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Efficacy and Safety of Catheter-Based Renal Denervation for Patients With Hypertension: A Systematic Review and Meta-Analysis

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ABSTRACT

This meta-analysis evaluates the efficacy and safety of renal denervation (RDN) for patients with hypertension. PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were systematically searched to identify relevant studies published before December 31, 2024. Review Manager 5.3 software was used to assess the results of the meta-analyses and the risk of bias plot. We pooled 2208 participants from 13 studies. The RDN was superior to the sham surgery group in the change in 24 h ambulatory systolic blood pressure (ASBP) and the change in 24 h ambulatory diastolic blood pressure (ADBP) (MD: −4.55 mmHg, 95% CI: −5.65 to −3.44; MD: −2.37 mmHg, 95% CI: −3.06 to −1.68, respectively). For the change in daytime ASBP and ADBP, significant differences were found between the RDN group and the sham group (MD: −6.21 mmHg, 95% CI: −7.61 to −4.80; MD: −2.96, 95% CI: −3.85 to −2.07). Compared to the sham surgery group, the RDN group showed better results in the change in night-time ASBP and ADBP (MD: −4.67 mmHg, 95% CI: −6.32 to −3.03; MD: −2.28 mmHg, 95% CI: −3.33 to −1.24). No significant differences were found between the RDN group and the sham group in terms of adverse events (AEs) and serious adverse events (SAEs) ($p = 0.39$ and 0.07). Subgroup analyses showed that RDN remains effective at long-term follow-up, and both ultrasound and radiofrequency RDN were effective. Current evidence shows that RDN is an effective treatment for patients with hypertension and does not increase the risk of AEs and SAEs.

1 | Introduction

Hypertension is the number one diagnosis for primary clinicians and is a major risk factor for cardiovascular disease [1, 2]. Hypertension is responsible for 85 million deaths worldwide from stroke, ischemic heart disease, other vascular diseases, and kidney disease [3]. Hypertension remains the leading cause of death from non-communicable diseases globally [4]. Improving the effectiveness of treatment for people with hypertension is a goal in many regions and countries. Lifestyle interventions and medication are the mainstays of hypertension treatment, however, rates of hypertension control remain low [1].

Resistant hypertension is defined as the inability to lower blood pressure to <140/90 mmHg despite the use of 3 or more antihypertensive medications at the maximum tolerated dose, including

Abbreviations: ADBP, ambulatory diastolic blood pressure; AE, adverse event; ASBP, ambulatory systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MD, mean difference; RAAS, renin-angiotensin-aldosterone system;; RCT, Randomized clinical controlled trials; RDN, renal denervation; SAE, serious adverse event; SBP, systolic blood pressure.

Xiao Chen and Jie Meng contributed equally to this work.

diuretics, and in combination with lifestyle changes [5, 6]. The prevalence of resistant hypertension among hypertensive patients is 10%, and these patients have a higher risk of cardiovascular disease and a greater need for aggressive treatment [7]. Surgical sympathectomy is an effective treatment for patients with resistant hypertension [8, 9]. Renal sympathetic nerves are located in the outer membrane of the renal arteries and regulate blood pressure through many important mechanisms [10, 11]. Activation of renal sympathetic nerves leads to constriction of small renal arteries, increased renin secretion, and subsequent activation of the renin-angiotensin-aldosterone system (RAAS), thereby leading to increased tubular sodium and water reabsorption and elevated blood pressure [10, 12]. Therefore, in recent years, renal denervation (RDN) has emerged as a potential treatment for resistant hypertension [11].

RDN is a percutaneous endovascular catheter-based neuromodulation approach that can be performed using radiofrequency, ultrasound, or a neurolytic agent (e.g., alcohol) to ablate renal sympathetic fibers [13]. Radiofrequency ablation is the most commonly used technique for RDN. An endovascular catheter is placed into the distal renal artery, and radiofrequency waves are used to ablate the renal sympathetic nerves in the outer membrane of the renal artery while minimizing damage to the outer membrane. Ultrasound RDN uses a balloon-type ultrasound catheter to denervate the renal arteries using thermal energy generated by high-frequency sound waves without damaging the renal artery wall [13]. Many previous clinical trial results have shown that RDN can effectively lower the blood pressure of patients with hypertension. However, the results of the SYMPLICITY HTN-3 trial showed that the main outcome indicators did not show significant differences 6 months after RDN. In addition, the final results of the SPYRAL HTN-ON MED trial showed that 6 months after surgery, the difference in 24-h dynamic systolic blood pressure (SBP) changes between the RDN and sham surgery groups no longer existed. The negative results of these key trials have cast doubt on the effectiveness of RDN [14, 15]. Therefore, we constructed this meta-analysis to examine the efficacy and safety of RDN in patients with hypertension. Hope to provide an update on the current evidence regarding the safety and efficacy of RDN in the treatment of hypertension and consider its prospects.

2 | Methods

2.1 | Study Protocol

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [16]. Before the project started, we drafted a research protocol following the Cochrane Collaboration format, and the protocol for this systematic review was registered on PROSPERO with the number CRD42024583980.

2.2 | Study Selection

We set the inclusion criteria as follows: (a) study type: Randomized clinical controlled trial (RCT); (b) language restriction: only available in English; (c) participants: patients with hypertension; (d) intervention: RDN or sham operation; (e) outcomes: primary outcomes included the change in 24 h ambulatory systolic blood pressure (ASBP); the change in 24 h ambulatory diastolic blood pressure (ADBP). Secondary outcomes: the change in daytime ASBP; the change in daytime ADBP; the change in night-time ASBP; the change in night-time ADBP; the change in office SBP; the change in office diastolic blood pressure (DBP); the change in home SBP; the change in home DBP. Safety outcomes included adverse events (AEs) and serious adverse events (SAEs).

2.3 | Search Strategy

PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov were systematically searched to identify relevant studies published before December 31, 2024. The following search strategy was employed: “Hypertension” AND “renal denervation” in the title, abstract, or keywords. The comprehensive search strategy is in the Supporting Information (Table S1). To ensure a more thorough search, the reference lists of RCTs, relevant systematic reviews, and meta-analyses were independently and manually screened.

2.4 | Study Selection and Data Collection

Two reviewers (X.C. and Q.F.Z.) independently reviewed all titles, abstracts, and full-text articles searched from the four databases, as well as the reference lists of RCTs and relevant systematic reviews or meta-analyses, following the eligibility criteria mentioned above. Duplicates and research articles for which the full text was unavailable were excluded. Disagreements between the two authors were settled through discussion or, if necessary, by a third author (Y.H.N.) not involved in data collection. Following selection and evaluation, the following data were extracted from the included RCTs: study characteristics, baseline characteristics, and outcome events included for each RCT (Table 1); inclusion and exclusion criteria, study design, and all efficacy and safety outcomes are shown in Supporting Information (Table S2).

