Hypertension

Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension
One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

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Background—Renal sympathetic nerve activation contributes to the pathogenesis of hypertension. Symplicity HTN-2, a multicenter, randomized trial, demonstrated that catheter-based renal denervation produced significant blood pressure lowering in treatment-resistant patients at 6 months after the procedure compared with control, medication-only patients. Longer-term follow-up, including 6-month crossover results, is now presented.

Methods and Results—Eligible patients were on ≥3 antihypertensive drugs and had a baseline systolic blood pressure ≥160 mm Hg (∼150 mm Hg for type 2 diabetics). After the 6-month primary end point was met, renal denervation in control patients was permitted. One-year results on patients randomized to immediate renal denervation (n=47) and 6-month postprocedure results for crossover patients are presented. At 12 months after the procedure, the mean fall in office systolic blood pressure in the initial renal denervation group (−28.1 mm Hg; 95% confidence interval, −35.4 to −20.7; P=0.001) was similar to the 6-month fall (−31.7 mm Hg; 95% confidence interval, −38.3 to −25.0; P=0.16 versus 6-month change). The mean systolic blood pressure of the crossover group 6 months after the procedure was significantly lowered (from 190.0±19.6 to 166.3±24.7 mm Hg; change, −23.7±27.5; P<0.001). In the crossover group, there was 1 renal artery dissection during guide catheter insertion, before denervation, corrected by renal artery stenting, and 1 hypotensive episode, which resolved with medication adjustment.

Conclusions—Control patients who crossed over to renal denervation with the Symplicity system had a significant drop in blood pressure similar to that observed in patients receiving immediate denervation. Renal denervation provides safe and sustained reduction of blood pressure to 1 year.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00888433.

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Key Words: catheter ablation ■ hypertension ■ nervous system, sympathetic ■ renal denervation ■ sympathetic nervous system

The prevalence of hypertension is increasing worldwide, with an estimated 972 million adults with hypertension in 2000 that is predicted to grow to 1.56 billion by 2025.1 Despite the availability of numerous effective antihypertensive medications, many hypertensive adults remain uncontrolled for various reasons, including inadequate treatment. Among hypertensive patients receiving treatment, the estimated proportion of patients with blood pressure uncontrolled to <140/90 mm Hg ranges from 47% to 84% in Europe and North America.1 Furthermore, a subset of patients who adhere to a prescribed pharmacological regimen of ≥3 drugs, including a diuretic, continue to have uncontrolled or resistant hypertension.2 The proportion of patients with resistant hypertension is uncertain. In the United States, estimates of resistant hypertension prevalence range from 13% to 30% of adults receiving drug treatment for hypertension.3,4 These numbers reflect a serious global health challenge given the observation that with every 20/10-mm Hg increase in blood pressure, cardiovascular mortality doubles.5

Clinical Perspective on p 2982

The sympathetic nervous system plays an important role in the pathogenesis of hypertension. Early studies demonstrated
activation of renal sympathetic outflow in patients with essential hypertension, as evidenced by increased norepinephrine spillover rates from the sympathetic nerves of the kidneys to plasma. Increased efferent sympathetic outflow to the kidneys causes elevation of blood pressure via release of renin, with subsequent activation of the renin-angiotensin-aldosterone system, increased tubular sodium retention, and reduced renal blood flow. Afferent nerve signaling from the kidneys, with renal injury stimuli, additionally stimulates sympathetic outflow from the central nervous system, indicating the primacy of the sympathetic nerves of the kidneys in the pathogenesis of hypertension.

