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Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Short title: Renal denervation for Chinese patients with resistant hypertension

Abstract:

Introduction: Available data show that approximately 8-18% of patients with primary hypertension will develop resistant hypertension. In recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated its potential safety and efficacy.

Methods and Analysis: This is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated radiofrequency ablation (RFA) catheter used for RDN in the treatment of Chinese patients with resistant hypertension. A total of 254 patients who have failed pharmacological therapy will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to undergo RDN using the RFA catheter plus antihypertensive medication, or to receive treatment with antihypertensive medication alone. The primary outcome measure is the change in 24-hour ambulatory systolic blood pressure from baseline to 3 months, comparing the RDN-plus-medication group with the medication-alone group. Important secondary endpoints include the change in office blood pressure from baseline to 6 months after randomization. Safety endpoints will also be evaluated. The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population.

Conclusion: This study is designed to investigate the efficacy and safety of RDN using a 5F saline micro-irrigated RFA catheter in Chinese patients with hypertension who are resistant to medication. It aims to provide clinical evidence that RDN with the RFA catheter is both safe and effective in Chinese patients. (Words: 248)

Trial registration: ClinicalTrials.gov ID: NCT02900729

Key words: resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

Abbreviations: RDN, renal denervation; RFA, radiofrequency ablation

Strengths and limitations of this study

- A micro-irrigated catheter used for renal denervation;
- A randomized controlled trial accords in principle with recommendations by European Expert Group;
- Enroll Chinese hypertensive patients only, which might affect generability of study findings

Introduction

Hypertension represents a significant global public health problem, contributing to vascular and renal morbidity, cardiovascular mortality, and economic burden. Although there are many methods for treating primary hypertension, more than half of the patients are still unable to achieve their treatment goal[1, 2].Available data show that 8-18% of patients will develop resistant hypertension[3, 4], defined as a systolic blood pressure (SBP) of 140mmHg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose[5]. Compared with those with controlled blood pressure (BP), patients with resistant hypertension are at greater risk for developing adverse cardiovascular events, leading to an unfavorable prognosis without adequate treatment[6]. Because of the complex pathophysiology of resistant hypertension, however, there are limited strategies available to treat it efficiently.

Following the clinical use of radiofrequency ablation (RFA) catheters in recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. This technique delivers low-level radiofrequency energy throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some extent. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated both the safety and the potential efficacy of this new therapy[7-15], whereas several other studies failed to show extra benefits when RDN was applied[16-18]. Whenever doubts arise concerning the effectiveness of a therapeutic approach, rigorously designed studies are warranted to furnish conclusive evidence. According to the clinical consensus from the European Expert Group[19], many factors could affect the results of RDN in clinical trials, including procedural aspects, patient populations, and design considerations. Many aspects of the RDN procedure may affect the success of the ablation; furthermore, whether denervation has been completely achieved in a specific patient remains the key factor for the efficacy of RDN.

Together with these key recommendations[19], we present the rationale and methodology for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA catheter for the treatment of hypertension in Chinese patients who have failed standardized pharmacologic therapy.

Methods/design

Study design

This trial (ClinicalTrials.gov ID: NCT02900729) is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated RFA catheter used in RDN for the treatment of Chinese patients with resistant hypertension. It will be conducted in accordance with the principles outlined in the Declaration of Helsinki and will follow the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/). Approximately 13 clinical centers will participate in this trial, which has been approved by the Independent Ethics Committee for each site. All subjects will be required to sign a written informed consent document before their participation in the trial. A brief flow chart of this trial is provided in Figure 1.

Study patients

A total of 254 patients who have failed pharmacological therapy will be enrolled. The following are the inclusion criteria:

1. Subject with primary hypertension has 24-hour ambulatory SBP≥135 mmHg and office SBP ≥140 mmHg /office diastolic blood pressure (DBP) ≥90 mmHg after 4weeks' standardized triple therapy.
2. Subject is ≥18 and <80 years old at the time of randomization.
3. Subject agrees to have all study procedures performed, and is willing to provide written informed consent to participate in this clinical study.

The exclusion criteria are as follows:

1. Subject has acute or serious systemic infection.
2. Subject has a history of renal artery interventional therapy.
3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve RFA surgery, including but not limited to the presence of serious aorta or renal-artery tortuosity or renal-artery stenosis.
4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within three months of the screening period, or has widespread atherosclerosis, with documented intravascular thrombosis.
5. Subject has aortic dissection aneurysm.
6. Subject has primary pulmonary hypertension.
7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease formula.
8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
10. Subject has atrial fibrillation.
11. Subject has a significant bleeding tendency or blood system disease(s).
12. Subject has a malignancy or end-stage disease(s).
13. Subject has secondary hypertension.
14. Subject has type 1 diabetes mellitus.
15. Subject has other conditions inappropriate for participation, at the investigator's discretion.
16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as presence of an average SBP≥170 mmHg on 24-hour ambulatory BP monitoring after 4weeks'standardized triple therapy.

Recruitment process

Before enrollment, there will be two screening visits. Each participant will be assigned a unique identification number during the first screening visit. In addition to the above mentioned entry criteria, patients with primary hypertension who meet any of the three following criteria will be considered for further evaluation at the second screening visit:

- Adherence to 3 kinds of antihypertensive medication, office SBP ≥140mmHg or office DBP ≥90mmHg, and office SBP <180mmHg, office DBP <100mmHg.
- Adherence to two kinds of antihypertensive medication, office SBP ≥140 mmHg, or office DBP ≥90mmHg.
- Adherence to one kind of antihypertensive medication, office SBP ≥160mmHg, or office DBP ≥100mmHg.

For any initially eligible patients as mentioned above, three basic kinds of antihypertensive medication, e.g. standardized triple antihypertensive medications consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who meet the following BP threshold criteria will then be eligible for randomized assignment after the second screening period: 24h ambulatory BP ≥135mmHg and office SBP ≥140mmHg, or office DBP ≥90mmHg.

Randomization process

Eligible patients with resistant hypertension will be randomly assigned to one of two study treatment groups in a 1:1 ratio. A stratified block randomization with randomly varying block size will be performed, stratified according to study site. Random assignment is generated by an independent statistician and implemented via random envelopes assigned to each site. In order to avoid potential selection bias, the sequence is concealed from both clinical staff and patients until assignment. Hence, neither investigators nor participants can influence which group the study patients are assigned to.

Description of the interventions

The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-irrigated RFA catheter plus antihypertensive medication, or to be treated with antihypertensive medication alone. RDN will be performed according to the device's instructions for use.

The study patients will be advised to maintain baseline antihypertensive medication in the first 90 days after randomization. However, the three baseline antihypertensive

medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be adjusted after randomization when clinically necessary. Criterion for dosage reduction: subjects experience a sudden reduction in BP within a short time, meanwhile accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these symptoms disappear and 72-hour average home SBP is ≥140mmHg or DBP ≥90mmHg, the antihypertensive medication may be restored to the original type and dosage. Criterion for dosage increase: if home SBP is ≥170mmHg for an observational period of 72 hours from randomization through 90 days, or from 91 days through 180 days if average home SBP is ≥140mmHg or DBP is ≥90mmHg based on three consecutive daily measurements, the following three kinds of drugs could be added, one per month in sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

For patients receiving antihypertensive medication alone, after maintenance of baseline standardized triple antihypertensive medications for 90 days post randomization and then medically necessary adjustment of antihypertensive medications for another 90 days, subjects will be allowed to cross over to undergo RDN if they still meet the original inclusion criteria for the study.

Renal denervation procedure

Under local anesthesia, RDN procedures are to be performed by interventionists at each study site after a unified training session. Following preoperative preparation, the ablation catheter will be advanced to the distal segment of the renal artery through the 7F guidance catheter.

The ablation involves at least six applications to each renal artery, according to the length of the artery's main stem. If the main renal artery is less than 15 mm, two ablations should be delivered to the main bifurcation with diameter >3mm in order to ensure six ablation lesions on each side. Treatment begins from the distal end of the artery or the main bifurcation in a helical pattern as the catheter is pulled back.

For every renal artery ostium, the catheter must be maneuvered to at least one position in each of the distal, middle and proximal segments. The ablation energy will be 8-10 W in

the distal segment, 10-11 W in the middle segment and 12 W in the proximal segment. Each ablation will last 60s. The ideal target outcome is for the energy titration to achieve a 10% to 20% drop in impedance at each location. If the drop in impedance is less than 5%, or the ablation energy is unable to achieve the preset wattage, the ablation will be stopped and the catheter will be repositioned.

