JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 13, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.01.038

EDITORIAL COMMENT

The Setback of Renal Denervation Should Not Backfire on Sympathetic Overactivity in Hypertension*

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The SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) study was a randomized, sham-controlled clinical study of the blood pressure (BP)-lowering effects of renal sympathetic denervation (RDN), which included ambulatory BP measurements (ABPM) as part of the inclusion criteria and as a secondary endpoint. The primary results of the study failed to show a larger reduction in office BP and ABPM compared with those of sham treatment at 6 months (1). In this issue of the *Journal*, the SYMPLICITY HTN-3 investigators report office systolic BP (SBP) and ABPM after 1 year in most of the patients originally randomized to RDN and in patients in the sham group who did and did not undergo RDN after 6 months (2).

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In the original RDN patients (n = 319), office SBP was slightly lower at 12 months than at 6 months (−15.5 vs. −18.9 mm Hg, respectively; $p < 0.025$), but ABPM was not different. Patients who did not undergo RDN (n = 48) had −32.9 mm Hg reduction in office SBP at 6 months but only −21.4 mm Hg at 12 months. As for the patients from the sham group who underwent RDN at 6 months (n = 93), they showed −17.7 mm Hg drop in office SBP and −9.2 mm Hg in ABPM at 1 year after randomization. These data support no further BP reductions after 1 year of follow-up (2).

RDN has been proposed as a new treatment modality for patients with treatment-resistant hypertension (TRH), a condition defined as persistent BP elevation despite use of at least 3 antihypertensive drugs including a diuretic agent. In the earlier SYMPLICITY HTN-2 trial (3), until recently the only randomized and controlled study of RDN, it is unfortunate that both the patient selection and the evaluation of efficacy were based on office BP rather than on ABPM, which is a state-of-the art assessment, particularly in TRH (4). Notwithstanding the contribution of poor drug adherence to TRH (5,6), drug adherence was not monitored, either at baseline or during follow-up. This made SYMPLICITY HTN-2 study vulnerable to the Hawthorne effect (i.e., patients started taking their drugs as prescribed in response to the attention devoted to them) (7). The lack of BP decrease in the control group also raises concerns that these patients may not have taken their medications properly in order to keep their BP at a level that made them eligible for crossover to the RDN group (8,9). In SYMPLICITY HTN-3, the use of a sham procedure and wider use of ABPM balanced the impact of the Hawthorne, white-coat, placebo, and regression-to-the-mean effects in both arms, disclosing the size of BP decrease attributable to RDN to be <2 mm Hg based on ABPM.

It has been suggested that the lack of efficacy of RDN in SYMPLICITY HTN-3 (1) may be due to lack of statistical power, to chance (10), or to the fact that the trial was not rigorously executed (11). Concerns were raised about whether the RDN was suboptimal because of

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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insufficient delivery of appropriate energy in the renal arteries as a consequence of investigator inexperience (12,13). However, the corresponding analyses are post-hoc, and the SYMPLICITY HTN-3 findings are in line with the results of other recent randomized clinical trials (14–17). Additionally, despite increased technical experience of the operators, the BP decrease 6 months after RDN in the crossover group was not substantially larger than that observed in the group initially randomized to RDN (2).

Does the failure of SYMPLICITY HTN-3 mean the end of RDN? Probably not; it has been shown in cohorts recruited from the third (18) to the fifth decades of the last century (19,20) that abdominal sympathectomy associated with splanchnicectomy is effective in the treatment of severe hypertension. The role of the sympathetic system in the pathophysiology of hypertension is substantiated by a wealth of experimental and clinical arguments (21–25). Accordingly, research should go on to find the minority of patients who are true responders to RDN. A European network included a large numbers of patients and suggested that it may be worthwhile searching for potential predictors of response to RDN (26,27). However, many patients have probably undergone unnecessary procedures. By a careful estimate, 20,000 renal arteries have been exposed to RDN in people with hypertension, and in these patients, investigators are reporting an increasing number of cases of renal artery stenosis (28). We must make sure that RDN is beneficial and does no harm.

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KEY WORDS ambulatory blood pressure monitoring, diastolic blood pressure, renal sympathetic denervation, systolic blood pressure