2.5 | Risk of Bias

To evaluate the risk of bias in RCTs, the updated Cochrane Collaboration’s uniform criteria RoB 2.0 were used [17], which included randomization process, intervention adherence, missing outcome data, outcome measurement, and selective reporting. Each bias criterion was classified as “low risk of bias,” “high risk of bias”, or “some risk of bias.” Two authors conducted the evaluation independently. Disagreements were settled with the help of a third author.

2.6 | Statistical Analysis

We used Review Manager 5.3 software to perform pairwise meta-analyses of direct evidence. The mean difference (MD) with a 95% confidence interval (95% CI) was analyzed and calculated

TABLE 1 | Characteristics of the included studies and outcome events.

Study	Treatment group (No. of participants)	Female (%)	Mean age ± SD (year)	Study period	Body-mass index (kg/m^2)	Baseline SBP ± SD (mm Hg)	Baseline DBP ± SD (mm Hg)	Outcome Events	The types of antihypertensive drugs
Symplicity HTN-2 2010 [18]	RDN (52) vs. Sham (54)	RDN: 35 Sham: 50	RDN: 58 ± 12 Sham: 58 ± 12	6 months	RDN: 31 ± 5 Sham: 31 ± 5	RDN: 178 ± 18 Sham: 178 ± 16	RDN: 97 ± 16 Sham: 98 ± 17	g, h, k, l	ACE-I, ARB, DARI, CCB, Diuretics, Aldosterone antagonist, Vasodilators, α-1 blockers, CAD
Symplicity HTN-3 2014 [19]	RDN (364) vs. Sham (171)	RDN: 41 Sham: 36	RDN: 57.9 ± 10.4 Sham: 56.2 ± 11.2	36 months	RDN: 34.2 ± 6.5 Sham: 33.9 ± 6.4	NR	NR	a, b, g, h, i, j, k, l	ACE-I, Aldosterone antagonist Beta-blocker, CAD, Direct-acting vasodilator, Alpha-adrenergic blocker, ARB, CCB, DARI, Diuretic
DENERHTN 2015 [20]	RDN (53) vs. Sham (53)	RDN: 36 Sham: 40	RDN: 55.2 ± 10.8 Sham: 55.2 ± 10.1	6 months	RDN: 30.7 ± 4.8 Sham: 29.7 ± 4.5	RDN: 151.6 ± 16.3 Sham: 146.8 ± 15.2	RDN: 90.2 ± 15.3 Sham: 88.8 ± 10.6	a, b, c, d, e, f, g, h, i, j, k, l	Indapamide, Ramipril, Irbesartan, Amlodipine, Amlodipine,
Desch et al. 2015 [21]	RDN (35) vs. Sham (36)	RDN: 23 Sham: 31	RDN: 64.5 ± 7.6 Sham: 57.4 ± 8.6	6 months	RDN: 31.9 ± 4.4 Sham: 31.2 ± 4.6	RDN: 140.2 ± 4.6 Sham: 140.4 ± 5.6	RDN: 78.2 ± 7.4 Sham: 80.6 ± 7.1	a, b, c, d, e, f	Beta blocker, ACE-I, ARB, CCB, Diuretic, Aldosterone antagonist, Vasodilator, Alpha blocker, Sympatholytic agent
ReSet 2016 [22]	RDN (36) vs. Sham (33)	RDN: 25 Sham: 27	RDN: 54.3 ± 7.8 Sham: 57.1 ± 9.6	6 months	RDN: 28.2 ± 5.0 Sham: 28.8 ± 3.9	RDN: 152 ± 12 Sham: 153 ± 13	RDN: 91 ± 9 Sham: 89 ± 11	a, b, c, d, e, f, k, l	ACE-I, ARB, CCB, Beta-blocker, Diuretic, Thiazide diuretic, Loop diuretic, Aldosterone inhibitor, Alpha-adrenergic blocker, DARI, Direct-acting vasodilator, CAD
RADIANCE-HTN SOLO 2018 [23]	RDN (74) vs. Sham (72)	RDN: 38 Sham: 46	RDN: 54.4 ± 10.2 Sham: 53.8 ± 10.0	2 months	RDN: 29.9 ± 5.9 Sham: 29.0 ± 5.0	RDN: 142.6 ± 14.7 Sham: 144.6 ± 15.9	RDN: 92.3 ± 10.1 Sham: 93.6 ± 8.3	a, b, c, d, e, f, g, h, i, j, k, l	ACE-I, ARB, Direct renin inhibitor, Diuretic, Beta blocker, Alpha-1 receptor blocker, Spironolactone
SPYRAL HTN-ON MED 2018 [24]	RDN (38) vs. Sham (42)	RDN: 13 Sham: 19	RDN: 53.9 ± 8.7 Sham: 53.0 ± 10.7	36 months	RDN: 31.4 ± 6.4 Sham: 32.5 ± 4.6	RDN: 152.1 ± 7.0 Sham: 151.3 ± 6.8	RDN: 97.2 ± 6.9 Sham: 97.9 ± 8.4	a, b, c, d, e, f, g, h, k, l	Diuretic, CCB, ACE-I /ARB, Beta blocker

(Continues)

TABLE 1 | (Continued)

Study	Treatment group (No. of participants)	Female (%)	Mean age ± SD (year)	Study period	Body-mass index (kg/m^2)	Baseline SBP ± SD (mm Hg)	Baseline DBP ± SD (mm Hg)	Outcome Events	The types of antihypertensive drugs
SPYRAL HTN-OFF MED 2020 [25]	RDN (166) vs. Sham (165)	RDN: 36 Sham: 32	RDN: 52.4 ± 10.9 Sham: 52.6 ± 10.4	3 months	RDN: 31.1 ± 6.0 Sham: 30.9 ± 5.5	RDN: 151.4 ± 8.1 Sham: 151.0 ± 7.5	RDN: 98.0 ± 7.7 Sham: 99.0 ± 7.4	a, b, g, h, k, l	NR
REDUCE HTN: REINFORCE 2020 [26]	RDN (34) vs. Sham (17)	RDN: 47 Sham: 24	RDN: 58.5 ± 10.1 Sham: 58.2 ± 9.8	12 months	NR	RDN: 148.3 ± 10.9 Sham: 149.1 ± 7.2	RDN: 85.7 ± 9.1 Sham: 86.4 ± 9.8	a, b, c, d, e, f, g, h, k, l	NR
RADIANCE-HTN TRIO 2021 [27]	RDN (69) vs. Sham (67)	RDN: 19 Sham: 21	RDN: 52.3 ± 7.5 Sham: 52.8 ± 9.1	2 months	RDN: 32.8 ± 5.7 Sham: 32.6 ± 5.4	RDN: 143.9 ± 13.4 Sham: 145.4 ± 14.0	RDN: 88.9 ± 8.2 Sham: 89.5 ± 9.5	a, b, c, d, e, f, g, h, i, j, k, l	ACE-I/ARB, Diuretics, CCB, β blockers, Aldosterone antagonists, CAD, α1 receptor blockers, Vasodilators
REQUIRE 2021 [28]	RDN (69) vs. Sham (67)	RDN: 30 Sham: 21	RDN: 50.7 ± 11.4 Sham: 55.6 ± 12.1	3 months	RDN: 29.5 ± 5.5 Sham: 28.4 ± 4.5	RDN: 161.9 ± 13.4 Sham: 161.5 ± 13.1	RDN: 94.9 ± 9.3 Sham: 92.7 ± 9.4	a, b, c, d, e, f, g, h, i, j, k, l	Renin angiotensin system blocker, CCB, Diuretic, Mineralocorticoid receptor blocker, α-blocker, β-blocker α-/β-blocker, CAD, Vasodilator
RADIANCE II 2023 [29]	RDN (150) vs. Sham (74)	RDN: 31 Sham: 23	RDN: 55.1 ± 9.9 Sham: 54.9 ± 7.9	2 months	RDN: 30.1 ± 5.2 Sham: 30.6 ± 5.2	RDN: 143.2 ± 9.0 Sham: 144.5 ± 9.7	RDN: 88.4 ± 5.8 Sham: 88.2 ± 5.8	a, b, c, d, e, f, g, h, i, j	ACE-I/ARB, CCB, Diuretics, β-Blockers, Aldosterone antagonists, α1 receptor blockers, CAD, Vasodilators.
Jiang 2024	RDN (107) vs. Sham (110)	RDN: 21.5 Sham: 20	RDN: 46.4 ± 10.2 Sham: 44.3 ± 10.2	6 months	RDN: 27.7 ± 3.6 Sham: 27.8 ± 3.3	RDN: 148.0 ± 10.0 Sham: 146.5 ± 8.9	RDN: 91.3 ± 10.4 Sham: 93.1 ± 8.8	a, b, c, d, e, f, g,h	ACE-I, Angiotensin receptor blocker, CCB, Diuretic, Thiazide or thiazide-like, Beta-blocker

