

Huatan Dingji Decoction Intervening in Atrial Fibrillation : Protocol for a Randomized Double-Blind Single-Simulated Placebo-Controlled Clinical Trial

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Study protocol

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Abstract

Background: Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and can lead to heart failure(HF), stroke, pulmonary embolism(PE) and other complications, seriously affecting people's quality of life and health. Western medicine is limited in the treatment of AF, while Traditional Chinese Medicine(TCM) has unique advantages, such as low side effects, low toxicity, long effect duration and high compliance. Huatan Dingji Decoction(HTDJ) is commonly used in the treatment of AF in our hospital, and its clinical efficacy is confirmed, but a comprehensive evaluation of the clinical efficacy is currently lacking.

Method: This study adopts a randomized double-blind, single-simulated, placebo-controlled research method. Participants were randomly assigned in a 1:1 ratio through a centrally controlled, computer-generated, simple randomization schedule. Participants would take the medicine for one month and the curative effect would be evaluated. Subsequently, the participants would not take TCM and only receive western medicine treatment. They would be followed up for another 8 weeks, and a clinical evaluation would be conducted. The evaluation includes the frequency of palpitation, cumulative attack time, increase and decrease rate of western medicine, TCM symptoms, clinical quality of life, clinical endpoint events and safety. Cases are derived from outpatient and inpatient with AF in the Cardiology Department of Longhua Hospital. Evaluations would be conducted at baseline and at week 4 and 12 after randomization.

Discussion: In this study, the efficacy and safety of HTDJ plus western medicine in the treatment of AF (palpitation of Qi deficiency-caused phlegm stagnation) were evaluated, so as to provide medicine evidence of short-term and medium-term clinical efficacy for the treatment of AF with integrated traditional and western medicine, and lay a foundation for further clinical development and application.

Trial registration: The trial has been registered on March 5, 2020 at Chinese Clinical Trial Registry (www.chictr.org.cn; ID: ChiCTR2000030517).

Trial registration: This study was registered on May 15, 2019 at ClinicalTrials.gov with the identifier number NCT03952676.

Introduction:

AF refers to supraventricular tachyarrhythmia characterized by rapid, disorganized atrial electrical activity and is one of the most common cardiac arrhythmias today. It is estimated that approximately 2% of the total global population suffers from AF, and its prevalence is increasing annually. The incidence rate is expected to increase 5 times in the next 40 years [1]. AF can exacerbate HF, increase the risk of ischemic stroke and malignant arrhythmic events. Meanwhile, with the change of age, cardiac structure and function and the increase of incidence of a variety of basic diseases and bad living habits, AF will lead to the increase of hospitalization days, medical expenses and overall mortality [2].

The current western medical treatments for AF are drug therapy, Percutaneous Left Atrial Appendage Closure(LAAC) and Radiofrequency Ablation(RF). Drug therapy includes reversal of sinus rhythm and ventricular rate control. And it needs to be combined with anticoagulation therapy. However, in the course of pharmacological treatment of AF, the majority of the causes of AF cannot be removed. And the electrical and anatomical reconstructions caused by AF itself make it difficult to revert and maintain sinus rhythm. Therefore, ventricular rate control has become a choice of clinical treatment[3]. LAAC prevents the formation of thrombus during AF by blocking the left atrium, thereby reducing the risk of long-term disability or death from thromboembolism in patients with AF. RF is now the most effective method for the eradication of paroxysmal tachycardia. RF has been clinically successful in immediately restoring sinus rhythm in more than 70% of patients with paroxysmal AF, but the long-term success rate is low. And the means to treat persistent or permanent AF are limited and the effect is poor[4-5]. In recent years, through a large number of clinical studies, it has been found that TCM has unique advantages in the treatment of AF, such as low side effects, low toxicity, long effect duration and high compliance, which has played a positive role and is widely used in clinical practice.

