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Efficacy of Yuxintong capsule on cardiorespiratory fitness in patients with stable coronary heart disease: A multicentre, randomized, double-blind, placebo-controlled, parallel-group clinical trial

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ABSTRACT

Ethnopharmacological relevance: Yuxintong capsule, a traditional Chinese patent medicine, has been widely used in the treatment of coronary heart disease (CHD). However, whether it can improve cardiopulmonary fitness (CRF) in patients with CHD remains unclear.

Aim of the study: To evaluate the efficacy and safety of Yuxintong capsule in CRF in patients with stable CHD.

Materials and methods: A multicentre, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in 13 hospitals in China from March 2021 to November 2021, and 404 patients with stable CHD were randomly assigned to receive either Yuxintong capsule and conventional Western medicine (Yuxintong group) or placebo and conventional Western medicine (placebo group) in a 1:1 ratio for 12 weeks (ChiCTR2000041293, December 23, 2020). The primary outcomes were peak oxygen uptake (VO_2peak) and anaerobic threshold (AT). The secondary outcomes were metabolic equivalents (METs), duration and onset time of 1-mm ST-segment depression on electrocardiography (ECG), and 36-Item Short Form Health Survey (SF-36) scores. The main

Abbreviations: AT, anaerobic threshold; ACS, acute coronary syndrome; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; CRF, cardiopulmonary fitness; CPET, cardiopulmonary exercise test; CYTA, corydalis yanhusuo total alkaloids; CONSORT, Consolidated Standards of Reporting Trials; CRO, contract research organization; DSMB, data and safety monitoring board; ECG, electrocardiography; FAS, full analysis set; LSMD, least squares mean difference; METs, metabolic equivalents; MedDRA, Medical Dictionary for Regulatory Activities; NYHA, New York Heart Association; PPS, per protocol set; ROS, reactive oxygen species; RER, respiratory exchange ratio; SAQ, Seattle Angina Questionnaire; SF-36, 36-Item Short Form Health Survey; SS, safety set; SUSARs, suspected unexpected serious adverse reactions; VO_2peak, peak oxygen uptake.

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safety indicators included complete blood count, urinalysis, liver function, renal function, coagulation function, and 12-lead electrocardiogram. And adverse events were recorded throughout the trial.
Results: 369 patients, 187 in the Yuxintong group and 182 in the placebo group, were finally included for analysis. Compared with placebo group, 12-week treatment with Yuxintong showed an improvement in AT (0.98 ± 2.88 vs. 0.12 ± 2.79 mL kg^{-1}·min^{-1}; LSMD, 0.80 [95 % CI: 0.28 to 1.32]; $P < 0.025$), and general health (13.61 ± 15.13 vs. 8.29 ± 14.14; LSMD 5.30, [95 % CI: 2.33 to 8.31]; $P < 0.05$) and vitality scores (12.46 ± 11.32 vs. 6.01 ± 11.41; LSMD 6.43, [95 % CI: 4.13 to 8.31]; $P < 0.05$) on SF-36 scale. The other outcomes did not significantly differ between the two groups. The adverse events were similar between the two groups.
Conclusions: Yuxintong capsule, as an adjunctive therapy to conventional treatment, improved AT, and general health and vitality scores on SF-36 scale in patients with stable CHD. However, the improvements in VO_2peak, METs, and the duration and onset time of 1-mm ST-segment depression on ECG were not statistically significant.

1. Introduction

Despite recent advances in drugs and interventions for coronary heart disease (CHD), many patients continue to experience reduced quality of life and impaired cardiopulmonary fitness (CRF) (Al-Lamee et al., 2018; Rezende et al., 2013; Boden et al., 2007). CRF is a critical physiological indicator of the integrated capacity of the circulatory and respiratory systems to deliver oxygen during exercise (Fan et al., 2020) and is recognized as an independent predictor of cardiovascular disease (CVD) mortality (Ross et al., 2016). In patients with CHD, coronary artery stenosis induces ischemic and hypoxic injury to cardiomyocytes and triggers elevated intracellular reactive oxygen species (ROS), Ca^{2+} overload, and impaired mitochondrial energy synthesis, which contribute to a decline the patients' CRF (Levraut et al., 2003; Chang et al., 2023).

