Letter to the Editor

Renal denervation for hypertension: we've come a long way!

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Renal sympathetic denervation (RSD), a therapeutic intervention for patients with hypertension (HTN), is undergoing active investigation. Prospective cohort studies and first-generation randomized controlled studies established the safety of RSD but its impact on blood pressure was variable (1-3). Perhaps the most infamous of these studies was SYMPLICITY HTN-3, a randomized, sham-controlled trial. Much to the surprise and dismay of many hypertension experts, RSD failed to meet its primary efficacy endpoint in this trial (3). Manifold potential explanations were offered for the absence of benefit. These included but were not limited to use of operators with little procedural experience, less than optimal patient selection, incomplete denervation, inappropriate selection of endpoints and variable use of antihypertensives (2,4,5). As a consequence, the second-generation trials were designed with these limitations in mind. They recruited operators with prior RSD procedural experience, included patients with blood pressures that were not as elevated and in whom combined systolic-diastolic HTN was present, employed catheters and strategies that provided more comprehensive renal nerve ablation, selected dynamic ambulatory instead of static office blood pressure measurements as the primary efficacy endpoint, and some even allowed patients to remain off of antihypertensive medications altogether.

The second-generation trials resulted in more modest yet significant reductions in blood pressure (2,5). In particular, SPYRAL and RADIANCE-HTN, invoked optimism after demonstrating significant blood pressure reductions with either radiofrequency- or ultrasound-mediated RSD and in on- and off-antihypertensive populations (1,2). Our recent meta-analysis (2), of six first- and second-generation randomized trials (n=977 patients) found that 24-hour ambulatory systolic blood pressure (ASBP) was reduced by 3.7 mmHg when compared with sham. Similarly, daytime RSD also significantly lowered ASBP, office systolic BP and office and ambulatory measures of diastolic BP *vs.* sham treatment. In fact, reductions in daytime ASBP were significantly larger for the three second-generation studies (6.1 mmHg greater than sham) than in first-generation trials (2.1 mmHg), where procedures were performed by experienced operators, patients with isolated systolic HTN were excluded, advanced catheters and ablation techniques were employed, medical therapy was modified to better discern treatment effect, and 24-hour ambulatory blood pressure was designated as the primary endpoint.

Importantly, the ability of RSD to lower blood pressure, even if less than once anticipated, approximates that observed with many approved antihypertensives. Blood pressure reductions of this magnitude should translate into a significantly lower risk of cardiovascular events. In addition, a single intervention with permanent impact on something as common as HTN would represent a tremendous public health advance for our field. Despite all the hype, many questions remain. What is the long-term safety and effectiveness of RSD? How might it be integrated into our lifestyle and pharmacological toolbox for treating HTN? Will it replace or bolster medication

regimens? Is it destined to become an elective procedure for those who are poorly adherent or who prefer to avoid medications or will it be reserved for those who 'fail' medical therapy? The answers to these and other questions remain to be seen (6). Much work is also needed to define the optimal responders and to develop point-of-care tests for establishing RSD success at the time of the procedure (2,6). In spite of these many uncertainties, we suspect that this technology will become integrated into mainstream therapy for hypertensive patients around the world upon conclusion of ongoing pivotal RSD studies.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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