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Alcohol-mediated renal denervation in patients with hypertension in the absence of antihypertensive medications

Atul Pathak[1]*, MD; Ulrike M. Rudolph[2], MD; Manish Saxena[3], MBBS; Thomas Zeller[4], MD; Jochen Müller-Ehmsen[5], MD; Erik Lipsic[6], MD; Roland E. Schmieder[7], MD; Horst Sievert[8], MD; Marcel Halbach[9], MD; Faisal Sharif[10], MBBS; Helen Parise[11], ScD; Tim A. Fischell[12], MD; Michael A. Weber[13], MD; David E. Kandzari[14], MD; Felix Mahfoud[15,16], MD

1. Department of Cardiovascular Medicine, Princess Grace Hospital, Principality of Monaco; 2. Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Universität Leipzig, Leipzig, Germany; 3. Barts NIHR Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, London, UK; 4. Universitäts-Herzzentrum Bad Krozingen, Bad Krozingen, Germany; 5. Asklepios Klinik Altona, Hamburg, Germany; 6. Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; 7. Universitätsklinikum Erlangen, Erlangen, Germany and Friedrich Alexander University Erlangen/Nürnberg, Erlangen, Germany; 8. CardioVasculäres Centrum (CVC) Frankfurt, Frankfurt, Germany; 9. University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinic III for Internal Medicine, Cologne, Germany and Herzzentrum der Uniklinik Koln, Koln, Germany; 10. Saolta University Healthcare Group, University Hospital Galway, Galway, Ireland; 11. Yale University School of Medicine, New Haven, CT, USA; 12. Ablative Solutions Inc., Wakefield, MA, USA; 13. Division of Cardiovascular Medicine, State University of New York (SUNY), New York, NY, USA; 14. Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, GA, USA; 15. Department of Internal Medicine III - cardiology, angiology and internal intensive care medicine, Saarland University Medical Center, Homburg, Germany; 16. Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA

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KEYWORDS

- miscellaneous
- resistant hypertension
- uncontrolled hypertension

Abstract

Background: Ultrasound and radiofrequency renal denervation (RDN) have been shown to safely lower blood pressure (BP) in hypertension.

Aims: The TARGET BP OFF-MED trial investigated the efficacy and safety of alcohol-mediated renal denervation (RDN) in the absence of antihypertensive medications.

Methods: This randomised, blinded, sham-controlled trial was conducted in 25 centres in Europe and the USA. Patients with a 24-hour systolic BP of 135-170 mmHg, an office systolic BP 140-180 mmHg and diastolic BP ≥90 mmHg on 0-2 antihypertensive medications were enrolled. The primary efficacy endpoint was the change in mean 24-hour systolic BP at 8 weeks. Safety endpoints included major adverse events up to 30 days.

Results: A total of 106 patients were randomised; the baseline mean office BP following medication washout was 159.4/100.4±10.9/7.0 mmHg (RDN) and 160.1/98.3±11.0/6.1 mmHg (sham), respectively. At 8 weeks post-procedure, the mean (±standard deviation) 24-hour systolic BP change was –2.9±7.4 mmHg (p=0.009) versus –1.4±8.6 mmHg (p=0.25) in the RDN and sham groups, respectively (mean between-group difference: 1.5 mmHg; p=0.27). There were no differences in safety events between groups. After 12 months of blinded follow-up, with medication escalation, patients achieved similar office systolic BP (RDN: 147.9±18.5 mmHg; sham: 147.8±15.1 mmHg; p=0.68) with a significantly lower medication burden in the RDN group (mean daily defined dose: 1.5±1.5 vs 2.3±1.7; p=0.017).

Conclusions: In this trial, alcohol-mediated RDN was delivered safely but was not associated with significant BP differences between groups. Medication burden was lower in the RDN group up to 12 months.

**Corresponding author: Department of Cardiovascular Medicine, Princess Grace Hospital, 1 Av. Pasteur, 98000 Principality of Monaco. E-mail: atul.pathak@chpg.mc*

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Abbreviations

BP	blood pressure
CTA	computed tomography angiography
DBP	diastolic blood pressure
DDD	defined daily dose
eGFR	estimated glomerular filtration rate
HTN	hypertension
MRA	magnetic resonance angiography
RDN	renal denervation
SBP	systolic blood pressure

Introduction

Hypertension (HTN) remains a major cardiovascular risk factor, affecting approximately one-third of adults worldwide[1]. Lowering systolic and diastolic blood pressure (BP) to recommended targets is associated with a substantial reduction in cardiovascular outcomes including stroke, heart failure, and myocardial infarction[2]. HTN management is challenging because of non-adherence to prescribed antihypertensive medications and lifestyle interventions, and more recently by the coronavirus disease 2019 (COVID-19) pandemic[1,3-6].

The renal sympathetic nerves are involved in the development and maintenance of HTN[7,8]. Catheter-based renal denervation (RDN) using radiofrequency or ultrasound energy has been demonstrated to safely lower BP in patients not receiving[9,10] or receiving[11,12] antihypertensive medications.

The Peregrine System Infusion Catheter (Ablative Solutions, Inc.,) delivers microdoses (0.6 mL per treatment site) of dehydrated alcohol, as a neurolytic agent, locally into the perivascular space of the renal artery to achieve ablation of the afferent and efferent sympathetic nerves[13-16]. A previous open-label trial using this catheter demonstrated that alcohol-mediated RDN was delivered safely and significantly lowered ambulatory and office BP in patients with severe uncontrolled HTN taking medications[13]. The TARGET BP program is a series of randomised, sham-controlled, assessor-blinded trials investigating the safety and efficacy of alcohol-mediated RDN for the treatment of uncontrolled HTN in the absence (TARGET BP OFF-MED) or presence (TARGET BP I, pivotal) of antihypertensive medications[17]. We report the results of the multicentre, blinded, sham-controlled, TARGET BP OFF-MED trial (ClinicalTrials.gov: NCT03503773) at 2 months and up to 12 months of follow-up.

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Methods

This randomised, blinded, sham-controlled, trial conducted in 25 trial centres in Europe and the USA was approved by national regulatory authorities and local independent ethics committees (IECs)/institutional review boards (IRBs).

INFORMED CONSENT AND ELIGIBILITY

Patients provided written informed consent and underwent eligibility screening assessments. Patients (18-80 years old) with a mean office systolic blood pressure (SBP) between 140 and 180 mmHg and a mean diastolic blood pressure (DBP) ≥90 mmHg who were taking 0-2 antihypertensive medications were recruited. Patients entered a 4-week run-in period during which they took no antihypertensive medications leading up to randomisation. Before randomisation, patients were required to have a mean 24-hour ambulatory systolic blood pressure (ASBP) of 135-170 mmHg with ≥70% valid readings (determined by ambulatory blood pressure monitoring [ABPM]). Patients with 1 or more accessory renal arteries that were deemed too small for treatment (<4 mm diameter), but supplying >20% of the renal parenchyma, were excluded. A complete list of eligibility criteria is presented in **Supplementary Appendix 1**.

RANDOMISATION AND PROCEDURE

After confirmation of their anatomical eligibility, patients were randomised in a 1:1 ratio to either the alcohol-mediated RDN or sham control. Randomisation was stratified by trial site and was performed centrally using an interactive web response system. Patients were blinded to treatment status by sensory deprivation and sedation during the procedure. The patients, the sponsor, and the outcome assessors who performed the screening and follow-up assessments, were blinded up to 12 months post-procedure. The interventionalist performing the procedure, and associated personnel, were unblinded but not involved in patient follow-up. Unblinding to treatment assignment and ABPM results took place after the last patients had completed the 12-month follow-up visit. Patient blinding effectiveness was assessed using a treatment perception questionnaire and the James and Bang blinding indices[18,19] **(Supplementary Table 1)**.

If an anatomically suitable renal artery anatomy was confirmed, patients were randomised to receive RDN using the Peregrine Catheter (RDN group) or diagnostic renal angiography only (sham control group). Significant renal accessory arteries (supplying >20% perfusion of the renal parenchyma) that were 4-7 mm in diameter were also treated, with a maximum of 1 accessory artery treated per side. Each treatment involved administration of 0.6 mL alcohol per treated renal artery with a maximum dose of 2.4 mL alcohol per patient. Total procedure time was defined as the time from femoral artery access to sheath removal.

For those patients randomised to the RDN group, the catheter was inserted via the femoral artery and advanced to the renal artery. Three microneedles were deployed through the media of the vessel, and the alcohol was delivered into the perivascular space surrounding the renal artery. Further details regarding the Peregrine System Infusion Catheter and its use have been previously described[13].

FOLLOW-UP

Patient follow-up was conducted at 1, 2, 3 and 6 months and 1 and 2 years post-procedure and included ABPM, office BP, and safety assessments (adjudicated by a clinical events committee [CEC] and reviewed via an independent Data Safety Monitoring Board [DSMB]). At 6 months post-procedure, renal

duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), or renal angiography were performed to assess renal artery patency and the presence of new stenosis. Adherence to the discontinuation of antihypertensive medications per protocol was assessed by tandem high-performance liquid chromatography and mass spectroscopy of urine and plasma by an independent laboratory at baseline and 2 months[20]. Antihypertensive medication utilisation was assessed by the mean number of antihypertensive medications prescribed, the daily defined dose (DDD), medication index, and the proportion of patients on ≥2 antihypertensive medications. Prescribed antihypertensive medications were summarised according to the sum of the DDD to assess and compare the total drug consumption between groups[21]. The prescribed dose of each antihypertensive medication was divided by the DDD, which was summed across all prescribed medications. The medication index was defined as a composite index based on the doses of medications and is a proportional measure of prescribed to maximum daily dose, as recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[22], calculated for each antihypertensive medication.

The primary efficacy endpoint was the change in the mean 24-hour ASBP from baseline to 8 weeks post-procedure as compared between the RDN and the sham control groups. After 8 weeks, antihypertensive medications were titrated to a target office SBP of ≤140 mmHg according to a protocol-defined titration scheme **(Supplementary Appendix 2)**. A full list of study endpoints in provided in **Supplementary Appendix 3**.

The safety endpoint was the occurrence of major adverse events (MAE) up to 30 days post-procedure. MAE included all-cause death, end-stage renal disease, significant embolic event resulting in end-organ damage or requiring intervention, major vascular complications, major bleeding events, postprocedural renal artery stenosis (>60% diameter stenosis), hypertensive crisis, and symptomatic hypotension requiring medication. Device success was defined as the ability to insert the catheter into the lumen of the renal artery (target vessel), deploy the guide tubes inside the renal artery, deploy the needles through the arterial wall, deliver the intended dose of alcohol, retract the needles and the guide tubes into the catheter, and remove the catheter from the access site without any related complications or events. Procedural success was defined as device success with freedom from periprocedural MAE.

