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

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Services Are Considered Investigational
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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

RESISTANT HYPERTENSION

Hypertension 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, despite treatment with at least 3 antihypertensive agents at optimal doses. Resistant hypertension is also a relatively common condition, given a large number of individuals with hypertension. In large clinical trials of hypertension treatment, 20% to 30% of participants meet the definition for resistant hypertension, and in tertiary care hypertension clinics, the prevalence is estimated at 11% to 18%. Resistant hypertension is associated with a higher risk for adverse outcomes such as stroke, myocardial infarction, heart failure, and kidney failure.

A number of factors may contribute to uncontrolled hypertension, and they should be considered and addressed in all patients with hypertension before labeling a patient resistant. They 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 control blood pressure adequately.

Treatment

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 events of treatment. As a result, there is a large unmet need for additional treatments that 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 blood pressure but is limited by the adverse events of surgery and was largely abandoned after effective medications for hypertension became available. The renal sympathetic nerves arise from the thoracic nerve roots and innervate the renal artery, the renal pelvis, and the renal parenchyma. Radiofrequency ablation (RFA) is thought to decrease both the afferent sympathetic signals from the kidney to the brain and the efferent signals from the brain to the kidney. This procedure decreases sympathetic activation, decreases vasoconstriction, and decreases activation of the renin-angiotensin system.

The procedure is performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery, and a controlled energy source, most commonly low-power RF energy, is delivered to the arterial walls where the renal sympathetic nerves are located. Once adequate RF energy has been delivered to ablate the sympathetic nerves, the catheter is removed.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

No RFA devices have been approved by the U.S. Food and Drug Administration (FDA) for ablation of the renal sympathetic nerves as a treatment for hypertension. Several devices have been developed for this purpose and are in various stages of application for FDA approval (FDA product code: DQY):

- Symplicity™‡ Renal Denervation System (Medtronic). In April 2018, FDA approved an investigational device exemption pivotal trial, SPYRAL HTN. The trial will be randomized and sham-controlled.
- The EnligHTN™‡ Multi-Electrode Renal Denervation System (St. Jude Medical) is an RFA catheter using a 4-point multiablation basket design. In January 2014, the EnligHTN™‡ Renal Guiding Catheter was cleared for marketing by FDA through the 510(k) process, based on substantial equivalence to predicate devices for the following indication: percutaneous use through an introducer sheath to facilitate a pathway to introduce interventional and diagnostic devices into the renal arterial vasculature.
- The OneShot™‡ Renal Denervation System (Covidien) is an irrigated RFA balloon catheter, consisting of a spiral-shaped electrode surrounding a balloon. (In 2014, Covidien abandoned development of its OneShot™‡ Renal Denervation program.)
- The Vessix™‡ Renal Denervation System (Boston Scientific; formerly the V2 renal denervation system, Vessix Vascular) is a combination of an RF balloon catheter and bipolar RF generator technologies, intended to permit a lower voltage intervention.

Other RFA catheters (eg, Thermocouple Catheter™‡ [Biosense Webster]) used for other types of ablation procedures (eg, cardiac electrophysiology procedures) have been used off-label for RFA of the renal arteries.

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

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

RADIOFREQUENCY ABLATION

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

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome in patients with resistant hypertension compared with continued medical therapy?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with hypertension that is resistant to standard medical management.

Interventions
The therapy being considered is RFA. RFA is a minimally invasive procedure performed percutaneously with access at the femoral artery. A flexible catheter is threaded into the renal artery and a controlled low-power energy is delivered to the arterial walls to ablate the renal sympathetic nerves.

Comparators
The following therapy is currently being used to make decisions about treating those with resistant hypertension: continued medical therapy.

Outcomes
The general short-term outcomes of interest are change in systolic (SBP) and diastolic (DBP) blood pressure and medication use. Blood pressure measurements may include daytime ambulatory blood pressure, 24-hour average SBP, and office SBP.

A longer term outcome of interest is the effect on cardiovascular outcomes such as myocardial infarction and stroke.

Timing
Short-term outcomes (changes in blood pressure and medication use) can be measured to at least 6 months. Long-term outcomes (reduction in cardiovascular adverse events) would require follow-up to at least 3 years.

