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Original Article

Shenzhu Guanxin Recipe Granules (参术冠心方颗粒) for Improving Exercise Tolerance in Patients with Stable Angina (SERIES Trial): A Protocol of Multicenter, Randomized, Double-Blind, Placebo Parallel Controlled Clinical Trial*

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ABSTRACT **Background:** Many patients with chronic angina experience anginal episodes despite successful recanalization, antianginal and antiischemic medications. Empirical observations suggested that Shenzhu Guanxin Recipe Granules (参术冠心方颗粒, SGR), a Chinese herbal compound, exerted potential impacts on increased treadmill exercise performance and angina relieve. However, there has been no systematic study to clarify the impact of SGR on exercise tolerance in patients with stable angina. The SERIES (ShEnzhu guanxin Recipe for Improving Exercise tolerance in patients with Stable angina) trial is designed to determine the effects of SGR on exercise duration, electrocardiographic (ECG) evidence of myocardial ischemia, and incidence of major adverse cardiac events (MACE) in stable anginal patients. **Methods:** A total of 184 eligible patients with stable angina will be randomly assigned to receive placebo or SGR (10 g/day for 12 weeks) in a 1:1 ratio. The primary outcome will be the change from baseline in total exercise tolerance duration, time to onset of angina and ECG ischemia during exercise treadmill testing performed over a 12-week study period. The secondary outcome will include ECG measures, the occurrence and composite of MACE and the Seattle Angina Questionnaire score. Moreover, the coronary microcirculation will be evaluated to explore the possible effects in response to treatment of SGR. After the procedure, all participants will be followed up by interview at 3 and 6 months, enquiring about any cardiac events, hospitalizations, cardiac functional level and medication usage. Additionally, the occurrence of adverse events will be evaluated at each follow-up. **Discussion:** This study may provide novel evidence on the efficacy of SGR in improving exercise tolerance and potentially reducing clinical adverse events. (Trial registration No. ChiCTR-TRC-14004504)

KEYWORDS exercise tolerance, stable angina, Shenzhu Guanxin Recipe, coronary microcirculation, trial protocol, randomized controlled trial

Chronic stable angina due to atherosclerotic coronary disease is a debilitating illness affecting more than 100 million people all over the world with approximately 2 million new cases occurring each year.[1] With the adoption of a westernized diet and subsequent increase of metabolic syndrome, and other risk factors, angina and related diseases in China have increased.[2] Patients with angina report greater physical limitations and diminished quality of life compared with general population. Despite of the continued explosive growth in myocardial revascularization and great advances in pharmacotherapy, up to one quarter of patients still experience heart attacks and require multi-drug regimens.[3,4] Currently, the available anti-ischemic agents include beta-blockers, calcium channel blockers, and short- or long-acting nitrates, which were limited by the hemodynamic and electrophysiologic effect.[5,6] Hence, novel complementary agents or

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therapies to reduce symptoms of angina and improve prognosis are urgently needed.

A series of studies have suggested Chinese herbal compound bought multiple benefits to patients with coronary heart disease.[7-10] In particular, Shenzhu Guanxin Recipe Granules (参术冠心方颗粒, SGR) , a potent herbal compound including *Radix Ginseng*, *Rhizoma Atractylodis*, *Radix Notoginseng*, *Rhizoma Pinelliae*, *Hirudo medicinalis*, *Radix Panacis* quinquefolium, and *Folium Nelumbinis*, have great potential of accelerating blood circulation, enhancing qi, and eliminating intravascular phlegm which all play critical roles in managing the ischemic disease based on Chinese medicine (CM) theory.[11,12] An increasing number of studies have been conducted to elucidate the cardioprotective effects of this Chinese herbal compound. A multicenter randomized controlled trial (RCT) demonstrated that administration of SGR reduced the angina pectoris scores and stabilized atherosclerotic plaque subsequently prevented in thrombotic events including restenosis in patients with angina pectoris after percutaneous coronary intervention (PCI).[13] From the pilot study, it has been proven that SGR could relieve the clinical symptoms of stable angina and improve the quality of life.[14] Recent experimental research also indicated that SGR may improve vascular endothelial function, reduce myocardial necrosis area and improve the myocardial microcirculation in rats with myocardial infarction.[15] Inspired by these supportive clinical and experimental evidence, we therefore hypothesized that treatment with SGR may provide an alternative therapeutic strategy to relive angina pectoris and improve exercise tolerance among patients with chronic stable angina, subsequently improve quality of life and lead to the reduction of major coronary adverse events finally.

