



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

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension. This is considered investigational.

When Policy Topic is covered

n/a

When Policy Topic is not covered

Radiofrequency ablation of the renal sympathetic nerves is considered **investigational** for the treatment of resistant hypertension.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With hypertension resistant to standard medical management 	Interventions of interest are: <ul style="list-style-type: none"> Radiofrequency ablation of the renal sympathetic nerves 	Comparators of interest are: <ul style="list-style-type: none"> Continued medical therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Medication use Treatment-related morbidity

Summary

Radiofrequency ablation (RFA) 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.

For individuals who have hypertension resistant to standard medical management who receive RFA of the renal sympathetic nerves, the evidence includes at least 10 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. Results from Symplicity HTN-3 are supported by a subsequent sham-controlled trial. 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 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 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.

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, 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, 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.² Also, sometimes it is necessary to address comorbid conditions, ie, obstructive sleep apnea, to adequately control blood pressure.

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 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 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. 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 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. Several devices 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, 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. Jude Medical, Plymouth, MN) 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 (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.

Rationale

This evidence review was created in August 2012 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through July 20, 2017.

A determination of the efficacy of this technology requires high-quality randomized controlled trials (RCTs). RCTs are necessary because of the natural variability in blood pressure, the heterogeneity of the patient populations with increased blood pressure, and the presence of many potential confounders of the outcome. A sham-controlled RCT is ideal because it also controls 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 the 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, 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 were also a number of nonrandomized controlled trials and case series, which are not the focus of this review.

RADIOFREQUENCY ABLATION

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.(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 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 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. The analysis was conducted using a modified intention-to-treat design, after excluding five 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 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 two patients, mild groin hematoma in one patient).

Prague-15 Study

Rosa et al reported on 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 α of 0.05, the study was prematurely halted after enrollment of 112 subjects (56 in each group), following the publication of the results of the Symplicity HTN-3 trial. 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 six 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.(6) 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, 1 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 six-month follow-up unless they were considered clinically necessary. The primary efficacy end point was the mean change in office SBP from baseline to six 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 six-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; $p=0.26$ with a superiority margin of 5 mm Hg). At 6-month follow-up, the change in ambulatory blood pressure was -6.75 mm Hg in the denervation group vs -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; $p=0.98$ with a superiority margin of 2 mm Hg). Major adverse event rates were similar between the denervation (1.4%) and control (0.6%) groups.

Strengths of this trial include 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 study subjects, including those who do not cross over to renal denervation, will be followed for five years to assess longer term outcomes.

Bakris et al (2014) reported on more detailed ambulatory blood pressure results from the Symplicity HTN-3 trial.⁽⁷⁾ The change in average 24-hour ambulatory SBP and diastolic blood pressure (DBP) were as reported by Bhatt et al. 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/m² or more, estimated glomerular filtration rate 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 (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.⁽⁸⁾ 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 12-month follow-up, the changes in office SBP compared with baseline (-18.9 mm Hg) were significantly greater than at 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 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 ($p < 0.001$ 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.

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.(9-11)

Symplicity HTN-2

Symplicity HTN-2 was a multicenter, unblinded RCT evaluating renal sympathetic denervation and standard pharmacologic treatment for patients with resistant hypertension.(12) 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 six 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 effects 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 (SD=23) SBP and 12 mm Hg (SD=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 six-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 one 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 in 2012.(13) 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 six-month follow-up of patients originally randomized to the control group, who were offered crossover to RFA after six 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 two 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.⁽¹⁴⁾ 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 are 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 allow better determination of whether the treatment effect was due to a placebo effect, or other nonspecific effects of being in a trial. The six-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 provide 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 post-treatment. 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.

Mathiassen et al

In 2016, Mathiassen et al reported on results of an additional sham-controlled, double-blind randomized trial to evaluate the efficacy of renal denervation in patients with treatment-resistant refractory hypertension.⁽¹⁵⁾ 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 systolic ambulatory blood pressure (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, $p=0.35$).

