Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO)

Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial

Michel Azizi, Kintur Sanghvi, Manish Saxena, Philippe Gosse, John P Reilly, Terry Levy, Lars C Rump, Alexandre Persu, Jan Basile, Michael J Bloch, Joost Daemen, Melvin D Lobo, Felix Mahfoud, Roland E Schmieder, Andrew S P Sharp, Michael A Weber, Marc Sapoval, Pete Fong, Atul Pathak, Pierre Lantelme, David Hsi, Sripal Bangalore, Adam Witkowski, Joachim Weil, Benjamin Kably, Neil C Barman, Helen Reeve-Stoffer, Leslie Coleman, Candace K McClure, Ajay J Kirtane*, on behalf of the RADIANCE-HTN investigators†*

Lancet 2021; 397: 2476–86

Published Online May 16, 2021 https://doi.org/10.1016/S0140-6736(21)00788-1

See Comment page 2441

*Contributed equally to the manuscript

†RADIANCE-HTN investigators are listed in the appendix

Université de Paris, Paris, France (Prof M Azizi MD, Prof M Sapoval MD); **Hypertension Department and DMU CARTE, AP-HP Hôpital Européen Georges-Pompidou, Paris, France** (Prof M Azizi, Prof M Sapoval); **INSERM, CIC1418, Paris, France** (Prof M Azizi); **Deborah Heart and Lung Center, Browns Mills, NJ, USA** (K Sanghvi MD); **Barts NIHR Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, London, UK** (M Saxena MBBS, Prof M D Lobo PhD); **Hôpital Saint-André CHU, Bordeaux, France** (P Gosse MD); **Ochsner Heart and Vascular Institute, New Orleans, LA, USA** (J P Reilly MD); **Royal Bournemouth Hospital, Bournemouth, UK** (T Levy MBChB); **University Clinic Dusseldorf, Dusseldorf, Germany** (Prof L C Rump MD); **Division of Cardiology, Cliniques Universitaires Saint-Luc** (Prof A Persu MD) **and Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique** (Prof A Persu), **Université Catholique de Louvain, Brussels, Belgium; Seinsheimer Cardiovascular Health Program, Medical University of South Carolina, Ralph H Johnson VA Medical Center, Charleston, SC, USA** (Prof J Basile MD); **Department**

Summary

Background Endovascular renal denervation reduces blood pressure in patients with mild-to-moderate hypertension, but its efficacy in patients with true resistant hypertension has not been shown. We aimed to assess the efficacy and safety of endovascular ultrasound renal denervation in patients with hypertension resistant to three or more antihypertensive medications.

Methods In a randomised, international, multicentre, single-blind, sham-controlled trial done at 28 tertiary centres in the USA and 25 in Europe, we included patients aged 18–75 years with office blood pressure of at least 140/90 mm Hg despite three or more antihypertensive medications including a diuretic. Eligible patients were switched to a once daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic. After 4 weeks of standardised therapy, patients with daytime ambulatory blood pressure of at least 135/85 mm Hg were randomly assigned (1:1) by computer (stratified by centres) to ultrasound renal denervation or a sham procedure. Patients and outcome assessors were masked to randomisation. Addition of antihypertensive medications was allowed if specified blood pressure thresholds were exceeded. The primary endpoint was the change in daytime ambulatory systolic blood pressure at 2 months in the intention-to-treat population. Safety was also assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT02649426.

Findings Between March 11, 2016, and March 13, 2020, 989 participants were enrolled and 136 were randomly assigned to renal denervation (n=69) or a sham procedure (n=67). Full adherence to the combination medications at 2 months among patients with urine samples was similar in both groups (42 [82%] of 51 in the renal denervation group *vs* 47 [82%] of 57 in the sham procedure group; p=0·99). Renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure (–8·0 mm Hg [IQR –16·4 to 0·0] *vs* –3·0 mm Hg [–10·3 to 1·8]; median between-group difference –4·5 mm Hg [95% CI –8·5 to –0·3]; adjusted p=0·022); the median between-group difference was –5·8 mm Hg (95% CI –9·7 to –1·6; adjusted p=0·0051) among patients with complete ambulatory blood pressure data. There were no differences in safety outcomes between the two groups.

Interpretation Compared with a sham procedure, ultrasound renal denervation reduced blood pressure at 2 months in patients with hypertension resistant to a standardised triple combination pill. If the blood pressure lowering effect and safety of renal denervation are maintained in the long term, renal denervation might be an alternative to the addition of further antihypertensive medications in patients with resistant hypertension.

Funding ReCor Medical.

Introduction

Endovascular catheter-based denervation of the renal efferent and afferent nerves was initially investigated as a novel blood pressure lowering treatment for patients with resistant hypertension. The first randomised, open-label trial[1] using catheter-directed radiofrequency ablation, as well as immediate subsequent trials,[2] overestimated its office blood pressure lowering efficacy in this clinical setting. Subsequently, a larger, sham-controlled trial (SYMPLICITY HTN-3) did not show improvement in office or ambulatory blood pressure control,[3] whereas the renal denervation for hypertension (DENERHTN) open-label trial,[4] which included a strict and standardised drug escalation protocol, showed a plausible reduction of daytime ambulatory systolic blood pressure by around 6 mm Hg in favour of renal denervation, irrespective of adherence to antihypertensive medications.[5]

Since 2017, three sham-controlled trials with more optimised designs to reduce variability of adjunctive medications, procedural performance, and endpoint ascertainment,[2] consistently confirmed the ambulatory and office blood pressure lowering efficacy of both

Research in context

Evidence before this study

We searched PubMed for papers published between Jan 1, 2017, and March 7, 2021, using the search terms "renal denervation", "hypertension", "randomised", "sham", "hypertension", and various combinations of those words with no language restrictions. We aimed to identify systematic reviews and meta-analyses of blood pressure lowering efficacy of renal denervation that specifically included second generation trials. We identified 11 meta-analyses, six of which included sham-controlled randomised trials in patients with uncontrolled hypertension in the absence or presence of antihypertensive medications. A 2021 meta-analysis that included six eligible sham-controlled studies using both first and second generation devices showed that renal denervation significantly reduced 24-h ambulatory systolic blood pressure versus a sham procedure. Other meta-analyses reported a more pronounced blood pressure lowering effect with second generation devices compared with the earlier generation systems.

Added value of this study

The RADIANCE-HTN TRIO trial was designed to overcome the methodological limitations of previous studies in patients with resistant hypertension. It showed a greater reduction in daytime, night-time, and 24-h ambulatory systolic blood pressure in patients with hypertension resistant to a guideline-approved single-pill, triple combination therapy with the second generation endovascular ultrasound renal denervation than a sham procedure. The difference between the renal denervation and the sham procedure group was independent of the adherence of patients to the antihypertensive medications, and its magnitude was consistent with the results of meta-analyses of second generation, sham-controlled trials.

