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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation in Chinese Patients With Uncontrolled Hypertension: The Randomized, Sham-Controlled, Multi-Center Iberis-HTN Trial

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BACKGROUND: Renal denervation (RDN) can lower blood pressure (BP) in patients with hypertension in both the presence and absence of medication. This is a sham-controlled trial investigating the safety and efficacy of RDN in China.

METHODS: This prospective, multicenter, randomized, patient- and outcome-assessor-blinded, sham-controlled trial investigated radiofrequency RDN in patients with hypertension on standardized triple antihypertensive therapy. Eligible patients were randomized 1:1 to undergo RDN using a multi-electrode radiofrequency catheter (Iberis; Shanghai Angiocare Medical Technology, Shanghai, China) or a sham procedure. The primary efficacy outcome was the between-group difference in baseline-adjusted change in mean 24-hour ambulatory systolic BP from randomization to 6 months.

RESULTS: Of 217 randomized patients (mean age, 45.3±10.2 years; 21% female), 107 were randomized to RDN and 110 were randomized to sham control. At 6 months, there was a greater reduction in 24-hour systolic BP in the RDN (−13.0±12.1 mm Hg) compared with the sham control group (−3.0±13.0 mm Hg; baseline-adjusted between-group difference, −9.4 mm Hg [95% CI, −12.8 to −5.9]; $P<0.001$). Compared with sham, 24-hour diastolic BP was lowered by −5.0 mm Hg ([95% CI, −7.5 to −2.4]; $P<0.001$) 6 months after RDN, and office systolic and diastolic BP was lowered by −6.4 mm Hg ([95% CI, −10.5 to −2.3]; $P=0.003$) and −5.1 mm Hg ([95% CI, −8.2 to −2.0]; $P=0.001$), respectively. One patient in the RDN group experienced an access site complication (hematoma), which resolved without sequelae. No other major device- or procedure-related safety events occurred through follow-up.

CONCLUSIONS: In this trial of Chinese patients with uncontrolled hypertension on a standardized triple pharmacotherapy, RDN was safe and reduced ambulatory and office BP at 6 months compared with sham.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02901704.

Key Words: antihypertensive agents ■ blood pressure ■ denervation ■ hypertension

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Clinical Perspective

What Is New?

- This trial is the first sham-controlled trial conducted in China investigating radiofrequency renal denervation using the Iberis catheter system.
- Radiofrequency renal denervation is safe and decreases office and ambulatory blood pressure in patients with uncontrolled hypertension despite standardized 3-drug antihypertensive therapy.

What Are the Clinical Implications?

- This trial provides evidence for the safety and efficacy of catheter-based renal denervation for the treatment of hypertension in Chinese patients with uncontrolled hypertension.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
eGFR	estimated glomerular filtration rate
RDN	renal denervation

In China, hypertension can be found in about 1 of 4 adults 18 to 69 years of age, and the prevalence has increased from 2004 through 2018.[1] High blood pressure (BP) associates with major cardiovascular events and mortality.[2] In 2018, 2.67 million cardiovascular deaths in China alone were attributed to high systolic BP.[3] Although hypertension awareness, treatment, and control have recently improved modestly, BP control rates remain as low as 16.8%,[1] and are worse than in Western populations.[4] At the population level in China, a modest 5-mm Hg decrease in BP could prevent ≈350 000 deaths per year among individuals <80 years of age and ≈200 000 deaths at <70 years of age.[2] Several device-based approaches have been introduced as additional treatment options in the management of hypertension.[5] One such approach is catheter-based renal denervation (RDN), which has undergone extensive preclinical and clinical investigation.[5,6] Recent sham-controlled trials have demonstrated that RDN safely and consistently reduces office and ambulatory BP.[6] Most patients included in these trials were recruited in Europe and the United States.[6] The Iberis-HTN trial (Renal Denervation by Iberis Multi-Electrode Renal Denervation System in Patients With Primary Hypertension) is a sham-controlled trial conducted in China to evaluate the safety and efficacy of a novel multielectrode radiofrequency RDN catheter system in patients with uncontrolled hypertension despite a standardized triple pharmacotherapy.

METHODS

Iberis-HTN was a prospective, multicenter, randomized, patient- and outcome assessor-blinded, sham-controlled, pivotal trial evaluating the safety and BP-lowering efficacy of catheter-based, radiofrequency RDN patients with hypertension in the presence of standardized antihypertensive medications. Details of the study protocol are included in the Supplemental Methods. The trial was conducted at 16 centers in China. Local ethics committees approved the protocol, and the trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. This trial is registered with ClinicalTrials.gov (URL: https://clinicaltrials.gov; Unique identifier: NCT02901704). The data of this study will be available from the corresponding author and study steering committee on reasonable request at the end of the study.

Patients

Patients 18 to 65 years of age with uncontrolled primary hypertension diagnosed for ≥6 months at the first screening visit were eligible if they had an office systolic BP ≥180 mm Hg and diastolic BP ≥110 mm Hg. After signing the informed consent at enrollment, patients were switched to a standardized antihypertensive therapy of 5 mg of amlodipine and a 2-drug fixed-dose single pill with 80 mg of valsartan and 12.5 mg of hydrochlorothiazide combined. At the second screening visit, after 4 weeks of standardized antihypertensive treatment, patients with an office systolic BP ≥150 but ≤180 mm Hg and an office diastolic BP ≥90 mm Hg, mean ambulatory 24-hour systolic BP ≥135 and ≤170 mm Hg, and suitable renal artery anatomy (renal artery diameter ≥3 mm, length ≥20 mm) on preprocedural computed tomographic angiography underwent renal angiography to confirm anatomical eligibility. Key exclusion criteria were patients with type 1 diabetes, secondary hypertension, a creatinine-based estimated glomerular filtration rate (eGFR) <45 m/min/1.73 m², previous implantation of an active implantable defibrillator or pacemaker, and myocardial infarction, syncope, cerebral hemorrhage, or cerebral infarction ≤6 months before signing the informed consent. The complete list of inclusion and exclusion criteria is provided in the Supplemental Methods.

