Chin J Integr Med 2019 Sep;25(9):684-690

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Clinical Experience

# Effect and Safety of Guanxinning Tablet (冠心宁片) for Stable Angina Pectoris Patients with Xin (Heart)-Blood Stagnation Syndrome: A Randomized, Multicenter, Placebo-Controlled Trial*

SUN Ming-yue[1], MIAO Yang[2], JIN Min[3], DONG Yao-rong[4], LIU Shu-rong[5], WANG Mu-lan[3], and GAO Rui[1]

**ABSTRACT** **Objective**: To investigate the effect and safety of Guanxinning Tablet (冠心宁片, GXN) for the treatment of stable angina pectoris patients with Xin (Heart)-blood stagnation syndrome (XBSS). **Methods**: One hundred and sixty stable angina pectoris patients with XBSS were randomly assigned to receive GXN (80 cases) or placebo (80 cases, Guanxinning simulation tablets, mainly composed of lactose), 4 tablets (0.38 g/tablet), thrice daily for 12 weeks. After treatment, an exercise stress test (treadmill protocol), Chinese medicine (CM) syndrome score, electrocardiogram (ECG), and nitroglycerin withdrawal rate were evaluated and compared in the patients between the two groups. Meanwhile, adverse events (AEs) were evaluated during the whole clinical trial. **Results**: Compared with the control group, the time extension of exercise duration in the GXN group increased 29.28±17.67 s after treatment ($P>0.05$); moreover, the change of exercise duration in the GXN group increased 63.10±96.96 s in subgroup analysis ($P<0.05$). The effective rates of angina pectoris, CM syndrome and ECG as well as nitroglycerin withdrawal rate were 81.33%, 90.67%, 45.76%, and 70.73%, respectively in the GXN group, which were all significantly higher than those in the control group (40.58%, 75.36%, 26.92%, 28.21%, respectively, $P<0.05$). **Conclusion**: GXN was a safe and effective treatment for stable angina pectoris patients with XBSS at a dose of 4 tablets, thrice daily.

**KEYWORDS** Guanxinning Tablet, coronary heart disease, stable angina pectoris, Xin (Heart)-blood stagnation syndrome, Chinese medicine

According to the World Health Organization, coronary heart disease (CHD) is one of the major causes of death whose incidence is increasing worldwide. Treatment of CHD has been improved with new technologies, including thrombolysis, percutaneous coronary intervention, and coronary artery bypass surgery. Despite their success, problems with these treatments persist, including in-stent restenosis, antiplatelet drug resistance, and poor myocardial tissue perfusion, limited their clinical applications.

Chinese medicine (CM) is effective at preventing and treating CHD because it acts on multiple targets and pathways, creating a symbiotic effect that promotes blood circulation and removes blood-stasis with few side effects.[1,2] Guanxinning Tablet (冠心宁片, GXN), contains compounds extracted from the plants *Salvia miltiorrhiza* and *Ligusticum chuanxiong*, and is used to treat CHD. In order to clarify the structures of the chemical components of *S. miltiorrhiza* and *L. chuanxiong*, a sample of GXN was subjected to high-performance liquid chromatography as shown in pervious patent.[3]

GXN exhibits a variety of pharmacological activities, including decreasing blood viscosity, reducing arterial plaque, improving myocardial ischemia, reducing oxidative stress, protecting



*Supported by the National Major Scientific and Technological Special Project for Significant New Drugs Development (No. 2012ZX09303-010-002), China

1. Good Clinical Practice Center, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing (100091), China; 2. Department of Cardiology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing (100091), China; 3. Chiatai Qingchunbao Pharmaceutical Co., Ltd., Hangzhou (310023), China; 4. Department of Cardiology, Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai (200071), China; 5. Department of Cardiology, the First Clinical Hospital of Jilin Academy of Chinese Medical Sciences, Changchun (130021), China
Correspondence to: Prof. GAO Rui, Tel: 86-10-62835653, E-mail: ruigao@126.com

DOI: https://doi.org/10.1007/s11655-019-3069-8

vascular endothelial cells, and prohibiting platelet aggregation, all of which improve coronary perfusion and cardiac function.[4-6] In this multi-center, randomized, double-blinded, and parallel-controlled trial, the effect and safety of GXN were investigated in patients with stable angina pectoris and Xin (Heart)-blood stagnation syndrome (XBSS).

