term after renal denervation.	
Azretovich YA, Dzhoshibaev S, Baymagambetov AK et al. (2016) Experience of one-electrode symplicity flex catheter and multi-electrode symplicity spyral catheter in Kazakhstan. Research Journal of Pharmaceutical, Biological and Chemical Sciences 7(4): 2698-704	Non-randomised comparative study n=58 (one-electrode Symplicity Flex catheter, n=44; multi-electrode Symplicity Spyral catheter, n=14) follow up: 6 months	Application of multi-electrode catheter in clinical practice helps to significantly reduce the total duration of intervention and improve efficiency.	Small sample
Bakris GL, Townsend RR, Liu M et al. (2014) Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. Journal of the American College of Cardiology 64(11): 1071-8	RCT n=535 (RDN, n=364; sham, n=171) follow up: 6 months	The current trial confirms the safety of renal denervation with the Symplicity catheter; however, a significant BP-lowering effect on 24-h ambulatory BP was not observed. Further clinical research using rigorous trial design will be required to understand whether renal denervation has any role in the	SYMPLICITY HTN-3 was included in Pisano (2021).

		treatment of resistant hypertension.	
Bakris GL, Townsend RR, Flack J M et al. (2015) 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension: the SYMPLICITY HTN-3 trial. Journal of the American College of Cardiology 65(13): 1314-21	RCT n=535 (RDN, n=364; crossover, n=101; non-crossover, n=70) Follow up: 12 months	The data support no further reduction in office or ambulatory BP after 1-year follow-up. Loss of BP reduction in the non-crossover group may reflect decreased medication adherence or other related factors.	SYMPLICITY HTN-3 was included in Pisano (2021).
Beeftink MMA, Spiering W, De Jong MR et al. (2017) Renal denervation beyond the bifurcation: The effect of distal ablation placement on safety and blood pressure. Journal of clinical hypertension (Greenwich, Conn.) 19(4): 371-8	Case series (registry) n=97 follow up: 12 months	Authors found no reason to believe that renal denervation distal to the bifurcation poses additional risks over the currently advised approach of proximal denervation, but improved efficacy remains to be conclusively established.	Studies with larger samples and better designs are included in the key evidence.
Bergland OU, Soraas CL, Larstorp ACK, et al. (2020). The randomised Oslo study of renal denervation vs. Antihypertensive drug adjustments: efficacy and safety through 7 years of follow-up. Blood Pressure. 30(1): 41-50.	Long-term follow up of Oslo RDN (2014) n=19 (RDN, n=9; drug adjustment group, n=10) Follow up: 7 years	BP changes up to 7 years show a tendency towards a smaller difference in BPs between the RDN and drug adjustment patients. Our data support RDN as a safe procedure, but it remains non-superior to intensive drug adjustment 7 years after the intervention.	Oslo RDN was included in Pisano (2021)

Bergland OU, Soraas CL, Larstorp ACK et al. (2021) The randomised Oslo study of renal denervation vs. antihypertensive drug adjustments: efficacy and safety through 7 years of follow-up. Blood pressure 30(1): 41-50	RCT n=19 (RDN, n=9; drug adjustment, n=10) follow up: 7 years	Blood pressure changes up to 7 years show a tendency towards a smaller difference in BPs between the RDN and drug adjustment patients. The data support RDN as a safe procedure, but it remains non-superior to intensive drug adjustment 7 years after the intervention.	Oslo RDN was included in Pisano (2021).
Bergland OU, Larstorp ACK, Lund Soraas C et al. (2021) Changes in sympathetic nervous system activity after renal denervation: results from the randomised Oslo RDN study. Blood pressure 30(3): 154-64	RCT n=19 (RDN, n=9; drug adjustment, n=10) follow up: 6 months	The data suggest that RDN reduces SNS activity after 6 months. The finding warrants investigation in a larger study.	Oslo RDN was included in Pisano (2021).
Bhatt DL, Kandzari DE, O'Neill WW et al. (2014) A controlled trial of renal denervation for resistant hypertension. The New England journal of medicine 370(15): 1393-401	RCT n=535 (RDN, n=364; sham, n=171) follow up: 6 months	This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control.	This study was included in Pisano (2021).
Bohm M, Mahfoud F, Ukena C et al. (2015) First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled	Case series (Global SYMPLICITY Registry) n=998 follow up: 6 months	Renal denervation was associated with low rates of adverse events. After the procedure through 6 months, there was 1 new renal artery stenosis >70% and 5 cases of hospitalisation for a	Analysis of this registry with a larger sample (Mahfoud 2019) is included in the key evidence.

hypertension. Hypertension (Dallas, Tex.: 1979) 65(4): 766-74		hypertensive emergency. In clinical practice, renal denervation resulted in significant reductions in office and 24-hour BPs with a favourable safety profile. Greater BP-lowering effects occurred in patients with higher baseline pressures.	
Bohm M, Ukena C, Ewen S et al. (2016) Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry. Journal of hypertension 34(12): 2480-6	Case series (registry) n=846 follow up: 12 months	RDN reduces BP independent from HR. A HR reduction is dependent on baseline HR and unchanged by b-blocker treatment. The effects of RDN on SBP and HR are durable up to 1 year. HR reduction might be a target for RDN in patients with high HR at baseline, which needs to be scrutinized in prospective trials	Analysis of this registry with a larger sample (Mahfoud 2019) is included in the key evidence.
Brandt MC, Reda S, Mahfoud F et al. (2012) Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. J Am Coll Cardiol. 60(19): 1956-65	Non-randomised comparative study n=120 (RDN, n=110; control, n=10) follow up: 6 months	Besides the known effect of RD on brachial blood pressure, the study showed for the first time that this novel approach significantly improves arterial stiffness and central hemodynamics, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk.	Studies with larger samples or better designs are included in the key evidence.

Cai,H, Fang Z, Lin R et al. (2022) Insight on efficacy of renal artery denervation for refractory hypertension with chronic kidney diseases: a long-term follow-up of 24-hour ambulatory blood pressure. Journal of Interventional Cardiology 2022: 6895993	Non-randomised comparative study n=54 Follow up: 48 months	RDN can safely reduce SBP in CKD patients combined with RHT for 48 months, with the most pronounced reduction in the GFR15 to 45 ml/min group. The variety of antihypertensive drugs was significantly reduced after RDN. This was particularly evident in patients with GFR 15 to 45 ml/min	Studies with larger samples or better designs are included in the key evidence.
Chen S, Kiuchi MG, Schmidt B et al. (2019) Renal denervation for mild-moderate treatment-resistant hypertension: A timely intervention? Herz 44(5): 412-8	Meta-analysis n=4 studies (185 patients) follow up: 6 months	New antihypertensive strategies to achieve better BP control even in less severe forms of RH are needed and should be carefully evaluated. RDN appears to be an effective and safe therapeutic option for patients with MMRH. However, the data from this patient group remain preliminary and need to be validated in large randomised studies with long-term follow up.	Meta-analysis with a larger sample is included in the key evidence. Of the 4 studies, 1 RCT was included in Pisano (2021) and 3 studies were case series with small samples.
Chen S, Kiuchi MG, Acou WJ et al. (2017) Feasibility of catheter ablation renal denervation in "mild" resistant hypertension. Journal of clinical hypertension (Greenwich, Conn.) 19(4): 361-8	Meta-analysis n=3 studies follow up: 6 months	The present study suggests that RDN seems feasible to treat mild RH. Further research of RDN in this patient group is needed.	Meta-analysis with a larger sample is included in the key evidence. Of the 3 studies, 1 RCT was included in Pisano (2021), and 2 studies were case series with small samples.

Chen W, Ling Z, Du H et al. (2016) The effect of two different renal denervation strategies on blood pressure in resistant hypertension: Comparison of full-length versus proximal renal artery ablation. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 88(5): 786-95	RCT n=47 (full-length ablation, n=23; proximal ablation, n=24) follow up: 12 months	The results indicate that proximal RDN has a similar efficacy and safety profile compared with full-length RDN, and propose the proximal artery as the key portion for RDN.	RCTs with larger samples are included in the key evidence.
Cheng XCh, Zhang DY, Luo SX et al. (2019) Effect of catheter-based renal denervation on uncontrolled hypertension: a systematic review and meta-analysis. Mayo Clinic proceedings 94(9): 1695-706	Systematic review and meta-analysis n=12 studies	Catheter-based RDN was associated with a significant BP-lowering benefit without increasing major adverse events.	All relevant studies of percutaneous transluminal RDN for resistant hypertension in this systematic review were included in Pisano (2021) and the outcomes for resistant hypertension were not reported separately.
Coppolino G, Pisano A, Rivoli L et al. (2017) Renal denervation for resistant hypertension. The Cochrane database of systematic reviews 2: cd011499	Cochrane review n=12 RCTs	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	The updated review (Pisano 2021) is included in the key evidence.

		not change blood pressure and low-quality evidence that it caused an increase of bradycardia episodes. Future trials measuring patient-centred instead of surrogate outcomes, with longer follow-up periods, larger sample size and more standardised procedural methods are necessary to clarify the utility of this procedure in this population.	
Daemen J, Mahfoud F, Kuck KH et al. (2019) Safety and efficacy of endovascular ultrasound renal denervation in resistant hypertension: 12-month results from the ACHIEVE study. Journal of hypertension 37(9): 1906-12	Case series n=96 follow up: 12 months	The therapy appeared safe and resulted in sustained reductions in both office BP and 24-h ambulatory BP through 12 months	Small sample
Dahal, K., Khan, M., Siddiqui, N. et al. (2020) Renal denervation in the management of hypertension: a meta-analysis of sham-controlled trials. Cardiovascular Revascularization Medicine 21(4): 532-537	Meta-analysis n=7 sham-controlled trials	Current meta-analysis shows that RD reduces ambulatory BP and office DBP in patients with hypertension. Future trials with longer follow-up should confirm these findings	All relevant studies of percutaneous transluminal RDN for resistant hypertension in this meta-analysis were included in Pisano (2021). The outcomes for resistant hypertension were not reported separately.

de Jager RL, van Maarseveen EM, Bots ML et al. (2018) Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial. British journal of clinical pharmacology 84(1): 18-24	Substudy of SYMPATHY n=98 Follow up: 6 months	Objective methodology, using a bioanalytical screening assay, to assess adherence to BP lowering drugs, provides a valuable tool to define true resistant hypertension and, when applicable, refine a treatment plan in consultation with the patient.	SYMPATHY was included in Pisano (2021).
de Sousa Almeida M, de Araujo Goncalves P, Branco P et al. (2016) Impact of renal sympathetic denervation on left ventricular structure and function at 1-year follow-up. PloS one 11(3): e0149855	Case series n=57 follow up: 12 months	In this study, renal denervation was associated with significant reduction in both office and ABPM blood pressure and a significant decrease in left ventricle mass evaluated by transthoracic echocardiogram at 1 year follow-up.	Studies with larger samples and better designs are included in the key evidence.
Denegri A, Naduvathumuriyil T, Luscher TF et al. (2018) Renal nerve ablation reduces blood pressure in resistant hypertension: Long-term clinical outcomes in a single-center experience. Journal of clinical hypertension (Greenwich, Conn.) 20(4): 627-33	Case series n=57 follow up: 24 months	In this study, in all patients with resistant hypertension, RNA, if performed adequately in the number of ablations and energy delivery, is an efficient and safe treatment option to lower office and 24-hour blood pressure. Whether these blood pressure–lowering effects will lead to a reduction of cardiovascular morbidity and mortality will require further studies.	Studies with larger samples or better designs are included in the key evidence.

