Is there any role for device therapies in resistant hypertension? Commentary

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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 non-partisan 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 blood pressure control is achieved but requires four or more medications\(^1\). Using the blood pressure target of <130/80 mm Hg, the prevalence of resistant hypertension among U.S. 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 blood pressure, 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 blood pressure.\(^3\) Thus there is a large unmet need for blood pressure management strategies that are not predicated on the patient swallowing additional pills.

### Device Therapies for Resistant 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 blood pressure of 20-30 mm Hg\(^4\). However, enthusiasm for renal denervation was significantly dampened with the publication of SYMPLICITY 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 blood pressure at 6 months (14 vs 12 mm Hg change from baseline in denervation vs. sham, for a difference of 2 mm Hg; p=0.3). Critics of the study cited variable medication adherence and incomplete renal denervation as potential reasons for the negative results of SYMPLICITY 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 SYMPLICITY HTN-3, only 6 patients overall experienced a major adverse event of any kind (5/361 in the denervation arm; 1/171 in the sham arm). The SYMPLICITY Global Registry reported 3-year outcomes for 1742 patients treated with renal denervation and showed very low rates of end-stage renal disease (1.5%) or renal artery stenosis (0.1%)\(^9\).

Another target of device therapies for resistant hypertension are 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 $\leq 140$ 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 showed a reduction in blood pressure of 26/12 mm Hg at 6 months, with 3 minor procedure-related complications that resolved\cite{10}. However, the Barostim Neo Pivotal trial (NCT01679132) for treatment of resistant hypertension was suspended, and the company appears 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 different 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 blood pressure. In a proof-of-principle clinical study (CALM-FIM_EUR), 30 patients with resistant hypertension underwent MobiusHD implant and were followed for six months: mean baseline 24-hour ambulatory systolic blood pressure fell by 21 mm Hg. Five serious adverse events occurred in four (13%) patients, including hypotension in 2 patients\cite{11}. A randomized, double-blind, sham-controlled pivotal trial of the MobiusHD device to treat resistant hypertension (CALM-2) is currently underway (NCT03179800).

Conclusions

Blood pressure control remains suboptimal worldwide, despite the widespread availability of antihypertensive medications, with non-adherence playing a major role. In one randomized trial\cite{12}, 68% of patients with resistant hypertension were non-adherent to their antihypertensive medications, which is associated with poorer cardiovascular outcomes. Antihypertensive medication non-adherence is also estimated to cost Medicare $13.7 billion dollars annually, with over 100,000 emergency department visits and 7 million inpatient hospital days\cite{13} related to poorly controlled hypertension. As you read Drs. Townsend and Peixoto arguments 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 U.S. Nonetheless, researchers continue to strive towards developing a blood pressure treatment device that can safely and reliably reduce blood pressure, without relying on the person’s willingness or ability to ingest multiple pills multiple times per day.
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