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# Renal Denervation for Uncontrolled Hypertension

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| Related Policies (if applicable) |
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| None |
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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Coverage

Radiofrequency ablation of the renal sympathetic nerves **may be considered medically necessary** for individuals:

- Whose blood pressure remains above >130/80 mmHg despite use of 3 or more antihypertensive medications from 3 classes (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers) at maximally tolerated doses; or
- With intolerance to antihypertensive medications whose blood pressure remains uncontrolled despite attempting lifestyle modifications (see Policy Guidelines).

Ultrasound ablation of the renal sympathetic nerves **may be considered medically necessary** for individuals

- Whose blood pressure remains above >130/80 mmHg despite use of 3 or more antihypertensive medications from 3 classes (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, and beta blockers) at maximally tolerated doses; or

- With intolerance to antihypertensive medications whose blood pressure remains uncontrolled despite attempting lifestyle modifications (see Policy Guidelines).

## Policy Guidelines

Priority for renal denervation of the renal sympathetic nerves 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.

The procedure should only be performed in experienced, specialized centers with multidisciplinary hypertension teams involving experts in hypertension (HTN) and percutaneous cardiovascular interventions after shared decision-making about the risks and benefits of treatment with the individual.

There is too little data to support the use of renal denervation for the following: stage 1 HTN, isolated systolic HTN, stage 4 or 5 chronic kidney disease, single kidney, kidney transplant recipients, or redo renal denervation in individuals who fail to respond to initial renal denervation.

Contraindications include: pregnancy, fibromuscular dysplasia, stented renal artery, renal artery aneurysm, significant renal artery stenosis, known kidney or secreting adrenal tumors, and unaddressed causes of secondary hypertension.

## Description

**Uncontrolled Hypertension**

Recommendations for blood pressure generally target <130/80 mmHg, although the blood pressure goal can vary (e.g., comorbidities, life-expectancy). (1) High blood pressure, or hypertension (HTN) is estimated to affect approximately 30% of the population in the United States. (2) It accounts for a high burden of morbidity related to strokes, 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. (3) Uncontrolled hypertension is diagnosed when an individual's blood pressure remains above targeted levels (typically ≥140/90mmHg) when a patient either is not using, or unable to use, treatments to control blood pressure or when hypertension persists despite antihypertensive therapies. (1, 4) 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. (4) 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. (5) Also, sometimes it is necessary to address comorbid conditions (i.e., obstructive sleep apnea) to control blood pressure adequately.

Treatment

*Radiofrequency (RF) 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. Radiofrequency ablation (RFA) 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. (6)

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 for 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.

## Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Treatment for hypertension consists of behavioral modifications and antihypertensive medications. For individuals with uncontrolled hypertension despite the use of antihypertensive medications, treatment is mainly intensified drug therapy, sometimes with the use of nontraditional antihypertensive medications such as spironolactone and/or minoxidil. However, treatment of hypertension which has not been adequately controlled with additional medications is often challenging and can lead to high costs and frequent adverse events of treatment. As a result, there is a large unmet need for additional treatments that can control uncontrolled hypertension. Nonpharmacologic interventions for uncontrolled hypertension despite medical management include modulation of the baroreflex receptor and/or radiofrequency (RF) denervation of the renal nerves. Broadly defined, health outcomes are the 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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. Randomized controlled trials 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 (RFA)**

Clinical Context and Therapy Purpose

The purpose of 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 policy.

*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. Radiofrequency ablation 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 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 six 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 (24-h) average SBP, and office SBP.

A longer-term outcome of interest (follow-up to at least three 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 event 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.

<u>Study Selection</u>
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.

Systematic Reviews

Multiple systematic reviews with overlapping studies, one of which is a Cochrane review by Coppolino et al. (2017), (7) have summarized the key RCTs evaluating renal denervation. The characteristics of the 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. (7) The evidence for clinical endpoints (e.g., all-cause mortality, hospitalization, cardiovascular events) was of low-quality. Comparisons of clinical outcomes in sham vs renal denervation groups showed no significant differences between groups in myocardial infarction (relative risk, 1.3; 95% confidence interval [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. (2021) pooled the results of 20 RCTs of varying approaches to renal denervation compared to sham or antihypertensive medications or one another. (8) 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-h 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 Review of Controlled Trials Assessing Renal Denervation**

| Study | Dates | Trials | N (Range) | Design | Duration, months |
|---|---|---|---|---|---|
| Silverwatch et al. (2021) (8) | 2010-2020 | 20 | 2152 (20-535) | RCT | 2 - 6 |
| Ogoyama et al. (2021) (9) | 2014-2021 | 9 | 1555 (51-535) | RCT, CT | 2 - 6 |

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|---|---|---|---|---|---|
| Pappaccogli et al. (2018) (10) | 2010-2016 | 11 | 1236 (19-535) | RCT, CT | 6 |
| Coppolino et al. (2017) (7) | 2010-2016 | 12 | 1149 (16-535) | RCT, CT | 6 |

CT: controlled trial; RCT: randomized controlled trial.

