Renal Denervation—Ready for Prime Time!?

The Steep SPYRAL Stairs to RADIANCE in Hypertension Treatment

Markus P. Schlaich, Marcio G. Kiuchi, Murray D. Esler

Two successive presentations at this year's EuroPCR in Paris with simultaneous publication of the SPYRAL HTN-ON MED (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)[1] and the RADIANCE-HTN SOLO (Endovascular ultrasound renal denervation to treat hypertension [RADIANCE-HTN SOLO]: a multicentre, international, single-blind, randomised, sham-controlled trial)[2] trials in *The Lancet* may well go down as a turning point in the renal denervation saga. After much controversy around the efficacy of renal denervation as an interventional approach to lower blood pressure (BP), both studies, one performed with a multielectrode radiofrequency ablation device in hypertensive patients on concurrent medication (SPYRAL HTN-ON MED) and the other using a high-frequency ultrasound device in drug-naive hypertensive patients (RADIANCE-HTN SOLO), show a convincing and clinically relevant reduction of ambulatory BP compared with respective sham control groups. In concert with the recently published SPYRAL HTN-OFF MED[3] study (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), robust evidence is now available from 3 consecutive and adequately designed randomized, sham-controlled trials confirming the BP-lowering efficacy of catheter-based renal denervation approaches.

This represents an important milestone in the development of catheter-based ablation of renal sympathetic nerves and lays to rest the concerns that the experimentally well-established concept of therapeutically targeting these nerves[4] may not apply in human hypertension.[5] Similarly important in this context is the finding that various treatment modalities, that is, transluminal ablation achieved either by applying radiofrequency or ultrasound energy, seem to be safe and similarly effective in lowering BP in patients with hypertension.

Indeed, as observed in all renal denervation studies conducted thus far, the safety profile of each ablation approach was favorable without significant vascular, renal, or procedural adverse effects,[5–9] as also confirmed in the real-world experience within the Global Symplicity Registry.[10,11] Furthermore, although background treatment and baseline BP levels differed between the recent 3 sham-controlled studies, the magnitude of the baseline-adjusted fall in ambulatory BP would clearly be considered as clinically significant: SPYRAL HTN-ON MED: 24-hour systolic BP (SBP), −7.0 mm Hg (95% confidence interval [CI], −12.0 to −2.1; *P*=0.0059), 24-hour diastolic BP, −4.3 mm Hg (95% CI, −7.8 to −0.8; *P*=0.0174); RADIANCE-HTN SOLO: 24-hour SBP, −7.0±8.6 mm Hg; *P*=0.006, 24-hour diastolic BP, −4.4±5.8 mm Hg; *P*=0.07; and SPYRAL HTN-OFF MED: 24-hour SBP, −5.3 mm Hg (95% CI, −8.6 to −2.0; *P*=0.0020), 24-hour diastolic BP, −4.8 mm Hg (95% CI, −6.8 to −2.8; *P*=0.001; Figure 1). Moreover, the effect in drug naïve patients seems similar when comparing SPYRAL HTN-OFF MED with RADIANCE-HTN SOLO.

Timing of the BP end point may be an important aspect to take into account when interpreting the available data. Indeed, data from the SPYRAL HTN-ON MED trial[1] demonstrate a trend toward more pronounced BP lowering over time, as indicated by a further reduction in 24-hour SBP of ≈4 mm Hg (from −4.3 mm Hg at 3 months to −8.8 mm Hg at 6 months; Figure 2A). Given that RADIANCE-HTN SOLO and SPYRAL HTN-OFF MED assessed the primary BP end point already at 2 and 3 months, respectively, paired with the expectation that any effect seen with a sham procedure is likely to diminish over time, longer-term follow-up of both studies may reveal even more pronounced and sustained BP reductions compared with the sham control groups. It is noteworthy that accumulating results from the Global Symplicity Registry, the largest collection of real-world data on renal denervation, demonstrated similar results in regard to the BP lowering efficacy at 3 months post-procedure.[10,11]

