07.01.100 Renal Denervation for Uncontrolled Hypertension

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Related Policies:

- 02.02.19 Baroreflex Stimulation Devices Components and Ancillary Services

Summary

Description

Radiofrequency ablation (RFA) or ultrasound of the renal sympathetic nerves is thought to decrease both the afferent sympathetic signals from the kidney to the brain and the efferent signals from the brain to the kidney. This procedure decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system. RFA or ultrasound of the renal sympathetic nerves may act as a nonpharmacologic treatment for hypertension and has been proposed as a treatment option for individuals with uncontrolled hypertension despite the use of anti-hypertensive medications.

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Summary of Evidence

For individuals who have uncontrolled hypertension, despite the use of anti-hypertensive medications, who receive RFA of the renal sympathetic nerves, the evidence includes several randomized controlled trials (RCTs), numerous systematic reviews of the RCTs, and a multinational registry study. Relevant outcomes are symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. The proof of principle SPYRAL HTN-OFF MED study found that multielectrode renal denervation was superior to sham in the absence of background antihypertensive medication therapy, with between-group differences of -4.0 mmHg for 24-h SBP and -6.6 for office SBP at 3 months. The unpowered SPYRAL HTN-ON MED Pilot study also found significant between-group differences of -7.4 mmHg for 24-h SBP and -6.8 mmHg for office SBP at 6 months; however, results were only significant for the subgroup of individuals' non-adherent to medications. Long-term data from the SPYRAL HTN-ON MED study suggest that blood pressure reductions with multielectrode renal denervation are progressive and sustained over time. The SPYRAL HTN-ON MED Expansion study failed to meet its primary efficacy endpoint and found only 0.03 mmHg difference between renal denervation and sham control groups at 6 months follow-up. A significant reduction in office blood pressure was noted at 6 months (-4.1 mmHg). Confounding of these outcome estimates by unbalanced medication changes, missing 24-h SBP outcome data, and timing of antihypertensive medications related to 24-h SBP assessment may explain the discordant results between the pilot and expansion phases of this trial. Study interpretation is also complicated by short-term blinded follow-up and imputation of excluded crossover patient data. A pooled patient-level analysis of 4 RCTs with 3-year follow-up demonstrated a sustained and statistically significant reduction in both office SBP (−4.7 mmHg) and 24-h SBP (−3.6 mmHg) in the renal denervation group compared to sham, with a low incidence of adverse events. It is unclear which individuals are most likely to derive benefit, and currently, there is no practical method to verify nerve destruction following ablation. Evidence from systematic reviews and meta-analyses are conflicting, but all available studies included evidence from both first and second-generation Symplicity catheters as well as multiple renal denervation methodologies such as ultrasound. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have uncontrolled hypertension, despite the use of anti-hypertensive medications, who receive ultrasound renal denervation (usRDN), the evidence includes 4 randomized sham-controlled trials, 1 RCT comparing usRDN to radiofrequency-based renal denervation, and a pooled analysis of 3 sham-controlled RCTs. Relevant outcomes are changes in blood pressure, medication use, and treatment-related morbidity. Two trials, RADIANCE-HTN SOLO and RADIANCE II evaluated usRDN in patients with no antihypertensive medication usage for 2 months post-intervention. The RADIANCE-HTN SOLO trial demonstrated that usRDN was superior to sham, with a between-group difference of -6.3 mmHg for daytime ambulatory systolic blood pressure (SBP) at 2 months. The RADIANCE II trial showed similar results, also showing a -6.3 mmHg difference in daytime ambulatory SBP at 2 months. The RADIANCE-HTN TRIO trial, focusing on resistant hypertension in individuals with a standardized triple combination antihypertensive treatment, found a -4.5 mmHg difference in daytime ambulatory SBP at 2 months. The durability of this effect was confirmed over 36 months of open-label follow-up, with significant reductions in office SBP from baseline levels in the usRDN group. The REQUIRE trial, conducted in Asian populations, did not show a significant difference between usRDN and sham control, possibly due to study design limitations. Long-term data from these trials show mixed results: while studies suggest that BP reductions with usRDN are sustained over time, the differences between usRDN and sham control groups diminished at 6 or 12 months after medication titration in some trials. However, the FDA's summary of safety and effectiveness data for the RADIANCE-HTN TRIO and SOLO trials demonstrated superior office systolic blood pressure reductions with usRDN compared to sham control at 24 and 36 months. Notably, these improved outcomes in the usRDN group were achieved despite individuals using fewer antihypertensive medications than the sham control group. A meta-analysis of the sham-controlled

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RADIANCE trials showed that fewer usRDN individuals required additional antihypertensive medications and demonstrated significant reductions in ambulatory, home, and office SBP at 6 months. Adverse events were infrequent and similar between usRDN and sham groups across studies. The RADIOSOUND-HTN trial compared 3 renal denervation techniques in individuals with resistant hypertension who were on a stable regimen of antihypertensive medications. The trial found that usRDN showed superiority over radiofrequency ablation (RFA) of main renal arteries in reducing daytime ambulatory SBP at 3 months, while RFA of main arteries plus branches did not significantly differ from the other groups. While these results are promising, there was high variability in individuals responses suggesting that further research may be needed to identify who is most likely to benefit from usRDN. Additionally, there is currently no practical method to verify nerve destruction following ablation. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2025 Input

Clinical input was sought to help determine whether the use of renal denervation for individuals who have uncontrolled hypertension provides a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 4 respondents, including: 3 physician-level responses with academic affiliations identified by specialty medical societies and 1 society-level response.

For individuals with uncontrolled hypertension, clinical input provides consistent support that the use of renal denervation provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Respondents were supportive of both ultrasound and radiofrequency approaches (see Policy Guidelines section).

Further details from clinical input are included in the Appendix.

OBJECTIVE

The objective of this evidence review is to determine whether the use of radiofrequency ablation or ultrasound of the renal sympathetic nerves improves the net health outcome in individuals with uncontrolled hypertension.

PRIOR APPROVAL

Not applicable.

POLICY

Radiofrequency ablation of the renal sympathetic nerves is considered **investigational** for the treatment of uncontrolled hypertension because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Ultrasound ablation of the renal sympathetic nerves is considered **investigational** for the treatment of uncontrolled hypertension because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Coding

See the Codes table for details.

BACKGROUND

Uncontrolled Hypertension

Recommendations for blood pressure generally target <130/80 mmHg, although blood pressure goal can vary (e.g., comorbidities, life-expectancy). High blood pressure, or hypertension is estimated to affect approximately 30% of the population in the U.S. It accounts for a high burden of morbidity related to stroke, ischemic heart disease, kidney disease, and peripheral arterial disease. An estimated 1 in 4 adults with hypertension have their hypertension under control, but the remaining 77% (93 million) remain uncontrolled. Uncontrolled hypertension is diagnosed when an individual's blood pressure remains above targeted levels (typically ≥140/90 mmHg) when an individual either is not using, or unable to use, treatments to control blood pressure or when hypertension persists despite antihypertensive therapies. The definition of uncontrolled hypertension is inclusive of resistant hypertension in which blood pressure remains above the targeted range despite the use of 3 or more antihypertensive medications, including a diuretic, with complementary mechanisms of action. A number of factors may contribute to uncontrolled hypertension including nonadherence to medications, excessive salt intake, inadequate doses of medications, excess alcohol intake, volume overload, drug-induced hypertension, and other forms of secondary hypertension. Also, sometimes it is necessary to address comorbid conditions (i.e., obstructive sleep apnea) to control blood pressure adequately.

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Treatment

Radiofrequency Denervation of the Renal Sympathetic Nerves

Increased sympathetic nervous system activity has been linked to essential hypertension. Surgical sympathectomy has been shown to be effective in reducing blood pressure but is limited by the adverse events of surgery and was largely abandoned after effective medications for hypertension became available. The renal sympathetic nerves arise from the thoracic nerve roots and innervate the renal artery, the renal pelvis, and the renal parenchyma. RFA is thought to decrease both the afferent sympathetic signals from the kidney to the brain and the efferent signals from the brain to the kidney. This procedure decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system.

The procedure is performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery, and a controlled energy source, most commonly low-power RF energy, is delivered to the arterial walls where the renal sympathetic nerves are located. Once adequate RF energy has been delivered to ablate the sympathetic nerves, the catheter is removed.

Ultrasound Denervation of the Renal Sympathetic Nerves

Ultrasound renal denervation (usRDN) is a minimally invasive procedure designed to treat hypertension by disrupting renal sympathetic nerves. The procedure targets the same physiological mechanism as radiofrequency ablation, aiming to decrease both afferent and efferent sympathetic signaling between the kidneys and the brain. This reduction in sympathetic activation is thought to decrease vasoconstriction and inhibit the renin-angiotensin system, ultimately leading to blood pressure reduction. The usRDN procedure is typically performed under local anesthesia with conscious sedation. Access is obtained through the femoral artery, and the catheter is advanced to the renal artery under fluoroscopic guidance. Once positioned, the catheter's balloon is inflated with cooling fluid, and ultrasound energy is delivered. Usually, 2-3 ultrasound emissions are delivered per renal artery, with the ability to treat both main renal arteries and accessory renal arteries when present.

Regulatory Status

Two renal denervation devices have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypertension (FDA product code: QYI):

The Paradise® Ultrasound Renal Denervation System (ReCor Medical, Inc) was approved by the FDA on November 7, 2023 and the Symplicity Spyral™ Renal Denervation System (Medtronic, Inc) was approved by the FDA on November 17, 2023. Both systems are indicated to reduce blood pressure as an adjunctive treatment in hypertension patients in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

No other renal denervation devices are currently FDA approved for the treatment of hypertension. Several other devices that were previously in development such as the EnligHTN™ system (St. Jude Medical) and Vessix™ system (Boston Scientific), are no longer being marketed for this indication.

Verve™ Renal Denervation System (Verve Medical Inc.) delivers radiofrequency energy to renal nerves through the renal pelvis of the kidney via a retrograde ureteral approach. Per Verve Medical July 2023 they announced they would initiate a randomized sham-controlled trial to evaluate the safety and efficacy

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of the Verve™ RPD System and the results of this trial would support the applications for the FDA Approval. As of September 2025, NCT05440513 trial status is unknown, see clinicaltrials.gov.

RATIONALE

This evidence review was created in January 2024 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Radiofrequency Ablation

Clinical Context and Therapy Purpose

The purpose of radiofrequency ablation (RFA) in individuals who have uncontrolled hypertension is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hypertension that is uncontrolled despite the use of antihypertensive medications or who poorly tolerate blood pressure lowering therapy. There is no widely accepted definition of uncontrolled hypertension. Furthermore, in real-world settings, it is difficult to distinguish uncontrolled hypertension from poor medication adherence.

Interventions

The therapy being considered is RFA. RFA is a minimally invasive procedure performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery and a controlled low-power energy is delivered to the arterial walls to ablate the renal sympathetic nerves. The updated

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Symplicity Spyral system employs a multielectrode, spiral-shaped RFA catheter intended to permit more complete, circumferential ablations.

Comparators

The following therapy is currently being used to treat those with uncontrolled hypertension: continued medical therapy.

Outcomes

The general short-term outcomes of interest (follow-up to at least 6 months) are a change in systolic and diastolic blood pressure (SBP and DBP) and medication use. Blood pressure measurements may include daytime ambulatory blood pressure, 24-hour average SBP, and office SBP.

A longer-term outcome of interest (follow-up to at least 3 years) is the effect on cardiovascular outcomes such as myocardial infarction and stroke.

Table 1. Outcomes of Interest for Individuals with Hypertension

Outcomes	Details	Timing
Morbid events	Outcomes of interest include adverse events such as end-stage renal disease, and embolic events resulting in end-organ damage, renal artery or other vascular complications, or hypertensive crisis.	≥30 days
Treatment-related morbidity	Outcomes of interest include decrease in daytime ambulatory SBP, nighttime SBP, and 24-hour average SBP	≥30 days

SBP: systolic blood pressure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
- Studies of the Symplicity Spyral catheter were reviewed, but evidence from the first-generation Symplicity Flex catheter was excluded.

Review of Evidence

Systematic Reviews

Multiple systematic reviews with overlapping studies, 1 of which is a Cochrane review by Coppolino et al (2017), have summarized the key RCTs evaluating renal denervation. The characteristics of the

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systematic reviews are summarized in Table 2, and the key results are summarized in Table 3. The overall results vary depending on the inclusion of earlier, unblinded studies and controlled but nonrandomized studies, with some systematic reviews reporting significant improvements with renal denervation and some reporting no significant improvement.

The Cochrane review reported that none of the trials was designed to evaluate clinical endpoints as primary outcomes. The evidence for clinical endpoints (e.g., all-cause mortality, hospitalization, cardiovascular events) was of low-quality. Comparisons of clinical outcomes in sham versus renal denervation groups showed no significant differences between groups in myocardial infarction (relative risk, 1.3; 95% CI, 0.5 to 3.8), ischemic stroke (relative risk, 1.1; 95% CI, 0.4 to 3.7), or unstable angina (relative risk, 0.6; 95% CI, 0.1 to 5.1).

A network meta-analysis by Silverwatch et al (2022) pooled the results of 20 RCTs of varying approaches to renal denervation compared to sham or antihypertensive medications or one another. Trials enrolled participants with uncontrolled hypertension treated with radiofrequency main renal artery denervation (n=10 studies), radiofrequency of the main renal artery plus branches (n=4), radiofrequency of main renal artery plus antihypertensive therapy (n=5), ultrasound of the main renal artery (n=3), sham control (n=8), and antihypertensive therapy alone (n=9). The authors found that radiofrequency renal denervation had the greatest improvement in 24 ambulatory, daytime, and nighttime BPs compared to other interventions (p-scores ranging from 0.83 to 0.97), with significant effects found versus both sham and antihypertensive therapies.

Table 2. Characteristics of Systematic Reviews of Controlled Trials Assessing Renal Denervation

Study	Dates	Trials	N (Range)	Design	Duration, mo
Silverwatch et al (2022)	2010-2020	20	2152 (20-535)	RCT	2 - 6
Ogoyama et al (2021)	2014-2021	9	1555 (51-535)	RCT, CT	2 - 6
Pappaccogli et al (2018)	2010-2016	11	1236 (19-535)	RCT, CT	6
Coppolino et al (2017)	2010-2016	12	1149 (16-535)	RCT, CT	6

CT: controlled trial; RCT: randomized controlled trial.