Implications of all the available evidence

Overall, the RADIANCE-HTN TRIO trial enrolled largely different patient populations from previous studies, and yet yielded consistent results, suggesting that catheter-based renal denervation, using ultrasound or radiofrequency, lowers blood pressure across a spectrum of hypertension severity, from mild hypertension among patients off antihypertensive medications to more severe hypertension among patients resistant to multiple antihypertensive medications.

radiofrequency and ultrasound renal denervation in the absence or the presence of medications in patients with less severe hypertension.[6–9] Among these trials, the RADIANCE-HTN trial compared endovascular ultrasound renal denervation with a sham procedure in two separate cohorts.[10] Among the first (SOLO) cohort of patients with mild-to-moderate hypertension who were weaned off medications, a 6·3 mm Hg greater reduction in daytime ambulatory systolic blood pressure was shown with renal denervation versus a sham procedure at 2 months.[7] The blood pressure lowering effect of ultrasound renal denervation was maintained at 6 and 12 months, even when patients were restarted on antihypertensive medications.[11,12] We report the primary efficacy and safety results of ultrasound renal denervation in the TRIO cohort of patients with more severe hypertension resistant to three or more antihypertensive medications.[10]

Methods

Study design and participants

The randomised, international, multicentre, single-blind, sham-controlled RADIANCE-HTN TRIO trial was done in 28 tertiary centres in the USA and 25 in Europe (France, the UK, Germany, Poland, Belgium, the Netherlands) and has been described previously.[10]

Eligible participants[10] were men or women aged 18–75 years with resistant hypertension defined as seated office blood pressure of at least 140 mm Hg systolic and 90 mm Hg diastolic despite a stable regimen of three or more antihypertensive medications including a diuretic, and an estimated glomerular filtration rate of at least 40 mL/min per 1·73 m². At enrolment, patients were switched to a single-pill, fixed-dose, daily combination of amlodipine 10 mg (or 5 mg in the event of severe leg oedema), valsartan 160 mg (or olmesartan 40 mg depending upon medication availability in each country), and hydrochlorothiazide 25 mg. No other antihypertensive medications were allowed except β blockers for chronic coronary syndrome or heart failure. After 4 weeks of standardised therapy, patients with daytime ambulatory blood pressure of at least 135 mm Hg systolic and 85 mm Hg diastolic and suitable renal artery anatomy on renal CT angiography or magnetic resonance angiography had renal angiography to confirm anatomical eligibility. A full list of inclusion and exclusion criteria are in the appendix (pp 7–8).

All participants provided written informed consent. The study was approved by local ethics committees or institutional review boards.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive ultrasound renal denervation or a sham procedure. The randomisation sequence was generated by computer and stratified by centre using randomised blocks of four or six and permutation of treatments within each block. To maintain masking, participants were sedated and wore headphones and eye covers. Patients completed a masking questionnaire at discharge and at the 2-month follow-up. Patients and clinicians

of Medicine, University of Nevada School of Medicine, Vascular Care, Renown Institute of Heart and Vascular Health, Reno, NV, USA (M J Bloch MD)**; Erasmus MC, Department of Cardiology, University Medical Center Rotterdam, Rotterdam, Netherlands** (J Daemen MD)**; Klinik für Innere Medizin III, Saarland University Hospital, Homburg/Saar, Germany** (Prof F Mahfoud MD)**; Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA** (Prof F Mahfoud)**; Nephrology and Hypertension, University Hospital Erlangen, Friedrich Alexander University, Erlangen, Germany** (Prof R E Schmieder MD)**; Cardiology Department, University Hospital of Wales, Cardiff, UK** (A S P Sharp MD)**; NIHR Clinical Research Facility, University of Exeter, Exeter, UK** (A S P Sharp)**; Division of Cardiovascular Medicine, State University of New York, Downstate Medical Center, New York, NY, USA** (Prof M A Weber MD)**; Vanderbilt University Medical Center, Nashville, TN, USA** (P Fong MD)**; Department of Cardiovascular Medicine, Princess Grace Hospital, Monaco** (Prof A Pathak MD)**; UMR UT3 CNRS 5288, University of Toulouse, Toulouse, France** (Prof A Pathak)**; Hôpital de la Croix Rousse, Lyon, France** (Prof P Lantelme MD)**; Stamford Hospital, Stamford, CT, USA** (Prof D Hsi MD)**; NYU School of Medicine, New York, NY, USA** (Prof S Bangalore MD)**; Institute of Cardiology, Warsaw, Poland** (Prof A Witkowski MD)**; Sana Kliniken Lübeck, Lübeck, Germany** (Prof J Weil MD)**; Université de Paris, Paris, France** (B Kably PharmD)**; AP-HP Hôpital Européen Georges-Pompidou, Pharmacology Unit and DMU CARTE, Paris, France** (B Kably)**; ReCor Medical, Palo Alto, CA, USA** (N C Barman MD, H Reeve-Stoffer PhD, L Coleman DVM)**; NAMSA, Minneapolis, MN, USA** (C K McClure PhD)**; Columbia University Medical Center/New York-Presbyterian Hospital and the Cardiovascular Research Foundation,**

New York, NY, USA
(Prof A J Kirtane MD)
Correspondence to:
Prof Michel Azizi, Hypertension Department and DMU CARTE, AP-HP Hôpital Européen Georges-Pompidou, 75015 Paris, France
michel.azizi@aphp.fr
See Online for appendix

involved in follow-up care were masked to treatment allocation for 6 months after random assignment.

Procedures

The Paradise System (ReCor Medical, Palo Alto, CA, USA) was used for ultrasound renal denervation. The full details of the renal denervation and sham procedures have been previously reported.[7] Pain was assessed post-procedure using a visual analogue scale. Participants were evaluated at monthly visits to the clinic between 0800 h and 1000 h, before ingestion of their standardised antihypertensive treatment. Attended seated office blood pressure and heart rate (Omron M10-IT, Kyoto, Japan), analysis of 7-day home blood pressure recordings (Omron M10-IT), medication lists, and adverse events were recorded. Laboratory assessments as well as urine samples for chemical adherence testing were done at baseline and 2 months, as previously described.[7,10] All participants were to remain on the single-pill triple combination (with or without β blocker) until 2 months after random assignment unless specified blood pressure criteria were exceeded (180/110 mm Hg for office blood pressure or 170/105 mm Hg for home blood pressure), in which case participants received escape antihypertensive treatment (mainly spironolactone 25 mg). 24-h ambulatory blood pressure measurements (Microlife WatchBP, Taipei, Taiwan) were done at baseline and at 2 months after random assignment, as previously described.[7,10] All blood pressure recordings were sent to a core laboratory (dabl Health, Dublin, Ireland), which was masked to treatment assignment. Urine samples were sent to a core laboratory (Pharmacology Department of the Georges Pompidou Hospital, Paris, France). Adherence to antihypertensive medications was directly assessed using ultra-high performance liquid chromatography tandem mass spectrometry to detect drugs or their metabolites in urine at baseline and 2 months by an independent pharmacologist (BK), who was masked to the treatment assignment, as previously described.[5,13] Full adherence to medications was defined as the presence of all prescribed drugs in the sample. Renal duplex ultrasound was done at 2 months in all randomly assigned participants.

Outcomes

The primary efficacy endpoint was the change in daytime ambulatory systolic blood pressure from baseline to 2 months. Secondary efficacy endpoints specified for hierarchical testing at 2 months were change in 24-h ambulatory systolic and diastolic blood pressures, nighttime ambulatory systolic and diastolic blood pressures, and daytime ambulatory diastolic blood pressure. Other prespecified observational assessments were change at 2 months in all other office and home blood pressure and heart rate measurements; the proportion of patients with at least 5, 10, or 15 mm Hg decrease in daytime ambulatory systolic blood pressure and with controlled daytime blood pressure at 2 months (<135/85 mm Hg); and change in estimated glomerular filtration rate at 2 months.