SPYRAL HTN-ON MED

The primary results from the SPYRAL HTN-ON MED trial[1] are those obtained from the first 80 patients (n=38 in the renal denervation group and n=42 in the sham-control group). Although most previous studies included hypertensive patients being prescribed at least 3 antihypertensive drugs (resistant hypertension), SPYRAL HTN-ON MED allowed participation of hypertensive patients on 1 to 3 antihypertensive drugs with stable doses during the previous 6 weeks. In the renal denervation group, 53% of patients were on 3 drugs, 18% on 2 drugs, and 29% on 1 drug. The change in BP was significantly

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Dobney Hypertension Centre, School of Medicine-Royal Perth Hospital Unit, University of Western Australia (M.P.S., M.G.K.); Departments of Cardiology and Nephrology, Royal Perth Hospital, Australia (M.P.S.); and Neurovascular Hypertension and Kidney Disease Laboratory and Human Neurotransmitter Laboratory, Baker Heart and Diabetes Institute, Melbourne, Australia (M.P.S., M.D.E.).

Correspondence to Markus Schlaich, Dobney Hypertension Centre, School of Medicine-Royal Perth Hospital Unit, The University of Western Australia Level 3, MRF Bldg, Rear 50 Murray St, Perth WA 6000, Australia. E-mail markus.schlaich@uwa.edu.au

(*Hypertension*. 2018;72:287-290.
DOI: 10.1161/HYPERTENSIONAHA.118.11532.)

