Hypertension

AHA SCIENTIFIC STATEMENT

Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association

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ABSTRACT: Hypertension is a leading risk factor for cardiovascular morbidity and mortality. Despite the widespread availability of both pharmacological and lifestyle therapeutic options, blood pressure control rates across the globe are worsening. In fact, only 23% of individuals with high blood pressure in the United States achieve treatment goals. In 2023, the US Food and Drug Administration approved renal denervation, a catheter-based procedure that ablates the renal sympathetic nerves, as an adjunctive treatment for patients in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure. This approval followed the publication of multiple randomized clinical studies using rigorous trial designs, all incorporating renal angiogram as the sham control. Most but not all of the new generation of trials reached their primary end point, demonstrating modest efficacy of renal denervation in lowering blood pressure across a spectrum of hypertension, from mild to truly resistant. Individual patient responses vary, and further research is needed to identify those who may benefit most. The initial safety profile appears favorable, and multiple ongoing studies are assessing longer-term efficacy and safety. Multidisciplinary teams that include hypertension specialists and adequately trained proceduralists are crucial to ensure that referrals are made appropriately with full consideration of the potential risks and benefits. Incorporating patient preferences and engaging in shared decision-making conversations will help patients make the best decisions given their individual circumstances. Although further research is clearly needed, renal denervation presents a novel treatment strategy for patients with uncontrolled blood pressure.

Key Words: AHA Scientific Statements ■ blood pressure ■ catheters ■ denervation ■ hypertension ■ kidney ■ patient care team

Hypertension is the leading risk factor for cardiovascular disease in the United States and globally, and it has been well established that treatment of hypertension reduces cardiovascular morbidity and mortality and slows progression to end-stage kidney disease. Despite treatment with lifestyle modifications, antihypertensive medications, or both, blood pressure (BP) control rates remain poor. Of the nearly 120 million adults in the United States with hypertension, only 23% have controlled BP to the recommended target of <130/80 mm Hg, and ≈45% of those with uncontrolled hypertension have BP readings of ≥140/90 mm Hg.[1] These numbers vary according to sex, race, other associated comorbidities, and geography but nonetheless contribute significantly to adverse health outcomes and increased health costs. The reasons for poor control are multiple, including medication nonadherence; medication intolerances; clinical inertia; cultural, financial, and psychological factors; as well as true resistant hypertension (RH). Novel approaches are needed to help achieve BP control.

The sympathetic nervous system is an important contributor to hypertension, partly through renal sympathetic nerve activity. Antihypertensive medications that work by sympathetic nervous system modulation are often ineffective in inhibiting sympathetic outflow; renal nerve denervation (RDN) is a therapeutic alternative or adjunct

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to pharmacological therapy to achieve this effect and treat uncontrolled hypertension.[2]

Our knowledge of the role that renal nerves play in BP control dates back to the mid-1800s. More recently, work using direct electrical stimulation or complete denervation has delineated the physiological effects of alterations in renal sympathetic nerve activity and informed our understanding today. The effect that renal sympathetic nerve activity has on kidney function and ultimately BP depends on the level of sympathetic activation. Low levels of sympathetic activation give rise to renin release; moderate levels increase sodium reabsorption (antinatriuresis); and at the highest levels of activation, renal vascular resistance is increased.[3] From this knowledge, a strong interest in developing percutaneous methods of RDN has developed.

At the present time, 3 main RDN devices have been studied (Figure 1) using different modalities to treat the renal nerves. The current Symplicity Spyral System (Medtronic) uses a catheter with 4 electrodes arranged in a spiral sequence to deliver a medium-frequency alternating current that generates sufficient heat to destroy the nerves in the renal artery periadventitial space without injuring the arterial wall. Earlier prototypes of radiofrequency ablation catheters used a monoelectrode (Symplicity Flex, Medtronic) or bipolar electrode technology (Vessix, Boston Scientific; neither shown). The Paradise System (Recor Medical) delivers ultrasound energy to the main renal arteries through a catheter with an inflatable balloon system that simultaneously irrigates the lumen of the vessel with a cooling solution, thus maintaining a lower temperature within the renal artery and preventing injury to the arterial wall. A third approach with less published experience, the Peregrine System (Ablative Solutions), delivers small amounts of dehydrated alcohol through a catheter with 3 embedded, concentrically placed microneedles that pass through the renal artery into the perivascular space before releasing alcohol to treat the renal nerves. In November 2023, the Medtronic Simplicity Spyral System and the Recor Medical Paradise System were approved by the US Food and Drug Administration for adjunctive treatment in patients with hypertension in whom lifestyle and antihypertensive medications do not adequately control BP.

EFFICACY

Since 2010, multiple randomized clinical trials (RCTs) of RDN with a sham-controlled arm and ambulatory systolic BP (SBP) as an outcome have been conducted in various patient subgroups with hypertension (Table 1 and Figure 2). It is important to note that both the RDN technology and study protocols have evolved over time. For example, later trials with radiofrequency ablation have provided more extensive denervation by incorporating branching or accessory renal arteries in addition to the main renal arteries. More recent study protocols often include the institution of therapeutic drug surveillance to ensure adherence to prescribed antihypertensive regimens when appropriate. As a result, comparing contemporary trials and earlier studies is challenging.