Study visits

Nine study visits will be scheduled following the baseline visit: once every 15 days in the first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits patients will return to the clinic office; for the remaining visits, the patients will be consulted by phone. At every visit, data relating to BP, medication, adverse events, etc., will be collected.

The subjects may withdraw from the study if any of the following conditions occur:

- After 4 weeks post randomization, the office or home SBP is ≥180mmHg for more than one week while standardized antihypertensive medications are maintained.
- Based on the investigator's discretion, the subject is no longer eligible for the study for any reason.

Outcome measures

Primary outcome

The primary outcome of this study is the change in 24-hour ambulatory SBP from baseline to 3 months compared between the RDN-plus-medication group and the medication-only group. This outcome will be strictly standardized in terms of uniform validated devices, appropriate cuff, identical clinical setting, and resting condition prior to BP measurement after mandatory one-day stay in participating site, etc.

Secondary outcomes

1. Change in office systolic/diastolic BP from baseline to 6 months post-randomization.
2. Incidence of achieving target BP at 6 months post-randomization. Target BP is defined as daytime ambulatory BP <135/85mmHg, nighttime ambulatory BP <120/70mmHg, or average 24-hour ambulatory BP <130/80mmHg.
3. Incidence of substantially adjusting antihypertensive medications at 6 months post-randomization. A substantial adjustment of antihypertensive medications is defined as any change in the number or type of antihypertensive medications, or a ≥50% dose change in the last two weeks with respect to any ongoing antihypertensive medications.
4. Incidence of achieving reductions of ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, and ≥20 mmHg in BP, including ambulatory, office, and home BP at 6 months post-randomization.

Safety endpoints

The safety endpoints mainly include any adverse events, a change in renal function (serum creatinine, urea nitrogen, serum uric acid, etc.), other laboratory tests (liver function, serum biochemistry), and cardiovascular complications.

Sample size calculation

We used R V.3.2.3 (R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2014.http://www.R-project.org/: last accessed June 2016) to estimate sample size. The trial is designed to compare the difference in average ambulatory SBP as a change from baseline to 3 months between the RDN-plus-medication group and the medication-alone group. With a sample size of 108 randomized patients per group, the between-group comparison will be powered at 90% to establish the superiority of added RDN for the primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP difference is 8mmHg with a common standard deviation of 18mmHg. Given an expected dropout rate of 15% in the first 3 months post randomization, a total of 254 patients (127 patients per group) must be enrolled in the study.

Results of 10,000 simulations using this estimated sample size for each study showed that an empirical power of 98% would be reached for the analysis of the BP target rate (56% versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

Statistical analysis

The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population. A two-sided p-value of <0.05 will be considered to indicate significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute, North Carolina, USA) will be used for statistical analysis. Such data as demographics, baseline characteristics, and safety will be summarized according to treatment group.

The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA) with treatment group as fixed factor and BP values at baseline as covariate. The paired and unpaired t-tests will further be used to test BP reduction within each group and between groups, respectively. The 95% confidence intervals for the differences between treatment groups will also be calculated. Subgroup analyses are prespecified according to the following prognostic factors: sex, age, diabetes, body mass index, estimated glomerular filtration rate, and aldosterone use at baseline.

Blood pressure target rate at 6 months will be analyzed using the CMH test, with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor. Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test, as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the primary endpoint. Mixed-model repeated measures analysis including terms for treatment group, time, baseline measurement, and time by treatment group interaction will be considered to compare BP reduction in the study.

Discussion

The design and methods of this trial satisfy the requirements to test whether a 5F saline micro-irrigated RFA catheter used in RDN is safe and effective for patients who remain hypertensive despite adherence to polypharmacy.

With the recognition of the role of the sympathetic nervous system in the development and progression of hypertension[20, 21], catheter-based RDN has been developed to reduce sympathetic nervous activity and subsequently reduce BP, as well as morbidity and mortality, in patients with uncontrolled hypertension[22-25]. However, the clinical evidence in support of RDN as an effective interventional technique in patients with resistant hypertension appears conflicting. Several large studies support both the safety and the efficacy of this new therapy[7-15], but some smaller studies failed to show the superiority resulting from added RDN[16-18]. In view of this controversy, the European Expert Group convened a clinical consensus conference and agreed on recommendations for future randomized controlled trials of RDN in hypertension. The design and methods of our trial accord in principle with the recommendations.

The RDN procedure is so complex that the efficacy of ablation may be influenced by many factors, such as renal artery anatomy, the depth of the ablation lesion, atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator, the equipment, and the procedure. A study of the anatomic assessment of sympathetic peri-arterial renal nerves showed that the greatest number of nerves were observed in the proximal and middle segments of the renal artery, while the smallest number were seen in the distal segment. However, in the main renal artery, the distance from the nerve to the renal artery lumen is shorter than in the proximal and middle segments, being approximately4.28mm[26]. Another study showed that, for a patient with atherosclerosis, the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface, leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the vascular lumen[27]. An animal study showed that the ablation zone geometries varied in arc, area, and depth, depending on the composition of the adjacent tissue substructure[28]. In addition, the delivered power density was influenced by tissue substructure, and peaked at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not

at the electrode-tissue interface[28]. With a greater recognition of nerve distribution, the ablation depth and location should be taken carefully into account.

In previous studies, a non-irrigated catheter was usually used and the ablation energy was usually 8W. Increasing ablation energy or prolonging ablation time could make the ablation deeper. However, using a non-irrigated catheter could raise the temperature of the luminal surface too much to increase the ablation power. In this study, radiofrequency energy delivery with the use of cold saline irrigation seems safe and effective. By actively cooling the ablation electrode during RFA, it is possible to minimize the possibility of char formation and also decrease the probability of vasospasm. These advantages to saline irrigation are so significant that most cardiac ablations are now performed using irrigated ablation catheters[29]. Ahmed et al., in a small single-arm study, demonstrated that RND can be performed safely and effectively using a saline-irrigated RFA catheter in patients with hypertension[30]. Using a saline-irrigated catheter, with the protection of cold saline, higher ablation energy can be delivered, ensuring the ablation depth. Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

In most clinical trials involving RDN, a renal artery less than 4mm in diameter could not be ablated because of the limited operation equipment. In this study, the 5F saline micro-irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries with diameter <4mm, while minimizing the possibility of peripheral artery-related complications.

In this study, the operation procedure will also be unified. A similar spiral ablation will be used and at least one site must be ablated at each of the distal segments of the renal artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There are a total of 6 ablation points on each side of the renal artery. The ablation energy will also be standardized to ensure sufficient ablation.

In this trial, patients with 24-hour ambulatory SBP ≥135mmHg and office SBP <170mmHg will be eligible for enrollment, while patients with high-risk characteristics will be excluded. Given this restriction, the patients enrolled in this study will mostly have mild to moderate hypertension and might be more responsive to RDN-induced

changes in sympathetic tone. In addition, it will be safer for these patients to strictly follow a standardized medication regimen. Moreover, higher drug adherence will be expected in this study, because of the lower level of discomfort occurring in the management of mild to moderate rather than severe hypertension.

In the study period, the antihypertensive medications administered are explicitly specified: standardized triple antihypertensive medications include a calcium channel blocker, a renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study[16], the maximum doses were administered, and 39% patients required medication adjustment because of adverse events; this may be related to the negative conclusions of that study. Conversely, in the DENERHTN study[15], the antihypertensive medications in the RDN group and control group were strictly regulated, and the study results supported the superiority of RDN. The rigorous specification of medication may be an important factor influencing the study results.

For this study, ambulatory BP is used as the primary endpoint, and office BP as the secondary parameter. In fact, several previous studies have documented a better prognostic value of ambulatory over office BP in different populations[31-35]. Among the previous trials conducted on RDN, only the DENERHTN study[15]successfully used the change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN to have superior efficacy. The Expert Group also strongly recommended ambulatory BP as the primary measure of response to RDN. Using ambulatory BP monitoring to measure efficacy could exclude pseudo-resistance due to a “white-coat” effect.

There is also one limitation regarding the selection of the control group. Because of the poor acceptability by patients in our routine clinical practice and potential ethical problems, a sham operation will not be performed in this study; its omission might thus be a potential confounder for study outcomes. Although a sham procedure could reduce some Hawthorne effects, it could not eliminate other biases that are considered as reasons for the lack of benefit from RDN.

This study is designed to investigate the efficacy and safety of RDN using a 5F saline-irrigated RFA catheter in Chinese patients with hypertension who are resistant to

medication therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-irrigated RFA catheter is both safe and effective in Chinese patients with drug-resistant, systemic hypertension.

Trial status

The study is not yet recruiting as of the date of submission.

Competing interests

None.