Sympathetic nerves were not specifically targeted, although there is no doubt that they were often surgically interrupted. Subsequent preclinical studies of selective renal denervation in animal models of hypertension provide direct evidence of blood pressure lowering, indicating the primacy of the sympathetic nerves of the kidneys in the pathogenesis of hypertension. Catheter-based renal denervation is a minimally invasive procedure involving the application of radiofrequency energy in short bursts along the length of the main renal arteries to ablate the renal nerves that lie within and just beyond the adventitia of the renal artery as they pass to the kidneys. Two-year results from a nonrandomized proof-of-principle cohort study (Symplicity HTN-1) and a larger group of registry patients with resistant hypertension treated by renal denervation have demonstrated substantial reductions in office-based blood pressure without serious adverse events. The Symplicity HTN-2 trial randomized patients with resistant hypertension, who met all clinical and anatomic eligibility criteria, to renal denervation or no renal denervation, with both groups maintained for 6 months on unchanged antihypertensive medications. The primary end point, change in office-based systolic blood pressure (SBP) at 6-month follow-up, demonstrated a significant difference in reduction of SBP between the treatment and control groups (33/11 mm Hg; P<0.0001). After assessment of the primary end point, patients in the control group had the option to receive the renal denervation procedure. We now report the 1-year results from the Symplicity HTN-2 trial, which includes 6-month outcomes for the crossover control patients who were treated with renal denervation after the primary end point was assessed.

Methods

Symplicity HTN-2 is a multicenter, randomized trial conducted at 24 centers across Europe, Australia, and New Zealand. The primary objective of the trial was to evaluate the safety and effectiveness of catheter-based renal denervation for the treatment of resistant hypertension. The trial was approved by each of the site ethics committees in accordance with the Declaration of Helsinki. All patients gave written informed consent for participation in the trial. Details of the study design and methodology have been published previously. Briefly, adult patients (aged 18–85 years) with essential hypertension, with a SBP ≥160 mm Hg (≥150 mm Hg if they had type 2 diabetes mellitus) were eligible for inclusion. Patients had to be on a stable drug regimen of at least 3 antihypertensive medications with no changes for 2 weeks before enrollment. Patients were excluded if they had received a prior renal artery intervention, if they had main renal arteries <4 mm in diameter or ≤20 mm in length, or if hemodynamically or anatomically significant renal artery abnormalities were present. Other exclusion criteria included renal insufficiency, with estimated glomerular filtration rate ≤45 mL/min per 1.73 m² as calculated by the Modification of Diet in Renal Disease formula and type 1 diabetes mellitus, stenotic valvular heart disease, and myocardial infarction, unstable angina, or cerebrovascular accident within 6 months of enrollment.

All patients underwent a 2-week screening period before randomization and again before their 6-month follow-up. During the screening period, patients were asked to document their medication use and record automated home blood pressure measurements twice a day. Office baseline and follow-up blood pressure measurements were taken with an automated Omron HEM-705 monitor, and the average of 3 measurements was reported. Before randomization, all patients underwent renal artery imaging (renal artery duplex imaging, computed tomography, magnetic resonance imaging, or angiography) to establish anatomic eligibility. Eligible patients were randomized 1:1 to immediate renal denervation with the Symplicity renal denervation system or to the control group (Figure 1). Study personnel and patients were not blinded to the study group allocation. Both groups were maintained on their baseline antihypertensive medication regimen during the first 6 months of the trial.

The primary end point was change in office SBP measured at 6-month follow-up. At the 6-month visit, control patients became eligible to receive the renal denervation treatment; these patients form the crossover treatment group. The per-protocol crossover patients proceeding to renal denervation described here had a SBP ≥160 mm Hg at the 6-month visit. Control patients choosing to proceed to renal denervation after the 6-month visit but who now had SBP <160 mm Hg (Figure 1) are excluded from the blood pressure analysis, but safety data for these patients are included in the analysis.

Details of the denervation procedure have been described previously. After the initial 6-month trial, periodic adjustments in antihypertensive medications were allowed if medically indicated by clinically important changes in blood pressure or if a medication-related complication occurred.

Patients in the initial renal denervation group and crossover patients receiving the renal denervation procedure at 6 months were followed to 12 months. Changes in office-based blood pressure measurements, the proportion of patients with a SBP reduction from baseline of ≥10 mm Hg, and chronic procedural safety end points (including new renal artery stenosis, the need for dialysis, hypotensive or hypertensive events requiring hospitalization, cardiovascular events including myocardial infarction, new-onset heart failure, stroke, or cardiac death) were analyzed. Antihypertensive medication changes, serum electrolytes, estimated glomerular filtration rate, serum creatinine, and cystatin C levels were collected at each follow-up visit.