Yuxintong capsule was approved by the China Food and Drug Administration in 2002 (GYZZ20020089) for the treatment of CHD. It is produced by Dalian Shengguang Pharmaceutical Group Co., Ltd., and is composed of Red ginseng (Ginseng Radix et Rhizoma Rubra), *Panax notoginseng* (Burkill) F.H.Chen, and *Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu in a ratio of 3:3:4. The studies indicated that red ginseng extract reduced mitochondrial swelling and membrane permeability, enhanced mitochondrial biogenesis, and improved mitochondrial dysfunction (Zhang et al., 2022; Yang et al., 2022). Ginsenosides Rg1 and Rb1 from red ginseng promoted aerobic respiration and SIRT1-driven mitochondrial biogenesis in cardiomyocytes (Huang et al., 2022). Notoginsenosides, the primary active components of *Panax notoginseng*, enhanced mitophagy, reduced mitochondrial ROS, increased mitochondrial membrane potential and oxygen consumption rate, and diminished oxidative stress injury (Zhou et al., 2018; Zhang et al., 2022). *Corydalis yanhusuo* total alkaloids (CYTA), the primary active components of *Corydalis yanhusuo*, possess both analgesic and cardioprotective properties. CYTA can reduce myocardial infarction area and improve cardiac function by suppressing oxidative stress, mitochondrial damage, apoptosis, and Ca^{2+} overload (Ling et al., 2006; Qi et al., 2024). Our previous studies with acute myocardial ischaemic dogs showed that Yuxintong capsule significantly reduced the area of myocardial infarction, increased the coronary blood flow (Lei et al., 1996), and inhibited the increase in creatine phosphokinase (Lei et al., 1997). The clinical studies demonstrated that Yuxintong capsule inhibited the inflammatory reaction, decreased the reliance on nitroglycerin consumption, alleviated angina symptoms, and promoted the recovery of ischaemic ST-segment changes on electrocardiography (ECG) in CHD patients (Wu et al., 2018; Wei, 2009). However, whether it improves CRF in patients with CHD remains unknown. Therefore, we conducted this clinical trial to evaluate the effects of Yuxintong capsule in combination with conventional Western medication treatment on CRF in patients with stable CHD.

2. Materials and methods

2.1. Study design

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial registered with the Chinese Clinical Trial Registry (ChiCTR2000041293; December 23, 2020). Centralized randomization was performed, stratified by prescribed exercise intensity (low vs. moderate), using permuted blocks within strata (1:1 allocation). Following a 1-week screening period at 13 Grade A tertiary hospitals in mainland China, eligible patients were randomly assigned to the Yuxintong group or the placebo group at a 1:1 ratio for 12 weeks of treatment. Follow-up assessments were conducted at 8 and 12 weeks (±3 days) (Supplementary material 1).

2.2. Ethics

The study adhered to the guidelines of the Declaration of Helsinki of the World Medical Association (World Medical Association, 2013). Ethical approval was obtained from the ethics committees of each study center. All participants provided written informed consent and agreed to the publication of their data. We strictly adhered to the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010) guidelines to report the results of this study (Supplementary material 2).

2.3. Study population

Patients were included in the present study if they met the following criteria: (1) aged between 18 and 75 years; (2) diagnosed with stable CHD according to the 2018 Chinese guidelines (Interventional Cardiology Group of Cardiovascular Branch of Chinese Medical Association, 2018), defined by coronary artery stenosis ≥50 % on coronary angiography or coronary computed tomography angiography, or a clinically stable status for ≥3 months after percutaneous coronary intervention; (3) had symptoms of fatigue or shortness of breath, and typical effort angina; (4) had a history of previous myocardial infarction, or a documented diagnosis of heart failure with New York Heart Association (NYHA) functional class II or less (including heart failure with preserved ejection fraction); and (5) provided written informed consent.

The exclusion criteria were as follows: (1) left main coronary artery stenosis (5th segment) ≥ 50 % or proximal left anterior descending coronary artery stenosis (6th segment) > 70 %; (2) severe aortic stenosis, acute aortic dissection, acute myocarditis or pericarditis, aneurysm, severe pulmonary hypertension, acute pulmonary embolism, pulmonary infarction, emphysema, respiratory failure or other cardiorespiratory diseases; (3) uncontrolled blood pressure with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg; (4) uncontrolled arrhythmia with clinical symptoms or haemodynamic disorders; (5) severe primary hepatic, renal, or haematopoietic system disorders, acute infectious diseases, mental disorders, or other diseases that would render the patient unsuitable for the CPET; (6) pregnancy, planning to achieve pregnancy or lactation; (7) major surgical intervention on the skull or chest and abdomen within 4 weeks and a

bleeding tendency; (8) participated in other clinical trials within the past one month; and (9) allergy to the test drug or its known components.

