Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension
Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Abstract—Renal sympathetic hyperactivity is seminal in the maintenance and progression of hypertension. Catheter-based renal sympathetic denervation has been shown to significantly reduce blood pressure (BP) in patients with hypertension. Durability of effect beyond 1 year using this novel technique has never been reported. A cohort of 45 patients with resistant hypertension (systolic BP ≥160 mm Hg on ≥3 antihypertension drugs, including a diuretic) has been originally published. Herein, we report longer-term follow-up data on these and a larger group of similar patients subsequently treated with catheter-based renal denervation in a nonrandomized manner. We treated 153 patients with catheter-based renal sympathetic denervation at 19 centers in Australia, Europe, and the United States. Mean age was 57±11 years, 39% were women, 31% were diabetic, and 22% had coronary artery disease. Baseline values included mean office BP of 176/98±17/15 mm Hg, mean of 5 antihypertension medications, and an estimated glomerular filtration rate of 83±20 mL/min per 1.73 m². The median time from first to last radiofrequency energy ablation was 38 minutes. The procedure was without complication in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae. Postprocedure office BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively. In conclusion, in patients with resistant hypertension, catheter-based renal sympathetic denervation results in a substantial reduction in BP sustained out to ≥2 years of follow-up, without significant adverse events. (Hypertension. 2011;57:00-00.)

Key Words: hypertension • blood pressure • renal sympathetic denervation

Hypertension remains a major global public health burden, affecting more than a quarter of adults in developed societies.1 It is the leading attributable cause of mortality worldwide, causing 7.5 million deaths annually. Every 20/10 mm Hg increase in blood pressure (BP) is associated with a doubling of cardiovascular mortality.2,3 Epidemiological studies have shown that awareness of the condition is poor, with approximately half of hypertensives adequately treated to target BP levels.4–6 Furthermore, among patients with hypertension, there exists a subgroup who are unable to achieve adequate BP control despite the use of multiple medications and dietary and lifestyle modifications. These patients (termed “refractory” or “resistant”) are, by common definition, receiving ≥3 different classes of antihypertensive therapy, with 1 being a diuretic, and at maximal recommended or maximal tolerated doses.7

Among such patients, treatment options are few. Additional pharmacological strategies have been proposed. Device or procedure-based therapies have also been studied recently. One such approach involves a percutaneous, catheter-based renal sympathetic denervation procedure to disrupt renal afferent and efferent nerves using radiofrequency ablation. Initial proof-of-concept studies have demonstrated both reductions in BP (out to 12 months), as well as evidence of organ-specific sympathetic denervation. Furthermore, the procedure was found to be both simple to perform and safe (minimal procedure-related adverse events).8,9 Recently a randomized, controlled clinical trial of renal denervation in patients with treatment-resistant hypertension showed a 33/11-mm Hg reduction of 6-month office BP compared with control.8 An outstanding question with regard to renal denervation in general and the radiofrequency approach taken in particular is the durability of the BP-lowering effect. This is because efferent nerves have been demonstrated to anatomically regrow over a period of months to years without consistent demonstration of functional reinnervation.10,11 Therefore, it is of great interest and importance to evaluate the long-term safety and the durability of BP reduction that may follow the denervation procedure. Accordingly, the aim of the present analysis was to examine long-term outcomes among the entire initial cohort of refractory hypertension patients who

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underwent the nonrandomized, open-label, catheter-based renal denervation procedure.

Methods

Study Setting
This open-label, proof-of-concept study enrolled 153 patients at 19 investigational sites in Australia, Europe, and the United States between June 6, 2007, and May 1, 2010. Ethics committees at each site approved the study, and written informed consent was obtained from all of the patients.

Patient Population
Patients were enrolled based on having an elevated office systolic BP (≥160 mm Hg) despite taking ≥3 antihypertensive drug classes, 1 of which was a diuretic, at target or maximal tolerated dose. Patients were excluded if they had an estimated glomerular filtration rate (eGFR) of <45 mL/min per 1.73 m², type 1 diabetes mellitus or a known secondary cause of hypertension other than sleep apnea or chronic kidney disease. Patients with significant renovascular abnormalities were not permitted to undergo the intervention. This was assessed by various methods, including angiography, magnetic resonance angiography, computed tomography angiography, and duplex ultrasound. Such anatomic abnormalities included multiple main renal arteries, short length main renal artery, and hemodynamically significant renal artery stenosis. Patients had to be >18 years of age.