Statistical Analysis

Formal between-group comparisons were not conducted. Descriptive statistics were used to present results for the immediate treatment and crossover groups. Comparisons of blood pressure measurements at each follow-up with preprocedure blood pressure were performed with a paired t test. A change was considered significant if the 2-sided α level was ≤0.05. Statistical analysis was done with the use of SAS version 9.2.

Results

One hundred six patients were randomized to the renal denervation or control group after baseline screening for eligibility. The 6-month primary effectiveness end point was reported for 49 patients in the renal denervation group and 51 patients in the control group. At the 6-month follow-up visit,
46 control patients elected to proceed to renal denervation. The SBP of 9 of these patients was <160 mm Hg at the time of crossover despite being ≥160 mm Hg at baseline. These subjects underwent renal denervation off label on compassionate grounds and are excluded from the present analysis. Two control group subjects were lost to follow-up, leaving 35 crossover patients who underwent the renal denervation procedure per protocol (SBP <160 mm Hg) (Figure 1). The outcomes for 47 patients in the primary renal denervation group and the 35 per-protocol crossover patients are reported at 1-year postrandomization follow-up. Hence, the primary cohort has 12-month and the crossover patients have 6-month post-renal denervation results available.

Baseline patient demographics at the time of initial randomization for the 2 groups were similar for mean office-based SBP and diastolic blood pressure, race, age, body mass index, and heart rate (Table 1). More patients in the initial renal denervation group had a history of coronary artery disease and type 2 diabetes mellitus. In the crossover group, estimated glomerular filtration rate was higher, and more patients were female. Distribution of baseline antihypertensive medications in the 2 groups was similar (Table 2). At the 6-month follow-up visit, before renal denervation, the mean SBP of the crossover group had increased from 182.9±16.3 mm Hg at baseline to 190.0±19.6 mm Hg (+7 mm Hg; P=0.026), and the mean diastolic blood pressure had increased from 99.1±17.0 mm Hg to 99.9±15.1 mm Hg (P=0.066) (Table 3).

At 12 months after the procedure, the mean SBP of the initial renal denervation group continued to be significantly lower than baseline; change from baseline (−28.1±24.9 mm Hg; P<0.001) was not different from the 6-month postprocedure change of −31.7±23.1 mm Hg (P=0.16). The mean SBP of the crossover group 6 months after the procedure was significantly higher than baseline; change from baseline (7.1±31.7 mm Hg; P=0.21) was not different from the 6-month postprocedure change of −3.1±23.1 mm Hg (P=0.92). The mean difference between the groups was −29.3±25.5 mm Hg (95% CI: −37.6 to −21.0 mm Hg; P<0.001) (Figure 1).

Figure 1. Patient disposition. At 12 months, follow-up data from 47 patients allocated to immediate renal denervation and 35 crossover patients meeting the same preprocedure eligibility criteria are available for analysis. BP indicates blood pressure; PI, principal investigator; and SBP, systolic blood pressure.

Table 1. Baseline Patient Demographics at Time of Randomization

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation Group (n=49)</th>
<th>Crossover Group* (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mm Hg</td>
<td>187.3±18.2</td>
<td>182.8±16.3</td>
<td>0.250</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>96.1±15.5</td>
<td>99.1±17.0</td>
<td>0.402</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.0±11.5</td>
<td>58.1±13.0</td>
<td>0.741</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>32.7</td>
<td>60.0</td>
<td>0.015</td>
</tr>
<tr>
<td>Race, % white</td>
<td>98.0</td>
<td>97.1</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index</td>
<td>30.8±5.2</td>
<td>31.5±5.3</td>
<td>0.559</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, %</td>
<td>42.9</td>
<td>28.6</td>
<td>0.252</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>18.4</td>
<td>5.7</td>
<td>0.111</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>53.1</td>
<td>45.7</td>
<td>0.658</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.5±15</td>
<td>73±15</td>
<td>0.568</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m2†</td>
<td>76.9±19.3</td>
<td>88.8±20.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.03±0.29</td>
<td>0.84±0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>0.91±0.25</td>
<td>0.78±0.17</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*The crossover group did not receive renal denervation until 6 months after randomization when the primary end point was reached.
†Estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease formula.
in both treatment groups (Table 5). In the majority of patients in the initial renal denervation group experienced a reduction in SBP at 6 and 12 months with a reduction in SBP of ≥10 mm Hg (83.7% [41/49] at 6 months and 78.7% [37/47] at 12 months). The crossover group demonstrated similar outcomes with a fall in SBP of ≥10 mm Hg at 6 months after renal denervation in 62.9% (22/35).