Note: a: change in 24 h ambulatory systolic blood pressure; b: change in 24 h ambulatory diastolic blood pressure; c: change in daytime ambulatory systolic blood pressure; d: change in daytime ambulatory diastolic blood pressure; e: change in night-time ambulatory systolic blood pressure; f: change in night-time ambulatory diastolic blood pressure; g: change in office systolic blood pressure; h: change in office diastolic blood pressure; i: change in home systolic blood pressure; j: change in home diastolic blood pressure; k: adverse events; l: serious adverse events.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, centrally acting drugs; CCB, Calcium channel blocker; DARI, direct-acting renin inhibitor; DBP, diastolic blood pressure; NR, not reported; RDN, renal denervation; SBP, systolic blood pressure.

for the outcomes. We then estimated heterogeneity through the I^2 statistic as follows: $I^2 < 30\%$ suggests "low heterogeneity"; I^2 between 30% and 50% indicates "moderate heterogeneity"; $I^2 > 50\%$ denotes "substantial heterogeneity". The data were analyzed with a fixed effects model when heterogeneity was less than 50%, and for heterogeneity greater than 50%, a random effects model was used. We also implemented subgroup analyses to detect the effect of different follow-up times (>6 months and <6 months) and different types of RDN (radiofrequency and ultrasound). We investigated the statistical significance of the associated results using Egger's regression test and looked at the distribution of effect sizes on a funnel plot to see whether publication bias may be present. For all the analyses, two-tailed tests were performed, and p value <0.05 was considered to be statistically significant.

3 | Results

3.1 | Study Characteristics

PubMed, EMBASE, the Cochrane Library, and Clinicaltrials.gov together provided 1423 titles and abstracts. In addition, references from relevant studies were manually scanned, and an additional RCT was discovered. A total of 1340 articles were excluded due to duplication and irrelevance after a quick review, and 83 full articles were assessed for eligibility. Among these, 70 articles were excluded due to the inapplicable publication types: review ($n = 19$); case report ($n = 27$); meta-analysis ($n = 10$); excluded RCTs ($n = 14$). Finally, a total of 13 studies were included in the meta-analysis [18–30]. The selection process is summarized in the flow diagram (Figure 1). The main characteristics of the included studies are summarized in Table 1.

3.2 | Primary Outcome Analyses

As shown in Table 2, the RDN was significantly superior to the sham surgery group in the change in 24 h ASBP and the change in 24 h ADBP (MD = −4.55 [−5.65, −3.44], $p < 0.00001$; MD = −2.37 [−3.06, −1.68], $p < 0.00001$, respectively). Forest plots are shown in Figure 2.

3.3 | Secondary Outcome Analyses

The RDN group showed superior effectiveness compared to the sham group in secondary outcomes. For the change in daytime ASBP and ADBP, significant differences were found between the RDN group and the sham group (MD = −6.21 [−7.61, −4.80], $p < 0.00001$; MD = −2.96 [−3.85, −2.07], $p < 0.00001$, respectively). Compared to the sham surgery group, the RDN group showed better results in the change in night-time ASBP and ADBP (MD = −4.67 [−6.32, −3.03], $p < 0.00001$; MD = −2.28 [−3.33, −1.24], $p < 0.0001$, respectively). The RDN group was superior to the sham group in the change in office SBP and DBP (MD = −7.65 [−10.85, −4.45], $p < 0.00001$; MD = −4.02 [−5.54, −2.49], $p < 0.00001$, respectively), as well as the change in home SBP and DBP (MD = −4.81 [−7.56, −2.05], $p < 0.0006$; MD = −2.25 [−4.43, −0.16], $p = 0.04$, respectively). In the change in office SBP and the change in home DBP, our results show a high degree of heterogeneity, 77% and 78%, respectively. Table 2 shows the detailed results of the secondary outcomes analyses. Forest plots are shown in the Supporting Information (Figures S1–S8).

3.4 | Safety Outcome Analyses

No significant differences were found between the RDN group and the sham group in terms of AEs and SAEs (RR = 1.10 [0.88, 1.37], $p = 0.39$; RR = 1.50 [0.96, 2.34], $p = 0.07$, respectively). The detailed results are presented in Table 2, and Figures S9–S10.

3.5 | Subgroup Analyses

To assess the influence of different follow-up times and different RDN types, we implemented subgroup analyses according to the characteristics at baseline. In the primary outcome, we found the RDN group was superior to the sham group regardless of follow-up time ≥6 months group and <6 months group (Figure 3A). For the change in night-time ADBP, no significant differences were found between the RDN group and the sham group in both follow-up times ($p = 0.13$ and 0.30, respectively). In terms of the change in home SBP and DBP, the difference between the RDN group and the sham group was not statistically significant in the follow-up time ≥6 months group, but in the follow-up time <6 months group, the RDN group was superior to the sham group. At the same time, we found the RDN group was superior to the sham group regardless of radiofrequency subgroup and ultrasound subgroup (Figure 3B). For the change in 24 h ADBP, the RDN group outperformed the sham group in the radiofrequency subgroup, and there was no difference between the RDN group and sham group in the ultrasound subgroup (MD = −2.08 [−3.25, −0.91]; MD = −2.33 [−4.75, 0.09], respectively). The radiofrequency RDN group was not superior to the sham group in the change in night-time ADBP, and in the change in home SBP and DBP, but the ultrasound RDN group was better than the sham group in the outcomes mentioned before. In all subgroups, the RDN group had a safety profile that was noninferior to that of the sham group. The detailed results of the subgroup analyses are shown in Table 3. Forest plots are shown in the Supporting Information (Figures S11–S30).