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Contributors

ZJL, LS and JBG conceived and designed the study. ZJL, LS and SZ supervised the power analyses and wrote the data analysis section. ZJL and JBG bear overall responsibility for the design, ethical conduct and publication of the study. Administrative, technical and material support was provided by ZJL and LS. All authors involved the protocol discussion and they will take responsibility for study data gathering and verification. All authors edited the draft and contributed substantially to the manuscript; they all approved this submission.

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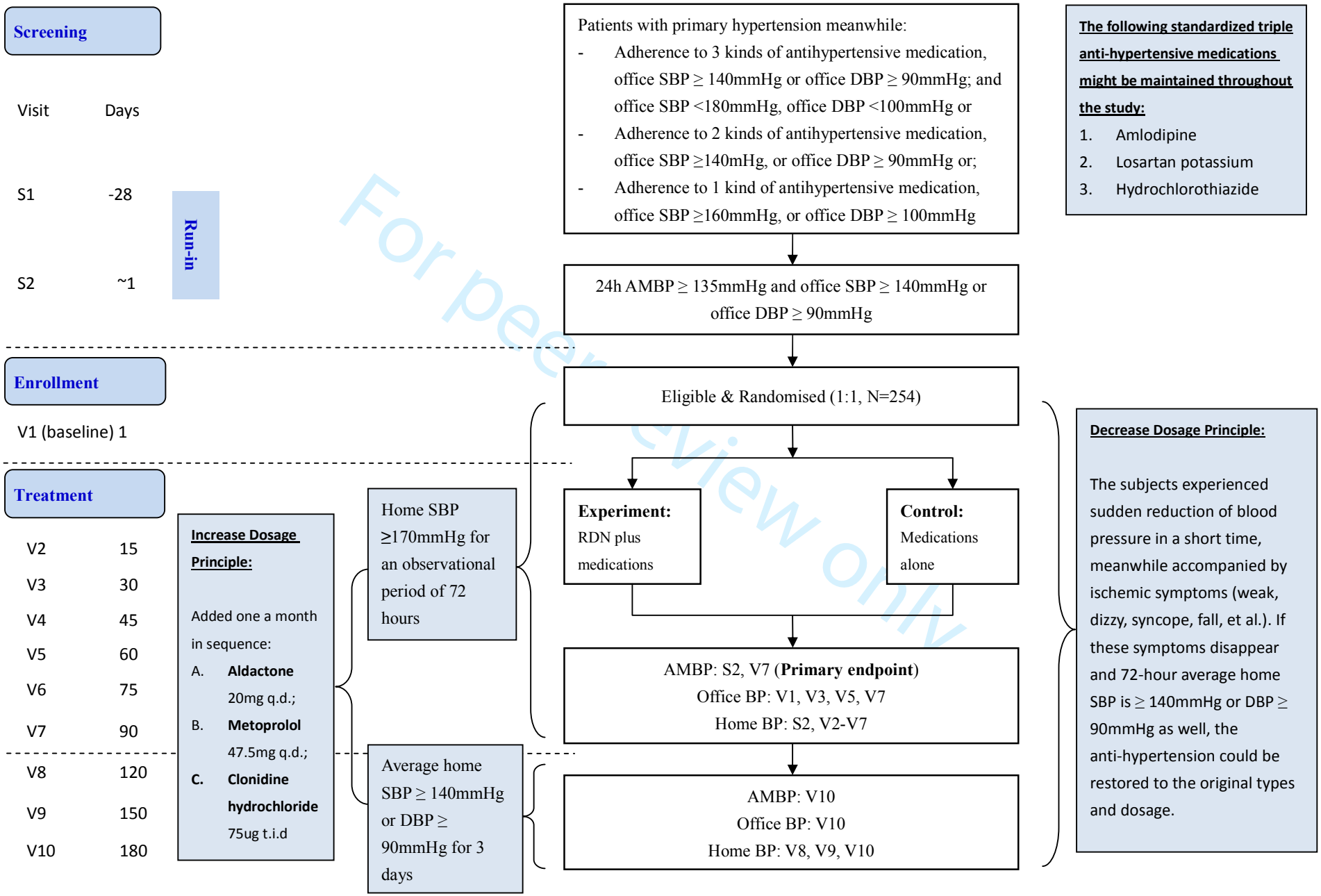
Figure 1: Study flowchart and principles of adjusting antihypertensive medications

Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure



SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n.a.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n.a.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	Item No	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see fig 1[f1])	figure 1

Section/item	Item No	Description	Addressed on page number
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if	Figure 1

Section/item	Item No	Description	Addressed on page number
		not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n.a.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n.a.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators	n.a.

Section/item	Item No	Description	Addressed on page number
		and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n.a.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n.a.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n.a.

Section/item	Item No	Description	Addressed on page number
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Short title: Renal denervation for Chinese patients with resistant hypertension

Abstract:

Introduction: Available data show that approximately 8-18% of patients with primary hypertension will develop resistant hypertension. In recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated its potential safety and efficacy.

Methods and Analysis: This is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated radiofrequency ablation (RFA) used for RDN in the treatment of Chinese patients with resistant hypertension. A total of 254 patients who have failed pharmacological therapy will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to undergo RDN using the RFA catheter plus antihypertensive medication, or to receive treatment with antihypertensive medication alone. The primary outcome measure is the change in 24-hour ambulatory systolic blood pressure from baseline to 3 months, comparing the RDN-plus-medication group with the medication-alone group. Important secondary endpoints include the change in office blood pressure from baseline to 6 months after randomization. Safety endpoints such as changes in renal function will also be evaluated. The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population.

Ethics and Dissemination: All participants will provide informed consent; the study protocol has been approved by the Independent Ethics Committee for each site. This study is designed to investigate the efficacy and safety of RDN using a 5F saline micro-irrigated RFA catheter. Findings will be shared with participating hospitals, policymakers and the academic community to promote the clinical management of resistant hypertension in China. (Words: 267)

Trial registration: ClinicalTrials.gov ID: NCT02900729

Key words: resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

Abbreviations: RDN, renal denervation; RFA, radiofrequency ablation

Strengths and limitations of this study

- A randomized controlled trial accords in principle with recommendations by European Expert Group;
- Strict standardization of anti-hypertensive medications during the study;
- Enroll Chinese hypertensive patients only, which might affect generability of study findings
- Failure to implement sham procedure as control might introduce Hawthorne effects.

Introduction

Hypertension represents a significant global public health problem, contributing to vascular and renal morbidity, cardiovascular mortality, and economic burden. Although there are many methods for treating primary hypertension, more than half of the patients are still unable to achieve their treatment goal[1, 2].Available data show that approximately 8-18% of patients with primary hypertension present with resistant hypertension[3, 4], defined as a systolic blood pressure (SBP) of 140mmHg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose[5].Compared with those with controlled blood pressure (BP), patients with resistant hypertension are at greater risk for developing adverse cardiovascular events, leading to an unfavorable prognosis without adequate treatment[6]. Because of the complex pathophysiology of resistant hypertension, however, there are limited strategies available to treat it efficiently.

Following the clinical use of radiofrequency ablation (RFA) catheters in recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. This technique delivers low-level radiofrequency energy throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some extent. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated both the safety and the potential efficacy of this new therapy[7-15], whereas several other studies failed to show extra benefits when RDN was applied[16-18]. Whenever doubts arise concerning the effectiveness of a therapeutic approach, rigorously designed studies are warranted to furnish conclusive evidence. According to the clinical consensus from the European Expert Group[19], many factors could affect the results of RDN in clinical trials, including procedural aspects, patient populations, and design considerations. Many aspects of the RDN procedure may affect the success of the ablation; furthermore, whether denervation has been completely achieved in a specific patient remains the key factor for the efficacy of RDN.

Together with these key recommendations[19], we present the rationale and methodology for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA catheter for the treatment of hypertension in Chinese patients who have failed standardized pharmacologic therapy.

Methods/design

Study design

This trial (ClinicalTrials.gov ID: NCT02900729) is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated RFA catheter used in RDN for the treatment of Chinese patients with resistant hypertension. The RFA catheter under study is manufactured by Shanghai WiseGain Medical Devices Co., Ltd Approximately 13 clinical centers will participate in this trial. A brief flow chart of this trial is provided in Figure 1.

Study patients

A total of 254 patients who have failed pharmacological therapy will be enrolled. The following are the inclusion criteria:

1. Subject with primary hypertension has 24-hour ambulatory SBP≥135 mmHg and office SBP ≥140 mmHg /office diastolic blood pressure (DBP) ≥90 mmHg after 4weeks'standardized triple therapy.
2. Subject is ≥18 and <80 years old at the time of randomization.
3. Subject agrees to have all study procedures performed, and is willing to provide written informed consent to participate in this clinical study.

