

Renal Denervation: A Review

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Uncontrolled hypertension persists as an important health issue despite the availability of many medications and nondrug therapies that lower blood pressure. Increasingly, nonadherence to medication is found in approximately 2 of every 5 patients with uncontrolled hypertension. In the search for interventions that lower blood pressure that do not rely on adherence to a regimen requiring daily ingestion of medication or repeated physical activity, device-based methods that denervate the renal arteries have emerged as a potential complement to standard antihypertensive treatments. At least 3 different approaches to renal artery denervation are under active investigation, including the use of radiofrequency energy, ultrasound, or the injection of neurolytic agents into the renal perivascular tissue. In this review, we cover what is currently known about the mechanisms of antihypertensive effects of renal denervation, summarize the efficacy and safety of renal denervation using recent controlled trial publications in a number of hypertensive populations, and conclude with some thoughts about challenges in the field, including the optimization of patient selection for the procedure and what the reader can expect in the near future in this rapidly developing field.

Complete author and article information provided before references.

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Background

The original Veterans Administration Cooperative Trials^{1,2} established the value of detecting and treating increased blood pressure (BP) and formed the basis of the first Joint National Committee report on the detection and management of hypertension.³ These milestone studies were enabled by the availability of oral antihypertensive agents. Before the Veterans Administration (now Veterans Affairs) studies demonstrated the feasibility of management of essential hypertension, it was largely not undertaken in clinical practice. It was only when hypertension entered an accelerated phase, typically with the emergence of heart, brain, or kidney problems, that interventions were considered. Among these interventions, there were several surgical approaches, including sympathetic denervation (“Smithwick procedure”)⁴ and bilateral adrenalectomy.⁵ Surgical morbidity and mortality limited the widespread acceptance of these techniques. In addition, there was early work undertaken to lower BP using device-based therapies such as carotid baroreceptor stimulation.⁶ However, signal spread and infections reduced the appeal of this approach. Another strategy emerged with extremely stringent diets that practically eliminated sodium intake using a diet of rice, fruit, and distilled water,⁷ but these suffered from a lack of long-term sustainability. These limitations of these approaches contributed to the search for safe and tolerable medications.

As antihypertensive pharmacology blossomed in the 1970s through the 1990s, with attendant investigations supporting these new agent classes, the growing portfolio of clinical trials led to multiple revisions of the Joint National Committee reports. These focused on medication therapy as the cornerstone of antihypertensive intervention. Although the Joint National Committee reports acknowledged the benefits of concurrent lifestyle modifications (less salt, less weight, less alcohol, more exercise)

that were useful when successfully achieved, clinical experience has shown them to often be difficult to maintain.

Despite widely available antihypertensive agents, drug-resistant hypertension (no matter how defined) remains a difficult issue in clinical hypertension care.⁸ The frequency of office BP measurements exceeding current guideline-directed BP goals has been reported to range from as low as 2% (Daugherty et al⁹) to >20% (Egan et al¹⁰). With the decrease in new antihypertensive medication classes available in the clinic (there have been no additions since 2007¹¹), the search for more effective ways to manage drug-resistant hypertension was diverted into revisiting device-based approaches. The success of early renal denervation (RDN) trials fueled this initiative.^{12,13} In this review, we will discuss the current state of this field, with an emphasis on studies undertaken in patients with kidney disease.

Mechanisms of Denervation

Currently, 3 approaches that use a percutaneous access route to the kidney artery are in development in the United States. These approaches use radiofrequency ablation (RFA), ultrasound, or a neurotoxin injected through the wall of the kidney artery into the perivascular space.

RFA uses a catheter to position electrodes (typically 4 spaced approximately 6 mm apart in a spiral sequence) that generate heat using medium-frequency alternating current. The heat generated seems well tolerated by the kidney arterial wall, but is toxic to the nerves surrounding the kidney artery that are in the heat energy field. The energy field ranges as far as 7 mm from the kidney artery lumen.

