kcj
Korean Circulation Journal

State of the Art Review

🔄 Check for updates

Current Status and Future Perspectives of Renal Denervation

Ki Hong Choi 🔟**, MD, and Seung-Hyuk Choi** 🔟**, MD, PhD**

Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

🔓 **OPEN ACCESS**

Correspondence to
Seung-Hyuk Choi, MD, PhD
Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: sh1214.choi@samsung.com

ORCID iDs
Ki Hong Choi 🔟
https://orcid.org/0000-0001-7511-9581
Seung-Hyuk Choi 🔟
https://orcid.org/0000-0002-0304-6317

Conflict of Interest
The authors declare that there is no conflict of interest relevant to this work.

AUTHOR'S SUMMARY

Despite the availability of numerous antihypertensive medications, hypertension treatment and control rates remain low, and uncontrolled hypertension is well-known to be one of the most important cardiovascular risk factors. Endovascular catheter-based renal denervation (RDN) has been developed to be a complementary or alternative treatment option for patients who cannot take medication, poor adherence, or have resistant hypertension despite the use of maximal doses of medications. Recently, several randomized trials for evaluating the efficacy and safety of second-generation RDN devices consistently show solid evidence for their blood pressure-lowering efficacy. This review summarizes the current evidence and future perspectives of RDN.

ABSTRACT

Catheter-based renal denervation (RDN) therapy, a new procedure that uses radiofrequency ablation to interrupt efferent and afferent renal sympathetic nerve fibers, is a complementary or alternative treatment to antihypertensive medications for optimal control of blood pressure (BP). Although several single-arm early proof-of-concept studies showed significant BP reduction, the largest sham-controlled study using the first-generation RDN device (SYMPLICITY HTN-3) failed to significantly reduce BP in patients with resistant hypertension who were taking the guideline-based combination of antihypertensive medications. Since then, new devices and techniques have been developed to improve the efficacy and safety of RDN procedures. Sham-controlled trials using second-generation RDN devices (radiofrequency- and ultrasound-based) have provided solid evidence for their BP-lowering efficacy with and without the use of concomitant antihypertensive medication. Moreover, the safety profile of RDN in several registries and clinical trials appears to be excellent. This review summarizes the current evidence for RDN and discusses its current issues, future trials, Asian perspectives, and potential roles in both hypertension and other morbidities.

Keywords: Renal denervation; Blood pressure; Resistant hypertension; Asia

INTRODUCTION

Hypertension (HTN) is a well-known, powerful risk factor of cardiovascular disease (CVD), and its prevalence has been rising worldwide.[1-3] Previous clinical trials have shown that treating HTN reduced the risk of all-cause mortality and CVD, including stroke, myocardial infarction, and heart failure.[4-7] More importantly, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that intensive blood pressure (BP) control (targeting a systolic BP of less than 120 mmHg), compared with standard control (targeting a systolic BP of less than 140 mmHg), reduced rates of major adverse cardiovascular events in patients at high risk for CVD without diabetes mellitus.[8] Based on that result, the current relevant guidelines recommend treatment thresholds for the initiation of antihypertensive drugs and target BP ranges that are lower than those in the previous guidelines as long as patients tolerate the treatment.[9-11] Nevertheless, in real-world practice, BP control rates are still low, and the prevalence of resistant HTN continues to increase globally.[12][13] One of the factors affecting that result is poor adherence to prescribed antihypertensive medications. In fact, previous large observational studies have shown that roughly half of participants stop taking their antihypertensive drugs within a year for various reasons, including poor patient compliance, adverse effects of drug therapy, and socioeconomic factors,[14][15] and non-persistence or low adherence to antihypertensive treatment was associated with future adverse outcomes.[16-19] In this regard, patients who cannot take medication or poorly adhere to their prescribed regimen might need additional or alternative treatment options for adequate BP control, and device-based BP-lowering therapy such as renal denervation (RDN) could be a complementary or alternative treatment option for those patients.[20-22] In this review, we discuss the current evidence, issues, future trials, and potential roles of RDN as an attractive treatment option for HTN.

PATHOPHYSIOLOGICAL RATIONALE

Although the pathophysiology of HTN is complicated, the renal sympathetic nervous system, which contains both afferent and efferent sympathetic nerve fibers, plays an essential role in the development of HTN.[23] Concretely, activation of the efferent sympathetic nerves in the renal artery can lead to renal arteriolar vasoconstriction, decreased renal blood flow, increased renin secretion, subsequent activation of the angiotensin-aldosterone system, and increased sodium and water absorption, resulting in increased intravascular volume and the maintenance of systemic HTN.[24] On the other hand, activation of renal afferent nerves can lead to increased systemic sympathetic activity and hormone release in the hypothalamus, resulting in increased systemic vascular resistance and HTN.[25] Therefore, RDN, which interrupts both efferent and afferent sympathetic sensory nerve pathways in the renal artery, has been developed for the treatment of HTN.

EVIDENCE FOR THE FIRST-GENERATION DEVICE

The first-generation radiofrequency (RF) ablation system for performing RDN was a single unipolar electrode on a flexible (4 French) catheter (SYMPLICITY Flex™; Medtronic, Minneapolis, MN, USA). In 2009, Krum et al.[26] conducted a proof-of-concept study (SYMPLICITY HTN-1) and demonstrated the feasibility of RDN in patients with resistant HTN. In that study, office BP was decreased by up to 27 mmHg (systolic BP) and 17 mmHg

(diastolic BP) 12 months after the RDN procedure without serious procedure-related adverse events. Subsequently, the open-label randomized controlled SYMPLICITY HTN-2 trial also showed that the RDN group was associated with significant BP reduction at the 6-month follow-up, compared with control group (RDN vs. control group, −32/12 mmHg vs. 1/0 mmHg, p<0.001) in patients with treatment-resistant essential HTN (defined as office systolic BP ≥160 mmHg despite the prescription of ≥3 antihypertensive drugs).[27] Most observational studies and registries showed similarly promising findings.[28-30]

