EDITORIAL

Renal Denervation for Resistant Hypertension?

Franz H. Messerli, M.D., and Sripal Bangalore, M.D.

Ever since Schlaich et al.[1] first reported on a patient with a blood pressure of 161/107 mm Hg (despite treatment with seven different antihypertensive drugs) that decreased to 127/81 mm Hg after renal denervation, the medical community has been enamored with this procedure. Resistant hypertension evolved into a fashionable diagnosis, and the number of publications pertaining to it grew rapidly.[2] Medical-device companies fancied renal denervation as the next big innovation and as a blockbuster therapy for millions of patients. A press release from the American Heart Association even touted renal denervation as a potential "cure" for mild hypertension.[3] Trials such as the SYMPLICITY HTN-1[4] and HTN-2[5] studies showed impressive decreases in blood pressure, seemingly attesting to the efficacy and safety of renal denervation. Three-year follow-up of the SYMPLICITY HTN-1 study revealed a decrease in blood pressure of 32/14 mm Hg.[6] These unprecedented results seemed to surpass what was achievable with drug therapy and continued to fan the flames of renal denervation.

The SYMPLICITY HTN-3 study, a blinded, sham-controlled study now reported in the *Journal* by Bhatt et al.,[7] brings the renal-denervation train to a grinding halt. After 6 months, office systolic blood pressure decreased from baseline to a similar extent in the renal-denervation and sham-procedure groups ($P<0.001$ for both comparisons of the change from baseline); the difference in the change in blood pressure between the two groups was a paltry –2.39 mm Hg (Table 1). In addition, a prespecified difference in 24-hour ambulatory systolic pressure of only 2 mm Hg was not met. Thus, in the SYMPLICITY HTN-3 study, renal denervation had no significant effect on office or 24-hour ambulatory systolic blood pressure, findings that contradict most published data on renal denervation, although a recent trial even suggested inferiority of renal denervation, as compared with adjusted drug treatment.[8]

At first blush, the most likely explanation for the findings of the SYMPLICITY HTN-3 study is the inclusion of a sham-control group. In clinical trials testing interventional procedures and medical devices, sham procedures are seminal, analogous to the use of a placebo in pharmaceutical trials. However, for ethical reasons sham procedures are frowned upon[9]; neither the SYMPLICITY HTN-1 study nor the HTN-2 study had a sham-control cohort. For this reason, placebo effects may well explain all or most of the blood-pressure differences noted in the first two trials. Lack of efficacy could also be caused by incomplete or ineffective denervation. No reliable markers of renal denervation are available, and questions remain as to what exactly the procedure accomplishes. Nevertheless, the ablation catheter used in the SYMPLICITY HTN-3 study was no different from that used in the SYMPLICITY HTN-1 and HTN-2 studies.

A decrease in systolic blood pressure was observed in both the renal-denervation group and the control group, a finding that is in marked contrast to the findings in previous trials. At 6 months, the decrease in office systolic blood pressure from baseline in the renal-denervation group in the SYMPLICITY HTN-3 study was about half that observed in the corresponding group in the SYMPLICITY HTN-2 study, despite the fact that baseline blood pressures were similar in the two studies. This is puzzling, because the degree of reduction in blood pressure is related to pretreatment blood-pressure levels (unpublished data). In addition, there was a larger decrease in blood pressure in the control group of the SYMPLICITY HTN-3 study, as compared

Table 1. Selected Findings of the SYMPLICITY HTN-2 and HTN-3 Studies.

Variable	SYMPLICITY HTN-2		SYMPLICITY HTN-3	
	Renal Denervation	No Renal Denervation	Renal Denervation	Sham Procedure
No. of patients	52	54	364	171
No. of antihypertensive medications at baseline	5.2±1.5	5.3±1.8	5.1±1.4	5.2±1.4
Aldosterone antagonist at baseline (% of patients)	17	17	22.5	28.7
Office systolic blood pressure at baseline (mm Hg)	178±18	178±16	179.7±16.1	180.2±16.8
Heart rate at baseline (beats/min)	75±15	71±15	NR	NR
Change in office systolic blood pressure at 6 mo (mm Hg)				
Absolute change	−32±23	1±21	−14.1±23.9	−11.7±25.9
Change relative to control group	−33		−2.4	
Change in home systolic blood pressure at 6 mo (mm Hg)				
Absolute change†	−20±17	2±21	−7.4	−6.0
Change relative to control group	−22		−1.3	
Change in 24-hr ambulatory systolic blood pressure at 6 mo (mm Hg)				
Absolute change‡	−11±15	−3±19	−6.8±15.1	−4.8±17.2
Change relative to control group	−8		−1.96	
Change in antihypertensive medication (% of patients)				
Decrease in dose or no. of medications	20	6	NR	NR
Increase in dose or no. of medications	8	12	NR	NR