***Hypertension* is available at http://hyper.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.118.11532

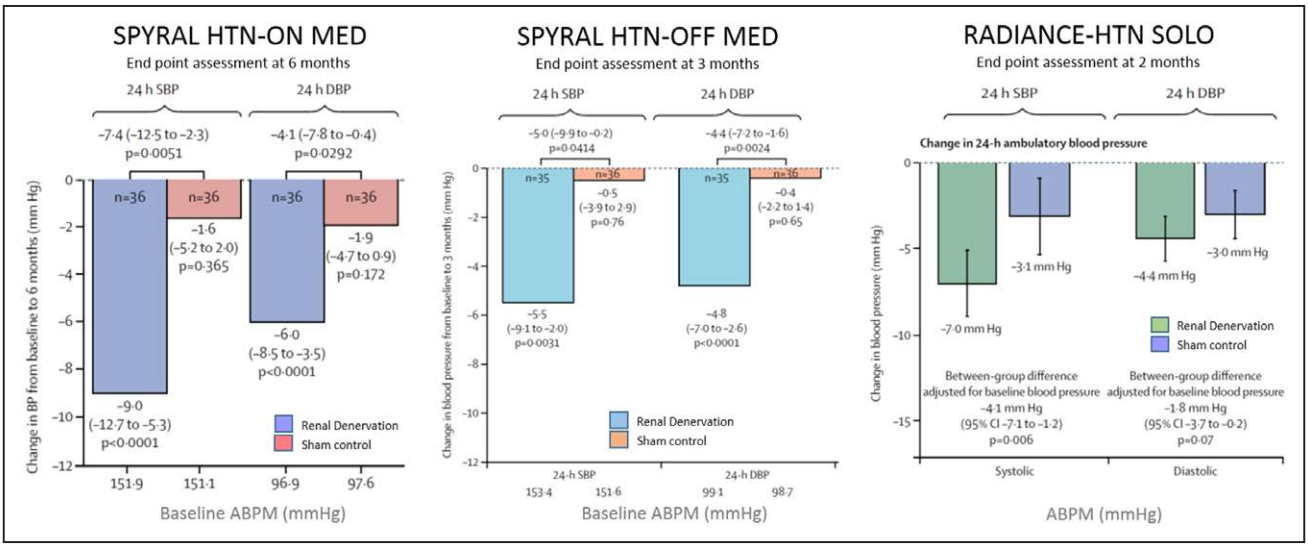

Figure 1. Comparison 24-h systolic and diastolic blood pressure (SBP and DBP) changes in renal denervation vs sham-control groups in the 3 recent randomized, sham-controlled clinical trials. ABPM indicates ambulatory BP monitoring; CI, confidence interval; HTN-ON MED, Spyral Hypertension on Medication trial; HTN-OFF MED, Spyral Hypertension OFF Medication trial; and RADIANCE-HTN SOLO, RADIANCE hypertension solo (off medication) trial. Reprinted from Kandzari et al,[1] Azizi et al,[2] and Townsend et al[3] with permission. Copyright © 2018, Elsevier.

greater at 6 months in the renal denervation group than in the sham control group for 24-hour SBP (difference, –7·4 mm Hg; 95% CI, –12·5 to –2·3; *P*=0·0051) and 24-hour diastolic BP (difference, –4·1 mm Hg; 95% CI, –7·8 to –0·4; *P*=0·0292). Adherence with prescribed medication was monitored, and analysis of urine and blood samples revealed that adherence rates were only ≈60%, despite patients being informed that respective testing would occur, thereby highlighting the averseness of many patients to maintain a stable and usually life-long medication regimen. In this context, it is reassuring that renal denervation seems to facilitate improved BP control that is sustained during the 24-hour period, including those periods during which hypertensive patients are most vulnerable to experience cardiovascular events (Figure 2B). Furthermore, if the longevity of the BP lowering effect of renal denervation can be demonstrated in longer-term follow-up studies, this is likely to translate into improved cardiovascular outcomes.

RADIANCE-HTN SOLO

While SPYRAL HTN-OFF[3] and ON MED[1] demonstrate the safety of extensive radiofrequency ablation of renal nerves in the main renal artery and its branches and provide