In 2014, to overcome the methodologic shortcomings, particularly the lack of blinding, in the SYMPLCITY HTN-2 trial, an additional multicenter, single-blind, randomized sham-controlled trial (the SYMPLICITY HTN-3 trial) was conducted in patients with resistant HTN (defined as office systolic BP ≥160 mmHg despite the prescription of ≥3 antihypertensive drugs).[31] In that study, 535 patients with resistant HTN were randomly assigned in a 2:1 ratio to undergo RDN or a sham procedure. Unexpectedly, the early excitement about RDN ended abruptly when the results of the SYMPLICITY HTN-3 trial failed to demonstrate the superiority of RDN over sham treatment for office BP changes at 6 months. In the SYMPLICITY HTN-3 trial, the mean change in office systolic BP at 6 months was −14.13 ± 23.93 mmHg in the RDN group (p<0.001 for comparisons with baseline) and −11.74 ± 25.94 mmHg in the sham-procedure group (p<0.001 for comparisons with baseline), without a significant between-group difference (difference of −2.39 mmHg; 95% confidence interval [CI], −6.89 to 2.12 mmHg; p for superiority=0.26 with a margin of 5 mmHg), although the safety endpoints did not differ significantly between the two groups either.[31] Several possible explanations have been proposed to account for the discrepancy between the results of the SYMPLICITY HTN-3 trial and the results of previous studies and registries, including the SYMPLICITY HTN-1 and -2 trials. First, 39% of patients underwent antihypertensive medication changes during the study period. Furthermore, trial participation might have affected the high degree of adherence to antihypertensive therapy found among the participants because of close follow-up, which might be associated with the unexpectedly large BP reduction in the sham group. Second, patients with isolated systolic HTN were included in the SYMPLICITY HTN-3 trial. Mahfoud et al. reported that changes in isolated systolic HTN following RDN was less pronounced than BP reduction in patients with combined systolic and diastolic HTN.[32] Third, due to the limitations of operator experience with RDN, only a few patients in the RDN group received the complete circumferential ablation pattern in the main renal arteries recommended in the protocol. Actually, the number of ablations was associated with the degree of BP reduction in post-hoc analysis of SYMPLICITY HTN-3 trial data.[33]

Beyond the SYMPLCITY HTN-1, -2, and -3 trials, several other randomized controlled trials and registries have been published about the first-generation RDN device, and **Table 1** summarizes the results of those studies.[34-43] Among them, the issue of adherence, which is one of the weaknesses of the SYMPLICITY HTN-3 trial, was adequately addressed in the well-designed open-label randomized controlled Renal Denervation for Hypertension (DENERHTN) trial. That trial included 106 patients with well-defined and truly resistant HTN, and the patients were randomized 1:1 to receive either RDN plus standardized stepped-care antihypertensive treatment (SSAHT) or SSAHT alone. That study showed that RDN plus SSAHT reduced ambulatory systolic BP significantly better than SSAHT alone (RDN vs. control, −15.8 mmHg vs. −9.9 mmHg; baseline-adjusted difference of −5.9 mmHg; 95% CI, −11.3 to −0.5 mmHg; p=0.033). Of note, although about 50% of the patients in both the RDN and control groups were partially or completely non-adherent to

Table 1. Results from trials that used the first-generation RDN device (SYMPLICITY Flex™)

Trial	Publication year	Inclusion criteria	Follow-up	RDN group (No.)	Control group (No.)	Primary outcome	ΔSBP (RDN) (mmHg)	ΔSBP (Control) (mmHg)	Difference between RDN and control (mmHg)	p value
Randomized, sham-controlled trials										
SYMPLICITY HTN-3	2014	Resistant HTN (SBP ≥160 mmHg on ≥3 antihypertensive drugs)	6 months	364	171	Office SBP change	−14.13±23.93	−11.74±25.94	−2.39 (−6.89 to 2.12)	0.26
Leipzig-RSD	2015	Mild resistant HTN (mean 24-hour SBP 135-149 or DBP 90-94 mmHg on ≥3 antihypertensive drugs)	6 months	35	36	24-hour SBP change	−7.0 (−10.8 to −3.2)	−3.5 (−6.7 to −0.2)	−3.5	0.15
ReSET	2016	Daytime SBP ≥145 mmHg on ≥3 antihypertensive drugs	3 months	36	33	Daytime SBP change	−6.2±18.8	−6.0±13.5	−0.2	0.95
Randomized controlled trials										
SYMPLICITY HTN-2	2010	Resistant HTN (SBP ≥160 mmHg on ≥3 antihypertensive drugs)	6 months	52	54	Office SBP change	−32±23	1±21	−33	<0.001
RDN Oslo	2014	Resistant HTN (SBP ≥140 mmHg on ≥3 antihypertensive drugs)	6 months	9	10	Office SBP change	−8	−28 (drug-adjusted)	16	0.002
Prague-15	2015	Resistant HTN (SBP ≥140 mmHg on ≥3 antihypertensive drugs)	6 months	52	54	24-hour SBP change	−8.6 (−11.8 to −5.3)	−8.1 (−12.7 to −3.4) (spironolactone add)	−0.5 (−6.1 to 5.2)	0.87
SYMPLICITY HTN-JAPAN	2015	Resistant HTN (SBP ≥160 mmHg on ≥3 antihypertensive drugs)	6 months	22	19	Office SBP change	−16.6±18.5	−7.9±21.0	−8.64 (−21.12 to 3.84)	0.169
DENERHTN	2015	Resistant HTN (SBP ≥140 mmHg or DBP ≥90 mmHg on ≥3 antihypertensive drugs)	6 months	53	53	Daytime SBP change	−15.8 (−19.7 to −11.9)	−9.9 (−13.6 to −6.2)	−5.9 (−11.3 to −0.5)	0.033
DENERVHTA	2016	Resistant HTN (office SBP ≥150 or 24-hour SBP ≥140 mmHg on ≥3 antihypertensive drugs)	6 months	11	14	24-hour SBP change	−5.7 (−14.8 to 3.4)	−23.6 (−31.9 to −15.3) (spironolactone add)	17.9 (4.9 to 30.9)	0.010
SYMPATHY	2017	Daytime SBP ≥135 mmHg on ≥3 antihypertensive drugs	6 months	95	44	Daytime SBP change	−6.0 (−10.7 to −1.2)	−7.9 (−14.7 to −1.3)	2.0 (−6.1 to 10.2)	0.625
RDN OSA	2018	Office SBP ≥140 mmHg, daytime ambulatory SBP ≥135 mmHg, and moderate-to-severe OSA	3 months	30	30	Office SBP change	−22 (−31 to −13)	−5 (−12 to −1)	−17 (−27 to −6)	0.002
Key registries										
SYMPLICITY HTN-1	2009	Resistant HTN (SBP ≥160 mmHg on ≥3 antihypertensive drugs)	1, 3, 6, 9, 12 months	45	NA	Office SBP change	−22 (−32 to −12) at 6 months	NA	NA	NA
Global SYMPLICITY Registry	2019	Treated with the SYMPLICITY Flex™ catheter	6 months and up to 36 months	2,237	NA	Office SBP change	−12.8±26.2 (6 months)	NA	NA	NA