Prespecified major adverse events assessed in the intention-to-treat population were all-cause mortality, renal failure, an embolic event, renal artery or vascular complications requiring intervention, or hypertensive crisis within 30 days of the study procedure, and new onset renal artery stenosis greater than 70% within 6 months of the study procedure.[7,10]

Statistical analysis

At the time of the design of the study in 2015, the sample size calculations were based on the DENERHTN study,[4] as well as the 2015 guidelines on renal denervation.[2] We therefore calculated that a sample size of 128 participants would yield 80% power to detect a 6 mm Hg difference in change in daytime ambulatory systolic blood pressure at 2 months between the renal denervation and sham groups (common standard deviation 12 mm Hg, two-sided type I error rate of 5%). To account for up to 10% missing observations, we initially planned to randomly assign 146 participants. However, the decision was made to stop enrolment on May 8, 2020, after random assignment of 134 patients with evaluable follow-up at 2 months due to the COVID-19 pandemic constraining further recruitment. The decision was consistent with guidance from the US Food and Drug Administration.[14]

The primary endpoint was analysed in the intention-to-treat population. Patients with missing 2-month ambulatory blood pressure or who met protocol criteria for escape antihypertensive treatment for elevated blood pressure had their baseline blood pressure imputed as their 2-month ambulatory blood pressure value. Further, a tipping point analysis was done on the primary endpoint to evaluate the effect of missing observations. For the secondary endpoints specified for hierarchical analysis, tests were done in order, until the first non-significant test, such that subsequent secondary endpoints would not be used to make claims; however, these results and corresponding significance tests are provided for descriptive purposes. Analyses in the per-protocol, modified intention-to-treat, and as-treated populations, as well as a post-hoc analysis of participants with complete ambulatory blood pressure monitoring data are also described.

Treatment differences between groups from baseline to 2 months were assessed using analysis of covariance, including the baseline value as a covariate. When the change of a parameter from baseline was not normally distributed, a baseline-adjusted analysis of covariance based on the ranks was done as detailed in the statistical analysis plan.[15]

Exploratory analyses of prespecified subgroups were done using linear regression analyses with change in daytime ambulatory systolic blood pressure at 2 months as the dependent variable. Baseline daytime ambulatory

systolic blood pressure, treatment group, subgroup, and treatment group by subgroup interaction term were included as independent variables in the models. Adjusted mean daytime ambulatory systolic blood pressure by subgroup and p value for the treatment by subgroup interaction term are shown.

Comparisons between groups were made using unpaired t tests or Wilcoxon tests for continuous variables and Fisher's exact test or χ^2 for categorical variables, as appropriate. Continuous variables are expressed as mean with SD or median with IQR if not normally distributed. Between-group differences are expressed as means with their two-sided 95% CI or medians with their 95% CIs estimated using the Hodges-Lehmann method where appropriate. Analyses were done using SAS version 9.4. All statistical analyses were predefined in the protocol or statistical analysis plan unless specifically indicated as being post-hoc analyses. All statistical analyses were independently validated (Baim Institute for Clinical Research, Boston, MA, USA). An independent data safety and monitoring board reviewed study data quarterly for all enrolled participants. This trial is registered with ClinicalTrials.gov, NCT02649426.

Role of the funding source

The executive committee designed the protocol with the funder of the study, who did data collection, monitoring, and data analysis. The funder of the study had no role in data interpretation or writing of the report, other than providing assistance in formatting and copy editing.

Results

Between March 11, 2016, and March 13, 2020, 989 participants were enrolled, 136 of whom met all eligibility criteria for random assignment (renal denervation, n=69; sham procedure, n=67; figure 1).

Baseline characteristics were similar across both study groups (table 1). Mean office blood pressure across both groups was 163/104 mm Hg despite a mean of 4·0 (SD 1·0) antihypertensive drugs at screening. After switching patients from their non-standardised therapy to a single-pill triple therapy, 99 (73%) of 136 patients received a single-pill combination containing valsartan 160 mg for 4 weeks until baseline; the remaining patients were treated with a combination containing olmesartan 40 mg (table 1). The distribution of valsartan versus olmesartan in the single-pill combination was well balanced between the two groups at baseline (table 1). Importantly, once the single-pill combination with valsartan or olmesartan was selected, it remained the same throughout the trial. A total of 117 (86%) patients received a single-pill combination containing amlodipine 10 mg for 4 weeks, the remaining being treated with a combination containing amlodipine 5 mg (table 1). The distribution of amlodipine 10 mg versus 5 mg in the single-pill combination was well balanced between the two groups at baseline (table 1). After 4 weeks of standardised treatment with the single-pill triple therapy

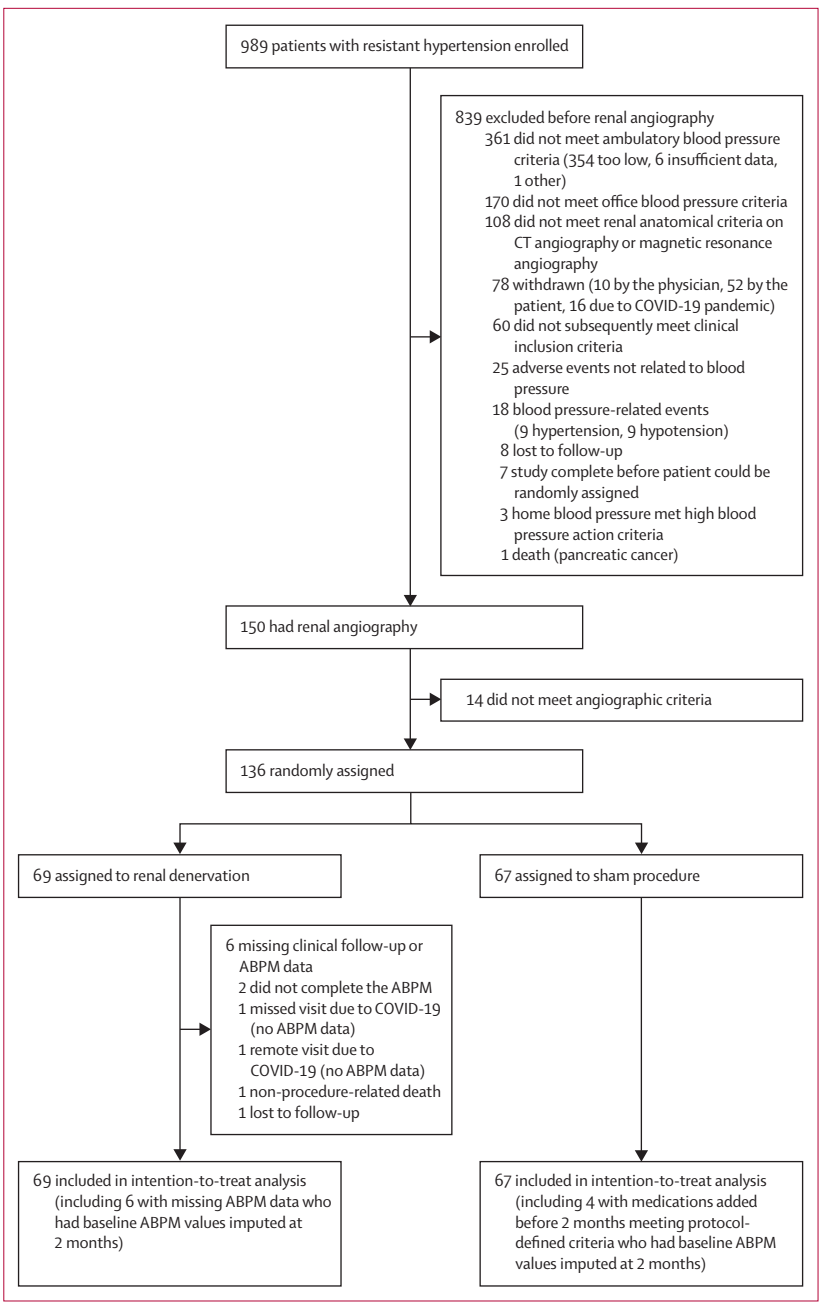

Figure 1: **Trial profile**
ABPM=ambulatory blood pressure monitoring.

