Renal artery denervation has captured the imagination of cardiologists as few recent technologies have done.1 The underlying pathophysiological construct seemed persuasive because evidence of sympathetic overactivity in the genesis of hypertension and heart failure has been clearly documented. Moreover, initial nonrandomized studies using different catheter systems in patients with hypertension deemed treatment resistant almost uniformly found large drops in office blood pressure measurements. The initial assessment of those very impressive results was surprisingly noncritical in many parts of the world in which the procedure was adopted into clinical practice. Subsequently, the neutral results of the SYMPLICITY-HTN 3 trial (Renal Denervation in Patients With Uncontrolled Hypertension),2 which was the first to incorporate a “sham procedure” control arm, came as a stunning surprise to some and generated a wide spectrum of responses, including denial, disbelief, abrogation of the entire concept, a critique of several technical and operator-dependent issues, and an increasing awareness of the power of placebo, regression to the mean, and methods of assessing blood pressure control. As is so often the case after the initial furor, it is a time for sober reflection, and a more circumspect view of renal artery denervation has been adopted that in turn has led to the design of more sophisticated ongoing trials.

Since the first studies, there is now a much greater understanding of resistant hypertension. Many of these lessons came from the SYMPLICITY HTN-3 trial.2 First, reports of the prevalence of resistant hypertension may have been greatly exaggerated. When studied rigorously, it appears that poor adherence is the root cause of the majority of cases initially felt to be resistant hypertension.3 The salutary role of aldosterone blockade in many instances of resistant hypertension has also now been fully appreciated. Partnership with dedicated hypertension experts based in cardiology, nephrology, or endocrinology greatly aids in the management of patients with difficult-to-treat hypertension. If interventional approaches to hypertension do eventually enter routine clinical practice, the collaborative approach to care pioneered in SYMPLICITY HTN-3 will serve as a useful model, somewhat akin to the collaborative, multidisciplinary approach for structural heart disease adopted at many centers.

As in all trials and particularly in hypertension, we should not underestimate the importance of the Hawthorne effect and regression to the mean. In evaluations of hypertension, it is essential to include ambulatory blood pressure measurements.4 Other lessons spawned by SYMPLICITY HTN-3 include “going back to the drawing board.” With the benefit of hindsight, it was premature to launch into large trials without understanding the underlying biology more completely. Since the time of the initial renal artery denervation studies, the anatomy and distribution of the renal sympathetic nerves have become clearer.5 This knowledge, coupled with better catheter design, should allow more complete denervation. Of course, it remains to be seen if there is a price to pay with respect to safety and the rate of complications because the newer trials will incorporate more extensive circumferential ablations, delivery of higher levels of cumulative energy, and both proximal and distal ablations (including
renal artery branches). In an older era, more complete nonselective surgical denervation appeared to be effective in lowering blood pressure but was also plagued by a high rate of unacceptable complications, including orthostatic hypotension.

SYMPLICITY HTN-3 serves as a powerful reminder of the value of sham-controlled trials in device evaluation and, regardless of the outcome, was a landmark trial that will have a lasting impact on clinical trial design in the device world. Although placebo-controlled trials are the standard of care in the drug development world, in the device world, this approach is the exception. Indeed, as the trial was starting, there were prominent accusations that SYMPLICITY HTN-3 was unethical because of its sham control. Questions were raised about feasibility and cost also. Nevertheless, with proper design considerations, sham-controlled device trials are possible and can be conducted ethically and efficiently. That is not to say that every single device or strategy trial needs a sham control, but for areas with a degree of subjectivity in end-point ascertainment or where beneficial placebo effects (or the opposite, harmful nocebo effects) can occur, sham controls are essential. For a variety of reasons, hypertension appears to be one of these areas.4

The clinical use of renal artery denervation in certain regions of the world before proper scientific vetting provides another lesson. In a time of globally spiraling healthcare costs, it falls on physicians to insist on adequate evidence before deploying expensive therapies. Linking reimbursement to sufficient prior demonstration of efficacy would be one way of ensuring that devices that come to market really do provide incremental benefit. The counterargument that this will slow innovation is a weak one given the alternative that expensive, ineffective, invasive therapies may otherwise be used on patients, potentially exposing them to risks and certainly escalating healthcare costs.

Despite this somber tone, there is reason for cautious optimism about the ultimate fate of renal artery denervation. Next-generation renal artery denervation catheters such as multipolar radiofrequency catheters and ultrasound catheters are being evaluated in preclinical studies and small clinical trials. These trials, which are meant to be proof-of-concept studies that definitively establish whether more complete renal artery denervation reduces blood pressure, are the first step in the renal denervation re boot. Some of these trials will test the technology in patients not on antihypertensive drugs, which removes the uncertainty of medication adherence. Ambulatory blood pressure will be used as the primary end point. The hope is that all these modifications in the ongoing and planned trials will overcome previously identified limitations. The next step after those series of trials will be comparative effectiveness studies versus drug therapy. It will be important to determine whether any noted reductions in these sham-controlled trials are of a magnitude that justifies an expensive, invasive therapy. Larger trials will also be necessary to establish any beneficial effects in more diverse populations of patients, coupled with long-term safety and efficacy data, as well as actual cardiovascular outcome data. It is likely that any blood pressure reduction achieved with a device should provide benefit similar to that provided by a drug, but this cannot be assumed and needs to be proved. Future areas of investigation will focus on the hypertension phenotypes most likely to benefit from denervation as opposed to drug therapy. Also needed and currently unavailable outside an experimental setting are methods of assessing the efficacy of denervation while in the catheterization laboratory.

Alternative procedural approaches to resistant hypertension and associated conditions are also being evaluated in a rigorous manner. For example, baroreflex activation therapy is being evaluated in carefully designed trials. Furthermore, renal artery denervation is still being tested in other disease states such as atrial fibrillation and heart failure. When this ongoing series of trials is complete, the medical community will finally have a thorough assessment of renal artery denervation and an answer to what its possible role may be in clinical practice. The results of SYMPLICITY-HTN 3 and the questions it generated have spawned a new series of well-designed and ongoing trials that we believe will answer the question of whether these procedures work. We have seen the rise and fall of renal artery denervation, and we hope that we shall witness the resurrection.

DISCLOSURES

Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; Board of Directors: Boston VA Research Institute and Society of Cardiovascular Patient Care; chair: American Heart Association Quality Oversight Committee; Data Monitoring Committee: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org), Belvoir Publications (editor in chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (guest editor, associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); other: Clinical Cardiology (deputy editor), NCDR ACTION Registry Steering Committee (vice-chair), and VA CART Research and Publications Committee (chair); research funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic (including for his role as coprincipal investigator of SYMPLICITY HTN-3), Pfizer, Roche, Sanofi Aventis, and The Medicines Company; royalties:
Elsevier (editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); site coinvestigator: Biotronik, Boston Scientific, and St. Jude Medical; trustee: American College of Cardiology; and unfunded research: FlowCo, PLx Pharma, and Takeda. Dr Gersh has served on data safety monitoring boards or other trial committees for Boston Scientific and Medtronic (including as chair of the data safety monitoring board for SYMPLICITY HTN-3).

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FOOTNOTE
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