3.6 | Risk of Bias in Included Studies

The risk of bias for 13 enrolled studies is illustrated in Table 4. The risks of bias in random sequence generation were low in 11 clinical trials. For intervention adherence, the risk of bias was low in all trials. One study showed a high risk of outcome measurement bias. In conclusion, one trial has a high overall risk of bias, two trials have some risk of overall bias, and the remaining studies had a low risk of bias.

There was no indication of publication bias based on a funnel plot analysis of all observed outcomes (Figures S31–S32). A p value of more than 0.05 was found for every result, indicating that the distribution of effect sizes was symmetric, as demonstrated by Egger's regression test.

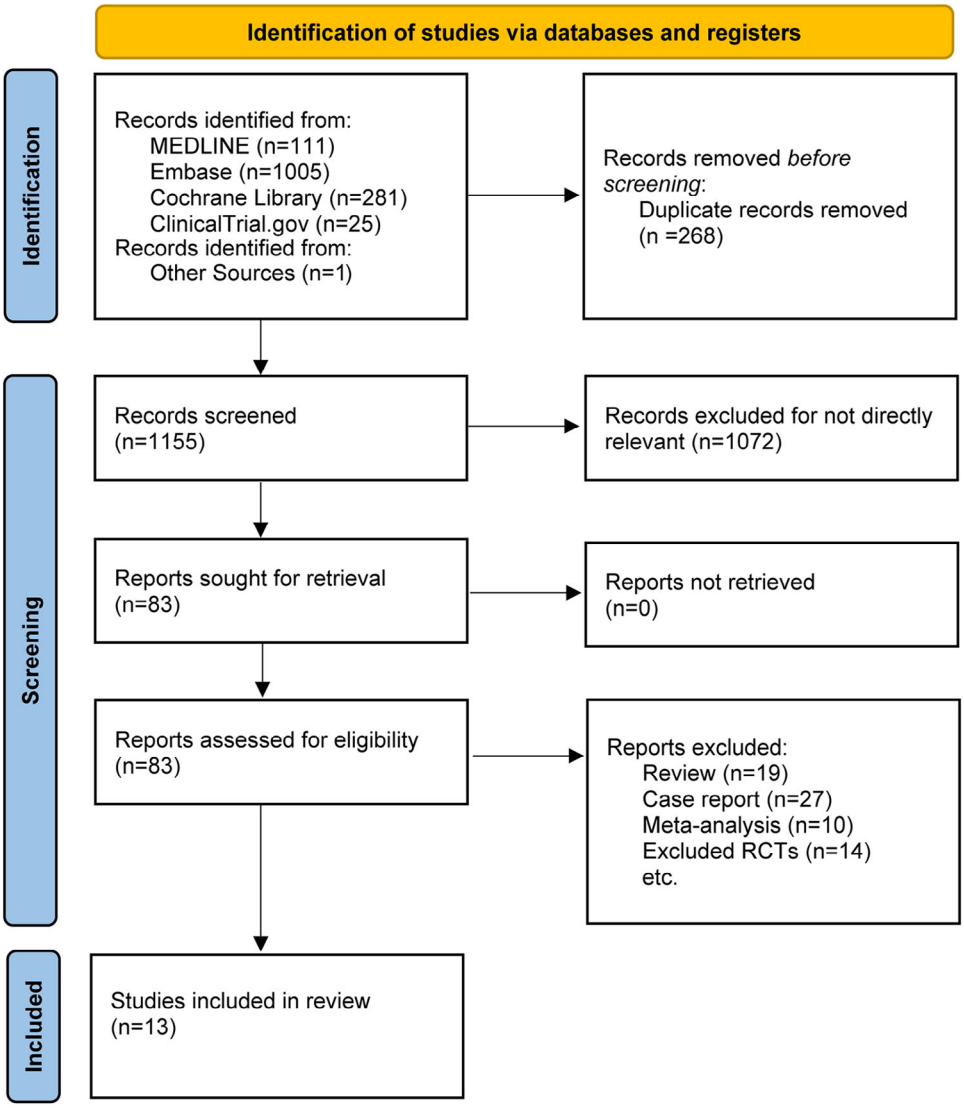

FIGURE 1 | The study search, selection, and inclusion process.

4 | Discussion

The present study included 13 studies with 2208 individuals randomly assigned to the RDN group or sham group. Our results showed that RDN was effective in lowering 24 h, daytime, and night-time ambulatory and office and home blood pressures, and was equally effective on SBP and DBP, compared with the sham-operated group. Our subgroup analyses showed that RDN lowered blood pressure in both short-term and long-term follow-up subgroups, and the short-term effect appeared to be more significant than the long-term effect. We categorized the different types of RDN into two subgroups: the ultrasound group and the radiofrequency group. Although both ultrasound and radiofrequency RDN had good efficacy, the ultrasound RDN was superior to the sham-operated group in more measures of effectiveness.

Hypertension remains the leading cause of death from non-communicable diseases globally, and low adherence may be the main reason for suboptimal hypertension control rates, including failure to take medication as prescribed or adhere to treatment [4]. Our results showed that RDN was effective in reducing systolic as well as DBP and that its antihypertensive effect may be independent of patient cooperation and adherence [31]. In addition, the antihypertensive effect of RDN was consistent across 24 h, daytime, and nighttime, and was not affected by location. Compared to short-acting antihypertensive drugs, RDN achieves a sustained and stable reduction in blood pressure [29].

Interestingly, in the present study, we found that although RDN also presented an effective blood pressure-lowering effect in the long-term follow-up subgroup, the results did not seem to be as significant as in the short-term follow-up subgroup. This is similar to the results of some previous studies, where the long-term efficacy of RDN has been questioned [32]. Peripheral nerves may have regenerative potential after injury, and partial regeneration and functional recovery of renal nerves after RDN have been observed in some animal studies [33, 34]. In contrast, others suggest that functional nerve regeneration is unlikely to occur [35]. Thus, data on renal nerve regeneration have been inconclusive to date. Current clinical evidence suggests that the antihypertensive effect of RDN lasts for at least 3 years

TABLE 2 | Detailed effects sizes from the meta-analysis of efficacy and safety outcomes.