According to the clinical symptoms and signs, AF corresponds to “palpitation” in TCM. Since Inner Canon of the Yellow Emperor, doctors of all generations have discussed palpitation. Many prescriptions and medicines have been recorded and can be used to treat palpitation, such as Zhigancao Decoction, Erchen Decoction, Taoren Honghua Decoction, etc. Modern medicine has found TCM to be effective in reducing ventricular rate, increasing the diversion rate, and improving cardiac function and its clinical symptoms. Professor Lin Zhongxiang, a famous TCM doctor in Shanghai, has been engaged in various cardiovascular diseases including AF for a long time, and has accumulated rich clinical experience. “Huatan Dingji Decoction” is the prescription for AF (palpitation of Qi deficiency-caused phlegm stagnation) established by Professor Lin Zhongxiang in combination with his long-term clinical treatment experience. It is composed of Pinellia ternata, Chen Pei, Astragalus membranaceus, Atractylodes macrocephala, Poria cocos, Coptis chinensis, Cinnamon, Keel, Oyster, Sophora flavescens, Artemisia annua, Radix Po lygala, Ophiopogon, Xianling spleen, Peony skin, Jujube. HTDJ is effective in treating palpitation and has been taken by lots of patients for a long period of time, but is limited to individual clinical cases and lacking in related evidence. Therefore, this study aims to evaluate the efficacy and safety of HTDJ plus western medicine in the treatment of AF, provide medicine evidence of short-term and medium-term clinical efficacy for the treatment of AF with integrated traditional and western medicine on the basis of TCM syndrome differentiation and lay the foundation for further clinical development and application.

Methods/design

Study objectives

The purpose of the experiment is to evaluate the efficacy and safety of HTDJ plus western medicine in the treatment of AF, provide medicine evidence of short-term and medium-term clinical efficacy for the

treatment of AF with integrated traditional and western medicine on the basis of TCM syndrome differentiation and lay the foundation for further clinical development and application.

Study design and settings

The study will be conducted in the Department of Cardiology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, to achieve the goal of 76 participants with AF (palpitation of Qi deficiency-caused phlegm stagnation) in total. Each participant can only be grouped once. The study will include five phases: screening/enrollment, allocation, treatment/intervention, end of intervention, and follow-up. During enrollment, all participants will undergo physical examination and assessment of eligibility in the cardiology clinics and wards before being recruited. The maximum time allowed between the assessment and the intervention is 1 week (week 0). If more than a week has passed since the assessment, the participant will have to undergo repeat assessment before being allowed to start the intervention. Eligible participants will be invited to sign the written informed consent regarding participation in the trial (procedures, risks, options for dropping out), regarding the use of laboratory data, and regarding the collection, storage, and use of biological specimens. A study investigator or medical staff member that has received adequate training will provide the participant with extensive explanations. Upon agreeing to provide consent, the participant will be invited to sign and date the informed consent form, at which time a participant identification (PID) number will be assigned to facilitate PID throughout the study.

The participants will be randomly assigned to the experimental or control group and undergo the corresponding intervention for a total of two treatment cycles. Participants in the experimental group will receive HTDJ, whereas those in the control group will receive placebo granules. The participants will continue to receive systemic therapy, as judged by their treating physician. All changes in symptoms, prescriptions, relevant scores, and macroscopic characteristics (based on photographic evidence), along with any adverse events (AEs), will be recorded. The experimental design is shown in Figure 1.

Diagnostic criteria

The diagnosis of atrial fibrillation can be confirmed based on clinical manifestations, physical examination and electrocardiographic characteristics as follows: (1) Clinical manifestations: palpitation, chest tightness, decreased exercise tolerance. (2) Physical

examination: heart auscultation varies in heart rate, heart sounds vary in strength,

rhythm is absolutely irregular, and pulse is short. (3) Electrocardiogram: P wave disappear, the f wave replaces it, the frequency is about 350-600 times, and the QRS complex rhythm is absolutely irregular.