Table 3. Systematic Review Results at 6-Month Follow-up for Controlled Trials Assessing Renal Denervation

Study	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I^2, %
Silverwatch et al (2022)	RD (radiofrequency of main renal artery, main renal artery plus branch, main renal artery plus antihypertensive treatment or ultrasound of	Sham or AHT (network meta-analysis)	20	*Outcome:* *Group* 24-h SBP: rfMRA+B 24-h SBP: rfMRA 24-h SBP: rfMRA+AHT 24-h SBP: usMRA 24-h SBP:	 -7.2 0.6 -4.7 -1.2 -12.9 5.9 -1 -6.9 -6.9 -0.2	 -13.6 to -0.8 -4.4 to 5.5 -5.5 to 14.8 -8.6 to 6.2 -22.6 to -3.2	 SS NS NS NS SS NS NS NS NS NS	*Comparison**: Sham Sham Sham Sham AHT AHT AHT Sham Sham

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Study	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I^2, %
	main renal artery)			rfMRA+B 24-h SBP: rfMRA 24-h SBP: rfMRA+AHT 24-h SBP: usMRA Office SBP: rfMRA+B Office SBP: rfMRA Office SBP: rfMRA+AHT Office SBP: usMRA Office SBP: rfMRA+B Office SBP: rfMRA Office SBP: rfMRA+AHT Office SBP: usMRA	-10.5 2.3 -7.3 -0.7 -10.1 -1.8	-11.4 to 1.3 -7.2 to 5.2 -17.8 to 4.1 -19.9 to 6.3 -13.4 to 13.1 -30.7 to 9.7 -12.9 to 17.5 -26.4 to 11.8 -11.7 to 10.4 -21.4 to -0.6 -21.2 to 24.8	NS NS NS NS SS NS	Sham Sham AHT AHT AHT AHT
Ogoyama et al (2021)	rf RD (1st or 2nd generation device)	Control	6	24-h SBP (N=1137) 24-h DBP (N=1137) Office SBP (N=997) Office DBP (N=997)	 -3.17 -1.58 -4.93 -3.33	-5.22 to -1.11 -3.11 to -0.04 -7.81 to -2.06 -4.88 to -1.78	 SS SS SS SS	 30 47 26 16
Pappaccogli et al (2018)	RD	Control	9 9 10 10	Office SBP Office DBP ASBP ADBP	-3.5 -2.8 -1.8 -0.6	-13.0 to 6.1 -6.0 to 0.4 -4.5 to 0.9 -2.3 to 1.2	NS NS NS NS	 90 74 47 63
Coppolino et al (2017)	RD	Control	5 4 6 5	24-h SBP 24-h DBP Office SBP Office DBP	0.3 0.9 -4.1 -1.3	-3.7 to 4.3 -4.5 to 6.4 -15.3 to 7.1 -7.3 to 4.7	NS NS NS NR	 NR NR NR NR

*Value reflects comparison group for network meta-analysis not I^2

ADBP: ambulatory diastolic blood pressure; ASBP: ambulatory systolic blood pressure; AHT: antihypertensive therapy; B: branch of renal artery; CI: confidence interval; DBP: diastolic blood pressure; MRA: main renal artery; NR: not reported; NS: not significant; RD: renal

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Sham-controlled Randomized Controlled Trials

Characteristics and results of sham-controlled RTCs are summarized in Tables 4 through 6.

Table 4. Sham-controlled Randomized Controlled Trials Characteristics

Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
				RDN	Sham	
SPYRAL HTN-OFF MED Pilot	80	Symplicity Spyral multielectrode RDN (n=38) vs. sham (n=42) following 3-4 week medication wash-out	Age 20-80 y with office SBP 150-180, DBP ≥90, and 24-h SBP 140-170; treatment-naïve individuals eligible	Mean Age: 55.8 Sex: Male, 68.4% Mean BMI: 29,8 Mean office BP: 162/100 Mean 24-h BP: 153/99 Prior Medications: NR	Mean Age: 52.8 Sex: Male, 68.4% Mean BMI: 30.2 Mean office BP: 161/102 Mean 24-h BP: 152/99 Prior Medications: NR	Change in mean office and 24-h BP at 3 months and between groups (unpowered)
SPYRAL HTN-OFFMED Pivotal	331	Symplicity Spyral multielectrode RDN (n=166) vs. sham (n=165) following 3-4 week medication wash-out	Same as above	Mean Age: 52.4 Sex: Male, 64% Race: White, 28%; Black, 22%; NR, 44% Mean BMI: 31.1 Mean office BP: 163/101 Mean 24-h BP: 151/98 Prior Medications: NR	Mean Age: 52.6 Sex: Male, 68% Race: White, 30%; Black, 19%; NR, 48% Mean BMI: 30.9 Mean office BP: 163/102 Mean 24-h BP: 151/99 Prior Medications: NR	Change in mean 24-h SBP at 3 months; superiority margin of -4.0 for 24-hr SBP and -6.5 for office SBP
SPYRAL HTN-ON MED **Pilot**	80	Symplicity Spyral multielectrode RDN (n=38) vs. sham (n=42) on stable doses for at least 6 weeks	Age 20-80 y with office SBP 150-180, DBP ≥90, 24-h SBP 140-170 despite use of 1-3 medications at ≥50% of maximum dose	Mean Age: 53.9 Sex: Male, 87% Race: White, 34%; Black, 11%; NR, 47% Mean BMI: 31.4 Mean office BP: 165/100 Mean 24-h BP: 152/97 Medications: 2.13	Mean Age: 53.0 Sex: Male, 81% Race: White, 36%; Black 12%; NR, 48% Mean BMI: 32.5 Mean office BP: 164/103 Mean 24-h BP: 151/98 Medications: 1.98	Change in mean office and 24-h BP from baseline to 6 months and between groups (unpowered)
SPYRAL HTN-ON MED Expansion	257	Symplicity Spyral multielectrode RDN (n=168) vs. sham (n=89) on	Same as above	Mean Age: 55.5 Sex: Male, 80% Race: White, 36%; Black,	Mean Age: 55 Sex: Male, 78% Race: White, 37%; Black	Change in mean 24-h BP from baseline to 6

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Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
		stable doses for at least 6 weeks		12%; NR, 37% Mean BMI: 31.4 Mean office BP: 163/102 Mean 24-h BP: 149/97 Medications: NR	17%; NR, 39% Mean BMI: 32 Mean office BP: 163/101 Mean 24-h BP: 148/95 Medications: NR	months and between groups

BP: blood pressure; BMI: body mass index; DBP: diastolic blood pressure; NR: not reported; RDN: renal denervation; SBP: systolic blood pressure.

Table 5. Primary Sham-Controlled Randomized Controlled Trials Results

Trial	24-h SBP Change (SD or 95% CI)	24-h DBP Change (SD or 95% CI)	Office SBP Change (SD or 95% CI)	Office DBP Change (SD or 95% CI)
SPYRAL HTN-OFF MED Pilot	**3 months**			
RDN	-5.5 (-9.1 to -2.0)	-4.8 (-7.0 to -2.6)	-10.0 (-15.1 to -4.9)	-5.3 (-7.8 to -2.7)
Sham	-0.5 (-3.9 to 2.9)	-0.4 (-2.2 to 1.4)	-2.3 (-6.1 to 1.6)	-0.3 (-2.9 to 2.2)
MD (95% CI); p	-5.0 (-9.9 to -0.2);.0414	-4.4 (-7.2 to -1.6);.0024	-7.7 (-14.0 to -1.5);.0155	-4.9 (-8.5 to -1.4);.0077
SPYRAL HTN-OFF MED Pivotal	**3 months**			
RDN	-4.7 (-6.4 to -2.9)	-3.7 (-4.8 to -2.6)	-9.2 (-11.6 to -6.9)	-5.1 (-6.4 to -3.8)
Sham	-0.6 (-2.1 to 0.9)	-0.8 (-1.7 to 0.1)	-2.5 (-4.6 to -0.4)	-1.0 (-2.3 to 0.3)
MD (95% CI); p	-4.0 (-6.2 to -1.8);.0005	-3.1 (-4.6 to -1.7);<.0001	-6.6 (-9.6 to -3.5); <.0001	-4.4 (-6.2 to -2.6); <.0001
SPYRAL HTN-ON MED Pilot	**6 months**			
RDN	-9.0 (-12.7 to -5.3)	-6.0 (-8.5 to -3.5)	-9.4 (-13.5 to -5.3)	-5.2 (-7.7 to -2.7)
Sham	-1.6 (-5.2 to 2.0)	-1.9 (-4.7 to 0.9)	-2.6 (-6.7 to 1.6)	-1.7 (-4.2 to 0.9)
MD (95% CI); p	-7.4 (-12.5 to -2.3);.0051	-4.1 (-7.8 to -0.4);.0292	-6.8 (-12.5 to -1.1);.0205	-3.5 (-7.0 to 0);.0478
SPYRAL HTN-ON MED Expansion	**6 months**			
RDN	-5.9	NR	-10.1	NR
Sham	-5.8	NR	-6.2	NR
MD (95% CI); p	0.0 (-2.8 to 2.9);.974	NR	-4.0 (-7.6 to 0.4);.028	NR

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Trial	24-h SBP Change (SD or 95% CI)	24-h DBP Change (SD or 95% CI)	Office SBP Change (SD or 95% CI)	Office DBP Change (SD or 95% CI)
SPYRAL HTN-ON MED Expansion (Full Cohort)	**6 months**			
RDN	-6.5	NR	-9.9	NR
Sham	-4.5	NR	-5.1	NR
MD (95% CI); p	-1.9 (-4.4 to 0.5);.110	NR	-4.9 (-7.9 to -1.9);.001	NR

CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; NR: not reported; RDN: renal denervation; SBP: systolic blood pressure; SD: standard deviation.

Table 6. Long-Term and Subgroup Sham-Controlled Randomized Controlled Trials Results

Trial	24-h SBP MD (95% CI); p	24-h DBP MD (95% CI); p	Office SBP MD (95% CI); p	Office DBP MD (95% CI); p
SYMPLICITY OFF MED (Full-Cohort)				
3 months ± SD, N, p-value	RDN: -4.5 ± 10.8, N=153; p<.001 Sham: -0.6± 8.7, N=147	NR	RDN: -9.4 ± 14.8, N=170; p<.001 Sham: -2.3 ±12.7, N=164	NR
6 months ± SD, N, p-value	RDN: -15.3 ± 13.7, N=150 Sham:-17.1 ± 12.3, N=159	NR	RDN: -20.8 ± 13.9, N=174 Sham: -21.9 ± 14.3, N=177	NR
12 months ± SD, N, p-value	RDN: -14.3 ± 11.9, N=146 Sham: -19.2 ± 12.l, N=92; p=.03	NR	RDN: -21.3 ± 14.2, N=171 Sham: -22.4 ± 13.6, N=104	NR
SPYRAL HTN-ON MED Pilot				
3 months	-4.6 (NR);.10	-3.7 (NR);.06	-1.6 (NR); 0.59	-1.5 (NR);.44
6 months	-7.4 (-12.5 to -2.3);.0051	-4.1 (-7.8 to -0.4);.0292	-6.8 (-12.5 to -1.1);.0205	-3.5 (-7.0 to 0);.0478
6 months (adherent subgroup)	-6.0 (NR);.99	-3.3 (NR);.249	-5.1 (NR);.144	-2.7 (NR);.241
6 months (non-adherent subgroup)	-8.3 (NR);.029	-4.6 (NR);.062	-7.9 (NR);.087	-4.0 (NR);.135
12 months	-1.9 (NR);.553	-0.8 (NR);.695	NR	NR
24 months	-11.2 (-18.4 to -4.0);.0031	-5.7 (-10.6 to -0.7);.025	-12.9 (-21.1 to -4.7);.0026	-8.5 (-15.0 to -2.1);.010
24 months (without imputation)	-11.2 (-18.4 to -4.0);.003	NR	-11.1 (-21.6 to -0.5);.11	NR

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Trial	24-h SBP MD (95% CI); p	24-h DBP MD (95% CI); p	Office SBP MD (95% CI); p	Office DBP MD (95% CI); p
36 months	-10.0 (-16.6 to -3.3);.0039	-5.9 (-10.1 to -1.8);.0055	-11.8 (-19.0 to -4.7); [0].0017	-3.9 (-9.8 to 1.9);.186
36 months (without imputation)	-6.1 (-13.6 to 1.4);.11	NR	0.5 (-8.8 to 9.7);.92	NR

CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; NR: not reported; SBP: systolic blood pressure.

Symplicity Spyral OFF-MED Pilot and Pivotal Trials

In 2015, Kandzari and coworkers noted several shortcomings of the failed SYMPLICITY HTN-3 trial, including the use of complex antihypertensive medications regimens, heterogeneous study populations, procedure variability, and choice of primary endpoint. As a result, investigators first aimed to conduct a proof-of-concept trial of renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED) utilizing the redesigned multielectrode Symplicity Spyral RFA catheter system. The multielectrode design was intended to provide more complete, circumferential treatments with automated 4-quadrant ablations, and operators were tasked with applying additional ablations in the branch and accessory renal arteries. Studies shifted to enroll patients with less severe and combined systolic-diastolic hypertension. Additionally, the primary endpoint now focused on 24-h ambulatory blood pressure measurements. Subsequent SPYRAL studies also monitored medication adherence.

In 2017, Townsend and coworkers published findings from the unpowered, proof-of-concept SPYRAL HTN-OFF MED pilot trial, in which 80 patients were randomized to renal denervation (n=38) or sham treatment (n=42). Patients were followed for 3 months following a 3–4-week medication washout period. Eligibility criteria included mild to moderate hypertension defined as office SBP ≥150 mmHg and <180 mmHg and office DBP ≥90 mmHg in addition to mean 24-h ambulatory SBP ≥140 mmHg and <170 mmHg. Both mean 24-h ambulatory and office blood pressure measurements significantly decreased from baseline in the renal denervation group at 3 months. No significant reductions in blood pressure were found in the sham control group. Between-group difference in blood pressure changes were also significant. Trial investigators concluded that these data provide biological proof of principle that renal denervation lowers blood pressure in untreated hypertensive patients, supporting prior data regarding the correlation between reduction in sympathetic tone and blood pressure reduction. No composite safety events were reported through 3 months of the pilot study, defined as the composite of all-cause mortality, end-stage renal disease, embolic event resulting in end-organ damage, renal artery perforation requiring reintervention, renal artery dissection requiring reintervention, vascular complications, hospitalization for hypertensive crisis or emergency, or new renal artery stenosis >70%.

Utilizing a Bayesian study design, Bohm et al (2020) published findings from the SPYRAL HTN-OFF MED Pivotal trial, in which pilot trial data (n=80) was used as an informative prior and combined with data from an additional 251 subjects to constitute an overall primary analysis population (N=331). Patients were randomly assigned to either renal denervation (n=166) or sham procedure (n=165). Significant between-group differences were found for the primary 24-h SBP and secondary office SBP endpoints in favor of renal denervation at 3 months. These primary and secondary endpoints were each met with a posterior probability of superiority greater than 0.999 with a treatment difference of -3.9 mmHg and -6.5 mmHg, respectively. Superiority of renal denervation was confirmed via both Bayesian and frequentist statistical methods. One composite safety event was reported in each study arm, neither of which were attributed to the device or trial procedures. Longer-term follow-up for the full cohort of pilot plus pivotal trial patients found that at 6 months, significant differences in 24-h SBP and office SBP were no longer observed, likely as a result of trial participants beginning or resuming antihypertensive medications at 3 months follow-

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up. By 12 months, the sham control group had a superior 24-h SBP, although no between-group differences were reported at 1-year post-treatment for office SBP (Table 4).

Symplicity Spyral ON-MED Pilot and Expansion Trials

Kandzari et al (2018) published initial findings from the unpowered SPYRAL HTN-ON MED pilot trial, in which 80 patients were randomized to renal denervation (n=38) or sham treatment (n=42). Eligibility criteria were consistent with those for the SPYRAL HTN-ON MED trial, but additionally required patients to be on 1-3 antihypertensive medications with stable doses at 50% or more of the maximum manufacturer's recommended dosage for at least 6 weeks. Patients were knowingly screened for antihypertensive drug adherence and medications changes were not permitted through 6 months unless patients met prespecified escape criteria (office SBP ≥180 mmHg or <115 mmHg with symptoms of hypotension). Baseline patient characteristics were similar except for a 19% higher incidence of obstructive sleep apnea in the sham control group. At 6 months for the overall population, the key efficacy outcome of mean 24-h SBP was significantly reduced by -9.0 mmHg with renal denervation, with a statistically significant between-group difference of -7.4 mmHg in favor of renal denervation. Between-group differences were also statistically significant for 24-h DBP, office SBP, office DBP, daytime SBP and DBP, and night-time SBP and DBP in favor of renal denervation. In contrast to prior findings from the SPYRAL HTN-OFF MED trial, no significant between-group differences were noted at 3 months. Medication adherence at 6 months was 60.5% and 64.3% in renal denervation and sham control groups, respectively. Importantly, between-group differences for 24-h SBP and DBP were only significant for the subgroup of non-adherent patients. Additionally, between-group differences for office SBP and DBP were not statistically significant in either adherent or non-adherent subgroup analyses. On an individual patient level, 6-month 24-h SBP reductions were reported for 75% and 58% of patients in renal denervation and sham control groups, respectively.