## METHODS

### Diagnostic Criteria

CHD was diagnosed by one of the following at least: a history of remote infarct, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery; significant coronary stenosis (>50%); or cardiac radionuclide measurement.[7]

### Inclusion Criteria

Patients who fulfilled the following criteria were enrolled in the study: (1) diagnosis of CHD; (2) a positive result in the treadmill exercise test; (3) diagnosis of stable angina pectoris grade Ⅰ–Ⅲ;[8] (4) weekly frequency of angina pectoris attack ≥2 times; (5) diagnosis of XBSS in CM;[9] (6) aged 30–70 years; (7) signed the written informed consents.

### Exclusion Criteria

Patients with any of the following conditions were excluded: (1) acute myocardial infarction within the past 3 months, acute coronary syndrome, New York Heart Association (NYHA) class Ⅳ; (2) heart disease other than stable angina pectoris, chest pain caused by severe cardiopulmonary insufficiency, severe neurosis, menopausal syndrome, or cervical spondylosis; (3) systolic pressure ≥160 mm Hg or diastolic pressure ≥100 mm Hg; (4) severe arrhythmia (rapid atrial fibrillation, atrial flutter, paroxysmal ventricular tachycardia, sinus bradycardia, severe atrioventricular block, complete bundle branch block); (5) patients with comorbid severe primary disease, psychosis, or abnormal liver or kidney function; (6) fasting plasma glucose >7.0 mmol/L or diabetes complications; (7) pregnancy, planned pregnancy, or lactation; (8) patients undergoing major orthopedic surgeries on head, chest, or abdomen within 4 weeks, and patients with a risk of bleeding; (9) allergic constitution, particularly to *S. miltiorrhiza*; (10) participation in other clinical trials within the past month.

### Rejection Criteria

Patients with false acceptance, misdiagnosis, no medication, or no inspection records were rejected.

### Patients

Eligible patients were recruited from 6 clinical centers located in different regions of China between December 2010 and October 2011, including Xiyuan Hospital of China Academy of Chinese Medical Sciences, Jilin Integrated Chinese and Western Hospital, Affiliated Hospital of Changchun University of Chinese Medicine, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Inner Mongolia University for the Nationalities, and Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine. Participants were randomly assigned to the GXN group or control group in a ratio of 1:1 via central randomization. The study protocol was reviewed and approved by the Ethic Committee of Xiyuan Hospital (Approval No. 2010XL029). The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

### Interventions

The study period included a 2-week start-up period and a 12-week treatment period. During the start-up period, patients were prohibited from taking other CM to activate blood or dissolve stasis. Both GXN (batch No. 1009001, containing 0.889 g of *S. miltiorrhiza* and *L. chuanxiong*, respectively) and the GXN simulation tablets (batch No. 1009001, mainly composed of lactose) were manufactured and supplied by Chiatai Qingchunbao Pharmaceutical Co., Ltd., China (0.38 g/tablet). During the treatment period, patients in the GXN group took 4 tablets of GXN thrice daily, while patients in the control group took 4 tablets of GXN simulation tablets thrice daily. All the study drugs passed a quality inspection. Basic treatment for CHD remained unaltered with a regular lifestyle including appropriate diet and rest. Factors inducing angina pectoris were strictly avoided. When angina pectoris attacks occurred, sublingual nitroglycerin (Pharmaceutical Factory of Hebei Medical University, China, batch No. 100103) was taken immediately and the nitroglycerin consumption was recorded.

