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Guanxinning for Residual Inflammation of Stable Coronary Artery Disease: A Pilot Randomized Controlled Trial

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Background: Despite statins and other medications central to atherosclerotic cardiovascular disease (ASCVD) secondary prevention, stable coronary artery disease (SCAD) patients remain at significant cardiovascular risk, partly due to residual inflammation risk (RIR). This study aims to assess if adding Guanxinning to standard ASCVD therapy further mitigates RIR in SCAD patients.

Methods: In a prospective, randomized, single-blind endpoint design, 50 patients with SCAD who received ASCVD standardized treatment strategy were randomly assigned to either take Guanxinning tablets (4 tablets, thrice daily) or no Guanxinning tablets and were followed up for an average of 12 weeks. The primary outcomes were changes in inflammation-related indicators, including interleukin-2 (IL-2), IL-4, IL-6, tumor necrosis factor-α (TNF-α), and high sensitivity C-reactive protein (hs-CRP).

Results: Compared with the control group, the intervention group showed significantly greater decreases in the levels of IL-2, IL-6, TNF-α, and hs-CRP (all $P < 0.05$). However, there was no significant difference in the IL-4 level between the two groups ($P > 0.05$). Compared with the control group, there were also significant improvements in endothelial function-related indicators (vascular endothelial growth factor (VEGF), nitric oxide (NO), and peroxisome proliferator-activated receptor-γ (PPAR-γ)), blood lipid profile (total cholesterol (Tch), low-density lipoprotein cholesterol (LDL-C)), and chest pain related scores (angina and Traditional Chinese medicine syndrome scores) in the intervention group (all $P<0.05$). There was no significant difference in the triglyceride (TG) and carotid intima-media thickness between the two groups ($P<0.05$). Compared to the control group, there was no significant difference in the white blood cell line, liver and kidney function, anemia, and bleeding in the intervention group (all $P<0.05$).

Conclusion: The addition of Guanxinning tablets (4 tablets, thrice daily) to the standard treatment strategy for ASCVD was associated with a reduction in the RIR in patients with SCAD and demonstrated good safety.

Plain Language Summary: In the quest for a heart-healthy life, even with statins at our side, some folks with stable heart troubles still face a sneaky foe: lingering inflammation. Our study explored whether adding Guanxinning, a traditional Chinese medicine, to the standard treatment might help. Over 12 weeks, patients who took Guanxinning along with their usual heart meds showed promising signs of reduced inflammation and improved heart health markers. These preliminary positive signs hint at the potential benefits of Guanxinning, which, however, need further studies to confirm. Fortunately, it appears to be safe to use Guanxinning alongside conventional treatments for now. As we delve deeper into the mysteries of heart health, every promising discovery brings us one step closer to developing better therapeutic strategies.

Keywords: Guanxinning, stable coronary artery disease, risk of residual inflammation, secondary prevention

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is considered to be a chronic low-grade inflammatory disease of arterial intima driven by lipids.[1–5] Current guidelines[6–8] advocate for intensified lipid-lowering therapy. However, a multitude of clinical trials[9–11] involving statins, non-statin medications, and combination therapies demonstrated that despite significant reductions in low-density lipoprotein cholesterol (LDL-C) levels, a residual risk of cardiovascular disease (CVD) persists. This residual risk may be associated with ongoing inflammation that remains after intensified LDL-C lowering treatments.[12,13] Ridker et al[13] conducted a collaborative analysis of three large-scale randomized trials, and the results showed that in patients receiving contemporary statin therapy, the risk of residual inflammation (RIR) assessed by high-sensitivity C-reactive protein (hs-CRP) was a stronger predictor of future cardiovascular events and mortality risk compared to LDL-C assessed cholesterol. In addition to hs-CRP, many inflammation-related indicators have been found to be associated with the prognosis of stable coronary artery disease (SCAD).[14–17] Anti-inflammatory treatment has the potential to become part of the standard treatment strategy for ASCVD in the future. Colchicine, a traditional anti-inflammatory drug, has recently been found to improve the residual cardiovascular risk in patients with SCAD, but its potential suppressive effect on the leukocyte series still raises concerns about its safety, making the search for a milder anti-inflammatory drug an urgent priority.[18,19]

Guanxinning tablets, composed of two commonly used traditional Chinese medicines, Salvia miltiorrhiza and Ligusticum chuanxiong, are mainly used to treat stable angina pectoris.[20,21] The network pharmacology study for Guanxinning found that it may exert anti-inflammatory effects through targets such as interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) to improve stable angina.[22] However, further study was needed to determine whether it could reduce the RIR.