Efficacy in Patients Who Are Not on Antihypertensive Medications

The efficacy of RDN has been examined in 6 RCTs in either drug-naive patients or previously treated patients after a washout period of 4 weeks.[4–9] The SPYRAL HTN-OFF MED pilot trial (Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications)[4] and SPYRAL HTN-OFF MED Pivotal trial (Efficacy of Catheter-Based Renal Denervation in the Absence of Antihypertensive Medications),[5] using the Symplicity Spyral system, showed a reduction in 24-hour SBP by 4 to 5 mm Hg compared with the sham control arm. In contrast, REDUCE HTN: REINFORCE (Randomized, Sham-Controlled Trial of Bipolar Radiofrequency Renal Denervation for the Treatment of Hypertension), using the Vessix catheter, failed to detect a difference in

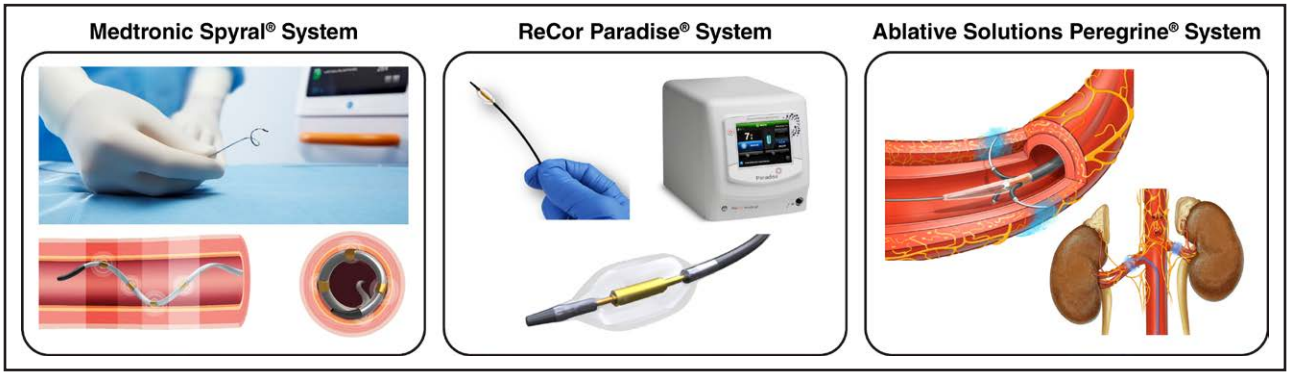

Figure 1. Three main renal denervation devices demonstrating different modalities to treat renal nerves.
The devices listed here serve only to illustrate examples of these types of devices. This is not intended to be an endorsement of any commercial product, process, service, or enterprise by the American Heart Association.

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Table 1. Characteristics of Patients and Clinical Outcomes After RDN in RCTs

Trial, year published	Sample size, n	RDN system	Exclusion criteria*	Standardized medication	Sham control	MRA use (RDN vs control), %	Follow-up duration, mo	Δ24-h SBP RDN, mm Hg	Δ24-h SBP control, mm Hg	*P* value	Drug surveillance
Absence of medication											
SPYRAL OFF-MED pilot, 2017[4]	80	Spyral	eGFR <45 mL/min/1.73m^2, OH, secondary hypertension, recent vascular events	NA	Yes	NA	3	5.5	0.5	0.04	Yes
SPYRAL OFF-MED Pivotal, 2020[5]	331	Spyral	eGFR <45 mL/min/1.73m^2, OH, secondary hypertension, recent vascular events	NA	Yes	NA	3	4.7	0.6	<0.01	Yes
REDUCE HTN: REINFORCE, 2020[6]	51	Vessix	eGFR <40 mL/min/1.73m^2, secondary hypertension	NA	Yes	NA	3	5.3	8.5	0.3	No
RADIANCE-HTN SOLO, 2018[7]	146	Paradise	eGFR <40 mL/min/1.73m^2, secondary hypertension, history of cardiac or cerebrovascular disease	NA	Yes	NA	2	Daytime 8.5	Daytime 2.2	<0.01	Yes
RADIANCE II, 2023[8]	150	Paradise	eGFR <40 mL/min/1.73m^2, secondary hypertension, history of cardiac or cerebrovascular disease	NA	Yes	NA	2	Daytime 7.9	Daytime 1.8	<0.01	Yes
TARGET BP OFF- MED, 2023[9]	106	Peregrine	eGFR ≤45 mL/min/1.73m^2, recent MI, unstable angina, stroke, OSA	NA	Yes	NA	2	2.9	1.4	0.25	Yes
1–5 medications											
SPYRAL HTN-ON MED pilot, 2018[10]	80	Spyral	eGFR <45 mL/min/1.73m^2, OH, secondary hypertension, recent vascular events	No	Yes	Not allowed	6	9	1.6	<0.01	Yes
SPYRAL HTN-ON MED Expansion, 2023[11]	257	Spyral	eGFR <45 mL/min/1.73m^2, OH, night shift work, T1D, secondary hypertension, poorly controlled T2D	No	Yes	Not allowed	6	6.5	4.5	0.12	Yes
TARGET BP I, 2024[12]	301	Peregrine	eGFR <45 mL/min/1.73m^2, OH, secondary hypertension, recent vascular events	No	Yes	Yes	3	10.0	6.8	0.049	Yes
RH											
SYMPLICITY HTN-3, 2014[13]	535	Flex single	eGFR <40 mL/min/1.73m^2, secondary hypertension	No, ≥3 drugs	Yes	28.7/22.5 continued 16/6	6	6.75	4.79	0.26	No
DENERHTN, 2015[14]	106	Flex single	eGFR <40 mL/min/1.73m^2, secondary hypertension	Yes, indapamide, amlodipine and ramipril or irbesartan	No	65/53	6	Daytime 15.8	Daytime 9.9	0.03	Yes
DENERVHTA, 2016[15]	24	Flex single	Secondary hypertension, previous MRA therapy	No	No (RDN vs spironolactone)	0/92	6	5.1	23.6	0.01	No

