Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Renal Denervation for Uncontrolled Hypertension

Description/Background

Uncontrolled Hypertension

Recommendations for blood pressure generally target <130/80 mmHg, although 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 U.S.[2,] It accounts for a high burden of morbidity related to stroke, ischemic heart disease, kidney disease, and peripheral arterial disease. An estimated 1 in 4 adults with hypertension have their hypertension under control, but the remaining 77% (93 million) remain uncontrolled.[3,]Uncontrolled hypertension is diagnosed when an individual's blood pressure remains above targeted levels (typically ≥140/90 mmHg) when a patient either is not using, or unable to use, treatments to control blood pressure or when hypertension persists despite antihypertensive therapies.[4,1,] 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 (ie, obstructive sleep apnea) to control blood pressure adequately.

Treatment

Radiofrequency Denervation of the Renal Sympathetic Nerves

Increased sympathetic nervous system activity has been linked to essential hypertension. Surgical sympathectomy has been shown to be effective in reducing blood pressure but is limited by the adverse effects 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) 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 decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system.[5] Radiofrequency ablation of the renal sympathetic nerves may act as a nonpharmacologic treatment for hypertension and has been proposed as a treatment option for patients with uncontrolled hypertension despite the use of anti-hypertensive medications.

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 (uRDN) 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 uRDN procedure is typically performed under local anesthesia with conscious sedation. Access is obtained through the femoral artery, and the catheter is advanced to the renal artery under fluoroscopic guidance. Once positioned, the catheter's balloon is inflated with cooling fluid, and ultrasound energy is delivered. Usually, 2-3 ultrasound emissions are delivered per renal artery, with the ability to treat both main renal arteries and accessory renal arteries when present.

Regulatory Status

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

The Paradise® Ultrasound Renal Denervation System (ReCor Medical, Inc) was approved by the FDA on November 7, 2023. The Symplicity Spyral™ Renal Denervation System (Medtronic, Inc),which uses radiofrequency energy to accomplish renal denervation, 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.

Medical Policy Statement

Renal denervation by radiofrequency ablation or ultrasound ablation of the renal sympathetic nerves as a treatment of uncontrolled hypertension is considered **experimental/investigational.** The evidence is insufficient to determine that the technology results in improvements in net health outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0338T 0339T

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

RADIOFREQUENCY ABLATION

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with hypertension that is uncontrolled despite the use of antihypertensive medications or who poorly tolerate blood pressure lowering therapy. There is no generally 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 (SBP) and diastolic (DBP) blood pressure and medication use. Blood pressure measurements may include daytime ambulatory blood pressure, 24-hour average SBP, and office SBP.

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

Study Selection

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

Review of Evidence

Systematic Reviews

Multiple systematic reviews with overlapping studies, 1 of which is a Cochrane review by Coppolino et al (2017),[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 (eg, all-cause mortality, hospitalization, cardiovascular events) was of low-quality. Comparisons of clinical outcomes in sham versus renal denervation groups showed no significant differences between groups in

myocardial infarction (relative risk, 1.3; 95% CI, 0.5 to 3.8), ischemic stroke (relative risk, 1.1; 95% CI, 0.4 to 3.7), or unstable angina (relative risk, 0.6; 95% CI, 0.1 to 5.1).

A network meta-analysis by Silverwatch et al (2022) pooled the results of 20 RCTs of varying approaches to renal denervation compared to sham or antihypertensive medications or one another.[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 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, mo
Silverwatch et al (2022)[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
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 3. Systematic Review Results at 6-Month Follow-Up for Controlled Trials Assessing Renal Denervation