Ultrasound approaches deliver a series of ultrasound-emitting sources (again typically 4) that are typically mounted on a catheter with an inflatable balloon system that allows irrigation of the portion of the catheter in

contact with the kidney arterial wall with a solution that maintains a cooler temperature in the kidney artery lumen than in the perivascular space.

The third approach introduces a smaller catheter with 3 tiny concentrically placed microneedles embedded in it. When the catheter is properly positioned, the microneedles are extended, penetrating the kidney artery wall into the perivascular space, and a small amount of liquid neurotoxin (typically a total of 0.6 mL of absolute ethanol) is injected through the 3 needles simultaneously.

Denervation effects are thought to result from interruption of renal sympathetic nerves. Progressively intense stimulation of the renal sympathetic nerves results in an increase in renin release at low stimulation levels, a reduction in sodium excretion at intermediate levels, and an increase in renal vascular resistance at the highest levels.¹⁴

Developments in Renal Artery Anatomy

When RDN studies were first undertaken in humans, the empirical approach was to denervate only within the main renal artery before branching based on the reasoning that the nerves governing BP-related signals to and from the kidney were largely accessible by this approach.¹⁵ Among the many reconsiderations undertaken after the failure of the SYMPLICITY HTN-3 study,¹⁶ more attention was paid to the actual human neural anatomy. Summarized briefly, some nerves that innervate the kidney do extend from the sympathetic ganglia near the origins of the renal artery from the aorta and travel on the surface of the kidney artery. However, some of these nerves from periaortic ganglia touch down on the renal artery surface and then divert away from the kidney artery before entering the kidney. Moreover, some nerves that innervate the kidney join the renal arterial vessels after the first bifurcation of the main kidney artery and are not among those in the perivascular space of the renal artery before the bifurcation. Further information is available in a recent summary of the current understanding of renal perivascular neural anatomy.¹⁷ Given the fundamental differences among the RDN approaches—the ultrasound and neurolytic approaches are currently directed to the main renal artery, whereas RFA now treats the main artery and the early branches—rigorous head-to-head comparisons are needed to understand if these anatomic issues are critical to clinical benefit.

Additionally, little is known about renal sympathetic nerve regrowth after denervation in humans. Although renal nerves appear to regrow in denervated rodents, tissue levels of norepinephrine do not recover to predenervation levels,¹⁸ and beneficial effects of RDN on a model of heart failure are not lessened with nerve regrowth.¹⁹ If renal sympathetic nerves regrow in humans, there is no evidence of functional recovery within the first 3 years (the extent of published follow-up intervals in human RDN studies) because the decrease in BP is maintained over time.²⁰

Efficacy of Renal Denervation

When RDN was first applied to people with hypertension, often in the presence of 5 or more medications with office-measured systolic BPs (SBPs) >160 mm Hg, the subsequent BP reductions were typically in the range of 25–30 mm Hg after approximately 6 months. The early trials lacked a sham control and relied on office BP measurements.^{12,13} The large, sham-controlled SYMPLICITY HTN-3 study was undertaken in a similar population and observed that, although office SBP measurements were reduced by 14 mm Hg in those who received RFA, those in the sham control group had a reduction of 12 mm Hg. More recent RDN trial designs employed more careful control of nonprotocol medication use (assured by urine and blood screening for antihypertensive medications), a redesigned ablation catheter (when using RFA), a diastolic BP requirement of ≥ 90 mm Hg in-office, and the use of ambulatory BP monitoring to ensure exclusion of “white-coat effects” (which are common in this population⁸). The results of newer RDN trials show lesser reductions of office and ambulatory SBP in the intervention and sham arms than earlier RDN trials. In addition, assumptions about the nerves in the kidney perivascular space were also revisited, and the technique for the RFA approach now includes the main renal artery and branches with lumen sizes of ≥ 3 mm, as well as suitable accessory arteries.²¹ The ultrasound and injection techniques remain focused on the main renal artery.^{22,23}

We will cover efficacy in several domains. These will include uncontrolled hypertension (treated and untreated with medications), resistant hypertension, and denervation in patients with hypertension and chronic kidney disease (CKD), including those receiving hemodialysis.

