Investigation of catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications: Results from the randomised, sham-controlled, proof of concept SPYRAL HTN-OFF MED Trial

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Word Count: 4,477

SUMMARY (322 of 300 words)

BACKGROUND: Previous randomised renal denervation studies failed to show consistent efficacy ~~benefit~~ in reducing blood pressure (BP).

METHODS: SPYRAL HTN-OFF MED is a multicentre, international, single-blind, randomised, sham-controlled, proof of concept trial (clinicaltrials.gov: NCT02439749). The objective was to evaluate the effect of renal denervation on BP in the absence of anti-hypertensive medications. Patients were enrolled at 21 centres in the USA, Europe, Japan and Australia. Eligible patients were drug naïve or discontinued their anti-hypertensive medications. 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 or sham control. Patients, caregivers, and those assessing BP were blinded to randomisation assignments. Changes in office and 24-hour BP at three months were compared between groups. Drug surveillance was employed to ensure patient compliance with medication ~~withdrawal~~absence. Safety events were assessed through three months.

FINDINGS: Eighty patients were randomis~~z~~ed and followed through three months. Office and 24-hour ambulatory BP decreased significantly from baseline to three months in the renal denervation group (n=38); 24-hour SBP (-5·5 mmHg [-9·1, -2·0]), 24-hour DBP (-4·8 mmHg [-7·0, -2·6]), office SBP (-10·0 mmHg [-15·1, -4·9]), and office DBP (-5·3 mmHg [-7·8, -2·7]). There were no significant changes in the sham-control group (n=42); 24-hour SBP (-0·5 mmHg [-3·9, 2·9]), 24-hour DBP (-0·4 mmHg [-2·2, 1·4]), office SBP (-2·3 mmHg [-6·1, 1·6]), and office DBP (-0·3 mmHg [-2·9, 2·2]). The difference between groups favoured renal denervation for both office and 24-hour three-month change from baseline; 24-hour SBP (-5·0 mmHg [-9·9, -0·2]), 24-hour DBP (-4·4 mmHg [-7·2, -1·6]), office SBP (-7·7 mmHg [-14·0, -1·5]) and office DBP (-4·9 [-8·5, -1·4]). Baseline-adjusted analysis gave very similar findings. There were no major adverse events in either group.

INTERPRETATION: Results from SPYRAL HTN-OFF MED provide biologic proof of principle for the BP lowering efficacy of renal denervation.

FUNDING: Medtronic.

INTRODUCTION

While the ability of renal denervation to decrease renal and systemic sympathetic tone was established by Esler et al[1] and early clinical trials were promising[2,3], ~~The encouraging results reported from the SYMPLICITY HTN-1 and HTN-2 trials[1,2] led to substantial interest in percutaneous renal denervation as a potential device-related non-pharmacological method to treat hypertension. However, despite meeting its safety endpoint~~, the randomised, blinded, sham-controlled SYMPLICITY HTN-3 trial failed to demonstrate a statistically significant blood pressure lowering effect of renal denervation when compared with sham treatment.[4] Post-hoc ~~sub-~~analyses ~~suggested~~ postulated that variance in medication adherence, incomplete renal denervation ~~of the renal arteries~~ and the inclusion of patients with isolated systolic hypertension might have contributed to the ~~surprisingly~~ absence of an observable blood pressure reduction.[5] Hence, the SPYRAL HTN-OFF MED was initiated to demonstrate that renal denervation could indeed impact blood pressure in a blinded, sham-controlled study. A new proof of concept trial was warranted due to dramatic trial design differences from previous studies. These differences included the unknown impact on ~~BP~~blood pressure reduction due to a different population (not "treatment resistant"), unknown impact on blood pressure~~BP~~ reduction of a new procedure, and unknown impact on the variability of what had previously been a secondary endpoint but was now the main focus of measurement, namely 24-hour ambulatory blood pressure monitoring (ABPM). Since the actual blood pressure reduction relative to sham could not be predicted, a study of 120 evaluable patients randomised 1:1 was designed to demonstrate a clinically meaningful signal focused on ABPM.

Given the uncertainty of both the blood pressure reduction and standard deviation, analyses were pre-specified at 40, 60, 80, and/or 100 subjects followed to three months so that if a clinically meaningful reduction was observed there could be rapid advancement to design and initiation of a powered, pivotal study. We present here the primary three-month analysis of ~~the~~ 80 subjects enrolled in the SPYRAL HTN-OFF MED trial.

METHODS

Trial design and patients

The design of the multicentre, international, single-blind, randomised, sham-controlled SPYRAL HTN-OFF MED proof of concept trial has been described previously and is illustrated in appendix **Figure S1**.[68] Briefly, we enrolled patients 20 to 80 years old with mild to moderate hypertension, 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 21 centres: ten in the USA, four in Germany, two in Japan, two in the United Kingdom, one in Australia, one in Austria, and one in Greece. The trial complied with the Declaration of Helsinki, all local ethics committees approved the research protocol and written informed consent was obtained from all patients. The trial is registered at www.clinicaltrials.gov as NCT02439749.

