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Commentary

SYMPLICITY HTN-3 results to be announced: a mystery or a story foretold?

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The SYMPLICITY HTN-1[1] and HTN-2 studies[2] showed that renal denervation (RDN) is feasible as a novel treatment for resistant hypertension. Despite great enthusiasm toward this new treatment modality[3], until now the current evidence rests on only one randomized controlled trial[2]. SYMPLICITY HTN-3[4] is a pivotal study started for regulatory purposes in the United States with the goal to evaluate the efficacy and safety of RDN in treatment of resistant hypertension. It is a randomized trial including 535 resistant hypertensive patients randomized to RDN or control (sham) in a ratio of 2:1. On 9 January 2014, Medtronic announced that SYMPLICITY HTN-3 failed to meet its primary endpoint of efficacy (http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1889335&highlight) and that the final scientific results will be reported at the 63th Scientific Meeting of the American Cardiology College, to be held in Washington DC on 29–31 March 2014. In the wake of this announcement, Medtronic suspended SYMPLICITY HTN-4 in the United States, HTN-Japan and HTN-India. Other manufacturers halted on-going studies (Covidien) or put their research programs on hold (St Jude Medical and Boston Scientific), because of the uncertainty about what SYMPLICITY HTN-3 will report.

In contrast to the desperation reigning in the company headquarters, we are convinced that now the time has come that scientists instead of marketers and shareholders take the lead in clinical research on RDN. In our view, there is little uncertainty about what SYMPLICITY HTN-3 will report at the end of March, based on the published sample size calculations for the primary efficacy endpoint based on office systolic blood pressure[4]. These calculations state that "*assuming a true difference between treatment means of 15 mmHg with a 25 mmHg standard deviation of systolic blood pressure change per group, a sample size of 316 treated and 158 control patients provides over 95% statistical power to demonstrate a difference of more than 5 mmHg between treatment groups with a 1-sided α-level of 0.025*". Assuming a standard deviation of 25 mmHg, the baseline-adjusted between-group difference in SYMPLICITY HTN-3 should be around 7 mmHg. The confidence interval around 7 mmHg must pass through zero (no effect) and 5 mmHg, so that RDN remains inferior to control (sham). Furthermore, the baseline-adjusted between group difference in the daytime systolic ambulatory blood pressure should be approximately 65% of 7 mmHg (~5 mmHg)[5]. We wonder whether the SYMPLICITY HTN-3 investigators will report any results on ambulatory blood pressure. They stated that if the primary effectiveness endpoint is met, the major secondary endpoint, change in average 24-h systolic blood pressure by ambulatory monitoring from baseline to 6 months, will

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be tested[4]. This statement implies that if the primary efficacy endpoint fails to be met, the analysis plan does not include the ambulatory blood pressure.

While SYMPLICITY HTN-3 was ongoing, thousands of patients underwent RDN in Europe, based on inconclusive evidence from a single randomized control led trial[2] and on CE label certification. RDN was therefore deemed safe enough to be deployed on a large scale in Europe, where this intervention is currently reimbursed in several countries. From this view point, the primary endpoint for safety as tested in SYMPLICITY HTN-3 is completely obsolete. It encompassed severe events occurring within 1 month after the procedure. These encompassed death, decrease of estimated glomerular filtration rate (eGFR) to below 15 mL/min·m^2, need for renal replacement therapy, major lesions of the renal artery (perforation, dissection, and more than 70% stenosis occurring up to 6 months after RDN), major cardiovascular complications, and hospitalization for hypertensive crisis not related to confirmed nonadherence. European registries did not report such severe events, although there were occasional reports of renal arterial lesions[6]. In our view, the primary safety endpoint should have included changes in renal artery structure, as picked up by computed tomography or magnetic resonance angiography and changes in eGFR. As reviewed by our group[7], one of the SYMPLICITY reports[8] already showed a fall in eGFR of 16 mL/min/1.73m^2. In the long-term follow-up of SYMPLICITY HTN-1[9] patients, eGFR declined (P= 0.05) from 83.6 to 74.3 mL/(min·1.73 m^2). Taking these observation into account, the SYMPLICITY HTN-3 investigators should report on eGFR changes. We presume that eGFR will show some decline in both treatment groups, for example, as a consequence of using contrast media, but the decline in eGFR might be larger in the intervention than control group.

Finally, the SYMPLICITY HTN-3 analysis plan also calls for subgroup analysis according to race, diabetes mellitus, sex, age and body mass index to evaluate the consistency of the results. Before randomization, SYMPLICITY HTN-3 patients were stratified for center and ethnicity. Thus, only the subgroup analysis by race was predefined. All other subgroup analysis are therefore post-hoc, vulnerable to chance findings with large margins of type 1 error. Moreover, because the primary efficacy endpoint was not met, one wonders what consistency is left over to be evaluated by subgroup analyses.

In conclusion, in most countries worldwide, the routine application of RDN in patients with treatment resistant hypertension is not evidence based but driven by market forces based on observational studies and deficient regulation. The first regulatory trial conducted under the guidance of the Food and Drug Administration in the United States removed the smoke curtain hiding the large variability in the blood pressure responses to RDN[10] and emphasized that one size will not fit all, but that only a small niche of carefully selected patients are likely to benefit from this procedure. New randomized clinical trials designed and led by scientists should now identify the indications of RDN in treatment resistant hypertension, so that the SYMPLICITY debacle and the shortcoming of device validation process in Europe will not lead to the abandonment of a potentially promising technique.

References

[1] Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension : a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275–81.

[2] Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial) : a randomised controlled trial. *Lancet* 2010;376:1903–9.

[3] Santiapillai GR, Ferro A. Renal denervation as an option for the management of hypertension. *J Biomed Res* 2014;28:18–24.

[4] Kandzari DE, Bhatt DL, Sobotka PA, O′Neill WW, Esler M, Flack JM, et al. Catheter-based renal denervation for resistant hypertension : rational and design of the SYMPLICITY HTN-3 trial. *Clin Cardiol* 2012;35:528–35.

[5] Staessen JA, Byttebier G, Buntinx F, Celis H, O′Brien ET, Fagard R, et al. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. *JAMA* 1997;278:1065–72.

[6] Kaltenbach B, Id D, Franke JC, Sievert H, Hennersdorf M, Maier J, et al. Renal artery stenosis after renal sympathetic denervation. *J Am Coll Cardiol* 2012;60:2694–5.

[7] Persu A, Renkin J, Thijs L, Staessen JA. Renal denervation — Ultima ratio or standard in treatment-resistant hypertension. *Hypertension* 2012;60:596–606.

[8] Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension. Durability of blood pressure reduction out to 24 months. *Hypertension* 2011;57:911–7.

[9] Krum H, Schlaich MP, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resitant hypertension : final 3-year report of the SYMPLICITY HTN-1 study. *Lancet* 2014;383:622–9.

[10] Persu A, Jin Y, Azizi M, Baelen M, Völz S, Elvan A, et al: Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens* 2014;28:150–6.