Renal Denervation: A New Therapy for Resistant Hypertension

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ABSTRACT:
The Food and Drug Administration (FDA) recently approved renal denervation to treat resistant hypertension. This procedure is a minimally invasive procedure that starts by placing a catheter in the renal artery. This catheter is used to send either radiofrequency heat or ultrasound waves to burn the superficial nerves surrounding the renal arteries while making certain no damage happens to the renal arteries themselves. This procedure is done after a renal angiogram to ensure patency of the renal artery. Each radiofrequency ablation will take 1–2 minutes, depending on the device used. The radiofrequency balloon generator requires one single application of the radiofrequency pulse. The radiofrequency generator that uses a catheter tube will need more than one pulse. The second approved option uses ultrasound to generate an electrical signal that is converted into ultrasound vibration, that occurs at the distal end of the catheter. This vibration heats the system around the nerves, disrupting the superficial nerves that communicate with the central nervous system. This will result in lowering the blood pressure. We will review the studies that led to FDA approval, and the current guidelines for use. The FDA now approves both devices.

Renal denervation (RDN) is approved to treat resistant hypertension. RDN targets the superficial sympathetic nerves that surround the renal arteries. The ablation of these superficial nerves has been shown to modulate the blood pressure (BP) pathways.[1,2] It was approved for resistant hypertension but has gained a lot of popularity as an additional avenue in the hypertension armamentarium for BP control. We will review here the history of RDN and the trials that resulted in Food and Drug Administration (FDA) approval. A third procedure that is not yet approved involves the injection of neurolytic agents to destroy the same superficial renal nerves. Each of the procedures has its own pros and cons, and ongoing studies are needed to refine the patient populations they can be applied to. Only radiofrequency and ultrasound ablation are currently approved by the FDA.[1,2] We will review the trials that resulted in FDA approval and who might benefit from this procedure.[3]

HISTORICAL BACKGROUND:

The efferent nerves of the sympathetic nervous system exit the thoracolumbar spinal cord and can significantly increase BP, especially when there is increased sympathetic outflow to the kidneys; this is especially the case in essential hypertension.[4] Activation of the efferent renal sympathetic nerves causes increased sympathetic outflow, which increases renin secretion, sodium reabsorption, and renal vasoconstriction, decreasing renal blood flow. RDN has direct effects on the cardiovascular system by denervation of both efferent and afferent nerves. Before the advances in antihypertensive medications, thoracolumbar sympathectomy was tried but limited because of the significant side effects of postural hypotension.

RDN was first performed in 1924 by Papin and Ambard for pain relief.[5] In 1935, at the Hospital of the Rockefeller Institute for Medical Research in New York, in collaboration with the Department of Surgery at the New York Hospital, a young woman was found to have uncontrolled hypertension, reaching 208/110, with little tendency to improve despite rest or pharmacological intervention with sodium thiocyanate therapy. They suspected the etiology could lie in the nervous impulses produced in the kidney. They performed bilateral denervation without improvement in arterial BP, which did not support the hypothesis that essential hypertension originates in the nervous mechanism of the kidneys.[6]

In the 1940s through 1950s, several surgical approaches were made for sympathetic denervation—splanchnic, intraspinal, thoracic, and lumbar—to treat resistant hypertension.[7] Even at that time, the risk of intraoperative and postoperative mortality remained low. They found it impossible to predict whether the fall in BP after the operation would be temporary or sustained. Whatever extent of sympathectomy they performed, there was almost always a reduction in BP during the following months. They theorized that this reduction may have allowed hypertrophy of the arteriolar wall—preventing arteriolar necrosis of malignant hypertension.[8] After the 1950s, initial drug therapy focused on addressing the sympathetic input as the etiology of hypertension; this was deemed chemical sympathectomy. These initial medications included: tetraethylammonium chloride, mecamlamide, guanethidine, and more.[9] Although these medications were valuable and helpful in the treatment of hypertension, they were associated with severe and adverse side effects, which limited their use. The late 1950s saw the introduction of thiazide diuretics, bringing innovation to hypertensive management.[10] In 1964, Sir James Black synthesized the first clinically significant beta blockers—propranolol and pronethalol—which revolutionized the medical management of hypertension and angina.[11] In 1975, Cushman and Ondetti's[12] discoveries on peptide analogs led to the discovery of captopril, the first orally active angiotensin-converting enzyme (ACE) inhibitor, and its approval by the FDA in 1981. In 1983, Fleckenstein[13] identified the first calcium channel blocker.[13] Losartan was approved in 1995.[14]