Uncontrolled Hypertension

Figure 1 shows the office systolic and 24-hour ambulatory SBP responses to RDN in various studies. Table 1 conveys further information about the studies in Fig 1. In the absence of antihypertensive medication (RADIANCE-HTN SOLO,²⁴ SPYRAL HTN-OFF MED²⁵), RDN produces an average of 9–11 mm Hg of office SBP reduction and 5–7 mm Hg of ambulatory SBP reduction. In the presence of antihypertensive medication (RADIANCE-HTN TRIO,²⁶ SPYRAL HTN-ON MED Pilot²⁷), RDN produces an average of 9 mm Hg of office SBP reduction and 9 mm Hg of ambulatory SBP reduction. These results are predicated on office SBPs of 150–180 mm Hg, office diastolic BPs >90 mm Hg, and ambulatory SBPs >135 mm Hg over 24 hours at baseline.

CKD

CKD affects 10% of the world’s population²⁸ and is within the top 10 noncommunicable diseases contributing to disability and premature death.²⁹ Although numerous factors contribute to hypertension in CKD,^{30,31} sustained activation of the sympathetic nervous system is crucial in

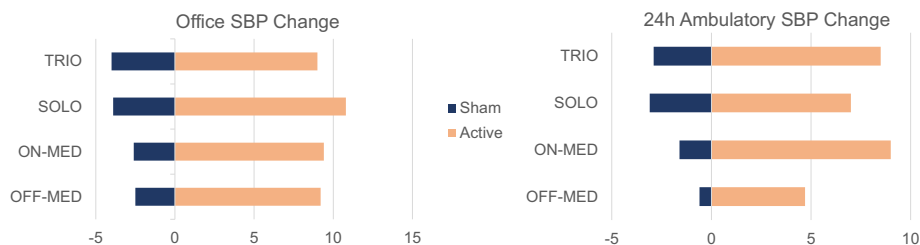


Figure 1. Office and ambulatory systolic blood pressure (SBP) changes. Tornado plots of changes in office and ambulatory SBP following sham or active intervention in double-masked randomized sham-controlled trials of renal denervation in patients with uncontrolled hypertension in the period following the SYMPLICITY HTN-3 study. Trial names are indicated on the left side of each panel.

the pathogenesis and maintenance of hypertension and in CKD progression.³² Therefore, it seems to be a potential strong pathophysiological rationale for RDN in the CKD population.³³

Because of safety concerns in regard to iodinated contrast agent use, reduced estimated glomerular filtration rate (eGFR; <45 mL/min/1.73 m²) is an exclusion criterion in the pivotal RDN trials.³⁴ Even though there are few data available regarding the safety of RDN in patients with CKD, no safety signal has surfaced in any of the sham-controlled trial registries and meta-analyses that included patients with CKD stages 3a and 3b.^{33,35}

Data from the Global SYMPLICITY Registry suggests similar BP-lowering efficacy by RDN in patients with CKD compared with patients with normal kidney function.³⁵ Further, a meta-analysis of 48 study cohorts detected no statistically different change in eGFR over an average 9 months of follow-up.³⁶

A recent meta-analysis of 11 single-center non-randomized, uncontrolled studies including 238 patients has been published.³³ Its aim was to evaluate the efficacy and safety of RDN for patients with hypertension and CKD. It showed a post-RDN decrease of office BP and 24-hour ambulatory BP monitoring, including office SBP and