METHODS

Study Design Overview

The SERIES (ShEnzhu guanxin Recipe for Improving Eexercise tolerance in patients with Stable angina) trial is a multi-center, prospective, randomized, double-blind, placebo parallel controlled trial in which patients with stable angina will be randomly assigned to receive twice-daily placebo or SGR for 12 weeks. The primary aim of the study is to investigate the effects of SGR *vs*. placebo on treadmill exercise duration, times to angina onset and to 1-mm ST segment depression during exercise treadmill testing performed over a 12-week study period.

The scientific design, organization and conduct of the study will be supervised by a steering committee. The participating centers of this study comprise 4 institutions across Guangdong Province, including Guangdong Provincial Hospital of Chinese Medicine, Ersha Island Hospital, Hospital of Guangzhou Higher Education Mega Center, and Guangzhou Mercy Hospital. Each participating center will have a nominated research assistant responsible for local data collection. Study monitoring, data management and statistical analysis will be carried out by Tianjin Institute of Clinical Evaluation for Chinese Medicine, a contract research organization. The study protocol and consent forms received ethics approval from the Guangdong Provincial Hospital of Chinese Medicine Institutional Review Board (No.B2013-100-01). The protocol was registered at Chinese Clinical Trial Registry (No. ChiCTR-TRC-14004504). The investigation will conform to the principles outlined in the Declaration of Helsinki and the relevant provisions of national regulatory agencies, and all participants will sign a written informed consent form that explained the risks and benefits of study particiption.

Inclusion and Exclusion Criteria

Potential trial participants fulfilling the inclusion criteria will be recruited consecutively. (1) aged 18–70 years-old; (2) stable coronary artery disease (CAD) confirmed by coronary angiography, a positive stress echocardiography showing regional wall motion abnormalities at least 3 months before inclusion according to American College of Cardiology/American Heart Association guidelines;[16] (3) repeatable ischemic ST-segment depression of at least 1 mm and limited exercise capacity on treadmill testing (3–9 min on a modified Bruce protocol); (4) Chinese medicine syndrome of phlegm and blood stasis due to qi deficiency;[17] (5) normal resting ECG in sinus rhythm without bundle branch aberration or other conduction disturbance; and (6) provide voluntary informed consent prior to enrollment.

Exclusion criteria will included: (1) electrocardiographic (ECG) abnormalities confounding the interpretation of ST-changes (e.g., left bundle-branch block, resting ST-segment depression ⩾1 mm, atrial fibrillation, flutter, pacemaker or implantable defibrillator); (2) severe congestive heart failure [the New York Heart

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Association (NYHA) class Ⅲ or Ⅳ, left ventricular ejection fractions (LVEF) <35%]; (3) an acute coronary syndrome or coronary revascularization procedure or bypass surgery within the prior 3 months; (4) significant left main stem stenosis; (5) anticipated revascularization procedures; (6) significant valvular disease; (7) uncontrollable symptomatic hypotension or hypertension, renal or hepatic insufficiency; (8) malignant tumor or other significant life-limiting comorbidities and (9) unable to perform exercise test for outcome assessment or use of an investigational drug within 30 days of inclusion.

Recruitment Strategies

To ensure adequate enrollment of a diverse study population, recruitment advertisements will be placed in a wide range of media outlets including the flyers within the hospital and advertisements in the local newspapers and website of Chinese Clinical Trials Registry. Any interested respondents will receive information about the trial and finish a screening survey to determine their eligibility. Each potential participant will be provided with informed consent addressed that participation is completely voluntary and declining to take part in the study will not influence the quality of patient care. After that, the principal investigator or study staff will screen participants to confirm that potential participants meet the eligibility criteria.

