Efficacy and safety of sympathetic mapping and ablation of renal nerves for the treatment of hypertension (SMART): 6-month follow-up of a randomised, controlled trial

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Summary

Background Previous trials of renal denervation (RDN) have been designed to investigate reduction of blood pressure (BP) as the primary efficacy endpoint using non-selective RDN without intraoperatively verified RDN success. It is an unmet clinical need to map renal nerves, selectively denervate renal sympathetic nerves, provide readouts for the interventionalists and avoid futile RDN. We aimed to examine the safety and efficacy of renal nerve mapping/selective renal denervation (msRDN) in patients with uncontrolled hypertension (HTN) and determine whether antihypertensive drug burden is reduced while office systolic BP (OSBP) is controlled to target level (< 140 mmHg).

Methods We conducted a randomized, prospective, multicenter, single-blinded, sham-controlled trial. The study combined two efficacy endpoints at 6 months as primary outcomes: The control rate of patients with OSBP < 140 mmHg (non-inferior outcome) and change in the composite index of antihypertensive drugs (Drug Index) in the treatment versus Sham group (superior outcome). This design avoids confounding from excess drug-taking in the Sham group. Antihypertensive drug burden was assessed by a composite index constructed as: Class N (number of classes of antihypertensive drugs) × (sum of doses). 15 hospitals in China participated in the study

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and 220 patients were enrolled in a 1:1 ratio (msRDN vs Sham). The key inclusion criteria included: age (18–65 years old), history of essential HTN (at least 6 months), heart rate (≥70 bpm), OSBP (≥150 mmHg and ≤180 mmHg), ambulatory BP monitoring (ABPM, 24-h SBP ≥130 mmHg or daytime SBP ≥135 mmHg or nighttime SBP ≥120 mmHg), renal artery stenosis (< 50%) and renal function (eGFR > 45 mL/min/1.73 m^2). The catheter with both stimulation and ablation functions was inserted in the distal renal main artery. The RDN site (hot spot) was selected if SBP increased (≥5 mmHg) by intra-renal artery (RA) electrical stimulation; an adequate RDN was confirmed by repeated electronic stimulation if no increase in BP otherwise, a 2nd ablation was performed at the same site. At sites where there was decreased SBP (≥5 mmHg, cold spot) or no BP response (neutral spot) to stimulation, no ablation was performed. The mapping, ablation and confirmation procedure was repeated until the entire renal main artery had been tested then either treated or avoided. After msRDN, patients had to follow a predefined, vigorous drug titration regimen in order to achieve target OSBP (< 140 mmHg). Drug adherence was monitored by liquid chromatography-tandem mass spectrometry analysis using urine. This study is registered with ClinicalTrials.gov (NCT02761811) and 5-year follow-up is ongoing.

Findings Between July 8, 2016 and February 23, 2022, 611 patients were consented, 220 patients were enrolled in the study who received standardized antihypertensive drug treatments (at least two drugs) for at least 28 days, presented OSBP ≥150 mmHg and ≤180 mmHg and met all inclusion and exclusion criteria. In left RA and right RA, mapped sites were 8.2 (3.0) and 8.0 (2.7), hot/ablated sites were 3.7 (1.4) and 4.0 (1.6), cold spots were 2.4 (2.6) and 2.0 (2.2), neutral spots were 2.0 (2.1) and 2.0 (2.1), respectively. Hot, cold and neutral spots was 48.0%, 27.5% and 24.4% of total mapped sites, respectively. At 6 M, the Control Rate of OSBP was comparable between msRDN and Sham group (95.4% vs 92.8%, p = 0.429), achieved non-inferiority margin –10% (2.69%; 95% CI –4.11%, 9.83%, p < 0.001 for non-inferiority); the change in Drug Index was significantly lower in msRDN group compared to Sham group (4.37 (6.65) vs 7.61 (10.31), p = 0.010) and superior to Sham group (–3.25; 95% CI –5.56, –0.94, p = 0.003), indicating msRDN patients need significantly fewer drugs to control OSBP <140 mmHg. 24-hour ambulatory SBP decreased from 146.8 (13.9) mmHg by 10.8 (14.1) mmHg, and from 149.8 (12.8) mmHg by 10.0 (14.0) mmHg in msRDN and Sham groups, respectively (p < 0.001 from Baseline; p > 0.05 between groups). Safety profiles were comparable between msRDN and Sham groups, demonstrating the safety and efficacy of renal mapping/selective RDN to treat uncontrolled HTN.

Interpretation The msRDN therapy achieved the goals of reducing the drug burden of HTN patients and controlling OSBP <140 mmHg, with only approximately four targeted ablations per renal main artery, much lower than in previous trials.

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Keywords: Hypertension; Renal denervation; Renal nerve mapping; Selective ablation; Drug burden; Medication adherence

Introduction

Hypertension continues as a major risk factor for morbidity and mortality of cardiovascular, neurologic and renal diseases in both industrial and developing countries.[1,2] Thus, hypertension is a global burden and needs better management with safe and efficient therapeutic approaches. Despite the availability of pharmacotherapy to treat hypertension with the therapy resulting in well documented reduction of the associated mortality and morbidity, more than 50% of hypertensive patients cannot attain target BP in both industrialized and developing countries[3–6]; poor drug compliance is one of the major causes.[3] Furthermore, even with demonstrated adherence and persistence with three or more anti-hypertensive medications, nearly 9% of patients with hypertension still cannot control their BP, a condition referred to as drug resistant hypertension.[7,8] Therefore, therapeutic solutions for hypertensive patients with features of no compliance issues, persistent antihypertensive effect and minor BP fluctuation remain a clinical need.

In recent years, catheter-based renal denervation (RDN) has been hotly pursued as a patient compliance-independent treatment for uncontrolled hypertension with features of 24-h always-on BP reduction and one-time treatment to gain long-term benefits.[9] Data from Symplicity studies, Spyral HTN Global Clinical Trial program and RADIANCE program have demonstrated the initial safety and efficacy of RDN to treat patients with either resistant[10–15] or uncontrolled[16–18] hypertension.

Research in context

Evidence before this study

We used "renal denervation", "hypertension" and "clinical trial" to search PubMed for papers published in English between January 1, 2018, and March 20, 2024. We found 53 clinical trial reports, 57 reviews and meta-analyses, 7 design papers and 3 position papers or consensus. Adding the term "drug burden" resulted in identifications of 4 clinical trials, 2 design papers, 1 guideline, one statement and 1 clinical trial report.

Previous trials of renal denervation (RDN) were to investigate reduction of blood pressure (BP) as only primary efficacy endpoint using blind (non-selective) ablation without verified RDN success intraoperatively and the effects of RDN on BP were severely interfered by antihypertensive drugs. There was no pivotal trial to answer the critical question whether RDN might reduce drug burden and properly control BP to target level using renal mapping, selective denervation approach.

Added value of this study

This pivotal trial investigated the safety and efficacy effects of renal mapping and selective renal denervation (msRDN) in patients with uncontrolled hypertension who received a standardized antihypertensive drug treatment. Combined dual primary outcomes were control rate of office systolic BP (OSBP) to achieve level of <140 mmHg and change in the composite drug index of antihypertensive medications. After msRDN, patients had to follow a predefined, vigorous drug titration regimen in order to achieve target OSBP (< 140 mmHg). This design eliminated the confounding effects of changes in antihypertensive medication on BP. RDN sites were selected by intra-renal artery electronic for ablation or to avoid ablation. The therapy achieved the goals to reduce drug burden of hypertension patients with 3.7 (1.4) and 4.0 (1.6) targeted ablations on left and right side renal main artery, respectively, and to control OSBP < 140 mmHg.

Implications of all the available evidence

This trial demonstrated the safety and efficacy of targeted renal denervation in patients with uncontrolled hypertension. The therapy achieved the goals to reduce drug burden of HTN patients with approximately 4 targeted ablations per side renal main artery and to control OSBP < 140 mmHg.

However, all previous trials of RDN have been designed to investigate reduction of BP as the primary efficacy endpoint using non-selective ablation without verified RDN success intraoperatively. Several issues have not been addressed: there was no pivotal trial to answer the critical question of whether RDN might reduce drug burden as a primary efficacy endpoint, and achieve the goal of controlling BP to a target level in hypertensive patients; the interferences of antihypertensive drugs were still persistent, Furthermore, there were no methods to confirm proper ablation sites and successful sympathetic denervation.[12]

Recent studies of the anatomy, physiology and histology of renal nerves have detailed the physiologic and anatomic heterogeneity of renal sympathetic nerves and justified the rationale to map renal nerves for selective RDN. van Amsterdam et al. and Mompeo et al.[19,20] demonstrated three nerve types around renal arteries: sympathetic, parasympathetic (or sympathetic inhibitory) and afferent nerve components. We[21–24] and other investigators[25–29] have demonstrated that BP was increased, decreased or unchanged once electronic stimulation was delivered to specific intra-renal artery sites[30]; thus, sites that increase in BP due to stimulation may represent dominant sympathetic fibers and are considered to be "hot spots" for RDN to treat hypertension. Sites that decrease in BP due to stimulation may represent dominant parasympathetic innervations or depressor nerves,[30] are considered to be "cold spots" and are inappropriate sites for ablation. Sites along the renal arteries that do not show significant effects on BP when stimulated are considered to be "neutral spots" and may represent the absence of renal nerves adjacent to the site or balanced sympathetic and parasympathetic innervations; ablation of these sites would provide no clinical benefit and add only therapeutic risk by futile denervations.[21]

Thus, we conducted this pivotal trial to examine the safety and efficacy of renal nerve mapping/selective RDN in patients with uncontrolled HTN, and to test whether patient's BP can be controlled following msRDN while reducing anti-hypertensive drug burden.