Setting
RFA is administered in a tertiary care center.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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, and another that compared renal denervation with stepped-care antihypertensive treatment. A third RCT compared renal denervation plus cardiac ablation with cardiac ablation alone for patients with resistant hypertension and atrial fibrillation (AF). There are also a number of non-RCTs and case series, but they are not detailed in this review.

Randomized Controlled Trials

DENERHTN Trial

Azizi et al (2015) published results of the Renal Denervation for Hypertension (DENERHTN) trial, a prospective, open-label RCT with blinded end point evaluation. The trial 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 a cough), and amlodipine to either renal denervation or control. Both groups received standardized stepped-care antihypertensive treatment, which involved the sequential addition of spironolactone, bisoprolol, and sustained-release prazosin for SBP and DBP of 135 mm Hg or higher or 85 mm Hg or higher, respectively. Spironolactone could be started for home SBP and DBP of 170 mm Hg or higher or 105 mmHg or higher, respectively. The analysis was conducted using a modified intention-to-treat design, after excluding 5 patients in the intervention group who were missing primary end point measurements. For the study's primary efficacy end point, the mean decrease in daytime ambulatory SBP after 6 months of follow-up 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 also 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).

Courand et al (2017) conducted a post hoc exploratory analysis using data from the DENERHTN trial to determine if abdominal aortic calcifications (AAC) had an impact on patients' response to renal denervation. AAC was measured in 90 patients. Analyses showed that patients with a lower AAC burden experienced larger decreases in daytime ambulatory SBP than patients who had a higher AAC burden.

Gosse et al (2017) also conducted an analysis to evaluate factors that may predict response to renal denervation. Comparing responders and nonresponders in the renal denervation group, average nighttime SBP and standard deviation were predictors of response to renal denervation. However, in the control group, these 2 variables did not discriminate between responders and nonresponders.

Prague-15 Study

Rosa et al (2015) reported on results of the Prague-15 study, an open-label RCT comparing renal sympathetic denervation with intensified pharmacologic treatment in patients who had resistant hypertension. Although trial enrollment was planned for 120 subjects and to have a 90% power in detecting a difference in treatment response between the 2 groups with an α of 0.05, the trial was prematurely halted after enrollment of 112 subjects (56 in each group), following the publication of the results of the Symplicity HTN-3 trial (discussed below). 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 or 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 SBP of 160 mm Hg or higher, on maximally tolerated doses of at least 3 antihypertensive medications of complementary classes, one of which had to be a diuretic at an appropriate dose. Five-hundred thirty-five patients were randomized to renal denervation with the Symplicity renal denervation catheter or to renal angiography only (sham control).

Changes in antihypertensive medication were not allowed during the 6-month follow-up unless they were considered 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 sham control group. The secondary efficacy end point was the change in mean 24-hour ambulatory SBP 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 blood pressure. There was a change in SBP of -14.13 mm Hg in the denervation group vs -11.74 mm Hg in the sham control group, for an absolute difference of -2.39 mm Hg (95% CI, -6.89 to 2.12 mm Hg; p=0.26; superiority margin, 5 mm Hg). At 6-month follow-up, the change in ambulatory blood pressure was -6.75 mm Hg in the denervation group and -4.79 mm Hg in the sham control group, for an absolute difference of -1.96 mm Hg (95% CI, -4.97 to 1.06 mm Hg; p=0.98; superiority margin, 2 mm Hg). Major adverse event rates were similar between the denervation (1.4%) and control (0.6%) groups.

Strengths of this trial included its large size and blinded, sham-controlled design, which reduced the likelihood of a placebo effect. A limitation of the initial publication is that the follow-up period reported was relatively short, leading to an underdetection of a treatment benefit differences between the groups over time. The trial 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 (2014) reported on more detailed ambulatory blood pressure results from the Symplicity HTN-3 trial. The change in average 24-hour ambulatory SBP and DBP were as reported by Bhatt et al (2014; discussed above). There were no significant differences in change in ambulatory blood pressure between the renal denervation and control groups for any of the prespecified subgroup analyses. Included among these prespecified subgroup analyses were the presence of coexisting diabetes, sex, race, body mass index of 30 kg/m^2 or more, estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or more, age of 60 years or older, or any medication change during the study.

