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Research status and frontiers of renal denervation for hypertension: a bibliometric analysis from 2004 to 2023

Jiaran Li[1†], Xiaohan Zhang[1†], Yuchen Jiang[1], Huan Wang[1], Xiongyi Gao[1], Yuanhui Hu[1*] and Bai Du[1*]

Abstract

Background Renal Denervation (RDN) is a novel non-pharmacological technique to treat hypertension. This technique lowers blood pressure by blocking the sympathetic nerve fibers around the renal artery, then causing a decrease in system sympathetic nerve excitability. This study aimed to visualize and analyze research hotspots and development trends in the field of RDN for hypertension through bibliometric analysis.

Methods In total, 1479 studies were retrieved on the Web of Science Core Collection (WoSCC) database from 2004 to 2023. Using CiteSpace (6.2.R4) and VOSviewer (1.6.18), visualization maps were generated by relevant literature in the field of RDN for hypertension to demonstrate the research status and frontiers.

Results The number of publications was found to be generally increasing. Europe and the United States were the first countries to carry out research on different techniques and related RDN clinical trials. The efficacy and safety of RDN have been repeatedly verified and gained increasing attention. The study involves multiple disciplines, including the cardiovascular system, peripheral vascular disease, and physiological pathology, among others. Research hotspots focus on elucidating the mechanism of RDN in the treatment of hypertension and the advantages of RDN in appliance therapy. Additionally, the research frontiers include improvement of RDN instruments and techniques, as well as exploration of the therapeutic effects of RDN in diseases with increased sympathetic nerve activity.

Conclusion The research hotspots and frontiers reflect the status and development trend of RDN in hypertension. In the future, it is necessary to strengthen international collaboration and cooperation, conduct long-term clinical studies with a large sample size, and continuously improve RDN technology and devices. These measures will provide new options for more patients with hypertension, thereby improving their quality of life.

Keywords Renal denervation, Hypertension, CiteSpace, VOSviewer, Knowledge mapping

[†]Jiaran Li and Xiaohan Zhang contributed equally to this work and share the first authorship.

*Correspondence:
Yuanhui Hu
huiyuhui55@sohu.com
Bai Du
dubaidubai@sina.com
[1]Department of Cardiovascular Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Introduction

Hypertension is an extremely common chronic condition and public health event, affecting roughly 25% of the population [1].Poor blood pressure control may occur due to irregular adherence to pharmacological treatments and the subsequent lifestyle modifications required. This leads to increased risk for adverse cardiovascular events, longer hospital stays, and increased cost of treatment [2, 3].The development of catheter-based renal denervation (RDN) is expected to address this limitation [4, 5].

A strong correlation between blood pressure levels and the excessive activity of the sympathetic nervous system has been observed [6, 7]. Activation of efferent renal sympathetic nerves results in renal arteriolar vasoconstriction, reducing renal blood flow and the release of renin [8]. Additionally, this process results in water-sodium retention due to activation of the renin-angiotensin-aldosterone system (RAAS), thereby increasing plasma volume and blood pressure [9]. RDN employs various techniques, including the use of radiofrequency energy, freezing energy, chemical denervation, or ultrasound-guided approaches. This technique aims to disrupt and interrupt the activity of the renal sympathetic nervous system and ultimately inhibit the sympathetic system throughout the body, leading to a reduction in arterial blood pressure [10]. According to the European Society of Hypertension (ESH) guidelines [11], RDN is a class II (level of evidence B) recommendation, and has become a therapeutic option for patients with uncontrolled or resistant hypertension.

The bibliometric analysis first emerged in the early 20th century and has become widely used as an analytical technique [12, 13]. This method can evaluate the productivity of countries, institutions, and authors to track the development trends and hotspots in a specific research field [14]. The visualization software CiteSpace (6.2.R4) and VOSviewer (1.6.18) are widely used in the field of bibliometrics. In this paper, CiteSpace was mainly used to create visual graphs of literature keywords, and VOSviewer was used to visually analyze basic information such as countries, authors, etc. Hence, this study aimed to conduct a comprehensive summary and analysis of the field of treatment of hypertension in RDN.

Materials and methods

Data retrieval and collection

Research data were obtained from the Web of Science Core Collection (WoSCC) database, which covers comprehensive research fields [15]. The retrieval strategy was (TS = (Hypertension OR "high blood pressure" OR hypertonic OR HPN OR HBP OR hyperpiesis OR hyperpiesia) AND TS= ("Renal Denervation")) AND LA=(English). The retrieval time was set from January 1, 2004, to August 1, 2023, and 2288 works of literature were initially retrieved. Of these, 383 meeting abstracts, 244 editorial materials, 128 letters, 19 proceeding papers, 11 corrections, 10 early accesses, 9 book chapters, and 5 news items were excluded. Thus, a total of 1479 papers (433 review papers and 1046 research papers) were exported in the form of plain text files and saved in "download_***.txt" format within 1 day (August 9, 2023).

Data analysis

We conducted a visualization analysis of countries, authors, institutions, and journals through the VOSviewer software. A lower distance between the nodes in the visualization map corresponded to a closer similarity between the two themes [16]. In addition, to observe cooperation between countries more clearly, country co-occurrence maps formed by VOSviewer were first exported in GML format. Following this, Scimago Graphica software was used for the subsequent operations, resulting in the generation of a geographical distribution map of country cooperation.

CiteSpace software performs visualization analysis of keywords, to demonstrate the development process and trends in the research field. In the maps, the size of the node is related to the frequency of the keyword, the purple and the red rings in the outer area of the node represent the centrality and burstiness of the keyword, respectively [17]. The centrality of the keyword reflects the important role of keywords in this field, while its burstiness indicates the research hotspots.

Results

The 1479 research papers used in this study were published across 351 journals in the period between 2004 and 2023, written by 5359 authors from 1890 organizations in 69 countries, and cited by 29,398 literature documents across 3721 journals.

Temporal distribution map of publications

Figure 1 shows the three phases in the development of this research field. The first phase, from 2004 to 2012, was characterized by an annual output of no more than 100 articles; this indicates that the field of treatment of hypertension in RDN was in its infancy and did not receive high attention. The number of papers being published increased from 2012 onwards and reached a peak in 2016; this reflected that RDN entered a rapid development stage between 2012 and 2017.

