

Efficacy and safety of renal denervation for hypertension in patients with chronic kidney disease: a meta-analysis

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ABSTRACT

Background: Renal denervation (RDN) is a new treatment for hypertension in patients with chronic kidney disease (CKD), but its efficacy is still debated. This meta-analysis aimed to evaluate the efficacy and safety of RDN for hypertension in patients with CKD.

Methods: PubMed, Web of Science, EMBASE, and Ovid databases were searched for relevant studies published. We performed both fixed- and random-effects meta-analyses of the changes in blood pressure, estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR) after RDN.

Results: The meta-analysis included 238 patients from 11 single-center, non-randomized, uncontrolled studies. Office blood pressure and 24-hour ambulatory blood pressure (24 h-ABP) showed a significant reduction 1 month after RDN ($p < 0.05$). This decrease of 24 h-ABP persisted for 24 months after RDN showed difference systolic blood pressure ($p < 0.001$) and diastolic blood pressure ($p = 0.001$). The 24 h-ABP exhibited a similar trend in the subgroup analysis. eGFR measurements obtained at each time point of analysis after RDN were not significantly different from those obtained before ($p > 0.05$). UACR levels were significantly reduced at 3 months and 6 months after RDN ($p < 0.001$). After RDN, the heart rate showed no significant changes ($p > 0.05$), and few major complications were encountered.

Conclusions: 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 its impact on clinical outcomes.

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Introduction

Chronic kidney disease (CKD) is a progressive chronic disease that carries a high burden of morbidity and mortality and affects more than 10% of the world's population [1,2]. CKD often coexists with several chronic conditions, including diabetes, hypertension, and heart failure [3]. Hypertension is also a major factor that causes both CKD mortality and cardiovascular diseases [4].


In patients with CKD, hypertension establishment and maintenance are often critically dependent on numerous factors, including volume overload, activation of the renin-angiotensin system, increased endothelin levels, reduced nitric oxide bioavailability and/or medullary vasodilating factors, and oxidative stress [5]. For a long time, volume overload and renin-angiotensin axis activation have been

acknowledged as the most actively involved parameters in the pathogenesis of renal hypertension. However, in clinical practice, treatments for these aspects are not always accompanied by the expected reduction in blood pressure (BP). After years of research, sustained activation of the sympathetic nervous system (SNS) in CKD has been demonstrated to play a crucial role in the pathogenesis and maintenance of hypertension and the progression of CKD [6].

In CKD, stimulation of the renal afferent nerves is caused by factors such as ischemia, and uremic toxins increase systemic sympathetic outflow. Sustained overactivity of SNS increases BP and aggravates further deterioration of the renal function at the same time [7]. Under such circumstances, even with several antihypertensive drugs, drug therapy is usually ineffective in patients with CKD [8].

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 Supplemental data for this article can be accessed [here](#).

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The kidney is an effector organ for sympathetic nerve outflow and an important regulator of SNS activity; thus, blocking overactivity of the renal sympathetic nerve in CKD may be a reasonable treatment option for lowering BP and delaying the deterioration of kidney function [9].

Renal denervation (RDN), also called catheter-based renal denervation, has been developed in recent years [10]. Compared with surgical denervation, most commonly splanchnicectomy, this more minimally invasive and efficient radiofrequency-induced RDN has been shown to benefit patients with resistant hypertension [11], and convincing results of many experimental hypertension with CKD animal model studies have shown that it effectively reduce BP and protect the kidneys [9]. RDN appears to be a sensible treatment approach for CKD patients with hypertension. Some subgroup analyses from larger clinical trials and smaller research on mechanisms have started to explore this further. Although a comprehensive review on this topic has been published by Schmieder [12], studies have reported inconsistent conclusions regarding the efficacy and safety of RDN, and there is no comprehensive review on RDN for CKD hypertension. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of RDN in the treatment of hypertension in patients with CKD.

Materials and methods

Search strategy

We performed a systematic search in PubMed, Web of Science, Embase, and Ovid databases from their inception to 30 November 2020. The terms used were ('renal sympathetic denervation' OR 'renal nerve ablation' OR 'renal denervation') AND ('chronic kidney disease' OR 'end stage renal disease') AND ('blood pressure' OR 'hypertension'). We did not impose any filter on text availability or the publication date. This meta-analysis is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and was registered in the International Prospective Register of Systematic Reviews (registration number: CRD42020189455).

Study selection criteria

Participants

This review focused on patients with CKD, including those with CKD stages 1–5 and CKD5D stage, and those older than 18 years of age with hypertension.

Intervention

In this review, we included any transcatheter renal sympathetic denervation procedure performed using contemporary percutaneous catheters and radiofrequency probes.

Design

Prospective or retrospective studies were included.

Comparison

The comparison between the investigated group and the comparator group is not yet possible since there has been no comparator group in the vast majority of included studies.

Outcome measures

The primary outcome measure was BP control (change in office or clinic, 24-h mean ambulatory, ambulatory daytime mean, and night mean systolic and diastolic BPs). Secondary outcomes were kidney function (change in the estimated glomerular filtration rate [eGFR] and urinary albumin-to-creatinine ratio [UACR], and the need for renal replacement therapy), heart rate, use rate of antihypertensive drugs, and adverse effects, including but not limited to bleeding, femoral artery pseudoaneurysm, renal artery dissection, transient dizziness, and flank pain.

Eligibility criteria

The criteria for inclusion of a study in the meta-analysis were as follows. (1) Original research papers written in English. (2) The study participants were humans. (3) The studies were prospective or retrospective. (4) The study compared pre-ablative and post-ablative clinical results, including the primary or secondary outcomes described above. (5) The follow-up period was at least 3 months after ablation. The following publications were excluded: (1) abstracts, case reports, case series, editorials, reviews; (2) studies based on animal experiments; (3) studies based on pediatric populations; and (4) studies lacking relevant outcome data. The included studies were selected independently by two investigators (M.X. and T.L.). A third investigator (Y.H.) was the arbitrator in cases of disagreement.

Data extraction and quality assessment

Two investigators (M.X. and T.L.) independently performed data extraction using a standard electronic data extraction form. The abstracted data included the period, country, and type of study and the baseline characteristics of the included patients, such as age, sex, body mass index, follow-up time, CKD stage, and the aforementioned main outcomes (BP, eGFR, adverse events, and so on).

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which is an effective tool for evaluating non-randomized studies, including case-control and cohort studies. This 'star system' was judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. A study with five or more stars in total was defined as high quality.