Screening and randomisation

Randomisation to renal denervation or sham procedure was stratified by trial centre at a 1:1 ratio, using block randomisation with a block size of four. Randomisation was performed by ICON plc using SAS-based software to generate the lists of randomisation codes. Participants were assigned to interventions through ICON's website. Prior to randomisation, patients were required to be off all anti-hypertensive medications (**Figure S1**).[68] An initial screening visit was conducted to verify initial eligibility criteria and initiate medication washout, if needed.

After a three- to four-week period of medication washout, screening visit two confirmed patients' eligibility for randomisation. Absence of anti-hypertensive medication usage was evaluated using tandem high performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory.[79] Office blood pressure and heart rate measurements were obtained using an automatic blood

pressure monitor (Omron, see appendix), and patients whose office blood pressure remained within range (SBP ≥150 mmHg and <180 mmHg and DBP ≥90 mmHg) underwent 24-hour ambulatory blood pressure monitoring (ABPM; Mobil-O-Graph; I.E.M GmbH, Stolberg, Germany). Blood pressure was measured every 30 minutes and 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. Patients had one opportunity to repeat ABPM data collection if they failed to record 21 daytime and 12 night-time readings, or the average 24-hour SBP was between 135-140 or 170-175 mmHg. Mean 24-hour heart rate was also determined from the ABPM record as the average of all heart rates measured during the cuff pressure measurement cycle.

Patients who satisfied all inclusion and exclusion criteria at the second screening visit were scheduled for renal angiogram and, if anatomical suitability was confirmed, proceeded to randomisation.

Procedure

The Symplicity Spyral™ multielectrode catheter (Medtronic, Galway, Ireland), and the Symplicity G3™ generator were used to provide radiofrequency ablation treatments. The four electrodes on the catheter are positioned to apply radiofrequency energy circumferentially in all four quadrants of the renal artery and branch vessels (**Figure 1**). All proceduralists had prior renal denervation experience and all cases were proctored based on detailed pre-specified treatment plans including a standardized approach to all accessible renal arterial vessels, including branch vessels and accessory arteries having a diameter of greater than three and less than eight mm. To minimize procedural variability, the number of proceduralists was restricted to one per trial centre.

In the control group, the sham procedure consisted of only a renal angiogram. Patients were also required to remain on the procedure table for at least 20 minutes post-angiogram to help prevent possible unblinding of randomisation allocation.

Follow-up

Patients' blood pressure was assessed at two-week intervals post-randomisation to ensure safety. If a patient's SBP surpassed the pre-specified escape criteria threshold (≥180 mmHg), and this was confirmed by repeated measurement within 72 hours, they could receive anti-hypertensive drug therapy at the discretion of the investigator. Otherwise, patients remained off anti-hypertensive medications post-randomisation until follow-up at three months, when a prespecified drug titration protocol was initiated if SBP was greater than 140 mmHg.

Maintenance of blinding

Trial patients were not informed of their randomisation assignments and were blinded during the renal angiogram by a combination of conscious sedation, sensory isolation (blindfolding and music), and lack of familiarity to the procedural details and duration of the angiogram (i.e., patients were not expected to know the difference between the renal angiography procedure alone and the renal angiography and denervation procedure). The proceduralist performing the angiogram and designated trial staff were blinded to the randomisation assignment until the angiography was completed and inclusion/exclusion criteria were confirmed. Blinded trial staff conducted all trial follow-up visits and the patient's referring/managing physicians were not informed of a patient's treatment assignment. Per protocol, blinding of patients and BP assessors was maintained to 12 months post-randomisation. Patients were asked to guess which randomisation group they were in at discharge and three months to evaluate the strength of the blinding procedures.

Efficacy endpoints

The primary efficacy endpoint of blood pressure reduction based on ABPM measurements was assessed at three months, judged to be an acceptable amount of time for patients to withhold their anti-hypertensive medications and to observe a decrease in blood pressure. The change from baseline (blood pressure

measured at screening visit two) in SBP and DBP measurements obtained in-office and with 24-hour ABPM was assessed for the renal denervation and sham control groups at three-months post randomisation. The three-month change in BP measurements were then compared between the two treatment groups in order to assess if the ABPM sham-control subtracted SBP and the corresponding standard deviation was sufficient to justify design of a larger, powered pivotal trial. Continued absence of anti-hypertensive medication usage was assessed by urine and plasma sampling at baseline and at three months. Plasma samples were also analysed for sodium, potassium, renin activity, aldosterone, serum creatinine, and other relevant laboratory values. 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.[8,10]

Safety endpoints

Safety endpoints collected at three months included all-cause mortality, end-stage renal disease, any significant embolic event resulting in end-organ damage, hospitalization for hypertensive crises not related to medication nonadherence, new myocardial infarction, new stroke, renal artery re-intervention, major bleeding, major vascular complications 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

The current proof-of-concept trial was designed in collaboration with the FDA and influenced by recommendations in the 2014 Scientific Statement by the American Society of Hypertension[9] which suggested a Phase Two type trial in a small group of patients. ~~To conduct a properly powered~~

after 40, 60, ~~and~~ 80 and/or 100 patients completed three-month follow up, respectively. The purpose of each interim analysis was to determine if there was an adequate treatment effect with a reduction in variability after this decision point are planned to be included in the pivotal dataset, as discussed with the FDA, and thus this report represents the ~~primary~~ results of the SPYRAL HTN-OFF MED trial.