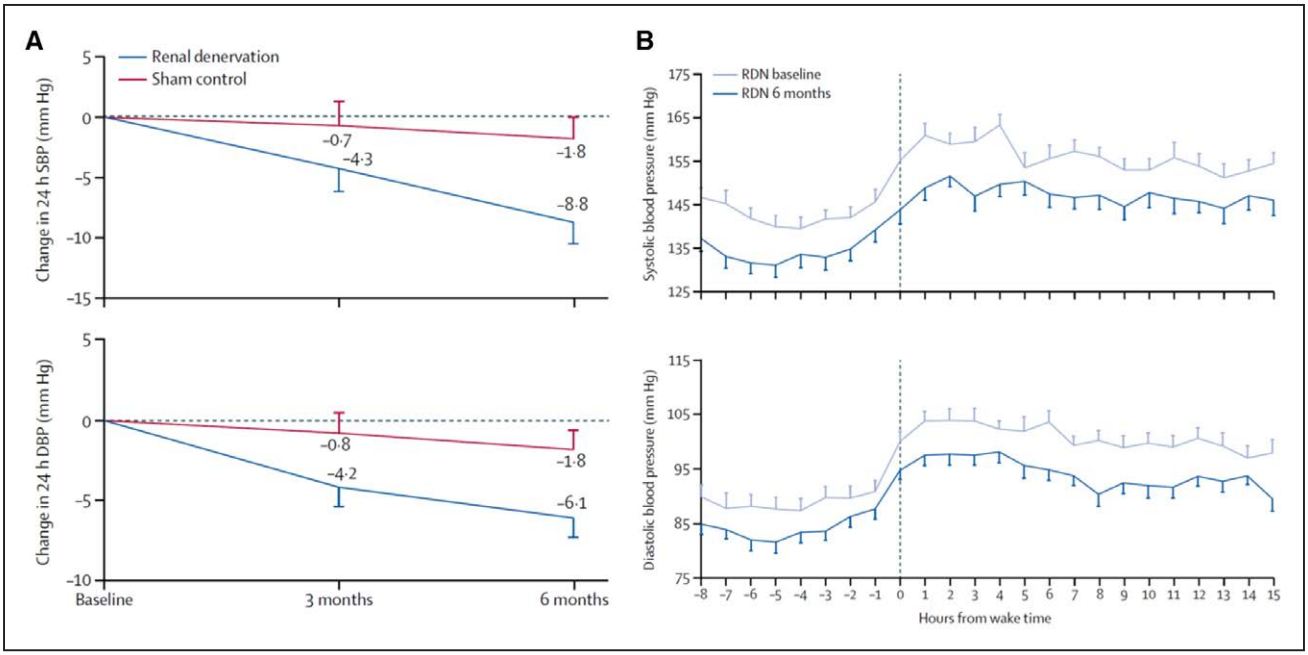

Figure 2. Time course of blood pressure lowering after renal denervation and its impact on 24-h blood pressure profile. **A**, Baseline-adjusted mean changes in 24-h systolic and diastolic blood pressure (SBP and DBP) in the SPYRAL HTN-ON MED[1] study at 3 and 6 mo follow up after renal denervation. **B**, Comparison of hourly ambulatory SBP and DBP at baseline and 6 mo after renal denervation based on patient-reported wake times. RDN indicates renal denervation. Reprinted from Kandzari et al[1] with permission. Copyright © 2018, Elsevier.

evidence for its BP lowering efficacy across a wider spectrum of hypertensive patients, including those who are drug-naive or treated with 1, 2, or 3 antihypertensive drugs, RADIANCE-HTN SOLO expands the field further with the first sham-controlled evidence for safety and efficacy of an alternative approach to successfully denervate the human kidney, namely endovascular ultrasound.[2] The circumferential energy delivery achieved by percutaneous placement of the endovascular catheter centred in the lumen of the main renal artery by a low pressure, water-filled cooling balloon creates a ring of ablation at a depth of 1 to 6 mm. A total of 5.4±1.0 ultrasound emissions were delivered with a total ablation time of 37.9±6.7 s in 74 drug-naive patients with combined hypertension, who were randomized to undergo renal denervation, whereas 72 patients underwent a sham procedure. The reduction in daytime ambulatory SBP was greater with renal denervation (–8.5±9.3 mm Hg) than with the sham procedure (–2.2±10.0 mm Hg), with a baseline-adjusted difference between groups of –6.3 mm Hg (95% CI, –9·4 to –3·1; *P*=0·0001).

This study is an important milestone in the evolving evidence around renal denervation as a safe and effective BP lowering therapy. The study was rigorously designed and executed with stringent inclusion criteria and ambulatory BP monitoring as the measure of the primary outcome. Importantly, the study was prospectively powered to demonstrate a difference in daytime ambulatory SBP compared with sham control. Adherence was only assessed through patient reporting, but no blood or urine analysis for drug metabolites was performed. Although one would perhaps anticipate that assessment of medication adherence by these means is not warranted in drug-naive patients and those whose medication was withdrawn 4 weeks before randomization, experience from the SPYRAL HTN-OFF MED[3] study demonstrated that around 10% of patients in either the renal denervation or the sham control group did use antihypertensive drugs.

Although some of the major questions have been addressed by the findings from these 2 studies, several others remain open and require further investigation to help to adequately position renal denervation as an alternative means to lower BP in the current environment: Clearly, renal denervation lowers BP in the absence and presence of concomitant antihypertensive medication. This is important as it offers a BP-lowering treatment for those patients who are intolerant to antihypertensive medication, who may elect not to take antihypertensive medication (nonadherence), as well as for those with true drug-resistant hypertension. Either way, if a reduction of ≈5 to 9 mm Hg in ambulatory SBP can reliably be achieved, as the latest studies indicate, treated patients would almost certainly benefit in the form of cardiovascular risk reduction, particularly so if the effects of a one-off procedure are sustained during a prolonged period of time, as seems to be the case based on follow-up reports out to 3 years.[8,9] However, nerve regeneration is possible, and longer term follow up is required.[12]

Of note, results from the HOPE-3 trial (Heart Outcomes Prevention Evaluation-3 [HOPE-3] Randomized Controlled Trial) in a patient cohort that is comparable to the one investigated in RADIANCE-HTN SOLO revealed that a 6/3 mm Hg office BP reduction achieved by prescription of a fixed dose combination of candesartan 16 mg/hydrochlorothiazide 12.5 mg during a period of 5.6 years was associated with a reduction in major cardiovascular events with the largest effect in those patients with a baseline systolic office BP of ≥150 mm Hg.