Data synthesis and statistical analysis

Before the analysis, data were standardized into equivalent units, and the median and extreme values or quartile data were converted to mean and standard deviation [13]. For continuous variables, weighted mean differences (WMD) with 95% confidence intervals (CIs) were calculated for each study. For categorical variables, each single proportion is expressed as an effect size (ES) and 95% CIs [14]. Heterogeneity was evaluated using the Cochrane Q test and I^2 statistic to assess the degree of inter-study variation. I^2 values of 0–24.9%, 25–49.9%, 50–74.9%, and 75–100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity, respectively. A fixed-effects model was applied when there was no or low heterogeneity ($I^2 < 50\%$), whereas a random-effects model was applied when there was moderate or high heterogeneity ($I^2 > 50\%$) [15,16]. Publication bias was assessed using the Egger's test [17]. Sensitivity analysis was performed to identify the influence of an individual study on pooled estimates by removing one study at a time [15]. Data analysis was performed using STATA 14.0 (StataCorp, College Station, TX, USA), with $p < 0.05$ considered statistically significant.

Results

Included studies

We retrieved 444 articles from the databases, and 246 articles remained after eliminating duplicate articles. After reviewing the titles and abstracts, 214 patients were excluded after implementing the eligibility criteria. Of the 35 studies included in the full-text evaluation, seven were excluded because they were case reports, three were excluded because of the study protocol, two were excluded for insufficient data, two were excluded for duplicate patient data, and

10 did not meet the inclusion criteria. Finally, 11 single-center, non-randomized, uncontrolled studies were included in the meta-analysis (Figure 1) [18–28]. These 11 studies included 238 patients and are summarized in Table 1. The NOS assessments are presented in Table 2. All studies had NOS scores of more than five stars, which were considered to indicate high quality.

Blood pressure

As shown in Table 3 and Figures 2 and 3, the results of the summary analysis of office BP and 24-h ambulatory BP monitoring (24 h ABPM), including office systolic BP (SBP) and office diastolic BP (DBP), showed a decreasing trend between before and after RDN. Among them, two articles [21,28] reported 24 h ABP 1 month after RDN. There was a significant difference in office SBP and office DBP between before and 1 month after RDN (all, $p < 0.001$), with no heterogeneity (Table 3). This significant difference in office SBP continued at 3, 6, and 12 months. By 24 months, there were still two articles [21,24] that recorded 24 h ABP, and there was a significant difference in 24 h ABP between before and 24 months after RDN (SBP: $p < 0.001$, DBP: $p = 0.001$), with mild and no evidence of heterogeneity, respectively (Table 3).

Only two trials [26,28] in which the 24-h ambulatory SBP and DBP could be calculated from the data reported were included in the subgroup analysis of patients with end-stage renal disease (ESRD). The results showed that the treatment may lower 24-h ambulatory SBP and DBP between before and 6 months after RDN for hypertension in patients with ESRD (all $p < 0.001$), with no significant heterogeneity (Figure 4).

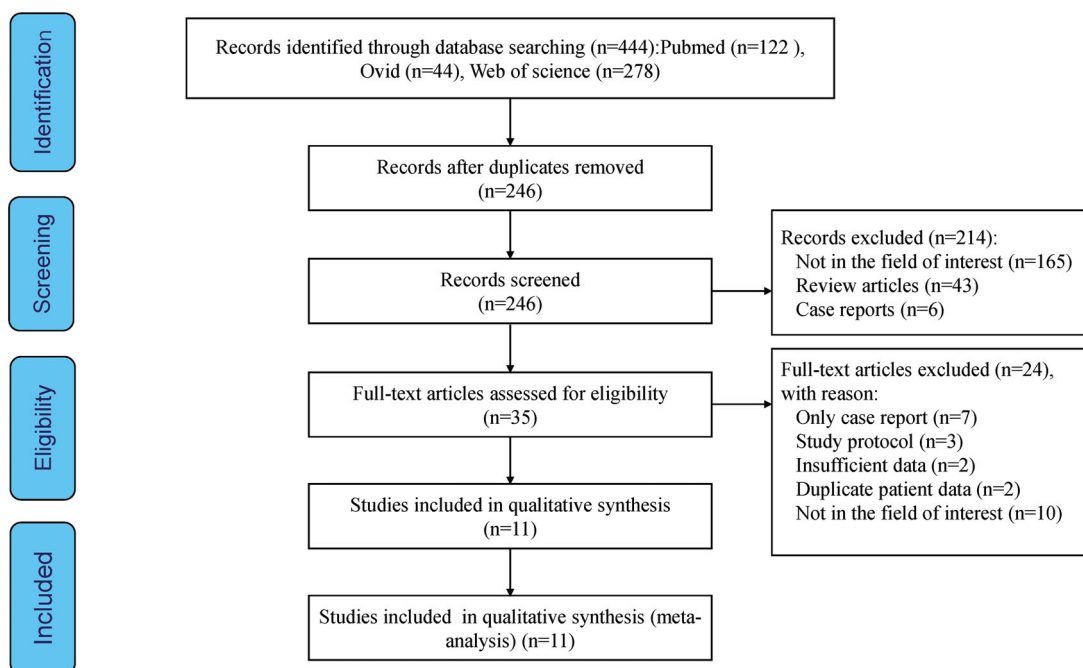


Figure 1. Flow diagram outlining article selection process.

Table 1. Base characteristics of included studies.

Study	Country	Period (Year)	Patient (n)	Age (Year)	BMI (kg/m ²)	Gender (M/F)	Diabetes (%)	CKD stage	eGFR (mL/min/1.73 m ²)	Follow-up (m)
Hering 2012	Germany/Australia	NR	15	61 ± 9	33 ± 8	9/ 6	73	CKD3–4	31.2 ± 8.9	12
Ott 2015	Germany	NR	27	63.4 ± 9.4	31.2 ± 4.8	22/5	56	CKD3–4	48.5 ± 12	12
Schlaich 2013	Germany	NR	9	47.4 ± 13.0	24.1 ± 2.7	NR	NR	CKD5D	<15	24
Kiuchi 2016	Brazil/USA	2011–2012	30	55 ± 10	NR	23/17	37	CKD2–4	61.9 ± 23.9	24
Kiuchi 2016'	Brazil	2012–2016	48	57.5 ± 10.2	26.8 ± 5.4	NR	22	CKD2–4	55.7 ± 33.0	6
Hering 2017	Australia	NR	46	66 ± 9	NR	28/18	48	CKD3–4	46.2 ± 13.0	24
Hoye 2017	New Zealand	2012–2013	9	59 ± 9	25 ± 2	8/1	22.2	CKD5D	<15	12
Hameed 2017	UK	NR	11	57.3 ± 4.9	32.5 ± 3.8	8/3	45.5	CKD3–4	29.3 ± 6.6	6
Ott 2019	Germany	NR	6	42.5 ± 15.2	22.7 ± 3.1	4/2	16.7	CKD5D	<15	6
Prasad 2019	Canada	2013–2014	25	62.8 ± 12.4	33.5 ± 6	NR	NR	CKD3–4	37.5 ± 4.8	24
Scalise 2020	Italy	2017–2018	12	56.5 ± 16.5	NR	8/4	33.3	CKD5D	<15	12

Abbreviations: BMI: Body Mass Index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; NR: not available; M: male; F: female; m: month.