Desch S, Okon T, Heinemann D et al. (2015) Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension (Dallas, Tex.: 1979) 65(6): 1202-8	RCT n=71 (RDN, n=35; sham, n=36) follow up: 6 months	In patients with mild resistant hypertension, renal sympathetic denervation failed to show a significant reduction in the primary end point of 24-hour systolic BP at 6 months between groups in the intention to treat analysis.	This study was included in Pisano (2021).
Dorr O, Liebetrau C, Mollmann H et al. (2016) Long-term verification of functional and structural renal damage after renal sympathetic denervation. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 87(7): 1298-303	Case series n=62 Follow up: 36.9 months	The results of the present study show a sustained effect of RSD on BP reduction after a three-year follow-up, and there was no evidence of renal failure. These results provide verification of the long-term safety and effectiveness of RSD, even in patients with impaired renal function.	Small sample
Fadl Elmula FEM, Jin Y, Yang WY et al. (2015) Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension. Blood pressure 24(5): 263-74	Meta-analysis n=7 studies follow up: 6 months	In selected rHT patients maintained on antihypertensive drugs, RDN with the SYMPLICITY systems does not significantly decrease BP but is safe. Future trials with next-generation catheters should aim at identifying responders in patients with evidence of sympathetic nervous overactivity.	All studies were included in Pisano (2021).

Esler MD, Bohm M, Sievert H et al. (2014) Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. European heart journal 35(26): 1752-9	RCT n=106 (RDN, n=52; control, n=54) follow up: 36 months	Renal denervation resulted in sustained lowering of blood pressure at 3 years in a selected population of subjects with severe, treatment-resistant hypertension without serious safety concerns.	This study was included in Pisano (2021).
Ewen S, Dorr O, Ukena C et al. (2015) Blood pressure variability after catheter-based renal sympathetic denervation in patients with resistant hypertension. Journal of hypertension 33(12): 2512-8	Case series n=84 follow up: 6 months	RDN reduces office and ambulatory BP and BP variability in patients with resistant hypertension. Improvement in BP variability was also documented in patients characterized as office BP non-responders after 6 months.	Studies with larger samples or better designs are included in the key evidence.
Ewen S, Mahfoud F, Linz D et al. (2014) Effects of renal sympathetic denervation on exercise blood pressure, heart rate, and capacity in patients with resistant hypertension. Hypertension 63(4): 839-45	Non-randomised comparative study n=60 (RDN, n=50; control, n=10) follow up: 12 months	Renal denervation reduced blood pressure and heart rate during exercise, improved mean workload, and increased exercise time without impairing chronotropic competence.	Small sample
Ewen S, Meyer MR, Cremers B et al. (2015) Blood pressure reductions following catheter-	Non-randomised comparative studies	Renal denervation can reduce office and ambulatory blood pressure in patients with resistant	Studies with larger samples or better designs are included in the key evidence.

based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis. Clinical research in cardiology: official journal of the German Cardiac Society 104(12): 1097-105	n=100 (adherent, n=52; non-adherent, n=48) follow up: 6 months	hypertension despite a significant reduction in adherence to antihypertensive treatment after 6 months.	
Fadl Elmula FEM, Feng YM, Jacobs L et al. (2017) Sham or no sham control: that is the question in trials of renal denervation for resistant hypertension. A systematic meta-analysis. Blood pressure 26(4): 195-203	Meta-analysis n=10 studies follow up: 6 months	The overall meta-analysis of 10 randomized and controlled studies showed no significant effect on BP of RDN in resistant hypertension. Moreover, the analysis does not support the use of sham control but rather suggests extensive use of 24-hour ambulatory BP in studies of RDN in resistant hypertension.	All studies in this meta-analysis were included in Pisano (2021).
Fengler, Karl, Ewen, Sebastian, Hollriegel, Robert et al. (2017) Blood pressure response to main renal artery and combined main renal artery plus branch renal denervation in patients with resistant hypertension. Journal of the	Non-randomised comparative studies n=50 (combined ablation, n=25; main artery ablation, n=25) follow up: 3 months	Combined ablation of the main renal artery and branches appears to improve BP-lowering efficacy and should be further investigated.	Studies with larger samples or better designs are included in the key evidence.

American Heart Association 6(8)			
Fengler K, Rommel KP, Blazek S et al. (2018) Predictors for profound blood pressure response in patients undergoing renal sympathetic denervation. Journal of hypertension 36(7): 1578-84	Non-randomised comparative studies n=190 (profound BP response, n=33; no or regular BP response, n=157) follow up: 3 months	Younger vascular age, higher baseline BP, treatment with ultrasound RDN and combined diuretic therapy were found as predictors for a pronounced BP reduction following RDN, improving BP control at follow-up.	Studies with larger samples or better designs are included in the key evidence.
Fengler K, Rommel KP, Lapusca R et al. (2019) Renal denervation in isolated systolic hypertension using different catheter techniques and technologies: insights from a randomized trial. Hypertension 74(2): 341-348	Post-hoc analysis of RCT n=120 follow up: 3 months	Using adjusted BP values, RDN seems to be equally effective in patients with ISH and CH, irrespective of the RDN technology and technique used. The role and potential of RDN in ISH patients should be evaluated in appropriately designed trials. In the meantime, the quest for the ideal candidate for RDN continues.	RADIOSOUND-HTN is included in the key evidence (Fengler 2019)
Fengler K, Hollriegel R, Okon T et al. (2017) Ultrasound-based renal sympathetic denervation for the treatment of therapy-resistant hypertension: a single-center experience. Journal of hypertension 35(6): 1310-7	Non-randomised comparative studies n=50 (responder, n=31; non-responder, n=19) follow up: 6 months	Ultrasound-based RDN seems to be well tolerated and effective for the treatment of patients with therapy-resistant hypertension.	Studies with larger samples or better designs are included in the key evidence.
Fengler K, Rommel KP, Lapusca R et al. (2019) Renal	Post-hoc analysis of RADIOSOUND-HTN	Using adjusted BP values, RDN seems to be equally	RADIOSOUND-HTN is included in

denervation in isolated systolic hypertension using different catheter techniques and technologies: insights from a randomized trial. Hypertension 74(2): 341-8	n=120 (USM-RDN, n=42; RFM-RDN, n=39; RFB-RDN, n=39) follow up: 3 months	effective in patients with ISH and CH, irrespective of the RDN technology and technique used. The role and potential of RDN in ISH patients should be evaluated in appropriately designed trials. In the meantime, the quest for the ideal candidate for RDN continues.	the key evidence (Fengler 2019)
Fengler K, Rommel KP, Hoellriegel R et al. (2017) Pulse wave velocity predicts response to renal denervation in isolated systolic hypertension. Journal of the American Heart Association 6(5)	Non-randomised comparative study n=109 (combined hypertension, n=69; isolated systolic hypertensin, n=40) follow up: 3 months	Extended assessment of arterial stiffness can help improve patient preselection for renal sympathetic denervation and identify a subgroup of isolated systolic hypertension patients who benefit from sympathetic modulation.	Studies with larger samples or better designs are included in the key evidence.
Flack JM, Bhatt DL, Kandzari DE et al. (2015) An analysis of the blood pressure and safety outcomes to renal denervation in African Americans and Non-African Americans in the SYMPLICITY HTN-3 trial. Journal of the American Society of Hypertension: JASH 9(10): 769-79	Subgroup analysis of SYMPLICITY HTN-3 trial n=140 (RSN, n=90; sham, n=50) follow up: 6 months	AA race did not independently predict SBP response in either sham or RDN. There appears to be effect modification by race with individual-level patient characteristics in both treatment arms that affect the observed pattern of SBP responses.	SYMPLICITY HTN-3 trial was included in Pisano (2021).
Gao JQ, Zhang H, Li LY et al. (2021) Comparison of a 5 F microtube-irrigated	Non-randomised comparative study	The microtube-irrigated ablation catheter is more effective in treating	Studies with larger samples or better designs are

ablation catheter and a general ablation catheter in the treatment of resistant hypertension with renal denervation. Cardiovascular Innovations and Applications 6(2): 81-89	n=65 follow up: 12 months	hypertension than the general ablation catheter at the 6-month follow up and thus fewer antihypertensive drugs were used in the microtube-irrigated ablation catheter group than in the general ablation catheter group.	included in the key evidence.
Gosain P, Garimella PS, Hart PD et al. (2013) Renal sympathetic denervation for treatment of resistant hypertension: a systematic review. Journal of clinical hypertension (Greenwich, Conn.) 15(1): 75-84	Systematic review n=19 studies (2 RCTs, 4 case-control studies, and 13 case series published between 2009 and 2012)	Data from short-term studies suggest that RSD is a safe and effective therapeutic option in carefully selected patients with resistant hypertension. Long-term studies with large patient populations are needed to study whether this benefit is sustained with a demonstrable difference in cardiovascular disease event rates.	Both RCTs referred to SYMPLICITY HTN-2 and were included in Pisano (2021). No meta-analyses were performed. More recent RCTs were included in Pisano (2021).
Gosse P, Cremer A, Pereira H et al. (2017) Twenty-four-hour blood pressure monitoring to predict and assess impact of renal denervation: the DENERHTN study (renal denervation for hypertension). Hypertension (Dallas, Tex.: 1979) 69(3): 494-500	Analysis of DENERHTN n=97 (RDN, n=44; control, n=53) follow up: 6 months	This detailed analysis of ABPM data in the DENERHTN trial confirms the efficacy of RD with the Simplicity flex catheter in addition to a SSAHT in lowering BP in patients with RH, with a homogenous effect over 24 hours. Nighttime SBP and its variability in patients being treated with a renin angiotensin system	DENERHTN was included in Pisano (2021).

