Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy #  00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers radiofrequency ablation (RFA) of the renal sympathetic nerves for the treatment of resistant hypertension to be investigational.*

Background/Overview
Radiofrequency 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 decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system. RFA of the renal sympathetic nerves may act as a nonpharmacologic treatment for hypertension and has been proposed as a treatment option for patients with resistant hypertension.

Resistant Hypertension
Hypertension is a widely prevalent condition, which is estimated to affect approximately 30% of the population in the United States. It accounts for a high burden of morbidity related to strokes, ischemic heart disease, kidney disease, and peripheral arterial disease. Resistant hypertension is defined as elevated blood pressure (BP), despite treatment with at least 3 antihypertensive agents at optimal doses. Resistant hypertension is also a relatively common condition, given the large number of individuals with hypertension. In large clinical trials of hypertension treatment, up to 20% to 30% of participants meet the definition for resistant hypertension, and in tertiary care hypertension clinics, the prevalence has been estimated to be 11% to 18%. Resistant hypertension is associated with a higher risk for adverse outcomes such as stroke, myocardial infarction (MI), heart failure, and kidney failure.

There are a number of factors that may contribute to uncontrolled hypertension, and these should be considered and addressed in all patients with hypertension before labeling a patient resistant. These include nonadherence to medications, excessive salt intake, inadequate doses of medications, excess alcohol intake, volume overload, drug-induced hypertension, and other forms of secondary hypertension. Also, sometimes it is necessary to address comorbid conditions, ie, obstructive sleep apnea, to adequately control BP.

Treatment for resistant hypertension is mainly intensified drug therapy, sometimes with the use of nontraditional antihypertensive medications such as spironolactone and/or minoxidil. However, control of resistant hypertension with additional medications is often challenging and can lead to high costs and frequent adverse effects of treatment. As a result, there is a large unmet need for additional treatments that

* Disclaimer: The information provided in this policy is for general information purposes only and is not intended to replace the advice of a qualified health care provider. Before making any decisions regarding medical treatment, it is important to consult with a qualified health care provider. The Company reserves the right to review and update this policy periodically.

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

can control resistant hypertension. Nonpharmacologic interventions for resistant hypertension include modulation of the baroreflex receptor and/or radiofrequency (RF) denervation of the renal nerves.

**RF Denervation of the Renal Sympathetic Nerves**

Increased sympathetic nervous system activity has been linked to essential hypertension. Surgical sympathectomy has been shown to be effective in reducing BP but is limited by the side 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. 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.

The procedure is performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery and 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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration

No RFA devices have been approved for ablation of the renal sympathetic nerves as a treatment for hypertension. There are several devices that have been developed for this purpose and are in various stages of application for U.S. FDA approval.

- The Symplicity™ renal denervation device (Medtronic Inc., Minneapolis, MN) consists of a flexible catheter that is specifically intended for use in the renal arteries, and an external power generator.
- The EnligHTN™ multielectrode renal denervation system (St. Judge Medical, Plymouth, MN) is an RFA catheter using a 4-point multiablation basket design. In January 2014, the EnligHTN Renal Guiding Catheter received clearance for marketing through the 510(k) process based on substantial equivalence to predicate devices (product code: DQY) 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 One-Shot Renal Denervation System™ (Covidien, Dublin) is an irrigated RFA balloon catheter, consisting of a spiral shaped electrode surrounding a balloon that is intended to ablate using 1 application. On January 21, 2014, Covidien announced it will exit its OneShot Renal Denervation program.
- The Vessix™ Renal Denervation System (Boston Scientific, Marlborough, MA; formerly the V2 renal denervation system, Vessix Vascular) is a combination of a RF balloon catheter and bipolar RF generator technologies, intended to permit a lower voltage intervention.
- The Thermocouple Catheter™ (Biosense Webster, Diamond Bar, CA) is an RFA catheter that is in clinical use for cardiac electrophysiology procedures, and also has been used for RFA of the renal arteries.
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy #  00465
Original Effective Date:  08/19/2015
Current Effective Date:  08/17/2016

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
This evidence review is updated periodically with literature reviews, most recently through August 3, 2015.