Even with these dynamic changes in the field of hypertension management, there are continued issues of uncontrolled hypertension resistant to pharmacological therapy. From noncompliance to lack of pharmacological treatment, there are a multitude of reasons why hypertension is poorly managed.[15] Given the modern-day lack of hypertensive improvement with up-to-date pharmacological sympathectomy, surgical and now endovascular interventions have been evaluated for resistant hypertension management.[16,17]

THE PROCEDURE:

RDN is a minimally invasive procedure that starts with a renal angiogram to ensure renal artery patency. The RDN procedure is a fluoroscopically guided angiographic procedure done in an interventional catheterization laboratory. Typically, significant data about renal anatomy is ascertained before the patient arrives for their procedure. After informed consent, the patient is taken to the cardiac catheterization operating table. Standard procedure for sterile draping is performed with either left or right femoral arterial process. Femoral arterial access is obtained by ultrasound-guided access. Either a 6Fr or 7Fr arterial sheath is placed in the femoral artery. Subsequently, a 0.035 wire is retrograde placed in the abdominal aorta with a guide catheter that is appropriately suited for the renal anatomy. Multiple different types of guide catheters exist depending on renal artery anatomy. The guide catheter is then engaged in each renal artery selectively. A renal angiogram is typically taken in an anteroposterior projection and the renal arterial distribution is seen on cineangiography. Subsequently, a 0.014 guidewire is placed in appropriate renal arteries. Afterward, angiographically or with standard rotational ultrasound devices, the size of the renal arteries is determined to select the appropriate size of the device for RDN. The device is brought over the 0.014 guidewire, and the procedure is performed. The nerves surrounding the renal arteries are ablated by radiofrequency or by ultrasound. This interrupts the connection between the renal nerves and the central nervous system. The ablation

is performed on 4–12 spots on each renal artery. Typically, versed and fentanyl are used for conscious sedation before the beginning of the ablation procedure to limit discomfort and pain. After one kidney is completed, the guide catheter and guidewire are removed, and a final renal angiogram is performed. This is then carried out in the contralateral kidney in the same manner. After this, the guide catheter and guidewire are removed along with the femoral arterial sheath in a standard manner. The patient is then anticoagulated with intravenous unfractionated heparin at 50 μ/kg[18] (Fig. 1).

