Renal denervation in the presence of antihypertensive medications: Blood pressure results through six months follow-up from the randomised, blinded, sham-controlled SPYRAL HTN-ON MED trial

David E. Kandzari, MD,[1] Prof. Michael Böhm, MD,[2] Prof. Felix Mahfoud, MD,[2,3] Prof. Raymond R. Townsend, MD,[4] Prof. Michael A. Weber, MD,[5] Stuart Pocock, PhD,[6] Konstantinos Tsioufis, MD,[7] Dimitrios Tousoulis, MD,[7] James W. Choi, MD,[8] Cara East, MD,[8] Sandeep Brar, MD,[9] Sidney A. Cohen, MD,[4,9] Martin Fahy, MS,[9] Garrett Pilcher, MS,[9] and Prof. Kazuomi Kario, MD,[10] on behalf of the SPYRAL HTN-ON MED Trial Investigators*

[1]Piedmont Heart Institute, Atlanta, GA, USA; [2]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [3]Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA;[4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]SUNY Downstate College of Medicine, Brooklyn, NY ; [6]London School of Hygiene and Tropical Medicine, London, UK; [7] National and Kapodistrian University of Athens, Hippocration Hospital, Athens, Greece; [8]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX, USA; [9]Medtronic PLC, Santa Rosa, CA; [10]Jichi Medical University School of Medicine, Tochigi, Japan

Corresponding author:

David E. Kandzari, MD

Piedmont Heart Institute

Suite 2065, 95 Collier Road NW

Atlanta, Georgia 30309

USA

Tel: +1 404 605 5526

Fax: +1 404 720 0911

E-mail: david.kandzari@piedmont.org

*Members listed at end of paper

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SUMMARY

BACKGROUND: Previous catheter-based renal denervation studies reported variable efficacy results. Our study evaluated the effect of renal denervation on blood pressure (BP) in the presence of specified anti-hypertensive medications and assessment of adherence.

METHODS: SPYRAL HTN-ON MED is a multicentre, international, blinded, randomised, sham control, proof-of-concept trial (clinicaltrials.gov: NCT02439775). Patients were enrolled at 25 centres worldwide. Eligible patients were on one to three anti-hypertensive medications with stable doses for at least six weeks. Patients with an office systolic BP (SBP) ≥150 mmHg and <180 mmHg, a diastolic BP (DBP) ≥90 mmHg and a 24-hour ambulatory SBP ≥140 mmHg and <170 mmHg at second screening underwent renal angiography and were randomised to renal denervation with the Symplicity Spyral™ multielectrode catheter or sham control. Patients, caregivers, and those assessing BP were blinded to randomisation assignments. The primary endpoint, change in 24-hour blood pressure at six months, was compared between groups. Drug surveillance was used to assess medication adherence. The primary analysis was done in the intention-to-treat population. Safety events were assessed through six months.

FINDINGS: Eighty patients were randomised and followed through six months. Office and 24-hour ambulatory BP decreased significantly from baseline to six months in the renal denervation group (n=38). Mean baseline-adjusted treatment differences [95% confidence intervals] are: 24-hour SBP (-7·0 mmHg [-12·0, -2·1], p=0.0059), 24-hour DBP (-4·3 mmHg [-7·8, -0·8], p=0.0174), office SBP (-6·6 mmHg [-12·4, -0·9], p=0.0250), and office DBP (-4·2 mmHg [-7·7, -0·7], p=0.0190). Evaluation of hourly changes in 24-hour SBP and DBP showed BP reduction throughout 24 hours for the renal denervation group. Three-month BP reductions were not

significantly different between groups. Medication adherence was ~60% and varied for individual patients throughout the study. There were no major adverse events.

INTERPRETATION: Renal denervation in the main renal arteries and branches significantly reduced BP compared to sham control with no major safety events. Incomplete medication adherence was common.

FUNDING: Medtronic.

INTRODUCTION

Against the background of preclinical and early human feasibility studies demonstrating reductions in renal and systemic sympathetic tone with catheter-based renal denervation,[1,2] subsequent trials of variable size, design and method have demonstrated inconsistent blood pressure results in the setting of treatment resistant hypertension.[3–5] More recently, as an exploratory trial intended to verify biologic proof-of-concept in the absence of antihypertensive therapy, the blinded, sham-controlled SPYRAL HTN-OFF MED trial demonstrated statistically significant and meaningful blood pressure reductions in a hypertension population utilizing a revised procedural method.[6]

Despite these promising results, uncertainty regarding the efficacy of renal denervation in the setting of concurrent antihypertensive medications persists. Previous study of renal denervation amidst prescribed antihypertensive therapy has been challenged by variability in medication classes, frequent medication and dose changes and unpredictable patient adherence.[7,8] although one of these trials, performed open label, did report a significant effect of renal denervation compared with control in patients receiving antihypertensive medications.[3] However, whether changes in blood pressure associated with this method of catheter-based therapy are amplified or instead muted by pharmacotherapy is unstudied. Further, estimates regarding the temporal pattern and magnitude of blood pressure change, and comparison of these measures with those observed in the SPYRAL HTN-OFF MED trial population are only speculative.

In parallel with the SPYRAL HTN-OFF MED study, a trial of similar design was performed to evaluate the application of renal denervation in a setting more representative of

clinical practice for which integrating drug and procedural strategies may be anticipated. To this purpose, the SPYRAL HTN-ON MED study[9] was conducted to evaluate the safety and efficacy of catheter-based renal denervation for treatment of moderate, uncontrolled hypertension despite ongoing therapy with commonly prescribed antihypertensive medications.

METHODS

Trial design and patients

SPYRAL HTN-ON MED is a global, multicentre, blinded (patient and assessor), randomised, sham-controlled, proof-of-concept trial. Details of the design have been reported (Appendix, **Figure S1)**.[9] In brief, eligible patients were 20 to 80 years old with uncontrolled hypertension on one, two, or three standard antihypertensive medications. Medications were required to be prescribed at 50% or more of the maximum manufacturer's recommended dosage of a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-inhibitor/angiotensin receptor blocker (ACE-I/ARB), or a beta blocker. In Japan, patients could be prescribed less than 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care. Uncontrolled hypertension was defined as office systolic blood pressure (SBP) ≥150 and <180 mmHg, office diastolic blood pressure (DBP) ≥90 mmHg, and a mean 24-hour ambulatory SBP ≥140 and <170 mmHg. Patients were enrolled at 25 centres in the USA, Germany, Japan, United Kingdom, Australia, Austria, and Greece. The protocol was approved by all local ethics committees and all patients provided written informed consent to participate in the trial. The trial was designed in accordance with the Declaration of Helsinki and is registered at www.clinicaltrials.gov as NCT02439775

Screening and randomisation

The first screening visit was conducted to confirm that patients had been prescribed antihypertensive pharmacotherapy without change in dose for a minimum of 6 weeks and met the office blood pressure criteria for inclusion. During screening visit 2 patients knowingly underwent drug screening to assess antihypertensive mediation adherence using tandem high performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory.[10] If office blood pressure, measured using an automatic blood pressure monitor (Omron, see appendix), remained within the required range (SBP ≥150 mmHg and <180 mmHg and DBP ≥90 mmHg) patients underwent 24-hour ambulatory blood pressure monitoring (ABPM, Mobil-O-Graph; I.E.M GmbH, Stolberg, Germany). Before the ABPM was initiated, study personnel documented pill identity and observed the patient swallowing their antihypertensive medication(s) (directly observed therapy). Ambulatory blood pressure was measured every 30 minutes. A minimum of 21 daytime (7:00 to 21:59) and 12 night-time (22:00 to 6:59) measurements were required for inclusion in the analysis. The ABPM could be repeated once if the required number of readings was not reached or the average 24-hour SBP was between 135-140 mmHg or between 170-175 mmHg. Patients who met all inclusion and exclusion criteria at the second screening visit were scheduled for renal angiogram and, if anatomical suitability was confirmed, proceeded to randomisation.

