ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

ABSTRACT

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

RESULTS

A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was –14.13±23.93 mm Hg in the denervation group as compared with –11.74±25.94 mm Hg in the sham-procedure group ($P<0.001$ for both comparisons of the change from baseline), for a difference of –2.39 mm Hg (95% confidence interval [CI], –6.89 to 2.12; $P=0.26$ for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was –6.75±15.11 mm Hg in the denervation group and –4.79±17.25 mm Hg in the sham-procedure group, for a difference of –1.96 mm Hg (95% CI, –4.97 to 1.06; $P=0.98$ for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School (D.L.B., L.M.), Boston University School of Public Health (R.D.), and Harvard Clinical Research Institute (R.D., L.M.) — all in Boston; Piedmont Heart Institute, Atlanta (D.E.K.); the Division of Cardiology, Henry Ford Hospital (W.W.O.), and Wayne State University and the Detroit Medical Center (J.M.F.) — all in Detroit; Baptist Cardiac and Vascular Institute, Miami (B.T.K.); New York Presbyterian Hospital, Columbia University Medical Center, and Cardiovascular Research Foundation, New York (M.B.L.); Medtronic CardioVascular, Santa Rosa, CA (M.L., M.N., S.A.C.); University of Alabama at Birmingham, Birmingham (S.O.); Prairie Heart Institute, Springfield, IL (K.R.-S.); Perelman School of Medicine, University of Pennsylvania, Philadelphia (S.A.C., R.R.T.); and University of Chicago Medicine, Chicago (G.L.B.). Address reprint requests to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

*A complete list of investigators in the SYMPLICITY HTN-3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Because of the aging of the population and rising rates of obesity, hypertension is increasing in prevalence worldwide.[1] Approximately 10% of patients with diagnosed hypertension have resistant hypertension, defined as a systolic blood pressure of 140 mm Hg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose.[1-4] Patients with resistant hypertension who are receiving appropriate medical therapy have high rates of cardiovascular complications, with few treatment options.

The sympathetic nervous system — in particular, sympathetic cross-talk between the kidneys and the brain — appears to play an important role in resistant hypertension.[5] In an earlier era, nonrandomized studies showed that surgical sympathectomy was an effective treatment for some patients with uncontrolled hypertension, but profound orthostasis commonly occurred after the procedure, and it fell into obsolescence.[6,7]

In recent years, catheter-based radiofrequency denervation of the renal arteries has emerged as a potential treatment for resistant hypertension and is already in clinical use in more than 80 countries, including parts of Europe, South America, Australia, and Canada.[8-10] Initial nonrandomized studies and randomized, unblinded trials have shown large reductions in blood pressure, as measured at an office visit, after renal denervation.[11,12] However, several limitations of these studies, including small sample sizes, limited assessment of ambulatory blood pressure, lack of blinding, and lack of a sham procedure as a control, make broad application of the findings unreliable. The SYMPLICITY HTN-3 study was carefully designed to overcome these methodologic shortcomings.[13]

Methods

Study Design and Oversight

The design of the SYMPLICITY HTN-3 trial has been reported previously.[13] In brief, patients 18 to 80 years of age with resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal-artery denervation or a sham procedure and were followed for 6 months, at which time the primary efficacy and safety end points were ascertained. All patients provided written informed consent.

The trial was designed by the first and last authors and the sponsor (Medtronic). The data were collected by the sponsor. Harvard Clinical Research Institute independently validated the analyses, with funding from the sponsor. The first and last authors prepared the first draft of this manuscript, which was then reviewed and edited by the coauthors. The sponsor had the right to review but not approve the final manuscript. The first and last authors accept full responsibility for the accuracy and completeness of the reported analyses and interpretations of the data, and they vouch for the fidelity of the study to the protocol (available with full text of this article at NEJM.org).

