Medical Policy Manual Surgery, Policy No. 235

Radiofrequency and Ultrasound Ablation of the Renal Sympathetic Nerves as a Treatment for Uncontrolled Hypertension

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Radiofrequency ablation (RFA) or ultrasound ablation 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. 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.

MEDICAL POLICY CRITERIA

Radiofrequency or ultrasound ablation of the renal sympathetic nerves is considered **investigational** for the treatment of uncontrolled hypertension.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

UNCONTROLLED HYPERTENSION

Hypertension is estimated to affect approximately 30% of the population in the U.S.[1] 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.[2] Uncontrolled hypertension is diagnosed when an individual's blood pressure remains above targeted levels when a patient either is not using, or unable to use, treatments to control blood pressure or when hypertension persists despite antihypertensive therapies.[3] 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[3]. 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.[4] Also, sometimes it is necessary to address comorbid conditions (i.e., 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 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) or ultrasound ablation 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.[5]

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 or ultrasound energy, is delivered to the arterial walls where the renal sympathetic nerves are located. Once adequate energy has been delivered to ablate the sympathetic nerves, the catheter is removed.

Regulatory Status

The Symplicity Spyral™ Renal Denervation System (Medtronic) is a multielectrode RFA catheter system designed to deliver 4-quadrant ablations and received FDA approval on November 17th, 2023.

Several other devices have been developed for this purpose and are in various stages of application for FDA approval (FDA product code: DQY):

- The EnligHTN™ Multi-Electrode Renal Denervation System (St. Jude Medical) is an RFA catheter using a 4-point multiablation basket design. In January 2014, the EnligHTN™ Renal Guiding Catheter was cleared for marketing by the FDA through the 510(k) process, based on substantial equivalence to predicate devices for the following indication: percutaneous use through an introducer sheath to facilitate a pathway to introduce interventional and diagnostic devices into the renal arterial vasculature.
- The Vessix™ Renal Denervation System (Boston Scientific; formerly the V2 renal denervation system, Vessix Vascular) is a combination of an RF balloon catheter and bipolar RF generator technologies, intended to permit a lower voltage intervention.
- Other RFA catheters (eg, Thermocouple Catheter™ [Biosense Webster]) used for other types of ablation procedures (eg, cardiac electrophysiology procedures) have been used off-label for RFA of the renal arteries.

The Paradise™ Ultrasound Renal Denervation System (Recor Medical) received FDA premarket approval on November 7, 2023.[6] The device is 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 (FDA product code QYI).

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health treatment for hypertension, which 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 denervation of the renal nerves by radiofrequency or ultrasound ablation. 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.

RENAL DENERVATION FOR THE TREATMENT OF HYPERTENSION

Systematic Reviews

Multiple systematic reviews with overlapping studies, one of which is a Cochrane review by Coppolino (2017), updated by Pisano (2021)[7, 8] have summarized the key RCTs evaluating renal denervation. The characteristics of the systematic reviews are summarized in Table 1, and the key results are summarized in Table 2. 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.

Singh (2023) published a systematic review with meta-analysis which included nine RCTs that compared RDN with sham treatment in adult patients with hypertension.[9] The RCTs, which included a total of 1,643 patients, reported on various blood pressure outcomes, including 24-hour ambulatory, daytime ambulatory, and office blood pressure. The results showed that RDN significantly reduced systolic and diastolic blood pressure compared to sham treatment, with mean differences of -4.20 mmHg (95% CI -5.36 to -3.03) and -2.38 mmHg (95% CI -3.42 to -1.35), respectively. Office blood pressure was also significantly reduced for both systolic and diastolic blood pressure (MD -5.46; 95% CI -7.12 to -3.81; $p<0.00001$ and MD -3.17; 95% CI -4.23 to -2.12; $p<0.00001$). These findings were consistent across different blood pressure measurements, including daytime ambulatory and office blood pressure. There was no significant difference in the effect of RDN on blood pressure between RFA and ultrasound-based treatments. This review did not assess cardiovascular endpoints.