Data are presented as the mean±standard deviation or median (95% confidence interval).
DBP = diastolic blood pressure; HTN = hypertension; NA = not applicable; OSA = obstructive sleep apnea; RDN = renal denervation; SBP = systolic blood pressure.

antihypertensive medications, no differences in doses or adherence rates were found between the two randomized groups.[44)] Interestingly, a post-hoc analysis of the DENERHTN trial demonstrated that antihypertensive medication nonadherence was a major determinant of the difference between office systolic and daytime ambulatory BP.[45)]

SECOND-GENERATION RENAL DENERVATION TRIALS

Radiofrequency ablation-based treatment

Because the results of trials using a first-generation RDN device for the treatment of HTN were controversial, several subsequent preclinical and clinical studies explored ways to improve the effectiveness of RDN.[46-48)] For example, a second-generation RF ablation device (SYMPLICITY Spyral™; Medtronic), a flexible 4-electrode catheter design used to perform 4 simultaneous ablations with a helical pattern, was developed. This system can perform a comprehensive RDN procedure that includes ablation in the distal main renal artery and arterial branches. Based on the lessons learned from the pitfalls of the SYMPLICITY HTN-3 study, two well-designed, randomized, sham-controlled, pilot trials of the second-generation multielectrode SPYRAL RF ablation device were conducted.[49)50)] Those trials enrolled patients with mild to moderate combined systolic and diastolic HTN (defined as office systolic BP ≥150 mmHg and <180 mmHg, office diastolic BP ≥90 mmHg, and mean 24-hour ambulatory systolic BP ≥140 mmHg and <170 mmHg) in the absence (SPYRAL HTN-OFF MED trial) or presence (SPYRAL HTN-ON MED trial) of antihypertensive medication. Based on the previous results of a randomized trial comparing the effectiveness of BP reduction between RF ablation at distal renal arterial branches beyond the main renal artery vs. conventional main renal artery treatment,[51)] all previously experienced RDN operators who participated in these studies were advised to perform RF ablation at all accessible renal arteries, including distal segments and subsequent branches, using a multi-electrode catheter. Furthermore, medication adherence was strictly evaluated by urine or serum assays both before and after the RDN or sham treatment in the SPYRAL HTN-ON MED study to identify the effect that adherence had on the endpoints. In the prospectively planned interim analyses of the first 80 patients enrolled in the SPYRAL HTN-OFF MED study, the RDN group showed a significant reduction in mean 24-hour ambulatory systolic BP from baseline to 3 months (−5.5 mmHg; 95% CI, −9.1 to −2.0 mmHg; p=0.003), but the sham procedure group saw no significant difference (−0.5 mmHg; 95% CI, −3.9 to 2.9 mmHg; p=0.76; difference between groups −5.0 mmHg; 95% CI, −9.9 to −0.2 mmHg; p=0.041). The SPYRAL HTN-ON MED trial of patients taking one to three antihypertensive medications also demonstrated that 24-hour ambulatory systolic BP decreased significantly from baseline to 6 months in the RDN group (−9.0 mmHg; 95% CI, −12.7 to −5.3 mmHg; p<0.001) but not in the sham procedure group (−1.6 mmHg; 95% CI, −5.2 to 2.0 mmHg; p=0.365), with significant between-group differences (−7.4 mmHg; 95% CI, −12.5 to −2.3 mmHg; p=0.005). Interestingly, similar to the DENERHTN trial, the patient adherence rate to the prescribed antihypertensive medications was about 60% and did not differ significantly between the RDN and control groups at 3 or 6 months. Recently, the sham-controlled SPYRAL HTN-OFF MED Pivotal trial was published and was adequately powered for the primary efficacy endpoint.[52)] A total of 331 patients was recruited using a combination of data from pilot (n=80) and pivotal (n=251) trials. A Bayesian approach was used for the primary analyses. The treatment difference between the RDN and sham control groups for 24-hour systolic BP was −4.0 mm Hg (Bayesian 95% credible interval, −6.2 to −1.8 mmHg; p=0.001), and for office systolic BP, the difference was −6.6 mm Hg (Bayesian 95% credible interval, −9.6 to −3.5 mmHg; p<0.001). There was no difference in

major device-related or procedural-related safety events between the two groups for up to 3 months. The prospectively powered sham-controlled SPYRAL HTN-ON MED Expansion trial is currently ongoing (ClinicalTrials.gov, NCT02439775). The results of these trials are expected to consolidate support for RDN as a treatment for HTN. Beyond the SYMPLICITY Flex™ and Spyral™ ablation catheters, other RF ablation systems have been developed and approved for use in Europe (EnligHTN [St. Jude Medical, St. Paul, MN, USA], Vessix [Boston Scientific, Marlborough, Massachusetts, USA], OneShot [Covidien, Dublin, OH, USA], and Iberis [Terumo, Ann Arbor, MI, USA]), China (GL-06E15WA ablator and GL-6W ablation catheter [Shanghai Golden Leaf Medtech Company, Shanghai, China]), and Korea (DENEX™ [Handok Kalos Medical, Seoul, Korea]).[53-58] However, those devices still need their efficacy and safety proven in well-designed, randomized, sham-controlled trials. Among them, the recent randomized, sham-controlled Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension (REDUCE HTN REINFORCE) trial evaluated the efficacy of balloon-type bipolar RF-based RDN devices (Vessix; Boston Scientific).[59] Although enrollment was terminated early for apparent futility before a sample sufficient for powered efficacy comparisons was enrolled, a significant difference in office systolic BP reduction in favor of RDN was reported at 6 and 12 months.