(including ten patients who were also treated with a β blocker; table 1), ambulatory blood pressure values confirmed treatment resistance (table 2). 93 (79%) of 117 patients with urine samples had full adherence to the standardised combination medication as measured by urine chromatography at baseline (appendix p 15).

Of the 53 study centres, 35 centres with 40 different interventionalists had patients assigned to the renal denervation group; each interventionalist did a mean of two (range 1–6) renal denervation procedures. Successful

	Renal denervation (n=69)	Sham procedure (n=67)
Age, years	52·3 (7·5)	52·8 (9·1)
Sex		
Female	13 (19%)	14 (21%)
Male	56 (81%)	53 (79%)
Race		
White	44 (64%)	50 (75%)
Black	14 (20%)	13 (19%)
Other or unknown*	11 (16%)	4 (6%)
Body-mass index, kg/m²	32·8 (5·7)	32·6 (5·4)
Abdominal obesity†	54 (82%)‡	55 (82%)
eGFR, mL/min per 1·73 m²§	86·0 (25·2)	82·2 (19·2)
eGFR <60 mL/min per 1·73 m²§	8 (12%)	7 (11%)
Type 2 diabetes	21 (30%)	17 (25%)
Sleep apnoea syndrome	19 (28%)	11 (16%)
Previous admission to hospital for hypertensive crisis	15 (22%)	11 (16%)
Previous cardiovascular or cerebrovascular event	8 (12%)	9 (13%)
History of heart failure	1 (1%)	3 (4%)
Office blood pressure and heart rate at screening		
Systolic blood pressure, mm Hg	161·9 (15·5)	163·6 (16·8)
Diastolic blood pressure, mm Hg	105·1 (11·6)	103·3 (12·7)
Heart rate, beats per minute	74·5 (11·0)	77·6 (12·9)
Number of antihypertensive medications at screening	4·0 (1·0)	3·9 (1·1)
3 medications	27 (39%)	28 (42%)
4 medications	22 (32%)	24 (36%)
≥5 medications	20 (29%)	15 (22%)
Antihypertensive medications at screening		
Renin angiotensin system blockers	67 (97%)	63 (94%)
Diuretics	63 (91%)	64 (96%)
Calcium channel blocker	61 (88%)	56 (84%)
β blockers	37 (54%)	29 (43%)
Aldosterone antagonists	25 (36%)	21 (31%)
Centrally acting drugs	9 (13%)	10 (15%)
α1 receptor blockers	6 (9%)	10 (15%)
Vasodilators	4 (6%)	4 (6%)
Antihypertensive medications at baseline before random assignment		
Valsartan 160 mg	50 (72%)¶	49 (73%)
Olmesartan 40 mg	19 (28%)	18 (27%)
Amlodipine 10 mg	59 (86%)	58 (87%)
Amlodipine 5 mg	10 (14%)	9 (13%)
Hydrochlorothiazide 25 mg	69 (100%)‖	67 (100%)‖
β blocker	7 (10%)	3 (4%)

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. *Two patients in the renal denervation group and two patients in the sham procedure group did not have race reported. †Abdominal obesity was defined as a waist circumference greater than 102 cm for men and greater than 88 cm for women. ‡Data available for 66 patients in the renal denervation group. §eGFR using the Modification of Diet in Renal Disease equation adjusted on race could not be recalculated in two patients in each group because of missing race data (data available for 67 patients in the renal denervation group and 65 patients in the sham procedure group); however, study centres reported eGFR values greater than 60 mL/min per 1·73 m² for all four patients before randomisation—these data were not added for the eGFR recalculated at baseline. ¶One patient given valsartan 320 mg in the renal denervation group. ‖One patient in each group given hydrochlorothiazide 12·5 mg.

Table 1: **Baseline demographics and clinical characteristics of the intention-to-treat population**

bilateral renal nerve ablations with mean 5·8 (SD 1·2) ultrasound emissions were done in 67 (97%) of 69 patients. 17 (25%) patients in the renal denervation group had accessory renal artery ablations (appendix p 16). There was no difference between groups in post-procedure pain and masking was maintained (appendix pp 16–17).

Between baseline and 2 months, 64 (93%) of 69 patients in the renal denervation group and 57 (85%) of 67 patients in the sham group had no change in their baseline antihypertensive treatment (p=0·15). Three (4%) patients in the renal denervation group and eight (12%) patients in the sham group received additional antihypertensive medications (spironolactone for two [3%] patients in the renal denervation group and for seven [10%] patients in the sham group; appendix p 18). Four (6%) patients in the renal denervation group and one (1%) patient in the sham group had a down-titration of the amlodipine dose from 10 mg to 5 mg in the single-pill combination done by the treating physician. Full adherence to the combination medications remained high at 2 months among patients with urine samples, with no difference between the renal denervation and sham groups (42 [82%] of 51 *vs* 47 [82%] of 57; p=0·99, appendix p 15). Three patients in the renal denervation group who were non-adherent at baseline became fully adherent at 2 months versus four patients in the sham group. Three patients in the renal denervation group who were fully adherent at baseline became non-adherent at 2 months versus one patient in the sham group.

In the intention-to-treat population, there was a greater reduction in daytime ambulatory systolic blood pressure at 2 months with renal denervation compared with the sham procedure (median –8·0 mm Hg [IQR –16·4 to 0·0] *vs* –3·0 mm Hg [–10·3 to 1·8]; median between-group difference –4·5 mm Hg [95% CI –8·5 to –0·3]; baseline-adjusted p=0·022; table 2; appendix p 12). Changes in all other systolic blood pressure parameters also favoured renal denervation (table 2), including 24-h ambulatory blood pressure (median between-group difference –4·2 mm Hg [95% CI –8·3 to –0·3]; adjusted p=0·016; appendix p 12). There was a larger systolic blood pressure lowering effect over the 24-h circadian cycle with renal denervation versus the sham procedure (figure 2).

Changes in diastolic blood pressure parameters are shown in table 2. There was no between-group difference in heart rate at 2 months (appendix p 19). Analyses of blood pressure in additional study populations were consistent with the intention-to-treat analysis (appendix pp 20–22). The median between-group difference in daytime ambulatory systolic blood pressure in the per-protocol population was –5·4 mm Hg (95% CI –9·5 to –1·3; adjusted p=0·011; appendix p 21) and was –5·8 mm Hg (–9·7 to –1·6; adjusted p=0·0051) among patients with complete ambulatory blood pressure data (appendix p 22). Tipping-point analysis showed the results to be robust (appendix p 23).