Table 1. Completed Trials of Renal Denervation^{24-27,41-44}

Study	Method	N	Active:Sham	Inclusion	Primary Outcome	Results
Trials excluding patients with reduced eGFR^a						
SPYRAL HTN-OFF MED Pivotal ²⁵	RFA	331	1:1	Office BP 150-179/ ≥90 mm Hg on no BP meds	24-h ABPM SBP at 3 mo	RDN: ↓5 mm Hg; sham: ↓1 mm Hg
RADIANCE-HTN SOLO ²⁴	US	146	1:1	Office BP 140-180/ 90-110 mm Hg on no BP meds	Daytime ABPM SBP at 2 mo	RDN: ↓7 mm Hg; sham: ↓2 mm Hg
SPYRAL HTN-ON MED Pilot ²⁷	RFA	80	1:1	Office BP 150-179/ ≥90 mm Hg on 1-3 stable BP meds	24-h ABPM SBP at 6 mo	RDN: ↓9 mm Hg; sham: ↓2 mm Hg
RADIANCE-HTN TRIO ²⁶	US	136	1:1	Office BP ≥140/ ≥90 mm Hg on 3 stable BP meds	Daytime ABPM SBP at 2 mo	RDN: ↓8 mm Hg; sham: ↓3 mm Hg
Studies in patients with CKD						
Ott et al ⁴¹	RFA	27	No sham	CKD 3-4 with resistant HTN (ESH/ESC definition)	Nephroprotection	eGFR slope improved at 1 y post intervention
Kiuchi and Chen ⁴²	RFA	108	No sham	CKD with or without controlled HTN	Nephroprotection	CKD with uncontrolled HTN had better eGFR outcome vs CKD with controlled HTN at 6 mo
Hering et al ⁴³	RFA	46	No sham	eGFR ≤60 mL/min/1.73 m ²	Nephroprotection	eGFR stabilized over 12-24 mo follow-up
Ott et al ⁴⁴	RFA	6	No sham	HD and 24 h ABPM ≥135/85 mm Hg on 3 meds	Δ24-h ABPM	24-h ABPM: ↓20/15 mm Hg at 6 mo

Abbreviations: ABPM, ambulatory blood pressure measurement; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESH/ESC, European Society of Hypertension/European Society of Cardiology; HD, hemodialysis; HTN, hypertension; RDN, renal denervation; RFA, radiofrequency ablation; SBP, systolic blood pressure; US, ultrasound.

^aDefined variously as eGFR <40-45 mL/min/1.73 m².

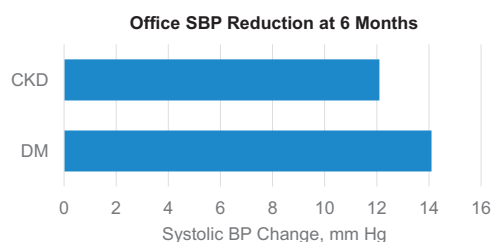


Figure 2. Office systolic blood pressure (SBP) reductions at 6 months compared with baseline in 766 patients with diabetes mellitus (DM) and 364 with chronic kidney disease (CKD; defined as an estimated glomerular filtration rate <60 mL/min/ 1.73 m²). Data are adapted from the 6-month time point reported in the Global SYMPLICITY Registry.²⁰ This is a real-world registry of patients who underwent renal denervation with radiofrequency ablation. Ambulatory blood pressure (BP) monitoring was not required for inclusion in the registry and was performed in only a modest number of registry participants, so these data are not shown. Note: The office SBP changes here are not directly comparable to those obtained in rigorous clinical trials shown in Figure 1.

office diastolic BP. eGFR values at 1, 3, 6, 12, and 24 months after RDN were not significantly different from those determined before the procedure ($P > 0.05$). Four trials included in this meta-analysis³⁷⁻⁴⁰ had reported data on antihypertensive medications before and after RDN and showed a significant decrease in these drugs after RDN ($P < 0.001$). RDN did not heighten the risk of rapid decline in kidney function or other major adverse events.³³

Some small studies have analyzed whether RDN could exert nephroprotective effects (Table 1). Ott et al reported results of an observational study of 27 patients with CKD stages 3/4 and resistant hypertension.⁴¹ All patients underwent catheter-based RDN using the Symplicity Flex RDN System (Medtronic). eGFR was monitored for as long as 3 years before and 1 year after RDN. The annual eGFR change before RDN was -4.8 mL/min/ 1.73 m². Following the procedure, the significant reduction in BP was accompanied by a halt in eGFR decrease, with an average annual change in eGFR of $+1.5$ mL/min/ 1.73 m².⁴¹ Similar results were reported by Kikuchi and Chen.⁴²