		blocker, a thiazide, and a calcium channel blocker seem as the best candidates that can be derived from ABPM recordings to predict responders to RD. Therefore, 24-hour ABPM should systematically precede any decision of RD as recommended by consensus guidelines.	
Hamdidouche I, Gosse P, Cremer A et al. (2019) Clinic versus ambulatory blood pressure in resistant hypertension: impact of antihypertensive medication nonadherence: a post hoc analysis the DENERHTN study. Hypertension (Dallas, Tex.: 1979) 74(5): 1096-1103	Post-hoc analysis of DENERHTN n=97 follow up: 6 months	This analysis indicates that antihypertensive medication nonadherence impacts greatly the clinic-SBP–day-SBP difference in patients with apparent resistant hypertension. Medication nonadherence should be considered in resistant hypertensive patients who have substantially higher clinic SBP recordings than ambulatory or home SBP recordings.	DENERHTN was included in Pisano (2021).
Hamza M and Khamis H (2014) Renal sympathetic denervation for treatment of resistant hypertension: Egyptian experience. J Interven Cardiol 27: 423-7	Case series n=55 follow up: 6 months	In this observational study, catheter-based renal denervation causes sustained blood pressure reduction in patients with resistant hypertension, without serious adverse events.	Small sample

Heradien M, Mahfoud F, Greyling C et al. (2022) Renal denervation prevents subclinical atrial fibrillation in patients with hypertensive heart disease: Randomized, sham-controlled trial. Heart Rhythm	RCT n=80 (RDN, n=42; sham, n=38)	RD reduced incident subclinical atrial fibrillation (SAF) events, SAF burden, and fast atrial fibrillation in patients with hypertensive heart disease. The observed effects may occur independent of BP lowering.	RCTs with larger samples are included in the key evidence. This study included some patients with non-resistant hypertension.
Hering D, Lambert EA, Marusic P et al. (2013) Renal nerve ablation reduces augmentation index in patients with resistant hypertension. Journal of hypertension 31(9): 1893-900	Non-randomised comparative studies n=50 (RDN, n=40; control, n=10)	RDN results in a substantial and rapid reduction in augmentation index, which appears to be independent of BP and muscle sympathetic nerve activity changes. These findings are indicative of a beneficial effect of RDN on arterial stiffness in patients with resistant hypertension and may contribute to the sustained BP-lowering effect of RDN.	Small sample
Hering, Dagmara, Marusic, Petra, Walton, Antony S et al. (2016) Renal artery anatomy affects the blood pressure response to renal denervation in patients with resistant hypertension. International journal of	Non-randomised comparative studies n=91 (65 patients with single renal arteries bilaterally, 16 patients with dual renal arteries on either one or both sides, and 10 patients with other anatomical constellations or	While RDN can be performed safely irrespective of the underlying renal anatomy, the presence of single renal arteries with or without structural abnormalities is associated with a more pronounced BP and muscle sympathetic nerve activity lowering effect than the	Studies with larger samples or better designs are included in the key evidence.

cardiology 202: 388-93	structural abnormalities) follow up: 6 months	presence of dual renal arteries in patients with RH. However, when patients with dual renal arteries received renal nerve ablation in all arteries there was trend towards a greater BP reduction. Insufficient renal sympathetic nerve ablation may account for these differences.	
Id D, Bertog SC, Ziegler AK et al. (2016) Predictors of blood pressure response: Obesity is associated with a less pronounced treatment response after renal denervation. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 87(1): e30-8	Case series n=101 follow up: 6 months	Blood pressure reductions after RDN were more pronounced in patients with higher baseline blood pressure and lower BMI. These findings may have implications regarding patient selection for renal denervation.	Studies with larger samples and better designs are included in the key evidence.
Id D, Kaltenbach B, Bertog S C et al. (2013) Does the presence of accessory renal arteries affect the efficacy of renal denervation? JACC. Cardiovascular interventions 6(10): 1085-91	Non-randomised comparative study n=74 (bilateral single renal arteries, n=54; accessory renal arteries, n=20) follow up: 6 months	BP reduction achieved after renal denervation in patients with accessory renal arteries is less pronounced than in patients with bilateral single renal arteries.	Studies with larger samples and better designs are included in the key evidence.
Ionov MV, Emelyanov IV, Yudina YS et al.	Case series n=22	The RDN shows a pronounced clinical effect in patients with	Small sample

(2021) Renal sympathetic denervation in patients with resistant hypertension. Results of long-term prospective follow-up. Arterial'naya Gipertenziya (Arterial Hypertension) 27(3): 318-32	Follow up: 5 years	resistant HTN up to 5 years, and is not accompanied by an AHT intensification, but is not associated with QoL changes. The initial positive trend for QoL completely harked back after 5 years which may be associated with the development of MACE. The only predictor of RDN positive effect is baseline SBP level.	
Jacobs L, Persu A, Huang QF et al. (2017) Results of a randomized controlled pilot trial of intravascular renal denervation for management of treatment-resistant hypertension. Blood pressure 26(6): 321-31	RCT (INSPiRED pilot trial) n=18 follow up: 6 months	The INSPiRED pilot suggests that RDN with the EnligHTN™ system is effective and safe and generated insights useful for the design of future RDN trials.	INSPiRED was included in Pisano (2021).
Juknevicius V, Berukstis A, Jukneviciene R et al. (2021) Long-term effects of renal artery denervation. Medicina (Kaunas, Lithuania) 57(7)	Case series n=73 follow up: 48 months	Antihypertensive effect after renal denervation lasts up to 48 months with no worsening of arterial stiffness compared to baseline. In this study, polypharmacy was associated with increased arterial stiffness 48 months after the procedure.	Studies with larger samples and better designs are included in the key evidence.
Kaiser L, Beister T, Wiese A et al. (2014) Results of the ALSTER BP real-world registry on renal denervation employing the	Case series (ALSTER BP Registry) n=93	This real-world analysis of renal sympathetic denervation confirms the procedure to be safe and efficient in most patients. Non-responders may	Studies with larger samples and better designs are included in the key evidence.

Symplicity system. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 10(1): 157-65	follow up: 6 months	profit from a second ablation, arguing in favour of the hypothesis that the procedure did not destroy sufficient amounts of sympathetic innervation in these patients. However, repeated denervations may also increase side effects.	
Kandzari DE, Hickey GL, Pocock SJ et al. (2021) Prioritised endpoints for device-based hypertension trials: the win ratio methodology. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 16(18): e1496-e1502	Win ratio analysis of the data from SPYRAL HTN-ON MED pilot study n=80 (RDN, n=38; sham control, n=42)	The win ratio method addresses prior limitations by enabling inclusion of more patient-oriented results while prioritising those endpoints considered most clinically important. Applying these methods to the SPYRAL HTN-ON MED pilot study, RDN was determined to be superior regarding a hierarchical endpoint and a “winner” compared with sham control patients.	Outcomes for resistant hypertension were not reported separately.
Kandzari DE, Bohm M, Mahfoud F et al. (2018) Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial.	RCT n=80 (RDN, n=38; sham, n=42) follow up: 6 months	Renal denervation in the main renal arteries and branches significantly reduced blood pressure compared with sham control with no major safety events. Incomplete medication adherence was common.	Outcomes for resistant hypertension were not reported separately.

Lancet 391(10137): 2346-55			
Karbasi-Afshar R, Noroozian R, Shahmari A et al. (2013) The effect of renal arterial sympathectomy on refractory hypertension. Tehran University Medical Journal 71(3): 179-84	Non-randomised comparative study n=212 (RDN, n=117; control, n=95) follow up: 6 months	It seems that the sympathetic renal denervation can be an effective and safe method for treatment of refractory hypertensive patients indeed of routine medications although further studies with longer follow up duration and more cases are suggested for confirming this issue.	Studies with larger samples and better designs are included in the key evidence.
Kario K, Ogawa H, Okumura K et al. (2015) SYMPLICITY HTN-Japan - first randomized controlled trial of catheter-based renal denervation in Asian patients. Circulation journal: official journal of the Japanese Circulation Society 79(6): 1222-9	RCT n=41 (RDN, n=22; control, n=19) follow up: 6 months	SYMPLICITY HTN-Japan, the first randomized controlled trial of RDN in an Asian population, was underpowered for the primary endpoint analysis and did not demonstrate a significant difference in 6-month BP change between RDN and control subjects.	SYMPLICITY HTN-Japan was included in Pisano (2021).
Kario K, Bhatt DL, Brar S et al. (2015) Effect of catheter-based renal denervation on morning and nocturnal blood pressure: Insights from SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan. Hypertension (Dallas, Tex.: 1979) 66(6): 1130-7	Pooled analysis n=2 studies (576 patients) follow up: 6 months	In SYMPLICITY HTN-3, compared with controls (n=159), patients treated with renal denervation (n=325) experienced a significantly greater change in morning (−7.3±19.8 mm Hg, P<0.001) and night-time (−6.1±18.2 versus −1.6±19.7 mm Hg, P=0.02) but not daytime systolic BP (−7.2±16.2 versus −6.4±18.6	SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan were included in Pisano (2021).