Study Patients

Patients with severe resistant hypertension were prospectively enrolled in the study. On initial screening, patients were required to have a systolic blood pressure of 160 mm Hg or higher (average of three measurements at an office visit [hereafter referred to as office blood pressure] while the patient was seated) and to be taking maximally tolerated doses of three or more antihypertensive medications of complementary classes, one of which had to be a diuretic at an appropriate dose. No changes in antihypertensive medication in the previous 2 weeks were allowed. For the next 2 weeks, patients recorded their blood pressure at home (hereafter referred to as home blood pressure) in the morning and in the evening and kept a diary indicating their adherence to medical therapy. Then a confirmatory screening visit occurred, during which the systolic blood pressure of 160 mm Hg or higher was confirmed, adherence to medications was documented, and automated 24-hour ambulatory blood-pressure monitoring was performed to ensure a systolic blood pressure of 135 mm Hg or higher. Clinical exclusion criteria were known secondary causes of hypertension and more than one hospitalization for a hypertensive emergency in the previous year. Anatomical exclusion criteria were renal-artery stenosis of more than 50%, renal-artery aneurysm, prior renal-artery intervention, multiple renal arteries, a renal artery of less than 4 mm in diameter, or a treatable segment of less than 20 mm in length.

Patients underwent renal angiography before randomization. At 6 months, patients in the control group were allowed to cross over to undergo

denervation if they still met the inclusion criteria for the study.

STUDY TREATMENT

Patients in the treatment group underwent renal-artery denervation with the use of radiofrequency energy delivered by the Symplicity renal-denervation catheter (Medtronic). Patients were unaware of whether they underwent renal-artery denervation or renal angiography only (sham control). (The blinding procedure is detailed in the Supplementary Appendix, available at NEJM.org.) Blood-pressure assessors were also unaware of the study-group assignments. A blinding index, based on responses to a questionnaire, was calculated at hospital discharge and at 6 months to verify the effectiveness of blinding.[14] The blinding index ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients did not know their study-group assignments), with values greater than 0.5 indicating successful blinding. Changes in antihypertensive medication were not allowed during the 6-month follow-up period unless they were considered to be clinically necessary.

END POINTS

The primary efficacy end point was the mean change in office systolic blood pressure from baseline to 6 months in the denervation group, as compared with the mean change in the sham control group, with a superiority margin of 5 mm Hg. The study was also powered for assessment of a secondary efficacy end point: the change in mean 24-hour ambulatory systolic blood pressure at 6 months. The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data. All patients are to be followed semiannually through 5 years after randomization.

STATISTICAL ANALYSIS

This trial was powered for the primary safety and efficacy end points and for the change in mean 24-hour ambulatory systolic blood pressure at 6 months (secondary efficacy end point). On the basis of the 9.8% safety performance criterion, 316 patients were required in the renal-denervation group to provide 80% power, with the use of a one-sided significance level of 0.05. Owing to the 2:1 randomization ratio, 158 patients were required for the control group. After accounting for expected patient attrition, we calculated that we would need to enroll a total of 530 patients. In agreement with the Food and Drug Administration, the superiority of denervation over the sham procedure was established by a margin of 5 mm Hg for the primary efficacy end point and by a margin of 2 mm Hg for the secondary efficacy end point. The superiority margin of 5 mm Hg for the primary efficacy end point was considered a clinically meaningful blood-pressure reduction on the basis of the observed decreases in cardiovascular morbidity with small reductions in systolic blood pressure (2 to 5 mm Hg) with pharmacologic therapy.[15] The detailed power and sample-size calculations have been published previously.[13]

The analyses were performed on the basis of the intention-to-treat principle. Means and standard deviations of continuous variables are presented according to treatment group. Between-group differences and differences from baseline to the 6-month follow-up assessment were tested with the use of unpaired and paired t-tests, respectively. For categorical variables, counts and percentages are presented according to treatment group; values were tested with the use of the exact test for binary variables and the chi-square test for multilevel categorical variables. All reported subgroup analyses were prespecified.