STATISTICAL ANALYSIS

This study was not formally powered for statistical comparisons of efficacy or safety events as this was designed as a proof-of-concept study, the purpose of which was to determine the treatment effect to inform future trial designs. Thus, the sample size was small. The primary efficacy endpoint analysis was conducted on the intention-to-treat (ITT) population and was compared between treatment groups using an analysis of covariance, which was adjusted for the baseline value. The per-protocol (PP) population consisted of patients meeting all eligibility criteria who were not taking antihypertensive medications prior to the primary endpoint collection and did not include RDN group patients with unilateral RDN. The null hypothesis was that there was no difference in the change in 24-hour ASBP between the RDN and sham control groups. The type I error rate for rejecting the null hypothesis is set at a 2-sided alpha level of 0.05. The primary analysis included only available data, and no data imputation was applied. The effect of the COVID-19 pandemic was assessed by exploring results before and after randomisations were paused (11 March 2020). This cutoff date was selected based on coincidence with the implementation of public health measures (e.g., lockdowns) and a pause in study randomisations that followed this date **(Supplementary Figure 1)**.

Results

PATIENT CHARACTERISTICS

Between March 2019 and December 2020, a total of 350 patients were consented, and 106 were randomised (50 and 56 patients in the RDN and sham control groups, respectively) **(Figure 1)**. The majority of patients (81 [76%]; 37 RDN, 44 sham control) were randomised during the COVID-19 pandemic era (the post-COVID group) **(Supplementary Figure 1)**.

Baseline characteristics were similar in both groups **(Table 1)**. Overall, 74% of patients were male with a mean (±standard deviation [SD]) age of 54.1±11.3 years, a mean body mass index of 28.6±4.3 kg/m^2, and normal renal function (estimated glomerular filtration rate [eGFR] 85.8±13.4 mL/min/1.73 m^2). Before medication washout, the number of patients on 0, 1, or 2 antihypertensive medications was 27 (25.5%), 32 (30.2%), and 47 patients (44.3%), respectively. The baseline mean office SBP/DBP following medication washout was 159.4/100.4±10.9/7.0 mmHg for the RDN group and 160.1/98.3±11.0/6.1 mmHg for the sham control group with a corresponding mean 24-hour SBP/DBP of 147.6/92.2±8.6/7.6 mmHg and 148.8/91.0±9.6/6.8 mmHg for the RDN and sham control groups, respectively **(Table 2)**.

Treatment perception questionnaires, evaluated by the James and Bang indices, indicated successful patient blinding at the time of the procedure and at 8 weeks post-procedure.

EFFICACY RESULTS

At 8 weeks, there was a change from baseline in the 24-hour SBP in the RDN group of –2.9±7.4 mmHg (p=0.009) versus –1.4±8.6 mmHg in the sham group (p=0.25) with a mean difference between groups of –1.5 mmHg (95% confidence interval [CI]: –4.8 to 1.7; p=0.27) **(Table 2, Supplementary Figure 2, Central illustration)**. The change in office SBP from baseline to 8 weeks was –4.0±12.6 mmHg (p=0.03) in the RDN group versus 0.6± 3.2 mmHg (p=0.73) in the sham group with a mean between-group difference of –4.6 mmHg (95% CI: –9.7 to 0.4; p=0.06) **(Figure 2, Table 2)**. A primary endpoint analysis using the per-protocol population was consistent with observations in the ITT population **(Supplementary Table 2)**. The individual 24-hour BP responses are presented in **Supplementary Figure 3**.

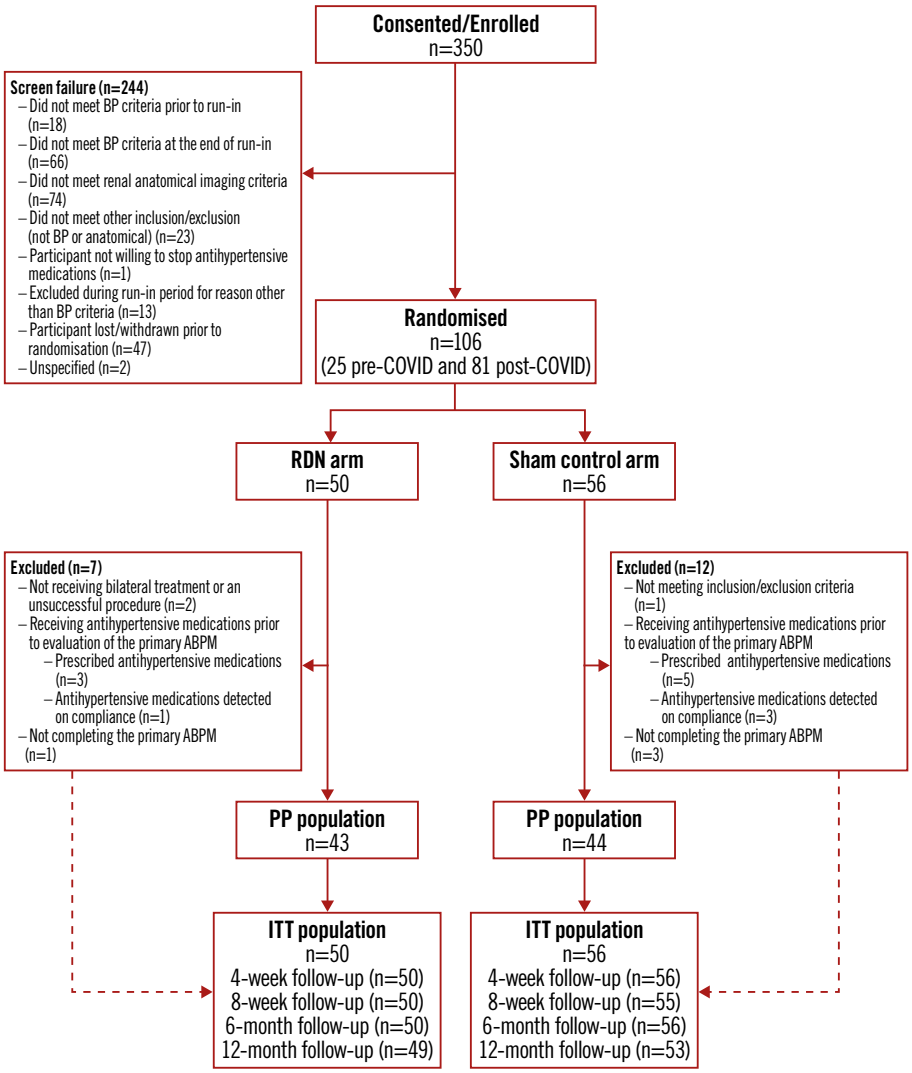

Figure 1. *Trial flowchart. The flow of patients through the trial. ABPM: ambulatory blood pressure measurement; BP: blood pressure; COVID: coronavirus disease; ITT: intention-to-treat; PP: per protocol; RDN: renal denervation*

Table 1. Baseline patient characteristics.

	RDN (n=50)	Sham control (n=56)
Age	53.8±11.0	54.4±11.5
Male	40 (80.0)	38 (67.9)
Body mass index, kg/m^2	28.1±4.2	28.9±4.4
eGFR, mL/min per 1.73 m^2	85.8±14.0	85.9±13.0
eGFR <60 mL/min per 1.73 m^2	3 (6.0)	2 (3.6)
Diabetes (all type 2)	2 (4.0)	5 (8.9)
Smoking (current)	8 (16.0)	3 (5.4)
Peripheral artery disease	1 (2.0)	1 (1.8)
Chronic coronary syndrome	2 (4.0)	1 (1.8)
24-hour systolic blood pressure, mmHg	147.6±8.6	148.8±9.6

Table 1 (cont'd).

	RDN (n=50)	Sham control (n=56)
24-hour diastolic blood pressure, mmHg	92.2±7.6	91.0±6.8
Office systolic blood pressure, mmHg	159.4±10.9	160.1±11.0
Office diastolic blood pressure, mmHg	100.4±7.0	98.3±6.1
Office heart rate, bpm	76±11	77±14
Number of antihypertensive medications at screening		
0	12 (24.0)	15 (26.8)
1	17 (34.0)	15 (26.8)
2+	21 (42.0)	26 (46.4)

Numbers are reported as mean±standard deviation or frequency (percentage). bpm: beats per minute; eGFR: estimated glomerular filtration rate; RDN: renal denervation

Table 2. 24-hour ambulatory and office SBP summary (ITT population).

	Baseline		8 weeks		6 months		12 months	
	RDN	Sham control	RDN	Sham control	RDN	Sham control	RDN	Sham control
Ambulatory SBP								
Mean±SD, mmHg (n)	147.6±8.6 (50)	148.8±9.6 (55)	144.6±10.1 (48)	147.0±11.5 (52)	134.1±11.6 (45)	135.1±11.7 (48)	137.6±11.4 (41)	133.7±11.3 (44)
Change from baseline mean±SD, mmHg (n)			–2.9±7.4 (48)	–1.4±8.6 (51)	–13.9±11.6 (45)	–13.4±12.9 (47)	–10.6±11.5 (41)	–15.9±13.1 (43)
P-value from baseline to 8 weeks[a]			0.0089	0.25	<0.0001	<0.0001	<0.0001	<0.0001
Difference between groups (95% CI)			–1.5 (–4.8 to 1.7)		–0.55 (–5.7 to 4.6)		5.3 (–0.1 to 10.7)	
P-value for between-group difference[b]			0.2682		0.6964		0.0775	
Office SBP								
Mean±SD, mmHg (n)	159.4±10.9 (50)	160.1±11.0 (56)	155.4±14.3 (50)	160.6±16.3 (54)	146.1±16.4 (45)	145.7±14.3 (51)	147.9±18.5 (41)	147.8±15.1 (50)
Change from baseline mean±SD, mmHg (n)			–4.0±12.6 (50)	0.63±13.24 (54)	–12.9±15.6 (45)	–14.7±15.7 (51)	–11.0±15.3 (41)	–13.2±16.6 (50)
P-value from baseline to 8 weeks[a]			0.029	0.73	<0.0001	<0.0001	<0.0001	<0.0001
Difference between groups (95% CI)			–4.6 (–9.7 to 0.4)		1.8 (–4.5 to 8.2)		2.2 (–4.5 to 8.9)	
P-value for between-group difference[b]			0.0605		0.724		0.6823	
Ambulatory DBP								
Mean±SD, mmHg (n)	92.2±7.6 (50)	91.0±6.8 (55)	90.0±7.3 (48)	90.1±9.7 (52)	83.0±8.4 (45)	83.4±9.0 (48)	85.6±8.7 (41)	81.0±7.9 (44)
Change from baseline mean±SD, mmHg (n)			–2.0±5.1 (48)	–1.1±6.6 (51)	–9.3±6.9 (45)	–8.0±8.5 (47)	–7.3±7.5 (41)	–9.8±8.3 (43)
P-value from baseline to 8 weeks[a]			0.0086	0.2443	<0.0001	<0.0001	<0.0001	<0.0001
Difference between groups (95% CI)			–0.9 (–3.3 to 1.4)		–1.3 (–4.5 to 1.9)		2.5 (–0.9 to 6.0)	
P-value for between-group difference[b]			0.4734		0.5386		0.0341	
Office DBP								
Mean±SD, mmHg (n)	100.4±7.0 (50)	98.3±6.1 (56)	97.0±9.4 (50)	97.3±10.9 (54)	90.4±9.4 (45)	89.7±10.5 (51)	91.0±11.0 (41)	88.5±11.5 (50)
Change from baseline mean±SD, mmHg (n)			–3.5±7.6 (50)	–1.1±8.8 (54)	–10.0±9.0 (45)	–8.4±9.5 (51)	–9.4±9.4 (41)	–9.6±11.0 (50)
P-value from baseline to 8 weeks[a]			0.0022	0.3578	<0.0001	<0.0001	<0.0001	<0.0001
Difference between groups (95% CI)			–2.3 (–5.6 to 0.9)		–2.5 (–6.1 to 1.2)		–1.6 (–5.4 to 2.1)	
P-value for between-group difference[b]			0.1843		0.3575		0.6375	