There are no powered endpoints in the trial. To conduct a properly powered randomised trial assuming a 5 mmHg SBP reduction with a standard deviation of 12, it was determined that 246 patients would be required. Considering the failure of SYMPLICITY HTN-3 it was agreed to proceed with a smaller proof of concept trial that would minimize exposure of patients to an interventional procedure and provide sufficient evidence to move forward with a larger, powered trial. Statistical analyses were performed based on the intention-to-treat principle. A modified intention-to-treat cohort excluded patients who met escape criteria (SBP ≥180 mmHg). For patients meeting escape criteria, the last observation was carried forward for three-month blood pressure assessment. A per-protocol analysis was also performed which excluded patients meeting escape criteria, who had antihypertensive medications measured in urine or serum, and who had at least one non-standardized blood pressure assessment. To adjust for baseline blood pressure measurements, Analysis of Covariance (ANCOVA) was employed as an additional analysis of blood pressure changes.

Means and standard deviations of continuous variables are presented per treatment group. Between group differences and differences from baseline to the three-month follow-up assessment were tested with the use of unpaired and paired t-tests, respectively. For categorical variables, counts and percentages are presented per treatment group; values were tested with the use of the exact test for binary variables and the chi-square test for multilevel categorical variables. All reported subgroup analyses were prespecified.

Commented [FM[1]: We have 90% power with 246 patients under these assumptions.

Correlation of office with 24-hour SBP measurements per patient was analysed using regression methods. A blinding index, based on responses to a questionnaire, was calculated at hospital discharge and at three months to verify the effectiveness of blinding.[10]

Role of the funding source

The SPYRAL HTN-OFF MED trial was funded by Medtronic (Santa Rosa, CA, USA). The trial executive committee designed the protocol in conjunction with the funder. The funder was responsible for selection of clinical sites, in collaboration with the executive committee, as well as collection, monitoring and analysis of the data. The manuscript was written by the lead author with substantial 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 had full responsibility for the decision to submit for publication.

RESULTS

The current analysis presents results from the first 80 patients randomised (38 to renal denervation and 42 to sham) from a total of 353 patients enrolled and screened between June 2015 and May 2017 (**Figure 2**). At the interim analysis of 80 patients, a reduction in BP, as well as in variability of 24-hour BP measurements was seen; all patients randomised after these 80 patients will contribute to the pivotal dataset. There were no significant differences in baseline clinical characteristics, weight, heart rate, office, or mean 24-hour SBP and DBP between the renal denervation and sham control groups although there were more current smokers in the sham-control group than the renal denervation group (23.8% vs 10.5%) (**Table 1**).

All patients underwent aortography and selective renal angiography. Angiographic documentation of catheter position for the renal denervation group was required. During the procedure, a mean of 251·0 ± 99·4 cc of contrast was used in the renal denervation group and 83·3 ± 38·5 cc in the sham control group.

For the renal denervation group, on a patient basis, proceduralists performed an average of 43·8 ± 13·1 total ablations, and treated an average of 2·2 main arteries (17·9 ± 10·5 ablations) and 5·2 branch vessels (25·9 ± 12·8 ablations).

The blinding index was 0·65 (0·56, 0·75) at discharge and 0·59 (0·49, 0·70) at three months, indicating proper blinding.[101]

Drug testing was performed at baseline and three months to identify whether patients were taking any anti-hypertensive medications. At baseline, 92·1% (35/38) of renal denervation patients and 88·1% (37/42) of sham control patients had no evidence of anti-hypertensive medication use (p=0·72). At three months, for available data, 94·3% (33/35) of renal denervation and 92·7% (38/41) of sham control patients had no anti-hypertensive medications detected (p>0·99). Overall compliance with the requirement to be off antihypertensive medications at baseline and 3 months was 85.5%. Of the six patients who met escape criteria following randomisation, three had drugs measured at three months, drugs were not detected in two patients, and one patient did not undergo drug testing. There were no significant differences in baseline laboratory values or in the three-month change in values between the renal denervation and sham control groups (Appendix, **Table S2**).

The three month SBP and DBP change from baseline for both 24-hour ambulatory and office measurements in the renal denervation and sham control groups is displayed in **Figure 3, and Table 2**. The change in blood pressure was greater at three months for the renal denervation group vs. sham control for 24-hour ambulatory SBP (difference -5·0 mmHg [-9·9, -0·2], p=0·04) as well as office SBP (difference -7·7 mmHg [-14·0, -1·5], p=0·02). The same was documented for 24-hour DBP (difference -4·4 mmHg [-7·2, -1·6] p=0·002) and office DBP (difference -4·9 mmHg [-8·5, -1·4] p=0·008). Comparison of office and 24-hour blood pressure measurements at baseline and three months for renal denervation and sham control groups are included in appendix **Table S3**.

