Healthy Blue

Medical Policy

Subject:	Radiofrequency Ablation of the Renal Sympathetic Nerves		
Document #:	SURG.00135	**Publish Date:**	09/27/2023
Status:	Reviewed	**Last Review Date:**	08/10/2023

Description/Scope

This document addresses use of radiofrequency ablation (RFA) of the renal sympathetic nerves for all indications, including but not limited to, treatment for resistant hypertension.

Note: For information related to other techniques for the treatment of resistant hypertension, please see:

- SURG.00124 Carotid Sinus Baroreceptor Stimulation Devices

Position Statement

Investigational and Not Medically Necessary:

Radiofrequency ablation of the renal sympathetic nerves is considered **investigational and not medically necessary** for all indications.

Rationale

Radiofrequency ablation (RFA) is a minimally invasive surgical procedure utilizing low power radiofrequency (RF) energy to ablate (or destroy) various tissues of the body. There are many RFA procedures that utilize specially designed ablation devices to treat multiple organ systems and disorders, such as cardiac arrhythmias, Barrett's esophagus, malignant tumors, varicose veins and for pain management. This document only addresses RFA procedures and devices specifically designed to ablate (or denervate) the sympathetic renal nerves for any indication, including but not limited to, the treatment of resistant hypertension (HTN).

Resistant HTN is defined as blood pressure (BP) above goal despite treatment with three antihypertensive agents of different classes, ideally including a diuretic, all prescribed at optimal dose amounts (Calhoun, 2008). Resistant HTN is a relatively common condition, estimated to affect approximately 30% of the adult population in the United States. In large clinical trials of HTN treatment, up to 20-30% of participants meet the definition for resistant HTN, and in tertiary care HTN clinics, the prevalence has been estimated to be 11-18% (Acelajado, 2010).

Resistant HTN is associated with a higher risk for adverse outcomes, such as stroke, myocardial infarction (MI), heart failure (HF), and kidney failure. Notably, resistant HTN is not the same as uncontrolled HTN. Uncontrolled HTN is a lack of BP control due to factors, such as poor adherence to the medication schedule, insufficient doses of antihypertensive medications, excessive salt or alcohol intake, volume overload, drug-induced HTN, and other forms of secondary HTN, due to comorbid conditions (Doumas, 2010).

RFA for the treatment of HTN is theorized to decrease both the afferent sympathetic signals from the kidneys to the brain and the efferent signals from the brain to the kidneys. This decreases sympathetic activation, decreases

vasoconstriction, and decreases activation of the renin-angiotensin system, which potentially lowers the BP (Zile, 2012).

There are several devices that have been developed for renal sympathetic denervation as a proposed treatment option for resistant HTN. To date, no proposed RFA device has been cleared by the U.S. Food and Drug Administration (FDA) for ablation of the renal sympathetic nerves as a treatment for HTN. The EnligHTN™ Renal Guide Catheter (St. Jude Medical, Plymouth, MN) received clearance from the FDA in 2014 for marketing 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" (FDA, 2014). The Symplicity™ Renal Denervation (RDN) System (Medtronic, Inc., Plainfield, IN) was launched commercially in April 2010 and is currently available in countries outside the U.S. The Symplicity RDN System consists of a flexible catheter for percutaneous use in the renal arteries and an external power generator. At the present time, the Symplicity RDN System is limited to *investigational use only* in the U.S. Other similar catheter-based devices with FDA clearance for the same indications include the St. Jude Medical EnligHTN™ Multi-electrode RDN System (St. Jude Medical, Inc., St. Paul, MN) and the Vessix™ Guide Sheath (Boston Scientific Corp., Maple Grove, MN).