Outcomes	No. of trials contributing to the meta-analysis	No. of participants contributing to the meta-analysis	MD (95% CI)/RR (95% CI)	*p* value	I^2 (%)
Change in 24 h ASBP	12	1998	−4.55 (−5.65, −3.44)	<0.00001	50
Change in 24 h ADBP	12	1998	−2.37 (−3.06, −1.68)	<0.00001	45
Change in daytime ASBP	10	1201	−6.21 (−7.61, −4.80)	<0.00001	21
Change in daytime ADBP	10	1201	−2.96 (−3.85, −2.07)	<0.00001	15
Change in night-time ASBP	10	1209	−4.33 (−6.97, −1.70)	0.001	55
Change in night-time ADBP	10	1209	−2.28 (−3.33, −1.24)	<0.0001	49
Change in office SBP	11	2040	−7.65 (−10.85, −4.45)	<0.0001	77
Change in office DBP	11	2040	−4.02 (−5.54, −2.49)	<0.00001	57
Change in home SBP	6	1217	−4.81 (−7.56, −2.05)	0.0006	61
Change in home DBP	6	1216	−2.25 (−4.43, −0.16)	0.04	78
AEs	11	1937	1.10 [0.88, 1.37]	0.39	10
SAEs	10	1581	1.50 [0.96, 2.34]	0.07	0

Abbreviations: ADBP, ambulatory diastolic blood pressure; AEs, adverse events; ASBP, ambulatory systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MD, mean difference; RR, risk ratio; SAEs, serious adverse events; SBP, systolic blood pressure.

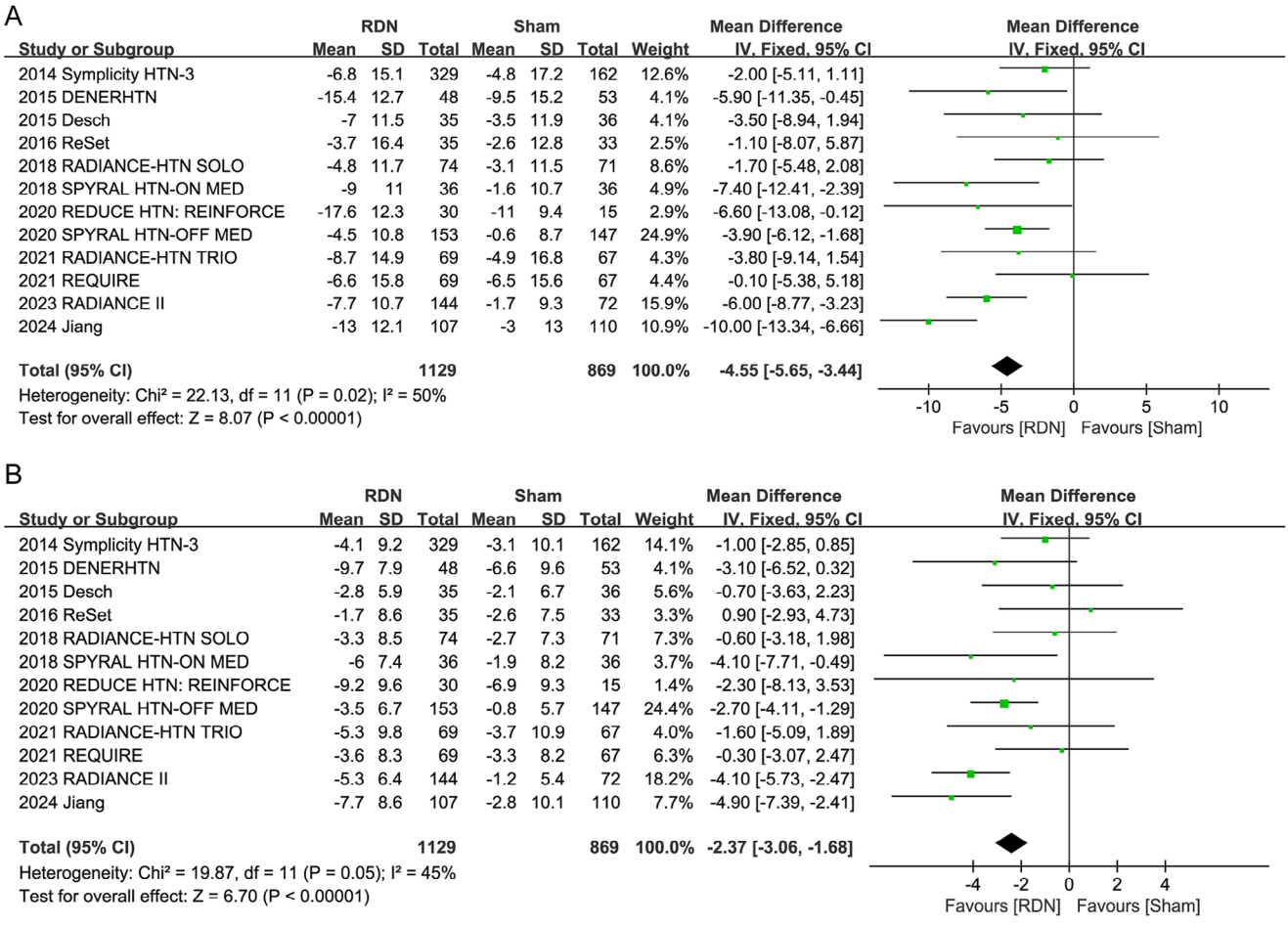

FIGURE 2 | Forest plots for the primary outcomes. (A) Change in 24 h ambulatory systolic blood pressure. (B) Change in 24 h ambulatory diastolic blood pressure.