(*Continued*)

Table 1. Continued

Trial, year published	Sample size, n	RDN system	Exclusion criteria*	Standardized medication	Sham control	MRA use (RDN vs control), %	Follow-up duration, mo	Δ24-h SBP RDN, mm Hg	Δ24-h SBP control, mm Hg	*P* value	Drug surveillance
Prague-15, 2015[16]	106	Flex single	eGFR <40 mL/min/1.73m^2, secondary hypertension, drug noncompliance by drug levels	No	No (RDN vs spirono-lactone)	25/61	6	8.6	8.1	0.87	Yes
Desch, 2015[17]	71	Flex single	eGFR <45 mL/min/1.73m^2	No	Yes	6/3	6	7	3.5	0.15	No
ReSET, 2016[18]	69	Flex single	eGFR <30 mL/min/1.73m^2, secondary hypertension, orthostatic syncope	No	Yes	22/21	3	Daytime 6.2	Daytime 6.0	0.95	No
WAVE IV, 2018[19]	81	External ultrasound system	Secondary hypertension, obesity, recent MI, unstable angina or stroke	No	Yes	33.3/25.6	6	Office 18.9	Office 13.2	0.18	Yes
RADIANCE-HTN TRIO, 2021[20]	989	Paradise	eGFR <40 mL/min/1.73m^2, secondary hypertension	Yes, HCTZ, amlodipine and valsartan or olmestartan	Yes	40/61	2	Daytime 8.0	Daytime 3.0	0.02	Yes
RADIOSOUND-HTN, 2019[21]	120	Paradise vs Spyral main vs Spyral main+side branch	eGFR <40 mL/min/1.73m^2, secondary hypertension, drug noncompliance by physician discretion	No	No, 3 active arms	23 (15/31/24)	3	Daytime 13.2 (Paradise)	Daytime main alone 6.7; main + branch 8.3 (Spyral)	0.04	No
REQUIRE, 2022[22]	72	Paradise	eGFR <40 mL/min/1.73m^2, secondary hypertension except OSA	No	Yes but single blind	24.6/14.9	3	6.6	6.5	0.97	No

DENERHTN indicates Optimum and Stepped Care Standardised Antihypertensive Treatment With or Without Renal Denervation For Resistant Hypertension; DENERVHTA, Spironolactone Versus Sympathetic Renal Denervation to Treat True Resistant Hypertension; Desch, randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension; eGFR, estimated glomerular filtration rate; HCTZ, hydrochlorothiazide; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; OH, orthostatic hypotension; OSA, obstructive sleep apnea; Prague, Randomized Comparison of Renal Denervation Versus Intensified Pharmacotherapy Including Spironolactone in True-Resistant Hypertension; RADIANCE II, Endovascular Ultrasound Renal Denervation to Treat Hypertension; RADIANCE-HTN SOLO, Endovascular Ultrasound Renal Denervation to Treat Hypertension; RADIANCE-HTN TRIO, Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill; RADIOSOUND-HTN, A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension; RCT, randomized clinical trial; RDN, renal denervation; REDUCE HTN: REINFORCE, Randomized, Sham-Controlled Trial of Bipolar Radiofrequency Renal Denervation for the Treatment of Hypertension; REQUIRE, Catheter-Based Ultrasound Renal Denervation in Patients With Resistant Hypertension; ReSET, Renal Denervation in Treatment-Resistant Essential Hypertension; RH, resistant hypertension; SBP, systolic blood pressure; SPYRAL HTN-ON MED Expansion, Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications; SPYRAL HTN-ON MED pilot, Effect of Renal Denervation on Blood Pressure in the Presence of Antihypertensive Drugs; SPYRAL OFF-MED pilot, Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications; SPYRAL OFF-MED Pivotal, Efficacy of Catheter-Based Renal Denervation in the Absence of Antihypertensive Medications; SYMPLICITY HTN-3, A Controlled Trial of Renal Denervation for Resistant Hypertension; T1D, type 1 diabetes; T2D, type 2 diabetes; TARGET BP I, Effect of Alcohol-Mediated Renal Denervation on Blood Pressure in the Presence of Antihypertensive Medications; TARGET BP OFF-MED, Alcohol-Mediated Renal Denervation in Patients With Hypertension in the Absence of Antihypertensive Medications; and WAVE IV, Phase II Randomized Sham-Controlled Study of Renal Denervation for Individuals With Uncontrolled Hypertension.

*All studies exclude renal artery stenosis of >50% and renal artery anatomical criteria, including renal artery size <3 or >8 mm.