Ultrasound-based treatment

An alternative technology using balloon-type ultrasonic RDN catheters (ReCor Medical, Palo Alto, CA, USA) allows complete circumferential denervation in a more reliable fashion than RF ablation by generating frictional heating through the interaction of high-frequency sound waves that pass through the surrounding fluids.[60] The multicenter, randomized, sham-controlled RADIANCE-HTN SOLO (patients with mild to moderate HTN without antihypertensive medications) and TRIO (patients with uncontrolled HTN receiving 3 antihypertensive medications) trials were conducted to evaluate the safety and efficacy of the ultrasound-based RDN procedure. In the RADIANCE HTN Solo trial, 146 patients with combined systolic and diastolic HTN (daytime ambulatory BP ≥135/85 mmHg and <170/105 mmHg) after discontinuing a maximum of two antihypertensive medications for 4 weeks before the ambulatory BP assessment were recruited.[61] After 2 months, the reduction in daytime ambulatory systolic BP was significantly greater with RDN (−5.9±9.3 mmHg) than with the sham procedure (−2.2±10.0 mmHg, baseline-adjusted difference between groups: −6.3 mm Hg; 95% CI, −9.4 to −3.1; p<0·001). Between 2 and 6 months after randomization, patients in both groups were restarted on antihypertensive drugs according to a standardized drug titration protocol if their average home BP was ≥135/85 mmHg. At 6 months, greater reduction in daytime ambulatory systolic BP was maintained in the RDN group than in the sham control group (difference adjusted for baseline BP and number of medications −4.3 mmHg; 95% CI, −7.9 to −0.6 mmHg; p=0.024), despite being prescribed fewer antihypertensive medications than in the sham group (RDN vs. sham procedure, 65.2% vs. 84.5%; p=0.008).[62] Between 6 and 12 months (unblinded phase), patients received antihypertensive medications at their physicians' preference. The decrease in daytime ambulatory systolic BP from baseline to 12 months in the RDN group was stably maintained, despite taking fewer prescribed medications than the sham procedure group (number of medications for RDN vs. sham, 1.0 vs. 1.4; p=0.015). However, the mean between-group difference in daytime ambulatory systolic BP change adjusted for the number of antihypertensive medications was not significant at 12 months (−2.3 mmHg; 95% CI, −5.9 to 1.3; p=0.201).[63] In the recently published RADIANCE HTN TRIO trial, 136 patients with resistant HTN (defined as office BP ≥140/90 mmHg despite the prescription of ≥3 antihypertensive drugs, and daytime ambulatory BP ≥ 135/85 mmHg 4 weeks after switching a single-pill, fixed-dose, daily combination of amlodipine 10

mg, valsartan 160 mg [or Olmesartan 40 mg], and hydrochlorothiazide 25 mg) were finally enrolled.[64] Full adherence to the combination medications at 2 months were similar between the two groups (RDN vs. sham, 82% vs. 82%; p=0.99). After 2 months, RDN procedure significantly reduced daytime ambulatory systolic BP more than the sham procedure (RDN vs. sham, −8.0 mmHg [interquartile range from −16.4 to 0.0 mmHg], vs. −3.0 mmHg [interquartile range from −10.3 to 1.8 mmHg]; group difference −4.5 mmHg; 95% CI, −8.5 to −0.3; adjusted p=0.022) without serious procedure-related adverse events. The currently ongoing REQUIRE (Korea and Japan, ClinicalTrials.gov, NCT02918305) trials will be helpful in determining the safety and efficacy of ultrasound-based RDN procedures for Asian patients with drug-resistant HTN taking standard antihypertensive medicines.

Ethanol injection-based treatment

The Peregrine catheter (Ablative Solutions, San Jose, CA, USA) was developed to deliver ethanol directly into the adventitial and periadventitial tissue of renal arteries. The preclinical study in a porcine model identified a linear dose-response between the injected alcohol volume and norepinephrine reduction in the renal artery.[65] A prospective, multi-center, open-label trial showed that 6 months after performing the Peregrine catheter procedure, the mean 24-hour ambulatory BP was significantly reduced compared with baseline.[66] This device is currently under investigation in a randomized, sham-controlled trial in hypertensive patients taking (TARGET BP I, ClinicalTrials.gov, NCT02910414) and not taking (TARGET BP OFF-MED, ClinicalTrials.gov, NCT03503773) antihypertensive medications.

COMPARISON BETWEEN RADIOFREQUENCY ABLATION AND ULTRASOUND BASED RENAL DENERVATION

A recent randomized, single-blind trial was conducted to compare the BP lowering effects of three treatment arms: ultrasound-based (PARADISE catheter) and RF ablation-based (SYMPLICITY Spyral™ catheter) RDN of the main renal artery, and RF ablation-based RDN of the main renal arteries, side branches, and accessories in patients with resistant HTN (office systolic BP >160 mm Hg or diastolic BP >90 mm Hg diastolic despite treatment with ≥3 different classes of antihypertensive drugs, including at least 1 diuretic unless intolerant to diuretics).[67] Although daytime ambulatory systolic BP was reduced more in the ultrasound-based treatment group at 3 months than in the group with RF ablation of the main renal artery (−13.2±13.7 vs. −6.5±10.3 mmHg; mean difference, −6.7 mmHg; p=0.038), no significant difference in systolic BP change was observed between the ultrasound-based treatment group and the group with main renal artery and side branch ablation (−8.3±11.7 mmHg for additional side branch ablation; mean difference −1.8 mmHg; adjusted p>0.99). This result might be because ultrasound energy has deeper penetration and offers more complete renal nerve ablation of the main renal artery than the RF ablation of the main renal artery alone. Nevertheless, this result should be interpreted with caution due to the limitations of this study, including the lack of a sham-control, lack of information about drug adherence tracking, and small sample size.

SAFETY OF RENAL DENERVATION

In contrast to antihypertensive medications, the safety of device-based therapies for HTN focuses on procedural complications. Renal artery injury, vascular access site complications, and deterioration in kidney function were the most anticipated complications after the RDN

procedure. However, the safety profile of RDN in several registries and clinical trials appears to be excellent. A recent meta-analysis of 50 published RDN trials reported on procedural safety.[68] Among 5,769 subjects with 10,249 patient-years of follow-up, only 26 patients were found to have renal artery stenosis or dissection (0.45%). The 3-year safety data from the largest database, the prospective, open-label Global SYMPLICITY registry, also demonstrated an extremely low incidence of peri-procedural complications and adverse events.[43]

ETHNIC DIFFERENCES FOR ASIANS

It is well-known that there are significant ethnic differences in the determinants of HTN and the risk of HTN-related CVD.[69-71] In general, the prevalence of HTN in Asia is similar to that in other countries, despite a lower prevalence of metabolic syndrome. In addition, the association between BP and CVD, especially for hemorrhagic stroke and non-ischemic heart failure, is stronger in Asian patients than in white patients.[71-73] Masked HTN (defined as normal office BP and elevated out-of-office BP), which is associated with increased sympathetic activity, is more prevalent in Asians than in Westerners.[74-76] East Asian populations in particular have at least a 2-fold higher sensitivity to the β-blocking effects of propranolol than white populations.[77] Taken together, these ethnic differences indicate that Asian populations might be particularly sensitive to sympathetic modulation, thereby making the RDN procedure an attractive BP-lowering strategy for Asian patients.[78]