Inclusion Criteria

The inclusion criteria are as follows: (1) Patient's age is 18–85 years. (2) Paroxysmal atrial fibrillation, seizure frequency ≥ 2 times a month or persistent atrial fibrillation (at least one ECG diagnosis). (3) The main syndrome of TCM syndrome differentiation was Qi deficiency-caused phlegm stagnation. (4) Have

a correct understanding of the significance of the study, have good compliance with the observation and evaluation of the researcher, voluntarily accept the clinical trial and fill in the clinical consent form.

Exclusion Criteria

The exclusion criteria are as follows: (1) Patients with primary diseases such as severe lung, liver, renal insufficiency and hematopoietic system or severe cardiac dysfunction (NYHA IV grade). (2) Atrial fibrillation caused by obvious incentives such as fatigue, mental stress, mood swings, drug poisoning, and electrolyte disturbance. (3) Mental illness and poor control of the condition. (4) Patients whose heart rate is less than 50 beats per minute (such as sick sinus syndrome, atrioventricular or intraventricular block, etc., who intend to install a pacemaker). (5) Pregnant or lactating women. (6) Cachexia in the terminal stage of malignant tumor. (7) For various reasons, the efficacy cannot be determined or the data is incomplete.

Termination of test cases

Patients who are enrolling but have not completed clinical observations: (1) In case of serious adverse events, the clinical experimenter should be stopped according to the doctor's judgment. (2) If the disease worsens in the course of the disease, or there are other conditions affecting the observation of the study, the clinical experimenter should be stopped and invalid cases should be treated according to the doctor's judgment. (3) Important deviations occurred in the implementation of clinical trial protocols, such as poor compliance, making it difficult to evaluate drug effects. (4) The subject is unwilling to continue the clinical trial during the clinical trial, and proposes to the doctor in charge to withdraw from the clinical trial.

Suspension criteria

The trial will be suspended in case of the following: (1) Those who have not used research drugs or combined with other Traditional Chinese medicines or proprietary Chinese medicines. (2) Misdiagnosis. (3) Those without any test records.

Case drop and treatment

The enrolled cases with incomplete clinical protocols due to the following reasons shall be deemed as shedding, with the shedding rate not exceeding 20%: (1) Patients withdraw spontaneously (unsatisfactory efficacy, adverse reactions, etc.). (2) Loss of follow-up. (3) The researcher ordered to withdraw (did not take medicine as prescribed; Severe comorbidities and complications occur; Serious adverse events).

For abscission cases, the reasons for abscission shall be recorded in detail. If there is a review, the results of the last major efficacy test shall be taken as the final results for statistical analysis, and the CRF table shall be kept for future reference.

Interventions

This subject adopts randomized, double-blind, single-simulated, placebo-controlled research method. 72 cases with AF (palpitation of Qi deficiency-caused phlegm stagnation) were randomly divided into two groups according to the 1:1 distribution principle. The first group was treated with HTDJ plus western medicine. The second group was treated with placebo granules plus western medicine. Western medicine includes cardioversion drugs and heart rate control drugs, as well as myocardial energy metabolism drugs, must be in keeping with "the 2015 Atrial Fibrillation: Current Understanding and Treatment Recommendations". The HTDJ and placebo were produced and packed in a single batch (production batch number: HTDJ: 1070649; Placebo: 1070649) by Shanghai Wan Shicheng Pharmaceutical Co., Ltd, which has no conflicts of interest relevant to this study. The test results of drug quality were consistent with the Chinese Medicine Standards of the State Food and Drug Administration. The placebo is composed of 10% crude HTDJ and 90% starch, which have the same appearance and scent as the active treatment drugs. Participants will take one bag twice a day for 4 weeks, while avoiding oral administration of other traditional Chinese medicine for efficacy evaluation. Then do not accept traditional Chinese medicine, only western medicine treatment, followed up for 8 weeks, another clinical evaluation.