24-hour SBP.[6] The RADIANCE HTN SOLO trial (Endovascular Ultrasound Renal Denervation to Treat Hypertension) demonstrated a 6.3 mm Hg reduction in daytime ambulatory SBP compared with the sham control group using the Paradise System.[7] This finding was later confirmed in the RADIANCE II trial (Endovascular Ultrasound Renal Denervation to Treat Hypertension) using the same technology with an identical difference in daytime SBP that favored RDN by 6.3 mm Hg.[8] The reduction in office BP was also remarkably similar, with 5.5 mm Hg lower SBP in the RDN group compared with the control group in both trials.[7,8] In contrast, the TARGET BP OFF-MED trial (Alcohol-Mediated Renal Denervation in Patients With Hypertension in the Absence of Antihypertensive Medications), done with the Peregrine System, showed no difference in 24-hour SBP compared with the sham control arm at 8 weeks (primary outcome), although lower medication burden was observed at 12 months when the medications were reinitiated in a single-blinded manner.[9] Taken together, the majority of clinical trials have demonstrated that RDN is efficacious in lowering BP in untreated patients with hypertension to a degree

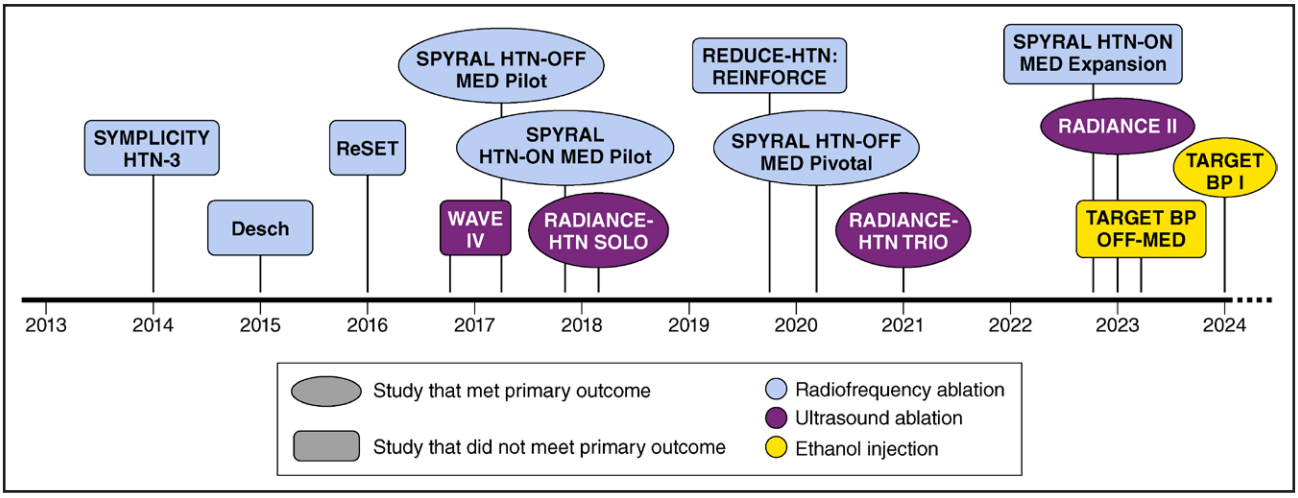

Figure 2. Timeline of renal denervation trials.
Timeline of renal denervation trials that had randomized double blind, sham-control arms indicating the type of device used (radiofrequency, ultrasound, or ethanol injection) and whether each study did (oval) or did not (rectangle) meet the primary outcome. RADIANCE II indicates Endovascular Ultrasound Renal Denervation to Treat Hypertension; RADIANCE-HTN SOLO Endovascular Ultrasound Renal Denervation to Treat Hypertension; RADIANCE-HTN TRIO, Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill; REDUCE HTN: REINFORCE, Randomized, Sham-Controlled Trial of Bipolar Radiofrequency Renal Denervation for the Treatment of Hypertension; ReSET, Renal Denervation in Treatment-Resistant Essential Hypertension; SPYRAL HTN-ON MED, Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications; SPYRAL OFF-MED pilot, Global Clinical Study of Renal Denervation With the Symplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications; TARGET BP OFF-MED, Alcohol-Mediated Renal Denervation in Patients With Hypertension in the Absence of Antihypertensive Medications; and WAVE IV, Phase II Randomized Sham-Controlled Study of Renal Denervation for Individuals With Uncontrolled Hypertension.

similar to the BP reduction achieved with 1 antihypertensive drug. Notably, the primary endpoint of these trials was typically assessed at 2 to 3 months, which was justifiable because enrolled patients were not allowed to take antihypertensive pharmacological treatment unless their BP reached unsafe values above the prespecified safety thresholds. Additional studies with longer duration of follow-up are needed to verify the prolonged effect of RDN in the absence of antihypertensive medications.