A determination of the efficacy of this technology requires high-quality randomized controlled trials (RCTs). This is due to the natural variability in blood pressure, the heterogeneity of the patient populations with increased blood pressure, and the presence of many potential confounders of outcome. A sham-controlled RCT is ideal, because it would also control for any placebo effects, or other nonspecific effects of treatment of hypertension. Case series have limited utility for determining efficacy. They can be useful for demonstrating potential of the technique, for determining the rate of short- and long-term adverse effects of treatment, and to evaluate the durability of the treatment response.

The literature review identified several RCTs, the largest of which compared renal denervation with sham control for patients with treatment-resistant hypertension. Several other smaller RCTs have also been conducted, one that compared renal denervation with standard care for patients with resistant hypertension, and a second that compared renal denervation plus cardiac ablation versus cardiac ablation alone for patients with resistant hypertension and atrial fibrillation. There were also a number of nonrandomized controlled trials and case series. These relevant studies are reviewed next.

Randomized Controlled Trials
DENERHTN Trial
In 2015, Azizi et al published results of the Renal Denervation for Hypertension (DENERHTN) trial, a prospective, open-label RCT with blinded end point evaluation. The study randomized 106 adults with confirmed resistant hypertension who had undergone 4 weeks of standardized triple antihypertensive therapy with sustained-release indapamide, ramipril (or irbesartan in cases of cough), and amlodipine to either renal denervation or control. Both groups received standardized stepped-care antihypertensive treatment (SSAHT), which involved the sequential addition of spironolactone, bisoprolol, sustained-release prazosin for systolic and diastolic pressures of 135 mm Hg or higher or 85 mm Hg or higher, respectively. Spironolactone could be started for home systolic and diastolic pressures of 170 mm Hg or higher or 105 mmHg or higher, respectively. Analysis was conducted using a modified intention-to-treat design, after excluding 5 patients in the intervention group who were missing primary endpoint measurements. For the study’s primary efficacy end point, the mean decrease in daytime ambulatory systolic blood pressure (SBP) was greater in the renal denervation group than in the control group (mean baseline-adjusted difference between groups, -5.9 mm Hg; 95% confidence interval [CI] -11.3 to -0.5 mm Hg; p=0.033). There were similarly greater decreases in nighttime and 24-hour SBP in the renal denervation group than in the control group. Nighttime blood pressure control was achieved at 6 months in 31.3% of renal denervation patients (vs 11.3% of controls; p=0.012) and 24-hour ambulatory blood pressure control was achieved in 39.6% of renal denervation patients (vs 18.9% of controls; p=0.013). Rates of daytime blood pressure control did not differ significantly between groups. The number of antihypertensive treatments at 6 months did not differ significantly between groups (mean, 5.25 for renal denervation patients vs 5.36 for control patients;
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

p=0.701). Three renal denervation-related adverse events were reported (lumbar pain in 2 patients, mild groin hematoma in 1 patient).

**Prague-15 Study**
Rosa et al reported results of the Prague-15 study, an open-label RCT comparing renal sympathetic denervation with intensified pharmacologic treatment in patients with resistant hypertension. Although study enrollment was planned for 120 subjects to have a 90% power in detecting a difference in treatment response between the 2 groups with an alpha of 0.05, the study was prematurely halted after the results of the Symplicity HTN-3 trial were published after enrollment of 112 subjects (56 in each group). Patients in the renal denervation group were maintained on baseline medical therapy; those in the control group received baseline medical therapy plus spironolactone. After 6 months, both groups demonstrated significant reductions in 24 hour average SBP (-8.6 mm Hg, p<0.001 [vs baseline] for renal denervation patients; -8.1 mm Hg, p=0.001 [vs baseline] for control patients). After 6 months, there were no significant differences in the absolute value of or the change in any of the blood pressure parameters reported between the renal denervation and control group.

**Symplicity HTN-3**
Results of the Symplicity HTN-3 trial, a multicenter, single-blinded, randomized, sham-controlled trial of renal denervation were published in 2014. Included patients had severe, resistant hypertension, with a systolic BP (SBP) of 160 mm Hg or higher, on maximally tolerated doses of at least 3 antihypertensive medications of complementary classes, 1 of which had to be a diuretic at an appropriate dose. Five-hundred thirty-five patients were randomized to renal denervation with the Medtronic Symplicity renal denervation catheter or to renal angiography only (sham control).