Randomization and Masking

Immediately after renal angiography, eligible patients were randomized in a 1:1 ratio to receive radiofrequency RDN or a sham procedure. The randomization sequence was generated centralized by computer using the Interactive Web Response System and stratified by center using block randomization of unknown block size. During the trial procedures (renal angiogram with RDN or renal angiogram only), patients were sedated and wore headphones playing music and eye masks. Patients randomized to the sham group remained on the table for ≥10 minutes to prevent unmasking. Before discharge, and again at 6 months, patients were asked to guess the treatment allocation using a questionnaire. Patients and staff involved in follow-up care and outcome assessment were masked to treatment allocation 6 months after randomization.

Procedures

The multielectrode, unipolar Iberis RDN catheter and generator system (Iberis, Shanghai Angiocare Medical Technology, Shanghai, China) for transfemoral access was used for treating the left and right main and accessory renal arteries, including their branches, with diameters between 3 and 8 mm using low-level radiofrequency energy. The over-the-wire catheter is 90 cm long and compatible with a 6F guiding catheter. The catheter's self-expanding distal tip has four electrodes arranged in a helical configuration (diameter, 10.5 mm) to ensure reliable wall contact and circumferential treatment. The helical tip straightens when the guidewire is inserted. Notably, the catheter is nonocclusive, maintaining blood flow to cool the vessel's intima during radiofrequency delivery. To assess adequate wall contact, the generator measures temperature changes after a short (10 s) low-energy (0.5 W per electrode) output before treatment. During the treatment, the generator utilizes real-time temperature and impedance monitoring to safely deliver low-level radiofrequency energy (maximum of 6 W per electrode) for 60 s. Each electrode can be deactivated individually. Unfractionated heparin was used to maintain an activated clotting time of ≥250 s during the procedure. Experienced interventionalists performed all procedures.

After randomization, clinical in-person follow-up visits were conducted at 1, 3, and 6 months. All participants were required to take their antihypertensive medications while observed by study personnel. Office BP and heart rate, medication lists, and adverse events were recorded at every follow-up visit. Attended seated office BP was measured using an automated, validated oscillometric device (Omron HEM-7081-IT, Omron HBP-1100U, and Omron HBP-1120U) with an appropriately sized cuff after a 5-minute rest. Three office BP measurements were taken 1 minute apart, with the mean of the last 2 readings used as the office BP reading. The 24-hour ambulatory BP monitoring device was placed immediately after the observed drug intake. Each site was permitted to use its own validated ambulatory BP monitor for the measurements (Table S1). However, the same device had to be used for both the patient's baseline and follow-up measurements. BP measurements were obtained every 20 minutes during the daytime (7:00 AM to 9:59 PM) and every 30 minutes during nighttime (10:00 PM to 6:59 AM). A minimum of 20 valid daytime and 7 valid nighttime measurements were required for inclusion in the analyses.[7] Ambulatory BP monitoring could be repeated once if the required number of valid readings was not reached. Laboratory tests, including serum creatinine, were performed at baseline and 6 months. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Computed tomographic angiography of the renal arteries was performed at baseline and 6 months to assess vascular safety. No antihypertensive medication changes were allowed during the 6 months after randomization unless they were deemed clinically necessary for safety reasons. In patients with symptomatic hypertension or systolic BP ≥180 mm Hg or symptomatic hypotension or systolic BP <120 mm Hg, changes in drug doses and changes in medications were permitted at the physician's discretion, while blinding to treatment allocation was maintained. Priority should be given to adjusting the drug dose over changing BP medications. Initially, the trial protocol did not require toxicologic adherence testing. After randomization of the first 32 patients, the trial protocol (version 3.0) was amended, and toxicologic adherence testing in spot urine at baseline and 6 months was included as required by the China Food and Drug Administration (now the National Medical Products Administration). Adherence was defined as having detectable levels of only and all prescribed antihypertensive medications in urine.

Outcomes

The primary efficacy outcome was the difference in mean 24-hour systolic BP change from baseline to 6 months after the procedure between the RDN and sham groups. The primary efficacy outcome was changed from 3 to 6 months on July 4, 2018 (protocol version 3.0), after randomizing 32 patients. Secondary efficacy outcomes included the between-group differences in the: (1) change in mean 24-hour diastolic BP from baseline to 6 months after procedure; (2) change in office systolic BP between baseline and 1, 3, and 6 months after procedure; (3) mean number of prescribed antihypertensive drugs at 1, 3, and 6 months after procedure; and (4) proportion of patients achieving office systolic BP <140 mm Hg at 6 months.

Safety outcomes collected through 6 months of follow-up were the incidence of: (1) procedural complications; (2) all-cause mortality; (3) cardiovascular (including acute myocardial infarction or any coronary revascularization) and cerebrovascular events (including stroke, transient ischemic attack, and cerebrovascular accident); (4) renal events, including eGFR <15 ml/min/1.73 m², renal replacement therapy, renal artery re-intervention, or new-onset renal artery stenosis (>50%), confirmed by CT angiography; and (5) adverse events and serious adverse events.