Mahfoud et al (2022) published long-term outcomes from the SPYRAL HTN-ON MED pilot trial through 36 months. Medication adjustments were permitted after 6 months and patients were unblinded and permitted to crossover after 12 months. No significant between-group differences were reported at 12 months, which investigators attributed to a higher medication burden in the sham control group as confirmed by 2 out of 4 post-hoc analyses. Progressive and sustained reductions in blood pressure were noted over time, with significant between-group differences at 24 and 36 months in favor of renal denervation. Between 6 and 36 months, mean 24-h SBP was reduced by an additional 5.9 mmHg with renal denervation. Kario et al. (2024) reported significantly lower 24-hour, morning, and nighttime ambulatory systolic blood pressure in the renal denervation group compared to sham control, with greater reductions of 10.0 mmHg, 15.9 mmHg, and 13.6 mmHg, respectively ($p<0.05$ for all), and a higher proportion of patients achieving blood pressure control in the renal denervation group (40% vs 6%, $p=.021$). However, during this period, the mean number of antihypertensive medications prescribed for patients in both renal denervation and sham control groups increased by approximately 1 additional medication. Sham control measurements at 36 months included 13 imputed crossover patients' blood pressure measurements from the last observation prior to the renal denervation procedure. Between-group differences in mean office SBP lost statistical significance at 24 months without imputation. Additionally, both mean 24-h and office SBP between-group differences lost statistical significance without imputation at 36 months. At 36 months, 6 (20%) of 30 patients in the renal denervation group and 1 (3%) of 32 patients in the sham control group had mean 24-h SBP <130 mmHg and DBP <80 mmHg ($p=.05$). However, between-group differences for the proportion of patients achieving target 24-h blood pressure were not statistically significant at 24 months. One composite safety event was reported in renal denervation and sham control arms through 36 months, occurring at 427 days and 693 days post-procedure, respectively. Changes in eGFR, serum creatinine, sodium levels, and potassium levels from baseline to 24 and 36 months were not significantly different between groups. Overall, study interpretation is complicated by short-term blinded follow-up and imputation of excluded crossover patient data. It is

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unclear which patients are most likely to derive benefit and whether such benefit is clinically meaningful in the context of increased medication use over time.

The HTN-ON MED Expansion trial was first reviewed by the FDA in August 2023 and has been reported on in several publications since. The eligibility criteria and primary efficacy endpoint were identical to the HTN-ON MED pilot study described above, with similar baseline characteristics (Table 4). The expansion trial randomized participants 2:1 to renal denervation (n=168) or sham treatment (n=89) and assessed patients as part of the expansion study alone or as part of a merged full cohort incorporating pilot data. A total of 12 patients in the renal denervation group and 13 in the sham group met escape criteria. Additionally, few patients from the pilot cohort were able to be incorporated into the full analysis due to large discrepancies outcome effects. Medtronic postulated that these differences might be due to unbalanced antihypertensive medication changes between groups, which showed that a higher proportion of sham control patients increased BP medications (17% in the renal denervation group vs. 30% in the sham group), non-evaluable 24-h SBP data (11.5% in the sham group vs. 6.8% in the renal denervation group), or confounding due to timing of BP medication use in relation to 24-h ambulatory monitoring.

The primary efficacy endpoint of baseline adjusted change in 24-h SBP from baseline to 6-months post-procedure, compared between renal denervation and sham groups did not show a significant difference in the expansion cohort or the full cohort of patients on Baysesan analysis (mean Bayesian posterior treatment effect, -0.03 mmHg; 95% CI, -2.92 to 2.76, posterior probability of superiority, =0.51). However, 6-month office SBP did show a significant difference favoring the renal denervation group (mean Bayesian posterior treatment effect, -4.1 mmHg; 95% CI, -7.4 to 0.75, posterior probability of superiority, =0.99), but the outcome assessment was non-powered. These results were mirrored in the frequentist ANCOVA analysis in both the expansion and full cohorts, which showed no differences in 24-h SBP but favored renal denervation for office SBP (Table 3). Between-group differences were also statistically significant for night-time SBP at 6 months (mean difference, -3.7; 95% CI, -6.5 to -0.9; p=.0095) in favor of renal denervation, but no differences were noted for daytime or 24-h SBP. At 6 months, the expansion cohort was unblinded, and the addition of medications was permitted; however, a high proportion of participants did not remain on stable medication usage during the trial. The FDA performed an assessment of differences in medication burden between groups at baseline, 3 months, and 6 months follow-up and did not find a significant between-group difference at any time point between groups. A subgroup analysis found that at 6 months follow-up 24-h SBP was significantly different between patients based on geography (United States vs. outside United States, p-value for interaction=.011). Patients in the U.S. sham control group had a greater absolute 24-h SBP reduction (6.7 mmHg) compared to those outside the U.S. (2.6 mmHg). Patients in the HTN-ON MED trial reported few major adverse events at 6 months, with only 2 (1%) in the renal denervation group and 1 (0.8%) event in the sham control group.

The primary safety analysis pooled patients from both the HTN-OFF MED and HTN-ON MED trials (n=253) and was defined as the composite incidence of major adverse events at 1-month post-randomization as adjudicated by a clinical events committee. Adverse events of interest included all-cause mortality, end-stage renal disease, significant embolic events resulting in end-organ damage, renal artery perforation requiring intervention, renal artery dissection requiring intervention, vascular complications, hospitalization for a hypertensive crisis not related to non-adherence with BP medications or study protocol as well as the 6-month incidence of renal artery stenosis (>70 diameter stenosis by angiography). The primary safety endpoint result was met with only a single vascular complication of a pseudo aneurysm being reported (event rate, 0.4%; 95% CI, 0% to 1.9%, p<.001) and is lower than the pre-specified performance goal of 7.1%. No renal artery stenoses were identified in the first 6 months of analysis; a sub-study using data from 180 renal denervation patients with CTA or MRA studies at 12 months found that potential stenoses were identified in 31 subjects at 12 months follow-up. Of these, 2 had stenoses of 51-75%, and 5 had stenoses of >76%; on follow-up angiography, 5 reported no stenosis 1 had confirmed 60% diameter stenosis, and 1 had no follow-up imaging.

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Kandzari et. al. (2023) have also published pooled analysis of data from Symplicity Spyral ON-MED Pilot and Expansion Trials and key findings are the following: The treatment difference in the mean 24-hour ambulatory systolic BP from baseline to 6 months between the RDN group (n = 206; -6.5 ± 10.7 mm Hg) and sham control group (n = 131; -4.5 ± 10.3 mm Hg) was -1.9 mm Hg (95% CI: -4.4 to 0.5 mm Hg; p = 0.12). There was no significant difference between groups in the primary efficacy analysis with a posterior probability of superiority of 0.51 (Bayesian treatment difference: -0.03 mm Hg [95% CI: -2.82 to 2.77 mm Hg]). However, there were changes and increases in medication intensity among sham control patients. RDN was associated with a reduction in office systolic BP compared with sham control at 6 months (adjusted treatment difference: -4.9 mm Hg; p = 0.0015). Night-time BP reductions and win ratio analysis also favored RDN. One adverse event (AE) was reported, one patient receiving RDN required right femoral pseudoaneurysm repair at the access site. The same limitations described below for the individual Pilot and Expansion trials apply to the combined analysis.

A follow-up pooled analysis by Mahfoud et al (2025) synthesized individual patient data from 4 randomized trials in the SYMPLICITY program (HTN-3, SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO) to evaluate the long-term durability and safety of renal denervation in a total cohort of 4,155 patients. The primary analysis focused on the adjusted change in office and 24-hour ambulatory SBP over 36 months post-procedure. Among patients treated with renal denervation, office SBP was reduced by a mean of -13.2 mmHg (95% CI, -13.9 to -12.5) at 36 months, compared to -8.5 mmHg (95% CI, -9.4 to -7.6) in sham controls, yielding a between-group difference of -4.7 mmHg (95% CI, -5.9 to -3.5; p<.001). Similarly, 24-hour SBP showed a mean reduction of -7.5 mmHg (95% CI, -8.1 to -6.9) for renal denervation treated patients versus -3.9 mmHg (95% CI, -4.7 to -3.1) in the sham group (-3.6 mmHg; 95% CI, -4.6 to -2.6; p<.001). These effects were sustained and appeared independent of changes in antihypertensive medication usage, which increased similarly across groups during follow-up. Safety outcomes demonstrated a low rate of major adverse events over 3 years, with renal artery stenosis requiring intervention reported in 0.4% of renal denervation patients, no significant differences in renal function decline between groups, and comparable rates of mortality (2.7% vs. 3.0%) and hospitalization for hypertensive crises (0.7% vs. 0.9%) for renal denervation and sham groups, respectively.

Sham-controlled study relevance, design, and conduct limitations are summarized in Tables 7 and 8 below.

Table 7. Sham-Controlled Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
SPYRAL HTN-OFF MED Pilot	3. Study population not representative of intended use; 4. Racial demographics of enrolled population not reported for over half of participants.	5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal.		3. Short duration of follow-up (3 months).
SPYRAL HTN-OFF	3. Study population not representative of intended use; 4, Racial	5. Number of ablations at main, branch, and	2. Not standard or optimal.		3. Short duration of blinded

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
MED Pivotal	demographics of enrolled population not reported for nearly half of participants.	accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.			follow-up (3 months).
SPYRAL HTN-ON MED Pilot	1. Intended use population is unclear as patients were permitted to take 1-3 medications at baseline with submaximal dosing; 4. Low enrollment of women (16%) and racial demographics of enrolled population not reported for nearly half of participants.	5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal.	6. Clinically significant difference for mean 24-h blood pressure observed only in adherent subgroup population. No clinically significant difference for mean office blood pressure observed in either adherent or non-adherent subgroup analyses.	3. Short duration of blinded follow-up for primary efficacy outcome (6 months).
SPYRAL HTN-ON MED Expansion	4. Low enrollment of women and racial demographics of enrolled population not reported for nearly half of participants.	5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal. Different rates of hypertension medication changes in renal denervation and sham groups post-randomization.	6. Clinically significant difference for mean office blood pressure only observed; no difference in primary 24-hr blood pressure. Sub-group analysis shows discordant BP reductions for US and non-US participants on primary outcome.	3. Short duration of blinded follow-up for primary efficacy outcome (6 months).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.
RFA: Radiofrequency ablation.

Table 8. Sham-Controlled Study Design and Conduct Limitations

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Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
SPYRAL HTN-OFF MED Pilot					4. Unpowered pilot study.	
SPYRAL HTN-OFF MED Pivotal						
SPYRAL HTN-ON MED Pilot				4-5. Inadequate handling of crossovers with inappropriate exclusion of blood pressure measurements at crossover. LOCF may not be the most appropriate approach.	4. Unpowered pilot study.	.
SPYRAL HTN-ON MED Expansion				4-5. Inadequate handling of crossovers with inappropriate exclusion of blood pressure measurements at crossover. LOCF may not be the most appropriate approach.	4. Unpowered key secondary endpoint of change in office BP.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.
LOCF: last observation carried forward.

Global Symplicity Registry

The Global Symplicity Registry (GSR) is a prospective, multi-center, single-arm, non-interventional and open-label registry that aims to document the long-term safety and effectiveness of renal denervation in a real-world population. Since 2012, a total of 3,077 patients have been enrolled in the GSR, but this includes a larger proportion of patients with the first-generation Symplicity Flex catheter. A subset of patients treated with the second-generation Symplicity Spyral device (n=846) was considered for this review. However, only a small group of these patients have 24-h SBP measurements, and fewer still have longer-term follow-ups. Patients generally had more co-morbidities and a greater baseline level of anti-hypertensive medications (mean 4.8) than those included in the Symplicity HTN-ON MED and HTN-OFF MED trials. Significant improvements from baseline in 24-hour ambulatory SBP and office SBP were observed at 6 months, 12 months, 24 months, and 36 months follow-up (Table 9). The magnitude of change in blood pressure from baseline was greater than that observed in sham-controlled trials, which may be suggestive of a potential placebo effect.

A stratified analysis of the GSR (n=2746 evaluable patients) by the number of antihypertensive medications taken (0 to 3, or ≥3) was published by Mahfoud et al (2023). At 36 months post-treatment, office SBP significantly decreased by -19.0 ± 28.3 in the 0 to 3 medication group and -16.2 ± 28.6 mmHg in the ≥4 group (p<.0001). Similarly, 24-h SBP was also significantly (p<.0001) decreased in both the 0 to

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3 and ≥4 medication groups (-10.7 ± 19.7 and -8.9 ±2 0.5 mmHg), respectively with a similar magnitude of decrease in both groups. The overall composite adverse event rate was 11.1%, consisting of 2.4% spontaneous myocardial infarction, 4.6% stroke, 3.9% hospitalizations for new-onset heart failure, 2.9% cardiovascular death, and 5.7% all-cause death. Only the rate of myocardial infarction varied significantly between groups, with those taking 4 or more medication classes experiencing a higher myocardial infarction rate compared to those taking fewer medications (1.8% vs. 0.3%, p=.023).

Table 9. Outcomes of Global Symplicity Registry

Outcome	Baseline Blood Pressure	6 Months	12 Months	24 Months	36 Months
24-h SBP MD±SD, N	155.20 ± 20.10, N=542	-7.69 ± 18.72, N=289	-8.77 ± 18.04, N=242	-8.83 ± 17.96, N=l32	-14.39 ± 2 1.93, N=74
24-h DBP MD±SD, N	88.10± 15.18, N=542	-4.88 ± 10.76, N=289	4.90 ± 10.62, N=242	-4.42 ± 10.05, N=l32	-6.12 ± 12.33, N=74
Office SBP MD±SD, N	165.83 ± 24.82, N=792	-14.23 ± 25.76, N=517	-15.18±26.54, N=475	-13.99 ± 27.59, N=331	-18.07 ± 26.76, N=200
Office DBP MD±SD, N	91.19 ± 17.44, N=792	-5.52 ± 14.07, N=515	-6.42 ± 14.77, N=473	-7.67 ± 15.06, N=326	-7.79 ± 15.68, N=195

MD: mean difference; SBP: systolic blood pressure; SD: standard deviation

Section Summary: Radiofrequency Ablation Denervation

Several RCTs have compared multielectrode renal denervation to sham with or without concomitant antihypertensive drug therapy for the treatment of a broader population of individuals with mild to moderate uncontrolled and combined systolic-diastolic hypertension. The SPYRAL HTN-OFF MED Pivotal trial found significant between-group differences of -4.0 mmHg for 24-h SBP and -6.6 mmHg for office SBP at 3 months, each meeting a posterior probability of superiority greater than 0.999. Investigators noted that these data provide biological proof of principle that renal denervation lowers blood pressure in untreated hypertensive patients, supporting prior data regarding the correlation between reduction in sympathetic tone and blood pressure reduction. It is unclear whether these trials results are generalizable to a real-world population. The SPYRAL HTN-ON MED pilot trial also found significant between-group differences of -7.4 mmHg for 24-h SBP and -6.8 mmHg for office SBP at 6 months for the overall population in favor of renal denervation. However, the 24-h SBP results were only significant for the subgroup of medication non-adherent patients. Subgroup analyses of both the non-adherent and adherent populations failed to find a significant between-group difference for office SBP and DBP. Long-term data from the SPYRAL HTN-ON MED study suggest that blood pressure reductions with multielectrode renal denervation are progressive and sustained over time, with between-group differences of -10.0 mmHg for 24-h SBP and -11.8 for office SBP for the overall population at 36 months. These differences lost significance without imputation. The SPYRAL HTN-ON MED Expansion study did not meet its primary effectiveness endpoint. No difference in 24-h SBP (0.03 mmHg) between the renal denervation and sham groups in HTN-ON MED was observed, although there was a significant difference in reduction for office SBP (4.1 mmHg), which favored the renal denervation group. Several confounders may have impacted the HTN-ON MED outcomes, including unbalanced medication changes between the 2 treatment groups, unbalanced missing 24-h SBP data, and timing of antihypertensive medication related to ABPM monitoring. Study interpretation is also complicated by short-term blinded follow-up and imputation of excluded crossover patient data, and it is unclear which patients are most likely to derive benefit. Currently, there is no practical method to verify nerve destruction following ablation. A safety analysis on a subset of HTN-ON and HTN-OFF MED participants found only 0.4% had a major adverse

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event at 1 month follow-up and met its pre-specified performance goal. pooled patient-level analysis of 4 RCTs with 3-year follow-up demonstrated a sustained and statistically significant reduction in both office SBP (−4.7 mmHg) and 24-h SBP (−3.6 mmHg) in the renal denervation group compared to sham, with a low incidence of adverse events.

