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Effect of Combined Renal Denervation and Pulmonary Vein Isolation on Atrial Fibrillation: A Systematic Meta-Analysis

ABSTRACT

Background: Atrial fibrillation (AF) is the most common type of heart arrhythmia. Hypertension (HTN) is known as the most common risk factor for AF. The purpose of this study is to compare clinical results of combined renal denervation (RDN) and pulmonary vein isolation (PVI) in AF patients with HTN.

Methods: A systematic search was conducted on patients with AF and HTN, comparing the differences between RDN and PVI with PVI alone. The risk ratio (RR) of categorical variables and the mean difference of continuous variables with a 95% confidence interval were applied.

Results: This meta-analysis included 10 studies with a total of 875 patients. 420 patients were in the RDN + PVI group (48%) while 455 (52%) were in the PVI group. 694 patients had paroxysmal AF (79.3%) and 181 patients had persistent AF (20.7%). At 12 months follow-up, the treatment of RDN + PVI reduced the overall risk of AF recurrence in HTN patients (RR = 0.64, $P < .001$, 95% confidence interval: 0.55-0.75). When pooled, the patients in the RDN + PVI group showed significant mean reductions in systolic blood pressure (BP) (−13.39 mm Hg, $P < .001$) and diastolic BP (−7.14 mm Hg, $P < .001$) compared to PVI alone. Meanwhile, PVI + RDN significantly increased the estimated glomerular filtration rate (+8.72 mL/min/1.73 m^2, $P < .001$) compared with PVI alone. There was no significant difference in complications between the 2 groups.

Conclusion: Combined therapy of RDN + PVI seems more efficacious and superior to PVI alone in treating AF. Further and larger trials are needed to fully prove these outcomes.

Keywords: Atrial fibrillation, hypertension, pulmonary vein isolation, renal denervation

META-ANALYSIS

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia characterized by irregular and disordered atrial electrical activity, which inhibits normal sinus rhythm. It affects up to 1% of the general population worldwide.[1] Hypertension (HTN) often accompanies many kinds of comorbidities and cardiac end-organ damage, such as arrhythmias caused by long-term exposure to elevated blood pressure (BP). Uncontrolled HTN plays an important role in the pathogenesis and prognosis of AF.[2] Yet, HTN is the most important independent predictor of recurrent AF after catheter ablation.[3,4] The sympathetic nervous system is also considered to have important implications in the occurrence and maintenance of AF. Overactivation of the sympathetic nervous system can predict AF recurrences after catheter ablation. There may be a synergism between sympathetic overactivation and HTN, resulting in abnormal atrial electrical conduction and facilitating AF. Therefore, a new method for controlling BP and sympathetic nervous system activity in patients with AF and HTN is feasible and potentially beneficial. The evidence-based and most mature technique is pulmonary vein isolation (PVI) for AF, including radiofrequency or cryoballoon ablation. Nevertheless, the failure rate of AF recurrences after PVI, typically 40%-50%, remains unacceptably high and repeat operation are often needed.[5]

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Renal denervation (RDN) is a novel nonpharmacologic catheter-based intervention therapy that ablates the renal sympathetic nervous system, including both efferent fibers that regulates renin-angiotensin aldosterone axis and afferent fibers that adjusts systemic sympathetic nervous tone. Renal denervation has been demonstrated to suppress sympathetic activity and reduce BP in certain patients with HTN.[6,7] It is firmly believed that RDN might influence the results of patients with AF and HTN after PVI. However, the data about the effects of combined RDN and PVI for AF are currently limited. Several analyses from randomized controlled trials (RCTs) have added new evidence concerning the efficacy and safety of RDN in HTN patients. Given this fresh data, the aim was to summarize the published evidence of RDN therapy to assess the effect and safety of RDN associated with PVI on AF.

METHODS

Search Strategy and Selection Criteria

We performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8,9] This included the use of prior study design, a detailed literature search, duplicate study screening, selection and data extraction, scientific quality and bias assessment of included studies, reporting of study features, and appropriate statistical methods to evaluate research results. The original strategy was executed by 2 authors. A systematic search was conducted using PubMed, Web of Science, EMBASE, SCOPUS, Cochrane, Ovid, Proquest, ClinicalTrials, CBM, CKNI WANFANG, VIP, DUXIU, Chinese Clinical Trial Registry without language restriction up until April 18, 2024. Studies comparing RDN with PVI versus PVI alone were analyzed. The search used the following combination of keywords: RSDN, RDN, renal denervation, renal sympathetic denervation, renal sympathetic nerve denervation, renal ablation, renal artery denervation, catheter ablation, catheter-based RDN, kidney denervation, pulmonary vein isolation, AF, afib, atrial fibrillations, auricular fibrillation, auricular fibrillations, fibrillation, auricular, fibrillations, auricula, persistent atrial fibrillation, persistent atrial fibrillations, familial atrial fibrillation.

The studies were screened during the 3 stages (titles, abstracts, and full-text of papers) independently, duplicated, and assessed for risk of bias by 2 authors. Internal discussions were held on disagreements before entering the next stage of screening. Studies that met the following criteria were included: (1) the study assessed and compared RDN with PVI and PVI alone in patients, (2) the study involved adult human subjects aged ≥ 18 years, (3) the study reported at least 1 clinical result, (4) RCTs and prospective comparative studies. Exclusion criteria included: (1) studies with no control groups; (2) retrospective studies; (3) editorials; (4) case reports; (5) expert opinions; (6) reviews; and (7) studies with overlapping data. Non-English studies were searched but ultimately excluded due to the inability to analyze them. A PRISMA flowchart of the literature screening is shown in Figure 1.

A review protocol was not registered. Artificial intelligence-assisted technologies (such as large language models, chatbots, or image creators) were not used in the production of the submitted work.

Clinical Outcomes

The following clinical outcomes were collected: (1) AF recurrence, (2) changes in BP, (3) changes in estimated glomerular filtration rate (eGFR), and (4) complications including major adverse events. Atrial fibrillation recurrence (including atrial flutter or atrial tachycardia) was defined as episodes of atrial tachyarrhythmias lasting >30 seconds during the follow-up period. The first 3 months after ablation were considered a blanking period and excluded from the analysis. Major adverse events included vascular complications requiring intervention or surgery, pericardial tamponade requiring drainage, renal artery complications requiring intervention, phrenic nerve palsy, pneumothorax, stroke, and death.

The following information, if available, was extracted from the studies: primary author and year, study design and purpose, sample size, age and gender information, country of study, follow-up time frame, baseline study sample characteristics (number of HTN medications, eGFR, presence of type 2 diabetes, coronary artery disease (CAD), left-ventricular ejection fraction, left-atrial diameter (LAD), AF type, systolic blood pressure (SBP) and diastolic blood pressure (DBP)), follow-up data on AF recurrence, BP, eGFR, and safety complications.

