Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial

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Summary

Background Catheter-based renal denervation has significantly reduced blood pressure in previous studies. Following a positive pilot trial, the SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial was designed to assess the efficacy of renal denervation in the absence of antihypertensive medications.

Methods In this international, prospective, single-blinded, sham-controlled trial, done at 44 study sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the UK, and the USA, hypertensive patients with office systolic blood pressure of 150 mm Hg to less than 180 mm Hg were randomly assigned 1:1 to either a renal denervation or sham procedure. The primary efficacy endpoint was baseline-adjusted change in 24-h systolic blood pressure and the secondary efficacy endpoint was baseline-adjusted change in office systolic blood pressure from baseline to 3 months after the procedure. We used a Bayesian design with an informative prior, so the primary analysis combines evidence from the pilot and Pivotal trials. The primary efficacy and safety analyses were done in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT02439749.

Findings From June 25, 2015, to Oct 15, 2019, 331 patients were randomly assigned to either renal denervation (n=166) or a sham procedure (n=165). The primary and secondary efficacy endpoints were met, with posterior probability of superiority more than 0·999 for both. The treatment difference between the two groups for 24-h systolic blood pressure was –3·9 mm Hg (Bayesian 95% credible interval –6·2 to –1·6) and for office systolic blood pressure the difference was –6·5 mm Hg (–9·6 to –3·5). No major device-related or procedural-related safety events occurred up to 3 months.

Interpretation SPYRAL Pivotal showed the superiority of catheter-based renal denervation compared with a sham procedure to safely lower blood pressure in the absence of antihypertensive medications.

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Introduction

Catheter-based renal denervation is intended to lower blood pressure by reducing sympathetic activity through renal nerve ablation.[1] Although significant blood pressure reductions were observed in early proof of concept studies,[2,3] the results from the randomised, sham-controlled trial Symplicity HTN-3 in patients with uncontrolled hypertension despite multidrug treatment regimens showed significant blood pressure reduction in both the treatment and control groups versus baseline, but no significant difference between groups.[4] Analysis of the trial data indicated that variations in procedural methods as well as changes in medication use after randomisation might have diminished the ability of the trial to distinguish the effects of renal denervation.[5] To address these concerns, smaller sham-controlled, randomised trials were designed to assess whether catheter-based renal denervation is effective in hypertensive patients with and without antihypertensive medications.[6] Results from these trials showed proof of concept of catheter-based renal denervation to reduce blood pressure in the absence and presence of antihypertensive medications.[7,8]

The SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial is a randomised, sham-controlled trial statistically powered to assess the efficacy of catheter-based renal denervation in the absence of antihypertensive medications.[9] This analysis uses a Bayesian study design to combine data from this trial (n=251) with an informative prior from the previous randomised pilot trial (n=80) to constitute the overall primary analysis population of 331 randomly assigned patients.

Methods

Study design

The SPYRAL Pivotal trial is a multicentre, international, prospective, single-blind, randomised, sham-controlled

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Jan 5, 2020, using the search terms "renal denervation", "hypertension", and "clinical trial". We searched for clinical trials published in English between Nov 1, 2012, and Jan 1, 2020.

Results from early clinical studies of renal denervation suggested promise for the therapy to reduce blood pressure. The first randomised sham-controlled study to assess renal denervation, SYMPLICITY HTN-3, did not show a significant treatment effect between renal denervation and sham procedure groups, prompting subsequent post-hoc analyses of the data to establish the future of this therapy. Two pilot studies were designed to overcome limitations of HTN-3 and assess the safety and efficacy of catheter-based renal denervation in the absence and presence of antihypertensive medications. Although results from these pilot studies were positive and showed safe and effective blood pressure reduction after catheter-based renal denervation, these studies were not powered to test for a significant treatment effect.

Added value of this study

The SPYRAL Pivotal trial was powered to show that catheter-based renal denervation successfully lowers blood pressure in the absence of antihypertensive medications. Additionally, subgroup analyses showed similar reductions in blood pressure for various baseline characteristics.