In a longer observational study of 46 patients with CKD (baseline eGFR ≤ 60 mL/min/ 1.73 m²), Hering et al reported on eGFR from 60 months before denervation and then at 3, 6, 12, and 24 months after RDN.⁴³ Compared with baseline, RDN was associated with improved eGFR at 3 months ($+3.73 \pm 1.64$ mL/min/ 1.73 m²; $P = 0.02$), with no further significant changes at 6 ($+2.54 \pm 1.66$ mL/min/ 1.73 m²; $P = 0.13$), 12 ($+1.78 \pm 1.64$ mL/min/ 1.73 m²; $P = 0.28$), or 24 (-0.24 ± 2.24 mL/min/ 1.73 m²; $P = 0.91$) months after RDN.

Little evidence is available for RDN in patients with kidney failure who are receiving maintenance hemodialysis. Ott et al conducted a pilot study to show the effects of RDN in this population.⁴⁴ Ambulatory BP was significantly

reduced over 6 months, and there was no change in hemodialysis parameters during follow-up. More recently, Scalise et al published results comparing drug therapy versus RDN in 24 patients who had been receiving hemodialysis for approximately 6 years and had resistant hypertension despite an average of 5.4 BP-lowering medications.⁴⁰ RDN was associated with a significant BP-lowering effect. The reduction persisted over a 1-year follow-up, and there were no significant periprocedural complications.

The small CKD populations included in the available studies makes it difficult to infer conclusions as a result of a general absence of sham controls (Table 1). However, there is an ongoing sham-controlled trial, the RDN-CKD study (ClinicalTrials.gov identifier NCT04264403). This prospective, double-blind, sham-controlled, multicenter feasibility study seeks to determine if RDN effectively reduces 24-hour ambulatory SBP in 80 patients with CKD stage 3a or 3b.

Diabetes

The percentages of enrolled patients with diabetes vary among pivotal RDN trials. In the SYMPLICITY HTN-3 trial, 47% of the participants in the intervention group were diabetic, compared with 40% of those receiving the sham procedure¹⁶; these respective values were 4% versus 5% in SPYRAL HTN-OFF MED,²⁵ 13% versus 19% in SPYRAL HTN-ON MED,²⁷ 3% versus 7% in RADIANCE-HTN SOLO,²⁴ and 30% versus 25% in RADIANCE-HTN TRIO.²⁶ In the subgroup analyses of the SYMPLICITY HTN-3 trial, the difference in the changes in office SBP was -4.53 (95% CI, -11.51 to 2.46) mm Hg in the diabetic population ($P = 0.20$), compared with -3.46 mm Hg (95% CI, -9.55 to 2.62) in the nondiabetic population ($P = 0.26$).¹⁶ Figure 2 shows SBP changes 6 months after RDN in the Global SYMPLICITY Registry.²⁰

Beyond improved BP control, some RDN research indicates a decrease in fasting glucose level and an increase in insulin sensitivity,^{45,46} likely as a result of attenuation of sympathetic nervous system activity.⁴⁷ However, in the DREAMS Study, RDN did not lead to a significant improvement of insulin sensitivity within 12 months of treatment.⁴⁸ All these studies were completed by 2015. The systematic review of Pan et al⁴⁷ concluded that, as a result of the contradictory results, more clinical trials are needed before any definite conclusion can be drawn. Some clinical trials are ongoing in an effort to determine if RDN has some role in glycemic control in diabetes. Since 2018, Gao-Jun et al have been recruiting patients for a clinical trial whose aim is to measure changes in glucose metabolism from baseline at 6 months and 2 years after RDN (ClinicalTrials.gov identifier NCT03418415).