Statistical Analysis

The sample size calculations were based on previous trial results in a similar population.[8] After accounting for up to 15% of missing observations, it was estimated that a sample size of 216 patients would yield 80% power to detect a 5-mm Hg difference in change in 24-hour ambulatory systolic BP from baseline to 6 months between the RDN and sham groups (with a common SD of 12 mm Hg and 2-sided type-I error rate of 5%).

Continuous variables are summarized as mean±SD, and categorical variables as counts (percentage). For categorical variables, comparisons between independent groups were performed using Pearson chi square test or Fisher exact test. For between-group comparisons of continuous baseline variables, an unpaired *t* test was used. Treatment differences between the groups were compared using ANCOVA, adjusting for baseline measurements, and are presented as mean (95% CI). The last observation carried forward method was used for patients with missing observations for the primary efficacy evaluation. A tipping point analysis was performed on the primary endpoint as a sensitivity analysis to evaluate the potential effect of missing observations. Exploratory post hoc subgroup analyses with tests of interaction for the primary outcome (dependent variable) were done for subgroups defined according to sex; age (at or above the median and below the median); body mass index (≥30 kg/m² or <30 kg/m²); history of diabetes; baseline 24-hour systolic BP (≥median and <median); heart rate (≥median and <median) and night-time dipping pattern (mean ambulatory systolic BP night-to-day ratio ≥0.9 or <0.9).

Antihypertensive medication burden was assessed using medication indices, described in detail in the Supplemental Methods.[9] Blinding indices of randomized patients were calculated as previously described.[10] The blinding index used is scaled to an interval of −1 to 1.[10] An index of 1 indicates no blinding, 0 is perfect blinding, and −1 means opposite guessing, possibly related to unblinding.[10]

Unless otherwise indicated, the analyses were performed in the intention-to-treat population, including all randomized patients to the treatment group to which they were randomly allocated. An independent data safety and monitoring board reviewed the study data. A 2-sided *P* value <0.05 was considered statistically significant. *P* values were not adjusted for multiple testing. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Role of the Funding Source

The Iberis-HTN trial was funded by AngioCare Medical (Shanghai, China). The executive committee designed the protocol and identified clinical sites in collaboration with the funder. The funding source was responsible for collecting, monitoring, and analyzing the data. The manuscript was written by the lead authors with contributions from the trial executive committee and all co-authors. The funder assisted in figure and table generation, copyediting, and formatting. All authors had unrestricted access to the data and were responsible for the decision to submit for publication.

RESULTS

Between June 14, 2017, and January 21, 2022, there were 873 patients enrolled. Of these, 217 patients fulfilled the inclusion and exclusion criteria and were randomly assigned to the RDN (n=107) or sham control groups (n=110; Figure 1). Baseline clinical characteristics, including office BP and heart rate, did not differ between both groups (Table 1). The mean age was 45.3±10.2 years, mean body mass index was 27.7±3.5 kg/m^2, and 21% were of female sex. At the time of enrollment, patients in the RDN and sham groups were prescribed a mean of 3.0±0.2 and 3.0±0.1 antihypertensive medications, respectively (Table 1). Most patients were prescribed 3 antihypertensive drugs (RDN, 96.3%; sham, 98.2%).

The blinding index for the RDN group was −0.224 (95% CI, −0.395 to −0.054) after the procedure and 0.076 (95% CI, −0.088 to 0.240) at 6 months. The sham group blinding index was 0.101 (95% CI, −0.084 to 0.286) after the procedure and −0.157 (95% CI, −0.314 to 0.001) at 6 months. The blinding indices are indicative of effective blinding.[10,11]

Procedures

The mean procedure time was 69.4±32.9 minutes in the RDN and 27.4±16.4 minutes in the sham control group (Table 2). All patients assigned to RDN successfully received a bilateral procedure. For patients undergoing RDN, an average of 6.2±2.2 and 6.4±1.9 successful ablation cycles, each consisting of 4 ablation spots, were delivered to the left and right renal arteries, including the branch arteries, respectively.

Antihypertensive Medication Changes and Adherence

The mean number of prescribed antihypertensive medications did not differ between the treatment groups at baseline and all follow-up time points. At 6 months, the average numbers of prescribed antihypertensive drugs were 3.0±0.2 and 3.1±0.7 in the RDN and the sham groups (*P*=0.166), respectively. There was also no between-group difference when accounting for medication classes and drug dosages (Tables S2 through S5). Although no antihypertensive medication changes were allowed for 6 months after randomization unless patients met the protocol-defined escape criteria, physicians who were blinded to treatment allocation adjusted antihypertensive medication in 4 (3.7%) patients in the RDN group and 12 (11.0%) patients in the sham procedure group. Of these, 1 (0.9%) patient in the RDN and 3 (2.8%) patients in the sham group had an increase in the number of medications, whereas 3 (2.8%) patients in the RDN and 8 (7.2%) patients in the sham group had an increase in drug doses. Of note, medications were changed for 0 (0%) patients in the RDN and only one (0.9%) patient in the sham group after meeting the protocol-defined escape criteria of having a systolic BP ≤120 mm Hg. None of the patients met the escape criterion of high systolic BP.

