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Position Statement on Renal Denervation in South Africa 2020

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INTRODUCTION

The recent publication of 4 Randomized Sham-controlled studies has greatly renewed interest in Renal Denervation (RDN) as an effective therapy for hypertension. Three of the studies, SPYRAL HTN-OFF MED Pilot (1), SPYRAL HTN-OFF MED Pivotal (2) and RADIANCE HTN SOLO (3), were performed in patients off medication, and a fourth, SPYRAL HTN-ON MED (4), with patients on medication. The prospective, randomized, double-blind, sham controlled SPYRAL HTN-OFF MED studies included patients with hypertension with an office systolic blood pressure (SBP) between 150 to 180mmHg, office diastolic BP >90mmHg, and ambulatory SBP of 140 to 170mmHg with no concomitant antihypertensive therapy.

The SPYRAL study procedures were performed with a radiofrequency multi-electrode catheter (SPYRAL, Medtronic, Ireland), designed to enable reliable circumferential four-quadrant ablation. Compliance with remaining off anti-hypertensive medications was confirmed by urine analysis in each patient in both the RDN and sham-control groups. In addition to in-office measurement, BP assessment was performed by 24-hour ambulatory BP to avoid bias and superadded white coating.

At 3 months in the SPYRAL OFF MED Pivotal, there was a significant difference in BP between patients treated with RDN and sham - office systolic BP by – 6.6 mmHg and diastolic BP (DBP) -4.4 mmHg and 24-hour ambulatory systolic BP -4.0mmHg and diastolic BP -3.1 mmHg (Figure 1). Differences were minimized due to 17% of sham compared to 9.6% RDN treated patients being withdrawn due to BP > 180/110 mmHg as part of pre-determined safety escape criteria. BP was also reduced throughout the 24-hour period, including the early morning period (Figure 2). RADIANCE HTN-SOLO ablated renal sympathetic nerves circumferentially using ultrasound energy and demonstrated a similar magnitude of BP reduction to SPYRAL HTN-OFF MED.

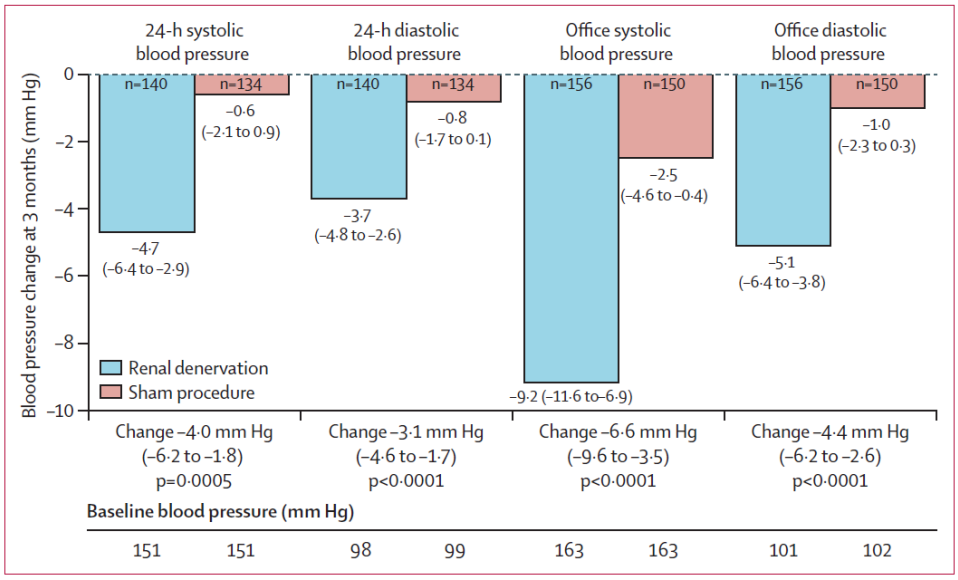


Figure 1: Change in 24-h and office systolic and diastolic blood pressure at 3 months (2).