We designed the trial to test the hypothesis that the combination of Guanxinning and ASCVD standard treatment strategy is more effective in reducing the RIR than the ASCVD standard treatment strategy alone, with acceptable safety, in patients with SCAD.

Methods

The data supporting the findings of this investigator-initiated trial are available from the corresponding author upon reasonable request.

Subjects

This is a prospective, randomized, single-blind endpoint trial. Fifty patients with SCAD were selected from the outpatient and inpatient departments of cardiovascular medicine at Hangzhou traditional Chinese medicine (TCM) Hospital Affiliated to Zhejiang Chinese Medical University between November 2021 and May 2022. This study was approved by the Ethics Committee of Hangzhou TCM (traditional Chinese medicine) Hospital Affiliated to Zhejiang Chinese Medical University (ethics approval number 2021LL013). The clinical trial was registered prospectively with the Chinese Clinical Trial Registry (ChiCTR2200055916), which can be accessed at https://www.chictr.org.cn/. All patients signed informed consent forms.

Inclusion Criteria

(1) Patients with a history of obstructive coronary artery disease and stable symptoms; (2) meeting the diagnostic criteria for blood stasis obstruction pattern of coronary heart disease in TCM; (3) age 30–80 years; (4) voluntarily participating in this trial and signing the informed consent form. The specific diagnostic criteria were detailed in Appendix 1 of the supplementary materials.

Exclusion Criteria

Key exclusion criteria included infection or polyarteritis nodosa, severe cardiopulmonary dysfunction, recent (within 6 months) history of acute myocardial infarction, acute cerebrovascular accident or other craniocerebral injury, and hepatic or renal dysfunction. The specific diagnostic criteria were detailed in Appendix 1 of the supplementary materials.

Dropout Criteria

(1) Poor compliance, not taking medication as instructed or self-adjusting medication, inability to follow-up regularly or insufficient follow-up; (2) occurrence of severe adverse reaction during the trial; (3) patients who voluntarily withdraw informed consent or are lost to follow-up.

Randomization and Interventions

The 50 enrolled patients with stable angina pectoris were randomly divided into intervention and control groups using random number table method.

After enrollment, detailed clinical data of patients were recorded, including gender, age, past medical history, chief complaint, medical history, symptoms and signs, laboratory and examination results, etc. Informed consent forms were signed.

ASCVD standard treatment strategy was used based on the independent decision-making of clinical physicians. (1) Antiplatelet agents: bayaspirin 75–100mg once daily. For patients intolerant to bayaspirin, hydroclopidogrel may be used instead. Patients with percutaneous coronary intervention (PCI) in the past year took both medications concurrently. (2) Lipid-lowering agents: Statins were preferred, such as atorvastatin calcium 10–20mg once daily. (3) Anti-myocardial ischemia medications: angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), such as irbesartan 75~150mg once daily, and β receptor blockers, such as metoprolol succinate 47.5–90mg once daily.

In addition to ASCVD standard treatment strategy, the intervention group also added Guanxinning tablets (Zhengda Chunqiubao Pharmaceutical Co., Ltd., State Food and Drug Administration approval number Z20150028, specifications: 0.38g) 4 tablets three times daily,[23] for a treatment duration of 12 weeks. Two researchers who evaluated the outcomes were blinded and did not participate in the randomization protocol and implementation process of this trial at all. All data analysis was completed by them. The first author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Efficacy Outcomes

The primary efficacy outcomes include inflammation-related indicators such as interleukin-2 (IL-2), IL-4, IL-6, tumor necrosis factor-α (TNF-α), and hs-CRP. The second efficacy outcomes included endothelial function-related indicators (vascular endothelial growth factor (VEGF), nitric oxide (NO), and peroxisome proliferator-activated receptor-γ (PPAR-γ)), blood lipid (total cholesterol (Tch), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)), carotid intima-media thickness, angina pectoris scores, and TCM syndrome differentiation scores. The methods for various testing indicators, and the scoring standards related to chest pain were detailed in Appendices 2 and 3, and Supplementary Tables 1 and 2 of the supplementary materials. All indicators were tested before and 12 weeks after treatment.

Safety Outcomes

The safety outcomes included white blood cell line (number of white blood cells and neutrophils), anemia indicators (hemoglobin and platelet count), bleeding indicators (urinary occult blood and fecal occult blood), liver function (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), and renal function (estimated glomerular filtration rate (eGFR)).