Pisano (2021) published a Cochrane systematic review which evaluated the effectiveness and safety of renal sympathetic denervation (RDN) for treatment of resistant hypertension.[8] The review included 15 randomized controlled trials (RCTs) and quasi-RCTs that compared RDN with standard medical therapy or sham intervention (n=1,416). Included studies assessed adults with refractory or resistant hypertension, defined as clinic blood pressure above target despite the concomitant use of three or more antihypertensive drugs of different classes, including a diuretic and had a duration of at least six months. Studies of both RFA and ultrasound ablation methods were included. In four studies, RDN was compared to a sham procedure; in the remaining studies, RDN was tested against standard or intensified antihypertensive therapy. Most studies had unclear or high risk of bias for allocation concealment and blinding. The reviewers concluded that, when compared to sham controls, there is low-certainty evidence that RDN has little or no effect on the risk of myocardial infarction (4 studies, 742 participants; RR 1.31, 95% CI 0.45 to 3.84), ischemic stroke (5 studies, 892 participants; RR 0.98, 95% CI 0.33 to 2.95), unstable angina (3 studies, 270 participants; RR 0.51, 95% CI 0.09 to 2.89) or hospitalization (3 studies, 743 participants; RR 1.24, 95% CI 0.50 to 3.11). Based on moderate-certainty evidence, RDN may reduce 24-hour ambulatory blood pressure monitoring (ABPM) systolic BP (9 studies, 1,045 participants; MD -5.29 mmHg, 95% CI -10.46 to -0.13), ABPM diastolic BP (8 studies, 1,004 participants; MD -3.75 mmHg, 95% CI -7.10 to -0.39) and office diastolic BP (8 studies, 1,049 participants; MD -4.61 mmHg, 95% CI -8.23 to -0.99). However, this procedure had little or no effect on office systolic BP (10 studies, 1,090 participants; MD -5.92 mmHg, 95% CI -12.94 to 1.10). Moderate-certainty evidence suggested that RDN may not reduce serum creatinine (5 studies, 721 participants, MD 0.03 mg/dL, 95% CI -0.06 to 0.13) and may not increase the estimated glomerular filtration rate (eGFR) or creatinine clearance (6 studies, 822 participants; MD -2.56 mL/min, 95% CI -7.53 to 2.42). The reviewers concluded that in patients with resistant hypertension, there is low-certainty evidence that RDN does not improve major cardiovascular outcomes and renal function, and moderate-certainty evidence suggests that RDN may improve 24-hour ABPM and diastolic office-measured BP. Future trials with longer follow-up, larger sample sizes, standardized procedural methods, and measurement of patient-centered outcomes instead of surrogate outcomes are needed to determine the utility of RDN for the treatment of hypertension.

Coppolino (2017) published a Cochrane review which reported that none of the trials were 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 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).

Most analyses included 6-month follow-up measurements, while a review by Chen (2017),[10] calculated change in blood pressure for subgroups at 12-month follow-up. The 12-month analysis showed no difference at the longer follow-up. A network meta-analysis by Silverwatch (2022) pooled the results of 20 RCTs of varying approaches to renal denervation compared to sham or antihypertensive medications or one another.[11] 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 1. Characteristics of Systematic Review of Controlled Trials Assessing Renal Denervation

Study	Dates	Trials	N (Range)	Design	Duration, mo
Silverwatch et al (2022)[11]	2010-2020	20	2152 (20-535)	RCT	2 - 6
Singh et al (2023)[9]	2010-2023	9	1643 (51-535)	RCT	2 - 6
Ogoyama et al (2021)[12]	2014-2021	9	1555 (51-535)	RCT, CT	2 - 6
Pisano et al (2021)[8]	2010-2020	15	1416 (32-535)	RCT	6
Pappaccogli et al (2018)[13]	2010-2016	11	1236 (19-535)	RCT, CT	6
Coppolino et al (2017)[7]	2010-2016	12	1149 (16-535)	RCT, CT	6
Chen et al (2017)[10]	2010-2016	9	1068 (19-535)	RCT	6
Fadl Elmula et al (2017)[14]	2010-2017	10	1174 (19-524)	RCT, CT	6
Sun et al (2016)[15]	2010-2015	9	2932 (67-622)	RCT, CT	6
Zhang et al (2016)[16]	2013-2015	11	1160 (19-535)	RCT, CT	6
Yao et al (2016)[17]	2010-2015	8	1059 (19-535)	RCT	6
Fadl Elmula et al (2015)[18]	2010-2015	7	985 (20-535)	RCT	6

CT: controlled trial; RCT: randomized controlled trial.