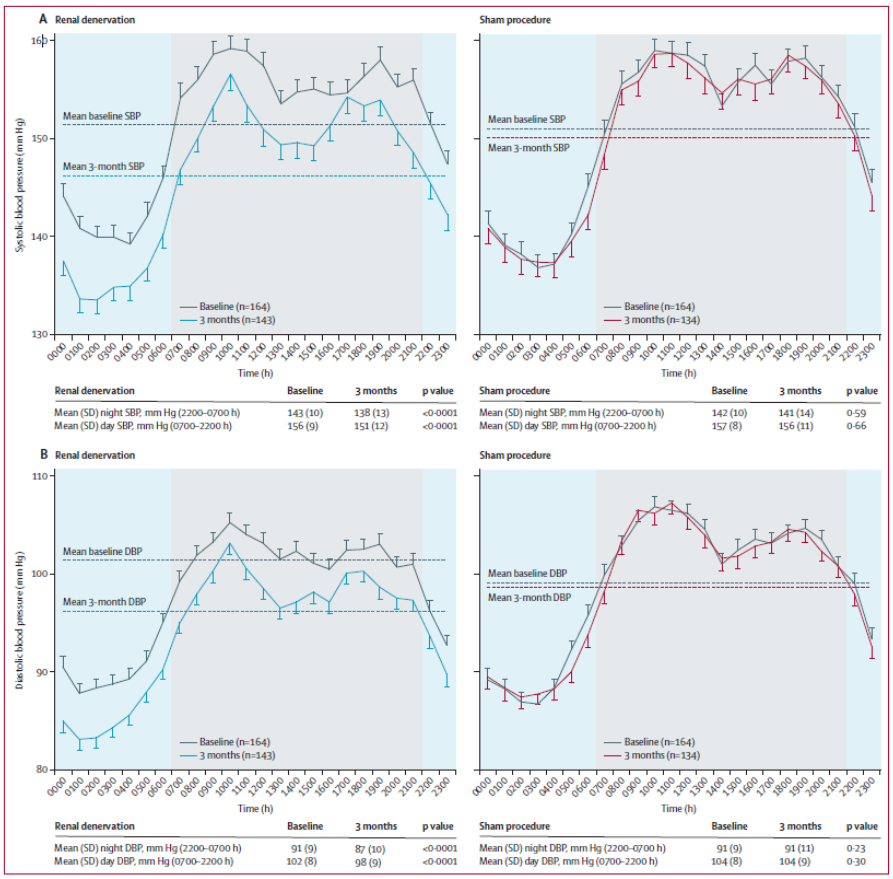


Figure 2: 24 Hour ambulatory SBP (A) and DBP (B) at Baseline and 3 months for renal denervation (2)

SPYRAL HTN-ON MED was a prospective, randomized, double-blind, sham-controlled study using the same blood pressure inclusion criteria as for the SPYRAL OFF MED study, but included uncontrolled hypertensive patients on 1 to 3 commonly prescribed antihypertensive drugs. At 3 months there was a significant difference in BP between

patients treated with RDN and sham - office systolic BP by – 6.6 mmHg and diastolic BP -4.2 mmHg and 24-hour ambulatory systolic BP -7.0 mmHg and diastolic BP -4.3 mmHg (4).

The above sham-controlled randomized studies were mandated by the United States Federal Drug Administration (FDA) following a series of studies with contradictory results and which failed to provide a clear answer to the question of whether RDN lowers blood pressure. The Symplicity HTN-1 and Symplicity HTN-2 studies (5, 6) showed profound and long-lasting office BP reduction (approximately 30/15 mmHg) after renal denervation in patients with resistant hypertension. This was followed by the single blind randomised trial, Symplicity HTN-3, which was also performed with a first-generation catheter. Ambulatory BP monitoring was the end point and it showed no significant benefit of RDN over sham procedure on ambulatory or office BP (7).

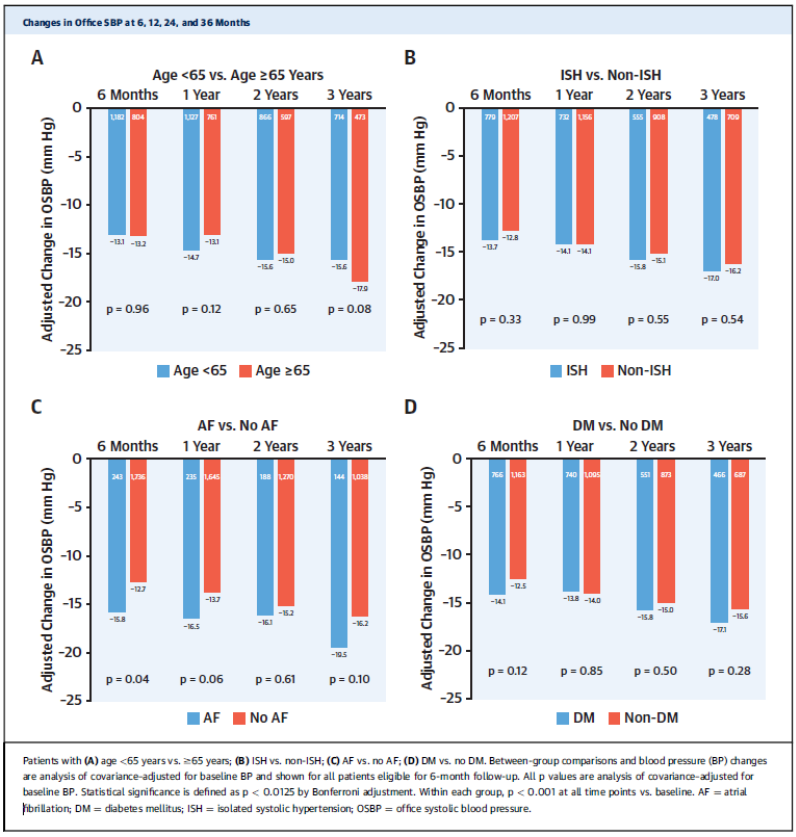
Following these results, the South African Hypertension Practice guideline in 2014 and European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) hypertension guideline did not recommend device-based Intervention for treatment of hypertension (8, 9). There were several problems with Symplicity HTN-3 that may have explained the negative result.