The SYMPLICITY HTN-3 was a Phase 3, single blinded, prospective, sham-controlled, randomized controlled trial (RCT) that was designed to evaluate the safety and effectiveness of RDN with the Symplicity RDN System in subjects with resistant HTN. A total of 535 study subjects underwent randomization. The mean (± standard deviation [SD]) change in systolic blood pressure (SBP) at 6 months was -14.13 ± 23.93 mm Hg in the RDN group, as compared with -11.74 ± 25.94 mm Hg in the sham-procedure group ($p<0.001$ for both comparisons of the change from baseline), for a difference of -2.39 mm Hg (95% confidence interval [CI], -6.89 to 2.12; $p=0.26$ for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory SBP was -6.75 ± 15.11 mm Hg in the RDN group and -4.79 ± 17.25 mm Hg in the sham-procedure group, for a difference of -1.96 mm Hg (95% CI, -4.97 to 1.06; $p=0.98$ for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups. The investigators concluded that this trial did not show a significant reduction in SBP in individuals with resistant HTN 6 months after RDN, as compared with a sham control (Bhatt, 2014). Additional articles have been published with up to 12 month results of the SYMPLICITY HTN-3 trial, in which they also concluded that the trial did not demonstrate a benefit from RDN or reduction in ambulatory SBP in either the 24-hour or day-and-night periods, as compared with sham (Bakris, 2014; Bakris, 2015).

In January 2014, Medtronic, Inc. announced that its pivotal trial in the U.S., the SYMPLICITY HTN-3 trial, failed to meet its primary and secondary efficacy endpoints, as described above. As a result, Medtronic's intends to formulate a panel of independent advisors made up of physicians and researchers who will be asked to make recommendations about the future of the global HTN clinical trial program, now known as the SPYRAL HTN Global Clinical Program. This program is described by the manufacturer, Medtronic's as, "A multi-phased clinical study strategy aimed to establish the safety and efficacy of RDN to lower blood pressure." Panel members will also provide advice on continued physician and patient access to the SYMPLICITY technology in countries with regulatory approval for this device. According to this announcement from Medtronic's, pending the panel review determinations, the company will suspend enrollment in the three countries where RDN HTN trials were being conducted, as part of the application process for regulatory approval, (which were SYMPLICITY HTN-4 in the U.S., HTN-Japan and HTN-India). In light of the results of the SYMPLICITY HTN-3 trial, Medtronic's will discontinue the already suspended SYMPLICITY HTN-4 trial. Medtronic's also announced that it would continue to enroll individuals in the Global SYMPLICITY Registry.

Since results of the SYMPLICITY HTN-3 trial were published, the manufacturer has modified and redesigned the catheter, which is now known as the SYMPLICITY SPYRAL™ System. This catheter device now has more electrodes to deliver up to four simultaneous RFAs in a helical pattern, and treatment of branch vessels has been added to the technique. According to Medtronic's, the FDA has provided investigational device exemption (IDE) approval for the two initial trials of the SPYRAL HTN Global Clinical Trial Program, which are randomized, sham-controlled studies evaluating the device in up to 433 subjects at 50 sites in the U.S., Europe, Australia, and Japan.