At randomization, 81% (72 of 89) of the patients in the RDN and 71% (68 of 96) of the patients in the sham control group with toxicological analyses completely adhered to the prescribed medications (*P*=0.263). In 5 patients (1 in the RDN and 4 in the sham group), none of the antihypertensive drugs or their compounds were detected in urine at randomization, indicating complete nonadherence to the study medication. Drug adherence did not differ between treatment groups at 6 months after the procedure (RDN, 79% [75 of 95] vs sham 73% [73 of 100]; *P*=0.578). At 6 months, in 6 patients (4 in the RDN and 2 in the sham group), none of the prescribed antihypertensive drugs or their compounds were detected in urine. The detection rates for each antihypertensive drug are provided in Table S6.

Blood Pressure Reductions

The primary efficacy outcome, the between-group difference in mean 24-hour systolic BP change from baseline, was changed from 3 to 6 months after randomizing 32 patients. Therefore, most patients (88.9%) had ambulatory BP monitoring only at baseline and 6 months. Office BP was measured in 214 (98.6%), 208 (95.9%), and 212 (97.7%) patients at 1, 3, and 6 months of follow-up, respectively.

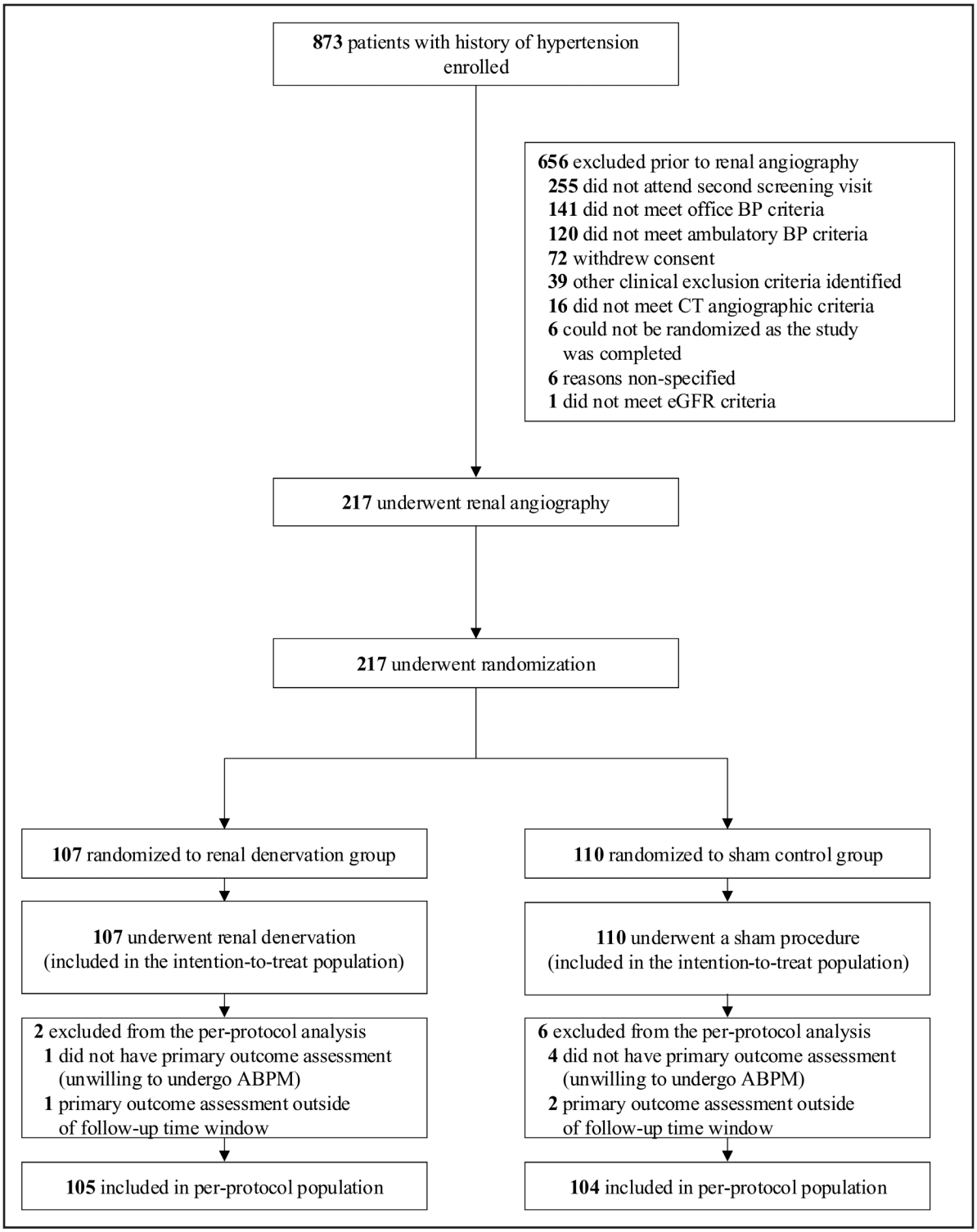

Figure 1. Patient flow chart.
ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; CT, computed tomography; and eGFR, estimated glomerular filtration rate.