Methods

Detail design of the SMART study has been reported previously[31] and is shown in Fig. 1; brief descriptions are as below.

Study design, patients and screening

The SMART Study is a prospective, randomized, multicenter, single-blinded and sham procedure controlled trial (RCT) using a renal stimulation/mapping and ablation system (SyMap Medical (Suzhou), LTD, Suzhou, China) in patients with uncontrolled hypertension (OSBP ≥150 mmHg) and was conducted at 15 hospitals in China.

One unique feature of the trial was that the protocol did not freeze antihypertensive drug regime; instead after obtaining informed consent, the patient's current antihypertensive medications were replaced by drugs per a standardized antihypertensive drug regimen

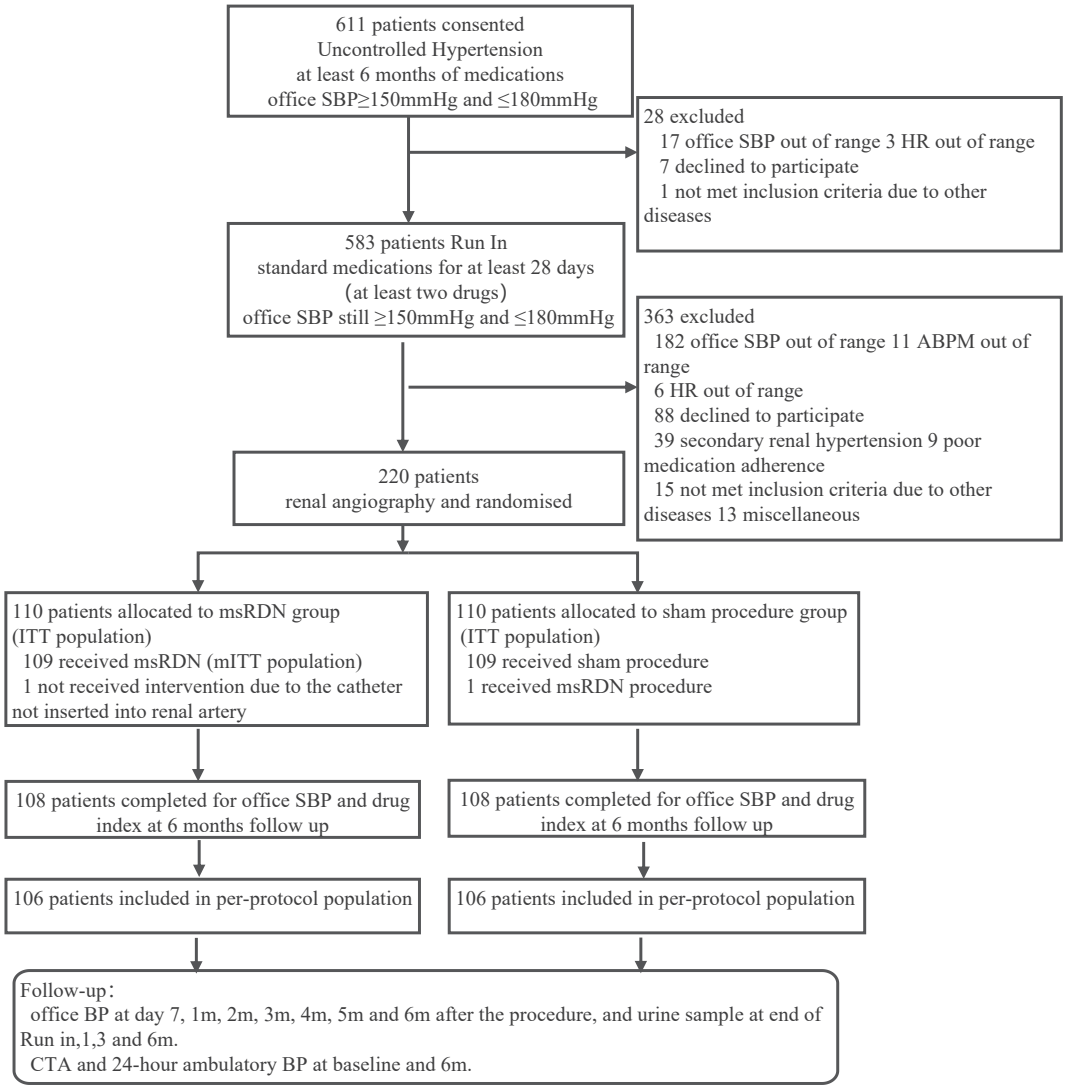


Fig. 1: **The trial design, profile and patient flowchart**. BP, blood pressure; HR, heart rate; ABPM, ambulatory blood pressure monitoring; ITT, intention-to-treat; mITT, modified intension-to-treat; msRDN, mapping/selective renal denervation; OSBP, office systolic blood pressure. Standard medications were stable for at least 28 days. SBP, systolic blood pressure; BP, blood pressure; CTA, computed tomography angiography.

including classes, doses and manufacturers of the medications (Table 1) and all medications were supplied by the study sponsor (SyMap Medical (Suzhou), LTD, Suzhou, China).

If patients had one antihypertensive medication, this drug was replaced by the same class of drug at a standard dose, and one more class of drug with a standard dose was added in the order shown in Fig. 2; for instance, the angiotensin-II receptor blocker (ARB), irbesartan, was the first option. Thus, patients were treated with least two drugs.

If patients previously had two classes of antihypertensive medications, their medications were replaced with the formulary supplied by the protocol.

If patients had three or more classes of antihypertensive medications, these drugs were replaced by the same classes of medications at standard dose from Table 1. In cases where patients were enrolled with compound antihypertensive medications, the medications were replaced by coaprovel (Irbesartan + Hydrochlorothiazide). Therapeutic substitutions of angiotensin converting-enzyme inhibition drugs were replaced by irbesartan.[31]

Patients were entered into a screen period for at least 28 days without changing antihypertensive medications, medication persistence and adherence was confirmed using urine samples for liquid chromatography-tandem mass spectrometry (LC-MS/MS) by an independent, qualified laboratory (Hangzhou Calibra Diagnostic Ltd,

	Class	Name	Manufacturer	Standard dose	Maximum dose
1	ARB	Irbesartan	Sanofi	150 mg/Day	300 mg/Day
2	CCB	Amlodipine	Pfizer	5 mg/Day	10 mg/Day
3	β Receptor Blocker	Metoprolol Sustained Release	AstraZeneca	47.5 mg/Day	95 mg/Day
4	Diuretic	Hydrochlorothiazide	Changzhou Pharmaceutical	25 mg/Day	50 mg/Day
5	α Receptor Blocker	Terazosin Hydrochloride	Abbott	2 mg/Day	4 mg/Day
6	Combination Drug	Irbesartan + Hydrochlorothiazide	Sanofi	Irbesartan 150 mg + Hydrochlorothiazide 12.5 mg/Day	Irbesartan 300 mg + Hydrochlorothiazide 25 mg/Day

Standardized drugs, doses and manufacturers, supplied by study sponsor. ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 1: **Standardization of anti-hypertension drug regimen.**

Hangzhou, China).[32] If their OSBP remained ≥150 mmHg, ≤180 mmHg after the screening period, all of the inclusion and exclusion criteria were met (Key inclusion criteria and key exclusion criteria are provided in Table 2), and the anatomy of renal artery as examined by computerized tomographic angiography (CTA) met specified criteria, patients were enrolled in the study. Patients (n = 220) underwent renal angiography then were randomly assigned in blocks by a central computer allocation system to either the renal nerve mapping and selective denervation group (n = 110, msRDN-Treatment) or the intensive drug therapy (n = 110, Sham) group in a 1:1 ratio. Follow-up was performed at 7 days after the procedure or at discharge from hospital, and 1, 2, 3, 4, 5 and 6 months after the procedure for BP measurements, antihypertensive medication analysis and adherence management. CTA was performed at 6 months for possible msRDN-related renal stenosis. In order to ensure adherence to the standardized antihypertensive drug regimen, urine samples were collected at the end of the screening period, 3 months and 6 months for LC-MS/MS and results were obtained within 48 h. Data collecting, management, statistical analysis and laboratory tests were done by independent, qualified organizations (Tiger Medical, Hangzhou, China; Peking University Clinical Research Institute, Beijing, China).