Changes in antihypertensive medication regimens occurred in both treatment groups (Table 5). The majority of patients from the crossover group experienced hypertensive dosing. The patient was discharged with no further sequelae, and the patient was discharged after the denervation procedure without prolonged hospitalization. In another crossover patient, hospitalization after renal denervation was needed because of a hypotensive episode requiring intravenous fluids and reduction in antihypertensive dosage. The patient was discharged with no further problems.

There were no significant changes in estimated glomerular filtration rate or cystatin C in either group (Table 6). Two patients from the crossover group experienced hypertension problems.

Table 2. Antihypertensive Medication Use at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation Group (n=49)</th>
<th>Crossover Group (n=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>51.0 (25/49)</td>
<td>48.6 (17/35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>67.3 (33/49)</td>
<td>82.9 (29/35)</td>
<td>0.136</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>77.6 (38/49)</td>
<td>77.1 (27/35)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diuretic</td>
<td>89.8 (44/49)</td>
<td>91.4 (32/35)</td>
<td>0.001</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>18.4 (9/49)</td>
<td>22.9 (8/35)</td>
<td>0.784</td>
</tr>
<tr>
<td>Centrally acting sympatholytics</td>
<td>51.0 (25/49)</td>
<td>42.9 (15/35)</td>
<td>0.511</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>16.3 (8/49)</td>
<td>22.9 (8/35)</td>
<td>0.575</td>
</tr>
<tr>
<td>β-blockers</td>
<td>81.6 (40/49)</td>
<td>62.9 (22/35)</td>
<td>0.078</td>
</tr>
<tr>
<td>α-adrenergic blocker</td>
<td>8.2 (4/49)</td>
<td>2.9 (1/35)</td>
<td>0.396</td>
</tr>
<tr>
<td>Direct-acting vasodilators</td>
<td>8.2 (4/49)</td>
<td>2.9 (1/35)</td>
<td>0.396</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

Table 3. Mean Office-Based Blood Pressure Before Renal Denervation and 6 and 12 Months After Renal Denervation Procedure

<table>
<thead>
<tr>
<th></th>
<th>Renal Denervation Group (n=49)</th>
<th>Crossover Group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before procedure*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>178.3±18.2</td>
<td>190.0±19.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>96.1±15.5</td>
<td>99.9±15.1</td>
</tr>
<tr>
<td>6 mo after procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>146.7±23.3</td>
<td>166.3±24.7</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>84.4±17.0</td>
<td>91.5±14.6</td>
</tr>
<tr>
<td>12 mo after procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>150.7±21.9†</td>
<td>N/A</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>87.0±16.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and N/A, not applicable.

*Preprocedure blood pressure is at randomization for the initial renal denervation group and 6 mo after randomization for the crossover group. †P=0.16 for difference from 6-mo SBP.
controlled trial of renal denervation in patients with drug-resistant essential hypertension.