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

| Study | Treatment | Comparator | Trials |
|---|---|---|---|
| Silverwatch et al. (2021) (8) | RD (radiofrequency of main renal artery, main renal artery plus branch, main renal artery plus antihypertensive treatment or ultrasound of main renal artery) | Sham or AHT (network meta-analysis) | 20 |
| Ogoyama et al. (2021) (9) | rf RD (1st or 2nd generation device) | Control | 6 |
| Pappaccogli et al. (2018) (10) | RD | Control | 9<br>9<br>10<br>10 |
| Coppolino et al. (2017) (7) | RD | Control | 5<br>4<br>6<br>5 |

AHT: antihypertensive therapy; RD: renal denervation; rf: radiofrequency.

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

| Study | Outcomes | SMD, mm HG | 95% CI, mm Hg | p | $I^2$, % |
|---|---|---|---|---|---|
| Silverwatch et al. (2021) (8) | *Outcome: Group* | | | | *Comparison**: |
| | 24-h SBP: RFA MRA+B | -7.2 | -13.6 to -0.8 | SS | Sham |
| | 24-h SBP: RFA MRA | 0.6 | -4.4 to 5.5 | NS | Sham |
| | 24-h SBP: RFA MRA+AHT | -4.7 | -5.5 to 14.8 | NS | Sham |
| | 24-h SBP: usMRA | -1.2 | -8.6 to 6.2 | NS | Sham |
| | 24-h SBP: rfMRA+B | -12.9 | -22.6 to -3.2 | SS | AHT |
| | 24-h SBP: rfMRA | 5.9 | -11.4 to 1.3 | NS | AHT |
| | 24-h SBP: rfMRA+AHT | -1 | -7.2 to 5.2 | NS | AHT |
| | 24-h SBP: usMRA | -6.9 | -17.8 to 4.1 | NS | AHT |
| | Office SBP: rfMRA+B | -6.9 | -19.9 to 6.3 | NS | Sham |
| | Office SBP: rfMRA | -0.2 | -13.4 to 13.1 | NS | Sham |
| | Office SBP: rfMRA+AHT | -10.5 | -30.7 to 9.7 | NS | Sham |
| | Office SBP: usMRA | 2.3 | -12.9 to 17.5 | NS | Sham |
| | Office SBP: rfMRA+B | -7.3 | -26.4 to 11.8 | NS | AHT |
| | Office SBP: rfMRA | -0.7 | -11.7 to 10.4 | NS | AHT |

| | | | | | |
|---|---|---|---|---|---|
| | Office SBP: rfMRA+AHT<br>Office SBP: usMRA | -10.1<br>-1.8 | -21.4 to -0.6<br>-21.2 to 24.8 | SS<br>NS | AHT<br>AHT |
| Ogoyama et al. (2021) (9) | 24-h SBP (N=1137)<br>24-h DBP (N=1137)<br>Office SBP (N=997)<br>Office DBP (N=997) | -3.17<br>-1.58<br>-4.93<br>-3.33 | -5.22 to -1.11<br>-3.11 to -0.04<br>-7.81 to -2.06<br>-4.88 to -1.78 | SS<br>SS<br>SS<br>SS | 30<br>47<br>26<br>16 |
| Pappaccogli et al. (2018) (10) | Office SBP<br>Office DBP<br>ASBP<br>ADBP | -3.5<br>-2.8<br>-1.8<br>-0.6 | -13.0 to 6.1<br>-6.0 to 0.4<br>-4.5 to 0.9<br>-2.3 to 1.2 | NS<br>NS<br>NS<br>NS | 90<br>74<br>47<br>63 |
| Coppolino et al. (2017) (7) | 24-h SBP<br>24-h DBP<br>Office SBP<br>Office DBP | 0.3<br>0.9<br>-4.1<br>-1.3 | -3.7 to 4.3<br>-4.5 to 6.4<br>-15.3 to 7.1<br>-7.3 to 4.7 | NS<br>NS<br>NS<br>NR | NR<br>NR<br>NR<br>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; rf: radiofrequency; RFA: radiofrequency ablation; SBP: systolic blood pressure; SMD: standardized mean difference; SS: statistically significant; usMRA: ultrasound denervation of main renal artery; mm HG: millimeters of mercury; 24-h: 24-hour.

Sham-Controlled Randomized Controlled Trials

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

**Table 4a. Sham-Controlled RCT Characteristics**

| Trial | N | Intervention | Eligibility Criteria |
|---|---|---|---|
| **SPYRAL HTN-OFF MED Pilot (11)** | 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 |
| **SPYRAL HTN-OFF MED Pivotal (12)** | 331 | Symplicity Spyral multielectrode RDN (n=166) vs. sham (n=165) following 3–4-week medication wash-out | Same as above |
| **Spyral HTN-ON MED Pilot (13, 14)** | 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 |
| **SPYRAL HTN-ON MED Expansion (4)** | 257 | Symplicity Spyral multielectrode RDN (n=168) | Same as above |

| | | | |
|---|---|---|---|
| | | vs. sham (n=89) on stable doses for at least 6 weeks | |

BP: blood pressure; BMI: body mass index; DBP: diastolic blood pressure; n: number; NR: not reported; RCT: randomized controlled trial; RDN: renal denervation; SBP: systolic blood pressure; y: year(s); 24-h: 24-hour.