There was a greater reduction in mean 24-hour ambulatory systolic BP between baseline and 6 months in the RDN (−13.0±12.1 mm Hg) compared with the sham group (−3.0±13.0 mm Hg), resulting in a baseline-adjusted between-group difference in change of −9.4 mm Hg ([95% CI, −12.8 to −5.9]; *P* from ANCOVA <0.001; Table 3; Figure 2). The tipping point sensitivity analysis on the primary end point (Table S7) and a sensitivity analysis, which only included patients with ambulatory BP measurements at baseline and 6 months (Table S8),

Table 1. Baseline Demographics and Clinical Characteristics (Intention-to-Treat Population)

Patient characteristic	Renal denervation (n=107)	Sham procedure (n=110)
Age, y, mean±SD	46.4±10.2	44.3±10.2
Female sex	23 (21.5)	22 (20.0)
Body mass index, kg/m², mean±SD	27.7±3.6	27.8±3.3
Creatinine-based eGFR,* ml/min/1.73 m², mean±SD	100.0±20.5	103.7±16.2
Creatinine-based eGFR* <60 ml/min/1.73 m²	6 (5.6)	0 (0)
Type 2 diabetes	21 (19.6)	14 (12.7)
Active smoker	29 (27.1)	31 (28.2)
History of coronary artery disease	14 (13.1)	6 (5.5)
Hyperlipidemia	29 (27.1)	35 (31.8)
Vitals on screening visit 2, mean±SD		
Office systolic BP, mm Hg	159.1±7.2	159.4±7.5
Office diastolic BP (screening visit 2), mm Hg	98.8±7.2	99.4±7.3
Heart rate (screening visit 2), beats/min	81.7 ±11.7	82.4 ±12.1
Prescribed antihypertensive drugs at screening, mean±SD	3.0±0.2	3.0±0.1
0	0 (0)	0 (0)
1	0 (0)	0 (0)
2	4 (3.7)	2 (1.8)
3	103 (96.3)	108 (98.2)
Prescribed medications at screening		
Renin angiotensin system blocker	80 (74.8)	80 (72.7)
ACE inhibitor†	1 (1.3)	0 (0)
Angiotensin receptor blocker†	79 (98.8)	80 (100)
Calcium channel blocker	87 (81.3)	91 (82.7)
Diuretic	77 (72.0)	76 (69.1)
Thiazide or thiazide-like‡	77 (100)	76 (100)
Beta-blocker	3 (2.8)	6 (5.5)
Other	4 (3.7)	0 ()

Values presented n (%) unless otherwise indicated. ACE indicates angiotensin-converting enzyme; and eGFR, estimated glomerular filtration rate.

*Calculated using Chronic Kidney Disease Epidemiology Collaboration equations.

†Percentage of patients treated with a renin angiotensin system blocker.

‡Percentage of patients treated with diuretics.

showed the primary results to be robust. Compared with the sham group, ambulatory systolic BP was continuously reduced during daytime and nighttime in the RDN group (Figure 3). Individual 24-hour systolic BP reductions of each patient in the RDN and sham groups are shown in Figure S1. In an exploratory subgroup analysis, the between-group differences for mean 24-hour ambulatory BP change from baseline to 6 months were consistent across all subgroups (Figure S2). The baseline-adjusted between-group difference for office systolic BP change was −6.4 mm Hg ([95% CI, −10.5 to −2.3]; *P*=0.003).

Table 2. Procedural Characteristics

Characteristic	Renal denervation (N=107)	Sham procedure (N=110)
Procedure time, min*	69.4±32.9	27.4±16.4
Treatment successfully delivered to both renal arteries	107 (100)	N/A
Complete ablation cycles† to left renal artery	6.2±2.2	N/A
Complete ablation cycles† to right renal artery	6.4±1.9	N/A
Total successful ablation cycles†	12.6±3.7	N/A

Data presented as mean±SD or frequency (%). N/A indicates not applicable.

*Procedure time defined as the time from arterial sheath placement to sheath removal.

†Ablation cycle is defined as the delivery of 4 ablation lesions.

In the RDN and the sham groups, mean 24-hour ambulatory diastolic BP were reduced by −7.7±8.6 mm Hg and −2.8±10.1 mm Hg from baseline to 6 months, respectively. The baseline-adjusted between-group difference of change in 24-hour diastolic BP was −5.0 mm Hg ([95% CI, −7.5 to −2.4]; *P*<0.001; Figure 2). Changes in all other ambulatory and office diastolic BP parameters also favored RDN (Table 3). The office systolic and diastolic BP changes between baseline and 1 and 3 months are reported in Tables S9 and S10. At 6 months, 29.2% (31 of 106) of the patients in the RDN group and 7.5% (8 of 106) patients in the sham group had a 24-hour systolic BP <130 mm Hg and diastolic BP <80 mm Hg. Similarly, 55.7% (59 of 106) of patients in the RDN group and 37.7% (40 of 106) in the sham group had an office systolic BP <140 mm Hg.

The mean 24-hour pulse rate change measured by the ambulatory BP monitor did not differ between both treatment groups (baseline-adjusted difference, 0.5 beats per minute [95% CI, −2.0 to 3.0]; *P*=0.695).

Safety Outcomes

Between baseline and 6 months, 3 major adverse events occurred in the RDN group and 1 in the sham control group. One event in the RDN was adjudicated as procedure-related (Table 4). One patient had a hematoma at the femoral access site, which resolved without sequelae. None of the 104 (97.2%) patients in the RDN group and 104 (94.5%) patients in the sham group who underwent computed tomography of the renal arteries developed new-onset renal artery stenosis >50%. Importantly, no patient developed end-stage renal disease.