Study	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I^2, %
Silverwatch et al (2022)[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	*Outcome: Group*				*Comparison*:*
				24-h SBP: RFA MRA+B	-7.2 0.6	-13.6 to -0.8 -4.4 to 5.5	SS NS	Sham Sham
				24-h SBP: RFA MRA	-4.7 -1.2	-5.5 to 14.8 -8.6 to 6.2	NS NS	Sham Sham
				24-h SBP: RFA MRA+AHT	-12.9 5.9 -1	-22.6 to -3.2 -11.4 to 1.3 -7.2 to 5.2	SS NS NS	AHT AHT AHT
				24-h SBP: usMRA	-6.9 -6.9	-17.8 to 4.1 -19.9 to 6.3	NS NS	AHT Sham
				24-h SBP: rfMRA+B	-0.2 -10.5	-13.4 to 13.1 -30.7 to 9.7	NS NS	Sham Sham
				24-h SBP: rfMRA	2.3 -7.3	-12.9 to 17.5 -26.4 to 11.8	NS NS	Sham AHT
				24-h SBP: rfMRA+AHT	-0.7 -10.1	-11.7 to 10.4 -21.4 to -0.6	NS SS	AHT AHT
				24-h SBP: usMRA	-1.8	-21.2 to 24.8	NS	AHT

				Office SBP: rfMRA+B Office SBP: rfMRA Office SBP: rfMRA+AHT Office SBP: usMRA Office SBP: rfMRA+B Office SBP: rfMRA Office SBP: rfMRA+AHT Office SBP: usMRA				
Ogoyama et al (2021)[9]	rf RD (1st or 2nd generation device)	Control	6	24-h SBP (N=1137) 24-h DBP (N=1137) Office SBP (N=997) Office DBP (N=997)	 -3.17 -1.58 -4.93 -3.33	-5.22 to -1.11 -3.11 to -0.04 -7.81 to -2.06 -4.88 to -1.78	 SS SS SS SS	 30 47 26 16
Pappaccogli et al (2018)[10]	RD	Control	9 9 10 10	Office SBP Office DBP ASBP ADBP	-3.5 -2.8 -1.8 -0.6	-13.0 to 6.1 -6.0 to 0.4 -4.5 to 0.9 -2.3 to 1.2	NS NS NS NS	90 74 47 63
Coppolino et al (2017)[7]	RD	Control	5 4 6 5	24-h SBP 24-h DBP Office SBP Office DBP	0.3 0.9 -4.1 -1.3	-3.7 to 4.3 -4.5 to 6.4 -15.3 to 7.1 -7.3 to 4.7	NS NS NS NR	NR NR NR NR

*Value reflects comparison group for network meta-analysis not I^2
ADBP: ambulatory diastolic blood pressure; ASBP: ambulatory systolic blood pressure; AHT: antihypertensive therapy; B: branch of renal artery; CI: confidence interval; DBP: diastolic blood pressure; MRA: main renal artery; NR: not reported; NS: not significant; RD: renal denervation; rf: radiofrequency: SBP: systolic blood pressure; SMD: standardized mean difference; SS: statistically significant; usMRA: ultrasound deneveration of main renal artery.

Sham-controlled Randomized Controlled Trials

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

Table 4. Sham-controlled RCT Characteristics

Trial	N	Intervention	Eligibility Criteria	Baseline Characteristics		Primary Outcome
				RDN	Sham	