Changes in antihypertensive medication were not allowed during the 6-month follow-up period unless they were considered to be clinically necessary. The primary efficacy end point was the mean change in office SBP from baseline to 6 months in the denervation group, compared with the mean change in the sham control group. The secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure at 6 months. The primary safety end point was a composite of major adverse events, defined as death from any cause, end stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months.

At the 6-month follow-up point, there was no significant between-group difference in the change in office BP. There was a change in SBP of -14.13±23.93 mm Hg in the denervation group versus -11.74±25.94 mm Hg in the sham control group, for a difference of -2.39 mm Hg (95% CI, −6.89 to 2.12; p=0.26 with a superiority margin of 5 mm Hg). At 6-month follow-up, the change in ambulatory BP was -6.75±15.11 mm Hg in the denervation group versus -4.79±17.25 mm Hg in the sham control group, for a difference of -1.96 mm Hg (95% CI, -4.97 to 1.06; p=0.98 with a superiority margin of 2 mm Hg). Major adverse event rates were similar between the denervation and control groups (1.4% and 0.6%, respectively).

Strengths of this study include its large size and blinded, sham-controlled design, which reduce the likelihood of a placebo effect. A limitation of the present publication is that the follow-up period reported is...
relatively short, leading to an underdetection of a treatment benefit differences between the groups manifest over time. The study subjects, including those who do not cross over to renal denervation, will be followed for 5 years to assess longer term outcomes.

Bakris et al reported more detailed ambulatory BP results from the Symplicity HTN-3 trial. The change in average 24-hour ambulatory SBP and diastolic BP (DBP) were as reported by Bhat et al. There were no significant differences in change in ambulatory BP between the renal denervation and control groups for any of the prespecified subgroup analyses, including the presence of coexisting diabetes mellitus; sex; race; body mass index of 30 kg/m2 or more; eGFR of 60 mL/min/1.73 m2 or more; age of 60 years or older; or any medication change during the study.

Bakris et al also reported 12-month follow-up from the Symplicity HTN-3 trial, including the original denervation group, the sham subjects who crossed over to renal denervation, and the sham subjects who did not cross over. The 12-month follow-up was available for 319 of 361 denervation subjects and 48 of 101 non−crossover subjects and 6-month denervation follow-up was available for 93 of 101 crossover subjects. At 12-month follow-up, the changes in office SBP compared with baseline were significantly greater than at 6-month follow up in the renal denervation group (-18.9 mm Hg vs -15.5 mm Hg, p=0.025). However, there were no significant differences in ambulatory blood pressure monitoring between the 12 and 6 months results in the renal denervation group. In the crossover group, the 6-month drop in office SBP and 24-hour ambulatory SBP were -17.7 mm Hg (p<0.001 for comparison with baseline) and -9.2 mm Hg (p<0.001 for comparison with baseline), respectively. In the non−crossover group, 48 subjects had 12-month data available. Among those, the change in office SBP from baseline to 6 months was -32.9 mm Hg; the change in office SBP from 6 to 12 months was an increase of 11.5 mm Hg, for an overall SBP drop from baseline to 12 months of -21.4 mm Hg.

Symplicity HTN-2
The Symplicity HTN-2 trial was a multicenter, unblinded RCT evaluating renal sympathetic denervation versus standard pharmacologic treatment for patients with resistant hypertension. A total of 106 patients with an SBP of at least 160 mm Hg, despite 3 or more antihypertensive medications were enrolled. The trial was unblinded, and clinicians ascertaining outcomes were not blinded to treatment assignment. Patients were followed for 6 months with the primary end point being the between-group difference in the change in BP over the course of the trial. Secondary outcomes included a composite outcome of adverse cardiovascular events and adverse effects of treatment. Baseline BP was 178/98 in the RFA group and 178/97 in the control group.