Table 2. Quality Assessment of the Included Studies

Study	Selection	Comparability	Outcome	Scores
Hering 2012	☆☆☆	☆☆	☆☆	7
Ott 2015	☆☆☆	☆☆	☆☆	7
Schlaich 2013	☆☆☆	☆☆	☆☆	7
Kiuchi 2016	☆☆☆	☆☆	☆☆☆	8
Kiuchi 2016'	☆☆☆	☆☆	☆☆☆	8
Hering 2017	☆☆☆	☆☆	☆☆	7
Hoye 2017	☆☆☆	☆☆	☆☆	7
Hameed 2017	☆☆☆	☆☆	☆☆	7
Ott 2019	☆☆☆	☆☆	☆☆☆	8
Prasad 2019	☆☆☆	☆☆	☆☆	7
Scalise 2020	☆☆☆	☆☆	☆☆☆	8

Renal function

As shown in Table 4, two articles reported eGFR values at 1 month [21,23], four articles reported eGFR values at 3 months and 6 months [18,21,23,27], three articles reported eGFR values at 12 months [20,21,27], and two articles reported eGFR values at 24 months after RDN [21,27]. The heterogeneity among the studies was significant; therefore, the random-effects model was used for the analysis (Table 4). The eGFR measurements obtained at 1 month, 3 months, 6 months, 12, and 24 months after RDN were not significantly different from those obtained before RDN (all, $p > 0.05$), as shown in Figure 5 and Table 4.

Data on UACR levels were reported in four studies [18,21,23,27] (Table 4). UACR levels were significantly reduced at 3 months and 6 months after RDN (all, $p < 0.001$). There was no heterogeneity among the studies; therefore, the fixed-effects model was used for the analysis (Figure 6 and Table 4). However, UACR levels at 12 and 24 months after RDN were not significantly different from those obtained before RDN (all $p > 0.05$) (Table 4). The heterogeneity among the studies was moderate at 12 months and significant at 24 months after RDN; therefore, the random-effects model was used for the analysis (Figure 6 and Table 4).

Heart rate

Two articles [18,24] reported changes in the heart rate at 3 months, and three trials [18,24,26] reported data at 6 months after RDN. No difference was found before and after the procedure (all, $p > 0.05$), with no heterogeneity among the studies (Figure S1).

Antihypertensive drugs

Overall, four trials [19,21,27,28] reported data on antihypertensive medications before and after RDN. The results of the summary analysis showed a significant decrease in antihypertensive medications after RDN ($p < 0.001$), with moderate heterogeneity among the studies (Figure S2).

Adverse events

Three major complications (hematoma, femoral pseudoaneurysm, and bleeding) were reported after RDN [19,21,23,25]. Only one article reported the data of the bleeding complication [21]. The incidence of pseudoaneurysm was 1.3% (3/238, $p = 0.07$), with no heterogeneity among the studies, and the incidence of hematoma was 2.9% (7/238, $p = 0.206$), with significant heterogeneity among the studies (Figure S3).

Two cases of progression to ESRD and one case of dialysis-related complications were recorded in two trials [23,25]; however, these events occurred several months after the procedure, and their occurrence was related to the patients' kidney disease. One patient had a myocardial infarction that was not ruled out to be related to his own disease [25]. Therefore, they were not considered as procedure-related events.

Sensitivity analyses and publication bias

Sensitivity analyses for changes in the BP, eGFR, and UACR level at each month after RDN were used to judge the dependability of the results. One study was deleted at a time, and no such deletion had any significant impact on the results, as shown in Figure 7.

Publication bias analyses were conducted for primary outcomes. No evidence of publication bias was detected for the BP using the Egger test (Table 5).

Discussion

To our knowledge, the present study is the first meta-analysis to evaluate the efficacy and safety of RDN for hypertension in patients with CKD. The overall outcome showed that individuals treated with RDN experienced significantly greater 24-h BP and diastolic BP reductions, and RDN did not

Table 3. Pooled effect on different type blood pressure at different timepoint.