Patients were randomised 1:1 to renal denervation or sham procedure. Randomisation was stratified by trial centre, using block randomisation with a block size of four. SAS-based software was used to generate the lists of randomisation codes and participants were assigned to an intervention by ICON plc via the website.

Procedure

Details of the renal denervation procedure were identical to those described in the SPYRAL HTN-OFF MED trial.[9] In brief, the Symplicity Spyral™ multielectrode renal denervation catheter (Symplicity Spyral catheter, Medtronic, Galway, Ireland), and the Symplicity G3™ renal denervation RF generator (Symplicity G3 generator) were used to provide circumferential radiofrequency ablation treatments in a spiral pattern in the four quadrants of the renal artery and branch vessels between three and eight mm in diameter. All cases were performed by experienced proceduralists and proctored using detailed treatment plans.

The control group received a sham procedure consisting of only a renal angiogram and were required to remain on the procedure table for at least 20 minutes with sensory masking post-angiogram to help prevent possible unblinding of randomisation allocation.

Maintenance of blinding

Patients and selected trial staff were blinded to the randomisation allocation. During the procedures (renal angiogram alone or followed by renal denervation) blinding was maintained by the use of conscious sedation, blindfolding, music and patients' lack of familiarity with the procedures. The blinded trial staff conducted all follow-up visits and the patient's referring/managing physicians were unaware of a patient's treatment assignment. A blinding assessment form was completed by patients and the blinded blood pressure assessors prior to discharge and at three and six-month follow-up visits. In accordance with the study protocol, blinding of patients and blood pressure assessors was maintained for up to 12 months after randomisation.

Follow-up

Patients returned for office follow-up visits at one, three and six-months post procedure. All patients underwent urine and blood analysis to assess adherence to their prescribed medications and staff witnessed patients taking their medication prior to the 24-hour ABPM at three and six months. Adherence was defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected. No antihypertensive medication changes were allowed through six months unless the escape criteria were met (office SBP exceeded 180 mmHg or was below 115 mmHg with symptoms of hypotension). Blood chemistries, including sodium, potassium, glucose and serum creatinine, were obtained at each follow-up visit as well. Estimated glomerular filtration rate (eGFR) was calculated using the four variable Modification of Diet in Renal Disease (MDRD) Formula or the local Japanese criteria for patients enrolled in Japan.[11] Renal artery imaging using duplex ultrasound was performed at the six-month office visit. MRA, CT or angiogram was suggested if the duplex ultrasound was deemed non-diagnostic.

Efficacy endpoints

The key efficacy endpoint was the blood pressure change from baseline (measured at screening visit two) based on ABPM measurements assessed at six months. This endpoint was based on the prespecified requirement for patients to be maintained on the same specified antihypertensive medication regimen through six-months follow-up. Office and 24-hour SBP and DBP were measured at three and six months post randomisation. The change in office and 24-hour blood pressure measurements were then compared between the two treatment groups.

Office and 24-hour heart rate change from baseline was assessed at six months. The rate pressure product (RPP) was then calculated using 24-hour heart rate and SBP measurements as follows: heart rate x SBP = RPP.[12,13]

Safety endpoints

Safety endpoints included all-cause mortality, end-stage renal disease, new renal artery stenosis >70% (assessed at six months), any significant embolic event resulting in end-organ damage, hospitalization for hypertensive crises not related to medication non-adherence, new myocardial infarction, new stroke, renal artery re-intervention, major bleeding, major vascular complications, dissections, perforations and increase in serum creatinine >50% from screening assessment. End-stage renal disease is defined as two or more eGFR measurements <15 mL/min/1·73 m^2 at least 21 days apart and requiring dialysis.

Statistical analysis

Like the SPYRAL HTN-OFF MED trial, the current proof-of-concept trial was designed in collaboration with and approved by the U.S. FDA with consideration of the recommendations in the 2014 Scientific Statement by the American Society of Hypertension[14] and by a consortium of investigators[15–17] that suggested a phase two-type trial in hypertensive patients. Given the uncertainty regarding the future role of renal denervation for management of hypertension after the results of SYMPLICITY HTN-3 it was decided to proceed with two smaller proof-of-concept trials that would minimize exposure of patients to an interventional procedure but have the potential to establish sufficient evidence to justify moving to a larger, powered trial. The

SPYRAL HTN-OFF MED proof-of-concept trial has been published, and this report represents the primary results of the SPYRAL HTN-ON MED trial. The protocol allowed up to 110 patients to be randomised with prospectively planned interim analyses after 40, 60, and 80 patients completed at three follow up, respectively. Because the current study prespecified that patients should be maintained on the same medication regimen through six-months follow-up, analysis of the 80-patient cohort was then performed to assess the pattern and progression of blood pressure change over time. The purpose of each interim analysis was to confirm the safety of the procedure and determine if the blood pressure lowering effect of renal denervation was sufficient to support design of future trials.

There are no powered endpoints in the trial. Statistical analyses were performed based on the intention-to-treat principle. For patients meeting escape criteria, the last observation was carried forward for the six-month blood pressure assessment. A modified intention-to-treat cohort excluded patients who met escape criteria (SBP ≥180 mmHg or <115 mmHg with symptoms). A per-protocol analysis was also performed which excluded patients meeting escape criteria, were non-adherent with their baseline anti-hypertensive regimen and who had at least one non-standardised blood pressure assessment. Analysis ofCovariance (ANCOVA) was employed to adjust for baseline blood pressure measurements. For specific daytime and night-time BP measurements, daytime was defined as 7:00AM to 9:59 PM, and night-time defined as 10:00 PM to 6:59 AM. Individual sleep/wake times were used to compare hourly BP measurements between patients where time zero was specified as wake time for patients who self-reported wake times. If a patient did not report a wake time, they were assigned a waking time of 7:00AM. Continuous variables are presented as means and standard deviations. Between group differences and blood pressure differences from baseline to the three- and six-month follow-up assessment

were tested using unpaired and paired t-tests, respectively. Counts and percentages are presented per treatment group for categorical variables; values were tested using the exact test for binary variables and the chi-square test for multilevel categorical variables.

A blinding index was calculated from the completed blinding assessment forms at hospital discharge and at three and six months to verify the effectiveness of blinding.[10]

Role of the funding source

The SPYRAL HTN-ON MED trial was funded by Medtronic. The executive committee designed the protocol and identified clinical sites in collaboration with the funder. The funder was responsible for collection, monitoring and analysis of the data. The manuscript was written by the lead author with contributions from the executive committee and co-authors. The funder assisted in figure and table generation, copy editing and formatting. The authors had unrestricted access to the data and were responsible for the decision to submit for publication.

