Netherlands
The Journal of Medicine

EDITORIAL

Renal denervation revised

A.H. van den Meiracker

Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands,
email: a.vandenmeiracker@erasmusmc.nl

In this issue of the Netherlands Journal of Medicine, a consensus document concerning recommendations for the performance of catheter-assisted renal denervation is provided.[1] This document, issued under the auspices of the Dutch Society of Cardiology, serves as a guide for implementation of renal denervation with care and caution in the Netherlands. Patient safety and creation of transparency are the important achievable aims when performing renal denervation according to the recommendations issued by the Dutch Society of Cardiology. Transparency can be achieved by participation in the independent national registry. In this registry essential clinical data and technical aspects related to the procedure as well as outcome data are documented. The idea behind this database is that we can determine which hypertensive patients will benefit and what kind of immediate and long-term risks are associated with renal denervation.

Patient safety is guaranteed by selecting the right patients to subject to the procedure. The right patient has treatment-resistant hypertension, an eGFR of at least 35 ml/min/1.73 m^2, and renal artery anatomy suitable for intervention. White coat hypertension or a strong white coat effect must be excluded by performing 24-hour ambulatory blood pressure monitoring, as must secondary forms of hypertension requiring other therapeutic approaches. Last but not least, the interventionalist (in most centres a cardiologist) is well experienced in performing this procedure and the multidisciplinary team should include a vascular medicine internist or a nephrologist specialised in hypertension treatment to help to select the right patients and take care of follow-up,

Publication of this document may give the wrong impression that renal denervation is already an accepted and established treatment for patients with resistant hypertension. Although in individual patients renal denervation is sometimes associated with an impressive blood pressure reduction, the recently published Simplicity HTN-3 has shown that the intervention above all has a strong placebo effect.[2] In Simplicity HTN-3, a randomised, controlled trial performed in the United States, 535 hypertensive patients were assigned in a 2:1 ratio to renal denervation or an invasive sham procedure. The mean decrease in systolic office blood pressure at six months was 14.1 mmHg in the renal denervation group as compared with 11.7 mmHg in the sham group (difference of 2.4 mmHg in favour of renal denervation). Reduction in 24-hour systolic ambulatory blood pressure was less than the reduction in office systolic blood pressure, 6.8 and 4.8 mmHg in the renal denervation and sham group, respectively (difference of 2 mmHg in favour of renal denervation). Based on this large controlled study it has to be concluded that, on average, renal denervation is an ineffective treatment. As mentioned, some patients may benefit but at this moment we do not know which ones. Previous results indicate that elderly patients, patients with isolated systolic hypertension and, unexpectedly, patients with impaired renal function are unlikely to respond.[3]

Besides lack of proof of efficacy with regard to blood pressure reduction, evidence of a favourable effect on (cardiovascular) morbidity or mortality, the ultimate goal of treatment of hypertension, is not available for renal denervation and the chance that such information will ever come is small. More importantly, safety issues are also arising. At least 13 cases of *de novo* renal artery stenosis have been reported 3-6 months after renal denervation was performed.[4] Renal artery stenosis is most likely a direct consequence of thermal injury of the renal artery wall induced by the radiofrequency catheter. In addition, a larger than anticipated reduction in eGFR was observed in the Symplicity HTN-1 registry after a follow-up of 36 months, although no difference in change in eGFR between the intervention and sham group was observed in Symplicity HTN-3 after the six-month follow-up period.[5]

Based on the present knowledge we must ask the question whether we should still offer renal denervation to a patient with resistant hypertension. Obviously, different professionals will have different views and considerations. What we at least should do is to inform our patients in an unbiased way. Although renal denervation has already frequently been performed in various European countries and Australia, it is still an experimental treatment, and

after publication of the Simplicity HTN-3 findings, a treatment with minimal efficacy. At least written informed consent from every patient should be required after a full explanation of the technique, including information about the doubtful efficacy and potential immediate and long-term harmful effects.

It remains possible that the disappointing results of Simplicity HTN-3 are in part related to the device used to perform renal nerve ablation. With other devices or techniques a more intensive degree of renal denervation than the maximal 50% denervation obtainable with the Simplicity catheter can probably be achieved, hopefully translating into a larger blood pressure lowering effect.[6] Obviously, before being certain that such a new device really works a new trial with a sham control as done in Simplicity HTN-3 is required. This is also advocated in a recent 'perspective' in the New England Journal of Medicine.[7]

Finally, in the past the proportion of patients with treatment-resistant hypertension suitable for renal denervation has been considerably overestimated. After careful selection, excluding patients with secondary hypertension, patients who are poorly adherent, patients with white coat hypertension or a pronounced white coat effect and patients with an inappropriate anatomy of the renal arteries, only a small fraction of the patients remain suitable for renal denervation.[8] In most of these remaining patients, blood pressure can be controlled by medical treatment when the patient is referred to an expert in the management of hypertension. Thus, although from a scientific point of view it is very disappointing that renal denervation seems to be much less efficacious than initially thought, from a clinical point of view the problem of resistant hypertension is surmountable as in almost all patients with severe hypertension control of the blood pressure can be obtained by lifestyle improvement and optimal pharmacotherapy.

REFERENCES

1. Verloop W, Agema W, Allaart C, et al. Renal denervation for the treatment of hypertension: the Dutch Consensus. Neth J Med. 2014;9:449-454.
2. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393-401.
3. Persu A, Jin Y, Azizi M, et al. Blood pressure changes after renal denervation at 10 European expert centers. J Hum Hypertens. 2014;28:150-6.
4. Persu A, Jin Y, Fe FE, Jacobs L, Renkin J, Kjeldsen S. Renal denervation after Symplicity HTN-3: An update. Curr Hyperten Rep. 2014;16:460.
5. Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383:622-9.
6. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;374:1275-81.
7. Redberg RF. Sham controls in medical device trial. N Engl J Med. 2014;371:892-3.
8. Savard S, Frank M, Bobri G, Plouin PF, Sapoval M, Azizi M. Eligibility for renal denervation in patients with resistant hypertension: when enthusiasm meets reality in real-life patients. J Am Coll Cardiol. 2012;60:2422-4.