[a]P-value from t-test of the hypothesis that the change from baseline is different than 0, by visit and trial group. [b]P-value for comparing RDN and sham control for the difference in the change from baseline from the ANCOVA model adjusted for baseline blood pressure. ANCOVA: analysis of covariance; CI: confidence interval; DBP: diastolic blood pressure; ITT: intention-to-treat; RDN: renal denervation; SBP: systolic blood pressure; SD: standard deviation

For daytime and night-time ambulatory SBP, the changes from baseline to 8 weeks in the RDN group were –3.2±9.5 mmHg compared with –1.7±9.9 mmHg in the sham group with a mean between group difference of –1.5 mmHg (95% CI: –5.4 to 2.4; p=0.2660) and –3.3±9.4 mmHg in the RDN group versus –0.6±12.2 mmHg in the sham group with a mean between-group difference of –2.8 mmHg (95% CI: –7.1 to 1.6; p=0.1908), respectively.

ANTIHYPERTENSIVE MEDICATIONS

Three patients in the RDN group and 5 patients in the sham group were prescribed antihypertensive medications for safety reasons, per the discretion of the treating investigator, before the 8-week 24-hour BP measurement. After 8 weeks, the most widely used antihypertensive medications in the RDN group were calcium channel blockers in 16 (32.0%), 23 (46.0%), and 23 (46.0%) of participants at 3, 6, and 12 months, respectively. This drug class was also the most frequently used of the antihypertensive medications in the sham group at 3 and 6 months, respectively (19 [33.9%] and 24 [42.9%] participants). At 12 months, sham patients used angiotensin II receptor blockers most frequently (26 [46.4%] participants) **(Supplementary Table 3)**.

In addition, antihypertensive drug metabolites were detected in the urine or plasma of 1 RDN and 3 sham group patients. Sensitivity analyses exploring multiple imputation techniques for these data points did not materially alter the conclusions regarding the BP changes **(Supplementary Table 4)**.

Following primary endpoint collection at 8 weeks, antihypertensive medication was uptitrated to achieve a target office SBP ≤140 mmHg while the patient and treating physician were blinded to treatment group assignment up to 12 months post-procedure.

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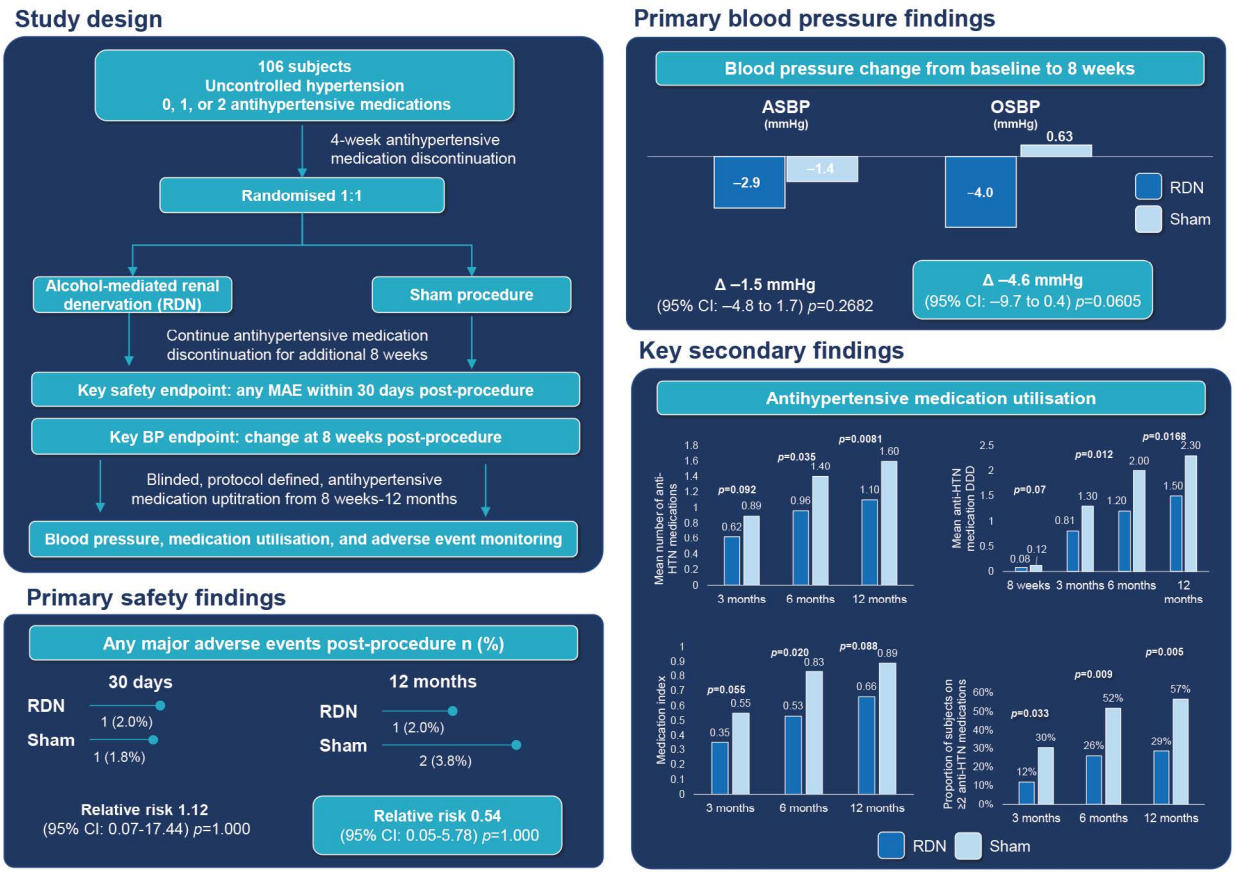
CENTRAL ILLUSTRATION Alcohol-mediated renal denervation effects in the absence of antihypertensive medications.



Fifty subjects were randomised to the alcohol-mediated renal denervation arm and 56 subjects were randomised to the sham control. Up to 12 months, there were no differences in safety events between groups. At 8 weeks post-procedure, there were no significant BP differences between groups despite a non-significant trend for a greater office BP reduction in the RDN group. After 12 months of blinded follow-up, the medication burden was lower in the RDN group. ASBP: ambulatory systolic blood pressure; BP: blood pressure; CI: confidence interval; DDD: defined daily dose; HTN: hypertension; MAE: major adverse event; OSBP: office systolic blood pressure; RDN: renal denervation

Antihypertensive medication utilisation, measured by the mean number of antihypertensive medications prescribed, the DDD, medication index, and the proportion of patients on ≥2 antihypertensive medications, increased from 8 weeks to 12 months in both groups. However, antihypertensive medication use was lower in the RDN group at 3, 6, and 12 months post-procedure **(Figure 3)**. The corresponding BP outcomes are reported in **Table 2**.

Patients randomised to RDN or sham before the start of the COVID-19 pandemic (pre-COVID group n=13; 11 March 2020) had larger 24-hour SBP decreases at 8 weeks post-procedure than patients randomised during the COVID-19 pandemic (post-COVID group) (RDN: –7.0±7.0 mmHg pre-COVID vs –1.5±7.2 mmHg post-COVID; p=0.02; sham: –5.1±5.8 mmHg pre-COVID vs –0.5±9.0 mmHg post-COVID) **(Supplementary Table 5)**. However, notable BP differences between the groups were not observed during the pre- and post-COVID-19 pandemic periods. Further, baseline SBP appeared to be more variable in the post-COVID group for both the RDN and sham groups (RDN: 24-hour SBP SD: 9.2 mmHg and office SBP SD: 11.5 mmHg; sham: 24-hour SBP SD: 9.9 mmHg and office SBP SD: 11.1 mmHg) than in the pre-COVID group (RDN: 24-hour SBP SD: 6.6 mmHg and office SBP SD: 9.1 mmHg; sham: 24-hour SBP: 8.8 mmHg and office SBP SD: 7.6 mmHg) **(Supplementary Table 6)**.

Further *post hoc* analysis showed treatment of all renal accessory arteries (n=5) was associated with a larger decrease in 24-hour SBP compared with subjects with untreated renal accessory arteries (n=8) (change from baseline: –6.6 mmHg versus –0.7 mmHg; p=0.0127) **(Supplementary Table 7, Supplementary Table 8)**.