Statistical Analysis

Sample size calculations were conducted using PASS 11 power analysis and sample size calculation software. Based on observations from the preliminary primary endpoint, with a sample size of 20 in the intervention group and 21 in the control group, the study would provide a statistical power of 91% at a 5% two-sided significance level. Considering potential dropouts during follow-up, we therefore planned to recruit 25 participants per group at the time of formal registration. SPSS 26.0 statistical software was used for analysis. Enumeration data were expressed as numbers (%). Measurement data conforming to normal distribution were expressed as means ± standard deviation (means ± SD), and non-normally distributed data were expressed as medians (interquartile range). The method of Shapiro-Wilk was used for

the test of normality. Data that conform to a normal distribution were compared between groups using an Independent Samples *T*-Test, and differences within groups before and after treatment were compared using a Paired Samples *T*-Test. Data that did not conform to a normal distribution was compared between groups using a Mann–Whitney *U*-Test, and differences within groups before and after treatment were compared using a Wilcoxon Signed-Rank Test. Pearson chi-square was used for enumeration data. Bilateral P values <0.05 were considered statistically significant.

Results

Baseline Patient Characteristics

From November 2021 through May 2022, a total of 50 persons participated this study (Figure 1). Five patients in the control group dropped out midway. A total of 45 patients were included in the final analysis, with 25 in the intervention group (median age 66 years, 15 males, 10 females) and 20 in the control group (median age 65 years, 14 males, 6 females). The mean duration of follow-up of these participants was 12 weeks. There were no statistically significant differences in the gender, age, disease course, BMI, hypertension, diabetes, smoking, history of PCI, number of vascular lesions, degree of vascular stenosis, and medication use between the two groups (all P>0.05) (Table 1).

The Levels of Inflammation Related Indicators

Before treatment, there was no statistically significant difference in the levels of IL-2, IL-4, IL-6, TNF-α, and hs-CRP between the two groups (all P>0.05). After treatment, the levels of IL-2, IL-6, TNF-α, and hs-CRP in both groups