Ultrasound Renal Denervation

Clinical Context and Therapy Purpose

The purpose of ultrasound renal denervation in individuals who have uncontrolled hypertension is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hypertension that is uncontrolled despite the use of antihypertensive medications or who poorly tolerate blood pressure lowering therapy. There is no widely accepted definition of uncontrolled hypertension. Furthermore, in real-world settings, it is difficult to distinguish uncontrolled hypertension from poor medication adherence.

Interventions

The therapy being considered is ultrasound renal denervation. Ultrasound renal denervation is a minimally invasive procedure performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery and ultrasound energy is delivered circumferentially to the arterial walls to thermally ablate and disrupt the renal sympathetic nerves.

Comparators

The following therapy is currently being used to treat those with uncontrolled hypertension: continued medical therapy.

Outcomes

The general short-term outcomes of interest (follow-up to at least 6 months) are a change in systolic and diastolic blood pressure (SBP and DBP) and medication use. Blood pressure measurements may include daytime ambulatory blood pressure, 24-hour average SBP, and office SBP.

A longer-term outcome of interest (follow-up to at least 3 years) is the effect on cardiovascular outcomes such as myocardial infarction and stroke.

Table 10. Outcomes of Interest for Individuals with Hypertension

Outcomes	Details	Timing
Morbid events	Outcomes of interest include adverse events such as end-stage renal disease, and embolic events resulting in end-organ damage, renal artery or other vascular complications, or hypertensive crisis.	≥30 days

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Treatment-related morbidity	Outcomes of interest include decrease in daytime ambulatory SBP, nighttime SBP, and 24-hour average SBP	≥30 days

SBP: systolic blood pressure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Azizi et al (2023) reported findings from a pooled analysis of the RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and RADIANCE II trials, which included 506 patients randomized to ultrasound renal denervation (usRDN, n=293) or sham procedure (n=213). The characteristics of the review are summarized in Table 11, and the key results are summarized in Table 12. Patients had mild to moderate or resistant hypertension, with baseline daytime ambulatory systolic blood pressure (SBP) of 150.5 ± 9.8 mmHg. From 2-6 months post-procedure, standardized antihypertensive treatment (AHT) was added if monthly home BP was ≥135/85 mmHg. At 6 months, fewer usRDN patients required added AHT (66.3% vs 77.0%; p=.002). After adjustment for baseline SBP and number of AHT medications, the between-group difference in daytime ambulatory SBP at 6 months favored usRDN by -3.0 mmHg (95% CI, -5.7 to -0.2; p=.033). Adjusted differences for home and office SBP also favored usRDN (-5.4 mmHg and -5.2 mmHg, respectively, p<.001 for both). No significant heterogeneity was detected between trials for these outcomes according to the I^2 statistic. Adverse events were infrequent and similar between groups.

Table 11. Characteristics of Pooled Analysis of Sham-Controlled Trials Assessing Ultrasound Renal Denervation

Study	Dates	Trials	N (Range)	Design	Duration, mo
Aziz et al. 2024	2018-2023	3 (RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, RADIANCE II)	506 (136-150)	RCT	2 - 6

RCT: randomized controlled trial.

Table 12. Pooled Analysis Results for Sham-Controlled Trials Assessing Ultrasound Renal Denervation

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Study	Daytime ambulatory SBP, mean change from BL (95% CI)	Daytime ambulatory SBP, mean change from BL (95% CI)	Home SBP, mean change from BL (95% CI)	OfficeSBP, mean change from BL (95% CI)	Safety, n
Aziz et al. 2024	**2 months**	**6 months**			
usRDN	-10.2 (-11.7 to -8.7)	-13.1 (-14.6 to -11.5)	NR	NR	Site reported AE: 8
Sham	-4.2 (-5.8 to -2.6)	-10.1 (-12.0 to -8.3)	NR	NR	Site reported AE: 9
SMD (95% CI), p (adjusted for BL value and # of antihypertensive medications)	-6.0 (-8.6 to -3.3), p<.0001	-3.0 (-5.7 to -0.2), p=.033	-5.3 (-6.69 to -3.91), p<.0001	-5.16 (-7.01 to -3.31), p<.001	

*Value reflects comparison group for network meta-analysis not I^2

AE: Adverse event; CI: confidence interval; DBP: diastolic blood pressure; NR: not reported; NS: not significant; RD: renal denervation; SBP: systolic blood pressure; SMD: standardized mean difference; SS: statistically significant; usRDN: ultrasound renal denervation.

Randomized Controlled Trials

Characteristics and results of RCTs are summarized in Tables 13 and 14.

Fengler et al (2019) conducted the RADIOSOUND-HTN trial, comparing three renal denervation techniques in 120 patients with resistant hypertension: radiofrequency ablation (RFA) of main renal arteries (n=39), RFA of main arteries plus branches (n=39), and ultrasound-based ablation of main arteries (usRDN, n=42). The mean age was 63.5 years, 69% were male, and the mean estimated glomerular filtration rate (eGFR) was 77.4 mL/min/1.73 m^2. At 3 months, the primary endpoint of change in daytime ambulatory SBP differed significantly between groups, with usRDN showing superiority over RFA renal denervation of the main renal arteries, but RFA of the main arteries plus branches did not differ between groups. Response rates (≥5 mmHg decrease at 3 months) were similar across groups. Minor procedural safety incidents occurred but were resolved without lasting effects. Adverse events during follow-up included cases of symptomatic hypotension, hypertension requiring treatment, and 1 death unrelated to the procedure.

Azizi et al (2022) published findings from the RADIANCE-HTN TRIO trial, in which 136 patients with resistant hypertension were randomized to usRDN (n=69) or a sham procedure (n=67). Eligibility criteria included daytime ambulatory BP ≥135/85 mmHg after 4 weeks of single-pill triple combination treatment, with an eGFR of ≥40 mL/min/1.73 m^2. From 2-5 months post-procedure, standardized AHT was initiated if monthly home BP was ≥135/85 mmHg. The mean age was 52.4 years, 80.6% were male, 16.1% self-identified as Black or African American, and mean eGFR was 81.5 mL/min/1.73 m^2. At 2 months follow-up, usRDN showed greater reductions in daytime ambulatory SBP compared to the sham procedure, with a median between-group difference of -4.5 mmHg (95% CI, -8.5 to -0.3; p=.022). At 6 months post-treatment, fewer AHT medications were added in the usRDN group (mean 0.7 vs. 1.1; p=.045), and fewer usRDN patients received aldosterone antagonists (40.0% vs. 60.9%; p=.02). Mean daytime ambulatory SBP at 6 months was similar between groups (138.3 vs. 139.0 mmHg). However, home SBP was lowered to a greater extent with usRDN by 4.3 mmHg (95% CI 0.5 to 8.1; p=.03) in a model adjusting for baseline and medications. Out-of-office BP control was achieved more frequently with uRDN (Odds Ratio [OR], 10.0, 95% CI 2.7-37.2; p=0.03 for home BP; OR 1.8, 95% CI 0.9 to 3.6; p=.07 for daytime ambulatory

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BP). Adverse events were infrequent and similar between groups. The FDA's summary of safety and effectiveness data demonstrated sustained benefits at 24 months follow-up. The ultrasound renal denervation (usRDN) group showed a reduction in office SBP of approximately 13 mmHg, compared to only 3 mmHg in the sham control group. Additionally, usRDN patients required fewer blood pressure medications, averaging 3.31 medications compared to 4.05 in the sham group.[24,] Bloch et al (2024) published 36 month data for 49 (71%) of usRDN arm participants in the trial, but did not report any information for the sham-controlled patients.[25,] A significant reduction in office SBP from baseline was noted (-8 ± 24.5 mmHg; p=.007) with patients who were on a mean of 3.7 anti-hypertensive medications.

Kario et al (2022) published findings from the REQUIRE trial, in which 143 patients from Japan or South Korea with resistant hypertension were randomized to usRDN (n=72) or a sham procedure (n=71). Eligibility criteria included office SBP ≥150 mmHg and 24-hour ambulatory systolic blood pressure ≥140 mmHg despite treatment with ≥3 AHT medications. The mean age was 53 years, 74% were male, and mean eGFR was 74.2 mL/min/1.73 m^2. The primary endpoint was change in 24-h ambulatory SBP at 3 months. At 3 months, the reduction in 24-h ambulatory SBP was not significantly different between the renal denervation (-6.6 mmHg) and sham control (-6.5 mmHg) groups (mean difference [MD], -0.1 mmHg, 95% CI -5.5 to 5.3; p=.971). Reductions in home and office SBP were also not significantly different between groups. The procedure was safe with no major device-related or procedure-related adverse events. While the BP reduction in the renal denervation group was similar to other sham-controlled studies, the sham group showed a much greater reduction than expected.

Azizi et al (2023) published findings from the RADIANCE II trial, in which 224 patients were randomized to usRDN (n=150) or sham treatment (n=74). Eligibility criteria included office SBP ≥140 mmHg and DBP ≥90 mmHg despite taking up to 2 antihypertensive medications, and ambulatory SBP/DBP ≥135/85 mmHg and <170/105 mmHg after a 4-week medication washout. Patients had an eGFR ≥40 mL/min/1.73m^2 and suitable renal artery anatomy. Patients were instructed to stop taking blood pressure medications for 2 months post-procedure unless their blood pressure exceeded specific thresholds. The mean age of participants was 55 years, 28.6% were female, and 16.1% self-identified as Black or African American. More patients in the sham group (13.5% vs. 8.0%) received AHT medications before 2 months. The primary efficacy outcome of mean daytime ambulatory SBP change from baseline to 2 months follow-up was significantly reduced by -7.9 mmHg with usRDN versus -1.8 mmHg with sham, with a baseline-adjusted between-group difference of -6.3 mmHg (95% CI, -9.3 to -3.2 mmHg; p<.001). Six of 7 secondary BP outcomes significantly favored renal denervation: 24-h ambulatory SBP, home SBP, office SBP, daytime ambulatory DBP, 24-hour ambulatory DBP, and home DBP. Only office DBP did not reach statistical significance. The BP-lowering effect was consistent across subgroups and throughout the 24-hour period. No major adverse events occurred in either group. A total of 64.1% in the usRDN group had a ≥ 5 mmHg reduction in daytime ambulatory SBP at 2 months versus 34.2% in the sham group. The FDA's summary of safety and effectiveness data showed that at 6 months, both groups achieved similar reductions in office SBP of approximately 22 mmHg. However, patients who received usRDN achieved this blood pressure reduction while using fewer antihypertensive medications compared to the sham control group (1.33 vs.1.73 medications).

Azizi et al reported findings from the RADIANCE-HTN SOLO trial, in which 146 patients with combined systolic-diastolic hypertension were randomized to endovascular ultrasound renal denervation (n=74) or a sham procedure (n=72).[28,] Eligibility criteria included daytime ambulatory SBP ≥135/85 mmHg and <170/105 mmHg after a 4-week discontinuation of up to 2 AHT medications. Participants were to remain off AHT medications throughout the 2 months of follow-up unless specified BP criteria were exceeded. The mean age was 54 years, 58% were male, 17% self-identified as Black or African American, and the mean eGFR was 84 mL/min/1.73 m^2. The primary endpoint was change in daytime ambulatory systolic BP at 2 months. At 2 months, the reduction in daytime ambulatory SBP was greater with usRDN (-8.5 mmHg) versus sham (-2.2 mmHg) (adjusted MD, -6.3 mmHg; p=.0001). Between 2-5 months, a

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standardized stepped-care AHT treatment protocol was implemented while maintaining blinding. At 6 months, mean daytime ambulatory BP remained lower in the usRDN group, with fewer medications required (0.9 vs. 1.3; p=.010).

At 12 months, following unblinding at 6 months, the BP-lowering effect of usRDN was maintained with fewer prescribed medications compared to sham. The proportion of patients on ≥2 medications (27.7% vs. 44.8%; p=.041), mean number of medications (1.0 vs. 1.4; p=.015), and defined daily medication dose (1.4 vs. 2.2, p=.007) remained lower with usRDN versus sham. The decrease in daytime ambulatory SBP from baseline in the usRDN group (-16.5 mmHg) remained stable at 12 months. Follow-up data from 36 months was reported for 51 (69%) of usRDN group participants; the authors found that office SBP had a 17.7 mmHg decrease (p<.001) and DBP had a 11.3 mmHg decrease from mean baseline BP. The authors reported that visit-to-visit variability in SBP was significantly smaller in the usRDN group across ambulatory, home, and office measurements. No significant differences in the rate of adverse events were observed through 12 months of follow-up. At the 36-month follow-up, the usRDN group had experienced 4 separate events: 1 case of renal artery stenosis requiring stent placement 6 months post-treatment, 1 right renal artery ostium issue 2 years post-procedure, 1 transient ischemic attack, and 1 hypertensive event.·The FDA's summary of safety and effectiveness data revealed sustained long-term benefits. At 2 and 3 years follow-up, the ultrasound renal denervation (usRDN) group showed blood pressure reductions of approximately 17 mmHg and 18 mmHg from baseline SBP, compared to 15 mmHg and 14 mmHg in the sham group. Additionally, after 3 years, usRDN patients required fewer blood pressure medications, averaging 1.28 medications compared to 1.79 in the sham group.