### Primary Outcome

All the patients took the exercise tolerance tests (ETTs) at baseline and 12 weeks after treatment following the standard protocol of Bruce, et al.[10] The index difference between the two groups was

Chin J Integr Med 2019 Sep;25(9):684-690

compared according to the following formulae: change value=duration before treatment–duration after treatment, change rate (%)=(change value/duration before treatment) × 100%. The ETT result was considered positive when one of the following occurred: S-T-segment depression of at least 1 mm (horizontal or down sloping); typical angina occurred during exercise; a drop in blood pressure of ⩾10 mm Hg from baseline blood pressure despite an increase in workload.[11]

A subgroup analysis was conducted to further elucidate the effect of GXN on the primary efficacy index and obtain more valid evidence.[12] It was performed in patients with a history of coronary artery disease (CAD), PCI, coronary computed tomography angiogram, and positive result in the ETT.

## Secondary Outcomes

### Curative Effect on Angina Pectoris

The effect on angina pectoris symptoms were evaluated at 2 weeks before treatment, baseline, as well as 2, 4, 6, 8, 10 and 12 weeks after treatment. Symptoms of angina pectoris, including frequency, duration and attack severity, and an angina pectoris symptom score were calculated, in accordance with the Guiding Principle of Clinical Research on New Drugs of Traditional Chinese Medicine.[13] The effect index was also determined according to the following formula. Effect index (%)=[(symptom score before treatment–symptom score after treatment)/symptom score before treatment] × 100%. A value of effect index ⩾70% suggested a significant effect; 30%–69% as an effect; 0–29% as no effect; <0 as a worsening effect.

### Effect on CM Symptoms

Effect on CM symptoms were measured at baseline, 4, 8 and 12 weeks after treatment. The symptoms of XBSS include chest pain, chest distress, palpitation, and a dark-purple tongue.[14,15] Each symptom was given a score, the individual scores were summed and the CM effect index was calculated. Effect index (%)=[(total symptom score before treatment–total symptom score after treatment)/total symptom scores before treatment] × 100%. A value of effect index ⩾70% suggested a significant effect; 30%–69% as an effect; 0–29% as no effect; <0 as a worsening effect.

### Curative Effect on Electrocardiogram Results

A significant effect occurred if the electrocardiogram (ECG) returned to the normal range at baseline, 4, 8 and 12 weeks after treatment. An effect occurred if the S-T segment depression recovered above 0.05 mV but did not return to the normal range, if negative T waves became shallow (⩾25%), if a flattened T wave became positive, or if an atrioventricular block or intraventricular block improved. No effect occurred if the ECG stayed the same or worsened, if the S-T segment depression decreased by 0.05 mV after treatment, if the negative T waves deepened (⩾25%), if positive T wave flattened, flattened T wave becomes negative, or if ectopic cardiac rhythm, atrioventricular block or intraventricular block appeared.

### Nitroglycerin Use

The nitroglycerin use was evaluated at baseline, 2, 4, 6, 8, 10 and 12 weeks and results were divided into 4 categories: stop: if the patient stopped taking nitroglycerin completely after treatment; decrease: if the patient reduced his/her nitroglycerin intake by more than 50% after treatment; same: if nitroglycerin intake was reduced by less than 50% after treatment; increase: if nitroglycerin intake increased after treatment.

### Safety Evaluation

The safety indices observed included vital signs, urinalysis, blood biochemical indices, blood coagulation indices, and the incidence of adverse events (AEs).

## Randomization and Blinding

The participants were randomly assigned to two groups using a block randomization. Random numbers based on the allocation sequence were generated using SAS (Version 9.1.3) by an independent statistician at Nanjing Medical University. The experiment was designed with a two-level blind method and blinded concealment was performed at the same time. The allocation sequence will be kept in an opaque, sealed and stapled envelope and will be kept concealed until end of outcome assessment. During the trial, the blinding method will be strictly applied to the investigator and the subject.

## Sample Size Estimation

It is assumed that the exercise time of the test group is longer than that of the control group after treatment. The following assumptions were made for calculation of valid sample size based on previous literature: according to the one-sided test: $\alpha = 0.25$ $\beta = 0.2$, using the ETT as the primary measure, the

difference of the exercise time between the positive drug and the placebo group was 23.7 s,[16] and average difference and standard deviation between the two groups specified as 23.7 s, a superiority margin of 12 s was chosen. The treatment and control groups were arranged in the ratio of 1:1, assuming a potential dropout rate of 20%, at least 66 cases would be required for each group of the study. We enrolled 80 cases each for the test group and control group.