Outcomes

1. General information: gender, age, weight, heart rate, heart rhythm, blood pressure, etc.
2. Clinical symptoms: The number and duration of atrial fibrillation episodes were recorded using a scoring method before and after treatment.
3. TCM syndromes: The changes in heart palpitations, shortness of breath, fatigue, coughing, spitting, salivation, body condition, tongue condition, and pulse condition were recorded before and after treatment.
4. The weekly cumulative number and duration of palpitations.
5. Electrocardiogram: trace the changes of resting ECG before and after treatment.
6. Holter ECG: Use Holter ECG to record the dynamic changes of the patient's cardiac electrical activity, record the number of ectopic beats, and evaluate the patient's arrhythmia.
7. Cardiac ultrasound: Ejection fraction (EF), stroke volume (SV), left ventricular end diastolic diameter (LVEDD), etc. before and after treatment in each group were detected by echocardiography.
8. Heart function: proBNP
9. The rate of increase or decrease of western medicines to transfer to the law and to control the room law.
10. Evaluation of Hamilton Anxiety and Depression Scale. The Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) are used to evaluate the emotional state of patients. HAMA is mainly

used to assess the severity of the patient's anxiety symptoms, and is generally considered to be greater than 14 points Meaningful. HAMD is currently one of the most commonly used clinical scales to assess depression, and 20 points or more are considered meaningful.

11.SF-36 EVALUATION

Use the MOS item short from health survey (SF-36) to assess changes in the quality of life of patients.

12. Safety indicators: detect changes in blood routine, urine routine, liver and kidney function before and after treatment.

During the experiment, closely observe any adverse reactions/events that may occur and record them in detail and truthfully.

Observation records of adverse events

During the trial period, the adverse event record form should be filled in truthfully. The occurrence, severity, duration, measures taken and outcome of the adverse event should be recorded. Adverse events should be recorded in the designated clinical case observation form (CRF) adverse event form. The person uses mild, moderate, and severe to describe the intensity of the adverse event, and evaluates the possible association between the adverse event and the study drug and combination drug to determine whether it is an adverse reaction.

Research process record points

The subject content and data at each time point, according to the patient's hospitalization period, will be recorded as shown in Table.1. Specifically, the screening period (-3~0 days) will be 0 to 3 days before recruitment. The 4-week treatment period was planned in two cycles of 2 weeks, with a return visit between cycles to check for AEs and monitor compliance. All interventions will be stopped after 4 weeks. Follow-up will be conducted on weeks 4 and 12.

Sample size

In order to study the efficacy and safety of HTDJ in the treatment of atrial fibrillation, we collected cases from outpatient and inpatient atrial fibrillation in Longhua

Table 1 Research flowchart

Activity	Phase(time points)	Screening stage	baseline period	intervention	Follow-up	
		-3d~0d	0d	4w	8w	12w
enrolment	Sign informed Consent	✓				
	Inclusion and exclusion criteria	✓				
	Demographic data	✓				
	Medical history and treatment history	✓				
	Basic data collection	✓				
Outcome assessment	TCM clinical syndrome integral		✓	✓	✓	✓
	ECG and Hotler		✓	✓		
	ultrasonic cardiogram		✓	✓		
	Palpitations index		✓	✓	✓	✓
	Rate of increase and decrease of anti-arrhythmia western medicine		✓	✓	✓	✓
	NT-proBNP		✓	✓		
	Hamilton Anxiety Scale		✓	✓	✓	✓
	Hamilton Depression Scale		✓	✓	✓	✓
	SF-36		✓	✓	✓	✓
	PVO		✓	✓		
Safty assessment	Anaerobic threshold		✓	✓		
	physical examination		✓	✓		
	blood routine examination		✓	✓		
	Urine routine and urinary sediment		✓	✓		
	Liver function		✓	✓		
	renal function		✓	✓		
	blood lipid		✓	✓		
	GLU		✓	✓		
	INR		✓	✓		
	CHA2DS2-VAS		✓	✓		
	HAS-BCED		✓	✓		
	Other information	randomization	✓			
hemorrhage			✓	✓	✓	✓
readmission			✓	✓	✓	✓

Hospital, 30 cases in the test group and 30 cases in the control group, a total of two groups, considering 20% clinical shedding rate, a total of 76 patients are planned to be included.