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 and DBP ≥90 and 24-h SBP 140-170; treatment-naïve individuals eligible	Mean Age: 55.8 Sex: Male, 68.4% Mean BMI: 29,8 Mean office BP: 162/100 Mean 24-h BP: 153/99 Prior Medications: NR	Mean Age: 52.8 Sex: Male, 68.4% Mean BMI: 30.2 Mean office BP: 161/102 Mean 24-h BP: 152/99 Prior Medications: NR	Change in mean office and 24-h BP at 3 months and between groups (unpowered)
SPYRAL HTN-OFFMED Pivotal[12]	331	Symplicity Spyral multielectrode RDN (n=166) vs. sham (n=165) following 3-4 week medication wash-out	Same as above	Mean Age: 52.4 Sex: Male, 64% Race: White, 28%; Black, 22%; NR, 44% Mean BMI: 31.1 Mean office BP: 163/101 Mean 24-h BP: 151/98 Prior Medications: NR	Mean Age: 52.6 Sex: Male, 68% Race: White, 30%; Black, 19%; NR, 48% Mean BMI: 30.9 Mean office BP: 163/102 Mean 24-h BP: 151/99 Prior Medications: NR	Change in mean 24-h SBP at 3 months; superiority margin of -4.0 for 24-hr SBP and -6.5 for office SBP
SPYRAL HTN-ON MED Pilot [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 and DBP ≥90 and 24-h SBP 140-170 despite use of 1-3 medications at ≥50% of maximum dose	Mean Age: 53.9 Sex: Male, 87% Race: White, 34%; Black, 11%; NR, 47% Mean BMI: 31.4 Mean office BP: 165/100 Mean 24-h BP: 152/97 Medications: 2.13	Mean Age: 53.0 Sex: Male, 81% Race: White, 36%; Black 12%; NR, 48% Mean BMI: 32.5 Mean office BP: 164/103 Mean 24-h BP: 151/98 Medications: 1.98	Change in mean office and 24-h BP from baseline to 6 months and between groups (unpowered)
SPYRAL HTN-ON MED Expansion[4]	257	Symplicity Spyral multielectrode RDN (n=168) vs. sham (n=89) on stable doses for at least 6 weeks	Same as above	Mean Age: 55.5 Sex: Male, 80% Race: White, 36%; Black, 12%; NR, 37% Mean BMI: 31.4 Mean office BP: 163/102 Mean 24-h BP: 149/97 Medications: NR	Mean Age: 55 Sex: Male, 78% Race: White, 37%; Black 17%; NR, 39% Mean BMI: 32 Mean office BP: 163/101 Mean 24-h BP: 148/95 Medications: NR	Change in mean 24-h BP from baseline to 6 months and between groups

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

Table 5. Primary Sham-controlled RCT Results

Trial	24-h SBP Change (SD or 95% CI)	24-h DBP Change (SD or 95% CI)	Office SBP Change (SD or 95% CI)	Office DBP Change (SD or 95% CI)
SPYRAL HTN-OFF MEDPilot[11]	3 months			
RDN	-5.5 (-9.1 to -2.0)	-4.8 (-7.0 to -2.6)	-10.0 (-15.1 to -4.9)	-5.3 (-7.8 to -2.7)
Sham	-0.5 (-3.9 to 2.9)	-0.4 (-2.2 to 1.4)	-2.3 (-6.1 to 1.6)	-0.3 (-2.9 to 2.2)
MD (95% CI); p	-5.0 (-9.9 to -0.2); 0.0414	-4.4 (-7.2 to -1.6); 0.0024	-7.7 (-14.0 to -1.5); 0.0155	-4.9 (-8.5 to -1.4); 0.0077
SPYRAL HTN-OFF MEDPivotal[12]	3 months			
RDN	-4.7 (-6.4 to -2.9)	-3.7 (-4.8 to -2.6)	-9.2 (-11.6 to -6.9)	-5.1 (-6.4 to -3.8)
Sham	-0.6 (-2.1 to 0.9)	-0.8 (-1.7 to 0.1)	-2.5 (-4.6 to -0.4)	-1.0 (-2.3 to 0.3)
MD (95% CI); p	-4.0 (-6.2 to -1.8); 0.0005	-3.1 (-4.6 to -1.7);<0.0001	-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	-9.0 (-12.7 to -5.3)	-6.0 (-8.5 to -3.5)	-9.4 (-13.5 to -5.3)	-5.2 (-7.7 to -2.7)
Sham	-1.6 (-5.2 to 2.0)	-1.9 (-4.7 to 0.9)	-2.6 (-6.7 to 1.6)	-1.7 (-4.2 to 0.9)
MD (95% CI); p	-7.4 (-12.5 to -2.3); 0.0051	-4.1 (-7.8 to -0.4); 0.0292	-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	-5.9	NR	-10.1	NR
Sham	-5.8	NR	-6.2	NR
MD (95% CI):p	0.0 (-2.8 to 2.9); 0.974	NR	-9.9	NR