Risk of Bias Assessments

The Cochrane risk of bias tool (The Cochrane Collaboration, Copenhagen, Denmark) was used to assess the quality and publication bias of the individual studies that were randomized. Studies that were non-randomized but prospective were assessed for quality and publication bias using The Methodological Index for Non-Randomized Studies (MINORS). The quality of the included studies was evaluated independently by 2 authors according to the Cochrane's risk of bias 2.0. If there were disagreements, a third researcher was consulted. Each quality item was graded as low risk, high risk, or no clear risk. The evaluation content included 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

HIGHLIGHTS

- The failure rate of atrial fibrillation (AF) recurrences after pulmonary vein isolation (PVI) remains unacceptably high and repeat operation are often needed.
- Renal denervation (RDN) intervenes in the contact between the kidney and autonomic nervous system to reduce blood pressure (BP).
- Renal denervation could be a safe and effective antihypertensive therapy option for patients with hypertension and chronic kidney disease.
- Combined RDN + PVI therapy significantly lowered AF recurrence and BP compared to PVI alone, without increasing complication rates.

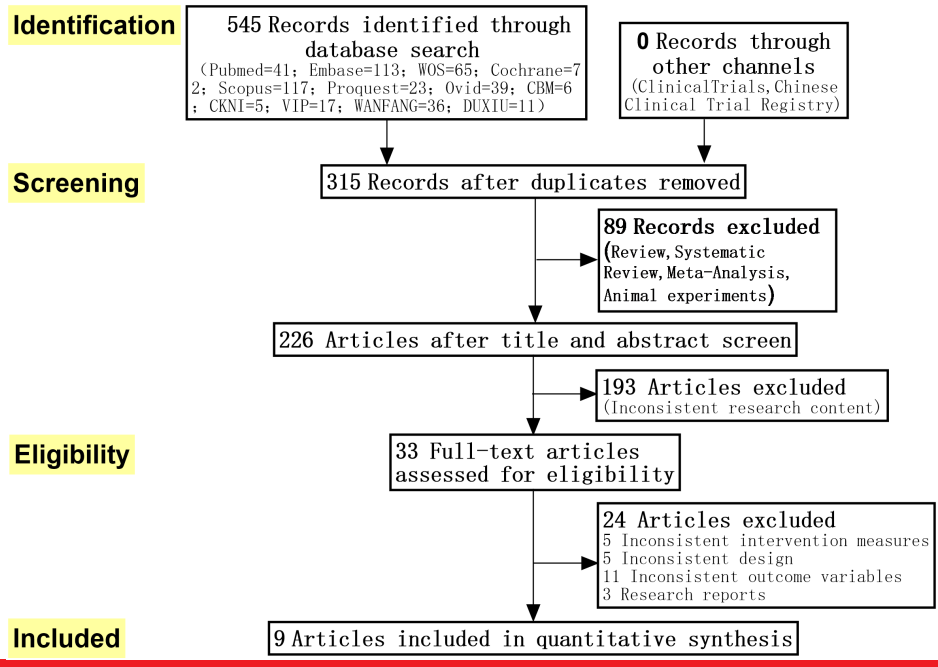

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis chart. Flow chart outlining the screening process for the included/excluded studies and detailing the results following each screening stage.

Data Analysis

The main outcomes were AF recurrence, the antihypertensive effect of RDN, and the effect of RDN on eGFR. Secondarily, the analysis was to appraise the efficacy, safety, and durability of RDN. Statistical analysis was done with Review Manager (RevMan), version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and Stata 16. The DerSimonian Laird random-effects model was used to estimate the risk ratios and mean difference (MD) with the corresponding 95% confidence interval (CI). A bilateral *P*-value <.05 is considered statistically significant. Heterogeneity was evaluated using Higgins and Thompson I^2 statistic with I^2 values of 25%, 25%-75%, and 75% respectively matching low, moderate, and high levels of heterogeneity. The risk of bias was assessed in STATA 16. Sensitivity analyses were conducted on the primary endpoint by excluding trials with bias risk and applying the Hartung Knap adjustment. Egger's regression test and a funnel plot were used to assess publication bias for the outcomes. Outcome pooling required at least 3 studies.[10,11]

RESULTS

Literature Screening Results and Literature Quality Evaluation

Figure 1 is a PRISMA chart shows the results of the literature search.[12] A total of 226 citations were identified after a thorough and detailed search procedure. Thirty-three full-text articles were evaluated for eligibility, and 24 were excluded after screening. Nine eligible articles were included after screening according to the inclusion criteria (Figure 1). Table 1 summarizes the characteristics of 10 included studies are summarized owing to 1 of the 9 aticles reporting 2 separate studies. According to MINORS, the literature quality score of Kiuchi et al,[15] 2017 is shown in Table 2. According to the Cochrane's risk of bias, the quality of the other literature is shown in Figure 2.

Baseline Study Characteristics

Table 3 outlines the inclusion criteria and the procedural methods utilized by the studies. The 10 trials included a total of 875 patients, with 420 in the PVI + RDN group and 455 in the PVI-only group (Table 1). The follow-up time ranged from 12 to 24 months (Table 1). There was a total of 695 patients with paroxysmal AF (PAF) and 181 patients with persistent AF (Table 1).

Effect of Renal Denervation on Atrial Fibrillation Recurrence

All the included studies reported AF recurrence rates during the follow-up period (Table 4). The rate of AF recurrence was significantly reduced across 7 trials in the RDN + PVI group (Table 4). Although AF recurrence rates were lower in the PVI + RDN groups of HFIB-1, HFIB-2, and Kirstein trials, they failed to show significant differences (Table 4). The overall pooled results indicated a significantly lower AF recurrence rate in the PVI + RDN (36.0%) group compared to the PVI-only (57.1%) group ($P < .001$) (Figure 3). The 10 contained studies were subjected to heterogeneity testing, with $I^2 = 0\%$ (<50%) and a *P*-value of .79 (>0.1) in the Q-test, indicating that the heterogeneity between the selected literature in this study is not statistically significant. Therefore, fixed effects were chosen for combined effect size. The combined effect showed a RR of 0.64 (95% CI: 0.55-0.75) and statistical significance ($Z = 5.62$, $P < .001$), demonstrating that the efficacy of RDN + PVI for AF appears significantly better than PVI alone (Figure 3A). The funnel plot is symmetrical and shows no publication bias, suggesting that the conclusion of this study is accurate and reliable (Figure 3B).