Randomization

This study uses a center-based stratification and block randomization method. The randomization sequence will be generated by study investigators who are statisticians. Patients will be allocated in a 1:1 ratio, aiming to balance baseline characteristics between the groups. Participants will be assigned a PID number, which will be used for subject identification throughout the study. Information regarding the random-number block will be delivered to the participating centers along with the intervention drugs.

Double-blind

The study is designed as a double-blind investigation. The participants, study monitors, and study investigators will be blinded throughout the duration of the study. The PID will be the only information linked to group allocation. Random codes will be maintained by Cui Xuejun, associate researcher, and director of the Office of National Traditional Chinese Medicine Clinical Research Base of Longhua Hospital to ensure concealment.

Statistical analysis

All data are entered using excel worksheets, and SPSS22.0 statistical software is used for statistical analysis. For measurement data, t-tests are performed for those that conform to the normal distribution,

and the data are represented by the mean \pm standard deviation; the row-rank conversion that does not conform to the normal distribution For non-parametric test, the data are represented by M (QR). The constituent ratio data uses the χ^2 test. The one-way ordered data uses the rank sum test. $P > 0.05$ is not statistically significant, $P < 0.05$ is statistically significant, two-sided test .

Data management and monitoring

In this study, the CRF will be filled out by the researchers in a timely manner, and by a third party is responsible for checking and checking, patient data confidentiality and

through the ethics committee, the ethics committee reviews drug clinical trial scheme

is scientific and ethical rationality, audit and supervision of drug clinical trials researchers qualification, supervision of drugs in clinical trials, ensure the independent, objective, fair and ethical review process.

Discussion

AF is the most common arrhythmia disease, with palpitate, chest tightness, shortness of breath, dizziness, amaurosis and weakness as the main clinical symptoms, which has serious complications and seriously affects people's quality of life and health[6]. AF is currently treated by western medicine, mainly through drugs and surgery, but anti-arrhythmic drugs have significant toxic side effects. RF is unstable and easy to relapse. People are now paying more attention to its treatment defects. The deficiency and risk of drug and surgical treatment are emerging and the advantages of TCM in the treatment of AF are gradually prominent. In recent years, through a large number of clinical studies, it has been found that TCM to be effective in reducing ventricular rate, increasing the diversion rate, and improving cardiac function and its clinical symptoms[7-10].

At present, Wenxin Granule and Shensong Yangxin Capsule are mainly aimed at patients with Qi and Yin Deficiency and Blood Stasis, while "deficiency" and "phlegm" are important pathogenesis for AF. Due to the characteristics of aging population and diet structure, patients with TCM pathogenesis ("deficiency" and "phlegm") account for a certain proportion. Currently, western medicine and surgery for patients with AF cannot fundamentally change the trend of atrial fibrosis and body degeneration. Patients need to be maintained on drugs for a long period of time and the relapse rate is high. Long term use of amiodarone, sotalol and other western medicine has certain side effects and limitations. Therefore, this kind of treatment can not solve the practical problems of many patients, and it is in urgent need of better treatment.