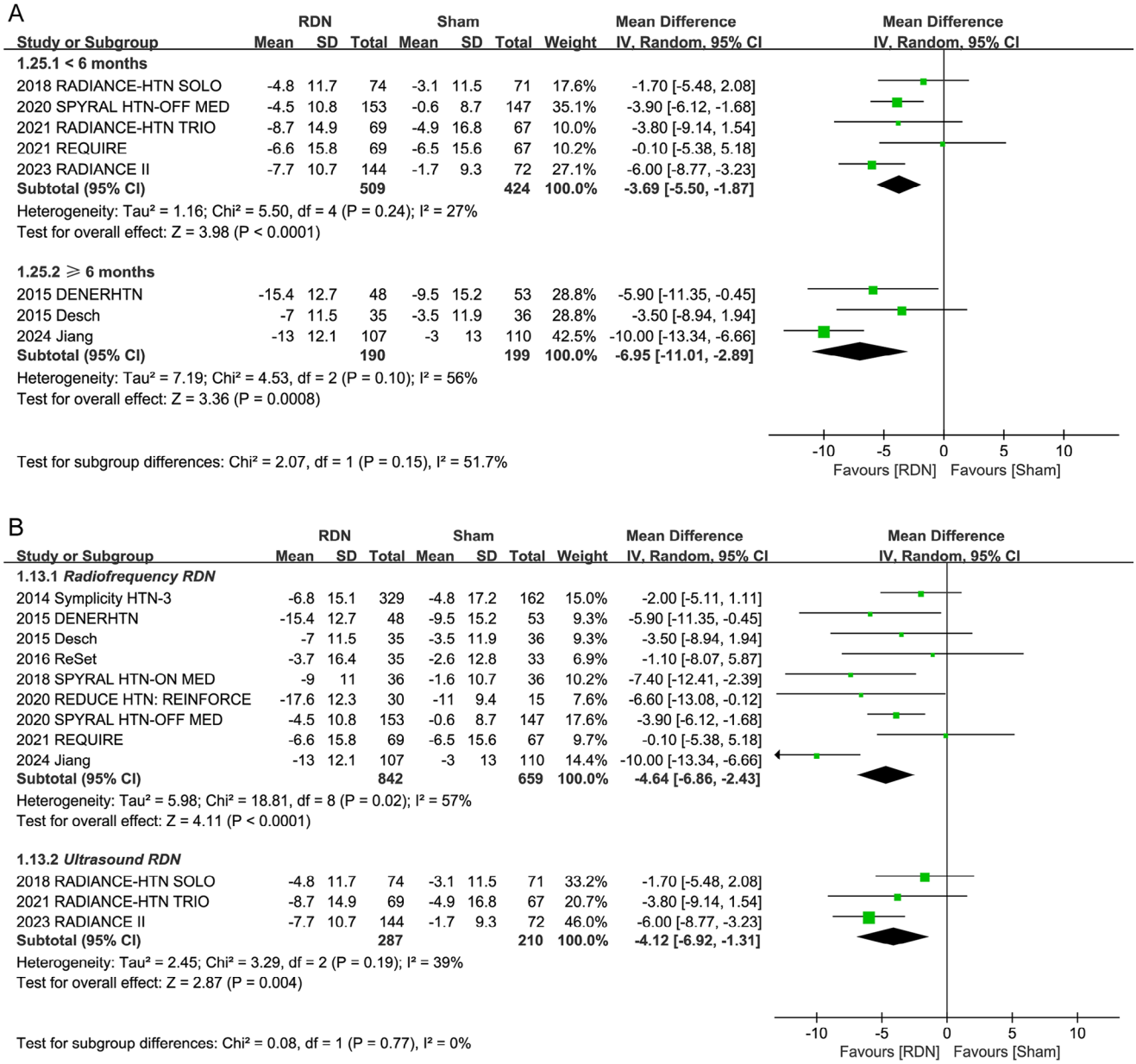

FIGURE 3 | Forest plots for the subgroup analysis of 24 h ambulatory systolic blood pressure. (A) Subgroup analysis of follow-up time. (B) Subgroup analysis of renal denervation type.

[36, 37]. Therefore, in patients who are poorly treated with antihypertensive medications or who have poor adherence, RDN can be effective in controlling blood pressure, thereby reducing all-cause mortality and adverse cardiovascular events [38].

The results of the subgroup analysis based on the type of RDN showed that both ultrasound RDN and radiofrequency RDN had good efficacy. The results of a previous study showed that RDN based on endovascular ultrasound was superior to radiofrequency ablation of the main renal artery [39]. However, due to the lack of additional head-to-head clinical trials, we were unable to directly compare the differences between the two types of RDN, and therefore, it is unclear whether RDN with endovascular ultrasound is superior. Additionally, RDN includes chemical neurolytic agent ablation, but this type of RDN was not included in our subgroup analysis due to a lack of relevant trials.

The antihypertensive effect of RDN on individual patients is difficult to predict, which may be one of the reasons affecting the clinical application of RDN. Patients with hypertension caused by sympathetic overactivity may benefit more from RDN, and patients with atherosclerosis and simple systolic hypertension are less likely to benefit [13, 40]. Thus, patient selection for RDN therapy is critical, and patients with high plasma renin activity (plasma renin activity ≥0.65 ng/mL/h) may respond better to RDN [41]. In addition, a faster heart rate and higher nocturnal blood pressure may be potential indicators of sympathetic overactivity [42].

Inevitably, there were several limitations of the present meta-analysis. First, although a comprehensive literature search was conducted, only 13 studies were included in the current meta-analysis. We must acknowledge that including only English

TABLE 3 | Subgroup analysis of efficacy outcomes.

	RDN type		Follow-up time	
	Radiofrequency	**Ultrasound**	**< 6 months**	**≥ 6 months**
Change in 24 h ASBP	−4.64 (−6.86, −2.43)***	−4.12 (−6.92, −1.31)**	−3.69 (−5.50, −1.87)***	−6.95 (−11.01, −2.89)***
Change in 24 h ADBP	−2.08 (−3.25, −0.91)***	−2.33 (−4.75, 0.09)n.s.	−2.19 (−3.62, −0.77)**	−2.98 (−5.54, −0.43)*
Change in daytime ASBP	−6.51 (−8.53, −4.50)***	−5.91 (−7.88, −3.94)***	−5.36 (−7.21, −3.51)***	−8.06 (−10.74, −5.38)***
Change in daytime ADBP	−2.67 (−3.99, −1.36)***	−3.20 (−4.42, −1.99)***	−2.85 (−3.97, −1.73)***	−3.55 (−5.32, −1.78)***
Change in night-time ASBP	−4.55 (−8.63, −0.48)*	−3.70 (−6.03, −1.37)**	−3.17 (−5.54, −0.80)**	−5.13 (−11.36, 1.11)n.s.
Change in night-time ADBP	−1.72 (−3.88, 0.44)n.s.	−2.47 (−4.91, −0.02)*	−1.80 (−4.12, 0.52)n.s.	−1.96 (−5.63, 1.71)n.s.
Change in office SBP	−8.55 (−13.10, −3.99)***	−5.94 (−8.68, −3.20)***	−4.90 (−6.75, −3.06)***	−14.57 (−30.03, 0.89) n.s.
Change in office DBP	−4.25 (−6.38, −2.11)***	−3.48 (−5.28, −1.68)***	−2.71 (−3.90, −1.53)***	−6.83 (−11.96, −1.70)**
Change in home SBP	−1.85 (−4.41, 0.71)n.s.	−7.26 (−9.26, −5.25)***	−6.49 (−8.35, −4.63)***	−1.67 (−4.61, 1.27)n.s.
Change in home DBP	−0.20 (−1.55, 1.14)n.s.	−4.28 (−5.44, −3.13)***	−3.05 (−5.13, −0.98)**	−0.28 (−1.78, 1.22)n.s.

Note: Data are presented as mean difference (95% confidence interval).

Abbreviations: ADBP, ambulatory diastolic blood pressure; ASBP, ambulatory systolic blood pressure; DBP, diastolic blood pressure; RDN, renal denervation; SBP, systolic blood pressure.

n.s. not significant.

*$p \leq 0.05$.

**$p \leq 0.01$.

***$p \leq 0.001$.

TABLE 4 | Risk of bias in included studies.