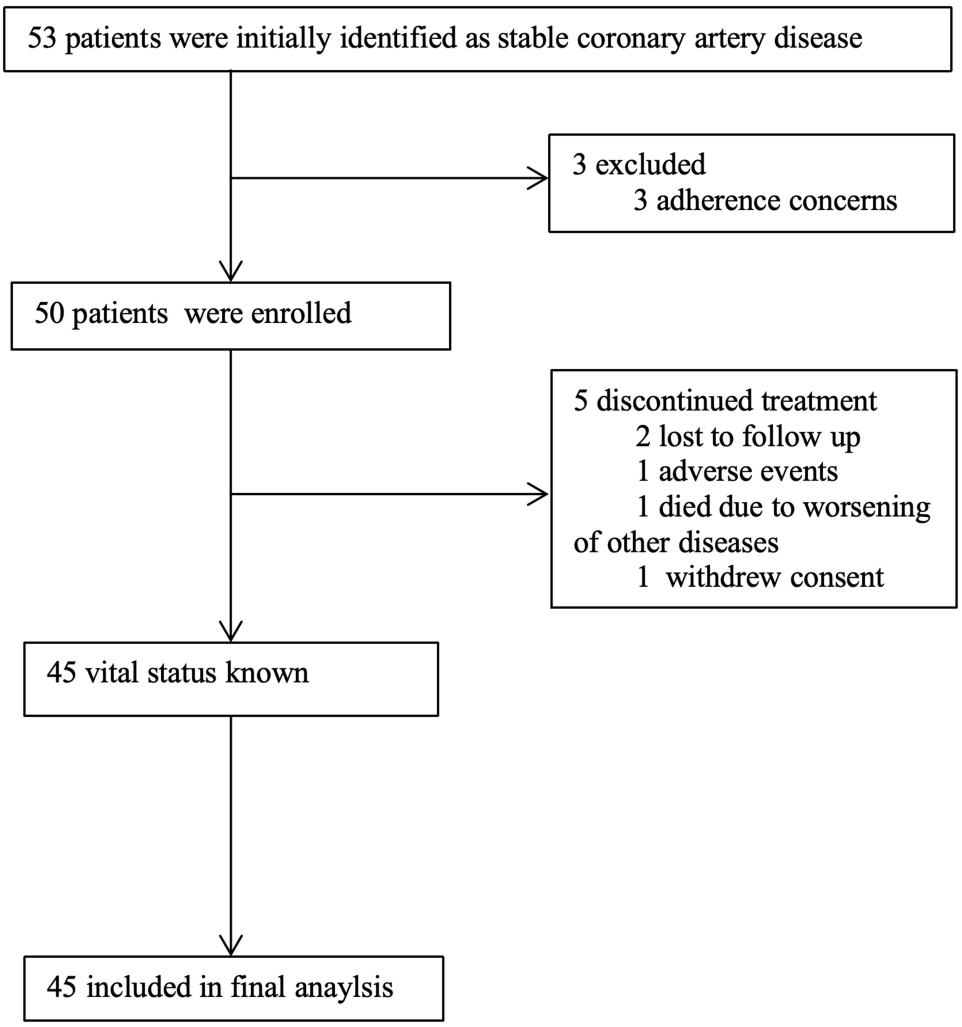

Figure 1 Flow diagram for recruitment of patients.

Table 1 Baseline Characteristics

Characteristics	Intervention Group (N=25)	Control Group (N=20)	*P*
Age, years	66.00 (61.50–69.00)	65.00 (58.25–71.50)	0.954
Male sex, no. (%)	15 (60)	14 (70)	0.486
Female sex, no. (%)	10 (40)	6 (30)	0.486
BMI, kg/m^2	26.06±2.96	24.04±3.05	0.030
Hypertension, n (%)	15 (60)	13 (65)	0.731
Diabetes, n (%)	6 (24)	3 (15)	0.453
Smoking, n (%)	11 (44)	9 (45)	0.947
History of PCI, n (%)	14 (56)	11 (55)	0.947
Number of vascular lesions, n (%)			0.874
Single branch	10 (40)	9 (45)	
Double branch	7 (28)	6 (30)	
Three or more	8 (32)	5 (25)	
The degree of vascular stenosis, n (%)			0.592
50%-70%	12 (48)	8 (7140)	
70%-90%	13 (52)	12 (60)	
Medication use, n (%)			
Antiplatelet agents	25 (100)	20 (100)	–
Lipid-lowering agents	25 (100)	20 (100)	–
β receptor blockers	20 (80)	15 (75)	0.688
ACEI/ARB	9 (36)	8 (40)	0.783
PPI	18 (72)	12 (60)	0.396

Note: Values are numbers (%), medians (interquartile ranges), or means ± standard deviation.
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

decreased compared to before (all P<0.05), but there was no significant statistical difference in the level of IL-4 in both groups compared to before (both P>0.05). After treatment, the intervention group showed a more significant decrease in the levels of IL-2, IL-6, TNF-α, and hs-CRP than the control group (all P<0.05), but there was no significant statistical difference in the level of IL-4 compared to the control group (P>0.05) (Table 2).

The Levels of Endothelial Function Related Indicators

Before treatment, there was no statistically significant difference in the levels of VEGF, NO, and PPAR-γ between the two groups (all P>0.05). After treatment, the levels of VEGF, NO, and PPAR-γ in both groups decreased compared to before (all P<0.05). The levels of VEGF, NO, and PPAR-γ in the intervention group showed a more significant decrease than in the control group after treatment (all P<0.05) (Table 3).

Table 2 The Levels of Inflammation-Related Indicators

	Intervention Group (N=25)	Control Group (N=20)	*P*
IL-2, ng/mL			
Before treatment	1.17 (1.00–1.40)	1.34 (1.26–1.50)	0.071
After treatment	0.88 (0.58–1.14)	1.25 (1.10–1.33)	0.002
P	<0.001	<0.001	
IL-4, pg/mL			
Before treatment	66.51±19.18	62.74±23.36	0.555
After treatment	58.30±19.47	58.87±18.19	0.920
P	0.07	0.282	
IL-6, pg/mL			
Before treatment	59.24 (49.94–83.56)	86.94 (62.24–91.19)	0.584
After treatment	58.24 (38.88–73.98)	70.39 (53.97–83.62)	0.022
P	<0.001	0.002	
TNF-α, pg/mL			
Before treatment	75.58±26.61	76.63±20.75	0.886
After treatment	52.09±19.83	68.44±17	0.005
P	<0.001	0.009	
Hs-CRP, mg/L			
Before treatment	1.09 (0.53–2.65)	0.99 (0.51–2.50)	0.749
After treatment	0.61 (0.41–1.95)	1.03 (0.64–5.39)	0.039
P	<0.001	0.117	

Note: Values are medians (interquartile ranges), or means ± standard deviation.
Abbreviations: Hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α.