Comparison of three-month change, adjusted for baseline measures using ANCOVA, provide similar results with a 24-hour SBP between group difference of -4.6 mmHg [-9·2, 0·1], p=0·053 and 24-hour DBP between group difference of -4·3 mmHg [-7·1, -1·5], p=0·003. Office SBP difference was -7·1 [-13·2, -1·1], p=0·021 and office DBP difference was -5·0 mmHg [-8·6, -1·4], p=0·008 (**Table 2**). Results were consistent using unadjusted and baseline-adjusted analysis for the modified ITT and per-protocol populations (Appendix **Table S4**).

Individual patient responses to renal denervation or sham procedure via office and 24-hour BP measurements are illustrated in **Figure 4**. As expected, the three-month change in blood pressure after renal denervation was correlated between 24-hour and office measurements (r=0·41, p=0·01) but this correlation was not observed in the sham control group (r=0·06, p=0·72) (Appendix **Figure S2**).

There were no major procedural or clinical safety events in either the renal denervation or sham control groups out to three months **(**Appendix **Table S5).** Specifically, there were no cases of death or occurrences of myocardial infarction, stroke, major bleeding, serum creatinine elevation >50%, significant embolic events, vascular complications, renal artery re-intervention, new or worsening renal failure, or hypertensive emergency/crisis.

DISCUSSION

This novel trial differs substantially from previous renal denervation trials in the hypertensive population enrolled, the renal denervation technique employed, and the absence of concomitant anti-hypertensive medications. To our knowledge, this is the first rigorously conducted sham controlled clinical trial to assess BP reduction in hypertensive patients in the absence of anti-hypertensive medications. These data provide the biologic proof of principle that renal denervation as performed in this trial lowers blood

pressure in untreated hypertensive patients and supports the prior data from Esler et al about the correlation of reduction in sympathetic tone and blood pressure reduction.[1] While not powered for efficacy endpoints, a substantial difference in both office and mean 24-hour ambulatory SBP and DBP change was observed between the renal denervation and sham control groups at three months. In addition, the renal denervation group had significant changes from baseline to three months in office and mean 24-hour ambulatory blood pressures. Of note, the sham control group had a small, non-significant change in blood pressure.

A new proof of concept trial was warranted due to substantial trial design differences from the previous SYMPLICITY HTN-1 proof of concept trial[11] based on key learnings from subsequent clinical trials. ~~The current trial design was influenced by several key learnings.~~ These included recent advances in our understanding of renal nerve anatomy[12], the potential impact of concurrent drug therapy[5,4,13], the importance of operator experience and an individual procedural treatment plan[14], and the biological difference between combined systolic-diastolic hypertension and isolated systolic hypertension (office DBP <90 mmHg with a SBP ≥140 mmHg).[15] Most prior renal denervation trials enrolled patients with resistant[1,3,4,2,3,15] or moderate hypertension[13,16] while patients continued their anti-hypertensive regimen without excluding isolated systolic hypertension patients. Unlike earlier SYMPLICITY trials that utilized a single electrode renal denervation catheter in main renal arteries exclusively, the current trial utilized a multi-electrode catheter that delivered up to four simultaneous, radiofrequency ablations in a helical pattern and included branch vessel treatment. Further clinical studies are needed to evaluate the effect of different catheters and treatment protocols on efficacy of BP reduction.

Elimination of anti-hypertensive medications as a confounding factor in the evaluation of efficacy of renal denervation was important as adherence to anti-hypertensive medications has been well documented to be unpredictable over time in hypertension clinical studies[17,18] and specifically in renal denervation clinical

studies.[19,20] Several hypertension studies found an association between a higher number of detected anti-hypertensive medications and lower blood pressure in patients,[12,20–23] underscoring the importance of objective measurement of medication adherence in an interventional therapy trial. The standard deviations for blood pressure change were notably tighter in this compared to~~than in~~ previous trials and may be attributed to removing drug adherence confounding of blood pressure measurement, to patient selection, as well as to proctoring to ensure consistency in performance of renal denervation and the addition of branch vessel treatment. Moreover, in the SPYRAL HTN-OFF MED trial, despite known drug surveillance, compliance with the requirement to remain off antihypertensive drugs through three months was 85·5%, illustrating the value of drug surveillance.