Firstly, it was clinically underpowered because of the impressive results of Symplicity HTN-1 and HTN-2; secondly, many operators were extremely inexperienced only performing one procedure; thirdly full bilateral denervation was not achieved in many of cases; and fourthly non-adherence at baseline and adherence in the study reduced differences between sham and active treatment (10).

Following the successful demonstration that the circumferential four quadrant ablation of both kidneys with distal and branch denervation of the kidneys performed by experienced interventionalists at high volume centres (10) as evidenced by SPYRAL HTN-OFF and ON MED studies, there have been calls by both clinicians and patients alike for guidance about the place and role of Renal Denervation in the therapy for hypertension.

The authors of this position statement believe that these studies provide evidence that RDN is effective in lowering BP in humans with or without concomitant antihypertensive medication, and the pathophysiological contribution of the renal efferent and afferent nerves in hypertension has been confirmed(10.) Although the numbers of patients enrolled in current studies are small and the duration of follow up has not been long no. major signals of harm have been noted.

The randomised sham-controlled data is supported by the real-world data from the Global Symplicity Registry (11). This showed long term BP reduction of RDN over a 3-year period including those in high risk sub-populations. Furthermore, there again was no safety signal (Figure 3).



Patients with **(A)** age <65 years vs. ≥65 years; **(B)** ISH vs. non-ISH; **(C)** AF vs. no AF; **(D)** DM vs. no DM. Between-group comparisons and blood pressure (BP) changes are analysis of covariance-adjusted for baseline BP and shown for all patients eligible for 6-month follow-up. All p values are analysis of covariance-adjusted for baseline BP. Statistical significance is defined as $p < 0.0125$ by Bonferroni adjustment. Within each group, $p < 0.001$ at all time points vs. baseline. AF = atrial fibrillation; DM = diabetes mellitus; ISH = isolated systolic hypertension; OSBP = office systolic blood pressure.

Figure 3: Changes in Office SBP at 6, 12, 24, and 36 months (11)

POSITIONING

It is now clear that Renal Denervation is as effective as a single antihypertensive drug. The great advantage of renal denervation is that efficacy is independent of adherence by the patient. It is also free of side effects related to taking drugs and has a good safety profile in the intermediate term. In real world data, it is also effective across most high-risk sub-populations. Although no long-term major outcome data on hard events are available, a 5-10 mmHg reduction in BP is likely to have substantial long-term benefits (12).

Given that recent major HTN guidelines were published before the recent RDN study results confirming efficacy and safety, the significant upfront expense of the procedure, the need for high levels of expertise and the current lack of universally available recommendations, there is an important need to provide guidance to clinicians and funders on the optimal place and role of RDN in the management of hypertensive patients.

CLINICAL PREREQUISITES

The following are the prerequisites for consideration of Renal Denervation:

1. Uncontrolled systolic hypertension with an office systolic blood pressure reading ≥150 mmHg despite patients taking optimal doses of ARB/ACE inhibitor, Calcium Channel Blocker and a diuretic plus low dose spironolactone (if not contra-indicated – eGFR < 45ml/min and serum K+ > 4.8 mmol/L
2. A 24-hour ambulatory BP monitor has to be performed to confirm uncontrolled hypertension and excluding pseudo-resistance or white coating. An abnormal BP is defined according to the SA Hypertension Guidelines 2014 as any of the following: Day time mean BP > 135/85 or night-time mean > 120/70 mm
3. The patient has had a detailed assessment by a specialist physician or sub-specialist (e.g., cardiologist, nephrologist, or endocrinologist) who is not the person performing the RDN procedure.
4. Secondary causes of hypertension have been excluded
5. RDN should be performed by an interventionalist with certified training in the procedure*.