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

A total of 1441 patients were assessed for eligibility; of these patients, 535 (37.1%) from 88 sites in the United States were enrolled in the trial between October 2011 and May 2013 (Fig. S1A and Fig. S1B in the Supplementary Appendix). The baseline characteristics are shown in Table 1. There were no significant differences between the two groups. Table S1 in the Supplementary Appendix shows the procedural characteristics for the two groups. Patients were receiving an average of five antihypertensive medications, and

on average, four of these medications were at maximally tolerated doses (Table S2 in the Supplementary Appendix). The majority of patients were receiving hydrochlorothiazide (Table S3 in the Supplementary Appendix). The numbers and types of antihypertensive medications at 6 months were similar to those at baseline in both groups. Table S4 in the Supplementary Appendix shows that the blinding index was significantly greater than 0.5 at discharge and at the 6-month follow-up visit, indicating proper blinding.

END POINTS

The results with regard to the primary efficacy end point (change in office systolic blood pressure at 6 months) and the secondary efficacy end point for which the study was powered (change in ambulatory blood pressure at 6 months) are shown in Figures 1 and 2, respectively. There was no significant between-group difference in the change in office blood pressure at 6 months: –14.13±23.93 mm Hg in the denervation group and –11.74±25.94 mm Hg in the sham-procedure group, for a difference of –2.39 mm Hg (95% confidence interval [CI], –6.89 to 2.12; P=0.26 with a superiority margin of 5 mm Hg). The change in ambulatory blood pressure at 6 months was –6.75±15.11 mm Hg in the denervation group and –4.79±17.25 mm Hg in the sham-procedure group, for a difference of –1.96 mm Hg (95% CI, –4.97 to 1.06); P=0.98 with a superiority margin of 2 mm Hg). Figure S2 in the Supplementary

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4

Table 1. (Continued.)

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Type of antihypertensive medication — no. (%)		
ACE inhibitor		
Patients taking medication	179 (49.2)	71 (41.5)
Patients taking maximally tolerated dose	167 (45.9)	64 (37.4)
Angiotensin-receptor blocker		
Patients taking medication	182 (50.0)	91 (53.2)
Patients taking maximally tolerated dose	180 (49.5)	88 (51.5)
Aldosterone antagonist	82 (22.5)	49 (28.7)
Alpha-adrenergic blocker	40 (11.0)	23 (13.5)
Beta-blocker	310 (85.2)	147 (86.0)
Calcium-channel blocker		
Patients taking medication	254 (69.8)	125 (73.1)
Patients taking maximally tolerated dose	208 (57.1)	109 (63.7)
Centrally acting sympatholytic agent	179 (49.2)	75 (43.9)
Direct-acting renin inhibitor	26 (7.1)	12 (7.0)
Direct-acting vasodilator	134 (36.8)	77 (45.0)
Diuretic		
Patients taking medication	363 (99.7)	171 (100)
Patients taking maximally tolerated dose	351 (96.4)	167 (97.7)

* Plus–minus values are means ±SD. All differences in characteristics between groups were nonsignificant. ACE denotes angiotensin-converting enzyme.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was determined by self-report.
§ Renal insufficiency was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Appendix shows the change in home systolic blood pressure; there was no significant difference between the two groups.

The observations regarding systolic blood pressure were consistent when diastolic blood pressure was examined (Table S5 in the Supplementary Appendix). The proportions of patients with a reduction in office systolic or diastolic blood pressure of at least 5 mm Hg or at least 10 mm Hg are shown in Table S6 in the Supplementary Appendix. The responses with regard to systolic and diastolic blood pressure were significantly greater in the denervation group than in the sham-procedure group.