DISCUSSION

The Iberis-HTN trial is the first multi-center, sham-controlled trial investigating the Iberis radiofrequency RDN catheter system in patients with uncontrolled hypertension. The key findings of this pivotal trial conducted

Table 3. Blood Pressure Change Between Baseline and 6 Months

Measurement	Renal denervation			Sham procedure			Baseline-adjusted between-group difference*	*P* value†
	Baseline	6 months	Difference from baseline to 6 months	Baseline	6 months	Difference from baseline to 6 months		
Ambulatory BP, mm Hg								
24-h systolic‡	148.0±10.0	135.1±14.4	−13.0±12.1	146.5±8.9	143.4±13.8	−3.0±13.0	−9.4 (-12.8 to −5.9)	<0.001
Daytime systolic	150.8±10.6	137.9±15.2	−12.9±13.6	149.1 ±9.3	146.4±14.2	−2.6±13.6	−10.3 (−14.0 to −6.6)	<0.001
Nighttime systolic	140.1±13.5	127.1±14.9	−13.1±13.9	139.1±12.0	135.1±15.6	−3.7±16.7	−9.4 (−13.6 to −5.3)	<0.001
24-h diastolic	91.3±10.4	83.7±11.4	−7.7±8.6	93.1±8.8	90.5±10.2	−2.8±10.1	−5.0 (−7.5 to −2.4)	<0.001
Daytime diastolic	93.4±10.7	85.8±11.6	−7.7±9.3	95.0 ±9.0	92.6±10.7	−2.5±10.4	−5.2 (−7.9 to −2.5)	<0.001
Nighttime diastolic	85.3±12.0	78.1±12.3	−7.3±10.2	87.8±10.5	84.8±11.3	−3.0±12.6	−4.4 (−7.5 to −1.3)	0.006
Office BP, mm Hg								
Systolic	159.1±7.2	137.4±14.0	−21.7±14.5	159.4±7.5	143.7±14.8	−15.4±15.8	−6.4 (−10.5 to −2.3)	0.003
Diastolic	98.8±7.2	85.9±10.6	−12.9±10.9	99.4±7.3	91.6±10.6	−7.8±11.8	−5.1 (−8.2 to −2.0)	0.001

Data are presented as mean±SD unless otherwise indicated. BP indicates blood pressure.
*Data shown as mean (95% CI).
†*P* value from baseline-adjusted ANCOVA.
‡Primary efficacy outcome.

in China are that RDN with the Iberis RDN catheter system was safe and associated with significant and clinically meaningful and consistent reductions in ambulatory and office BP in patients with uncontrolled hypertension despite standardized 3-drug antihypertensive pharmacotherapy. The BP lowering was observed continuously throughout the day and night, a phenomenon described as the always-on effect of RDN, which appears to be unrelated to medication intake.[6] The reduction in nighttime BP is of particular interest, as nighttime BP is more closely associated with cardiovascular morbidity and death than office BP.[12,13]

With the positive outcomes of this trial, the Iberis RDN system represents the third catheter and the second radiofrequency device[9,14,15] proving its BP-lowering in office and ambulatory BP in a high-quality randomized, sham-controlled trial as defined by the European Society of Cardiology Council on Hypertension and the European Association of Percutaneous Coronary Intervention clinical Consensus Statement[6] and the Hypertension Academic Research Consortium.[16] The Iberis and Symplicity Spyral radiofrequency catheter systems are both 6F-compatible and have a helical tip with 4 independent ablation electrodes, facilitating reliable wall contact and circumferential treatment of renal arteries with diameters between 3 mm and 8 mm. The Iberis RDN catheter is available in 90-cm and 160-cm lengths for transfemoral and transradial procedures. Therefore, it is currently the only European Conformity (marked RDN catheter available for radial access).

Compared with the SPYRAL HTN-ON MED trial (Global Clinical Study of Renal Denervation With the

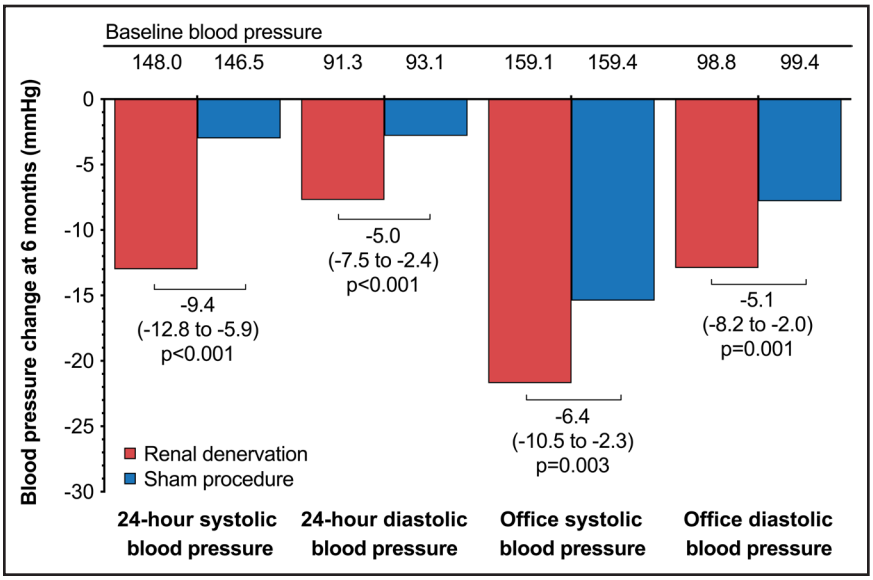

Figure 2. Changes in 24-hour and office systolic and diastolic blood pressure from baseline to 6 months. Between-group differences were adjusted for baseline measurements and are presented as mean (95% CI).