**Table 4b. Sham-Controlled RCT Characteristics**

| Trial | Baseline Characteristics | | Primary Outcome |
|---|---|---|---|
| | **RDN** | **Sham** | |
| **SPYRAL HTN-OFF MED Pilot (11)** | Mean Age: 55.8<br>Sex: Male, 68.4%<br>Mean BMI: 29.8<br>Mean office BP: 162/100<br>Mean 24-h BP: 153/99<br>Prior Medications: NR | Mean Age: 52.8<br>Sex: Male, 68.4%<br>Mean BMI: 30.2<br>Mean office BP: 161/102<br>Mean 24-h BP: 152/99<br>Prior Medications: NR | Change in mean office and 24-h BP at 3 months and between groups (unpowered) |
| **SPYRAL HTN-OFF MED Pivotal (12)** | Mean Age: 52.4<br>Sex: Male, 64%<br>Race: White, 28%; Black, 22%; NR, 44%<br>Mean BMI: 31.1<br>Mean office BP: 163/101<br>Mean 24-h BP: 151/98<br>Prior Medications: NR | Mean Age: 52.6<br>Sex: Male, 68%<br>Race: White, 30%; Black, 19%; NR, 48%<br>Mean BMI: 30.9<br>Mean office BP: 163/102<br>Mean 24-h BP: 151/99<br>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 (13, 14)** | Mean Age: 53.9<br>Sex: Male, 87%<br>Race: White, 34%; Black, 11%; NR, 47%<br>Mean BMI: 31.4<br>Mean office BP: 165/100<br>Mean 24-h BP: 152/97<br>Medications: 2.13 | Mean Age: 53.0<br>Sex: Male, 81%<br>Race: White, 36%; Black 12%; NR, 48%<br>Mean BMI: 32.5<br>Mean office BP: 164/103<br>Mean 24-h BP: 151/98<br>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 (4)** | Mean Age: 55.5<br>Sex: Male, 80%<br>Race: White, 36%; Black, 12%; NR, 37%<br>Mean BMI: 31.4 | Mean Age: 55<br>Sex: Male, 78%<br>Race: White, 37%; Black 17%; NR, 39%<br>Mean BMI: 32 | Change in mean 24-h BP from baseline to 6 months and between groups |

| | | | |
|---|---|---|---|
| | Mean office BP: 163/102<br>Mean 24-h BP: 149/97<br>Medications: NR | Mean office BP: 163/101<br>Mean 24-h BP: 148/95<br>Medications: NR | |

BP: blood pressure; BMI: body mass index; DBP: diastolic blood pressure; NR: not reported; RCT: randomized controlled trial; RDN: renal denervation; SBP: systolic blood pressure; 24-h: 24-hour.

**Table 5a. Primary Sham-Controlled RCT Results**

| Trial | 24-h SBP Change (SD or 95% CI) | 24-h DBP change (SD or 95% CI) |
|---|---|---|
| **SPYRAL HTN-OFF MED Pilot (11)** | **3 months** | |
| RDN | -5.5 (-9.1 to -2.0) | -4.8 (-7.0 to -2.6) |
| Sham | -0.5 (-3.9 to 2.9) | -0.4 (-2.2 to 1.4) |
| MD (95% CI), p | -5.0 (-9.9 to -0.2); 0.0414 | -4.4 (-7.2 to -1.6); 0.0024 |
| **SPYRAL HTN-OFF MED Pivotal (12)** | **3 months** | |
| RDN | -4.7 (-6.4 to -2.9) | -3.7 (-4.8 to -2.6) |
| Sham | -0.6 (-2.1 to 0.9) | -0.8 (-1.7 to 0.1) |
| MD (95% CI), p | -4.0 (-6.2 to -1.8); 0.0005 | -3.1 (-4.6 to -1.7); <0.0001 |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | **6 months** | |
| RDN | -9.0 (-12.7 to -5.3) | -6.0 (-8.5 to -3.5) |
| Sham | -1.6 (-5.2 to 2.0) | -1.9 (-4.7 to 0.9) |
| MD (95% CI), p | -7.4 (-12.5 to -2.3); 0.0051 | -4.1 (-7.8 to -0.4); 0.0292 |
| **SPYRAL HTN-ON MED Expansion (4)** | **6 months** | |
| RDN | -5.9 | NR |
| Sham | -5.8 | NR |
| MD (95% CI); p | 0.0 (-2.8 to 2.9); 0.974 | NR |
| **SPYRAL HTN-ON MED Expansion (Full Cohort) (4)** | **6 months** | |
| RDN | -6.5 | NR |
| Sham | -4.5 | NR |
| MD (95% CI); p | -1.9 (-4.4 to 0.5); 0.110 | NR |

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

**Table 5b. Primary Sham-Controlled RCT Results**

| Trial | Office SBP Change (SD or 95% CI) | Office DBP Change (SD or 95% CI) |
|---|---|---|