Other RCTs

Desch et al reported on 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).(16) 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 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 and 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 may have been underpowered to detect a significant SBP effect. A predefined subgroup analysis of this study reported on exercise blood pressure.(17)

Kario et al (2015) reported on results of the SYMPPLICITY HTN-Japan trial, which was an RCT comparing renal sympathetic denervation with standard pharmacotherapy in subjects with treatment-resistant hypertension.(18) Enrollment was initially planned for 100 subjects, but the trial was halted early after results of the SYMPPLICITY HTN-3 trial were published, at which time 41 subjects (22 to renal denervation, 19 to control) had been randomized. At six 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; 95% CI, -21.1 to 3.8; $p=0.169$). No major adverse events occurred. The authors noted that the trial was underpowered due to the early termination.

Fadl Elmula et al (2014) reported on 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.(19) 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 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 (1 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 changed 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 six-month follow-up.

An additional randomized study (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.(20) 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%, $p = 0.033$).

In 2015, Schneider et al 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.(21) The study 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.

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 ($n = 14$). (22) Subjects and investigators were unblinded. Eleven and 12 subjects in the renal denervation and spironolactone groups, respectively, completed the study; 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.

Section Summary: Randomized Controlled Trials

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, and which has been confirmed by another sham-controlled trial. 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 difference 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 may have been better in Simplicity HTN-3 trial than in earlier studies.

Systematic Reviews

Multiple systematic reviews 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.

Table 1. Systematic Review Characteristics for Controlled Trials on Renal Denervation

Study (Year)	Dates	Trials	N (Range)	Design	Duration, mo	Outcomes
Fad Elmula et al (2015) ²³	2010-2015	7	985 (20-535)	RCT	6	Office SBP
Sun et al (2015) ²⁴	2010-2015	9	2932 (67-622)	RCT, CT	6	SBP, DBP
Zhang et al (2016) ²⁵	2013-2015	11	1160 (19-535)	RCT, CT	6	Change in BP
Yao et al (2016) ²⁶	2010-2015	8	1059 (19-535)	RCT	6	Change in BP

BP: blood pressure; CT: controlled trial; DBP: diastolic blood pressure; RCT: randomized controlled trial; SBP: systolic blood pressure.

Table 2. Systematic Review Outcomes for Controlled Trials of Renal Denervation

Study (Year)	Treatment	Comparator	Trials	Outcomes	SMD, mm Hg	95% CI, mm Hg	p	I ² , %
Fad Elmula (2015) ²³	RD	Control	15	SBP	-4.89	-20.9 to 11.1	0.47	91.7
Sun (2015) ²⁴	RD	Control	9	SBP	-12.81	-22.77 to -2.85	0.01	92
	RD	Control	8	DBP	-5.56	-8.15 to -2.97	<0.001	63
Zhang (2016) ²⁵	RD	Control	11	SBP	-13.9	-21.17 to -6.63	<0.001	93
Yao (2016) ²⁶	RD	Control	8	SBP	-8.23	-16.86 to 0.39		
				DBP	-3.77	-7.21 to -0.32		

CI: confidence interval; DBP: diastolic blood pressure; RCT: randomized controlled trial; RD: renal denervation; SBP: systolic blood pressure; SMD: standardized mean difference.

Several systematic reviews that have included RCTs and nonrandomized studies have been published. In 2014, Kwok et al 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, described in the Randomized Controlled Trials section), 8 prospective observational studies, and 1 observational study with

matched controls.(27) Similarly, Pancholy et al published a meta-analysis of renal denervation that included the same three RCTs, along with two nonrandomized controlled trials.(28) Previous systematic reviews and meta-analyses, including those by Davis et al(29) and Shantha et al,(30) 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.

Multiple additional 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.(31-34)

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 ten randomized controlled trials, 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, 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 are supported by a subsequent sham-controlled trial. 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 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 body of evidence for the use of renal denervation to treat hypertension consists of randomized controlled trials 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Heart Association et al

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(35): The guideline noted that the SYMPPLICITY HTN-3 trial did not find a significant benefit from renal denervation and stated that additional RCTs are needed.

Joint UK Societies

In 2015, the Joint UK Societies issued an expert consensus statement on renal denervation for resistant hypertension, which concluded(36): "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."

Eighth Joint National Committee

In 2014, the Eighth Joint National Committee, which was appointed to provide recommendations on hypertension treatment, published an evidence-based guideline for the management of hypertension in adults.(37) These recommendations did not discuss the use of renal denervation.

