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

Description

Radiofrequency ablation (RFA) of the renal sympathetic nerves is a non-pharmacologic treatment for hypertension and has been proposed as a treatment option for patients with resistant hypertension. This treatment is intended to reduce sympathetic nerve activity in the renal system, thus leading to lower blood pressure. There are currently no devices that have FDA-approval for this indication.

Background

Resistant Hypertension:

Hypertension is a widely prevalent condition, which is estimated to affect approximately 30% of the population in the United States. (1) 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%. (1) 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 prior to labeling a patient resistant. These include non-adherence to medications, excessive salt intake, inadequate doses of medications, excess alcohol intake, volume overload, drug-induced hypertension, and other forms of secondary hypertension. (2) Also, sometimes it is necessary to address comorbid conditions, ie, obstructive sleep apnea, in order to adequately control BP.

Treatment for resistant hypertension is mainly intensified drug therapy, sometimes with the use of non-traditional 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 can control resistant hypertension. Non-pharmacologic interventions for resistant hypertension
include modulation of the baroreflex receptor, and/or radiofrequency (RF) denervation of the renal nerves.

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 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. (3)

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.

Regulatory Status

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. Food and Drug Administration (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™ multi-electrode renal denervation system (St. Jude Medical, Plymouth, MN) is an RFA catheter using a 4-point multi-ablation 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 is considered investigational for the treatment of resistant hypertension.

Rationale

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 (BP), the heterogeneity of the patient populations with increased BP, and the presence of many potential confounders of outcome. A sham-controlled RCT is ideal since it would also control for any placebo effects, or other non-specific, effects of BP treatment. 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, including one that compared renal denervation with standard care for patients with resistant hypertension, a second that compared renal denervation with stepped-care antihypertensive treatment, and a third 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 (RCTs)

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. (4) 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; 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. (5) 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. (6) Included patients had severe, resistant hypertension, with a systolic BP 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 systolic BP 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 systolic BP (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 initial 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. (7) The change in average 24-hour ambulatory systolic and diastolic BP 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. (8) 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.

**SYMPPLICITY 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. (9) A total of 106 patients with a systolic blood pressure 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 endpoint 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 systolic BP and no change for diastolic BP (p<0.001 for both systolic blood pressure (SBP) and SBP differences). The percent of patients who achieved an SBP of 140 or less was 39% (19/49) in the radiofrequency ablation (RFA) group compared to 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 to 2 in the control group (p=NS). 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.

One-year follow-up data from the Symplicity HTN-2 trial were reported in 2013. (10) 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 diastolic BP. These decreases in BP were not significantly different from those reported at the 6-month time point (31.7 ± 23.1 mm Hg systolic and 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, one patient with a dissection of the renal artery and one patient with a hypotensive episode.

Three-year follow-up data from the Symplicity HTN-2 trial were reported in 2014.11 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 received renal denervation 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 non-specific 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 myocardial infarction (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 re-innervation of the renal sympathetic nerves occurs post-treatment. If re-innervation 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 re-innervation 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 (daytime SBP 135-149 mm Hg and DBP 90-94 mm Hg on 24 ambulatory monitoring). (12) 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. (13) 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.(14) 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. (10) Endpoints 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 diastolic BP (96±6 mm Hg to 87±4 mm Hg), compared to no reduction in the control group (p<0.001). The percentage of patients who were free of atrial fibrillation at 12 months post-treatment was higher in the group receiving renal artery denervation (69% versus 29%, p=0.033).

**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. (16) 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. (17) Similarly, Pancholy et al published a systematic review of renal denervation that included the same 3 RCTs, along with 2 nonrandomized controlled trials.18 Previous systematic reviews and meta-analyses, including those by Davis et al19 and Shantha et al,20 did not include the Symplicity HTN-3 trial or subsequently-reported RCTs.
Non-randomized 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 blood pressure.

An echocardiographic sub-study was published in 2012. (20) This trial compared 46 patients who underwent RFA to 18 control patients from the larger control group in the trial. The selection of patients for the control group was not specified. The main endpoints of this trial were echocardiographic measures of left ventricular hypertrophy (LVH) and diastolic dysfunction at 6 months post-treatment. 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 sub-study published in 2011 evaluated the response to exercise in 46 patients treated with RFA compared to 9 patients in the control group at 3 months post-treatment. (21) There were significant improvements in the achieved workload, and recovery from exercise in heart rate and blood pressure compared to 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 and n=9 control patients) and also included another 20 treated patients and 4 control patients who met the same eligibility criteria used in the Symplicity 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 (22) 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 discernible 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 BP, 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). (23) At 6-month follow-up, office BP 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 BP in the control group (BP 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 systolic BP 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. (24, 25) A total of 153 patients with resistant hypertension were treated at 19 clinical centers in the US, 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 endpoint being reduction in BP. Procedural complications occurred in 4 patients (3%), including 3 cases of groin pseudoaneurysms and one renal artery dissection. The mean BP reductions at 6 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. (26) 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 non-randomized studies and case series have been published, reporting BP outcomes and adverse events from the procedure. (22, 27-44) These case series generally report similar BP reductions, as do the controlled studies with few complications. Some studies have reported on different populations such as the elderly population, (45) those with moderately resistant HTN (33) and in patients with chronic kidney disease, (34, 46) or with an accessory renal artery. (47) Other studies report additional outcomes, including improvements in quality of life (QOL) (32) favorable changes in renal hemodynamics, (23) changes in neurohormonal measurements, (49) improvements in LV mass and function, (50, 51) improvements in atrial remodeling, (52) changes in PR interval and heart rate, (53) reduction in microalbuminuria, (54) and improvements in measures of vascular function. (36)