RESULTS

Between July 2015 and September 2017, 467 patients were screened and enrolled. This analysis presents results for the first 80 patients randomly assigned to renal denervation (n=38) and sham control (n=42; **Figure 1**). Baseline clinical characteristics were similar between groups, except there were more patients with obstructive sleep apnea in the sham control group (ten vs. two patients, p=0·0277; **Table 1**). Mean baseline office and 24-hour SBP, DBP and heart rate were similar between groups.

There was no difference in the number of prescribed anti-hypertensive medication classes at baseline between groups (2·2 ± 0·9 for renal denervation and 2·3 ± 0·8 for sham control, p=0·70; **Table 1**). The proportion of patients in each treatment group prescribed 3 classes of antihypertensive medications was also similar (52·6% in the renal denervation group and 52·4% in the sham control group; p=1·00). Calcium channel blockers were prescribed in 71·1% of the renal denervation group and 73·8% of the sham control group (p=0·81), ACE-I/ARB for 81·6% and 83·3% (p=1·00), and diuretics for 57.9% and 59.5% (p=1.00). Subject adherence to prescribed medications was not consistent at different time points (**Appendix Figure S2**).

All patients underwent renal angiography and angiographic documentation of catheter position for the renal denervation group was required. During the procedure, a mean of 270·8 ± 101·6 cc of contrast was used in the renal denervation group compared with 86·0 ± 50·0 cc in the sham control group. For the renal denervation group, proceduralists performed an average of 45·9 ± 13·7 total ablations and treated an average of 2·3 ± 0·5 main arteries (19·3 ± 8·9 ablations) and 5·8 ± 2·2 branch vessels (26·6 ± 11·7 ablations; Appendix, **Table S2**).

The blinding index was 0·78 (95% CI 0·70, 0·85) at discharge, 0·68 (0·57, 0·79) at 3 months and 0·64 (0·54, 0·74) at 6 months, indicative of effective blinding.[18]

Adherence was similar between groups (at baseline, 65·8% for renal denervation and 59·5% for sham control, p=0·65; at three months, 52·6% vs. 57·1%, p=0·82; at six months, 60·5% vs. 64·3%, p=0·82; **Appendix Table S3**). Anti-hypertensive medications not prescribed by

physicians were detected in 10-15% of patients at each time point. There were no significant differences in baseline laboratory values or in six-month change in values between renal denervation and sham control groups (Appendix, **Table S4**).

Changes in SBP and DBP from baseline to six months for both 24-hour ambulatory and office measurements in the renal denervation and sham control groups are displayed in **Figure 2 and Table 2**. The change in blood pressure was significantly greater at six months for the renal denervation group vs. sham control for office SBP (difference -6·8 mmHg [-12·5, -1·1], p=0·0205), 24-hour SBP (difference -7·4 mmHg [-12·5, -2·3], p=0·0051), office DBP (difference -3·5 mmHg [-7·0, -0·0], p=0·0478) and 24-hour DBP (difference -4·1 mmHg [-7·8, -0·4] p=0·0292). Individual changes in 24-hour and office BP at six months are displayed in Appendix **Figure S3**. Comparison of changes in 24-hour blood pressure measurements at three and six months for renal denervation and sham control groups is shown in **Figure 3**, where blood pressure reduction for the renal denervation group was greater at six months compared to three months. Three-month changes in office and 24-hour ambulatory BP are listed in Appendix **Table S5**, and BP measurements at baseline and three and six months for all available patients in Appendix **Table S6**. Hourly changes in ambulatory SBP and DBP for renal denervation and sham control groups at baseline and six months are presented in **Figure 4**.

Six-month changes in 24-hour and office SBP and DBP in the two treatment groups for the adherent patients and those incompletely or not adherent are shown in Appendix **Figure S4**. All patients receiving renal denervation had a significant drop from baseline at six months but between group differences are not significant in the adherent patients. The sham control response was minimal in the incomplete/nonadherent group and 24-hour SBP was significantly different between renal denervation and sham in these patients.

Comparison of six-month changes, adjusted for baseline measures using ANCOVA, also showed significant differences, with a 24-hour SBP between group difference of -7.0 mmHg [-12·0, -2·1], p=0·0059 and 24-hour DBP between group difference of -4·3 mmHg [-7·8, -0·8], p=0·0174. Office SBP difference was -6·6 [-12·4, -0·9], p=0·0250 and office DBP difference was -4·2 mmHg [-7·7, -0·7], p=0·0190 (**Table 2**). Results for the modified ITT population provided similar outcomes (**Appendix, Table S7**). The small number of patients in the per-protocol population (15 renal denervation and 14 control patients) limits comparison of outcomes.

There was no significant difference in office or 24-hour heart rate at six months (**Table 2**). To further explore the effect of renal denervation on heart rate and blood pressure the RPP was analysed (**appendix Figure S5**). The hourly 24-hour RPP change at six months was lower in the renal denervation patients at all time points. This consistent change over time was not observed in the sham control group.

Similar to reported results for SPYRAL HTN-OFF MED,[6] there were no procedural or safety events through six months follow up in SPYRAL HTN-ON MED (Appendix, **Table S8)**.

DISCUSSION

In this trial designed to explore the safety and efficacy of catheter-based renal denervation in moderate, uncontrolled hypertension despite specified antihypertensive therapy, the salient findings of this study are: (1) in patients receiving medical therapy, renal denervation extending into branch arteries was associated with statistically significant and clinically relevant reductions

in office and ambulatory measures compared with a sham procedure; (2) the extent of blood pressure reduction with renal denervation increased over temporal follow-up through six months; (3) no procedural- or intermediate-term adverse safety events associated with renal denervation were observed; and (4) non-adherence to antihypertensive medications was common. These promising results both encourage further study with this method of renal denervation for persistent hypertension despite the prescription of medical therapy and inform the design and conduct of subsequent trials.

Similar to the SPYRAL HTN OFF-MED study[6] and unlike prior investigations of renal denervation,[3–5] the ON MED trial differs considerably regarding the patient population enrolled, procedural method and restriction to selected antihypertensive medication classes. Regarding the latter feature, antihypertensive therapy was limited to four pharmaceutical categories (ACE inhibitors/ARBs, calcium channel blockers, beta blockers, and thiazide diuretics) routinely prescribed in clinical practice in part to minimize potential confounding suggested in previous studies.[4,19] Further, enrolled patients had moderate, combined hypertension[20] (mean office SBP 164·6 ± 7·1 mm Hg and DBP 99·9 ± 6·9 mm Hg) requiring up to three antihypertensive agents in comparison, for example, with the SYMPLICITY HTN-3 study in which the mean office SBP was 179·7 ± 16·1 mm Hg with no diastolic requirement in patients prescribed an average 5·1 medications. Also, like the SPYRAL HTN-OFF MED study, renal denervation using a multi-electrode catheter that permitted simultaneous or sequential energy delivery to the main renal arteries with extension into distal renal artery branches was performed to enable more complete, circumferential ablative treatment based on an evolving understanding in renal nerve anatomy[1,21,22] and procedural technique.[8]

Investigation of renal denervation in the setting of concurrent medical therapy for hypertension was necessary to better understand the role of device therapy in clinical indications anticipated to be common in routine patient care. Specifically, in the treatment of difficult to control hypertension, consideration of an interventional therapy may factor into the decision process after patients have been prescribed guideline-recommended drug therapy[11,23–25] that commonly begins with one or two medications and may eventually include a third agent in more difficult cases. By 24-hour ambulatory measurement at six months, average systolic and diastolic blood pressure reductions were 9 and 6 mm Hg, respectively, with a corresponding similar magnitude of decline in office systolic and diastolic measures. Importantly, the magnitude of blood pressure decline is clinically significant, associated with lower rates of both cardiovascular events and mortality in prior studies.[26–28] Notably, the absolute reduction in 24-hour ABPM at three months in this study was similar that observed in the SPYRAL HTN-OFF MED study,[6] despite greater variance in the sham control cohorts. Yet a progressive trend for the fall in blood pressure was observed across all blood pressure measures in the renal denervation cohort between three and six months raising the possibility that further time may be required to fully realize the benefit of renal denervation therapy associated with resetting of systemic sympathetic tone.