Bakris et al (2015) also reported on 12-month follow-up data 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 data were 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 the 12-month follow-up, the changes in office SBP compared with baseline (-18.9 mm Hg) were significantly greater than at the 6-month follow-up in the renal denervation group (-15.5 mm Hg; p=0.025). However, there were no significant differences in ambulatory blood pressure monitoring between the 12- and 6-month 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 vs baseline) and -9.2 mm Hg (p<0.001 vs 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.

Using pooled data from the Symplicity HTN-3 trial and the Global Symplicity Registry, Mahfoud et al (2017) investigated the response to renal denervation in patients with isolated systolic hypertension and patients with combined systolic-diastolic hypertension. A total of 1103 patients were included in the analysis, 429 with isolated systolic hypertension and 674 with combined hypertension. At 6 months, SBP reduction in patients with combined hypertension was -18.7 mm Hg compared with -10.9 mm Hg in patients with isolated systolic hypertension (p<0.001).

Additional analyses from Symplicity HTN-3 have reported on the effects of renal denervation on nocturnal blood pressure and cardiac physiology and analyses of population subgroups.

Symplicity HTN-2and Symplicity HTN-Japan

Symplicity HTN-2 was a multicenter, unblinded RCT (2010) evaluating renal sympathetic denervation and 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. Patients were followed for 6 months with the primary end point being the between-group difference in the change in blood pressure during the trial. Secondary outcomes included a composite outcome of adverse cardiovascular events and adverse events of treatment. Baseline blood pressure was 178/98 in the RFA group and 178/97 in the control group.

At 6-month follow-up, blood pressure reductions in the RFA group were 32 mm Hg (standard deviation, 23) SBP and 12 mm Hg (standard deviation, 11) DBP. 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 percentage of patients who achieved an SBP of 140 mm Hg or less was 39% (19/49) in the 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 period. Three patients in the RFA group had adverse cardiovascular events compared with two 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, and hypotension.

One-year follow-up data from the Symplicity HTN-2 trial were reported by Esler et al (2012). 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 offered crossover to RFA after 6 months. Forty-six of 54 patients accepted crossover to RFA; 35 were available at 12 months. For the patients originally randomized to RFA, the decrease in blood pressure at 12 months was 28.1 mm Hg for SBP and 9.7 mm Hg for DBP. These decreases did not differ significantly from those reported at 6 months (31.7 mm Hg systolic, 11.7 mm Hg diastolic). For the crossover group, the decrease in blood pressure 6 months after renal denervation was 23.7 mm Hg systolic and 8.4 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 by Esler et al (2014). Follow-up was available for 40 of 52 subjects in the initial RFA group and for 30 of 37 subjects in the initial control group who crossed over to renal denervation 6 months after enrollment. After 30 months, the mean change in SBP was -34 mm Hg (95% CI, -40 to -27 mm Hg; $p<0.01$) and the mean change in DBP was -13 mm Hg (95% CI, -16 to -10 mm Hg; $p<0.01$). The degree of blood pressure 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 mm Hg; $p<0.01$) and the mean change in DBP was -14 mm Hg (95% CI, -17 to -10 mm Hg; $p<0.01$). 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 AF requiring hospitalization; 1 case of acute renal failure due to acute interstitial nephritis deemed unrelated to renal denervation treatment; and 3 deaths deemed unrelated to the device or therapy.

The main limitations of the Symplicity HTN-2 trial was its small size, unblinded design, and a relatively short follow-up for the controlled portion of the trial. A trial with a sham control would have allowed 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 was too short to ascertain whether the reduction in blood pressure would reduce adverse cardiovascular outcomes such as myocardial infarction and stroke. The 12- and 36-month follow-up reports provided some insight into longer term outcomes following the procedure, although comparison with a control group was no longer possible due to the crossover design.