The SYMPLICITY HTN-Japan randomized trial using the first-generation RDN device (SYMPLICITY Flex™; Medtronic) was the first published information specifically about the efficacy of RDN in an Asian population with resistant HTN.[38] Although this trial did not provide conclusive information about the effects of RDN due to its small sample size and early discontinuation, the magnitude of office systolic BP reduction 6 months after the RDN procedure (−16.6±18.5 mmHg) was numerically greater than that in the SYMPLICITY HTN-3 trial (−14.13±23.93 mm Hg), in which the study population was mainly white and Black people. In Korea, the first successful percutaneous RDN using the first-generation device was used to treat a hypertensive patient with congestive heart failure in 2013.[79] After that, a sub-analysis of the Global SYMPLICITY Registry evaluated the outcomes of the RDN procedure among patients from Korea.[80] Compared with Caucasians with uncontrolled HTN, the Korean patients were younger, had a lower body mass index, a lower baseline systolic BP, and a higher prevalence of CVD, such as stroke, myocardial infarction, or angina. After propensity score matching, the Koreans had a systolic BP change similar to that of Caucasians at 6 months (−19.4±17.2 mmHg vs. −20.9±21.4 mmHg; adjusted p=0.998), whereas the change in BP reduction was significantly higher in Koreans than in Caucasians (−27.2±18.1 mmHg vs. −20.1±23.9 mmHg; adjusted p=0.002) at 12 months. The RDN procedural characteristics did not differ significantly between the two ethnic groups. Thus, the responsiveness of Asian patients to the RDN procedure appears to be at least equivalent to that of Westerners for the reduction of BP. Nevertheless, more evidence using the current generation of RDN devices is needed to confirm these findings.

FUTURE DIRECTIONS OF RENAL DENERVATION BEYOND HYPERTENSION

The randomized, sham-controlled trial results for multipolar RF- and ultrasound-based second-generation RDN devices are summarized in **Figure 1**. Although these trials and

|	SPYRAL HTN-ON MED Pilot	SPYRAL HTN-OFF MED Pilot	SPYRAL HTN-OFF MED Pivotal	REDUCE HTN REINFORCE	RADIANCE-HTN SOLO	RADIANCE-HTN TRIO
Inclusion criteria	SBP 150–180, DBP ≥90, and mean 24-hour ambulatory SBP 140–170 on med	SBP 150–180, DBP ≥90, and mean 24-hour ambulatory SBP 140–170 off med	SBP 150–180, DBP ≥90, and mean 24-hour ambulatory SBP 140–170 off med	SBP 150–180 and mean 24-hour ambulatory SBP 135–170 off med	Daytime ambulatory BP ≥135/85 mmHg, and <170/105 mmHg off med	SBP ≥140, DBP ≥90, and mean 24-hour ambulatory BP ≥135/85 on med
Device	SYMPLICITY Spyral™	SYMPLICITY Spyral™	SYMPLICITY Spyral™	Vessix	PARADISE	PARADISE
Follow-up	6 months	3 months	3 months	6 months	2 months	2 months
Sample size	80	80	331 (251 pivotal + 80 pilot)	51	146	136
Group	RDN Sham	RDN Sham	RDN Sham	RDN Sham	RDN Sham	RDN Sham
Baseline SBP	152 151	153 152	151 151	166 166	143 144	162 164
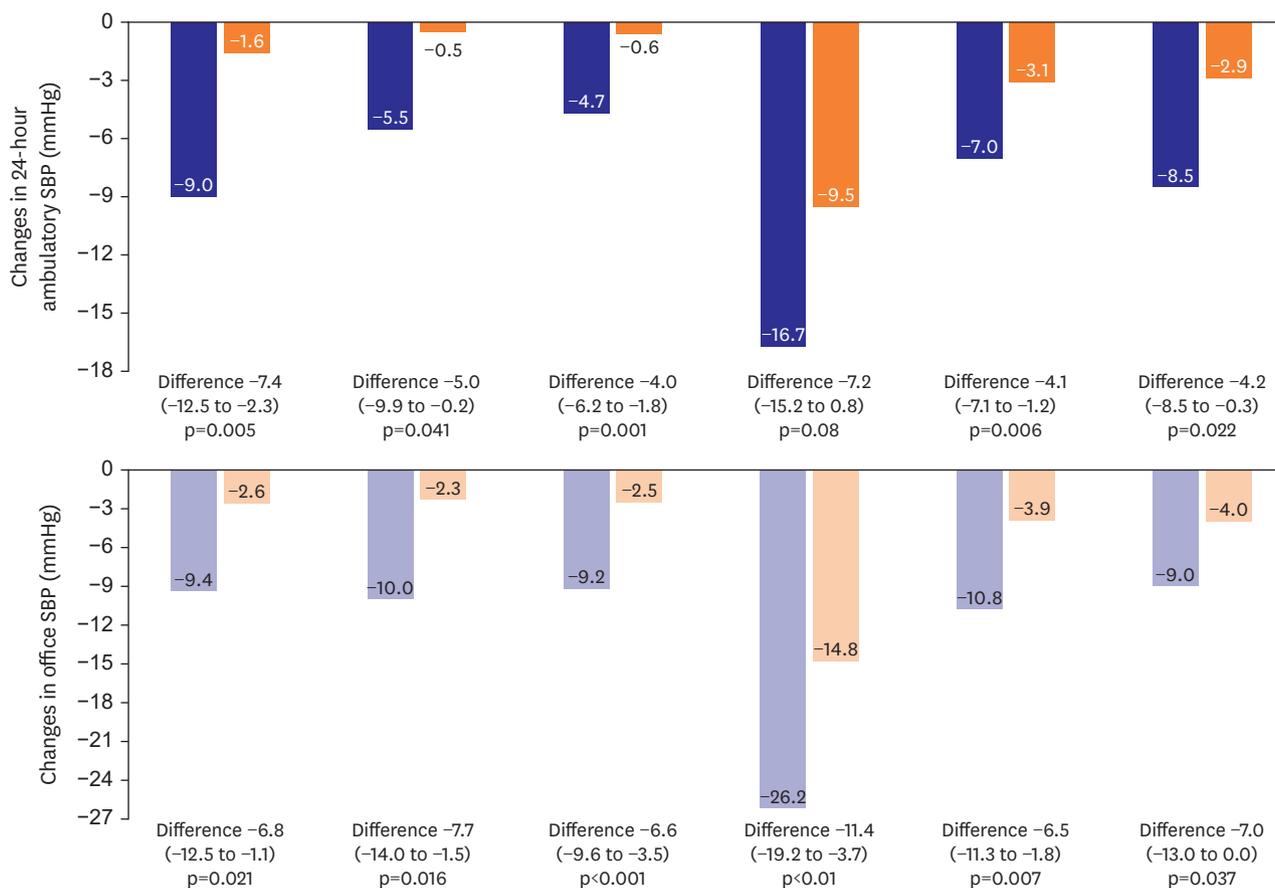
Figure 1. BP Changes with second-generation RDN devices in recently published randomized, sham-controlled trials.
Changes in 24-hour ambulatory systolic BP and office SBP in the landmark randomized, sham-controlled trials using second-generation RDN devices are presented.
BP = blood pressure; DBP = diastolic blood pressure; RDN = renal denervation; SBP = systolic blood pressure.

several meta-analyses have shown that RDN was associated with reduced BP without serious complications, several problems with those results, including small sample sizes, highly selected patients, and short-term follow-up results, still limit its application in clinical practice.[81-83] Thus, future trials should include large samples, less-selected patients, and longer follow-up times. Furthermore, clinical outcomes should be assessed following the RDN procedure to identify the benefits of RDN as a potential game-changer.