Table 1. Baseline Characteristics of Included Studies

Study Author (Year)	Design	Follow-Up (Months)	RDN + PVI (N)	PVI (N)	Age (Years)	Number of Females	Antihypertens-ives	LVEF ± SD (%)	LAD ± SD mm	Patients with T2D (%)	Patients with CAD (%)	Types of AF
Kirstein et al, (2022)[13]	RCT	12	39	22	RDN: 66.3 ± 7.9 PVI: 63.0 ± 9.9	RDN: 10 PVI:19	RDN: ACEi/ARB 89.7% CCB 69.2% BB 87.2% Diuretic 97.4% PVI: ACEi/ARB 100% CCB 45.5% BB 95.5% Diuretic 100%	RDN: 58.2 ± 9.5 PVI: 58.8 ± 8.9	RDN: 45.4 ± 6.2 PVI: 44.5 ± 5.7	RDN: 41.0 PVI: 31.8	RDN: 12.8 PVI: 31.8	Paroxysmal 50.8%, Persistent 49.2%
Kiuchi et al, (2016)[14]	RCT	12	21	24	RDN: 68 ± 9 PVI: 66 ± 9	RDN: 8 PVI: 8	RDN: ACEi/ARB 100% CCB 100% BB 67% Diuretic 76% PVI: ACEi/ARB 100% CCB 100% BB 63% Diuretic 67%	RDN: 62.7 ± 6.6 PVI: 63.5 ± 6.8	RDN: 45.1 ± 3.2 PVI: 44.9 ± 3.9	RDN: 76.2 PVI: 54.2	RDN: 57.1 PVI: 58.3	Paroxysmal 60%, Persistent 40%
Kiuchi et al, (2017)[15]	Prospe-ctive Nonra-ndomized	12	39	96	RDN: 60 ± 14 PVI: 59 ± 15	RDN:15 PVI:31	RDN: ACEi/ARB 100% CCB 33% BB 56% Diuretic 69% PVI: ACEi/ ARB 100% CCB 32% BB 52% Diuretic 71%	RDN: 65.8 ± 12.8 PVI: 66.5 ± 10.0	RDN: NR PVI: NR	RDN: 35.9 PVI: 37.5	RDN: NR PVI: NR	Paroxysmal 100%
Kiuchi et al, (2018)[16]	RCT	12	33	36	RDN: 56.8 ± 6.5 PVI: 58.4 ± 5.1	RDN:8 PVI:6	RDN: ACEi/ARB 100% CCB 100% BB 55% Diuretic 100% PVI: ACEi/ARB100% CCB 100% BB 69% Diuretic 100%	RDN: 62.2 ± 7.20 PVI: 61.2 ± 5.70	RDN: NR PVI: NR	RDN: 4.2 PVI: 27.8	RDN: 15.2 PVI: 25.0	Paroxysmal 100%
Pokushalov et al, (2012)[17]	RCT	12	13	14	RDN: 57 ± 8 PVI: 56 ± 9	RDN:2 PVI:4	RDN: ACEi/ARB 92% CCB 76% BB 77% Diuretic 100% PVI: ACEi/ARB 100% CCB 71% BB 78% Diuretic 92%	RDN: 65 ± 5 PVI: 66 ± 4	RDN: 49 ± 7 PVI: 50 ± 6	RDN: 7.7 PVI: 14.2	RDN: 15.3 PVI: 14.2	Paroxysmal 33%, Persistent 66%

Pokushalov et al, (2014)[18]	RCT	12	41	39	RDN: 56 ± 6 PVI: 56 ± 6	RDN:10 PVI:15	RDN: ACEi/ARB 98% CCB 76% BB 37% Diuretic 98% PVI: ACEi/ARB 100% CCB 72% BB 44% Diuretic 100%	RDN: 60 ± 4 PVI: 61 ± 5	RDN: 47.0 ± 5.0 PVI: 47.0 ± 4.0	RDN: 12.2 PVI: 22.5	RDN: 12.2 PVI: 10.3	Paroxysmal 43.75%, Persistent 56.25%
Romanov et al, (2016)[19]	RCT	12	39	37	RDN: 56 ± 6 PVI: 56 ± 5	RDN: 10 PVI:11	RDN: ACEi/ARB 97.4% CCB 76.9% BB 35.9% Diuretic 97.4% PVI: ACEi/ARB 100% CCB 72.9% BB 43.2% Diuretic 100%	RDN: 60 ± 4 PVI: 61 ± 4	RDN: 47 ± 6 PVI: 47 ± 5	RDN: 10.2 PVI: 8.1	RDN: 10.2 PVI: 10.8	Paroxysmal 40.78%, Persistent 59.21%
Steinberg et al, (2020)[20]	RCT	12	154	148	RDN: 59 (54-65) PVI: 60 (58-65)	RDN: 63 PVI:57	RDN: ACEi/ARB 100% CCB 67.5% BB 23.3% Diuretic 17.5% PVI: ACEi/ARB 100% CCB 70.9% BB 23.6% Diuretic 18.2%	RDN: 62.0 ± 5.0 PVI: 62.0 ± 5.0	RDN: 48 ± 3 PVI: 47 ± 3	RDN: 10.4 PVI: 12.2	RDN: 9.1 PVI: 6.8	Paroxysmal, 100%
Turagam-HFIB1 et al, (2021)[21]	RCT	24	13	17	RDN: 59 ± 10 PVI: 68 ± 9	RDN: 5 PVI:8	RDN: ACEi/ARB 38% CCB 38% BB 77% Diuretic 69% PVI: ACEi/ARB 42% CCB 42% BB 83% Diuretic 59%	RDN: 60.0 ± 6.0 PVI: 61.0 ± 5.0	RDN: 51.0 ± 0.9 PVI: 46.0 ± 0.7	RDN: 0 PVI: 17.6	RDN: NR PVI: NR	Paroxysmal 66.7%, Persistent 33.3%
Turagam-HFIB2 et al, (2021)[21]	RCT	24	28	22	RDN: 64 ± 7 PVI: 65 ± 8	RDN:12 PVI:8	RDN: ACEi/ARB 54% CCB 46% BB 4% Diuretic 75% PVI: ACE/ARB 41% CCB 59% BB 0% Diuretic 41%	RDN: 62.0 ± 6.0 PVI: 64.0 ± 5.0	RDN: 54.0 ± 0.9 PVI: 47.0 ± 1.3	RDN: 17.9 PVI: 57.3	RDN: NR PVI: NR	Paroxysmal 70.0%, Persistent 30.0%

Data for age, left-atrial diameter and left-ventricular ejection fraction are displayed as means and SD.
AF, atrial fibrillation; CAD, coronary artery disease; HTN, hypertension; IQR, interquartile range; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; BB, Beta-blocker; LAD, left-atrial diameter; LVEF, left-ventricular ejection fraction; NR, not reported; PVI, pulmonary vein isolation; RCT, randomized control trial; RDN, renal denervation; T2D, type 2 diabetes.

Table 2. Literature quality evaluation of 1 study[15]

Methodological Items for Non-Randomized Studies	Score†
1. A clearly stated aim	2
2. Inclusion of consecutive patients	1
3. Prospective collection of data	1
4. Endpoints appropriate to the aim of the study	2
5. Unbiased assessment of the study endpoint	0
6. Follow-up period appropriate to the aim of the study	1
7. Loss to follow-up less than 5%	2
8. Prospective calculation of the study size	1
9. An adequate control group	2
10. Contemporary groups	1
11. Baseline equivalence of groups	2
12. Adequate statistical analyses	2

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).

Effects of Renal Denervation on Blood Pressure

All included studies reported follow-up data on BP following the procedure (Table 4). One of the studies without follow-up BP[19] and 2 with follow-up BP displayed without standard deviation[21] were excluded from the meta-analysis. Two of the studies that included patients with drug-controlled HTN were also excluded.[14,15] For merged analysis, 12-month follow-up data was used to compare changes in BP. Three studies reported a significant decrease in both office SBP and DBP in the PVI + RDN group vs. the PVI alone group.[17,18,20] One study reported no significant decrease in office SBP in the 2 groups.[13] One study reported a significant reduction in ambulatory SBP in the 2 groups.[16] When merged, the overall outcomes showed a significant MD in SBP of −13.39 mm Hg in the PVI + RDN group vs. the PVI alone group ($P < .001$) (Figure 4A). The merged DBP analysis also showed a significant difference between the groups ($P < .001$) (Figure 5A). The combined analysis of both SBP and DBP showed a high heterogeneity of $I^2 = 93\%$ and 76% respectively. A sensitivity analysis was performed by deleting each study in turn and evaluating its impact on the SBP and DBP pooled analyses (Figures 4 and 5D). For asymmetric funnel plots of DBP, the trim-and-fill analysis was chosen for correction. After 3 iterations, the results of 2 virtual articles were generated, and a total of 7 articles were trimmed without publication bias (Figure 6). The adjusted MD = −8.12 mm Hg (95% CI: −6.24 to −9.99) (Figure 6). Comparing the results before and after pruning, it can be considered that the existing meta-analysis results are not stable. If there are new research results or reports in the future, they may cause changes in the meta-analysis results.