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

Kario et al (2015) reported on results of the SYMPLICITY HTN-Japan trial, 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, at which time 41 subjects (22 to renal denervation, 19 to control) had been randomized. At 6 months, the change in SBP in renal denervation subjects did not differ significantly from the change in SBP in control subjects (between-group difference, -8.6 mm Hg; 95% CI, -21.1 to 3.8 mm Hg; p=0.169). No major adverse events occurred. The authors noted that the trial was underpowered due to the early termination.

SYMPATHY

De Jager et al (2017) conducted a trial in which patients with resistant hypertension were randomized to usual care based on European Society Hypertension guidelines (n=44) or usual care plus renal denervation (n=95) (SYMPATHY trial). Six-month follow-up analyses showed no significant difference between groups in daytime SBP (2.0 mm Hg; 95% CI, -6.1 to 10.2 mm Hg), 24-hour SBP (1.0 mm Hg; 95% CI, -7.1 to 9.1 mm Hg), or office SBP (-8.2 mm Hg; 95% CI, -17.1 to 0.7 mm Hg).

De Jager et al (2018) evaluated medication adherence as a post hoc analysis of data from the SYMPATHY trial. Serum screening for BP-lowering drugs was conducted on samples taken at baseline (n=98) and at the 6-month follow-up (n=83. Most patients (68%) were found to be nonadherent. Factors related to nonadherence were a higher number of prescribed BP-lowering drugs, higher baseline BP, and younger age. As adherence decreased, office BP increased significantly.

Other RCTs

In the DENERVHTA study (2016), 27 patients with hypertension resistant to 3 drugs were randomized 1:1 to renal denervation (n=13) or the addition of spironolactone (n=14). Subjects and investigators were unblinded. Eleven and 12 subjects in the renal denervation and spironolactone groups, respectively, completed the trial; analysis was intention-to-treat. At 6 months, after adjusting for age, sex, and baseline 24-hour SBP, there was a significantly greater reduction in 24-hour ambulatory SBP in the spironolactone group of -17.9 mm Hg (95% CI, -30.9 to -4.9 mm Hg; p=0.01), with similar reductions in 24-hour ambulatory DBP. There were no statistically significant differences in office blood pressure between groups.

Mathiassen et al (2016) reported results of a sham-controlled, double-blind randomized trial to evaluate the efficacy of renal denervation in patients with treatment-resistant refractory hypertension. In this trial, 69 patients with treatment-resistant hypertension were randomized to renal denervation (n=36) or sham treatment (n=33). For the study's primary efficacy end point, reduction in daytime ambulatory SBP (after adjustment for changes in antihypertensive medications), there were no significant between-group differences at 3 months (-6.1 mm Hg for renal denervation vs -4.7 mm Hg for sham, p=0.73) or at 6 months (-6.9 mm Hg for renal denervation vs -2.6 mm Hg for sham, p=0.35).

Desch et al (2015) reported on results from a smaller RCT comparing renal sympathetic denervation with sham control among patients who had treatment-resistant hypertension but only mildly elevated blood pressures (daytime SBP 135-149 mm Hg and daytime DBP 90-94 mm Hg on 24-hour 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 trial's primary end point, in the intention-to-treat analysis, the mean change in 24-hour SBP at 6 months was -7.0 mm Hg for 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 3 patients (2 patients in the renal denervation group, 1 patient in the sham control group), 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 noted that the trial might have been underpowered to detect a significant SBP effect. A 2016 predefined subgroup analysis of this study reported on exercise blood pressure.

Schneider et al (2015) published the ISAR-denerve study, which evaluated the results of renal denervation in patients after renal transplantation. Eighteen patients were randomized 1:1 to renal denervation or best medical therapy alone. The trial was unblinded. Office blood pressure was measured at 30 days and 6 months postprocedure. For the primary efficacy end point of mean change in office blood pressure from baseline to 6 months postrandomization, a difference of 24/11 in reduction in office-based blood pressure was noted between groups (p<0.001 for SBP and p=0.09 for DBP; CIs not reported) at 6-month follow-up. There was no change in mean 24-hour ambulatory blood pressure monitoring for either group.