2.4. Sample size

The primary outcomes were peak oxygen uptake (VO_2peak) and the anaerobic threshold (AT). The trial hypothesis would be supported if a statistically significant between-group difference favoring the Yuxintong group over the placebo group was observed for either outcome. Superiority was tested using a two-sided α of 0.025 to control for multiplicity, with a superiority margin of 0 (Stefanos et al., 2020). The test power (1-β) was set at 80 % with a 1:1 allocation ratio between groups. Based on clinical experience and previous literature (Li et al., 1999), we assumed that after 12 weeks of treatment, the changes in VO_2peak would be 4.5 ± 4.9 mL kg^{-1}·min^{-1} in the Yuxintong group and 2.8 ± 4.9 mL kg^{-1}·min^{-1} in the placebo group. The corresponding changes in AT were assumed to be 0.25 ± 0.28 mL kg^{-1}·min^{-1} and 0.15 ± 0.28 mL kg^{-1}·min^{-1}, respectively. The sample size calculation indicated that 160 participants per group were needed for VO_2peak and 151 for AT. To ensure adequate power for both outcomes and account for a 20 % dropout rate, the final planned sample size was set at 404 participants.

2.5. Randomization and blinding

Randomization was centralized with stratification by prescribed exercise intensity (low vs. moderate) and permuted blocks within strata (1:1 allocation). Allocation was concealed using a secure interactive web-response system. An independent statistician generated the randomization schedule using SAS. Separate sequences for subjects and drug packs were created based on exercise intensity and the allocation ratio. Due to the unfixed sample size per stratum, block randomization was used independently for each, generating 404 codes per stratum (moderate: 001–404; low: 405–808) to accommodate the extreme scenario of all participants being enrolled in one stratum. Participants, investigators, care providers, endpoint adjudicators, and statisticians remained blinded. Placebo was indistinguishable from active product in appearance, taste, and packaging.

2.6. Intervention

The specification of Yuxintong capsule/placebo is 0.33 g/capsule. Patients received treatment with 12 capsules (3.96 g) of Yuxintong capsule/placebo daily (4 capsules, 3 times daily for 12 weeks). High-performance liquid chromatography (HPLC) showed that the main active ingredients of Yuxintong capsule included tetrahydropalmatine, notoginsenoside R1, ginsenoside Rg1, ginsenoside Re, palmatine chloride, berberine hydrochloride, ginsenoside Rf, and ginsenoside Rb1, and we also used Liquid Chromatography Mass Spectrometer (LC/MS) to identify potential active ingredients in Yuxintong capsule (Supplementary material 3).

In accordance with the 2018 ″Guidelines on the Diagnosis and Treatment of Stable CHD" published by the Chinese Medical Association (Interventional Cardiology Group of Cardiovascular Branch of Chinese Medical Association, 2018), all patients in this study were treated with symptom-relieving agents (nitrates), anti-ischaemic drugs (beta blockers and/or calcium channel blockers), antiplatelet drugs (aspirin or clopidogrel), and lipid-lowering drugs (statins). In addition, throughout the study, all participants received low-intensity or moderate-intensity exercise rehabilitation guidance based on their own circumstances (Fletcher et al., 2013). The patients were required to follow the guidance for home exercise three times a week. During the follow-up period, detailed information on the patient's rehabilitation exercise was recorded in a case report form.

All participants underwent CPET on an electronically braked cycle ergometer (Jaeger MasterScreen CPX, Germany). A personalized ramp protocol was employed with the goal of eliciting exhaustion within 8–12 min. The protocol began with a 3-min warm-up at 20 W, followed by a continuous increase in work rate (10, 15, or 20 W per minute) until volitional exhaustion. The criteria for terminating the CPET included reaching the volitional exhaustion criterion (respiratory exchange ratio, RER ≥1.10) or the emergence of limiting symptoms, such as ischemic ECG changes, abnormal elevation or reduction in blood pressure, angina. The reasons for CPET termination and their respective proportions were detailed in supplementary material 4. During the test, a cardiologist continuously monitored the participants' ECG. The VO_2peak was defined as the highest value averaged over eight breathing cycles. AT was determined using the V-slope method by two independent physicians who were blinded to allocation; discrepant readings were adjudicated by a third reviewer. Inter-reader agreement was assessed.