At 6-month follow-up, the BP reductions in the RFA group were 32 mm Hg systolic (SD=23) and 12 mm Hg diastolic (SD=11). In the control group, there was a 1 mm Hg increase in SBP and no change for DBP (p<0.001 for both SBP and DBP differences). The percent of patients who achieved an SBP of 140 or less was 39% (19/49) in the radiofrequency ablation (RFA) group compared with 6% (3/51) in the control group (p=0.001). There was no difference in renal function, as measured by serum creatinine, between groups at the 6-month time period. There were 3 patients in the RFA group who had adverse cardiovascular events compared with 2 in the control group (p=NS). Other serious adverse events requiring admission in the RFA.
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

One-year follow-up data from the Symplicity HTN-2 trial were reported in 2013. This report included 47 of the 52 patients originally randomized to the RFA group, who were subsequently followed in an uncontrolled fashion after the 6-month follow-up. It also included 6-month follow-up of patients originally randomized to the control group, who were then offered crossover to RFA after 6 months. A total of 46 of 54 patients accepted crossover to RFA; 35 were available at the 12-month time point. For the patients originally randomized to RFA, the decrease in BP at 12 months was 28.1±24.9 mm Hg for SBP and 9.7±10.6 mm Hg for DBP. These decreases in BP were not significantly different from those reported at the 6-month time point (31.7±23.1 mm Hg systolic, 11.7±11.2 mm Hg diastolic). For the crossover group, the decrease in BP 6 months after renal denervation was 23.7±27.5 mm Hg systolic and 8.4±12.1 mm Hg diastolic. There were 2 procedural complications in the crossover group, 1 patient with a dissection of the renal artery and 1 patient with a hypotensive episode.

Three-year follow-up data from the Symplicity HTN-2 trial were reported in 2014. Follow-up was available for 40 of 52 subjects in the initial RFA group and for 30 of 37 subjects who were initially in the control group but who crossed over and were offered RFA treatment 6 months after enrollment. After 30 months, the mean change in SBP was -34 mm Hg (95% CI, -40 to -27, p<0.01) and the mean change in DBP was -13 mm Hg (95% CI, -16 to -10, p<0.01). The degree of BP change was similar between the randomized and crossover subjects. Subjects in the initial RFA group had follow-up available at 36 months; at that point, the mean change in SBP was -33 mm Hg (95% CI, -40 to -25, p<0.01) and the mean change in DBP was -14 mm Hg (95% CI, -17 to -10, p<0.01). Beyond 12 months of follow-up, safety events included 5 hypertensive events requiring hospitalization; 1 case of mild transient acute renal failure due to dehydration; 2 episodes of atrial fibrillation requiring hospitalization; 1 case of acute renal failure due to acute interstitial nephritis that was deemed unrelated to renal denervation treatment; and 3 deaths that were deemed unrelated to the device or therapy.

The main limitations of this RCT are that it is small in size, unblinded, and has only a relatively short follow-up for the controlled portion of the trial. A trial with a sham control would allow better determination of whether the treatment effect was due to a placebo effect, or other nonspecific effects of being in a trial. The 6-month follow-up reported for the controlled portion of the trial is too short to ascertain whether the reduction in BP is likely to reduce adverse cardiovascular outcomes such as MI and stroke. The 12- and 36-month follow-up reports provide some insight into longer-term outcomes following the procedure, although comparison with a control group is no longer possible due to the crossover design.

It is unknown whether reinnervation of the renal sympathetic nerves occurs post-treatment. If reinnervation does occur, the efficacy of the procedure will diminish over time. The BP change appears to be stable over the longer-term follow-up studies, suggesting that reinnervation did not occur in the 36-month follow-up.

Other RCTs
Desch et al reported results from a smaller RCT comparing renal sympathetic denervation with sham control among patients with treatment-resistant hypertension but only mildly elevated blood pressures
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

(daytime SBP 135-149 mm Hg and DBP 90-94 mm Hg on 24 ambulatory monitoring). Seventy-one patients were randomized to denervation (n=35) or sham control (n=35). Subjects and all investigators except for the physicians performing the active and sham procedures were blinded to treatment group. For the study’s primary end point, in intention-to-treat analysis, the mean change in 24-hour SBP at 6 months was -7.0 mm Hg for patients in the renal denervation group, compared with -3.5 mm Hg in the sham control group (p=0.15). In a per protocol analysis, which excluded 2 patients in the renal denervation group who had incomplete procedures due to difficult anatomy or technical problems and 1 patient for preexisting severe renal artery stenosis detected at 6 months, and 1 patient in the sham control group who did not receive the sham procedure, the change in 24-hour SBP at 6 months was -8 mm Hg in the renal denervation group, compared with -3.5 mmHg in the sham control group (p=0.042). The authors note that the trial may have been underpowered to detect a significant SBP effect.