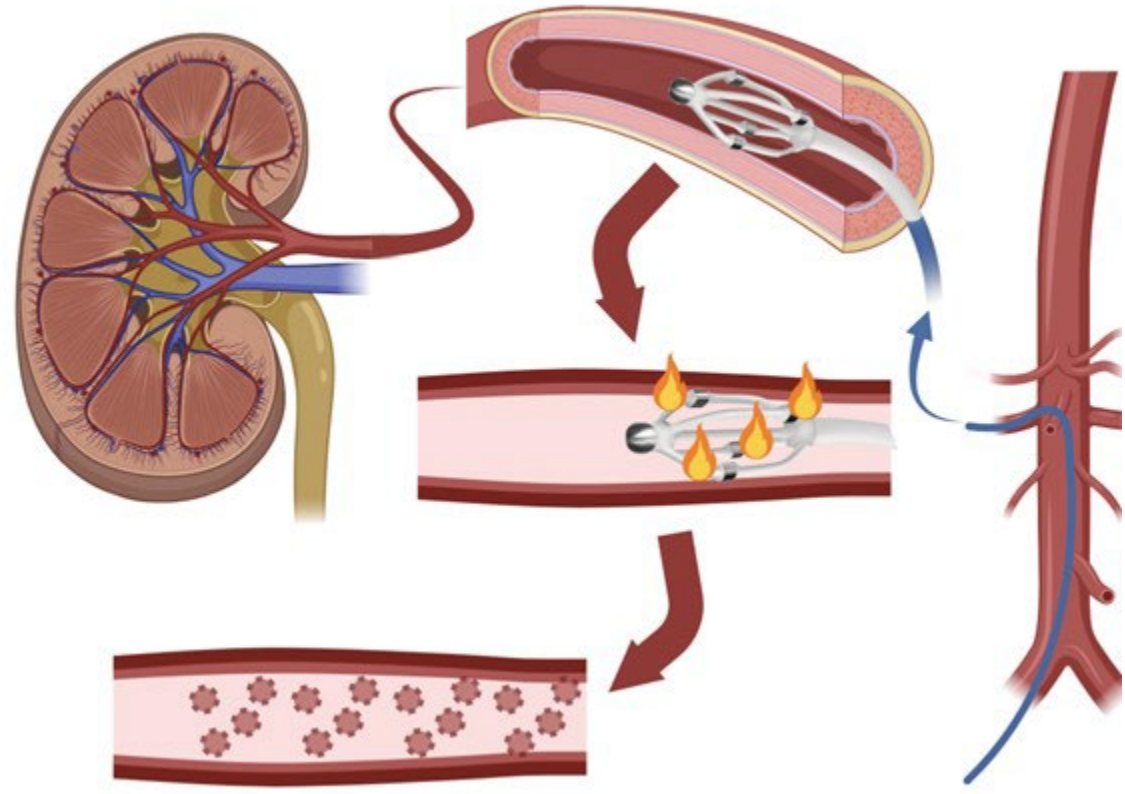

Figure 1: The nerves surrounding the renal arteries are ablated by radiofrequency or by ultrasound. This interrupts the connection between the renal nerves and the central nervous system. (Stars = post-ablation sites).

PHYSIOLOGY OF RENAL DENERVATION:

The renin-angiotensin-aldosterone system (RAAS) regulates arterial BP control, sodium balance, extracellular fluid volume, and vascular resistance.[1,19] Angiotensin (ANG) I act on the RAAS. ANG I is cleaved to ANG II, by ACE, primarily in the pulmonary endothelium.[20] In the nephron, ANG II induces salt and water retention by controlling renal blood flow and controlling glomerular filtration rates.[19]

PHYSIOLOGIC MECHANISMS:

While renin has a role in regulating the RAAS, it is also controlled by ANG II's negative feedback loop. Renin is synthesized in the juxtaglomerular region of the renal afferent arterioles.

These cells express the mineralocorticoid receptor for aldosterone.[21] When bound by prorenin, it causes conformation changes, enabling enzymatic activation. The prorenin receptor has demonstrated utility by activating prorenin and enhancing the effect of renin, promoting ANG II formation.[22,23] Although the body of evidence in brain prorenin receptor function remains low, sympathetic regulatory mechanisms may be worth investigating. Angiotensinogen is found in the plasma at high concentrations and functions at a cellular level.[24] Angiotensinogen is now thought to regulate BP through renin binding with high selectivity.[25] ANG I is the enzymatic byproduct of the union of renin and angiotensinogen. ANG I is converted to ANG II by ACE. ANG I is cleaved by ACE 2, to produce several other ANG analogs and derivatives.[26]