Table 2. 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)[11]	RD (radio-frequency of main renal artery, main renal artery plus branch, main renal artery plus anti-hypertensive treatment or ultrasound of main renal artery)	Sham or AHT (network meta-analysis)	20	*Outcome: Group*				*Comparison**:
				24-h SBP: rfMRA+B	-7.2	-13.6 to -0.8	SS	Sham
				24-h SBP: rfMRA	0.6	-4.4 to 5.5	NS	Sham
				24-h SBP: rfMRA+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	-10.1	-21.4 to -0.6	SS	AHT
				Office SBP: usMRA	-1.8	-21.2 to 24.8	NS	AHT
Ogoyama et al (2021)[12]	rf RD (1st or 2nd generation device)	Control	6	24-h SBP (N=1137)	-3.17	-5.22 to -1.11	SS	30
				24-h DBP (N=1137)	-1.58	-3.11 to -0.04	SS	47
				Office SBP (N=997)	-4.93	-7.81 to -2.06	SS	26
				Office DBP (N=997)	-3.33	-4.88 to -1.78	SS	16
Pappaccogli et al (2018)[13]	RD	Control	9	Office SBP	-3.5	-13.0 to 6.1	NS	90
			9	Office DBP	-2.8	-6.0 to 0.4	NS	74
			10	ASBP	-1.8	-4.5 to 0.9	NS	47
			10	ADBP	-0.6	-2.3 to 1.2	NS	63
Coppolino et al (2017)[7]	RD	Control	5	24-h SBP	0.3	-3.7 to 4.3	NS	NR
			4	24-h DBP	0.9	-4.5 to 6.4	NS	NR
			6	Office SBP	-4.1	-15.3 to 7.1	NS	NR
			5	Office DBP	-1.3	-7.3 to 4.7	NR	NR
Chen et al (2017)[10]	RD	Control	9	24-h SBP	-1.1	-4.7 to 2.5	.55	67
			7	Office SBP	-2.5	-12.9 to 7.8	.63	90
Fadl Elmula et al (2017)[14]	RD	Control	8	Office SBP	-3.6	-12.8 to 5.6	.45	NR
			10	24-h SBP	-1.0	-4.3 to 2.3	.54	NR

Study	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I^2, %
Sun et al (2016)[15]	RD	Control	9 8	Office SBP Office DBP	-12.81 -5.56	-22.77 to -2.85 -8.15 to -2.97	.01 <.001	92 63
Zhang et al (2016)[16]	RD	Control	11	Office SBP	-13.9	-21.17 to -6.63	<.001	93
Yao et al (2016)[17]	RD	Control	8 8	Office SBP Office DBP	-8.23 -3.77	-16.86 to 0.39 -7.21 to -0.32	NR NR	93 90
Fadl Elmula et al (2015)[18]	RD	Control	15	Office SBP	-4.89	-20.9 to 11.1	.47	92

*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.

RADIOFREQUENCY ABLATION

Randomized Controlled Trials

Characteristics and results of sham-controlled RCTs are summarized in Tables 3 through 5.