Fadl Elmula et al (2014) reported on the results of a smaller RCT that compared renal denervation with clinically adjusted drug treatment in treatment-resistant hypertension after patients who had poor drug adherence were excluded. The trial enrolled patients with office SBP greater than 140 mm Hg, despite maximally tolerated doses of at least 3 antihypertensive drugs, including a diuretic, and required that patients have 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 (one of whom was subsequently excluded due to a diagnosis of secondary hypertension). In the drug-adjusted group, the office SBP changed from 160 mm Hg at baseline to 132 mm Hg at 6-month follow-up (p<0.000); in the renal denervation group, the office SBP improved from 156 mm Hg at baseline to 148 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.

Pokushalov et al (2012) compared RFA of the renal arteries plus cardiac ablation for AF (pulmonary vein isolation) with ablation for AF alone in 27 patients with refractory AF and resistant hypertension. End points of this trial included blood pressure control and recurrence of AF. Patients who received RFA of the renal arteries had significant reductions in SBP (181 mm Hg to 156 mm Hg) and DBP (96 mm Hg to 87 mm Hg) compared with no reduction in the control group (p<0.001). The percentage of patients free of AF at 12 months posttreatment was higher in the group receiving renal artery denervation (69% vs 29%, p=0.033).

Section Summary: Randomized Controlled Trials

Several RCTs have compared renal denervation with drug therapy for the treatment of resistant hypertension, with inconsistent 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 small trial, which used a 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 not using a sham control design, including the DENERHTN and Symplicity HTN-2 trials, did find a significant benefit in patients treated with renal denervation. Potential explanations for the differences in the treatment effect between the Symplicity HTN-3 trial and the unblinded trials may be a placebo effect or other nonspecific effects of participating in a trial. Alternatively, blood pressure control in the control arm might have been better in Simplicity HTN-3 trial than in earlier studies.

Systematic Reviews

Multiple systematic reviews with overlapping studies, one of which is a Cochrane review by Coppolino et al (2017), have summarized the key RCTs evaluating renal denervation. The characteristics of the systematic reviews are summarized in Table 1, and the key results are summarized in Table 2. The overall results vary depending on the inclusion of earlier, unblinded studies and controlled but nonrandomized studies, with some systematic reviews reporting significant improvements with renal denervation and some reporting no significant improvement.

The Cochrane review reported that none of the trials was designed to evaluate clinical end points as primary outcomes. The evidence for clinical endpoints (eg, all-cause mortality, hospitalization, cardiovascular events) was low quality. Comparisons of clinical outcomes in sham vs renal denervation groups showed no significant differences between groups in myocardial infarction (relative risk, 1.3; 95% CI, 0.5 to 3.8), ischemic stroke (relative risk, 1.1; 95% CI, 0.4 to 3.7), or unstable angina (relative risk, 0.6; 95% CI, 0.1 to 5.1).

Most analyses included 6-month follow-up measurements, while a review by Chen et al (2017), calculated change in BP for subgroups at 12-month follow-up. The 12-month analysis showed no difference at the longer follow-up.

Table 1. Characteristics of Systematic Review of Controlled Trials Assessing Renal Denervation

Study	Dates	Trials	N (Range)	Design	Duration, mo	Outcomes
Pappaccogli et al (2018)	2010-2016	11	1236 (19-535)	RCT, CT	6	Change in BP
Coppolino et al (2017)	2010-2016	12	1149 (16-535)	RCT, CT	6	Change in BP; myocardial infarction; ischemic stroke; unstable angina
Chen et al (2017)	2010-2016	9	1068 (19-535)	RCT	6	Change in BP
Fadl Elmula et al (2017)	2010-2017	10	1174 (19-524)	RCT, CT	6	Change in BP
Sun et al (2016)	2010-2015	9	2932 (67-622)	RCT, CT	6	Change in BP
Zhang et al (2016)	2013-2015	11	1160 (19-535)	RCT, CT	6	Change in BP
Yao et al (2016)	2010-2015	8	1059 (19-535)	RCT	6	Change in BP
Fadl Elmula et al (2015)	2010-2015	7	985 (20-535)	RCT	6	Change in BP

BP: blood pressure; CT: controlled trial; RCT: randomized controlled trial.