SPYRAL HTN-ON MED Expansion (Full Cohort)[4]	6 Months			
RDN	-6.5	NR	-9.9	NR
Sham	-4.5	NR	-5.1	NR
MD (95% CI); p	-1.9 (-4.4 to 0.5); 0.110	NR	-4.9 (-7.9 to -1.9); 0.001	NR

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

Table 6. Long-term and Subgroup Sham-controlled RCT Results

Trial	24-h SBP MD (95% CI); p	24-h DBP MD (95% CI); p	Office SBP MD (95% CI); p	Office DBP MD (95% CI); p
SYMPLICITY OFF MED (Full-Cohort)[4],				
3 months ± SD, N, p-value	RDN: -4.5 ± 10.8, N=153; p<0.001 Sham: -0.6± 8.7, N=147	NR	RDN: -9.4 ± 14.8, N=170; p<0.001 Sham: -2.3 ±12.7, N=164	NR
6 months ± SD, N, p-value	RDN: -15.3 ± 13.7, N=150 Sham:-17.1 ± 12.3, N=159	NR	RDN: -20.8 ± 13.9, N=174 Sham: -21.9 ± 14.3, N=177	NR
12 months ± SD, N, p-value	RDN: -14.3 ± 11.9, N=146 Sham: -19.2 ± 12.l, N=92; p=0.03	NR	RDN: -21.3 ± 14.2, N=171 Sham: -22.4 ± 13.6, N=104	NR
SPYRAL HTN-ON MED Pilot [13,14]				
3 months	-4.6 (NR); 0.10	-3.7 (NR); 0.06	-1.6 (NR); 0.59	-1.5 (NR); 0.44
6 months	-7.4 (-12.5 to -2.3); 0.0051	-4.1 (-7.8 to -0.4); 0.0292	-6.8 (-12.5 to -1.1); 0.0205	-3.5 (-7.0 to 0); 0.0478
6 months (adherent subgroup)	-6.0 (NR); 0.99	-3.3 (NR); 0.249	-5.1 (NR); 0.144	-2.7 (NR); 0.241
6 months (non-adherent subgroup)	-8.3 (NR); 0.029	-4.6 (NR); 0.062	-7.9 (NR); 0.087	-4.0 (NR); 0.135
12 months	-1.9 (NR); 0.553	-0.8 (NR); 0.695	NR	NR
24 months	-11.2 (-18.4 to -4.0); 0.0031	-5.7 (-10.6 to -0.7); 0.025	-12.9 (-21.1 to -4.7); 0.0026	-8.5 (-15.0 to -2.1); 0.010
24 months (without imputation)	-11.2 (-18.4 to -4.0); 0.003	NR	-11.1 (-21.6 to -0.5); 0.11	NR

36 months	-10.0 (-16.6 to -3.3); 0.0039	-5.9 (-10.1 to -1.8); 0.0055	-11.8 (-19.0 to -4.7); 0.0017	-3.9 (-9.8 to 1.9); 0.186
36 months (without imputation)	-6.1 (-13.6 to 1.4); 0.11	NR	0.5 (-8.8 to 9.7); 0.92	NR

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

Symplicity Spyral OFF-MED Pilot and Pivotal Trials

In 2015, Kandzari and coworkers noted several shortcomings of the failed SYMPLICITY HTN-3 trial, including the use of complex antihypertensive medications regimens, heterogeneous study populations, procedure variability, and choice of primary endpoint.[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 six 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.[3,] 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 Trial 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 medications changes were not permitted through 6 months unless patients met prespecified escape criteria (office SBP ≥180 mmHg or <115 mmHg with symptoms of hypotension). Baseline patient characteristics were similar except for a 19% higher incidence of obstructive sleep apnea in the sham control group. At 6 months for the overall population, the key efficacy outcome of mean 24-h SBP was significantly reduced by -9.0 mmHg with renal denervation, with a statistically significant between-group difference of -7.4 mmHg in favor of renal denervation. Between-group differences were also statistically significant for 24-h DBP, office SBP, office DBP, daytime SBP and DBP, and night-time SBP and DBP in favor of renal denervation. In contrast to prior findings from the SPYRAL HTN-OFF MED trial, no significant between-group differences were noted at 3 months. Medication adherence at 6 months was 60.5% and 64.3% in renal denervation and sham control groups, respectively. Importantly, between-group differences for 24-h SBP and DBP were only significant for the subgroup of non-adherent patients. Additionally, between-group differences for office SBP and DBP were not statistically significant in either adherent or non-adherent subgroup analyses. On an individual patient level, 6-month 24-h SBP reductions were reported for 75% and 58% of patients in renal denervation and sham control groups, respectively.

