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CONGRESS COVERAGE

Renal Sympathetic Denervation for Resistant Hypertension: Symplicity HTN-3 and the Power of PlaceboKonstantinos Tziomalos¹, Vasilios G. Athyros² and Michael Doumas^{2,3,*}

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DEAR EDITOR

The results of the Symplicity HTN-3 trial have been presented a few days ago in the 2014 Scientific Meeting of the American College of Cardiology and simultaneously published in the *New England Journal of Medicine* [1]. The Symplicity HTN-3 trial was the first placebo-controlled (via sham procedure) study evaluating the effects of renal sympathetic denervation (RSD) in patients with resistant hypertension. The study met its primary safety endpoint but failed to achieve its primary and secondary efficacy endpoints generating major disappointment in the scientific community and raised significant concerns about the future of this novel interventional approach for the management of patients with resistant hypertension.

The Symplicity HTN-3 trial was a multicenter, prospective, randomized, single-blind, sham-controlled study conducted in the United States of America. The study was performed in patients with uncontrolled resistant hypertension, i.e. office systolic blood pressure >160 mmHg despite the use of at least three antihypertensive drugs (one of which was a diuretic) in maximally tolerated doses. Moreover, home blood pressure monitoring for two weeks and 24h ambulatory blood pressure monitoring ensured the diagnosis of true resistant hypertension, excluding patients with pseudo-resistance due to the white-coat effect. From a total of 1,441 patients screened for eligibility, 535 patients fulfilled the inclusion/criteria and were randomly assigned to either RSD or a sham procedure (placebo) in a 2 to 1 ratio and were then followed-up for 6 months.

The primary safety endpoint was a composite of hard and surrogate events (all-cause mortality, end-stage renal failure, embolic episodes leading to target organ damage, renovascular complications and new-onset renal artery stenosis, and hypertensive crises) less of approximately 10%, based on

prior information. The office blood pressure reduction at 6 months with a superiority margin of 5 mmHg for renal nerve ablation was the primary efficacy endpoint and the ambulatory blood pressure reduction at the same time point was the secondary efficacy endpoint.

The study achieved its primary safety endpoint, since no significant differences in adverse events were observed between RSD and sham procedure. In total, there were 5 significant adverse events in the active treatment group compared with one significant adverse event in the placebo group, and the difference was not significant ($p=0.67$). Moreover, no significant deterioration of renal function was observed with RSD, even in patients with chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73m²). The reassuring renal safety profile confirms the short-term safety of RSD that was observed in previous studies [2-5], but does not totally exclude potential long-term detrimental effects on renal function [6, 7].

The major disappointment however comes from the efficacy endpoints. The study failed to achieve both its primary and secondary efficacy endpoints. In particular, the mean reduction in office blood pressure was 14.1 mmHg with active therapy and 11.7 mmHg with placebo at 6 months, and was highly significant for both groups compared to baseline ($p<0.001$). However, the between-group difference in systolic blood pressure reduction was small (2.4 mmHg) and was not significant ($p=0.26$) in terms of the pre-defined superiority of 5 mmHg. Similarly, the mean reduction in ambulatory blood pressure at 6 months was 6.8 mmHg with active therapy and 4.8 mmHg with placebo compared to baseline, and the small between-group difference (2.0 mmHg) was not significant ($p=0.98$) for a superiority margin of 2 mmHg.

Several points need to be highlighted and evaluated in the context of previous knowledge in order to avoid misleading conclusion.

Firstly, the magnitude of office blood pressure reduction was almost half than in previous studies (14.1 mmHg versus 25-30 mmHg) [2, 3, 5, 8-11]. The inferior efficacy of RSD in the Symplicity-3 might be attributed to differences in study

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populations and several other factors. It has to be noted however that all previous studies were uncontrolled. It has been estimated that the anticipated blood pressure reduction with RSD is approximately 15 mmHg, when all other factors are taken in consideration [12].

Secondly, the ambulatory blood pressure reduction was significantly lower than the office blood pressure reduction (6.8 mmHg versus 14.1 mmHg), and this also was not an unexpected finding. A marked disparity between office and ambulatory blood pressure reduction with RSD has been observed in all previous RSD studies [13], and this disparity is significantly higher than with antihypertensive drug therapy [14].

Thirdly, the main factor contributing to the negative findings of the study was the impressive blood pressure reduction with the sham procedure (11.7 mmHg). However, this was also not an unexpected finding and it should have been anticipated based on previous data. Indeed, two studies performed in patients with resistant hypertension and similar baseline characteristics, revealed a strong placebo effect: the Rheos pivotal trial and the darusentan study [15, 16]. The powerful placebo effect almost “killed” both carotid baroreceptor activation and endothelin receptor antagonism for the treatment of resistant hypertension [17, 18].

Finally, potential disadvantages in study design cannot be entirely excluded. The study design was very meticulous and of the highest quality, and included sham procedure and ambulatory blood pressure monitoring overcoming previous concerns [19, 20]. However, one factor might have significantly influenced the findings of the study: the absence of familiarity with this novel procedure. The study was conducted in 88 sites all over the United States and more than 100 interventional cardiologists performed the procedure, for a mean of 3 to 4 procedures for each interventionalist. This raises the concern of a learning curve, especially because RSD was performed with the single-tip Symplicity catheter, which needs a lot of manipulations.

Overall, the negative findings of the Symplicity-3 trial “turned-off” the initial enthusiasm about RSD in many physicians, both hypertension specialists and primary care doctors. However, a sober and dispassionate approach seems more rational, avoiding overwhelming enthusiasm and excessive pessimism. Carefully designed clinical trials along with intensive research about response predictors are eagerly awaited in order to identify patient subgroups that will benefit from RSD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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