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METHODS PAPER

Rationale and Design of Sympathetic Mapping/Ablation of Renal Nerves Trial (SMART) for the Treatment of Hypertension: a Prospective, Multicenter, Single-Blind, Randomized and Sham Procedure-Controlled Study

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Abstract

Renal denervation (RDN) is proposed as a durable and patient compliance independent treatment for hypertension. However, 20–30% non-responder after RDN treatment weakened the therapeutic effect, which may be due to blind ablation. The renal nerve mapping/selective ablation system developed by SyMap Medical Ltd (Suzhou), China, has the function of mapping renal sympathetic/parasympathetic nerve sites and selectively removing renal sympathetic nerves and is expected to meet the urgent unmet clinical need of targeted RDN. The "Sympathetic Mapping/Ablation of Renal Nerves Trial" (SMART) is a prospective, multicenter, randomized, single-blinded, sham procedure-controlled trial, to evaluate the safety and efficacy of targeted renal sympathetic denervation in patients with essential and uncontrolled hypertension. The study is the first clinical registry trial using a targeted RDN for the treatment of uncontrolled hypertension; the dual-endpoint design can answer the question of how many antihypertensive drugs can be reduced in patients after RDN. The trial is registered on clinicaltrials.gov NCT02761811.

Keywords Hypertension · Renal denervation · Study design · Renal nerve mapping · Selective ablation

Abbreviations

ACEI	Angiotensin-converting enzyme inhibition
AE	Adverse event
ARB	Angiotensin-II receptor blocker
BP	Blood pressure
CCB	Calcium channel blocker
CTA	Computerized tomographic angiography
FAS	Full analysis set
ITT	Intention-to-treat

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LC-M/M	Liquid chromatography with tandem mass spectrometry
PPS	Per-protocol set
RDN	Renal denervation
RF	Radiofrequency
SAE	Serious adverse event
SS	Safety set

Background

The prevalence of hypertension continues to rise worldwide, remaining the principle underlying risk factor for cardiovascular, neurologic, and renal morbidity and mortality. Hypertension is directly correlated with the incidence of stroke, coronary artery disease, congestive heart failure with either preserved or reduced ejection fraction, vascular disease, chronic kidney disease, and end-stage renal failure [1]. Despite demonstrated adherence and persistence with 3 or more antihypertensive medications, nearly 9% of hypertensive patients still cannot attain target blood pressures (BP), a condition referred to as drug-resistant hypertension [2, 3]. Alarmingly, only less than 50% of cases control of hypertension is achieved in both industrial and developing countries [4–7] despite persistent efforts to educate patients on the importance of lifestyle modification and compliance with pharmacological therapy. In USA, 40% of hypertension patients do not receive long-term pharmaceutical therapy; among the patients with antihypertensive medications, nearly 65% of them cannot reach the target BP level due to non-adherence [8]. In the countries of the European Union, failure to control BP is attributed in 23% of cases to poor adherence to pharmacological therapy [4]. In China, a study by Lu et al. [9] showed that the prevalence of hypertension has exceeded 200 million individuals; among these patients, 23% are managed with antihypertensive medications and only 5.7% attain target BP [9]. Therefore, despite the availability of life-long poly-pharmacy for the treatment of hypertension and the well-documented reduction of the associated mortality and morbidity risk, therapeutic solutions for a life-long silent clinical condition remain an unmet clinical need.

Catheter-based renal denervation (RDN) is proposed as a durable and patient compliance independent treatment for hypertension offering hope of reducing the multi-systemic morbidity and mortality associated with elevated BP. Several milestone studies have been completed examining the treatment. The open-label Symplicity HTN-1 [10] and the randomized Symplicity HTN-2 [11] demonstrated efficacy with the earliest iteration of a therapeutic RDN device and treatment strategy. Forty-five patients with resistant hypertension were enrolled in Symplicity HTN-1; the results showed that compared with baseline BP, after RDN procedure, office BP was decreased by 21/10 mmHg, 22/11 mmHg, 24/11 mmHg, and 27/17 mmHg at 3, 6, 9, and 12 months, respectively. The results were further confirmed by Symplicity HTN-2 trial with expanded number of the patient enrollment ($n = 160$). Patients were randomized to RDN or drug therapies; patients treated with RDN showed an office BP reduction of 33/11 mmHg at 6 months. However, results from Symplicity HTN-3 [12], a prospective, randomized, single-blind, sham procedure-controlled study, were disappointing. Utilizing a relatively untested new catheter design, patients ($n = 535$) were randomized to the RDN group (active medication treatment and RDN) or control group (active medication treatment and sham procedure). The primary effectiveness endpoint was not achieved at 6 months; office systolic BP in the RDN group was decreased by 14.13 mmHg, while a reduction of 11.74 mmHg was observed in the sham group, indicating the fail of the study to achieve its primary efficacy endpoint, although the primary safety endpoint was achieved. Investigators concluded [13] that several major trial execution and analytic factors contributed to the negative result of Symplicity HTN-3:

1) Poor adherence to medical therapy and unpredictable changes in the use of antihypertensive drugs during the trial in both treatment and control arms interfered with RDN treatment effects. A significant number of patients in the control group appeared to increase their exposure to antihypertensive drugs, and medications were reduced in the RDN arm. Both trends likely contributed to the obfuscation of the potential clinical benefits of RDN.
2) The study failed to adequately confirm patient compliance with medication prior to enrollment and subsequently enrolled patients when their recorded BP likely represented outlier values and not representative of their usual BP. Thereby, the study enrollment design inculcated migration to the mean following enrollment for patients in both RDN and control populations, obscuring identification of statistical changes due to the enrollment strategy.
3) The trial used a new catheter design and arduous treatment protocol, and the experiment did not confirm successful renal nerve ablation, raising the specter of inadequate denervation and operator technical failure rather than failure of the treatment strategy. There was no confirmation of an effective renal sympathetic denervation [14].
4) Retrospective analysis demonstrated a plethora of inadequate treatments, largely due to failure to complete circumferential ablations, possibly due to inadequate operator training.