The SPYRAL HTN-OFF MED study (NCT02439749) has primary efficacy and safety endpoints, which are 24-hour BP at 3 months and major adverse events through 1 month after randomization, respectively. The second trial utilized a separate cohort of 80 trial subjects; the SPYRAL HTN ON-MED study (NCT02439775) required eligible subjects to be treated with a consistent medical therapy of up to 3 antihypertensive drugs during the study. The SPYRAL HTN OFF-MED study included a 3- to 4-week drug washout period followed by a 3-month efficacy and safety endpoint in the absence of antihypertensive medications. In 2017, Townsend and colleagues reported 3-month results of the SPYRAL HTN OFF-MED trial. This study included subjects with a mean 24-hour ambulatory systolic (SBP) of 140 mm Hg or greater and less than 170 mm Hg at second screening who underwent renal angiography and were randomly assigned to RDN or sham control. Results at 3 months reflected 24-hour ambulatory BP decreased from baseline to 3 months in the RDN group (24-hour SBP -5.5 mm Hg [95% CI, -9.1 to -2.0; p=0.0031], and 24-hour diastolic blood pressure [DBP] -4.8 mm Hg [-7.0 to -2.6; p<0.0001]; office SBP -10.0 mm Hg [-15.1 to -4.9; p=0.0004], and office DBP -5.3 mm Hg [-7.8 to -2.7; p=0.0002]). No significant changes were seen in the sham-control group (24-hour SBP -0.5 mm Hg [95% CI, -3.9 to 2.9; p=0.7644], 24-hour DBP -0.4 mm Hg [-2.2 to 1.4; p=0.6448], and office SBP -2.3 mm Hg [-6.1 to 1.6; p=0.2381], and office DBP -0.3 mm Hg [-2.9 to 2.2; p=0.8052]). The mean difference between the groups favored RDN for 3 month change in both office and 24-hour BP from baseline: 24-hour SBP -5.0 mm Hg (95% CI, -9.9 to -0.2; p=0.0414), 24-hour DBP -4.4 mm Hg (-7.2 to -1.6; p=0.0024), office SBP -7.7 mm Hg (-14.0 to -1.5; p=0.0155), and office DBP -4.9 mm Hg (-8.5 to -1.4; p=0.0077). There were no major adverse events in either group (Townsend, 2017).

In the SPYRAL HTN-ON MED trial, 80 subjects with uncontrolled HTN (office SBP, 150–180 mm Hg; DBP, 90 mm Hg or higher) were randomized to RDN with RFA or a sham procedure with angiography. Trial participants were taking up to 3 antihypertensive drugs. Office and 24-hour ambulatory BP decreased significantly from baseline to 6 months in the RDN group (mean baseline-adjusted treatment differences in 24-hour SBP -7.0 mm Hg, 95% CI, -12.0 to -2.1; p=0.0059, 24-hour DBP -4.3 mm Hg, -7.8 to -0.8; p=0.0174, office SBP -6.6 mm Hg, -12.4 to -0.9; p=0.0250, and office DBP -4.2 mm Hg, -7.7 to -0.7; p=0.0190). The change in BP was significantly greater at 6 months in the RDN group than the sham-control group for office SBP (difference -6.8 mm Hg, 95% CI, -12.5 to -1.1; p=0.0205), 24-hour SBP (difference -7.4 mm Hg, -12.5 to -2.3; p=0.0051), office DBP (difference -3.5 mm Hg, -7.0 to -0.0; p=0.0478), and 24-hour DBP (difference -4.1 mm Hg, -7.8 to -0.4; p=0.0292). Evaluation of hourly changes in 24-hour SBP and DBP showed BP reductions throughout 24 hours for the RDN group. At 3 months, BP reductions were not significantly different between groups. It was also noted that medication adherence was about 60% and varied for individual trial subjects throughout the study. No major adverse events were recorded in either group (Kandzari, 2018). The primary estimated completion dates for these two trials are as follows: for SPYRAL HTN ON-MED study – January 2021; SPYRAL HTN OFF-MED study – June 2020.

Additional studies have investigated confounding factors that potentially affected the early results of RFA trials. In 2016, the DENERHTN trial (Renal Denervation for Hypertension) attempted to report the influence of adherence to

