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EDITORIAL COMMENT

"Won't Get Fooled Again"*

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Early trials demonstrated that renal artery denervation (RDN), delivered with a catheter in the renal artery, reduced blood pressure by reducing sympathetic tone in patients with hypertension, as measured by renal norepinephrine spillover and muscular sympathetic nerve activity (1). SYMPLICITY HTN 1, an early RDN trial, demonstrated safety and efficacy in 153 patients with resistant hypertension (2). Subsequent preliminary clinical trials created significant enthusiasm for RDN as a novel and effective treatment for hypertension and led to a profusion of companies developing a variety of technologies.

Unfortunately, the enthusiasm for RDN was significantly tempered with the unfavorable results of the pivotal SYMPLICITY HTN 3 trial (3). This large, multicenter, randomized, and sham-controlled trial failed to support RDN as a preferred modality in this hypertensive population. It failed to fulfill our hopes for this new technology. In fact, many of us were fooled. Some proponents continue to be hopeful that there are subgroups of patients who will benefit from RDN, or that a more complete denervation procedure will be effective, but at this time, there is no comparative evidence to support RDN as a superior treatment option for hypertension.

In this issue of *JACC: Cardiovascular Interventions*, Neuzil et al. (4) present early safety and efficacy results of a noninvasive, externally delivered ultrasound RDN system (Surround Sound; Kona Medical, Bellevue, Washington) for the treatment of resistant hypertension (average 4.57 blood pressure medications per patient). Compared with baseline, systolic blood pressure was reduced by 23.8 ± 24.1 mm Hg and diastolic pressure by 10.3 ± 13.1 mm Hg at 1 year. The third and final phase of the trial (wave III) reported 22 patients who underwent completely noninvasive, externally delivered, focused ultrasound treatment. In this subgroup, reductions in blood pressure were comparable with those in the patients enrolled in the earlier phases of the trial (waves I and II), in which an invasive renal artery catheter was used to enhance targeting of the ultrasound.

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The most common adverse event reported in the 3 waves was back pain, reported in 32 of 69 patients (46%). Post-treatment magnetic resonance imaging demonstrated inflammation in the paraspinal muscles and adjacent tissues, but neurological examination revealed no sensory or motor deficits. Although 5 patients required narcotic pain relief, none reported life-style limitations due to back pain. The pain was not restricted to the periprocedural period. Six of the 21 patients (28.6%) in waves I and II reported back pain for more than 30 days. In the noninvasive cohort (wave III), 41% of the patients reported postprocedural back pain, similar to the waves I and II groups. Back pain persisted for more than 30 days in 1 of the 11 subjects (9%) in wave III.

This feasibility study of the Surround Sound system is of interest because it suggests that a noninvasive RDN tool can achieve a significant reduction in blood pressure. Developing a completely noninvasive RDN technology eliminates the risks for complications inherent in performing invasive endovascular procedures. However, we have been down this road before, and there will be skepticism regarding the utility of noninvasive RDN for blood pressure control until proved in a more rigorous trial.

The perceived veracity of the data reported will influence the informed reader's skepticism. A majority of the investigators voluntarily disclosed some

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level of financial relationship or conflict of interest with the trial's sponsor, Kona Medical; 3 of the investigators are employees of Kona Medical. In a peer-reviewed journal, the voluntary disclosure of financial and nonfinancial conflicts is intended to mitigate the impact of an investigator's potential bias. How many readers actually look at disclosures of conflicts of interest, rather than relying on journal editors to act as surrogate screeners for impartiality?

There are varying degrees of bias among conflicted investigators, ranging from inconsequential to insurmountable. One wonders what courage is required for an employee investigator to voluntarily report damaging information regarding his or her company's product? Preserving one's livelihood is an example of financial conflict that cannot be extinguished by voluntary disclosure. An informed reader should understand the conflict being disclosed by the investigators and put that degree of conflict into perspective when determining how much confidence to place in the data reported, the recommendations made, and the conclusions reached by the investigators.

Most would agree that the earliest "proof of principle" data on a novel device are appropriately presented by an investigator who understands the process best, often the inventor of the device, who is expected to have a very strong bias. As the device matures, the inventor must hand the device off to independent operators to ensure its generalizability (i.e., that other operators can achieve the same results as the inventor). The acceptance of this report by the journal editors suggests their willingness to accept the participation of strongly biased employee investigators at this stage of the research. Informed readers will judge the credibility of this report, consider the data offered, and ultimately form opinions regarding this technology. Very likely, they will ask for more independent reporting of a larger dataset while humming a few bars of Pete Townshend's (The Who) "Won't Get Fooled Again."

CONCLUSIONS

Although the preliminary data for this noninvasive RDN technology for hypertension are encouraging, this early promise, including its safety, efficacy, and tolerability, will need to be confirmed in a large, randomized, sham-controlled trial.

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