		mm Hg, P=0.67). This same trend was observed in the pooled analysis with HTN-Japan.	
Kario K, Bhatt DL, Kandzari DE et al. (2016) Impact of renal denervation on patients with obstructive sleep apnea and resistant hypertension - insights from the SYMPLICITY HTN-3 Trial. Circulation journal: official journal of the Japanese Circulation Society 80(6): 1404-12	Post-hoc analysis of SYMPLICITY HTN-3 trial n=535 follow up: 6 months	Obstructive sleep apnoea patients appeared to be responsive to renal denervation therapy. However, this hypothesis requires prospective testing.	SYMPLICITY HTN-3 was included in Pisano (2021).
Kario K, Mahfoud F, Kandzari DE et al. (2022) Long-term reduction in morning and nighttime blood pressure after renal denervation: 36-month results from SPYRAL HTN-ON MED trial. Hypertension Research, 15: 1-9	RCT n=80 (RDN, n=38; sham, n=42) of the 80 patients, 46 patients with resistant hypertension (RDN, n=23; sham, n=23) Follow up: 36 months	In summary, morning and nighttime SBP were significantly reduced in patients prescribed at least 3 antihypertensive medications at 36 months in the SPYRAL HTN-ON MED trial after RDN compared to sham control. The results during these times of high sympathetic tone suggest that radiofrequency RDN has significant long-term benefit when the plasma levels of drug concentrations are the lowest and the risk of cardiovascular events is highest.	Small sample
Kario K, Yamamoto E, Tomita H et al.	RCT	SYMPLICITY HTN-Japan is the first	SYMPLICITY HTN-Japan was

(2019) Sufficient and persistent blood pressure reduction in the final long-term results from SYMPLICITY HTN-Japan - safety and efficacy of renal denervation at 3 years. Circulation journal: official journal of the Japanese Circulation Society 83(3): 622-9	n=41 (RDN, n=22; control, n=19) follow up: 36 months	randomised controlled trial to evaluate RDN in an Asian population. Despite the small number of enrolments, results show patients who received RDN therapy maintained SBP reduction out to 36 months.	included in Pisano (2021).
Kim BK, Bohm M, Mahfoud F et al. (2016) Renal denervation for treatment of uncontrolled hypertension in an Asian population: results from the Global SYMPLICITY Registry in South Korea (GSR Korea). Journal of human hypertension 30(5): 315-21	Case series (GSR-Korea registry) n=262 follow up: 12 months	RDN provided a significant reduction in 6- and 12-month office SBP among Asian patients, with a favourable safety profile. The 12-month SBP reduction was larger than that observed in Caucasian patients.	Analysis of this registry with a larger sample was presented in Mahfoud (2019).
Kindermann I, Wedegartner SM, Mahfoud F et al. (2017) Improvement in health-related quality of life after renal sympathetic denervation in real-world hypertensive patients: 12-month outcomes in the Global SYMPLICITY Registry. Journal of clinical	Case series (registry) n=934 follow up: 12 months	Renal denervation was associated with a significant improvement in health-related quality of life, particularly anxiety/ depression.	Analysis of this registry with a larger sample was presented in Mahfoud (2019).

hypertension (Greenwich, Conn.) 19(9): 833-839			
Kiuchi MG, Chen S, Rodrigues PLM et al. (2018) Number of ablated spots in the course of renal sympathetic denervation in CKD patients with uncontrolled hypertension: EnligHTN vs. Standard irrigated cardiac ablation catheter. Hipertension y riesgo vascular 35(2): 54-63	Non-randomised comparative studies n=112 (EnligHTN, n=56; Flexability, n=56) follow up: 6 months	The RSD reduced the mean 24-h ABPM in subjects with CKD and uncontrolled hypertension and improved the renal function in both groups. These effects were more marked and important in subgroups underwent a great number of ablated spots using the SICAC.	Outcomes for resistant hypertension were not reported separately.
Krum H, Schlaich MP, Sobotka PA et al. (2014) Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet (London, England) 383(9917): 622-9	Case series (Symplicity HTN-1) n=88 follow up: 3 years	Changes in blood pressure after RDN persist long term in patients with treatment-resistant hypertension, with good safety.	Studies with larger samples and better designs are included in the key evidence.
Krum HK, Schlaich M, Whitbourn R et al. (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373:1275-81	Case series n=50 follow up: up to 1 year	Catheter-based RDN causes substantial and sustained BP reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the	Small sample

		management of this condition.	
Kwok CS, Loke YK, Pradhan S et al. (2014) Renal denervation and blood pressure reduction in resistant hypertension: A systematic review and meta-analysis. Open Heart 1(1): e000092	Systematic review and meta-analysis n=12 studies (3 RCTs, 8 prospective observational studies and 1 observational study with matched controls) follow up: 3 months	Evidence for the efficacy of renal denervation using catheter-based systems in reducing blood pressure in resistant hypertension is derived from unblinded studies that are at risk of bias. The highest quality single blinded randomised controlled trial did not show efficacy in office blood pressure reduction, although it did meet its safety end point. Future studies investigating the efficacy of renal denervation in the treatment of drug-resistant hypertension should be undertaken in a blinded manner, with sham procedures in the control group and ambulatory monitoring to reduce the potential for bias.	Of the 3 RCTs included in this study, 2 RCTs were included in Pisano (2021) and 1 RCT compared pulmonary vein isolation with RDN with pulmonary vein isolation alone in patients with refractory symptomatic atrial fibrillation and resistant hypertension. Other studies were observational studies with small samples.
Lambert GW, Hering D, Marusic P et al. (2015) Health-related quality of life and blood pressure 12 months after renal denervation. Journal of hypertension 33(11): 2350-8	Non-randomised comparative studies n=97 (resistant hypertension, n=69; pseudoresistent, n=11; masked uncontrolled hypertension, n=17)	These results indicate that in patients with confirmed resistant hypertension, RDN is associated with a reduction in BP and a sustained improvement in mental health-related aspects of QoL.	Studies with larger samples and better designs are included in the key evidence.

	follow up: 12 months		
Lambert T, Nahler A, Reiter C et al. (2015) Influence of pseudo-resistance on the effect of renal denervation on 24-hour ambulatory blood pressure levels. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 86(3): e126-30	Case series n=106 follow up: 6 months	There was a significant BP reduction in almost 60% of patients with true-resistant hypertension, but only in 10% in patients with pseudoresistant hypertension. According to our results, patient selection seems to be crucial for acceptable response rates after RDN.	Studies with larger samples and better designs are included in the key evidence.
Lambert T, Blessberger H, Gammer V et al. (2014) Effects of renal denervation on ambulatory blood pressure measurements in patients with resistant arterial hypertension. Clinical cardiology 37(5): 307-11	Case series n=86 follow up: 6 months	Office BP and AMBP levels can be significantly lowered by RDN in patients with resistant hypertension.	Studies with larger samples and better designs are included in the key evidence.
Lambert T, Nahler A, Reiter C et al. (2015) Frequency of renal artery stenosis after renal denervation in patients with resistant arterial hypertension. The American journal of cardiology 115(11): 1545-8	Case series n=76 follow up: 6 months	The incidence of significant renal artery stenosis 6 months after RAD seems to be very low. However, late-onset development of nonsignificant renal artery narrowing cannot be excluded in some patients and should be anticipated in the case of RAH relapse	Studies with larger samples and better designs are included in the key evidence.

		or worsening of renal function after successful RAD.	
Lauder L, Ewen S, Tzafriri AR et al. (2018) Anatomical and procedural determinants of ambulatory blood pressure lowering following catheter-based renal denervation using radiofrequency. Cardiovascular revascularization medicine: including molecular interventions 19(7ptb): 845-851	Non-randomised comparative study n=150 follow up: 6 months	24h-ambulatory BP lowering was most pronounced in patients with smaller renal artery diameter but not related to renal artery length, accessory arteries or renal artery disease. Further, there was no dose-response relationship observed with increasing number of ablations.	Studies with larger samples and better designs are included in the key evidence.
Lenski D, Kindermann I, Lenski M et al. (2013) Anxiety, depression, quality of life and stress in patients with resistant hypertension before and after catheter-based renal sympathetic denervation. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 9(6): 700-8	Case series n=119 follow up: 6 months	RDN is associated with reduced anxiety and depression, intensity of headache and with improved QOL and stress tolerance in patients with resistant hypertension.	Studies with larger samples and better designs are included in the key evidence.
Linz D, Mancia G, Mahfoud F et al. (2017) Renal artery denervation for treatment of patients with self-	Non-randomised comparative study (Registry)	RDN resulted in significant BP reductions at 6 months in hypertensive patients with and without	Analysis of this registry with a larger sample was presented in Mahfoud (2019).

reported obstructive sleep apnea and resistant hypertension: results from the Global SYMPLICITY Registry. Journal of hypertension 35(1): 148-53	n=1,868 (non-OSA, n=1,663; OSA, n=205) follow up: 6 months	OSA, and regardless of continuous positive airway pressure usage in OSA patients.	
Luo D and Lu CZ (2022) Renal denervation reduces blood pressure and improves cardiac function: results from a 12-month study. BioMed research international 2022: 2620876	Non-randomised comparative study n=26 (RDN, n=13; drugs, n=13) Follow up: 12 months	Both RDN and drug regiments resulted in significant reduction from baseline in SBP/DBP at 12-month follow-up (all p<0.01), and the decline due to 2 interventions showed no statistically significant difference (F=1:64, p=0:213 and F=0:124, p=0:853 for SBP and DBP, respectively). RDN significantly reduced mean LV mass index (LVMI) from 151:43 ± 46:91 g/m2 to 136:02±37:76 g/m^2 (p=0.038) and ejection fraction (LVEF) increased from 57:15 ± 5:49% at baseline to 59:54 ± 4:18% at 12 months (p=0.039). No similar changes were detected in the drug group (P values, 0.90 for EF and 0.38 for LVMI). Renal parameters including BUN, Cr, UA, and eGFR at baseline, 3 months, and 12 months	Small sample

		showed no marked difference.	
Lyu TJ, Li LY, Wang X et al. (2021) Main renal artery plus branch ablation in the treatment of resistant hypertension with renal denervation. Cardiovascular Innovations and Applications 6(2): 91-8	RCT n=60 (main renal artery plus branch ablation, n=30; main renal artery ablation, n=30) Follow up: 2 years	The results of this study show that main renal artery plus branch ablation is a safe interventional method, but there was no obvious advantage on long-term follow-up compared with only main renal artery ablation.	RCTs with larger samples are included in the key evidence.
Mahfoud F, Ukena C, Schmieder RE et al. (2013) Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. Circulation 128(2): 132-40	Non-randomised comparative study n=346 (true resistant, n=303; pseudoresistant, n=43) follow up: 12 months	RDN reduced office BP and improved relevant aspects of ambulatory BP monitoring, commonly linked to high cardiovascular risk, in patients with true-treatment resistant hypertension, whereas it only affected office BP in pseudoresistant hypertension.	Studies with larger samples and better designs are included in the key evidence
Mahfoud F, Bakris G, Bhatt DL et al. (2017) Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. European heart journal 38(2): 93-100	Non-randomised comparative study n=1,103 (isolated systolic hypertension, n=429; combined systolic-diastolic hypertension, n=674) follow up: 6 months	In the hitherto largest analysed population of patients with uncontrolled hypertension considered for RDN therapy, patients with ISH and CH appear to exhibit a reduction in SBP after RDN. However, patients with ISH who underwent RDN in SYMPLICITY HTN-3 and GSR had a significantly smaller reduction in office and ambulatory BPs after RDN than	SYMPLICITY HTN-3 was included in Pisano (2021), and data from the registry were included in Mahfoud (2019).