Implications of all the available evidence

This trial provides evidence of the safety and efficacy of catheter-based renal denervation in the absence of antihypertensive medications. A companion ongoing trial (NCT02439749) will assess safety and efficacy in the presence of antihypertensive medications.

trial, the design of which has been previously described.[9] Patients were enrolled at 44 study sites in Australia, Austria, Canada, Germany, Greece, Ireland, Japan, the UK, and the USA. A complete list of study sites and investigators is in the appendix (pp 4–9). Members of the steering committee and other administrative committees for the trial are in the appendix (p 18). The trial was conducted in accordance with the Declaration of Helsinki and the trial protocol was approved by the institutional review board or ethics committee at each study site.

Patients

Complete inclusion and exclusion criteria are in the appendix (pp 19–20).[9] Patients were aged 20–80 years at the time of enrolment, had office systolic blood pressure from 150 mm Hg to less than 180 mm Hg and office diastolic blood pressure of at least 90 mm Hg. Furthermore, patients were required to have mean 24-h systolic blood pressure of at least 140 mm Hg but less than 170 mm Hg using ambulatory blood pressure monitoring. 24-h blood pressure measurements were considered valid if at least 21 daytime readings and 12 night-time readings had been recorded. Daytime was defined as 0700 h to 2200 h and night-time defined as 2200 h to 0700 h.[10] Patients were excluded if they had stable or unstable angina or myocardial infarction within 3 months of enrolment or a history of heart failure, cerebrovascular accident or transient ischaemic attack, or atrial fibrillation. Other key exclusion criteria were renal artery anatomy ineligible for treatment, presence of fibromuscular dysplasia, more than 50% stenosis in any treatable vessel, renal artery stent placed less than 3 months before the procedure, and previous renal denervation. Before randomisation, if patients were on antihypertensive medications, they were required to discontinue them, as described in the appendix (p 12). Written informed consent was provided by all patients before enrolment.

Randomisation and masking

All patients had renal angiography and were then randomly assigned 1:1 to renal denervation or a sham procedure, stratified by study centre if renal anatomy met all inclusion and no exclusion criteria.[9] Patients as well as study staff conducting blood pressure assessments and clinical follow-up were masked to the treatment assignment until 6 months after randomisation. Operators were not masked to random group assignment and were not involved in patient care from randomisation until after clinical assessment 6 months later. During renal denervation or sham procedure, patients had conscious sedation, sensory isolation, and no familiarity with the procedural details, so they remained masked to their assignment. For the sham procedure, patients were required to remain on the table for at least 20 min after renal angiography to help prevent unmasking.

Procedures

For the renal denervation procedure, the Symplicity Spyral multielectrode renal denervation catheter (Medtronic; Galway, Ireland) and the Symplicity G3 radiofrequency generator (Medtronic; Minneapolis, MN, USA) were used. The catheter has four electrodes designed to simultaneously or individually deliver radiofrequency ablation (intended duration of 60 s) to all four quadrants of the renal arteries and branch vessels with each activation; 45 s or longer was considered a successful ablation. Ablations were recommended in all accessible renal arterial vessels between 3 mm and 8 mm in diameter. Angiography was repeated throughout the procedure to verify anatomy and catheter positioning. Procedure time was defined as the time from arterial access until the patient was removed from the table. Only one operator per centre did the renal denervation procedure to minimise procedural variability. All procedures were proctored according to specific treatment plans.

Patients were followed up every 2 weeks after randomisation by phone or in person to assess safety and measure blood pressure in person if warranted. Office and 24-h blood pressure were measured at baseline and 3 months as outlined in the appendix (pp 10–11). Additionally, urine and blood were tested for the absence of antihypertensive medications at baseline and 3 months with patient awareness, and quality of life assessment and masking assessment were also done.

Safety was assessed every 2 weeks until 3 months after randomisation.

Outcomes

The primary safety events assessed up to 3 months included all-cause mortality, end-stage renal disease, significant embolic event resulting in end-organ damage, renal artery perforation or dissection requiring intervention, vascular complications, hospital admission for hypertensive crisis not related to confirmed non-adherence with medications or the protocol, and new renal artery stenosis of more than 70% confirmed by the angiographic core laboratory.

The primary efficacy endpoint was the change in mean 24-h systolic blood pressure from baseline to 3 months after the procedure, adjusted for baseline 24-h systolic blood pressure.