Study Procedures and Assessments
The primary efficacy end point of the study was change in office BP. Patients had office BP measurements performed in accordance with Joint National Committee VII guidelines. Measurements were performed sitting, in triplicate, and then averaged. The primary safety assessments were based on physical examination, basic blood chemistries, and anatomic assessment of the renal vasculature. Renal evaluations were performed via angiography in initial patients (at 14 to 30 days after procedure) and via renal magnetic resonance angiography, computed tomography angiography, or duplex scan at 6 months.

Physicians could alter background BP-lowering medication at any time for clinical reasons but were encouraged not to do so unless considered absolutely necessary, to carefully assess the effect of the procedure, per se. This was more strictly applied during the initial 12 months of the follow-up study and less so after this time.

Baseline measurements included physical examination, vital signs, basic blood chemistries, and pregnancy testing as appropriate. Follow-up assessments occurred at 1, 3, 6, 12, 18, and 24 months. Assessment of routine biochemistry, including eGFR (using the Modification of Diet in Renal Disease formula), was performed within the individual laboratories of participating hospitals.

Renal Denervation Procedure
The denervation procedure itself involves an endovascular catheter-based approach to disrupt renal sympathetic nerves using radiofrequency (RF) ablation applied via an electrode at the catheter tip. The central arterial tree is accessed via the femoral artery. The lumen of the main renal artery is catheterized using a 6F or 8F guide. The Symplicity Catheter (Ardian, Inc) is connected to an RF generator, and multiple RF treatments are applied in a manner devised to maximize renal sympathetic nerve disruption within the individual artery. Specifically, the first RF treatment is applied distally in the renal artery, and the catheter is then retracted by 5 mm and rotated circumferentially before the energy is reapplied. This is continued until 4 to 6 treatments have been applied within each renal artery and across the full circumference of the vessel. Each low-power treatment lasts ≥2 minutes.

As described in the initial report of this open-label experience, the first 10 patients underwent staged sequential procedures involving a single renal artery followed by the contralateral artery 1 month later. Subsequent patients underwent bilateral procedures in the 1 session.

Statistical Analysis
BP levels from baseline to the above time points were evaluated to calculate mean change, as well as 95% CIs. This was assessed by repeated-measures ANOVA with pairwise comparison of significant values. A 2-tailed paired t test of P < 0.05 was regarded as statistically significant. Multivariate stepwise backward regression analysis of key demographic and procedural characteristics that may predict increased systolic BP response was performed. Baseline variables entered into the model were age, sex, race, body mass index, systolic BP, diastolic BP, pulse pressure, heart rate, drug class, number of antihypertensive medications, eGFR, hypercholesterolemia, and coronary artery disease. Change in eGFR was evaluated in comparison with baseline at various time points using the paired t test. All of the statistical analysis was performed using SPSS version 15.0.

Patient Characteristics
We treated 153 patients in this open-label, proof-of-concept study. Baseline characteristics of the study subjects including demographics and background medication are listed in Tables 1 and 2. Mean baseline BP values were 176/98 ± 17/14 mm Hg. Patients were taking an average of 5.1 ± 1.4 antihypertensive drug classes.

Procedure Characteristics
A 6F guide was used in 55 patients and an 8F guide in 98 patients. The median time from first to last RF energy application was 2 minutes.

Table 1. Demographics of Treated Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD, y</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>39%</td>
</tr>
<tr>
<td>Ethnic origin (non-white)</td>
<td>5%</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>31%</td>
</tr>
<tr>
<td>CAD</td>
<td>22%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68%</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>83 ± 20</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>176/98 ± 17/15</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate.