The Spyral Global HTN Off-Med and On-Med studies were initiated after the failure of Symplicity HTN-3 trial,

utilizing an improved enrollment methodology, medication management, a new catheter, and ablation treatment design with hopes of addressing the trial execution flaws of the Symplicity HTN-3 trial. The migration to mean statistical issue was addressed by lengthening the period of prior observation to assure stable enrollment BP. The issue of drug compliance was partially addressed by establishing two separate cohorts of patients in the study: (1) drug-naïve antihypertensive drugs (Off-Med cohort) and (2) a controlled drug regimen during the study (On-Med cohort) [15–17]. Both studies have further confirmed the efficacy and safety of RDN. However, the amplitude of office systolic BP reduction was moderate only around 10 mmHg. This reduced treatment effect is likely related to a large portion of non-responders in the treatment arm, estimated to be 20–30% [15–17]. Whether this non-responder rate represents patients in whom renal nerves do not contribute to hypertension, or inadequate treatments or operator errors are not known [15–17]. This non-responder phenomenon has been consistently observed across various energy-based device RDN. Townsend and Sobotka [18] pointed out that either radiofrequency ablation or ultrasound ablation had an over-all success rate of about 63%. Similarly, Mahfoud et al. reported approximately 30% non-responder rate was also observed among patients using alcohol-mediated RDN; however, that decreases of ≥ 5 and ≥ 10 mm Hg in office systolic BP at 6 months were observed in 70% and 61% of patients, respectively [19]. Townsend and Sobotka believed that the approximate 30% non-responder rates may reflect either a technical failure or suboptimal patient selection given the lack of predictors for BP-lowering success [18]. Non-responders may represent inadequate operator treatment, intrinsic device failures, or patients in whom the renal nerves do not participate in hypertension. Esler pointed out that failure to test an effective renal sympathetic denervation represents "the Achilles heel of the field" [12]. Selection of patients with confirmed renal nerve participation in hypertension and identification of proper ablation site, with subsequent confirmation of a successful sympathetic denervation, is an urgent unmet clinical need for this therapy. Resources to confirm proper treatment sites and adequate nerve ablation could reduce the rates of non-responders and result in a statistical increase in the response rates.

One of the under-considered "the Achilles heel of the field" [12] with the so-called blind RDN is the heterogeneity of nerves in the renal artery adventitia. Renal ablation sites include nerves which may either cause a rise or fall of BP, the former are appropriate ablation targets, and the later are certainly not. Hence, the treatment effect of RDN is dependent upon the mix of hypertensive and cardioprotective fibers ablated during the procedure.

Mapping Renal Nerves by Renal Stimulation: Anatomy, Physiology and Histology Evidence

Recent studies of the anatomy, physiology, and histology of renal nerves have detailed the physiologic and anatomic heterogeneity of renal sympathetic nerves and justify the clinical mapping and selective ablation. Amsterdam et al. and Mompeo et al. [20, 21] examined neural anatomy structures around renal artery and revealed three nerve types: sympathetic, parasympathetic, and afferent nerve components, although Kuichi et al. had different views about the types of these nerves and named these nerves as "pressor nerves," "depressor nerves," and "neutral" depending upon whether BP was increased, decreased, or not changed in responses to electronic stimulation [14]. We [22–24] and other investigators [25, 26] have demonstrated that systemic hemodynamics in particular, BP, was increased, decreased, or unchanged once an electronic stimulation was delivered to specific intra-renal artery sites. Several studies have illustrated BP responses to renal nerve stimulation in corresponding to the different nerve distributions around renal artery providing rational for selective RDN following renal nerve stimulation [23–29]. We have demonstrated a substantial reduction in both BP [24, 30] and serum norepinephrine levels in Chinese Kunming dogs, a canine model with spontaneous high sympathetic tone, after ablating the sites which caused significant rises in BP evoked by renal nerve stimulation, and confirmed that the BP-lowering effects were proportional to the increases in BP by the stimulation. Histological evidence implied that these sites were innervated by nerve bundles containing sympathetic fibers [23, 24]; the amplitudes of increases in BP to renal stimulation were proportionally determined by the total area and number of renal nerves in stimulated site. The changes in observed systemic BP following renal artery stimulation depend upon the balance of targeted fibers. Sites with increase in BP to stimulation represent dominant sympathetic fibers and are considered to be "hot spots" [22] for the purpose of RDN to treat hypertension. Sites which observe a lowering in BP with stimulation represent dominant parasympathetic innervations or depressor nerves and are considered to be "cold spots" and thus are considered to be inappropriate sites for the purpose of therapeutic RDN. Locations along the renal artery which do not show any significant effects on BP when stimulated are considered to be "neutral spots" may present the absence of renal nerves adjacent to the site or balanced sympathetic and parasympathetic innervations. Ablation of these sites would provide no therapeutic benefit and add only therapeutic risk by futile denervations. The concepts of "hot spots," "cold spots,"