Results from the current trial are supported by data from several important trials that suggest an effect of renal denervation in treating hypertension. Symplicity HTN-1, an open-label proof-of-principle study, was among the first to report a significant BP reductions in patients with resistant hypertension, that were evident by 1 month and sustained through three years.[2,11] The Renal Denervation for Hypertension (DENERHTN) prospective, open-label, randomised, controlled trial reported a significant difference in reduction in daytime ambulatory SBP after renal denervation plus antihypertensive medication compared to a control medication alone group.[24] A second recent retrospective, *non*-randomised analysis of renal denervation in a non-medicated hypertensive population documented a reduction in 24-hour SBP of -5·7 mmHg after renal denervation treatment.[25]

The choice of 24-hour SBP as the primary endpoint resulted from consensus that it is less prone to bias~~,~~ and, due to the multiple measurements, not only better reflects a patient's blood pressure but also demonstrates less variability of measurement;[9,29-31] for these reasons it was the endpoint recommended by regulatory authorities including the FDA. There was a significant correlation between ambulatory and office blood pressure changes in patients after renal denervation. This observation suggests that either measure may be appropriate for future clinical trials when office BP measurements are blinded. In line with expectations, a numerically smaller decrease was observed in the 24-hour ambulatory measurements.

The minimal blood pressure reductions in the sham control group did not show a similar relationship supporting the reduction of blood pressure specifically in response to renal denervation rather than other confounding factors.

The magnitude of the presently observed SBP reductions in the renal denervation arm, -10·0 mmHg for office (p<0·001) and -5·5 mmHg for 24-hour ABPM (p=0·003), represent clinically meaningful reductions in blood pressure. Blood pressure reductions of similar magnitudes have been associated with reduced rates of cardiovascular death, coronary death and stroke.[32-34~~29–31~~] For example, a recent meta-analysis predicts an approximate 20% reduction in relative risk for cardiovascular events with the presently observed 7.7 mmHg sham-adjusted reduction in office SBP.[3~~0~~] Likewise, the observed reduction in 24-hour ambulatory blood pressure is also associated with relative risk reductions and meets the criteria recommended by an expert panel.[~~27,29,35,36,32–34~~] It is noteworthy that ~~unclear why~~ there is a greater reduction in DBP after renal denervation in our trial. It is possible that this is related to the mechanism of action of renal denervation related to vascular tone or may be due to the exclusion of patients with isolated hypertension, but this is only speculation at this point.

Changes in renal denervation procedural requirements in SPYRAL HTN-OFF MED may have also contributed to the reduction in blood pressure observed in the treatment group. Based on more recent preclinical and clinical data a greater number of ablations were delivered in a circumferential pattern within the main artery, renal artery branches and accessory arteries of greater than three to less than eight mm in diameter, whereas in previous studies only the main renal artery was treated, the total number of ablations were fewer, ablations were not applied in a circumferential pattern and accessory renal arteries were not treated.[5,8,14] In SPYRAL HTN-OFF MED, 17·9 ± 10·5 ablations were attempted in the main renal arteries and 25·9 ± 12·8 ablations in branch vessels as compared with 11·2 ± 2·8 ablation attempts and no branch treatments in SYMPLICITY HTN-3. Nevertheless, not all patients responded to renal denervation treatment in this trial, which could be explained by variations in the degree of renal nerve innervation between patients,[12] or differences in the underlying pathophysiology.

There are several limitations to our trial. As a ~~feasibility~~ proof of concept trial, it was designed with a small sample size, and was not powered for statistical significance given the uncertainty of the placebo-subtracted blood pressure reduction and of the standard deviation of these measurements. Some patients had anti-hypertensive medications measured in their urine or serum, met escape criteria, or had blood pressure measured in a non-standardized manner; however, the findings were consistent in the primary intention to treat analysis as well as the modified intention to treat and per protocol analyses when these patients were excluded from analysis (Appendix **Table S3**). The three-month follow-up was relatively short; however, a short off-med period was specified per-protocol for safety reasons. After three-months antihypertension medications could be titrated as needed and thus there was not a substantial cohort of truly off-med patients after this time point. While renal denervation was performed to achieve complete and comprehensive denervation of the kidneys, no practical methods to verify nerve destruction are currently available. As previously described and similarly to trials of pharmacological therapies, not all participants experienced a blood pressure reduction post-renal denervation treatment. Furthermore, the method employed in this trial may not be generalizable to other renal denervation technologies or other populations not studied.

In conclusion, results from SPYRAL HTN-OFF MED provide biologic proof of principle for the efficacy of catheter based renal denervation to reduce blood pressure in hypertensive subjects not treated with antihypertensive medications. We demonstrated a clinically significant reduction in office and 24-hour ambulatory SBP and DBP at three months in mild to moderate hypertensive patients following renal denervation in the absence of anti-hypertensive medications that was not observed in the sham control group. There were no major safety events in either group despite lack of pharmacologic therapy from enrolment to three- month follow-up and a more aggressive renal denervation procedure that extended into renal artery branch vessels. The results of this trial ~~will be useful in informing~~serve as the basis to inform on ~~a~~design of a pivotal trial design.