Randomization and Blinding

Clinical Research Center for Design, Measurement and Evaluation (DME) from Guangzhou University of Chinese Medicine, generated separate randomization schedules using a random number generator in SAS version 6.12 (SAS Institute, Cary, NC) in a 1:1 randomization ratio. The schedules will be sent to Tianjiang Pharmaceuticals Co, Ltd. for drug packaging and preparation of the code break envelopes. A disk-based electronic backup will be filed securely in a sealed envelope at Data Safety Monitoring Board. DME center will provide the sealed medication assignment envelope to the clinical units for each patient randomized in the study. Randomization envelopes should not be opened unless a participant meets the eligibility criteria, completes the informed consent, and undergoes a baseline assessment.

Blinding will be ensured using a matched placebo granule (a patent from Tianjiang Pharmaceutical Factory, Jiangyin, China) identical in color, size, shape, and taste. The quality of the matched trial supplies, such as contents, solubility, and bacteria contaminations, should be controlled rigorously according to the good manufacturing practice standards, and be tested and verified by researchers.

Study medication (including both placebo and SGR) will be dispensed by the Hospital Central Pharmacy as a set of boxes at the beginning of each study month. Patients will be asked to store these. The boxes will be brought to the next study visit to check to reinforce compliance.

Throughout the duration of this trial, all study participants and attending physician will be blinded to treatment assignment. Moreover, staff performing the exercise test and echocardiography, investigator responsible for the follow-up assessment, all core laboratories, the biostatisticians performing the analysis as well as the members of the Data Safety Monitoring Board will remain blinded until after the database has been locked.

Intervention

Eligible participants will be randomized to receive placebo or SGR (10 g/day for 12 weeks). Simultaneously, all patients after intervention will receive standard anti-ischemic therapy according to patients' conditions, such as aspirin, clopidogrel, angiotensin converting enzyme inhibitors or beta-blockers, calcium channel blockers and nitrate esters irrespective of the initial randomization assignment. All procedures as well as medicines prescription will be under responsibility of physicians according to the clinical guidelines.[13] The date of any medical therapy change and the reasons will be documented in the case record form.

Outcome Assessment

At baseline (prior to starting either intervention), after completing the intervention (12-week treatment later), and at 6-month follow-up, exercise tolerance testing, echocardiographic cardiac function, and quality of life questionnaire will be undertaken in all participants (Table 1). In the event that the participants enrolled will not be able to continue the study in the treatment or follow-up period, they will remain in their randomized group to perform an intention to treat (ITT) analysis. Primary and secondary endpoints of the trial are listed in Table 2.

Additional efficacy endpoints will include

Table 1. Study Procedures of the SERIES Trial

	Screening	Baseline	Month 3	Month 6
Informed consent	×		×	×
Basic characteristic variables	×			
Medical history	×		×	×
Physical exam	×		×	×
Medications	×		×	×
Randomization and allocation	×			
Exercise treadmill testing		×	×	
Rest electrocardiography		×	×	×
Incidence of MACE			×	×
Seattle Angina Questionnaire		×	×	
NYHA assessment		×	×	×
Echocardiographic cardiac function		×	×	
Coronary microcirculation assessment		×	×	
Blood work		×	×	×
Safety assessment			×	×
Adherence			×	×

Notes: MACE: major adverse cardiac event; NYHA: New York Heart Association

Table 2. Outcomes of the SERIES Trial

Primary endpoints	1. Change from baseline in total treadmill exercise duration, time to angina onset and time to 1 mm ST segment depression after 12 weeks of treatment
Secondary endpoints	1. Change from baseline in maximum ST-segment depression and maximal workload during exercise treadmill testing performed over a 12-week study period
	2. Echocardiographic cardiac function and NT-proBNP
	3. Incidence of MACE
	4. Seattle Angina Questionnaire scores
	5. NYHA functional classification
	6. Coronary microcirculation assessment (in selected centers only)

Notes: NT-proBNP: N-terminal pro-brain natriuretic peptide; MACE: major adverse cardiac event; NYHA: New York Heart Association

echocardiographic measures of global LV ejection fraction, ventricular volumes (LV end-systolic/diastolic volume) and ventricular wall motion score, and wall thickening during the same interval at the 3-month follow-up to evaluate the efficacy of SGR treatment.