The secondary efficacy endpoint was the change in mean office systolic blood pressure from baseline to 3 months after the procedure, adjusted for baseline office systolic blood pressure. Other secondary endpoints were changes in systolic and diastolic blood pressure from baseline at 3, 6, 12, 24, and 36 months; and changes in office systolic and diastolic blood pressure from baseline and incidence of achieving target systolic blood pressure (<140 mm Hg) at 1, 3, 6, 12, 24, and 36 months. Acute or procedural safety secondary endpoints were assessed at 1 month after randomisation and chronic safety secondary endpoints were assessed at 3, 6, 12, 24, and 36 months after randomisation. All primary and secondary endpoints and definitions are in the appendix (p 21).

Statistical analysis

The statistical methods for this trial have been previously described in detail.[9] In brief, the trial utilises a Bayesian design that allows for prespecified interim analyses with predetermined stopping rules for efficacy or futility of the primary and secondary efficacy endpoints. The primary and secondary efficacy endpoints will be assessed and enrolment will only stop at an interim analysis if both endpoints meet prespecified stopping criteria. The first prespecified interim analysis was planned when 210 evaluable patients had 3-month efficacy follow-up data. The randomised pilot trial (n=80), done under similar enrolment and treatment criteria,[8] provided data for the informative prior in the Bayesian power prior method.[9] Weighting of the pilot trial data was established by the degree of similarity between the pilot and pivotal datasets.

For the primary and secondary efficacy endpoints, the overall type I error and power for this adaptive study design were calculated using simulations.[9] The protocol specified interim analyses when 210 and 240 patients had completed 3-month follow-up, with a maximum study size of 300 patients. The overall power to detect a mean treatment difference of –4·0 mm Hg (SD 12) for 24-h systolic blood pressure and –6·5 mm Hg (16) for office systolic blood pressure was 94%. The overall one-sided type I error was predetermined as 2·9% for 24-h systolic blood pressure and 2·6% for office systolic blood pressure, and power was established at the first interim analysis to be 83%. The primary and secondary efficacy endpoints were met if the posterior probabilities of superiority were more than 0·975. Treatment differences are presented with Bayesian 95% credible intervals (95% BCIs).

The intention-to-treat (ITT) population was used for the primary efficacy analysis and consists of all randomly assigned patients in this trial and the previous randomised pilot trial, analysed according to their assigned treatment. Patients who met antihypertensive medication escape criteria (office systolic blood pressure >180 mm Hg or safety reasons) were analysed using last observation carried forward for their blood pressure measurements at 3 months in the ITT population. Missing office and ambulatory primary endpoint outcomes were imputed using multiple imputation as a sensitivity analysis (appendix p 13). Primary and secondary efficacy endpoints were assessed in other prespecified analysis populations, including the modified ITT population, as treated population, and per-protocol population as defined in the appendix (p 22).

Continuous variables are presented as means with SDs. Categorical variables are presented as counts and percentages. Statistical comparisons between treatment groups were made using *t* tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Within each treatment group, paired *t* tests were used to compare changes in continuous variables from baseline to follow-up. Comparisons of blood pressure changes between treatment groups were done using frequentist ANCOVA analyses adjusting for baseline blood pressure. For prespecified subgroup analyses, the interaction between treatment group and subgroup was assessed using a linear regression model adjusting for baseline systolic blood pressure, treatment indicator, subgroup indicator, and the treatment–subgroup interaction. A masking index was calculated after the procedure and at 3 months to verify the effectiveness of masking for patients and assessors.[11]

Statistical analyses were performed using SAS for Windows (version 9.4 or higher) and R (version 3.6.0 or higher).[9] The independent data monitoring committee reviewed safety and efficacy data at prespecified timepoints

and provided recommendations regarding continuation of the study to the funder. The trial is registered at ClinicalTrials.gov, NCT02439749.

Role of the funding source

The funder of the study was involved in study design, data collection, validation of the data analyses, and writing of the report (figure and table generation, copy editing, and formatting). The manuscript was written by the lead author with substantial contributions from the trial's executive committee and all co-authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From June 25, 2015, to Oct 15, 2019, 1519 patients were enrolled, of whom 1188 were excluded because they did not meet inclusion criteria. 166 were randomly assigned to renal denervation and 165 to the sham procedure (80 were included in the pilot and 251 in Pivotal; appendix p 14). Baseline characteristics were well balanced between the renal denervation and sham groups (table). Baseline characteristics across the individual pilot and Pivotal groups were also well balanced (appendix p 23).