SAFETY RESULTS

Forty-eight patients (96.0%) were successfully treated with bilateral, alcohol-mediated RDN using the Peregrine System Infusion

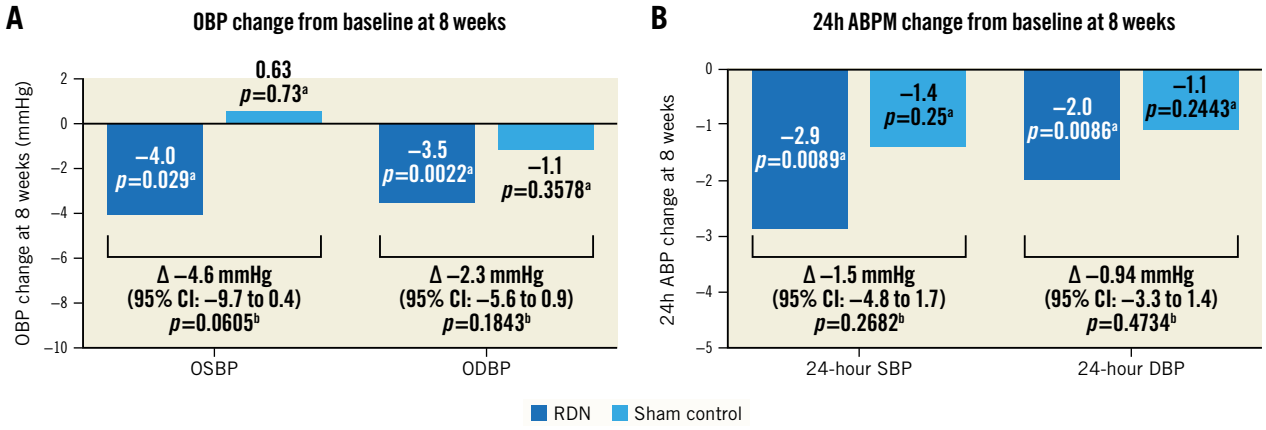


Figure 2. *Blood pressure change from baseline at 8 weeks. A) Office and (B) ambulatory BP changes from baseline at 8 weeks post-procedure for the RDN group (blue) and sham control group (light blue). [a]P-value from t-test of the hypothesis that the change from baseline is different than 0, by trial group. [b]P-value for comparing RDN and sham control for the difference in the change from baseline from the ANCOVA model adjusted for baseline blood pressure. ABPM: ambulatory blood pressure measurement; ANCOVA: analysis of covariance; CI: confidence interval; DBP: diastolic blood pressure; OBP: office blood pressure; ODBP: office diastolic blood pressure; OSBP: office systolic blood pressure; RDN: renal denervation; SBP: systolic blood pressure*

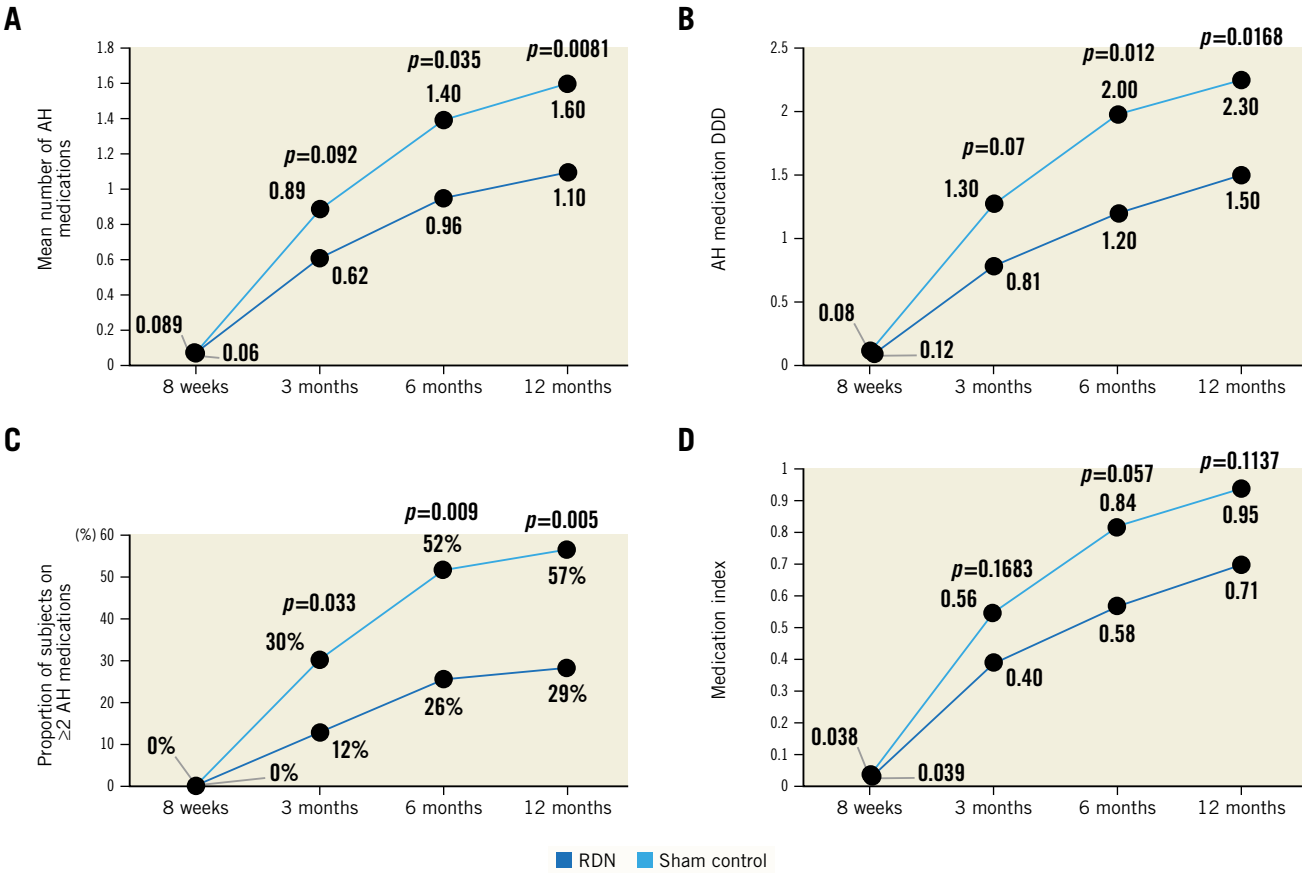


Figure 3. *Antihypertensive medication utilisation. Up to 12 months, the RDN group (blue) were on fewer antihypertensive medications than the sham control group (light blue) as measured by (A) the mean number of antihypertensive medications, (B) defined daily dose (DDD), (C) the proportion on ≥2 antihypertensive medications, and (D) antihypertensive medication index. P-value for comparing the RDN group to the sham control group from the t-test for continuous variables and from the chi-square or Fisher's exact test, as appropriate, for categorical variables. AH: antihypertensive; RDN: renal denervation*

Catheter. The mean±SD (range) procedure time was 62.3±24.0 (18-115) minutes with the mean±SD (range) total volume of contrast used 100.0±55.5 (28-300) mL. In 2 patients, challenging anatomies, due to vessel angulation/tortuosity, permitted only unilateral RDN. The incidence of MAE, up to 30 days post-procedure, was similar between groups (RDN: 2.0%, sham: 1.8%). Up to 30 days post-procedure, 1 RDN patient experienced a hypertensive crisis, and 1 sham control patient experienced a vascular complication (the patient developed a small subcutaneous haematoma; aneurysma spurium was subsequently diagnosed). No evidence of renal artery stenosis was identified at 6 months post-procedure via any of the imaging modalities.

eGFR remained stable in the RDN group but decreased in the sham group up to 12 months post-procedure **(Supplementary Table 9)**.

Discussion

The TARGET BP OFF-MED trial investigated the safety and efficacy of alcohol-mediated RDN in hypertensive patients without antihypertensive medications. Alcohol-mediated RDN safety observations were consistent with prior experience with the Peregrine catheter[14,23] and other RDN modalities[9,24]. At 8 weeks post-procedure, the 24-hour ambulatory BP was not statistically significantly different between groups. During blinded follow-up at 3, 6 and 12 months, the use of antihypertensive medication was found to be lower in the RDN group when compared to the sham control group despite similar office BP measurements.

The BP reductions observed in the RDN group were less than those observed in the prior open-label, alcohol-mediated RDN studies with the Peregrine System in patients taking antihypertensive medications[14,23]. After 12 months of blinded follow-up, with medication escalation, office systolic BP values were similar between groups despite a significantly lower medication burden in the RDN group. The mean office systolic BP did not reach guideline-recommended target levels <140 mmHg in either group. However, the present study was a proof-of-concept trial, not formally powered to assess alcohol-mediated RDN in a different, off-medication, study design including a washout period for antihypertensive medications. Based upon prior studies, we anticipated a clinically meaningful change of 5 mmHg between groups[25,26]. Although unlikely (based upon other clinical trial data), one cannot exclude that alcohol-mediated RDN had no effect on BP in patients not taking concomitant antihypertensive medication in this trial cohort. It is important to note that, unlike prior alcohol-mediated RDN studies, the majority of patients in the present trial were recruited during the COVID-19 pandemic. Population-based studies in hypertensive patients during the COVID-19 pandemic have reported increases in SBP as high as 5.6 mmHg[4-6]. Other randomised controlled cardiovascular clinical trials have reported similar dichotomous outcomes when subgrouping primary endpoint results by pre- or post-COVID-19 pandemic[27,28]. Similarly, in this trial, larger and clinically meaningful BP changes were observed in patients that were enrolled prior to the start of the COVID-19 pandemic. Results also suggest that 24-hour ABPM may be sensitive to COVID-19 stressors and public health measures which may have affected lifestyle (e.g., sleep deprivation, activity, diet, etc.) and social living. The individual impact is difficult to measure or control in a clinical trial setting. It is possible that this confounding effect was not evenly distributed between patients and treatment groups.

The completeness of renal artery treatment may have also played a role in the smaller than anticipated BP decrease in the RDN group. The treatment of accessory arteries has previously been shown to be related to the magnitude of BP reduction[29], and this is consistent with the present trial's results. This reiterates the importance of complete renal artery treatment on BP reduction, in particular treating accessory arteries, which has been shown to contribute to the sympathetic innervation of the renal parenchyma. For future studies, a Peregrine System Infusion Catheter that facilitates treatment of smaller renal arteries (3-4 mm) is now available and may improve the ability to achieve more complete RDN. Although the mean office SBP was similar between treatment groups at 3, 6, and 12 months, there were fewer antihypertensive medications used in the RDN group than in the sham control group. Importantly, the reduced antihypertensive medication utilisation in the RDN group occurred while the patients and the treating physicians remained blinded to treatment status. The reduced medication burden observed in the RDN group, relative to the sham control group, may be due to better BP control associated with RDN and a reduced need for medications. This observation suggests an RDN treatment effect and potential benefit for the patient up to 12 months post-procedure[30-33].

The pivotal, randomised, powered, sham-controlled TARGET BP I trial (ClinicalTrials: NCT02910414) for patients taking antihypertensive medications is currently ongoing and will further assess the efficacy of alcohol-mediated RDN in the management of HTN.

