



THE SYMPLICITY HTN-3 TRIAL FOR HYPERTENSION; AN UPDATE

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Editor's Note: During the past year, this Journal has published two "Calls for Participants" in SYMPLICITY HTN-3, a multi-institutional trial of renal denervation via catheter for medically intractable hypertension. However, shortly after the most recent "Call" appeared in the Journal, the SYMPLICITY HTN-3 was terminated coincident with the presentation of the 6 month interim results of the GLOBAL SYMPLICITY Registry, and the publication of the 6 months interim results of the randomized trial.

I have asked Dr. Rupal Dumasia, who led the Lancaster Heart and Vascular Institute's participation in this study, to provide an update and perspective on these developments, which are somewhat surprising in view of the effectiveness of renal denervation in lowering blood pressure experimentally and in previous clinical studies. Herewith his comments:

Resistant hypertension is a difficult problem with substantial morbidity that is becoming increasingly important as obesity and diabetes rise. Resistant hypertension may be mediated by the sympathetic nervous system, and several decades ago surgical sympathectomy was shown to be effective in treating resistant hypertension. Though its use at that time was limited by severe orthostatic hypotension, interest in sympathectomy for resistant hypertension has recently been renewed by the availability of a percutaneous approach. Since the kidney's sympathetic nerves surround and invest the adventitia of the renal arteries, renal denervation is presumed to have been performed by the application of radiofrequency energy to the endoluminal surface of the renal arteries.

Renal denervation for the treatment of resistant hypertension has been shown in unblinded, non-randomized clinical trials to be effective compared with baseline measurements of blood pressure. On this basis, renal denervation has been used in many countries throughout the world including many countries in Europe, South America, Australia, and Canada. The SYMPLICITY HTN-3 trial was conducted in the United States in order to more

rigorously evaluate the safety and efficacy of this procedure. The ongoing Global SYMPLICITY Registry is also attempting to evaluate the efficacy of this procedure in a non-randomized fashion in "real world" patients.

SYMPLICITY HTN-3 randomized 535 patients with severe resistant hypertension. Patients had to be on three anti-hypertensive drugs including a diuretic. They had to have an office SBP ≥ 160 mmHg followed by two weeks of ambulatory BP monitoring followed by a confirmatory office BP ≥ 160 mmHg followed by a 24 hour automated ambulatory BP > 135 mmHg. Patients were then randomized 2:1 to renal denervation or a sham procedure. The sham procedure was a renal angiogram.

The primary efficacy endpoint was a change in office SBP at 6 months. The secondary efficacy endpoint was a change in mean 24 hour ambulatory SBP. The primary safety endpoint was the composite of death, end stage renal disease, embolic events resulting in organ damage, renovascular complications, hypertensive crisis at 1 month, or new renal artery stenosis $> 70\%$ at 6 months.

The mean reduction in office SBP was 14.1 mmHg in the treatment group and 11.7 mmHg in the sham group. The mean reduction in 24 hour ambulatory SBP was 6.8 mmHg in the treatment group and 4.8 mmHg in the sham group. Neither of these endpoints reached statistical significance. There was no difference between the trial arms in the composite safety endpoint. Overall, the investigators concluded that renal denervation is safe but not efficacious for the treatment of resistant hypertension compared to continued optimal medical therapy.

The 6 month interim results of the GLOBAL SYMPLICITY Registry were revealed at the 2014 ACC meeting. The patients in the registry had a mean reduction in office SBP of 11.9 mmHg at 6 months. Those patients who had a baseline office SBP ≥ 160 , had a mean reduction in office SBP of 19.8 mmHg. There was a mean reduction in 24 hour ambulatory SBP of

7.9% in those patients with a baseline office SBP \geq 140 mmHg and a mean reduction in 24 hour ambulatory SBP of 9.2% in those patients with a baseline office SBP \geq 160 mmHg.

The results of the GLOBAL SYMPLICITY REGISTRY should not be viewed as contradictory to those of the SYMPLICITY HTN-3 trial. The registry is a comparison of post-treatment BP to baseline BP. The trial is a comparison of the effect of treatment to a sham procedure. The difference is perhaps subtle but important. The registry indicates that patients have improvements in SBP compared to baseline. The trial indicates that patients who undergo treatment do not have improvement in SBP compared to similar patients who undergo a sham procedure. The point is that there is significant improvement in SBP in the sham procedure arm. This may reflect a significant placebo effect or may simply be a reflection of the meticulous attention to hypertension treatment by virtue of participation in a clinical trial.

The authors of the SYMPLICITY HTN-3 trial also suggest other potential explanations for the trial

results. The lack of a control group in SYMPLICITY HTN-2 may explain the difference in the results. There was also a lack of blinding in prior trials. Finally, the operator learning curve may have played a role in the lack of efficacy in SYMPLICITY HTN-3.

Overall, the results of the SYMPLICITY HTN-3 trial raise several important questions and concerns. The inability to confirm that renal denervation has actually been accomplished as a result of the procedure is a significant limitation of the current state of the technology. In addition, it is unclear whether the lack of efficacy in the SYMPLICITY HTN-3 trial is a reflection of the lack of efficacy of the Medtronic device, operator inexperience, or a true lack of efficacy of renal denervation. Finally, it is unclear whether there are certain subgroups of patients in whom denervation may be beneficial. While it is premature to determine whether there is any role at all for renal denervation, it is clear that any additional denervation procedures should be carried out within a well-designed clinical trial that addresses the shortcomings of the SYMPLICITY HTN-3 trial.

REFERENCES

1. Bohm, M. Presentation at the Annual Meeting of the American College of Cardiology, Washington, DC, 2014.
2. Bhatt, DL, Kandzari, DE, O'Neill, WW, et al. A controlled trial of renal denervation for resistant hypertension. *New Engl J Med.* 2014; 370(15):1393-1401

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