This follow-up of the initial renal denervation cohort of patients confirms that the significant drop in mean blood pressure seen at 6 months after renal denervation (−32 mm Hg) is sustained at 12-month follow-up (−28 mm Hg), with no significant difference between blood pressure reductions at 6 and 12 months (P=0.16). These results are consistent with the longer-term responses observed in the Symplicity HTN-1 trial and an associated renal denervation registry that reported substantial drops in SBP at 12 (−23 mm Hg) and 24 months (−32 mm Hg) for 153 patients with resistant hypertension.16

At 6 months after randomization, 35 of the 51 control patients available for follow-up underwent renal denervation per protocol (SBP >160 mm Hg). Before renal denervation treatment (6 months after randomization), the mean SBP of the crossover group had increased from 182.8±16.3 to 190.0±19.6 mm Hg. This increase in blood pressure while patients are on a stable antihypertensive regimen may represent a natural tendency for blood pressure to increase in patients with treatment-resistant hypertension and suggests a potential cost in delaying renal denervation treatment. However, these patients represent a subset of the original control group; removal of subjects who chose not to undergo renal denervation or who no longer had a SBP >160 mm Hg introduces selection bias that may account for the differences in preprocedure blood pressure and renal function. Nevertheless, the crossover group experienced a significant drop in blood pressure at 6 months after treatment (−24 mm Hg; P<0.001 for difference from before the procedure) similar to that seen in the immediate renal denervation group, demonstrating the reproducibility of the primary end point results. It should be noted that the crossover patients did not repeat the 2-week compliance period before their 6-month visit after the procedure, which was required by the patients randomized to immediate renal denervation before their 6-month follow-up visit. It may be that the greater, albeit nonsignificant, drop in SBP in the initial renal denervation group compared with the crossover group at 6 months is related to this difference in patient management before the 6-month postprocedure office visit. Crossover group outcomes after renal denervation are consistent with results reported in the Symplicity HTN-1 trial (−25 mm Hg at 6 months).16

These data further substantiate the safety of renal sympathetic denervation via delivery of controlled radiofrequency energy bursts. Measures of renal function were unchanged 6 and 12 months after renal denervation (Table 6), suggesting no adverse consequences of the renal denervation on kidney function. Of note, preliminary data from a small series of patients with resistant hypertension and stage 3 to 4 kidney disease are indicative of a similar favorable safety profile even in a setting of moderate to severe renal impairment.20

In the crossover group, the renal denervation procedure resulted in 1 renal artery dissection that occurred before insertion of the Symplicity catheter and 1 hypotensive episode requiring hospitalization and adjustment of antihypertensive drugs. In the period from 6 to 12 months after initial randomization, 2 crossover patients experienced episodes of

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**Table 6. Renal Function at Baseline and 6 and 12 Months**

<table>
<thead>
<tr>
<th>Renal Function Data</th>
<th>Renal Denervation Group</th>
<th>Crossover Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>Baseline: 76.9±19.3 (n=49)</td>
<td>88.8±20.7 (n=35)</td>
</tr>
<tr>
<td></td>
<td>6 mo: 77.1±18.8 (n=49)</td>
<td>89.3±19.5 (n=35)</td>
</tr>
<tr>
<td></td>
<td>12 mo: 78.2±17.4 (n=45)</td>
<td>85.2±18.3 (n=35)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>Baseline: 1.03±0.29 (n=49)</td>
<td>0.84±0.21 (n=35)</td>
</tr>
<tr>
<td></td>
<td>6 mo: 1.04±0.32 (n=49)</td>
<td>0.83±0.18 (n=35)</td>
</tr>
<tr>
<td></td>
<td>12 mo: 1.01±0.28 (n=45)</td>
<td>0.86±0.20 (n=35)</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>Baseline: 0.91±0.25 (n=38)</td>
<td>0.78±0.17 (n=27)</td>
</tr>
<tr>
<td></td>
<td>6 mo: 0.98±0.36 (n=40)</td>
<td>0.82±0.16 (n=26)</td>
</tr>
<tr>
<td></td>
<td>12 mo: 0.98±0.30 (n=38)</td>
<td>0.89±0.20 (n=26)</td>
</tr>
</tbody>
</table>

Values are mean±SD. eGFR indicates estimated glomerular filtration rate.
hypertension requiring hospitalization (1 patient experienced 2 events).