		patients with CH. There was no difference in response to RDN between the patients with ISH who were younger than or older than 65 years of age. Patients with CH may represent good candidates for testing this procedure.	
Mahfoud F, Kandzari DE, Kario K et al. (2022) Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. The Lancet.	RCT n=80 (RDN, n=38; control, n=42) follow up: 36 months	Radiofrequency RDN compared with sham control produced a clinically meaningful and lasting blood pressure reduction up to 36 months of follow-up, independent of concomitant antihypertensive medications and without major safety events. RDN could provide an adjunctive treatment modality in the management of patients with hypertension.	Outcomes for patients with resistant hypertension were not reported separately.
Makai P, IntHout J, Deinum J et al. (2017) A network meta-analysis of clinical management strategies for treatment-resistant hypertension: making optimal use of the evidence. Journal of general internal medicine 32(8): 921-930	Network meta-analysis n=20 studies (RDN, n=8 studies) follow up: 8 to 24 weeks	When compared to MRA as anchor, darusentan, CAA and RDN are not more effective in achieving a clinically significant reduction in ambulatory blood pressure in individuals with apparent treatment resistant hypertension.	All 8 studies on the effect of RDN for resistant hypertension were included in Pisano (2021).
Mathiassen ON, Vase H, Bech JN et al. (2016) Renal denervation in	RCT (ReSET)	Further, clinical use of RDN for treatment of resistant hypertension should	This study was included in Pisano (2021).

treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. Journal of hypertension 34(8): 1639-47	n=69 (RDN, n=36; sham, n=33) follow up: 6 months	await positive results from double-blinded, SHAM-controlled trials with multipolar ablation catheters or novel denervation techniques.	
Naduvathumuriyil T, Held U, Steigmiller K et al. (2020) Clinical benefits and safety of renal denervation in severe arterial hypertension: A long-term follow-up study. Journal of Clinical Hypertension	Case series n=50 follow up: 36 months	Renal denervation is a safe and effective procedure for patients with treatment-resistant hypertension with a clinically significant antihypertensive effect. Further randomized trials are needed to determine the specific context within which renal denervation should be considered a therapeutic option in antihypertensive care.	Small sample
Neumann JT, Ewen S, Mortensen K et al. (2016) Effects of renal denervation on heart failure biomarkers and blood pressure in patients with resistant hypertension. Biomarkers in medicine 10(8): 841-51	Case series n=157 follow up: 6 months	In this multicentre analysis RDN did significantly reduce systolic BP. However, NT-proBNP, ST-2, galectin-3 and hs-TnI did not correspond to BP reduction 6 months after RDN.	Studies with larger samples and better designs are included in the key evidence.
Ogoyama Y, Tada K, Abe M et al. (2022) Effects of renal denervation on blood pressures in patients with hypertension: a	Systematic review and meta-analysis n=9 studies (1,555 patients)	These data from randomised sham-controlled trials showed that renal denervation significantly reduced all BP metrics in	Outcome for resistant hypertension were not reported separately. All relevant studies in this systematic

systematic review and meta-analysis of randomized sham-controlled trials. Hypertension research: official journal of the Japanese Society of Hypertension 45(2): 210-20		medicated or unmedicated patients with hypertension, including resistant/uncontrolled hypertension. Future trials should investigate the long-term efficacy and safety of renal denervation.	review are included in the key evidence (Pisano 2021; Azizi 2021; Kario 2022).
Oliveras A, Armario P, Clara A et al. (2016) Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study - a randomized controlled trial. Journal of hypertension 34(9): 1863-71	RCT n=24 (RDN, n=11; spironolactone, n=13) follow up: 6 months	Authors conclude that spironolactone is more effective than RDN to reduce 24-h SBP and 24-h DBP in patients with resistant hypertension. Therefore, spironolactone should be the fourth antihypertensive drug to prescribe if deemed well tolerated' in all patients with resistant hypertension before considering RDN.	DENERVHTA was included in Pisano (2021).
Oliveras A, Armario P, Sans L et al. (2018) Organ damage changes in patients with resistant hypertension randomized to renal denervation or spironolactone: The DENERVHTA (Denervacion en Hipertension Arterial) study. Journal of clinical hypertension 20(1): 69-75	RCT n=24 (RDN, n=11; spironolactone, n=13) follow up: 6 months	At 6 months there was a reduction in albuminuria in patients with resistant hypertension treated with spironolactone as compared with renal denervation.	DENERVHTA was included in Pisano (2021).
Orekhov AU, Sabitov YT and	Non-randomised comparative study	The results demonstrated the	Studies with larger samples or better

Karazhanova LK (2022) Renal denervation in resistant hypertension treatment. Bratislavske lekarske listy 123(10): 710-5	n=81 (monopolar catheter, n=36; spiral catheter, n=45) Follow up: 5 years	efficiency and safety of renal denervation in both short-term and long-term follow-up using monopolar and spiral catheters in the treatment of uncontrolled hypertension with combined antihypertensive therapy. The most significant is the demonstrated stability of the effect after the procedure. In addition, the survival rate of the patients with resistant hypertension after the intervention has been carried out.	designs are included in the key evidence.
Ott C, Mahfoud F, Mancia G et al. (2022) Renal denervation in patients with versus without chronic kidney disease: results from the Global SYMPLICITY Registry with follow-up data of 3 years. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 37(2): 304-10	Case series (registry) n=1,980 follow up: 3 years	After adjusting for baseline data, 24-h systolic and diastolic ABP reduction were similar in patients with and without CKD after RDN, whereas office systolic but not diastolic BP was reduced less in patients with CKD. Authors conclude that RDN is an effective antihypertensive treatment option in CKD patients.	Mahfoud (2019) included a larger sample (n=2,237) from the Global SYMPLICITY Registry.
Ott C, Mahfoud F, Schmid A et al. (2013) Renal	Case series	The data indicate that RDN may reduce office and 24-	Small sample

denervation in moderate treatment-resistant hypertension. Journal of the American College of Cardiology 62(20): 1880-6	n=54 follow up: 6 months	h ambulatory BP substantially in patients with moderate treatment-resistant hypertension.	
Ott C, Franzen KF, Graf T et al. (2018) Renal denervation improves 24-hour central and peripheral blood pressures, arterial stiffness, and peripheral resistance. Journal of clinical hypertension (Greenwich, Conn.) 20(2): 366-72	Case series n=94 follow up: 12 months	The results suggest that RDN improves both peripheral and central BP, as well as aortic stiffness and total vascular resistance in 24-hour measurements under ambulatory conditions. Hence, RDN may improve CV prognosis of patients with true treatment resistant hypertension.	Studies with larger samples and better designs are included in the key evidence.
Ott C, Schmid A, Toennes SW et al. (2015) Central pulse pressure predicts BP reduction after renal denervation in patients with treatment-resistant hypertension. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 11(1): 110-6	Case series n=63 follow up: 6 months	The data suggest that cPP, indicative of the degree of large arterial stiffening, may be helpful to identify responders to RDN	Studies with larger samples and better designs are included in the key evidence.
Panchavinnin P, Wanthong S, Roubsanthisuk W et al. (2022) Long-term outcome of renal nerve	Case series n=17	Effectiveness of the RDN outcome was defined by either (1) a reduction in office systolic BP ≥ 10 mmHg, (2) a	Small sample

denervation (RDN) for resistant hypertension. Hypertension research: official journal of the Japanese Society of Hypertension 45(6): 962-6	Follow up: mean 52 months	reduction in the number of antihypertensive drugs taken, or (3) both outcomes being achieved. Effectiveness of the RDN outcome was achieved in 88% of the patients at 1 year and in >80% of the patients during the entire follow-up at each time point up to 9 years.	
Pancholy SB, Shantha GPS, Patel TM et al. (2014) Meta-analysis of the effect of renal denervation on blood pressure and pulse pressure in patients with resistant systemic hypertension. The American journal of cardiology 114(6): 856-61	Meta-analysis n=5 studies follow up: 6 months	This meta-analysis shows that RD is superior to MMT in lowering BP, but heterogeneity among study populations in this pooled sample is high, and further data are needed to better compare these treatment strategies.	Of the 3 RCTs, 2 RCTs were included in Pisano (2021) and 1 RCT compared pulmonary vein isolation with RDN with pulmonary vein isolation alone in patients with refractory symptomatic atrial fibrillation and resistant hypertension. Two studies were non-randomised comparative studies with small samples.
Pappaccogli M, Covella M, Berra E et al. (2018) Effectiveness of renal denervation in resistant hypertension: a meta-analysis of 11 controlled studies. High blood pressure & cardiovascular prevention: the official journal of	Meta-analysis n=11 studies (1,236 patients) follow up: 6 months	In spite of promising results in early reports, renal denervation fails to show superiority to a sham procedure or to medical therapy in recently published controlled studies. Lack of a sham control in most publications and heterogeneity in assessment of	Ten of the 11 studies were included in Pisano (2021) and 1 study with a small sample and being stopped early for ethical reasons because RDN had uncertain BP-lowering effect.