Table 3 The Levels of Endothelial Function-Related Indicators

	Intervention Group (N=25)	Control Group (N=20)	*P*
VEGF, pg/mL			
Before treatment	235.61 (215.85–254.94)	237.13 (224–244.12)	0.918
After treatment	268.29 (249.07–287.83)	253.52 (244.57–265.45)	0.032
P	<0.001	<0.001	
NO, pg/mL			
Before treatment	41.68 (37.11–45.40)	36.51 (34.44–41.94)	0.068
After treatment	50.84 (44.93–54.94)	43.15 (39.91–48.05)	0.021
P	<0.001	<0.001	

(*Continued*)

Table 3 (Continued).

	Intervention Group (N=25)	Control Group (N=20)	*P*
PPAR-γ, pg/mL			
Before treatment	329.84±15.77	327.88±16.06	0.683
After treatment	348.60±16.13	338.66±16.35	0.047
P	<0.001	<0.001	

Note: Values are medians (interquartile ranges), or means ± standard deviation.
Abbreviations: NO, nitric oxide; PPAR-γ, proliferator-activated receptor-γ; VEGF, vascular endothelial growth factor.

The Levels of Blood Lipid and Carotid Intima-Media Thickness

Before treatment, there was no statistically significant difference in the levels of Tch, LDL-C, HDL-C, and carotid intima-media thickness between the two groups (all P>0.05). After treatment, both groups exhibited a significant decrease in the levels of Tch and LDL-C compared to pre-treatment levels (both $P < 0.05$). However, there were no significant differences in the levels of TG, HDL-C, or carotid intima-media thickness in the intervention group (all $P > 0.05$). Similarly, the levels of HDL-C and carotid intima-media thickness in the control group did not show significant changes ($P > 0.05$). In contrast, the level of TG in the control group significantly increased compared to before ($P < 0.05$).

After treatment, the intervention group showed a more significant decrease in the levels of Tch and LDL-C than the control group (both P<0.05), but there was no significant statistical difference in the levels of TG, HDL-C, and carotid intima-media thickness compared to the control group (all P>0.05) (Table 4).

Table 4 The Levels of Blood Lipid and Carotid Intima-Media Thickness

	Intervention Group (N=25)	Control Group (N=20)	*P*
Tch, mmol/L			
Before treatment	3.69 (3.25–4.69)	3.83 (3.33–4.43)	0.964
After treatment	3.29 (3.09–3.59)	3.62 (3.25–4.01)	0.036
P	0.001	0.011	
TG, mmol/L			
Before treatment	1.51 (1.22–1.79)	1.06 (0.80–1.30)	0.005
After treatment	1.20 (0.85–2.04)	1.23 (0.91–1.50)	0.758
P	0.353	0.033	
LDL-C, mmol/L			
Before treatment	2.23 (1.98–3.06)	2.73 (2.16–2.94)	0.392
After treatment	1.88 (1.64–2.04)	2.27 (1.82–2.61)	0.006
P	<0.001	0.002	
HDL-C, mmol/L			
Before treatment	0.93 (0.89–1.09)	0.92 (0.81–1.04)	0.749
After treatment	0.9 (0.79–1.01)	0.89 (0.81–1.02)	0.973
P	0.192	0.370	

(*Continued*)

Table 4 (Continued).

	Intervention Group (N=25)	Control Group (N=20)	*P*
Carotid intima-media thickness, mm			
Before treatment	1 (0.9–1.1)	0.9 (0.9–1)	0.213
After treatment	1 (0.9–1.1)	0.9 (0.8–1)	0.219
P	0.317	0.236	

Note: Values are medians (interquartile ranges).
Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Tch, total cholesterol; TG, triglyceride.

Adverse Event

Before treatment, there were no statistically significant differences in white blood cell count, neutrophil count, hemoglobin, platelet count, urinary occult blood, fecal occult blood, ALT, AST, and eGFR (all P>0.05). After treatment, there were no significant statistical differences in the aforementioned indicators between the two groups compared to before treatment (all P>0.05). Similarly, after treatment, compared to the control group, there were no significant statistical differences in the aforementioned indicators for the intervention group (all P>0.05) (Table 5).