This was found to be related to the neutral results of the SYMPLICITY-3 HTN trial in 2014 on one hand, and the increased number of patients with hypertension on the other [18]. Meanwhile, research on hypertension in RDN reached the maturation stage in 2017. According to a citation analysis of 1479 articles, 29,398 citations

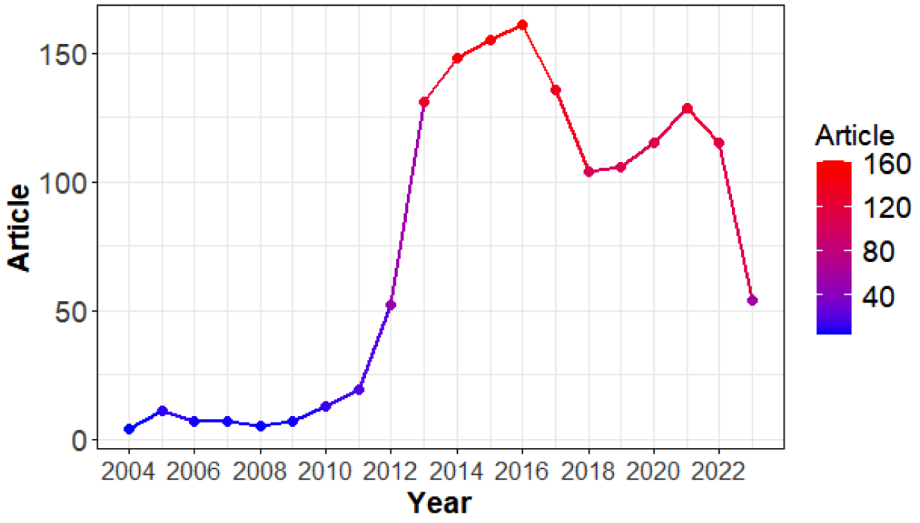


Fig. 1 The trend of publications from 2004 to 2023

Table 1 Top 10 contributing countries/regions in the field of RDN for hypertension

Rank	Country/Regions	Articles	H-index	Citations	Average per item
1	USA	559	75	12,730	22.77
2	Germany	329	60	7310	22.22
3	Australia	185	49	8122	43.90
4	China	166	21	1100	6.63
5	England	138	43	2399	17.38
6	Netherland	125	35	1244	9.95
7	Italy	117	33	2086	17.83
8	Japan	96	28	1376	14.33
9	Poland	93	30	602	6.47
10	Greece	72	23	342	4.75

were involved between 2004 and 2023, with an average of 29.55 citations per paper (h-index=92).

Distribution of co-authorship-countries/regions, institutions, and scholar authors

Two countries (USA and Germany) published more than half of all literature, demonstrating that the study of RDN was investigated more thoroughly in these countries (Table 1; Fig. 2A and C). Figure 2B shows the locations and collaboration of each country in this field have been shown in Fig. 2B. America ranked first in total citations and h index, with 559 and 75 respectively. Figure 2D indicates that the USA and Germany were early starters in the research of this field; although research in Asian countries began relatively later, they have made important contributions to the research field. In 2020, the Asia Renal Denervation Consortium fully affirmed the role of RDN and actively promoted this treatment as the initial choice for hypertension [19].

As shown in Table 2, five top scholar authors and institutions with the largest number of published research papers were listed. Figure 3A describes the follow-up survey of patients with or without complications after RDN surgery conducted by Monash University, confirming the safety and efficacy of RDN in clinical applications [20]. In addition, this university has been involved in many experimental studies on RDN [21]. Figure 3B shows inter-agency partnership, with the size of the nodes representing the number of posts and the lines representing the linkages, by dividing the 25 institutions that met the threshold into 2 clusters. As the most representative author, Mahfoud F was involved in the SYMPLICITY HTN-2 randomized clinical trial, and worked on the study of RDN for other cardiovascular diseases [22, 23].

Distribution of disciplines and journals

Figure 4A shows the top 15 subject categories in the field of RDN for hypertension. As shown in Table 3; Fig. 4B, the journal with the largest number of publications was *Hypertension* (105 papers), which publishes research on the regulation, clinical treatment, and prevention of hypertension. *Hypertension* also had the largest number of citations (5936 papers), followed by the *European Heart Journal* (2606 papers) and *Journal of the American*