	Renal denervation (n=166)	Sham procedure (n=165)
Age, years		
All	52·4 (10·9)	52·6 (10·4)
Females	53·1 (11·2)	49·7 (9·2)
Males	52·0 (10·7)	53·9 (10·6)
Sex		
Female	59 (36%)	52 (32%)
Male	107 (64%)	113 (68%)
Body-mass index, kg/m^2	31·1 (6·0)	30·9 (5·5)
Race		
White	47 (28%)	50 (30%)
Black or African American	36 (22%)	31 (19%)
Asian	9 (5%)	4 (2%)
Other	1 (1%)	1 (1%)
Not reported	73 (44%)	79 (48%)
Diabetes (all type 2)	6 (4%)	9 (5%)
Current smoker	28 (17%)	27 (16%)
Obstructive sleep apnoea	14 (8%)	12 (7%)
Peripheral artery disease	1 (1%)	0
Coronary artery disease*	0	8 (5%)
Myocardial infarction or acute coronary syndrome*	0	2 (1%)
Stroke or transient ischaemic attack*	1 (1%)	0
Office systolic blood pressure, mm Hg	162·7 (7·8)	162·9 (7·5)
Office diastolic blood pressure, mm Hg	101·2 (7·0)	102·0 (7·1)
Office heart rate, beats per min	73·3 (10·6)	74·0 (9·9)
Mean 24-h systolic blood pressure, mm Hg	151·4 (8·1)	151·0 (7·5)
Mean 24-h diastolic blood pressure, mm Hg	98·0 (7·7)	99·0 (7·4)

The primary analysis consists of pilot (n=80) and Pivotal (n=251) patients. *These events occurred more than 3 months before randomisation.

Table: **Patient characteristics at baseline**

Aortography and renal angiography were done in all patients to confirm anatomic eligibility for the trial before randomisation. Mean procedure time was 99·6 min (SD 37·3) for the renal denervation group and 52·9 min (16·6) for the sham control group. In the renal denervation group, on an individual patient basis, proceduralists did a mean of 46·9 (15·6) total ablations and treated a mean of 2·2 main arteries (18·3 ablations [9·9]) and 5·8 (2·7) branch vessels (28·6 ablations [15·4]). Nine (5%) of 166 renal denervation patients had accessory arteries that were not treated and in seven of these nine patients, the accessory artery was less than 3 mm in diameter. The mean time between initial catheter insertion and final guide catheter removal was 60·2 min (25·0).

The patient masking index was 0·66 (95% CI 0·61–0·71) after the procedure and 0·53 (0·48–0·59) at 3 months. The assessor masking index was 0·82 (0·78–0·86) after the procedure and 0·73 (0·68–0·78) at 3 months. The upper CI above 0·5 at both baseline and 3 months for all of these indices indicates that proper masking was achieved.[11]

Patients were assessed at baseline and 3 months for the requirement to abstain from all antihypertensive medications. At baseline, no antihypertensive medications were detected in 150 (91%) of 165 renal denervation patients and 144 (87%) of 165 sham procedure patients (p=0·38). 16 renal denervation patients and 28 sham control patients met escape criteria related to increased blood pressure between baseline and 3 months (p=0·049; appendix p 24). Among those not meeting escape criteria, at 3 months, 135 (91%) of 148 renal denervation patients and 129 (95%) of 136 of sham control patients had no antihypertensive medications detected (p=0·25).

For the primary efficacy endpoint of changes from baseline in 24-h systolic blood pressure at 3 months, there was a significant difference between the renal denervation and sham procedure groups. This endpoint was met with a posterior probability of superiority greater than 0·999 and a treatment difference of –3·9 mm Hg (95% BCI –6·2 to –1·6; appendix p 15). For the secondary efficacy endpoint of difference in 3-month changes in office systolic blood pressure between the two groups, the difference was significant and the endpoint was met (difference –6·5 mm Hg (95% BCI –9·6 to –3·5), with posterior probability of superiority of more than 0·999 (appendix p 15). The blood pressure changes analysed using the prespecified ANCOVA-adjusted frequentist analysis of the overall population show similar changes in blood pressure

to Bayesian results (figure 1). Treatment differences were consistent across the pilot, Pivotal, and overall populations for systolic and diastolic blood pressure changes calculated using frequentist ANCOVA analyses adjusting for baseline blood pressure (figure 2).