Costs

RDN procedures are not approved for clinical use in the United States, but there is one cost-effectiveness study undertaken by Australian investigators in which the cost of

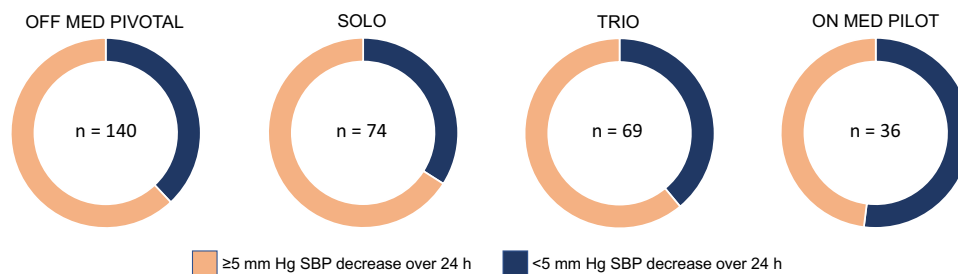


Figure 3. Renal denervation responders. Donut graphs of participants who did or did not experience a ≥ 5 -mm Hg reduction in 24-hour ambulatory systolic blood pressure (SBP) in double-blinded randomized controlled trials of renal denervation. Within each circle, the number of patients in the denervation arm in that trial is shown.

the RDN procedure was estimated to be €6,573 (approximately \$9,530 Australian or \$7,300 US).⁴⁹

Clinical Predictors of BP Response to RDN

As shown in Figure 3, most randomized, controlled studies of RDN in uncontrolled hypertension observed that approximately 2 of every 3 patients have a ≥ 5 -mm Hg SBP reduction over 24 hours.⁵⁰ The identification of predictors that identify patients who are more or less likely to show a response has remained a significant challenge to this field. As shown in the center of Figure 4, the most significant predictor of denervation efficacy to date has been SBP at the time of intervention, with higher SBP levels associated with a greater SBP reduction, a phenomenon often cited as Wilder’s law.⁵¹ A number of other candidate predictors have been proposed. These typically fall into 2 categories: those that likely reflect greater underlying sympathetic activity and those that reflect a stiffer arterial vasculature. Because the RDN procedure is thought to reduce BP through downregulation of sympathetic activity,⁵² this makes sense. On the contrary, arterial stiffness is often associated with an increase in the ratio of collagen to

elastin in large vessels, and patients with indicators of arterial stiffness such as isolated systolic hypertension⁵³ may be less responsive because of a “fixed” element of inelasticity (ie, more collagen) in the vessel wall. Such reasoning was used in recent study designs that used an inclusion criterion of diastolic BP ≥ 90 mm Hg in the office. Clinical markers of arterial stiffness include higher pulse wave velocity in the aorta and greater wave reflection resulting in a proportionately higher central artery systolic pressure. Although these studies are suggestive, they are usually small in number and await confirmation in larger and more diverse hypertensive populations.

Patient Acceptability of RDN

No matter how effective a therapy is, if patients are unwilling to try it, any therapeutic benefit will remain hypothetical. Investigations into patient preference information for competing treatments have become more common and are encouraged by regulatory agencies like the US Food and Drug Administration, particularly when a device-based intervention is involved.⁵⁴ A recent international study of patient preference information conducted in the United