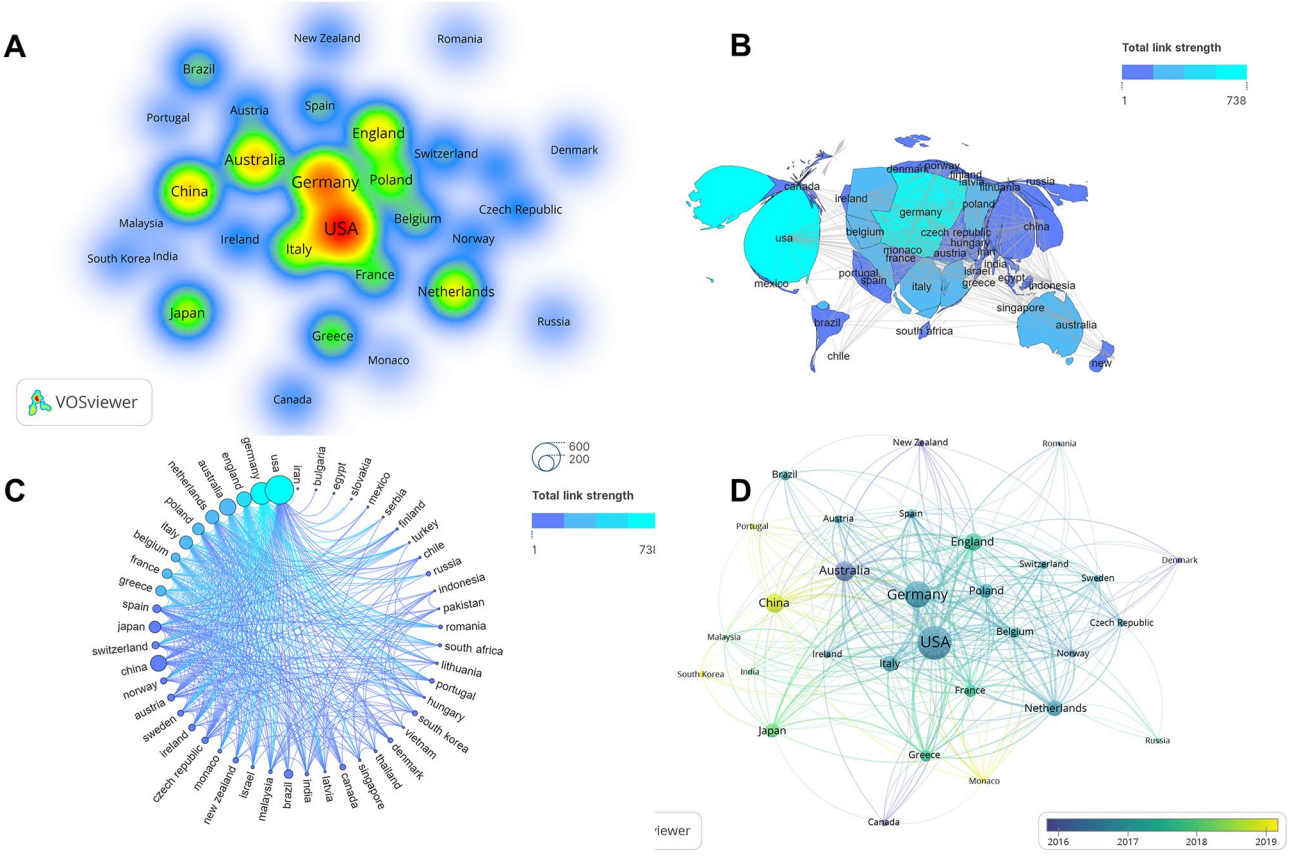


Fig. 2 Distribution map of countries/regions. **A** Density visualization of countries. **B** Collaboration of all countries by Scimago. **C** Occurrence of contributing countries. **D** Time overlay of main countries

Table 2 Top 5 contributing authors and institutions in the field of RDN for hypertension

Rank	Authors			Institutions		
	Name	Documents	H-index	Description	Documents	Citations
1	Mahfoud F	155	50	Monash Univ	73	6786
2	Bohm M	126	45	Univ Western Australia	59	1237
3	Schmieder RE	93	33	Baker heart and diabetes ins	58	6826
4	Schlaich MP	73	36	Saarland Univ	57	4629
5	Ewen S	53	24	Jichi med Univ	55	2655

College of Cardiology (2498 papers). As the journal with the maximum number of publications and citations, *Hypertension* is authoritative and scientific in the field of treatment of hypertension in RDN.

Distribution of highly cited literature and co-cited reference

The analysis of highly cited literature

A greater number of citations was understood to indicate greater academic value of the paper. As of August 2023, 24 highly cited studies were finally retrieved, with a total of 7625 citations. Table 4 listed the top 10 most highly cited studies. The most cited study is "A Controlled Trial of Renal Denervation for Resistant Hypertension" published in the *New England Journal of Medicine* in 2014, conducted by Bakris et al. This study was a prospective, randomized, single-blind, randomized, sham-operated, controlled trial (SYMPLICITY HTN-3 clinical trial), conducted to show that RDN surgery for the treatment of resistant hypertension failed to achieve the expected results. This publication caused a great deal of controversy at the time, but also spurred the development of more randomized controlled trials [18].

Only one review, titled "The Autonomic Nervous System and Hypertension", describes in detail the effect of the mechanism of adrenergic and vagal abnormalities on the characteristic structure of hypertension, leading to essential hypertension and organic damage [24]. In this study, Mancia and Grassi noted that the activation of adrenergic nerves is an unstable process, and can be

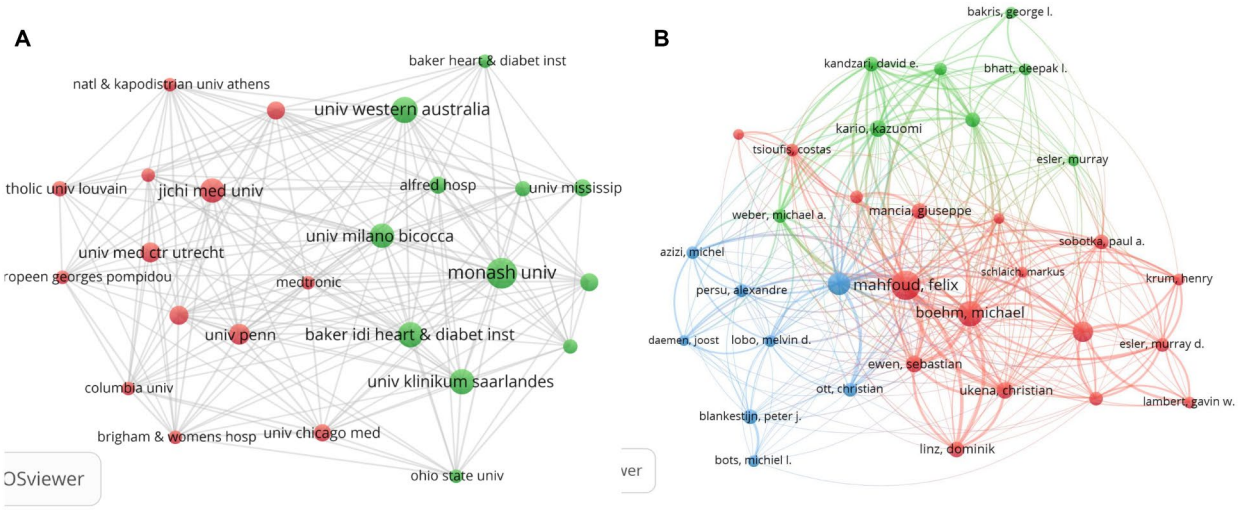


Fig. 3 Distribution map of institutions and scholar authors. **A** The occurrence of contributing institutions. **B** The occurrence of contributing scholar authors