Mahfoud et al (2022) published long-term outcomes from the SPYRAL HTN-ON MED pilot trial through 36 months.[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. (2024) reported significantly lower 24-hour, morning, and nighttime ambulatory systolic blood pressure in the renal denervation group compared to sham control, with greater reductions of 10.0 mmHg, 15.9 mmHg, and 13.6 mmHg, respectively ($p<0.05$ for all), and a higher proportion of patients achieving blood pressure control in the renal denervation group (40% vs 6%, p=.021).[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 was first reviewed by the 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 CTA or MRA studies at 12 months found that potential stenoses were identified in 31 subjects at 12 months follow-up. Of these, 2 had stenoses of 51-75%, and 5 had stenoses of >76%; on follow-up angiography, 5 reported no stenosis 1 had confirmed 60% diameter stenosis, and 1 had no follow-up imaging.

Sham-controlled study relevance, design, and conduct limitations are summarized in Tables 7and 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 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.		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 submaximal dosing, 4. Low enrollment of women (16%) and racial demographics of enrolled population not reported for nearly half of participants.	5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal.	6. Clinically significant difference for mean 24-h blood pressure observed only in adherent subgroup population.	3. Short duration of blinded follow-up for primary efficacy outcome (6 months).

				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-hr blood pressure. Sub-group analysis shows discordant BP reductions for US and non-US participants on primary outcome.	3. Short duration of blinded follow-up for primary efficacy outcome (6 months).

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

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 at crossover. LOCF may not be the most appropriate approach.	4. Unpowered key secondary endpoint of change in office BP.	

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

Global Symplicity Registry

The Global Symplicity Registry (GSR) is a prospective, multi-center, single-arm, non-interventional and open-label registry that aims to document the long-term safety and effectiveness of renal denervation in a real-world population.[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).[19,] At 36 months post-treatment, office SBP significantly decreased by -19.0 ± 28.3 in the 0 to 3 medication group and -16.2 ± 28.6 mmHg in the ≥4 group (p<.0001). Similarly, 24-h SBP was also significantly (p<.0001) decreased in both the 0 to 3 and ≥4 medication groups (-10.7 ± 19.7 and -8.9 ±2 0.5 mmHg), respectively with a similar magnitude of decrease in both groups. The overall composite adverse event rate was 11.1%, consisting of 2.4% spontaneous myocardial

infarction, 4.6% stroke, 3.9% hospitalizations for new-onset heart failure, 2.9% cardiovascular death, and 5.7% all-cause death. Only the rate of myocardial infarction varied significantly between groups, with those taking 4 or more medication classes experiencing a higher myocardial infarction rate compared to those taking fewer medications (1.8% vs. 0.3%, p=.023).

Table 9. Outcomes of Global Symplicity Registry

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

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

Section Summary: Radiofrequency 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-groups 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 two treatment groups, unbalanced missing 24-h SBP data, and timing of antihypertensive medication related to ABPM monitoring. Study interpretation is also complicated by short-term blinded follow-up and

imputation of excluded crossover patient data, and it is unclear which patients are most likely to derive benefit. Currently, there is no practical method to verify nerve destruction following ablation. A safety analysis on a subset of HTN-ON and HTN-OFF MED participants found only 0.4% had a major adverse event at 1 month follow-up and met its pre-specified performance goal.