Table 2. Baseline Antihypertensive Medications and Antihypertensive Medications at Last Available Follow-Up

<table>
<thead>
<tr>
<th>Antihypertensive Medications</th>
<th>Baseline (n = 153)</th>
<th>Last Available Follow-Up (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of antihypertension medications</td>
<td>5.1 ± 1.4</td>
<td>5.0 ± 1.5</td>
</tr>
<tr>
<td>Diuretic</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>Aldosterone blocker</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Direct renin inhibitor</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>β-blocker</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>75%</td>
<td>72%</td>
</tr>
<tr>
<td>Centrally acting sympatholytic</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>α1-blocker</td>
<td>19%</td>
<td>19%</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
delivery was 38 minutes, with an average of 4 ablations in each renal artery. There were no device malfunctions. Conscious sedation using IV narcotics and anxiolytics were commonly used to prevent and manage expected pain during the procedure. Episodes of bradycardia observed during the procedure were managed with administration of atropine in 10% patients (15 of 153 patients).

Efficacy

BP-Lowering Efficacy

Ninety-two percent of patients had an office BP reduction of \( \geq 10 \) mm Hg. Within-patient changes in both systolic and diastolic BPs were highly significant \((P < 0.0001)\) for all systolic and diastolic changes except 24-month diastolic BP, where \( P = 0.002 \) at all time points postprocedure with BPs reduced on average by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively (Figure 1A). When patient BP values were censored for medication increases postprocedure, there was little change in BP values over time compared with the uncensored values (Figure 1B). Similarly, when BP values over time were analyzed for the 18 patients who had data out to 2 years (Figure 1C), there was, again, little change in BP values compared with the uncensored values. Figure 2 illustrates the distribution of BP levels at baseline preprocedure and at 12 and 24 months postprocedure.

Baseline Predictors of BP Response

Significant independent predictors of greater systolic BP response on multivariate analysis were higher baseline systolic BP \((P < 0.0001)\) and use of central sympathetic agents \((P = 0.018)\). All of the other baseline parameters fell out as nonsignificant on multivariate analysis.

Antihypertensive Medication Changes Postprocedure

The number of antihypertensive medications at last available follow-up was unchanged as compared with baseline (5.0 versus 5.1; \( P = 0.11)\). In addition, classes of antihypertensive drugs were similar to baseline at last available follow-up (Table 2). Twenty-seven patients were on a reduced number of medications at last follow-up compared with baseline; 18 were on increased medications. Of the 18 patients with medication increases, 10 had their medications increased after drops in BP, presumably in an attempt to achieve additional reductions in BP. To ascertain the BP-lowering effect of renal denervation in the absence of increased medications, office BP data censored after an increase in the number of medications is presented in Figure 1B. The magnitude of the mean BP reduction in response to the procedure was unchanged when data from patients with increased antihypertension medications were censored.

Safety

Periprocedural Safety

The procedure was without complication in 97% of patients (149 of 153 patients). One patient experienced the renal artery dissection on placement of the treatment catheter before RF energy delivery was delivered in that artery. The dissection was treated with renal artery stenting without any subsequent complication or delay in hospital discharge. Three other patients developed a pseudoaneurysm/hematoma in the femoral access site; all had had an 8F guide and were treated without any subsequent complication. In all of the cases, the procedure was performed with standard techniques for femoral artery access using commercially available introducers.

Renal Vascular Safety

As mentioned, follow-up renal artery imaging was performed to evaluate structural abnormalities that may have occurred postprocedure in the treated renal arteries. Some minor focal renal artery irregularities attributed to minor spasm and/or edema were noted immediately after RF energy delivery. None were considered flow limiting at procedure termination. Of the short-term follow-up angiography performed in the first 20 patients, no evidence of renal artery stenosis or abnormalities was noted in treated arteries. In the 81 patients with 6-month magnetic resonance angiography, computed tomography angiography, or duplex evaluation, no irregularities or stenoses at any treatment site were identified that were not present on pretreatment angiography. One patient had a 6-month postprocedure computed tomography angiography that identified progression of a preexisting renal artery stenosis in the proximal portion of the renal artery. This stenosis was successfully stented; the location of the stenosis was quite proximal and well away from sites of RF energy application.