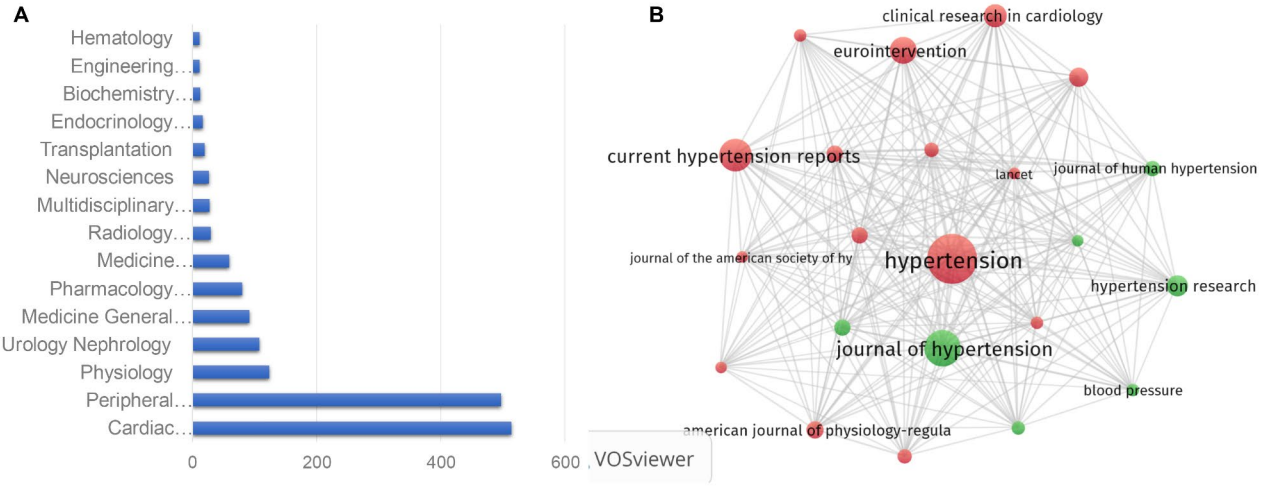


Fig. 4 Distribution map of subject categories and journals. **A** Top 15 subject categories in the field of RDN for hypertension. **B** Occurrence of contributing journals

overdriven by the progression of hypertension [25, 26]. Moreover, previous studies have confirmed that in the adrenergic system, sympathetic nervous system hyperactivity may be the determinant of blood pressure variability [27, 28], This is generally considered an independent risk factor for cardiovascular diseases such as heart failure and severe arrhythmias. In addition to traditional medical therapy, invasive approaches, such as continuous carotid baroreceptor stimulation and renal denervation, have been proven to effectively reduce blood pressure levels in patients with resistant hypertension [29, 30], supplementing the mechanism of RDN for hypertension.

The analysis of co-cited references

According to the citation analysis of the publications listed in Fig. 5A, the top three co-cited references revealed the effectiveness and safety of RDN for treating resistant hypertension through randomized controlled trials. After 6 months of assessing the patient's blood pressure levels, the efficacy of RDN in the treatment of resistant hypertension was confirmed [31, 32]. This study can provide an important clinical rationale for this research field. Using VOSviewer software to visualize and analyze the co-cited references, 25 references reaching the threshold were finally included and co-citation mapping was generated. Figure 5B shows the division of the 25 kinds of literature into two clusters based on the

Table 3 Top 5 contributing journals in the field of RDN for hypertension

Rank	Journal title	Quantity	Citations	Average Citation/Publication	IF_{2023}
1	Hypertension	105	5936	56.53	9.897
2	Journal of Hypertension	71	2234	31.46	4.9
3	Current Hypertension Reports	61	933	15.30	4.592
4	Eurointervention	46	973	21.15	6.2
5	Clinical Research in Cardiology	38	1138	29.95	6.138

Table 4 Top 10 highly cited literatures in the field of RDN for hypertension

Rank	Literature title	Citations	Journal	Year
1	A Controlled Trial of Renal Denervation for Resistant Hypertension	1511	New England Journal of Medicine	2014
2	Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial	479	Lancet	2017
3	Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial	475	Lancet	2018
4	Hypertension	466	Lancet	2015
5	Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study	447	Lancet	2014
6	Predictors of blood pressure response in the SYMPLICITY HTN-3 trial	403	European Heart Journal	2019
7	Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial	378	Lancet	2018
8	The Sympathetic Nervous System Alterations in Human Hypertension	362	Circulation Research	2015
9	Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial	360	Lancet	2015
10	The Autonomic Nervous System and Hypertension	345	Circulation Research	2015

intensity of collaboration. Most of these were clinical research studies in the field of cardiovascular systems, with a few in the field of physiology.

Distribution of keywords

Analysis of keyword co-occurrence

Keywords represent the core of the article, and their visual analysis plays an important role in exploring the frontiers and the development directions of this field. Figur6A shows the formation of eight clusters by running with a k-means clustering algorithm. Figure 6B shows the co-occurrence map of 150 keywords with times of occurrence greater than 15, created using VOSviewer software. Additionally, the top 20 keywords in terms of number of occurrences were also listed in Table 5. Apart from renal denervation and hypertension, keywords with high frequency included resistant hypertension, blood pressure, sympathetic nervous system, and trial, which are terms frequently used in the cardiovascular field (Fig. 6C and D).

According to Fig. 6B, keywords were mainly concentrated in the fields of cardiovascular system and physiology, and three clusters were formed. The red cluster consisted of 64 nodes, including hypertension, renin-angiotensin system, oxidative stress, resistant hypertension, and nervous system, and was focused on the mechanism of hypertension. For example, development of neurogenic hypertension is closely related to elevated angiotensin-II, inflammation, and vascular dysfunction [33].

The green cluster mainly consisted of renal denervation, controlled trial, prevalence, management, and blood-pressure reduction, and concentrates on the