Contributors

RT, FM, DK, KK, SP, MW, SC, VD, DJ, and MB participated in the design of the study. FM, DK, SE, KT, DT, ASh, AFW, RS, ASc, JC, CE, AWal, IH, DC, RW, DL, AM, CD, JL, PL, KF, JD, and NC participated in patient data collection. All authors were involved in interpretation of the data. MF was the study biostatistician responsible for the statistical analyses. RT, FM, DK, SP, MW, SC, VD, MF, DJ, MR, and MB 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

RT receives institutional support for conduct of clinical trials from Medtronic and consultant fees for trial design and management from Medtronic. FM is supported by Deutsche Hochdruckliga and Deutsche Gesellschaft für Kardiologie, and has received speaker honoraria and consultancy fees from St. Jude Medical, and Medtronic. DK receives institutional support for conduct of clinical trials from Medtronic and research/grant support and consulting honoraria for work unrelated to present submission. KK receives personal fees from Medtronic during the conduct of the study; grants from Teijin Pharma, Omron Helthcare, FUKUDA DENSHI, Bayer Yakuhin, A & D, Daiichi Sankyo, Mochida Pharmaceutical, EA pharma, Boehringer Ingelheim Japan, Tanabe Mitsubishi Pharma Corporation, Novartis Pharma K.K., Shionogi & Co., Terumo Corporation, MSD K.K., and Sanwa Kagaku Kenkyusho; personal fees from Bristol-Myers Squibb K.K., Takeda Pharmaceutical, Daiichi Sankyo, Omron Healthcare, Bayer Yakuhin, Mochida Pharmaceutical, and Sumitomo Dainippon Pharma outside the submitted work. SP receives consultant fees from Medtronic during the conduct of the study. MW receives research/consultant fees from Medtronic, Boston Scientific and ReCor outside the submitted work. SE receives speaker honorarium from Medtronic, Pfizer, Servier and Novartis outside the submitted work. KT receives

payments from Medtronic for work as centre PI. ASh receives research grants, consultant and speakers fees from Medtronic outside the submitted work. RS receives grant support from Medtronic and Kona Medical, and personal fees from Medtronic, Kona Medical and ReCor outside the submitted work. ASc receives institutional support for conduct of clinical trials from Medtronic and speakers fees from Medtronic outside the submitted work. JC, AWal and CD receive personal fees from Medtronic for advisory board participation outside the submitted work. DL receives grant support and personal fees for advisory board participation from Medtronic outside the submitted work. PL receives personal fees from Medtronic outside the submitted work. JD receives grants and personal fees from Medtronic during the conduct of the study, and grants and personal fees from Phillips Volcano outside the submitted work. NC receives institutional support for conduct of clinical trials from Medtronic. SC, VD, MF, DJ and MR are employees of Medtronic. MR is Chief Medical Officer of Medtronic. MB receives honoraria for lectures and scientific advice from Abbott, Astra-Zeneca, Boehringer-Ingelheim, Medtronic, Servier and Vifor. The other authors have nothing to disclose.

Acknowledgements

Manuela Negoita, MD, Sandeep Brar, MD and Garrett Pilcher, MS, all Medtronic employees, provided study oversight and expert review of the manuscript. Beth Ferri, PhD and Colleen Gilbert, PharmD of Medtronic, provided editorial support including creation of tables, figures and copy editing of text.

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Research in Context

Evidence before this study

Early uncontrolled and unblinded trials reported large reductions in blood pressure following renal denervation in patients with uncontrolled hypertension. However, the results of the randomised, sham-controlled SYMPLICITY HTN-3 trial showed no statistically significant blood pressure lowering benefits over sham treatment although continued follow-up of patients from multiple studies has confirmed the safety of renal denervation. Subsequent post-hoc analyses of SYMPLICITY HTN-3 suggested that ablation of the renal nerves, patient non-adherence to anti-hypertensive medications and patient selection might have impacted these results. Continued pre-clinical and clinical research provided evidence for the importance of circumferential ablations in both the main renal arteries and vessel branches.

Added value of this study

The SPYRAL HTN-OFF MED trial was designed to evaluate the effect~~feasibility~~ of renal denervation to influence blood pressure in non-medicated patients with mild to moderate hypertension. While not powered for efficacy endpoints, patients randomised to renal denervation experienced significant reductions in office and 24-hour ambulatory blood pressure compared to much smaller, non-significant blood pressure reductions in the sham control patients. These results provide the biologic proof of concept for the effect of renal denervation on blood pressure when performed by the described method.

Implications of all the available evidence

The results of this proof of concept~~feasibility~~ trial will inform the design of a larger pivotal trial that will be important to establish the role of renal denervation in the treatment of hypertension.

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Table 1: Patient characteristics and blood pressure measurements at baseline.