In comparison with office measurement that has been associated with greater variability,[29] 24-hour ABPM demonstrated directionally consistent findings at three and six months with progressive blood pressure decrease in the treatment group and in parallel, relatively modest change in the control group. Compared with traditional office measurement changes, variance in 24-hour ambulatory blood pressure is less susceptible to measurement bias, placebo effects, and day-to-day variability. This method provides more stable and reproducible blood

pressure values than office or random home measurements,[30] and the ability to provide frequent, serial blood pressure readings permits dynamic assessment over a time course that yields prognostic relevance associated with reduced nocturnal blood pressure fall,[31] increased short-term blood pressure variability[32] and excessive morning blood pressure surge.[33] In addition, ambulatory blood pressure is also more strongly correlated with cardiovascular risk than office measures,[34,35] and the extent of ambulatory blood pressure reduction in the present study is consistent with that deemed clinically meaningful by expert consensus.[15,16]

As another revision to trial conduct compared with most prior renal denervation studies, inclusion of surveillance methods to objectively document protocol adherence was important to interpreting results of an interventional therapy in the presence of prescribed pharmacologic therapy. Monitoring is informative given that imbalances in drug adherence between treatment groups may either over- or underestimate the treatment effect observed with the experimental therapy. Indeed, in both previous pharmacologic and renal denervation studies for hypertension, medical adherence despite protocol mandate is largely unpredictable as it was not objectively measured. Among contemporary studies involving renal denervation, for example, the prevalence of medical non-adherence commonly approaches 50%, with 5% to 30% of patients demonstrating complete absence of prescribed medical therapy by biochemical assay.[36] For those patients treated with a standardised antihypertensive regimen and randomised in open-label fashion to renal denervation or control in the DENER HTN trial, only half of patients were fully adherent to drug therapy by urine and blood analysis performed at six months.[7] The present study confirms observations regarding the frequency of medical non-adherence in hypertension trials and also highlights the dynamic pattern and influences of patient behaviour in the context of protocol mandate and pre-existing awareness of drug surveillance. Despite documentation of a

stable drug regimen for at least two months prior to randomisation and requirement of only 50% maximal dose, adherence with prescribed medical therapy was approximately 60% with highly variable individual patient adherence at all timepoints (**Appendix, Figure S2**). If the benefit of renal denervation is proven consistent and durable in future study, a constant, 'always on' treatment effect distinguishes it from pharmaceutical therapy reliant upon patient daily action and complicated by intolerances, dosing frequency or other common issues that challenge adherence. Further, the more constant reduction in sympathetic tone with renal denervation may reduce variation in blood pressure control associated with pharmaceutical trough levels, especially at early morning and evening levels. Supporting this premise, ambulatory readings demonstrate persistent blood pressure suppression at all time points during the 24-hour period for patients treated with renal denervation. Combining blood pressure with heart rate, 24-hour lowering of the RPP may also support a more consistent reduction in sympathetic activity.

Altogether, these results reaffirm the safety and efficacy of renal denervation observed in previous trials but further extend our understanding in the context of medical therapy and with a modified procedural technique. Nevertheless, limitations exist to the present study. As an exploratory, proof-of-concept trial, the study did not prespecify a hypothesis for differences in blood pressure measurements at any particular time interval. If the analyses were prespecified, however, assuming a treatment difference of 7 ± 11 mm Hg between renal denervation and sham control groups, and two-sided alpha level of 0·05, a sample size of 80 patients (40 per cohort) would provide 80% statistical power to reject the null hypothesis of no treatment difference between groups. Instead, the investigational plan included prospectively planned interim analyses to ascertain whether an adequate treatment effect with acceptable reduction in blood

pressure variability in the control cohort could be achieved and therefore inform further study. To this purpose, a particular limitation—and challenge for future investigation— relates to the prevalence of medical non-adherence despite patient education and awareness of drug testing. Although absence of detectable drug at a single timepoint implies more frequent non-adherence, it is not predictable for a single patient at interval assessments, and increasing recognition of this potential confounder as common among both pharmaceutical and device trials raises the question whether such assays should be imposed as common practice in hypertension trials. In part related to this issue, the present findings are suggestive of effect in both adherent and non-adherent populations but cannot confirm the benefit of renal denervation among patients with higher drug adherence given the small sample size. Nevertheless, the prevalence of both number of medications and adherence were similar in both groups, and critically, as previously stated, ambulatory blood pressure measurements were obtained only following witnessed pill ingestion in all patients. For the same reasons related to size of the study population, the safety of renal denervation involving main artery and branch treatment cannot be confirmed; however, the absence of safety events through six months in the current study is consistent with none observed at three months applying the same procedural method in the SPYRAL HTN-OFF MED trial.[6] Also, as in prior studies of renal denervation, there is no measure of effective renal nerve ablation; however, the number of ablations per patient and procedural technique were similar to those observed in the SPYRAL HTN-OFF MED trial that demonstrated similar and significant reductions in 24-hour blood pressure at three months using the same procedural method and technology. In addition, the inclusion criteria in the protocol for number of required antihypertensive medications was revised during enrollment to allow patients to be on up to three medications, instead of exactly three, to facilitate enrollment. We did not assess sodium intake or

impose any restrictions on dietary or lifestyle habits (e.g., smoking), and these factors could have influenced blood pressure measurements. Finally, the results observed with this therapy and in this specific population may not be generalizable to more varied clinical populations and alternative interventional therapies for hypertension or medication classes not represented in this trial.

In conclusion, we found clinically and statistically significant greater reductions in blood pressure six months post-renal denervation compared to the sham control group. Both main renal arteries and branches were treated with no major safety events. Although patients were aware of planned medication adherence assessments, roughly half the patients were not adherent to their prescribed anti-hypertensive medication regimen.

Contributors

DK, MB, FM, RT, MW, SP, GP, SB, SC, and KK participated in the design of the study. DK, KT, DT, JC and CE participated in patient data collection. All authors were involved in interpretation of the data. MF was the study biostatistician responsible for the statistical analyses. DK, MB, FM, RT, MW, SP, GP, SB, SC and MF participated in writing of the report. All authors agreed on the content of the manuscript, reviewed drafts, and approved the final version.