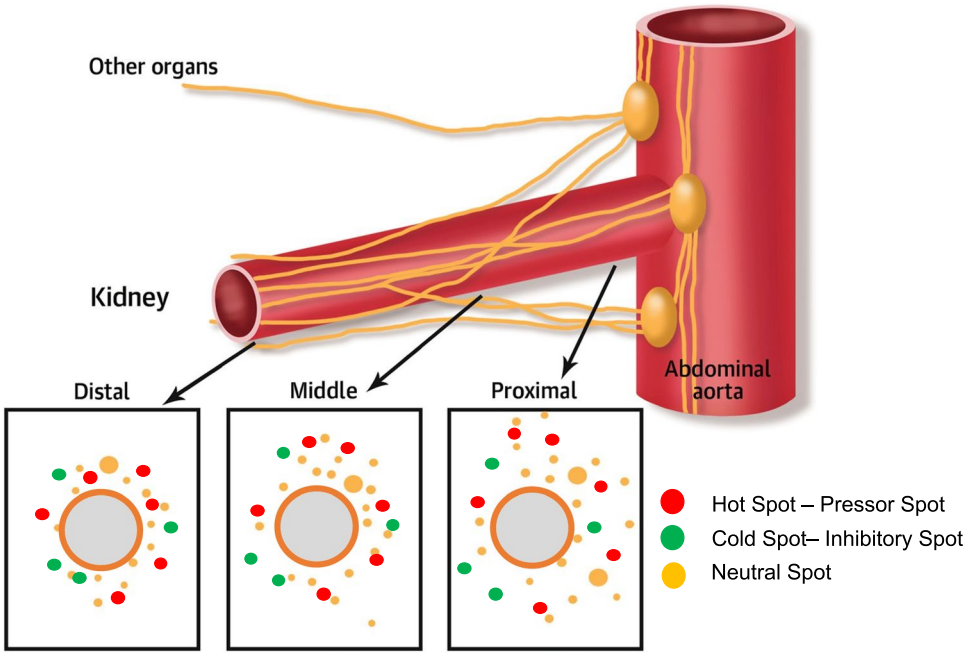


Fig. 1 Theoretical framework for selective vs global RDN: red lines/dots represent "hot spots"—pressor spots. These are nerves that raise the BP when stimulated. They are the ideal target of RDN. Green line/spots represent "cold spots"—inhibitory spots, which lower the BP when stimulated. The majority of nerve fibers (here in yellow) are neutral in their contribution for BP physiology and do not show BP effects when stimulated. Adapted from Fudim M et al. Curr Hypertens Rep. 2018; 20: 37 [22], and Sakakura K et al. *Journal of the American College of Cardiology* 2014;64:635–643 [29]

and "neutral spots" are illustrated in Fig. 1 [22]. Identification of sympathetic/pressor nerves or hot spots for selective ablations is expected to cause a significant fall in BP, whereas ablations of parasympathetic/depressor nerves or cold spots may result in either no beneficial effect or even a paradoxical post ablation increase in BP [22, 27], and neutral spots should not be ablated since these sites do not seem to play a role in the regulation of BP [14]. Results from clinical trials consistently identify increased BP in some patients after RDN at 6-month follow-up [15–17] and may be driven by inappropriate ablations of parasympathetic fibers.

Confirmation of successful treatments remains a critical component of the procedure after a RDN; BP response to stimulation should be significantly blunted; otherwise, it suggests an inadequate denervation at the target sites and informs the operator that a repeat treatment is justified.

Thus, renal nerve stimulation while observing changes in BP in response to the stimulation has the potential for selecting optimal ablation sites while avoiding denervation of cardioprotective fibers and thereby reducing futile ablations or ablations that risk raising BP, as well as intraprocedural confirmation of successful ablation of targeted sites allowing repeat treatments of those sites.

The SMART trial examines the utility of intraprocedural renal sympathetic mapping with selective renal denervation and confirmation of successful ablation in patients with uncontrolled office systolic hypertension, ≥ 150 mmHg and ≤ 180 mmHg for at least 6 months. The SMART trial mitigates the trial risks of pharmacologic non-compliance and different medication use in the treatment and control arms by providing medications and assessing persistence and adherence to mediations throughout the trial. Prespecified primary trial endpoints include (1) percentage of patients within each cohort reaching target BP, including active drug titration within specific protocols, and (2) changes in antihypertensive drug burden within both cohorts. Procedural safety and clinical outcomes are assessed for 6 months following the procedure.