ACE converts ANG I to ANG II.[27] ANG II is a vasoconstrictor that raises BP, is pro-inflammatory, and increases reactive oxygen species (ROS). In 2000, a new monocarboxypeptidase was reported: ACE 2. ACE 2 degrades angiotensinogen II (ANG II) into a vasodilator and anti-antiproliferative ANG I metabolite.[1–7] ANG II is degraded to a vasodilator that reverses this process, reducing inflammation and reducing ROS.[28] The oxidative stress induced by ANG II reduces nitric oxide and causes hypertension.[29] Aldosterone is manufactured in the outer layer of both adrenal glands and mediates electrolyte homeostasis.[30] It also functions through sodium channels in the principal cells of the nephron and by utilizing the mineralocorticoid receptors to regulate the salt and water balance.[31]

CLASSICAL RAS PATHWAY VS. EXPANDED RAS PATHWAY:

In the early 1970s, the renin-angiotensin system was identified in the regulation of fluid balance and BP. In this pathway, renin converts angiotensinogen to ANG I and its metabolites. These productions are once again converted to ANG II by ACE to synthesize ANG II and achieve vasoconstriction, aldosterone release, antidiuretic hormone release, and central nervous system stimulation. Alongside this pathway, bradykinin is the proteolytic byproduct of kininogen and is equally important, with bradykinin reduced to inactive fragments by ACE.[32] The role of bradykinin is expanded with ACE inhibition and ANG II receptor blockade. The expanded renin-angiotensin system pathway recognizes the benefits of drugs acting on the ACE2/ANG$^{1–7}$/G-protein–coupled Mas receptor (MasR) pathways.[33] These drugs bind as MasR agonists to enhance the effects of ANG.[1–7] It is theorized that the key to understanding the RAS pathway may lie in the panel of ANG peptides. Further inspection of the parallel cascading pathways has recently shown benefits in antagonizing the decarboxylated byproducts of ANG II.[34]

TECHNOLOGICAL ADVANCES:

Since the 1920s and the surgically performed sympathectomies and splanchnicectomy, technology has advanced drastically to provide similar effects with minimal invasion. In 2013, endovascular catheter-based radiofrequency ablation was shown to be effective in disrupting the neurogenic reflexes involved in BP control.[35] This concept originated from the retroperitoneal location of the renal system and the proximity of the renal afferent and efferent nerves to the renal arterial wall, as verified by postmortem histological studies.[36] These studies confirmed that over 90% of the renal sympathetic nerves were identified within 2 mm of the renal arterial lumen and roughly 50% within 1 mm. Further animal studies were performed to evaluate lesion depth, concluding that radiofrequency ablation at 6 watts for 60 seconds using fine sectioning at 500-micrometer intervals, provided the greatest RDN at 6.4 mm depth.[37,38] Recently, pulse field

ablation has gained stride in electrophysiology and atrial fibrillation. Although limited, studies have been incorporating and evaluating the impact of adjunctive renal sympathetic denervation with pulse field ablation to modify hypertension and sympathetic tone as upstream therapy in treating atrial fibrillation and hypertension.[39] Data was obtained from 2 prospective randomized pilot studies [HFIB (Adjunctive RDN to Modify Hypertension and Sympathetic Tone as Upstream Therapy in the Treatment of Atrial Fibrillation)-1 and HFIB-2] and compared those receiving renal sympathetic denervation versus pulmonary-vein isolation alone. Although the studies showed atrial fibrillation recurrence was not statistically significant between these groups, those receiving sympathetic denervation were found to have a statistically significant reduction in BP.