The exclusion criteria are as follows:

1. Subject has acute or serious systemic infection.
2. Subject has a history of renal artery interventional therapy.

3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve RFA surgery, including but not limited to the presence of serious aorta or renal-artery tortuosity or renal-artery stenosis.
4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within three months of the screening period, or has widespread atherosclerosis, with documented intravascular thrombosis.
5. Subject has aortic dissection aneurysm.
6. Subject has primary pulmonary hypertension.
7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease formula.
8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
10. Subject has atrial fibrillation.
11. Subject has a significant bleeding tendency or blood system disease(s).
12. Subject has a malignancy or end-stage disease(s).
13. Subject has secondary hypertension.
14. Subject has type 1 diabetes mellitus.
15. Subject has other conditions inappropriate for participation, at the investigator's discretion.
16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as presence of an average SBP≥170 mmHg on 24-hour ambulatory BP monitoring after 4weeks'standardized triple therapy.

Recruitment process

Before enrollment, there will be two screening visits. Each participant will be assigned a unique identification number during the first screening visit. In addition to the above-mentioned entry criteria, patients with primary hypertension who meet any of the three following criteria will be considered for further evaluation at the second screening visit:

- Adherence to 3 kinds of antihypertensive medication, office SBP ≥140mmHg or office DBP ≥90mmHg, and office SBP <180mmHg, office DBP <100mmHg.

- Adherence to two kinds of antihypertensive medication, office SBP ≥140 mmHg, or office DBP ≥90mmHg.
- Adherence to one kind of antihypertensive medication, office SBP ≥160mmHg, or office DBP ≥100mmHg.

For any initially eligible patients as mentioned above, three basic kinds of antihypertensive medication, e.g. standardized triple antihypertensive medications consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who meet the following BP threshold criteria will then be eligible for randomized assignment after the second screening period: 24h ambulatory BP ≥135mmHg and office SBP ≥140mmHg, or office DBP ≥90mmHg.

Randomization process

Eligible patients with resistant hypertension will be randomly assigned to one of two study treatment groups in a 1:1 ratio. A stratified block randomization with randomly varying block size will be performed, stratified according to study site. Random assignment is generated by an independent statistician and implemented via random envelopes assigned to each site. In order to avoid potential selection bias, the sequence is concealed from both clinical staff and patients until assignment. Hence, neither investigators nor participants can influence which group the study patients are assigned to.

Description of the interventions

The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-irrigated RFA catheter plus antihypertensive medication, or to be treated with antihypertensive medication alone. RDN will be performed according to the device's instructions for use.

The study patients will be advised to maintain baseline antihypertensive medication in the first 90 days after randomization. However, the three baseline antihypertensive medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be adjusted after randomization when clinically necessary. Criterion for dosage reduction:

subjects experience a sudden reduction in BP within a short time, meanwhile accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these symptoms disappear and 72-hour average home SBP is ≥140mmHg or DBP ≥90mmHg, the antihypertensive medication may be restored to the original type and dosage. Criterion for dosage increase: if home SBP is ≥170mmHg for an observational period of 72 hours from randomization through 90 days, or from 91 days through 180 days if average home SBP is ≥140mmHg or DBP is ≥90mmHgbased on three consecutive daily measurements, the following three kinds of drugs could be added, one per month in sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

For patients receiving antihypertensive medication alone, after maintenance of baseline standardized triple antihypertensive medications for 90 days post randomization and then medically necessary adjustment of antihypertensive medications for another 90 days, subjects will be allowed to cross over to undergo RDN if they still meet the original inclusion criteria for the study.

Renal denervation procedure

Under local anesthesia, RDN procedures are to be performed by interventionists at each study site after a unified training session. Following preoperative preparation, the ablation catheter will be advanced to the distal segment of the renal artery through the 7F guidance catheter.

The ablation involves at least six applications to each renal artery, according to the length of the artery's main stem. If the main renal artery is less than 15 mm, two ablations should be delivered to the main bifurcation with diameter>3mm in order to ensure six ablation lesions on each side. Treatment begins from the distal end of the artery or the main bifurcation in a helical pattern as the catheter is pulled back.

For every renal artery ostium, the catheter must be maneuvered to at least one position in each of the distal, middle and proximal segments. The ablation energy will be 8-10W in the distal segment, 10-11Win the middle segment and 12Win the proximal segment. Each ablation will last 60s. The ideal target outcome is for the energy titration to achieve a 10%

to 20% drop in impedance at each location. If the drop in impedance is less than 5%, or the ablation energy is unable to achieve the preset wattage, the ablation will be stopped and the catheter will be repositioned.

Study visits

Nine study visits will be scheduled following the baseline visit: once every 15 days in the first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits patients will return to the clinic office; for the remaining visits, the patients will be consulted by phone. At every visit, data relating to BP, medication, adverse events, etc., will be collected. The 8-item Morisky Medication Adherence Scale (MMAS-8) will be provided at 1st, 3rd, 5th, 7th, and 10th visits.

The subjects may withdraw from the study if any of the following conditions occur:

- After 4 weeks post randomization, the office or home SBP is ≥180mmHg for more than one week while standardized antihypertensive medications are maintained.
- Based on the investigator's discretion, the subject is no longer eligible for the study for any reason.

Outcome measures

Primary outcome

The primary outcome of this study is the change in 24-hour ambulatory SBP from baseline to 3 months compared between the RDN-plus-medication group and the medication-only group. The department of laboratory other than the clinical department at each participating site will undertake the ambulatory blood pressure monitoring (ABPM) during the study period. The ABPM machine will record and report ABPM results automatically. This outcome will be strictly standardized in terms of uniform validated devices, appropriate cuff, identical clinical setting, and resting condition prior to BP measurement after mandatory one-day stay in participating site, etc.

Secondary outcomes

1. Change in office systolic/diastolic BP from baseline to 6 months post-randomization.
2. Incidence of achieving target BP at 6 months post-randomization. Target BP is defined as daytime ambulatory BP<135/85mmHg, nighttime ambulatory BP<120/70mmHg, or average 24-hour ambulatory BP<130/80mmHg.
3. Incidence of substantially adjusting antihypertensive medications at 6 months post-randomization. A substantial adjustment of antihypertensive medications is defined as any change in the number or type of antihypertensive medications, or a ≥50% dose change in the last two weeks with respect to any ongoing antihypertensive medications.
4. Incidence of achieving reductions of≥5 mmHg,≥10 mmHg, ≥15 mmHg, and ≥20 mmHg in BP, including ambulatory, office, and home BP at 6 months post-randomization.

Safety endpoints

The safety endpoints mainly include any adverse events (e.g. puncture hematoma, thrombosis, renal artery stenosis and renal artery dissection as adverse event of special interest, etc), a change in renal function (serum creatinine, urea nitrogen, serum uric acid, creatinine clearance, etc.), other laboratory tests (liver function, serum biochemistry), and cardiovascular complications.

Sample size calculation

We used R V.3.2.3 (R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2014.http://www.R-project.org/: last accessed June 2016) to estimate sample size. The trial is designed to compare the difference in average ambulatory SBP as a change from baseline to 3 months between the RDN-plus-medication group and the medication-alone group. With a sample size of 108 randomized patients per group, the between-group comparison will be powered at 90% to establish the superiority of added RDN for the primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP difference is 8mmHg with a common standard deviation of 18mmHg. Given an expected

dropout rate of 15% in the first 3 months post randomization, a total of 254 patients (127 patients per group) must be enrolled in the study.

Results of 10,000 simulations using this estimated sample size for each study showed that an empirical power of 98% would be reached for the analysis of the BP target rate (56% versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

Statistical analysis

The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population. A two-sided p-value of<0.05 will be considered to indicate significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute, North Carolina, USA) will be used for statistical analysis. Such data as demographics, baseline characteristics, and safety will be summarized according to treatment group.

The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA) with treatment group as fixed factor and BP values at baseline as covariate. The paired and unpaired t-tests will further be used to test BP reduction within each group and between groups, respectively. The 95% confidence intervals for the differences between treatment groups will also be calculated. Subgroup analyses are prespecified according to the following prognostic factors: sex, age, diabetes, body mass index, estimated glomerular filtration rate, and aldosterone use at baseline.

Blood pressure target rate at 6 months will be analyzed using the CMH test, with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor. Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test, as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the primary endpoint. Mixed-model repeated measures analysis including terms for treatment group, time, baseline measurement, and time by treatment group interaction will be considered to compare BP reduction in the study.