Effect of Renal Denervation on Estimated Glomerular Filtration Rate

Every study reported eGFR at baseline. However, 1 study only reported eGFR changes for the PVI + RDN group and was therefore excluded.[18] Only 5 studies reported eGFR during the follow-up period (Table 5).[13-17] To conduct a pooled analysis, the eGFR at the 6-month follow-up period was compared(Figure 7). The combined analysis showed a MD of +8.72 mL/min/1.73 m^2 (95% CI: 4.10-13.33) significantly in favor of the PVI + RDN group ($Z = 3.70$, $P < .001$) (Figure 7A). Sensitivity analysis was performed owing to the high heterogeneity ($I^2 = 93\%$). The trim-and-fill analysis was chosen for correction because of asymmetric funnel plots of eGFR. No studies were imputed after trim-and-fill, thus publication bias was minimal ($P = .044$) (Figure 8).

Complications

Nine trials reported data about complications following the procedure and during the follow-up period in the 2 gro ups.[13-18,20,21] The total incidence of complications between the 2 groups was 4.99% (n = 381) and 3.59% (n = 418) respectively. There were no significant differences in complications (RR = 1.11, $P = .74$, 95% CI: 0.61-2.02), further indicating the safety of RDN (Figure 9).

DISCUSSION

The results from 10 studies investigating the use of combined RDN and PVI in the treatment of paroxysmal and/or persistent AF in 876 patients with HTN and AF were examined. On the basis of the available evidence, the main findings of the study favoring the following favoring RDN and PVI treated group are the following: (1) the risk of AF recurrence is significantly reduced at follow-up; (2) SBP and DBP are significantly reduced at the 12-month follow-up; (3) eGFR is significantly increased at the 6-month follow-up; (4) the total rate of complications in the 2 groups, both during the procedures and during the follow-up period, is low; (4) there is no significant difference in complications.

Atrial fibrillation is related to an increased risk of cardiovascular events, mortality, and cognitive decline.[22] Hypertension is one of the major modifiable and independent risk factors for the development and progression of AF.[23] Atrial fibrillation increases BP beat-to-beat variability,[24] which raises concerns about the potential risk of hypoperfusion and its influence on vascular and cognitive function. A recent meta-analysis of clinical trials showed that patients with AF had a reduced risk of dementia from BP-lowering treatment.[25] There may be a synergistic effect between HTN and sympathetic overactivation, leading to abnormal atrial electrical conduction and promoting AF. A novel treatment regulating both BP and sympathetic activity in patients with AF and HTN is desirable and may be potentially beneficial.

Renal denervation has been proved to be effective in lowering BP in resistant HTN patients in multiple trials and network meta-analysis.[26,27] With recent continuous trials, RDN is under investigation for comorbidities associated with increased sympathetic nervous system (SNS) activity.[28] Various epidemiological studies further support the use of RDN in AF, demonstrating that lowering BP into a lower category of HTN can reduce the odds of AF recurrence, where HTN is an established risk factor.[29] This study found a significant reduction in the rate of AF recurrence in the RDN + PVI group (36.9%) compared to the PVI alone group (57.7%). If proved effective, the added cost and time of RDN would need to be justified by reduced AF recurrences and possibly fewer repeat ablations in the long run. Of note, freedom from

Figure 2. Literature quality evaluation of 9 studies. A. Risk of bias graph. B. Risk of bias summary.

AF recurrence at 12 and 24 months after catheter ablation in the RDN + AF group and the PVI-only group did not reach statistical significance in the recently published RDN + AF study.[13] Although the exact mechanism behind the antiarrhythmic effects of RDN remains elusive, it was proposed that autonomic nervous system modulation plays a central role.[30] An increase in the activation of SNS was related to the promotion of atrial arrhythmia genesis[31] by exacerbating left atrial structural modifications and hence electrical remodeling into AF. In the studies included in this meta-analysis, a significant reduction in SBP and DBP at the 12-month follow-up was observed. However, Kiuchi et al[14,15] did not report significant BP differences in-group on follow-up compared to baseline for both arms, as shown in Kirstein's study.[13]

It remains unclear whether RDN improved AF outcomes by better BP control, a direct antiarrhythmic effect mediated by sympathetic inhibition, or both. Kirstein's study provided evidence that among patients with multidrug-resistant arterial HTN and paroxysmal or persistent AF, concomitant

Table 3. Criteria and Intervention Method of Included Studies

Study Author (Year)	Study Population	AF Definition	PVI Method	RDN Method
Kirstein et al, (2022)[13]	• Refractory paroxysmal or persistent AF • Drug-resistant HTN (ASBP > 135) • At least 3 antihypertensive (including 1 diuretic) • eGFR ≥ 45	PAF = AF duration up to 7 days, Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	EnligHTN
Kiuchi et al, (2016)[14]	• Refractory paroxysmal or persistent AF • Drug-controlled HTN (130 > ASBP ≥ 100) • eGFR between 30 and 89 and if >60 microalbuminuria	PAF = AF duration up to 7 days, Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	Irrigated tip
Kiuchi et al, (2017)[15]	• Paroxysmal AF • Drug-controlled HTN • (130 > ASBP ≥ 100) • eGFR >15 (if eGFR > 60 Have microalbuminuria)	PAF = AF duration up to 7 days	Radiofrequency ablation	Irrigated tip
Kiuchi et al, (2018)[16]	• Paroxysmal AF or symptomatic refractory AF • Drug-resistant HTN (ASBP ≥ 130, ADBP ≥ 80) • At least 3 antihypertensiv • eGFR ≥ 60 and microalbuminuria	PAF = AF duration up to 7 days	Radiofrequency ablation	EnligHTN
Pokushalov et al, (2012)[17]	• Refractory paroxysmal or persistent AF • Drug-resistant HTN (Office SBP ≥ 160) • At least 3 antihypertensive (including 1 diuretic) • eGFR ≥ 45	PAF = AF duration up to 7 days, Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	Thermocool
Pokushalov et al, (2014)[18]	• Refractory paroxysmal or persistent AF • Moderate drug-resistant HTN (office BP ≥ 140/90) or severe drug-resistant HTN (office BP ≥ 160/100) • At least 3 antihypertensive (including 1 diuretic) • eGFR ≥ 45	PAF = AF duration up to 7 days, Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	ThermoCool (n = 20), Symplicity (n = 21)
Romanov et al, (2016)[19]	• Refractory paroxysmal or persistent AF • Drug-resistant HTN (Office BP ≥ 160/100) • At least 3 antihypertensive (including 1 diuretic) • eGFR ≥ 60	PAF = AF duration up to 7 days, Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	ThermoCool
Steinberg et al, (2020)[20]	• Paroxysmal AF • Drug-resistant HTN (Office SBP ≥ 130 or DBP ≥ 80) • At least 1 antihypertensive	PAF = AF duration up to 7 days	Cryoballoon catheter	Irrigated tip and RDN catheter
Turagam-HFIB1 et al, (2021)[21]	• Paroxysmal and persistent AF • Drug-resistant HTN (Office SBP ≥ 160 or DBP ≥ 100) • At least 1 antihypertensive • eGFR > 45	Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	ThermoCool
Turagam-HFIB2 et al, (2021)[21]	• Paroxysmal and persistent AF • Drug-resistant HTN (Office SBP ≥ 160 or DBP ≥ 100) • At least 1 antihypertensive • eGFR > 45	Persistent AF = AF ≥ 7 Days	Radiofrequency ablation	Vessix

Units for blood pressure and estimated glomerular filtration rate are in mmHg and mL/min per 1.73 m^2 respectively.
ADBP, ambulatory diastolic blood pressure; AF, atrial fibrillation; ASBP, ambulatory systolic blood pressure; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN,hypertension; PAF, paroxysmal atrial fibrillation; PVI, pulmonary vein isolation; RDN, renal denervation; SBP, systolic blood pressure.