Renal Mapping and Ablation System

The combined renal stimulation/mapping and ablation system developed by SyMap Medical Ltd (Suzhou, China) consists of a dedicated electric stimulation/mapping and ablation SyMapCath I®™ catheter and a SYMPIONEER S1®™ Stimulator/Generator [31]. The stimulation/ablation catheter has a steer tip, within a sheath that can be manipulated to advance or return while rotating 360 degrees in the sheath, at 90-degree intervals confirmed by a marker in the handle. The sheath can be used for contrast injection (Fig. 2A). The stimulator/generator (Fig. 2B) can perform both electronic stimulation and radiofrequency (RF) ablation with the catheter. The system could facilitate appropriate patient selection through screening for candidates whose BP is driven by renal sympathetic nerve activity. Further, operators may target only optimal ablation sites (hot spots/sympatho-stimulatory)

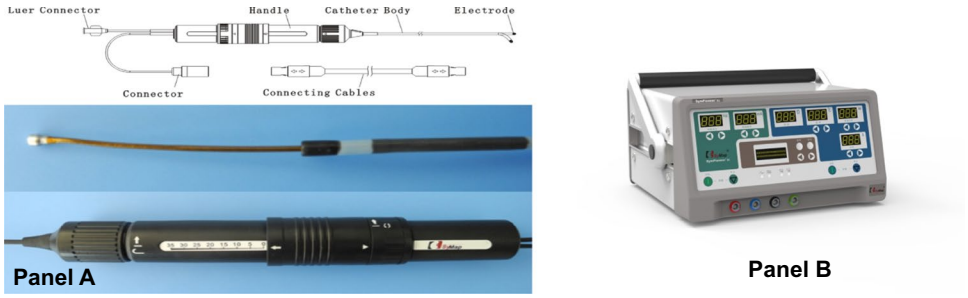


Fig. 2 The combined renal stimulation/mapping and ablation system developed by SyMap Medical Ltd (Suzhou, China) consists of a dedicated electric stimulation/mapping and ablation SyMapCath I®™ catheter and a SYMPIONEER S1®™ Stimulator/Generator. **A** Mapping/ ablation SyMapCath I ®™ catheter. **B** stimulator/generator SYMPIONEER S1 ®™

Panel A. Mapping/ ablation SyMapCath I ®™ catheter

Panel B. stimulator/ generator SYMPIONEER S1 ®™

avoiding futile or counterproductive ablations of cold spots/sympatho-inhibitor sites and confirming technical success through the loss of systemic BP changes when stimulated again after RDN.

Study Design

The SMART Study is a prospective, multicenter, single-blinded, sham procedure-controlled and randomized trial to evaluate the safety and efficacy of targeted renal sympathetic denervation using SyMapCath I®™ (mapping and ablation catheter) and SymPioneer ®™ (renal nerve stimulator and RF generator) in patients with uncontrolled hypertension for at least 6 months of the disease history and pharmacotherapy; however, their BP still cannot be controlled (≥ 150 mmHg). The study design is shown in Fig. 3.

Following informed consent, patients enter a screening phase. During the screening period, patients will receive a standardized antihypertensive drug treatments (at least two drugs) for at least 28 days; if their office systolic BP remains ≥ 150 mmHg and ≤ 180 mmHg and all of the inclusion and exclusion criteria are met (key inclusion criteria and key exclusion criteria are provided in Table 1), patients will be enrolled in the study. Since electronic renal stimulation may increase BP by 10 mmHg or more, safety concerns have to be taken into consideration; thus, if patient's systolic BP is 180 mmHg or higher, the patient is excluded from the study. At end of the screening period, computerized tomographic angiography (CTA) will be obtained to determine whether the anatomy of renal arteries meets the including criteria for RDN. Patients ($n = 220$, 110 pairs) who meet all inclusion and exclusion criteria will undergo renal angiography with visual and auditory blinding to the procedure and then randomly assigned by a central computer allocation system to either renal nerve mapping and selective denervation group (RDN treatment) or renal artery angiography (sham) group in a 1:1 ratio in blocks of 4 patients at each site. After RDN or sham procedure, scheduled follow-up and data collection are at 7 days after the procedure or at discharge from hospital, 1, 2, 3, 4, 5, 6, 9, and 12 months for BP measurements, antihypertensive medications analysis and management. Urine samples are collected at the end of screening period, 3 months and 6 months for LC-M/M. Data collecting, managements, statistical analysis, and laboratory tests will be done by independent, qualified organizations.