Discussion

The design and methods of this trial satisfy the requirements to test whether a 5F saline micro-irrigated RFA catheter used in RDN is safe and effective for patients who remain hypertensive despite adherence to polypharmacy.

With the recognition of the role of the sympathetic nervous system in the development and progression of hypertension[20, 21], catheter-based RDN has been developed to reduce sympathetic nervous activity and subsequently reduce BP, as well as mortality and morbidity, in patients with uncontrolled hypertension[22-25] and the prevention of recurrences of atrial fibrillation[26], the improvement of glycemic control[27] and the mitigation of pulmonary arterial hypertension as well[28]. However, the clinical evidence in support of RDN as an effective interventional technique in patients with resistant hypertension appears conflicting. Several large studies support both the safety and the efficacy of this new therapy[7-15], but some studies failed to show the superiority resulting from added RDN[16-18]. In view of this controversy, the European Expert Group convened a clinical consensus conference and agreed on recommendations for future randomized controlled trials of RDN in hypertension. The design and methods of our trial accord in principle with the recommendations.

The RDN procedure is so complex that the efficacy of ablation may be influenced by many factors, such as renal artery anatomy, the depth of the ablation lesion, atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator, the equipment, and the procedure. A study of the anatomic assessment of sympathetic peri-arterial renal nerves showed that the greatest number of nerves were observed in the proximal and middle segments of the renal artery, while the smallest number were seen in the distal segment. However, in the main renal artery, the distance from the nerve to the renal artery lumen is shorter than in the proximal and middle segments, being approximately4.28mm[29].Another study showed that, for a patient with atherosclerosis, the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface, leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the vascular lumen[30]. An animal study showed that the ablation zone geometries varied in arc, area, and depth, depending on the composition of the adjacent tissue substructure[31]. In

addition, the delivered power density was influenced by tissue substructure, and peaked at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not at the electrode-tissue interface[31]. With a greater recognition of nerve distribution, the ablation depth and location should be taken carefully into account.

In previous studies, a non-irrigated catheter was usually used and the ablation energy was usually 8W. Increasing ablation energy or prolonging ablation time could make the ablation deeper. However, using a non-irrigated catheter could raise the temperature of the luminal surface too much to increase the ablation power. In this study, radiofrequency energy delivery with the use of cold saline irrigation seems safe and effective. By actively cooling the ablation electrode during RFA, it is possible to minimize the possibility of char formation and also decrease the probability of vasospasm. These advantages to saline irrigation are so significant that most cardiac ablations are now performed using irrigated ablation catheters[32]. Ahmed et al., in a small single-arm study, demonstrated that RND can be performed safely and effectively using a saline-irrigated RFA catheter in patients with hypertension[33]. Using a saline-irrigated catheter, with the protection of cold saline, higher ablation energy can be delivered, ensuring the ablation depth. Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

In most clinical trials involving RDN, adrenal artery less than 4mm in diameter could not be ablated because of the limited operation equipment. In this study, the 5F saline micro-irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries with diameter <4mm, while minimizing the possibility of peripheral artery-related complications.

In this study, the operation procedure will also be unified. A similar spiral ablation will be used and at least one site must be ablated at each of the distal segments of the renal artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There are a total of 6 ablation points on each side of the renal artery. The ablation energy will also be standardized to ensure sufficient ablation.

In this trial, patients with 24-hour ambulatory SBP ≥135mmHg and office SBP <170mmHg will be eligible for enrollment, while patients with high-risk characteristics

will be excluded. Given this restriction, the patients enrolled in this study will mostly have mild to moderate hypertension and might be more responsive to RDN-induced changes in sympathetic tone. In addition, it will be safer for these patients to strictly follow a standardized medication regimen. Moreover, higher drug adherence will be expected in this study, because of the lower level of discomfort occurring in the management of mild to moderate rather than severe hypertension.

In the study period, the antihypertensive medications administered are explicitly specified: standardized triple antihypertensive medications include a calcium channel blocker, a renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study[16], the maximum doses were administered, and 39% patients required medication adjustment because of adverse events; this may be related to the negative conclusions of that study. Conversely, in the DENERHTN study[15], the antihypertensive medications in the RDN group and control group were strictly regulated, and the study results supported the superiority of RDN. The rigorous specification of medication may be an important factor influencing the study results.

For this study, ambulatory BP is used as the primary endpoint, and office BP as the secondary parameter. In fact, several previous studies have documented a better prognostic value of ambulatory over office BP in different populations[34-38].Among the previous trials conducted on RDN, only the DENERHTN study[15]successfully used the change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN to have superior efficacy. The Expert Group also strongly recommended ambulatory BP as the primary measure of response to RDN. Using ambulatory BP monitoring to measure efficacy could exclude pseudo-resistance due to a “white-coat” effect.

There is also one limitation regarding the selection of the control group. Because of the poor acceptability by patients in our routine clinical practice and potential ethical problems, a sham operation will not be performed in this study; its omission might thus be a potential confounder for study outcomes. Although a sham procedure could reduce some Hawthorne effects, it could not eliminate other biases that are considered as reasons for the lack of benefit from RDN.

Ethics and dissemination

This trial will be conducted in accordance with the principles outlined in the Declaration of Helsinki and will follow the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/). It has been approved by the Independent Ethics Committee for each site (Approval No 2016-46). All subjects will be required to sign a written informed consent document before their participation in the trial.

This study is designed to investigate the efficacy and safety of RDN using a 5F saline-irrigated RFA catheter in Chinese patients with hypertension who are resistant to medication therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-irrigated RFA catheter is both safe and effective in Chinese patients with drug-resistant, systemic hypertension. Findings will be shared with participating hospitals, policymakers and the academic community to promote the clinical management of resistant hypertension in China.

Trial status

The study enrolled the first patient in March 2017 and is expected to finish patient enrolment within 1.5 years.

Competing interests

None. All of the authors report receiving no honoraria from the sponsor.

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Contributors

ZJL, LS and JBG conceived and designed the study. ZJL, LS and SZ supervised the power analyses and wrote the data analysis section. ZJL and JBG bear overall responsibility for the design, ethical conduct and publication of the study. Administrative,

technical and material support was provided by ZJL and LS. All authors involved the protocol discussion and they will take responsibility for study data gathering and verification. All authors edited the draft and contributed substantially to the manuscript; they all approved this submission.

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Figure 1: Study flowchart and principles of adjusting antihypertensive medications

Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

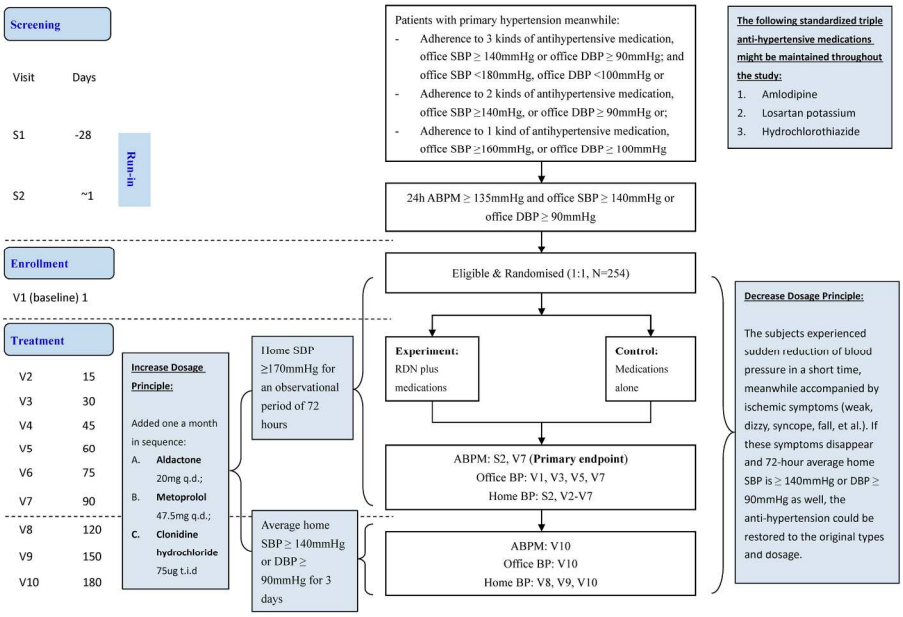

Figure 1: Study flowchart and principles of adjusting antihypertensive medications
Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

209x148mm (300 x 300 DPI)

SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p.21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	ItemNo	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants.	figure 1

Section/item	ItemNo	Description	Addressed on page number
		A schematic diagram is highly recommended (see fig 1[f1])	
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	Figure 1

Section/item	ItemNo	Description	Addressed on page number
		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.18-19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.15

Section/item	ItemNo	Description	Addressed on page number
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.18
Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and	p.20

Section/item	ItemNo	Description	Addressed on page number
policy		other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	resistant hypertension, renal denervation, radiofrequency ablation catheter, ambulatory blood pressure, Chinese patients

Efficacy and Safety of Renal Denervation for Chinese Patients with Resistant Hypertension Using a Micro-irrigated Catheter: Study Design and Protocol for a Prospective Multicenter Randomized Controlled Trial

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Short title: Renal denervation for Chinese patients with resistant hypertension

Abstract:

Introduction: Available data show that approximately 8-18% of patients with primary hypertension will develop resistant hypertension. In recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated its potential safety and efficacy.