Similar results were observed for the prespecified ANCOVA-adjusted frequentist analysis of the modified ITT, as treated, and per-protocol populations (appendix pp 25–27). Sensitivity analyses done to account for missing data yielded conclusions consistent with the primary analysis (appendix p 28). Individual patient responses to renal denervation or sham control are shown for 24-h systolic blood pressure and office systolic blood pressure (appendix p 16).

Mean 24-h blood pressure measurements for the renal denervation group show consistent reductions in systolic (figure 3A) and diastolic (figure 3B) blood pressure across 24 h, with non-significant changes in 24-h blood pressure measurements in the control group. Results were similar when analysed using patient-reported wake times. The renal denervation group had significantly lower mean daytime and night-time systolic and diastolic blood pressure measurements compared to sham control. Treatment differences between groups for 24-h systolic blood pressure in key baseline characteristic subgroups demonstrate no significant interactions between subgroups (appendix p 17).

No major safety events were reported at 1 month. There was one major safety event in each treatment group up to 3 months (one admission to hospital for hypertensive crisis or emergency in the renal denervation group and one new stroke in the sham procedure group), and neither was attributed to the device or trial procedures (appendix p 29).

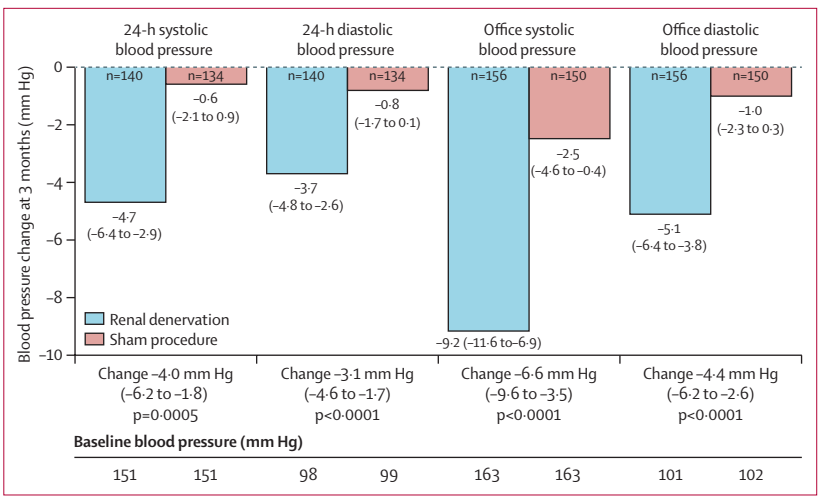


Figure 1: **Changes in 24-h and office systolic and diastolic blood pressure from baseline to 3 months**
Data in parentheses are 95% CI.