Table 13. RCT Characteristics

Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
				usRDN	Control	
RADIOSOUND-HTN	120	Paradise Recor ultrasound (n=42) vs. radiofrequency RDN with the Symplicity Spyral catheter (n=78) either with RFA RDN to the main branch (n=39) or to multiple branches (n=39). Two or more ultrasound emissions were delivered in the main right and left renal arteries.	Age 18-75 y with SBP > 135 on ABPM; participants were on 4 weeks of stable antihypertensive medications prior to enrollment	Mean Age: 64.6 Sex: Male, 76% Mean BMI: 32.6 Mean 24-h BP: 151.3/83 # antihypertensive drug classes: 5	Mean Age: 62.1 or 63.8 Sex: Male, 62% or 67% Mean BMI: 30.6 or 31.6 Mean 24-h BP: 147.4/83.6 or 150.6/83.5 # antihypertensive drug classes: 4.7 or 5.3	Change in daytime ambulatory SBP at 3 months
RADIANCE-HTN SOLO	146	Paradise Recor ultrasound (n=74) vs. sham (n=72) following 4-week AHT medication wash-out. Guideline-based stepped-care hypertensive	Age 18-75 y with office BP ≥ 140/90 and <180/110; EGFR ≥ 40 mL/min per 1.73m^2; patients were eligible if hypertension	Mean Age: 54.4 Sex: Male, 62% Mean BMI: 29.9 Mean office BP: 154.5/99.7 Mean 24-h BP: 142.6/87.3 Prior	Mean Age: 53.8 Sex: Male, 54% Mean BMI: 29 Mean office BP: 153.6/99.1 Mean 24-h BP: 143.8/88.6 Prior	Change in daytime ambulatory SBP at 2 months

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Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
		treatment began at 2 months if BP remained uncontrolled. Mean number of ultrasound emissions delivered was 5.4±1.	was controlled or uncontrolled on 0 to 2 antihypertensive medications	Medications: 0-2 antihypertensive medications; 1 participant in each group was found to be on 3 medications at BL	Medications: 0-2 antihypertensive medications; 1 participant in each group was found to be on 3 medications at BL	
RADIANCE-II	150	Randomized 1:1 to Paradise Recor ultrasound (n=150) vs. sham (n=74) following 4-week antihypertensive medication wash-out. Individuals remained off AHT medications for 2 months as long as BP was controlled. Participants remained masked to treatment allocation through 6 months follow-up. Mean number of ultrasound emissions delivered was 5.6.	Aged 18 to 75 years with office BP ≥ 140/90 despite 2 or more antihypertensive medications; eGFR ≥ 40 mL/min/1.73 m^2	Mean Age: 55.1 Sex: Male, 68.7% Mean BMI: 30.1 Mean office BP: 155.8/101.3 Prior Medications: 1: 38.5% 2: 32.3% ≥2: 0%	Mean Age: 54.9 Sex: Male, 77% Mean BMI: 30.6 Mean office BP: 154.3/99.1 Prior Medications: 1: 33.8% 2: 33.8% ≥2: 1.4%	Change in daytime ambulatory SBP at 2 months
RADIANCE-HTN TRIO[,]	136	Paradise Recor ultrasound (n=65) vs. sham (n=64); at enrollment all participants switched to standard AHT regimen (single-pill, fixed-dose, daily combination of valsartan, 160 mg (or olmesartan, 40 mg), amlodipine, 10 mg (or 5 mg in the event of severe leg edema), and hydrochlorothiazide, 25 mg). Guideline-based stepped-care hypertensive treatment began at 2 months if BP remained	Aged 18 to 75 years with office BP ≥ 140/90 despite 3 or more antihypertensive medications; eGFR ≥ 40 mL/min/1.73 m^2	Mean Age: 51.9 Sex: Male, 82% Mean BMI: 32.8 Mean office BP: 161.7/104.9 Prior Medications: 3: 38.5% 4: 32.3% 5: 29.2%	Mean Age: 53 Sex: Male, 80% Mean BMI: 32.7 Mean office BP: 163.3/102.8 Prior Medications: 3: 42.2% 4: 35.9% 5: 21.9%	Change in daytime ambulatory SBP at 2 months

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Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
		uncontrolled. Mean number of ultrasound emissions delivered was 5.8±1.2.				
REQUIRE	143	Paradise Recor ultrasound (n=72) vs. sham (n=71) following 4-week AHT medication wash-out. Two or more ultrasound emissions were delivered in the main right and left renal arteries.	Aged 20 to 75 years with office BP ≥ 150/90 and 24-hr ambulatory BP ≥140 despite ≥ 3 antihypertensive medications from different classes including a diuretic; eGFR ≥ 40 mL/min/1.73 m^2. The study population was recruited from multiple centers in Japan and Korea.	Mean Age: 50.7 Sex: Male, 69.6% Mean BMI: 29.5 Mean office BP: 157.6/97.7 Prior Medications: 3: 46.4% 4: 29% ≥5: 24.6%	Mean Age: 55.6 Sex: Male, 79.1% Mean BMI: 28.4 Mean office BP: 160.4/95.3 Prior Medications: 3: 43.3% 4: 34.3% ≥5: 22.4%	Change in ambulatory SBP at 3 months

ABPM: ambulatory blood pressure monitoring; AHT: antihypertensive; BP: blood pressure; BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; NR: not reported; RDN: renal denervation; RFA: radiofrequency ablation; SBP: systolic blood pressure; usRDN: ultrasound renal denervation.

Table 14. Primary RCT Results

Trial	Daytime ambulatory SBP Change, mmHg (SD or 95% CI)	Daytime ambulatory DBP Change, mmHg (SD or 95% CI)	24-h ambulatory SBP Change, mmHg (SD or 95% CI)	24-h ambulatory DBP Change, mmHg (SD or 95% CI)
RADIOSOUND-HTN[22,]	**3 months**			
usRDN	-13.2	~-8	~-12	~-7
RFA RDN main artery	-6.5	~-3.5	~-5.2	~-3
RFA RDN main artery and branches	-8.3	~-6	~-7	~-6
p	.043 for usRDN vs RFA of main artery >.99 for usRDN vs RFA of main artery and branches	.025 for usRDN vs RFA of main artery NS for usRDN vs RFA of main artery and branches	.029 for usRDN vs RFA of main artery NS for usRDN vs RFA of main artery and branches	.015 for usRDN vs RFA of main artery NS for usRDN vs RFA of main artery and branches
RADIANCE-HTN SOLO[27,29,30,]	**2; 6; and 12**			

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Trial	Daytime ambulatory SBP Change, mmHg (SD or 95% CI)	Daytime ambulatory DBP Change, mmHg (SD or 95% CI)	24-h ambulatory SBP Change, mmHg (SD or 95% CI)	24-h ambulatory DBP Change, mmHg (SD or 95% CI)
usRDN	-8.5 ± 9.3; -18.1 ± 12.2; -16.5 ± 12.9;	-5.1 ± 5.9; −10.7±7.8; -9.8 ± 8.3	-7.0 ± 8.6; -16.5±11.8; -15.1 ± 12.4	-4.4 ± 5.8; -9.7 ±7.3;
Sham	-2.2 ± 10.0; -15.6 ± 13.2; -15.8 ± 13.1	-2.6 ± 6.5; −9.7±8.1; -9.6 ± 7.9;	-90.9 ± 7.9; -14.9±12.8; -15.3 ± 12.4	-3.0 ± 6.1; -9.4 ± 7.8;
MD (95% CI), p (adjusted for BL value and # of antihypertensive medications)	-6.3 (-9.4 to -3.1), p=.0001; -4.3 (-7.9 to -0.6), p=.024; -2.3 (-5.9 to 1.3), p=.201	-2.6 (-4.6 to -0.6), p=.01; −1.3 (-3.7 to 1.2), p=.018; -2.0 (-4.3 to 0.4), p=.103	-2.6 (-4.6 to -0.6), p=.01; -4.3 (-7.7 to -1.0), p=.012; -2.4 (-5.8 to 0.9), p=.156	-1.8 (-3.7 to 0.2), p=.07: -2.6 (-4.6 to -0.5), p=.017; -1.7 (-3.9 to 0.6), p=.142
RADIANCE-II[28]	**2 months**			
usRDN	-7.9 ± 11.3	-5.4 ± 6.5	-7.7 ± 10.7	-5.3 ± 6.4
Sham	-1.8 ± 9.5	-1.3 ± 5.7	-1.7 ± 9.3	-1.2 ± 5.4
MD (95% CI), p (adjusted for BL values and multiple imputations for missing data)	-6.3 (-9.3 to -3.2), p <.001	-3.9 (-5.6 to -2.2), p <.001	-6.2 (-9.1 to -3.4), p <.001	-4.1 (-5.7 to -2.4), p<.001
RADIANCE-HTN TRIO[23,32]	**2 months; 6 months (additional decrease from 2 months)**			
usRDN	-8.0 (-16.4 to 0.0); -2.4 ± 16.6	-4.9 (-10.4 to 0.0)	-8.5 (-15.1 to 0.0)	-5·4 (-10.4 to 0.0)
Sham	-3.0 (-10.3 to 1.8); -7.0 ± 16.7	-2.0 (-7.8 to 1.0)	-2.9 (-12.6 to 2·5)	-2·4 (-7.8 to 0.5)
MD (95% CI), p (adjusted for BL value and # of antihypertensive medications)	-4.5 (-8.5 to -0.3), p=.022; -2.5 (-6.7 to 1.7), p=.25	-1.8 (-4.5 to 0.8), p=.18	-4.2 (-8.3 to -0.3), p=.016	-2·0 (-4.5 to 0.6), p=.12
REQUIRE [33]	**3 months**		**Home SBP 1 month; 3 months**	
usRDN	-6.6 (-10.4 to -2.8)		-10.2; -8.7	
Sham	-6.5 (-10.3 to -2.7)		-4.8; -6	
MD (95% CI), p (adjusted for BL value and # of antihypertensive medications)	-0.1 (-5.5 to 5.3), p=.971		p=.046; p=.488	

ABPM: ambulatory blood pressure monitoring; BL: baseline; BMI: body mass index; BP: blood pressure; CI: confidence interval; DBP: diastolic blood pressure; NR: not reported; RDN: renal denervation; RFA: radiofrequency ablation; SBP: systolic blood pressure; usRDN: ultrasound renal denervation. ~indicates value estimated from figure

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RCT study relevance, design, and conduct limitations are summarized in Tables 15 and 16 below.

Table 15. RCT Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
RADIOSOUND-HTN	3. Study population not representative of intended use (only larger renal artery diameters were included and single center experience) 4. Racial demographics not reported.	5. Number of ultrasound emissions not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal. Different rates of hypertension medication changes in ultrasound and radiofrequency renal denervation groups post-randomization. Adherence to medication measured by self-reporting only.	6. Clinically significant difference for blood pressure outcomes observed only versus radiofrequency renal denervation of main artery and not for radiofrequency renal denervation of the main artery and branches.	3. Short duration of follow-up (3 months).
RADIANCE-HTN SOLO	3. Study population not representative of intended use	5. Number of ultrasound emissions not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal. Different rates of hypertension medication changes in renal denervation and sham groups at 6 months post-randomization. Adherence to antihypertensive medication was not measured.		3. Short duration of blinded follow-up for primary efficacy outcome (6 months). Follow-up of trial population for 36 months in FDA SSED post-treatment.
RADIANCE-II	3. Study population not representative of intended use; 4. Low enrollment of women.	5. Number of ultrasound emissions not standardized and no practical methods to verify nerve destruction are available.			3. Short duration of follow-up (6 months).
RADIANCE-HTN TRIO		5. Number of ultrasound emissions not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal. Different rates of hypertension medication changes in renal denervation and sham groups at 6 months post-randomization.		3. Short duration of blinded follow-up for primary efficacy outcome (6 months). Follow-up of trial population

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
					for 24 months in FDA SSED post-treatment and 36 months in the usRDN group only in a subsequent publication.
REQUIRE	4. Enrolled populations are only from Japan and South Korea	5. Number of ultrasound emissions not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal. Adherence to medication measured by self-reporting only.		3. Short duration of follow-up (3 months).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 16. RCT Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
RADIOSOUND-HTN		1. Study staff not blinded				
RADIANCE-HTN SOLO		1. Study staff not blinded		1. High loss to follow-up at 36 months post-treatment	4. Per-protocol analyses fell below the number of participants calculated in power calculations for the primary outcome	
RADIANCE-II		1. Study staff not blinded				
RADIANCE-HTN TRIO		1. Study staff not blinded				

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Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
REQUIRE		1. Study staff not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Ultrasound Renal Denervation

Ultrasound renal denervation (usRDN) has been evaluated in individuals with uncontrolled hypertension despite antihypertensive therapy through several randomized controlled trials, including sham-controlled studies, a comparison with radiofrequency-based renal denervation, and pooled analyses. Two trials, RADIANCE-HTN SOLO and RADIANCE II evaluated usRDN in individuals with no antihypertensive medication usage for 2 months post-intervention. The RADIANCE-HTN SOLO trial demonstrated that usRDN was superior to sham, with a between-group difference of -6.3 mmHg for daytime ambulatory systolic blood pressure (SBP) at 2 months. The RADIANCE II trial showed similar results, also showing a -6.3 mmHg difference in daytime ambulatory SBP at 2 months. The RADIANCE-HTN TRIO trial, focusing on resistant hypertension in individuals with a standardized triple combination antihypertensive treatment, found a -4.5 mmHg difference in daytime ambulatory SBP at 2 months. The durability of this effect was confirmed over 36 months of open-label follow-up, with significant reductions in office SBP from baseline levels in the usRDN group. The REQUIRE trial, conducted in Asian populations, did not show a significant difference between usRDN and sham control, possibly due to study design limitations. Long-term data from these trials show mixed results: while studies suggest that BP reductions with usRDN are sustained over time, the differences between usRDN and sham control groups diminished at 6 or 12 months after medication titration in some trials. However, the FDA's summary of safety and effectiveness data for the RADIANCE-HTN TRIO and SOLO trials demonstrated superior office systolic blood pressure reductions with usRDN compared to sham control at 24 and 36 months, respectively. Notably, these improved outcomes in the usRDN group were achieved despite patients using fewer antihypertensive medications than the sham control group. A meta-analysis of the sham-controlled RADIANCE trials showed that fewer usRDN individuals required additional antihypertensive medications and demonstrated significant reductions in ambulatory, home, and office SBP at 6 months. Adverse events were infrequent and similar between usRDN and sham groups across studies. The RADIOSOUND-HTN trial compared 3 renal denervation techniques in individuals with resistant hypertension who were on a stable regimen of antihypertensive medications. The trial found that usRDN showed superiority over radiofrequency ablation (RFA) of main renal arteries in reducing daytime ambulatory SBP at 3 months, while RFA of main arteries plus branches did not significantly differ from the other groups.

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SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology

In 2025, the 2017 joint committee guideline by the ACC/AHA/AANP/AAPA/ABC/ACCP/AGS/AMA/ASPC/NMA/PCNA/SGIM was updated for the prevention, detection, evaluation and management of high blood pressure in adults, which included the following new recommendations regarding resistant hypertension and renal denervation:

- "In carefully selected patients with systolic and diastolic hypertension (office SBP 140-180 mm Hg and DBP $\geq$ mm Hg) and eGFR $\geq$ 40 mL/min/1.73 m^2 who have resistant hypertension despite optimal treatment, or intolerable side effects to additional antihypertensive drug therapy, renal denervation (RDN) may be reasonable as an adjunct treatment to BP medications and lifestyle medication to reduce BP." (2b [Weak])
- "All patients with hypertension who are being considered for RDN should be evaluated by a multidisciplinary team with expertise in resistant hypertension and RDN." (B-NR [Nonrandomized])
- For patients with hypertension for whom RDN is contemplated, the benefits of lowering BP and potential procedural risks compared with continuing medical therapy should be discussed as part of shared decision-making process to ensure patients choose the therapy that meets their expectations." (C-EO [Expert Opinion])

American Heart Association

In 2024 the American Heart Association (AHA) published a Scientific Statement on renal denervation for the treatment of hypertension in which they concluded the following:

- "Although further research is needed, particularly in the realms of patient selection and long-term efficacy, renal denervation is a promising new therapeutic approach for some patients with uncontrolled hypertension, particularly patients with resistant hypertension who have multiple medication intolerances.
- 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.
- A multidisciplinary team approach that includes hypertension specialists and proceduralists is important both for identifying the right candidates for renal denervation and for following them after the procedure.

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- Much if not all of our current literature and experience with renal denervation in the United States have been in the context of clinical trials. Therefore, little is currently known about the cost of renal denervation as it compares with conventional treatment options, many of which are now generic and lower-cost pharmacological options."