Between-group differences in the change in office systolic blood pressure from baseline to 6 months in various prespecified subgroups are shown in Figure 3. Although the differences between groups in some subgroups were nominally significant, the absolute magnitude of the differences was small (<10 mm Hg), and the differences were not significant with the use of a superiority margin of 5 mm Hg or after adjustment for multiple comparisons. There were no significant differences between the denervation and sham-procedure groups as a function of baseline systolic blood pressure. There was also no significant between-group difference in the change in heart rate from baseline to 6 months (–3.8±11.2 beats per minute in the denervation group and –2.7±10.9 beats per minute in the sham-procedure group, P=0.30).

Table 2 shows the primary safety end point and other safety events. There were few major adverse events in the trial: five in the denervation group (1.4%) and one in the sham-procedure group (0.6%), for a difference of 0.8 percentage points (95% CI, −0.9 to 2.5; P=0.67). Table S5 in the Supplementary Appendix lists details of the office, ambulatory, and home

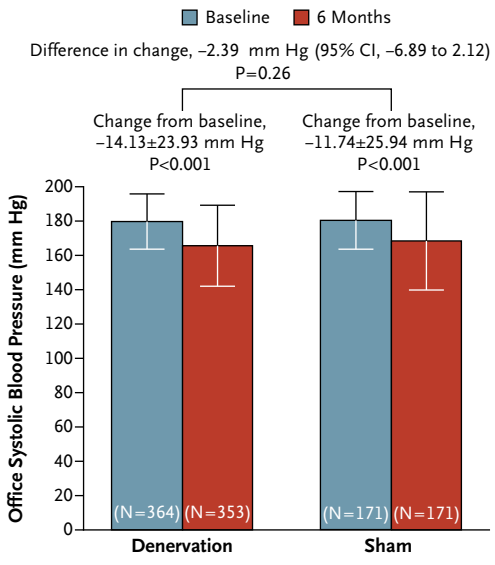

Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

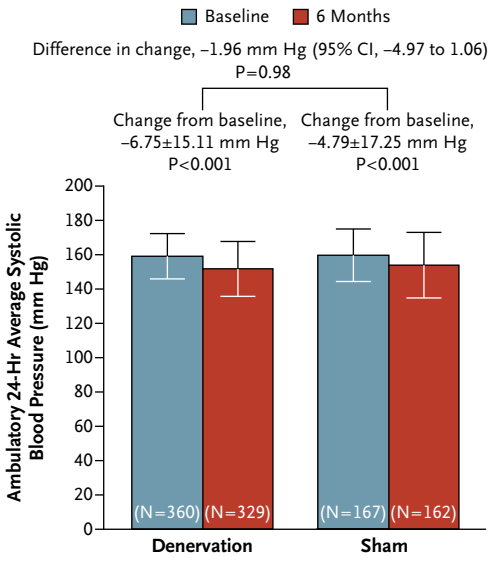

Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

blood-pressure measurements at baseline and 6 months. As shown in Table S7 in the Supplementary Appendix, there were no significant differences between the two groups in kidney function at any time point; there were also no significant differences in the subgroup of patients with an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area. There was no significant between-group difference in the change in glycated hemoglobin levels from baseline to 6 months overall (0.06±0.93% in the denervation group and –0.06±0.87% in the sham-procedure group, P=0.19) or in the subgroup of patients with diabetes (0.12±1.15% in the denervation group and –0.22±1.14% in the sham-procedure group, P=0.051). Table S8 in the Supplementary Appendix shows the percentages of patients who had "notching" on angiography, signifying energy delivery sufficient to cause spasm of the artery.