Measure	No. of studies	Heterogeneity		Estimate	
		I ² (%)	p Value ^a	Pooled WMD [95% CI]	p Value ^b
1-Month					
Office SBP	3	95.2	<0.001	-25.719 [-47.175, -4.264]	0.019
Office DBP	3	85.2	0.001	-10.561 [-19.612, -1.511]	0.022
24h ABPM SBP	2	0	0.912	-17.186 [-24.094, -10.278]	<0.001
24h ABPM DBP	2	0	0.746	-9.353 [-13.968, -4.738]	<0.001
3-Month					
Office SBP	5	95.8	<0.001	-22.678 [-37.538, -7.819]	0.003
Office DBP	4	91.6	<0.001	-9.734 [-20.071, 0.602]	0.065
24h ABPM SBP	3	71.8	0.029	-9.465 [-18.712, -0.218]	0.045
24h ABPM DBP	3	15.5	0.306	-4.715 [-7.888, -1.543]	0.004
Ambulatory daytime SBP	3	96.9	<0.001	-13.687 [-36.951, 9.577]	0.249
Ambulatory daytime DBP	3	70.3	0.034	0.712 [-4.934, 6.358]	0.805
Ambulatory nighttime SBP	3	38.5	0.197	-3.412 [-6.688, -0.136]	0.041
Ambulatory nighttime DBP	3	65.6	0.055	-1.774 [-6.313, 2.764]	0.444
6-Month					
Office SBP	6	94.1	<0.001	-23.746 [-35.464, -12.029]	<0.001
Office DBP	5	90.9	<0.001	-10.314 [-18.419, -2.209]	0.013
24h ABPM SBP	6	90.8	<0.001	-11.716 [-23.270, -0.163]	0.047
24h ABPM DBP	6	79.3	<0.001	-6.103 [-12.273, -0.067]	0.053
Ambulatory daytime SBP	6	81.1	<0.001	-4.658 [-10.475, 1.158]	0.116
Ambulatory daytime DBP	6	78.6	<0.001	-3.908 [-9.617, 1.801]	0.180
Ambulatory nighttime SBP	6	89.0	<0.001	-8.970 [-18.797, 0.856]	0.074
Ambulatory nighttime DBP	6	80.7	<0.001	-4.046 [-9.265, 1.173]	0.129
12-Month					
Office SBP	5	95.6	<0.001	-28.479 [-45.519, -11.440]	0.001
Office DBP	4	88.8	<0.001	-13.111 [-21.353, -4.870]	0.002
24h ABPM SBP	4	80.4	0.002	-14.325 [-24.153, -4.497]	0.004
24h ABPM DBP	4	60.3	0.056	-6.915 [-11.849, -1.981]	0.006
Ambulatory daytime SBP	3	62.3	0.070	-4.747 [-11.732, 2.237]	0.183
Ambulatory daytime DBP	3	76.6	0.014	-5.725 [-12.757, 1.306]	0.110
Ambulatory nighttime SBP	3	87.4	<0.001	-11.031 [-24.092, 2.031]	0.098
Ambulatory nighttime DBP	3	78.2	0.010	-3.589 [-10.135, 2.958]	0.283
24-Month					
Office SBP	2	98.5	<0.001	-35.285 [-71.542, 0.972]	0.056
Office DBP	2	96.0	<0.001	-10.895 [-28.534, 6.743]	0.226
24h ABPM SBP	2	38.0	0.204	-17.102 [-23.591, -10.613]	<0.001
24h ABPM DBP	2	0	0.329	-6.896 [-10.907, -2.885]	0.001
Ambulatory daytime SBP	2	81.6	0.020	-4.009 [-17.591, 9.572]	0.563
Ambulatory daytime DBP	2	90.4	0.001	-2.707 [-12.490, 7.076]	0.588
Ambulatory nighttime SBP	2	81.9	0.019	3.472 [-13.930, 20.874]	0.696
Ambulatory nighttime DBP	2	0	0.356	1.674 [-0.649, 3.996]	0.158

SBP: systolic blood pressure; DBP: diastolic blood pressure; 24 h ABPM: 24 h mean ambulatory blood pressure monitoring.

^aHeterogeneity was defined as I² >50% or p < 0.10; ^bSignificance was set at p < 0.05.

Bold values indicate statistically significant results.

increase the risk of rapid deterioration of renal function and other major adverse events.

In our study, a significant decrease in the average 24-h and office BP was observed 1 month after RDN. Similar to previous studies on the renal sympathetic nerve in patients with resistant hypertension, our review of ABPM and office BP obtained during a follow-up period of 24 months showed a significant decrease in the ambulatory BP, especially the systolic ambulatory BP after RDN. This difference was maintained until 1, 3, 6, 12, and 24 months postoperatively [29,30]. As a more selective method of reducing renal sympathetic secretion, RDN effectively removes sympathetic nerve overactivity and leads to a systemic decrease in sympathetic tone [31]. In particular, sympathetic nerve activity is more obvious in CKD, and the degree of sympathetic nerve overdrive increases with disease progression [32]. Previous research also suggests that the role of sympathetic overactivity in driving sustained hypertension is derived from its effects on renal function; RDN interrupts renal afferent and efferent sympathetic nerves, which modulate central sympathetic outflow and renal physiology to achieve sustained BP

reduction in patients with CKD [33,34]. RDN can also reduce increased renin secretion and increased renal tubular sodium reabsorption caused by renal sympathetic nerve activity, thereby inhibiting the renin-angiotensin system and achieving the purpose of lowering BP [35,36]. Furthermore, RDN may affect peripheral vascular resistance by significantly reducing the sympathetic trophic effect on arteriolar walls and arterial stiffness in patients with CKD, which is more conducive to lowering BP [18,37]. However, it is unknown how long BP reduction is maintained as sympathetic nerves recover after the lesion [38]. Data showed that DBP and SBP levels were significantly lower at 24 months after RDN, and neither the recovery of nerve fibers nor the effective counter-regulatory mechanism that elevates BP was found [39]. Even 36 months after RDN, BP was significantly lower than before RDN [40].

Subgroup analysis of ESRD patients with hypertension showed similar changes in the BP after RDN treatment. This finding is in line with those of previous reports in patients with ESRD, and shows that BP reduction accompanying renal denervation was greater than that during the whole CKD

