HYPERTENSION

Renal denervation—promising data from the DENERHTN trial

Wen-Yi Yang and Jan A. Staessen

Refers to Azizi, M. *et al.* Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* [http://dx.doi.org/10.1016/S0140-6736\(14\)61942-5](http://dx.doi.org/10.1016/S0140-6736(14)61942-5)

In patients with resistant hypertension, renal denervation plus standardized stepped-care antihypertensive treatment (SSAHT) resulted in significant blood-pressure lowering compared with SSAHT alone. These new data from the DENERHTN trial may indicate that despite the failure of SYMPLICITY HTN-3, there is light at the end of the tunnel for renal denervation.

The DENERHTN trial investigators report that in patients with resistant hypertension, renal denervation together with standardized step-care antihypertensive treatment (SSAHT) resulted in approximately 6 mmHg greater reductions in 24 h, daytime and night-time systolic blood pressure levels at 6 months than did SSAHT alone.¹ These data are in contrast to the findings of the SYMPLICITY HTN-3 trial,² which failed to reach its efficacy end point and showed baseline-adjusted differences in systolic blood pressure between renal denervation and sham-operated groups of only 2.4 mmHg and 2.0 mmHg on office and 24-h ambulatory blood pressure monitoring, respectively. The DENERHTN consortium sailed against the tide by continuing their trial despite the negative findings of SYMPLICITY HTN-3, but they have been rewarded by the generation of novel insights into the effects of renal denervation on resistant hypertension.

Design characteristics that differentiate the DENERHTN trial from previous studies of renal denervation (Table 1)^{2–5}—and increase the reliability of the findings—include blinded assessment of daytime systolic blood pressure, the primary end point, recruitment and monthly follow-up of patients at specialized tertiary referral centres, and assessment of drug adherence at every clinic visit using the eight-item Morisky Medication Adherence Scale (MMAS-8) questionnaire. The highly standardized drug treatment regimen, which reduces confounding by concomitant antihypertensive therapy, is particularly relevant for the interpretation of the DENERHTN trial results.² Patients who maintained a

daytime blood pressure of ≥ 135 mmHg systolic or ≥ 85 mmHg diastolic despite triple therapy with indapamide 1.5 mg, ramipril 10 mg (or irbesartan 300 mg) and amlodipine 5–10 mg daily for 4 weeks ($n=106$) were randomly assigned to renal denervation and control groups.¹ From month two to five after randomization, if home blood pressure was ≥ 135 mmHg systolic or ≥ 85 mmHg diastolic, spironolactone 25 mg, bisoprolol 10 mg, prazosin 5 mg and rilmenidine 1 mg per day were sequentially added. Similar proportions of patients in the renal denervation and control groups received these add-on medications; overall 27.7% of participants reached the last step in the treatment algorithm. During follow-up, the median number

of drugs increased from three to five and the proportion of patients with high adherence (MMAS-8 score 8) increased from ~63% to ~73% in both groups.

Notwithstanding the merits of the DENERHTN trial, a number of issues limit interpretation of the data. The drop-out rates in the intention-to-treat and per-protocol analyses were higher in the renal denervation than in the control group (9.4% versus 0% and 17.0% versus 0%, respectively). At the time of randomization, blood pressure was also consistently, albeit not significantly, higher in the renal denervation group. In the modified intention-to-treat analysis, daytime, night-time and 24 h systolic blood pressures were respectively 4.5 mmHg ($P=0.15$), 5.9 mmHg ($P=0.059$) and 4.8 mmHg ($P=0.12$) higher in the denervation group than in the control group (P values calculated using t -tests of data reported in Table S1 of the original article¹). The between-group baseline-adjusted differences in ambulatory blood pressure, therefore, partly depend on the higher baseline blood pressure levels in the denervation group; there was no significant difference in blood pressure levels at 6 months in the study groups ($P\geq 0.45$). According to the regression model derived in the per-protocol analysis, a 4.5 mmHg higher daytime systolic pressure by itself accounts for a ~2 mmHg lower blood pressure at 6 months. The between-group