DISCUSSION

This randomized, sham-controlled, blinded trial did not show a benefit of renal-artery denervation with respect to either of the efficacy end points for which the study was powered (reduction in office or ambulatory systolic blood pressure at 6 months). These findings contradict the published clinical data regarding renal denervation, which showed larger reductions in blood pressure 6 months after denervation and, in the unblinded SYMPLICITY HTN-2 trial, no reduction of systolic blood pressure in control patients.[8,9,16] A meta-analysis of antihypertensive-drug trials predicted that the change in office systolic blood pressure would be smaller than reported in two early renal-denervation trials (–22 mm Hg[11] and –28 mm Hg[16]) when a more rigorous study design was used to reduce bias.[17] The current trial underscores the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption.[18]

There are several possible explanations for the discrepancy between our findings and the results of previous renal-denervation studies.[11,12] Prior nonrandomized studies compared the treatment results with baseline observations rather than with the results in a control group, leading to a false impression of treatment efficacy. Regression to the mean may have been in play such that patients who had an elevated sys-

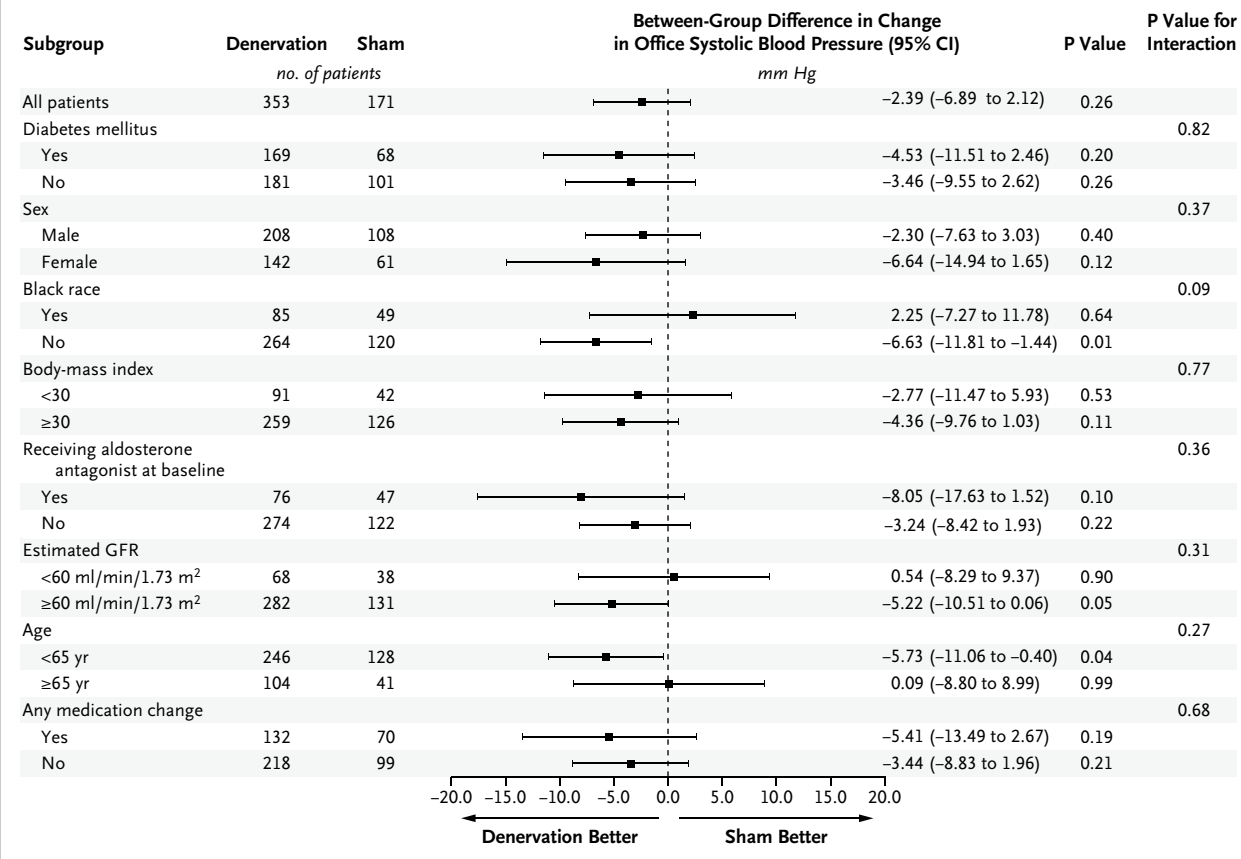

Figure 3. Selected Subgroup Analyses.