Protocol Details

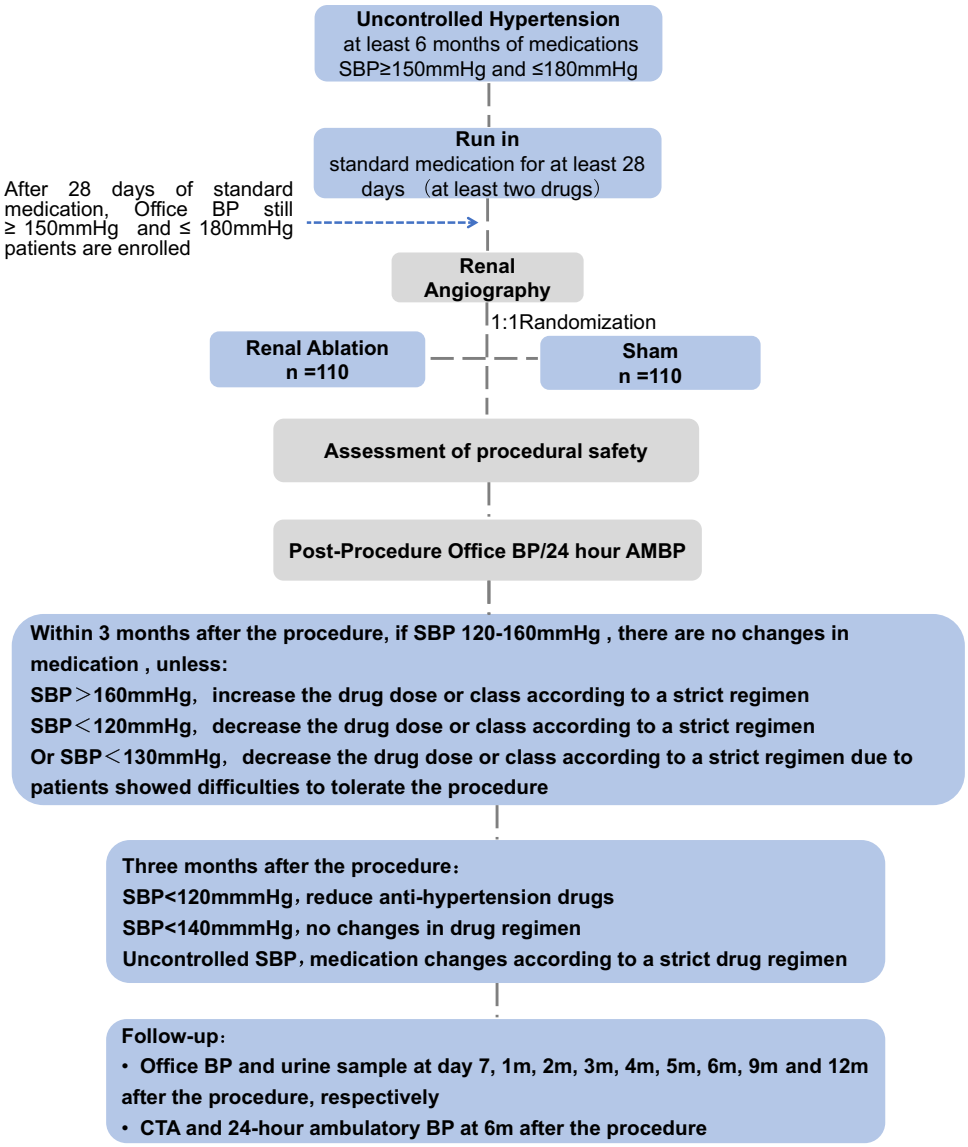
Patient *Screening*

After obtaining informed consent, patients are entered into a period of 28 observation days, tested for medication persistence and adherence with a predefined formulary of antihypertensive medications. Patients are required to use a standardized antihypertensive medication regimen: classes, doses, and manufacturers of the medications are predefined (Table 2). The medications are supplied by the study sponsor.

At the first visit, after the history of hypertension is confirmed for at least 6 months and the patient's BP is ≥ 150 mmHg, the patient's current antihypertensive medications will be replaced by drugs from Table 2. The protocol is detailed as below:

- If the patient has one antihypertensive medication and the drug should be replaced by the same class of drug at a standard dose, then one more class of drug with a standard dose will be added, and angiotensin-II receptor blocker (ARB), irbesartan, is provided.
- For example, if the patient takes a calcium channel blocker (CCB), it will be replaced by amlodipine and irbesartan at a protocol standard doses.

Fig. 3 The study design



- Patients enrolled with two classes of antihypertensive medications will have their medications replaced with the formulary supplied by the protocol.
- If the patient have three classes of antihypertensive medications, these drugs are replaced by the same classes of medications at standard dose. In the cases where patients are enrolled with compound antihypertensive medications, the medication will be replaced by CoAprovel (irbesartan + hydrochlorothiazide), a formulary combination product in Table 2. Therapeutic substitution of angiotensin-converting enzyme inhibition (ACEI) drugs will be replaced by irbesartan.
- Run-in period will be at least for 28 days, and antihypertensive medications cannot be changed during the run-in period.

Blinding and Sham Protocol for Patients and Physicians

Patients and managing physicians are blinded to the treatment allocation; the quality of blinding is assessed throughout the trial. Randomization and blinding occur in the procedure laboratory from a computer random assignment. For the procedure, physicians are aware of treatment allocation; however, neither patients nor treating ambulatory physicians are informed of the treatment allocation.

Patient blinding to treatment allocation begins upon entry to the procedure laboratory when a noise-canceling headset is placed on each patient. Patients randomized to sham group receive renal artery angiography only, with a sham procedure of stimulation/mapping and ablation equipment

Table 1 SMART study: key inclusion and exclusion criteria

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; and 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) Have 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/1.73m^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 contraindications and are not tolerant to significantly reduced blood pressure
    (4) Within half a 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 contraindications to conduct renal artery stimulation and ablation

mimicking stimulation/mapping and ablation procedure. Those patients randomized to treatment receive the same in-laboratory treatment and post-procedure follow-up. Physicians who perform post-procedure patient management are not informed about the treatment allocation, and neither study physicians nor patients will have access to procedure notes or blinding notes.

An assessment of blindness via questionnaire is filled by patients at discharge from the hospital and at 6- month follow-up, the results of the questionnaire might be taken into considerations of statistical analyses if regulatory authority requests. Because patients and managing physicians will be aware of medications and changes in medications and BP following the procedure, it is appreciated that some participants may develop personal hypothesis to their treatment allocation without formal confirmation of their allocation until the end of the trial.