	Renal denervation (n=69)			Sham procedure (n=67)			Unadjusted median between-group difference (95% CI)*	Baseline-adjusted p value†
	At random assignment	2 months	Difference from random assignment to 2 months	At random assignment	2 months	Difference from random assignment to 2 months		
Systolic blood pressure parameters								
Daytime ambulatory blood pressure, mm Hg‡	150·0 (11·9)	141·0 (16·1)	−8·0 (−16·4 to 0·0)	151·1 (12·6)	146·3 (18·8)	−3·0 (−10·3 to 1·8)	−4·5 (−8·5 to −0·3)	0·022
24-h ambulatory blood pressure, mm Hg	143·9 (13·4)	135·2 (16·0)	−8·5 (−15·1 to 0·0)	145·4 (14·0)	140·5 (18·7)	−2·9 (−12·6 to 2·5)	−4·2 (−8·3 to −0·3)	0·016
Night-time ambulatory blood pressure, mm Hg	134·4 (18·0)	126·3 (18·4)	−8·3 (−15·7 to 0·0)	136·4 (18·6)	131·9 (20·9)	−1·8 (−16·2 to 5·0)	−3·9 (−8·8 to 1·0)	0·044
Office blood pressure, mm Hg§	155·6 (16·7)	147·1 (20·3)	−9·0 (−19·5 to −1·5)	154·9 (16·8)	152·1 (22·0)	−4·0 (−12·0 to 9·0)	−7·0 (−13·0 to 0·0)	0·037
Home blood pressure, mm Hg¶	152·0 (16·2)	144·6 (18·2)	−6·0 (−17·0 to 1·5)	153·1 (17·0)	149·9 (18·9)	−2·0 (−9·5 to 2·0)	−4·0 (−8·0 to 0·0)	0·052
Diastolic blood pressure parameters								
Daytime ambulatory blood pressure, mm Hg	93·8 (7·7)	88·5 (11·6)	−4·9 (−10·4 to 0·0)	94·6 (9·1)	90·7 (12·2)	−2·0 (−7·8 to 1·0)	−1·8 (−4·5 to 0·8)	0·18
24-h ambulatory blood pressure, mm Hg	88·9 (8·2)	83·6 (10·9)	−5·4 (−10·4 to 0·0)	89·5 (9·5)	85·8 (12·0)	−2·4 (−7·8 to 0·5)	−2·0 (−4·5 to 0·6)	0·12
Night-time ambulatory blood pressure, mm Hg	81·3 (10·7)	76·2 (12·2)	−5·1 (−12·7 to 0·0)	81·3 (12·1)	78·4 (13·2)	−2·0 (−9·5 to 4·1)	−2·8 (−6·1 to 0·2)	0·053
Office blood pressure, mm Hg§	101·4 (11·6)	96·6 (13·9)	−5·0 (−13·5 to 2·5)	99·4 (10·9)	98·7 (13·8)	−1·0 (−7·0 to 6·0)	−4·0 (−9·0 to 0·0)	0·16
Home blood pressure, mm Hg¶	96·5 (11·2)	93·2 (14·7)	−4·0 (−9·0 to 2·0)	96·7 (11·4)	96·0 (12·8)	−1·0 (−5·0 to 4·0)	−3·0 (−6·0 to 0·0)	0·053

Data are mean (SD) or median (IQR) unless otherwise stated. *Hodges-Lehmann estimate of location shift and 95% asymptotic CI. †As change from baseline in either cohort was non-normal, the p value from baseline-adjusted analysis of covariance (ANCOVA) on the ranks is provided for all parameters, except for home systolic and diastolic blood pressure for which the p value from baseline adjusted ANCOVA is reported. ‡Primary efficacy endpoint. §64 patients in the renal denervation group and 66 patients in the sham group with office blood pressure measurements were included in the intention-to-treat population. ¶There were 60 patients in the renal denervation group and 64 patients in the sham group with home blood pressure measurements included in the intention-to-treat population.

Table 2: **Primary and secondary efficacy endpoints in the intention-to-treat population**

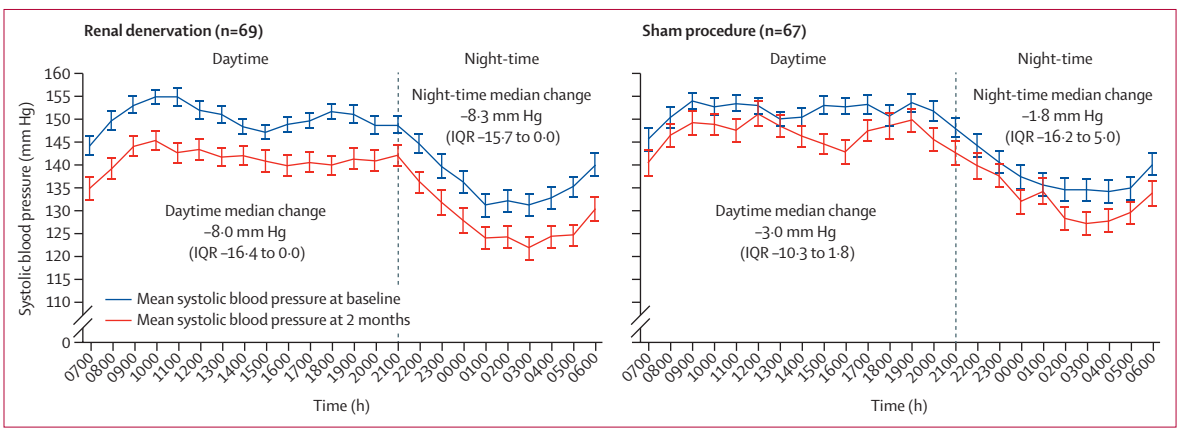

Figure 2: **24-h ambulatory profiles of systolic blood pressure at baseline and 2 months in the renal denervation group and the sham group in the intention-to-treat population**

Between baseline and 2 months, 64 (93%) of 69 patients in the renal denervation group and 57 (85%) of 67 patients in the sham procedure group had no change in their baseline antihypertensive treatment. Error bars represent standard errors.

Individual patient changes in daytime ambulatory systolic blood pressure are shown in the appendix (p 13). In the intention-to-treat population, 24 (35%) of 69 patients in the renal denervation group had controlled daytime ambulatory blood pressure at 2 months versus 14 (21%) of 67 patients in the sham procedure group. The effect of renal denervation on the primary efficacy endpoint was consistent across sex, ethnicity, age, abdominal circumference, and baseline blood pressures (appendix p 14). In a post-hoc analysis using linear mixed models with the change in daytime systolic blood pressure as the dependent variable, we found no significant interaction with the type of angiotensin II receptor blocker (valsartan or olmesartan) or the dose of amlodipine used (data not shown). The number of ultrasound emissions, the presence of non-ablated accessory renal arteries, and the number of renal denervation procedures per interventionalist did not influence the blood pressure response to renal denervation (data not shown). The between-group difference