Table 3. Sham-controlled RCT Characteristics

Trial	N	Intervention	Eligibility criteria	Baseline characteristics		Primary Outcome
				RDN	**Sham**	
SPYRAL HTN-OFF MED Pilot[19]	80	Symplicity Spyral multielectrode RDN (n=38) vs. sham (n=42) following 3-4 week medication wash-out	Age 20-80 y with office SBP 150-180, DBP ≥90, and 24-h SBP 140-170; treatment-naïve individuals eligible	Mean Age: 55.8 Sex: Male, 68.4% Mean BMI: 29,8 Mean office BP: 162/100 Mean 24-h BP: 153/99 Prior Medications: NR	Mean Age: 52.8 Sex: Male, 68.4% Mean BMI: 30.2 Mean office BP: 161/102 Mean 24-h BP: 152/99 Prior Medications: NR	Change in mean office and 24-h BP at 3 months and between groups (unpowered)
SPYRAL HTN-OFFMED Pivotal[20]	331	Symplicity Spyral multielectrode RDN (n=166) vs.	Same as above	Mean Age: 52.4 Sex: Male, 64% Race: White, 28%; Black, 22%;	Mean Age: 52.6 Sex: Male, 68% Race: White, 30%; Black, 19%; NR,	Change in mean 24-h SBP at 3 months; superiority margin of -

Trial	N	Intervention	Eligibility criteria	Baseline characteristics		Primary Outcome
				RDN	**Sham**	
		sham (n=165) following 3-4 week medication wash-out		NR, 44% Mean BMI: 31.1 Mean office BP: 163/101 Mean 24-h BP: 151/98 Prior Medications: NR	48% Mean BMI: 30.9 Mean office BP: 163/102 Mean 24-h BP: 151/99 Prior Medications: NR	4.0 for 24-hr SBP and -6.5 for office SBP
SPYRAL HTN-ON MED **Pilot**[21, 22]	80	Symplicity Spyral multielectrode RDN (n=38) vs. sham (n=42) on stable doses for at least 6 weeks	Age 20-80 y with office SBP 150-180, DBP ≥90, 24-h SBP 140-170 despite use of 1-3 medications at ≥50% of maximum dose	Mean Age: 53.9 Sex: Male, 87% Race: White, 34%; Black, 11%; NR, 47% Mean BMI: 31.4 Mean office BP: 165/100 Mean 24-h BP: 152/97 Medications: 2.13	Mean Age: 53.0 Sex: Male, 81% Race: White, 36%; Black 12%; NR, 48% Mean BMI: 32.5 Mean office BP: 164/103 Mean 24-h BP: 151/98 Medications: 1.98	Change in mean office and 24-h BP from baseline to 6 months and between groups (unpowered)
SPYRAL HTN-ON MED Expansion[3]	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; BMI: body mass index; DBP: diastolic blood pressure; NR: not reported; RDN: renal denervation; SBP: systolic blood pressure.

Table 4. 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)	24-h SBP Change (SD or 95% CI)
SPYRAL HTN-OFF MED Pilot[19]	**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)	RDN
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)	Sham
MD (95% CI); p	-5.0 (-9.9 to -0.2);.0414	-4.4 (-7.2 to -1.6);.0024	-7.7 (-14.0 to -1.5);.0155	-4.9 (-8.5 to -1.4);.0077	MD (95% CI); p
SPYRAL HTN-OFF MED Pivotal[20]	**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)	RDN
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)	Sham
MD (95% CI); p	-4.0 (-6.2 to -1.8);.0005	-3.1 (-4.6 to -1.7);<.0001	-6.6 (-9.6 to -3.5); <.0001	-4.4 (-6.2 to -2.6); <.0001	MD (95% CI); p
SPYRAL HTN-ON MED Pilot[21, 22]	**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)	RDN
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)	Sham
MD (95% CI); p	-7.4 (-12.5 to -2.3);.0051	-4.1 (-7.8 to -0.4);.0292	-6.8 (-12.5 to -1.1);.0205	-3.5 (-7.0 to 0);.0478	MD (95% CI); p
SPYRAL HTN-ON MED Expansion[3]	**6 months**				
RDN	-5.9	NR	-10.1	NR	RDN
Sham	-5.8	NR	-6.2	NR	Sham
MD (95% CI); p	0.0 (-2.8 to 2.9);.974	NR	-4.0 (-7.6 to 0.4);.028	NR	MD (95% CI); p
SPYRAL HTN-ON MED Expansion (Full Cohort)[3]	**6 months**				
RDN	-6.5	NR	-9.9	NR	RDN
Sham	-4.5	NR	-5.1	NR	Sham
MD (95% CI); p	-1.9 (-4.4 to 0.5);.110	NR	-4.9 (-7.9 to -1.9);.001	NR	MD (95% CI); p