2.7. Outcomes

The primary outcomes included VO_2peak and AT. The secondary outcomes included metabolic equivalents (METs), the duration and onset time of 1-mm ST-segment depression on ECG, and 36-Item Short Form Health Survey (SF-36) scores. These outcomes were measured at baseline and at the 12-week endpoint. Additionally, at the 8-week time point, patient data on vital signs, rehabilitation exercise adherence, adverse events, and concomitant treatments were recorded. The safety of Yuxintong capsule was evaluated based on the incidence of all adverse events and adverse drug reactions observed throughout the trial.

2.8. Data management and quality control

An electronic data capture system was used for online data management in this study. Additionally, a Data and Safety Monitoring Board (DSMB) was convened to periodically review trial data, participant safety, study progress, and quality.

2.9. Statistical analysis

In accordance with the intention-to-treat principle, the randomized subjects who received the trial drugs at least once and had at least one follow-up visit were included in the full analysis set (FAS). Data for patients who were lost to follow-up were imputed using multiple imputation methods. The per protocol set (PPS) included patients who complete the trial without major deviations of protocol. The safety set (SS) included all patients who received at least one treatment after randomization and underwent the safety evaluation. To ensure the accuracy and representativeness of the research results, we analysed the FAS.

The significance level for the primary outcomes was set at 0.025 (two-sided), whereas for the secondary outcomes, it was set at 0.05 (two-sided). For primary and key secondary endpoints, Analysis of Covariance (ANCOVA) was used (with the change from baseline as the outcome; and age, gender, BMI, baseline value, study center, exercise-intensity stratum, and bate-blocker use as covariates). Categorical data were presented in frequency tables and reported as percentages, and between-group differences were assessed with the chi-square test or Fisher's exact test. Continuous variables with a normal distribution are presented as mean ± standard deviation; otherwise, they are presented as median with interquartile range. Student's t-test or the Wilcoxon rank-sum test was used, as appropriate, to analyse between-group differences. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics of patients

From March 2021 to November 2021, 422 patients were screened, of whom 18 did not meet the inclusion criteria. Finally, a total of 404

patients were enrolled and randomly divided into the Yuxintong group and the placebo group. A total of 60 patients (32 patients in the Yuxintong group and 28 patients in the placebo group) dropped out. According to the predefined statistical analysis plan, the full analysis set (FAS) comprised 369 patients, and the safety set (SS) comprised 393 patients (Fig. 1). There were no statistically significant differences in demographic information, comorbidities, beta-blocker use or exercise intensity between the two groups (Table 1).

3.2. Exercise adherence

Exercise adherence was summarized as sessions per week and the proportion achieving the prescribed intensity (heart-rate or RPE targets). The Yuxintong and placebo groups completed a median of 3 sessions per week, with target-intensity attainment of 91.4 % and 93.2 %, respectively.

3.3. Primary outcomes

The within-group comparisons showed that after 12 weeks of treatment, Yuxintong group demonstrated significant improvements from baseline in both VO_2peak (19.23 ± 4.97 vs. 19.98 ± 4.78 mL $kg^{-1}{\cdot}min^{-1}$, $P = 0.002$) and AT (12.44 ± 3.78 vs. 13.42 ± 3.54 mL $kg^{-1}{\cdot}min^{-1}$, $P = 0.001$). In contrast, no significant improvements were observed in placebo group for either VO_2peak (19.67 ± 4.43 vs. 19.79 ± 4.87 mL $kg^{-1}{\cdot}min^{-1}$, $P = 0.59$) or AT (12.76 ± 3.29 vs. 12.87 ± 3.37 mL $kg^{-1}{\cdot}min^{-1}$, $P = 0.57$). For the between-group comparison, the improvement in AT was significantly greater in the Yuxintong group