| | | |
|---|---|---|
| **SPYRAL HTN-OFF MED Pilot (11)** | **3 months** | |
| RDN | -10.0 (-15.1 to -4.9) | -5.3 (-7.8 to -2.7) |
| Sham | -2.3 (-6.1 to 1.6) | -0.3 (-2.9 to 2.2) |
| MD (95% CI), p | -7.7 (-14.0 to -1.5); 0.0155 | -4.9 (-8.5 to -1.4); 0.0077 |
| **SPYRAL HTN-OFF MED Pivotal (12)** | **3 months** | |
| RDN | -9.2 (-11.6 to -6.9) | -5.1 (-6.4 to -3.8) |
| Sham | -2.5 (-4.6 to -0.4) | -1.0 (-2.3 to 0.3) |
| MD (95% CI), p | -6.6 (-9.6 to -3.5); <0.0001 | -4.4 (-6.2 to -2.6); <0.0001 |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | **6 months** | |
| RDN | -9.4 (-13.5 to -5.3) | -5.2 (-7.7 to -2.7) |
| Sham | -2.6 (-6.7 to 1.6) | -1.7 (-4.2 to 0.9) |
| MD (95% CI), p | -6.8 (-12.5 to -1.1); 0.0205 | -3.5 (-7.0 to 0); 0.0478 |
| **SPYRAL HTN-ON MED Expansion (4)** | **6 months** | |
| RDN | -10.1 | NR |
| Sham | -6.2 | NR |
| MD (95% CI); p | -4.0 (-7.6 to 0.4); 0.028 | NR |
| **SPYRAL HTN-ON MED Expansion (Full Cohort) (4)** | **6 months** | |
| RDN | -9.9 | NR |
| Sham | -5.1 | NR |
| MD (95% CI); p | -4.9 (-7.9 to -1.9); 0.001 | NR |

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

**Table 6a. Long-term and Subgroup Sham-Controlled RCT Results**

| Trial | 24-h SBP MD (95% CI); p | 24-h DBP MD (95%CI); p |
|---|---|---|
| **SYMPLICITY OFF MED (Full-Cohort) (4)** | | |
| 3 months ± SD, N, p-value | RDN: -4.5 ± 10.8, N=153; p<0.001<br>Sham: -0.6± 8.7, N=147 | NR |
| 6 months ± SD, N, p-value | RDN: -15.3 ± 13.7, N=150<br>Sham: -17.1 ± 12.3, N=159 | NR |
| 12 months ± SD, N, p-value | RDN: -14.3 ± 11.9, N=146<br>Sham: -19.2 ± 12.1, N=92; p=0.03 | NR |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | | |
| 3 months | -4.6 (NR); 0.10 | -3.7 (NR); 0.06 |
| 6 months | -7.4 (-12.5 to -2.3); 0.0051 | -4.1 (-7.8 to -0.4); 0.0292 |
| 6 months (adherent subgroup) | -6.0 (NR); 0.99 | -3.3 (NR); 0.249 |

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|---|---|---|
| 6 months (non-adherent subgroup) | -8.3 (NR); 0.029 | -4.6 (NR); 0.062 |
| 12 months | -1.9 (NR); 0.553 | -0.8 (NR); 0.695 |
| 24months | -11.2 (-18.4 to -4.0); 0.0031 | -5.7 (-10.6 to -0.7); 0.025 |
| 24 months (without imputation) | -11.2 (-18.4 to -4.0); 0.003 | NR |
| 36 months | -10.0 (-16.6 to -3.3); 0.0039 | -5.9 (-10.1 to -1.8); 0.0055 |
| 36 months (without imputation) | -6.1 (-13.6 to 1.4); 0.11 | NR |

CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; NR: not reported; SBP: systolic blood pressure; RCT: randomized controlled trial; RDN: renal denervation.

**Table 6b. Long-term and Subgroup Sham-Controlled RCT Results**

| Trial | Office SBP MD (95% CI); p | Office DBP MD (95% CI); p |
|---|---|---|
| **SYMPLICITY OFF MED (Full-Cohort) (4)** | | |
| 3 months ± SD, N, p-value | RDN: -9.4 ± 14.8, N=170; p<.001<br>Sham: -2.3 ± 12.7, N=164 | NR |
| 6 months ± SD, N, p-value | RDN: -20.8 ± 13.9, N=174<br>Sham: -21.9 ± 14.3, N=177 | NR |
| 12 months ± SD, N, p-value | RDN: -21.3 ± 14.2, N=171<br>Sham: -22.4 ± 13.6, N=104 | NR |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | | |
| 3 months | -1.6 (NR); 0.59 | -1.5 (NR); 0.44 |
| 6 months | -6.8 (-12.5 to -1.1); 0.0205 | -3.5 (-7.0 to 0); 0.0478 |
| 6 months (adherent subgroup) | -5.1 (NR); 0.144 | -2.7 (NR); 0.241 |
| 6 months (non-adherent subgroup) | -7.9 (NR); 0.087 | -4.0 (NR); 0.135 |
| 12 months | NR | NR |
| 24months | -12.9 (-21.1 to -4.7); 0.0026 | -8.5 (-15.0 to -2.1); 0.010 |
| 24 months (without imputation) | -11.1 (-21.6 to -0.5); 0.11 | NR |
| 36 months | -11.8 (-19.0 to -4.7); 0.0017 | -3.9 (-9.8 to 1.9); 0.186 |
| 36 months (without imputation) | 0.5 (-8.8 to 9.7); 0.92 | NR |

CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; N: number; NR: not reported; SBP: systolic blood pressure; RCT: randomized controlled trial; RDN: renal denervation; 24-h: 24-hour.

*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. (15) 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). (11) 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). (12) 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-up. (4) 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). (13) 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 medication 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. (14) 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. (2023) 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). (16) 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 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 U.S. Food and Drug Administration (FDA) in August 2023 and has been reported on in several publications since. (4, 17, 18) The eligibility criteria and primary efficacy endpoint were identical to the HTN-ON MED pilot study described above, with similar baseline characteristics (Table 2). 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 computed tomography angiography (CTA) or magnetic resonance angiography (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.

