A New Era of Renal Denervation Trials for Patients With Hypertension?

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The field of renal denervation for the treatment of hypertension has undergone a substantial set of dynamics during the past decade. Early unblinded and essentially uncontrolled trials reported stunning reductions in clinic blood pressure (BP) following renal denervation in patients with uncontrolled and/or treatment-resistant hypertension.[1,2] However, the field fell apart when results of the first large, randomized, observer-blinded, and sham-controlled SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) trial[3] did not show a BP-lowering effect of renal denervation compared to sham-operator treatment. Post hoc analyses of this trial and other studies suggested a variety of factors that might have led to failure of renal denervation, including patient selection, variability in adherence to antihypertensive medications, incomplete renal denervation, or technical failure of denervation.[4] The heterogeneity in results from early studies in renal denervation and those from the SYMPLICITY HTN-3 trial led to an overhaul of clinical development processes for renal denervation devices similar to the approach that has been used for more than 40 years in drug development for antihypertensive agents (Fig 1).[5,6] With general agreement by academicians, regulatory agencies, and device sponsors, controlled early-phase studies have been initiated by the device manufacturers. The first of these studies, the SPYRAL HTN-OFF MED (Catheter-Based Renal Denervation in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications) trial,[7] reports an analysis that shows a significant effect of renal denervation on both clinic BP and ambulatory BP (ABP) in patients with stages 1 to 2 hypertension who were not using antihypertensive medications.

Commentary on Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised-sham-controlled, proof of concept trial. Lancet. 2017;390(10108):2160-2170.

What Does This Important Study Show?

The SPYRAL HTN-OFF MED was a randomized, sham-controlled, proof-of-concept trial evaluating the effects of renal denervation on BP in the absence of antihypertensive medications. There were 80 patients randomly assigned: 38 to the renal-denervation group and 42 to the sham-control group. To evaluate study participants without antihypertensive drugs, non–treatment-resistant patients who could safely discontinue antihypertensive medications over a 3- to 4-week period were chosen as the study population. Drug surveillance using quantitative assays ensured that patients were not on therapy. The absence of antihypertensive medication use was evaluated by the use of tandem high-performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory (notably, adherence to remaining off treatment with antihypertensive drugs was 85.5%). An early-phase device trial in patients off antihypertensive therapies makes both clinical and regulatory sense because it avoids the confounding effects of the drugs and heterogeneity in adherence to treatment seen in SYMPLICITY HTN-3.[8,9] Importantly, it makes sense to determine the efficacy and short-term safety of a new renal denervation device in a smaller well-characterized sample before it is tested in a larger heterogeneous randomized trial population with increased cardiorenal risk.[6,10]

Patients, caregivers, and those assessing BP were blinded to randomization assignments. Blinding of study patients and BP assessors was maintained for up to 12 months after randomization. Importantly, and in contrast to many prior studies of renal denervation, all interventionists performing the procedure had previous experience performing renal denervation and all procedures were proctored on the basis of detailed prespecified procedural plans involving a standardized approach to target all accessible renal arterial vessels. To minimize technical variability, the number of physicians performing the renal denervation procedure was restricted to 1 per trial center. Additionally, study patients in the sham and experimental groups both remained on the catheterization table for 20 minutes after the angiogram to prevent possible unblinding of randomization allocation. This is the approximate time that it takes to perform an ablation procedure with a multinodal catheter. The primary end point for SPYRAL HTN-OFF MED was change from baseline in 24-hour ABP at 3 months. Because of the multiple measurements obtained with ABP monitoring and removal of observer bias seen in clinical measurements, ABP is more reproducible than clinic measurements and has the ability to determine nocturnal BP values at a time when sympathetic nervous system activity is theoretically lower than while awake.[10,11] SPYRAL HTN-OFF MED was also performed with more than 1 catheter per site, according to international consensus recommendations.[5,6]

Results of SPYRAL HTN-OFF MED showed that the renal-denervation group had small but both statistically and clinically significant reductions from baseline to 3 months in both clinic BPs and ABPs, whereas the sham