* Plus–minus values are means ±SD. NR denotes not reported.
† In the SYMPLICITY HTN-2 study, data were available for 32 patients who underwent renal denervation and 40 patients who did not.
‡ In the SYMPLICITY HTN-2 study, data were available for 20 patients who underwent renal denervation and 25 patients who did not.

with the meager decrease in the SYMPLICITY HTN-2 study. Is it conceivable that greater exposure to spironolactone in the SYMPLICITY HTN-3 study facilitated this decrease (and possibly contributed to a neutral outcome)?

Could we have predicted the outcome of the SYMPLICITY HTN-3 study? The standard deviations of the change in office systolic blood pressure from baseline in both study groups in both trials were remarkably similar, indicating a wide variation in response. In fact, in the SYMPLICITY HTN-2 study, the change in blood pressure from baseline in 95% of patients was between −78 mm Hg and 14 mm Hg in the renal-denervation group and between −43 mm Hg and 41 mm Hg in the control group. The mean blood-pressure reduction in the SYMPLICITY HTN-3 study is well within this range for both study groups. The wide variability in response to renal denervation begs the question of whether this procedure could be more efficacious in selected patients with increased sympathetic drive only, such as those with heart failure. Regardless of this conjecture, the SYMPLICITY HTN-3 study certainly has raised the bar.

To be enrolled in a study, patients need to fulfill predefined blood-pressure criteria on a particular day. Patients whose blood pressure is above their usual average will preferentially be enrolled. Thus, subsequent blood-pressure measurements are prone to be lower regardless of whether there was an intervention. This phenomenon, although unlikely to fully explain the differences in blood-pressure decrease among various studies, occurs only when inclusion criteria require a certain blood-pressure level. It should not be confused with regression to the mean or a placebo effect, both of which could also have contributed to

the uneven blood-pressure response in the SYMPLICITY trials. Indeed, regression to the mean was probably responsible for a less extreme decrease in office systolic blood pressure in the renal-denervation group and a more impressive decrease in the control group, as compared with changes observed in prior studies.

Exuberance about renal denervation has been widespread, as is illustrated by these statements: "The potential of renal denervation is enormous" and it "may be used not only to treat hypertension, but also . . . diseases that are characterized by high sympathetic activity such as diabetes and hyperinsulinemia, heart failure, arrhythmias, and chronic kidney disease."[10] These words, thoroughly referenced, tout the benefits of renal denervation in these metabolic or cardiovascular disorders. In contrast, the conclusions of the SYMPLICITY HTN-3 study by one of the same authors now 6 months later soberingly state that "a significant effect on systolic blood pressure was not observed. Further evaluation in rigorously designed clinical trials will be necessary . . . to confirm previously reported benefits of renal denervation in patients with resistant hypertension." Should this statement indeed hold true, we will have to come to grips with two facts: the SYMPLICITY studies merely document the natural history of resistant hypertension in clinical trials, and the time has come to turn the page on renal denervation for hypertension but by all means, let's not close the book.

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

From the Division of Cardiology, Mount Sinai Roosevelt Hospital, Icahn School of Medicine (F.H.M.), and the Leon H. Charney Division of Cardiology, New York University School of Medicine (S.B.) — both in New York.

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1. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med 2009;361:932-4.
2. Messerli FH, Bangalore S. Treatment-resistant hypertension: another Cinderella story. Eur Heart J 2013;34:1175-7.
3. Radio waves to kidneys lower persistent high blood pressure. Press release of the American Heart Association, Dallas, December 17, 2012.
4. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373:1275-81.
5. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the SYMPLICITY HTN-2 Trial): a randomised controlled trial. Lancet 2010;376:1903-9.
6. Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the SYMPLICITY HTN-1 study. Lancet 2014; 383:622-9. [Erratum, Lancet 2014;383:602.]
7. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. DOI: 10.1056/NEJMoa1402670.
8. Elmula F, Hoffmann P, Larstorp AC, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension 2014 March 3 (Epub ahead of print).
9. Gottlieb S. The FDA wants you for sham surgery: there are better ways to test medical devices than by having patients be placebos who get fake operations. Wall Street Journal. February 18, 2014.
10. Mahfoud F, Bhatt DL. Catheter-based renal denervation: the black box procedure. JACC Cardiovasc Interv 2013;6:1092-4.

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