The occurrence and composite of major adverse cardiac events (MACE) will be evaluated (defined as cardiogenic death, stroke, myocardial infarction, readmission on account of deterioration of congestive heart failure or unstable angina, target vessel revascularization, and major arrhythmias) during the treatment and up to 6 months thereafter. According to the consensus statement, unstable angina defined as rest angina, new-onset severe angina and increasing angina within 1 month will be diagnosed. In patients with normal baseline levels of troponin-I, myocardial infarction will be defined as a post-procedural troponin-I ⩾2 × upper limits of normal. Conversely, in patients with elevated baseline levels of troponin-I, higher than 2-fold of baseline value will be consider as myocardial infarction.[18] Target vessel revascularization will be done either by the repeated PCI, or by the bypass surgery of the target vessel.

The Seattle Angina Questionnaire (SAQ) score[19] will be used to assess quality of life at baseline and 3 and 6 months. At the same time, the investigators will compare the number of patients who experienced an improvement in cardiac functional classes in more than 1 NYHA grades 1 month after the intervention. To avoid bias, questions to the patients about their condition will be scripted to ensure that every investigator asked in an identical manner to each participant. The safety assessment will be based on vital signs, blood test, and the incidence of major adverse events in the duration of the study.

Exercise Treadmill Testing

Each exercise treadmill test will be performed using a computer-assisted treadmill system (Marquette Electronics Inc. Illinois, USA), and modified Bruce protocol at approximately the same time of day.[20] During testing, standing torso ECG data from 3 leads (Vi, Vs and avF) will be continuously recorded throughout the exercise. A core ECG laboratory (Guangdong Provincial Hospital of Chinese Medicine) blinded to treatment assignment will analyze all exercise ECG data using customized software as previously described.[21] A positive exercise-induced ECG ischemia will be defined as the new occurrence of limiting angina with ST-segment depression more than 1 mm between 3 and 9 min of initiation of an testing. For patients with permitted baseline ST-depression at rest (<1 mm), qualifying ST-segment depression will be defined as additional ST depression of at least 1 mm below the resting value. Neither ST-segment depression nor target heart rate will be used as an indication for stopping the test in the baseline period. If the patients would be free of angina until the target heart rate is achieved, the target heart rate will be used as an indication for stopping the exercise test during the period of treatment. The following intervals will be documented: time to onset of angina, time to limiting angina (exercise duration beyond which the patient would not be able to continue with the exercise due to anginal pain), and time to 1 mm

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ST-segment depression.[22]

Coronary Microcirculation Assessment (Sub-Study)

Participant enrolled in selected centers also will participate in a sub-study aimed at evaluating the coronary microcirculation in response to 12-week treatment of SGR. Primary measurements, performed at baseline and at 3-month following treatment, included coronary flow velocity (CFV) pattern and CFV reserve (CFVR) measured with a Doppler guidewire.[23] After completion of the diagnostic coronary angiography and left ventriculography, myocardial contrast echocardiography (MCE) was performed as previously reported.[24] Two microliter of biocompatible ultrasound contrast agents containing microbubbles of a mean size of 12 μmol/L will be injected into the left coronary artery while two-dimensional echocardiograms will be recorded by use of a commercially available scanner (Philips Medical Systems, Andover, MA, USA). Recorded MCE images will be the parasternal short-axis view at the mid-papillary muscle level and the apical 2-chamber view. MCE will be repeated with injection into the right coronary artery. The echocardiograms will be analyzed centrally according to predefined procedures in the core laboratory at the Guangdong Provincial Heart Center by technicians supervised by 2 cardiologists, all of them will be blinded to randomization assignment and examination sequence (baseline *vs*. follow-up assessment).