Efficacy in Patients With Hypertension Managed With 1 to 5 Antihypertensive Medications

Among patients with hypertension with uncontrolled BP despite treatment with 1 to 5 medications, the efficacy of RDN appears to be more variable. Although the SPYRAL HTN-ON MED pilot trial (Effect of Renal Denervation on Blood Pressure in the Presence of Antihypertensive Drugs)[10] showed a sham-corrected reduction in 24-hour SBP that favored RDN therapy by 7.4 mm Hg, the SPYRAL HTN-ON MED Expansion trial (Safety and Efficacy of Renal Denervation in Patients Taking Antihypertensive Medications) did not show a difference between the 2 groups.[11] This lack of difference was ascribed to a larger-than-expected reduction in 24-hour SBP (by 4.5 mm Hg) in the sham control arm compared with a 6.5 mm Hg reduction in the RDN arm. The unexpectedly larger decrease in BP in the sham control arm was attributed to intensification of background antihypertensive medication treatment in the control arm (29.9% in the sham control arm compared with 17.3% in the RDN arm; P=0.02), which, although not permitted per protocol, was detected by chemical adherence testing in urine or plasma samples. In the TARGET BP I trial (Effect of Alcohol-Mediated Renal Denervation on Blood Pressure in the Presence of Antihypertensive Medications), RDN was found to have a modest but statistically significant benefit of a 3.2 mm Hg reduction in 24-hour SBP at 3 months compared with the sham control arm.[12]

Efficacy in Patients With Medication-Resistant Hypertension

All of the early RDN trials were done in patients with RH, defined as BP above goal despite concurrent use of 3 antihypertensive agents or BP at goal but requiring ≥4 medications of different classes at maximum or maximally tolerated doses. The prevalence of RH in adults with treated hypertension is ≈19.7% (10.3 million).[23] Those with RH are more frequently characterized by demographic correlates of Black race, older age, and male sex and show evidence of multiple comorbidities, vascular disease/dysfunction, and metabolic abnormalities. Patients with RH have a 2-fold increased risk of cardiovascular disease events compared with patients whose hypertension is responsive to treatment.

Efficacy of RDN in RH despite treatment with at least 3 drugs at >50% of maximal dose was examined in 10 sham control RCTs.[13–22] Three trials using

the Symplicity Flex System showed no difference in 24-hour BP between the RDN and sham control groups.[13,17,18] Although the lack of efficacy was partly attributed to the use of a unipolar catheter causing incomplete denervation, some studies demonstrated a greater-than-expected SBP reduction in the sham control arm, thought to be related to intensification of medication treatment outside protocol or increased medication adherence in this group.[13] When the background medical therapy was standardized with triple combination pills and adherence was monitored with biochemical drug testing, a significant reduction in BP was observed with RDN in both the DENERHTN trial (Optimum and Stepped Care Standardised Antihypertensive Treatment With or Without Renal Denervation for Resistant Hypertension)[14] and RADIANCE HTN TRIO trial (Ultrasound Renal Denervation for Hypertension Resistant to a Triple Medication Pill).[20] In the DENERHTN trial, the Symplicity Flex System reduced daytime SBP by 5.9 mm Hg (95% CI, −11.3 to −0.5) compared with the sham control group (P=0.03). The Paradise System was also shown to be effective in reducing SBP in the RADIANCE HTN TRIO trial, with a between-group difference of −4.5 mm Hg (95% CI, −8.5 to −0.3) that favored the RDN group.[20] In RADIOSOUND-HTN (A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension), the only head-to-head randomized comparison of radiofrequency-based and ultrasound-based RDN, ultrasound-based RDN showed a larger SBP reduction than radiofrequency-based RDN.[21] The magnitude of SBP reduction achieved by unipolar radiofrequency denervation was shown to be either inferior or similar to the addition of spironolactone as the fourth agent in 2 RCTs, DENERVHTA (Spironolactone Versus Sympathetic Renal Denervation to Treat True Resistant Hypertension)[15] and Prague-15 (Randomized Comparison of Renal Denervation Versus Intensified Pharmacotherapy Including Spironolactone in True-Resistant Hypertension).[16] However, the effects of spironolactone on BP in the Prague-15 trial are likely underestimated because 25% of the RDN group also received spironolactone but only 61% of the spironolactone group remained on this drug at the end of the trial.[16] The effects of the combination of mineralocorticoid receptor antagonist plus RDN on BP compared with RDN alone or mineralocorticoid receptor antagonist alone have not yet been investigated in RH. Although the duration of RCTs in RH was also limited to 2 to 6 months, the Global SYMPLICITY Registry has reported a sustained reduction in office SBP of 16.5±28.6 mm Hg and decreases in 24-hour ambulatory SBP of 8.0±20.0 mm Hg from baseline for up to 3 years.[24] However, these data must be interpreted with caution because of the absence of a sham control group.

Efficacy in Patients With Diabetes and Chronic Kidney Disease

The impact of RDN has been examined among individuals with hypertension and type 2 diabetes,[25,26] including some with chronic kidney disease (CKD).[26–28] In the Global SYMPLICITY Registry, patients with CKD demonstrated a smaller reduction in office SBP but similar reductions in ambulatory BP monitoring after RDN compared with patients without CKD.[28] Subgroup analysis from the 3 ultrasound RDN trial RADIANCE cohorts[7,8,20] did not show an interaction between CKD or type 2 diabetes and BP response to RDN.[26] However, the power of subgroup analyses may be limited because the majority of trials excluded patients with more advanced CKD (estimated glomerular filtration rate <30–45 mL/min/1.73m^2).[4,5,10,13–16,18,20,21]

Overall Response Rate

It is important to note that the efficacy of RDN is not uniform among all patients. A meaningful reduction in office SBP or daytime ambulatory SBP of at least 5 mm Hg was observed in 60% to 70% of patients during 2 to 3 months of follow-up among patients undergoing ultrasound RDN. Although 24% of patients undergoing RDN achieved the target of daytime or home BP <135/85 mm Hg compared with 12% in the sham group, participants in the RDN arm received less medication.[26,29] Similar findings have been reported with RDN done with radiofrequency technology.