Based on Shanghai's famous TCM practitioner, Lin Zhongxiang's studio, combined with the literature and long-term clinical treatment summary, HTDJ is designed from the pathogenesis of AF (palpitation of Qi deficiency-caused phlegm stagnation). In this prescription, Huanglian Wendan Decoction can clear away heat and dampness and treat disturbance of the gastric qi. Pinellia ternata and Pericarpium Citri Reticulatae are used to regulate qi-flowing for removing the phlegm; Poria cocos can fortify the spleen

and percolate dampness. *Coptis chinensis* can purge intense heat and detoxicate; Chinese date can benefit spleen and stomach. LiuJunZi Decoction can replenish qi to invigorate the spleen and remove the phlegm. On the basis of Sijunzi Decoction, increasing the dosage of *Atractylodes macrocephala* can improve the effect of drying dampness and resolving phlegm. *Coptis chinensis*, cinnamon and Jiaotai Pill can coordinate the heart and the kidney. On this basis, adding fossilized concha ostreae can quiet the spirit by heavy settling. *Astragalus membranaceus* can tonify middle-Jiao and Qi, while dwarf lilyturf tuber can nourish yin and promote the secretion of saliva. *Herba Epimedii* can mildly reinforce the kidney yang and light yellow sophora root can clear away heat and dampness. The prescription can replenish qi to invigorate the spleen and remove the phlegm, nourish the heart and quiet the spirit, coordinate the heart and the kidney and balance yin and yang.

Clinical and pharmacological studies have shown that Jiaotai Pill has therapeutic and anti-arrhythmic effects on AF [11,12]. *Pinellia ternata* and its processed products are also anti-arrhythmic [13], and *Pericarpium Citri Reticulatae* has vasodilatory effects that help to induce an increase in coronary flow, which may have the effect of lowering blood pressure and slowing the heart rate [14]. The effects of *Coptis chinensis* include blood pressure lowering, antibiosis, anti-inflammatory, anti-tumor, regulating blood lipid, anti-arrhythmia, etc [15]. Icariin can effectively avoid the damage of myocardial cells and vascular endothelium caused by adverse factors. In addition to inhibiting apoptosis in cardiac myocytes, icariin can also effectively regulate blood lipid and protect the cardiovascular system [16]. In addition, Huanglian Wendan Decoction has a certain therapeutic effect on coronary heart disease with rapid AF [17]. Matrine has antiarrhythmic and electrophysiological effects [18]. *Artemisia apiacea* is the main drug for clinical treatment of arrhythmia [19] and arteannuin has electrophysiological characteristics of antiarrhythmia [20].

HTDJ is effective in treating palpitations, but is lacking in related research evidence. Therefore, this study aims to evaluate the efficacy and safety of "Huatan Dingji Prescription" plus western medicine in the treatment of AF, in order to provide preliminary data for the treatment of patients with AF. It can further provide evidence for the clinical application of TCM in the treatment of AF.

Trial status

The trial has been registered on Chinese Clinical Trial Registry (ID:ChiCTR2000030517). At the time of writing the trial protocol (version 1.0, May 24, 2019), the trial has not yet started registration. The start and end of recruitment are planned on July 1, 2019 and June 31, 2022, respectively.

Abbreviations

AF: Atrial fibrillation; HTDJ: Huatan Dingji Decoction; TCM: Traditional Chinese Medicine; HF: heart failure; PE: stroke, pulmonary embolism; LAAC: Left atrial appendage Closure; RF: Radiofrequency ablation; PID: Participant identification; AEs: Adverse events; EF: Ejection fraction; SV: Stroke volume; LVEDD: Left ventricular end diastolic diameter; HAMA: Hamilton anxiety scale and; HAMD: Hamilton depression scale; CRF: Case observation form.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

(I) Project design and implementation: TN and WQ. (II) Project supervision and management coordination: DB. (III) Traditional Chinese medicine prescription design, case collection: SL. (IV) Participation in project design, data statistics and case collection: WYH. (V) Case collection : ZN, ZS, ZP, ZC and MMJ. (VI) Case collection and statistics: XY, MZL, WXY. (VII) Manuscript writing: XY. (VIII) Final approval of manuscript: All authors.

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Availability of data and materials

We declare that the materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes without breaching participant confidentiality.