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. (19) 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-h 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 (11)** | 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 MED Pivotal (12)** | 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 blinded follow-up (3 months). |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | 1. Intended use population is unclear as patients were permitted to take 1-3 medications at baseline with | 5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical | 2. Not standard or optimal. | 6. Clinically significant difference for mean 24-h blood pressure observed only in adherent subgroup | 3. Short duration of blinded follow-up for primary efficacy outcome (6 months). |

| | | | | | |
|---|---|---|---|---|---|
| | submaximal dosing; 4. Low enrollment of women (16%) and racial demographics of enrolled population not reported for nearly half of participants. | methods to verify nerve destruction are available. | | population. No clinically significant difference for mean office blood pressure observed in either adherent or non-adherent subgroup analyses. | |
| **SPYRAL HTN-ON MED Expansion (4)** | 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-h blood pressure. Sub-group analysis shows discordant BP reductions for U.S. and non-U.S. participants on primary outcome. | 3. Short duration of blinded follow-up for primary efficacy outcome (6 months). |

BP: blood pressure; U.S.: United States; 24-h: 24 hour.

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 8. Sham-Controlled Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| **SPYRAL HTN-OFF MED Pilot (11)** | | | | | 4. Unpowered pilot study. | |
| **SPYRAL HTN-OFF MED Pivotal (12)** | | | | | | |
| **SPYRAL HTN-ON MED Pilot (13, 14)** | | | | 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)** | | | | 4-5. Inadequate handling of crossovers with inappropriate exclusion of blood pressure measurements | 4. Unpowered key secondary endpoint of change in office BP. | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | at crossover. LOCF may not be the most appropriate approach. | | |

LOCF: last observation carried forward; BP: blood pressure.
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.

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. (4) 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). (20) At 36 months post-treatment, office SBP significantly decreased by -19.0 ± 28.3 mmHg 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 3 and ≥4 medication groups (-10.7 ± 19.7 and -8.9 ± 20.5 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=132 | -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=132 | -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; DBP: diastolic blood pressure; SD: standard deviation: 24-h: 24-hour.

Section Summary: Radiofrequency Renal 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 ambulatory blood pressure 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 event at 1 month follow-up and met its pre-specified performance goal. 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.

**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 policy.

*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-h 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 |
| 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.

Systematic Reviews

Azizi et al. (2024) 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). (21) 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) (21) | 2018-2023 | 3 (RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, RADIANCE II) | 506 (136-150) | RCT | 2 - 6 |

RCT: randomized controlled trial; mo: month(s).

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

| 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) | Office SBP, mean change from BL (95% CI) | Safety, n |
|---|---|---|---|---|---|
| Aziz et al. (2024) (21) | **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 | |

AE: Adverse event; BL: baseline; CI: confidence interval; DBP: diastolic blood pressure; NR: not reported; RD: renal denervation; SBP: systolic blood pressure; SMD: standardized mean difference; 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). (22) 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. (2021) 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). (23) 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=.03 for home BP; OR 1.8, 95% CI 0.9 to 3.6; p=.07 for daytime ambulatory 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). (26) Eligibility criteria included office SBP ≥150 mmHg and 24-h 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). (28) 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-h 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). (24)

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). (27) 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 SBP 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 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). (29)

At 12 months, following unblinding at 6 months, the BP-lowering effect of usRDN was maintained with fewer prescribed medications compared to sham. (30) 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. (31) 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. (31) 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. (24)

**Table 13a. RCT Characteristics**

| Trial | N | Intervention | Eligibility Criteria |
|---|---|---|---|
| **RADIOSOUND-HTN (22)** | 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 24-h branches (n=39). Two or more ultrasound emissions were delivered in the main right and left renal arteries. | Age 18-75 years with SBP > 135 on ABPM; participants were on 4 weeks of stable antihypertensive medications prior to enrollment. |
| **RADIANCE-HTN SOLO (27, 29, 30)** | 146 | Paradise Recor ultrasound (n=74) vs. sham (n=72) following 4-week AHT medication wash-out. Guideline-based stepped-care hypertensive treatment began at 2 months if BP remained uncontrolled. Mean number of ultrasound emissions delivered was 5.4±1. | Age 18-75 years with office BP ≥ 140/90 and <180/110; eGFR ≥ 40 mL/min/1.73m$^2$; patients were eligible if hypertension was controlled or uncontrolled on 0 to 2 antihypertensive medications. |
| **RADIANCE-II (28)** | 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 | Aged 18 to 75 years with office BP ≥ 140/90 despite 2 or more antihypertensive medications; eGFR ≥ 40 mL/min/1.73 m$^2$. |

| | | | |
|---|---|---|---|
| | | number of ultrasound emissions delivered was 5.6. | |
| **RADIANCE-HTN TRIO (23, 25, 32)** | 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 uncontrolled. Mean number of ultrasound emissions delivered was 5.8±1.2. | Aged 18 to 75 years with office BP ≥ 140/90 despite 3 or more antihypertensive medications; eGFR ≥ 40 mL/min/1.73 $m^2$. |
| **REQUIRE (26)** | 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. |

ABPM: ambulatory blood pressure monitoring; AHT: antihypertensive; BP: blood pressure; eGFR: estimated glomerular filtration rate; RCT: randomized controlled trial; RDN: renal denervation; RFA: radiofrequency ablation; SBP: systolic blood pressure.