PATIENT SELECTION

As detailed previously, RCT data have shown benefit of RDN across a spectrum of patients with hypertension, including those with true RH[18] and those with disease ranging from mild hypertension in whom medications were withdrawn[5–7] to more moderate to severe hypertension.[11,20] That said, not all patients with hypertension are candidates for RDN (Table 2 lists specific considerations). RDN should be considered only for patients with sustained, uncontrolled hypertension, confirmed with 24-hour ambulatory BP monitoring or appropriate home BP measurements to eliminate the diagnosis of white-coat hypertension. Patients with true RH are the most obvious group who would benefit from RDN. A second group is patients with uncontrolled hypertension despite being on antihypertensive medication who are intolerant of or unable or unwilling to adhere to sufficient medication to control their BP. This group includes patients with apparent RH who are prescribed at least 3 medications but do not actually take them all as prescribed. It also includes patients who may be prescribed 2 or even only 1 medication, if they are not able to tolerate higher doses or sufficient additional

Table 2. Clinical Considerations for Selecting Candidates for Renal Denervation

Recommended for all patients
Out-of-office BP measurements to exclude white-coat hypertension/effect
Ongoing efforts at lifestyle modification
Shared decision-making on risks and benefits
Resistant hypertension or uncontrolled hypertension
BP not at goal despite taking ≥3 antihypertensive medications
BP not at goal and either unable to tolerate or unwilling to take additional antihypertensive medications
Contraindications
Pregnancy
Fibromuscular dysplasia
Stented renal artery
Renal artery aneurysm
Significant renal artery stenosis
Known kidney or secreting adrenal tumors
Limited data
Stage 1 hypertension
Isolated systolic hypertension
Stage 4 and 5 CKD
Single kidney
Kidney transplant recipients (on native nonfunctional kidneys)

BP indicates blood pressure; and CKD, chronic kidney disease.

medication to control their BP. The high frequency of partial or total medication nonadherence, particularly in patients with apparent RH (23%–66%), encompasses varied reasons, all of which limit the success of pharmacological treatment, including cost, fear, misunderstandings, side effects, forgetfulness, and cultural factors.[30] Clinicians can help alleviate any correctible challenges, but many of these patients could benefit from BP reduction from RDN and may prefer it. Therefore, shared decision-making between patient and clinician is necessary (Figure 3 and Supplemental Material).

Ideally, institutions performing RDN will provide a multidisciplinary team approach that includes clinicians with specialty training or expertise in the field who will screen patients with hypertension, refer appropriate patients, and manage their hypertension after the procedure. The proceduralists performing RDN, whether interventional radiologists, interventional cardiologists, or vascular surgeons, need to have sufficient relevant training and be directly involved in the decisions about the procedure. Specific recommendations for operator training and competency standards are beyond the scope of this scientific statement.

Ideally, results from RCTs would help predict which patients are most likely to benefit from RDN. However, to date, no clinical feature apart from high baseline BP has been consistently associated with greater response to RDN. Markers of increased sympathetic activity, including greater variability of BP, higher resting heart rate, and higher renin, have been proposed, but convincing evidence is lacking.[31–33] In a pooled analysis of the RADIANCE studies, orthostatic hypertension was associated with greater BP reduction after RDN.[29] When patients are selected for RDN, priority may be given to those with highest cardiovascular risk and thus greatest potential benefit from BP lowering. These include patients with end-organ damage such as left ventricular hypertrophy, CKD, albuminuria, cerebrovascular disease, and cardiovascular complications.

Patients with certain treatable secondary causes of hypertension, most commonly primary aldosteronism, which is prevalent and often undiagnosed, should not be directed to RDN. Screening should be performed in all eligible patients because targeted, effective treatment is available. Other secondary causes of hypertension such as Cushing syndrome, pheochromocytoma, thyroid disease, hyperparathyroidism, atherosclerotic renal artery stenosis (RAS), fibromuscular dysplasia, and coarctation of the aorta should be excluded if clinically suspected (Table 3). Common contributing factors such as sleep