Ethics approval and consent to participate

Ethical approval has been obtained from the Ethics Committee of the Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (approval no.19401970900). All participants will sign an informed consent before being enrolled in this study. No clinical data or bio-samples will be collected without the participants' consent. The study is conducted in accordance with national laws, Good Clinical Practice guidelines, and the Declaration of Helsinki as revised in 2013. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Hu SC, Gao RL, Liu LS, et al. " Chinese cardiovascular disease report 2018" profile. *China Circulation Journal*.2019,34(03):209–220.
2. January CT, Wann LS, Alpert J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology /American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1–76.
3. Yu XT. Research progress of traditional Chinese and western medicine in atrial fibrillation. *Journal of integrated traditional Chinese and western medicine*.2015,13(16):1847–1849.
4. Sorgente A, Tung P, Wylie J, et al. Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. *Am J Cardiol*. 2012;109(8):1179–86.
5. Tilz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. *J Am Coll Cardiol*,201276(6): 1921–1929.
6. Zhang R, Wei LB. Advances in Clinical Research of Traditional Chinese Medicine in the Treatment of Atrial Fibrillation. *Journal of Cardiovascular and Cerebrovascular Diseases*,2019,17(19):2962–2964.
7. Cai YP, Wang FY. Clinical effect and safety of wenxin granule combined with amiodarone and perindopril in the treatment of paroxysmal atrial fibrillation in the elderly. *hebei pharmaceutical*.201739(6): 847–853.
8. Du H, Dai HX. Meta-analysis on efficacy and safety of wenxin granules in the treatment of atrial fibrillation. *Journal of anhui university of Chinese medicine*. 2014;33(6):27–30.
9. Zhang JF, Wei C, Wang HT, et al. Research progress of integrated regulation of arrhythmia by shensong yangxin capsule. *Chinese journal of basic medicine of traditional Chinese medicine*. 2016;22(1):144–6.
10. Jia ZH. Characteristics of Integrated regulation of Shensong Yangxin Capsule for arrhythmia. *Chinese Community Physicians*.2011(2):10.
11. He YT, Bian KT, Yuan FR, et al. The treatment of 68 cases of rapid heart arrhythmia with Jiatai pill plus admixture. *Zhejiang journal of Chinese medicine*.1992,27(9):386.

12. Wang YX,Zou ZN,liu HH,et al.Effect of jiatai pill extract powder on cell membrane potential of guinea pig ventricular myometrium. Chinese journal of experimental formulae.2010,16(8):157–160.
13. Zhang MF,Shen YQ.Pharmacological effects of pinellia ternata and its processed products on the nervous and circulatory system.Anti-infective pharmacology.2017,14(09):1643–1648.
14. Li WX. Pharmacological analysis and clinical Application of Orange peel.Medical Theory and Practice.2012,31(10):1521–1522 + 1555.
15. Gai XH, Liu SX, Ren T,LIU, Yi,et al. Advances in chemical constituents and pharmacological effects of *Coptis chinensis*. Chinese Herbal Medicine. 2008;49(20):4919–27.
16. Lu MJ. Zhao YQ,Zhang BL.Clinical study of traditional Chinese medicine in the treatment of rapid atrial fibrillation of coronary heart disease. China medical guide. 2009;12(1):67–8.
17. Shi YP, Chen T, Li Det al. Wang Qiong.Advances in the pharmacological action of oxymatrine. Shaanxi Medical Journal. 2008;47(2):271–3.
18. Ding SW. Jiao HC.clinical study of qingshan jianxin tablet against premature cardiac beat. Chinese journal of traditional Chinese medicine. 2008;7(26):1365–7.
19. Li BX,Yang BF,li YR,et al.Anti-arrhythmia effect and mechanism of artemisinin.Chinese pharmacology bulletin.1999,15(5):449–452.
20. Xu JR, He Y, Shen L,et al. Experimental Study on Antiarrhythmic Antiarrhythmic Effect of FuLvning. GranulesJiangxi Traditional Chinese Medicine. 2014;45(11):18–20.