Renal mapping/ablation system and renal mapping/selective denervation procedure

The combined renal stimulation/mapping and ablation system consists of a dedicated electric stimulation/mapping and ablation catheter (SyMapCath I®) and a Stimulator/RF Generator (SYMPIONEER S1®).[33] The system allows operators to deliver intra-renal artery electronic stimulation for mapping renal nerves, target optimal ablation sites (hot spots/sympatho-stimulatory), avoid futile ablations of cold (parasympathetic or sympatho-inhibitor sites) and neutral spots, and to confirm technical success.

Standard operation procedure has been applied to msRDN.[31] The procedure was performed under deep sedation. Renal artery angiography was performed before the renal mapping/selective RDN procedure; the length of renal main artery was measured to determine the number of sites to be stimulated and possibly ablated; and per the predefined standard protocol, these sites span the length of the artery and rotate 90° at every 5 mm interval. The catheter sheath was designed to provide the visual aids and technical support necessary to ensure operator success in completing this circumferential stimulation-mapping and ablation of sites. The sheath has a graduated scale that guides the operator in advancing or retreating the catheter by 5 mm, and the handle has 90° markers for the operator to rotate the knob and

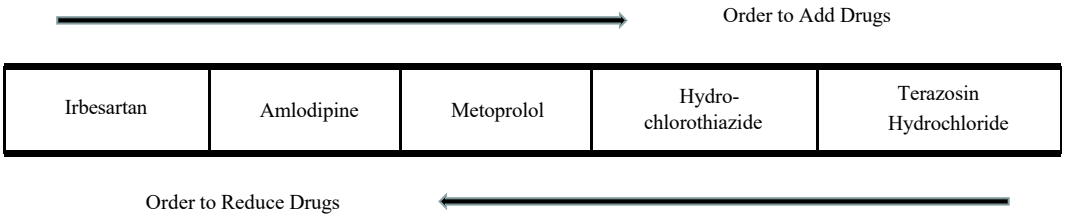


Fig. 2: **Antihypertensive medication titration regimen**. Once a drug needed to be adjusted, the dose was adjusted then class. For instance, an increase in dosing was first selected until the defined maximum dose; if systolic BP was still not controlled, then another class drug was added according to the order shown. If the class of drugs was not proper to the patient as evidenced by clinical signs, the class can be skipped and the next class of drug was used.

Key inclusion criteria
1 Male and non-pregnant female subjects, 18 ≤ age ≤ 65
2 Essential hypertension
3 Office systolic blood pressure ≥150 mmHg and ≤180 mmHg; and resting heart rate ≥70 bpm without taking beta blocker (Resting heart rate does not taken into account if beta blocker is taken)
4 Average 24-h ABPM systolic blood pressure ≥130 mmHg, or ABPM systolic blood pressure during daytime ≥135 mmHg, or ABPM systolic blood pressure during nighttime ≥120 mmHg
5 History of hypertension is longer than 6 months
6 Patient with poor blood pressure control after 6 months of drug therapy, understands the purpose of this study, and is willing to participate and sign the Informed Consent; then the patient receives standard antihypertensive drug treatment (at least two drugs) for at least 28 days, drug compliance ≥80%, office systolic blood pressure ≥150 mmHg and ≤180 mmHg.
7 Patient is compliant and willing to complete clinical follow-up
Key exclusion criteria
1 Renal artery anatomy is unqualified including:
(1) Diameter <4 mm or treatable length <25 mm,
(2) Multiple renal arteries and the main renal artery supplies a fraction of the blood flow less than 75%,
(3) Renal artery stenosis >50% or any renal artery aneurysms on either side,
(4) History of renal artery PTA, including balloon angioplasty and stenting.
2 eGFR <45 mL/min/1.73 m^2 (MDRD formula)
3 Hospitalized within one year due to hypertensive crisis
4 Average 24-h systolic blood pressure <130 mmHg and ABPM systolic blood pressure during daytime ≤135 mmHg, and ABPM systolic blood pressure during nighttime ≤120 mmHg
5 Pulse pressure > 80 mmHg
6 During run in period, using antihypertensive drugs other than standardized antihypertensive drugs
7 Participated in other clinical trials including both drug and medical device studies within 3 months of current study
8 Female with pregnant or lactating, or having plans for pregnancy within 1 year
9 Patients with sleep apnea who need chronic oxygen or mechanical ventilation support (for example, tracheostomy) during sleep
10 Patients previously or currently suffering from following diseases:
(1) Essential pulmonary arterial hypertension,
(2) Type I diabetes,
(3) Patients with severe cardiac valvular stenosis who have contradictions and cannot tolerant to significantly reduce blood pressure,
(4) Within half year, patients had myocardial infraction, unstable angina, syncope or cerebrovascular accidents,
(5) History of primary aldosteronism, pheochromocytoma, aorta stenosis, hyperthyroidism or hyperparathyreosis,
(6) Any disease conditions interfering the measurement of blood pressure (for instance, severe peripheral artery diseases, abdominal artery aneurysm, hemorrhagic disorders such as thrombocytopenia, hemophilia and severe anemia),
(7) Plans to have surgery or cardiovascular interventions within 6 months,
(8) Alcohol abuse or unknown drug dependence history,
(9) Neuroticisms such as depression or anxiety disorders.
11 non-compliant patients who are unable to follow the study protocol per physician's requests
12 Any contradictions to conduct renal artery stimulation and ablation
ABPM, ambulatory blood pressure monitoring; eGFR, estimated glomerular filtration rate; DMRD, Modification of Diet in Renal Disease.

Table 2: **Key patient inclusion and exclusion criteria.**

accurately aim the catheter tip to target the distinct treatment quadrants of the renal artery.

msRDN procedures had three steps: renal stimulation to map renal innervation, ablation of hot spot, and stimulation to confirm an effective or failed ablation. The procedure was started from the distal end of a main renal artery and repeatedly executed until the entire main renal artery had been tested then either treated or avoided.

The parameters used for intra-renal artery stimulation and mapping were as below:

Mode: electric current
Frequency: 20 Hz.
Pulse width: 5 ms
Amplitude: 10–20 mA.
Stimulation duration: < 120 s

The stimulation should be maintained for at least 10 s. During stimulation, invasive BP was monitored from a femoral artery. If systolic BP rise ≥5 mmHg during stimulation, the site was defined as a "hot spot" and ablated. At sites where there was a decrease in systolic BP (≥5 mmHg) following stimulation or no BP response (< 5 mmHg) to stimulation, the site was defined as "cold spots" or "neutral spots" without ablation and the operator would then withdraw the catheter to another site for stimulation/mapping and ablation procedure.

Renal ablation was conducted at "hot spots" using parameters as below:

Power: 8 W
Temperature: 50–55 °C
Duration: 120 s

An effective ablation was subsequently confirmed by a repeat stimulation. If systolic BP still rose more than 5 mmHg, a second ablation was performed at the same site; otherwise, if an effective ablation was defined, the

catheter was moved to the next site. After the second ablation, another stimulation was repeated, but no third ablation was allowed at one site. At least 1 min must be waited between the steps. We only mapped and treated renal main artery and accessary artery if its diameter was > 3 mm and length was >25 mm.

The procedure physicians were aware of patient allocation in msRDN or Sham group; however, neither physicians who were responsible for follow-up nor patients were informed of the treatment allocation. The blind was ensured by measures as below: patients were visual and auditory blind to the procedure with a noise-cancelling headset placed on each patient who entered the procedure laboratory; patients randomized to Sham group experienced a sham msRDN procedure using RF console to mimic steps of stimulation/mapping (30 s), ablation (120 s) and stimulation/confirmation (30 s) in 60 s intervals for a total of 10 cycles, resulting in a sham procedure duration of at least 50 min; patients in either msRDN or Sham group received the same in-laboratory treatment and post follow-up procedures; physicians who performed post-procedure management did not have access to procedure notes or blinding notes. A questionnaire was completed by patients to assess blindness at discharge from the hospital and at 6 months follow-up.

Key operators participated in preclinical experiments to learn how to perform msRDN procedure. Once these operators obtained experience and a certificate from the sponsor, they guided other physicians to perform the procedure for their first case.[21–23]

Standardized antihypertensive medication regimen, titration protocol and adherence monitoring

Persistence of and adherence to hypertensive medications were particularly important for this study because drug burden was one of two primary efficacy endpoints. Thus, rigorous measurements including standardized medications, titration protocol and adherence monitoring were taken to ensure the consistency, persistence of and adherence to antihypertensive drugs.

All enrolled patients had to follow a standardized antihypertensive medication regimen (Table 1) and an antihypertensive medication titration protocol (Fig. 2) in order to control OSBP <140 mmHg. At each follow-up point after msRDN procedure office BP was assessed; if the patient's OSBP had not achieved target level (<140 mmHg), the doses or classes of antihypertensive medications were titrated until OSBP was <140 mmHg. Once a patient's medication was titrated, the dose was adjusted firstly per the protocol; if maximum dose was achieved and OSBP was still not controlled to target level (<140 mmHg), another class of medication was added in the order shown by Fig. 2 unless the patient had a contraindication to a medication in the protocol, then the medication can be skipped in the titration order.