Questions that remain open and require further substantiation in future studies relate to the long-term safety of both the extended radiofrequency ablation approach, which currently includes branch treatment and that of ultrasound energy delivery in larger cohorts. A head-to-head comparison may be useful to determine the potential superiority of either approach, although the anatomy of the renal vasculature may dictate the preferential use of one or the other.

With pivotal trials now underway for many renal denervation devices, it is perhaps pertinent for the hypertension community to devise plans on how to best allocate the limited resources available to ensure the availability of renal denervation for those patients who are likely to benefit in a most cost-effective manner.

Disclosures

M.P. Schlaich is supported by an NHMRC (National Health and Medical Research Council of Australia) Research Fellowship and has received consulting fees and travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer-Ingelheim. M.D. Esler is supported by an NHMRC Research Fellowship and an NHMRC Program Grant and has received research support and consulting fees from Medtronic. The other author reports no conflicts.

References

1. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen SA, Fahy M, Pilcher G, Kario K; on behalf of the SPYRAL HTN-ON MED Trial Investigators. 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;391:2346–2355. doi: 10.1016/S0140-6736(18)30951–6.
2. Azizi M, Schmieder RE, Mahfoud F et al; on behalf of the RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet*. 2018;391:2335–2345. doi: 10.1016/ S0140-6736(18)31082-1.
3. Townsend RR, Mahfoud F, Kandzari DE, et al; SPYRAL HTN-OFF MED Trial Investigators. 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;390:2160–2170. doi: 10.1016/S0140-6736(17)32281-X.
4. Schlaich MP, Krum H, Sobotka PA. Renal sympathetic nerve ablation: the new frontier in the treatment of hypertension. *Curr Hypertens Rep*. 2010;12:39–46. doi: 10.1007/s11906-009-0078-6.
5. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393–1401. doi: 10.1056/NEJMoa1402670.
6. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275–1281. doi: 10.1016/S0140-6736(09)60566-3.
7. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet*. 2010;376:1903–1909.
8. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in

patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2014;383:622–629. doi: 10.1016/S0140-6736(13)62192-3.
9. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, Mahfoud F, Schlaich MP. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. *Eur Heart J*. 2014;35:1752–1759. doi: 10.1093/eurheartj/ehu209.
10. Linz D, Mancia G, Mahfoud F, Narkiewicz K, Ruilope L, Schlaich M, Kindermann I, Schmieder RE, Ewen S, Williams B, Böhm M; Global SYMPLICITY Registry Investigators. Renal artery denervation for treatment of patients with self-reported obstructive sleep apnea and resistant hypertension: results from the Global SYMPLICITY Registry. *J Hypertens*. 2017;35:148–153. doi: 10.1097/HJH.0000000000001142.
11. Böhm M, Ukena C, Ewen S, et al; Global SYMPLICITY Registry Investigators. Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry. *J Hypertens*. 2016;34:2480–2486. doi: 10.1097/HJH.0000000000001085.
12. Booth LC, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, May CN. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. *Hypertension*. 2015;65:393–400. doi: 10.1161/HYPERTENSIONAHA.114.04176.

Renal Denervation—Ready for Prime Time!?: The Steep SPYRAL Stairs to RADIANCE in Hypertension Treatment

Markus P. Schlaich, Marcio G. Kiuchi and Murray D. Esler

Hypertension. 2018;72:287-290; originally published online June 25, 2018;
doi: 10.1161/HYPERTENSIONAHA.118.11532
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563