Ultrasound Renal Denervation

Weber et al. (2019) reviewed the evolution of renal denervation (RDN) for hypertension. They found that early RDN using radiofrequency ablation (RFA) in main renal arteries showed RDN was effective in lowering blood pressure. However, the first randomized sham-controlled trial, SYMPLICITY-HTN-3 did not show significantly lower office or 24-h ambulatory systolic blood pressure compared with sham treatment. Subsequent studies revealed the importance of targeting distal and branch renal arteries with RFA and a second generation multielectrode system became available. Two randomized sham-controlled trials using this second-generation system that included treatment of the distal renal artery as well as the branch renal arteries in individuals not taking antihypertensive medications, SPYRAL HTN OFF MED, or continuing with antihypertensive medications, SPYRAL HTN-ON MED, demonstrated significant reductions in office and 24-H ambulatory blood pressures compared to sham treatments. Similarly, the RADIANCE-HTN SOLO trial, a randomized sham-controlled trial in patients not receiving medications who underwent ultrasound-based RDN in main renal arteries, also showed significantly lowered daytime ambulatory and office BP compared with sham treatment.[20] These findings have revived interest in defining the role of RDN in hypertensive treatment. Looking ahead, key challenges include developing methods to assess the extent of RDN at the time of the procedure and the potential for renal nerve regrowth after the ablation.

Azizi et al. (2021) published results of the Radiance-HTN TRIO trial, which was a randomized, multicenter, single-blind, sham-controlled study that evaluated the efficacy and safety of ultrasound renal denervation (uRDN) in patients with hypertension resistant to three or more antihypertensive medications. The trial included patients with resistant hypertension who were randomized (1:1) to either uRDN or a sham procedure. The addition of antihypertensive medications were allowed if specified blood pressure thresholds were exceeded. One hundred thirty-six participants were randomly assigned to renal denervation (n=69) or a sham procedure (n=67). Ultrasound renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure at two months.[21] There were no difference in safety outcome between the two groups. While these results are promising, longer term follow is needed to determine whether the blood pressure lowering effect of uRDN remains over time, especially when patients receive additional antihypertensive medications. Additionally, there was between-patient variability in patient response to uRDN suggesting that further research may be needed to identify who is most likely to benefit from uRDN. Last, there is currently no practical method to verify nerve destruction following ablation which may account for some of the variability in patient response. Longer-term studies are needed to confirm the blood pressure lowering effect and safety profile of uRDN. The authors concluded, if the blood pressure lowering effect and safety of u-RDN are maintained long-term, uRDN might be an alternative to the addition of further antihypertensive medications in patients with resistant hypertension.

Rader et al. (2022) assessed the long-term durability of lowering office blood pressure in 51 patients with mild-to-moderate hypertension who were randomized to uRDN as part of the RADIANCE-HTN SOLO trial and completed a 36-month follow-up. The RADIANCE-HTN SOLO trial was a multicenter, international, single-blind, randomized, sham-controlled trial done at 21 centers in the USA and 18 in Europe. Patients with combined systolic–diastolic hypertension aged 18–75 years were eligible if they had ambulatory blood pressure greater than or equal to 135/85 mm Hg and less than 170/105 mm Hg after a 4-week discontinuation of up to two antihypertensive medications and had suitable renal artery anatomy. One hundred and forty-six patients were randomized, 74 to the uRDN arm and 72 to the sham arm. The primary effectiveness endpoint of the original trial was the change in daytime ambulatory systolic blood pressure at 2 months in the intention-to-treat population. Patients were to remain off antihypertensive medications throughout the 2 months of follow-up unless specified blood pressure criteria were exceeded. Patients and physicians were unblinded at 6 months. Fifty-one of 74 patients (age: 53.9±11 years; 67% men) originally randomized to uRDN completed the 36-month follow-up. Initial screening office blood pressure upon study entry was 145/92 ± 14/10 mmHg on a mean of 1.2 antihypertensive medications (range: 0-2.0). Baseline office blood pressure after antihypertensive medication washout was 154/99 ±1 3/8 mmHg. At 36 months, patients were on an average of 1.3 antihypertensive medications (range: 0-3.0) with 8 patients on no antihypertensive medications. Office blood pressure decreased by 18/11±15/9 mmHg from baseline to 36 months ($p<0.001$ for both). Overall, office blood pressure control (<140/90 mmHg) improved from 29.4% at screening to 45.1% at 36 months ($p=0.059$). For patients uncontrolled at screening (n=36), systolic office blood pressure decreased by 10.8 mmHg ($p<0.001$) at 36 months on similar antihypertensive medications ($p=0.158$).[22] The authors concluded that the safety and effectiveness of uRDN was durable to 36 months, with reduced office blood pressure and improved office blood pressure control despite a similar starting medication burden. No new uRDN-related long-term safety concerns were identified. The study had several limitations including the fact that only office blood pressure measurements, not ambulatory blood pressure, were recorded after the 12-month follow-up visit and the study was not powered for office blood pressure at the long-term timepoints. In addition, chemical analysis for determination of medication adherence and measurement of eGFR as a measure of kidney function were no longer performed as a protocol requirement. Another limitation is that patients and physicians were unblinded after the 6-month visit and patients in the sham group could cross over after the primary endpoint was met (after 12 months) therefore, no between-group differences can be evaluated from the data. The authors concluded that their results suggest that long-term BP reductions and improvement of HTN control rates can be achieved with a combination of uRDN and antihypertensive medications.