Significant reductions in office-based blood pressure are sustained in patients who continue multidrug pharmacological treatment after renal denervation, and, importantly, to date there have been no observations of persistent symptomatic hypotension. The 1 episode of hypotension at the time of denervation was managed by the administration of intravenous fluids and alteration of the antihypertensive regimen. The sustained blood pressure–lowering effect of renal denervation in this and other studies with the Symplicity catheter suggests that there are unlikely to be overriding alterations in counterregulatory mechanisms or evidence of renal sympathetic reinnervation occurring up to 3 years after the procedure. An improvement in cardiac reflex adjusts to maintain the new lower blood pressure after patients or staff measuring the blood pressure response to the described in the Symplicity HTN-1 and HTN-2 human tent with the safety profile of renal sympathetic denervation component within the treated arteries as well as the absence reported in a patient with treatment-resistant hypertension.24 The lack of any persisting inflammatory component within the treated arteries as well as the absence of any stenosis or thrombosis in the swine arteries is consistent with the safety profile of renal sympathetic denervation described in the Symplicity HTN-1 and HTN-2 human trials. Furthermore, the Symplicity renal denervation system provides an additional level of safety by the incorporation of a specifically designed algorithm in the generator that measures and controls temperature, impendence, and duration of each energy application to maximize safety and efficacy.

Changes in antihypertensive medications were allowed as medically indicated after the 6-month primary end point was met. Although both increases and decreases in number of medications and prescribed dosage were observed, there was a trend toward decreases in antihypertensive medication use after renal denervation. It should be noted that the intent of the trial was to lower blood pressure and thereby reduce cardiovascular risk for patients with persistently elevated blood pressure; there was no intent to reduce medication use or to “cure” hypertension, which would surely be an unrealistic goal in hypertension of this severity.

Study Limitations
In this study, 24-hour blood pressure monitoring was lacking. There was an attempt to collect ambulatory blood pressure data during the initial 6 months of the trials, but because of patient nonadherence and incomplete records, these data are unavailable. After the 6-month end point, 24-hour blood pressure records were not collected. It is possible, although not definitively established, that with renal denervation, reactive elements in blood pressure, such as might operate with office blood pressure measurements, are lowered more than the less reactive components manifest in 24-hour blood pressure monitoring. Additionally, there was no blinding of patients or staff measuring the blood pressure response to the renal denervation intervention. These methodological shortcomings will be addressed directly in the ongoing Symplicity HTN-3 renal denervation trial in resistant hypertension, in which 24-hour blood pressure change is an important and powered secondary end point, the study is blinded, and a sham renal denervation procedure is incorporated into the study design.

Conclusions
Renal denervation with the use of the Symplicity catheter system results in sustained blood pressure reductions through 12 months in patients with severe hypertension unresponsive to ≥3 antihypertensive drugs. Patients crossed over to renal denervation from the control arm after 6 months experienced a similar significant drop in blood pressure. Procedure-related complications were uncommon and easily managed. At 12 months of follow-up, the Symplicity HTN-2 trial demonstrates safety and continued benefit with renal denervation used for the management of uncontrolled, treatment-resistant hypertension.

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Disclosures
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References

**CLINICAL PERSPECTIVE**

Patients with uncontrolled hypertension are at significant risk for cardiovascular events, and a subset of these patients who do not respond to aggressive pharmacological treatment (≥3 antihypertensive drugs including a diuretic) are considered to have treatment-resistant hypertension. It has been shown that activation of the sympathetic nervous system is involved in the pathogenesis and maintenance of hypertension. Renal denervation with the Symplicity catheter is a minimally invasive procedure based on the premise that interruption of renal afferent and efferent nerves with resultant decreased sympathetic outflow to the kidneys will reduce renin release and sodium retention, increase renal blood flow, and lower blood pressure. The Symplicity HTN-2 trial demonstrates that radiofrequency ablation of renal nerves can significantly lower blood pressure in patients with systolic blood pressures >160 mm Hg with no loss of treatment effect through 1 year and thus may provide a safe and effective adjunctive therapy for treatment-resistant hypertensive patients.

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