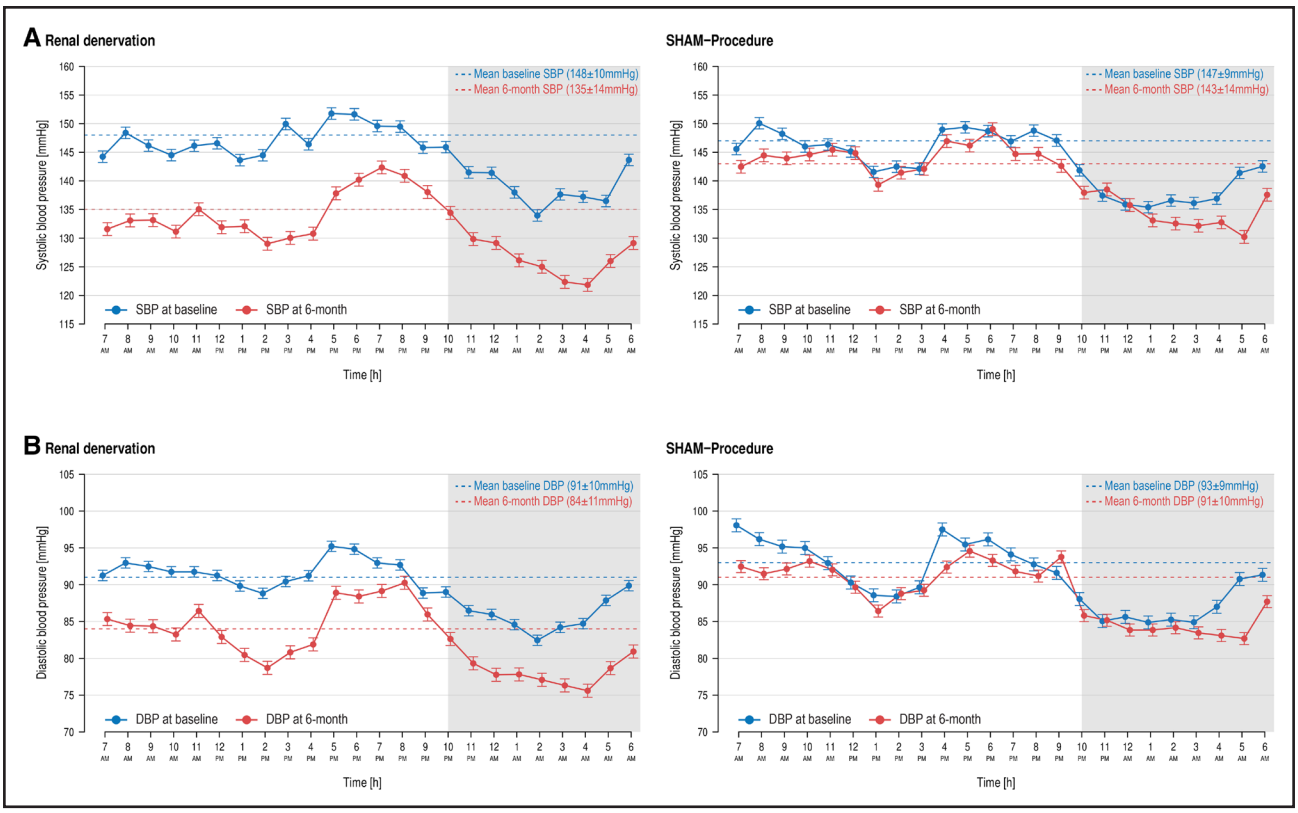

Figure 3. Ambulatory blood pressures: 24-hour profiles.
Depicted are 24-hour ambulatory systolic (**A**) and diastolic (**B**) blood pressures at baseline and 6 months of the renal denervation and sham control groups. Error bars show SEM.

Symplicity Spyral Multi-Electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications), which investigated the Symplicity Spyral radiofrequency catheter in patients with uncontrolled hypertension treated with 1, 2, or 3 antihypertensive drugs, the ambulatory BP reduction observed after 6 months were comparable.[17] In contrast to the SPYRAL HTN-ON MED trial,[17] patients enrolled in the present trial were switched to a standardized triple antihypertensive regimen. In both trials, changes in antihypertensive treatment were only allowed for safety reasons, if prespecified escape criteria were met, and performed by physicians blinded to treatment allocation. As the stable and symmetrical use of cointerventions was identified as a key methodologic characteristic of sham-controlled trials,[18] it is reassuring that the mean number of prescribed antihypertensive medication, the medication burden, and adherence rates did not differ between treatment groups at baseline and follow-up.

The differences in BP reductions are similar at 6 months with the SPYRAL HTN-ON MED trial, but the absolute BP reductions for both office and ambulatory BP were greater.[17] Compared with previous sham-controlled RDN trials,[8,15,19,20] the patients included in this trial were approximately ten years younger (mean age, 45 years) and had higher heart rates (mean heart rate, 79 bpm). One may speculate that the efficacy of RDN is more pronounced in younger age and patients with elevated heart rate[21] because both represent conditions of increased sympathetic nervous system activity. In the current trial, patients >65 years and patients with isolated hypertension were excluded.