Azizi et al (2023) published findings from the RADIANCE II trial, in which 224 patients were randomized to uRDN (n=150) or sham treatment (n=74).[23.] 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 antihypertensive 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 uRDN versus -1.8 mmHg with sham, with a baseline-adjusted between-group difference of -6.3 mmHg (95% CI, -9.3 to -3.2 mmHg; p<.001). Six of 7 secondary BP outcomes significantly favored renal denervation: 24-h ambulatory SBP, home SBP, office SBP, daytime ambulatory DBP, 24-hour ambulatory DBP, and home DBP. Only office DBP did not reach statistical significance. The BP-lowering effect was consistent across subgroups and throughout the 24-hour period. No major adverse events occurred in either group. A total of 64.1% in the uRDN 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 uRDN achieved this blood pressure reduction while using fewer antihypertensive medications compared to the sham control group (1.33 vs.1.73 medications).[24] The authors concluded that, in patients with hypertension, ultrasound renal denervation reduced daytime ambulatory SBP at 2 months in the absence of antihypertensive medications vs a sham procedure without postprocedural major adverse events.

Fulton et al. (2024) discuss the current landscape and future directions of renal denervation as a treatment for hypertension in the United States. They note that that hypertension is a significant contributor to cardiovascular morbidity and mortality in the USA, affecting nearly half of the US population, with over 40% continuing to have uncontrolled hypertension. They state that multiple randomized, placebo-controlled, randomized studies have shown the safety and efficacy of renal denervation, leading to the recent approval of two devices by the US Food and Drug Administration (FDA). However, there are still issues regarding the future of the technology in its applications and reimbursement landscapes.[25] The article emphasizes that despite the promising results of renal denervation in reducing blood pressure, there are challenges in its widespread adoption due to the lack of long-term data, identification of which patients will benefit most from the procedure, and what the magnitude of that benefit is.

Summary of Evidence:
For individuals who have uncontrolled hypertension, despite the use of anti-hypertensive medications, who receive RFA of the renal sympathetic nerves, the evidence includes numerous RCTs, numerous systematic reviews of the RCTs, as well as multiple nonrandomized comparative studies and case series. Relevant outcomes are symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. The proof of principle SPYRAL HTN-OFF MED study found that multielectrode renal denervation was superior to sham in the absence of background antihypertensive medication therapy, with between-group differences of -4.0 mmHg for 24-h SBP and -6.6 for office SBP at 3 months. The unpowered SPYRAL HTN-ON MED 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. However, 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 currently, there is no practical method to verify nerve destruction following ablation. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have uncontrolled hypertension, despite the use of anti-hypertensive medications, who receive ultrasound renal denervation (usRDN), the evidence includes 3 randomized sham-controlled trials. 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-HTNSOLO 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 inpatients with a standardized triple combination antihypertensive treatment, found a -4.5 mmHg difference in daytime ambulatory SBP at 2 months. 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. Adverse events were infrequent and similar between usRDN and sham groups across studies. 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. The evidence is insufficient to determine that the technology results in an improvement in net health outcomes.