Table 4. Atrial Fibrillation Recurrence Following Interventions and Baseline and 12-Month Follow-Up Blood Pressure

Study Author (Year)	Study Group	AF Recurrence at Follow-Up (%)	Baseline SBP (mm Hg)	SBP at Follow-Up (mm Hg)	Baseline DBP (mm Hg)	DBP at Follow-Up (mm Hg)
Kirstein et al, (2022)[13]	RDN + PVI	39.4	146.8 ± 11.9	138.3 ± 14.8	86.5 ± 10.6	80.1 ± 8.6
	PVI	46.7	148.5 ± 12.2	142.4 ± 15.3	88.5 ± 8.4	82.2 ± 8.2
	P	NS	NS	NS	NS	NS
Kiuchi et al, (2016)[a14]	RDN + PVI	23.8	119 ± 7	114 ± 7	80 ± 3	77 ± 3
	PVI	75.0	117 ± 8	112 ± 8	79 ± 3	77 ± 4
	P	.001	NS	NS	NS	NS
Kiuchi et al, (2017)[a15]	RDN + PVI	38.5	121 ± 9	118 ± 7	79 ± 6	78 ± 3
	PVI	61.5	119 ± 8	120 ± 10	79 ± 8	79 ± 5
	P	.015	NS	NS	NS	NS
Kiuchi et al, (2018)[a16]	RDN + PVI	39.4	142 ± 6	123 ± 4	103 ± 8	82 ± 4
	PVI	63.9	140 ± 6	130 ± 6	103 ± 7	89 ± 5
	P	0.043	NS	<.0001	NS	<.0001
Pokushalov et al, (2012)[17]	RDN + PVI	30.8	181 ± 7	156 ± 2	97 ± 6	87 ± 4
	PVI	71.4	178 ± 8	173 ± 2	96 ± 4	93 ± 2
	P	.033	NS	<.001	NS	<.001
Pokushalov et al, (2014)[18]	RDN + PVI	36.6	163 ± 18	142 ± 11	89 ± 11	79 ± 5
	PVI	59.0	164 ± 17	162 ± 10	88 ± 11	86 ± 5
	P	.046	NS	<.001	NS	<.001
Romanov et al, (2016)[19]	RDN + PVI	35.9	163 ± 20	–	88 ± 13	–
	PVI	59.5	164 ± 16	–	88 ± 12	–
	P	<.005	NS	–	NS	–
Steinberg et al, (2020)[20]	RDN + PVI	27.9	151 ± 9	134 ± 8	89 ± 7	78 ± 6
	PVI	43.2	150 ± 9.	148 ± 8	90 ± 7	88 ± 6
	P	.006	NS	<.001	NS	<.001
Turagam-HFIB1 et al, (2021)[21]	RDN + PVI	38.5	147.0 ± 31.0	152.3	84.1 ± 25.0	84.7
	PVI	52.9	153.0 ± 20.0	144.4	88.0 ± 12.0	82.5
	P	NS	NS	–	NS	–
Turagam-HFIB2 et al, (2021)[21]	RDN + PVI	25.0	146.6 ± 20.6	138.2	81.4 ± 13.4	82.6
	PVI	27.3	143.4 ± 18.4	142.8	79.1 ± 12.4	80.8
	P	NS	NS	–	NS	–

Data for blood pressures are displayed as means and SD.
AF, atrial fibrillation; DBP, diastolic blood pressure; NS, not significant; PVI, pulmonary vein isolation; RDN, renal denervation; SBP, systolic blood pressure.
[a]These studies reported ambulatory blood pressure data.

RDN + AF ablation was not associated with better BP control or rhythm outcomes in comparison to AF-only ablation and medical therapy.[13] In another single-center, randomized, sham-controlled pilot trial in patients with uncontrolled HTN at high risk of developing subclinical AF, RDN reduced subclinical AF events, subclinical AF burden, and fast AF compared to sham treatment.[32] However, no significant change in 24-hour ambulatory systolic or diastolic BP from baseline to 6 months after the procedure in either the RDN or sham group was observed, suggesting that the antifibrillatory effect of RDN in this study appeared unrelated to the improvements in BP or changes in antihypertensive medication.[32] A recently published study showed that RDN could represent an alternative therapy in AF by inhibiting atrial interstitial remodeling and atrial Receptor-for-Advanced-Glycation-End-products (RAGE)/soluble RAGE (sRAGE) dysbalance as well as inflammation in metabolic syndrome spontaneously hypertensive rats, not due to a decrease in BP.[33] On the other hand, both persistent and paroxysmal AF patients are included in this meta-analysis. Impressively, the Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial involved paroxysmal AF patients only and showed a recurrence rate of 28% in the RDN + PVI group vs. 43% in the PVI-only group, implying a lower recurrence in patients with paroxysmal AF as opposed to persistent AF.[20] Larger-scale clinical trials focusing on normotensive patients are necessary to assess the antiarrhythmic mechanism of RDN.

Beyond the impact on BP, improvement of renal function is highlighted. HTN may cause chronic kidney disease (CKD) and contribute to its progression, whereas CKD induces