European Society of Cardiology

The European Society of Cardiology (ESC) published guidelines on the management of elevated blood pressure and hypertension in 2024. The following recommendations were issued concerning renal denervation:

- "To reduce BP, and if performed at a medium-to-high volume center, catheter-based renal denervation may be considered for resistant hypertension patients who have BP that is uncontrolled despite a three BP-lowering drug combination (including a thiazide or thiazide-like diuretic), and who express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment. (Class: IIb, Level: B)
- To reduce BP, and if performed at a medium-to-high volume center, catheter-based renal denervation may be considered for patients with both increased CVD risk and uncontrolled hypertension on more than three drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment. (Class: IIb, Level: A)
- Due to a lack of adequately powered outcomes trials demonstrating its safety and CVD benefits, renal denervation is not recommended as a first-line BP-lowering intervention for hypertension. (Class: III, Level: C)
- Renal denervation is not recommended for treating hypertension in patients with moderate-to-severely impaired renal function (eGFR < 40 mL/min/1.73 m²) or secondary causes of hypertension, until further evidence becomes available. (Class: III, Level: C)"

European Society of Cardiology (ESC) Council on Hypertension and European Association of Percutaneous Cardiovascular Interventions (EAPCI)

In 2023, the ESC and EAPCI issued a clinical consensus statement regarding renal denervation in the management of hypertension in adults which included the following:

- “Renal denervation (RDN) may be used in adult patients with uncontrolled hypertension (office BP $\geq$ 140/$\geq$ 90 mmHg confirmed by 24-hour ambulatory systolic BP $\geq$ 130 mmHg or daytime systolic BP $\geq$ 135 mmHg) treated with $\geq$ 3 antihypertensive drugs and an eGFR $\geq$ 40 ml/min/1.73m^2.
- RDN may be a possible treatment option for patients unable to tolerate antihypertensive drugs in the long term or patients who express a preference to undergo RND in a tailored, shared decision-making process.
- The patient’s global CV risk should be evaluated, accounting for hypertension -mediated organ damage and CV complications. High CV risk favors the use of renal denervation.
- The decision-making process should incorporate the preference of a well-informed and educated patient. To optimize the shared decision-making, patients must be fully informed about the benefits/limitations and risks associated with renal denervation.
- Multidisciplinary hypertension teams involving experts on hypertension and percutaneous CV interventions should evaluate the indication and perform renal denervation.

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- Standard operating procedures are suggested for each device to achieve the most effective renal nerve ablation in optimal periprocedural patient security conditions.
- At present, there is no validated, easily applicable periprocedural clinical indicator of successful renal nerve ablation."

European Society for Hypertension (ESH)

The ESH, with endorsement by the European Renal Association and the International Society of Hypertension, issued guidance on the management of arterial hypertension in 2023. The following recommendations were issued concerning renal denervation:

- "Renal denervation can be considered as a treatment option in patients with an eGFR of > 40 ml/min/1.73m^2 who have uncontrolled blood pressure despite the use of anti-hypertensive drug combination therapy or if drug treatment elicits serious side effects. (Class of Recommendation: II, Level of Evidence: B)
- Renal denervation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is > 40 ml/min/1.73m^2. (Class of Recommendation: II, Level of Evidence: B)
- Selection of patients to whom renal denervation is offered should be done in a shared decision-making process after objective and complete patient information is collected. (Class of Recommendation: I, Level of Evidence: C)
- Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure. (Class of Recommendation: I, Level of Evidence: C)"

A class of recommendation I indicates a general consensus that the measure is useful, and a class II recommendation reflects that there is no general consensus and that only doubtful evidence exists. An 'A' level of evidence indicates that RCTs or meta-analyses with cardiovascular disease outcomes are available for this recommendation, a level 'B' suggests RCTs with surrogate measures, observational studies with cardiovascular disease outcomes or meta-analyses are available, and a C recommendation reflects either expert opinion or only observational or lower quality experimental evidence.

ESH recommendations did not discuss the specific use of radiofrequency renal denervation and included evidence from other modalities, such as ultrasound, in their evidence appraisal.

National Institute for Health and Care Excellence

In 2023, the National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance on the use of percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension, recommending that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research due to limited evidence. The guidance is scheduled for its next review in 2026.

Society for Cardiovascular Angiography and Interventions

In 2023, the Society for Cardiovascular Angiography & Interventions (SCAI) published a position statement on patient selection, operator competence, training and techniques, and organizational recommendations for the use of renal denervation for the treatment of hypertension. The following selection criteria were issued concerning renal denervation:

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- "Patients with resistant hypertension, defined by blood pressure >130/80 mmHg despite being on 3 medications with maximally tolerated doses from classes with outcomes data (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers)
- Patients with uncontrolled hypertension despite attempting lifestyle modification and antihypertensive medication but who are either intolerant of additional medication or do not wish to be on additional medications and who are willing to undergo renal denervation after shared decision-making
- Priority may be appropriately given to patients with higher cardiovascular risk (e.g., comorbidities of coronary artery disease, diabetes, prior transient ischemic attack/cerebrovascular accident, or chronic kidney disease) who may have the greatest benefit from blood pressure reduction"

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral

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Codes	Number	Description
	0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral
	0935T	Cystourethroscopy with renal pelvic sympathetic denervation, radiofrequency ablation, retrograde ureteral approach, including insertion of guide wire, selective placement of ureteral sheath(s) and multiple conformable electrodes, contrast injection(s), and fluoroscopy, bilateral (Verve RPD System)
HCPCS		
	C1735	Catheter(s), intravascular for renal denervation, radiofrequency, including all single use system components
	C1736	Catheter(s), intravascular for renal denervation, ultrasound, including all single use system components
Type of Service	Surgery	
Place of Service	Outpatient/Inpatient	

POLICY HISTORY

Date	Action	Action
September 2025	Annual Review	Policy Revised
February 2025	Annual Review	Policy Revised
January 2024		New Medical Policy

Appendix

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2025 Clinical Input

Objective

Clinical input was sought to help determine whether the use of renal denervation (RDN) in individuals with uncontrolled hypertension would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Kobayashi, Tai** , MD; Interventional Cardiology; Hospital of the University of Pennsylvania, identified by Society for Cardiovascular Angiography & Interventions (SCAI)
- Dmitry, Feldman, MD, FACC, FSCAI; Interventional Cardiology; Weill Cornell Medical College, identified by SCAI
- Uzoma N. Ibebuogu*, MD, FACC, FSCAI Cardiac Surgery; The University of Tennessee Health Science Center, identified by the American College of Cardiology (ACC)
- Cohen, Debbie**, MD; Hospital of the University of Pennsylvania, identified by Hospital of the University of Pennsylvania

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see below).

Ratings

			Confidence Level That Clinical Use is Expected to Provide a Clinically Meaningful Improvement in Net Health Outcome (Low – Intermediate – High)						Confidence Level That Clinical Use Is Consistent with Generally Accepted Medical Practice (Low – Intermediate – High)					
Clinical Indication	**Respondent**	**Identified by**	**Yes or No**	**1**	**2**	**3**	**4**	**5**	**Yes or No**	**1**	**2**	**3**	**4**	**5**
Radiofrequency ablation of the renal sympathetic nerves in individuals with uncontrolled hypertension despite the use of anti-hypertensive medications or who poorly tolerate blood pressure therapy	Dr. Kobayashi*	SCAI	Yes					■	Yes					■
	Dr. Feldman*	SCAI	Yes					■	Yes					■
	ACC		Yes					■	Yes					■
	Dr. Cohen*	Hospital of the University of Pennsylvania	Yes					■	Yes					■
Ultrasound ablation of the renal sympathetic nerves in individuals with uncontrolled hypertension despite the use of anti-hypertensive medications or who poorly tolerate blood pressure therapy	Dr. Kobayashi*	SCAI	Yes					■	Yes					■
	Dr. Feldman*	SCAI	Yes					■	Yes					■
	ACC		Yes					■	Yes					■
	Dr. Cohen*	Hospital of the University of Pennsylvania	Yes					■	Yes					■

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Respondent Profile

	Physician				
#	**Name**	**Degree**	**Institutional Affiliation**	**Clinical Specialty**	**Board Certification and Fellowship Training**
Identified by the Society for Cardiovascular Angiography & Interventions (SCAI)					
1	Kobayashi, Tai	MD	Hospital of the University of Pennsylvania	Interventional Cardiology	Cardiovascular Disease Interventional Cardiology
2	Dmitry, Feldman	MD, FACC, FSCAI	Weill Cornell Medical College, New York Presbyterian Hospital	Interventional Cardiology	Cardiovascular Disease Interventional Cardiology
Identified by The American College of Cardiology (ACC)					
3	Ibebuogu, Uzoma	MD, FACC, FSCAI	The University of Tennessee Health Science Center	Interventional Cardiology	Cardiovascular Disease Interventional Cardiology
Hospital of the University of Pennsylvania					
4	Cohen, Debbie*	MD	Hospital of the University of Pennsylvania	Interventional Cardiology and Nephrology	Cardiovascular Disease Interventional Cardiology and Nephrology

*Response given with Kobayashi, Tai

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	YES	Several research studies that utilize both of the current FDA approved	YES	I serve in an advisory role for Medtronic, Recor Medical	YES	please see response to answer 2	YES	please see response to answer 2

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#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
		platforms for renal denervation and another newer investigational renal denervation platform		and Sonivie Medical				
2	YES	Site PI, Spyral Affirm Study. Prior site PI of Spyral HTN ON MED trial.	NO		NO		NO	
3	NR	Input provided by the Renal Denervation coverage analysis workgroup.	NR		NR		NR	
4	YES	We have several research studies that utilize both of the current FDA approved platforms for renal denervation and another newer investigational renal denervation platform	YES	I receive research funding and serve in an advisory role for Medtronic, Recor Medical	YES	please see response to answer 2	YES	please see response to answer 2

NR: Not reported

Clinical Input Responses

Question 1. We are seeking your rationale on whether using radiofrequency ablation of the renal sympathetic nerves provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

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#	Rationale
1	SCAI has been instrumental in coordinating with leaders in the field and has been the first and most consistent society to publish guidelines for renal denervation in regards to patient eligibility considerations, work up and operator criteria for who should be undergoing/performing renal denervation that exist and should be incorporated into the coverage decisions. (PMID 39129887, 34343406)SCAI has felt that these guidelines were necessary and timely because of the discrepancy in language used by the US Food and Drug Administration's instructions for use for both device platforms and the strict criteria in how these devices were originally studied in research. In the SCAI guidelines, patient undergoing research trials underwent meticulous screening for secondary causes of hypertension, out of office blood pressure testing and seen by a multi-disciplinary hypertension group prior the procedure. Further, anatomical exclusions were set by the studies to exclude patients with fibromuscular dysplasia, renal artery aneurysms and significant renal artery stenosis. SCAI coordinated those instrumental to performing these research trials across both platforms to come up with a agreed upon expert consensus statement to help guide operators new to the field based upon experience and the above research trials.In these guidelines, the authors cover at least 8 randomized sham control trials investigating the use of renal denervation (both ultrasound and radiofrequency) that consistently show clinically meaningful drops in blood pressure in comparison to sham control. (PMID 322234534, 35390320, 29803589, 37914510, 29803590, 34010611, 36853627, 36350593) Previous randomized control trials show that even small drops in blood pressures can result in decreases in heart failure, deaths from cardiovascular causes and all cause mortality.(PMID 28564682, PMID 36223105) However, when these same patients came off trial protocol and returned to their baseline blood pressures, these mortality drops abated (PMID 36223105). Renal denervation offers a procedural method to lower blood pressures in a patient-independent manner creating an "always on" effect of being on at least one blood pressure medication. Long term registries in Europe (PMID 30907413) are showing not only durable blood pressure reductions but along the same scale of reductions seen in the SPRINT trial. These reductions in blood pressure have been modeled to reduce the rates of stroke and heart attack as well as mortality. (PMID 3605783).
2	Clinical trials have demonstrated the efficacy of RDN across a wide range of HTN severity, including patients with hypertension in whom medications have been withdrawn (SPYRAL HTN-OFF MED), and patients with more severe and resistant HTN (SPYRAL HTN-ON MED). 1. The efficacy of RDN for treatment of uncontrolled hypertensionhas been consistently demonstrated in sham-controlled, randomized trials both in the presence and absence of medications. 2. Current evidence with RDN suggests a constant reduction in BP over day and night ("always on" effect) that is distinct from pharmokinetic profiles and dosing regimens with medications and patient nonadherence. This observation may improve BP stability and TTR (time in target range). 3. Both randomized trials and registries support the early and late-term safety of RDN. 4. RDN is associated not only with improvements in BP but also reductions in medication number and/or dose. 5. Registry data suggest long-term durability in BP reduction following RDN. Longer-term surveillance of existing trials and additional studies may inform durability and impact on clinical outcome. References: 1. Kandzari DE, Townsend RR, Bakris G,Basile J, Bloch MJ, Cohen DL, et al. Renal denervation inhypertension patients: Proceedings from an expert consensusroundtable cosponsored by SCAI and NKF. CatheterCardiovasc Interv. 2021;98:416–26. 2. Swaminathan RV, East CA, Feldman DN, Fisher ND, Garasic JM, Giri JS, Kandzari DE, Kirtane AJ, Klein A, Kobayashi T, Koenig G, Li J, Secemsky E, Townsend RR, Aronow HD. SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations. J Soc Cardiovasc Angiogr Interv 2023 Aug 21;2(6Part A):101121. doi: 10.1016/j.jscai.2023.101121. 3. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renaldenervation in patients with uncontrolled hypertension in theabsence of antihypertensive medications (SPYRAL HTN-OFF MED): arandomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390:2160-2170. 4. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renaldenervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED pivotal): a multicentre, randomised, sham-controlledtrial. Lancet. 2020;395:1444-1451. 5. Kandzari DE, Böhm M, Mahfoud F, et al. SPYRAL HTN-ON MED TrialInvestigators. Effect of renal

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#	Rationale
	denervation on blood pressure in thepresence of antihypertensive drugs: 6-month efficacy and safetyresults from the SPYRAL HTN-ON MED proof-of-concept random-ised trial. Lancet. 2018;391:2346-2355. 6. Mufarrih SH, Qureshi NQ, Khan MS, Kazimuddin M, Secemsky E, Bloch MJ, Giri J, Cohen D, Swaminathan RV, Feldman DN, Alaswad K, Kirtane A, Kandzari D, Aronow HD. Randomized Trials of Renal Denervation for Uncontrolled Hypertension: An Updated Meta-Analysis. J Am Heart Assoc 2024 Aug 20;13(16):e034910. doi: 10.1161/JAHA.124.034910. 7. Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet. 2022;399(10333):1401–1410. https://doi.org/10.1016/S0140-6736(22)00455-X.
3	See attached.
4	There have been at least 8 randomized sham control trials investigating the use of renal denervation (both ultrasound and radiofrequency) that consistently show clinically meaningful drops in blood pressure in comparison to sham control. (PMID 322234534, 35390320, 29803589, 37914510, 29803590, 34010611, 36853627, 36350593) Please recall that even small drops in blood pressure can result in a large cardiovascular mortality change (PMID 28564682). In trials investigating the effect of blood pressure lowering and cardiovascular mortality such as the SPRINT trial, there were lower rates of heart failure, deaths from cardiovascular causes or death from any cause in the more intensive blood pressure arm achieved through medications. However, when the same group of patients were followed long term, most patients lost control of their blood pressure thus negating the early mortality effects due to a loss of adherence to blood pressure medication. (PMID 36223105)Renal denervation offers a procedural mechanism to lower blood pressures in a patient-independent manner creating an "always on" effect of being on at least one blood pressure medication. Long term registries in Europe (PMID 30907413) are showing not only durable blood pressure reductions but along the same scale of reductions seen in the SPRINT trial. These reductions in blood pressure have been modeled to reduce the rates of stroke and heart attack as well as mortality. (PMID 3605783).While the language from the US Food and Drug Administration's instructions for use for both device platforms are broad, consideration for how these devices were studies in research should be considered for coverage. Specifically, in the research trials cited above, patients underwent scrutinous screening for secondary causes of hypertension, out of office blood pressure testing and seen by a multi-disciplinary hypertension group prior the procedure. Further, anatomical exclusions were set by the studies to exclude patients with fibromuscular dysplasia, renal artery aneurysms and significant renal artery stenosis. Thus the need for a true multidisciplinary approach should be considered for eligibility prior to renal denervation. However, we would also caution to not limit to resistant hypertension alone given this may restrict the use of this life saving technology to a set of definitions not strictly studied in the research trials.Lastly, there are already societal guidelines for eligibility, work up and operator criteria for who should be undergoing/performing renal denervation that exist and should be incorporated into the coverage decisions. (PMID 39129887, 34343406)

- Respond YES or NO whether radiofrequency RDN would be expected to provide a clinically meaningful improvement in the indication; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Radiofrequency RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Radiofrequency RDN is consistent with generally accepted medical practice	Yes					X

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No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
2	Radiofrequency RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Radiofrequency RDN is consistent with generally accepted medical practice	Yes					X
3	Radiofrequency RDN results in a clinically meaningful improvement in net health outcome	Yes					
	Radiofrequency RDN is consistent with generally accepted medical practice	Yes					
4	Radiofrequency RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Radiofrequency RDN is consistent with generally accepted medical practice	Yes					X

Question 2. Would you agree that the following criteria for identifying individuals for radiofrequency ablation of the renal sympathetic nerves are clinically appropriate?