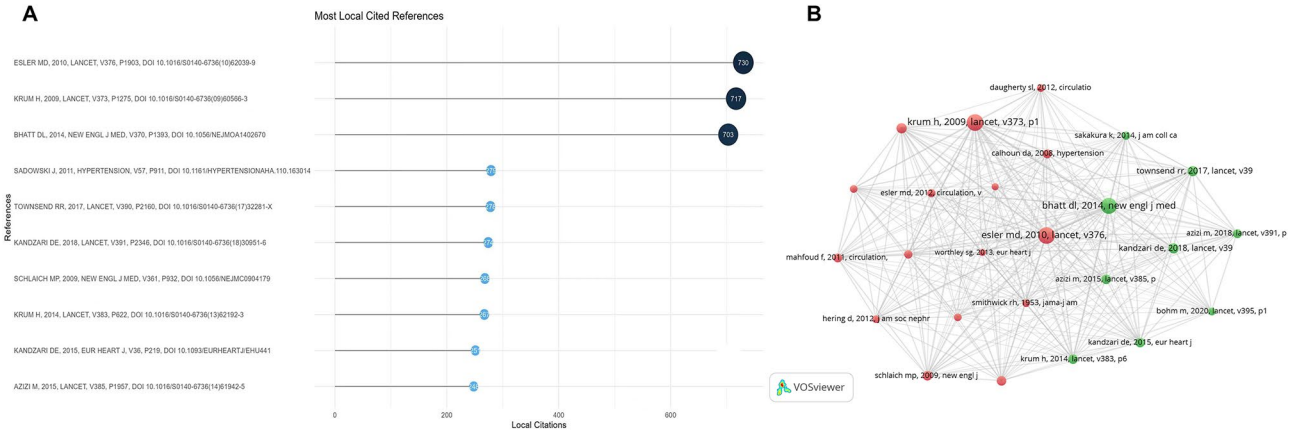


Fig. 5 Distribution map of co-cited reference. **A** Top 10 local cited references in the field of RDN for hypertension. **B** Visualization of co-cited references

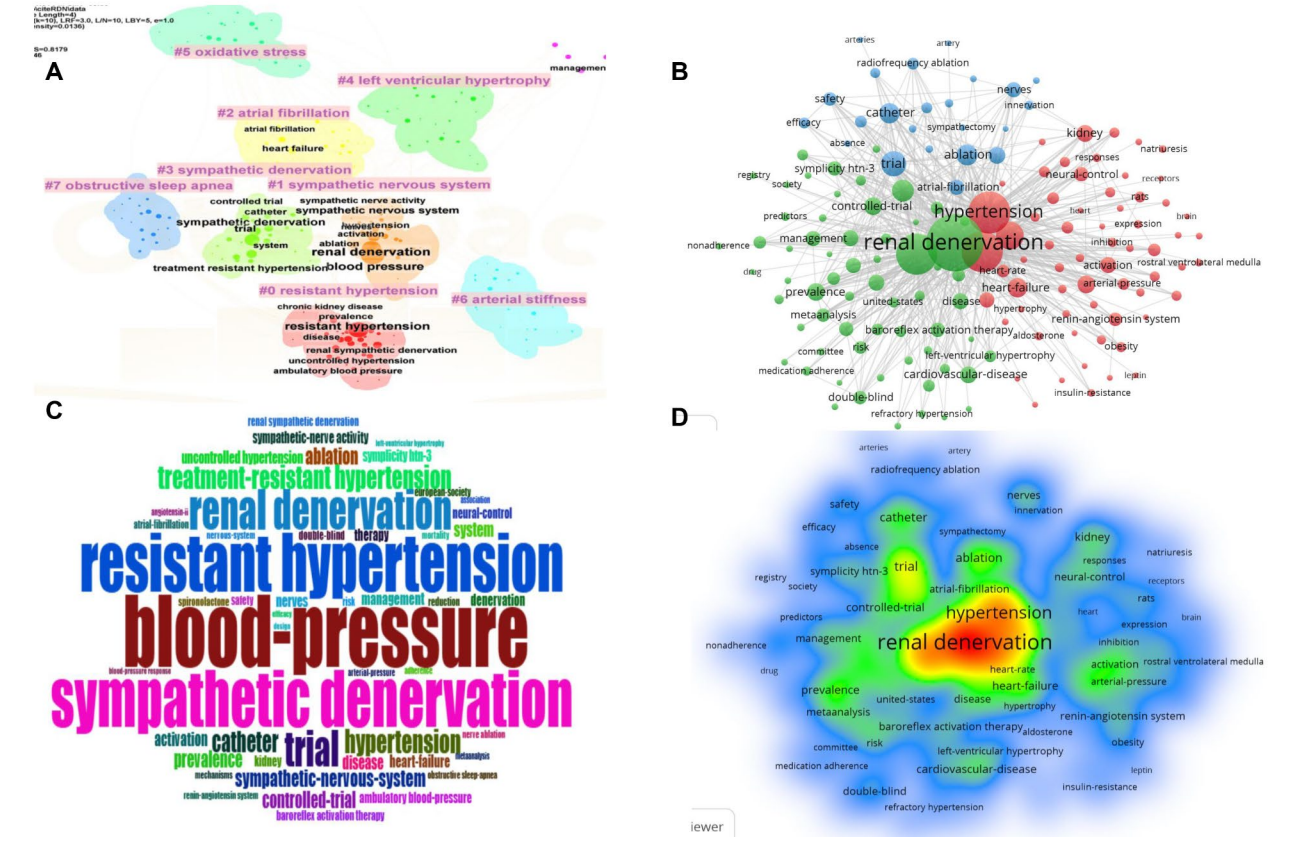


Fig. 6 Visualization of keywords. **A** Cluster map of keywords. **B** Occurrence map of keywords. **C** Word cloud map of the top 50 keywords. **D** Density visualization of keywords

analysis of clinical trials of hypertension and the therapeutic effects of RDN on hypertension. An animal study illustrated the therapeutic effect of RDN by reducing factors associated with hypertension, such as ang-II or actin-binding protein [34].

The blue cluster consisting of atrial fibrillation and pulmonary vein isolation, reflected that RDN can treat other diseases as well as hypertension [35]. A meta-analysis conducted by Ukena indicated the effectiveness of RDN as an adjunctive treatment for patients with atrial fibrillation [36].

Analysis of keywords timeline map

The timeline of keyword analysis explored the development and evolution of this research field. The time slice was set to 3 years, the g-index was set to 5, and the

Table 5 Top 20 keywords in the field of RDN for hypertension

Rank	Keyword	Occurrences	Total link strength
1	renal denervation	1192	6941
2	hypertension	633	3889
3	resistant hypertension	627	3897
4	blood-pressure	609	3928
5	sympathetic nervous system	283	1932
6	trial	239	1539
7	treatment-resistant hypertension	178	1275
8	ablation	163	1150
9	catheter	148	1088
10	heart-failure	135	891
11	prevalence	115	785
12	sympathetic-nerve activity	114	773
13	controlled-trial	112	774
14	kidney	107	702
15	cardiovascular-disease	106	746
16	system	101	710
17	activation	99	684
18	uncontrolled hypertension	99	711
19	disease	95	632
20	ambulatory blood pressure	92	636

threshold of occurrences of the keyword was set to 14; this formed the timeline map of keywords in this research field by using CiteSpace software (Fig. 7A). The size of the node represented the frequency of keyword occurrence, with the position related to the year. The purple and red of the outer ring of the node indicated the centrality and the strength of the keyword respectively, and the connecting line displayed a close association with the co-occurrence relationship between keywords.