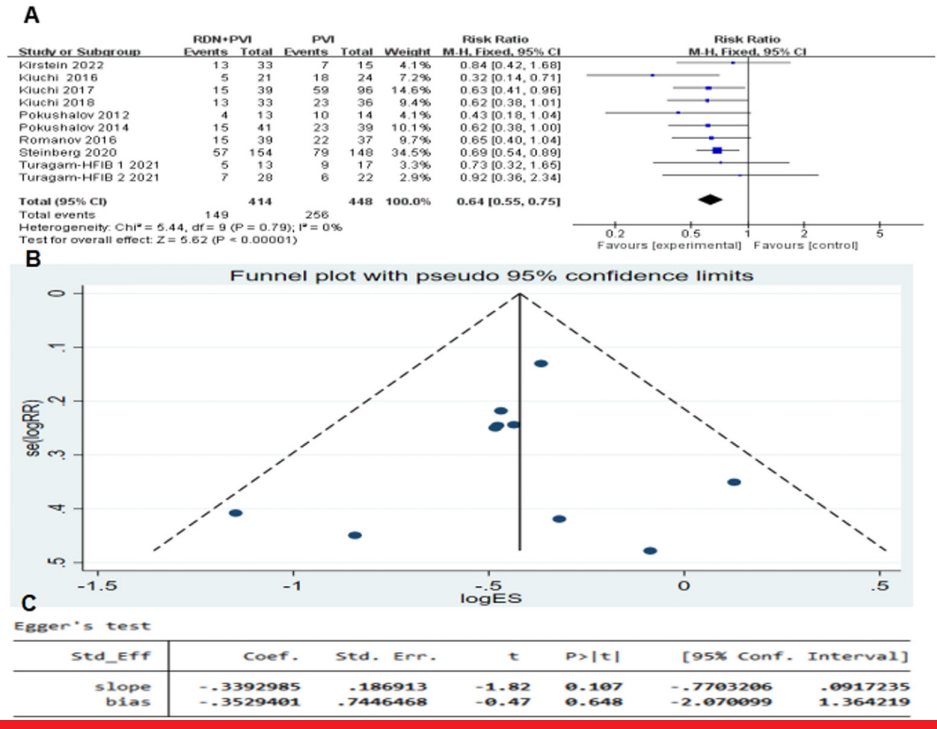

Figure 3. Effects of renal denervation on atrial fibrillation. A. Forest plot of the pooled comparison between PVI + RDN and PVI alone in the rate of AF recurrence of all included studies. B. Funnel plot of pooled comparison. C. Tests for publication bias. df, degrees of freedom; MH, Mantel–Haenszel; PVI, pulmonary vein isolation; RDN, renal denervation.

HTN conversely. For any given cause of CKD, including HTN itself, the elevation in BP values amplifies the degree to which glomerular filtration rate worsens, making the high BP state an independent risk factor for end-stage renal disease.[34,35] Because the prior RCTs have excluded patients with severe CKD, animal and human studies have proved that RDN is effective in lowering BP in mild and moderate CKD.[36] However, the amount of data including HTN patients with CKD is limited, even though patients with reduced renal function and HTN may benefit the most. Therefore, this meta-analysis addresses not only the pooled effect of RDN on AF recurrence and BP but also whether HTN patients with

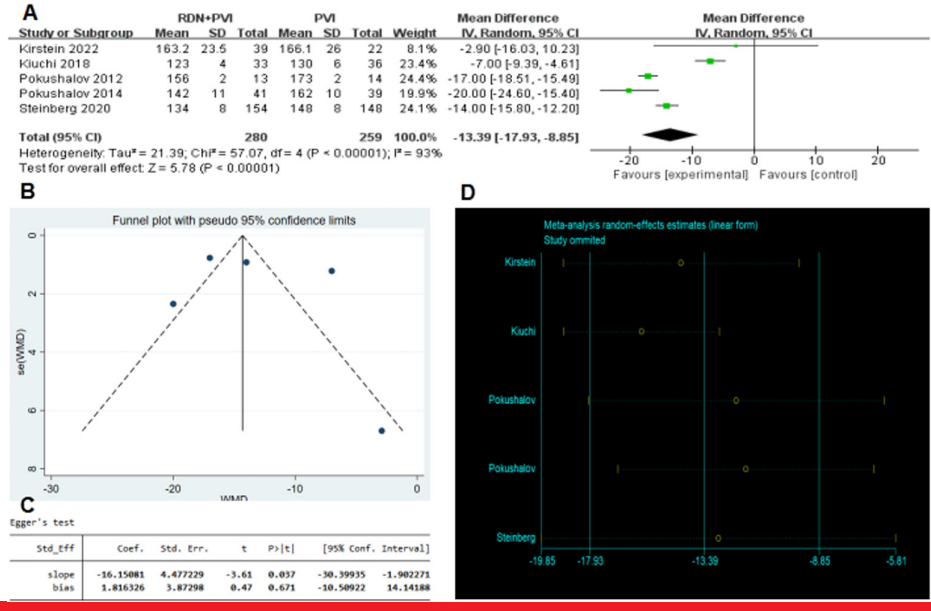

Figure 4. Effects of renal denervation on SBP. A. Forest plot of pooled comparison of SBP between PVI + RDN and PVI. B. Funnel plot of pooled comparison of SBP between PVI + RDN and PVI. C. Tests for Publication Bias. D. SBP sensitivity analysis. df, degrees of freedom; IV, inverse variance; PVI, pulmonary vein isolation; RDN, renal denervation; SBP, systolic blood pressure.

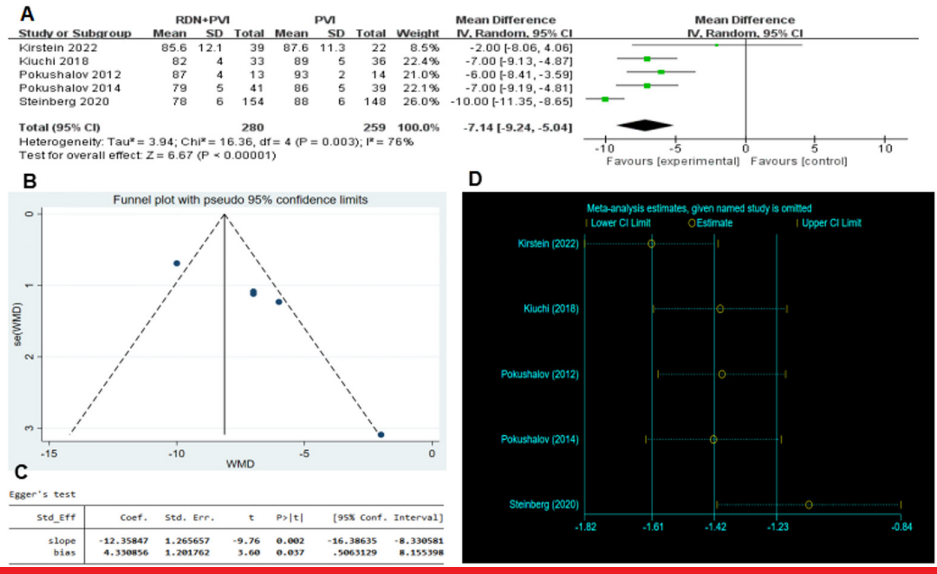

Figure 5. Effects of renal denervation on DBP. A. Forest plot of pooled comparison of DBP between PVI + RDN and PVI. B. Funnel plot of pooled comparison of DBP between PVI + RDN and PVI. C. Tests for Publication Bias. D. DBP sensitivity analysis. DBP, diastolic blood pressure; df, degrees of freedom; IV, inverse variance; PVI, pulmonary vein isolation; RDN, renal denervation.