### Statistical Analyses

Statistical analyses were conducted using SAS (Version 9.1.3). Descriptive statistics were reported as mean ± standard deviation ($\bar{x} \pm s$). Comparisons between the two groups were performed using Student's *t* test, and Chi-square test was used for the comparison of rate. Values of $P<0.05$ were considered significant. The primary analysis was conducted on the full analysis set (FAS), which comprised all randomized patients, regardless of whether the patients received any study medication.

## RESULTS

### Baseline Characteristics of Patients

A total of 160 patients were enrolled from 6 clinical centers in this study, 80 patients in each group (Figure 1). There was no significant difference on patients' demographic profiles between the two groups ($P>0.05$, Table 1).

### Comparison of ETT between Two Groups

Compared with baseline, the exercise duration in the GXN and control groups was both extended after treatment. The change of exercise duration in the GXN group was statistically significant ($P<0.05$), but there was no statistical difference in the control group ($P>0.05$). The subgroup analysis was the same (Table 2).

There was no statistical difference in the change of exercise duration between the GXN and control groups ($P>0.05$). However, the change of exercise duration in the GXN subgroup was better than that in the control subgroup ($P<0.05$, Table 2).

### Comparisons of Symptom Scores of Angina Pectoris between Two Groups

There was no statistical difference in angina pectoris symptom scores between GXN and control groups (11.73 ± 3.89 *vs*. 10.85 ± 4.25, $P>0.05$) at baseline. After 12-week treatment, the scores of GXN and control groups were both significantly decreased compared with before treatment ($P<0.01$), and the GXN group was superior to the control group at 10 and 12 weeks ($P<0.01$, Figure 2A). The effective rates

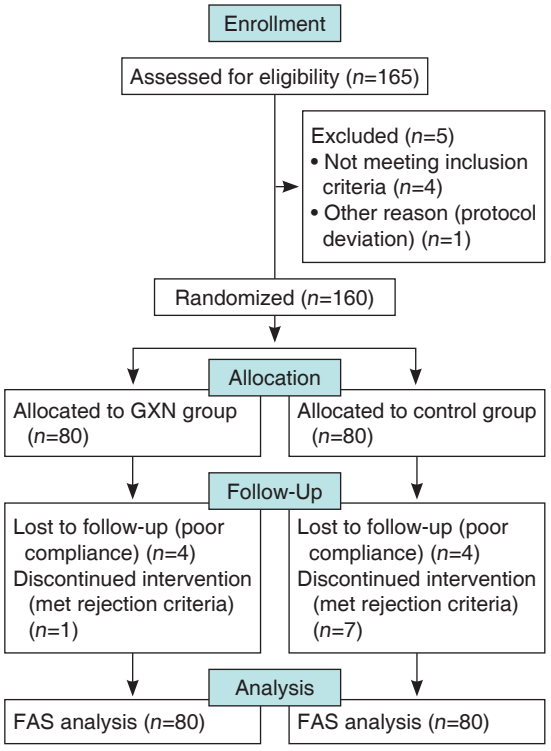


**Figure 1. Flow Chart of Participants Enrollment in GXN Trial**

**Table 1. Baseline Characteristics of Patients in Both Groups ($\bar{x} \pm s$)**

| Characteristic | Control (80 cases) | GXN (80 cases) |
|---|---|---|
| Age (Year) | 57.15 ± 6.07 | 57.83 ± 6.83 |
| Sex (Male/female, case) | 37/43 | 40/40 |
| Weight (kg) | | |
| Male | 72.55 ± 8.01 | 71.04 ± 6.60 |
| Female | 64.29 ± 8.05 | 62.54 ± 5.75 |
| Height (cm) | | |
| Male | 170.34 ± 4.10 | 169.84 ± 3.16 |
| Female | 160.33 ± 3.91 | 160.04 ± 3.77 |
| Body mass index (kg/m$^2$) | | |
| Male | 25.03 ± 2.82 | 24.62 ± 2.07 |
| Female | 24.98 ± 2.73 | 24.41 ± 2.07 |
| Pulse (Beat per min) | 70.74 ± 8.12 | 72.56 ± 8.41 |
| Systolic blood pressure (mm Hg) | 128.89 ± 9.52 | 128.82 ± 10.76 |
| Diastolic blood pressure (mm Hg) | 78.38 ± 6.99 | 79.25 ± 6.92 |
| Diabetes [Case (%)] | 2 (2.50) | 4 (5.00) |
| Hypertension [Case (%)] | 23 (28.75) | 26 (32.50) |
| Hyperlipidemia [Case (%)] | 13 (16.25) | 14 (17.50) |

