Taken together, current results do not support the use of chlorthalidone over hydrochlorothiazide. Of note, a randomized controlled study of hydrochlorothiazide versus chlorthalidone (ClinicalTrials.gov Identifier: NCT02185417) is currently in progress[2] and may clarify matters.

Thomas Kahan - thomas.kahan@sll.se

REFERENCES

1. Hripcsak G, Suchard MA, Shea S, Chen R, You SC, Pratt N, Madigan D, Krumholz HM, Ryan PB, Schuemie MJ. Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension. JAMA Intern Med. 2020;180(4):542-51. doi:10.1001/jamainternmed.2019.7454

2. Lederle FA, Cushman WC, Ferguson RE, Brophy MT, Fiore Md LD. Chlorthalidone versus hydrochlorothiazide: A new kind of Veterans Affairs cooperative study. Ann Intern Med. 2016;165(9):663-664. doi: 10.7326/M16-1208

HOT OFF THE PRESS: CLINICAL

Renal denervation lowers blood pressure – now what?

MARKUS P SCHLAICH

Dobney Hypertension Centre, School of Medicine - Royal Perth Hospital Unit / Medical Research Foundation, University of Western Australia and Departments of Cardiology and Nephrology, Royal Perth Hospital, Perth, Australia. Neurovascular Hypertension & Kidney Disease Laboratory. Baker Heart and Diabetes Institute, Melbourne, Australia

DOI: 10.30824/2006-6

The controversies around renal denervation over the last decade have undoubtedly shaped the hypertension world and have brought to light some hidden truths, stimulated extensive research efforts into the phenotype of "resistant hypertension", and helped to advance our approaches to diagnose and manage this complex aspect of hypertension medicine. Therapeutic drug monitoring revealed that a large proportion of patients requiring poly-pharmacy are indeed non-adherent with prescribed medication. The importance of 24-hour ambulatory blood pressure (BP) monitoring as a primary endpoint measure, adequate study designs including sham-procedures, optimization of procedural aspects, and the relevance of patient selection became apparent. While Symplicity HTN-1 and HTN-2 demonstrated a substantial reduction in BP, Symplicity HTN-3, the largest and first study to include a sham control failed to demonstrate a BP lowering effect beyond that observed in the sham control group and thereby questioned the utility of catheter-based renal denervation[1].

Since then, three sham-controlled studies using either radiofrequency ablation technology[2,3] or high frequency ultrasound[4] in both drug-naïve[2] or treated hypertensive patients[3,4] demonstrated clinically relevant reductions in ambulatory BP compared to respective sham control groups.

Most recently, results from the SPYRAL HTN-OFF MED Pivotal trial, an international, prospective, randomised controlled trial on the effects of renal denervation in unmedicated patients were reported[5]. In a cohort of 331 patients with hypertension assigned to either radiofrequency ablation (n=166)

or sham procedure (n=165), differences between treatments were -6.5mmHg (Bayesian 95% credible interval -9.6 to -3.5) for office systolic BP and -3.9 mmHg (-6.2 to -1.6) for 24 h systolic BP (Figure 1). Blood pressure reductions were persistent and sustained over 24 h (Figure 2) and no relevant procedure-related or short term safety events were reported after three months. Treatment differences in 24 h BP in key baseline characteristic subgroup measurements showed no significant interactions between subgroups.

Advocates of renal denervation will be pleased with the findings from the SPYRAL HTN-OFF MED Pivotal for a number of reasons: It provides further robust evidence to support the validity of the concept of therapeutically targeting renal sympathetic nerves to lower BP in humans and thereby extends the unambigious evidence from experimental studies into the clinical sphere. Furthermore, it is reassuring that there was no signal for safety concerns at 3 months follow up given the substantially more aggressive treatment approach with targeting of distal branches. Additionally, the apparent "always-on" effect (Figure 2) of renal denervation may prove advantageous particularly in patients on drugs that have short durations of action and in terms of mitigating the loss of BP control in patients who are non-adherent to drug therapy, which has become a major concern in hypertension management.

Skeptics may argue that the effects on BP observed with renal denervation, while clinically relevant, were relatively small and could equally be achieved with appropriate antihypertensive medication. They have a point... although renal denervation has been shown to exert more pronounced BP lowering effects beyond three months. Furthermore, is an interventional approach really something one would consider as an initial option in a drug-naïve patient in a real world setting? Probably not....at least at this stage. Patients however, who are intolerant to antihypertensive medication or chose not to take antihypertensive drugs may well benefit from such an approach, particularly in the long term if the BP lowering effect is sustained.