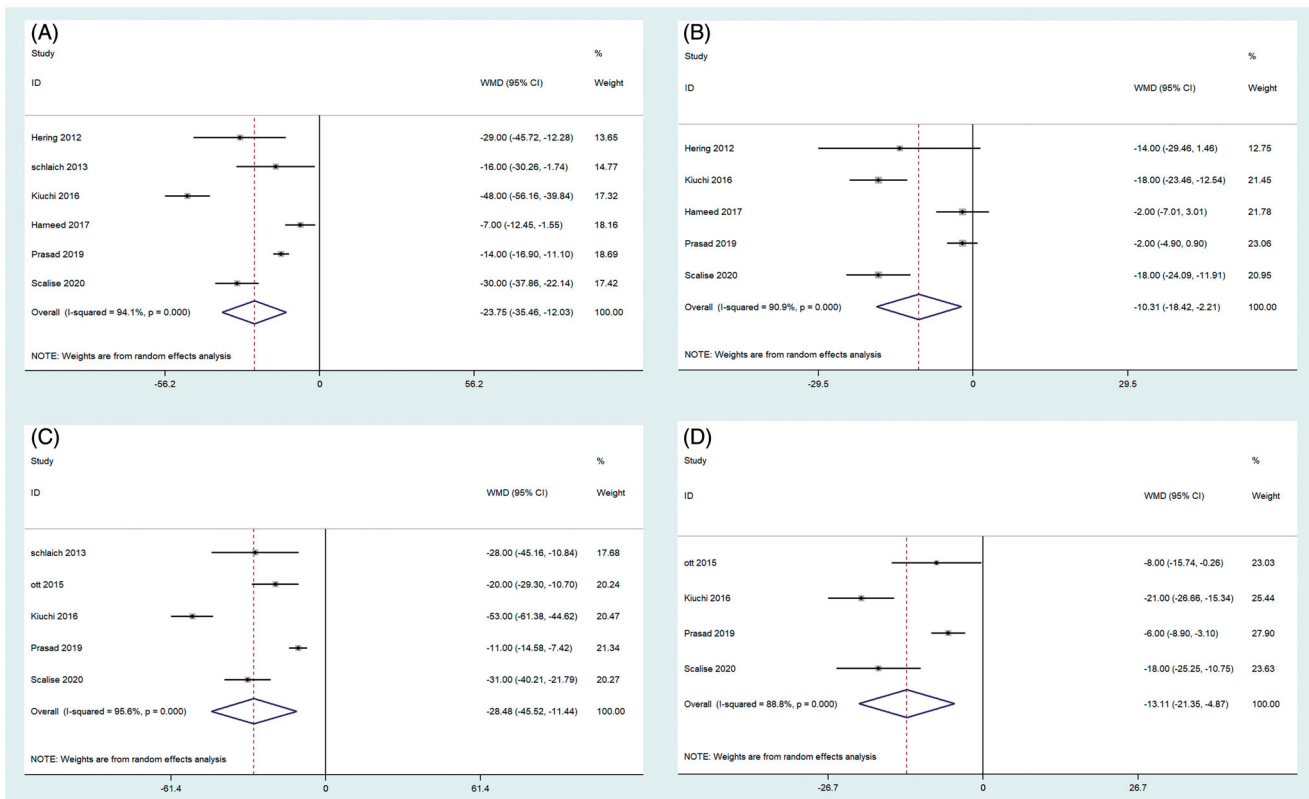


Figure 2. Forest plots of comparison between (A) office systolic-BP at six months after RDN and that of pre-ablation. (B) Office diastolic-BP at six months after RDN and that of pre-ablation. (C) Office systolic-BP at 12 months after RDN and that of pre-ablation. (D) Office diastolic-BP at 12 months after RDN and that of pre-ablation.

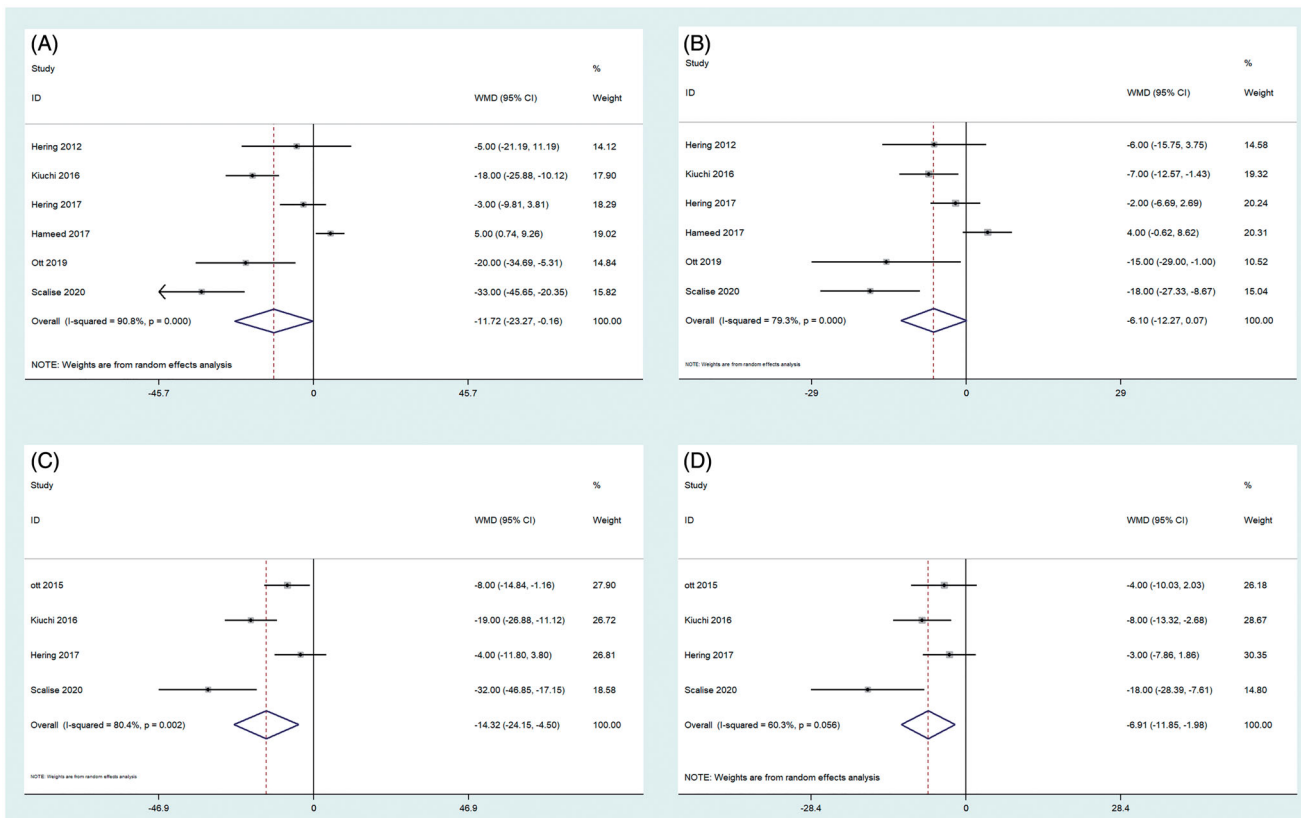


Figure 3. Forest plots of comparison between (A) 24-h ambulatory systolic-BP at six months after RDN and that of pre-ablation. (B) 24-h ambulatory diastolic-BP at six months after RDN and that of pre-ablation. (C) 24-h Ambulatory systolic-BP at 12 months after RDN and that of pre-ablation. (D) 24-h Ambulatory diastolic-BP at 12 months after RDN and that of pre-ablation.