Chin J Integr Med 2019 Sep;25(9):684-690

**Table 2. Comparison of Exercise Duration of Pre- and Post-Treatment between Two Groups (s, $\bar{x} \pm s$)**

| Group | Case | Exercise duration | | | In group | | $(d_1-d_2) \pm s$ | Between groups | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before treatment | After treatment | Change | *t* | *P* | | *F* | *P* |
| Control | 80 | 486.63 ± 293.12 | 495.39 ± 299.55 | –8.22 ± 98.36 | 0.74 | 0.4601 | 29.28 ± 17.67 | 2.75 | 0.0995 |
| GXN | 80 | 471.89 ± 275.95 | 509.42 ± 276.11 | –37.54 ± 120.56 | 2.78 | 0.0067 | | | |
| Sub-Control | 28 | 351.21 ± 75.15 | 366.89 ± 95.21 | –15.68 ± 80.05 | 1.04 | 0.3092 | 63.10 ± 96.96 | 2.23 | 0.0314 |
| Sub-GXN | 23 | 315.57 ± 110.57 | 394.35 ± 128.80 | –78.78 ± 114.35 | 3.30 | 0.0032 | | | |

Notes: GXN: Guanxinning Tablet; $d_1$: mean of control group, $d_2$: mean of GXN group

in the GXN group were significantly higher than those in the control group at 6, 8, 10 and 12 weeks after treatment (*P*<0.05 or *P*<0.01, Figure 2B and Table 3).

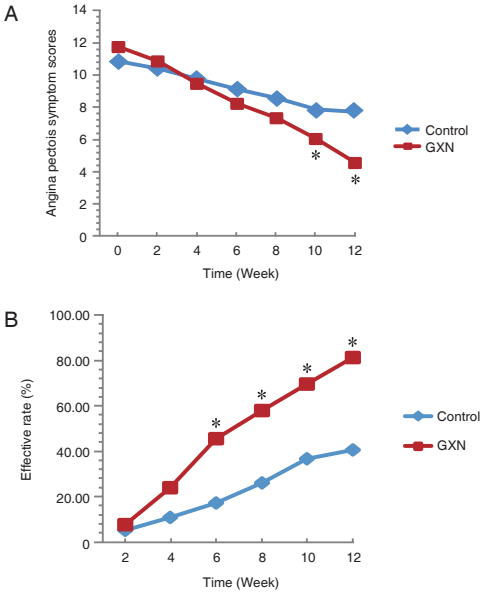


**Figure 2. Comparisons of Symptom Scores and Effective Rate of Angina Pectoris between Two Groups**

Notes: A: total angina pectoris symptom scores for each group; B: effective rate of angina pectoris. **P*<0.01 *vs*. control group

## Comparisons of CM Symptom Scores between Two Groups

There was no statistical difference in CM syndrome score between GXN group and control group (8.11 ± 2.22 *vs*. 7.54 ± 2.42, *P*>0.05) at baseline. The scores of two groups were decreased by 5.23 ± 2.37 and 3.29 ± 2.17, respectively after 12 weeks (*P*<0.01). The GXN group was superior to the control group at 10 and 12 weeks after treatment (*P*<0.05 or *P*<0.01, Figure 3A). The effective rates in the GXN group were significantly higher than those in the control group at 8, 10 and 12 weeks (*P*<0.05 or *P*<0.01, Figure 3B and Table 3).