Limitations

This trial was designed as a hypothesis-generating safety and efficacy trial and, hence, not formally powered for the primary efficacy endpoint. The sample size, in particular for subgroup analyses, was small. Larger, appropriately powered, trials are necessary to conclusively determine the BP-lowering effect of alcohol-mediated RDN in hypertensive patients. Alcohol-mediated RDN with the Peregrine System Infusion Catheter has no intraprocedural operator feedback confirming complete ablation of renal sympathetic nerves. This is currently a limitation for all modalities of RDN. Finally, the COVID-19 pandemic may have introduced additional confounding factors, which, at present, cannot be objectively quantified.

Conclusions

The results from this randomised, sham-controlled, assessor-blinded trial investigating the safety and efficacy of alcohol-mediated RDN for the treatment of uncontrolled HTN in the absence of antihypertensive medications demonstrated that alcohol-mediated RDN was safely delivered; however, there was not sufficient evidence to show a BP difference between groups. The antihypertensive medication burden was lower in the RDN group up to

12 months post-procedure. Studies of larger powered trials, not confounded by the COVID-19 pandemic, are underway to further assess the efficacy of alcohol-mediated RDN in the management of HTN.

Impact on daily practice

Catheter-based RDN using radiofrequency or ultrasound energy has been demonstrated to safely lower BP. Previous open-label trials have demonstrated that alcohol-mediated RDN is safe and has significantly lowered ambulatory and office BP in patients with severe uncontrolled HTN. Despite the results of this current trial not providing sufficient evidence to show a BP difference between groups, the results did demonstrate that alcohol-mediated RDN was safely delivered, and the medication burden was lower in the RDN group up to 12 months post-procedure.

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Conflict of interest statement

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Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria.

Supplementary Appendix 2. Proposed dose titration steps.

Supplementary Appendix 3. Study endpoints.

Supplementary Appendix 4. List of trial sites and investigators.

Supplementary Table 1. Treatment perception: Bang and James blinding indices (ITT analysis set).

Supplementary Table 2. 24-hour ambulatory BP (per-protocol population).

Supplementary Table 3. 24-hour ambulatory BP at 8 weeks post-procedure.

Supplementary Table 4. 24-hour ambulatory BP at 8 weeks post-procedure (sensitivity analyses).

Supplementary Table 5. COVID-19 era subgroup analyses on 24-hour SBP at 8 weeks (*post hoc*).

Supplementary Table 6. COVID-19 era subgroup analyses on baseline BP standard deviation (*post hoc*).

Supplementary Table 7. Renal artery treatment status effect on 24-hr SBP at 8 weeks (*post hoc*).

Supplementary Table 8. Accessory renal artery treatment status RDN group subgroup analyses effect on BP at 8 weeks (*post hoc*).

Supplementary Table 9. eGFR up to 12 months.

Supplementary Figure 1. Distribution of patient baseline and primary endpoint (8-week) visits relative to the onset of COVID-19.

Supplementary Figure 2. Systolic blood pressure by visit.

Supplementary Figure 3. Individual patient blood pressure changes.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00088

Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible and undergo the procedure:

Prior to run-in period

Patient has provided written informed consent.

Male or female patient, aged ≥18 and ≤80 years at time of enrollment.

If patient has a documented history of uncontrolled hypertension and is currently taking no (0) antihypertensive medications, he/she must:

- Have 3 office blood pressure measurements with a mean office SBP of ≥140 mmHg and ≤180 mmHg **AND** mean office DBP ≥90 mmHg, and
- Be willing to adhere to the no-medication regimen for at least 12 weeks (4-week run-in period and 8-week post-treatment period).

If patient has a documented history of uncontrolled hypertension and is currently taking 1 or 2 antihypertensive medications, he/she must:

- Have 3 office blood pressure measurements with a mean office SBP of ≥120 mmHg and ≤180 mmHg, and
- Be willing to discontinue his/her antihypertensive medication(s), and to adhere to the no medication regimen for at least 12 weeks (4-week run-in period and 8-week post-treatment period).

Investigator judges that the patient can be discontinued safely from all current antihypertensive medication (where applicable) and managed safely for at least 12 weeks (4-week run-in period and 8-week post-treatment period) without antihypertensive medication intake.

Female patients of childbearing potential must agree to use acceptable methods of contraception, from the time of informed consent through to the last follow-up visit.

Patient agrees to have all study procedures performed and is able and willing to comply with all study follow-up visits and protocol requirements.

End of run-in period

Patient has 3 office blood pressure measurements with a mean office SBP of ≥140 mmHg and ≤180 mmHg **AND** mean office DBP ≥90 mmHg.

Patient has a mean 24-hour ambulatory SBP of ≥135 mmHg and ≤170 mmHg with ≥70% valid readings (as determined by ABPM measurement device).

Exclusion Criteria

If **ANY** of the following exclusion criteria are met, the patient must be excluded from the trial and cannot be randomized or undergo the procedure:

1. Patient has a contraindication known for conventional percutaneous interventional procedures such as:

   Intolerance for antiplatelet/anticoagulant therapy

   Known allergy to contrast media that cannot be adequately pre-medicated

   Bleeding/coagulation disorders (such as bleeding diathesis, thrombocytopenia, and severe anemia)

   Occlusive peripheral vascular disease that would preclude percutaneous femoral access for the procedure.

2. Patient has an acute or sub-acute infection that the investigator judges would pose unacceptable procedural risks to the patient.

3. Patient has imaging-assessed renal artery anatomy abnormalities or variations based on investigator's evaluation of the screening images (i.e. MRA/CTA examination and/or renal angiography) meeting one of the following criteria:

   Main renal artery that has a diameter of <4 mm or >7 mm and length of <5 mm

   Accessory renal arteries with diameter >2 mm or <4 mm, which supply >20% of the whole kidney parenchyma on that side, per the investigator's judgment. Note: patients with more than one eligible accessory renal artery per side will be excluded.

   Renal artery stenosis >50% of the normal diameter segment (diameter stenosis, compared to the angiographically normal proximal or distal segment)

   Any renal artery abnormality or disease that, per the physician assessment, precludes the safe insertion of the guiding catheter (including, but not limited to, severe renal artery aneurysm, excessive tortuosity, severe renal artery calcification)

   Previous renal angioplasty associated with stenting or other implants, that, per the physician's assessment, precludes the safe deployment of the Peregrine Catheter components in the target treatment segment of the renal artery

   Previous renal denervation

   Fibromuscular dysplasia of the renal arteries.

4. Patient has documented severe untreated obstructive sleep apnea (apnea-hypopnea index [AHI] ≥30 per hour).

5. Patient has documented diagnosis of the following causes of hypertension: Cushing's disease or Cushing's Syndrome, hyperaldosteronism, pheochromocytoma, thyroid and parathyroid abnormalities, or onset of hypertension prior to the age of 18.

6. Patient has a history of pre-eclampsia.

7. Patient has orthostatic hypotension at screening, or documented history of orthostatic hypotension within 12 months prior to the planned procedure, defined as a drop in blood pressure that is >20 mmHg in SBP and/or >10 mmHg in DBP within 3 minutes upon standing from sitting or from a lying down face-up (supine) position.

8. Patient has Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus (defined as as hemoglobin A1c [HbA1c] ≥9.0%).

9. Patient has an eGFR of ≤45 mL/min/1.73 m^2, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; or is on chronic renal replacement therapy.

10. Patient has nephrotic syndrome.

11. Patient has a history of recurrent (>1 episode) kidney stones, or history of kidney stones within 12 months prior to the planned procedure.

12. Patient has a history of nephrectomy, a single kidney or kidney tumor, or urinary tract obstruction (with potential for hydronephrosis). Note: Simple renal cysts are not an exclusion.

13. Patient has a renal transplant, or is known to have a non-functioning kidney or unequal renal size (>2 cm difference in renal length between kidneys associated with a chronic kidney disease or a deterioration of the kidney function).

14. Patient has a history of myocardial infarction, unstable angina pectoris, or stroke/TIA within 6 months prior to the planned procedure.

15. Patient has any of the following conditions: severe cardiac valve stenosis, heart failure (New York Heart Association [NYHA] Class III or IV), chronic atrial fibrillation, and known primary pulmonary hypertension (>60 mmHg pulmonary artery or right ventricular systolic pressure).

16. Patient is allergic or intolerant to the neurolytic agent (i.e. dehydrated alcohol).

17. Patient is being treated chronically (e.g. daily use) with NSAIDs, immunosuppressive medications, or immunosuppressive doses of steroids. Aspirin therapy and nasal pulmonary inhalants are allowed.

18. Any contraindication to the imaging as required per the protocol.

19. Patient for whom an ABPM device cannot be used due to arm size (>42 cm arm circumference) or other reasons as identified by the investigator.

20. Patient has any other acute or chronic condition that the investigator believes will adversely affect the ability to interpret the data or will prevent the patient from completing the trial procedures, or has a life expectancy of <12 months.

21. Patient has a known history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions, or for any reason, in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements.

22. If female, patient is pregnant or lactating at the time of enrollment or planning to become pregnant during the trial time period.

23. Patient has participated in another clinical study involving an investigational drug or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an investigational drug or investigational device during the course of this study. Patients enrolled in observational registries not involving renal denervation may still be eligible.

24. Patient is in custody or an institution.

25. Patient has close affiliation with the study site or sponsor (e.g. employee, close relative of an employee).

26. Patient has a history of hypertensive emergency in the previous 3 months.

Supplementary Appendix 2. Proposed dose titration steps.

Proposed Dose Titration Steps to Maintain a Target Office SBP of <140 mmHg and ≥90 mmHg after Week 8 Visit

Step (Target SBP <140 mmHg and ≥90 mmHg)[a]	**Drug**	**Treatment Score[b]**
0 (not needed)	None	0
1 (if needed)	CCB: mid-dose	1
2 (if needed)	ACE inhibitor or ARB: full dose	2
3 (if needed)	Hydrochlorothiazide 12.5 mg	3
4 (if needed)	Hydrochlorothiazide 25 mg	4
5 (if needed)	CCB: increase to full dose	5
6 (if needed)	Spironolactone or beta-blocker or clonidine	6
7 (if needed)	Spironolactone or beta-blocker or clonidine	7
8 (if needed)	Spironolactone or beta-blocker or clonidine	8

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; SBP = systolic blood pressure.

a There will usually be 2 to 3 weeks between steps. If the target is reached, there are no further steps even if BP fluctuates above the target. For Steps 6, 7, and 8, the choice of drug and dose is at the investigator's discretion. If initial systolic BP is ≥160 mmHg, Steps 1 and 2 can be combined. Fixed-combination drug products can be used to decrease pill burden.

b The treatment score will be used for the purpose of the statistical analysis.