- Blood pressure >130/80 mmHg despite use of 3 or more antihypertensive medications from 3 classes at maximally tolerated doses; OR
- With intolerance to antihypertensive medications whose blood pressure remains uncontrolled despite attempting lifestyle modifications.

#	Yes/No	Rationale
1	Yes	The patient criteria represent both populations studied in the research for RDN.
2	No	Given that RCT data for patients on and off meds have confirmed BP benefits, criteria should also include:Patients with uncontrolled hypertension despite attempting lifestyle modification and antihypertensive medication but who are either intolerant of additional medication or do not wish to be on additional medications and who are willing to undergo renal denervation after shared decision-making.Priority may be appropriately given to patients with higher cardiovascular risk (eg, comorbidities of coronary artery disease, diabetes, prior transient ischemic attack cerebrovascular accident, or chronic kidney disease) who may have the greatest benefit from blood pressure reductionThe role that patient preference should play in choosing the most appropriate treatment strategy cannot be minimized. For some patients, medication treatment is limited by side effects, whereas in others, nonadherence is explained by cost, fear, or lack of understanding of the benefit. Importantly, a high burden of antihypertensive medications is associated with high rates of nonadherence in a stepwise fashion. Furthermore, a challenge for medication adherence among many younger hypertensive individuals is that HTN is often an asymptomatic condition until end-organ effects are manifest. Each of these factors should be considered when determining a patient's preference for alternative HTN treatment options.References: Fisher NDL, Mahfoud F. Medication adherence in hypertension: lessons learned from renal denervation trials. Eur J Prev Cardiol. 2023;30(1):34–36. https://doi.org/10.1093/eurjpc/zwac159 Schmieder RE, Kandzari DE, Wang TD, Lee YH, Lazarus G, Pathak A. Differences in patient and

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#	Yes/No	Rationale
		physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension. J Hypertens. 2021;39(1):162–168. https://doi.org/10.1097/HJH.0000000000002592. Kandzari DE, Weber MA, Poulos C, et al. Patient preferences for pharmaceutical and device-based treatments for uncontrolled hypertension: discrete choice experiment. Circ Cardiovasc Qual Outcomes. 2023;16(1), e008997. https://doi.org/10.1161/CIRCOUTCOMES.122.008997
3	Yes	See attached. Patients with resistant hypertension, characterized by blood pressure that still exceeds 130/80 mm Hg despite being on three maximally tolerated medications from classes with proven outcomes (such as mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers) benefit from RDN. Additionally, patients with uncontrolled hypertension who have tried lifestyle modifications and antihypertensive medications but are either intolerant of additional medications or for whom escalation of medications is ineffective, and who are willing to undergo renal denervation after shared decision-making, are also suitable candidates. When evaluating patients with elevated blood pressure who may be candidates for RDN, priority might be given to patients with higher cardiovascular risk (e.g., comorbidities of coronary artery disease, diabetes, prior transient ischemic attack/stroke, or chronic kidney disease), as they are likely to gain the most significant benefit from blood pressure reduction. However, payers should not limit coverage to resistant hypertension or intolerance to medication alone. Given the risk of untreated hypertension, additional populations and clinical scenarios where RDN can offer substantial benefits, coverage should reflect this broader applicability. As stated in the 2023 SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations, 10 RDN was initially tested in patients with resistant hypertension, where controlling blood pressure was challenging despite the use of at least three antihypertensive medications, including a diuretic. For patients who adhere to their medication regimen, these individuals have limited further medical treatment options and may benefit most from RDN. However, other groups, such as those who struggle with medication adherence, might also see significant benefits. Long-term follow-up has shown that reduced adherence to medication can negate the clinical benefits of blood pressure reduction. Many patients previously diagnosed with resistant hypertension are now more accurately identified as having 'apparent resistant hypertension,' as nearly half of these patients are not taking their prescribed medications one year later. Patient preference plays a crucial role in selecting the most appropriate treatment strategy. For some, medication treatment is limited by side effects, while for others, nonadherence is due to cost, fear, or lack of understanding of the benefits. Importantly, a high burden of antihypertensive medications is associated with increased rates of nonadherence. Before referring a patient for RDN, a multidisciplinary team should discuss the necessity of other efforts to control blood pressure, such as lifestyle modifications and optimizing medication regimens, in addition to the workup and management of secondary causes of hypertension.
4	Yes	The patient criteria represent both populations studied in the research for RDN.

Question 3.
Studies of radiofrequency RDN have found significant between-group differences of -7.4 mmHg for 24-h SBP and -6.8 mmHg for office SBP at 6 months; however, results were only significant for the subgroup of patients non-adherent to medications. Are there patient characteristics that help to predict treatment success with the Symplicity Spyral device?

#	Rationale
1	There are many challenges to predict success with renal denervation. Specifically the definition of success is difficult to define. First, most denervation studies report increasing durability and effect at 1 and 3 years however all primary endpoints for the initial trials concerning renal denervation stop at 2, 3 or 6 months. In addition, for the study aforementioned, if patient subgroups are investigated, patients were able to achieve more

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	time in targeted zone of optimal blood pressure with less medication burden than those in the sham arm thus favoring RDN over sham in secondary analyses. (PIMD 37914150)Second, the only predictive response to renal denervation appears to be the higher the starting blood pressure, the more likely a patient is to respond; however, how much blood pressure drop is needed to achieve "success" or confer a mortality benefit; these are questions that have yet to be answered.
2	To date, the most reliable predictor for the magnitude of antihypertensive response has been higher levels of baseline systolic blood pressure.
3	Please see attached.
4	There are many challenges to predict success with renal denervation. Specifically the definition of success is difficult to define. First, most denervation studies report increasing durability and effect at 1 and 3 years however all primary endpoints for the initial trials concerning renal denervation stop at 2, 3 or 6 months. In addition, for the study aforementioned, if patient subgroups are investigated, patients were able to achieve more time in targeted zone of optimal blood pressure with less medication burden than those in the sham arm thus favoring RDN over sham in secondary analyses. (PIMD 37914150)Second, the only predictive response to renal denervation appears to be the higher the starting blood pressure, the more likely a patient is to respond and more likely to have a larger decrease in BP ; however, how much blood pressure drop is needed to achieve "success" or confer a mortality benefit; these are questions that have yet to be answered. However data does show that even SBP reductions of 5-10 mm Hg confer CV morbidity and mortality benefits of 10-12% reduction so the reductions achieved have important clinical implications to reduce CV events (PMID: 26724178; PMID: 33933205).

Question 4. We are seeking your rationale on whether using ultrasound ablation of the renal sympathetic nerves provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID). Rationale

#	Rationale
1	We would like to call attention to the results of the 12 month RADIOSOUND-HTN study which is a three armed trial performed between rRDN (main artery alone), rRDN (main+distal arteries; the current way we perform rRDN) and uRDN (main alone). At 12 months, there were no statistical differences between the systolic and diastolic reductions in blood pressure in comparison to baseline.In addition, patient inclusion and exclusion criteria for entry into the uRDN trials were identical to the rRDN trials and the FDA's IFUs are also identical to rRDN. While there are some minor procedural differences, the efficacy, safety and durability of RDN are the same whether the patient undergoes uRDN or rRDN.Thus SCAI does not delineate between radiofreqeuncy and ultrasound renal denervation.
2	Clinical trials have demonstrated the efficacy of RDN across a wide range of HTN severity, including patients with hypertension in whom medications have been withdrawn (RADIANCE HTN SOLO, RADIANCE II), and patients with more severe and resistant HTN (RADIANCE HTN TRIO).1. The efficacy of RDN for treatment of uncontrolled hypertensionhas been consistently demonstrated in sham-controlled, randomized trials both in the presence and absence of medications. 2. Current evidence with RDN suggests a constant reduction in BP over day and night ("always on" effect) that is distinct from pharmokinetic profiles and dosing regimens with medications and patient nonadherence. This observation may improve BP stability and TTR (time in target range).

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#	Rationale
	3. Both randomized trials and registries support the early and late-term safety of RDN. 4. RDN is associated not only with improvements in BP but also reductions in medication number and/or dose. 5. Registry data suggest long-term durability in BP reduction following RDN, longer term surveillance of existing trials and addi-tional studies may inform durability and impact on clinical outcome. References: 1. Kandzari DE, Townsend RR, Bakris G,Basile J, Bloch MJ, Cohen DL, et al. Renal denervation inhypertension patients: Proceedings from an expert consensusroundtable cosponsored by SCAI and NKF. CatheterCardiovasc Interv. 2021;98:416–26. 2. Swaminathan RV, East CA, Feldman DN, Fisher ND, Garasic JM, Giri JS, Kandzari DE, Kirtane AJ, Klein A, Kobayashi T, Koenig G, Li J, Secemsky E, Townsend RR, Aronow HD. SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations. J Soc Cardiovasc Angiogr Interv 2023 Aug 21;2(6Part A):101121. doi: 10.1016/j.jscai.2023.101121. 3. Mufarrih SH, Qureshi NQ, Khan MS, Kazimuddin M, Secemsky E, Bloch MJ, Giri J, Cohen D, Swaminathan RV, Feldman DN, Alaswad K, Kirtane A, Kandzari D, Aronow HD. Randomized Trials of Renal Denervation for Uncontrolled Hypertension: An Updated Meta-Analysis. J Am Heart Assoc 2024 Aug 20;13(16):e034910. doi: 10.1161/JAHA.124.034910. 4. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, singleblind, randomised, sham-controlled trial. Lancet. 2018;391(10137):2335–2345. https://doi.org/10.1016/S0140-6736(18)31082-1. 5. Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021;397(10293):2476–2486. https://doi.org/10.1016/S0140-6736(21)00788-1. 6. Azizi M, Saxena M, Wang Y, et al. Endovascular ultrasound renal denervation to treat hypertension: the RADIANCE II randomized clinical trial. JAMA. 2023;329(8): 651–661. https://doi.org/10.1001/jama.2023.0713.
3	See attached. Patients with resistant hypertension, characterized by blood pressure that still exceeds 130/80 mm Hg despite being on three maximally tolerated medications from classes with proven outcomes (such as mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers) benefit from RDN. Additionally, patients with uncontrolled hypertension who have tried lifestyle modifications and antihypertensive medications but are either intolerant of additional medications or for whom escalation of medications is ineffective, and who are willing to undergo renal denervation after shared decision-making, are also suitable candidates. When evaluating patients with elevated blood pressure who may be candidates for RDN, priority might be given to patients with higher cardiovascular risk (e.g., comorbidities of coronary artery disease, diabetes, prior transient ischemic attack/stroke, or chronic kidney disease), as they are likely to gain the most significant benefit from blood pressure reduction. However, payers should not limit coverage to resistant hypertension or intolerance to medication alone. Given the risk of untreated hypertension, additional populations and clinical scenarios where RDN can offer substantial benefits, coverage should reflect this broader applicability. As stated in the 2023 SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations, 10 RDN was initially tested in patients with resistant hypertension, where controlling blood pressure was challenging despite the use of at least three antihypertensive medications, including a diuretic. For patients who adhere to their medication regimen, these individuals have limited further medical treatment options and may benefit most from RDN. However, other groups, such as those who struggle with medication adherence, might also see significant benefits. Long-term follow-up has shown that reduced adherence to medication can negate the clinical benefits of blood pressure reduction. Many patients previously diagnosed with resistant hypertension are now more accurately identified as having 'apparent resistant hypertension,' as nearly half of these patients are not taking their prescribed medications one year later. Patient preference plays a crucial role in selecting the most appropriate treatment strategy. For some,

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#	Rationale
	medication treatment is limited by side effects, while for others, nonadherence is due to cost, fear, or lack of understanding of the benefits. Importantly, a high burden of antihypertensive medications is associated with increased rates of nonadherence. Before referring a patient for RDN, a multidisciplinary team should discuss the necessity of other efforts to control blood pressure, such as lifestyle modifications and optimizing medication regimens, in addition to the workup and management of secondary causes of hypertension.
4	At present there is only one randomized control study looking at a comparative analysis between the two platform of uRDN (utlrasound) and rRDN (radiofrequency). In the RADIOSOUND-HTN study, a three pronged approach was performed between rRDN (main artery alone), rRDN (main+distal arteries; the current way we perform rRDN) and uRDN (main alone). At 12 months, there were no statistical differences between the systoluic and diastolic reductions in blood pressure in comparison to baseline.In addition, patient inclusion and exclusion criteria for entry into the uRDN trials were identical to the rRDN trials and the FDA's IFUs are also identical to rRDN. While there are some minor procedural differences, the efficacy, safety and durability of RDN are the same whether the patient undergoes uRDN or rRDN.Thus, the viewpoints described above in the rRDN section also apply to uRDN.

- Respond YES or NO whether ultrasound RDN would be expected to provide a clinically meaningful improvement in the indication; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Ultrasound RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Ultrasound RDN is consistent with generally accepted medical practice	Yes					X
2	Ultrasound RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Ultrasound RDN is consistent with generally accepted medical practice	Yes					X
3	Ultrasound RDN results in a clinically meaningful improvement in net health outcome	Yes					
	Ultrasound RDN is consistent with generally accepted medical practice	Yes					
4	Ultrasound RDN results in a clinically meaningful improvement in net health outcome	Yes					X
	Ultrasound RDN is consistent with generally accepted medical practice	Yes					X

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Question 5. Would you agree that the following criteria for identifying individuals for for ultrasound ablation of the renal sympathetic nerves are clinically appropriate?

- Blood pressure >130/80 mmHg despite use of 3 or more antihypertensive medications from 3 classes at maximally tolerated doses; OR
- With intolerance to antihypertensive medications whose blood pressure remains uncontrolled despite attempting lifestyle modifications.

