Editorial

Interventional Cardiology

Renal denervation revisited: complexity following Symplicity

"With the development of new catheters, procedural skills and technologies … the complexity following Symplicity HTN-3 may just require a tincture of time and further rigorous scientific testing to sort out."

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Hypertension is a worldwide epidemic currently affecting one in four adults. By 2025, its prevalence is expected to increase to one in three adults, totaling 1.56 billion individuals [1]. Resistant hypertension is defined as a blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of difference classes (one of which should be a diuretic) and appropriate lifestyle modifications. Prior to the development of effective antihypertensive medications, surgical lumbar sympathectomy was used for the treatment of resistant hypertension. In 1953, renal denervation by splanchniectomy was demonstrated to be an effective means to treat essential hypertension compared with conservative therapy [2]. However, this procedure was associated with significant morbidity and mortality. With the subsequent development of more effective antihypertensive drugs, interest in this surgical approach waned.

Advances in the knowledge of the anatomy and physiologic effect of renal sympathetic nerves on blood pressure regulation led to the development of localized endovascular approaches to treat hypertension [3]. This was tested in a proof-of-concept trial, Symplicity HTN-1. This first-in-man, nonrandomized trial performed localized renal artery radiofrequency ablation in an initial cohort of 45 patients that was later expanded to 153 patients. A significant and sustained reduction of blood pressure of 30/10 mmHg out to 24 months was observed [4]. These findings were further confirmed in Symplicity HTN-2 in which 106 patients were randomized 1:1 to renal denervation or medical therapy. At 3 years, a mean blood pressure reduction of 33/14 mmHg with an 85% response rate was observed after renal denervation [5].

Based upon on the results of 205 treated patients in Symplicity HTN-1 and the randomized Symplicity HTN-2, several devices obtained CE Mark in Europe since 2010. A recent ESC consensus document stated that renal artery denervation is indicated for blood pressure control in patients with treatment resistant hypertension (defined as systolic blood pressure >160 mmHg or >150 mmHg in Type 2 diabetes) despite treatment with at least three antihypertensive drugs of different types in adequate doses (including one diuretic) and lifestyle modification [6].

With all the enthusiasm generated by this technology, Medtronic launched Symplicity HTN-3, which was intended to be the pivotal US clinical trial of the Symplicity renal denervation system for uncontrolled hypertension. The inclusion criteria were similar to those of Symplicity HTN-2 but with more demanding medication requirements [7]. This prospective, randomized, double-blind trial of 535 patients across 90 US medical centers was initiated in September 2011 and completed enrollment in May 2013. The preliminary results of the Symplicity HTN-3 Trial were recently released [8]. Despite meeting its safety end point, it did not meet its primary efficacy end point of reducing office systolic blood pressure by 10 mmHg compared with a sham procedure. Although disappointing and unexpected, we must withhold judgment until the specific data become publically available to determine how the study results differed from the prior studies.

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To place the sobering outcome of Symplicity HTN-3 in perspective, several points should be considered. Unlike the first two trials, this was the only study of renal artery denervation to be blinded and tested against a sham procedure (the most rigorous of scientific testing to demonstrate an unbiased true effect). All blood pressures throughout the study were measured via an automated cuff by a blinded study coordinator and/or physician. This is extremely important, as was shown by the CONVERGE report illustrating that doctor-documented blood pressures are lower than automatically documented blood pressures in patients participating in drug trials. This difference was only observed when the doctor was unblinded to the study drug [9]. Medication compliance could also have been a confounding issue. This study was a renal denervation plus medication study, not a comparison of renal denervation versus antihypertensive therapy. Given recent studies that report only a 43–65.5% compliance with medications, patients who perceived they received the active therapy may have stopped their antihypertensive drugs [10]. Furthermore, differences in patient populations must be considered. In total, 95 and 99% of patients were caucasian in the Symplicity HTN-1 and HTN-2 trials, respectively. The percentage of non-caucasian patients was much higher in HTN-3. Could this difference in patient population have accounted for a different outcome?

The preliminary trial results have raised more questions than answers. Were there technical differences? We have found the renal artery denervation procedure to be relatively straightforward; however, it remains unknown whether sufficient radiofrequency energy to effectively injure the renal nerves was delivered. Were the number of ablations adequate? Was there a significant learning curve effect that hampered the outcomes of the 90 US sites in Symplicity HTN-3? Could a different catheter type mitigate the variables in both the patient and the operator? Most importantly, does Symplicity HTN-3 illustrate the true ineffectiveness of renal denervation given that it is the largest and most rigorous of all the studies to date?

> "The preliminary trial results have raised more questions than answers."

The status of renal denervation therapy has suddenly become more complicated after Symplicity HTN 3. Unfortunately, many have written off this technology altogether, as shown by subsequent trials being placed on hold or discontinued [8]. We must remember, as was described in a recent online viewpoint by Tim Fischell, that coronary stenting was initially deemed a total failure after the poor results with the Wallstent [11,12]. Not long afterwards, with the development of the Palmaz–Schatz stent, the STRESS and BENESTENT trials proved coronary stenting was a breakthrough technology that is now performed over 1 million times annually in Europe alone [13,14]. With the development of new catheters, procedural skills and technologies (high frequency ultrasound, cryoablation, injectable chemical ablation) the complexity following Symplicity HTN-3 may just require a tincture of time and further rigorous scientific testing to sort out.

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