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

Table 5. 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)[3]				
3 months ± SD, N, p-value	RDN: -4.5 ± 10.8, N=153; p<.001 Sham: -0.6± 8.7, N=147	NR	RDN: -9.4 ± 14.8, N=170; p<.001 Sham: -2.3 ±12.7, N=164	NR
6 months ± SD, N, p-value	RDN: -15.3 ± 13.7, N=150 Sham:-17.1 ± 12.3, N=159	NR	RDN: -20.8 ± 13.9, N=174 Sham: -21.9 ± 14.3, N=177	NR
12 months ± SD, N, p-value	RDN: -14.3 ± 11.9, N=146 Sham: -19.2 ± 12.l, N=92; p=.03	NR	RDN: -21.3 ± 14.2, N=171 Sham: -22.4 ± 13.6, N=104	NR
SPYRAL HTN-ON MED Pilot[21, 22]				
3 months	-4.6 (NR);.10	-3.7 (NR);.06	-1.6 (NR); 0.59	-1.5 (NR);.44
6 months	-7.4 (-12.5 to -2.3);.0051	-4.1 (-7.8 to -0.4);.0292	-6.8 (-12.5 to -1.1);.0205	-3.5 (-7.0 to 0);.0478
6 months (adherent subgroup)	-6.0 (NR);.99	-3.3 (NR);.249	-5.1 (NR);.144	-2.7 (NR);.241
6 months (non-adherent subgroup)	-8.3 (NR);.029	-4.6 (NR);.062	-7.9 (NR);.087	-4.0 (NR);.135
12 months	-1.9 (NR);.553	-0.8 (NR);.695	NR	NR
24 months	-11.2 (-18.4 to -4.0);.0031	-5.7 (-10.6 to -0.7);.025	-12.9 (-21.1 to -4.7);.0026	-8.5 (-15.0 to -2.1);.010
24 months (without imputation)	-11.2 (-18.4 to -4.0);.003	NR	-11.1 (-21.6 to -0.5);.11	NR
36 months	-10.0 (-16.6 to -3.3);.0039	-5.9 (-10.1 to -1.8);.0055	-11.8 (-19.0 to -4.7); ^{0}.0017	-3.9 (-9.8 to 1.9);.186
36 months (without imputation)	-6.1 (-13.6 to 1.4);.11	NR	0.5 (-8.8 to 9.7);.92	NR

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

Symplicity Spyral OFF-MED Pilot and Pivotal Trials

In 2015, Kandzari 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.[23] 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 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).[19] 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 (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).[20] 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.[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 6).

Symplicity Spyral ON-MED Pilot and Expansion Trials

Kandzari (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).[21] 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 (2022) published long-term outcomes from the SPYRAL HTN-ON MED pilot trial through 36 months.[22] 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. 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 has yet to be published, but results are available from material from the FDA August 23, 2023 Meeting of the Circulatory System Devices Panel for the Medtronic, Inc. Symplicity Spyral Renal Denervation System at the time of drafting this health assessment.[3] The eligibility criteria and primary efficacy endpoint were identical to the HTN-ON MED pilot study described above, with similar baseline characteristics (Table 4). The expansion trial randomized participants 2:1 to renal denervation (n=168) or sham treatment (n=89) and assessed patients as part of the expansion study alone or as part of a merged full cohort incorporating pilot data. A total of 12 patients in the renal denervation group and 13 in the sham group met escape criteria. Additionally, few patients from the pilot cohort were able to be incorporated into the full analysis due to large discrepancies outcome effects. Medtronic postulated that these differences might be due to unbalanced antihypertensive medication changes between groups, which showed that a higher proportion of sham control patients increased BP medications (17% in the renal denervation group vs. 30% in the sham group), non-evaluable 24-h SBP data (11.5% in the sham group vs. 6.8% in the renal denervation group), or confounding due to timing of BP medication use in relation to 24-h ambulatory monitoring.