the Italian Society of Hypertension 25(2): 167-76		treatment adherence may account for part the variability reported in the studies.	
Pekarskiy, Stanislav E, Baev, Andrei E, Mordovin, Victor F et al. (2017) Denervation of the distal renal arterial branches vs. conventional main renal artery treatment: a randomized controlled trial for treatment of resistant hypertension. Journal of hypertension 35(2): 369-375	RCT n=51 (main renal artery, n=26; distal branches, n=25) follow up: 6 months	Percutaneous renal denervation treatment was significantly less effective at lowering 24-h blood pressure in treatment-resistant hypertensive patients when therapy was applied conventionally in the trunk of renal artery as compared with when applied to distal segmental branches. This observation is in accordance with previous surgical and anatomical findings showing that most renal nerve fibres are distant from the lumen proximally and become available for endovascular treatment mainly in the distal portion of the vessel.	RCTs with larger samples are included in the key evidence.
Pekarskiy S, Baev A, Falkovskaya A et al. (2022) Durable strong efficacy and favorable long-term renal safety of the anatomically optimised distal renal denervation according to the 3 year follow-up extension of the double-blind randomized	Long-term extension of an RCT n=47 (distal RDN, n=23; main trunk RDN, n=24) Follow up: 3 years	The study effectively confirms that anatomical optimisation of percutaneous renal denervation by shifting treatment from the main trunk to distal branches of the renal artery results in a significant durable increase in the efficacy of the therapy without any	RCTs with larger samples are included in the key evidence.

controlled trial. Heliyon 8: e08747		compromise on its renal safety.	
Persu A, Jin Y, Azizi M et al. (2014) Blood pressure changes after renal denervation at 10 European expert centers. Journal of human hypertension 28(3): 150-6	Case series n=109 follow up: 6 months	The key findings were that the BP responses to RDN were: (i) highly variable in individual patients; (ii) on average considerably smaller on ambulatory than office measurement (iii) and smaller than reported in previous studies.	Small sample
Persu A, Azizi M, Jin Y et al. (2014) Hyperresponders vs. nonresponder patients after renal denervation: do they differ? Journal of hypertension 32(12): 2422-7	Case series n=109 follow up: 6 months	This study suggests a major overestimation of BP response after RDN in extreme responders defined according to office, but not ambulatory BP. The association of lower eGFR with poor response to RDN is consistent with our previous analysis. The increased proportion of women in extreme responders may reflect sex differences in drug adherence.	Small sample
Persu A, Gordin D, Jacobs L et al. (2018) Blood pressure response to renal denervation is correlated with baseline blood pressure variability: a patient-level meta-analysis. Journal of	Case series n=167 follow up: 6 months	RDN was associated with a decrease in BP variability independent of the BP level, suggesting that responders may derive benefits from the reduction in BP variability as well. Furthermore, baseline DBP variability estimates significantly correlated with mean	Studies with larger samples and better designs are included in the key evidence.

hypertension 36(2): 221-9		DBP decrease after RDN. If confirmed in younger patients with less arterial damage, in the absence of the confounding effect of drugs and drug adherence, baseline BP variability may prove a good predictor of BP response to RDN.	
Peters CD, Mathiassen ON, Vase H et al. (2017) The effect of renal denervation on arterial stiffness, central blood pressure and heart rate variability in treatment resistant essential hypertension: a substudy of a randomized sham-controlled double-blinded trial (the ReSET trial). Blood pressure 26(6): 366-80	RCT n=58 follow up: 6 months	In a sham-controlled setting, there were no significant effects of RDN on arterial stiffness, C-BP and HRV. Thus, the idea of BP-independent effects of RDN on large arteries and cardiac autonomic activity is not supported.	ReSET trial was included in Pisano (2021)
Petrov I, Tasheva I, Garvanski I et al. (2019) Comparison of standard renal denervation procedure versus novel distal and branch vessel ablation with brachial arterial access. Cardiovascular Revascularization Medicine 20: 38-42	Non-randomised comparative study n=119 (standard ablation, n=80; Y-patten ablation, n=39) follow up: 6 months	Renal denervation using a Y-pattern ablation strategy combined with a greater number of lesions is safe and resulted in significant greater decreases in mean 24-hour ambulatory systolic and diastolic blood pressure compared to the conventional approach in this single-centre matched cohort study. Brachial artery	Studies with larger samples and better designs are included in the key evidence.

		access was shown to be feasible and safe for renal denervation.	
Prochnau D, Otto S, Figulla HR et al. (2016) Renal denervation with standard radiofrequency ablation catheter is effective in 24-hour ambulatory blood pressure reduction - Follow-up at 1/3/6/12 months. Netherlands Heart Journal 24(78): 449-55	Case series n=70 follow up: 12 months	RDN with a standard RF catheter can be used safely to reduce mean ABP in resistant hypertension as shown in long-term follow-up.	Studies with larger samples or better designs are included in the key evidence.
Beeftink MMA, Spiering W, Bots ML et al. (2016) Renal denervation in a real life setting: a gradual decrease in home blood pressure. PloS one 11(9): e0162251	Case series n=70 follow up: 12 months	Blood pressure reduction after renal denervation occurs as a gradual decrease that extends to at least 1-year follow-up. Home monitoring seems a suitable alternative for ambulatory blood pressure monitoring after renal denervation.	Small sample
Qi X-Y, Cheng B, Li Y-L et al. (2016) Renal denervation, adjusted drugs, or combined therapy for resistant hypertension: A meta-regression. Medicine 95(30): e3939	Meta-analysis n=13 studies (6 RCTs and 7 cohort studies) follow up: 6 months	Compared with control, the meta-analysis showed that RDN significantly reduced office-based BP and ambulatory BP in 6 months in the unblinded studies, while no significant difference was found in the blinded studies. Meta-regression showed the significant influence of blinding method on BP reduction, and further analysis revealed a	Five of the 6 RCTs were included in Pisano (2021), and 1 with a small sample and being stopped early for ethical reasons because RDN had uncertain BP-lowering effect. Seven studies were cohort studies with small samples.

		significant BP reduction compared with baseline even in the control arm of blinded studies. RDN had similar effects compared with adjusted drugs, and combined therapy seemed to further reduce the level of BP.	
Rea F, Morabito G, Savare L et al. (2022) The impact of renal denervation procedure on use of antihypertensive drugs in the real-life setting. Blood pressure 31(1): 245-53	Case series n=136 Follow up: 3 years	In the real-life setting, patients who underwent renal denervation had a clearcut reduction in antihypertensive drug prescription over the following years.	Studies with larger samples or better designs are included in the key evidence.
Ripp TM, Mordovin VF, Pekarskiy SE et al. (2015) Predictors of renal denervation efficacy in the treatment of resistant hypertension. Current hypertension reports 17(12): 90	Non-randomised comparative study n=60 follow up: 24 weeks	The study found the associations between the initial LV wall dimensions and LV MM changes. Unlike LV EDD, arterial blood pressure, or heart rate, the initial values of LV wall thickness predicted LV MM regress.	Studies with larger samples or better designs are included in the key evidence.
Rodriguez-Leor O, Segura J, Donaire JAG et al. (2020) Renal denervation for the treatment of resistant hypertension in Spain. The Flex-Spyral registry. Rev Esp Cardiol.	Case series (FLEX-SPYRAL Registry) n=125 follow up: 12 months	In patients with resistant hypertension, treatment with renal denervation was related to a decrease in office blood pressure and, more importantly, in ambulatory blood pressure monitoring, with a significant reduction in	Studies with larger samples or better designs are included in the key evidence.

		pharmacological treatment.	
Rohla M, Nahler A, Lambert T et al. (2016) Predictors of response to renal denervation for resistant arterial hypertension: a single center experience. Journal of hypertension 34(1): 123-9	Case series n=103 follow up: 12 months	Out of a wide range of baseline variables, elevated systolic ABPM values, BMI and the number of antihypertensive drugs used were associated with response. One has to consider the Hawthorne effect, the regression to the mean phenomenon, the actual effect of sympathetic denervation and the interaction of therapy modification when interpreting data from RDN registries without a control arm.	Studies with larger samples or better designs are included in the key evidence.
Rosa J, Widimsky P, Waldauf P et al. (2016) Role of adding spironolactone and renal denervation in true resistant hypertension: one-year outcomes of randomized PRAGUE-15 study. Hypertension (Dallas, Tex.: 1979) 67(2): 397-403	RCT (PRAGUE-15) n=106 (RDN, n=52; PHAR, n=54) follow up: 12 months	This study shows that over a period of 12 months, RDN is safe, with no serious side effects and no major changes in the renal arteries. RDN in the settings of true resistant hypertension with confirmed compliance is not superior to intensified pharmacological treatment. Spironolactone addition (if tolerated) seems to be more effective in blood pressure reduction.	PRAGUE-15 was included in Pisano (2021).
Rosa J, Widimsky P, Tousek P et al. (2015) Randomized comparison of	RCT (PRAGUE-15) n=106 (RDN, n=52; PHAR, n=54)	The 6-month results of this study confirmed the safety of renal denervation. In conclusion, renal	PRAGUE-15 was included in Pisano (2021).

renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. Hypertension 65(2): 407-13	follow up: 6 months	denervation achieved reduction of blood pressure comparable with intensified pharmacotherapy.	
Rosa J, Widimsky P, Waldauf P et al. (2017) Renal denervation in comparison with intensified pharmacotherapy in true resistant hypertension: 2-year outcomes of randomized PRAGUE-15 study. Journal of hypertension 35(5): 1093-9	RCT n=106 (RDN, n=52; PHAR, n=54) follow up: 24 months	In the settings of true resistant hypertension, spironolactone addition (if tolerated) seems to be of better efficacy than RDN in BP reduction over a period of 24 months. However, by contrast to the 12-month results, BP changes were not significantly greater.	PRAGUE-15 was included in Pisano (2021).
Sardar P, Bhatt DL, Kirtane AJ et al. (2019) Sham-controlled randomized trials of catheter-based renal denervation in patients with hypertension. Journal of the American College of Cardiology 73(13): 1633-1642	Meta-analysis n=6 studies (977 patients) follow up: 2 to 6 months	RSD significantly reduced blood pressure compared with sham control. Results of this meta-analysis should inform the design of larger, pivotal trials to evaluate the long-term efficacy and safety of RSD in patients with hypertension.	This review included patients with hypotension and outcomes for resistant hypertension were not reported separately.
Sanders MF, Reitsma JB, Morpey M et al. (2017) Renal safety of catheter-based renal denervation: systematic review and meta-analysis.	Systematic review and meta-analysis n=66 studies follow up: 9 months	The results show that renal function does not significantly change up to at least 9 months after RDN.	This study assessed the change in renal function after RDN and outcomes for resistant hypertension were

Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 32(9): 1440-7			not reported separately.
Sata Y, Hering D, Head G A et al. (2018) Ambulatory arterial stiffness index as a predictor of blood pressure response to renal denervation. Journal of hypertension 36(6): 1414-22	Case series n=111 follow up: 12 months	We conclude that in patients with resistant hypertension, a lower AASI is an independent predictor of the BP response to RDN, possibly explained by a more pronounced neurogenic rather than biomechanical contribution to their BP elevation.	Studies with larger samples and better designs are included in the key evidence.
Schmieder RE, Mahfoud F, Mancia G et al. (2022) Clinical event reductions in high-risk patients after renal denervation projected from the Global SYMPLICITY Registry. European heart journal. Quality of care & clinical outcomes	Analysis of GSR data (model-based projections) n=2,651 Follow up: 3 years	Model-based projections suggest radiofrequency RDN for patients with uncontrolled hypertension adds considerable clinical benefit across a spectrum of different cohort characteristics.	This study projected clinical event reductions after RDN using a novel modelling approach. Significant patient overlap between this study and Mahfoud (2019; n=2,237) included in the key evidence.
Schirmer SH, Sayed MMYA, Reil JC et al. (2014) Improvements in left ventricular hypertrophy and diastolic function following renal denervation:	Case series n=66 follow up: 6 months	In patients with resistant hypertension, LV hypertrophy and diastolic function improved 6 months after RDN, without significant relation to SBP and HR. These	Studies with larger samples or better designs are included in the key evidence.

effects beyond blood pressure and heart rate reduction. Journal of the American College of Cardiology 63(18): 1916-23		findings suggest a direct effect of altered sympathetic activity in addition to unloading on cardiac hypertrophy and function.	
Schmid A, Schmieder R, Lell M et al. (2016) Mid-term vascular safety of renal denervation assessed by follow-up MR imaging. Cardiovascular and interventional radiology 39(3): 426-32	Case series n=51 follow up: 11 months	No vascular or parenchymal complications after radiofrequency based RDN were detected in 51 patients followed up by MRI.	Studies with larger samples or better designs are included in the key evidence.
Schmid A, Ditting T, Sobotka P A et al. (2013) Does renal artery supply indicate treatment success of renal denervation? Cardiovascular and interventional radiology 36(4): 987-91	Non-randomised comparative studies n=53 (one-vessel, n=32; multivessel, n=21) follow up: 6 months	In patients with multiple renal arteries, RDN of one renal artery - namely, the dominant one - is sufficient to induce BP reduction in treatment-resistant hypertension.	Studies with larger samples or better designs are included in the key evidence.
Schmieder RE, Ott C, Schmid A et al. (2016) Adherence to antihypertensive medication in treatment-resistant hypertension undergoing renal denervation. Journal of the American Heart Association 5(2)	Non-randomised comparative studies n=79 (adherent, n=44; partially adherent, n=22; non-adherent, n=13) follow up: 6 months	Nonadherence to medication among patients with TRH was relatively low: about 1 of 6 patients with TRH did not take ≥2 of the prescribed drugs. Adherence pattern did not change significantly after renal denervation and had no impact on the overall observed BP changes, supporting the concept that	Studies with larger samples or better designs are included in the key evidence.

		renal denervation is an effective treatment in patients with TRH.	
Schneider S, Promny D, Sinnecker D et al. (2015) Impact of sympathetic renal denervation: a randomized study in patients after renal transplantation (ISAR-denerve). Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 30(11): 1928-36	RCT n=18 follow up: 6 months	RDN is feasible and safe in renal transplant recipients. However, larger sham-controlled studies will be necessary to clarify the potential role of RDN in this population.	Small sample and focusing on RDN in patients with post-transplant hypertension.
Sievert H, Schofer J, Ormiston J et al. (2015) Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society	Single-arm trial n=146 follow up: 6 months	Renal artery denervation with the Vessix system reduced both office and ambulatory BP at 6 months in patients with resistant hypertension. Renal artery safety and renal function results are favourable.	Studies with larger samples or better designs are included in the key evidence.

of Cardiology 10(10): 1213-20			
Silverwatch J, Marti KE, Phan MT et al. (2021) Renal denervation for uncontrolled and resistant hypertension: Systematic review and network meta-analysis of randomized trials. Journal of Clinical Medicine 10(4): 1-14	Systematic review and network meta-analysis n=20 studies (resistant hypertension, n=15 studies; uncontrolled hypertension, n=5) follow up:	Radiofrequency in main renal artery (MRA) and branches ranked as the best treatment to reduce 24-h ambulatory, daytime, and nighttime SBP and DBP versus other interventions (p-scores: 0.83 to 0.97); significant blood pressure effects were found versus sham or antihypertensive therapy (AHT). Radiofrequency in MRA+AHT was the best treatment to reduce office SBP and DBP (p-scores: 0.84 and 0.90, respectively). Radiofrequency in MRA and branches was the most efficacious versus other interventions to reduce 24-h ambulatory SBP and DBP in uncontrolled or resistant hypertension.	Most of the relevant studies are included in the key evidence (Pisano 2021; Fengler 2019). Limited efficacy outcomes for resistant hypertension were reported via sensitive analyses.
Skowerski M, Roleder T, Banska-Kisiel K et al. (2016) Long-term follow-up after radio-frequency catheter-based denervation in patients with resistant hypertension. International journal of	Case series n=86 follow up: 24 months	Authors regard RND as a safe and effective procedure in resistant hypertension, although more studies and trials are needed to find the most adequate model of a patient that would be a good responder to RND.	Small sample

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Stavropoulos K, Patoulias D, Imprialos K et al. (2020) Efficacy and safety of renal denervation for the management of arterial hypertension: A systematic review and meta-analysis of randomized, sham-controlled, catheter-based trials. Journal of Clinical Hypertension 22(4): 572-84	Systematic review and meta-analysis n=6 studies	The results suggest that renal denervation works in the short term and may contribute to better management and control of uncontrolled hypertension. Nonetheless, the effect is relatively small and most likely diluted by non-responders. Further, well-designed studies are needed to better define the role of renal denervation in the treatment of hypertension in the general population.	All relevant studies of percutaneous transluminal RDN for resistant hypertension were included in Pisano (2021).
Stoiber L, Mahfoud F, Zamani SM et al. (2018) Renal sympathetic denervation restores aortic distensibility in patients with resistant hypertension: data from a multi-center trial. Clinical research in cardiology: official journal of the German Cardiac Society 107(8): 642-52	Case series n=65 follow up: 6 months	The results underline the direct neurohormonal influence of RDN on vascular tone and aortic stiffness and propose that CMR determined AD may be most suitable in the evaluation of aortic compliance in invasive BP therapy. Indeed, other parameters considered to integrate alterations of vascular compliance and arterial stiffness such as isolated systolic hypertension, augmentation index, and pulse wave velocity have been	Studies with larger samples and better designs are included in the key evidence.

		demonstrated to improve with RDN.	
Sun D, Li C, Li M et al. (2016) Renal denervation vs pharmacotherapy for resistant hypertension: a meta-analysis. Journal of clinical hypertension (Greenwich, Conn.) 18(8): 733-40	Meta-analysis n=9 studies (1,096 patients) follow up: 6 months	This pooled analysis shows that for patients with resistant hypertension, RD is more effective in reducing SBP and DBP than PHAR. RD may be more effective in special subgroups of patients, which needs to be identified in future investigations.	Most relevant RCTs of percutaneous transluminal RDN for resistant hypertension were included in Pisano (2021).
Syed M, Osman M, Alhamoud H et al. (2021) The state of renal sympathetic denervation for the management of patients with hypertension: A systematic review and meta-analysis. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions 97(4): e438-e445	Systematic review and meta-analysis n=8 studies	The use of RSD for the management of hypertension resulted in effective reduction in the ambulatory and office blood pressure compared to sham procedure. Adequately powered RCTs of RSD are needed to confirm safety, reproducibility and assess the impact on clinical outcomes.	Most studies for resistant hypertension were included in Pisano (2021).
Symplicity HTN-1 Investigators. (2011) Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months.	Case series n=153 follow up: up to 24 months	In patients with resistant hypertension, catheter-based RDN results in a substantial reduction in BP sustained out to ≥2 years of follow-up, without significant adverse events.	Studies with larger samples and better designs are included in the key evidence.