Table 5 Safety Outcomes

	Intervention Group (N=25)	Control Group (N=20)	*P*
WBC, $*10^9$/L			
Before treatment	6.92± 1.67	6.40± 1.86	0.328
After treatment	6.97± 1.82	6.54± 1.70	0.425
P	0.848	0.668	
Neutrophils, $*10^9$/L			
Before treatment	4.12±1.07	3.76± 1.35	0.334
After treatment	4.33±1.49	3.72± 1.00	0.124
P	0.433	0.846	
Hemoglobin, g/L			
Before treatment	140.76± 16.64	139.05± 17.54	0.740
After treatment	138.92± 20.10	139.35± 20.70	0.944
P	0.582	0.933	
Platelets, $*10^9$/L			
Before treatment	217 (182–270.5)	205.50 (168.00–241.75)	0.706
After treatment	225 (200.25–264.75)	217.5 (170.25–263.75)	
P	0.920	0.153	

(*Continued*)

Table 5 (Continued).

	Intervention Group (N=25)	Control Group (N=20)	*P*
UOB, no. (%)			
Before treatment	0 (0)	2 (10)	0.106
After treatment	0 (0)	1 (5)	0.258
P	–	0.548	
FOB, no. (%)			
Before treatment	2 (8)	1 (5)	0.688
After treatment	0 (0)	2 (10)	0.106
P	0.157	0.548	
ALT, U/L			
Before treatment	24 (16.5–37)	20.50 (14.25–31.25)	0.397
After treatment	28 (17.5–42.75)	20.00 (15.25–32.75)	0.105
P	0.103	0.614	
AST, U/L			
Before treatment	24 (20–33)	23.50 (19.00–33.75)	0.964
After treatment	23 (20.25–28.75)	25.00 (16.75–27.25)	0.688
P	0.879	0.559	
Estimated GFR, mL/min/1.73 m^2			
Before treatment	87.26±15.31	90.01±12.22	0.516
After treatment	89.39±16.48	86.96±15.07	0.612
P	0.176	0.087	

Note: Values are medians (interquartile ranges), or means ± standard deviation.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FOB, fecal occult blood; GFR, glomerular filtration rate; WBC, white blood cell count; UOB, urinary occult blood.

Angina Pectoris Scores and TCM Syndrome Differentiation Scores

Before treatment, there was no statistically significant difference in the overall mean angina pectoris scores and TCM syndrome differentiation scores between the two groups (both P>0.05). After treatment, the TCM syndrome differentiation scores and angina pectoris scores in both groups were significantly lower than before treatment (both P<0.05). After treatment, the decreases in angina pectoris scores and TCM syndrome differentiation scores were more significant in the intervention group compared to the control group (both P<0.05) (Supplementary Tables 3 and 4).

Discussion

With the popularization of ASCVD secondary prevention strategies, a large proportion of patients with SCAD receive treatment with proven effective secondary prevention strategies, namely standard treatment strategies. In these patients, compared with the ASCVD standard treatment strategy alone, the combination of Guanxinning (4 tablets, thrice daily) and ASCVD standard treatment strategy further reduced inflammation-related indicators (IL-2, IL-6, TNF-α, and hs-CRP), improved blood lipid profiles (Tch and LDL-C), further improved endothelial function-related indicators (VEGF, NO, and PPAR-γ), and further improved the score of angina pectoris, while the total effective rate of TCM syndrome score increased by 32%. However, there was no significant difference in IL-4, HDL-C, TG, and carotid intima-media

thickness. Compared with the ASCVD standard treatment strategy alone, the combination of Guanxinning (4 tablets, thrice daily) and ASCVD standard treatment strategy did not reduce the white blood cell line, increase the risk of liver and kidney dysfunction, anemia, and bleeding.

Atherosclerosis is an important link in the development of coronary artery disease. The pathogenesis of atherosclerosis is complex and involves multiple pathological factors. In addition to the theory of lipoprotein infiltration, inflammation is also considered one of the important theories, which was first proposed by Virchow et al in 1856. Atherosclerosis is believed to be an inflammatory response involving the arterial intima. Unlike typical inflammation, CRP can accumulate at the site of atherosclerotic lesions. This accumulation triggers endothelial cells to produce and display adhesion molecules and chemokines, which in turn attract monocytes and macrophages. These immune cells are then stimulated to release additional inflammatory mediators, such as interleukins and TNF-α. Furthermore, they engulf LDL-C, leading to the formation of foam cells. The accumulation of foam cells within the plaque not only thickens and hardens the arterial walls but also impairs the function of the vascular endothelium, thereby facilitating the progression of atherosclerosis.[1,24,25]

Various anti-inflammatory drugs combined with ASCVD standard treatment strategies have been tested for long-term cardiovascular prevention. Previous studies[18,19] suggested that the long-term oral administration of colchicine can reduce the risk of a variety of cardiovascular events in patients with a history of myocardial infarction or SCAD. Within these studies, certain data sets demonstrated an improvement in CRP levels following anti-inflammatory treatment. This finding indicated that a decrease in RIR may be an important factor in the reduction of residual cardiovascular risk. However, the use of colchicine was associated with an increased risk of certain adverse effects, including gastrointestinal discomfort, pneumonia, and rhabdomyolysis. Additionally, the Low-Dose Colchicine 2 (LoDoCo2)[19] trial reported a 1.51-fold increase in the risk of non-cardiovascular mortality associated with colchicine use, raising concerns about its safety profile.