Declarations of Interest

DK receives institutional support for conduct of clinical trials from Medtronic and research/grant support and consulting honoraria for work unrelated to present submission. MB receives honoraria for lectures and scientific advice from Abbott, Astra-Zeneca, BMS, Boehringer-Ingelheim, Medtronic and Servier. FM is supported by Deutsche Hochdruckliga and Deutsche Gesellschaft für Kardiologie and has received speaker honoraria and consultancy fees from Medtronic and Recor. SP receives consultant fees from Medtronic during the conduct of the study. RT receives institutional support for conduct of clinical trials from Medtronic and consultant fees for trial design and management from Medtronic. MW receives consultant fees for trial design and management from Medtronic and from Boston Scientific, ReCor and Omron. KT receives personal fees and institutional support for conduct of clinical trials from Medtronic. SB, SAC, MF and GP are employees of Medtronic. KK receives personal fees from Medtronic during the conduct of the study; grants from Teijin Pharma, Omron Healthcare, FUKUDA DENSHI, Bayer Yakuhin, A & D, Daiichi Sankyo, Mochida Pharmaceutical, EA pharma, Boehringer Ingelheim Japan, Tanabe Mitsubishi Pharma Corporation, Shionogi & Co., MSD K.K., Sanwa Kagaku Kenkyusho and Bristol-Myers Squibb K.K.; personal fees from Takeda Pharmaceutical and Omron Healthcare outside the submitted work. The other authors have nothing to disclose.

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***Collaborators:** Jiro Aoki, MD and Kengo Tanabe, MD from Mitsui Memorial Hospital , Tokyo, Japan; Bryan Batson, MD and Robert Wilkins, MD from Hattiesburg Clinic, Hattiesburg, MS, USA; Michael Böhm, MD and Felix Mahfoud, MD from Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes , Homberg/Saar, Germany; James W. Choi, MD and Cara East, MD from Baylor Jack and Jane Hamilton Heart and Vascular Hospital in Dallas, TX, USA; Debbie L. Cohen, MD and Robert Wilensky, MD from Perelman School of Medicine, University of Pennsylvania in Philadelphia, PA, USA; George Dangas, MD and Johanna Conteras, MD from The Mount Sinai Hospital, New York, NY, USA; Shukri David, MD and Susan Steigerwalt, MD from Providence Park Hospital, Southfield, MI, USA; Justin Davies, MD and Neil Chapman, MD from Imperial College and Hammersmith Hospital in London, United Kingdom; Chandan M. Devireddy, MD and Janice P. Lea, MD, MSc from Emory University School of Medicine, Atlanta, GA, USA; David Kandzari, MD and Denise Reedus, DNP from Piedmont Atlanta Hospital, Atlanta, GA, USA; Kazuomi Kario, MD and Satoshi Hoshide, MD from Jichi Medical University School of Medicine, Tochigi, Japan; David P. Lee, MD and Adrian Ma, MD from Stanford Hospital & Clinics, Stanford, CA, USA; Philipp C. Lurz, MD, PhD and Karl Fengler, MD from University of Leipzig – Heart Center, Leipzig, Germany; Vasilios Papademetriou, MD and Ping Li, MD from Veterans Affairs Medical Center, Washington, DC, USA; Manesh Patel, MD and Laura Svetkey, MD from Duke University Medical Center, Durham, NC, USA; Kiritkumar Patel, MD and Anjani Rao, MD from St. Joseph Mercy Oakland, Pontiac, MI, USA; Roland E. Schmieder, MD and Axel Schmid, MD from

Universitätsklinikum Erlangen, Erlangen, Germany; Andrew S.P. Sharp, MD and Anthony F Watkinson, MBBS from The Royal Devon and Exeter Hospital, Exeter, United Kingdom; Jasvindar Singh, MD and Angela Brown, MD from Barnes-Jewish Hospital, St. Louis, MO, USA; Konstantinos Tsioufis, MD and Dimitrios Tousoulis, MD from University of Athens, Hippocratio Hospital, Athens, Greece; Antony Walton, MD and Ingrid Hoppper, PhD from The Alfred Hospital, Melbourne, Australia; Thomas Weber, MD and Markus Suppan, MD from Klinikum Wels-Grieskirchen, Wels, Austria; Joachim Weil, MD and Tolga Agdirlioglu, MD from Sana Cardiomed Heart Center, Lübeck, Germany; Thomas Zeller, MD and Elias Noory, MD from Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany; Khaled Ziada, MD and Craig Chasen, MD from University of Kentucky Albert B Chandler Hospital, Lexington, KY, USA.

Research in Context

Evidence before this study

We searched PubMed using the search terms “renal denervation”, “hypertension” and clinical trial for papers published from November 1, 2012, to February 1, 2018. 34 clinical trial reports of renal denervation for treatment of hypertension were identified, as well as 46 systematic reviews, consensus statements, or meta-analyses published from Jan 1, 2015, to February 1, 2018. In addition, a search for “renal denervation,” “hypertension” and “medication adherence” identified 25 clinical trial reports of renal denervation in the presence of medication adherence assessment.

Added value of this study

This trial addresses the application of renal denervation in a setting representative of clinical practice for which integrating drug and procedural strategies may be anticipated. Although not powered for efficacy endpoints, renal denervation inpatients receiving medical therapy for moderate, uncontrolled hypertension, was safe and associated with significant and clinically relevant reductions in blood pressure measures compared with a sham procedure. The temporal pattern of blood pressure reduction with renal denervation is characterized with progressive reduction through six-month follow-up. Frequent non-adherence to medical therapy informs the design and conduct of future trials.

Implications of all the available evidence

The results of the proof of concept study reaffirm the safety and efficacy of renal denervation observed in previous trials but further extend our understanding in the context of medical therapy and with a modified procedural technique. The findings both encourage further study with this

method of renal denervation for persistent hypertension despite the prescription of medical therapy and inform the design and conduct of subsequent trials.

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641 **Table 1:** Patient characteristics, blood pressure measurements, and anti-hypertensive medications at

642 baseline.

Characteristic Mean (SD) or N (%)	**Renal Denervation Group (N=38)**	**Sham Procedure Group (N=42)**
Age (years)	53·9 (8·7)	53·0 (10·7)
Male	33 (86·8)	34 (81·0)
BMI (kg/m^2)	31·4 (6·4)	32·5 (4·6)
Race		
White	13 (34·2)	15 (35·7)
Black/African American	4 (10·5)	5 (11·9)
Asian	0 (0·0)	1 (2·4)
Not reportable per local laws/regulations	18 (47·4)	20 (47·6)
Diabetes (all type 2)	5 (13·2)	8 (19·0)
Current smoker	8 (21·1)	11 (26·2)
Obstructive sleep apnea	2 (5·3)	10 (23·8)
Peripheral artery disease	0 (0·0)	0 (0·0)
Coronary artery disease†	1 (2·6)	1 (2·4)
Stroke and transient ischemic attack†	0 (0·0)	1 (2·4)
Myocardial infarction/Acute coronary syndrome	0 (0·0)	0 (0·0)
Office SBP (mm Hg)	164·6 (7·1)	163·5 (7·5)
Office DBP (mm Hg)	99·6 (6·9)	102·7 (8·0)
Mean 24-hour SBP (mm Hg)	152·1 (7·0)	151·3 (6·8)
Mean 24-hour DBP (mm Hg)	97·2 (6·9)	97·9 (8·4)
Office heart rate (bpm)	75·6 (11·8)	73·5 (10·4)
24-hour heart rate (bpm)	75.3 (11.3)	75.6 (10.7)
Number of anti-hypertensive medication classes		
Mean (SD)	2·2 (0·9)	2·3(0·8)
Median [1st IQR, 3rd IQR]	3·0 [1·0, 3·0]	3·0 [1·0, 3·0]
Prescribed medication classes:		
1	11 (28·9)	9 (21·4)
2	7 (18·4)	11 (26·2)
3	20 (52·6)	22 (52·4)
4	0 (0·0)	0 (0·0)
Medication class:		
Diuretic	22 (57·9)	25 (59·5)
Calcium channel blocker	27 (71·1)	31 (73·8)

ACE-I/ARB	31 (81·6)	35 (83·3)
Beta blocker	4 (10·5)	6 (14·3)

643 †These events occurred more than six months before randomisation.