Figure 7A displays that research themes in the field of RDN for hypertension can be divided into 3 phases from 2004 to 2023. Firstly, from 2004 to 2010, research themes mainly involved theoretical exploration of RDN and research on the pathogenesis of hypertension [37], and included stimulation [38, 39], fetal origins [40] and receptors [41].

From 2010 to 2016, keywords were heavily concentrated. During this period, the range of research was further expanded, and the number of themes increased rapidly. Therefore, it can be concluded that this phase focused on clinical trial research on RDN for hypertension. High-frequency keywords reflecting this stage included controlled trial [42–44], double-blind [45, 46], meta-analyze [47], and simplicity htn 3 [48].

After 2016, the development of RDN has entered a phase of relative maturity, with further evidence of its effectiveness in treating hypertension. Therefore, this stage mainly involves exploring the extensive application of RDN in the cardiovascular field, while continuing to improve treatments for hypertension. This phase was analyzed around pulmonary vein isolation [36], baroreflex activation therapy [33], and rostral ventrolateral medulla [49]. Research around these themes is predicted to continue in the near future.

Analysis of keywords with high citation bursts

Figure 7B represents commencement and termination times as well as the intensity of keyword bursts, where the blue color denotes temporal placement of the retrieved keywords, and the red line signifies peak intensity of keyword bursts. The examination of keyword mutations aids in investigating the frontiers of the research field.

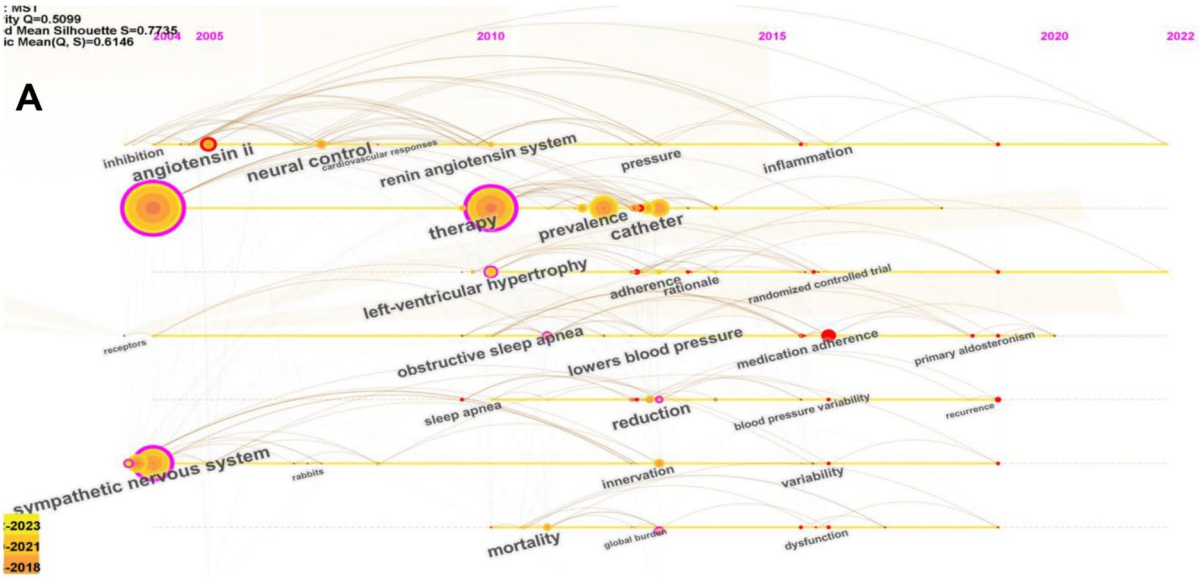
In Fig. 7B, uncontrolled hypertension had the highest burst intensity of 22.3, lasting from 2019 to the present. The subsequent keywords are neural control and the United States, respectively, which have already passed the period of highest outburst intensity. Early appearance of the sympathetic nervous system and arterial pressure confirmed that the mechanism of hypertension was a research hotspot in the early days of this phase. In addition to uncontrolled hypertension, keywords currently in the burst period include safety, hypertension, and cardiovascular disease, which represent the current frontiers in this field of research.

Discussion

General information

In this study, bibliometric methods were applied to examine the development and application of RDN in hypertension. Since the initial application of this technique in 2009 [50], RDN has undergone numerous clinical trials and has been validated as an effective modality to treat hypertension, in addition to pharmacologic therapy and lifestyle interventions. The technique encompasses three primary categories: radiofrequency ablation, ultrasound ablation, and chemical ablation. Meanwhile, radiofrequency ablation, ultrasound ablation. Meanwhile, radiofrequency ablation and ultrasound ablation were approved for hypertension treatment by the U.S. Food and Drug Administration (FDA) in November 2023. This represents a significant development in the field. Based on the bibliometric analysis, the following representative clinical studies are as follows:

Currently, radiofrequency ablation is the most advanced technique used in RDN. Large-scale prospective studies and clinical trials of radiofrequency based RDN (rRDN) have been conducted in the United States, Europe, and Asia; among these, the most prominent are the SYMPLICITY trials. Initial clinical studies provided evidence in support of the efficacy of rRDN in lowering blood pressure. However, the SYMPLICITY HTN-3 clinical trial did not confirm the efficacy of this technique in the treatment of resistant hypertension, as investigated by a 6-month follow-up of 535 patients from the



B

Keywords	Year	Strength	Begin	End	2004 - 2023
sympathetic nervous system	2004	7.53	2004	2009	
arterial pressure	2004	5.86	2004	2012	
neural control	2007	9.49	2007	2015	
nervous system	2008	6.38	2008	2015	
sleep apnea	2010	6.08	2010	2015	
scientific statement	2012	6.04	2012	2015	
united states	2013	8.1	2013	2015	
symplicity htn 3	2014	7.83	2016	2021	
predictors	2016	6.81	2016	2018	
outcm	2017	6.44	2017	2023	
artery denervation	2016	5.73	2016	2021	
uncontrolled hypertension	2016	22.3	2019	2023	
safety	2013	8.08	2019	2023	
Hypertension	2005	6.6	2019	2023	
pulmonary vein isolation	2019	6.01	2019	2021	