Four measurements were taken to rigorously monitor patient's adherence and persistence to our drug regimen during this trial:

1. Study sponsor provided all antihypertensive medications.
2. Patients recorded their medications daily in a medication diary.
3. Antihypertensive drugs were counted at each follow-up visit.
4. Antihypertensive drug adherence was monitored, managed and confirmed by using urine samples for LC-MS/MS at the end of running-in period, 1 month, 3 months and 6 months; the validation of the methods was reported previously.[32]

The execution of rigorous antihypertensive medication titration protocol was examined and performed monthly. Imperfect adherence or persistence with medication can exist in trials.

Measurements of office blood pressure

Office BP was measured according to standard American Heart Association recommendations[34] using an electronic calibrated automatic recording sphygmomanometer system consisting of a sphygmomanometer (OMRON HBP-1100U) and a dedicated computer. Within 30 min of measurements, patients were instructed to empty bladder and to avoid smoking, drink caffeinated beverages and exercise. After 5 min of quiet rest, measurements were conducted on sitting patients with straight supported back, feet flat on the floor, legs not crossed, and arms supported on a flat surface with the upper arm at heart level with the cuff applied directly to the skin. Three automated measurements were performed with at least 1-min interval between measures. If the difference between the highest and lowest systolic BP was more than 15 mmHg among the three measurements, another measurement was performed. However, if the difference was still higher than 15 mmHg after six measurements, the patient was excluded.[35,36] Three qualified BP measurements were automatically averaged and stored in the computer in a binary format.

Outcomes

The study used combined primary efficacy endpoints at 6 months post msRDN procedure: The control rate of patients to OSBP <140 mmHg, which was a non-inferior come,[37–40] and the change in the composite index of antihypertensive drugs between treatment and sham group, which was a superior outcome.[41]

Antihypertensive drug composite index was calculated as below:

Drug Composite Index = Class N (number of classes of antihypertensive drugs) × (sum of doses).

One standard dose of each drug was defined as 1, a half dose was defined as 0.5, and double dose was defined as 2.

For instance, if a patient took one dose of an angiotensin-II receptor blocker and one dose of a calcium blocker, the drug composite index was as follows: $2 \times (1 + 1) = 4$.

This design ensured that the comparison of drug burden was made at the same control rate of OSBP between msRDN and sham groups.

The secondary efficacy outcomes included changes in 24-h ABPM at 6 months, changes in 24-h ABPM one day immediately after the msRDN procedure, and change in composite index of antihypertensive drugs at 1 and 3 months.

The primary safety measures of the study were:

1. Success rate of the renal interventional therapy procedure during msRDN procedure.

The success rate was defined by whether the renal mapping/denervation catheter can be engaged in the correct position in the renal artery and renal nerve ablation procedure was successfully performed without related complications such as renal arterial perforation or renal artery embolization.

2. Acute infection and renal dysfunction during the time from msRDN procedure to the time the patient was discharged from the hospital or during 7 days after msRDN procedure.
3. All-cause death within 6 months.
4. Severe renal dysfunction (eGFR <15 mL/min/m^2) or renal function replacement therapy at 6 months.
5. Rate of renal artery stenosis (>70%) at 6 months.
6. Adverse events (AEs), serious adverse events (SAEs), and severe cardio-cerebrovascular events within 6 months.

Statistical analysis

The statistical analysis was performed by Peking University Clinical Research Institute, Beijing, China. Statisticians participated in the concept development, protocol design, study implementation, data management, analysis and summary of research results. The statistical analysis plan was formulated after the completion of the study protocol and the statistical analysis report was completed by statisticians in a blinded manner after the end of the trial.

Clinical compliance was defined as the OSBP of patients was controlled and achieved to target level: <140 mmHg[41] at 6 months after msRDN. The assumption was that the msRDN and Sham groups had the same clinical compliance rate of 95% at 6 months, the non-inferiority margin was 10% with the significance level at 0.05 (two-side test), and the power was 80%, then using PASS13 software and group sequential design to conduct simulation calculations (50,000 simulations and assuming half of the subjects reached the evaluable endpoint). Using O'Brien-Fleming method of type I error consumption, 85 pairs of subjects were needed. If 20% of drop-out rate was taken into consideration, 212 subjects (106 for each group) were needed. Because subgroup analyses might be utilized, the final sample size was thus further expanded to 220 patients (110 pairs).

The composite index of antihypertensive drugs, which was based on both the classes and the doses of antihypertensive medications, should have higher power to examine the drug burden than use of an index only considering the class or dose of antihypertensive drugs.[42,43]

Per the principle of intention-to-treat (ITT), the full analysis set (FAS) consists of all subjects who received treatments and had the baseline assessments. For subjects with missing efficacy assessments, these missing primary endpoints were imputed by worst case carry forward (WCCF) method.

Per-protocol (PP) set consisted of subjects who completed the study protocol and excluded the subjects who had serious protocol violations.

Safety set (SS) consisted of all randomized subjects who received treatments and had at least one baseline safety assessment.

The efficacy analysis was performed based on data from FAS and the analysis of safety were performed based on SS.

The efficacy analysis of the study was based on the combined primary outcomes at 6 months after the msRDN procedure. The control rate of patients with OSBP <140 mmHg was tested under non-inferiority hypothesis; the hypothesis was as following:

$$H_0 : \pi_T - \pi_C \leq -10\%$$

$$H_1 : \pi_T - \pi_C > -10\%$$

The difference in control rates between groups and corresponding 95% CI was computed and compared with significance level of 0.025 (one-side test) and power of 80%. The test hypothesis was significant if the lower bound of 95% CI was greater than –10% (non-inferiority margin). Cochran-Mantel-Haenszel (CMH) test was used to test the difference between treatment groups when considering multicenter factor.

The change in the composite index of antihypertensive drugs between treatment and Sham group was tested under superiority hypothesis and the change in the composite index was examined using analysis of covariance (ANCOVA) model to estimate the least-square means and 95% CI of the change in composite index when considering multicenter factor. ANCOVA model with center–group interaction was applied to assess the consistency between centers,

$p < 0.1$ was considered interaction significant. Only if both the non-inferiority test for the compliance of control rate of systolic BP and superiority test for drug burden indicated by the composite index of antihypertensive medications were statistically significant, the study was considered statistically significant.

Data presented in the current report were from FAS unless it is specified. Continuous variables were presented as mean and SD and compared using paired t-test or Wilcoxon rank test, as appropriate. Categorical variables were summarized with frequencies and percentages and compared using chi-square test or Fisher exact test, as appropriate. Ranked variables were compared using Wilcoxon rank test or CMH test.

Safety analyses were based on SS. Each safety endpoint was summarized using descriptive statistics and compared between groups. Events such as AEs, SAEs etc. were summarized by tabulating the number of each event, the number of subjects with each event, the incidences rate of each event, while listing each event. Comparisons of incidence rate of AEs between groups were conducted with the use of chi-square test. If the data did not conform to chi-square test, Fisher's exact test was used. All safety data including AEs reports and laboratory results from participants were assessed.

Statistical analysis was performed with SAS 9.4 (or higher version; SAS Institute, Cary, NC, USA). The sample size was calculated using PASS13 software (NCSS, Kaysville, UT, USA). A 2-tailed $p < 0.05$ was considered statistically significant in all statistical tests.

The protocol was approved by the Ethics Committees of all participating hospitals. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients previous to being included in the study.

The trial is registered on clinicaltrials.gov (NCT02761811) and follow-up for 5 years is ongoing.

Role of the funding source

The founder of the study identified clinical sites and was involved in data collection, monitoring and project administration via independent, qualified organizations (Hangzhou Tigermed Consulting Co., Ltd, Hangzhou, China; Peking University Clinical Research Institute, Beijing, China). The manuscript was written by the lead authors with contributions from the co-authors. The founding source assisted in figure and table generation, manuscript editing and formatting.

Results

From July 8, 2016 to February 23, 2022, 611 patients were consented and entered screening period, 391 patients were excluded due to various causes, 220 patients fulfilled all inclusion and exclusion criteria and were randomly assigned to either msRDN (n = 110) or Sham (n = 110) procedure. In msRDN and Sham control group 108 patients completed 6 months follow-up, respectively. The trial profile and the reasons why those patients were excluded from the trial are listed in Fig. 1. The baseline clinical characteristics are illustrated in Table 3. Age, body weight, BMI, sex, office BP, 24-h BP, heart rate, eGFR and left ventricular ejection fraction were similar between msRDN and Sham group. The major comorbidities of other major cardiovascular diseases are also listed in Table 3. There were no differences in the usages of antihypertensive medications in terms of number, class, dosing and drug composite index at baseline between msRDN and Sham groups (Table 4). At end of screening period, the percentages of patients prescribed 2, 3, 4 and 5 classes of antihypertensive drugs in msRDN and Sham groups were 47.7% vs 46.4%, 31.2% vs 30.0%, 18.4% vs 21.8% and 2.8% vs 1.8% (all $p > 0.05$), respectively. Drug composite indexes were not different between msRDN and Sham group (9.17 (7.11) vs 9.04 (6.11), $p > 0.05$).