Renal stimulation, mapping and ablation

The procedure will be performed under deep sedation. The agents for the sedation are not rigidly defined since each participating hospital may have its own routing clinical practice. Selective renal artery angiography is performed before the RDN procedure, the length of main branch of renal artery will be measured, and the numbers of stimulation/mapping/ablation are planned per the length of the artery and the predefined standard protocols: the minimum distance between stimulation/mapping/ablation sites is restricted to 5 mm and a rotation of 90 degrees. For complete circumferential mapping, stimulation/mapping sites include 4 distinct quadrants of the artery (superior, inferior, anterior, and posterior quadrants). The designs of our renal mapping and ablation catheter ensure the operators are at their best efforts who can apply circumferential treatment of renal artery because they can rotate the catheter in 360 degrees at 90 degrees intervals confirmed by a marker in the handle (Fig. 2A). The RDN procedure is delivered with a pre-programed testing of physiologic response and subsequent delivery of energy, followed by confirmation of the physiologic response to the treatment, including:

A. Stimulation/mapping
   Mode: electric current.
   Frequency: 20 Hz.
   Pulse width: 5 ms.
   Amplitude: 10–20 mA.
   Duration: 20–120 s.
   During stimulation, invasive BP is examined from a femoral artery. If systolic BP rises ≥ 5 mmHg during stimulation, the site is defined as a "hot spot" and marked as an ablation target site.

Table 2 Standardized antihypertensive medications and dose regimen

No	Class	Name	Standard dose	Maximum dose	Manufacture
1	ARB	Irbesartan	150 mg/day	300 mg/day	Sanofi
2	CCB	Amlodipine	5 mg/day	10 mg/day	Pfizer
3	β receptor blocker	Metoprolol sustained release	47.5 mg/day	95 mg/day	AstraZeneca
4	Diuretic	Hydrochlorothiazide	25 mg/day	50 mg/day	Changzhou Pharmaceutical
5	α receptor blocker	Terazosin hydrochloride	2 mg/day	4 mg/day	Abbott
6	Combination drug	Irbesartan + hydrochlorothiazide	Irbesartan 150 mg + hydrochlo 12.5 mg/day	Irbesartan 300 mg + hydrochlo 25 mg/day	Sanofi

At sites where there is decreased systolic BP following stimulation or no BP response to stimulation, the site is defined as "cold spots" or "neutral spots," and the operator advances the catheter to another site for stimulation/mapping and ablation procedure, excluding this site as a treatment target.

The ablation is conducted using pre-programed application of energy and time at the screened ablation site.

B. Ablation:
   Power: 8 W.
   Temperature: 50 °C.
   Duration: 120 s.
C. Confirmation of effective treatment

The stimulation/mapping site will start from the distal end of main renal artery and the stimulation should be maintained for at least 20 s. During stimulation, invasive BP is examined. Effective ablation is subsequently confirmed by repeating the initial stimulation. If systolic BP still rises more than 5 mmHg, a second ablation will be performed at the same location; otherwise, an effective ablation is defined.

IV. D. After the second ablation, there is neither further stimulation nor additional ablations performed at that site.

This procedure is repeatedly executed until the entire main renal artery has been tested and either treated or avoided, with each treated site having confirmation of technical success or failure.

Training of Operators

Key operators will have to participate in preclinical experiments to learn how to perform renal stimulation/mapping and ablation procedure. Once these operators obtain experience and a certificate from the sponsor, they will become instructors to guide other physicians for the procedure [22–24].

Dual Primary Efficacy Outcomes and Composite Antihypertensive Medication Index

The study has two primary efficacy endpoints at 6-month post-procedure:

1. The control rate of patients with office systolic BP <140 mmHg [32–35]
2. The change in the composite index of antihypertensive drugs between treatment and sham group [36]

Antihypertensive drug composite index is calculated as follows:

Drug Composite Index = Weight (number of classes of antihypertensive drugs) × (sum of doses)

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

For instance, if a patient takes one dose of an angiotensin-II receptor blocker and one dose of a calcium blocker, this patient's drug composite index is as follows: 2×(1+1)=4.

Our clinical trial allows active titration in medications for both RDN treatment and control groups to simultaneously achieve the same control rate of BP in patients of both groups attaining target BP and then assess the changes in the antihypertensive medication burden. Drug burden is a measurable endpoint of hypertension trials; the comparable pharmacologic profiles pre- and post-treatment in both RDN treatment and sham control groups will be evaluated at 6 months. Weber et at. have editorialized that reducing BP pharmacologic burden is an important endpoint for RDN trials [37]. Not only is this endpoint valued by patients, but if unmeasured may obscure the clinical utility of renal denervation in hypertension management. Kandzari et al. recently emphasized the importance of drug burden as a clinical endpoint for device-based therapies to treat hypertension [36]. Furthermore, in a clinical setting, the design using reduction in BP as the 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 6-month follow-up. If patients in the sham group take any antihypertensive drugs to manage their high BP, the difference of office systolic BP between RDN and sham group could be compromised since the efficacy of global RDN is around 10 mmHg [15–17]. This trial design will inform patients and physicians the percentage of patients anticipated to reach target BP and the anticipated changes of antihypertensive medications after RDN treatment compared to usual titrated care.