Characteristic* Mean±SD or % (N)	**Renal Denervation Group (N=38)**	**Sham Procedure Group (N=42)**
Age (years)	55·8 ± 10·1 (38)	52·8 ± 11·5 (42)
Male	68·4% (26/38)	73·8% (31/42)
BMI (kg/m^2)	29·8 ± 5·1 (38)	30·2 ± 5·1 (42)
Race		
White	26·3% (10/38)	23·8% (10/42)
Black/African American	13·2% (5/38)	11·9% (5/42)
Asian	7·9% (3/38)	7·1% (3/42)
Not reportable per local laws/regulations	52·6% (20/38)	57·1% (24/42)
Diabetes (all type 2)	2·6% (1/38)	7·1% (3/42)
Current smoker	10·5% (4/38)	23·8% (10/42)
Obstructive sleep apnea	7·9% (3/38)	7·1% (3/42)
Peripheral artery disease	2·6% (1/38)	0·0% (0/42)
Coronary artery disease†	0·0% (0/38)	4·8% (2/42)
Stroke and transient ischemic attack†	5·3% (2/38)	0·0% (0/42)
Myocardial infarction/Acute coronary syndrome†	0·0% (0/38)	2·4% (1/42)
Office SBP (mm Hg)	162·0 ± 7·6 (38)	161·4 ± 6·4 (42)
Office DBP (mm Hg)	99·9 ± 6·8 (38)	101·5 ± 7·5 (42)
Mean 24-hour SBP (mm Hg)	153·4 ± 9·0 (37)	151·6 ± 7·4 (42)
Mean 24-hour DBP (mm Hg)	99·1 ± 7·7 (37)	98·7 ± 8·2 (42)
Office heart rate (bpm)	71.1 ± 11.0 (38)	73.4 ± 9.8 (42)
24-hour heart rate (bpm)	72.3 ± 10.9 (37)	75.5 ± 11.5 (42)

*All comparisons between renal denervation and sham control groups were non-significant.

†These events occurred more than three months before randomisation.

BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute

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Table 2: Blood pressure changes at three months in intent-to-treat (ITT) population. 95% confidence intervals and p-values are included for each comparison.

BP Measure	Renal Denervation Group		Sham Control Group		Mean Difference: Renal Denervation vs Sham Control	
	Unadjusted[1]	Baseline Adjusted[2]	Unadjusted[1]	Baseline Adjusted[2]	Unadjusted[3]	Baseline Adjusted[4]
ITT Population						
	n=37		n=41			
3-Month Office SBP Change	-10·0 [-15·1, -4·9] p=0.0004	-9·7 [-14·1, -5·3] p<0·0001	-2·3 [-6·1, 1·6] p=0·2381	-2·5 [-6·7, 1·6] p=0·2273	-7·7 [-14·0, -1·5] p=0·0155	-7·1 [-13·2, -1·1] p=0·0212
3-Month Office DBP Change	-5·3 [-7·8, -2·7] p=0.0002	-5·3 [-7·9, -2·7] p=0·0001	-0·3 [-2·9, 2·2] p=0·8052	-0·3 [-2·8, 2·2] p=0·8158	-4·9 [-8·5, -1·4] p=0·0077	-5·0 [-8·6, -1·4] p=0·0076
	n=35	n=34	n=36			
3-Month 24-Hour SBP Change	-5·5 [-9·1, -2·0] p=0·0031	-5·3 [-8·6, -2·0] p=0·0020	-0·5 [-3·9, 2·9] p=0·7644	-0·7 [-4·0, 2·5] p=0·6523	-5·0 [-9·9, -0·2] p=0·0414	-4·6 [-9·2, 0·1] p=0·0528
3-Month 24-Hour DBP Change	-4·8 [-7·0, -2·6] p<0·0001	-4·8 [-6·8, -2·8] p<0·0001	-0·4 [-2·2, 1·4] p=0·6448	-0·5 [-2·4, 1·5] p=0·6433	-4·4 [-7·2, -1·6] p=0·0024	-4·3 [-7·1, -1·5] p=0·0028

BP: blood pressure; DBP: diastolic blood pressure; ITT: Intention-to-treat; SBP: systolic blood pressure

[1] p-value from paired t-test

[2] BP change and p-value from Least Squares Means estimation in ANCOVA model

[3] p-value from unpaired t-test

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

Figure legends

Figure 1: Angiographic images of multi-electrode denervation catheter applying circumferential ablations in renal arteries.

Figure 2: Trial profile

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

Figure 3: Change at 3 months in office and ambulatory SBP and DBP for treatment and sham control patients using un-adjusted p-values.

SBP: systolic blood pressure; DBP: diastolic blood pressure

Figure 4: Changes at three months for individual patients in renal denervation and sham control groups for**:**