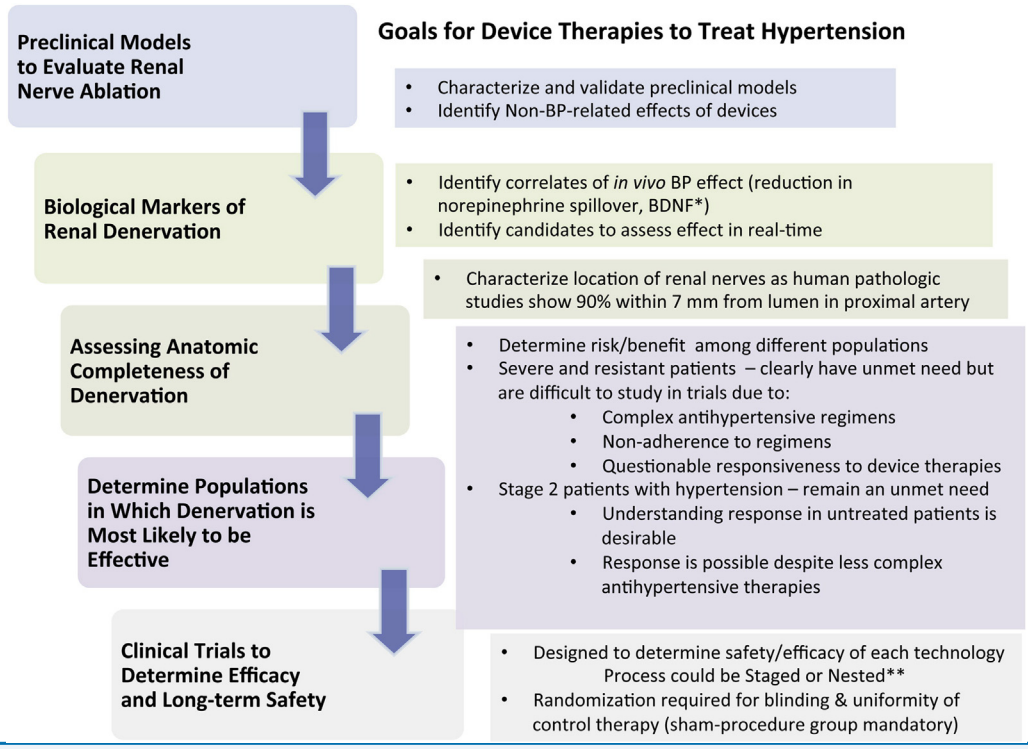

Figure 1. Summary of goals and pathways to address the goals for the development of device therapies in hypertension. *BDNF, brain-derived neurotrophic factor. **Phase 2 study could be performed before phase 3 or nested within the phase 3 trial. Abbreviation: BP, blood pressure. Reproduced from White et al[5] with permission of Elsevier.

group did not. Not surprisingly, a numerically smaller reduction from baseline was observed in ABP compared to BPs measured in the clinic.[5,7] Because a similar decline in BP was not found in the sham group, it can be concluded that the decline in BP was due to the effect of renal denervation. Clearly, the magnitude of the systolic BP reductions in the renal-denervation group, −10.0 mm Hg for clinic BP ($P = 0.0004$) and −5.5 mm Hg for ABP ($P = 0.0031$), are clinically meaningful. Similarly, there were significant reductions in clinic and ambulatory diastolic BPs in patients randomly assigned to renal denervation (sham-control–subtracted values of −4.9 and −4.4 mm Hg, respectively). This extent of BP reduction in patients with stages 1 to 2 hypertension is associated with reduced rates of cardiovascular mortality, heart failure, and stroke.[12-14]

There are important limitations to this study. By design, SPYRAL HTN-OFF MED had a small sample size and was not powered for complete efficacy end points because of the uncertainty of the sham-subtracted BP reduction. It was a difficult study to perform; even with just 80 randomly assigned patients, it was necessary to screen more than 340 potential study participants. This large-screen failure rate was due primarily to out-of-range clinic BPs or ABPs ($n = 171$ and $n = 49$, respectively) or renal artery anatomy that was not amenable to instrumentation and radiofrequency ablation ($n = 28$). It is understood that a 3-month follow-up time point was short for efficacy, but deemed necessary for safety considerations. Individual responder analyses demonstrated that 20% to 30% of patients randomly assigned to renal denervation had no reduction in ABPs (20% for diastolic and 28% for systolic BP measurements). This could be explained by varying degrees of success with renal nerve ablation or differences in the underlying hypertension pathophysiology of study participants.[4,5,15] Although the SPYRAL catheter improves the ability to completely interrupt renal nerves, there is no practical method available to verify nerve destruction/disruption while the patient is undergoing the procedure. A small proportion of patients was found to be taking antihypertensive medications (<10%), but this was balanced between the 2 treatment groups and not likely to have affected efficacy results.

How Does This Study Compare With Prior Studies?

The SPYRAL HTN-OFF MED trial differs substantially from previous renal denervation trials in terms of population enrolled, absence of antihypertensive therapy, and denervation technique. It is the first rigorously performed sham-controlled clinical trial to assess BP reductions in patients with untreated stages 1 to 2 hypertension. Virtually all prior renal-denervation trials enrolled patients with resistant[1-3] or moderately severe hypertension[16,17] using a multitude of antihypertensive drugs and did not exclude those with isolated systolic hypertension. Patients with both systolic and diastolic hypertension were enrolled in SPYRAL OFF-HTN MED, which likely increased the response rate because patients with diastolic BP elevations