It is particularly important that our active drug titration design eliminates the ethical quandary caused by freezing approved therapeutic intervention and by physicians or expecting patient/subjects to voluntarily accept their own excess cardiovascular risk due to uncontrolled hypertension. Resolving this ethical consideration requires allowing active drug titration coupled with the designs of SMART trial dual endpoints of the following: (1) to achieve the same control rate of patients reaching target BP and (2) change of drug burden, between RDN and sham group. Alternative trial designs mandate physicians and patient/subjects document and allow excess ongoing cardiovascular risk due to hypertension when there are readily available treatments. Neither patient/subjects nor treating physicians can be expected to remain compliant with protocols that deliberately deny available therapy. Thus, the SMART active drug titration protocol with dual endpoint is the preferred resolution to ethical violations inherent to alternative designs.

Standardized Antihypertensive Medication Regimen and Titration Protocol

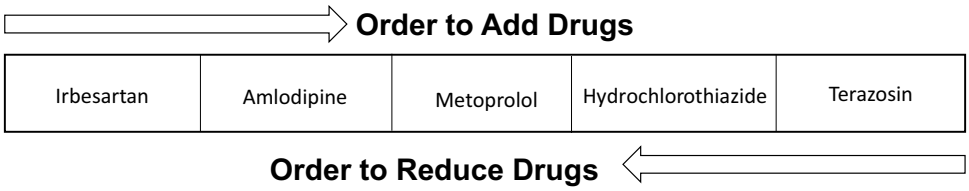
During the study, patients will have to follow a standardized antihypertensive medication regimen: classes, doses, and manufacturers of the medications are predefined (Table 2) and must follow an antihypertensive medication titration protocol (Figure 4).

Within 3 months after RDN procedure, the antihypertensive medications in principle should not be adjusted when office systolic BP varies between 120 and 160 mmHg unless:

If office systolic BP > 160 mmHg, dosing or a class of a medication will be added per the predefined rules.

If office systolic BP < 120 mmHg or office systolic BP < 130 mmHg but patient with symptoms due to low BP, dosing or a class of a medication will be decreased.

Three months after RDN procedure, patients with office systolic BP who have not achieved target BP level (< 140 mmHg) will titrate doses or classes of antihypertensive drugs per a specific predefined sequence (Fig. 4) until their office systolic BP is < 140 mmHg or if office systolic BP < 120 mmHg antihypertensive medications will be adjusted as well if patient complains clinical symptoms due to low BP. The principles are to adjust the dose first; once maximum dose is achieved, office systolic BP is still not controlled to target level (< 140 mmHg), another class of medication should be added (Fig. 4), and the titration procedure is performed monthly.



Regimen to Add Drugs：Increase in dosing is firstly selected until defined maximum dose; if systolic BP is still not controlled, then another class drug is added according to the order shown . If the class of drugs is not proper to the patient evidenced by clinical signs the class can be skipped and next class of drug is used. For instance, a patient with irbesartan 150mg/day + Amlodipine 5mg/day, SBP is still >160mmHg. HR is < 65 b/min, Metoprolol will be skipped and hydrochlorothiazide is used.

Regimen to Reduce Drugs: Decrease in dosing is considered first; if it is needed then the class of drug is reduced according to above order.

Fig. 4 Antihypertensive medication titration regimen. Regimen to add drugs: increase in dosing is firstly selected until defined maximum dose; if systolic BP is still not controlled, then another class drug is added according to the order shown. If the class of drugs is not proper to the patient evidenced by clinical signs, then the class can be skipped, and the next class of drug is used. For instance, a patient with irbesartan 150 mg/day + amlodipine 5 mg/day, SBP is still > 160 mmHg. HR is < 65 b/min, metoprolol will be skipped and hydrochlorothiazide is used. Regimen to reduce drugs: decrease in dosing is considered first; if it is needed, then the class of drug is reduced according to above order

The rigorous antihypertensive medication titration protocol (Fig. 4) must be followed unless the patient has contraindication to a medication in the protocol, and then the medication can be skipped.

Monitoring Adherence of Antihypertensive Medications

Adherence and persistence with hypertensive medications during the clinical trial are a crucial confounding factor potentially interfering with identification of the treatment effects. Some of the medication changes are captured by changes in prescription; many are concealed by changes in adherence or persistence by patients. Thus, antihypertensive medications are rigorously monitored to ensure patient's adherence and persistence to our drug regimen during this trial. The adherence is monitored by four approaches:

1. All antihypertensive medications are supplied by the study sponsor via physicians who are investigators of the trial at participating hospitals and records of drug supplies are documented.
2. Patients record their medications daily on a medication diary.
3. Antihypertensive drugs are counted at each follow-up visit.
4. Urine samples are taken from patients at the end of run-in period, 1, 3, 6, 9, and 12 months after RDN procedure and sent to a third party, independent laboratory (Hangzhou Calibra Diagnostic Ltd, Hangzhou, China) for assay using standard liquid chromatography with tandem mass spectrometry (LC-M/M) [38].

Measurements of Office Blood Pressure

Office BP is measured by an electronic calibrated automatic recording sphygmomanometer system consisting of a sphygmomanometer (OMRON HBP-1100U) and a dedicated computer. The standard American Heart Association recommendations for BP measurement will be applied. Patients are instructed to avoid smoking, drinking caffeinated beverages, or exercise within 30 min of measurements, the bladder will be emptied, and measurements are taken only after 10 min of quiet rest. Measurements will be 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 are performed with at least 1-min interval between measures. If the difference between the highest and lowest systolic BP is more than 15 mmHg among these three measurements, another measurement should be performed. However, if the difference is still higher than 15 mmHg after 6 measurements, the patient will be excluded [39, 40]. Three qualified BP measurements are automatically averaged and stored in the computer in a binary format.