644 Data are n (%), mean (SD) or median [1st IQR, 3rd IQR].

645 All comparisons of baseline medications between renal denervation and sham control groups were non-
646 significant.
647

648 BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per
649 minute; SD: standard deviation; IQR: interquartile range
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Table 2: Baseline blood pressure and changes at six months in intent-to-treat (ITT) population. 95% confidence intervals and p-values are included for each comparison. Baseline BP and changes at six months presented as mean ± SD, and mean differences expressed with [95% confidence intervals].

	Renal Denervation Group			Sham Control Group			Mean Difference: Renal Denervation vs Sham Control	
	N	Baseline BP	Change at six months	N	Baseline BP	Change at six months	Unadjusted[1]	Baseline Adjusted[2]
Office SBP	38	164·6 ± 7·1	-9·4 ± 12·5	40	163·1 ± 7·2	-2·6 ± 12·9	-6·8 [-12·5, -1·1] p=0·0205	-6·6 [-12·4, -0·9] p=0·0250
Office DBP	38	99·6 ± 6·9	-5·2 ± 7·6	40	102·3 ± 8·0	-1·7 ± 7·9	-3·5 [-7·0, -0·0] p=0·0478	-4·2 [-7·7, -0·7] p=0·0190
Office HR	38	75·6 ± 11·8	-5·1 ± 7·6	40	73·6 ± 10·3	-3·2 ± 7·9	-2·0 [-5·5, 1·5] p=0·2628	-1·4 [-4·7, 1·8] p=0·3863
24-Hour SBP	36	151·9 ± 7·1	-9·0 ± 11·0	36	151·1 ± 6·8	-1·6 ± 10·7	-7·4 [-12·5, -2·3] p=0·0051	-7·0 [-12·0, -2·1] p=0·0059
24-Hour DBP	36	96·9 ± 6·9	-6·0 ± 7·4	36	97·6 ± 8·3	-1·9 ± 8·2	-4·1 [-7·8, -0·4] p=0·0292	-4·3 [-7·8, -0·8] p=0·0174
24-Hour HR	36	75·5 ± 11·4	-3·7 ± 6·0	36	76·2 ± 10·2	-1·5 ± 6·6	-2·2 [-5·1, 0·8] p=0·1509	-2·3 [-5·1, 0·4] p=0·0944
Daytime SBP	36	156·4 ± 8·1	-8·8 ± 11·3	36	157·4 ± 8·4	-3·2 ± 11·4	-5·7 [-11·0, -0·3] p=0·0390	-6·1 [-11·2, -1·1] p=0·0181

Daytime DBP	36	101·0 ± 7·1	-6·3 ± 7·9	36	102·7 ± 9·3	-2·8 ± 8·3	-3·5 [-7·3, 0·3] p=0·0691	-4·1 [-7·7, -0·4] p=0·0297
Nighttime SBP	37	144·9 ± 11·0	-9·8 ± 13·9	38	141·0 ± 8·5	2·1 ± 13·5	-11·9 [-18·2, -5·6] p=0·0003	-10·0 [-16·0, -3·9] p=0·0016
Nighttime DBP	37	90·5 ± 10·6	-5·9 ± 9·7	38	89·5 ± 8·9	-0·3 ± 10·2	-5·6 [-10·2, -1·1] p=0·0167	-5·1 [-9·1, -1·1] p=0·0134

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation

[1] p-value from unpaired t-test

[2] Treatment difference and p-value from ANCOVA model, adjusting for baseline BP

Figure legends

Figure 1: Trial profile

ITT: Intention-to-treat; mITT: modified intention-to-treat; PPP: per-protocol population

Figure 2: Change at 6 months in office and ambulatory SBP and DBP for treatment and sham control patients. Results are expressed as mean (95% confidence intervals).

SBP: systolic blood pressure; DBP: diastolic blood pressure

Figure 3: Mean changes in ambulatory 24-hour blood pressure measurements at three and six months, adjusted for baseline values.

Figure 4:

Hourly measurements, according to patient-recorded individual wake times; error bars represent the standard error.

A) 24-hour ambulatory SBP at baseline and six months for renal denervation group. Wake time (W) was reported by 25 patients at baseline and 34 patients at six months and was set to 7:00AM for those patients not reporting.

B) 24-hour ambulatory SBP at baseline and six months for sham control group. Wake time (W) was reported by 33 patients at baseline and 37 patients at six months and was set to 7:00AM for those patients not reporting.

C) 24-hour ambulatory DBP at baseline and six months for renal denervation group. Wake time (W) was reported by 25 patients at baseline and 34 patients at six months and was set to 7:00AM for those patients not reporting.

D) 24-hour ambulatory DBP at baseline and six months for sham control group. Wake time (W) was reported by 33 patients at baseline and 37 patients at six months and was set to 7:00AM for those patients not reporting.

Figure 1: Trial profile

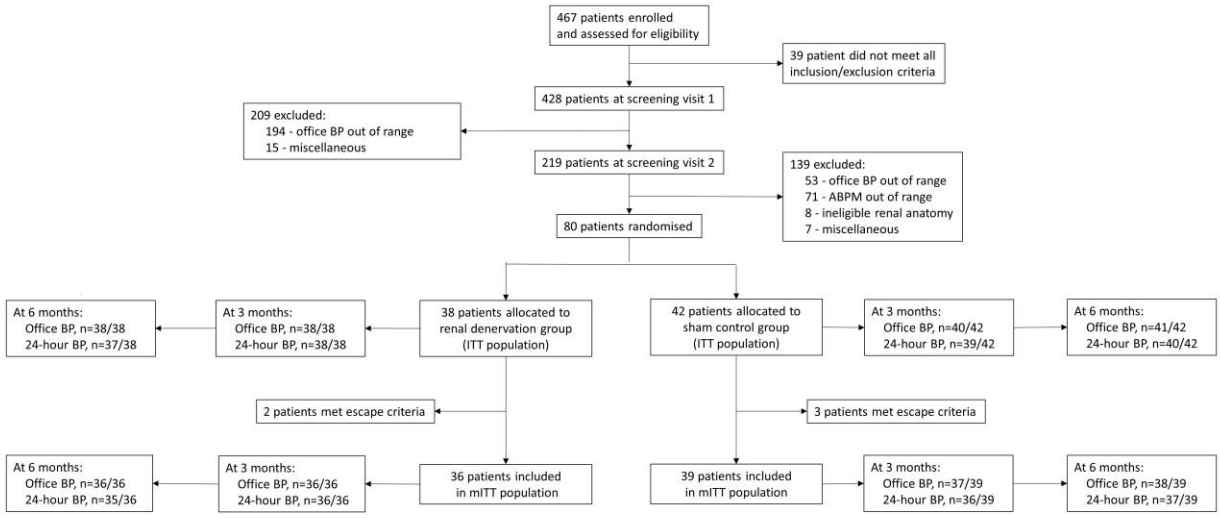


Figure 2: Change at 6 months in office and ambulatory SBP and DBP for treatment and sham control patients. Results are expressed as mean (95% confidence intervals).