Adverse Events and Additional Safety Assessments

Interim efficacy and safety analyses at approximately 50% and 100% recruitment will be performed by an independent Data and Safety Monitoring Board (DSMB), whom will be notified in the event of a serious adverse event. All adverse events will be recorded on an adverse event case report form during study interventions and evaluated for relevance to the intervention, reported to the Human Research Committee promptly in accordance with guidelines. The DSMB is entitled to recommend early termination of the trial in the event of evidence of overwhelming benefit or substantive detriment once sufficient data has been accumulated.

With respect to data security, deidentified ECG and echocardiograms data will be stored on a secure network. In addition, blood samples for biological parameters assessment will be managed and stored using appointed identifiers. All case report forms will be kept in a secure and lock-protected location. In accordance with our study protocol, extensive procedures are in place to ensure quality control of data entry, missing data minimization, and subject confidentiality. The statistician will review the database to ensure accurate data collection and correct data export for future analyses.

Sample Size Estimation

Based on the results of our pilot study, we hypothesized that the expected difference in the primary endpoint (treadmill exercise duration) between the SGR and placebo groups was estimated to be 10%. Under the assumptions of normally distributed data, on the basis of a two-sided test size of a level of 5% and a statistical power of 90%, it has been calculated by SPSS 11.0 software (NCSS, LLC, Kaysville, Utah, USA) that a minimum of 82 patients would be required for each group. After considering a potential 10% dropout rate within 6 months, it was estimated that 184 eligible cases would need to be enrolled.

Statistical Analysis

Results will be reported as means ± standard deviation or median and interquartile range for continuous variables, and numbers and percentages (%) for categorical variables. Continuous variables will be compared within each group using Student's *t*-test or the Wilcoxon nonparametric statistic (if non-normally distributed), while the categorical variables will be compared using Chi-square statistics or Fisher's exact test when appropriate. The primary efficacy parameter will be the change from baseline in exercise treadmill time, analyzed using an analysis of covariance with baseline values and background therapy as covariates, using the last observation carried forward after randomization on an ITT basis. To examine the unique contribution of SGR on exercise treadmill time, a hierarchical multiple regression analysis will be performed with a 2-stage, step-down procedure based on closed testing and union intersection principles. Because the data of angina frequency and nitroglycerin consumption per week will be not normally distributed, treatment comparisons between SGR and placebo will be obtained from a nonparametric analysis of variance model using ranked data with effects of treatment, baseline covariate and background therapy. A survival curve will be prepared using Kaplan-Meier estimates for all patients. All comparisons will be carried out using two-sided α of 0.05. Statistical analysis will be performed using SPSS (version 13.0, SPSS Inc, Chicago, IL).

DISCUSSION

The SERISE trial is a prospective exploratory study designed to determine the efficacy of application of Chinese herbal compound, SGR, in the stable angina patients with the goal of improving exercise tolerance and benefiting on clinical cardiovascular outcomes.

Chronic angina pectoris is the most common manifestation of atherosclerotic coronary heart disease which is the predominant cause of death in most countries. Stable angina pectoris typically characterized by a significant coronary stenosis in one or more epicardial vessels and evidence of reversible myocardial ischemia assessed by exercise tolerance testing. Despite many sophisticated and costly attempts, including an-tianginal drugs and coronary artery revascularization, to mitigate the syndrome, only modest benefits have thus far been identified with these therapies.[25] As symptom control improves the patients' quality of life, utmost consideration should be given to available management options that aim to relive angina pectoris and improve exercise tolerance. However, for many patients receiving treatment, angina pectoris still persists, illustrating the need for complementary drugs with novel anti-ischemic mechanism and potentially additive to those of the existing agents resulting in a more efficacious strategy.