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS)[26] included patients with a history of myocardial infarction and elevated baseline CRP levels. It demonstrated that the risk of cardiovascular events could be significantly reduced by combining the long-term oral anti-inflammatory drug Canakinumab with the standard treatment strategy for ASCVD. The CRP level in patients who received Canakinumab combined with the standard treatment strategy for ASCVD had decreased compared to those who received the ASCVD standard treatment strategy alone. This suggested the importance of reducing RIR. However, it was important to note that the use of Canakinumab may result in a reduction of neutrophil levels and consequently, an increased susceptibility to infections. The Cardiovascular Inflammation Reduction Trial (CIRT)[27] enrolled patients who had experienced a myocardial infarction or had multiple instances of obstructive coronary artery disease. However, the administration of the long-term oral anti-inflammatory medication methotrexate, when combined with the standard treatment strategy for atherosclerotic cardiovascular disease (ASCVD), did not demonstrate a reduction in the risk of subsequent cardiovascular events. In this study, the median CRP level at patient enrollment was 1.6 mg/L. After 8 months of treatment, no significant difference was observed in CRP levels between the group receiving methotrexate combined with the standard ASCVD treatment strategy and the group receiving the ASCVD standard treatment alone. The lack of reduction in CRP levels after treatment indicated that RIR was not diminished, which in turn suggested that residual cardiovascular risk remained unchanged. This highlighted the intimate link between RIR and residual cardiovascular risk, as the standard ASCVD treatment strategy did not effectively address the underlying inflammation. Moreover, the use of methotrexate was associated with an increase in liver enzyme levels, a higher incidence of non-melanoma skin cancer, and a decrease in both white blood cell count and hematocrit.

In this study, the combination of Guanxinning and ASCVD standard treatment strategy can effectively reduce the CRP level and other inflammatory indicators that affect the progression of atherosclerosis. Guanxinning is a traditional Chinese patent medicine approved by the China Food and Drug Administration for listing in 2015. It is a compound of salvia miltiorrhiza and Chuanxiong. Salvia miltiorrhiza is mainly composed of lipid-soluble compound tanshinone and water-soluble compound rosmarinic acid.[28] Many studies have reported the anti-inflammatory effects of tanshinone and rosmarinic acid. Tanshinone could inhibit the nuclear factor kappa-B (NF-κB) signaling pathway in macrophages to prevent the expression of inflammatory related factors (such as IL-2, IL-4, IL-6, and TNF-α), while rosmarinic acid could promote cholesterol efflux from macrophages through the PPAR-γ-related pathway.[29–32] The representative components of Chuanxiong are Shenqi lactone A (Z-ligustrazine) and ferulic acid (4-hydroxy-3-methoxycinnamic acid).[33] In animal experiments, it was found that Shenqi lactone A significantly reduced the levels of serum interleukin and TNF-α in

asthmatic rats, which may exert an anti-inflammatory response through upregulation of cAMP-PKA pathway activity.[34] And Ferulic acid is also believed to reduce interleukin levels and alleviate inflammation.[35,36] According to the inflammation theory, the key ingredients in Guanxinning act on multiple fronts to curb the inflammatory response. They prevent macrophages from producing inflammatory mediators and also reduce the absorption of LDL-C, which in turn decreases the formation of foam cells. This reduction in foam cell generation corresponds to fewer sites for CRP deposition, thereby effectively impeding the advancement of atherosclerosis. Although no significant changes in carotid intima-media thickness were found in this study, this may be attributed to the short follow-up period. It is important to highlight that while traditional anti-inflammatory medications such as colchicine, canakinumab, and methotrexate have been shown to decrease white blood cell or neutrophil counts and potentially increase the risk of infection, raising safety concerns.[18,19,26,27] Unlike other medications, Guanxinning does not appear to reduce the levels of white blood cells or neutrophils. This difference may be due to the fact that Guanxinning primarily exerts its anti-inflammatory effects by acting on inflammatory mediators, rather than by inhibiting the production of white blood cells. This mechanism not only lessens the potential suppression of the immune system but also may offer a safer approach to inflammation management, as it reduces the risk of infection associated with lowered white blood cell counts. Furthermore, Guanxinning has also shown good performance in other aspects of safety. It has few adverse reactions in clinical applications, and these reactions are typically mild and can be alleviated after discontinuation of the drug or symptomatic treatment.[23] Safety studies further confirm this, showing that the use of Guanxinning does not increase the risk of liver and kidney dysfunction, anemia, and bleeding. In animal models, Guanxinning has also demonstrated good safety. In acute toxicity tests, Guanxinning tablets have shown a high maximum tolerated dose and acute lethal dose 50, indicating that it is relatively safe for short-term use.[23] These research findings, combined with the safety record of Guanxinning in clinical applications, give us confidence that Guanxinning is a higher safety treatment option, especially suitable for patients who need to avoid the immunosuppressive side effects that traditional anti-inflammatory drugs may bring.