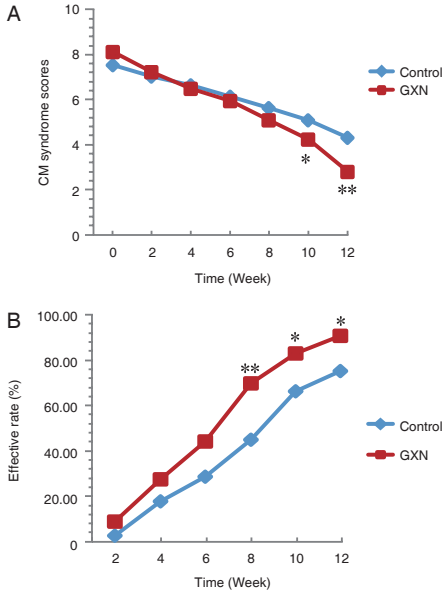


**Figure 3. Comparisons of CM Symptom Scores and Effective Rate between Two Groups**

Notes: A: total CM symptom scores for each group; B: effective rate of CM symptoms. **P*<0.05, ***P*<0.01 *vs*. control group

## Curative Effect on ECG

After treatment, the significant effective rate and effective rate of ECG in GXN group were significantly higher than those in the control group (*P*<0.05, Table 3).

**Table 3. Comparisons of Angina Pectoris, CM Symptom and ECG after 12 Weeks between Two Groups [Case (%)]**

| Group | Item | Case | Significant effect | Effect | No effect | Worsening | Effective rate |
|---|---|---|---|---|---|---|---|
| Control | Angina pectoris | 69 | 9 (13.04) | 19 (27.54) | 39 (56.52) | 2 (2.90) | 28 (40.58) |
| | CM symptom | 69 | 16 (23.19) | 36 (52.17) | 17 (24.64) | — | 52 (75.36) |
| | ECG | 52 | 0 | 14 (26.92) | 31(59.62) | 7 (13.46) | 14 (26.92) |
| GXN | Angina pectoris | 75 | 26 (34.67)* | 35 (46.66)* | 14 (18.67) | 0 | 61 (81.33)* |
| | CM symptom | 75 | 39 (52.00) | 29 (38.67) | 7 (9.33) | — | 68 (90.67)* |
| | ECG | 59 | 6 (10.17)* | 21 (35.59)* | 29 (49.15) | 3 (5.08) | 27 (45.76)* |

Note: **P*<0.05 *vs*. control group

### Comparisons of Nitroglycerin Intake of Patients between Two Groups

The nitroglycerin withdrawal rate in the GXN group was significantly higher than that in the control group ($P$<0.05, Table 4).

**Table 4. Comparisons of Nitroglycerin Intake between Two Groups [Case (%)]**

| Group | Case | Stop | Decrease | Same | Increase |
|---|---|---|---|---|---|
| Control | 39 | 11 (28.21) | 15 (38.46) | 12 (30.77) | 1 (2.56) |
| GXN | 41 | 29 (70.73)* | 9 (21.95) | 3 (7.32) | 0 |

Note: *$P$<0.05 *vs*. control goup

### Safety Evaluation

Throughout the study, no death or serious AE was reported. There were 6 cases of minor AEs in the GXN group (7.50%), including urinary infection, prostatitis, and upper respiratory tract infection. Eight of minor AEs were reported in the control group (10.00%), including abnormal liver function, vulva cotamination, urinary tract infection, and dry lips. These AEs were not considered to be causally related to the study drugs by the investigator judgement.