Systematic experimental and clinical evidence indicates the relation between myocardial ischemia and damages the coronary microvasculature. It's demonstrated that a substantial coronary microcirculation disturbance assessed by MCE was observed in about one fourth of patients with CAD despite angiographically successful coronary recanalization, which means little or no functional improvement was obtained in these patients.[26,27] Because of technical limitations, MCE was not widely performed previously. However, a recently developed Doppler guidewire with a 12-MHz Doppler transducer allows cardiologist to assess blood flow velocity pattern, which reflects severity of coronary microvascular dysfunction.[28] The rationale for evaluating the ability of SGR to improve exercise tolerance is based on constantly accumulated evidences indicating its induction of improving coronary microcirculation. In the SERISE study, we investigate the coronary blood flow velocity patterns in patients with stable angina to explore the mechanism of SGR from the viewpoint of coronary flow dynamics.

The SERIES trial will utilize a rigorous set of methods to minimize bias, such as randomization, parallel control design, blinding to the outcome evaluators and analyzers, and statistical analysis according to the ITT principle.

Potential limitation of SERIES trial is that it is not a mechanistic study and will not provide any physiologically plausible explanation for the effects of SGR. However, the findings will provide a promising evidence to develop an effective therapy additive to those of the existing agents. Also, the study has been designed based on the recommendation of the American College of Cardiology/ American Heart Association guideline for exercise treadmill testing. Enforcing a smaller threshold would have made recruitment more difficult and the study is less representative of the real world but would have reduced intraindividual sources of variability.

The SERIES trial is a randomized trial to demonstrate the efficacy of SGR in improving exercise tolerance in patients with stable angina. Both symptoms control and reducing the incidence of adverse clinical outcomes are the goals of stable angina management. Several studies have shown that optimal medical therapy along with revascularization was effective in reducing the risk of adverse coronary events. These results are expected to provide a reliable evidence for administration of this Chinese herbal compound, in addition to currently available antianginal and anti-ischemic therapy, in the cardiac rehabilitation program for patients with coronary artery disease.

Conflict of Interest

The authors declare that they have no competing interests. None of authors received funding from the relevant drug manufacturers in this research. The sponsors had no role in the project development, data collection, manuscript preparation, nor the decision to publish.

Author Contributions

Mao S drafted this manuscript; Dang XJ and Wu HL designed the described study, Xu DP made the statistical analysis; Wu HL and Li V made critical revision of the manuscript and contributed to the rationalization of the study. All authors read and approved the final version of this manuscript.