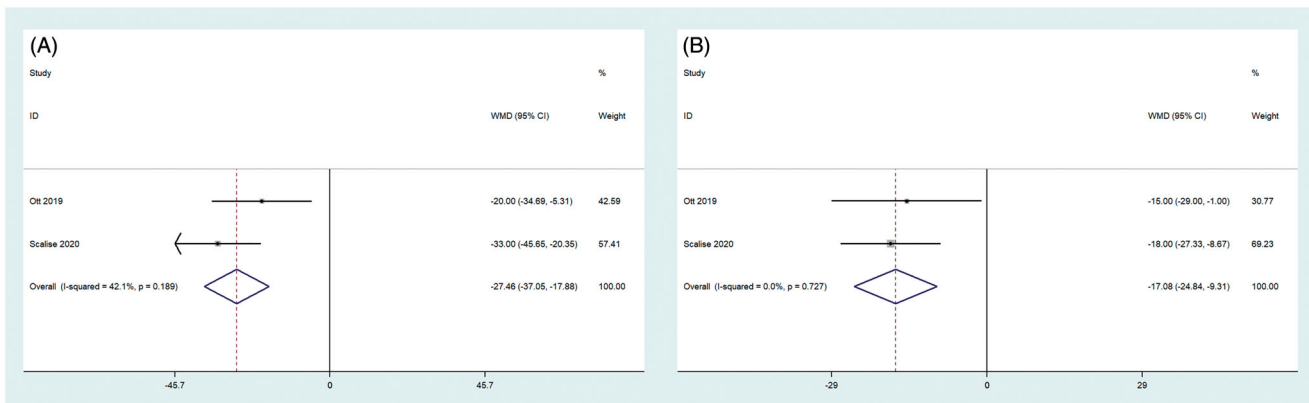


Figure 4. Forest plots of subgroup analysis in ESRD (A) 24-h ambulatory systolic-BP at six months after RDN and that of pre-ablation. (B) 24-h Ambulatory diastolic-BP at six months after RDN and that of pre-ablation.

Table 4. Pooled effect on renal function at different timepoint.

Measure	NO. of studies	Heterogeneity		Estimate	
		I^2 (%)	p Value ^a	Pooled WMD [95% CI]	p Value ^b
1-Month					
eGFR (mL/min/1.73 m ²)	2	71.1	0.063	5.301 [-8.536, 19.138]	0.453
3-Month					
eGFR (mL/min/1.73 m ²)	4	38.0	0.184	0.057 [-2.456, 2.571]	0.964
UACR (mg/g)	4	0	0.852	-51.731 [-71.197, 32.265]	<0.001
6-Month					
eGFR (mL/min/1.73 m ²)	4	69.7	0.019	0.801 [-4.795, 6.397]	0.779
UACR (mg/g)	4	0	0.796	-75.538 [-90.960, -60.115]	<0.001
12-Month					
eGFR (mL/min/1.73 m ²)	3	77.6	0.011	5.711 [-3.792, 15.215]	0.239
UACR (mg/g)	2	51.1	0.153	-51.328 [-152.367, 49.711]	0.319
24-Month					
eGFR (mL/min/1.73 m ²)	2	90.2	0.001	10.830 [-16.711, 38.370]	0.441
UACR (mg/g)	2	92.8	< 0.001	103.337[-301.147, 507.821]	0.617

eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio.

^aHeterogeneity was defined as $I^2 > 50\%$ or $p < 0.10$; ^bsignificance was set at $p < 0.05$.

Bold values indicate statistically significant results.

stage. This may originate from the fact that patients with advanced CKD and ESRD are more likely to have increased sympathetic nerve activity given their impaired capacity for sodium and fluid excretion and increased sympathetic drive [41,42]. Furthermore, in patients with ESRD, the increase in nerve density in the internal area of the periadventitial tissue may have also played a role [42]. This implies that RDN may target more nerves in patients with ESRD than in other hypertensive patients [43]. It is also possible that the increasing improvement and completion of RDN catheters and a higher number of renal artery ablations can be performed [28], thereby more effectively destroying sympathetic fibers within the renal tissue. However, compared to patients with CKD who are not undergoing long-term dialysis, the BP of patients with ESRD is affected by many factors, such as the volume load, electrolytes, and other interference factors [44]. Therefore, further well-designed large clinical trials are needed to determine the potential role of this in ESRD, given that activation of sympathetic nerve activity has been described as a crucial component in the development and progression of CKD [45].

There is growing evidence that therapeutic sympathetic nerve ablation aimed at targeting renal nerves may have potential benefits for CKD [20,24]. The BP-lowering effect of RDN can have a protective effect on the kidney, as the

detrimental effect of hypertension on renal function has been well established [46]. Inhibition of renal sympathetic nerve activity may lead to prominent vasodilatation in pre-glomerular arterioles, decreased renal vascular resistance, and increased renal blood flow, which may be the major determinants of improved renal function [47]. Our data showed that the eGFR was unchanged and urinary albumin excretion, usually expressed as total UACR [48], was significantly reduced at 1, 3, and 6 months after catheter-based RDN, suggesting that RDN and the associated hemodynamic changes have no adverse effects on the kidneys. Although it is unclear whether the unchanged eGFR was related to the progression of individual differences in CKD progression, urinary albumin excretion, as an early marker of CKD progression [49], is encouraging in the early postoperative follow-up.

Regarding complications and adverse effects after RDN, among the 238 patients in the 11 studies included, there was one case of bleeding, three cases of pseudoaneurysm, and seven cases of hematoma among the adverse reactions related to puncture-site complications, which are common with any percutaneous angiographic procedure [23]. The heart rate showed no significant changes after treatment. Moreover, no incidence of electrolyte disturbances, including hyperkalemia, hypokalemia, hypercalcemia, and