	Renal denervation (n=69)	Sham procedure (n=67)
Procedural safety events		
Death	0	0
Clinically significant embolic events resulting in end organ damage	0	0
Any renal artery complication requiring intervention (eg, dissection or perforation)	0	0
Acute renal injury*	0	0
Need for renal artery angioplasty or stenting	0	0
Major access site complications requiring intervention	1 (1%)†	0
Procedure-related pain lasting for >2 days‡	12 (17%)	10 (15%)
New onset renal artery stenosis greater than 50%§	0	0
Other safety events from baseline to 2 months		
All-cause mortality	1 (1%)¶	0
Hypertensive emergency resulting in hospital admission	0	0
Hypotensive emergency resulting in hospital admission	0	0
Hospital admission for heart failure	0	0
Stroke, transient ischaemic attack, cerebrovascular accident	0	0
Acute myocardial infarction (STEMI or non-STEMI)	1 (1%)	0
Any coronary revascularisation	0	1 (1%)
Doubling of plasma creatinine	1 (1%)‖	0
End stage renal disease, the need for permanent renal replacement therapy	0	0

Data are n (%). STEMI=ST-elevation myocardial infarction. *Acute renal injury defined as increase in plasma or serum creatinine concentration by ≥0·3 mg/dL (≥26·5 µmol/L) within 48 h of the procedure, increase in plasma or serum creatinine to ≥1·5 times baseline known to have occurred during 7 days post-procedure, or urine volume <0·5 mL/kg per h for 6 h. †One femoral access site pseudoaneurysm post-procedure treated with thrombin injection met the definition of a major adverse event. ‡In the renal denervation group, seven patients had pain at the femoral access site, four patients had back pain, and one patient had extremity pain. In the sham group, eight patients had pain at the femoral access site and two patients had back pain. §Diagnosed by duplex ultrasonography and confirmed by renal CT-angiography or magnetic resonance-angiography or as diagnosed or confirmed by CT-angiography or magnetic resonance-angiography; non-invasive renal imaging was available in 61 patients in the renal denervation group and 61 patients in the sham procedure group at 2 months. ¶One sudden death unrelated to device or procedure 21 days post-procedure met the definition of a major adverse event. ‖One transient acute renal injury at 25 days post-procedure associated with spironolactone use resolved on discontinuation of spironolactone and met the definition of a major adverse event.

Table 3: **Incidence of safety events from baseline to 2 months**

in daytime systolic blood pressure was in favour of renal denervation in patients who were fully adherent and patients who were non-adherent to medications in a post-hoc analysis (appendix p 24).

Three major adverse events occurred within 30 days after renal denervation, of which only one (access site pseudoaneurysm successfully treated) was adjudicated as being procedure-related (table 3). Estimated glomerular filtration rate was similar in both groups at 2 months (appendix p 25) and no new renal artery stenosis greater than 50% was detected (table 3).

Discussion

Among patients with hypertension confirmed to be resistant despite adherence to a 4-week, standardised, fixed-dose, single-pill, triple combination of a thiazide, an angiotensin II receptor blocker, and a dihydropyridine, there was a greater reduction in daytime ambulatory systolic blood pressure at 2 months in the ultrasound renal denervation group compared with the sham procedure group. The treatment effect of renal denervation was consistent for 24-h ambulatory systolic blood pressure, night-time ambulatory systolic blood pressure, and office and home systolic blood pressures. Patients in both groups remained on the same standardised, single-pill, triple combination (plus β blocker in ten patients), to which they were highly adherent. The greater blood pressure lowering effect of renal denervation versus the sham procedure was observed despite the more frequent use of add-on new antihypertensive drugs, including spironolactone, in the sham group. The effect of renal denervation was also consistent across various prespecified subgroups, including sex, ethnicity, age, abdominal obesity, and baseline blood pressures. There was only a single reversible procedure-related adverse event at the vascular access site.

The design of the RADIANCE-HTN TRIO trial attempted to overcome potential limitations of previous studies in resistant hypertension.[2,3] We randomly assigned patients with resistant hypertension confirmed by ambulatory blood pressure after adjusting their antihypertensive treatment to a single-pill, fixed-dose, triple combination consistent with current guidelines.[16,17] By reducing pill burden,[18] a high adherence to the standardised treatment was achieved at baseline, which was maintained at 2 months in both groups. We also took care to reduce confounding factors[19] by planning circumferential renal denervation treatment based on the pre-procedural imaging,[10] ensuring effective masking of patients and clinical staff, and strictly limiting any uncontrolled changes in the antihypertensive medications during follow-up. Altogether, these strengths in the design of our study increased its internal validity but led to an increase in the number of study centres and increased the enrolment period to 4 years, with the last year being influenced by the COVID-19 pandemic. In accordance with international guidelines[16] and with the approval of health authorities and ethics committees, we assessed the primary endpoint at 2 months to prioritise safety of our patients with resistant hypertension who were at higher risk than patients with mild-to-moderate hypertension uncontrolled with fewer than three medications. Indeed, the SYMPLICITY HTN-3 trial reported 84 (16%) major cardiovascular and cerebrovascular events among 535 randomly assigned patients with resistant hypertension, including three deaths, during a short follow-up of 6 months.[3] This is the main reason why an escape antihypertensive treatment could be prescribed in our study if blood pressure exceeded a specified threshold within the 2-month study period, and a standardised drug titration protocol was to be started in both groups while maintaining masking if blood pressure remained uncontrolled from the second month onwards.[10] The RADIANCE-HTN TRIO trial is continuing with a 3-year follow-up to assess longer-term safety and efficacy.

In the strictly controlled conditions of our trial, the renal denervation group had a reduction in daytime ambulatory systolic blood pressure of 8·0 mm Hg between baseline and 2 months, which was 4·5 mm Hg greater than with the sham procedure in the intention-to-treat population. This between-group difference was detected with patients maintained on the same standardised treatment as at baseline to which they were highly adherent. Of note, antihypertensive medications were more commonly added in the sham group (n=8) than in the denervation group (n=3) during the 2-month follow-up, either according to protocol-defined safety criteria or to patient or physician preference. The systolic blood pressure lowering effect of ultrasound renal denervation was consistent over the 24-h circadian cycle as shown by the 8·3 mm Hg decrease in night-time ambulatory systolic blood pressure, similar to findings in the RADIANCE-HTN SOLO[7] and SPYRAL HTN trials.[8,9]

The sham effect in the TRIO cohort, in which patients were on standardised triple-pill combination treatment, was larger than that observed in the SOLO cohort, in which patients were off treatment (–3·0 mm Hg *vs* –2·2 mm Hg in the intention-to-treat population; –3·3 *vs* –0·1 mm Hg in the per-protocol population when excluding patients who received medications for any reason and had missing ambulatory blood pressure data). The sham effect in the RADIANCE-HTN TRIO study might have been amplified by changes in adherence to medications from baseline to 2 months in some patients. Indeed, four patients who were non-adherent at baseline became fully adherent at 2 months in the sham group and contributed to large individual decreases in daytime systolic blood pressures (data not shown). Nevertheless, the overall sham effect in our trial was smaller than in the SYMPLICITY HTN-3 study[20] (which showed a 6·1 mm Hg decrease in daytime ambulatory systolic blood pressure in the sham procedure group) and other studies,[21] and was similar to the placebo effect reported in drug trials done in patients with resistant hypertension.[22] Indeed, the meta-analysis by Patel and colleagues[21] on the effect of placebo or sham procedures on blood pressure lowering in randomised controlled trials in patients with resistant hypertension reported that invasive sham procedures showed a trend towards a greater response in office systolic blood pressure (no ambulatory blood pressure data available) than a placebo pill in the treatment of resistant hypertension (–13·2 mm Hg [SD 2·4] *vs* –7·2 mm Hg [2·4]). The sham effect might have contributed to an underestimation of the blood pressure lowering effect of renal denervation in the RADIANCE-HTN TRIO study. Moreover, the large number of interventionalists might have increased the variability in how the procedure was done. However, the number of renal denervation procedures per interventionalist was not a predictor of the blood pressure response.