Heart failure

Theoretically, excessive and prolonged activation of the sympathetic nervous system plays a key role in the pathological remodeling of the cardiac structure in patients with heart failure,[84] and the use of a beta-blocker or renin-angiotensin system blockade, which affects the regulation of the sympathetic signaling pathway, has been associated with a reduced risk of morbidity in heart failure patients with reduced ejection fraction.[85-90] Furthermore, Brandt et al.[91] previously documented that RDN significantly reduced the left ventricular mass index, improved diastolic function, reduced interventricular septum thickness, decreased end-systolic volume, and improved ejection fraction. Therefore, the REACH-Pilot study was conducted to evaluate the efficacy and safety of the RDN procedure for patients with chronic systolic heart failure. Patients showed improvements in both symptoms and exercise capacity without peri-procedural complications 6 months after the RDN.[92] However, the Renal Denervation in Heart Failure with Preserved Ejection Fraction (RDT-PEF) trial was terminated early because of difficulties in recruitment, leaving it underpowered to detect whether RDN improved the endpoints of quality of life, exercise function, biomarkers, and left heart remodeling in patients with heart failure with preserved ejection fraction.[93] Therefore, future randomized, adequately powered, blinded, sham-controlled clinical trials are required to determine the effects of RDN on the morbidity of heart failure patients with reduced or preserved ejection fraction.

Atrial fibrillation

Sympathetic activation, particularly in association with para-sympathetic withdrawal, produces arrhythmias such as atrial fibrillation (AF).[94] A randomized trial to evaluate the adjunctive effects of RDN on pulmonary vein isolation (PVI) for the treatment of refractory AF and drug-resistant HTN demonstrated that RDN reduces systolic and diastolic BP in patients with drug-resistant HTN and reduces AF recurrence.[95] In addition, the larger Evaluate Renal Artery Denervation In Addition To Eliminate Atrial Fibrillation (ERADICATE-AF) trial also showed that adding RDN to PVI, compared with PVI alone, significantly increased the likelihood of freedom from AF 12 months later among patients with paroxysmal AF and HTN.[96] These results suggest that RDN could be an attractive new treatment addition to PVI for patients with AF.

Chronic kidney disease

Patients with chronic kidney disease (CKD) are often refractory to drug treatment, even with the combination of several antihypertensive medications.[97] Therefore, RDN might be a potentially beneficial intervention to treat the sympathetic activation associated with both HTN and CKD. However, most previous randomized trials of RDN have excluded patients with advanced CKD or end-stage renal disease due to concerns about renal safety. Observational studies have consistently shown that RDN was associated with significant BP-lowering effects without deteriorating the glomerular filtration rates of patients with CKD[98-100] or end-stage renal disease.[101] Future well-designed randomized outcomes studies in patients with CKD treated with and without RDN would provide interesting evidence about risk reduction in those patients.

CONCLUSION

Based on the lessons learned from the pitfalls of the SYMPLICITY HTN-3 trial, improvements in device design (spiral type or ultrasound-mediated), technique (main renal artery and

distal branch ablation), and trial design (control for adherence) have made RDN an attractive treatment option for HTN. Future trials need to focus on cardiovascular outcomes as well as BP reduction, adequate patient selection to show the greatest benefit, completeness of ablation without significant peri-procedural complications, and potential roles in treating other morbidities characterized by sympathetic overactivity. Furthermore, evidence is needed for the benefits of second-generation RDN devices in Asian patients.

REFERENCES

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1923-94.
   PUBMED | CROSSREF

2. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension* 2020;75:285-92.
   PUBMED | CROSSREF

3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol* 2020;16:223-37.
   PUBMED | CROSSREF

4. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957-67.
   PUBMED | CROSSREF

5. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
   PUBMED | CROSSREF

6. Neal B, MacMahon S, Chapman N; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955-64.
   PUBMED | CROSSREF

7. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997;277:739-45.
   PUBMED | CROSSREF

8. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
   PUBMED | CROSSREF

9. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104.
   PUBMED | CROSSREF

10. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension* 2020;75:1334-57.
    PUBMED | CROSSREF

11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127-248.
    PUBMED | CROSSREF

12. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016;134:441-50.
    PUBMED | CROSSREF

13. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet* 2017;389:37-55.
    PUBMED | CROSSREF

14. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ* 2008;336:1114-7.
    PUBMED | CROSSREF

15. Tajeu GS, Kent ST, Huang L, et al. Antihypertensive medication nonpersistence and low adherence for adults <65 years initiating treatment in 2007–2014. *Hypertension* 2019;74:35-46.
   PUBMED | CROSSREF

16. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940-8.
   PUBMED | CROSSREF

17. Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;29:610-8.
   PUBMED | CROSSREF

18. Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009;120:1598-605.
   PUBMED | CROSSREF

19. Yang Q, Chang A, Ritchey MD, Loustalot F. Antihypertensive medication adherence and risk of cardiovascular disease among older adults: a population-based cohort study. *J Am Heart Assoc* 2017;6:e006056.
   PUBMED | CROSSREF

20. Lauder L, Böhm M, Mahfoud F. The current status of renal denervation for the treatment of arterial hypertension. *Prog Cardiovasc Dis* 2021;65:76-83.
   PUBMED | CROSSREF

21. Weber MA, Mahfoud F, Schmieder RE, et al. Renal denervation for treating hypertension: current scientific and clinical evidence. *JACC Cardiovasc Interv* 2019;12:1095-105.
   PUBMED | CROSSREF

22. Akinseye OA, Ralston WF, Johnson KC, Ketron LL, Womack CR, Ibebuogu UN. Renal sympathetic denervation: a comprehensive review. *Curr Probl Cardiol* 2021;46:100598.
   PUBMED | CROSSREF

23. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. *Circ Res* 2015;116:976-90.
   PUBMED | CROSSREF

24. DiBona GF. Neural control of the kidney: functionally specific renal sympathetic nerve fibers. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R1517-24.
   PUBMED | CROSSREF