Shown are between-group differences in the change in office systolic blood pressure from baseline to 6 months in selected subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate.

tolic blood pressure on the day they were enrolled in the trial may have had a lower subsequent measurement, indicating a reduction that was actually an artifact of the study inclusion criterion regarding systolic blood pressure.[19] Furthermore, without a control group, the observed treatment effect may have been a result of trial participation, with the reduction in systolic blood pressure due to good care and a high degree of adherence to antihypertensive therapy as a result of close follow-up (i.e., the Hawthorne effect).[20,21]

A prior randomized trial included a control group, but lack of blinding may have introduced a bias. Both patients and assessors may be subject to bias in favor of a new treatment that is expected to have increased efficacy. The misattribution of a placebo effect as a treatment effect is a likely limitation of prior renal-denervation studies.[22,23] Our analysis revealed that an important placebo effect was present. Perhaps this placebo effect was accentuated by the use of an invasive procedure in the control group (i.e., a femoral-artery puncture and renal angiography), which may have increased adherence to medication and diet. Regardless, this finding has important therapeutic implications for the design of trials of antihypertensive (and other) medications, devices, and strategies.

A limitation of this trial is that medication adherence could not be confirmed. More than 50% of patients with resistant hypertension are known to be nonadherent to medications.[24] Although we did not measure urine levels of antihypertensive medications, patients had specific instructions to keep taking their antihypertensive medications at their current doses, and medication use was documented over a period of 2 weeks in diaries before baseline and before the 6-month follow-up visit. We found no evidence

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (–0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	–1.9 (–6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (–1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (–2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	–2.7 (–6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (–2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (–1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (–0.3 to 0.9)

* CI denotes confidence interval.
† 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. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data. The rate in the renal-denervation group was 1.4% with an upper boundary of the one-sided 95% CI of 2.9%; therefore, the performance criterion was met with a P value of <0.001.
‡ This end point was a composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis of more than 70% within 6 months.

of a significant difference in medication adherence between the groups. Medication changes between screening visits may have caused instability of baseline blood pressure, but only 31 patients (5.8%) had a medication change during this period, with no significant between-group difference in office blood pressure at screening visits (Table S2 in the Supplementary Appendix). Ideally, blood pressure would have been measured in the morning as recommended by the American Heart Association.[25] Although blood pressure was not always measured in the morning, it was measured at approximately the same time at both the baseline and the 6-month follow-up visits.

The 6-month period from baseline to ascertainment of the primary end point might be too short if a placebo effect declined with time, though prior studies showed a large effect by 6 months (which was sustained through 3 years); the patients in our study will be followed for up to 5 years, including those who did not cross over. The trial was not powered to detect small differences in systolic or diastolic blood pressure or any potential effects in subgroups. An operator learning curve can affect the success of interventional procedures, though all procedures were proctored. We observed no significant difference in outcomes between operators performing five or more procedures and those performing fewer than five procedures, and we found no evidence of a learning curve for high-volume operators when earlier procedures were compared with later ones. There was no direct measurement to confirm that the renal nerves were in fact denervated by the procedure, because there is no test that can be easily performed in a large trial. However, the Symplicity catheter system allowed confirmation of energy delivery, and the presence of angiographic notching indicated a bio-

logic effect of energy delivery on the artery. Finally, the results of this trial are specific to the catheter tested and cannot necessarily be generalized to other denervation systems.

Renal denervation in the current trial appeared to be safe, with no unanticipated side effects. However, a significant effect on systolic blood pressure was not observed. Further evaluation in rigorously designed clinical trials will be necessary to validate alternative methods of renal denervation or to confirm previously reported benefits of renal denervation in patients with resistant hypertension.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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