Supplementary Appendix 3. Study endpoints.

Primary efficacy endpoint

The primary efficacy endpoint is defined as the change in mean 24-hour ambulatory SBP from baseline to 8 weeks post-treatment. This will be summarized and compared between the 2 treatment groups using the independent two-sample t-test.

Secondary efficacy endpoints:

Change in mean 24-hour, daytime (07:00 to 21:59), and nighttime (22:00 to 06:59) ambulatory SBP and DBP from baseline to time points post-treatment.

Change in mean office SBP and DBP from baseline to time points post-treatment.

Percentage of subjects controlled to target blood pressure values.

Use of antihypertensive medication(s) from time of procedure to 8 weeks post-treatment (emergency use medication).

Use of antihypertensive medication(s) (including increases/decreases) from 8 weeks to 6 months and 1 year post-treatment (titrated according to standardized formula to maintain a target SBP of <140 mmHg and ≥90 mmHg).

Compliance with not taking antihypertensive medications through 8 weeks post-treatment.

Changes from baseline will be computed as the paired mean difference and will be summarized with descriptive statistics (n, mean, SD, range, median). The 95% confidence interval (CI) of the difference between treatment groups at each time point will be computed. Categorical data will be summarized as frequencies and percentages. Relative risks and 95% CIs will be computed. Secondary efficacy endpoints are considered supportive and thus there is no adjustment to alpha for multiplicity with a single primary efficacy endpoint. Analysis of efficacy endpoints will be conducted in the ITT and PP Analysis Sets. For the primary efficacy endpoint analysis, the main population is considered the ITT, and the PP is considered supportive.

For all continuous primary and secondary blood pressure endpoints, changes over time will be additionally explored in mixed effects repeated measures analyses, including the values at all time points.

It is planned to conduct an 8-week blinded interim analysis, a 6-month blinded interim analysis, and an unblinded 1-year interim analysis after all subjects have completed the 1-year follow-up visit and the study has been unblinded.

Secondary safety endpoints:

- Major adverse events (MAEs) through 30 days post-treatment, as adjudicated by the Clinical Events Committee (CEC). An MAE is defined as any of the following:

  All-cause death

  End-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2 or need for renal replacement therapy)

  Significant embolic event resulting in end-organ damage or requiring intervention to prevent it

  Major vascular complications, including major renal artery dissection, renal artery aneurysm or pseudoaneurysm that required intervention or led to renal artery stenosis (>60% diameter stenosis)

  Major bleeding related to renal denervation within the renal arteries, or related to the Peregrine Catheter when in the body (per protocol bleeding definition)

  Significant acute (post-procedural) renal artery stenosis (>60% diameter stenosis) as indicated by the renal angiogram post renal denervation, and confirmed by the angiography core laboratory, which led to one of the following: (i) acute kidney injury per modified Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) definition, as confirmed by renal function blood test, or (ii) percutaneous intervention.

  Hypertensive crisis (hypertensive emergency only)

Hypotensive crisis

Symptomatic hypotension that required a change in antihypertensive medications, or medications to increase blood pressure (e.g. persistent syncope, lightheadedness)

- Changes in eGFR from baseline to 8 weeks, 6 months, and 1-year post-treatment.
- Decreases in eGFR >25% from baseline to 8 weeks, 6 months, and 1-year post-treatment.
- Rate of adverse events (serious and non-serious), peri-procedurally, at discharge, and at each of the follow-up time points.
- Device success (defined as the ability to insert the Peregrine Catheter into the lumen of the renal artery [target vessel], deploy the guide tubes inside the renal artery, deploy the needles through the arterial wall, deliver the intended dose of alcohol, retract the needles and the guide tubes back in the catheter, and remove the catheter from the access site without any related complications or events)
- Procedure success (defined as device success with freedom from peri-procedural MAEs).

Supplementary Appendix 4. List of trial sites and investigators.

Dr. Manish Saxena
NIHR Barts Cardiovascular Biomedical Research Unit
William Harvey Research Institute, QMUL,
Centre for Clinical Pharmacology
Queen Mary University of London
Charterhouse Square
London
EC1M 6BQ
UK

Dr Clare Bent
Royal Bournemouth Hospital
BH7 7DW
UK

Dr. Benjamin Honton
Clinique Pasteur
Groupe CardioVasculaire Interventionnel
45, avenue du Lombez
BP 27617
31076 TOULOUSE Cedex 3
France

Prof. Philippe GOSSE
CHU de Bordeaux
Hôpital Saint-André
1, rue Jean Burguet
33075 Bordeaux
France

Dr Bernard BEYSSEN
Clinique CMC Ambroise Paré
25-27, boulevard Victor Hugo
92200 Neuilly sur Seine
France

Prof. Dr. med. Horst Sievert
CardioVasculäres Centrum (CVC) Frankfurt
Seckbacher Landstr. 65
60389 Frankfurt/Main
Germany

Prof. Peter J. Blankestijn
University Medical Center Utrecht (UMCU)
Dept. Of Nephrology
Heidelberglaan 100
3485 CX Utrecht
The Netherlends

Dr. Eric Lipsic
University Medical Center (UMCG)
Dept. Of Cardiology
Hanzeplein 1
9713 GZ Groningen
The Netherlands

Dr Maria ROUGIER
Centre Hospitalier de Pau
Service de Cardiologie
4 boulevard Hauterive
64000 Pau
France
Prof. Prof. h.c. Dr. med. Markus van der Giet
Charité-Universitaetsmedizin Berlin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
12203 Berlin
Germany

Dr. med. Ulrike Maria Rudolph
Universitätsklinikum Leipzig
Klinik and Poliklinik für Kardiologie
Liebigstrasse 20, Haus 4
04103 Leipzig
Germany

Prof. Dr. med. Thomas Zeller
UNIVERSITÄTSKLINIKUM FREIBURG
Universitäts-Herzzentrum
Klinik für Kardiologie und Angiologie II Bad Krozingen
Clinic of Cardiology and Angiology II Bad Krozingen
Südring 15 79189 Bad Krozingen
Germany

Professeur Xavier Girerd
Groupe Hospitalier Pitié-Salpêtrière
Institut IE3M
47-83 boulevard de l'Hôpital
75651 Paris Cedex 13
France

Dr. Faisal Sharif
Saolta University Healthcare Group
Newcastle Road
Galway H91 YR 71
Ireland

Prof. Dr. med. Marcel Halbach

Herzzentrum der Uniklinik Köln (Heart Center at University of Cologne)
Klinik für Kardiologie, Angiologie, Pneumologie und internistische Intensivmedizin
Hypertoniezentrum
Kerpenerstr. 6
50937 Cologne
Germany

Prof. Patrick Rossignol
Prof. Jean-Marc BOIVIN (from June 2022)
CHRU de Nancy, Hôpitaux de Brabois, Institut Louis Mathieu, Centre Investigation Clinique plurithématique, RDC, porte 3
4 rue du Morvan
54500 Vandoeuvre les Nancy, France"

Prof Alexandre Persu
Cliniques Universitaires Saint-Luc (UCL)
Division of Cardiology
10 avenue Hippocrate
1200, Brussels
Belgium

Prof. Dr. med. Felix Mahfoud
Universitätsklinikum des Saarlandes
Klinik für Innere Medizin III
Kardiologie, Angiologie und Internistische Intensivmedizin
Kirrbergerstr. 1, Geb. 41
66421 Homburg/Saar
Germany

Prof. Dr. Roland E. Schmieder
Universitätsklinikum Erlangen
Nephrologie und Hypertensiologie
Medizin 4
Ulmenweg 18,
91054 Erlangen
Germany

Dr. Eric Wyffels
Onze Lieve Vrouw Ziekenhuis Aalst
Moorselbaan 164
9300 Aalst
Belgium

Prof. Dr. med. Martin Bergmann
Paul-Ehrlich-Str. 1,3. Medizinische
Abteilung, Kardiologie,
Pneumologie und Internistische
Intensivmedizin
22763 Hamburg
Germany

Dr Asif Ali
Houston Cardiology Consultants
8830 Long Point Suite 507
Houston
TX 77055
USA

Dr Shukri David
Ascension Providence Hospital
16001 W. Nine Mile Rd
Southfield
MI 48075"
USA

Dr Nilesh Goswami
Prairie Cardiovascular Consultants, Ltd
701 East Mason Street
Springfield
IL 62769
USA

Dr Malcolm Foster
Tennova Healthcare - Turkey Creek Medical Center
10820 Parkside Drive
Knoxville
TN 37934
USA

Dr James Zidar
NC Heart and Vascular Research, LLC
4414 Lake Boone Trail
Suite 409 Raleigh
NC 27607
USA

Saihari Sadanandan
Tampa Cardiovascular Interventions & Research
4620 North Habana Ave,
Suite 203
Tampa FL 33614
USA

Supplementary Table 1. Treatment perception: Bang[a] and James[b] blinding indices (ITT analysis set).

	Patient Guess					
	RDN	**Sham Control**	**Do Not Know**	**Total**	**James' BI (95% CI)**	**Bang's BI (95% CI)**
Procedure						
RDN Group	13 (61.9%)	3 (60.0%)	32 (43.2%)	48 (48.0%)		0.21 (0.06,0.36)
Sham Control	8 (38.1%)	2 (40.0%)	42 (56.8%)	52 (52.0%)		-0.12 (-0.23,-0.00)
Total	21 (100.0%)	5 (100.0%)	74 (100.0%)	100 (100.0%)	0.87 (0.81,0.93)	
8 Weeks						
RDN Group	5 (45.5%)	8 (38.1%)	33 (51.6%)	46 (47.9%)		-0.07 (-0.22,0.09)
Sham Control	6 (54.5%)	13 (61.9%)	31 (48.4%)	50 (52.1%)		0.14 (-0.03,0.31)
Total	11 (100.0%)	21 (100.0%)	64 (100.0%)	96 (100.0%)	0.82 (0.75,0.90)	

[a] Bang's Blinding Index: Ranging from -1 to 1, -1 = opposite guessing, 1 = complete unblinding. Values close to 0 indicate random guessing.
[b] James' Blinding Index: Ranging from 0 to 1, 0 = total lack of blinding, 1 = complete blinding. If the upper bound of the confidence interval is greater than 0.5 then blinding is achieved.

Supplementary Table 2. 24-hour ambulatory BP (per-protocol population).