## DISCUSSION

The morbidity and mortality rates of CHD are increasing dramatically in China, and its prevention is of critical importance. Thus, treatment for CHD has gradually become a hot topic in medical field.[17] In recent years, many studies have indicated that blood stasis correlates with an abnormal hemorheology, which plays a key role in the development of CHD. Therefore, CMs that activate blood and dissolves stasis are important therapies in CHD.[18,19]

Either single CM or compound preparations can have multiple target effects in the prevention and treatment of cardiovascular disease. *S. miltiorrhiza* and *L. chuanxiong* have been widely used to treat cardiovascular disease, angina pectoris, and headache for hundreds of years in China.[20,21] A meta-analysis studying the effect of GXN Injection (冠心宁注射液) on angina pectoris showed that it was an effective treatment and had potentially beneficial effects on cardiovascular diseases by enhancing coronary blood flow, improving the myocardial systolic functions, and protecting myocardial cells.[22] Cheng, et al[23] investigated the effects of GXN Injection on rats suffering from myocardial infract, and found that GXN Injection protected the myocardium from ischemia-reperfusion injury and reduced the infract size via the improvement of HSP70 expression. In addition, Chen, et al[4,24] found that GXN significantly ameliorated abnormal blood viscosity and erythrocyte rheological characteristics. It inhibited platelet aggregation and lipid peroxidation to improve secretion from vascular endothelial cells, and protected vascular function in aged rats. Thus, the mechanism of GXN may be anti-platelet aggregation, improvement of blood rheology and anti-lipid peroxidation.

The results of this trial demonstrated that treatment with GXN improved the symptoms of angina pectoris and prolonged exercise duration. Exercise treadmill testing is an effective non-invasive method for diagnosing CAD with high sensitivity. This study used ETT as the primary outcome. After 12 weeks of treatment, the exercise duration of GXN group was significantly longer than baseline. Additionally, the symptoms of angina pectoris such as chest tightness, chest pain, and palpitation improved over time in the GXN group. The indices of CM symptoms were significantly better than those in the control group. There were no deaths or serious AEs occurred in the GXN group, neither did drug-related AEs. XBSS is the one of core pathogenesis of CAD. GXN has the effect of promoting circulation and removing stasis, which is consistent with the core pathogenesis. Based on the results of trial, GXN is effective for relieving the angina pectoris symptoms and improving the CM symptoms for stable angina pectoris patients with XBSS.

The limitation of this study is no follow-up after the trial. The effect of GXN on platelet aggregation may improve the long-term prognosis of patients with angina pectoris. Thus, a larger number of patients and long-term follow-up are required to validate the efficacy and safety of GXN in further study.

### Conflict of Interest

This research received a research grant from Chiatai Qingchunbao Pharmaceutical Co., Ltd., China.

### Author Contributions

Gao R and Miao Y were involved in the conception or design of the study; Miao Y, Dong YR, and Liu SR were involved in clinical observation; Wang ML and Jin M collected the data; Sun MY, Gao R, and Jin M analyzed the data and drafted the article.

### Acknowledgement

The authors would like to thank the staff at the Xiyuan Hospital of China Academy of Chinese Medical Sciences, Jilin

Integrated Chinese and Western Hospital, Affiliated Hospital of Changchun University of Chinese Medicine, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Inner Mongolia University for the Nationalities and Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, for their invaluable help in conducting this study.