The consistency of the primary endpoint results as shown by the similar magnitude in the decrease of ambulatory systolic blood pressure in patients in the ultrasound renal denervation group either on antihypertensive treatment (–8·0 mm Hg in TRIO) or off antihypertensive treatment (–8·5 mm Hg in SOLO) at baseline reinforces the validity of the present results. Interestingly, night-time systolic blood pressure decreased more in the renal denervation group in the TRIO cohort (–8·3 mm Hg) than in the renal denervation group in the SOLO cohort (–4·8 mm Hg), although baseline night-time blood pressure was 4·0 mm Hg lower in SOLO.[7] Both the higher baseline night-time blood pressure and the larger night-time blood pressure response to renal denervation might be consistent with the greater contribution of the sympathetic nervous system to the pathophysiology of resistant hypertension compared with less severe hypertension.[23] Given the strong association of night-time blood pressure with cardiovascular disease risk,[24] these results might have prognostic implications, especially for patients with resistant hypertension who are at risk. In a post-hoc analysis on the subgroup of patients with urine samples, renal denervation resulted in a greater decrease in blood pressure versus the sham procedure regardless of adherence to treatment (ie, in both adherent patients with consequently true resistant hypertension and non-adherent patients with apparent resistant hypertension), consistent with the results of the DENERHTN trial.[5] This result might have important clinical implications but should be considered as hypothesis generating and thus be confirmed in a larger study.

Overall, the positive results of the RADIANCE-HTN TRIO trial in patients with resistant hypertension expand the results of the pilot sham-controlled SPYRAL HTN-ON MED trial[8] to a larger population of patients with more severe and resistant hypertension to three or more antihypertensive medications. The SPYRAL HTN-ON MED trial enrolled 80 patients with moderate hypertension requiring up to three antihypertensive agents, who had multi-electrode radiofrequency-based renal denervation. The difference in 24-h ambulatory systolic blood pressure between these patients and the sham procedure group was significant at 6 months and not at 3 months while patients were maintained on a stable combination of antihypertensive treatments. Although both our study and the SPYRAL HTN-ON MED trial used a sham procedure for the control group, there were differences in study populations, hypertension severity, standardised medication protocol, and conduct. The method used for renal nerve ablation also differed, as endovascular ultrasound was used to ablate in the main renal artery, and radiofrequency ablation in that study ablated in the main and distal branches. The daytime ambulatory systolic blood pressure difference in favour of renal denervation versus the sham procedure in our study is consistent with results of

various meta-analyses on renal denervation with the second generation of catheters.[6,25,26]

If maintained in the long term as highlighted by the 3-year report of the Global SYMPLICITY Registry[27] as well as the 12-month results of the RADIANCE-HTN SOLO study,[12] the average 9·0 mm Hg reduction in office systolic blood pressure we observed after renal denervation in patients with resistant hypertension who are at high risk of a cardiovascular event,[28] is of a magnitude previously associated with a reduction in stroke, coronary heart disease, heart failure, and all-cause mortality for antihypertensive drug therapy.[29] A reduction in both cardiovascular and cerebrovascular events might also be expected if we confirm our previous observation in the RADIANCE-HTN SOLO trial of a reduced visit-to-visit variability in blood pressure after renal denervation.[12]

Our study has limitations. Additional follow-up will be required to determine whether the blood pressure lowering effect of ultrasound renal denervation remains durable over time, especially when patients receive additional antihypertensive medications (particularly the aldosterone antagonist spironolactone) to control their blood pressure in both masked (2–6 months) and unmasked conditions (after 6 months).[10] Although adverse events were infrequent, longer follow-up of this trial and more treated patients will be necessary to provide additional safety data. Additionally, similar to other trials of renal denervation, despite our efforts to reduce overall variability, there was still between-patient variation in the response to renal denervation (as well as to the sham procedure; see table 2 and appendix p 13), some of which might be attributed to variable medication adherence or other factors. We found none of the previously described patient-related factors (including age, sex, ethnicity, obesity, and baseline blood pressure levels) or procedure-related factors (including number of ablations or ablation of accessory arteries) to explain such variability.[30] Between-patient variability might still be due to variable renal nerve ablation despite the uniform use of circumferential ablations and treatment of accessory renal arteries, or might reflect differing contributions of renal nerve signalling to hypertension perpetuation. There is currently no reliable perioperative marker of successful renal denervation.[30] Also, we observed a very high adherence to antihypertensive medications, but the true adherence to medications might have been lower, because patients were fully informed that medication adherence was monitored throughout the trial, and this might have given rise to white coat adherence phenomenon. However, our assays enabled us to determine non-adherence to the medications with high specificity, because non-detection of the medications in the urine samples collected at trough indicates that the drugs had not been ingested by the patient for a duration that exceeded at least five plasma half-lives of that given drug. Despite this limitation, our analysis suggests that potential biases attributable to non-adherence to the treatment are likely to have had minimal consequences for the results of the RADIANCE-HTN TRIO study, because the exposure to the medications after 2 months of follow-up was not different in the two groups. We included patients with resistant hypertension and estimated glomerular filtration rates greater than 40 mL/min, of whom only 11% had estimated glomerular filtration rates less than 60 mL/min. Therefore, our results are not necessarily applicable to patients with more severe renal insufficiency, even though they often have resistant hypertension, or to other clinical settings (including patients with heart failure, sleep obstructive apnoea, or arrhythmias).

In conclusion, in this adequately powered, sham-controlled, randomised trial of patients with combined systolic–diastolic hypertension resistant to a fixed-dose, single-pill, triple combination antihypertensive therapy as recommended by current guidelines,[16] ultrasound renal denervation safely reduced ambulatory systolic blood pressure more than a sham procedure at 2 months. The 6-month (masked phase) and 12-month (unmasked phase) follow-up of the RADIANCE-HTN TRIO study, during which patients of both groups receive spironolactone as fourth line therapy according to guidelines, will also determine whether renal denervation could be an alternative to the addition of further antihypertensive medications to reduce the risk of drug-related side-effects and non-adherence to medications.[17,28] Follow-up of the present population for 3 years[10] as well as additional studies will be important to evaluate the durability, continued safety, and long-term clinical impact of ultrasound renal denervation in patients with various forms of hypertension.

Contributors

MA, AJK, JB, MJB, JD, MDL, FM, RES, ASPS, MAW, NCB, HR-S, LC, and CKM participated in the design of the study. MA, AJK, KS, MSax, PG, JPR, TL, LCR, APe, JB, MJB, JD, MDL, FM, RES, ASPS, MSap, PF, APa, PL, DH, SB, AW, JW, BK, NCB, HR-S, LC, and CKM participated in patient data collection. All authors analysed and interpreted the data. CKM was the study biostatistician responsible for the statistical analyses. MA and AJK wrote the first draft of the report with contributions from coauthors. All authors participated in the writing of the report, agreed on the content of the manuscript, reviewed drafts, and approved the final version. MA, AJK, NCB, HR-S, LC, and CKM had access to and verified the underlying data. All authors had unrestricted access to the data, and statistical analyses were independently validated (Baim Institute for Clinical Research, Boston, MA, USA). All authors had full responsibility for the decision to submit for publication.

