Is There Any Role for Device Therapies in Resistant Hypertension? Commentary

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Introduction
In this issue of Kidney360, two titans of hypertension, Drs. Ray Townsend and Aldo Peixoto, debate whether there is any role for device therapies in resistant hypertension. As the debate’s moderator, I will provide background information to set the stage for this epic showdown and offer a nonpartisan opinion on the topic.

First, what is meant by “resistant hypertension?” According to the most recent ACC/AHA High Blood Pressure Clinical Guidelines, the diagnosis of resistant hypertension is made when a patient takes three antihypertensive medications, including at least one diuretic, but does not achieve control or when BP control is achieved but requires four or more medications (1). Using the BP target of <130/80 mm Hg, the prevalence of resistant hypertension among United States adults taking antihypertensive medication is estimated at 20% or 10.3 million persons (2).

Second, with so many different types of antihypertensive medications that can effectively and reliably lower BP, why turn to device therapy for hypertension management given the inherent risks that come with these invasive procedures? Many patients cannot or will not take antihypertensive medications as prescribed due to unacceptable side effects or other factors. Moreover, even patients with perfect medication adherence to multiple antihypertensive medications will sometimes still have poorly controlled BP (3). Thus, there is a large unmet need for BP management strategies that are not predicated on the patient swallowing additional pills.

Device Therapies forResistant Hypertension
Most device therapies for treatment of resistant hypertension have focused on modulating sympathetic tone via the nerves located along the renal or carotid arteries. Catheter-based renal denervation is the best studied of the different types of device therapy for resistant hypertension. This treatment generally involves accessing the renal arteries via the femoral artery with subsequent radiofrequency ablation of the renal afferent nerves. Early open-label, uncontrolled trials of this radiofrequency-based renal denervation showed dramatic reductions in office systolic BP of 20–30 mm Hg (4). However, enthusiasm for renal denervation was significantly dampened with the publication of the SYMPLECTICITY HTN-3 in 2014, which was the first randomized, blinded, sham-controlled renal denervation trial (5). In the 535 trial participants, no significant difference was observed in mean change in systolic BP at 6 months (14 versus 12 mm Hg change from baseline in denervation versus sham for a difference of 2 mm Hg; P=0.30). Critics of the study cited variable medication adherence and incomplete renal denervation as potential reasons for the negative results of the SYMPLECTICITY HTN-3, and thus, studies of renal denervation continued. Since 2014, additional randomized, blinded, sham-controlled renal denervation trials have shown promising results in patients with uncontrolled (but not resistant) hypertension in the absence (6) and presence (7) of antihypertensive medications and in studies of renal denervation using endovascular ultrasound (8). Thus far, there have been no concerning safety signals with renal denervation. In the SYMPLECTICITY HTN-3, only six patients overall experienced a major adverse event of any kind (5 of 361 in the denervation arm and 1 of 171 in the sham arm). The SYMPLECTICITY Global Registry reported 3-year outcomes for 1742 patients treated with renal denervation and showed very low rates of ESKD (1.5%) and renal artery stenosis (0.1%) (9).

Another target of device therapies for resistant hypertension is the carotid baroreceptors. Baroreflex activation therapy (BAT) with the early Rheos System (CVRx, Inc., Minneapolis, MN) required surgical neck dissection to suture electrodes to the carotid arteries bilaterally, which were then connected to a programmable pulse generator. In the Rheos Pivotal Trial, 265 participants with resistant hypertension had the device implanted and were then randomly assigned to early (1-month) or deferred (6-month) device activation. There were no differences in acute efficacy, but more participants in the early activation arm attained SBP≤140 mm Hg at 6 months compared with the deferred BAT group. However, 25.5% of participants experienced a procedural complication, including surgical complications (4.8%), nerve injury with residual deficit (4.8%), or wound complication (2.6%). The company has since developed the Barostim Neo, a second generation BAT that requires electrode placement on only one carotid artery. An uncontrolled, single-arm study in 30 patients with resistant hypertension

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showed a reduction in BP of 26/12 mm Hg at 6 months, with three minor procedure-related complications that resolved (10). However, the Barostim Neo Pivotal trial (NCT01679132) for treatment of resistant hypertension was suspended, and the company seems to be focusing its efforts on using the device for treatment of heart failure (BeAT-HF; NCT 02627196).

The MobiusHD device (Vascular Dynamics, Mountain View, CA) uses a self-expanding nitinol implant to modulate carotid baroreceptor activity. The device is endovascularly delivered to the carotid sinus and works by increasing wall strain in the carotid sinus to reduce sympathetic outflow, thereby reducing BP. In a proof-of-principle clinical study (CALM-FIM_EUR), 30 patients with resistant hypertension underwent MobiusHD implant and were followed for 6 months: mean baseline 24-hour ambulatory systolic BP fell by 21 mm Hg. Five serious adverse events occurred in four (13%) patients, including hypotension in two patients (11). A randomized, double-blind, sham-controlled pivotal trial of the MobiusHD device to treat resistant hypertension (CALM-2) is currently underway (NCT03179800).

In conclusion, BP control remains suboptimal worldwide, despite the widespread availability of antihypertensive medications, with nonadherence playing a major role. In one randomized trial (12), 68% of patients with resistant hypertension were nonadherent to their antihypertensive medications, which is associated with poorer cardiovascular outcomes. Antihypertensive medication nonadherence is also estimated to cost Medicare $13.7 billion annually, with >100,000 emergency department visits and 7 million inpatient hospital days (13) related to poorly controlled hypertension. As you read the arguments of Drs. Townsend and Peixoto about the role of device therapies to treat resistant hypertension, it is important to remember that, to date, none of the device therapies discussed above are approved for use in the United States. Nonetheless, researchers continue to strive toward developing a BP treatment device that can safely and reliably reduce BP without relying on the person’s willingness or ability to ingest multiple pills multiple times per day.

Disclosures

T. Chang is a site co-investigator for controlling and lowering blood pressure with the MobiusHD (CALM-2), a trial which is sponsored by Vascular Dynamics, Inc.

References