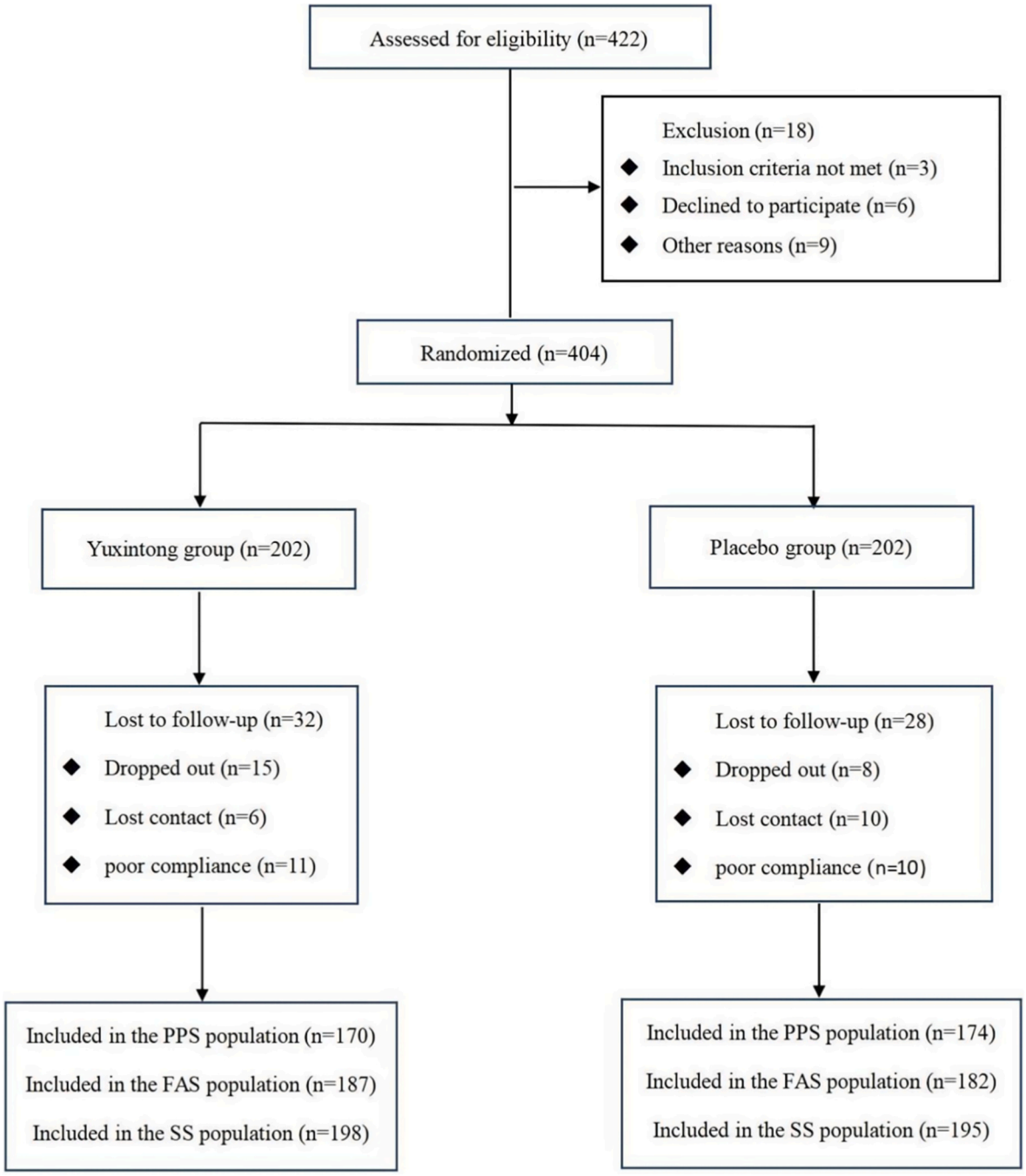

Fig. 1. Flowchart of patient enrolment.

Table 1
Baseline characteristics of the study population.

	Yuxintong group (n = 187)	Placebo group (n = 182)	*P* value
Male	137 (73.26 %)	144 (79.12 %)	0.19
Age (years)	58.83 ± 9.51	57.92 ± 9.85	0.37
Han nationality	179 (95.72 %)	174 (95.60 %)	0.96
Height (cm)	166.81 ± 8.33	167.95 ± 7.69	0.17
Weight (kg)	70.81 ± 11.60	71.88 ± 11.29	0.37
BMI (kg/m^2)	25.34 ± 3.13	25.41 ± 3.10	0.84
Systolic pressure (mmHg)	123.22 ± 13.25	123.80 ± 13.58	0.68
Diastolic pressure (mmHg)	75.33 ± 9.37	76.35 ± 9.05	0.29
Smoking	75 (40.11 %)	85 (46.70 %)	0.20
Drinking	50 (26.74 %)	65 (35.71 %)	0.06
Comorbidities			
Myocardial infarction	53 (28.34 %)	53 (29.12 %)	0.87
Hypertension	122 (65.24 %)	116 (63.74 %)	0.76
Heart failure	40 (21.39 %)	39 (21.43 %)	0.99
NYHA classification			0.55
NYHA Class I	24 (60.00 %)	21 (53.85 %)	
NYHA Class II	14 (35.00 %)	15 (38.46 %)	
NYHA Class III	2 (5.00 %)	3 (7.69 %)	
Arrhythmia	14 (7.49 %)	15 (8.24 %)	0.79
Diabetes	55 (29.41 %)	54 (29.67 %)	0.96
Hyperlipidaemia	116 (62.03 %)	111 (60.99 %)	0.84
Cerebral apoplexy	3 (1.60 %)	5 (2.75 %)	0.50
Beta-blocker use	105 (56.1 %)	99 (54.4 %)	0.74
Coronary CT angiography	42 (22.46 %)	33 (18.13 %)	0.30
Coronary angiography	150 (80.21 %)	150 (82.42 %)	0.59
Exercise intensity			0.67
Low intensity	73 (39.04 %)	75 (41.21 %)	
Medium intensity	114 (60.96 %)	107 (58.79 %)	
Disease diagnosis			0.86
Stable angina	164 (89.30 %)	161 (88.46 %)	
Postoperatively stable ACS	8 (4.28 %)	10 (5.49 %)	
Other	12 (6.42 %)	11 (6.04 %)	