CKD can benefit from RDN. The pooled analysis showed that RDN significantly improved eGFR compared to PVI alone (MD = 8.72; $P < .001$). Apart from lowering BP, this may be explained by the reduction in sympathetic overdrive following RDN. The renal nerves contain sympathetic efferent and sensory afferent fibers.[37] Previous evidence has indicated that renal injury can activate renal afferent nerves, and activation of renal afferent nerves increases sympathetic nerve activity by stimulating pre-sympathetic neurons in the brain. Renal denervation may not only regulate sodium/water retention and renin-angiotensin system activity in the kidney but also affect the brain, which determines sympathetic outflow. Thus, it is plausible that the eGFR improvement by RDN seems mediated mainly by inhibiting the sympathetic transmission from afferent nerve impulses to the central nervous system, leading to interruption of the progressive decline in renal function. Pilot studies in HTN patients with CKD have shown that the progression of renal functional loss could be slowed down or even stopped after RDN.[38,39]

On account of safety concerns, many previous studies have excluded patients with eGFR < 45 mL/min/1.73m^2 or eGFR < 40 mL/min/1.75m^2, respectively. In the study of Günes-Altan M, patients with eGFR ≥ 15 mL/min/1.73m^2 were included, and no major cardiovascular or renal adverse events or sustained eGFR decline were observed after a follow-up of 12 months. This single-center experience showed a similar reduction in 24-hour, day and night-time ambulatory BP as well as in-office BP in patients with and without CKD at any time point up to 12 months after RDN.[40] In the Global SYMPLICITY Registry, the largest dataset of patients treated with RDN (n = 1742), there was an insignificant difference in 24-hour ambulatory BP reduction between patients with and without CKD.[39] A meta-analysis also showed the efficacy and

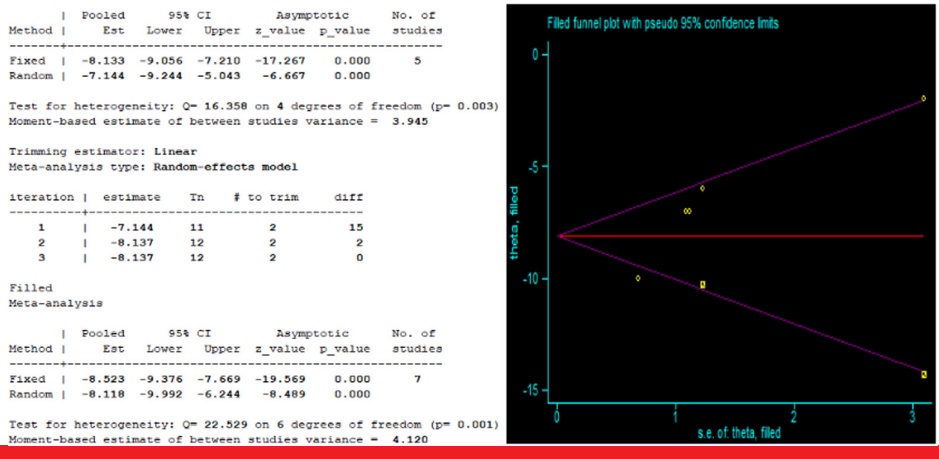

Figure 6. The trim-and-fill analysis for asymmetric funnel plots of diastolic blood pressure.

Table 5. Estimated Glomerular Filtration Rate at Baseline, 6-Month, and 12-Month Follow-Up

Study Author (Year)	Study Group	eGFR Baseline (mL/min per 1.73 m²)	eGFR 6-Month (mL/min per 1.73 m²)	eGFR 12-Month (mL/min per 1.73 m²)
Kirstein et al, (2022)[13]	RDN + PVI	77.6 ± 17.4	81.6 ± 17.7	78.7 ± 17.2
	PVI	72.7 ± 14.2	82.2 ± 14.9	76.8 ± 15.3
	P	NS	NS	NS
Kiuchi et al, (2016)[14]	RDN + PVI	59.3 ± 13.3	64.9 ± 13.4	65.7 ± 14.0
	PVI	60.5 ± 15.9	58.3 ± 14.0	56.6 ± 14.7
	P	NS	<.001	<.001
Kiuchi et al, (2017)[15]	RDN + PVI	47.9 ± 6.8	59.2 ± 5.0	NR
	PVI	50.0 ± 5.4	46.0 ± 5.0	NR
	P	NS	<.0001	–
Kiuchi et al, (2018)[16]	RDN + PVI	69.2 ± 6.7	76.2 ± 7.2	81.8 ± 6.8
	PVI	66.7 ± 7.7	66.4 ± 8.6	64.8 ± 9.9
	P	NS	<.05	<.0001
Pokushalov et al, (2012)[17]	RDN + PVI	78 ± 6.1	NR	NR
	PVI	80.2 ± 4.6	NR	NR
	P	NS	–	–
Pokushalov et al, (2014)[18]	RDN + PVI	75.5 ± 9.2	80.9 ± 4.3	NR
	PVI	77.0 ± 8.5	NR	NR
	P	NS	–	–
Romanov et al, (2016)[19]	RDN + PVI	75.7 ± 9.1	NR	NR
	PVI	77 ± 8.3	NR	NR
	P	NS	–	–
Steinberg et al, (2020)[20]	RDN + PVI	79 ± 11	NR	NR
	PVI	76 ± 11	NR	NR
	P	NS	–	–
Turagam-HFIB1 et al, (2021)[21]	RDN + PVI	>45[a]	NR	NR
	PVI	>45[a]	NR	NR
	P	NS	–	–
Turagam-HFIB2 et al, (2021)[21]	RDN + PVI	>45[a]	NR	NR
	PVI	>45[a]	NR	NR
	P	NS	–	–

Data are displayed as means and SD.
eGFR, estimated glomerular filtration rate; NR, not reported; NS, not significant; PVI, pulmonary vein isolation; RDN, renal denervation.
[a]This study did not report baseline eGFR data but as per the inclusion criteria eGFR of all patients were greater than 45 mL/min per 1.73 m².

safety of RDN for HTN in patients with CKD, with just an overall complication rate of 4.86%.[41] These findings support the viewpoint that RDN could be a safe and effective antihypertensive therapy option for patients with HTN and CKD. Yet, patients with CKD have a high risk of contrast-induced nephropathy after RDN surgery. If RDN surgery can be carried out without or with only a small amount of contrast agent, CKD patients may benefit more from RDN.[42] Furthermore, AF is highly prevalent among patients with CKD. An animal study suggested that CKD created a substrate for AF development in Nlrp3-/- and wildtype (WT) mice by activating the NLR-family pyrin domain-containing 3 (NLRP3) inflammasome in atria, which is associated with structural and electrical remodeling.[43] Renal denervation may directly prevent CKD-induced AF, not by lowering the BP.

Regarding the safety of RDN, there was no significant difference in complications between the ren studies. Previous research on patients receiving RDN has reported similar safety results,[35,36,44] which are consistent with ours. These findings support that RDN is a relatively safe treatment for AF, but the incidence of complications cannot be ignored, and reminds of the importance of carefully selecting RDN patients. In addition, this discovery is meaningful and important, since the selection of strategies can focus more on the patients' needs rather than fear of surgical complications. Moreover, it is worth noting that most RCTs are conducted by a large number of academic centers, which may lead to an underestimation of the complication risk, especially in more complex surgeries.[45]

Study Limitations

The current meta-analysis has the following limitations. First, despite the inclusion of 10 clinical trials, small observational studies were included,[17,21] and the results were primarily subject to the largest trial.[20] However,