SUPPLEMENTAL INFORMATION

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

Practice Guidelines and Position Statements

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

American Heart Association 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.[26] The following recommendations were issued concerning renal denervation:

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

European Society of 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.[27] 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 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.

European Society for Hypertension (ESH)

The ESH, with endorsement by the European Renal Association and the International Society of Hypertension, issued guidance on the management of arterial hypertension in 2023.[28] The following recommendations were issued concerning renal denervation:

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

A class of recommendation I indicates a general consensus that the measure is useful, and a class II recommendation reflects that there is no general consensus and that only doubtful evidence exists. An 'A' level of evidence indicates that RCTs or meta-analyses with cardiovascular disease outcomes are available for this recommendation, a level 'B' suggests RCTs with surrogate measures, observational studies with cardiovascular disease outcomes or meta-analyses are available, and a C recommendation reflects either expert opinion or only observational or lower quality experimental evidence.
ESH recommendations did not discuss the specific use of radiofrequency renal denervation and included evidence from other modalities, such as ultrasound, in their evidence appraisal.

National Institute for Health and Care Excellence

In 2023, the National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance on the use of percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension, recommending that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research due to limited evidence. [29]

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.[30.]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 (eg, comorbidities of coronary artery disease, diabetes, prior transient ischemic attack/cerebrovascular accident, or chronic kidney disease) who may have the greatest benefit from blood pressure reduction

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02439749[a]	Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications (SPYRAL HTN-OFF MED)		Dec 2023(ongoing)
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 (recruiting)
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 (active,not recruiting)

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 (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]	The 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)
NCT05027685a	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 (active)
NCT05988411a	ULTRA-HFIB-Redo: Ultrasound-based Renal Sympathetic Denervation vs Control in Redo Ablation Patients	200	Dec 2024 (recruiting)
Unpublished			
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.

Government Regulations

National:

There is no national coverage determination (NCD) on this topic.

Local:

There is no local coverage determination (LCD) on this topic.

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: Category III Codes (A56902)
Original effective date 08/29/2019; Revision effective date 11/17/2024

Procedure codes 0338T and 0339T as not included as covered procedures.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Radiofrequency Ablation of Miscellaneous Solid Tumors, Excluding Liver Tumors
- Radiofrequency Ablation of Primary or Metastatic Liver Tumors

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/28/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/14	2/18/14	2/28/14	Joint policy established
5/1/16	2/16/16	2/16/16	Routine maintenance
5/1/17	2/21/17	2/21/17	Routine maintenance
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance
5/1/21	2/16/21		Routine maintenance Added ref 4 and 47
5/1/22	2/15/22		Routine maintenance
5/1/23	2/21/23		Routine maintenance (jf) new references 4, 5, 6, 8,9, 10,11, 53, 54 Vendor Managed: NA Revised Title: added “Or uncontrolled”
5/1/24	2/20/24		Routine maintenance (jf) Vendor managed: NA Original Title: Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment resistant or for Uncontrolled Hypertension Revised to Title Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Uncontrolled Hypertension Edited title and medical policy statement. Ref: Added 2,3,13,14,25
5/1/25	2/18/25		Routine maintenance (jf) Vendor managed: NA • Edits to Description, Regulatory section, rationale

			section and summary of evidence • Edit to MPS “individuals” replaced “patients”, added “and ultrasound denervation” Title Change: Previous Title: Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Uncontrolled Hypertension Revised Title: Renal Denervation for Uncontrolled Hypertension Added Ref: 1,19.20, 21,22,23,24,25,26,27,28,29,30 1/31/25 We received a literature review from Medtronic for coverage of Symplicity Spyral renal denervation system. 19 references are already listed in our policy in support of continuing our E/I stance.

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: RENAL DENERVATION FOR UNCONTROLLED HYPERTENSION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.