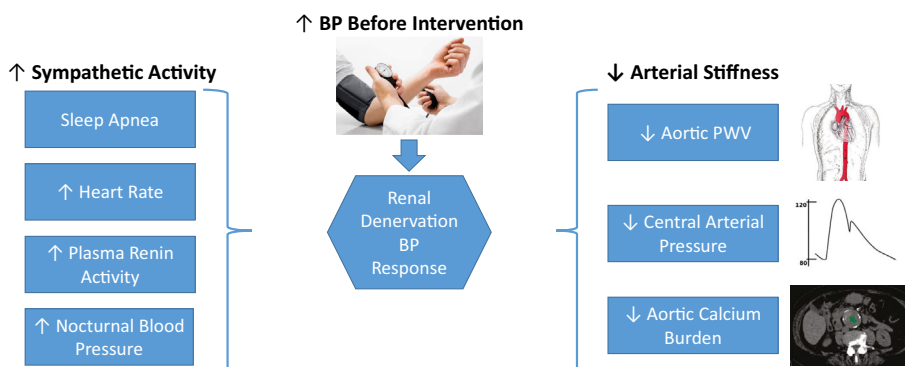


Figure 4. Predictors of renal denervation (RDN) response. The only established predictor of blood pressure (BP) reduction after RDN is BP level before intervention (top middle).⁶² Situations in which sympathetic activity may be increased such as sleep apnea,⁶³ higher heart rate,⁶⁴ higher plasma renin activity,⁶⁵ and increased nocturnal BP (and more variable nocturnal BP)⁶⁶ may also be useful in predicting RDN response. Situations in which arterial stiffness is less prevalent,⁶⁷ there is greater pulse wave reflection (PWV; ie, higher central aortic BPs),⁶⁸ or there is less evidence of aortic calcification by imaging⁶⁹ also seem to be predictive of BP reduction following RDN.

Table 2. Adverse Events Associated With Renal Denervation²⁴⁻²⁷

Event	RADIANCE-HTN SOLO (n = 64) ²⁴	SPYRAL HTN-OFF MED (n = 166) ²⁵	SPYRAL HTN-ON MED (n = 38) ²⁷	RADIANCE-HTN TRIO (n = 69) ²⁶
Periprocedural (denervation day and ≤30 d after)				
Death	0	0	0	1 (1%)
Acute kidney injury	0	0	0	0
Embolic event	0	0	0	0
Femoral vascular injury	0	0	0	1 (1%)
Renal artery stenosis	0	0	0	0
Pain >2 d post procedure	8 (11%)	NR	NR	12 (17%)
Hypertensive emergency	0	0	0	0
HF hospitalization	0	0	0	0
Postprocedural (1-6 mo after denervation)				
New RAS (>50%)	0	0	0	0
Scr doubling	0	0	0	1 (1%)
Hypertensive emergency	0	1 (1%)	0	0
Heart failure hospitalization	0	0	0	0
Stroke, TIA	0	0	0	0
AMI	0	0	0	1 (1%)
Coronary intervention	0	0	0	0
Renal angioplasty/stent	0	0	0	0
New orthostasis	0	0	0	0

Abbreviations: AMI, acute myocardial infarction; NR, not reported; RAS, renal artery stenosis; Scr, serum creatinine; TIA, transient ischemic attack.

States and Europe enrolled more than 2,700 patients and more than 1,900 physicians. The investigators made several interesting observations. Among the patients surveyed, those with unmedicated hypertension were more likely to opt for RDN compared with those taking medication, and this finding was not linked to the degree of increased BP. Also, patients who had medication side effects were also willing to consider RDN. Physicians, on the contrary, were more likely to consider RDN when BP was higher or when more medications were needed. Overall, approximately 40% of the patients and physicians surveyed would consider

RDN as an option instead of new or additional medication. A United States-based 400-person patient preference information study presented in November 2021 at the Transcatheter Therapeutics Conference⁵⁵ should provide more insight in this area when published.

Safety of RDN

Given that RDN is an invasive procedure, it is incumbent on those who are developing these technologies to ensure that the risk-benefit ratio is not skewed toward risk. Risk in RDN

Table 3. Listing of Ongoing Denervation Studies

Study/Registry	Sponsor	Method	Target Enrollment	Active: Sham	Primary Outcome	Expected Completion	Geographic Region
SPYRAL HTN-ON MED Pivotal	Medtronic	RFA	340	2:1	Δ24-h ABPM SBP at 6 mo	10/2022	Global
RADIANCE II	ReCor	Ultrasound	225	1:1	ΔDaytime ABPM SBP at 2 mo	7/2022	Europe, USA
TARGET BP OFF-MED	Ablative Solutions	Absolute ethanol injection	90	1:1	ΔABPM SBP at 2 mo	3/2023	Europe
TARGET BP I	Ablative Solutions	Absolute ethanol injection	300	1:1	ΔABPM SBP at 3 mo	12/2022	USA
CKD-RDN	University of Erlangen	Ultrasound	80	1:1	Δ24-h ABPM SBP at 6 mo	1/2023	Germany
GSR DEFINE Registry	Medtronic	RFA	5,000	All Active	Observation	10/2027	Global
Global Paradise System Registry	ReCor	Ultrasound	3,000	All Active	Observation	12/2031	Global

