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 and may clarify matters.

**REFERENCES**


**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

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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.

Since then, three sham-controlled studies using either radiofrequency ablation technology or high frequency ultrasound in both drug-naive or treated hypertensive patients 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. 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
unambiguous 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 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](image-url)
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

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