Kario et al reported results of the SYMPLICITY HTN-Japan study, which was an RCT comparing renal sympathetic denervation with standard pharmacotherapy in subjects with treatment-resistant hypertension. Enrollment was initially planned for 100 subjects, but the trial was halted early after results of the SYMPLICITY HTN-3 trial were published, after the randomization of 41 subjects (n=22 to renal denervation, n=19 to control). At 6 months, the change in SBP in renal denervation subjects was not significantly different than the change in SBP in control subjects (between-group difference, -8.6; 95% CI -21.1 to 3.8; p=0.169). No major adverse events occurred. The authors note that the study was underpowered due to the early termination.

Fadl Elmula et al reported results from a smaller RCT that compared renal denervation with clinically adjusted drug treatment in treatment-resistant hypertension after patients with poor drug adherence were excluded. The study enrolled patients with office SBP greater than 140 mm Hg, in spite of maximally tolerated doses of at least 3 antihypertensive drugs, including a diuretic, and required that patients had an ambulatory daytime SBP greater than 135 mm Hg after witnessed intake of antihypertensive drugs. Twenty patients were randomized, 10 to adjusted drug treatment and 10 to renal denervation with the Symplicity renal denervation catheter (1 of whom was subsequently excluded due to a diagnosis of secondary hypertension). In the drug-adjusted group, the office SBP changed from 160±14 mm Hg at baseline to 132±10 mm Hg at 6-month follow-up (p<0.000); in the renal denervation group, the office SBP changed from 156±13 mm Hg at baseline to 148±7 mm Hg at 6-month follow-up (p=0.42). SBP and DBP were significantly lower in the drug-adjusted group at 6-month follow-up.

An additional randomized study compared RFA of the renal arteries plus cardiac ablation for atrial fibrillation (pulmonary vein isolation) with ablation for atrial fibrillation alone in 27 patients with refractory atrial fibrillation and resistant HTN. End points of this study included both BP control and recurrence of atrial fibrillation. Patients who received RFA of the renal arteries had significant reductions in SBP (181±7 mm Hg to 156±5 mm Hg) and DBP (96±6 mm Hg to 87±4 mm Hg), compared with no reduction in the control group (p<0.001). The percentage of patients who were free of atrial fibrillation at 12 months posttreatment was higher in the group receiving renal artery denervation (69% vs 29%, p=0.033).
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

Section Summary: RCTs of Renal Denervation
Several RCTs have compared renal denervation with drug therapy for the treatment of resistant hypertension, with conflicting results. The most rigorous evidence about the efficacy of renal denervation comes from the largest of these trials, the Symplicity HTN-3 trial, which used a single-blinded, sham-controlled design to reduce the risk of placebo effect and showed no significant improvements in blood pressure control with renal denervation at 6 months. Another smaller trial which used sham control reported discrepant results between intention-to-treat and per-protocol analysis, but showed no significant improvements in SBP for patients treated with renal denervation compared with controls. Other trials which did not use a sham-control design, including the DENERHTN and Symplicity HTN-2 trials, did find a significant benefit in patients treated with renal denervation. A potential explanation for the difference in findings between the Symplicity HTN-3 trial and is that the treatment effect seen in nonblinded trials may have been due to a placebo effect, or other nonspecific effects of being in a trial. Alternatively, blood pressure control in the control arm may have been better in Simplicity HTN-3 trial compared with earlier studies.

Systematic Reviews
In 2015, Fad Elmula et al published a systematic review of RCTs evaluating renal denervation for hypertension, which included 7 trials, including the Symplicity HTN-3 trial, along with the RCTs reported by Desch et al, Kario et al, Rosa et al, and Azizi et al after the result of Symplicity HTN-3 were published. Across the 7 trials, a total of 985 patients were randomized to control (n=397) or renal denervation (n=588). In pooled analysis, for office systolic blood pressure, the effect size of renal denervation compared with control (defined as the treatment effect at 6 months in the renal denervation group subtracted from that in the control group) was -4.89 mm Hg (95% CI, -20.9 to 11.1 mm Hg; p=0.47). For 24-hour SBP, the pooled effect size of renal denervation compared with control was -2.81 mm Hg (95% CI, -6.46 to 0.83 mm Hg; p=0.11). Safety measures did not differ significantly between groups.