		Systolic				Diastolic			
		RDN Group	**Sham Group**	**Difference (95% CI)[a]**	**P-value[b]**	**RDN Group**	**Sham Group**	**Difference (95% CI)[a]**	**P-value[b]**
Baseline									
	Mean±SD (n)	147.9 ± 8.7 (43)	148.7 ± 9.9 (44)	-0.71 (-4.69, 3.28)	0.7245	92.4 ± 7.4 (43)	90.4 ± 6.4 (44)	1.9 (-1.0, 4.9)	0.1953
8 Weeks									
	Mean±SD (n)	145.9 ± 10.0 (43)	147.3 ± 11.4 (44)	-1.4 (-6.0, 3.1)	0.5353	90.8 ± 7.1 (43)	89.2 ± 8.6 (44)	1.6 (-1.8, 5.0)	0.3457
Change from Baseline									
	Mean±SD (n)	-2.1 ± 7.2 (43)	-1.4 ± 8.4 (44)	-0.72 (-4.06, 2.61)	0.6027	-1.6 ± 5.2 (43)	-1.3 ± 6.1 (44)	-0.34 (-2.77, 2.08)	0.9793

a. Difference between Peregrine Kit and Sham Control for changes from baseline.
b. P-value for comparing Peregrine Kit to Sham Control from the ANCOVA model adjusted for baseline blood pressure.

CI = confidence interval, RDN= renal denervation

Supplementary Table 3. 24-hour ambulatory BP at 8 weeks post-procedure.

	Screening (Wk -8)	Baseline (Wk -1)	4-week	8-Week	3-Month	6-Month	1-Year
Peregrine Kit							
Vasodilators Used In Cardiac Diseases	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antiadrenergic Agents, Centrally Acting	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
Antiadrenergic Agents, Peripherally Acting	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Low-Ceiling Diuretics, Thiazides	7 (14.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	4 (8.0%)	3 (6.0%)
Low-Ceiling Diuretics, Excl. Thiazides	2 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	3 (6.0%)	3 (6.0%)
High-Ceiling Diuretics	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Potassium-Sparing Agents	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
Beta Blocking Agents	4 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Selective Calcium Channel Blockers With Mainly Vascular Effects	16 (32.0%)	0 (0.0%)	1 (2.0%)	2 (4.0%)	16 (32.0%)	23 (46.0%)	23 (46.0%)
Selective Calcium Channel Blockers With Direct Cardiac Effects	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Ace Inhibitors, Plain	7 (14.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (6.0%)	4 (8.0%)	5 (10.0%)
Angiotensin II Receptor Blockers (ARBS), Plain	18 (36.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	9 (18.0%)	12 (24.0%)	15 (30.0%)
Sham Control							
Vasodilators Used In Cardiac Diseases	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antiadrenergic Agents, Centrally Acting	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antiadrenergic Agents, Peripherally Acting	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Low-Ceiling Diuretics, Thiazides	7 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	8 (14.3%)	8 (14.3%)
Low-Ceiling Diuretics, Excl. Thiazides	3 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
High-Ceiling Diuretics	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	2 (3.6%)
Potassium-Sparing Agents	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	3 (5.4%)
Beta Blocking Agents	6 (10.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	3 (5.4%)	4 (7.1%)
Selective Calcium Channel Blockers With Mainly Vascular Effects	14 (25.0%)	0 (0.0%)	2 (3.6%)	2 (3.6%)	19 (33.9%)	24 (42.9%)	22 (39.3%)
Selective Calcium Channel Blockers With Direct Cardiac Effects	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	2 (3.6%)	2 (3.6%)
Ace Inhibitors, Plain	13 (23.2%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	8 (14.3%)	14 (25.0%)	15 (26.8%)
Angiotensin II Receptor Blockers (ARBs), Plain	19 (33.9%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	17 (30.4%)	22 (39.3%)	26 (46.4%)

Supplementary Table 4. 24-hour ambulatory BP at 8 weeks post-procedure (sensitivity analyses).

		RDN Group			Sham Group				
		8 Weeks	**Matched Baseline**	**Change from Baseline**	**8 Weeks**	**Matched Baseline**	**Change from Baseline**	**Difference (95% CI)[a]**	**P-value[b]**
All Available Data (No Imputation)	Mean±SD (n)	144.6 ± 10.1 (48)	147.6 ± 8.6 (48)	-2.9 ± 7.4 (48)	147.0 ± 11.5 (52)	148.8 ± 9.4 (51)	-1.4 ± 8.6 (51)	-1.5 (-4.8, 1.7)	0.2682
	[min,max]	[129.4, 173.8]	[134.4, 167.2]	[-18.1, 15.9]	[122.1, 170.7]	[134.7, 169.9]	[-24.2, 23.0]		
	(95% CI)	(141.7,147.6)	(145.1,150.1)	(-5.1,-0.8)	(143.8,150.2)	(146.2,151.5)	(-3.8,1.0)		
Imputation #1 escape patients imputed[c]	Mean±SD (n)	145.2 ± 9.9 (49)	147.8 ± 8.6 (49)	-2.5 ± 7.3 (49)	146.9 ± 11.4 (53)	148.7 ± 9.3 (52)	-1.4 ± 8.2 (52)	-1.1 (-4.2, 1.9)	0.3849
	[min,max]	[131.0, 173.8]	[134.4, 167.2]	[-18.1, 15.9]	[122.1, 170.7]	[134.7, 169.9]	[-24.2, 23.0]		
	(95% CI)	(142.4,148.1)	(145.3,150.3)	(-4.6,-0.4)	(143.8,150.1)	(146.1,151.3)	(-3.7,0.9)		
Imputation #2 escape patients removed[d]	Mean±SD (n)	145.2 ± 10.0 (46)	147.9 ± 8.6 (46)	-2.7 ± 7.5 (46)	146.8 ± 11.8 (48)	148.8 ± 9.7 (47)	-1.5 ± 8.6 (47)	-1.2 (-4.5, 2.2)	0.4176
	[min,max]	[131.0, 173.8]	[134.4, 167.2]	[-18.1, 15.9]	[122.1, 170.7]	[134.7, 169.9]	[-24.2, 23.0]		
	(95% CI)	(142.2,148.1)	(145.3,150.4)	(-4.9,-0.5)	(143.3,150.2)	(145.9,151.6)	(-4.1,1.0)		
Imputation #3 any medications detected removed[e]	Mean±SD (n)	145.6 ± 10.0 (44)	147.9 ± 8.6 (44)	-2.3 ± 7.3 (44)	146.8 ± 11.8 (45)	148.7 ± 9.9 (44)	-1.4 ± 8.4 (44)	-0.96 (-4.29, 2.37)	0.5060
	[min,max]	[131.0, 173.8]	[134.4, 167.2]	[-15.9, 15.9]	[122.1, 170.7]	[134.7, 169.9]	[-24.2, 23.0]		
	(95% CI)	(142.6,148.6)	(145.3,150.5)	(-4.5,-0.1)	(143.3,150.3)	(145.6,151.7)	(-3.9,1.2)		
Imputation #4 Multiple Imputation for missing data[f]		144.4±1.4	147.6±1.2	-3.2±1.1	146.8±1.6	148.5±1.3	-1.7±1.3	-1.6 (-4.9, 1.6)	0.3239

	RDN Group			Sham Group				
	8 Weeks	Matched Baseline	Change from Baseline	8 Weeks	Matched Baseline	Change from Baseline	Difference (95% CI)[a]	P-value[b]
Imputation #5 Multiple Imputation for missing and escape patients[7]	144.7±1.4	147.6±1.2	-2.9±1.1	146.7±1.6	148.5±1.3	-1.8±1.3	-1.3 (-4.5, 2.0)	0.4347

a. Difference between Peregrine Kit and Sham Control for changes from baseline.
b. P-value for comparing Peregrine Kit to Sham Control from the ANCOVA model adjusted for baseline blood pressure.
c. Baseline value of ABPM imputed for subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within the 8 w eeks prior to assessment.
d. Subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks removed from the analysis.
e. Subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks, AND any subjects in whom anti-hypertensive
medications are detected via compliance analysis regardless of whether the protocol defined criteria was met removed from the analysis.
f. Missing data at 8 weeks imputed via multiple imputation techniques and combined over 5 imputed data sets using the MCMC algorithm. Covariates include: t reatment group,
age, gender, diabetes, BMI, length from ostium to bifurcation, # of baseline meds, 8-week office SBP, baseline 24-hour systolic ABP. Values are mean ± SE.
g. Missing data at 8 weeks and data for those subjects who meet the protocol defined criteria for antihypertensive drug treatment and receive treatment within 8 weeks imputed
via multiple imputation techniques.
Values are mean ± SE.

CI= confidence interval, RDN= renal denervation

Supplementary Table 5. COVID-19 era subgroup analyses on 24-hour SBP at 8 weeks (*post hoc*).

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		RDN		Sham Control	
		Patients randomized prior COVID- 19 pause[a]	**Patients randomized after COVID- 19 pause[a]**	**Patients randomized prior COVID- 19 pause[a]**	**Patients randomized after COVID- 19 pause[a]**
Change from Baseline (mmHg)	Mean±SD (n)	-6.9 ± 7.0 (13)	-1.5 ± 7.2 (35)	-5.1 ± 5.8 (10)	-0.5 ± 9.0 (41)
Subgroup P-value		0.008		0.141	

[a] 11 March 2020, COVID-19 = coronavirus disease 2019; RDN = renal denervation; SBP = systolic blood pressure; SD = standard deviation.

Supplementary Table 6. COVID-19 era subgroup analyses on baseline BP standard deviation (*post hoc*).

	RDN		Sham Control	
	Patients randomized prior COVID- 19 pause[a]	**Patients randomized after COVID- 19 pause[a]**	**Patients randomized prior COVID- 19 pause[a]**	**Patients randomized after COVID- 19 pause[a]**
Baseline 24 hour ASBP standard deviation; mmHg (n)	6.6 (13)	9.1 (37)	8.8 (11)	9.9 (44)
Baseline OSBP standard deviation; mmHg (n)	9.2 (13)	11.5 (37)	7.6 (12)	11.1 (44)

[a] 11 March 2020, ASBP = ambulatory systolic blood pressure; COVID-19 = coronavirus disease 2019; OSBP = office systolic blood pressure; RDN = renal denervation.

Supplementary Table 7. Renal artery treatment status effect on 24-hr SBP at 8 weeks (*post hoc*).