Throughout the trial, the adherences of antihypertensive medications were maintained at very high levels and comparable between msRDN and Sham group (Fig. 3), it was 98.2% and 95.5% in baseline, 89.9% and 90.9% at 6 months, respectively. The high adherences ensured the reliability of the major clinical outcome, Drug Composite Index. Using msRDN procedure, hot, cold and neutral spots was 48.0%, 27.5% and 24.4% of total mapped sites, 37.7% of total hot spots needed a second ablation. Specifically, in left and right main RA, mapped sites were 8.2 (3.0) and 8.0 (2.7), hot/ablated sites were 3.7 (1.4) and 4.0 (1.6), cold spots were 2.4 (2.6) and 2.0 (2.2), neutral spots were 2.0 (2.1) and 2.0 (2.1), 39.4% and 36.1% of hot spots needed a second ablation, respectively (Fig. 4). The percentage of hot, cold and neutral spots among mapped sites in right and left main RA was also shown in Fig. 4. Average time for msRDN procedure time was 76.4 (17.9) min (Mapping: 9.9 (5.7) min, Ablation: 16.6 (4.0) min, Confirmation/Stimulation: 4.3 (2.0) min, 2nd Ablation: 5.7 (4.2) min, 2nd Confirmation/Stimulation: 1.5 (1.3) min, Total Waiting: 38.4 (8.5) min). The amount of contrast used for msRDN and Sham procedure was 102.3 (38.3) mL and 56.6 (22.1) mL, respectively.

At 6 months, the Control Rate of OSBP was comparable between msRDN and Sham group (95.4% vs 92.8%, $p = 0.429$), achieving a non-inferiority margin −10% (2.69%; 95% CI -4.11%, 9.83%, $p < 0.001$ for non-inferiority). The change in Drug Composite Index, the pre-specified primary clinical endpoint presenting antihypertensive drug burden, was statistically significant lower in msRDN group (4.37 (6.65) vs 7.61 (10.31), $p = 0.010$) and superior to Sham group (−3.25; 95% CI −5.56, −0.94, $p = 0.003$), indicating patients in msRDN groups need significant fewer drugs to control OSBP < 140 mmHg (Fig. 5).

	msRDN group (n = 109)	Sham group (n = 110)
Age (years)	44.52 (10.96)	46.84 (9.49)
Male	93 (85.32%)	97 (88.18%)
Weight (kg)	85.01 (14.70)	82.58 (12.86)
Height (cm)	170.57 (6.78)	169.72 (6.54)
BMI, kg/m^2	29.14 (4.13)	28.57 (3.40)
Race/Han race	105 (96.33%)	108 (98.18%)
Minority race	4 (3.67%)	2 (1.82%)
Office SBP (mmHg)	158.49 (6.79)	160.35 (7.78)
Office DBP (mmHg)	99.57 (9.77)	101.62 (10.30)
Heart rate (bpm)	80.29 (13.25)	78.74 (11.25)
Mean 24 hSBP (mmHg)	146.79 (13.94)	149.75 (12.76)
Mean 24 hDBP (mmHg)	92.56 (10.93)	95.54 (9.13)
Mean 24 hSBP-Daytime (mmHg)	149.16 (14.23)	151.66 (13.07)
Mean 24 hDBP-Daytime (mmHg)	94.26 (10.87)	97.27 (9.38)
Mean 24 hSBP-Nighttime (mmHg)	141.64 (16.74)	143.95 (15.79)
Mean 24 hDBP-Nighttime (mmHg)	87.94 (12.82)	90.52 (10.48)
eGFR (%, MDRD formula)	98.20 (22.07)	98.83 (27.45)
LVEF (%)	65.12 (5.05)	65.20 (4.43)
Hyperlipidemia	40 (36.69%)	47 (42.73%)
Coronary artery disease & Coronary syndrome	6 (5.51%)	8 (7.27%)
Atrial fibrillation	1 (0.92%)	0 (0.00%)
Heart failure	1 (0.92%)	0 (0.00%)
Stroke	11 (10.10%)	16 (14.55%)
Diabetes (Type 2) & Glucose Metabolic Abnormality	20 (18.34%)	34 (30.91%)
Obstructive sleep apnea	7 (6.43%)	4 (3.64%)
Peripheral artery disease	2 (1.83%)	4 (3.64%)

Values are mean SD or n (%). msRDN, mapping selective renal denervation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; DMRD, Modification of Diet in Renal Disease; LVEF, left ventricular ejection fraction.

Table 3: **Baseline characteristics.**

Antihypertensive medications	Baseline		1 month		3 month		6 month	
	msRDN (n = 109)	Sham (n = 110)	msRDN (n = 109)	Sham (n = 109)	msRDN (n = 108)	Sham (n = 108)	msRDN (n = 108)	Sham (n = 108)
Drug index	9.17 (7.11)	9.04 (6.11)	9.33 (7.19)	9.74 (6.30)	9.78 (7.30)	10.34 (6.59)	13.16 (8.35)	16.03 (9.74)
Number								
1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
2	52 (47.7%)	51 (46.4%)	53 (48.6%)	44 (40.4%)	51 (47.2%)	41 (38.0%)	30 (27.8%)	21 (19.4%)
3	34 (31.2%)	33 (30.0%)	33 (30.3%)	39 (35.8%)	35 (32.4%)	40 (37.0%)	47 (43.5%)	44 (40.7%)
4	20 (18.4%)	24 (21.8%)	20 (18.4%)	24 (22.0%)	19 (17.6%)	24 (22.2%)	24 (22.2%)	34 (31.5%)
5	3 (2.8%)	2 (1.8%)	3 (2.8%)	2 (1.8%)	3 (2.8%)	2 (1.9%)	6 (5.6%)	8 (7.4%)
Average	2.76 (0.85)	2.79 (0.85)	2.75 (0.85)	2.85 (0.83)	2.76 (0.84)	2.86 (0.84)	3.04 (0.87)	3.25 (0.89)
Classes								
ARB	101 (92.7%)	100 (90.9%)	101 (92.7%)	102 (93.6%)	100 (92.6%)	101 (93.5%)	102 (94.4%)	105 (97.2%)
CCB	96 (88.1%)	101 (91.8%)	96 (88.1%)	104 (95.4%)	96 (88.9%)	103 (95.4%)	100 (92.6%)	104 (96.3%)
β-Blocker	69 (63.3%)	63 (57.3%)	69 (63.3%)	62 (56.9%)	67 (62.0%)	62 (57.4%)	75 (69.4%)	76 (70.4%)
Diuretic	31 (28.4%)	35 (31.8%)	30 (27.5%)	34 (31.2%)	31 (28.7%)	34 (31.5%)	43 (39.8%)	47 (43.5%)
α-Blocker	4 (3.7%)	8 (7.3%)	4 (3.7%)	9 (8.3%)	4 (3.7%)	9 (8.3%)	8 (7.4%)	17 (15.7%)

Values are mean SD or n (%). msRDN, mapping selective renal denervation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 4: **The status of antihypertensive medications.**

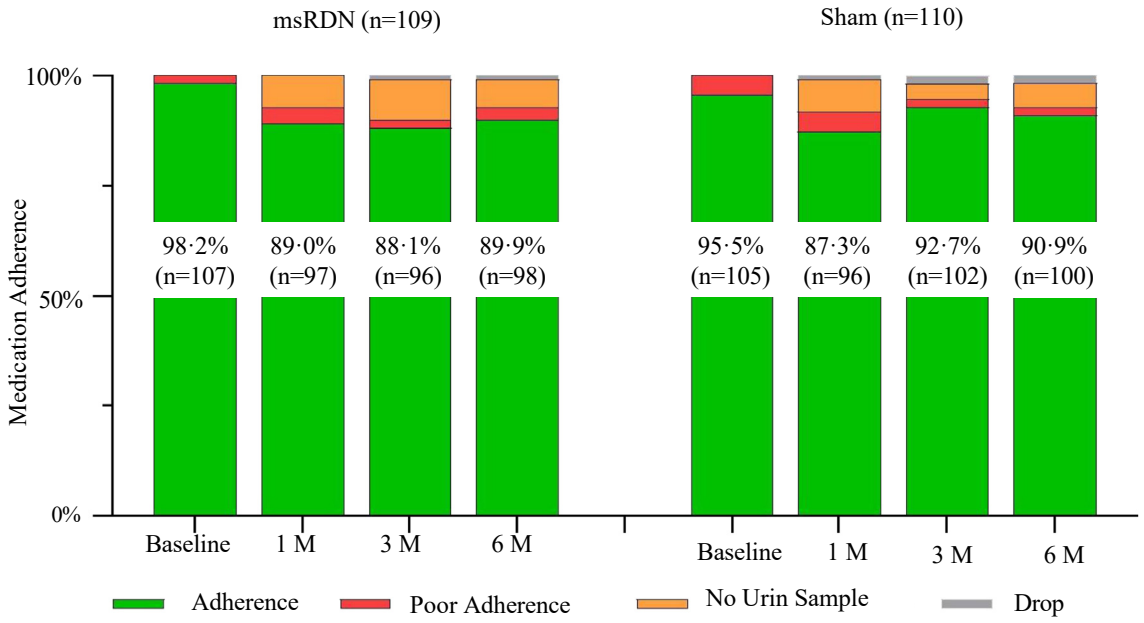


***Fig. 3:* Antihypertensive medication adherence**. Antihypertensive drug adherence was consistently high in msRDN (mapping/selective renal denervation) and Sham group throughout the trial. Per the design of the trial, physicians had to adjust patient's drug in order to control their office systolic blood pressure to target level < 140 mmHg, and this design is preferred solution for patient's willingness, ethical violation and avoids confounding from excess drug-taking in the sham group. Thus, high antihypertensive drug adherence was maintained. M, month.

