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Scientific Statement

Renal denervation therapy for hypertension: pathways for moving development forward

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Abstract

This scientific statement provides a summary of presentations and discussions at a cardiovascular Think Tank co–sponsored by the American Society of Hypertension (ASH), the United States Food and Drug Administration (FDA), and the National Heart, Lung, and Blood Institute (NHLBI) held in North Bethesda, Maryland, on June 26, 2014. Studies of device therapies for the treatment of hypertension are requested by regulators to evaluate their safety and efficacy during their development programs. Think Tank participants thought that important considerations in undertaking such studies were: (1) Preclinical

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assessment: how likely it is that both efficacy and safety data indicating benefit in humans will be obtained, and/or whether a plausible mechanism of action for efficacy can be identified; (2) Early human trial(s): the ability to determine that the device has an acceptable benefit–to–risk balance for its use in the intended patient population and without the influence of drug therapy during a short–term follow–up period; and (3) Pivotal Phase III trial(s): the ability to prove the effectiveness of the device in a broad population in which the trial can be made as non–confounded as possible while still allowing for the determination for benefits when added to antihypertensive therapies. J Am Soc Hypertens 2015;9(5):341–350.

Keywords: American Society of Hypertension; clinical trials; device therapy for hypertension; renal denervation.

Introduction

The American Society of Hypertension (ASH)[1] held an interactive forum with members of academic cardiology, hypertension, nephrology, and pathology, the United States (US) Food and Drug Administration (FDA), the National Heart, Lung, and Blood Institute (NHLBI), the US Centers for Medicare and Medicaid Services, and the medical device industry that focused on the basic and clinical processes needed to inform the development of novel safe and effective device therapies for the treatment of hypertension. The forum's multiple goals included: (1) Review of the present status of preclinical efficacy and safety models of renal denervation (RDN); (2) Design and rationale of a controlled Phase II (proof–of–concept) RDN trial in human hypertension not confounded by antihypertensive drug therapy; and (3) Evaluation of the most appropriate Phase III pivotal trial designs for future device trials in severe and/or drug–resistant hypertension.

Background Information

Novel research with radiofrequency thermal energy delivered to the renal arteries at the inner surface of the vascular wall was initially conducted using a single tip electrode catheter.[2,3] Because of high intravascular blood flow, the renal artery endothelium and muscular media were heated less with this approach, whereas the energy was transmitted more efficiently to the adventitial tissue, leading to functional disruption of visceral afferent and sympathetic nerves. Recent human anatomic research has shown that the renal nerves are located 1–8 mm from the endothelium, but sympathetic fibers are situated more distally in the artery, and hence closer to the renal hilum.[4] Therefore, it is possible that denervation could be incomplete in as many as half of the patients treated with the radiofrequency catheter, since the effectiveness of the procedure is based on adequate electrode–tissue contact, power delivery, temperature, and target tissue impedance, all of which affect lesion depth.[5] Circumferential application of energy deployment is also required for effective RDN.[6]

Resistant hypertension remains a major unmet medical need, and RDN has emerged to be a potential leading therapeutic intervention to address this challenge.[7] In the open–label, uncontrolled SYMPLICITY hypertension (HTN)–1 and HTN–2 studies undertaken in patients with severe hypertension resistant to at least three antihypertensive drugs, there were large and significant reductions in office blood pressure (BP) that have persisted for as long as 3 years post–denervation.[8–10] In contrast, data from these uncontrolled studies, as well as pooled analyses of patients who have undergone RDN, have shown much more modest changes in ambulatory BP.[11] Furthermore, in a randomized trial of 106 truly resistant hypertensive patients from the Prague–15 Study, intensified antihypertensive therapy including spironolactone was as effective as RDN in lowering 24–hour BP after 6 months with a mean increase of 0.3 antihypertensive drugs.[12]

The SYMPLICITY HTN–3 trial[13] was a landmark study in the field of RDN, recruiting patients with severe and treatment–resistant hypertension whose clinic systolic BP (SBP) averaged approximately 180 mm Hg and whose 24–hour mean SBP was approximately 160 mm Hg while on an average of five antihypertensive agents. The design used a sham–procedure control group (1:2 randomization to sham vs. active therapy), and the primary endpoint of change in clinic SBP was evaluated after 6 months. Reductions from baseline in digital clinic BPs were notably less in SYMPLICITY HTN–3 than in the prior two trials with the Symplicity catheter, and, most importantly, there was no difference observed between the RDN and sham–operated groups.[13] Also importantly, there were no differences observed between the randomized treatment groups in ambulatory BP. However, interestingly, there were reductions from baseline in the 24–hour SBP of approximately 5 ± 17 mm Hg in the sham–operated group.[14] This finding suggested a change in patient behavior regarding adherence to their multi–drug pharmacologic regimens.

The failure of SYMPLICITY HTN–3 to meet its primary (and secondary) efficacy endpoints was the source of much discussion during 2014.[6,13,15] In both pre–specified and post–hoc exploratory analyses of the SYMPLICITY HTN–3 trial data, changes in medication prescriptions, procedural technique regarding distribution and number of ablations, and differential outcomes among ethnic subgroups were identified as potential confounders.[16]