Methods and Analysis: This is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated radiofrequency ablation (RFA) used for RDN in the treatment of Chinese patients with resistant hypertension. A total of 254 patients who have failed pharmacological therapy will be enrolled. Eligible subjects will be randomized in a 1:1 ratio to undergo RDN using the RFA plus antihypertensive medication, or to receive treatment with antihypertensive medication alone. The primary outcome measure is the change in 24-hour average ambulatory systolic blood pressure from baseline to 3 months, comparing the RDN-plus-medication group with the medication-alone group. Important secondary endpoints include the change in office blood pressure from baseline to 6 months after randomization. Safety endpoints such as changes in renal function will also be evaluated. The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population.

Ethics and Dissemination: All participants will provide informed consent; the study protocol has been approved by the Independent Ethics Committee for each site. This study is designed to investigate the efficacy and safety of RDN using a 5F saline micro-irrigated RFA. Findings will be shared with participating hospitals, policymakers and the academic community to promote the clinical management of resistant hypertension in China. (Words: 268)

Trial registration: ClinicalTrials.gov ID: NCT02900729

Key words: resistant hypertension, renal denervation, radiofrequency ablation, ambulatory blood pressure, Chinese patients

Abbreviations: RDN, renal denervation; RFA, radiofrequency ablation

Strengths and limitations of this study

- A randomized controlled trial accords in principle with recommendations by European Expert Group;
- Strict standardization of anti-hypertensive medications during the study;
- Enroll Chinese hypertensive patients only, which might affect generability of study findings
- Failure to implement sham procedure as control might introduce Hawthorne effects.

Introduction

Hypertension represents a significant global public health problem, contributing to vascular and renal morbidity, cardiovascular mortality, and economic burden. Although there are many methods for treating primary hypertension, more than half of the patients are still unable to achieve their treatment goal[1, 2].Available data show that approximately 8-18% of patients with primary hypertension present with resistant hypertension[3, 4], defined as a systolic blood pressure (SBP) of 140 mmHg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose[5].Compared with those with controlled blood pressure (BP), patients with resistant hypertension are at greater risk for developing adverse cardiovascular events, leading to an unfavorable prognosis without adequate treatment[6]. Because of the complex pathophysiology of resistant hypertension, however, there are limited strategies available to treat it efficiently.

Following the clinical use of radiofrequency ablation (RFA) catheters in recent years, catheter-based renal denervation (RDN) has emerged as a potential treatment option for resistant hypertension. This technique delivers low-level radiofrequency energy throughout the renal artery wall to disrupt renal nerves and thereby modulate BP to some extent. A number of observational studies and randomized controlled trials among non-Chinese patients have demonstrated both the safety and the potential efficacy of this new therapy[7-15], whereas several other studies failed to show extra benefits when RDN was applied[16-18]. Whenever doubts arise concerning the effectiveness of a therapeutic approach, rigorously designed studies are warranted to furnish conclusive evidence. According to the clinical consensus from the European Expert Group[19], many factors could affect the results of RDN in clinical trials, including procedural aspects, patient populations, and design considerations. Many aspects of the RDN procedure may affect the success of the ablation; furthermore, whether denervation has been completely achieved in a specific patient remains the key factor for the efficacy of RDN.

Together with these key recommendations[19], we present the rationale and methodology for a randomized, controlled trial of RDN using a 5F saline micro-irrigated RFA for the treatment of hypertension in Chinese patients who have failed standardized pharmacologic therapy.

Methods/design

Study design

This trial (ClinicalTrials.gov ID: NCT02900729) is a multicenter, randomized, open-label, parallel-group, active controlled trial that will investigate the efficacy and safety of a 5F saline-irrigated RFA used in RDN for the treatment of Chinese patients with resistant hypertension. The RFA catheter under study is manufactured by Shanghai WiseGain Medical Devices Co., Ltd. Approximately 13 clinical centers will participate in this trial. A brief flow chart of this trial is provided in Figure 1.

Study patients

A total of 254 patients who have failed pharmacological therapy will be enrolled. The following are the inclusion criteria:

1. Subject with primary hypertension has 24-hour ambulatory SBP≥135 mmHg and office SBP ≥140 mmHg /office diastolic blood pressure (DBP) ≥90 mmHg after 4weeks'standardized triple therapy.
2. Subject is ≥18 and <80 years old at the time of randomization.
3. Subject agrees to have all study procedures performed, and is willing to provide written informed consent to participate in this clinical study.

The exclusion criteria are as follows:

1. Subject has acute or serious systemic infection.
2. Subject has a history of renal artery interventional therapy.

3. Subject lacks suitable renal artery anatomy for percutaneous renal sympathetic nerve RFA surgery, including but not limited to the presence of serious aorta or renal-artery tortuosity or renal-artery stenosis.
4. Subject has experienced a myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within three months of the screening period, or has widespread atherosclerosis, with documented intravascular thrombosis.
5. Subject has aortic dissection aneurysm.
6. Subject has primary pulmonary hypertension.
7. Subject has an estimated glomerular filtration rate of less than 40 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease formula.
8. Subject had a definite diagnose of coronary heart disease requiring beta-blockers
9. Subject has Class III-IV heart failure or left ventricular ejection fraction <45%.
10. Subject has atrial fibrillation.
11. Subject has a significant bleeding tendency or blood system disease(s).
12. Subject has a malignancy or end-stage disease(s).
13. Subject has secondary hypertension.
14. Subject has type 1 diabetes mellitus.
15. Subject has other conditions inappropriate for participation, at the investigator's discretion.
16. Subject has a medical ethics issue of concern, at the investigator's discretion, such as presence of an average SBP≥170 mmHg on 24-hour ambulatory BP monitoring after 4weeks'standardized triple therapy.

Recruitment process

Before enrollment, there will be two screening visits. Each participant will be assigned a unique identification number during the first screening visit. In addition to the above-mentioned entry criteria, patients with primary hypertension who meet one of the three following criteria will be considered for further evaluation at the second screening visit:

- Adherence to 3 kinds of antihypertensive medication, office SBP ≥140mmHg or office DBP ≥90mmHg, and office SBP <180mmHg, office DBP <100mmHg.

- Adherence to two kinds of antihypertensive medication, office SBP ≥140 mmHg, or office DBP ≥90mmHg.
- Adherence to one kind of antihypertensive medication, office SBP ≥160mmHg, or office DBP ≥100mmHg.

For any initially eligible patients as mentioned above, three basic kinds of antihypertensive medication, e.g. standardized triple antihypertensive medications consisting of amlodipine 5mg per day, losartan potassium 50mg, and hydrochlorothiazide 12.5mg per day, will be administered for at least 4 weeks (run-in period). Patients who meet the following BP threshold criteria will then be eligible for randomized assignment after the second screening period: 24h ambulatory BP ≥135mmHg and office SBP ≥140mmHg, or office DBP ≥90mmHg.

Randomization process

Eligible patients with resistant hypertension will be randomly assigned to one of two study treatment groups in a 1:1 ratio. A stratified block randomization with randomly varying block size will be performed, stratified according to study site. Random assignment is generated by an independent statistician and implemented via random envelopes assigned to each site. These envelopes are opaque and without any information identifying treatment assignment from appearance. Anyone is prohibited to open an envelope unless there is a real eligible subject requiring randomization. In order to avoid potential selection bias, the sequence is concealed from both clinical staff and patients until assignment. Hence, neither investigators nor participants can influence which group the study patients are assigned to.

Description of the interventions

The enrolled subjects will be randomized to undergo RDN using a 5F saline micro-irrigated RFA plus antihypertensive medication, or to be treated with antihypertensive medication alone. RDN will be performed according to the device's instructions for use.