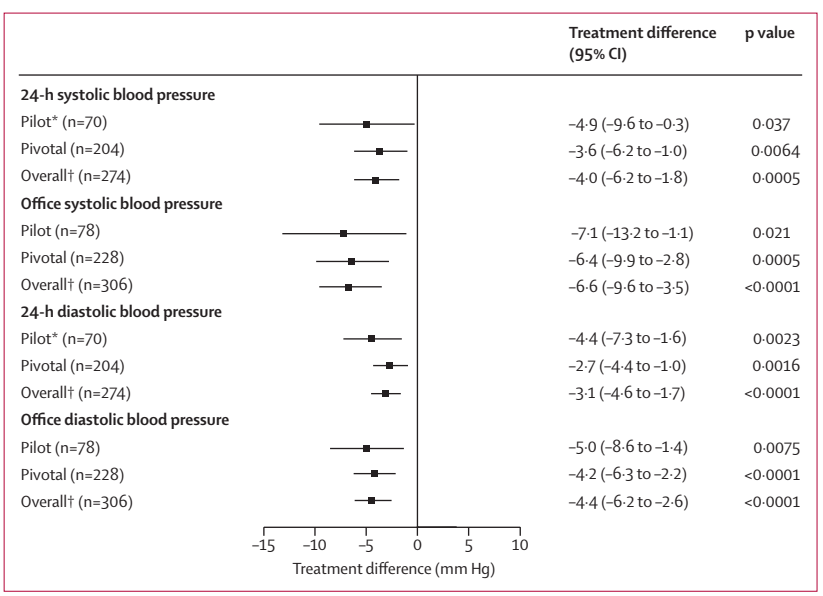


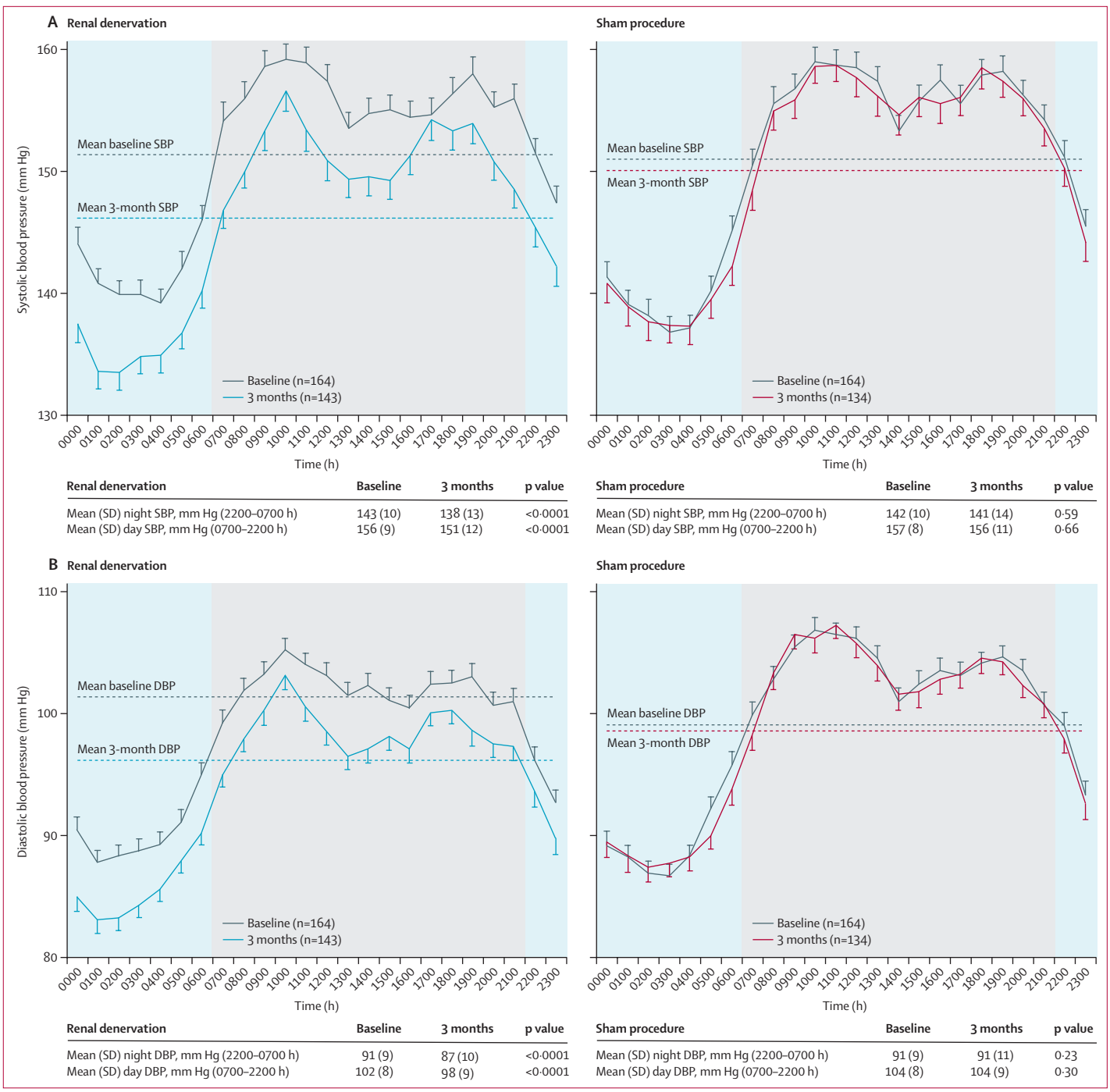
Figure 2: **Treatment differences between the renal denervation and sham procedure groups in the pilot (n=80), Pivotal (n=251), and overall (n=331) patient data**
*In the previous publication of pilot data results,[8] 71 pilot patients had 24-h blood pressure measurements at 3 months; further review excluded 24-h blood pressure measurements from one control patient who met escape criteria. †Results from stratified analysis of covariance (adjusting for Pivotal *vs* pilot) were similar to overall results.