Office BP and 24-h ambulatory BP were significantly reduced from baseline in both msRDN and Sham group at 6 months (Fig. 6); for instance, the reduction in OSBP and 24-h systolic BP was 25.2 (8.6) mmHg and 10.8 (14.1)mmHg in msRDN group, and 27.3 (10.0)mmHg and 10 (14.0)mmHg in Sham group, respectively. The results indicated msRDN plus significantly less antihypertensive drug treatment achieved a comparable BP lowering effect as intensive drug therapy in patients with uncontrolled hypertension.

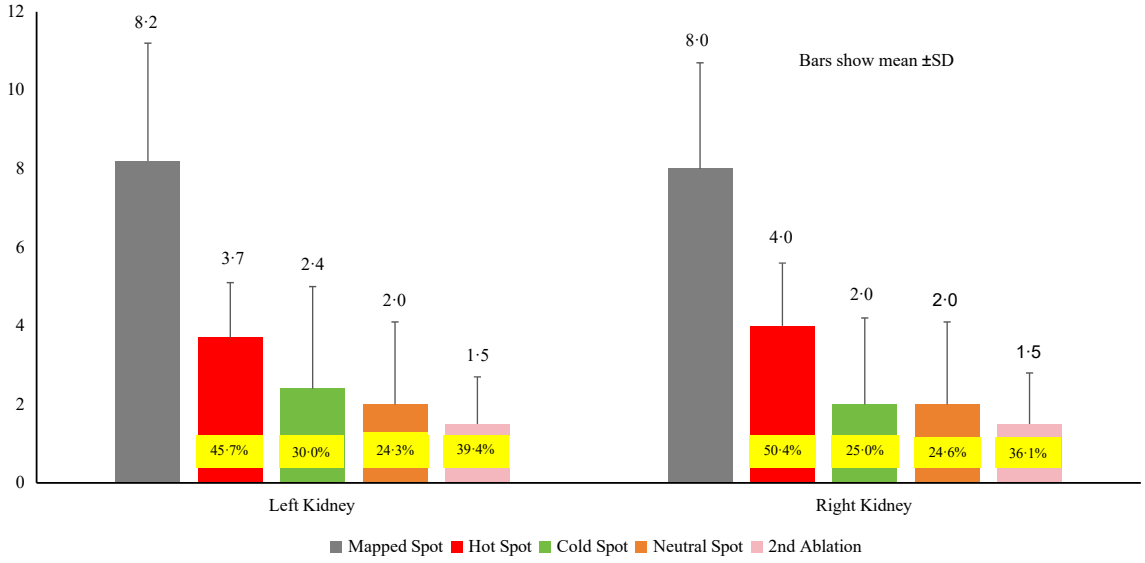
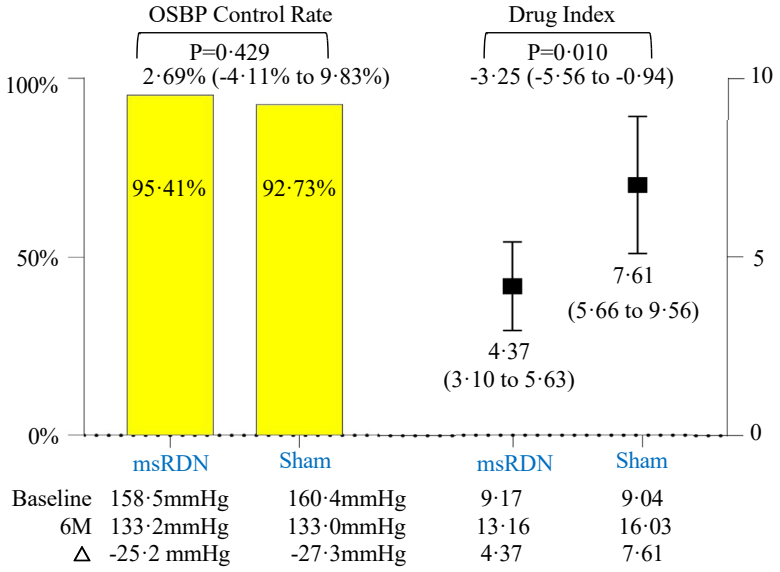


***Fig. 4:* Renal mapping selective renal denervation data**. Renal mapping/selective RDN procedure was utilized. Mapped sites were 8.2 and 8.0, hot/ablated sites were 3.7 and 4.0, cold spots were 2.4 and 2.0, neutral spots were 2.0 and 2.0, 39.4% in left and right renal main artery, respectively. Hot, cold and neutral spots was 48.0%, 27.5% and 24.4% of total mapped sites. 37.7% of total hot spots needed a second ablation.



	msRDN Group	Sham Group	*P*-value	Difference (95% CI)	Hypothesis Test
Control Rate Office SBP	95·41% (89·62%, 98·49%)	92·73% (86·17%, 96·81%)	P=0·429	2·69% (-4·11%, 9·83%)	P<0·001 (Non-inferiority Test)
Changes Drug Index	4·37 (SD, 6·65)	7·61 (SD, 10·31)	P=0·010	-3·25 (-5·56, -0·94)	P=0·003 (Superiority Test)

Fig. 5: **Combined primary outcomes**. At 6 month after msRDN (mapping/selective renal denervation) procedure, the control rate of office systolic blood pressure (OSBP) was comparable between msRDN and Sham group, 95 vs 93%, p = 0.429, it reached non-inferiority hypothesis test, p < 0.001. Drug burden, the change of Drug Index was significantly lower in msRDN group compared to Sham group: 4.37 vs 7.61, p < 0.01, it reached superiority test, p = 0.003. Thus, msRDN significantly reduced patient's drug burden and controlled office systolic blood pressure to target level: 140 mmHg, compared to sham group.

Based on PPS analysis, msRDN procedure resulted in 42.6% of patients having their OSBP controlled to target level <140 mmHg at 6 M with their drugs either unchanged or reduced, compared to only 27.8% of such patients in Sham group; the difference was statistically significant (p = 0.023) (Fig. 7).

The safety endpoints are presented in Table 5. The safety profiles were comparable between msRDN and Sham group. All-cause mortality and severe renal dysfunction were zero. One incidence of renal stenosis was observed in msRDN group; however, the stenosis already existed when the patient was enrolled in the trial. Adverse event rate, severe adverse rate and severe cardio-cerebrovascular events rate were similar between msRDN and Sham group. None of these events were related to renal mapping/selective renal ablation procedure. The data demonstrated the safety of the therapy.

Discussion

In this rigorous trial, we have demonstrated safety and efficacy of msRDN to treat patients with uncontrolled hypertension. There were three main findings of the trial: First, compared to Sham group, patients in msRDN group needed significantly less antihypertensive medications to control their OSBP to target level < 140 mmHg. Second, such effects of msRDN on drug burden and OSBP were achieved via only 3.7 and 4.0 ablations on left and right of renal main artery, respectively. Third, the comparable reduction in BP between msRDN group and Sham group revealed that the enrolled patients in the trial were uncontrolled hypertension since the patients in Sham group were in fact intensively pharmacologically treated and their OSBP was able to be controlled to < 140 mmHg.

The novel trial is distinguished from previous RDN trials to treat hypertension by several features: First, combined primary efficacy endpoints were used to assess the effects of msRDN therapy not only on BP but also on antihypertensive drug burden. This is the first rigorous trial with prespecified main clinical outcomes that demonstrated msRDN therapy can reduce drug burden in patients with uncontrolled hypertension. Second, this trial requested physicians to titrate the patient's antihypertensive drugs during the trial in order to control their OSBP to the level of less than 140 mmHg.