Fig. 7 **A** Timeline map of keywords from 2004 to 2023. **B** Top 15 keywords with the strongest citation bursts

United States [18]. However, a 3-year follow-up revealed a 24-hour ambulatory systolic blood pressure (SBP) change of −15.6 mmHg in the rRDN group, which is a significantly superior level of blood pressure compared to the sham control group (–0.3 mmHg) [51]. This trial corroborates the long-term efficacy of rRDN in patients with resistant hypertension, supported by the supplementary evidence provided for SYMPLICITY HTN-3. A total of 1,742 patients with uncontrolled hypertension were enrolled in the Global SYMPLICITY Registry at 196 active centers in 45 countries following the rRDN procedure [52]. The data from the three-year follow-up period indicated sustained the reductions in office blood pressure (–16.5 mmHg) and 24-hour ambulatory SBP (–8.0 mmHg) were sustained. Furthermore, the occurrence of cardiovascular mortality and major adverse events associated with rRDN was markedly reduced at the three-year follow-up. This study has demonstrated the durability and safety of this procedure.

The sham-controlled RADIANCE-HTN trials, conducted to investigate the efficacy of endovascular ultrasound RDN (uRDN) in lowering blood pressure, included two cohorts: the SOLO cohort [53] and the TRIO cohort [54]. In the RADIANCE-HTN SOLO study, 146 patients

with mild hypertension who had discontinued their antihypertensive medications were randomly assigned to the uRDN group and the sham-controlled group. In the RADIANCE-HTN TRIO trial, 136 patients with severe resistant hypertension resistant to three antihypertensive agents were randomized into groups. The results of the two-month follow-up indicated that the uRDN group had more pronounced reductions in 24-hour ambulatory SBP (SOLO cohort: −8.5 mmHg, TRIO cohort: −8.0 mmHg) compared to the sham procedure groups (SOLO cohort: −2.2 mmHg, TRIO cohort: −3.0 mmHg). These findings substantiated the efficacy and safety of uRDN in the treatment of hypertension.

Previous clinical studies [55] have demonstrated the feasibility of alcohol mediated RDN. However, these studies were limited by a small sample size and a lack of sufficient clinical evidence. In the TARGET-BP off-MED study [56], 106 patients with uncontrolled hypertension were recruited. No significant difference was observed in 24-hour ambulatory SBP reductions (−1.5 mmHg versus −4.6 mmHg). This trial confirmed the safety of alcohol mediated RDN; however, its efficacy has yet to be demonstrated. More recently, the TARGET BP I Randomized Clinical Trial was recently conducted [57], enrolling 301 patients with uncontrolled hypertension. These patients were prescribed 2–5 antihypertensive drugs, randomly assigned to RDN or sham control. The results of the trial demonstrated that after a three-month follow-up duration, a statistically significant difference in mean 24-hour ambulatory SBP between the RDN group and the sham-controlled group was observed (−10±14.2 mmHg versus −6.8±12.1 mmHg, P=0.0487). Additionally, the occurrence of adverse events during the six-month follow-up period was minimal; this substantiates the intermediate-term safety and efficacy of the alcohol-mediated RDN in patients with uncontrolled hypertension.

Hotspots and frontiers

Hotspots

The analysis of the co-citation relationship between the literature and cited reference can assist in the development of a knowledge framework and identification of research hotspots. Keywords, which represent the essence of an article, can be used to ascertain the hotspot direction of a research field. In conclusion, research hotspots identified through analysis of co-citation relationships and clustering and timeline analysis of keywords can be summarized as follows: mechanism of RDN for the treatment of hypertension and advantages of RDN in appliance therapy.

Mechanism of RDN for hypertension

Research on the mechanism of hypertension is mostly concentrated in the over-activation of the RAAS system, sympathetic dysfunction, and release of inflammatory factors [58–60]. As a pivotal organ and nervous system for regulating blood pressure, enhanced renal efferent sympathetic nerve activity promotes activation of beta1-adrenergic receptors of glomerular parietal cells. This influences turn on renin secretion, glomerular filtration rate, and renal tubular sodium reabsorption [61].The renal afferent nerve provides continuous feedback to the central autonomic nuclei and regulates the central sympathetic nervous system [62]. Therefore, the interaction between renal efferent and afferent sympathetic nerves constitutes renal sympathetic nerve activity (RSNA), which plays a pivotal role in the physiopathology of hypertension [63].

Distribution of renal efferent nerve fibers is particularly dense in the vicinity of renal arteries and veins, and some branches of these blood vessels are distributed around the arterial vascular segments outside the renal cortex and medulla [62]. The RDN technique reduces blood pressure by removing efferent and afferent fibers from the renal sympathetic nervous system, increasing water and sodium excretion, and decreasing the RSNA system and systemic sympathetic nervous system activity. In other words, the antihypertensive mechanism of RDN is equivalent to the combinations of antihypertensive agents, including beta-blockers, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEI), and thiazide-like diuretics. Hence, RDN is a more suitable treatment option for patients with resistant hypertension.

Advantages of RDN in appliance therapy

At present, in addition to the RDN technology, several devices have been proposed to treat resistant hypertension. These include a central iliac arteriovenous coupler, electrical baroreflex activation therapy, and others.

The prompt decline in blood pressure following treatment of the anastomosis may be attributed to the formation of a low-resistance, high-compliance venous segment into the central arterial tree [7, 64, 65]. In a randomized controlled trial (the ROX CONTROL HTN study) [66], 44 patients were randomly assigned to the arteriovenous coupler group and 39 to the medical therapy group. The six-month postoperative follow-up indicated that levels of blood pressure in the anastomosis group (office blood pressure: −23.2 mmHg systolic and −17.7 mmHg diastolic, 24-hour ambulatory blood pressure: −13.0 mmHg systolic and −13.0 mmHg diastolic) exhibited a notable decrease when compared with the control group (−1.5[16.7] mmHg systolic and −1.1[10.5] mmHg diastolic). While this study demonstrates the efficacy of the central iliac arteriovenous coupler for treating resistant hypertension, it is important to note that there 25 adverse events occurred among the patients

who underwent this surgical procedure; these included urinary retention, transient pain, anemia, and others. Twelve patients developed significant unilateral lower extremity edema and were subsequently diagnosed with iliac vein stenosis proximal to the anastomosis. To date, no reports or clinical trials have been published regarding the long-term safety of central iliac arteriovenous coupler treatment; hence, this needs to be investigated in the future.