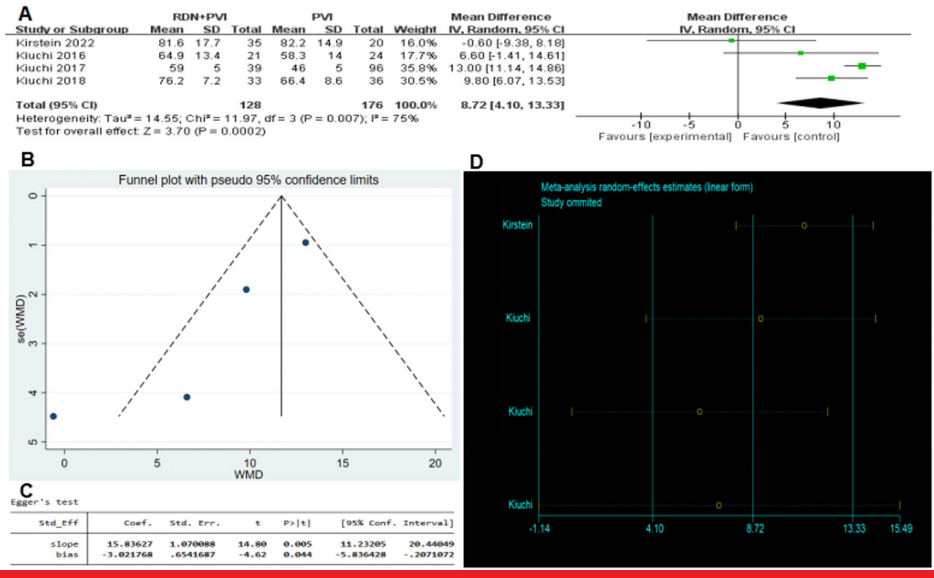

Figure 7. Effects of renal denervation on eGFR. A. Forest plot of pooled comparison of eGFR between PVI + RDN and PVI. B. Funnel plot of pooled comparison of eGFR between PVI + RDN and PVI. C. Tests for Publication Bias. D. eGFR sensitivity analysis. df, degrees of freedom; eGFR, estimated glomerular filtration rate; IV, inverse variance; PVI, pulmonary vein isolation; RDN, renal denervation.

the improvement of AF recurrence was consistent across every study. Second, catheter type and technique of RDN among different studies are variable. It is currently uncertain whether other technologies or the use of specialized RDN catheters will alter the results. Third, these trials contained patients with a history of HTN. These conclusions cannot, therefore, be hence extrapolated to AF patients with normal BP. Fourth, the patients included in this analysis underwent radiofrequency or cryoballoon ablation. It remains unclear whether these outcomes apply to other AF ablation methods, such as ganglion plexus ablation, laser balloon, or pulsed field electroporation. Fifth, the control situation of BP was not similar between the groups in any of the included studies. Thus, it is difficult to determine whether the antiarrhythmic effect of RDN is caused by a single decrease in BP or other mechanisms unrelated to BP, and its potential mechanisms remain elusive. Sixth, differences in the type of AF (paroxysmal AF, persistent AF, or mixed), the length of the blanking period between studies, and baseline BP add to the variability of the outcomes. Seventh, 16% of RCTs were considered to be at a high risk of bias. This observation is largely due to the issue of blinding, as operators cannot be blinded in the original research. Still, the sensitivity analysis leaving out these studies did not change the outcomes.

CONCLUSION

This meta-analysis revealed that adding RDN to PVI in patients with AF and HTN appears more effective and superior to using PVI alone to treat AF. Combination therapy showed improvement in BP and eGFR, and a reduced risk of AF recurrence. Moreover, the use of the technique proved to be safe. It is important to realize that while this novel and promising therapeutic modality shows potential

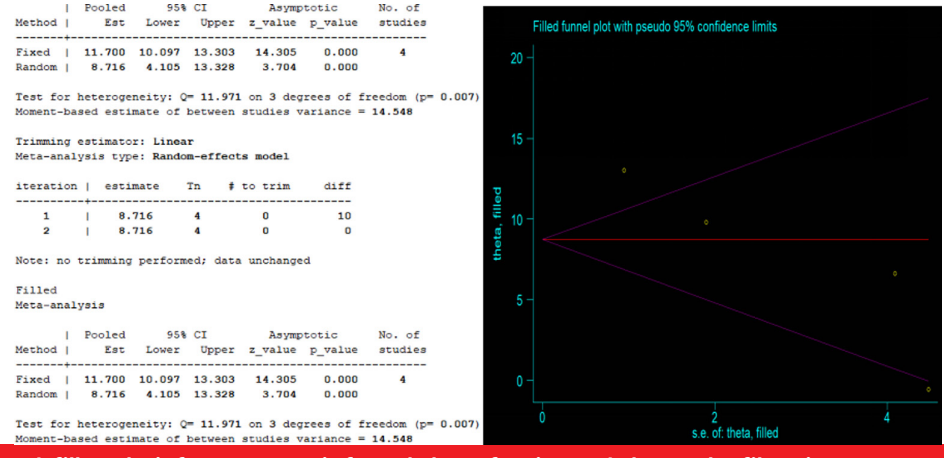

Figure 8. The trim-and-fill analysis for asymmetric funnel plots of estimated glomerular filtration rate.

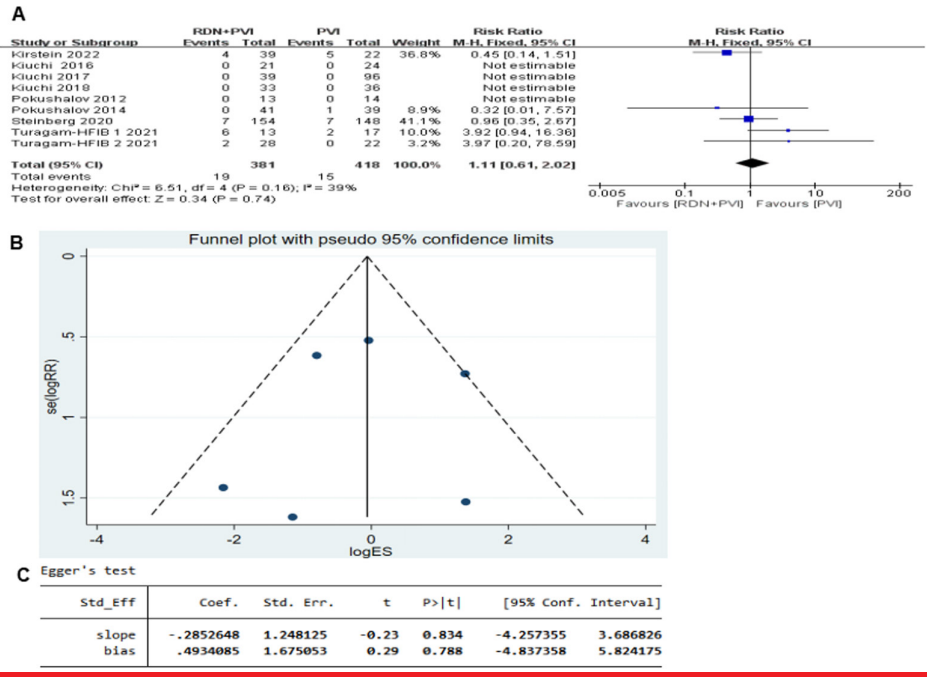

Figure 9. Effects of renal denervation on complications. A. Forest plot of pooled comparison. B. Funnel plot of pooled comparison. C. Tests for publication bias. df, degrees of freedom; MH, Mantel-Haenszel; PVI, pulmonary vein isolation; RDN, renal denervation.

as a treatment approach for AF, larger trials (including those enrolling patients with normal BP or different AF subtypes) are needed to confirm these findings and determine the patient groups that may benefit most from adjunctive RDN.

Ethics Committee Approval: As this is a meta analysis based on previously published literature, ethical approval was not required.

Informed Consent: As this is a meta analysis based on previously published literature, informed consent was not required.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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