Importantly, the data from this trial need to be interpreted in the broader context. With the uncertainties arising from Symplicity HTN-3[1] it was crucial to demonstrate in an appropriately designed clinical trial that renal denervation safely and reliably reduces BP. This has now been proven.

The next step is to identify patients who may benefit most from such an interventional approach and a complementary randomised trial in patients with uncontrolled hypertension despite anti-hypertensive therapy due to report in 2021 may provide some answers. Management of hypertension is a marathon, not a sprint and assessment of long term performance of renal denervation will further our understanding of the overall benefits of renal denervation.

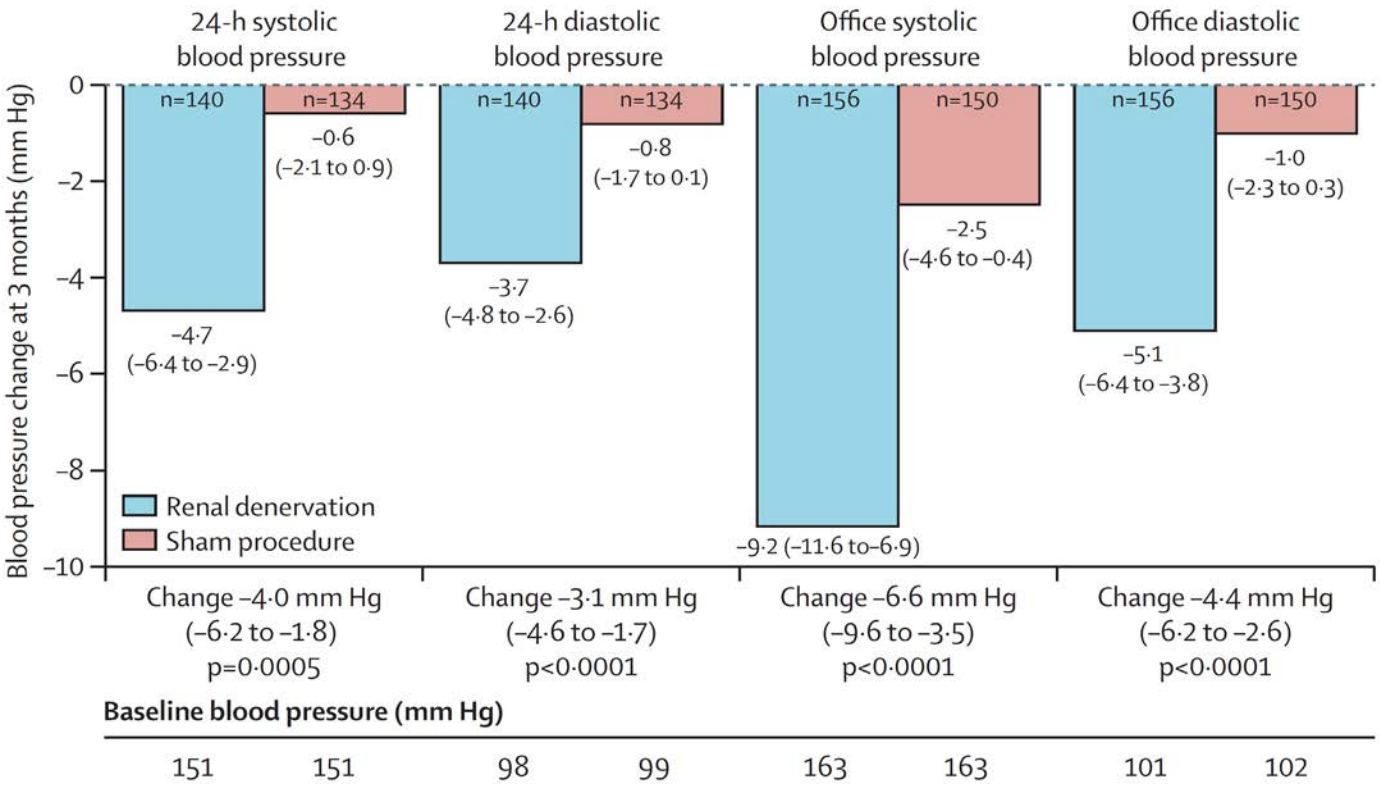
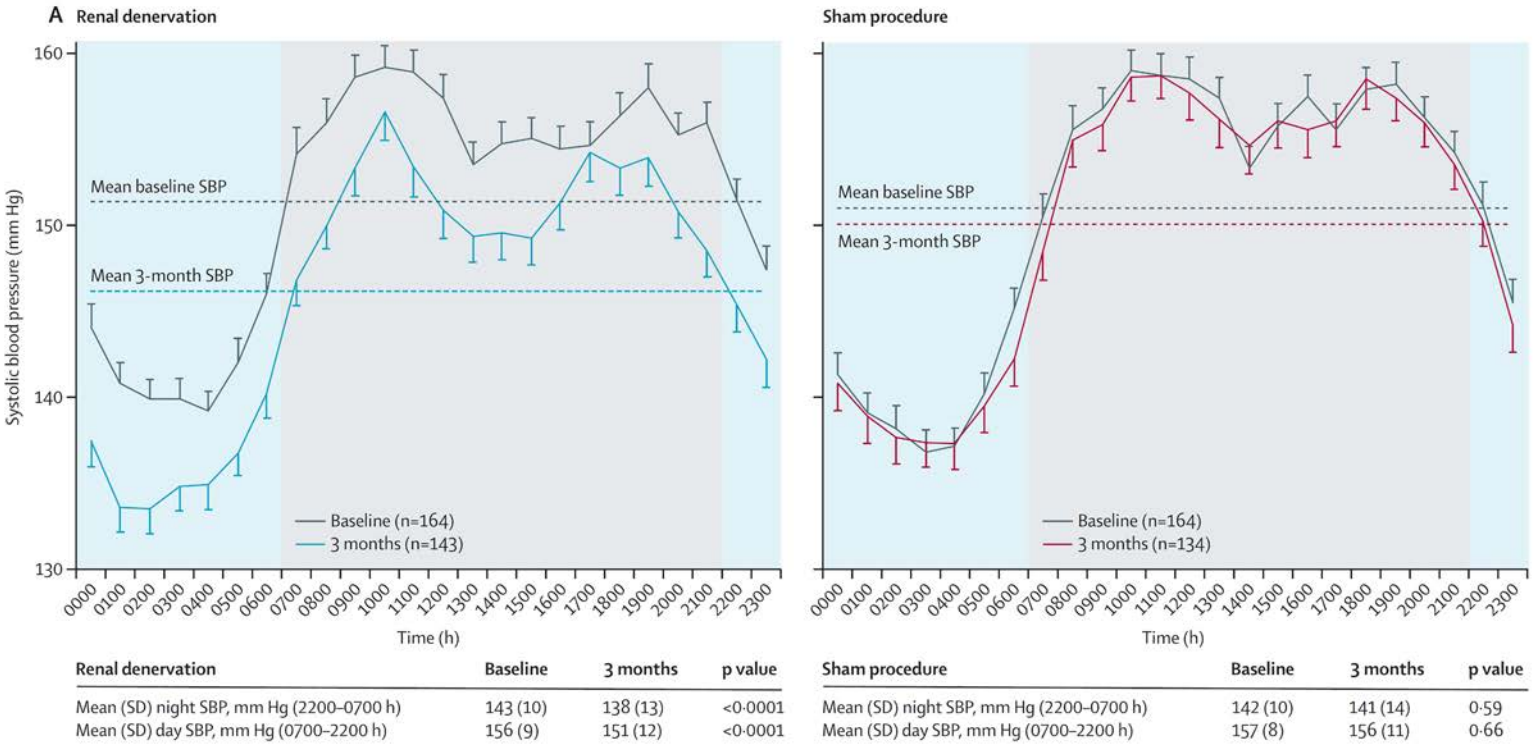