25. Ciriello J, de Oliveira CV. Renal afferents and hypertension. *Curr Hypertens Rep* 2002;4:136-42.
   PUBMED | CROSSREF

26. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275-81.
   PUBMED | CROSSREF

27. Symplicity HTN-2 Investigators, Esler MD, Krum H, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;376:1903-9.
   PUBMED | CROSSREF

28. Mahfoud F, Ukena C, Schmieder RE, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation* 2013;128:132-40.
   PUBMED | CROSSREF

29. Vogel B, Kirchberger M, Zeier M, et al. Renal sympathetic denervation therapy in the real world: results from the Heidelberg registry. *Clin Res Cardiol* 2014;103:117-24.
   PUBMED | CROSSREF

30. Kaiser L, Beister T, Wiese A, et al. Results of the ALSTER BP real-world registry on renal denervation employing the Symplicity system. *EuroIntervention* 2014;10:157-65.
   PUBMED | CROSSREF

31. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393-401.
   PUBMED | CROSSREF

32. Mahfoud F, Bakris G, Bhatt DL, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. *Eur Heart J* 2017;38:93-100.
   PUBMED | CROSSREF

33. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015;36:219-27.
   PUBMED | CROSSREF

34. Desch S, Okon T, Heinemann D, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015;65:1202-8.
PUBMED | CROSSREF

35. Mathiassen ON, Vase H, Bech JN, et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J Hypertens* 2016;34:1639-47.
PUBMED | CROSSREF

36. Fadl Elmula FE, Hoffmann P, Larstorp AC, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014;63:991-9.
PUBMED | CROSSREF

37. Rosa J, Widimský P, Toušek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015;65:407-13.
PUBMED | CROSSREF

38. Kario K, Ogawa H, Okumura K, et al. SYMPLICITY HTN-Japan: First randomized controlled trial of catheter-based renal denervation in Asian patients. *Circ J* 2015;79:1222-9.
PUBMED | CROSSREF

39. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015;385:1957-65.
PUBMED | CROSSREF

40. Oliveras A, Armario P, Clarà A, et al. Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study - a randomized controlled trial. *J Hypertens* 2016;34:1863-71.
PUBMED | CROSSREF

41. de Jager RL, de Beus E, Beeftink MM, et al. Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial. *Hypertension* 2017;69:678-84.
PUBMED | CROSSREF

42. Warchol-Celinska E, Prejbisz A, Kadziela J, et al. Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept phase II trial. *Hypertension* 2018;72:381-90.
PUBMED | CROSSREF

43. Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 2019;40:3474-82.
PUBMED | CROSSREF

44. Azizi M, Pereira H, Hamdidouche I, et al. Adherence to antihypertensive treatment and the blood pressure-lowering effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) trial. *Circulation* 2016;134:847-57.
PUBMED | CROSSREF

45. Hamdidouche I, Gosse P, Cremer A, et al. Clinic versus ambulatory blood pressure in resistant hypertension: impact of antihypertensive medication nonadherence: a post hoc analysis the DENERHTN study. *Hypertension* 2019;74:1096-103.
PUBMED | CROSSREF

46. Mahfoud F, Tunev S, Ewen S, et al. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. *J Am Coll Cardiol* 2015;66:1766-75.
PUBMED | CROSSREF

47. Fengler K, Ewen S, Höllriegel R, et al. Blood pressure response to main renal artery and combined main renal artery plus branch renal denervation in patients with resistant hypertension. *J Am Heart Assoc* 2017;6:e006196.
PUBMED | CROSSREF

48. Henegar JR, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation: location effects on renal norepinephrine. *Am J Hypertens* 2015;28:909-14.
PUBMED | CROSSREF

49. Townsend RR, Mahfoud F, Kandzari DE, et al. 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. *Lancet* 2017;390:2160-70.
PUBMED | CROSSREF

50. Kandzari DE, Böhm M, Mahfoud F, et al. 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. *Lancet* 2018;391:2346-55.
PUBMED | CROSSREF

51. Pekarskiy SE, Baev AE, Mordovin VF, et al. Denervation of the distal renal arterial branches vs. conventional main renal artery treatment: a randomized controlled trial for treatment of resistant hypertension. *J Hypertens* 2017;35:369-75.
PUBMED | **CROSSREF**

52. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020;395:1444-51.
PUBMED | **CROSSREF**

53. Worthley SG, Tsioufis CP, Worthley MI, et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J* 2013;34:2132-40.
PUBMED | **CROSSREF**

54. Sievert H, Schofer J, Ormiston J, et al. Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. *EuroIntervention* 2015;10:1213-20.
PUBMED | **CROSSREF**

55. Ormiston JA, Watson T, van Pelt N, et al. First-in-human use of the OneShot™ renal denervation system from Covidien. *EuroIntervention* 2013;8:1090-4.
PUBMED | **CROSSREF**

56. Kario K, Rumoroso JR, Okawara Y, et al. Renal sympathetic denervation in patients with resistant hypertension: a feasibility study. *Pulse (Basel)* 2019;6:137-43.
PUBMED | **CROSSREF**

57. Li Y, Nawabi AQ, Feng Y, Dai Q, Ma G, Liu N. Safety and efficacy of a new renal denervation catheter in hypertensive patients in the absent of antihypertensive medications: a pilot study. *Int J Hypertens* 2019;2019:7929706.
PUBMED | **CROSSREF**

58. Kim CJ, Chang K, Kim BK, Park CG, Jang Y. An open-label, single-arm, multicenter feasibility study evaluating the safety of catheter-based renal denervation with DENEX™ in patients with uncontrolled hypertension on standard medical therapy. *Korean Circ J* 2021;51:43-55.
PUBMED | **CROSSREF**

59. Weber MA, Kirtane AJ, Weir MR, et al. The REDUCE HTN: REINFORCE: randomized, sham-controlled trial of bipolar radiofrequency renal denervation for the treatment of hypertension. *JACC Cardiovasc Interv* 2020;13:461-70.
PUBMED | **CROSSREF**

60. Mabin T, Sapoval M, Cabane V, Stemmett J, Iyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. *EuroIntervention* 2012;8:57-61.
PUBMED | **CROSSREF**

61. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;391:2335-45.
PUBMED | **CROSSREF**

62. Azizi M, Schmieder RE, Mahfoud F, et al. Six-month results of treatment-blinded medication titration for hypertension control following randomization to endovascular ultrasound renal denervation or a sham procedure in the RADIANCE-HTN SOLO trial. *Circulation* 2019;139:2542-53.
PUBMED | **CROSSREF**