Several systematic reviews that have included RCTs and nonrandomized studies have been published. In 2014, Kwok et al published a systematic review of renal denervation that included 3 RCTs (the Symplicity HTN-3 trial, the Symplicity HTN-2 trial, and Pokushalov et al, described in the Randomized Controlled Trials section), 8 prospective observational studies, and 1 observational study with matched controls. Similarly, Pancholy et al published a systematic review of renal denervation that included the same 3 RCTs, along with 2 nonrandomized controlled trials. Previous systematic reviews and meta-analyses, including those by Davi et al and Shantha et al, did not include the Symplicity HTN-3 trial or subsequently-reported RCTs.

Nonrandomized Comparative Studies
Several nonrandomized studies with a control group have been published. The populations from some of these studies overlap to a large extent with the Symplicity HTN-2 trial. Additional cases may have been added to the study population using the same eligibility criteria, and only a small number of control patients were included in the analyses. Thus, these comparisons are not considered randomized. These studies examine different physiologic outcomes in addition to changes in BP.

An echocardiographic substudy was published in 2012. This trial compared 46 patients who underwent RFA with 18 control patients from the larger control group in the trial. The selection of patients for the control
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

group was not specified. The main end points of this trial were echocardiographic measures of left ventricular hypertrophy (LVH) and diastolic dysfunction at 6 months posttreatment. There was a significant decrease in the LV mass index for the treatment group at 6 months, from a baseline of 112.4±33.9 g/m² to 94.9±29.8 g/m². In the control group, there was a slight increase in LV mass index from 114.8±41.6 g/m² to 118.7±30.1 g/m² (p=0.009 for comparison with RFA group). There was also a significant improvement in measures of diastolic dysfunction for the RFA group compared with controls at 6 months.

Another substudy published in 2011 evaluated the response to exercise in 46 patients treated with RFA compared with 9 patients in the control group at 3 months posttreatment. There were significant improvements in the achieved workload, and recovery from exercise in heart rate and BP compared with controls. There were no differences in maximum oxygen uptake or maximum heart rate during exercise.

A third study that enrolled 50 patients measured parameters of glucose metabolism in treated and control patients. This population included a subset of patients from the Symplicity trial (n=17 treated, n=9 control patients) and also included another 20 treated patients and 4 control patients who met the same eligibility criteria used in the Simplicity HTN-2 trial. Outcomes at 3 months showed that there was an improvement in fasting glucose for the treated patients from a baseline of 118±3.4 mg/dL to 108±3.8 mg/dL (p=0.039). There was no change in the control group. Insulin levels and C-peptide levels were also reduced in the treatment group, as were peak glucose levels at 2 hours on a glucose tolerance test.

Mahfoud et al enrolled 100 patients in a study that evaluated the impact of RFA on renal function and renal hemodynamics, 87 treated with RFA and 13 control patients. This population also overlapped with the Symplicity HTN-2 trial and all patients met the eligibility criteria used in Symplicity HTN-2. There was no discernable impact of RFA on the glomerular filtration rate or mean urinary albumin excretion at 6-month follow-up. There were significant improvements for the treated patients on the incidence of microalbuminuria and the renal resistive index. There were no instances of renal artery stenosis, dissections, or aneurysms at the 6-month time point.

Ewen et al evaluated the impact of renal denervation on blood pressure, heart rate, and chronotropic index at rest, during exercise, and at recovery in 60 patients with resistant hypertension (50 who underwent renal denervation and 10 control patients). At 6-month follow-up, office blood pressure was reduced by 26/7 mm Hg to 138±3/84±2 mm Hg in the renal denervation group (p<0.001 for both), whereas there was no significant change in blood pressure in the control group (blood pressure reduced by 2/0 mm Hg to 153±5/87±1 mm Hg; p=0.750/p=0.611). At 6-month follow-up, the intervention group demonstrated a significant reduction in percent of maximum SBP from baseline during exercise and recover.