The data were presented as the means ± standard deviations (SDs) or frequencies (percentages).

than in the placebo group (LSMD, 0.80 [95 % CI: 0.28 to 1.32]; P < 0.025). However, the between-group difference for VO_2peak did not reach statistical significance (LSMD, 0.57 [95 % CI: 0.06 to 1.21]; P > 0.025). These results suggested that Yuxintong capsule may improve the AT in patients with stable CHD, but shows no significant improvement in VO_2peak. (Table 2 and Fig. 2).

3.4. Secondary outcomes

Within-group comparisons revealed that after 12 weeks of treatment, Yuxintong group showed a significant increase in METs (5.31 ± 1.62 vs. 5.57 ± 1.46 MET, $P = 0.001$), and the placebo group also exhibited a significant improvement (5.33 ± 1.53 vs. 5.51 ± 1.48 MET, $P = 0.026$). However, between-group comparison demonstrated that the difference in METs was not statistically significant (0.25 ± 1.03 vs. 0.18 ± 1.08 MET; LSMD, 0.09 [95 % CI: 0.10 to 0.29]; $P > 0.05$). These results suggest that Yuxintong capsule did not produce a statistically significant improvement in METs compared with placebo (Table 2 and Fig. 3).

Among the subgroup of patients who exhibited exercise-induced ST-segment depression, changes in the onset time and the duration of 1-mm ST-segment depression were analyzed between the two groups. In within-group comparisons, after 12 weeks of treatment, the changes in the onset time of 1-mm ST-segment depression did not reach statistical significance in either group (Yuxintong group: 6.23 ± 3.89 vs. 6.21 ± 4.15 min, $P = 0.94$; placebo group: 6.89 ± 2.89 vs. 6.75 ± 3.48 min, $P = 0.55$). Furthermore, the between-group difference in onset time was also not statistically significant ($P = 0.78$). Regarding the duration of 1-mm ST-segment depression, the Yuxintong group showed a slight shortening compared to baseline (4.68 ± 7.38 vs. 4.49 ± 7.44 min, $P = 0.55$), whereas the placebo group exhibited a slight prolongation (3.82 ± 3.44 vs. 3.97 ± 3.45 min, $P = 0.66$). But the between-group difference in duration was not significant ($P = 0.48$) (Table 3).

Compared with the baseline, the scores of general health, physiological function, role-physical, role-emotional, social function, bodily pain, vitality and mental health on the SF-36 were significantly improved in both Yuxintong and placebo groups after 12 weeks of treatment ($P < 0.05$). Compared with those of placebo group, there was a significant difference in the scores of general health (13.61 ± 15.13 vs. 8.29 ± 14.14; LSMD 5.30, [95 % CI: 2.33 to 8.31]; $P < 0.05$) and vitality (12.46 ± 11.32 vs. 6.01 ± 11.41; LSMD 6.43, [95 % CI: 4.13 to 8.31]; $P < 0.05$) in Yuxintong group (Fig. 4).