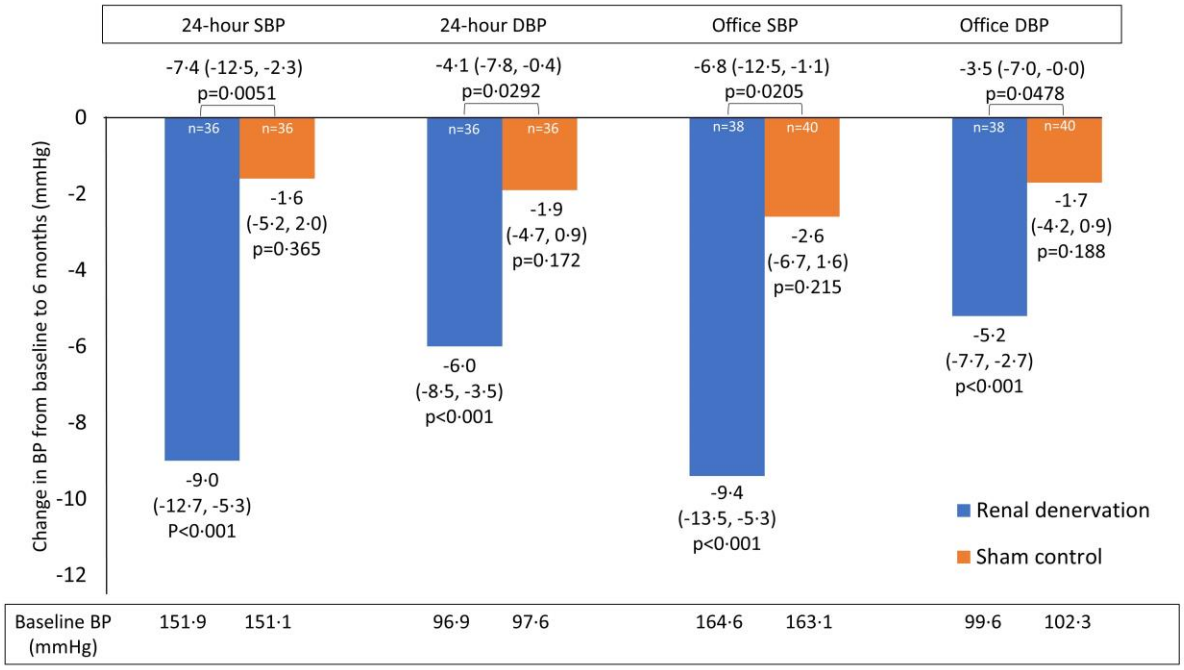


Figure 3: Mean changes in ambulatory 24-hour blood pressure measurements at three and six months, adjusted for baseline values.

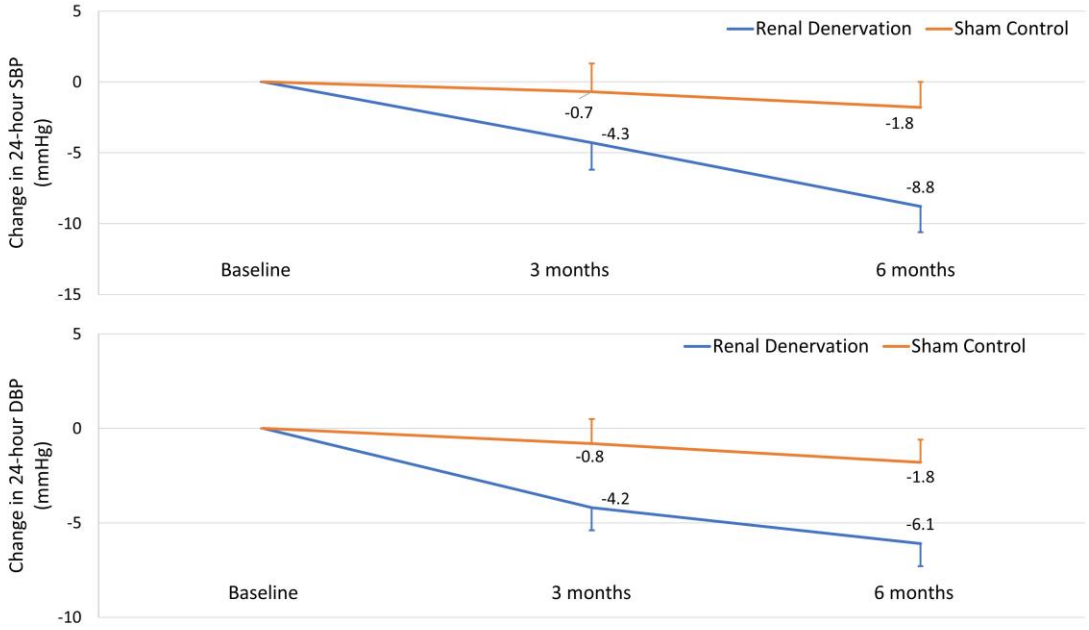
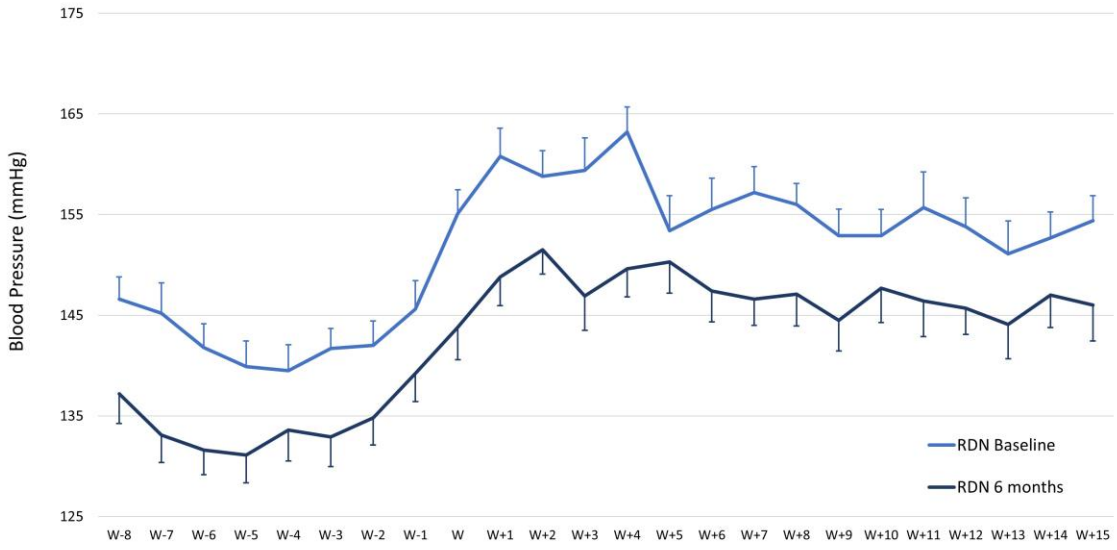