Case Series
The largest case series was the Symplicity HTN-1 study, which was a multicenter, single-arm trial sponsored by the manufacturer. A total of 153 patients with resistant hypertension were treated at 19 clinical centers in the United States, Europe, and Australia. The mean baseline BP was 176/98, and participants were taking a mean of 5 antihypertensive drugs. Patients were followed for up to 24 months with the main end point being reduction in BP. Procedural complications occurred in 4 patients (3%), including 3 cases of groin pseudoaneurysms and 1 renal artery dissection. The mean BP reductions at 6
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

months, 12 months, and 24 months were 25/11, 23/11, and 32/14, respectively. There was no evidence for a diminution of the treatment effect over time.

Krum et al reported 3-year follow-up for patients in the Symplicity HTN-1 study in 2014. Among 88 patients who had complete follow-up data at 36 months, the mean change in SBP was -32 mm Hg (95% CI, -35.7 to -28.2) and DBP was -14.4 mm Hg (95% CI, -16.9 to -11.9). The proportion of patients with a SBP decrease of 10 mm Hg or more was stable over time: 69% at 1 month; 81% at 6 months; 85% at 12 months; 83% at 24 months; and 93% at 36 months. Adverse events included 4 cases of possible or suspected renal artery stenosis, 1 of which required stenting; 3 deaths that were deemed unrelated to the device or procedure; 2 hospitalizations for acute renal failure in the setting of other illnesses; and 13 hospitalizations for hypertensive episodes.

Numerous other small nonrandomized studies and case series have been published, reporting blood pressure outcomes and adverse events from the procedure. These case series generally report similar blood pressure reductions, as do the controlled studies with few complications. Some studies have reported on different populations such as the elderly population, those with moderately resistant hypertension, with chronic kidney disease, or with an accessory renal artery. Other studies report additional outcomes, including improvements in quality of life, favorable changes in renal hemodynamics, changes in neurohormonal measurements, improvements in LV mass and function, improvements in atrial remodeling, changes in PR interval and heart rate, reduction in microalbuminuria, and improvements in measures of vascular function.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02439749</td>
<td>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)</td>
<td>120</td>
<td>Feb 2020</td>
</tr>
<tr>
<td>NCT02439775</td>
<td>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)</td>
<td>100</td>
<td>Oct 2019</td>
</tr>
<tr>
<td>NCT01366625</td>
<td>Effects of Renal Denervation on Blood Pressure and Clinical Course of Obstructive Sleep Apnea in Patients With Resistant Hypertension</td>
<td>60</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT01911078</td>
<td>Renal Sympathetic Denervation in Metabolic Syndrome</td>
<td>60</td>
<td>Jun 2016</td>
</tr>
</tbody>
</table>
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

(Reviewed: April 2016)

©2016 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association.
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Summary of Evidence
The evidence for the use of RFA of the renal sympathetic nerves for individuals with resistant hypertension includes 8 RCTs, along with multiple nonrandomized comparative studies and case series. Relevant outcomes are symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. The largest trial, the Symplicity HTN-3 trial, which used a sham-controlled design to reduce the likelihood of placebo effect, demonstrated no significant differences between renal denervation and sham-control patients in office-based or ambulatory blood pressure at 6-month follow-up. The Symplicity HTN-3 results were in contrast to additional studies, including Symplicity HTN-2 and DENERHTN, which reported efficacy in reducing blood pressure over a 6-month time period compared with a control group. Additional smaller RCTs, some of which were stopped early after results of the Symplicity HTN-3 trial became available.
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

available, did not demonstrate significantly improved outcomes with renal denervation. Single-arm studies with overlapping populations report improvements in blood pressure and related physiologic parameters, such as echocardiographic measures of left ventricular hypertrophy, that appear to be durable up to 24 months of follow-up. The body of evidence for the use of renal denervation to treat hypertension consists of RCTs that have conflicting results. The strongest evidence comes from sham-controlled trials, the largest of which found no significant benefits with renal denervation. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016


Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016


Policy History
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

08/06/2015 Medical Policy Committee review
08/19/2015 Medical Policy Implementation Committee approval. New Policy
08/04/2016 Medical Policy Committee review
08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 08/08/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.
Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

Policy # 00465
Original Effective Date: 08/19/2015
Current Effective Date: 08/17/2016

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0338T, 0339T</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or 
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

† Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific-based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.