3.5. Adverse events

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class/preferred term (Supplementary material 5), severity (graded by CTCAE criteria), and relationship to study drug. We report AE risk differences with 95 % CIs, AEs leading to discontinuation, and serious AEs with narratives and causality assessment. And there were no significant differences in the number of AEs between two groups (32 [16.16 %] vs. 24 [12.31 %]; $P = 0.27$; Table 4). Among them, the most common AEs were gastrointestinal disorders, including 10 cases in the Yuxintong group (3 cases of abdominal pain; 2 cases of dyspepsia; 2 cases of diarrhea; 2 cases of nausea/vomiting; 1 case of gastritis) and 4 cases in the control group (2 cases of gastric distension; 1 case of dyspepsia; 1 case of gastritis). Two Serious Adverse Events (SAEs) occurred in the placebo group (1 case of cholecystitis and 1 case of sudden death), while no SAEs were reported in the Yuxintong group. In the placebo group, a 68-year-old male patient (enrolled on April 30, 2021) with a history of myocardial infarction, percutaneous coronary intervention, hypertension, hyperlipidemia, and diabetes experienced sudden cardiac death on June 20,

Table 2
Primary and key secondary outcomes (ITT analysis).

	Yuxintong group (n = 187)	Placebo group (n = 182)	lsmeans difference(95 % CI)	unadjusted *P*-value	adjusted *P*-value
VO_2peak ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)					
baseline	19.23 ± 4.97	19.67 ± 4.43	–	–	–
12 weeks	19.98 ± 4.78	19.79 ± 4.87	–	–	–
difference	0.77 ± 3.35	0.13 ± 3.19	0.57 (−0.06, 1.21)	0.066	0.078
AT ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$)					
baseline	12.44 ± 3.78	12.76 ± 3.29	–	–	–
12 weeks	13.42 ± 3.54	12.87 ± 3.37	–	–	–
difference	0.98 ± 2.88	0.12 ± 2.79	0.80 (0.28, 1.32)	0.004	0.003
METs (MET)					
baseline	5.31 ± 1.62	5.33 ± 1.53	–	–	–
12 weeks	5.57 ± 1.46	5.51 ± 1.48	–	–	–
difference	0.25 ± 1.03	0.18 ± 1.08	0.09 (−0.10, 0.29)	0.49	0.34

adjusted *P*-value: adjusted for age, sex, BMI, baseline, center, exercise intensity, and bate-blocker use.

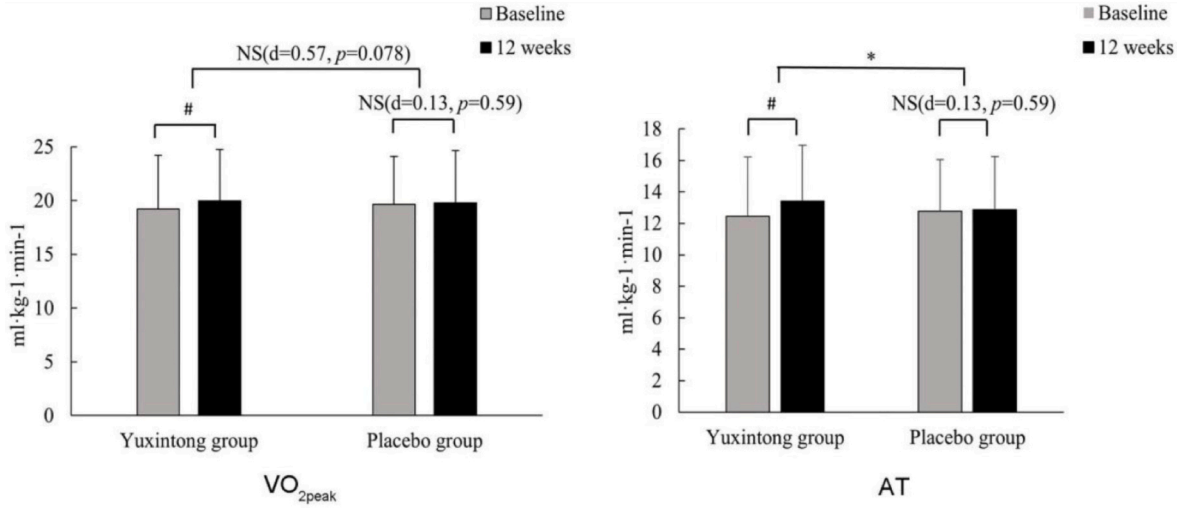

Fig. 2. VO_2peak and AT of the two groups. The data were presented as the means ± SDs. # baseline vs 12 weeks, $P < 0.025$; * Yuxintong group vs placebo group, $P < 0.025$; NS, Not Significant.