antihypertensive treatment regimens on BP control. Individual adherence to antihypertensive medical treatment was evaluated at 6 months with drug screening of urine and plasma samples from 85 trial subjects. The numbers of trial subjects who were fully adherent (20/40 versus 21/45), partially nonadherent (13/40 versus 20/45), or completely nonadherent (7/40 versus 4/45) to antihypertensive treatment did not differ significantly in the RDN and control groups, respectively (p=0.3605). The difference noted in the change in daytime ambulatory SBP from baseline to 6 months between the 2 groups was -6.7 mm Hg (p=0.0461) in the fully adherent and -7.8 mm Hg (p=0.0996) in the nonadherent group (made up of the partially nonadherent plus the completely nonadherent). The between-subject variability in daytime ambulatory SBP was greater for the nonadherent than for the fully adherent subjects. The authors concluded that the prevalence of nonadherence to antihypertensive drugs at 6 months was high (≈50%), but not different in the RDN and control groups. Regardless of adherence to medical treatment, RDN plus standardized stepped-care antihypertensive treatment resulted in a greater decrease in BP than with standardized antihypertensive medical treatment alone. The number of responders was greater in the RDN group (20/44, 44.5%) than in the control group (11/53, 20.8%; p=0.01). In the discriminant analysis, baseline average nighttime SBP and standard deviation were significant predictors of the SBP response in the RDN group only, allowing adequate responder classification of 70% of the trial participants. According to the investigators, this analysis indicated that RDN lowers ambulatory BP homogeneously over 24 hours in subjects with resistant HTN, which suggests that nighttime SBP and variability are predictors of the BP response to RDN (Azizi, 2016; Gosse, 2017).

Results of a prior small, short-term, RCT, the Symplicity HTN-2 trial, were published in 2010. This trial evaluated RDN using the Symplicity RDN System versus standard pharmacologic treatment for a total of 106 subjects with resistant HTN, (defined as having a SBP of at least 160 mm Hg despite regimens of three or more antihypertensive medications). The trial was unblinded, and subjects were followed for 6 months with a primary endpoint of between-group differences in the change in BP over the course of the 6-month trial. Secondary outcomes included a composite outcome of adverse cardiovascular events and adverse effects of treatment. Baseline BP was 178/98 in the RFA treatment group and 178/97 in the control group treated with medications alone. At 6 months, the BP reductions in the RFA group were 32 mm Hg systolic (standard deviation [SD] of 23) and 12 mm Hg diastolic (SD of 11). In the control group, there was a 1 mm Hg increase in SBP and no change for DBP (p<0.0001 for both SBP and DBP differences). The percent of subjects who achieved a SBP of 140 mm or less was 39% (19/49) in the RFA group, compared to 6% (3/51) in the control group (p<0.0001). There was no difference in renal function, as measured by serum creatinine, between groups at the 6-month follow-up time. In the RFA group, 3 subjects reported an adverse cardiovascular event compared to 2 in the control group (p=nonsignificant). Other serious adverse events requiring admission in the RFA group included 1 case each of nausea/vomiting, hypertensive crisis, transient ischemic attack (TIA), and hypotension. In each group, 3 subjects were lost to follow-up. It was noted that larger studies with longer outcomes data are needed to demonstrate the safety and efficacy of RFA of the renal nerves as a treatment of resistant HTN. The additional issue of durability of treatment effect also warrants investigation, due to the potential for post-treatment re-innervation of the treated renal nerves, which could potentially result in diminished therapeutic effect over time following the RFA procedure (Esler, 2010).

Follow-up outcomes data at 36 months were reported in 2014 in 40 of 52 subjects in the initial RDN group and at 30 months in 30 of 37 subjects who crossed over and received RDN at 6 months. Baseline BP was 184 ± 19/99 ± 16 mm Hg in all treated subjects. At 30 months post-procedure, SBP decreased 34 mm Hg (95% CI: -40, -27; p<0.01) and DBP decreased 13 mm Hg (95% CI: -16, -10; p<0.01). The systolic and diastolic BP reduction at 36 months for the initial RDN group was -33 mm Hg (95% CI: -40, -25; p<0.01) and -14 mm Hg (95% CI: -17, -10; p<0.01), respectively. Procedural complications included 1 hematoma and 1 renal artery dissection before energy delivery that were treated successfully. Later complications included 2 cases of acute renal failure, which fully

resolved, 15 hypertensive events requiring hospitalization, and 3 deaths that were deemed unrelated to the device or the therapy. The authors concluded that RDN resulted in sustained lowering of BP at 3 years in a selected population of subjects with severe, treatment-resistant HTN without serious safety concerns. These longer-term findings were limited by the lack of comparison to a control group, due to the crossover design (Esler, 2014).