Renal Function

During the first year of follow-up, eGFR remained stable, with a change at 1, 3, 6, and 12 months of -0.1 mL/min (95% CI: -2.8 to 3.0; \( N = 112)\), -1.6 mL/min (95% CI: -4.3 to 1.1; \( N = 102)\), -0.1 mL/min (95% CI: -2.9 to 2.8; \( N = 87)\), and -2.9 mL/min (95% CI: -6.2 to +0.3; \( N = 64)\), respectively. eGFR data were only available on 10 patients at 2 years. In these 10 patients, eGFR changed by -16.0 mL/min per 1.73 m² at 24 months postprocedure. Five of these 10 patients had spironolactone or other diuretic added after the first year of follow-up. In patients without newly added spironolactone or other diuretic, eGFR changed by -7.8 mL/min per 1.73 m² for an annualized change of -3.9 mL/min per 1.73 m². In no cases did serum creatinine double, the patient develop class IV chronic kidney disease (15 to 29 mL/min per 1.73 m²), or the patient require dialysis.

Postural Hypotension and Edema

No patients reported symptomatic orthostatic hypotension. Six patients reported transient dizziness, spread across the entirety of the study period; no patients had any loss of consciousness. Three patients reported pitting edema, which was considered to be related to medication adjustment. This responded to conservative care, use of diuretics, and/or reduction in minoxidil dose.

Pain

Bilateral flank pain was reported by a single patient. Extensive diagnostic evaluation did not identify a specific cause for this pain. It did respond to ibuprofen over a number of months but eventually completely resolved. Three other patients reported intermittent or transient flank or kidney pain; all resolved with or without analgesic intervention.
Death
Two patients died within the follow-up period postprocedure. Neither death was considered by the study investigator or Data Safety Monitoring Board to be related to the device or the procedure. The first patient had known coronary artery disease and died from a myocardial infarction. Clopidogrel had been stopped after an episode of reversible cerebral ischemia, which was thought to have occurred secondary to atrial fibrillation with rapid ventricular response. The second patient was a 61-year-old female with gastrointestinal disease and coronary artery bypass grafting who was thought to have had sudden death.

Discussion
The present analysis has found that the initial reported BP reduction out to 12 months postrenal sympathetic denervation procedure has now been observed to persist out to 24 months of follow-up postprocedure. Furthermore, this larger cohort
of denervated patients followed for a longer time period appeared to experience few, if any, adverse effects that could be attributed to the RF energy application.

It is worth remembering that these large and persistent BP reductions occurred in patients who, by definition, were refractory to standard medical therapies. Among this cohort, 92% of patients had a reduction in systolic BP.

The persistence of overall BP lowering out to 2 years is of considerable clinical and pathophysiological relevance. The findings of the present study, therefore, suggest that catheter-based renal denervation results in initial sustained BP reduction to >24 months. If there is any reinnervation or counter-regulatory mechanisms, they are not clinically relevant in this time frame. This is particularly important given the dramatic BP reductions compared with control reported in the Symplicity HTN-2 Trial.9

A key issue in the clinical application of the procedure is in prediction of which patients may best respond with regard to falls in their BP. Although a relatively small cohort of patients, it was of interest to perform multivariate analysis to determine independent predictors of BP reductions. It was of interest that, among baseline variables, only elevated BP and use of central sympatholytics were predictors. Although the former is intuitive, the latter does not appear to be so biologically plausible. With an underlying 90% response rate in conjunction with the low observed morbidity and the reasonable cost of the procedure, it is improbable that a screening demographic or test could be developed that might be of any clinical value. The search for a screening test to identify those few patients for which BP is not related to the sympathorenal axis may principally have scientific value.

The magnitude of BP lowering postprocedure at 24 months is no less than and appears to be numerically greater than that observed at 12 months. It is, therefore, of interest to speculate as to what may be driving this persistence of BP-lowering effect postprocedure. This may represent a predominant alteration in afferent signaling induced by the renal denervation procedure with a resetting of central sympathetic outflow, as demonstrated previously.12 This may be associated with a resetting of the baroreflex around a lower homeostatic set point. Vascular remodeling may have been reversed over the 24-month period, with that reversal sustained postprocedure. Whatever the mechanism, this appears to override any functional reinnervation that may be occurring postprocedure. However, further follow-up of this cohort is required beyond this time point to ascertain the status of BP lowering over an even longer time, as well implications regarding the need for repeat procedure(s).