Table 2. Systematic Review Results at 6-Month Follow-Up for Controlled Trials Assessing Renal Denervation

Study	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I^2, %
Pappaccogli et al (2018)	RD	Control	9	Office SBP	-3.5	-13.0 to 6.1	*NS*	90
			9	Office DBP	-2.8	-6.0 to 0.4	*NS*	74
				ASBP	-1.8	-4.5 to 0.9	*NS*	47
				ADBP	-0.6	-2.3 to 1.2	*NS*	63
Coppolino et al (2017)	RD	Control	5	24-h SBP	0.3	-3.7 to 4.3	*NS*	NR
			4	24-h DBP	0.9	-4.5 to 6.4	*NS*	NR
			6	Office SBP	-4.1	-15.3 to 7.1	*NS*	NR
			5	Office DBP	-1.3	-7.3 to 4.7	NR	NR
Chen et al (2017)	RD	Control	9	24-h SBP	-1.1	-4.7 to 2.5	0.55	67
			7	Office SBP	-2.5	-12.9 to 7.8	0.63	90
Fadl Elmula et al (2017)	RD	Control	8	Office SBP	-3.6	-12.8 to 5.6	0.45	NR
			10	24-h SBP	-1.0	-4.3 to 2.3	0.54	NR
Sun et al (2016)	RD	Control	9	Office SBP	-12.81	-22.77 to -2.85	0.01	92
			8	Office DBP	-5.56	-8.15 to -2.97	<0.001	63
Zhang et al (2016)	RD	Control	11	Office SBP	-13.9	-21.17 to -6.63	<0.001	93
Yao et al (2016)	RD	Control	8	Office SBP	-8.23	-16.86 to 0.39	NR	93
			8	Office DBP	-3.77	-7.21 to -0.32	NR	90
Fadl Elmula et al (2015)	RD	Control	15	Office SBP	-4.89	-20.9 to 11.1	0.47	91.7

ADBP: ambulatory diastolic blood pressure; ASBP: ambulatory systolic blood pressure; CI: confidence interval; DBP: diastolic blood pressure; NR: not reported; *NS*: not significant; RD: renal denervation; SBP: systolic blood pressure; SMD: standardized mean difference.

Several other systematic reviews have also included RCTs and nonrandomized studies. Kwok et al (2014) published a systematic review on renal denervation that included 3 RCTs (the Symplicity HTN-3 trial, the Symplicity HTN-2 trial, and Pokushalov et al (2012), described in the Randomized Controlled Trials section), 8 prospective observational studies, and 1 observational study with matched controls. Similarly, Pancholy et al (2014) published a meta-analysis of renal denervation that included the same 3 RCTs, along with 2 non-RCTs. Other systematic reviews and meta-analyses, including those by Davis et al (2013) and Shantha et al (2015), 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. 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 examined different physiologic outcomes in addition to changes in blood pressure.

Other nonrandomized comparative studies exist. Given the multiple randomized studies, these studies add little to the overall body of evidence and are not discussed further here.

SUMMARY OF EVIDENCE

For individuals who have hypertension resistant to standard medical management who receive RFA of the renal sympathetic nerves, the evidence includes at least 10 RCTs, numerous systematic reviews of the RCTs, as well as multiple nonrandomized comparative studies and case series. Relevant outcomes are symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. The largest trial, the Symplicity HTN-3 trial, used a sham-controlled design to reduce the likelihood of placebo effect and demonstrated no significant differences between renal denervation and sham control patients in office-based or ambulatory blood pressure at 6-month follow-up. Results from Symplicity HTN-3 have been supported by a subsequent sham-controlled trial. The Symplicity HTN-3 results were in contrast to other studies, including Symplicity HTN-2 and the Renal Denervation for Hypertension (DENERHTN) trial, which reported efficacy in reducing blood pressure over a 6-month period compared with a control group. Additional smaller randomized controlled trials, 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 have reported 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 strongest evidence comes from sham-controlled trials, the largest of which found no significant benefits with renal denervation. Meta-analyses of the systematic reviews have also reported inconsistent findings, with most analyses showing no significant benefit in blood pressure measurements following RFA. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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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
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension

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