Discussion

The SPYRAL Pivotal trial is, to the best of our knowledge, the largest randomised trial to show the superiority of catheter-based renal denervation, compared with a sham procedure, to lower blood pressure in the absence of antihypertensive medications. The trial met its primary and secondary efficacy endpoints, with significant reductions in 24-h and office systolic blood pressure measurements, and without significant differences in safety endpoints between patients who had renal denervation and those who had a sham procedure. Significant reductions in diastolic blood pressure measurements were observed as well as systolic and diastolic blood pressure reductions throughout the 24-h period.

In this trial, superiority of catheter-based renal denervation was shown in both the primary Bayesian analysis and frequentist statistical methods. The Bayesian approach used in this study allowed data from the pilot study to be used, resulting in a more efficient use of data and faster timelines.[9] This approach also allowed for a reduction in the number of patients enrolled than if only using a frequentist approach, limiting exposure of patients to sham treatment.

Office and 24-h blood pressure reductions were broadly consistent across the modified ITT, as-treated, and per-protocol populations. These findings are consistent with previous studies.[8,12] The small changes in blood pressure in the sham procedure group emphasise the importance of this rigorous trial design and execution for the assessment of device-based therapies for hypertension. Relative risk reductions of cardiovascular events have been shown to be proportional to the magnitude of blood pressure reduction achieved through treatment.[13] Given



Renal denervation	Baseline	3 months	p value
Mean (SD) night SBP, mm Hg (2200–0700 h)	143 (10)	138 (13)	<0·0001
Mean (SD) day SBP, mm Hg (0700–2200 h)	156 (9)	151 (12)	<0·0001

Sham procedure	Baseline	3 months	p value
Mean (SD) night SBP, mm Hg (2200–0700 h)	142 (10)	141 (14)	0·59
Mean (SD) day SBP, mm Hg (0700–2200 h)	157 (8)	156 (11)	0·66

Renal denervation	Baseline	3 months	p value
Mean (SD) night DBP, mm Hg (2200–0700 h)	91 (9)	87 (10)	<0·0001
Mean (SD) day DBP, mm Hg (0700–2200 h)	102 (8)	98 (9)	<0·0001

Sham procedure	Baseline	3 months	p value
Mean (SD) night DBP, mm Hg (2200–0700 h)	91 (9)	91 (11)	0·23
Mean (SD) day DBP, mm Hg (0700–2200 h)	104 (8)	104 (9)	0·30

Figure 3: **24-h ambulatory SBP (A) and DBP (B) at baseline and 3 months for renal denervation and sham control groups in the overall population**
Error bars show standard error. DBP=diastolic blood pressure. SBP=systolic blood pressure.

its continuous therapeutic effect, it is possible that the treatment effect of renal denervation could help reduce cardiovascular morbidity in patients that otherwise cannot consistently achieve goal blood pressure targets. Additionally, treatment differences between groups for 24-h systolic blood pressure were consistent among numerous baseline characteristic subgroups assessed, suggesting efficacy of renal denervation for patients of different age, sex, body-mass index, and smoking status. However, patients with higher baseline heart rate had slightly greater blood pressure reduction after renal denervation (although the difference did not reach significance), corroborating previously published results.[14]