## REFERENCES

1. Jia Y, Leung SW. Drug efficacy in treating stable angina pectoris: a protocol for network meta-analysis of randomised controlled trials. BMJ Open 2014;4:e005453.
2. Shang H, Zhang J, Yao C, Liu B, Gao X, Ren M, et al. Qi-shen-yi-qi Dripping Pills for the secondary prevention of myocardial infarction: a randomised clinical trial. Evid Based Complement Alternat Med 2013;2013:738391.
3. Lin XJ, Chai JG, Dai JM, Shi XP, Shen Y, Zhang WJ. A method and application for establishing the fingerprint of Guanxinning Tablet 2017;CN105158352B.
4. Chen ML, Wang H, Lin L, Shou QY, Zhou WM, Wang DJ, et al. Effect of Guanxinning Tablet on hemorrheology in aged rats. Lab Anim Comparat Med (Chin) 2006;26:231-233.
5. Pan YM, Ying HZ, Chen ML, Xu JQ, Zhou WM, Wang H, et al. Effects of Guanxinning Tablet on myocardial oxygen consumption in dogs. Lab Anim Comparat Med (Chin) 2007;27:190-191.
6. Wang ML, Pan YM, Jin M, Xu XP, Wang DJ, Ma QX, et al. Establishment of a zebrafish model of thrombosis and the intervention effect of Guanxinning Tablet. Acta Lab Anim Sci Sin (Chin) 2016;24:432-438.
7. The Society of Cardiovascular, Chinese Medical Association. Guidelines for the diagnosis and treatment of chronic stable angina pectoris. Chin J Cardiol (Chin) 2007;35:195-205.
8. McGillion M, Arthur HM, Cook A, Carroll SL, Victor JC, L'Allier PL, et al. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines. Canad J Cardiol 2012;28:S20-S41.
9. Zhang Q, Peng JH, Zhang XN. A clinical study of Safflower Yellow Injection in treating coronary heart disease angina pectoris with Xin-blood stagnation syndrome. Chin J Integr Med 2005;11:222-225.
10. Bruce RA, Hornsten TR. Exercise stress testing in evaluation of patients with ischemic heart disease. Prog Cardiovasc Dis 1969;11:371-390.
11. Association CM. Guideline for diagnosis and treatment of patients with chronic stable angina. Chin J Cardiol (Chin) 2007;35:195-206.
12. Wang YZ, Wang J, Huang Q. Application of subgroup analysis in drug clinical trial. Chin J Clin Pharmacol (Chin) 2012;28:477-480.
13. Zheng XY, ed. Guiding principle of clinical research on new drugs of traditional Chinese medicine. Beijing: China Medic-Pharmaceutical Sciences and Technology Publishing Press;2002:77-80.
14. State Food and Drug Administration. Traditional Chinese medicine, natural medicine treatment of coronary heart disease angina pectoris clinical trials technical guiding principles. Available at http://www.nmpa.gov.cn/WS04/CL2196/323849.html.
15. Chinese Association of the Integration of Traditional and Western Medicine. Diagnostic criteria of blood-stasis symptom-complex. Chin J Integr Tradit West Med (Chin) 1987;7:129.
16. Stone PH, Gratsiansky NA, Blokhin A, Huang Z, Meng LX. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566-575.
17. Shi ZW. Introduction and explanation of the Chinese 2007 guidelines on the diagnosis and treatment of chronic stable angina. Pract J Clin Med (Chin) 2008;5:7-9.
18. He J, Zhu HB, Zheng JH. Meta-analysis of clinical research literature on method of promoting blood circulation and removing blood-stasis for treatment of coronary heart disease. J Pract Tradit Chin Int Med (Chin) 2014;28:1-5.
19. Wu JR, Liu S, Zhang XM, Zhang B. Danshen Injection as adjuvant treatment for unstable angina pectoris: a systematic review and meta-analysis. Chin J Integr Med 2017;23:306-311.
20. Wu JR, Zhang XM, Zhang B, Zhai MD, Sheng XG. Systematic evaluation on Danshen Chuanxiongqin Injection in the treatment of angina pectoris. Chin J Inf Tradit Chin Med (Chin) 2015;22:39-43.
21. Wang Y, Guo G, Yang BR, Xin QQ, Liao QW, Lee SM, et al. Synergistic effects of Chuanxiong-Chishao herb-pair on promoting angiogenesis at network pharmacological and pharmacodynamic levels. Chin J Integr Med 2017;32:654-662.
22. Jia Y, Leung SW, Lee MY, Cui G, Huang X, Pan F. The efficacy of Guanxinning Injection in treating angina pectoris: systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2013;2013:282707.
23. Cheng XL, Yan XT, Tu ZL, Xiao MS, Wang XT, Luo DQ. Protective effect of Guanxinning Injection on myocardial ischemia reperfusion injury in rats and effect on heat shock protein 70 expression. Chin J Hosp Pharm (Chin) 2009;29:1080-1082.
24. Chen ML, Shou QY, Pan YM, Zhang JB, Sang R, Guan MW, et al. Inhibitive and protective effects of Guanxinning Tablets on platelet aggregation and vascular endothelium in qi stagnation and blood stasis rats. Chin J Clin Pharm Therap (Chin) 2005;10:586-589.

(Accepted May 5, 2017; First Online July 13, 2019)
Edited by YU Ming-zhu