63. Azizi M, Daemen J, Lobo MD, et al. 12-Month results from the unblinded phase of the RADIANCE-HTN SOLO trial of ultrasound renal denervation. *JACC Cardiovasc Interv* 2020;13:2922-33.
PUBMED | **CROSSREF**

64. Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet*. 2021 [Epub ahead of print].
PUBMED | **CROSSREF**

65. Fischell TA, Vega F, Raju N, et al. Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. *EuroIntervention* 2013;9:140-7.
PUBMED | **CROSSREF**

66. Mahfoud F, Renkin J, Sievert H, et al. Alcohol-mediated renal denervation using the peregrine system infusion catheter for treatment of hypertension. *JACC Cardiovasc Interv* 2020;13:471-84.
PUBMED | **CROSSREF**

67. Fengler K, Rommel KP, Blazek S, et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation* 2019;139:590-600.
PUBMED | **CROSSREF**

68. Townsend RR, Walton A, Hettrick DA, et al. Review and meta-analysis of renal artery damage following percutaneous renal denervation with radiofrequency renal artery ablation. *EuroIntervention* 2020;16:89-96.
PUBMED | CROSSREF

69. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008;118:2702-9.
PUBMED | CROSSREF

70. Wang TD, Goto S, Bhatt DL, et al. Ethnic differences in the relationships of anthropometric measures to metabolic risk factors in Asian patients at risk of atherothrombosis: results from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Metabolism* 2010;59:400-8.
PUBMED | CROSSREF

71. Kario K, Chen CH, Park S, et al. Consensus document on improving hypertension management in Asian patients, taking into account Asian characteristics. *Hypertension* 2018;71:375-82.
PUBMED | CROSSREF

72. Arima H, Murakami Y, Lam TH, et al. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific Region. *Hypertension* 2012;59:1118-23.
PUBMED | CROSSREF

73. Hoshide S, Wang JG, Park S, et al. Treatment considerations of clinical physician on hypertension management in Asia. *Curr Hypertens Rev* 2016;12:164-8.
PUBMED | CROSSREF

74. Uzu T, Ishikawa K, Fujii T, Nakamura S, Inenaga T, Kimura G. Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation* 1997;96:1859-62.
PUBMED | CROSSREF

75. Kario K, Bhatt DL, Brar S, Bakris GL. Differences in dynamic diurnal blood pressure variability between Japanese and American treatment-resistant hypertensive populations. *Circ J* 2017;81:1337-45.
PUBMED | CROSSREF

76. Omboni S, Aristizabal D, De la Sierra A, et al. Hypertension types defined by clinic and ambulatory blood pressure in 14143 patients referred to hypertension clinics worldwide. Data from the ARTEMIS study. *J Hypertens* 2016;34:2187-98.
PUBMED | CROSSREF

77. Zhou HH, Koshakji RP, Silberstein DJ, Wilkinson GR, Wood AJ. Racial differences in drug response. Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites. *N Engl J Med* 1989;320:565-70.
PUBMED | CROSSREF

78. Kario K, Kim BK, Aoki J, et al. Renal denervation in Asia: consensus statement of the Asia Renal Denervation Consortium. *Hypertension* 2020;75:590-602.
PUBMED | CROSSREF

79. Yang JH, Choi SH, Gwon HC. Percutaneous renal sympathetic denervation for the treatment of resistant hypertension with heart failure: first experience in Korea. *J Korean Med Sci* 2013;28:951-4.
PUBMED | CROSSREF

80. Kim BK, Böhm M, Mahfoud F, et al. Renal denervation for treatment of uncontrolled hypertension in an Asian population: results from the Global SYMPLICITY Registry in South Korea (GSR Korea). *J Hum Hypertens* 2016;30:315-21.
PUBMED | CROSSREF

81. Stavropoulos K, Patoulias D, Imprialos K, et al. Efficacy and safety of renal denervation for the management of arterial hypertension: a systematic review and meta-analysis of randomized, sham-controlled, catheter-based trials. *J Clin Hypertens (Greenwich)* 2020;22:572-84.
PUBMED | CROSSREF

82. Agasthi P, Shipman J, Arsanjani R, et al. Renal denervation for resistant hypertension in the contemporary era: a systematic review and meta-analysis. *Sci Rep* 2019;9:6200.
PUBMED | CROSSREF

83. Cheng X, Zhang D, Luo S, Qin S. Effect of catheter-based renal denervation on uncontrolled hypertension: a systematic review and meta-analysis. *Mayo Clin Proc* 2019;94:1695-706.
PUBMED | CROSSREF

84. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Intern Med* 1984;101:370-7.
PUBMED | CROSSREF

85. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;342:1441-6.
PUBMED | CROSSREF

86. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
    PUBMED | **CROSSREF**

87. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
    PUBMED | **CROSSREF**

88. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
    PUBMED | **CROSSREF**

89. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772-6.
    PUBMED | **CROSSREF**

90. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
    PUBMED | **CROSSREF**

91. Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012;59:901-9.
    PUBMED | **CROSSREF**

92. Davies JE, Manisty CH, Petraco R, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol* 2013;162:189-92.
    PUBMED | **CROSSREF**

93. Patel HC, Rosen SD, Hayward C, et al. Renal denervation in heart failure with preserved ejection fraction (RDT-PEF): a randomized controlled trial. *Eur J Heart Fail* 2016;18:703-12.
    PUBMED | **CROSSREF**

94. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011;91:265-325.
    PUBMED | **CROSSREF**

95. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012;60:1163-70.
    PUBMED | **CROSSREF**

96. Steinberg JS, Shabanov V, Ponomarev D, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020;323:248-55.
    PUBMED | **CROSSREF**

97. Sarafidis PA, Sharpe CC, Wood E, et al. Prevalence, patterns of treatment, and control of hypertension in predialysis patients with chronic kidney disease. *Nephron Clin Pract* 2012;120:c147-55.
    PUBMED | **CROSSREF**

98. Hering D, Mahfoud F, Walton AS, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012;23:1250-7.
    PUBMED | **CROSSREF**

99. Hering D, Marusic P, Duval J, et al. Effect of renal denervation on kidney function in patients with chronic kidney disease. *Int J Cardiol* 2017;232:93-7.
    PUBMED | **CROSSREF**

100. Kiuchi MG, Maia GL, de Queiroz Carreira MA, et al. Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension. *Eur Heart J* 2013;34:2114-21.
     PUBMED | **CROSSREF**

101. Scalise F, Sole A, Singh G, et al. Renal denervation in patients with end-stage renal disease and resistant hypertension on long-term haemodialysis. *J Hypertens* 2020;38:936-42.
     PUBMED | **CROSSREF**