Figure 4:

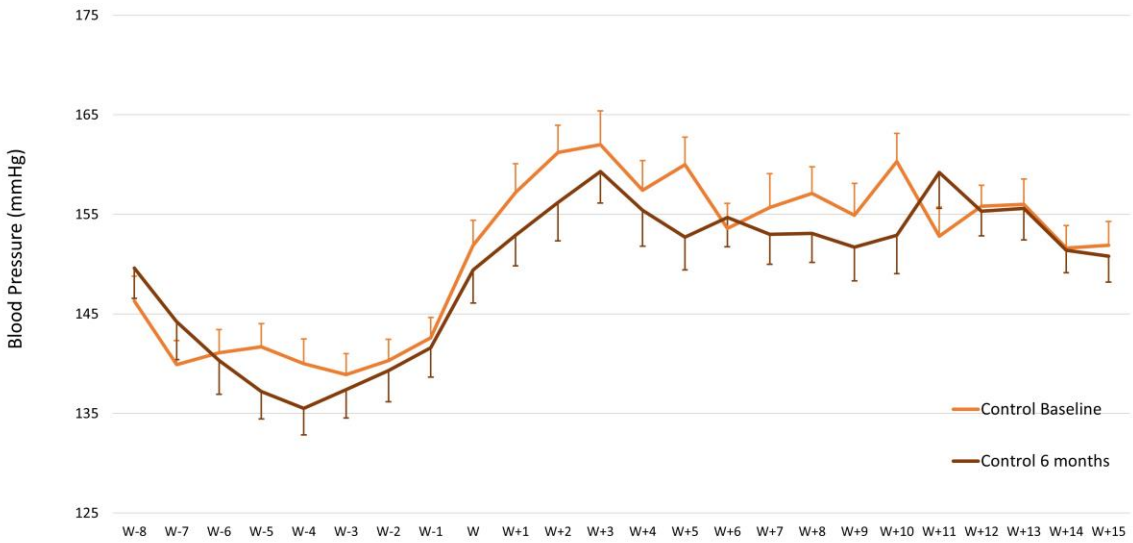
Hourly measurements, according to patient-recorded individual wake times; error bars represent the standard error.

A) 24-hour ambulatory SBP at baseline and six months for renal denervation group.



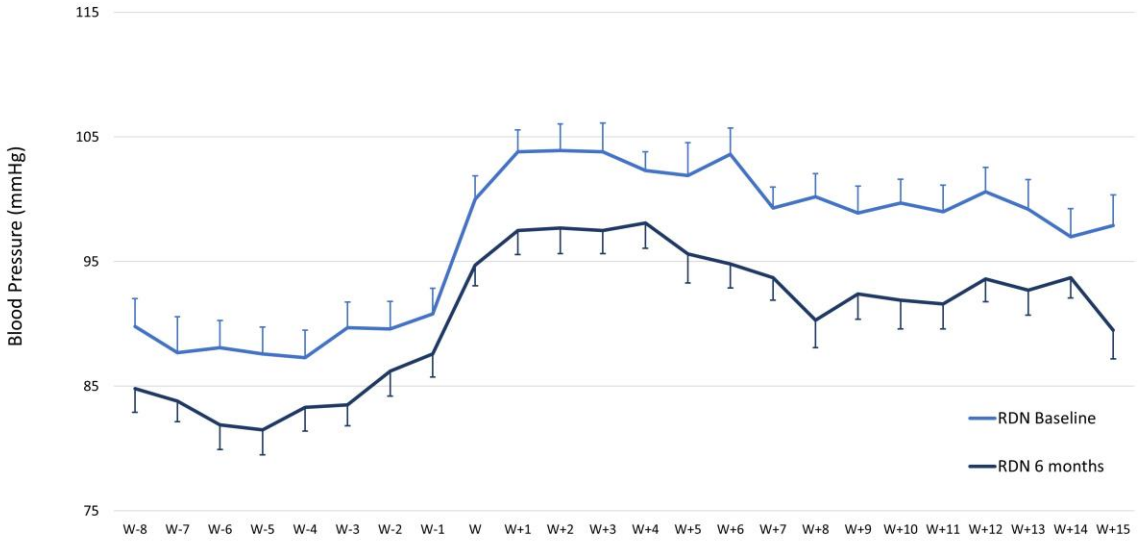
Wake time (W) was reported by 25 patients at baseline and 34 patients at six months and was set to 7:00AM for those patients not reporting.

B) 24-hour ambulatory SBP at baseline and six months for sham control group.



Wake time (W) was reported by 33 patients at baseline and 37 patients at six months and was set to 7:00AM for those patients not reporting.

C) 24-hour ambulatory DBP at baseline and six months for renal denervation group.



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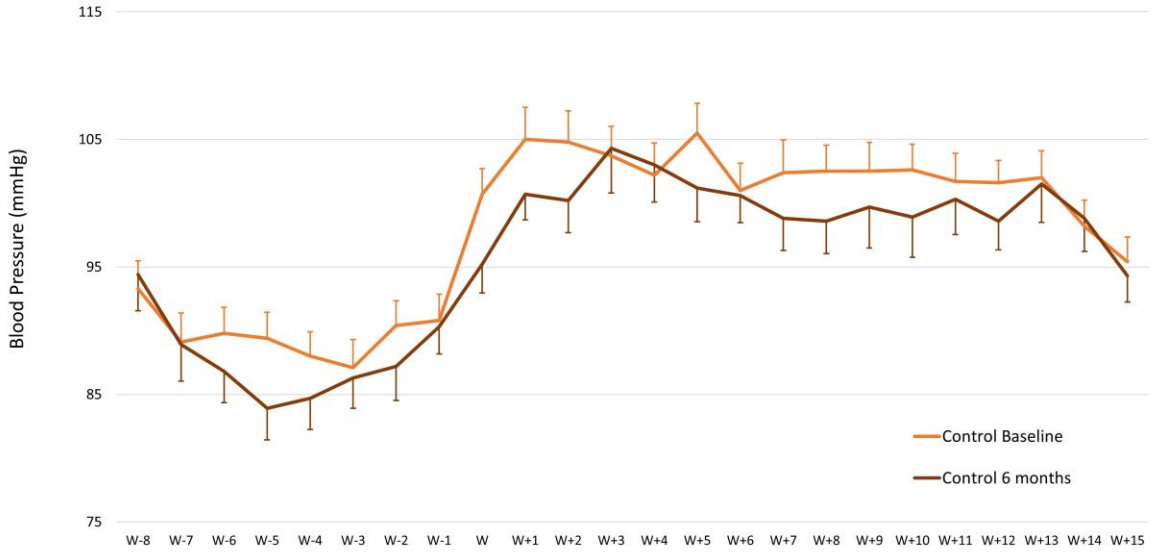
D) 24-hour ambulatory DBP at baseline and six months for sham control group.



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