Table 1 | Randomized clinical trials of renal denervation in patients with resistant hypertension

Characteristic	DENERHTN ¹	OSLO RDN ⁴	PRAGUE-15 ⁵	SYMPLICITY HTN-2 ³	SYMPLICITY HTN-3 ²
Number of patients					
Control/renal denervation (analysed)	53/53 (53/48)	10/10 (10/9)	54/52 (54/52)	52/54 (51/49)	171/364 (171/353)
Blood pressure criteria (mmHg)					
Office systolic/diastolic	$\geq 140/\geq 90$	$>140/\text{NS}$	$>140/\text{NS}$	$\geq 160/\text{NS}$	$>160/\text{NS}$
Ambulatory systolic/diastolic (period)	$\geq 135/\geq 85$ (Daytime)	$>135/\text{NA}$ (Daytime)	$>130/\text{NA}$ (24 h)	NS/NS (NS)	$\geq 135/\text{NA}$ (24 h)
Systolic blood pressure (mmHg)					
Office (control/renal denervation)					
Baseline	156/160	160/156	155/159	178/178	180/180
Change at 6 months	-9.5/-15.1	2/-8	-14.3/-12.4	1/-32	-11.7/-14.1
24 h (control/renal denervation)					
Baseline	147/152	152/152	147/149	NS/NS	160/159
Change at 6 months	-9.5/-15.4	21/-10	-8.1/-8.6	-3/-11	-4.8/-6.7

Abbreviation: NA, not applicable; NS, not specified.

difference in entry blood pressure levels might be the result of randomization of three or fewer patients at 10 of 15 centres.

A consensus exists in the literature that blood-pressure lowering effects assessed by home or daytime ambulatory monitoring are generally 30–40% lower than those observed on office measurement.⁶ By contrast, the DENERHTN investigators observed within-group changes in systolic blood pressures of similar magnitudes on office, home and daytime ambulatory measurement.¹ Titration of add-on medication based on self-measured home blood pressures might explain this finding. However, in 203 patients randomly assigned to treatment adjustment guided by home blood pressure in the THOP trial,⁶ in which the treatment regimen was as thoroughly standardized as in the DENERHTN trial, decreases in systolic pressure were larger on office than on out-of-office assessment, averaging 15.3 mmHg, 11.1 mmHg and 11.3 mmHg on office, home and daytime measurement, respectively. Alternative explanations for the similar treatment effects on systolic blood pressure across measurement platforms in the DENERHTN trial include assessment of office blood pressure in the morning before intake of medications and, at variance with other trials in the field,^{2–5} the use of both systolic and diastolic blood pressure as entry criteria and treatment goals. Patients with white-coat or masked systolic hypertension might have entered the trial based on a qualifying diastolic blood pressure on daytime ambulatory or office measurement, respectively.

A remarkable design feature of the DENERHTN trial is the stepwise add-on treatment with sympatholytic drugs. This protocol was probably based on the premise that these drugs would enhance the effects of renal denervation, which was apparently correct.¹ The increasing adherence to multiple drug treatment during the follow-up period might reflect a learning curve in completing the MMAS-8 questionnaire or exemplify the Hawthorne effect, by which patients improve their behaviour in response to their awareness of being observed.⁷ Measurement of drug concentrations in urine would be required to investigate these possibilities.

The data generated by the DENERHTN trial will substantially change the field of renal denervation as a treatment modality for hypertension. First, all renal denervation trials conducted to date^{1–5} have used the single-electrode radiofrequency Symplicity™ catheter (Medtronic, USA). The modest blood pressure reduction observed in the

DENERHTN trial confirmed that this device is too imprecise and operator dependent to meet the objective of effective renal sympathetic denervation. Ultrasound-based catheters and multi-electrode catheters with intelligent designs that include inflatable balloons or expandable baskets for stabilization may have greater efficacy than the Symplicity™ denervation system. Moreover, in contrast to radiofrequency ablation, circumferential delivery of ultrasound energy at an adjustable depth in the renal arterial adventitia does not damage the endothelium.