#	Yes/No	Rationale
1	Yes	Please see above
2	Yes	Given that RCT data for patients on and off meds have confirmed BP benefits, criteria should also include:Patients with uncontrolled hypertension despite attempting lifestyle modification and antihypertensive medication but who are either intolerant of additional medication or do not wish to be on additional medications and who are willing to undergo renal denervation after shared decision-making.Priority may be appropriately given to patients with higher cardiovascular risk (eg, comorbidities of coronary artery disease, diabetes, prior transient ischemic attack cerebrovascular accident, or chronic kidney disease) who may have the greatest benefit from blood pressure reduction.The role that patient preference should play in choosing the most appropriate treatment strategy cannot be minimized. For some patients, medication treatment is limited by side effects, whereas in others, nonadherence is explained by cost, fear, or lack of understanding of the benefit. Importantly, a high burden of antihypertensive medications is associated with high rates of nonadherence in a stepwise fashion. Furthermore, a challenge for medication adherence among many younger hypertensive individuals is that HTN is often an asymptomatic condition until end-organ effects are manifest. Each of these factors should be considered when determining a patient's preference for alternative HTN treatment options.References: Fisher NDL, Mahfoud F. Medication adherence in hypertension: lessons learned from renal denervation trials. Eur J Prev Cardiol. 2023;30(1):34–36. https://doi.org/10.1093/eurjpc/zwac159 Schmieder RE, Kandzari DE, Wang TD, Lee YH, Lazarus G, Pathak A. Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension. J Hypertens. 2021;39(1):162–168. https://doi.org/10.1097/HJH.0000000000002592. Kandzari DE, Weber MA, Poulos C, et al. Patient preferences for pharmaceutical and device-based treatments for uncontrolled hypertension: discrete choice experiment. Circ Cardiovasc Qual Outcomes. 2023;16(1), e008997. https://doi.org/10.1161/CIRCOUTCOMES.122.008997
3	Yes	See attached.
4	Yes	Please see above

Question 6. The RADIANCE-HTN TRIO trial of the ReCor Paradise device, focusing on resistant hypertension in patients with a standardized triple combination antihypertensive treatment, found a -4.5 mmHg difference in daytime ambulatory SBP at 2 months. The durability of this effect was confirmed over 36 months of open-label follow-up, with significant reductions in office SBP from baseline levels in the ultrasound RDN group. Do you agree that this decrease in blood pressure is clinically meaningful – particularly in the context of known issues with medication compliance?

#	Yes/No	Rationale
1	Yes	While current randomized control data from RDN studies have not shown mortality differences, there have been meta-analyses show that even a drop of 5mmHg in pressure confers both a mortality and major adverse cardiovascular event reduction which amplifies at 10mmHg. (PMID 26724178)In the trial cited above, there was a decrease of -8.6mmHg of 24 hour ambulatory blood pressures at 36 months thus meeting the criteria of clinical significance.

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#	Yes/No	Rationale
2	Yes	There is universal agreement that reducing BP will lower the risk of CV disease and mortality, as demonstrated in several meta-analyses.Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reductionand risk of cardiovascular disease and mortality: a systematic reviewand network meta-analysis. JAMA Cardiol. 2017;2:775-781. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure low-ering on outcome incidence in hypertension: 7. Effects of morevs. less intensive blood pressure lowering and different achievedblood pressure levels - updated overview and meta-analyses of ran-domized trials. J Hypertens. 2016;34:613-622.
3	Yes	See attached.
4	Yes	The 36 month follow up study of RADIANCE_HTN TRIO underscores several key points already made above. One, it shows increasing efficacy over time with a drop of -4.5mmHg at 2months and -8mmHg at 36 months from baseline. When comparing to screening visit this drop with uRDN was -14.5mmHg.Second, it shows that patients with higher starting blood pressures tended to get a more robust signal for efficacy with RDN.In context, meta-analyses show that even a drop of 5mmHg in pressure confers both a mortality and major adverse cardiovascular event reduction which amplifies at 10mmHg. As described here and below, there is no data to suggest a difference in outcomes between the two platforms and thus RDN should have the ability to reduce mortality and MACE with BP reductions in this range. (PMID 26724178)

Question 7. The evidence from the RADIANCE-HTN TRIO, RADIANCE-HTN SOLO and RADIANCE II trials overall suggests that ultrasound RDN may result in an improvement in net health outcomes for patients with uncontrolled hypertension despite the use of anti-hypertensive medications. Are there any patient characteristics that predict technical success and response to treatment with ultrasound RDN?

#	Yes/No	Rationale
1	No	To date, there has not been any pre-hoc predictors of technical success or response to treatment except that those with a higher starting systolic blood pressure tend to accrue the most benefit from RDN. These patterns seem to be device agnostic.
2	No	To date, the most reliable predictor for the magnitude of antihypertensive response has been higher levels of baseline systolic blood pressure.
3	Yes	See attached.
4	No	Please see response above for predictability of response to RDN (device or energy agnostic).

Question 8. Given the variability of individual patient responses to ultrasound RDN and the invasive nature of the procedure – should this intervention be limited to individuals with elevated cardiovascular risk?

#	Rationale
1	The research trials did not stratify those with elevated cardiovascular risk and in fact excluded those with the highest CV risk (CKD [eGFR <40], history of atrial fibrillation, congestive heart failure, stroke or heart attack within 3 months of the procedure, blood pressures of 180mmHg or higher, uncontrolled diabetes).
2	The procedure is minimally invasive, with minimal risks.The procedure should prioritize hypertensive individuals with elevated CV risk and those with established end organ damage. Those with hypertension who are unable to take medications, for whatever reason, should be another priority group. The procedure should be a shared decision that includes perspectives from the treating physician, a discussion of risk and benefits with the patient and incorporating patient preferences (for either RFA or ultrasound RDN).

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3	See attached.
4	The research trials did not stratify those with elevated cardiovascular risk and in fact excluded those with the highest CV risk (CKD [eGFR <40], history of atrial fibrillation, congestive heart failure, stroke or heart attack within 3 months of the procedure, blood pressures of 180mmHg or higher, uncontrolled diabetes). It would make empiric sense that these higher risk patients would benefit more from RDN but these were not the included in the research trials and would set precedent to extend/limit coverage to populations not studied.

Question 9. The RADIOSOUND-HTN trial compared 3 RDN techniques in patients with resistant hypertension who were on a stable regimen of antihypertensive medications. The trial found that ultrasound RDN showed superiority over radiofrequency ablation (RFA) of main renal arteries in reducing daytime ambulatory SBP at 3 months, while RFA of main arteries plus branches did not significantly differ from the other groups. While these results are promising, it is unclear which version of the Spyral device was used as well as high variability in patient responses suggesting that further research may be needed to identify who is most likely to benefit from ultrasound RDN. Additionally, there is currently no practical method to verify nerve destruction following ablation.

Are there concerns with the relative performance and technical success of treatment with the Symplicity Spyral device compared to ultrasound-based ReCor Paradise systems? Are there considerations to guide choice of radiofrequency versus ultrasound systems?

#	Rationale
1	Please refer to discussion of RADIOSOUND-HTN above.Based upon these results, SCAI remains device and modality agnostic in regards to current RDN platforms.
2	Based on limited data, the results from either RFA of the main arteries plus branches or ultrasound technique of main arteries are likely similar. The key to a successful procedure is to perform a complete bilateral renal denervation, which could be achieved with either technology. The intervention should be performed at an experienced specialist interventional center with catheter-based equipment and appropriate imaging.
3	See attached.
4	As alluded to earlier, there is a longer term follow up from RADIOSOUND-HTN (PMID 36792266) in which the 3 RDN techniques were compared to each other.It should be noted that the technique for performing contemporary rRDN (radiofrequency) is to treat main+distal branches thus one of the comparator arms is clinically irrelevant (rRDN main alone). Thus, if comparing rRDN (Main +distal) and uRDN (main alone) there were no differences between blood pressures measured at 12 months thus either modality was found to be efficacious, safe and durable.

Question 10. In patients who do not achieve adequate blood pressure control after initial treatment with either ultrasound or radiofrequency RDN, what is the safety, efficacy, and clinical rationale for repeat RDN?

#	Rationale
1	We are not aware of any patients undergoing a repeat RDN.
2	Currently, limited data exist to perform repeat RDN and patients should be considered non-responders if adequate BP response is not achieved.
3	The ACC does not believe there is sufficient data available to comment on repeat RDN.
4	While there have been anecdotes of repeat RDN procedures, this is not commonly performed and has not been studied.

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Question 11. Are there any contraindications to treatment with ultrasound or radiofrequency RDN systems?

#	Rationale
1	SCAI would like to highlight there are differences from FDA approval and the research eligibility criteria to perform RDN. Further, anatomical exclusion should be consistent with research protocols to ensure predictable efficacy with this procedure (FMD, renal artery aneurysms and renal artery stenosis should be avoided or treated appropriately prior to RDN).
2	To date, enrollment in clinical trials of RDN has been predicated on the absence of a secondary cause of HTN in patients with resistant HTN. Patients considered for RDN should undergo appropriate evaluation for secondary causes of HTN with specific treatment that may correct the etiology of their HTN.There are patient subsets in whom RDN has not been studied well. For this reason, caution should be used when extrapolating results to these populations.
3	See attached. For RDN to be effective, it is important to rule out conditions like white coat and secondary hypertension. White coat hypertension should be ruled out by confirming elevated blood pressures outside of the provider's office. Secondary hypertension, caused by underlying conditions such as kidney disease or hormonal disorders, must be identified and managed appropriately. Comprehensive workup and exclusion of these conditions are needed to ensure that the treatment outcomes align with those demonstrated in clinical studies. Patients with renal artery stenosis, end stage renal disease and fibromuscular dysplasia have been excluded from randomized trials and the safety and effectiveness of RDN in these patient populations is unknown. Those with treatable secondary causes of hypertension should not undergo RDN. Other secondary causes, like Cushing syndrome and thyroid disease, should be excluded if suspected. Common factors such as sleep apnea and obesity do not exclude patients from RDN, but optimization of these risk factors should be attempted prior to referral for RDN. There are limited data on RDN for certain subgroups, including those with stage 1 hypertension, end stage renal disease, and kidney transplant recipients.11
4	The FDA's instructions for use do not delineate any contraindications for treatment.In the research protocol as referenced in the response from Question 1, there are several components of research eligibility that should be considered before referring to RDN. Further, anatomical exclusion should be consistent with research protocols to ensure predictable efficacy with this procedure (FMD, renal artery aneurysms and renal artery stenosis should be avoided or treated appropriately prior to RDN).

Question 12. Is there any key evidence missing from the attached reference list on page 13 that demonstrates clinically meaningful improvement in net health outcome?

#	Rationale
1	While most of the discussion around RDN has been focused on clinical impact, there have been financial modeling around RDN.It should be noted first that the average age of patients undergoing RDN were in their 50s (references previously cited) and therefore the decision regarding coverage is timely. In cost analysis performed on patients in the SPYRAL HTN-ON MED trial, the ICER for RDN was 13,4782 pounds and 32,732 dollars in the UK and US respectively, well below the typical ICER cutoffs of 20,000 pounds or 50,000 dollars, showing that RDN is a high-value intervention for patients. (PMID 39525984, 38196127)
2	See references included with the answers to above questions.Kandzari DE, Townsend RR, Bakris G,Basile J, Bloch MJ, Cohen DL, et al. Renal denervation inhypertension patients: Proceedings from an expert consensus roundtable cosponsored by SCAI and NKF. CatheterCardiovasc Interv. 2021;98:416–26. Swaminathan RV, East CA, Feldman DN, Fisher ND, Garasic JM, Giri JS, Kandzari DE, Kirtane AJ, Klein A, Kobayashi T, Koenig G, Li J, Secemsky E, Townsend RR, Aronow HD. SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations. J Soc Cardiovasc Angiogr Interv 2023 Aug 21;2(6Part A):101121. doi: 10.1016/j.jscai.2023.101121.

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#	Rationale
3	1 Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. The Lancet. 2022; 399:1401- 1410. 2 Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet March 2020. 3 Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018 Jun 9;391(10137):2335-2345. doi: 10.1016/S0140-6736(18)31082-1. Epub 2018 May 23. Erratum in: Lancet. 2018 Sep 8;392(10150):820 4 Azizi M, Saxena M, Wang Y, Jenkins JS, Devireddy C, Rader F, Fisher NDL, Schmieder RE, Mahfoud F, Lindsey J, Sanghvi K, Todoran TM, Pacella J, Flack J, Daemen J, Sharp ASP, Lurz P, Bloch MJ, Weber MA, Lobo MD, Basile J, Claude L, Reeve-Stoffer H, McClure CK, Kirtane AJ; RADIANCE II Investigators and Collaborators. Endovascular Ultrasound Renal Denervation to Treat Hypertension: The RADIANCE II Randomized Clinical Trial. JAMA. 2023 Feb 28;329(8):651-661. doi: 10.1001/jama.2023.0713. Erratum in: JAMA. 2023 Jun 13;329(22):1989. 5 Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, Rump LC, Persu A, Basile J, Bloch MJ, Daemen J, Lobo MD, Mahfoud F, Schmieder RE, Sharp ASP, Weber MA, Sapoval M, Fong P, Pathak A, Lantelme P, Hsi D, Bangalore S, Witkowski A, Weil J, Kably B, Barman NC, Reeve-Stoffer H, Coleman L, McClure CK, Kirtane AJ; RADIANCEHTN investigators. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCEHTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021 Jun 26;397(10293):2476-2486. doi: 10.1016/S0140-6736(21)00788-1. 6 Vukadinović D, Lauder L, Kandzari DE, Bhatt DL, Kirtane AJ, Edelman ER, Schmieder RE, Azizi M, Böhm M, Mahfoud F. Effects of Catheter-Based Renal Denervation in Hypertension: A Systematic Review and Meta-Analysis. Circulation. 2024 Nov 12;150(20):1599-1611. 7 Mahfoud F, Böhm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L, Schlaich M, Williams B, Fahy M, Mancia G. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J. 2019 Nov 1;40(42):3474-3482. 8 Cluett JL, Blazek O, Brown AL, East C, Ferdinand KC, Fisher NDL, Ford CD, Griffin KA, Mena-Hurtado CI, Sarathy H, Vongpatanasin W, Townsend RR; American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on the Kidney in Cardiovascular Disease; and Council on Peripheral Vascular Disease. Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association. Hypertension. 2024 Oct;81(10):e135-e148. 9 Fisher NDL, Kirtane AJ. Renal denervation for hypertension. Nat Rev Cardiol. 2025 Jan 2. doi: 10.1038/s41569-024- 01104-z.10 Swaminathan RV, East CA, Feldman DN, Fisher ND, Garasic JM, Giri JS, Kandzari DE, Kirtane AJ, Klein A, Kobayashi T, Koenig G, Li J, Secemsky E, Townsend RR, Aronow HD. SCAI Position Statement on Renal Denervation for Hypertension: Patient Selection, Operator Competence, Training and Techniques, and Organizational Recommendations. J Soc Cardiovasc Angiogr Interv. 2023 Aug 21;2(6Part A):101121. 11 Cluett JL, Blazek O, Brown AL, East C, Ferdinand KC, Fisher NDL, Ford CD, Griffin KA, Mena-Hurtado CI, Sarathy H, Vongpatanasin W, Townsend RR; American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on the Kidney in Cardiovascular Disease; and Council on Peripheral Vascular Disease. Renal Denervation for the Treatment of Hypertension: A Scientific Statement From the American Heart Association. Hypertension. 2024 Oct;81(10):e135-e148.
4	While most of the discussion around RDN has been focused on clinical impact, there have been financial modeling around RDN.It should be noted first that the average age of patients undergoing RDN were in their 50s (references previously cited) and therefore the decision regarding coverage is timely. In cost analysis performed on patients in the SPYRAL HTN-ON MED trial, the ICER for RDN was 13,4782 pounds and 32,732 dollars in the UK and US respectively, well below the typical ICER cutoffs of 20,000 pounds or 50,000 dollars, showing that RDN is a high-value intervention for patients. (PMID 39525984, 38196127)

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New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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