Abbreviations: ABPM, ambulatory blood pressure measurement; CKD, chronic kidney disease; RDN, renal denervation; RFA, radiofrequency ablation; SBP, systolic blood pressure.

is divided into the periprocedural period (the time of the actual denervation and the ensuing 30 days) and the post-procedural risk, which is often the second through the sixth month following the procedure. Most RDN studies continue to assess patient status for 3 years after denervation. Fortunately, the risk profile in both periods demonstrates a low incidence of adverse events, as shown in [Table 2](#). The incidence of renal artery stenosis requiring an intervention has been studied in greatest detail in the RFA population, including those treated outside the clinical trial setting. We noted a 0.2%-per-year incidence of renal artery stenosis requiring intervention in more than 5,000 patients followed for 2 years.⁵⁶ Most cases of interval renal artery stenosis requiring intervention occur within the first 6 months after RDN. Importantly, kidney function appears to be unperturbed by denervation, even when denervation is undertaken in those with decreased kidney function (CKD stages 3b and 4).³³

RDN for Conditions Other Than Hypertension

RDN studies have been conducted in conditions in which denervation may have benefit separate from any reduction in BP, including heart failure,⁵⁷ arrhythmias,⁵⁸ and metabolic syndromes.⁵⁹ Another possible application is the kidney-related discomfort in patients with polycystic kidney disease, which, in a small subset of severe cases, requires opioids and profoundly affects quality of life. Although the pathophysiology of this pain is complex, RDN has been described in case reports as having a beneficial effect.⁶⁰ Notably, the benefits of RDN in these other contexts can be discerned on a time scale faster than seen in the treatment of hypertension, which takes months to produce an effect. Coverage of these topics has appeared recently.⁶¹

Upcoming Trials

The RDN portfolio includes several pending trials, as shown in [Table 3](#). Primary completion of the SPYRAL HTN-ON MED pivotal trial (ClinicalTrials.gov identifier [NCT02439775](#)), sponsored by Medtronic, is expected in October 2022. The SPYRAL AFFIRM trial ([NCT05198674](#)), also sponsored by Medtronic, initiated in February 2022. Primary completion of the RADIANCE II trial in stage 2 hypertension ([NCT03614260](#)), sponsored by ReCor, is anticipated in July 2022. Primary completion of the TARGET BP I trial ([NCT02910414](#)), sponsored by Ablative Solutions, is anticipated in December 2022.

The 3,000-person Global SYMPPLICITY Registry will be expanded to include an additional 2,000 people receiving RFA in what will be known as the GSR DEFINE registry ([NCT01534299](#)); as of April 2022, it was listed as recruiting. ReCor has announced a Global Paradise System Registry ([NCT05027685](#)) to follow people treated with the ultrasound approach to denervation; this study is also listed as recruiting. Both registries are thought to represent “real-world” follow-up, as neither collects information as

strictly as a protocol-driven randomized clinical trial. However, both registries will have repeated office BP measurements, some repeated ambulatory BP monitoring data, and measures of safety like kidney function estimates, along with a record of interval cardiovascular events, typically at yearly intervals.

Summary

RDN, regardless of approach, remains a research-only procedure in the United States. The BP-lowering efficacy of RDN appears similar to those of many single-agent antihypertensive medications. The safety profile of RDN, an invasive procedure, has remained at an acceptable level to date. In the absence of unanticipated findings in the pending trials, we anticipate that RDN could one day be an added to the antihypertensive toolbox.

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