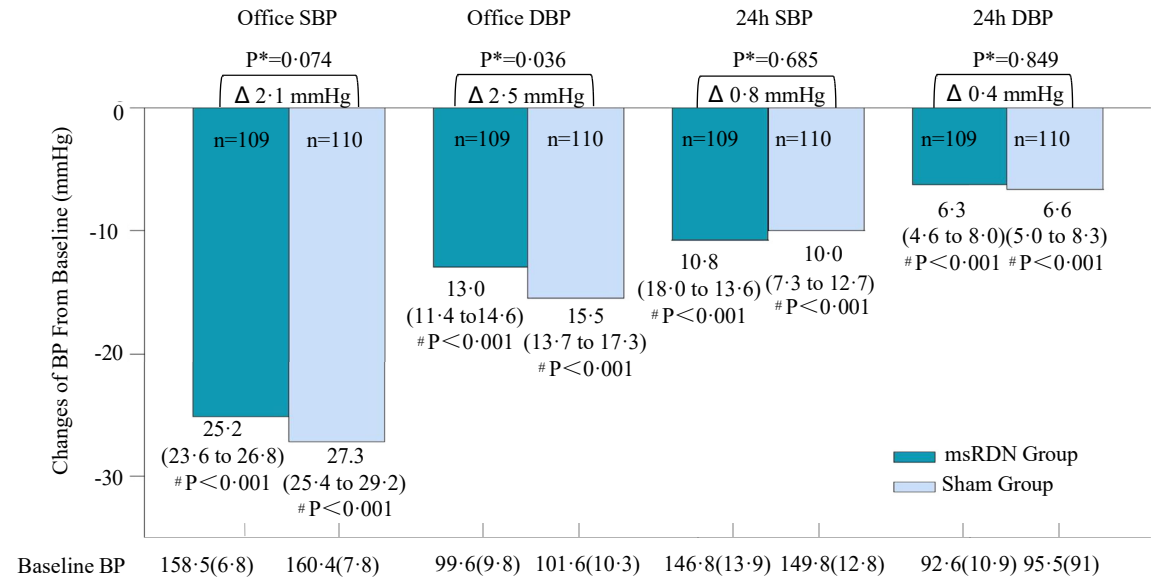


***Fig. 6:* Changes in office, ambulatory systolic and diastolic blood pressure**. The reductions of office systolic, diastolic, 24-h systolic and diastolic blood pressures were comparable between msRDN (mapping/selective renal denervation) and Sham group. The results indicated msRDN plus significantly less antihypertensive drug treatment achieved a comparable blood pressure lowering effect as intensive drug therapy in patients with uncontrolled hypertension. SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure. *, p value between msRDN and Sham group. #, p value from baseline within a group.

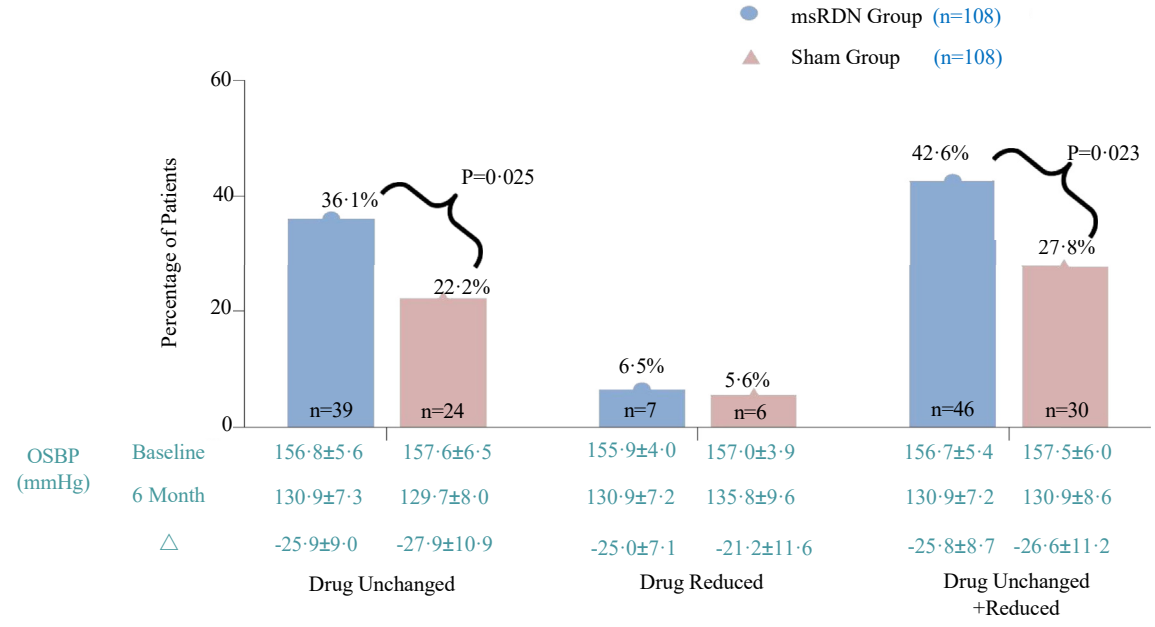


***Fig. 7:* Percentage of patient's blood presure was controlled to target level by msRDN treatment**. There were 42.6% patients (n = 46) in the msRDN (mapping selective renal denervation) group, their office systolic blood pressure (OSBP) was controlled to target level < 140 mmHg at 6 months due to msRDN treatment per se, because these patients did not change their drug regimen or reduce their drug taking during the trial. There were only 27.8% patients (n = 30) who did not change their antihypertensive drug regimen in Sham group; the difference was statistically significant (p = 0.023).

	msRDN group (n = 111)	Sham group (n = 109)	p value
Success rate of the interventional therapy	99.10% (n = 110)	NA	NA
Success rate of clinical treatment	100.00% (n = 111)	100.00% (n = 109)	NA
All-cause mortality	0.00%	0.00%	NA
Severe renal dysfunction	0.00%	0.00%	NA
Incidence of renal artery stenosis	1.00% (n = 1)	0.00%	0.495
Adverse events rate	67.57% (n = 75)	62.39% (n = 68)	0.480
Serious adverse events rate	9.91% (n = 11)	7.34% (n = 8)	0.633
Severe cardio-cerebrovascular events rate	0.90% (n = 1)	3.67% (n = 4)	0.210

msRDN, mapping selective renal denervation.

Table 5: **Safety endpoints within 6 months after the procedure (Based on safety set analysis).**

Third, the classes, doses, manufacturers and the order to titrate antihypertensive medications were rigorously defined and all these medications were supplied via the research pharmacy of the participating hospitals. Fourth, the abaseline usages of antihypertensive medications reflected real-world conditions of medical practice, because drug regimen was not mechanically predefined by numbers and combinations of antihypertensive medications; instead, medication regimen of each patient was determined by the patient's drug use history then their medications were replaced by predefined drugs. Fifth, LC-MS/MS urine assays were not only used to confirm drug adherence at end of the 6 months trial, but also used to monitor and manage antihypertensive drug adherence throughout the trial. Sixth, due to these five features, adherence to antihypertensive drugs was consistently maintained at a very high level, near or above 90%, throughout the 6 months trial period, and the control rate of OSBP was very high. Finally, msRDN was used for the trial in order to specifically ablate renal sympathetic nerves, provide readouts for the interventionalists and avoid futile ablation.

Weber et at. has editorialized that reducing BP pharmacologic burden is an important endpoint for RDN trials.[44] This endpoint is not only valued by both patients and physicians, but if unmeasured may obscure the clinical utility of RDN in hypertension management. Kandzari et al. recently emphasized the importance of drug burden as a clinical endpoint for device-based therapies such as RDN to treat hypertension[41] although the concept of drug burden in antihypertensive drug trial has been proposed.[45] Furthermore, in a clinical setting, the design using reduction in BP as the only major clinical endpoint faces an important challenge: convincing patients not to alter their antihypertensive regimen even when their BP is still ≥150 mmHg after RDN; this pertains particularly to patients in the sham group during six-months follow-up. If patients in the sham group take any antihypertensive drugs to manage their high BP, the difference of OSBP between RDN and Sham group could be compromised since the efficacy of global RDN is around 10 mmHg.[16,17] The beneficial effects of RDN on drug burden have been indeed reported recently by Mahfoud et al. and by Azizi et al., where the investigators demonstrated that antihypertensive medication classes significantly decreased after RDN therapy.[15,17,46] However, adopting reduction in antihypertensive drug burden as a primary endpoint is unique to here, a RDN randomized, sham-procedure controlled trial (RCT) and it is certainly justifiable. This would be a clinically worthy outcome because whether RDN reduces medication requirements is a critical question in the real world of clinical practice because both patients and physicians must ask the question if RDN is utilized to treat hypertension. There is additional virtue in using this endpoint. It allows drug noncompliance confounding to be avoided. In treatment trials of uncontrolled and drug resistant hypertension, drug noncompliance is common in the device sham arm or drug placebo arm, depending on the intervention type.[11,17,47] This drug noncompliance is of an unusual form, different to that of clinical practice, as it is the taking of additional medication. Home BP measurement by patients in the trials may mainly contribute to this drug noncompliance; in the sham and placebo arm the recorded pressures can be disappointing and worrying, triggering unauthorized antihypertensive drug taking. If BP reduction is the only clinical endpoint, the unauthorized antihypertensive drug taking will confound the trial, by lowering the BP in the sham or placebo group. With optimization of BP lowering medication use in both arms as the present trial designed, this form of error was avoided. The primary endpoint, based on justification of medication needed to achieve pre-specified BP lowering, was free from confounding. Meanwhile, the control rate of OSBP was combined as a co-primary endpoint and physicians had to titrate patient's antihypertensive drugs in order to control their OSBP < 140 mmHg. Thus, both antihypertensive drug burden and the control rate of OSBP must be achieved simultaneously, then the trial yielded positive outcomes.