**Table 13b. RCT Characteristics**

| **Trial** | **Baseline Characteristics** | | **Primary Outcome** |
|---|---|---|---|
| | **usRDN** | **Control** | |
| **RADIOSOUND-HTN (22)** | Mean Age: 64.6<br>Sex: Male, 76%<br>Mean BMI: 32.6<br>Mean 24-h BP: 151.3/83<br># antihypertensive drug classes: 5 | Mean Age: 62.1 or 63.8<br>Sex: Male, 62% or 67%<br>Mean BMI: 30.6 or 31.6<br>Mean 24-h BP: | Change in daytime ambulatory SBP at 3 months |

| | | | |
|---|---|---|---|
| | | 147.4/83.6 or 150.6/83.5<br># antihypertensive drug classes: 4.7 or 5.3 | |
| **RADIANCE-HTN SOLO (27, 29, 30)** | Mean Age: 54.4<br>Sex: Male, 62%<br>Mean BMI: 29.9<br>Mean office BP: 154.5/99.7<br>Mean 24-h BP: 142.6/87.3<br>Prior Medications: 0-2 antihypertensive medications; 1 participant in each group was found to be on 3 medications at BL | Mean Age: 53.8<br>Sex: Male, 54%<br>Mean BMI: 29<br>Mean office BP: 153.6/99.1<br>Mean 24-h BP: 143.8/88.6<br>Prior Medications: 0-2 antihypertensive medications; 1 participant in each group was found to be on 3 medications at BL | Change in daytime ambulatory SBP at 2 months |
| **RADIANCE-II (28)** | Mean Age: 55.1<br>Sex: Male, 68.7%<br>Mean BMI: 30.1<br>Mean office BP: 155.8/101.3<br>Prior Medications:<br>1: 38.5%<br>2: 32.3%<br>≥2: 0% | Mean Age: 54.9<br>Sex: Male, 77%<br>Mean BMI: 30.6<br>Mean office BP: 154.3/99.1<br>Prior Medications:<br>1: 33.8%<br>2: 33.8%<br>≥2: 1.4% | Change in daytime ambulatory SBP at 2 months |
| **RADIANCE-HTN TRIO (23, 25, 32)** | Mean Age: 51.9<br>Sex: Male, 82%<br>Mean BMI: 32.8<br>Mean office BP: 161.7/104.9<br>Prior Medications:<br>3: 38.5%<br>4: 32.3%<br>5: 29.2% | Mean Age: 53<br>Sex: Male, 80%<br>Mean BMI: 32.7<br>Mean office BP: 163.3/102.8<br>Prior Medications:<br>3: 42.2%<br>4: 35.9%<br>5: 21.9% | Change in daytime ambulatory SBP at 2 months |
| **REQUIRE (26)** | Mean Age: 50.7<br>Sex: Male, 69.6%<br>Mean BMI: 29.5<br>Mean office BP: 157.6/97.7<br>Prior Medications:<br>3: 46.4% | Mean Age: 55.6<br>Sex: Male, 79.1%<br>Mean BMI: 28.4<br>Mean office BP: 160.4/95.3<br>Prior Medications:<br>3: 43.3% | Change in ambulatory SBP at 3 months |

| | | | |
|---|---|---|---|
| | 4: 29%<br>≥5: 24.6% | 4: 34.3%<br>≥5: 22.4% | |

BL: baseline; BP: blood pressure; BMI: body mass index; RCT: randomized controlled trial; SBP: systolic blood pressure; usRDN: ultrasound renal denervation; 24-h: 24-hour.

**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<br>>.99 for usRDN vs RFA of main artery and branches | .025 for usRDN vs RFA of main artery<br>NS for usRDN vs RFA of main artery and branches | .029 for usRDN vs RFA of main artery<br>NS for usRDN vs RFA of main artery and branches | .015 for usRDN vs RFA of main artery<br>NS for usRDN vs RFA of main artery and branches |
| **RADIANCE-HTN SOLO (27, 29, 30)** | **2; 6; and 12** | | | |
| usRDN | -8.5 ± 9.3;<br>-18.1 ± 12.2;<br>-16.5 ± 12.9 | -5.1 ± 5.9;<br>−10.7 ±7.8;<br>-9.8 ± 8.3 | -7.0 ± 8.6;<br>-16.5 ± 11.8;<br>-15.1 ± 12.4 | -4.4 ± 5.8;<br>-9.7 ± 7.3 |
| Sham | -2.2 ± 10.0;<br>-15.6 ± 13.2;<br>-15.8 ± 13.1 | -2.6 ± 6.5;<br>−9.7 ± 8.1;<br>-9.6 ± 7.9; | -90.9 ± 7.9;<br>-14.9 ± 12.8;<br>-15.3 ± 12.4 | -3.0 ± 6.1;<br>-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;<br>-4.3 (-7.9 to -0.6), p=.024;<br>-2.3 (-5.9 to 1.3), p=.201 | -2.6 (-4.6 to -0.6), p=.01;<br>−1.3 (-3.7 to 1.2), p=.018;<br>-2.0 (-4.3 to 0.4), p=.103 | -2.6 (-4.6 to -0.6), p=.01;<br>-4.3 (-7.7 to -1.0), p=.012;<br>-2.4 (-5.8 to 0.9), p=.156 | -1.8 (-3.7 to 0.2), p=.07;<br>-2.6 (-4.6 to -0.5), p=.017;<br>-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 (26)** | **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 | |

BL: baseline; CI: confidence interval; DBP: diastolic blood pressure; MD: mean difference; NS: not significant; RCT: randomized controlled trial; RDN: renal denervation; RFA: radiofrequency ablation; SBP: systolic blood pressure; SD: standard deviation; usRDN: ultrasound renal denervation; 24-h: 24-hour. ~indicates value estimated from figure.