European Society of Cardiology

In 2013, the European Society of Cardiology issued an expert consensus statement on catheter-based renal denervation which concluded that, based on the available evidence, renal denervation can be considered as a treatment 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."(38):

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

- "Office-based systolic BP [blood pressure] ≥ 160 mmHg (≥ 150 mmHg diabetes type 2)
- ≥ 3 antihypertensive drugs in adequate dosage and combination (incl. diuretic)
- Lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ABPM [ambulatory blood pressure monitoring] (average BP > 130 mmHg or mean daytime BP > 135 mmHg)
- Preserved renal function (GFR [glomerular filtration rate] ≥ 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

Not applicable.

MEDICARE NATIONAL COVERAGE

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01901549	Renal Denervation in Patients After Acute Coronary Syndrome	80	Jun 2016 (ongoing)
NCT01583881	Sympathetic Renal Denervation in Heart Failure With Normal LV Ejection Fraction: Denervation of the renal sympathetic nerves in Heart Failure With normal LV Ejection Fraction	60	Jul 2016 (ongoing)
NCT02029885a	Wave IV Study: Phase II Randomized Sham Controlled Study of Renal Denervation for Subjects With Uncontrolled Hypertension	132	Mar 2018
NCT02439749	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)	120	Jul 2020
NCT02439775	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)	100	Sep 2020
Unpublished			
NCT01895140a	A Pragmatic Randomized Clinical Evaluation of Renal Denervation for Treatment Resistant Hypertension	104	Oct 2014 (terminated)
NCT01628172a	Renal Sympathetic Denervation for the Management of Chronic Hypertension	96	Mar 2014 (completed)
NCT01459900	Renal Sympathectomy in Treatment Resistant Essential Hypertension, a Sham Controlled Randomized Trial	69	Feb 2015 (completed)
NCT01932450	A Randomized, Open-label Study Investigating the Effect of Bilateral Renal Artery Sympathetic Denervation by Catheter-based Radiofrequency Ablation on Blood Pressure and Disease Progression in Autosomal Dominant Polycystic Kidney Disease	100	Jul 2015 (unknown)

NCT02039492	Sympathetic Renal Denervation Versus Increment of Pharmacological Treatment in Resistant Arterial Hypertension	50	Dec 2015 (completed)
NCT01505010	Investigator-Steered Project on Intravascular Renal Denervation for Management of Drug-Resistant Hypertension	240	Apr 2016 (unknown)
NCT01911078	Renal Sympathetic Denervation in Metabolic Syndrome (Metabolic Syndrome Study)	20	Jun 2016 (completed)
NCT01850901a	Renal Sympathetic Denervation as a New Treatment for Therapy Resistant Hypertension - A Multicenter Randomized Controlled Trial	300	Jun 2016 (unknown)
NCT01366625	Effects of Renal Denervation on Blood Pressure and Clinical Course of Obstructive Sleep Apnea in Patients With Resistant Hypertension	60	Nov 2016 (completed)
NCT02041130	Renal Sympathectomy in Heart Failure (the RESPECT-HF Study) - a Study of Renal Denervation for Heart Failure With Preserved Ejection Fraction	144	Dec 2016 (unknown)
NCT01522430	Denervation of Renal Sympathetic Activity and Hypertension Study	120	Dec 2016 (unknown)
NCT02021019	Renal Denervation to Improve Outcomes in Patients With End-stage Renal	100	Dec 2016 (unknown)

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

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Billing Coding/Physician Documentation Information

- 0338T** Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral
- 0339T** Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

ICD10 Codes

- I10-** Hypertensive disease code range
I15.9

Effective January 1, 2014, there are CPT category III codes for this procedure:
 0338T Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral

0339T bilateral

These CPT category III codes cannot be reported with codes 36251, 36252, 36253, and 36254.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

11/1/15 New Policy; considered investigational.
5/1/16 No policy statement changes.
11/1/16 No policy statement changes.
5/1/17 No policy statement changes.
11/1/17 No policy statement changes.
5/1/18 No policy statement changes.
11/1/18 No policy statement changes.

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