This present study not only found that Guanxinning reduced the risk of residual inflammation on the basis of ASCVD standard treatment strategy but also further improved blood lipid profile and endothelial cell function. Based on inflammatory theory, rosmarinic acid, a key component of Guanxinning, facilitates the removal of cholesterol from macrophages. This action, along with the reduction in multiple inflammatory markers, helps to minimize their penetration into the endothelial layer. Consequently, the observed enhancements in blood lipid profiles and endothelial cell functions could be attributed to the supplementary benefits provided by anti-inflammatory therapies. Moreover, the observed improvements in angina symptoms and TCM syndrome scores aligned with findings from earlier research.[37] Regarding the non-significant changes observed in IL-4 levels, it is possible that while Guanxinning has a significant reducing effect on other inflammatory factors such as IL-2, IL-6, and TNF-α, its impact on IL-4 may be minimal. Moreover, since IL-4 has an anti-inflammatory role in the body, changes in its levels may require a longer duration of treatment to be observed, and the follow-up period in this study may have been too short to capture such changes. As for the non-significant differences in carotid intima-media thickness, this could be because the progression of atherosclerosis is a long-term process, and the follow-up time in this study may not have been sufficient to observe significant changes in carotid intima-media thickness. Additionally, the measurement of carotid IMT is influenced by various factors, including technical errors, operator subjectivity, and biological variation, which may have affected the significance of the results.

In clinical practice, physicians may consider adding Guanxinning treatment for patients who still have residual inflammatory risk after standard therapy, such as those with higher CRP levels or other inflammatory markers. This could potentially help to reduce residual cardiovascular risk. Moreover, Guanxinning's improvement in endothelial cell function suggests that it may contribute to better vascular health. This implies that for patients at risk of endothelial dysfunction, such as those with hypertension, diabetes, or existing cardiovascular diseases, Guanxinning could be considered as an adjunctive treatment.

Our study carries several limitations that deserve attention. As a single-center, small-sample, single-blind pilot trial, it is possible that our findings are affected by ascertainment and reporting biases. Despite 5 participants dropping out during follow-up, the baseline data between the intervention and control groups stayed balanced. The objective measures we used, such as inflammation-related indicators, are not likely to have significantly swayed our results or conclusions. However, the short follow-up period constrained our capacity to detect substantial reductions in carotid intima-media thickness and other outcomes like major adverse cardiovascular events. The small sample size may also restrict the generalizability and statistical

power of our findings. The single-center nature of our study means that the patient population and treatment practices might not mirror those in other regions or settings, urging caution when applying our results to broader populations. Additionally, the lack of a placebo control in our study could have led to an overestimation of subjective outcomes in the intervention group, such as Traditional Chinese Medicine syndrome scores and angina scores. Future large-scale, multicenter clinical trials with longer follow-up periods are necessary to validate the effects of Guanxinning on these outcomes and to further elucidate its potential benefits and safety across diverse patient populations.

Overall, for patients with SCAD, the concurrent use of Guanxinning with the standard treatment strategy for ASCVD was shown to effectively lower RIR, improve blood lipid profiles and endothelial function, and alleviate chest pain symptoms, compared to the ASCVD standard treatment alone. Additionally, the adjunctive therapy with Guanxinning does not seem to elevate the risks of liver or kidney dysfunction, anemia, or bleeding, making it a potentially valuable addition to the management of SCAD.

Ethical Approval and Consent to Participate

All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors approved the final version of the manuscript.

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Disclosure

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