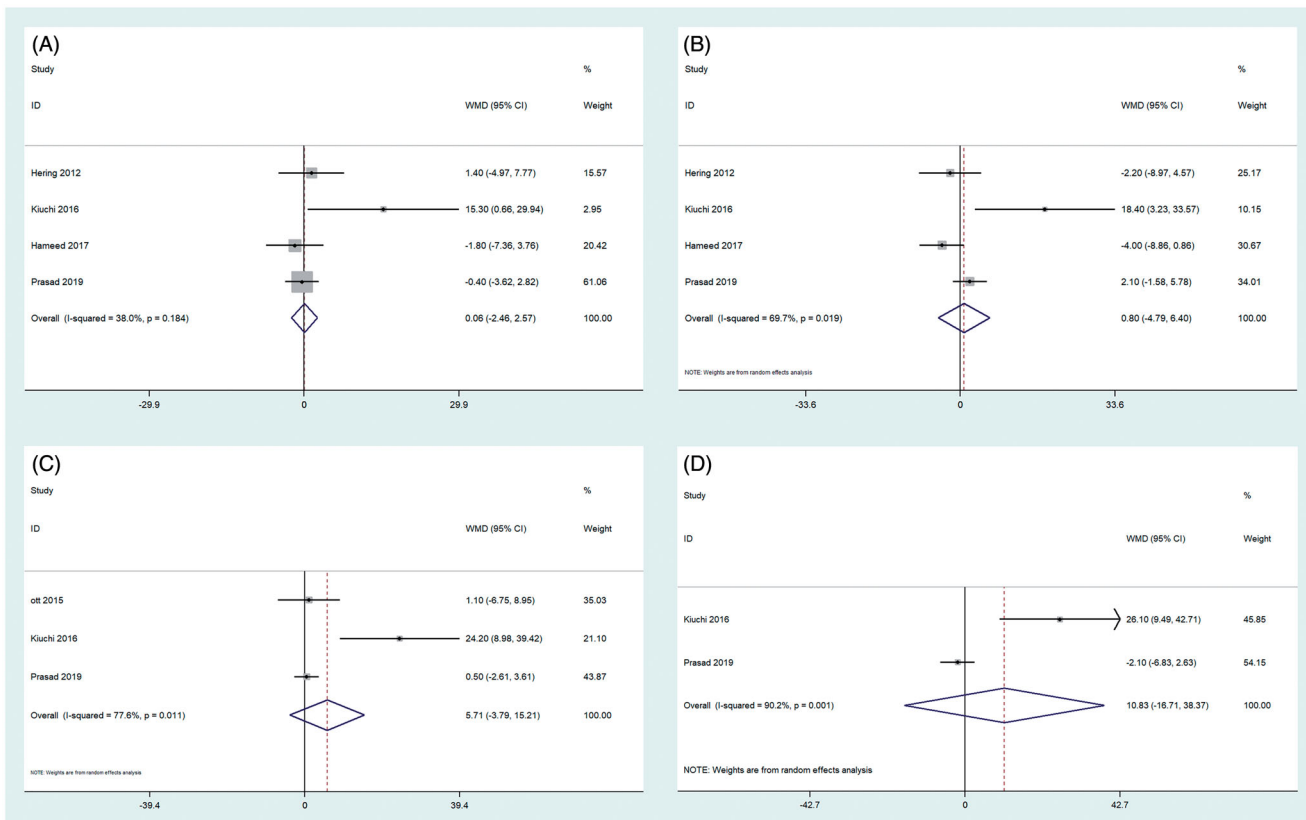


Figure 5. Forest plots of comparison between (A) eGFR at three months after RDN and that of pre-ablation. (B) eGFR at six months after RDN and that of pre-ablation. (C) eGFR at 12 months after RDN and that of pre-ablation. (D) eGFR at 24 months after RDN and that of pre-ablation.

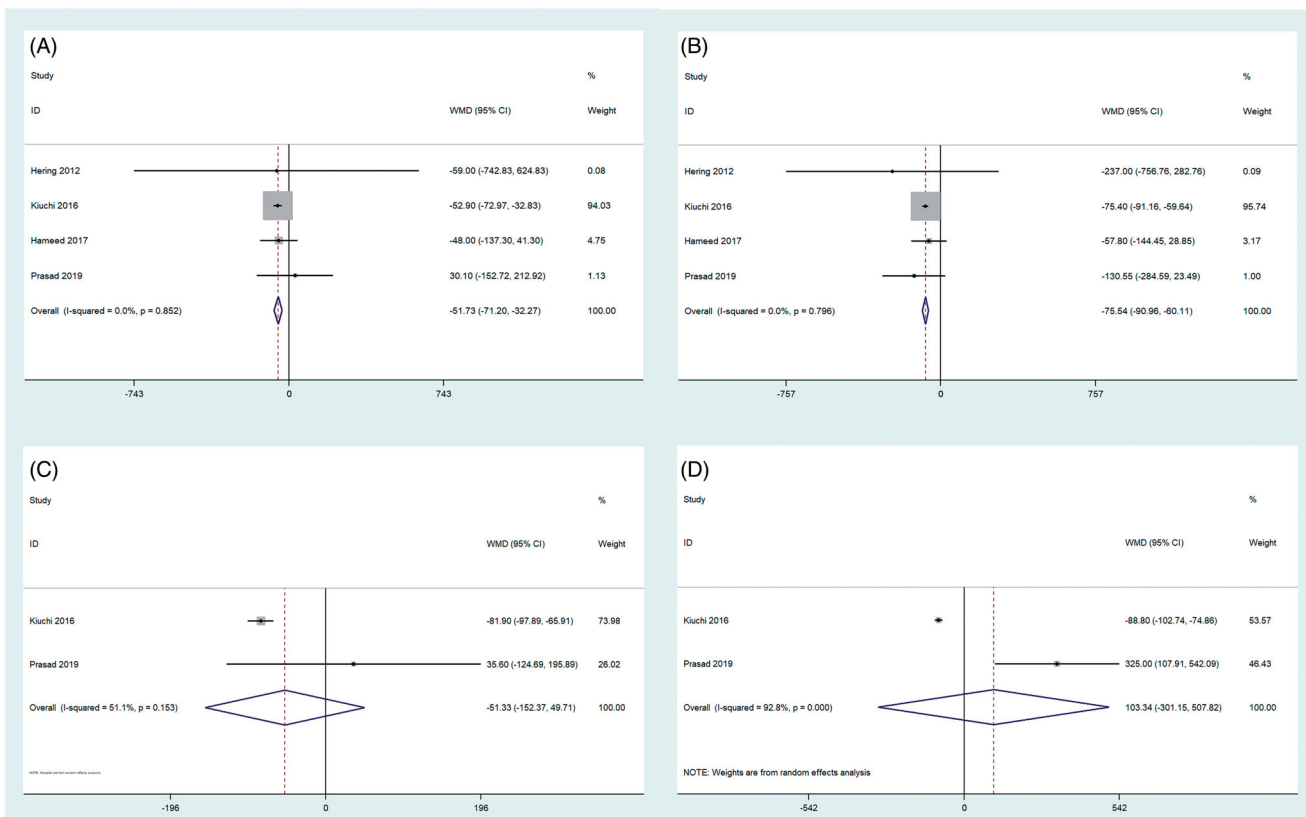


Figure 6. Forest plots of comparison between (A) UACR at three months after RDN and that of pre-ablation. (B) UACR at six months after RDN and that of pre-ablation. (C) UACR at 12 months after RDN and that of pre-ablation. (D) UACR at 24 months after RDN and that of pre-ablation.