The study patients will be advised to maintain baseline antihypertensive medication in the first 90 days after randomization. However, the three baseline antihypertensive

medications (e.g. calcium antagonist, angiotensin II receptor antagonist, diuretics) will be adjusted after randomization when clinically necessary. Criterion for dosage reduction: subjects experience a sudden reduction in BP within a short time, meanwhile accompanied by ischemic symptoms (weakness, dizziness, syncope, fall, etc.). If these symptoms disappear and 72-hour average home SBP is ≥140mmHg or DBP ≥90mmHg, the antihypertensive medication may be restored to the original type and dosage. Criterion for dosage increase: if home SBP is ≥170mmHg for an observational period of 72 hours from randomization through 90 days, or from 91 days through 180 days if average home SBP is ≥140mmHg or DBP is ≥90mmHgbased on three consecutive daily measurements, the following three kinds of drugs could be added, one per month in sequence: aldactone 20mg per day, metoprolol succinate sustained-release tablet 47.5mg per day, and clonidine hydrochloride tablets 75ug t.i.d (Figure 1).

For patients receiving antihypertensive medication alone, after maintenance of baseline standardized triple antihypertensive medications for 90 days post randomization and then medically necessary adjustment of antihypertensive medications for another 90 days, subjects will be allowed to cross over to undergo RDN if they still meet the original inclusion criteria for the study.

Renal denervation procedure

Under local anesthesia, RDN procedures are to be performed by interventionists at each study site after a unified training session. Following preoperative preparation, the ablation catheter will be advanced to the distal segment of the renal artery through the 7F guidance catheter.

The ablation involves at least six applications to each renal artery, according to the length of the artery's main stem. If the main renal artery is less than 15 mm, two ablations should be delivered to the main bifurcation with diameter>3mm in order to ensure six ablation lesions on each side. Treatment begins from the distal end of the artery or the main bifurcation in a helical pattern as the catheter is pulled back.

For every renal artery ostium, the catheter must be maneuvered to at least one position in each of the distal, middle and proximal segments. The ablation energy will be 8-10W in

the distal segment, 10-11Win the middle segment and 12Win the proximal segment. Each ablation will last 60s. The ideal target outcome is for the energy titration to achieve a 10% to 20% drop in impedance at each location. If the drop in impedance is less than 5%, or the ablation energy is unable to achieve the preset wattage, the ablation will be stopped and the catheter will be repositioned.

Study visits

Nine study visits will be scheduled following the baseline visit: once every 15 days in the first 90 days and then every 30 days until 180 days. For the 3rd, 5th, 7th, and 10th visits patients will return to the clinic office; for the remaining visits, the patients will be consulted by phone. At every visit, data relating to BP, medication, adverse events, etc., will be collected. The 8-item Morisky Medication Adherence Scale (MMAS-8) will be provided at 1st, 3rd, 5th, 7th, and 10th visits.

The subjects may withdraw from the study if any of the following conditions occur:

- After 4 weeks post randomization, the office or home SBP is ≥180mmHg for more than one week while standardized antihypertensive medications are maintained.
- Based on the investigator's discretion, the subject is no longer eligible for the study for any reason.

Outcome measures

Primary outcome

The primary outcome of this study is the change in 24-hour average ambulatory SBP from baseline to 3 months compared between the RDN-plus-medication group and the medication-only group. The department of laboratory other than the clinical department at each participating site will undertake the ambulatory blood pressure monitoring (ABPM) during the study period. The ABPM machine will record and report ABPM results automatically. This outcome will be strictly standardized in terms of uniform

validated devices, appropriate cuff, identical clinical setting, and resting condition prior to BP measurement after mandatory one-day stay in participating site, etc.

Secondary outcomes

1. Change in office systolic/diastolic BP from baseline to 6 months post-randomization.
2. Incidence of achieving target BP at 6 months post-randomization. Target BP is defined as daytime ambulatory BP<135/85mmHg, nighttime ambulatory BP<120/70mmHg, or average 24-hour ambulatory BP<130/80mmHg.
3. Incidence of substantially adjusting antihypertensive medications at 6 months post-randomization. A substantial adjustment of antihypertensive medications is defined as any change in the number or type of antihypertensive medications, or a ≥50% dose change in the last two weeks with respect to any ongoing antihypertensive medications.
4. Incidence of achieving reductions of≥5 mmHg,≥10 mmHg, ≥15 mmHg, and ≥20 mmHg in BP, including ambulatory, office, and home BP at 6 months post-randomization.

Safety endpoints

The safety endpoints mainly include any adverse events (e.g. puncture hematoma, thrombosis, renal artery stenosis and renal artery dissection as adverse event of special interest, etc), a change in renal function (serum creatinine, urea nitrogen, serum uric acid, creatinine clearance, etc.), other laboratory tests (liver function, serum biochemistry), and cardiovascular complications.

Sample size calculation

We used R V.3.2.3 (R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2014.http://www.R-project.org/: last accessed June 2016) to estimate sample size. The trial is designed to compare the difference in average ambulatory SBP as a change from baseline to 3 months between the RDN-plus-medication group and the medication-alone

group. With a sample size of 108 randomized patients per group, the between-group comparison will be powered at 90% to establish the superiority of added RDN for the primary endpoint at a two-sided significance level of 0.05, assuming that the true SBP difference is 8 mmHg with a common standard deviation of 18 mmHg. Given an expected dropout rate of 15% in the first 3 months post randomization, a total of 254 patients (127 patients per group) must be enrolled in the study.

Results of 10,000 simulations using this estimated sample size for each study showed that an empirical power of 98% would be reached for the analysis of the BP target rate (56% versus 44%) as the important efficacy endpoint, using the Cochran-Mantel-Haenszel (CMH) test with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor.

Statistical analysis

The full analysis set, according to the intent-to-treat principle, will be established as the primary analysis population. A two-sided p-value of<0.05 will be considered to indicate significance for any statistical tests. R, V.3.2.3 and SAS software, V.9.2 (SAS Institute, North Carolina, USA) will be used for statistical analysis. Such data as demographics, baseline characteristics, and safety will be summarized according to treatment group.

The primary efficacy outcomes will be analyzed using analysis of covariance (ANCOVA) with treatment group as fixed factor and BP values at baseline as covariate. The sensitivity analysis with stratifying variable centre as a fixed effect of ANCOVA will also be considered as appropriate. The paired and unpaired t-tests will further be used to test BP reduction within each group and between groups, respectively. The 95% confidence intervals for the differences between treatment groups will also be calculated. Subgroup analyses are prespecified according to the following prognostic factors: sex, age, diabetes, body mass index, estimated glomerular filtration rate, and aldosterone use at baseline.

Blood pressure target rate at 6 months will be analyzed using the CMH test, with antihypertensive medication adjusted or not within the last 2 weeks as stratification factor. Other categorical data will be tested using Pearson's chi-square test or Fisher's exact test, as appropriate. Other continuous efficacy endpoints will be analyzed similarly to the

primary endpoint. Mixed-model repeated measures analysis including terms for treatment group, time, baseline measurement, and time by treatment group interaction will be considered to compare BP reduction in the study.

Discussion

The design and methods of this trial satisfy the requirements to test whether a 5F saline micro-irrigated RFA used in RDN is safe and effective for patients who remain hypertensive despite adherence to polypharmacy.

With the recognition of the role of the sympathetic nervous system in the development and progression of hypertension[20, 21], catheter-based RDN has been developed to reduce sympathetic nervous activity and subsequently reduce BP, as well as mortality and morbidity, in patients with uncontrolled hypertension[22-25] and the prevention of recurrences of atrial fibrillation[26], the improvement of glycemic control[27] and the mitigation of pulmonary arterial hypertension as well[28]. However, the clinical evidence in support of RDN as an effective interventional technique in patients with resistant hypertension appears conflicting. Several large studies support both the safety and the efficacy of this new therapy[7-15], but some studies failed to show the superiority resulting from added RDN[16-18]. In view of this controversy, the European Expert Group convened a clinical consensus conference and agreed on recommendations for future randomized controlled trials of RDN in hypertension. The design and methods of our trial accord in principle with the recommendations.

The RDN procedure is so complex that the efficacy of ablation may be influenced by many factors, such as renal artery anatomy, the depth of the ablation lesion, atherosclerosis, etc. Achieving complete ablation will pose a challenge to the operator, the equipment, and the procedure. A study of the anatomic assessment of sympathetic peri-arterial renal nerves showed that the greatest number of nerves were observed in the proximal and middle segments of the renal artery, while the smallest number were seen in the distal segment. However, in the main renal artery, the distance from the nerve to the renal artery lumen is shorter than in the proximal and middle segments, being

approximately4.28mm[29].Another study showed that, for a patient with atherosclerosis, the RFA-induced damage did not penetrate deeper than 2mm from the luminal surface, leaving unaffected a large part of the nerves in (peri-) adventitial areas remote from the vascular lumen[30]. An animal study showed that the ablation zone geometries varied in arc, area, and depth, depending on the composition of the adjacent tissue substructure[31]. In addition, the delivered power density was influenced by tissue substructure, and peaked at the conductivity discontinuities between soft fatty adventitia and water-rich tissues, not at the electrode-tissue interface[31]. With a greater recognition of nerve distribution, the ablation depth and location should be taken carefully into account.