The primary efficacy endpoint of baseline adjusted change in 24-h SBP from baseline to 6-months post-procedure, compared between renal denervation and sham groups did not show a significant difference in the expansion cohort or the full cohort of patients on Baysesan analysis (mean Bayesian posterior treatment effect, -0.03 mmHg; 95% CI, -2.92 to 2.76, posterior probability of superiority, =0.51). However, 6 month office SBP did show a significant difference favoring the renal denervation group (mean Bayesian posterior treatment effect, -4.1 mmHg; 95% CI, -7.4 to 0.75, posterior probability of superiority, =0.99), but the outcome assessment was non-powered. These results were mirrored in the frequentist ANCOVA analysis in both the expansion and full cohorts, which showed no differences in 24-h SBP but favored renal denervation for office SBP (Table 5). 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 6 and 7 below.

Table 6. Sham-controlled Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
SPYRAL HTN-OFF MED Pilot[19]	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[20]	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[21, 22]	1. Intended use population is unclear as patients were permitted to take 1-3 medications at baseline with submaximal dosing; 4. Low enrollment of women (16%) and racial demographics of enrolled population not reported for nearly half of participants.	5. Number of ablations at main, branch, and accessory renal vessels not standardized and no practical methods to verify nerve destruction are available.	2. Not standard or optimal.	6. Clinically significant difference for mean 24-h blood pressure observed only in adherent subgroup population. No clinically significant difference for mean office blood pressure observed in either adherent or non-adherent subgroup analyses.	3. Short duration of blinded follow-up for primary efficacy outcome (6 months).
SPYRAL HTN-ON MED Expansion[3]	4. Low enrollment of women and racial	5. Number of ablations at main, branch, and accessory renal	2. Not standard or optimal. Different rates	6. Clinically significant difference for mean office	3. Short duration of blinded follow-up

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
	demographics of enrolled population not reported for nearly half of participants.	vessels not standardized and no practical methods to verify nerve destruction are available.	of hypertension medication changes in renal denervation and sham groups post-randomization.	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.	for primary efficacy outcome (6 months).

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

Table 7. 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[19]					4. Unpowered pilot study.	
SPYRAL HTN-OFF MED Pivotal[20]						
SPYRAL HTN-ON MED Pilot[21, 22]				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				4-5. Inadequate handling of crossovers with	4. Unpowered key	

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
MED Expansion[3]				inappropriate exclusion of blood pressure measurements at crossover. LOCF may not be the most appropriate approach.	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.[3] 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 8). 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.

Table 8. 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

Outcome	Baseline Blood Pressure	6 Months	12 Months	24 Months	36 Months
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

ULTRASOUND ABLATION

Randomized Controlled Trials

RCTs not included in the systematic reviews referenced above are discussed below.

Azizi (2023) published results from the RADIANCE II, sham-controlled RCT of 224 patients with hypertension (seated office systolic BP [SBP] ≥140 mm Hg and diastolic BP [DBP] ≥90 mm Hg despite taking up to two antihypertensive medications).[24] Participants were aged 18 to 75 years and were to abstain from antihypertensive medications until the two-month follow-up unless prespecified BP criteria were exceeded and were associated with clinical symptoms. Participants and accessors were blinded to treatment assignment. Participants were randomized 2:1 (treatment: sham). After 12-month follow-up, sham-treated participants were eligible to receive cross-over RDN treatment. After insertion of the catheter device, a minimum of two sonications were delivered to each the left and right renal arteries. The primary outcome was the mean change in daytime ambulatory systolic blood pressure (SBP) at two months. The results showed that RDN significantly reduced daytime ambulatory SBP compared to the sham procedure, with a mean difference of -6.3 mmHg (95% CI, -9.3 to -3.2 mmHg, p<0.001). Additionally, RDN improved six out of seven secondary blood pressure outcomes, including 24-hour ambulatory SBP, home SBP, office SBP, and diastolic blood pressure parameters. No major adverse events were reported in either group. This study is limited by a short follow-up period, lack of cardiovascular endpoints, lack of comparison to other treatments for uncontrolled hypertension, and the exclusion of patients with a history of cardiovascular or cerebrovascular events, which may limit the generalizability of the results.