In 2016, the Agency for Healthcare Research and Quality (AHRQ) issued a technical brief with results of a systematic review of the literature to assess the effectiveness of RDN in the Medicare population. This report was conducted by the Johns Hopkins University Evidence-based Practice Center at the request of the Centers for Medicare and Medicaid Services (CMS). Data was abstracted from 83 studies (n=7660); 9 were RCTs, 8 were comparative cohorts, and 66 were non-comparative cohorts. It was noted that the trial participants within the included studies were only partially comparable to the Medicare-eligible population, due to the multifactorial causes of treatment-resistant HTN. Additional limitations of the literature review included variable eligibility criteria between the studies, the fact that adherence to diet and medications was not routinely assessed in all the studies, and only 10 (12%) of all studies described a run-in period prior to randomization. None of the studies were designed or powered to detect a long-term difference between groups in clinical endpoints, such as stroke, MI, hospitalization, or mortality, and few studies reported these outcomes. Also beneficial clinical effects of RDN by specific subgroups (age, gender, race/ethnicity) were seldom and inconsistently reported. Details about different RDN techniques used and interventionalist training and experience were not uniformly reported. Only 6-month outcomes data was reported in the majority of included studies. The technical brief provided the following conclusions:

> Limited evidence suggests that renal denervation in patients with treatment-resistant HTN lowers systolic BP, but the results were highly variable and the studies reviewed were not designed to determine improvement in clinical endpoints. The most rigorously conducted RCTs showed much smaller BP reductions, as compared with observational non-comparative studies. Further research is needed to identify optimal candidates for renal denervation, refine next generation renal denervation technology, develop methods for assessing completeness of renal denervation procedures, and demonstrate the efficacy of renal denervation in reducing BP and improving clinical endpoints, including the risk of stroke, myocardial infarction, heart failure, and death in patients with HTN (Shafi, AHRQ, 2016).

A systematic review and meta-analysis included nine RCTs comprised of 674 individuals with hypertension who received sham RDN. The primary outcome was systolic and diastolic BP. The sham arms showed a significant decrease in both systolic and diastolic BP, highlighting the importance of RCTs to determine the magnitude of effect of RDN in resistant HTN (Fernandes, 2023).

In 2022, Bhatt and colleagues published 36-month follow-up results of the industry-sponsored SYMPLICITY HTN-3 trial, previously described as Medtronic's pivotal trial in the U.S. which failed to meet its primary and secondary efficacy endpoints. The original primary endpoint was the change in systolic BP from baseline to 6 months for the RDN group compared with the sham control group. Following the initial 6-month follow-up, participants were unmasked and those in the sham group who met the inclusion criteria (office BP ≥160 mm Hg, 24 h ambulatory systolic BP ≥135 mm Hg, and still prescribed three or more antihypertensive medications) could cross over to receive renal artery denervation. Changes in BP up to 36 months were analyzed in the original RDN group and in the sham control group, including those who crossed over to RDN and those who did not (remained in the control group). The study's safety endpoints were the incidence of all-cause mortality, end stage renal disease,

significant embolic event, renal artery perforation or dissection requiring intervention, vascular complications, hospitalization for hypertensive crisis unrelated to non-adherence to medications, or new renal artery stenosis of more than 70% within 6 months. Follow-up data from 36-months were available for 219 individuals in the original RDN group (originally, n=364), 63 in the crossover group, and 33 in the control group (originally, n=171). At 36 months, the change in office systolic BP and 24 h ambulatory systolic BP was significantly lower in the RDN group ($p \leq 0.0001$, for both outcomes). The rates of adverse events were similar across treatment groups. Given the trials failure to meet its original primary and secondary endpoints, and the high rate of attrition at 36 months, further study is warranted.