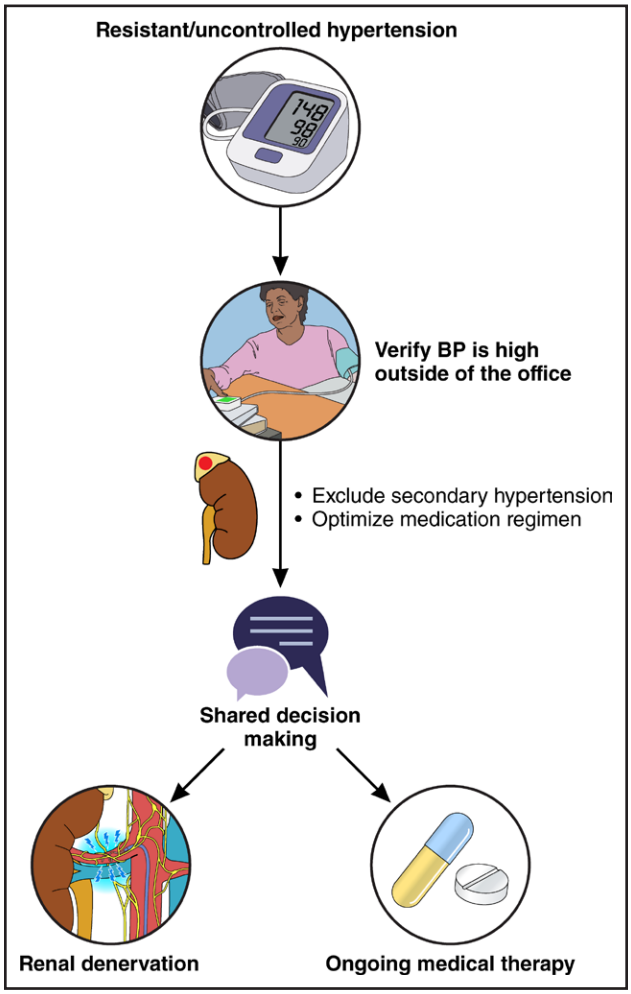

Figure 3. Steps to identify potential candidates for renal denervation.
BP indicates blood pressure.

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Table 3. Recommended Secondary Evaluation Before Renal Denervation

Recommended testing for all candidates
Serum creatinine and urinalysis to assess for CKD and eGFR
Screening for primary aldosteronism with further evaluation as indicated
Optional testing depending on clinical suspicion
Hormonal testing to screen for
Cushing syndrome
Pheochromocytoma
Hyperthyroidism
Hyperparathyroidism
Imaging to screen for
Atherosclerotic renal artery stenosis
Fibromuscular dysplasia
Coarctation of the aorta

CKD indicates chronic kidney disease; and eGFR, estimated glomerular filtration rate.

apnea, obesity, sedentary lifestyle, and excessive dietary sodium are not exclusionary. At this time, there are limited data on RDN in some patient subgroups such as those with stage 1 hypertension, patients with isolated systolic hypertension, kidney transplant recipients, and patients with a single kidney.

Some anatomical criteria preclude the procedure, including significant RAS, kidney tumors, renal artery aneurysm, and renal artery branches too small to accommodate current catheters. Although the large RCTs enrolled patients with estimated glomerular filtration rate >40 mL/min/1.73m^2, smaller studies have demonstrated safety and efficacy in those with lower kidney function.[34] Postmarketing studies and registries will likely provide more data in this subgroup; in the meantime, RDN must be considered with caution in patients with lower estimated glomerular filtration rate.

In conclusion, patients with RH should be the first but not only candidates who might be considered for RDN. Others who would likely benefit include patients with uncontrolled hypertension despite being prescribed antihypertensive medication and those who cannot tolerate or take sufficient medication to control their BP. Given the novelty of a device-based approach to the treatment of hypertension and the heterogeneity in existing study outcomes, thoughtful and informed discussions between experienced clinicians and patients who are candidates for this therapy are paramount.

SAFETY

RDN is a catheter-based procedure that is currently performed through the femoral artery, although technology that would allow a radial artery approach is under development. The total procedural length varies according to individual patient anatomy and the type of catheter used, but the procedure generally lasts ≈1 hour or less. There are no significant procedural risks from the procedure beyond those typically associated with femoral arterial access (including hemorrhage, infection, arterial dissection, thromboembolism, atheroembolism, and formation of a hematoma, pseudoaneurysm, or arteriovenous fistula), iodinated contrast, and radiation exposure.[35] Analgesics are administered during the procedure to minimize patient discomfort.

The immediate safety profile of RDN has been evaluated in several studies. Multiple meta-analyses of RCTs conducted between 2013 and 2022 reported no significant difference in the rates of major adverse events between the RDN and control groups.[36–38] The most common adverse event was pain lasting >2 days after the procedure (occurring in ≈12% of patients); rates of serious adverse events, including access site complications, renal artery dissection, and death, were all <1%. Current protocols for RDN do not mandate postprocedural imaging, although, depending on the clinical circumstances, it may be reasonable to consider renal artery duplex ultrasound, computed tomography angiogram, or magnetic resonance angiography if needed to assess for RAS or dissection.[39,40] Longer-term safety data after RDN procedures have also been examined. A recent review reported a low incidence of major adverse events beyond the initial 30-day period.[41] Adverse clinical events are more likely to occur in patients with higher baseline cardiovascular risk.[42] RAS, particularly after radiofrequency ablation, has been a concern, but the estimated incidence of stenosis requiring intervention is 0.2%/y, with the greatest risk occurring within the first 6 months.[43] This is similar to the natural rate of occurrence of RAS in patients with hypertension.[44] It is important to note that there does not appear to be any deleterious effect on kidney function after RDN regardless of baseline kidney function, including patients with moderate to severe CKD and those with systolic heart failure.[28,41,45–47] A 3-year analysis from the Global SYMPLICITY Registry did not demonstrate late safety concerns that arose after the procedure.[24]

Although most patients experience a modest sustained reduction in BP, others may exhibit a partial response or even a return to baseline values over time.[48] There is a theoretical concern that reinnervation may occur over time and lessen the effects of denervation. That said, animal studies that have shown evidence of partial or full reinnervation have demonstrated persistent reductions in BP, which raises questions about whether the reinnervation that occurs is functional.[49,50] Factors negatively influencing BP response to RDN remain incompletely understood but may include lower baseline BP (patients with higher baseline BPs often experience a greater reduction), higher arterial stiffness, and the presence of anatomical variants such as accessory arteries.[41,51] Similarly, the effectiveness of RDN in

maintaining BP control over time varies, likely because of a number of factors, including aging, development of comorbidities, medication changes, and potential regrowth of the renal nerves.[35]

In conclusion, RDN therapy appears to have a favorable immediate safety profile with a low incidence of major adverse events. Medium- to longer-term safety data suggest a continued absence of serious complications, with no evidence of kidney function impairment or RAS. Future work is needed to better understand the potential impact of reinnervation in humans and how to address any increases in BP over time after RDN.