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REFERENCES

1. Ohman EM. Clinical practice. chronic stable angina. N Engl J Med 2016;374:1167-1176.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2095-2128.
3. Serruys PW, Unger F, Sousa F. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. ACC Curr J Rev 2001;10:85.
4. Holubkov R, Laskey WK, Haviland A, Slater JC, Bourassa MG, Vlachos HA, et al. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. Am Heart J 2002;144:826-833.
5. Thadani U. Current medical management of chronic stable angina. J Cardiovasc Pharmacol Ther 2004;9:S11.
6. Kones R. Recent advances in the management of chronic stable angina Ⅱ. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization. Vasc Health Risk Manag 2010;6:749-774.
7. Qiu Y, Xu H, Shi D. Traditional Chinese herbal products for coronary heart disease: an overview of cochrane reviews. Evid-Based Complement Alternat Med 2012;2012:417387.
8. Mao S, Wang L, Ouyang W, Zhou Y, Qi J, Guo L, et al. Traditional Chinese medicine, Danlou Tablets alleviate adverse left ventricular remodeling after myocardial infarction: results of a double-blind, randomized, placebo-controlled, pilot study. BMC Complement Altern Med 2016;16:447.
9. Yu L, Qin Y, Wang Q, Zhang L, Liu Y, Wang T, et al. The efficacy and safety of Chinese herbal medicine, Rhodiola formulation in treating ischemic heart disease: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 2014;22:814-825.
10. Mao S, Wang L, Zhao X, Shang H, Zhang M, Hinek A. Sodium tanshinone ⅡA sulfonate for reduction of periprocedural myocardial injury during percutaneous coronary intervention (STAMP trial): rationale and design. Int J Cardiol 2015;182:329-333.
11. Ruan X, Jiang W, Lin Y. Clinical efficacy of treatment for regulating Pi and protecting Xin in treating patients after coronary artery bypass grafting and its effect on patients' quality of life. Chin J Integr Tradit West Med (Chin) 2006;26:28-32.
12. Wu H, Xu D, Luo W. Retrospective cohort study on the improvement of the prognosis of patients after coronary artery bypass grafting operation treated by the method for regulating Pi (Spleen) and protecting Xin (Heart). Jilin J Tradit Chin Med (Chin) 2009;29:27-29.
13. Xu D, Wu H, Lan T, Wang X, Sheng X, Lin Y, et al. Effect of Shenzhu Guanxin Recipe on patients with angina pectoris after percutaneous coronary intervention: a prospective, randomized controlled trial. Chin J Integr Med 2015;21:408-416.
14. Xu D, Wang X, Sheng X, Lin Y, Li S, Zheng C. Double-blind, randomized, controlled clinical trial of Shenzhu Guanxin Prescription for treatment of stable angina due to cronary heart disease. J Guangzhou Univ Tradit Chin Med (Chin) 2014;31:173-182.
15. Xu D, Wu H. Effect of Shenshu Guanxin Granules on coronary circulation in rats with myocardial infarction. Chin J Pathophysiol (Chin) 2014;30:438-443.
16. Fraker TD, Fihn SD, Members WC, Gibbons RJ, Abrams J, Chatterjee K, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol 2007;50:2264-2274.
17. Chen KJ. Blood stasis syndrome and its treatment with activating blood circulation to remove blood stasis therapy. Chin J Integr Med 2012;18:891-896.
18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:2264-2274.
19. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-341.
20. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee to update the 1997 exercise testing guidelines). J Am Coll Cardiol 2002;40:1531-1540.
21. Munzel T, Meinertz T, Tebbe U, Schneider HT, Stalleicken D, Wargenau M, et al. Efficacy of the long-acting nitro vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial. Eur Heart J 2014;35:895-903.
22. McInnis KJ, Balady GJ, Weiner DA, Ryan TJ. Comparison of ischemic and physiologic responses during exercise tests in men using the standard and modified Bruce protocols. Am J Cardiol 1992;69:84-89.
23. Kume T, Akasaka T, Kawamoto T, Yoshitani H, Watanabe N, Neishi Y, et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ J 2005;69:934-939.
24. Gaibazzi N, Rigo F, Lorenzoni V, Molinaro S, Bartolomucci F, Reverberi C, et al. Comparative prediction of cardiac events by wall motion, wall motion plus coronary flow reserve, or myocardial perfusion analysis: a multicenter study of contrast stress echocardiography. JACC Cardiovasc Imag 2013;6:1-12.
25. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: executive summary: the task force on the management of stable angina pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341-1381.
26. Thanigaraj S, Nease RF Jr., Schechtman KB, Wade RL, Loslo S, Perez JE. Use of contrast for image enhancement during stress echocardiography is cost-effective and reduces additional diagnostic testing. Am J Cardiol 2001;87:1430-1432.
27. Huqi A, He A, Klas B, Paterson I, Thompson R, Irwin M, et al. Myocardial deformation analysis in contrast echocardiography: first results using two-dimensional cardiac performance analysis. J Am Soc Echocardiogr 2013;26:1282-1289.
28. Shah BN, Chahal NS, Bhattacharyya S, Li W, Roussin I, Khattar RS, et al. The feasibility and clinical utility of myocardial contrast echocardiography in clinical practice: results from the incorporation of myocardial perfusion assessment into clinical testing with stress echocardiography study. J Am Soc Echocardiogr 2014;27:520-530.

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