In previous studies, a non-irrigated catheter was usually used and the ablation energy was usually 8W. Increasing ablation energy or prolonging ablation time could make the ablation deeper. However, using a non-irrigated catheter could raise the temperature of the luminal surface too much to increase the ablation power. In this study, radiofrequency energy delivery with the use of cold saline irrigation seems safe and effective. By actively cooling the ablation electrode during RFA, it is possible to minimize the possibility of char formation and also decrease the probability of vasospasm. These advantages to saline irrigation are so significant that most cardiac ablations are now performed using irrigated ablation catheters[32]. Ahmed et al., in a small single-arm study, demonstrated that RND can be performed safely and effectively using a saline-irrigated RFA in patients with hypertension[33]. Using a saline-irrigated catheter, with the protection of cold saline, higher ablation energy can be delivered, ensuring the ablation depth. Indeed, the saline-irrigated catheter has been widely used in cardiac ablation.

In most clinical trials involving RDN, adrenal artery less than 4mm in diameter could not be ablated because of the limited operation equipment. In this study, the 5F saline micro-irrigated RFA catheter is smaller and more flexible, so it can be used in renal arteries with diameter <4mm, while minimizing the possibility of peripheral artery-related complications.

In this study, the operation procedure will also be unified. A similar spiral ablation will be used and at least one site must be ablated at each of the distal segments of the renal artery, the middle segment, proximal, and opening. Four quadrants will be ablated. There

are a total of 6 ablation points on each side of the renal artery. The ablation energy will also be standardized to ensure sufficient ablation.

In this trial, patients with 24-hour ambulatory SBP ≥135mmHg and office SBP <170mmHg will be eligible for enrollment, while patients with high-risk characteristics will be excluded. Given this restriction, the patients enrolled in this study will mostly have mild to moderate hypertension and might be more responsive to RDN-induced changes in sympathetic tone. In addition, it will be safer for these patients to strictly follow a standardized medication regimen. Moreover, higher drug adherence will be expected in this study, because of the lower level of discomfort occurring in the management of mild to moderate rather than severe hypertension.

In the study period, the antihypertensive medications administered are explicitly specified: standardized triple antihypertensive medications include a calcium channel blocker, a renin-angiotensin system blocker, and a diuretic. In the Symplicity HTN-3 study[16], the maximum doses were administered, and 39% patients required medication adjustment because of adverse events; this may be related to the negative conclusions of that study. Conversely, in the DENERHTN study[15], the antihypertensive medications in the RDN group and control group were strictly regulated, and the study results supported the superiority of RDN. The rigorous specification of medication may be an important factor influencing the study results.

For this study, ambulatory BP is used as the primary endpoint, and office BP as the secondary parameter. In fact, several previous studies have documented a better prognostic value of ambulatory over office BP in different populations[34-38].Among the previous trials conducted on RDN, only the DENERHTN study[15] successfully used the change in mean daytime ambulatory SBP as primary endpoint, and that study found RDN to have superior efficacy. The Expert Group also strongly recommended ambulatory BP as the primary measure of response to RDN. Using ambulatory BP monitoring to measure efficacy could exclude pseudo-resistance due to a “white-coat” effect.

There is also one limitation regarding the selection of the control group. Because of the poor acceptability by patients in our routine clinical practice and potential ethical

problems, a sham operation will not be performed in this study; its omission might thus be a potential confounder for study outcomes. Although a sham procedure could reduce some Hawthorne effects, it could not eliminate other biases that are considered as reasons for the lack of benefit from RDN.

Ethics and dissemination

This trial will be conducted in accordance with the principles outlined in the Declaration of Helsinki and will follow the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/). It has been approved by the Independent Ethics Committee for each site (Approval No 2016-46). All subjects will be required to sign a written informed consent document before their participation in the trial.

This study is designed to investigate the efficacy and safety of RDN using a 5F saline-irrigated RFA in Chinese patients with hypertension who are resistant to medication therapy. Its goal is to provide clinical evidence that RDN with a 5F saline-irrigated RFA is both safe and effective in Chinese patients with drug-resistant, systemic hypertension. Findings will be shared with participating hospitals, policymakers and the academic community to promote the clinical management of resistant hypertension in China.

Trial status

The study enrolled the first patient in March 2017 and is expected to finish patient enrolment within 1.5 years.

Competing interests

None. All of the authors report receiving no honoraria from the sponsor.

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Contributors

ZJL, LS and JBG conceived and designed the study. ZJL, LS and SZ supervised the power analyses and wrote the data analysis section. ZJL and JBG bear overall responsibility for the design, ethical conduct and publication of the study. Administrative, technical and material support was provided by ZJL and LS. All authors involved the protocol discussion and they will take responsibility for study data gathering and verification. All authors edited the draft and contributed substantially to the manuscript; they all approved this submission.

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Figure 1: Study flowchart and principles of adjusting antihypertensive medications

Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

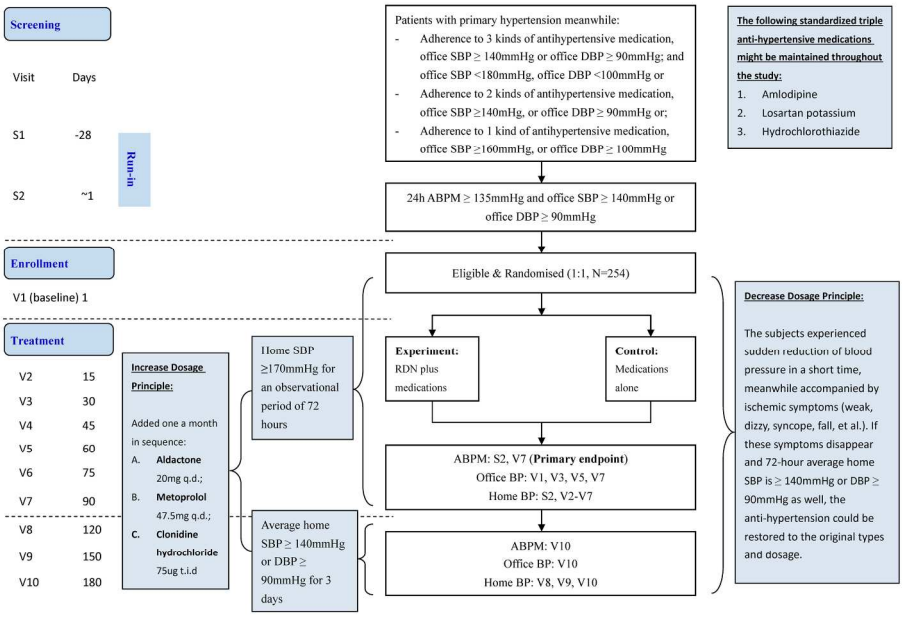

Figure 1: Study flowchart and principles of adjusting antihypertensive medications
Abbreviations: ABPM: Ambulatory Blood Pressure Monitoring; BP: Blood Pressure; DBP: Diastolic Blood Pressure; RDN: Renal Denervation; SBP: Systolic Blood Pressure

209x148mm (300 x 300 DPI)

SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p.3
	2b	All items from the World Health Organization Trial Registration Data Set	n.a.
Protocol version	3	Date and version identifier	n.a.
Funding	4	Sources and types of financial, material, and other support	p.16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p.1, 2, 16
	5b	Name and contact information for the trial sponsor	p.1, 2, 16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p.21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p.21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p.5, 6
	6b	Explanation for choice of comparators	p.5, 6

Section/item	ItemNo	Description	Addressed on page number
Objectives	7	Specific objectives or hypotheses	p.6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p.6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p.6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p.6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p.8,9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p. 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p.8, 9, 10, figure 1
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p.8, 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p.10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants.	figure 1

Section/item	ItemNo	Description	Addressed on page number
		A schematic diagram is highly recommended (see fig 1[f1])	
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p.11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n. a.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p.8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p.8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p.8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how	p.8
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial	p.8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	Figure 1

Section/item	ItemNo	Description	Addressed on page number
		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p.18-19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n.a.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p.12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p.12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p.12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n.a.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p.15

Section/item	ItemNo	Description	Addressed on page number
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n.a.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p.6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n.a.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p.20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p.20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p.16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p.20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	p.18
Dissemination	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and	p.20

Section/item	ItemNo	Description	Addressed on page number
policy		other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	p.16
	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n.a.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.