		RDN Group			Sham Control Group				
		Adjusted mean (95% CI)	**Within group p-value.[a]**	**Subgroup p p-value[b]**	**Adjusted mean (95%CI)**	**Within group p-value[a]**		**Difference bt Groups (95% CI)**	**Difference p-value[c]**
24-Hr Mean Systolic ABP at 8 weeks									
All Eligible Renal Arteries Treated	YES[d]	-3.7 (-6.4, -0.9)	0.012	0.422	-1.3 (-3.5, 0.9)	0.255		-2.4 (-5.9, 1.2)	0.186
	NO[e]	-1.6 (-6.1, 3.0)	0.439		-1.3 (-3.6, 1.0)	0.255		-0.2 (-5.4, 4.9)	0.932

a. Testing the within subgroup within treatment hypothesis that the difference is different from 0 from one sample t-test
b. Testing the hypothesis that subgroups are different within treatment from ANCOVA adjusting for baseline BP
c. Testing the hypothesis that treatments are different within subgroups from ANCOVA adjusting for baseline BP
d. Defined as bi-lateral main renal artery treatment and no accessories present or if accessories present all were treated
e. Defined as no bi-lateral main artery treatment or if accessories arteries were present only some or none were treated

ABP = ambulatory blood pressure, RDN= renal denervation

Supplementary Table 8. Accessory renal artery treatment status RDN group subgroup analyses effect on BP at 8 weeks (*post hoc*).

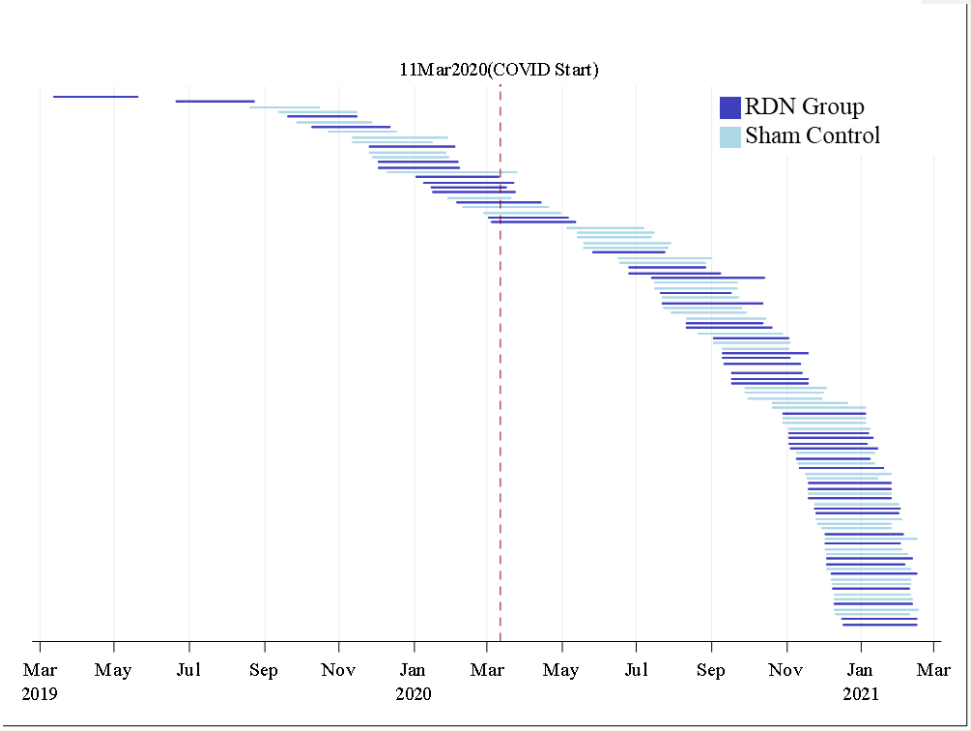
	n	24-hour ambulatory SBP at 8 weeks change from baseline (Mean, 95% CI, mmHg)	Subgroup P-value
Accessory Treatment Status			
Accessory renal arteries identified - all treated	5	-6.6 (-12.1, -1.2)	0.0127
Accessory renal arteries identified – none treated	8	-0.7 (-5.3, 3.9)	

BP= blood pressure, CI= confidence interval, RDN= renal denervation, SBP = systolic blood pressure

Supplementary Table 9. eGFR up to 12 months.

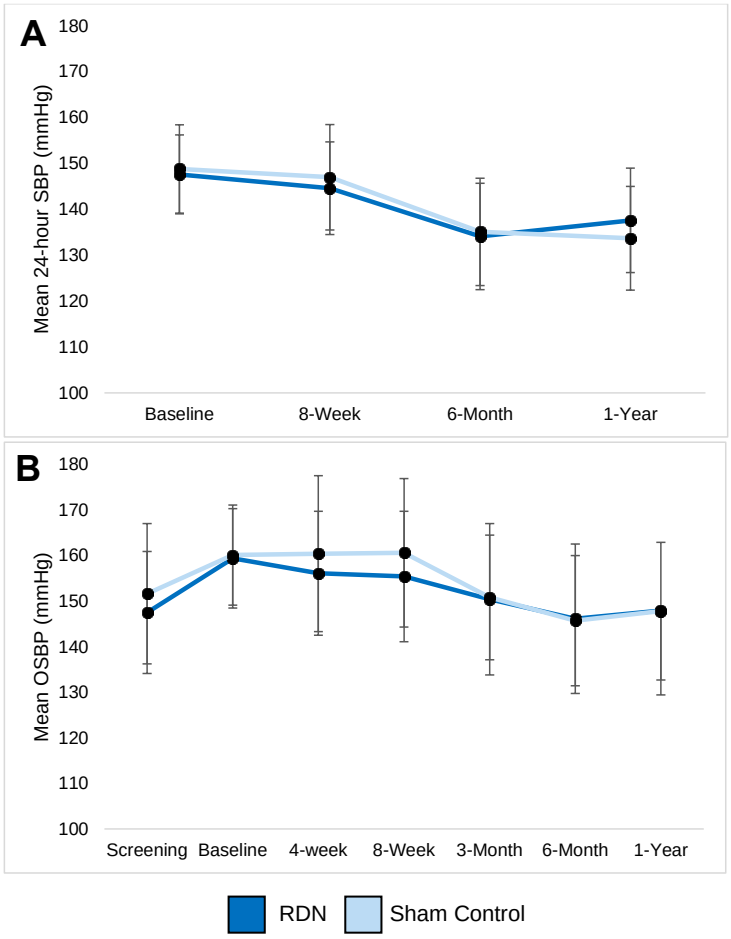
	Baseline		8 Weeks		6 Months		12 Months	
	RDN	**Sham Control**	**RDN**	**Sham Control**	**RDN**	**Sham Control**	**RDN**	**Sham Control**
eGFR (mean ± SD, mL/min/1.73m^2) (n)	85.8 ± 14.0 (50)	85.9 ± 13.0 (56)	84.6 ± 12.9 (47)	84.3 ± 13.6 (55)	85.7 ± 13.6 (48)	79.9 ± 13.8 (55)	83.5 ± 13.8 (48)	79.6 ± 15.8 (53)
Change from Baseline			-0.62 ± 9.90	-2.0 ± 9.8	-0.083 ± 9.1	-5.7 ± 8.5	-2.1 ± 8.9	-6.4 ± 10.0
p-value[a]			0.4813		0.0016		0.0224	

[a] P-value for comparing RDN to Sham Control from the t-test for change from baseline in eGFR.
eGFR = estimated glomerular filtration rate; RDN = renal denervation; SD = standard deviation.



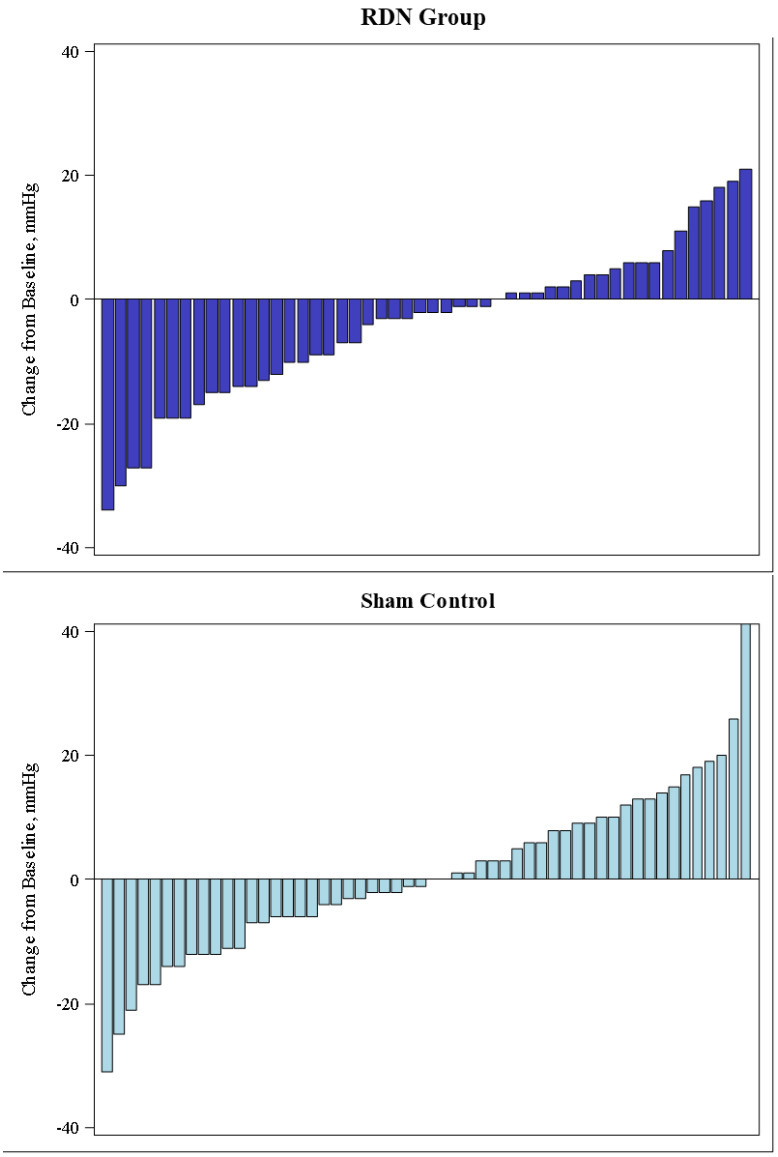
Supplementary Figure 1. Distribution of patient baseline and primary endpoint (8-week) visits relative to the onset of COVID-19.

The majority of the patients were randomized after the onset of the COVID-19 pandemic.



Supplementary Figure 2. Systolic blood pressure by visit.

24-h ambulatory systolic blood pressure (panel A) and office systolic blood pressure (panel B) show modest between group differences through 8 weeks and no difference at 12 months. OSBP = office systolic blood pressure, RDN = renal denervation, SBP=systolic blood pressure



Supplementary Figure 3. Individual patient blood pressure changes.

24-hour SBP change from baseline at 8 weeks (Waterfall Plot) for the RDN group (top) and sham control group (bottom)