RANDOMIZED CLINICAL TRIALS:

Randomized clinical trials (RCTs) started in 2010 (Fig. 2), but these were all sham (placebo) negative trials. Placebo-controlled RCTs only began in 2014 and the following decade saw multiple trials with inconsistent results due to confounders.[6,40–43] There were 5 very important clinical trials that resulted in FDA approval of RDN: Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pilot), Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED), Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO), Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal), and Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO).[41–44] The FDA approved the Paradise system (Ultrasound) based on the results of 3 sham-controlled trials showing the reduction in BP, RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and the RADIANCE II trial.[43,44] The Paradise system allowed for treatment of the main renal artery with a diameter of 3–8 mm, through femoral access (7 French) and the ability to perform 2–3 ablations per artery at 7 seconds per ablation.[45]

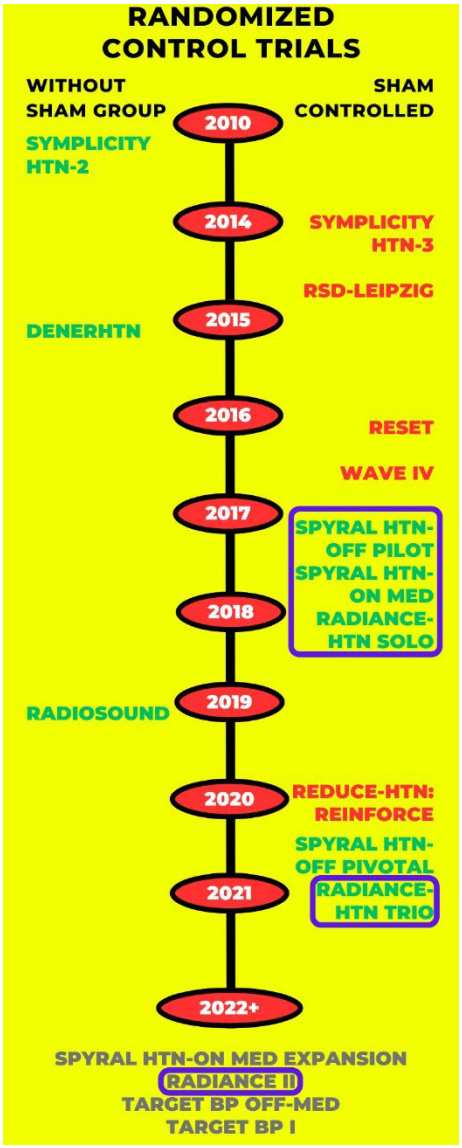

Figure 2: Timeline depicting randomized control trials. Green trials depict trials that met their primary outcomes, red indicates trials that did not meet primary efficacy outcomes, and circles indicate FDA-approved renal denervation systems.

The Simplicity Spyral system (Radiofrequency) is a second-generation RDN system that was approved by the FDA based on BP lowering in 2 sham-controlled clinical trials, HTN-OFF, and the SPYRAL HTN-ON trials. The HTN-OFF study was criticized for failure to lower BP at 6 months, which was seen in the pilot study, largely explained by higher medication doses in the sham group.[41,46] The Simplicity Spyral system allowed for the treatment of the main renal artery and its branches through femoral access (6 French), and the ability to perform simultaneous ablation at 4 points for at least 45–60 seconds.[45] Both systems achieved comparable results[47,48] (Fig. 2)

Paradise ultrasound RDN System Trials[43,44,49] (Table 1)

The Paradise Ultrasound RDN System Trials are Illustrated Including the Trial Sample Size, Primary Outcome Measure, and Blood Pressure Reduction in the Renal Denervation Group Versus the Control Group

Trial Name	Sample Size	Primary Efficacy Outcome	Blood Pressure Reduction in RDN vs Control Group
RADIANCE II, NCT03614260	225	Change in daytime ambulatory SBP at 2 months	-
RADIANCE-HTN SOLO	146	Change in daytime ambulatory SBP at 2 months	−8.5±9.3 vs −2.2±10.0 mm Hg; *P* = 0.0001
RADIANCE-HTN TRIO	136	Change in daytime ambulatory SBP at 2 months	−8.0 vs −3.0 mm Hg; *P* = 0.022

SBP indicates systolic blood pressure.