Secondary Efficacy Outcomes and Safety Outcomes

The secondary efficacy outcomes are as follows:

1. Changes in mean 24-h ambulatory BP monitoring (ABPM) at 6 months after RDN procedure.
2. Changes in mean, systolic, and diastolic 24-h ABPM 1 day immediately after the RDN procedure.
3. Office BP at 1, 3, 4, 5, 6, 9, and 12 months after RDN procedure
4. Change in composite index of antihypertensive drugs at 1, 3, 4, 5, 9, and 12 months after RDN procedure.

The primary safety measures of the study are as follows:

1. Successful rate of the renal interventional therapy procedure during RDN procedure.

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

2. Acute infection and renal dysfunction are assessed during the time from RDN procedure to the time which patient is discharged from the hospital or during 7 days after RDN procedure.
3. All-cause death is assessed at 1 month and 3, 6, 9, and 12 months, respectively.
4. Severe renal dysfunction is defined as eGFR < 15 mL/min/m^2, or renal function replacement therapy is needed at 6 months.
5. The rate of renal artery stenosis (> 70%) is assessed by CT angiography at 6 months.
6. Adverse events (AEs), serious adverse events (SAEs), and severe cardio-cerebrovascular events at 1 month and 3, 6, 9,and 12 months, respectively.

Statistical Analysis

The statistical analysis will be undertaken by the Department of Biostatistics, Peking University First Hospital. Statisticians will participate in the concept development, protocol design, study implementation, data management, analysis, and summary of research results. The statistical analysis plan shall be formulated after the completion of the research protocol and case report form, and the statistical analysis report will be completed after the end of the trial.

Clinical compliance is defined as the office systolic BP of patients is controlled and achieved to target level: < 140 mmHg [40] at 6 months after RDN. The assumption is that the RDN and sham groups will have the same clinical compliance rate of 95% at 6 months, the non-inferiority margin is 10% with the significance level at 0.05 (two-side test), and the power is 80% then using PASS13 software and group sequential design to conduct simulation calculations (50,000 simulations and assuming half of the subjects reach the evaluable endpoint). Using O'Brien-Fleming method of type I error consumption, 85 pairs of subjects will be needed. If 20% of drop-out rate is taken into consideration, 212 subjects (106 for each group) are needed. Because subgroup analyses might be utilized, the final sample size is further expanded to 220 patients (110 pairs).

In order to investigate the difference in drug burden between RDN and sham groups, all subjects will take 2 or more classes of antihypertensive drugs at baseline. The assumption is that the average numbers of antihypertensive drug classes are not changed in RDN group; however, one class of antihypertensive drug will be added in sham group at 6-month follow-up, and the standard error for classes of antihypertensive drugs is 2; in the conditions of the group sequential design along with 5000 simulations and the power of the sample size (85 pairs), it will reach the conclusion that the certainty to use less antihypertensive drugs in RDN group than sham group will be 89%.

We have constructed a composite index of antihypertensive drugs based on both the classes and the doses of antihypertensive medications. This composite index should have higher power to examine the drug burden than use of an index only considering the class or dose of antihypertensive drugs [41, 42].

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

Per-protocol set (PPS) consists of subjects who completed the study protocol and excludes subjects with serious protocol violations.

Safety set (SS) consists of all randomized subjects who receive treatments and have at least one baseline safety assessment.

The efficacy and safety analysis will be performed based on data from FAS and PPS, and the analysis of safety will be performed based on SS.

The efficacy analysis of the study is based on the dual primary outcomes at 6 months after the RDN procedure. 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 are statistically significant, the whole study is considered statistically significant.

Summary

The SMART trial is a prospective, multicenter, randomized, single-blinded, sham procedure-controlled trial to evaluate the safety and efficacy of targeted renal sympathetic denervation in patients with essential and uncontrolled hypertension among patients confirmed to have persistently elevated BP and receiving a standardized formulary of medications. Dual primary outcomes are control rate of office systolic BP to achieve level of < 140 mmHg and change in the composite index of antihypertensive medications. This design eliminates the confounding effects of antihypertensive medication changes on BP endpoints and able to assess meaningful changes in medications required to manage BP to target following RDN. Patients will follow a predefined medication regimen. All antihypertensive medications are supplied by study sponsor; drug adherence is monitored by multiple techniques. The study will both identify the utility of selective RDN in the successful management of chronic uncontrolled hypertension as well as assess the safety of the Symap device and procedure.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12265-022-10307-z.

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Declarations

Ethics Approval and Consent to Participate The protocol was approved by the Ethics Committees of all participated hospitals. All procedures followed are 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 is obtained from all patients previous to being included in the study.

Conflict of Interest Jie Wang is a co-founder of SyMap Medical Ltd (Suzhou).
Sun N, Jiang H, Yin Y, Chen M, and Huo Y are consultants and received consultant honoraria from SyMap Medical Ltd (Suzhou). Sobotka PA is a consultant and receives consultant honoraria from SyMap Medical Ltd (Suzhou). Yan X received consultant honoraria from SyMap Medical Ltd (Suzhou).

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