Study	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall RoB
2010 Symplicity HTN-2	L	L	L	H	L	H
2010 Symplicity HTN-2	L	L	L	L	L	L
2015 DENERHTN	L	L	L	L	L	L
2015 Desch	L	L	L	L	L	L
2016 ReSet	S	L	L	L	L	S
2018 RADIANCE-HTN SOLO	L	L	L	L	L	L
2018 SPYRAL HIN-ON MED	L	L	L	L	L	L
2020 REDUCE HIN: REINFORCE	L	L	S	L	S	S
2020 SPYRAL HTN-OFF MED	L	L	L	L	L	L
2021 RADIANCE-HIN TRIO	L	L	L	L	L	L
2021 REQUIRE	L	L	L	L	L	L
2023 RADIANCE II	L	L	L	L	L	L
2024 Jiang	L	L	L	L	L	L

Note: H: high risk of bias; L: low risk of bias; RoB: risk of bias; S: some risk of bias.

research may limit the comprehensiveness of the literature search. Second, although we performed subgroup analyses based on the type of RDN and the follow-up time, differences in study design, inclusion and exclusion criteria, and baseline characteristics (e.g., gender, study area, ethnicity) may also have contributed to differences. Most of the outcomes in our study had low heterogeneity; heterogeneity was higher in the change in office SBP and the change in home DBP, at 79% and 78%, respectively. In addition, although we performed subgroup analyses, they were only roughly grouped according to follow-up time greater or less than 6 months, and more long-term clinical trials are needed in the future to study the long-term effects of RDN on blood pressure.

5 | Conclusion

In conclusion, RDN is an effective treatment for controlling blood pressure and does not increase the risk of AEs and SAEs. Subgroup analyses showed that RDN remains effective at long-

term follow-up, and both ultrasound and radiofrequency RDN were effective.

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Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent

The authors have nothing to report.

Conflicts of Interest

All authors declared no conflict of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

References

1. N. K. Choudhry, I. M. Kronish, W. Vongpatanasin, et al., "Medication Adherence and Blood Pressure Control: A Scientific Statement From the American Heart Association," *Hypertension* 79 (2022): e1–e14, https://doi.org/10.1161/hyp.0000000000000203.

2. P. Muntner, S. T. Hardy, L. J. Fine, et al., "Trends in Blood Pressure Control Among US Adults With Hypertension, 1999–2000 to 2017–2018," *Jama* 324 (2020): 1190–1200, https://doi.org/10.1001/jama.2020.14545.

3. NCD Risk Factor Collaboration (NCD-RisC), "Worldwide Trends in Hypertension Prevalence and Progress in Treatment and Control From 1990 to 2019: A Pooled Analysis of 1201 Population-Representative Studies With 104 Million Participants," *Lancet* 2021; 398: 957–980, https://doi.org/10.1016/s0140-6736(21)01330-1.

4. M. Burnier and B. M. Egan, "Adherence in Hypertension," *Circulation Research* 124 (2019): 1124–1140, https://doi.org/10.1161/circresaha.118.313220.

5. G. Bakris and S. Nathan, "Renal Denervation and Left Ventricular Mass Regression," *Journal of the American College of Cardiology* 63 (2014): 1924–1925, https://doi.org/10.1016/j.jacc.2013.11.015.

6. A. Doroszko, A. Janus, E. Szahidewicz-Krupska, et al., "Resistant Hypertension," *Advances in Clinical and Experimental Medicine: Official Organ Wroclaw Medical University* 25 (2016): 173–183, 10.17219/acem/58998.

7. G. Lamirault, M. Artifoni, M. Daniel, et al., "Resistant Hypertension: Novel Insights," *Current Hypertension Reviews* 16 (2020): 61–72, https://doi.org/10.2174/1573402115666191011111402.

8. A. Myat, S. R. Redwood, A. C. Qureshi, et al., "Renal Sympathetic Denervation Therapy for Resistant Hypertension," *Circulation: Cardiovascular Interventions* 6 (2013): 184–197, https://doi.org/10.1161/CIRCINTERVENTIONS.112.000037.

9. M. Esler, "Renal Denervation for Hypertension: Observations and Predictions of a Founder," *European Heart Journal* 35 (2014): 1178–1185, https://doi.org/10.1093/eurheartj/ehu091.

10. G. F. DiBona, "Neural Control of the Kidney: Functionally Specific Renal Sympathetic Nerve Fibers," *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 279 (2000): R1517–1524, https://doi.org/10.1152/ajpregu.2000.279.5.R1517.

11. K. Sakakura, E. Ladich, Q. Cheng, et al., "Anatomic Assessment of Sympathetic Peri-Arterial Renal Nerves in Man," *Journal of the American College of Cardiology* 64 (2014): 635–643, https://doi.org/10.1016/j.jacc.2014.03.059.

12. M. P. Schlaich, E. Lambert, D. M. Kaye, et al., "Sympathetic Augmentation in Hypertension," *Hypertension* 43 (2004): 169–175, https://doi.org/10.1161/01.HYP.0000103160.35395.9E.

13. A. Rao and N. Krishnan, "Update on Renal Sympathetic Denervation for the Treatment of Hypertension," *Current Cardiology Reports* 24 (2022): 1261–1271, https://doi.org/10.1007/s11886-022-01753-x.

14. D. L. Bhatt, D. E. Kandzari, W. W. O'Neill, et al., "A Controlled Trial of Renal Denervation for Resistant Hypertension," *New England Journal of Medicine* 370 (2014): 1393–1401, https://doi.org/10.1056/NEJMoa1402670.

15. M. Azizi, R. E. Schmieder, F. Mahfoud, et al., "Endovascular Ultrasound Renal Denervation to Treat Hypertension (RADIANCE-HTN SOLO): A Multicentre, International, Single-Blind, Randomised, Sham-Controlled Trial," *Lancet* 391 (2018): 2335–2345, https://doi.org/10.1016/S0140-6736(18)31082-1.

16. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *Bmj* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

17. J. A. C. Sterne, J. Savovic, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *Bmj* 366 (2019): l4898, https://doi.org/10.1136/bmj.l4898.

18. H. Symplicity, M. D. Esler, H. Krum, et al., "Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension (The Symplicity HTN-2 Trial): A Randomised Controlled Trial," *Lancet* 376 (2010): 1903–1909, https://doi.org/10.1016/S0140-6736(10)62039-9.

19. D. L. Bhatt, D. E. Kandzari, W. W. O'Neill, et al., "A Controlled Trial of Renal Denervation for Resistant Hypertension," *New England Journal of Medicine* 370 (2014): 1393–1401, https://doi.org/10.1056/NEJMoa1402670.

20. M. Azizi, M. Sapoval, P. Gosse, et al., "Optimum and Stepped Care Standardised Antihypertensive Treatment With or Without Renal Denervation for Resistant Hypertension (DENERHTN): A Multicentre, Open-Label, Randomised Controlled Trial," *Lancet* 385 (2015): 1957–1965, https://doi.org/10.1016/S0140-6736(14)61942-5.

21. S. Desch, T. Okon, D. Heinemann, et al., "Randomized Sham-Controlled Trial of Renal Sympathetic Denervation in Mild Resistant Hypertension," *Hypertension* 65 (2015): 1202–1208, https://doi.org/10.1161/HYPERTENSIONAHA.115.05283.

