SYMPLICITY HTN-3: failure at 6 months, success at 3 years?

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In *The Lancet*, Deepak L Bhatt and colleagues report long-term outcomes of renal artery denervation in patients denervated by single-electrode radiofrequency within the SYMPLICITY HTN-3 study.[1] This large sham-controlled trial recruited 535 patients (210 [39%] women and 325 [61%] men; mean age in renal denervation group 57·9 years [SD 10·4]) with treatment-resistant hypertension enrolled in 88 centres in the USA. The trial was expected to provide definitive evidence of the efficacy of renal denervation in patients with treatment-resistant hypertension but did not meet its primary 6-month efficacy endpoint,[2] raising an unprecedented wave of scepticism about renal denervation.[3]

The results of the 3-year follow-up show a surprisingly large benefit,[1] of the same order of magnitude as that reported in the SYMPLICITY HTN-1[4] and SYMPLICITY HTN-2[5] trials, with a reduction in office systolic blood pressure at 36 months of 26·4 mm Hg (SD 25·9) in the renal denervation group versus 5·7 mm Hg (24·4) in the control group (p≤0·0001), and a reduction in 24 h ambulatory blood pressure of 15·6 mm Hg (20·8) in the renal denervation group versus 0·3 mm Hg (15·1) in the control group (p≤0·0001).[1] Furthermore, the long-term follow-up confirmed the safety of the procedure, with no differences in the composite safety endpoint between the two groups.[1] The investigators of SYMPLICITY HTN-3 deserve praise for their efforts and persistence to report 3-year outcomes of patients enrolled in an otherwise negative trial.

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However, such an optimistic interpretation should be tempered. Indeed, the current long-term analysis[1] unavoidably has lost the benefits of randomisation and blinding of the SYMPLICITY HTN-3 trial, with the potential drawbacks of patient-related and physician-related biases in an observational study. Patients who had renal denervation might have received more care and attention; therefore, they might have been better managed than patients in the sham control group in terms of implementation of lifestyle modification, patient–physician relationship, and antihypertensive treatment. These potential biases might have different consequences: for example, they might have led to an improved adherence to antihypertensive drug treatment in the renal denervation group. In the absence of direct assessment of drug adherence, this will never be known. Indeed, similar numbers of prescribed antihypertensive medications in the renal denervation and control groups do not necessarily imply similar adherence levels.

Additionally, the composition of the control group and the use of imputed data could have affected the results. Indeed, after unmasking at 6 months, patients from the initial sham control group were allowed to cross over to renal denervation, if they still met the inclusion criteria. In this way, 101 participants had crossover renal denervation and 70 participants remained in the non-crossover group. The comparison of long-term outcomes was not done between participants who underwent renal denervation, either after randomisation or after crossover, and participants who were not denervated, as could have been expected. The comparison group included non-crossover patients and data from crossover patients at 6 months, before renal denervation, using the most recent pre-crossover blood pressure to impute subsequent follow-up data, following the principle of the last observation carried forward.[6] This approach deserves caution, especially for non-random missing data,[6] because it crystallises the crossover patients at 6 months and does not consider the actual evolution of blood pressure over time. When only available data are considered and no imputed data are included in the analysis, no statistically significant difference in blood pressure reduction is present between the renal denervation and control group, as reported by the authors in supplementary table S4 (Article appendix p 5).[1]

Furthermore, data about crossover and non-crossover patients before and after unmasking provide interesting findings (supplemental figure S5, Article appendix p 14): the non-crossover group had a reduction in blood pressure when masked, with a subsequent increase in blood pressure after unmasking; this suggests a potential contribution of placebo and Hawthorne effects in this trend.[3] The crossover group did not show a variation of blood pressure while masked, with a reduction in blood pressure only after unmasking and renal denervation. The authors advocated this as additional evidence of the efficacy of renal denervation.[1] Nevertheless, mean blood pressure decrease appears to be similar in the crossover and non-crossover groups—approximately of 25 mm Hg. Therefore, also in the comparison between the crossover and non-crossover patients, renal denervation showed no additional benefit in reducing blood pressure.

Since the initial report of SYMPLICITY HTN-3,[2] second-generation sham-controlled trials of renal denervation with a rigorous and uniform design consistently documented a blood pressure lowering effect of renal denervation,[7] although not to the extent postulated in initial uncontrolled or unblinded studies.[3-5] The failure of SYMPLICITY HTN-3 to meet its 6-month primary endpoint[2] does not detract from these conclusions, and potential reasons for this failure have been extensively discussed previously.[8-9] The current 3-year follow-up study of the SYMPLICITY HTN-3 trial[1] is meritorious and physicians interested in renal denervation will find much relevant information here. Nevertheless, we are not fully convinced that these data "support the growing body of evidence of favourable, durable, and safe long-term results of renal artery denervation, with the potential for larger reductions in blood pressure with longer durations of follow-up", as reported by the authors.[1] While the 3-year outcome report of the SYMPLICITY HTN-3 trial[1] adds important evidence about the long-term safety of renal denervation, further blinded, randomised, sham-controlled trials are still needed to better define the efficacy of this technique over time, and to predict the patients who will benefit most from it.

AP is involved in the RADIANCE (RecorMedical, a commercial company) and TARGET BP (Ablative Solutions, a commercial company) renal denervation research programmes, which include clinical trials, and reports grants to his institution; is a member of the Steering Committee of the TARGET BP research programme (Ablative Solutions); and reports limited institutional support from Ablative Solutions and RecorMedical for a PhD student working on projects unrelated to renal denervation. EF declares no competing interests.

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Best time for administration of antihypertensive medications: morning or evening?

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Hypertension is a leading cause of cardiovascular morbidity and mortality, with more than 1 billion patients living with hypertension worldwide.[1] This high prevalence is associated with a huge burden on the health-care systems and economies globally.[2]

Neurohormonal variations result in diurnal changes in blood pressure, with peak blood pressure typically being recorded after awakening and lowest blood pressure during the night-time, a phenomenon commonly referred to as dipping.[3] The absence of