Second, resistant hypertension is currently defined as office blood pressure of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic despite treatment with three classes of antihypertensive drugs, including a diuretic, at maximal doses. The DENERHTN trial, in which patients needed a median of five drugs for blood pressure control, with or without renal denervation, proves that the current indication for the procedure is a misconception. In line with the pathophysiological evidence,⁸ signs of sympathetic dysregulation in the presence of hypertension—preferably in untreated patients—might become the prime indication for renal denervation rather than the number of antihypertensive drugs.

Renal nerve stimulation can be used to identify the anatomical sites where lesions should be delivered and to ascertain the completeness of denervation, thereby addressing the huge variability in the course of the renal sympathetic nerves along the renal arteries.⁹ Accessory renal arteries that cannot be engaged for denervation represent an anatomical constraint that has not been accounted for in most trials conducted to date. Short-term (6 month) blood pressure results or grossly incomplete follow-up¹⁰ cannot be translated into durability of the blood-pressure response or the prevention of cardiovascular complications. The DENERHTN investigators will likely soon report whether or not the need to continue or intensify antihypertensive treatment after renal denervation limits the cost-effectiveness of the procedure in treatment-resistant hypertension.¹

After years of market-driven research, the DENERHTN trial¹ has generated novel insights that suggest that there is light at the end of the tunnel for renal denervation. The experts who have led the trials conducted to date agree that a minority of highly selected patients experience a substantial blood-pressure response to the procedure. Full access to the available data should enable a patient-level meta-analysis to characterize

this small subgroup of responders, thereby informing future trials, preferably in never-treated patients with hypertension and evidence of sympathetic overactivity.⁸

Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium (W.-Y.Y., J.A.S.). Correspondence to: J.A.S. jan.staessen@med.kuleuven.be

doi:10.1038/nrneph.2015.28

Published online 10 March 2015

Acknowledgements

The authors are grateful to the investigators of the European Network Coordinating Research on Renal Denervation, who substantially contributed to the insights expressed in this commentary. They are especially indebted to Y. Jin (University of Leuven, Belgium), F. E. M. Fadl Elmula and S. E. Kjeldsen (both University of Oslo, Norway).

Competing interests

The authors declare no competing interests.

1. Azizi, M. *et al.* Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* **26**, [http://dx.doi.org/10.1016/S0140-6736\(14\)61942-5](http://dx.doi.org/10.1016/S0140-6736(14)61942-5).
2. Bhatt, D. L. *et al.* A controlled trial of renal denervation for resistant hypertension. *N. Engl. J. Med.* **370**, 1393–1401 (2014).
3. Symplicity HTN-2 Investigators *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* **376**, 1903–1909 (2010).
4. Fadl Elmula, F. E. M. *et al.* Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* **63**, 691–699 (2014).
5. Rosa, J. *et al.* Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* **65**, 407–413 (2014).
6. Staessen, J. A. *et al.* Antihypertensive treatment based on blood pressure measurement at home or in the physician's office. A randomized controlled trial. *JAMA* **291**, 955–964 (2004).
7. Colloca, L. & Finniss, D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA* **307**, 567–568 (2012).
8. Kjeldsen, S. E., Flaaten, B., Eide, I., Helgeland, A. & Leren, P. Increased peripheral release of noradrenaline and uptake of adrenaline in essential hypertension? *Clin. Sci. (Lond.)* **61** (Suppl. 7), 215s–217s (1981).
9. Gal, P. *et al.* Blood pressure response to renal nerve stimulation in patients undergoing renal denervation: a feasibility study. *J. Hum. Hypertens.* <http://dx.doi.org/10.1038/jhh.2014.91>.
10. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension. Durability of blood pressure reduction out to 24 months. *Hypertension* **57**, 911–917 (2011).