22. O. N. Mathiassen, H. Vase, J. N. Bech, et al., "Renal Denervation in Treatment-Resistant Essential Hypertension. A Randomized, SHAM-Controlled, Double-Blinded 24-h Blood Pressure-Based Trial," *Journal of Hypertension* 34 (2016): 1639–1647, https://doi.org/10.1097/HJH.0000000000000977.

23. M. Azizi, R. E. Schmieder, F. Mahfoud, et al., "Endovascular Ultrasound Renal Denervation to Treat Hypertension (RADIANCE-HTN SOLO): A Multicentre, International, Single-Blind, Randomised, Sham-Controlled Trial," *Lancet* 391 (2018): 2335–2345, https://doi.org/10.1016/S0140-6736(18)31082-1.

24. F. Mahfoud, D. E. Kandzari, K. Kario, et al., "Long-Term Efficacy and Safety of Renal Denervation in the Presence of Antihypertensive Drugs (SPYRAL HTN-ON MED): A Randomised, Sham-Controlled Trial," *Lancet* 399 (2022): 1401–1410, https://doi.org/10.1016/S0140-6736(22)00455-X.

25. M. Bohm, K. Kario, D. E. Kandzari, et al., "Efficacy of Catheter-Based Renal Denervation in the Absence of Antihypertensive Medications (SPYRAL HTN-OFF MED Pivotal): A Multicentre, Randomised, Sham-Controlled Trial," *Lancet* 395 (2020): 1444–1451, https://doi.org/10.1016/S0140-6736(20)30554-7.

26. M. A. Weber, A. J. Kirtane, M. R. Weir, et al., "The REDUCE HTN: REINFORCE: Randomized, Sham-Controlled Trial of Bipolar Radiofrequency Renal Denervation for the Treatment of Hypertension," *JACC Cardiovascular Interventions* 13 (2020): 461–470, https://doi.org/10.1016/j.jcin.2019.10.061.

27. M. Azizi, K. Sanghvi, M. Saxena, et al., "Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill (RADIANCE-HTN TRIO): A Randomised, Multicentre, Single-Blind, Sham-Controlled Trial," *Lancet* 397 (2021): 2476–2486, https://doi.org/10.1016/S0140-6736(21)00788-1.

28. K. Kario, Y. Yokoi, K. Okamura, et al., "Catheter-Based Ultrasound Renal Denervation in Patients With Resistant Hypertension: The Randomized, Controlled Require Trial," *Hypertension Research* 45 (2022): 221–231, https://doi.org/10.1038/s41440-021-00754-7.

29. M. Azizi, M. Saxena, Y. Wang, et al., "Endovascular Ultrasound Renal Denervation to Treat Hypertension: The RADIANCE II Randomized Clinical Trial," *Jama* 329 (2023): 651–661, https://doi.org/10.1001/jama.2023.0713.

30. X. Jiang, F. Mahfoud, W. Li, et al., "Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation in Chinese Patients With Uncontrolled Hypertension: The Randomized, Sham-Controlled, Multi-Center Iberis-HTN Trial," *Circulation* 150 (2024): 1588–1598, https://doi.org/10.1161/CIRCULATIONAHA.124.069215.

31. K. Fengler, P. Reimann, K. P. Rommel, et al., "Comparison of Long-Term Outcomes for Responders Versus Non-Responders Following Renal Denervation in Resistant Hypertension," *Journal of the American Heart Association* 10 (2021): e022429, https://doi.org/10.1161/jaha.121.022429.

32. A. Persu, M. S. Stoenoiu, F. Maes, et al., "Late Outcomes of Renal Denervation Are More Favourable Than Early Ones: Facts or Fancies?," *Clinical Kidney Journal* 16 (2023): 2357–2364, https://doi.org/10.1093/ckj/sfad231.

33. R. R. Singh, Z. M. McArdle, M. Iudica, et al., "Sustained Decrease in Blood Pressure and Reduced Anatomical and Functional Reinnervation of Renal Nerves in Hypertensive Sheep 30 Months After Catheter-Based Renal Denervation," *Hypertension* 73 (2019): 718–727, https://doi.org/10.1161/hypertensionaha.118.12250.

34. C. Templin, M. Jaguszewski, J. R. Ghadri, et al., "Vascular Lesions Induced by Renal Nerve Ablation as Assessed by Optical Coherence Tomography: Pre- and Post-Procedural Comparison With the Simplicity Catheter System and the EnligHTN Multi-Electrode Renal Denervation Catheter," *European Heart Journal* 34 (2013): 2141–2148, https://doi.org/10.1093/eurheartj/eht141.

35. A. S. P. Sharp, S. Tunev, M. Schlaich, et al., "Histological Evidence Supporting the Durability of Successful Radiofrequency Renal Denervation in a Normotensive Porcine Model," *Journal of Hypertension* 40 (2022): 2068–2075, https://doi.org/10.1097/hjh.0000000000003236.

36. K. R. L. Reyes and F. Rader, "Long-Term Safety and Antihypertensive Effects of Renal Denervation: Current Insights," *Integrated Blood Pressure Control* 16 (2023): 59–70, https://doi.org/10.2147/ibpc.S392410.

37. F. Mahfoud, M. Böhm, R. Schmieder, et al., "Effects of Renal Denervation on Kidney Function and Long-Term Outcomes: 3-Year Follow-Up From the Global SYMPLICITY Registry," *European Heart Journal* 40 (2019): 3474–3482, https://doi.org/10.1093/eurheartj/ehz118.

38. Y. Ahmad, D. P. Francis, D. L. Bhatt, et al., "Renal Denervation for Hypertension: A Systematic Review and Meta-Analysis of Randomized, Blinded, Placebo-Controlled Trials," *JACC: Cardiovascular Interventions* 14 (2021): 2614–2624, https://doi.org/10.1016/j.jcin.2021.09.020.

39. K. Fengler, K. P. Rommel, S. Blazek, et al., "A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients with Resistant Hypertension (RADIOSOUND-HTN)," *Circulation* 139 (2019): 590–600, https://doi.org/10.1161/circulationaha.118.037654.

40. G. Grassi, A. Mark, and M. Esler, "The Sympathetic Nervous System Alterations in Human Hypertension," *Circulation Research* 116 (2015): 976–990, https://doi.org/10.1161/circresaha.116.303604.

41. F. Mahfoud, R. R. Townsend, D. E. Kandzari, et al., "Changes in Plasma Renin Activity after Renal Artery Sympathetic Denervation," *Journal of the American College of Cardiology* 77 (2021): 2909–2919, https://doi.org/10.1016/j.jacc.2021.04.044.

42. H. Krum, M. P. Schlaich, P. A. Sobotka, et al., "Percutaneous Renal Denervation in Patients With Treatment-Resistant Hypertension: Final 3-Year Report of the Symplicity HTN-1 Study," *Lancet* 383 (2014): 622–629, https://doi.org/10.1016/s0140-6736(13)62192-3.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file 1: jch70080-sup-0001-SuppMat.docx. **Supporting file 2:** jch70080-sup-0002-SuppMat.docx.