Declaration of interests

MA has received research grants from the French Ministry of Health, Quantum Genomics, and the European Horizon 2020 programme; has received grant support and non-financial support from ReCor Medical and Idorsia; and has received personal fees from CVRx, AstraZeneca, Alnylam Pharmaceutical, and Poxel Pharma. KS has received grant support and personal fees from ReCor Medical and Medtronic, and has received grant support from Cardiovascular Systems. MSax has received grant support and personal fees from ReCor Medical. PG has received grant support from the University Hospital of Bordeaux. LCR has received personal fees from ReCor Medical. APe has received personal fees from Quantum Genomics and grant support from Ablative Solutions, Quantum Genomics, and ReCor Medical. JB has received grant support from ReCor Medical and Ablative Solutions. MJB has

received personal fees from ReCor Medical and Medtronic. JD has received grant support from ReCor Medical, Medtronic, Boston Scientific, Abbott Vascular, Acist Medical, AstraZeneca, Pie Medical, and Pulse Cath, and personal fees from ReCor Medical, Medtronic, Acist Medical, Boston Scientific, Pie Medical, and Pulse Cath. MDL has received personal fees from ReCor Medical, Medtronic, CVRx, Ablative Solutions, Vascular Dynamics, ROX Medical, and Tarilan Laser Technologies, and grants from Medtronic. FM is supported by Deutsche Gesellschaft für Kardiologie and Deutsche Forschungsgemeinschaft (SFB TRR 219); and has received grant support and personal fees from ReCor Medical, Medtronic, Berlin Chemie, Bayer, and Boehringer Ingelheim. RES has received grant support and personal fees from ReCor Medical, Medtronic, and Ablative Solutions. ASPS has received personal fees from ReCor Medical, Medtronic, Boston Scientific, and Philips. MAW has received personal fees from ReCor Medical, Medtronic, Boston Scientific, and Ablative Solutions. APa has received grant support and personal fees from ReCor Medical, Medtronic, and Ablative Solutions. DH reports institutional funding to Stamford Hospital from ReCor Medical. SB has received grant support from Abbott Vascular, the National Heart, Lung, and Blood Institute, and REATA; and personal fees from Abbott Vascular, Biotronik, REATA, Amgen, Pfizer, Boehringer Ingelheim, and Meril. JW has received personal fees from ReCor Medical and Medtronic. NCB is an employee of ReCor Medical and is the author on multiple patents in the field of renal denervation. HR-S is an employee of ReCor Medical. LC is an employee of ReCor Medical. CKM is an employee of North American Science Associates and a contractor for ReCor Medical. AJK reports institutional funding (in addition to research grants, institutional funding includes fees paid for speaking engagements or consulting) to Columbia University or the Cardiovascular Research Foundation (New York, NY, USA) from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, Cardiovascular Systems, CathWorks, Siemens, Philips, and ReCor Medical. AJK also reports travel expenses or meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, Cardiovascular Systems, CathWorks, Siemens, Philips, Chiesi, OpSens, Zoll, Regeneron, and ReCor Medical. All other authors declare no competing interests.

Data sharing

Data will be shared with researchers who submit a research proposal approved by the study principal investigators (MA and AJK). Individual patient data will be shared in data sets in a de-identified and anonymised format. Data will be made available after research completion and approval of the product and product use in the EU and the USA.

Acknowledgments

Lisa Claude (ReCor Medical) assisted with the preparation of tables and figures and copy editing. Chris Mullin (North American Science Associates) provided input on study design and statistical analysis. Damien Bergerot (Hôpital Européen Georges-Pompidou, Clinical Investigation Centre) supported the medication adherence analysis.

References

1 Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010; **376:** 1903–09.

2 Mahfoud F, Böhm M, Azizi M, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. *Eur Heart J* 2015; **36:** 2219–27.

3 Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370:** 1393–401.

4 Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; **385:** 1957–65.

5 Azizi M, Pereira H, Hamdidouche I, et al. Adherence to antihypertensive treatment and the blood pressure-lowering effects of renal denervation in the renal denervation for hypertension (DENERHTN) trial. *Circulation* 2016; **134:** 847–57.

6 Sardar P, Bhatt DL, Kirtane AJ, et al. Sham-controlled randomized trials of catheter-based renal denervation in patients with hypertension. *J Am Coll Cardiol* 2019; **73:** 1633–42.

7 Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018; **391:** 2335–45.

8 Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; **391:** 2346–55.

9 Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020; **395:** 1444–51.

10 Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: the RADIANCE-HTN and REQUIRE clinical study designs. *Am Heart J* 2018; **195:** 115–29.

11 Azizi M, Schmieder RE, Mahfoud F, et al. Six-month results of treatment-blinded medication titration for hypertension control following randomization to endovascular ultrasound renal denervation or a sham procedure in the RADIANCE-HTN SOLO trial. *Circulation* 2019; **139:** 2542–53.

12 Azizi M, Daemen J, Lobo MD, et al. 12-month results from the unblinded phase of the RADIANCE-HTN SOLO trial of ultrasound renal denervation. *JACC Cardiovasc Interv* 2020; **13:** 2922–33.

13 Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Routine urinary detection of antihypertensive drugs for systematic evaluation of adherence to treatment in hypertensive patients. *J Hypertens* 2017; **35:** 1891–98.

14 US Food and Drug Administration. Statistical considerations for clinical trials during the COVID-19 public health emergency guidance for industry (FDA-2020-D-1136). Rockville, MD: US Food and Drug Administration, 2020.

15 Conover WJ, Iman RL. Analysis of covariance using the rank transformation. *Biometrics* 1982; **38:** 715–24.

16 Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39:** 3021–104.

17 Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018; **72:** e53–90.

18 Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension* 2021; **77:** 692–705.

19 Kandzari DE, Mahfoud F, Bhatt DL, et al. Confounding factors in renal denervation trials: revisiting old and identifying new challenges in trial design of device therapies for hypertension. *Hypertension* 2020; **76:** 1410–17.

20 Bakris GL, Townsend RR, Liu M, et al. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. *J Am Coll Cardiol* 2014; **64:** 1071–78.

21 Patel HC, Hayward C, Ozdemir BA, et al. Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials: implications for trials of renal denervation. *Hypertension* 2015; **65:** 401–06.

22 Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; **386:** 2059–68.

23 Grassi G, Seravalle G, Brambilla G, et al. Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. *Int J Cardiol* 2014; **177:** 1020–25.

24 Kario K, Hoshide S, Mizuno H, et al. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP study. *Circulation* 2020; **142:** 1810–20.

25 Ahmad Y, Kane C, Arnold AD, et al. Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: a meta-analysis. *Cardiovasc Revasc Med* 2021; published online Jan 30. https://doi.org/10.1016/j.carrev.2021.01.031.

26 Syed M, Osman M, Alhamoud H, et al. The state of renal sympathetic denervation for the management of patients with hypertension: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2021; **97:** E438–45.

27 Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 2019; **40:** 3474–82.

28 Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; **125:** 1635–42.

29 Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387:** 957–67.

30 Mahfoud F, Azizi M, Ewen S, et al. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. *Eur Heart J* 2020; **41:** 1588–99.