The other important observation relates to renal function. Clearly, elevated BP is a major determinant of decline in renal function; BP lowering will have renoprotective effects. Bakris et al13 have published a meta-analysis on expected 1-year eGFR decline based on starting systolic BP. The decline in renal function observed in this 24-month follow-up analysis is less than would be predicted based on the BP response achieved, especially so over the first 12 months postprocedure before the introduction of diuretics, which may worsen renal function. Therefore, this suggests that there may be an intrinsic beneficial effect of the procedure on the kidney to maintain renal function, which is greater than that achieved via BP reduction alone. Clearly, these findings can only be considered hypothesis generating, however, because we do not have a control group in this study, and comparisons are based entirely on natural history studies from noncontemporary cohorts. Nonetheless, it is interesting to speculate mechanistically as to why this may be occurring. In particular, sympathetic nerves drive release of a number of key hormones regulating renal perfusion and glomerular filtration, including renin and adenosine. Blockade of renin has been documented as part of neurohormonal profiling postprocedure in this study.12 Blockade of adenosine (in particular, A1 receptors in the kidney) has been shown to maintain glomerular filtration while improving renal blood flow.12 Thus, renal sympathetic denervation theoretically (with some supporting data from this analysis) would appear to slow the BP- and time-related decline in eGFR in the hypertension setting.

The other important observation from this extended follow-up of renal denervation patients was the ongoing safety observed within the study. In this report, a larger cohort of patients is exposed to a longer period of postprocedure follow-up without any major safety signals emerging. In particular, in the cohort of 81 patients with 6-month follow-up imaging, no cases of major de novo renal artery stenosis have occurred, and only 1 case of progression of an existing stenosis is described. Even with that single case, it cannot be determined whether this was specifically related to the interventional procedure or natural progression of a baseline stenosis. No cases of renal artery aneurysm and no cases with cholesterol emboli were documented in this series. Furthermore, no late clinical sequelae (out to 2 years) could be attributed to development of renal artery stenosis.

Aldosterone antagonists, such as spironolactone, have been proposed for patients failing to attain target BP. It should be noted that, in this cohort, 22% of the patients were already...
taking spironolactone at baseline, yet failing to attain target. The presence of the aldosterone blocker did not alter the response to renal denervation. Baroreceptor stimulation, to reduce baroreceptor reflex, has been explored as a treatment for resistant hypertension. Comparisons with baroreceptor stimulation are foiled by the inherently different morbidity and cost of catheter-based renal denervation from a more invasive surgical procedure requiring implantation of a permanent foreign body.

Limitations
As with the initial published report regarding this procedure, this extended analysis has a number of important limitations. There is no control group with which to make comparisons regarding BP and eGFR responses over time. Therefore, factors such as regression to the mean and Hawthorne effect need to be considered in the interpretation of these results. This limitation has been recently addressed in a prospective, randomized control clinical trial (Symplicity HTN-2) that has recruited similar patients and then randomly assigned them to immediate or delayed (6-month) procedure to allow for such comparisons. In addition, only relatively small numbers of patients have reached the 24-month follow-up time point. However, the consistency of the BP reductions achieved at the differing time points postprocedure would suggest that the present findings would be unlikely to differ greatly with larger numbers reaching each follow-up time point.

In conclusion, this report, describing the prolonged renal denervation experience out to 2 years, demonstrates durable BP lowering over this period, in an extended cohort of patients in whom the procedure was safely applied. Therefore, renal sympathetic denervation appears to be a potentially useful option for patients with refractory hypertension. Baroreceptor stimulation, to the renal denervation procedure, at least out to 24 months.

Perspectives
A major issue with the renal denervation procedure is the question mark over its durability, given the potential for sympathetic nerves to regrow after damage to them. This analysis demonstrates that significant postprocedure office BP reductions were achieved by the renal denervation procedure and sustained out to 24 months in this group of resistant hypertensive patients. Thus, BP reductions, initially observed out to 12 months, appear to persist to ≥24 months, suggesting durability of the denervation. The procedure itself was well tolerated and generally safe; there were no periprocedural or late adverse events associated with the application of RF energy in this setting. Therefore, despite the potential for nerve regrowth and reinnervation, there appeared to be little if any impact on the functional (ie, BP-lowering) benefit of the renal denervation procedure, at least out to 24 months.

Appendix

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Paul A. Sobotka, Neil C. Barman, and Craig Straley are employees of Ardian, Inc. All of the other authors have worked at centers receiving per-patient payment for study involvement as part of the Symplicity HTN-1 Study.

References


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