Symplicity Spyral Multi-Electrode Catheter Trials[41,42] (Table 2)

The Symplicity Spyral Multi-Electrode Catheter Trials are Illustrated Including the Trial Sample Size, Primary Outcome Measure, and Blood Pressure Reduction in the Renal Denervation Group Versus the Control Group

Trial Name	Sample Size	Primary Efficacy Outcome	BP Reduction in RDN vs Control Group
SPYRAL HTN-OFF MED Pilot	80	Change in 24-hour SBP at 3 months	−5.5 (95% CI, −9.1 to −2.0) vs −0.5 mm Hg (95% CI, −3.9 to 2.9); *P* = 0.0414
SPYRAL HTN-ON MED	80	Change in 24-hour SBP at 6 months	−9.0 (95% CI, −12.7 to −5.3) vs −1.6 mm Hg (95% CI, −5.2 to 2.0); *P* = 0.006

CI indicates confidence interval; SBP, systolic blood pressure.

Symplicity HTN-3 Trial for Resistant Hypertension[2,50,51] (Table 3).

The Symplicity HTN-3 Trial for Resistant Hypertension are Illustrated Including the Trial Sample Size, Primary Outcome Measure, and Blood Pressure Reduction in Renal Denervation Group Versus Sham Group

Trial Name	Sample Size	Primary Efficacy Outcome	RDN vs Sham Arm
SYMPLICITY HTN-3	535	Change in office SBP from baseline to 6 months postrandomization	−14.13 ± 23.93 mm Hg vs −11.74 ± 25.94 mm Hg Absolute difference = −2.39 mmHg (95% CI, −6.89 to 2.12, *P* = 0.26)

Trial Name	Sample Size	Primary Efficacy Outcome	RDN vs Sham Arm
SYMPLICITY HTN-3	535	Change in office SBP from baseline to 12 months postrandomization	Original RDN arm (364): −18.9 mm Hg Crossover (101): −17.7 mm Hg Non-crossover[52]: −21.4 mm Hg ANCOVA (6-month difference): −4.11 mmHg (95% CI, −8.44 to 0.22, *P* = 0.064)
SYMPLICITY HTN-3	535	Change in office SBP from baseline to 36 months postrandomization	−26.4 vs −5.7 mm Hg (*P* < 0.0001)
SYMPLICITY HTN-3	535	Change in ambulatory SBP from baseline to 36 months postrandomization	−15.6 vs −0.3 mm Hg (*P* = 0.0001)

CI indicates confidence interval; RDN, renal denervation; SBP, systolic blood pressure.

Unblinded Denervation Trial (DENER-HTN)[53,54] (Table 4).

The Unblinded Denervation Trial (DENER-HTN) are Illustrated Including the Trial Sample Size, Primary Outcome Measure, and Blood Pressure Reduction in the Renal Denervation Group Versus the Control Group

Trial Name	Sample Size	Primary Efficacy Outcome	BP Reduction in RDN vs Control Group
Renal Denervation in Hypertension (DENER-HTN)	97	Mean Diurnal SBP Assessed by ABPM at 6 months	−16.36 ± 16.23 vs −9.26 ± 12.59; *P* = 0.02

BP indicates blood pressure; RDN, renal denervation; SBP, systolic blood pressure.

SYMPATHY Trial[55] (Table 5).

The SYMPATHY Trial is Illustrated Including the Trial Sample Size, Primary Outcome Measure, and Blood Pressure Reduction in the Renal Denervation Group Versus the Control Group

Trial Name	Sample Size	Primary Efficacy Outcome	BP Reduction in RDN vs Control Group
SYMPATHY	139	Change in Daytime SBP at 6 months	−6.0 mm Hg (95% CI, −10.7 to −1.2) vs −7.9 mm Hg (95% CI, −14.7 to −1.3); *P* = 0.625
	Change in office SBP		−7.5 mm Hg (95% CI, −12.5 to −2.5) vs 0.7 (95% CI, −6.9 to 8.3); *P* = 0.069

BP indicates blood pressure; CI, confidence interval; SBP, systolic blood pressure.