RCT study relevance, design, and conduct limitations are summarized in Tables 14 and 15 below.

**Table 14. RCT Study Relevance Limitations**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Duration of Follow-up[e] |
|---|---|---|---|---|---|
| **RADIOSOUND-HTN (22)** | 3. Study population not representa-tive of intended use (only larger renal artery diameters were included and single center experience).<br>4. Racial demo-graphics 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 radio-frequency renal denervation groups post-randomization. Adherence to medication measured by self-reporting only. | 6. Clinically significant difference for blood pressure outcomes observed only versus radio-frequency renal denervation of main artery and not for radio-frequency renal denervation of the main artery and branches. | 3. Short duration of follow-up (3 months). |
| **RADIANCE-HTN SOLO (27, 29, 30)** | 3. Study population not representa-tive 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 anti-hypertensive 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 (28)** | 3. Study population not representa-tive of intended use.<br>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 (23, 32)** | | 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 for 24 months in FDA SSED post-treatment and 36 months in the usRDN group only in a sub-sequent publication. |
| **REQUIRE (26)** | 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). |

FDA SSED: U.S. Food and Drug Administration Summary of Safety and Effectiveness Data; RCT: randomized controlled trial; usRDN: ultrasound renal denervation.
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 15. RCT Study Design and Conduct Limitations**

| Study | Allocation [a] | Blinding [b] | Selective Reporting [c] | Data Completeness [d] | Power[e] | Statistical [f] |
|---|---|---|---|---|---|---|
| **RADIOSOUND-HTN (22)** | | 1. Study staff not blinded | | | | |
| **RADIANCE-HTN SOLO (27, 29, 30)** | | 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 partici-pants calculate d in power calcula-tions for the primary outcome | |
| **RADIANCE-II (28)** | | 1. Study staff not blinded | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **RADIANCE-HTN TRIO (23, 32)** | | 1. Study staff not blinded | | | | |
| **REQUIRE (26)** | | 1. Study staff not blinded | | | | |

RCT: randomized controlled trial.
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 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 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 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 patients 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 patients 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.

**Summary of Evidence**

For individuals who have uncontrolled hypertension, despite the use of anti-hypertensive medications, who receive radiofrequency ablation (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 the 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 patients 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 patients 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 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 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 patients using fewer antihypertensive medications than the sham control group. A meta-analysis of the sham-controlled RADIANCE trials showed that fewer usRDN patients 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 patients 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 patient 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. Despite these limitations, the overall evidence suggests that usRDN may result in an improvement in net health outcomes for patients with uncontrolled hypertension despite the use of anti-hypertensive medications. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Clinical Input**

For individuals with uncontrolled hypertension, 2025 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.

**Practice Guidelines and Position Statements**

American Heart Association (AHA) et al.

The AHA (2024) published a Scientific Statement on renal denervation for the treatment of hypertension. (1) The AHA concluded:

- "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 or 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.
- 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. (33) 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 cardiovascular disease [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 $m^2$) or secondary causes of hypertension, until further evidence becomes available. (Class: III, Level: C)"

European Society of Hypertension (ESH) and European Association of Percutaneous Cardiovascular Interventions (EAPCI)

In 2023, the ESH, with the EAPCI, issued a clinical consensus statement on the use of renal denervation in the management of adults with hypertension. (34) The following recommendations were issued concerning renal denervation:

- "Renal denervation may be used in adult patients with uncontrolled resistant hypertension (office BP ≥140/≥90 mmHg confirmed by 24-hour ambulatory systolic BP ≥130 mmHg or daytime systolic BP ≥135 mmHg) treated with ≥3 antihypertensive drugs and an eGFR ≥40 ml/min/1.73 $m^2$.
- Renal denervation 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 renal denervation in a tailored, shared decision-making process.
- The patient's global cardiovascular [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.
- 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."

<u>European Society for Hypertension (ESH)</u>

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. (35) 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/1.73$m^2$ 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/1.73$m^2$. (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. (36)

Society for Cardiovascular Angiography & 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. (37) The following selection criteria were issued concerning renal denervation:

- "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 policy are listed in Table 16.