* Certification for the procedure will be obtained after an operator has completed formal training from the supplier of the device as well as performed proctored clinical cases to a standard sufficient to be signed off by the proctor as an independent operator.

RECOMMENDATIONS

Intervention through Renal Denervation should be considered in the following circumstances:

1. In patients with uncontrolled BP as defined above or uncontrolled BP with documented intolerance to one or several antihypertensives
2. In patients with uncontrolled BP that is not remediable to long term drug adherence despite extensive counselling.
3. In hypertensive patients considered to be at very high risk of a major adverse cardiac event (MACE) according to the 2018 ESC/ESH Hypertension Guidelines to improve BP control. (13)

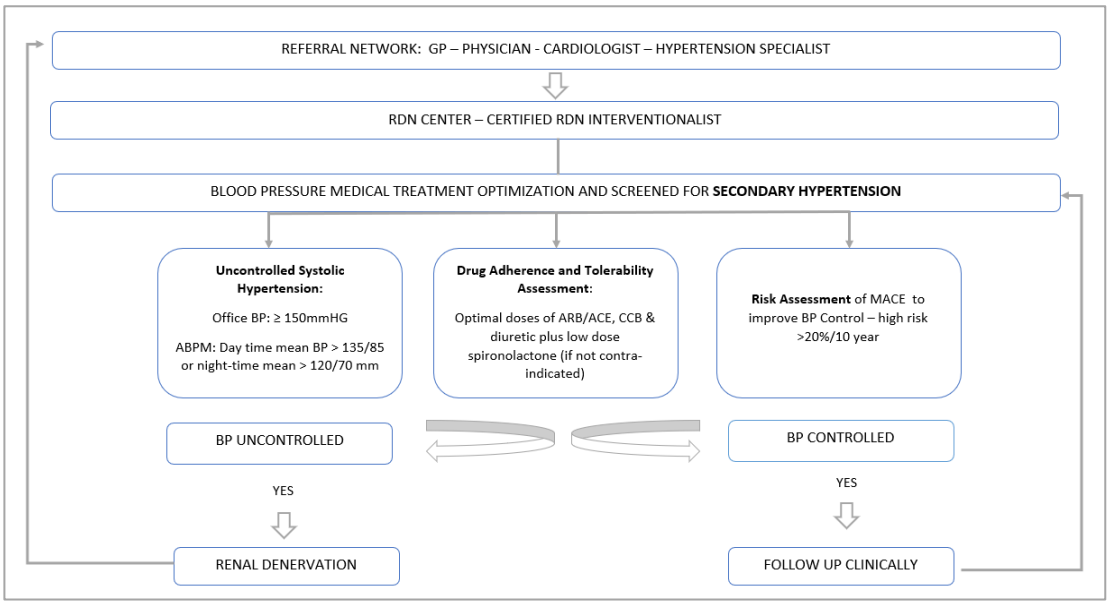


Figure 4: Proposed clinical treatment algorithm for selection of a renal denervation patient

RENAL DENERVATION CONTRA-INDICATIONS

1. Clinically significant renal artery stenosis on a pre-procedure CT renal angiogram or direct angiography at the time of the denervation. (The latter approach may reduce costs and exposure to contrast)
2. Complex renal vascular anatomy making denervation technically difficult
3. eGFR < 45mls/min
4. Pregnancy
5. Significant aortic stenosis

CONCLUSION

In conclusion, this document provides guidance to Clinicians and Funders for the indication and approval of Renal Denervation in a highly selected group of hypertensive patients. It is not meant to replace good clinical judgement in the individual patient.

REFERENCES

1. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, 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 Nov 11;390(10108):2160-2170.
2. 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 multicenter, randomised, sham-controlled trial. Lancet. 2020;395(10234):1444-51.

3. 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 multicenter, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391(10137):2335-45.
4. Kandzari DE, Bohm 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(10137):2346-55.
5. Krum H, Schlaich MP, Sobotka PA, Bohm M, Mahfoud F, Rocha-Singh K, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014;383(9917):622-9.
6. Esler MD, Bohm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. 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(26):1752-9.
7. 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.
8. Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. Cardiovasc J Afr. 2014;25(6):288-94.
9. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017.
10. Schmieder RE, Mahfoud F, Azizi M, Pathak A, Dimitriadis K, Kroon AA, et al. European Society of Hypertension position paper on renal denervation 2018. J Hypertens. 2018;36(10):2042-8.
11. Mahfoud F, Mancia G, Schmieder R, Narkiewicz K, Ruilope L, Schlaich M, et al. Renal Denervation in High-Risk Patients with Hypertension. J Am Coll Cardiol. 2020;75(23):2879-88.
12. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol 2017; 2:775–781
13. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953-2041.