SECTION SUMMARY: RANDOMIZED CONTROLLED TRIALS

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 trial results are generalizable to a real-world population. The SPYRAL HTN-ON MED pilot trial also found significant between-group differences of -7.4 mmHg for 24-h SBP and -6.8 mmHg for office SBP at 6 months for the overall population in favor of renal denervation. However, the 24-h SBP results were only significant for the subgroup of medication non-adherent patients. Subgroup analyses of both the non-adherent and adherent populations failed to find a significant between-group difference for office SBP and DBP. Long-term data from the SPYRAL HTN-ON MED study suggest that blood pressure reductions with multielectrode renal denervation are progressive and sustained over time, with between-group differences of -10.0 mmHg for 24-h SBP and -11.8 for office SBP for the overall population at 36 months. These differences lost significance without imputation. The SPYRAL HTN-ON MED Expansion study did not meet its primary effectiveness endpoint. No difference in 24-h SBP (0.03 mmHg) between the renal denervation and sham groups in HTN-ON MED was observed, although there was a significant difference in reduction for office SBP (4.1 mmHg), which favored the renal denervation group. Several confounders may have impacted the HTN-ON MED outcomes, including unbalanced medication changes between the 2 treatment groups, unbalanced missing 24-h SBP data, and timing of antihypertensive medication related to ABPM monitoring. Study interpretation is also complicated by short-term blinded follow-up and imputation of excluded crossover patient data, and it is unclear which patients are most likely to derive benefit. Currently, there is no practical method to verify nerve destruction following ablation. A safety analysis on a subset of HTN-ON and HTN-OFF MED participants found only 0.4% had a major adverse event at 1 month follow-up and met its pre-specified performance goal.

PRACTICE GUIDELINE SUMMARY

AMERICAN HEART ASSOCIATION

The American Heart Association (AHA), American College of Cardiology (AHA), and American Society of Hypertension (ASH; 2015) issued joint guidelines on the treatment of hypertension in patients with coronary artery disease.[25] The guidelines noted the Symplicity HTN-3 trial did not find a significant benefit from renal denervation and stated that additional randomized controlled trials would be needed.

The AHA, ACC, and 9 additional specialty societies (2018) published joint guidelines on the prevention, detection, evaluation, and management of high blood pressure in adults.[26] In discussing resistant hypertension, the guidelines indicated that studies using catheter ablation of renal sympathetic nerves "have not provided sufficient evidence to recommend the use of these devices."

The AHA (2018) published a Scientific Statement on the detection, evaluation, and management of resistant hypertension.[27] The AHA Statement discussed the lack of benefit found in the Symplicity HTN-3 trial, as well as its methodological limitations. The statement also referred to the more recent positive data from the SPYRAL HTN-OFF MED trial but noted that because the enrolled patients did not have resistant hypertension, "at best, this represents a proof-of-principle study demonstrating the role of the renal sympathetic nervous system in hypertension." The statement concluded that "the role of device-based sympatholytic treatments, as with renal denervation and baroreceptor stimulation, awaits clarification."

EIGHTH JOINT NATIONAL COMMITTEE

The Eighth Joint National Committee (2014), which was appointed to provide recommendations on hypertension treatment, published an evidence-based guideline on the management of hypertension in adults.[28] These recommendations did not discuss the use of renal denervation.

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.[29] 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/1.73m2 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/1.73m2. (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)

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.[30]

SUMMARY

There is not enough research to show that radiofrequency or ultrasound ablation of renal sympathetic nerves improves net health outcomes in patients with uncontrolled hypertension. Therefore, the use of radiofrequency ablation of renal sympathetic nerves for the treatment of uncontrolled hypertension is considered investigational.

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CODES

Codes	Number	Description
CPT	0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and

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

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