PROS AND CONS OF RENAL DENERVATION:

Although much research has been performed on RDN, arguments can be made on both sides to favor and oppose RDN. The main points arguing RDN include the safety, efficacy, and its' patient-centric approach. RDN has developed into a strategic and targeted science that has shown significantly low procedural complications, postprocedural complications, or a significant rise in major adverse cardiovascular events.[40,47,49,53,55–66] When analyzing the second-generation SPYRAL-HTN and RADIANCE-HTN RCTs, statistically significant reductions in outpatient systolic BPs were noted in all studies when compared to their sham counterparts.[41–44,49] Lastly, in a study evaluating patients' preferences in the management of their disease, it was shown that patients preferred to have RDN over drug therapy, likely to avoid taking extensive BP-control drug regimens; further investigation revealed a preference against drug therapy regardless of the number of pills or BP levels.[67,68]

The criticism against RDN arose post-SYMPLICITY HTN-3 trials in 2014 when initial trials did not meet primary efficacy outcomes. Three opposing arguments were made: the lack of hard endpoints in RCTs, poor predictors of intraoperative success, and lack of data for long-term success.[67] Ambulatory BP reductions limited the efficacy of RDN by showing minimal changes compared to antihypertensive drugs.[69] Denervation continues to be challenging to confirm intraoperatively, with a further lack of predictability arising from postoperative nerve regrowth.[70] In the long term, those who responded to RDN were identified by various degrees of BP reduction, which some may consider a large variance in RDN's efficacy.

GUIDELINES FROM THE CARDIAC SOCIETIES:

The European Clinical Consensus Statement concluded that RDN did not result in significant long-term increases in renal artery stenosis or worsening renal function. RDN is recommended for patients with uncontrolled or resistant hypertension who are on triple-drug therapy or are unable to tolerate long-term medications and resulted in an average BP-lowering effect of RDN lasting for 3 years, with a reduction of approximately 10 mm Hg.[48] The Society for Cardiovascular Angiography & Interventions stressed that when these factors are properly addressed, RDN can be provided optimally to the needed population.[71,72]

The European Society of Hypertension recommends considering RDN for patients with true-resistant hypertension and those with uncontrolled BP despite the use of combination antihypertensive drug therapy. It is also recommended for patients who experience serious medication side effects or who experience poor quality of life due to drug treatment.[52]

The American College of Cardiology and the European Society of Cardiology preliminarily recommend RDN to be used in those with true-resistant hypertension, with office BP ≥140/≥90 mm Hg confirmed by 24-hour systolic ambulatory BP ≥130 mm Hg or daytime systolic BP ≥135 mm Hg, with estimated glomerular filtration rate ≥40 ml/min/1.73m². RDN should be considered for patients who have been unable to tolerate the side effects of antihypertensive medications and very high-risk patients who have not achieved BP goals.[73]

CONCLUSION:
There are 2 devices that are approved by the FDA for RDN based on 5 clinical trials, an ultrasound device and a radiofrequency device. The RADIANCE trials showed that ultrasound was safe and effective, and the Simplicity Spyral trial showed excellent BP lowering in patients not on medication. Before considering this procedure, you must have considered secondary causes of resistant hypertension, like sleep apnea, renal artery stenosis, primary hyperaldosteronism, or fibromuscular dysplasia. This procedure would not be appropriate for systolic hypertension of the elderly with wide pulse pressures. The estimated glomerular filtration rate must be above 45 to consider this procedure as well. The procedure starts with a renal angiogram and is followed by RDN. The procedure has been shown to be safe in many patients in many trials. The average BP reduction is 5–6 mm, so they will unlikely be able to stop the medications they are already on. This procedure is an excellent addition to the treatment armamentarium for patients with resistant hypertension. However, cost issues may be a consideration with RDN going forward.

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