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Tsioufis C, Ziakas A, Dimitriadis K et al. (2017) Blood pressure response to catheter-based renal sympathetic denervation in severe resistant hypertension: data from the Greek Renal Denervation Registry. Clinical research in cardiology: official journal of the German Cardiac Society 106(5): 322-30	Case series (Greek registry) n=79 follow up: 12 months	In our ‘‘real-world’’ multicenter national registry, the efficacy of renal denervation in reducing BP as well as safety is confirmed during a 12-month follow-up. Moreover, younger age, obesity, and higher levels of baseline systolic BP are independently related to better BP response to RDN.	Studies with larger samples and better designs are included in the key evidence.
Ukena C, Seidel T, Rizas K et al. (2020) Effects of renal denervation on 24-h heart rate and heart rate variability in resistant hypertension. Clinical Research in Cardiology 109(5): 581-588	Case series n=105 follow up: 6 months	In patients with resistant hypertension and elevated heart rate or high burden of PACs, RDN was associated with a reduction of HR and number of PAC. Parameters of HRV were not changed after RDN nor were predictive of response to RDN.	Studies with larger samples and better designs are included in the key evidence.
Verheye S, Ormiston J, Bergmann MW et al. (2015) Twelve-month results of the rapid renal sympathetic denervation for resistant hypertension using the OneShotTM ablation system (RAPID) study. EuroIntervention: journal of EuroPCR in collaboration	Case series (RAPID) n=50 follow up: 12 months	The results showed safety delivery of RF energy by the OneShot Renal Denervation System for renal sympathetic denervation and sustained efficacy, as evidenced by a significant reduction in office and 4-hour ABPM for 6 months, which was sustained up to 12 months.	Studies with larger samples and better designs are included in the key evidence.

with the Working Group on Interventional Cardiology of the European Society of Cardiology 10(10): 1221-9			
Verloop WL, Vink EE, Spiering W et al. (2014) Renal denervation in multiple renal arteries. European journal of clinical investigation 44(8): 728-35	Case series n=69 follow up: 6 months	Based on our results and the high prevalence of multiple arteries, it seems reasonable not to exclude patients with multiple renal arteries from RDN. Current analysis suggests that BP reduction may be less pronounced in patients with multiple renal arteries of whom not all arteries were treated	Small sample
Verloop WL, Vink EE, Spiering W et al. (2015) Effects of renal denervation on end organ damage in hypertensive patients. European journal of preventive cardiology 22(5): 558-67	Case series n=54 follow up: 12 months	In the current study, authors observed a modest effect from renal denervation. Moreover, RDN did not result in a statistically significant effect on end organ damage 12 months after treatment.	Small sample
Vink EE, Verloop WL, Bost RBC et al. (2014) The blood pressure-lowering effect of renal denervation is inversely related to kidney function. Journal of hypertension 32(10): 2045-53	Case series n=67 follow up: 6 months	The present study shows an inverse relation between the BP-lowering effect of RDN and eGFR. Second, authors found relations between variables of the RAAS and SNS with the BP-lowering effect of RDN. The data complement current concepts on	Limited efficacy reported and small sample.

		pathophysiology of sympathetic hyperactivity and hypertension and may give some insight in the wide range of the effect of RDN.	
Vogel B, Kirchberger M, Zeier M et al. (2014) Renal sympathetic denervation therapy in the real world: results from the Heidelberg registry. Clinical research in cardiology: official journal of the German Cardiac Society 103(2): 117-24	Case series (Heidelberg registry) n=63 follow up: 12 months	RDN with the Symplicity™ system is safe and effective in patients with treatment-resistant hypertension also in a real-world setting.	Studies with larger samples and better designs are included in the key evidence.
Vogiatzakis N, Tsioufis C, Georgiopoulos G et al. (2017) Effect of renal sympathetic denervation on short-term blood pressure variability in resistant hypertension: a meta-analysis. Journal of hypertension 35(9): 1750-7	Meta-analysis n=6 studies (2 RCTs and 4 non-randomised comparative studies)	Catheter-based RDN in resistant hypertensive patients can favourably affect short-term BPV, independent of the level of BP reduction. Further investigation of the effect of RDN on BPV is needed with large, randomised trials.	3 studies in this meta-analysis were included in Townsend (2020) and both RCTs were included in Pisano (2021).
Volz S, Spaak J, Elf J et al. (2018) Renal sympathetic denervation in Sweden: a report from the Swedish registry for renal denervation. Journal of	Case series (Swedish registry) n=252 follow up: 24 months	In this complete national cohort, RDN was associated with a sustained reduction in office and ambulatory BP in patients with resistant hypertension. The procedure proved to be feasible and	This study was included in Townsend (2020).

hypertension 36(1): 151-8		associated with a low-complication rate, including long-term adverse events.	
Warchol-Celinska E, Prejbisz A, Kadziela J et al. (2018) Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept phase ii trial. Hypertension (Dallas, Tex.: 1979) 72(2): 381-90	RCT n=60 (RDN, n=30; control, n=30) follow up: 6 months	This study shows that catheter-based renal sympathetic denervation may lower BP in resistant hypertensive patients with sleep-disordered breathing. This was accompanied by improvement of the clinical course of sleep apnoea. Our data are in concordance with the post hoc analyses from Symplicity-HTN-3 and global registry studies suggesting that patients with OSA may be particularly responsive to RDN therapy. Further studies are warranted to assess the impact of RDN on sleep apnoea and its relation to BP decline and cardiovascular risk.	This RCT was included in Pisano (2021).
Xia M, Liu T, Chen D et al. (2021) Efficacy and safety of renal denervation for hypertension in patients with chronic kidney disease: a meta-analysis. International journal of hyperthermia: the official journal of European Society	Meta-analysis n=11 studies (238 patients with hypertension and CKD) follow up: 24 months	The meta-analysis showed that RDN may be effective and safe for treating CKD patients with hypertension. Well-designed randomized controlled trials of RDN are urgently needed to confirm the safety and reproducibility of RDN and to assess	This study evaluated the efficacy and safety of RDN for hypertension in patients with CKD, and the outcomes for resistant hypertension were not reported separately.

for Hyperthermic Oncology, North American Hyperthermia Group 38(1): 732-42		its impact on clinical outcomes.	
Xu H, Jiang Z, Jiang W et al. (2022) The effect of renal denervation on cardiac diastolic function in patients with hypertension and paroxysmal atrial fibrillation. Evidence-based complementary and alternative Medicine 2022: 2268591	Non-randomised comparative study n=190 Follow up: 12 months	RDN could improve the diastolic function in patients with refractory hypertension and PAF. Patients with HFPEF could receive benefits through RDN. It was speculated that RDN improved the diastolic function mainly through decreasing HR and MAP.	Studies with larger samples or better designs are included in the key evidence.
Xu Y, Xiao P, Fan J et al. (2018) Blood pressure elevation response to radiofrequency energy delivery: one novel predictive marker to long-term success of renal denervation. Journal of hypertension 36(12): 2460-70	Case series n=57 follow up: 12 months	Baseline SBP and BP-elevation response during radiofrequency ablation, as well as larger positive response points to radiofrequency energy delivery could be an effective intraprocedural predictive markers to long-term procedural success of RDN.	Studies with larger samples or better designs are included in the key evidence.
Yang X, Liu H, Chen S et al. (2022) Intravascular renal denervation reduces ambulatory and office blood pressure in patients with essential hypertension: a meta-analysis of randomized sham-	Meta-analysis n=8 studies	Intravascular RDN using second-generation catheters reduces ambulatory and office BP in patients with essential hypertension. The selection of appropriate hypertensive patients may be the major challenge	Most relevant studies of percutaneous transluminal RDN for resistant hypertension are included in the key evidence (Pisano 2021; Azizi, 2021). Outcomes for resistant hypertension were

controlled trials. Kidney Blood Press Res 47: 363–74		for the performance of intravascular RDN in routine clinical practice.	not reported separately.
Yang X, Liu H, Chen S et al. (2022) Intravascular renal denervation reduces ambulatory and office blood pressure in patients with essential hypertension: a meta-analysis of randomized sham-controlled trials. Kidney & blood pressure research 47(6): 363-374	Meta-analysis n=1,297 (8 RCTs)	Intravascular RDN using second-generation catheters reduces ambulatory and office BP in patients with essential hypertension. The selection of appropriate hypertensive patients may be the major challenge for the performance of intravascular RDN in routine clinical practice.	Four studies specifically for resistant hypertension are included in the key evidence (Pisano 2021; Azizi 2021), 1 RCT (SPYRAL HTN-ON MED pilot) for uncontrolled hypertension is in the appendix, and 3 studies are not for resistant hypertension.
Yao Y, Zhang D, Qian J et al. (2016) The effect of renal denervation on resistant hypertension: Meta-analysis of randomized controlled clinical trials. Clinical and experimental hypertension (New York, N.Y.: 1993) 38(3): 278-86	Meta-analysis n=9 studies follow up: 6 months	Radiofrequency RDN in a randomised manner did not have superiority compared with medical treatment at 6-month follow-up in general population. Current evidence provides insufficient evidence to support the use of such RDN strategy in the treatment of resistant hypertension. The result could not be used to extrapolate other strategies' effect.	Most studies in this meta-analysis were included in Pisano (2021).
Zhang X, Wu N, Yan W et al. (2016) The effects of renal denervation on resistant hypertension patients: a meta-analysis. Blood	Meta-analysis n=11 studies follow up: 6 months	This meta-analysis shows that RDN is superior to the control group in lowering office blood pressure rather than ambulatory SBP and might have other	Most relevant RCTs were included in Pisano (2021) and non-randomised comparative

pressure monitoring 21(4): 206-14		potential benefits to protect heart and renal function.	studies had small samples.
Zhang ZH, Yang K, Jiang FL et al. (2014) The effects of catheter-based radiofrequency renal denervation on renal function and renal artery structure in patients with resistant hypertension. Journal of clinical hypertension (Greenwich, Conn.) 16(8): 599-605	Non-randomised comparative studies n=77 (RDN, n=39; control, n=38) follow up: 12 months	RDN significantly and persistently reduced blood pressure and decreased urinary protein excretion rate in patients with resistant hypertension and did not exhibit any adverse effect on renal function and renal artery structure	Studies with larger samples or better designs are included in the key evidence.
Zeijen VJM, Feyz L, Nannan Panday R et al. (2022b) Long-term follow-up of patients undergoing renal sympathetic denervation. Clinical Research in Cardiology	Case series n=72 Follow up: median 3.5 years	The BP-lowering effect of RDN was safely maintained at least five years post-procedure as reflected by a significant decrease in ambulatory daytime BP in the absence of escalating antihypertensive drug therapy over time.	Studies with larger samples or better designs are included in the key evidence.
Zweiker D, Lambert T, Steinwender C et al. (2019) Blood pressure changes after renal denervation are more pronounced in women and nondiabetic patients: findings from the Austrian Transcatheter Renal Denervation Registry. Journal of	Case series (Registry) n=291 follow up: 12 months	Ambulatory BP reductions after RDN were substantially more pronounced in female and in nondiabetic patients despite lower baseline BP. It is concluded that in terms of efficacy female patients and nondiabetic patients might benefit more from RDN.	Studies with larger samples or better designs are included in the key evidence.

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