PATIENT ACCEPTANCE

As highlighted in current guidelines and position papers,[35,52–55] shared decision-making is imperative when considering the role of RDN among available treatment options for hypertension. Eliciting patient preferences is part of other previously published guidelines that are references in the prior sentence. The US Food and Drug Administration has emphasized the integration of patient preference initiative studies in their regulatory risk-benefit decision-making for medical devices and played an active role in developing the science of patient-initiated input.[56] Patient preference initiative, as defined by the US Food and Drug Administration Center for Devices and Radiological Health, involves assessing how patients view different options for health interventions.[57] Effective shared decision-making and patient preference initiative depend on valid, unbiased, and current treatment information.

Multiple patient preference studies were conducted in the past 10 to 12 years in the United States, Western European nations, China, and Japan.[58–63] Not all of these studies provided presurvey participant education or RDN updates and thus are not equivalent to shared decision-making discussions.[64] Nevertheless, they provide valuable information reflecting global attitudes about RDN compared with further medical management for hypertension. Findings appear largely consistent despite wide variation in ethnicities and health care access and use. The proportion interested in RDN for BP control averaged ≈30% among those taking antihypertensive medications and 35% to 40% among those with hypertension not on medication.[59–63] Predictors for preferring RDN were consistent across studies: younger age, male sex, higher office or home BP, need for more antihypertensive medication, cardiovascular comorbidities, medication side effects, and poor drug adherence. The majority of patients relied heavily on information and recommendations provided by their physicians. Older patients also considered input from pharmacists, whereas younger patients considered sources such as television, pharmaceutical websites, and internet searches. Although >30% of participants with untreated hypertension favored RDN, a survey conducted between 2016 and 2019 among Western European– and US-based physicians (cardiologists, proceduralists, and hypertension specialists) highlighted that physicians were more likely to refer patients with difficult-to-control BP and those on multiple antihypertensive medications. Moreover, this study alluded to cultural differences, with greater reluctance to accept RDN among American compared with Western European patients.[63] Physicians' concerns included the invasive nature of the procedure, limited data on long-term side effects, and continued reliance on oral medication. Overall, patients had high expectations for RDN treatment. In a cross-sectional survey in China, over 96% of patients expected that RDN would decrease their SBP by ≥10 mm Hg.[59] In a German series, 40% of patients expected to stop taking all antihypertensive medications after treatment.[61] Of note, lower increments of BP decrease of ≈2 to 3 mm Hg appeared more acceptable to US-based participants.[58] Participants favored medical management when faced with a possible 20% risk of injurious side effects from RDN.[63] In the single study addressing expectations about the long-term impact of RDN, >90% of patients expected a sustained BP decrease for >10 years.[59]

Overall, a 10 mm Hg BP reduction is associated with a 10% to 20% decline in cardiovascular morbidity and mortality.[65,66] With RDN, office and ambulatory SBP decreases of 5 to 10 mm Hg are often achieved and thus could be expected to have a similar risk reduction,[67,68] but further research in this area is needed. This contrasts with patients' expectations of achieving >10 mm Hg reduction in SBP after RDN. Given the real-world issues with medication adherence, sustained BP reduction with RDN may favorably decrease cardiovascular risk, but intensive patient education to align expectations with realistic outcomes will be key to wider adoption of RDN.

CONCLUSIONS

Although further research is needed, particularly in the realms of patient selection and long-term efficacy, RDN is a promising new therapeutic approach for some patients with uncontrolled hypertension, particularly patients with RH or who have multiple medication intolerances. Ideally, individual characteristics that predict response will be identified to enhance the success of the procedure. As with any procedure, safety remains a concern. That said, both short-term and ongoing medium- to longer-term studies have demonstrated reassuring safety profiles. Ensuring that clinicians who perform RDN have adequate training and experience will help mitigate the risks inherent in any invasive procedure. A multidisciplinary team approach that includes hypertension specialists and proceduralists is important both for identifying the right candidates for RDN and for following them after the procedure. Both patient and

clinician acceptance will be a critical factor in the widespread adoption of RDN. Efforts to educate patients and health care practitioners about how to realistically assess the benefits and risks of RDN for each individual person will be crucial for its uptake. Of note, much if not all of our current literature and experience with RDN in the United States have been in the context of clinical trials. Therefore, little is currently known about the cost of RDN as it compares with conventional treatment options, many of which are now generic and lower-cost pharmacological options. RDN holds promise as an adjunctive treatment for patients whose BP remains uncontrolled despite treatment with lifestyle and medications.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Wanpen Vongpatanasin	University of Texas Southwestern Medical Center	None	Inventors of the patent US-2017/0281578-Al under the application by the Board of Regents of the University of Texas System, Austin, TX (Patent is on the role potassium magnesium citrate in reversing metabolic side effect of thiazide.)*	None	None	None	None	None

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