Figure 1: Changes in 24-h and office systolic and diastolic BP from baseline to 3 months (95% CI). Source: Lancet 2020 May 2;395(10234):1444-1451



Renal denervation	Baseline	3 months	p value
Mean (SD) night SBP, mm Hg (2200–0700 h)	143 (10)	138 (13)	<0·0001
Mean (SD) day SBP, mm Hg (0700–2200 h)	156 (9)	151 (12)	<0·0001

Sham procedure	Baseline	3 months	p value
Mean (SD) night SBP, mm Hg (2200–0700 h)	142 (10)	141 (14)	0·59
Mean (SD) day SBP, mm Hg (0700–2200 h)	157 (8)	156 (11)	0·66

Figure 2: 24-h ambulatory systolic (SBP) at baseline and 3 months after renal denervation or sham-procedure in the overall population. Source: Lancet 2020 May 2;395(10234):1444-1451

Markus Schlaich - markus.schlaich@uwa.edu.au

REFERENCES

1.Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401. doi: 10.1056/NEJMoa1402670

2.Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017; 390:2160-70. doi: 10.1016/S0140-6736(17)32281-X

3.Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391:2346-55. doi: 10.1016/S0140-6736(18)30951-6.

4.Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391:2335-45. doi: 10.1016/S0140-6736(18)31082-1

5. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020;395:1444-1451. doi: 10.1016/S0140-6736(20)30554-7