In 2022, Mahfoud published results of a pre-specified analysis of the SPYRAL HTN-ON MED study, a single-blind, sham RCT which enrolled individuals with a 24-h ambulatory systolic BP between 140 mm Hg and less than 170 mm Hg, while taking one to three antihypertensive drugs with stable doses for at least 6 weeks. Study participants underwent renal angiography and were randomly assigned (1:1) to radiofrequency RDN or a sham control group. After 12-month follow-up, participants and physicians were unmasked and the sham group could cross over to the treatment arm. The primary endpoint was the treatment difference in mean 24-h systolic BP at 6 months between the RDN group and the sham control group. Statistical analyses were done on the intention-to-treat population. Long-term efficacy was assessed using ambulatory and office BP measurements up to 36 months. Among 467 enrolled participants, 80 fulfilled the qualifying criteria and were randomly assigned to undergo RDN (n=38) or a sham procedure (n=42). Mean ambulatory systolic and diastolic BP were significantly reduced from baseline in the RDN group and were significantly lower than the sham control group at 24 and 36 months, despite a similar treatment intensity of antihypertensive drugs. The medication burden at 36 months did not differ significantly between groups. At 36 months, the ambulatory systolic BP reduction was -18.7 mm Hg (SD 12.4) for the renal denervation group (n=30) and -8.6 mm Hg (14.6) for the sham control group (n=32; adjusted treatment difference -10.0 mm Hg, 95% CI -16.6 to -3.3; p=0.0039). There were no short-term or long-term safety issues associated with RDN. The study is ongoing with a target enrollment of an additional 260 participants (NCT02439775).

Despite modestly favorable results for RDN as treatment of drug-resistant uncontrolled HTN from several trials, benefit from renal nerve denervation compared with a sham procedure has not been consistently established. Additional, well-powered studies with sufficient long-term follow-up to assess net health outcomes data are warranted. There are multiple additional interventional trials in progress and ongoing RCTs of new RDN catheters as a treatment for resistant HTN (Azizi, 2018; de Jager, 2017; Kandzari, 2016; Mauri, 2018; Rader, 2022).

Background/Overview

RFA of the sympathetic renal nerves is performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery, and controlled, 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. It is anticipated that this procedure will be performed on an outpatient basis with the use of appropriate anesthesia. Potential complications of this procedure include, but are not limited to, vascular access problems, perforation of the renal artery and renal artery stenosis. Additional information is needed from the clinical trials currently in progress regarding the safety and efficacy associated with RFA of the renal nerves.

Definitions

Radiofrequency ablation (RFA): This minimally invasive surgical procedure utilizes low power radiofrequency energy to ablate (or destroy) various tissues of the body.

Resistant hypertension (HTN): Blood pressure (BP) above goal despite treatment with three antihypertensive agents, of different classes ideally including a diuretic, all prescribed at optimal dose amounts.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

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

ICD-10 Procedure

	For the following code when specified as ablation (or destruction) of renal sympathetic nerves:
015M3ZZ	Destruction of abdominal sympathetic nerve, percutaneous approach

ICD-10 Diagnosis

	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Description/Scope, Rationale and References updated.
Reviewed	08/11/2022	MPTAC review. References updated.
Reviewed	08/12/2021	MPTAC review. References updated.
Reviewed	08/13/2020	MPTAC review. The References were updated. Updated Coding section; removed 015L3ZZ, 015N3ZZ (not applicable).
Reviewed	08/22/2019	MPTAC review. The References updated.
Reviewed	09/13/2018	MPTAC review. The Rationale and References sections updated.
Reviewed	11/02/2017	MPTAC review. The document header wording was updated from "Current Effective Date" to "Publish Date." The Rationale and References sections updated.

Reviewed	11/03/2016	MPTAC review. Updated Rationale and References sections.
Reviewed	11/05/2015	MPTAC review. The Rationale and References were updated. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review. The Rationale and References updated.
Reviewed	11/14/2013	MPTAC review. The Rationale and References updated. Updated Coding section with 01/01/2014 CPT changes.
New	11/08/2012	MPTAC review. Initial document development.