It is particularly important that our active drug titration design eliminates the ethical quandary caused

by freezing antihypertensive drug regimen during a RDN trial although patient's BP is higher than 150 mmHg; thus, physicians or patients had to forcedly accept possible cardiovascular risks due to the uncontrolled high BP. The ethical consideration has been resolved by allowing active drug titration coupled with the combined, dual primary clinical outcomes of the trial: the control rate of patients to target BP level and the change of drug index between msRDN and Sham group. Thus, the active drug titration protocol with combined dual endpoints is a preferred resolution to potential ethical concerns inherent to alternative designs.

Current RDN devices cannot map renal nerves nor provide intraprocedural feedback or validation of an effective RDN; the unmet clinical needs remain fundamental challenges in the field.[30] SMART trial is the first rigorous RCT study to examine the effects of msRDN on drug burden and BP in patients with uncontrolled hypertension. The trial clearly demonstrated significantly fewer ablations on renal main arteries were needed to achieve clinically meaningful outcomes in both drug burden and BP compared to previous trials using unmapped RDN. Ablation of renal main artery using ultrasound energy achieved significant reductions in both BP and drug burden, which has been demonstrated by Azizi et all.[14,15,18] Here we showed that 4 selective RF ablations of the renal main artery can lower BP and drug burden once msRDN was applied. The fewer ablation sites provide benefits to avoid detrimental effects of unselective global RDN, such as not needing to treat branch vessels[21] and using less contrast compared to other RDN studies.[16,17] Whether msRDN can increase responder rate is still an unanswered question due to the limitation of current trial design because the trial required adjusting antihypertensive drugs in order to reduce OSBP to less than 140 mmHg; therefore, the pure effects of msRDN on the changes in BP were not able to be determined. Thus, further studies to examine the net effects of msRDN on BP in patients without antihypertensive medication treatment are warranted. However, our data showed that for 42.6% patients whose antihypertensive drugs were unchanged or decreased during the entire 6-month period after msRDN therapy, OSBP was lowered by 25.8 (8.7) mmHg and controlled to target level. The concepts of "hot, cold and neutral spots," representing sympathetic, parasympathetic and afferent innervations, respectively, have been used to guide ablation in the current trial. Surrounding the renal arteries there is dense innervation: sympathetic, parasympathetic and afferent. The sympathetic nerves are directed primarily to the kidneys, although also to the renal artery itself.[48] The renal sympathetic nerves are the primary ablation targets. Identification of sympathetic or hot spots for selective ablations in this trial have been showed to significantly reduce drug burden and resulted in 95.41% control rate of OSBP to achieve target level with a few ablations in each side renal main artery. New evidence proves the existence of renal parasympathetic nerves, which perhaps innervate the renal arteries and renal pelvis.[49] There is no direct proof that these parasympathetic nerves are responsible for "cold spots" with electrical arterial stimulation; however, preclinical experimental data did show ablations of "cold spots" resulting in elevation of BP.[50] The afferent nerves are diverse. These nerves are variously primarily non-myelinated or lightly myelinated and consisted of nociceptors, chemoreceptors and renorenal reflexes.[51–54]

A key question is whether the afferents that lower BP with electrical arterial stimulation have a chronic and persistent BP-lowering effect. Such case has been demonstrated in a canine model, ablating these nerves could persistently elevate BP or minimize RDN BP lowering.[50] Are there afferent nerves anywhere in the human body which do this: lowering BP with electronic stimulation and raising BP with ablation? A typical example is arterial baroceptor afferents: stimulation of the afferents causes BP-lowering effects and ablations of these afferents result in raised BP. Whether similar reflex mechanisms exist in the kidneys is still debatable. It has been demonstrated that a renal baroreflex controls renal renin release; however, this mechanism acts through BP distortion of the juxtaglomerular cells modifying connexin and integrins.[55] Whether this reflex has a neural loop, it has not been proven. The nature of nerves representing "cold spots" near the renal arteries remains to be identified. The decrease in BP induced by electronic stimulation could be due to triggering vagomimetic afferents leading to peripheral dilatation. Thus, this trial provided solid evidence to demonstrate clinical benefits of msRDN, such as proper control rate of OSBP with reduced drug burden, significantly fewer ablation sites by avoiding futile ablations and intraprocedural confirmation of successful ablation of targeted sites.

The trial reached its safety endpoints: all-cause mortality and severe renal dysfunction after msRDN treatment at 6 months were zero. One renal artery stenosis occurred in msRDN group; however, this stenosis was pre-existing when the patient was enrolled in the trial. Adverse event rates, serious adverse event rates and severe cardio-cerebrovascular event rates were comparable between msRDN and Sham group. The trial was a pivotal study and requested by regulatory agency of China (National Medical Products Administration) to report all medical conditions as adverse events or serious adverse events such as headache, cough, fever etc.; however, these events were not related to msRDN treatment. The design of mapping/ablation system and catheter satisfied the needs of operators, indicated by the success rate of the interventional therapy and success rate of clinical treatment, which was measured by whether the catheter can reach mapping and ablation

sites in the renal artery and whether the treatment procedures were completed using the system.

The study has several limitations. 1. Office systolic BP < 140 mmHg was designed as a primary treatment target because this was a pivotal study in China, and it has to be compliant with Chinese Hypertension Guidelines,[56,57] which maintains OSBP < 140 mmHg as a goal for BP control. However, we acknowledge that this is a major limitation of the study because the target BP is not the same as that recommended by ESH, ACC/AHA guidelines. 2. BP lowering effects of antihypertensive medications in our drug regimen are different, and Drug Index cannot reflect these differences. In particular, the non-linear relationship between antihypertensive medication doses and lowering BP effects was not able to be captured by the method used in the study for calculating Drug Index. However, both msRDN and Sham group used the same methods for Drug Index, so this may reduce the bias of the calculation and the Index. 3. Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR, which is not as accurate as the index based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIP). However, MDRD is one of the standards accepted by the regulatory agency (National Medical Products Administration) in China. 4. For some antihypertensive drugs, the detection time in urine exceeds 24 h; thus, results of urine samples may have bias. 5. Compared to other studies, patients enrolled in this study were relatively younger with high heart rates; in addition, only 29 female patients were enrolled; thus, it might lead to uncertainty whether this device would lower BP in older and female patients.

In conclusion, in this trial we have demonstrated the safety and efficacy of targeted renal sympathetic denervation in patients with uncontrolled hypertension and a standardized formulary of antihypertensive medications. Combined dual primary outcomes were control rate of OSBP to achieve level of <140 mmHg and change in the composite Drug Index of antihypertensive medications. This design eliminated the confounding effects of changes in antihypertensive medication on BP endpoints and was able to assess meaningful changes in medications required to manage BP to target level following msRDN. The therapy achieved the goals to reduce drug burden of hypertension patients with 3.7 (1.4) and 4.0 (1.6) targeted ablations on left and right side renal main artery, respectively, and to control OSBP < 140 mmHg. Drug adherence was consistently near 90% during the entire trial period. Based on these promising results, further studies to explore the net effects of msRDN on BP in patients without antihypertensive drug therapy are warranted.

Contributors

JW, YH, MC, YY, CL, ZL, NS and ME participated in the design of the study. YY, CL, JG, JH, HJ, ZL, WM, XQ, DY, YD, SC, JZ, DW, CD, WW, JL, YW, HL, ZP, KC, CL, XL, WC, MC and YH participated in data collection. All authors were involved in interpretation of the data. CY and XY were the biostatisticians responsible for the statistical analyses. JW, YH, JJZ, PAS and ME participated in writing of the report. JW, YW and JJZ participated in generating figures and tables. All authors agreed on the content of the manuscript, reviewed drafts and approved the final version. YH, CY and XY had accessed and verified the underlying data. All authors were responsible for the final decision to submit for publication. JW, YY, CL, ZL and JH contributed equally to the manuscript. YH, MC, NS, ME and JW are joint correspondences.

Data sharing statement

Data from this study are owned by the funder and are not available to other researchers for the purposes of reproducing the results or replicating the procedure.

Declaration of interests

Yin Y, Chen M, Yan X, Sobotka P and Esler M were consultants and received consultant honoraria from SyMap Medical (Suzhou), LTD. Sun N, Lu C, Ma W, Hu J and Huo Y received speaker honoraria from SyMap Medical (Suzhou), LTD. Huo Y, Ma W, Yin Y, Sun N, Hu J, Wang D, Li H, Pan Z, Li C, Liang X, Wang Y, Zhang JJ, Esler M and Wang J received travel grant from SyMap Medical (Suzhou), LTD for attending Euro PCR(2023) and TCT (2023). Chen S received grants from The National Scientific Foundation of China and speaker honoraria from Microport, Pulnovo, Boston International Scientific, Medtronic, Sanofi, and BioMed. Zhang JJ is an employee of SyMap Medical (Suzhou), LTD, receives salary and has stock options from SyMap Medical (Suzhou), LTD. Wang Y received consultant honoraria from SyMap Medical (Suzhou), LTD. Wang J is a co-founder of SyMap Medical (Suzhou), LTD, has equity of the company and receives consultant honoraria from SyMap Medical (Suzhou), LTD. Lu Z, Ge J, Jiang H, Yao C, Qi X, Dang Y, Zhu J, Ding C, Wang W, Liu J, Cui K and Chen W received grant and study materials from SyMap Medical (Suzhou), LTD.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102626.

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