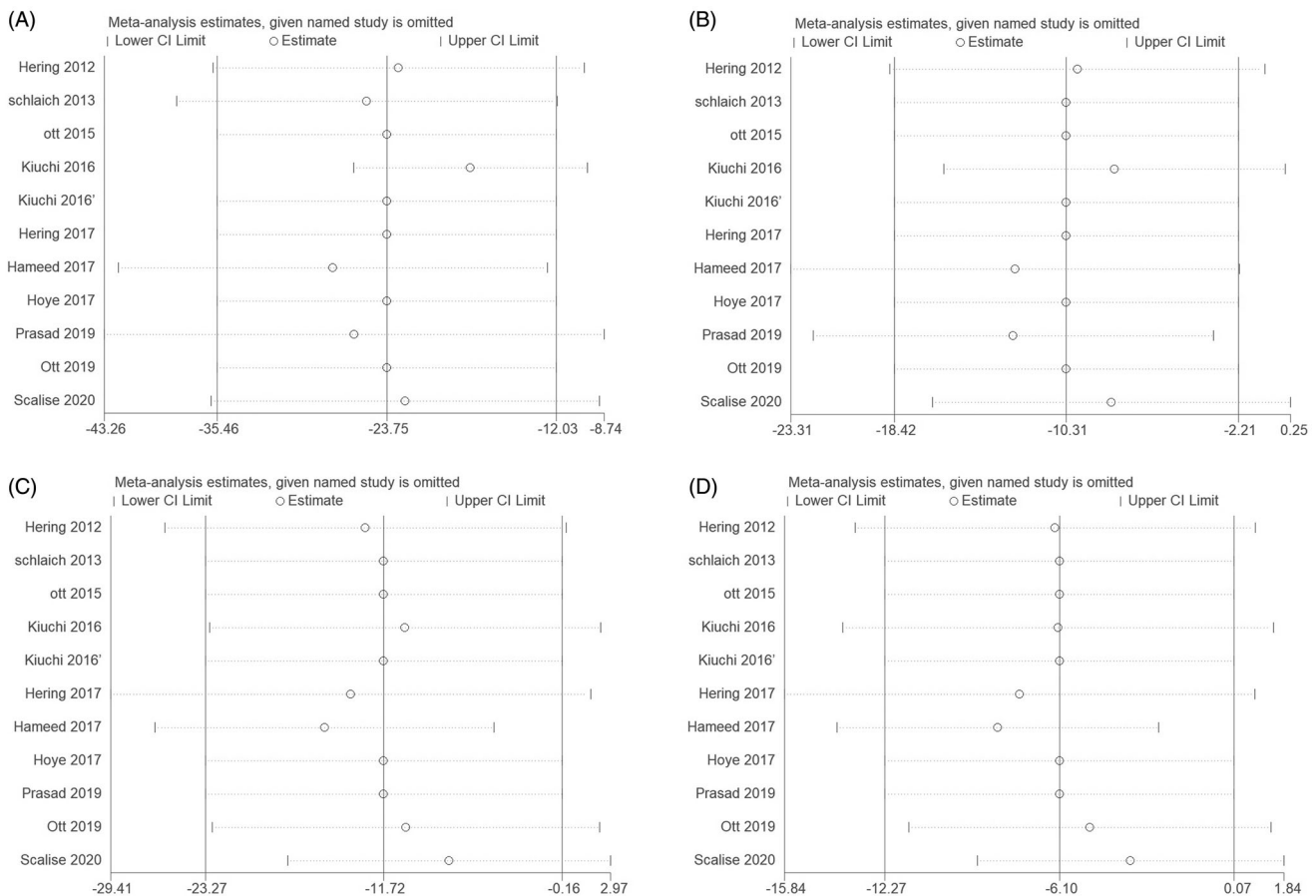


Figure 7. Results of sensitivity analyses. (A) Office systolic-BP at six months after RDN and that of pre-ablation. (B) Office Diastolic-BP at six months after RDN and that of pre-ablation. (C) 24-h ambulatory Systolic-BP at six months after RDN and that of pre-ablation. (D) 24-h ambulatory Diastolic-BP at six months after RDN and that of pre-ablation.

Table 5. Assessment of publication bias based on different outcome.

Primary outcomes	Follow-up time point	<i>t</i>	<i>p</i> Value ^a
Office SBP	1 months	6.42	0.987
	3 months	4.80	0.366
	6 months	3.97	0.302
	12 months	4.10	0.221
Office DBP	1 months	3.21	0.676
	3 months	3.94	0.641
	6 months	3.02	0.271
	12 months	2.66	0.313
24h ABPM SBP	3 months	2.66	0.968
	6 months	2.35	0.073
	12 months	1.85	0.255
	3 months	0.84	0.367
24h ABPM DBP	6 months	1.63	0.088
	12 months	1.04	0.154
	3 months	3.09	0.252
	6 months	2.02	0.191
Ambulatory daytime SBP	12 months	1.15	0.332
	3 months	1.10	0.278
	6 months	1.71	0.117
	12 months	0.70	0.154
Ambulatory daytime DBP	3 months	1.01	0.756
	6 months	0.69	0.390
	12 months	0.93	0.655
	3 months	0.87	0.235
Ambulatory nighttime SBP	6 months	1.62	0.073
	12 months	0.37	0.077

SBP: systolic blood pressure; DBP: diastolic blood pressure; 24 h ABPM: 24 h mean ambulatory blood pressure monitoring.

hypocalcemia, was reported in our included studies after the procedure, supporting that renal denervation may not adversely affect autoregulation of the kidneys [50]. No serious procedure-related complications (including all-cause death, major cardiovascular events, perioperative complications, and hypertension crisis) were reported.

There are several limitations to our analysis. First, significant heterogeneity was found in some pooled results, which may be due to the (1) source and number of populations, (2) different CKD stages, (3) varied ablation types, and (4) the heterogeneity of some measurement methods, such as the office BP measurement. We attempted to explore this relationship between studies by pooling the data using sensitive analysis and subgroup analysis. However, some heterogeneities could not be avoided because of the limited number of included studies. Second, the number of included studies and sample size were small; although this might not have caused obvious publication bias, there is still potential for bias. Third, most of the studies will focus on the efficacy of treatment more than 24 months after surgery in the future, so there is not enough current information to analyze the long-term efficacy of RDN. Finally, after searching the database thoroughly, no relevant randomized controlled trials were found. Thus, well-designed randomized controlled trials of RDN are urgently needed to confirm the safety and

reproducibility of this treatment and to assess its impact on clinical outcomes in the future.

Conclusions

In conclusion, our meta-analysis indicates that RDN may be effective and safe for treating CKD patients with hypertension. It helped achieve a highly significant reduction in BP with no adverse reaction to renal function and enabled a substantial reduction in the number of antihypertensive drugs used. Moreover, RDN was associated with reduced albumin excretion during this short follow-up period, and no major complications occurred.

Disclosure statement

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