Electrical baroreflex activation therapy (BAT) stimulates the baroreceptors in the carotid sinus, inhibiting the activity of sympathetic nerves and ultimately reducing blood pressure [67]. In a randomized, double-blind, placebo-controlled study [68], 256 patients with resistant hypertension were randomly assigned to one of two groups. Group A was administered immediate BAT, while Group B underwent BAT deferred for six months. While the second-generation BAT technique is a significant advance over existing approaches, further randomized treatment trials must be conducted to prove the durability and safety of this technique for patients with resistant hypertension. Other technologies are not yet sufficiently mature for widespread adoption, and further studies and clinical trials are needed to improve their theranostic applications. In contrast, RDN has been verified and analyzed in numerous randomized clinical trials; hence, it offers a more objective theoretical basis, and plays an invaluable role in the treatment of resistant hypertension.

Frontiers

By analyzing the keywords with high citation bursts in this paper, we can summarize the research frontiers of RDN can be summarized as follows:

Improvement of RDN instruments and techniques

Although the RDN technique has become relatively established and confirmed by multiple studies, some uncertainty about this surgery persists. A study conducted by De Jong et al. [69] showed that 30% of patients did not respond when undergoing the RDN procedure with the monopoly ablation catheter, this may be due to the different proportions of sympathetic and parasympathetic tissue around the renal arteries [70]. Therefore, improvements to RDN instrumentation and techniques remain an important direction for research.

Taking rRDN as an example, in the SPYRAL HTN-OFF MED trial [48], the Symplicity Spyral multielectrode ablation catheter and the Symplicity G3 ablation radiofrequency generator were applied to patients with uncontrolled hypertension. The Symplicity Spyral catheter can ablate renal arteries with vessel diameters ranging from 3 to 8 mm. The catheter is equipped with four helical electrodes, enabling ablation of four quadrants of the renal artery trunk and at least two quadrants of the renal artery branches. The results of this trial demonstrated a significant benefit of RDN in terms of 24-hour ambulatory blood pressure reduction in the absence of antihypertensive agents, with stable levels of blood pressure throughout the day and no adverse events during the six-month follow-up period. However, this catheter has certain limitations. These include the following: the relatively fixed spiral structure of the catheter makes conformation to the morphology of the blood vessels challenging; the continuity of the ablation energy field is less effective, resulting in a longer ablation time.

A recent Netrod-HTN clinical study conducted in China investigated the efficacy and safety of the Netrod Six-Electrode rRDN for the treatment of uncontrolled hypertension. The Netrod Six-Electrode catheter increased the diameter of the renal artery vessels to 2–12 mm and adapted intelligently to morphological changes in the blood vessels, ensuring continuity of the ablation energy field. The procedure time was shortened, and the surgical efficiency increased significantly. Further prospective studies are required to verify long-term efficacy and safety.

At present, the RDN technique still presents some limits such as vascular endothelial damage, severe pain, etc. Further improvement of the RDN instrument and conduction of more research studies with multi-center, large sample size, real world studies represent potential future research directions.

Exploration of the therapeutic effects of RDN in diseases with increased sympathetic nerve activity

The increased sympathetic nerve activity is closely linked to cardiovascular diseases and metabolic abnormalities. Christian Ukena et al. [36] randomized patients with hypertension combined with atrial fibrillation(AF) into the RDN combined pulmonary vein isolation(PVI) group as well as the PVI alone group, and after 12 months, the odds ratio for AF recurrence was 0.43 for the combined surgery group versus the PVI alone group, suggesting that RDN can significantly reduce the recurrence of AF.

The subcohort of the SYMPLICITY HTN-2 clinical trial showed reduced blood pressure in RDN treatment with a concomitant reduction in fasting glucose (from 118±3.4 to 108±3.8 mg/dL), insulin levels (from 20.8±3.0 to 9.3±2.5 μIU/mL), and C-peptide levels (from 5.3±0.6 to 3.0±0.9 ng/mL) at 3-month follow-ups [71]. As an important regulator of insulin resistance, excitation of the sympathetic nervous system is associated with increased risks of central obesity and diabetes. RDN can improve glucose metabolism and insulin sensitivity, which can be explained by reduction of noradrenaline and inhibition of renal sympathetic activity.

Furthermore, some pathophysiology studies and clinical trials have demonstrated the treatment efficacy of

RDN on chronic heart failure, left ventricular hypertrophy, and autonomic nerve dysfunction [61–63]. Thus, future research should explore the potential therapeutic effects of RDN in diseases with increased sympathetic nerve activity.

Limitations

Research data were obtained from the WoSCC. Only 433 review papers and 1,046 research papers were included in the analysis, as other types of literature and non-English sources were excluded; hence, there was a certain degree of source bias.

Conclusions

As the first bibliometric study of RDN for hypertension, this paper provided a comprehensive and objective summary of the status and clinical trials of the RDN technique, manifesting the efficacy, durability, and safety. The improvement of RDN ablation catheters and exploration of the therapeutic effects of RDN in diseases with increased sympathetic nerve activity will be the priority of future research. This will confirm the importance of RDN technology hypertension therapy and provide more treatment options to patients with hypertension or other diseases. Our study provides references and implications for future research into RDN for the treatment of hypertension.

Abbreviations

AF	Atrial fibrillation
ACEI	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
BAT	Baroreflex activation therapy
ESH	European Society of Hypertension
CCBs	Calcium channel blockers
FDA	Food and Drug Administration
RAAS	Renin-angiotensin-aldosterone system
RDN	Renal Denervation
rRDN	Radiofrequency-based Renal Denervation
RSNA	Renal sympathetic nerve activity
SBP	Systolic blood pressure
PVI	Pulmonary vein isolation
uRDN	Ultrasound Renal Denervation
WoSCC	Web of Science Core Collection

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Author contributions

JR and XH analyzed the data and prepared the first draft of the manuscript. YC and H collected and collated data. XY helped in visualization. B and YH conceptualized designed the study and involved in manuscript reviewed. All authors contributed substantively to the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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