Figures

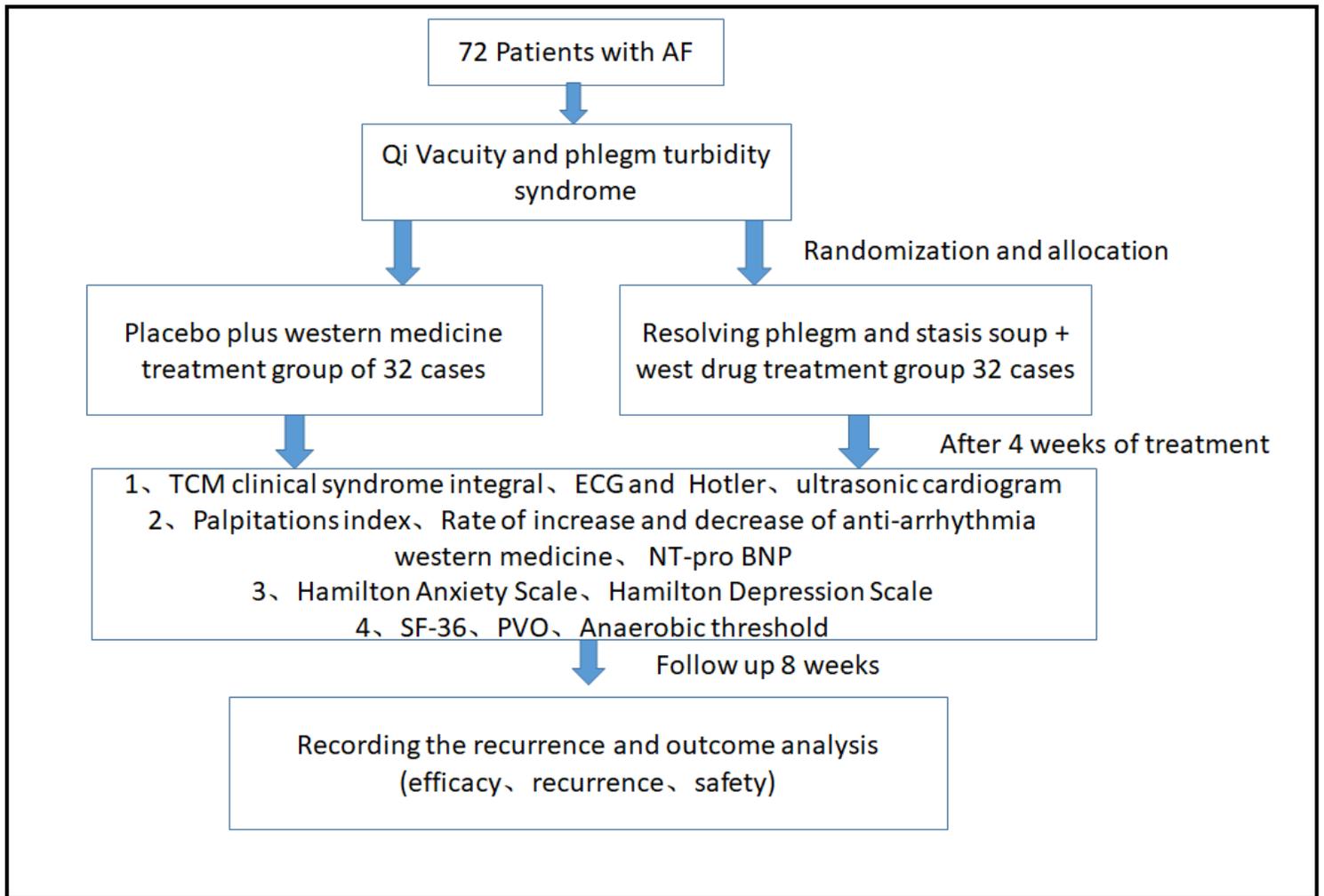


Figure 1

Trial flow chart