A) 24-hour ambulatory SBP and DBP

B) Office SBP and DBP

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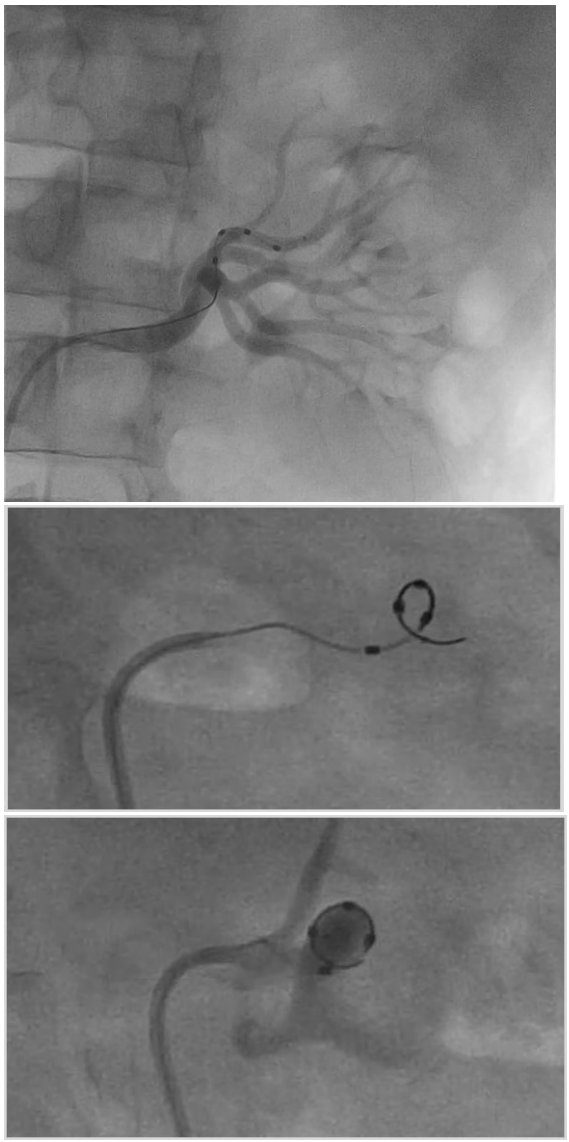

611 **Figure 2:** Trial profile

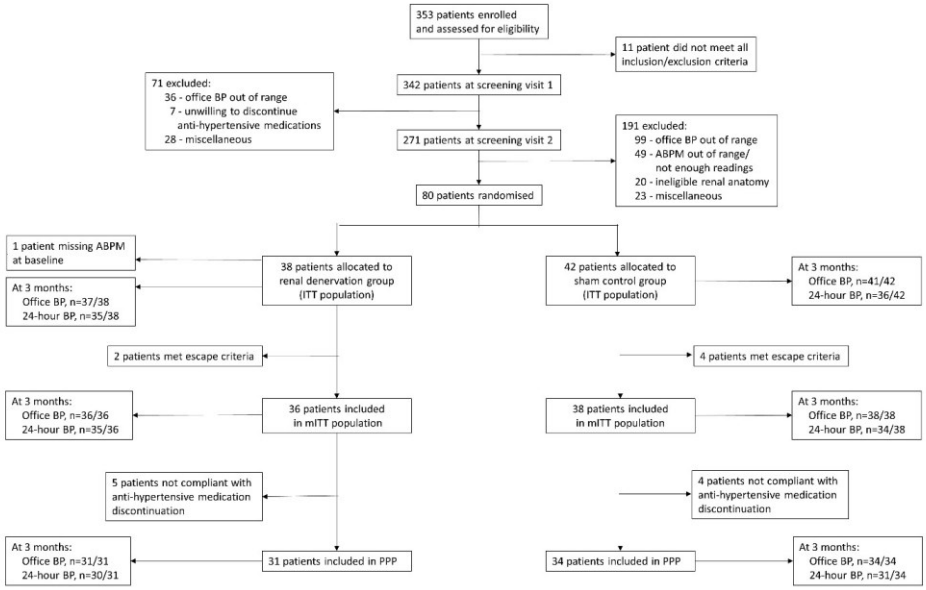

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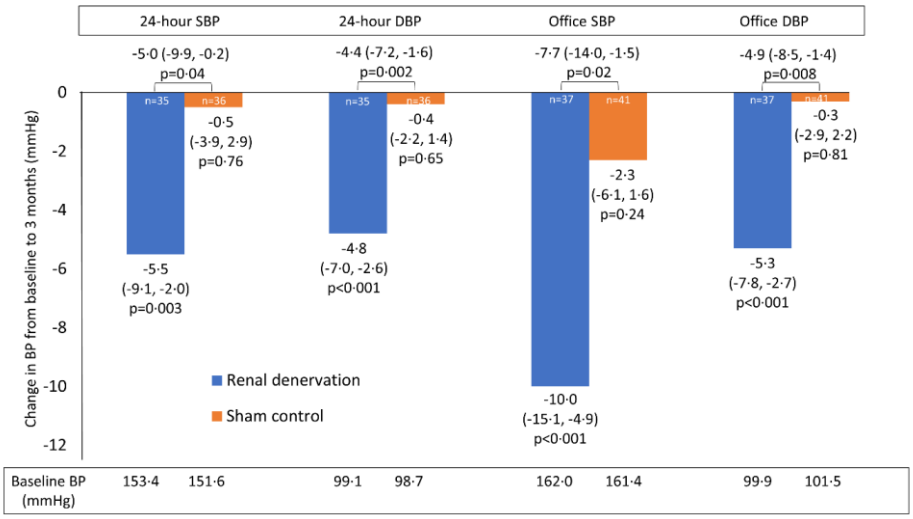
Figure 3: Change at 3 months in office and ambulatory SBP and DBP for treatment and sham control patients using un-adjusted p-values



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