Additional case series report safety and effectiveness outcomes after use of newer generation renal denervation systems, including the OneShot Renal Denervation System (55) and the Vessix Renal Denervation System. (56)

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

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<td>Sympathetic Renal Denervation in Heart Failure With Normal LV Ejection Fraction: Denervation of the renAI sympathetic nerves in Heart Failure With normal LV Ejection Fraction</td>
<td>60</td>
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<td>NCT02021019</td>
<td>Renal Denervation to Improve Outcomes in Patients With End-stage Renal Hypertension</td>
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<td>NCT01850901a</td>
<td>Renal Sympathetic Denervation as a New Treatment for Therapy Resistant Hypertension - A Multicenter Randomized Controlled Trial</td>
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<td>NCT01901549</td>
<td>Renal Denervation in Patients After Acute Coronary Syndrome</td>
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<td>NCT02041130</td>
<td>Renal Sympathectomy in Heart Failure (the RESPECT-HF Study) - a Study of Renal Denervation for Heart Failure With Preserved Ejection Fraction</td>
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<td>NCT01459900</td>
<td>Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Randomized Controlled Trial</td>
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<td>NCT01522430</td>
<td>Denervation of Renal Sympathetic Activity and Hypertension Study</td>
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<td>Dec 2016</td>
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<td>NCT: national clinical trial.</td>
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<td>a Denotes industry-sponsored or cosponsored trial.</td>
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Practice Guidelines and Position Statements

In 2015, the American Heart Association, American College of Cardiology, and American Society of Hypertension issued guidelines on the treatment of hypertension in patients with coronary artery disease, which makes the following statements regarding renal denervation: (57)

“In the first large-scale clinical trial of renal denervation in patients with resistant hypertension, with an appropriate control group, namely a sham procedure (Renal Denervation in Patients With Uncontrolled Hypertension [SYMPLICITY HTN-3]), there was no significant difference between the 2 groups in the reduction of SBP, which leaves the future of renal denervation in the management of hypertension uncertain. The impact of renal denervation in HF [heart failure] patients is also unclear, and future randomized trials are needed to clarify its role in this patient population.”

In 2015, the Joint UK Societies issued an expert consensus statement on renal denervation for resistant hypertension which concludes: (58)

“The Joint UK Societies does not recommend the use of renal denervation for treatment of resistant hypertension in routine clinical practice but remains committed to supporting research activity in this field.”

In 2013, the European Society of Cardiology issued an expert consensus statement(59) on catheter-based renal denervation that makes the following conclusions:

“Current evidence from the available clinical trials strongly support the notion that catheter-based radiofrequency ablation of renal nerves reduces blood pressure and improves blood pressure control in patients with drug-treated resistant hypertension, with data now extending out to 36 months. Accordingly, renal denervation can be considered as a therapeutic option in patients with resistant hypertension, whose blood pressure cannot be controlled by a combination of lifestyle modification and pharmacological therapy according to current guidelines.”

The statement outlined the following criteria patients should meet before renal denervation is considered:

- Office-based SBP ≥160 mm Hg (≥150 mm Hg in type 2 diabetes.)
- ≥3 antihypertensive drugs in adequate dosage and combination (including a diuretic).
- Lifestyle modification.
- Exclusion of secondary hypertension.
- Exclusion of pseudoresistance using ambulatory blood pressure monitoring (average BP >130 mm Hg or mean daytime BP >135 mm Hg)
- Preserved renal function (GFR ≥45 mL/min/1.73 m²)
- Eligible renal arteries: no polar or accessory arteries; no renal artery stenosis; no prior revascularization.
U.S. Preventive Services Task Force Recommendations

RFA of renal sympathetic nerves is not a preventive service.

Summary of Evidence

The evidence for the use of radiofrequency ablation (RFA) of the renal sympathetic nerves for individuals with resistant hypertension includes 8 randomized controlled trials (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, 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.

Medicare National Coverage

None

References

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


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<th>Date</th>
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<tr>
<td>March 2013</td>
<td>New Policy</td>
<td>Radiofrequency ablation of the renal sympathetic nerves is considered investigational for the treatment of resistant hypertension</td>
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<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review. References 5, 6, 17-20 added. No change in policy statement.</td>
</tr>
<tr>
<td>December 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review. References 4-5, 8-9, 11-12, 16, 19, 29-36, 38-43, and 46 added. No change to policy statement.</td>
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<td>March 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review through August 3, 2015; references 4-5, 8, 12-13, 16-17, 51, 54-55, and 57-58 added. Policy statement unchanged.</td>
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Keywords
Renal Denervation
EnligHTN
Simplicity
This policy was approved by the FEP\textsuperscript{®} Pharmacy and Medical Policy Committee on March 18, 2016 and is effective April 15, 2016.

Signature one file

Deborah M. Smith, MD, MPH