Renal denervation showed consistent blood pressure reduction throughout the 24-h period, a finding also observed in previous studies with this device.[7,8,15] These observations might have particular clinical relevance to patients whose 24-h blood pressure phenotype is associated with a high cardiovascular risk, particularly those with nocturnal or early morning hypertension.[16–21] Furthermore, the continuous nature of this therapy is distinguished from the pharmacokinetic profile of those drugs that have short durations of action. One important limitation of oral antihypertensive drug therapy is that medication levels might reach a relative trough during the night and early morning periods because of once daily (typically morning) dosing schedules and the pharmacokinetics of drug clearance. The feature of continuous effect with renal denervation could have particular relevance in mitigating the loss of blood pressure control in patients who are non-adherent to drug therapy, which has become a major concern in hypertension management.[22,23]

The observed treatment effects for 24-h and office blood pressure measured at 3 months could be conservative estimates for two reasons. The first is that we and others have seen in previous studies that the blood pressure-lowering signal increased from 3 months to 6 months.[7] This result is also supported by the observation of the time course of blood pressure reduction reported in the Global Symplicity Registry.[15] Thus, the need to assess blood pressure at 3 months for safety reasons might have led to an underestimate of the true treatment effect of renal denervation. Second, about twice as many patients in the sham group than in the renal denervation group resumed medications under protocol-defined escape criteria, either because of systolic blood pressures exceeding 180 mm Hg or blood pressure-related symptoms or complications. Therefore more patients with very high systolic blood pressure were not included in the control group, because those resuming medications were usually not able to complete 24-h ambulatory blood pressure monitoring for the primary endpoint assessment, and thereby disadvantaged the renal denervation group. The observation is also interesting because it suggests that renal denervation decreased the occurrence of high blood pressures, which led to the high number of patients who were eligible for escape in the control group, thus demonstrating an additional benefit of treatment.

Treatment with renal denervation in this trial was shown to be safe, with no major device-related or procedure-related safety events. These findings contribute further to the already established safety profile of catheter-based renal denervation.[7,8,15,24] Long-term efficacy and safety will continue to be followed up for 3 years, and a complementary randomised trial in patients with uncontrolled hypertension despite antihypertensive medication is ongoing (NCT02439775). Additional subgroup analyses with this large dataset are planned, to assess whether any predictors of response to renal denervation can be identified.

There are several limitations of this trial. Blood pressure assessment in patients not treated with medications was limited to 3 months to avoid prolonging medication withdrawal.[6] Because previous trials have shown an increasing treatment effect between 3 months and 6 months,[7,25] this shorter duration might have resulted in underestimation of the treatment effect. Not all patients followed protocol requirements to stay off medications, as assessed by drug and urine testing; although results in the per-protocol cohort were consistent with the ITT results. An intraprocedural indicator of successful renal denervation is not available for operator feedback. Patients with a history of heart failure, cerebrovascular accident or transient ischaemic attack, or atrial fibrillation were excluded from the study because these patients require medications such as renin–angiotensin–aldosterone system inhibitors for secondary prevention of hypertension, and it would have been unethical to withhold these medications. Furthermore, although not all patients had primary efficacy endpoint observations available (often related to meeting protocol-specified criteria for resuming medications, and more commonly observed in the sham group), the efficacy analyses were consistent when multiple imputation for missing values was performed.

In conclusion, among patients with uncontrolled hypertension in the absence of antihypertensive medication, the salient findings of this trial are as follows: (1) catheter-based renal denervation was associated with statistically significant and clinically meaningful reductions in 24-h and office blood pressure compared with a sham procedure; (2) renal denervation showed a persistent, sustained reduction in blood pressure over a 24-h period; and (3) no major procedural or device-related safety events were observed.

Contributors

MB drafted the manuscript. MB, KK, DEK, FM, MAW, RES, KT, SP, VD, SAC, SB, and RRT all participated in the design of the study and contributed to the writing of the first draft of the manuscript. MB, KK, DEK, FM, MAW, RES, KT, SP, DK, JWC, CE, DPL, AM, SE, DLC, RW, CMD, JL, AS, JW, TA, DRee, BKJ, DRey, RD'S, ASPS, and FS participated in patient data collection. MF performed the statistical analysis and contributed to the writing of the report. All authors were involved in interpretation of the data. All authors agreed on the content of the manuscript, reviewed drafts, and approved the final version.

Declaration of interests

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Data sharing

Data from this study will not be made available to others because of ownership by the sponsor.

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