**Table 16. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT04307836[a] | A Prospective, Multicenter, No-treatment Controlled, Randomized, Open-label, Pivotal Study to Evaluate the Safety and Efficacy of DENEX, Renal Denervation Therapy, in Patients with Hypertension on no or 1-3 Antihypertensive Medications | 140 | Jan 2024 (unknown) |

| | | | |
|---|---|---|---|
| NCT04535050[a] | A Prospective, Multicenter, Sham-controlled, Single-blinded, Randomized, Pilot Study to Evaluate the Safety and Effectiveness of DENEX Renal Denervation System in Patients With Uncontrolled Hypertension Not Treated With Antihypertensive Medication | 100 | Mar 2026 (not yet recruiting) |
| NCT02439775[a] | Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy (SPYRAL HTN-ON MED) | 337 | Jul 2026 (ongoing) |
| NCT05198674[a] | The SPYRAL AFFIRM Global Clinical Study of Renal Denervation With the Symplicity Spyral Renal Denervation System in Subjects With Uncontrolled Hypertension (SPYRAL AFFIRM) | 1200 | Jun 2027 (recruiting) |
| NCT05563337 | Renal Denervation in Hypertensive Women Planning to Become Pregnant (WHY-RDN) | 80 | Aug 2027 (not yet recruiting) |
| NCT01534299[a] | Global SYMPLICITY Registry (GSR) Denervation Findings in Real World (DEFINE) | 5000 | Oct 2027 (recruiting) |
| NCT05703620[a] | REducing Sympathetic Activity Through Ultrasound-based Renal deneRvation in Excessive Cardiovascular Risk populaTions. (RESURRECT) | 75 | May 2026 (recruiting) |
| NCT02649426[a] | A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN) | 282 | May 2025 (active) |
| NCT05460169[a] | Renal Denervation in ADPKD- RDN-ADPKD Study (RDN-ADPKD) | 44 | May 2027 (recruiting) |
| NCT05326230[a] | A Clinical Study of the Paradise™ Renal Denervation System in Patients With Hypertension (RADIANCE-HTN DUO) | 154 | Dec 2029 (recruiting) |
| NCT03614260[a] | he RADIANCE II Pivotal Study: A Study of the ReCor Medical Paradise System in Stage II Hypertension (RADIANCE-II) | 225 | July 2027 (active) |
| NCT06297291[a] | Global Paradise System US Post Approval Study (US GPS) | 1000 | July 2031 (recruiting) |
| NCT05017935[a] | RADIANCE Continued Access Protocol (RADIANCE CAP) | 300 | Dec 2028 (active) |
| NCT05027685[a] | The "Global Paradise System" Registry (GPS Registry) | 3000 | Dec 2031 (recruiting) |

| | | | |
|---|---|---|---|
| NCT05934383[a] | Safety and Efficacy of Ultrasound Renal Denervation in Kidney Transplantation Patients With Uncontrolled Hypertension (RESTART) | 40 | Sept 2030 (not yet recruiting) |
| NCT04182620[a] | Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy During Atrial Fibrillation Ablation (ULTRA-HFIB) | 160 | Mar 2025 (completed) |
| NCT05988411[a] | ULTRA-HFIB-Redo: Ultrasound-based Renal Sympathetic Denervation vs Control in Redo Ablation Patients | 200 | Dec 2027 (recruiting) |
| NCT04311086[a] | Global Clinical Study of Renal Denervation in the Distal Main and First Order Branch Renal Arteries Using the Symplicity Spyral™ Multi-electrode Renal Denervation System (SPYRAL DYSTAL) | 56 | Jan 2023 (completed) |
| NCT04722159 | Clinical Outcome of Patients With Resistant Hypertension Undergoing Renal Denervation: A Report From the Swedish Registry for Renal Denervation | 300 | Aug 2021 (unknown) |
| NCT05438446[a] | Effect of Renal Denervation on Stress, Hypertension and Anxiety Management (ERSHAM) | 60 | Dec 2023 (unknown) |

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | 0338T, 0339T |
| **HCPCS Codes** | C1735, C1736 |

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
|---|---|
| **Date** | **Description of Change** |
| 10/15/2025 | Document updated with literature review. The following change was made to Coverage: 1) Experimental, investigational and/or unproven statement removed; and 2) Added coverage criteria for radiofrequency ablation and ultrasound ablation of the renal sympathetic nerves. Added references 1, 16-34 and 37; others removed. Title changed from "Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Uncontrolled Hypertension". |
| 02/01/2025 | Reviewed. No changes. |
| 02/01/2024 | Document updated with literature review. The following change was made to Coverage: Removed "resistant" from coverage statement. References 2, 3, 11, 13, 14, and 25 added; others updated, some removed. Document title changed from "Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant or Uncontrolled Hypertension". |
| 01/15/2023 | Document updated with literature review. Minor editorial changes to Coverage to include patients with uncontrolled hypertension; intent unchanged. References 5, 6, 8, 9, 15, 53 and 54 added; others removed. Title changed from: Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension. |
| 12/01/2021 | Document updated with literature review. Coverage unchanged. References 4, 22, 46 and 47 added. |
| 01/15/2021 | Reviewed. No changes. |
| 05/15/2020 | Document updated with literature review. Coverage unchanged. References 5-6, 11, 19-20, 28-31, 45 added; two references removed. |
| 04/01/2019 | Reviewed. No changes. |
| 04/01/2018 | Document updated with literature review. Coverage unchanged. References 9-11, 15, 17, 21-22, 24-26, 37 and 39 were added, some references removed. |
| 03/01/2017 | Reviewed. No changes. |
| 03/01/2016 | Document updated with literature review. Coverage unchanged. |
| 04/01/2015 | Reviewed. No changes. |
| 01/01/2014 | New medical document. Radiofrequency ablation of the renal sympathetic nerves is considered experimental, investigational and/or unproven for the treatment of resistant hypertension. |