This is a multicenter, sham-controlled trial investigating RDN in China, where hypertension is highly prevalent, and BP control rates remain poor.[1,4,22] Lowering BP is of great importance not only to reduce cardiovascular

Table 4. Incidence of Safety Events From Baseline to 6 Months

	Renal denervation (n=107)	Sham procedure (n=110)
All-cause mortality	0 (0)	0 (0)
Acute myocardial infarction	0 (0)	0 (0)
Coronary revascularization	2 (1.9)	1 (0.9)
Cerebrovascular event	0 (0)	0 (0)
Renal artery re-intervention	0 (0)	0 (0)
New-onset renal artery stenosis >50% (confirmed by CT angiography)	0 (0)	0 (0)
End-stage renal disease*	0 (0)	0 (0)
Access site hematoma	1 (0.9)	0 (0)

Data are presented as n (%). CT indicates computed tomography.
*Defined as estimated glomerular filtration rate <15 ml/min/1.73 m² or the need for renal replacement therapy.

morbidity and mortality but also to reduce health care costs.[23] In addition to lifestyle modifications and pharmacotherapy, RDN represents an alternative, adjunct treatment option.[6] Particularly in regions without a well-developed primary health care system,[2,22] RDN might be a valuable addition to existing therapies because of the one-time procedure which associates with clinically relevant and continuous 24-hour BP reductions.[6] Clinical evidence from sham-controlled trials and registries suggests that the BP changes after RDN persist for ≤10 years after RDN.[9,24,25]

The Iberis-HTN trial adds to the large body of evidence derived from sham-controlled trials, registries, and nonrandomized studies, indicating that RDN has a favorable safety profile.[6] There is no evidence of procedure-related safety concerns beyond the risks associated with femoral arterial access (<1%).[6,26,27] In the current study, 1 access site complication (hematoma) occurred (0.9%) in the RDN group, corresponding to a complication rate of 0.5% (1 of 217) for all included patients undergoing transfemoral puncture. In contrast to other catheter systems, the Iberis RDN catheter is also available for transradial use and is currently under investigation for the treatment of uncontrolled hypertension in a clinical study comparing the safety and efficacy of radial versus femoral access (URL: https://clinicaltrials.gov/; Unique identifier: NCT05234788). As for percutaneous coronary and other noncoronary interventions,[28,29] radial access for RDN might reduce vascular complications, shorten the hospital stay, and increase patient comfort when compared with femoral access.

Limitations

Our trial has potential limitations. The Iberis RDN system was investigated in Chinese patients with uncontrolled hypertension despite standardized therapy with 3 antihypertensive drugs. This standardized treatment with half-maximum doses of valsartan, hydrochlorothiazide, and amlodipine follows current hypertension guidelines recommending low-dose combination therapy, with the advantages of fewer side effects and swifter BP control.[30] Of note, these patients did not have resistant hypertension. Although safety events rarely occurred, additional follow-up is warranted to assess long-term safety. In line with other sham-controlled RDN trials, patients with an eGFR <45 ml/min/1.73 m² were excluded, and only 6% of the patients in the RDN group had an eGFR between 45 and 59 ml/min/1.73 m². Therefore, the BP-lowering efficacy and renal safety can only be considered in patients with normal or mildly-to-moderately reduced kidney function (Kidney Disease Improving Global Outcomes [KDIGO] stage G1 to G3a). As with other RDN catheter systems, there is no periprocedural marker of successful RDN.[5,6] Although treating branches and accessory renal arteries supplying ≥20% of the renal parenchyma was recommended as the lowest number of nerves per quadrant and the shortest lumen-to-nerve distance are found in the distal postbifurcation segments,[31] the number of ablations performed in the accessory renal arteries and branches was not separately captured. Although the reductions in mean 24-hour BP in the sham group were negligible, the office BP reductions were higher compared with other clinical trials. These large reductions could have occurred for several reasons. First, office BP is known to be more prone to a placebo effect and regression to the mean than ambulatory BP.[6] Second, office BP is susceptible to the so-called *whitecoat phenomenon*, which might decrease with recurring study visits.[6] Third, although medication changes were not allowed, physicians who were blinded to treatment allocation adjusted antihypertensive medication in more patients in the sham (11.0%) than the RDN (3.7%) group. These medication changes were mostly escalations, which potentially biased BP reductions in the sham group. Finally, one may speculate that patients self-adjusted their medication in case they did not experience a relevant drop in BP after the procedure. Qualitative drug adherence measurements would not have detected such alterations. As defined in the statistical analysis plan, the last observation carried forward method, which does not account for informative missingness, was used for patients with missing observations for the primary efficacy outcome. However, only one patient in the RDN group and 4 in the sham did not undergo ambulatory BP monitoring after randomization and the tipping-point analysis suggests the data are robust. Finally, each site was permitted to use its own validated ambulatory BP monitor for the measurements. However, the same monitor had to be used for the patient's baseline and follow-up measurements. Given that the primary efficacy outcome was the difference in mean 24-hour systolic BP change from baseline to 6 months after the procedure, and this was measured with the same BP monitor in a randomized trial, any differences between the BP monitors would have affected both arms equally, making a significant impact on the outcomes unlikely.

Conclusions

This randomized, sham-controlled trial demonstrated the feasibility, safety, and BP-lowering efficacy of radiofrequency RDN with the Iberis system in Chinese patients with uncontrolled hypertension on a standardized triple antihypertensive therapy.

ARTICLE INFORMATION

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Supplemental Material

Iberis-HTN Trial Organization
Supplemental Methods
Tables S1 to S10
Figures S1 to S2

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