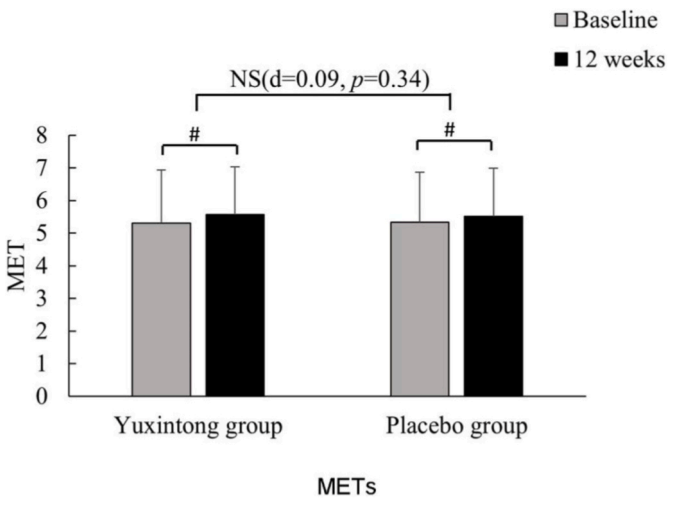

Fig. 3. METs of the two groups. The data were presented as the means ± SDs. # baseline vs 12 weeks, $P < 0.05$; * Yuxintong group vs placebo group, $P < 0.05$; NS, Not Significant.

2021. This event was assessed by the attending physician as unrelated to the study drug. No bleeding events or serious adverse reactions occurred. Participant safety was the primary concern in managing AEs. Based on the event's nature and severity, our responses included trial discontinuation, dose adjustment, symptomatic treatment, or observation. All Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported to relevant authorities by investigators within required timelines, and promptly disseminated to all trial sites and ethics committees by the Contract Research Organization (CRO). And all SAEs were followed until a definitive outcome was reached, such as resolution, stabilization, death, or attribution to non-trial-related causes.

4. Discussion

To our knowledge, this is the first multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy of the Yuxintong capsule on CRF in patients with stable CHD. Individualized exercise intensity was prescribed based on the each patient's condition, and randomization was stratified by exercise intensity. This approach ensured the balance of exercise intensity between the Yuxintong group and the placebo group, while also enhancing patient compliance. Compared with baseline, the Yuxintong group showed significant improvements in the primary outcomes, including VO_2peak and AT, as well as in secondary outcomes such as METs and SF-36 scores. Furthermore, compared with the placebo group, the Yuxintong group demonstrated superior improvement in the primary outcome of AT and in the general health and vitality domains of the SF-36.

In 2016, the American Heart Association recommended "CRF" as an important clinical "vital sign", urging healthcare providers to prioritize the assessment of this condition (Ross et al., 2016). CPET can objectively quantify the patient's CRF, and is commonly used to guide personalized exercise prescription for patients with CHD. It has high predictive value of recurrent cardiovascular events and is currently recognized as the best method to quantify CRF (Sun et al., 2010; Guazzi et al., 2012, 2017). VO_2peak and AT are the most crucial indicators for clinical evaluation of CRF. VO_2peak refers to the oxygen uptake at where the participants are unable to maintain a continuous increase in power during exercise, which is an accurate indicator for evaluating exercise ability (Lewis et al., 2017). Terence et al. followed 12,169 male patients with CHD for an average of 7.9 years and reported that VO_2peak was an independent predictor of the cardiac and all-cause mortality risks (Kavanagh et al., 2002). The AT, also well known as the lactic acid threshold or ventilation threshold, represents the point at where the body transitions from aerobic to anaerobic metabolism. The AT value can help patients safely engage in aerobic exercise within an appropriate range of CRF (Gibbons, 1987). According to U.S. epidemiological data,

Table 3
The start and duration of 1 mm ST-segment depression during CPET.

	Yuxintong group (n=25)			Placebo group (n=32)		
	baseline	12 weeks	difference	baseline	12 weeks	difference
ST-1 mm start time (min)	6.23 ± 3.89	6.21 ± 4.15	−0.03 ± 1.68	6.89 ± 2.89	6.75 ± 3.48	−0.14 ± 1.31
ST-1 mm duration (min)	4.68 ± 7.38	4.49 ± 7.44	−0.19 ± 1.54	3.82 ± 3.44	3.97 ± 3.45	0.16 ± 2.00

The data were presented as the means ± SDs. # baseline vs 12 weeks, $P < 0.05$; * Yuxintong group vs placebo group, $P < 0.05$.

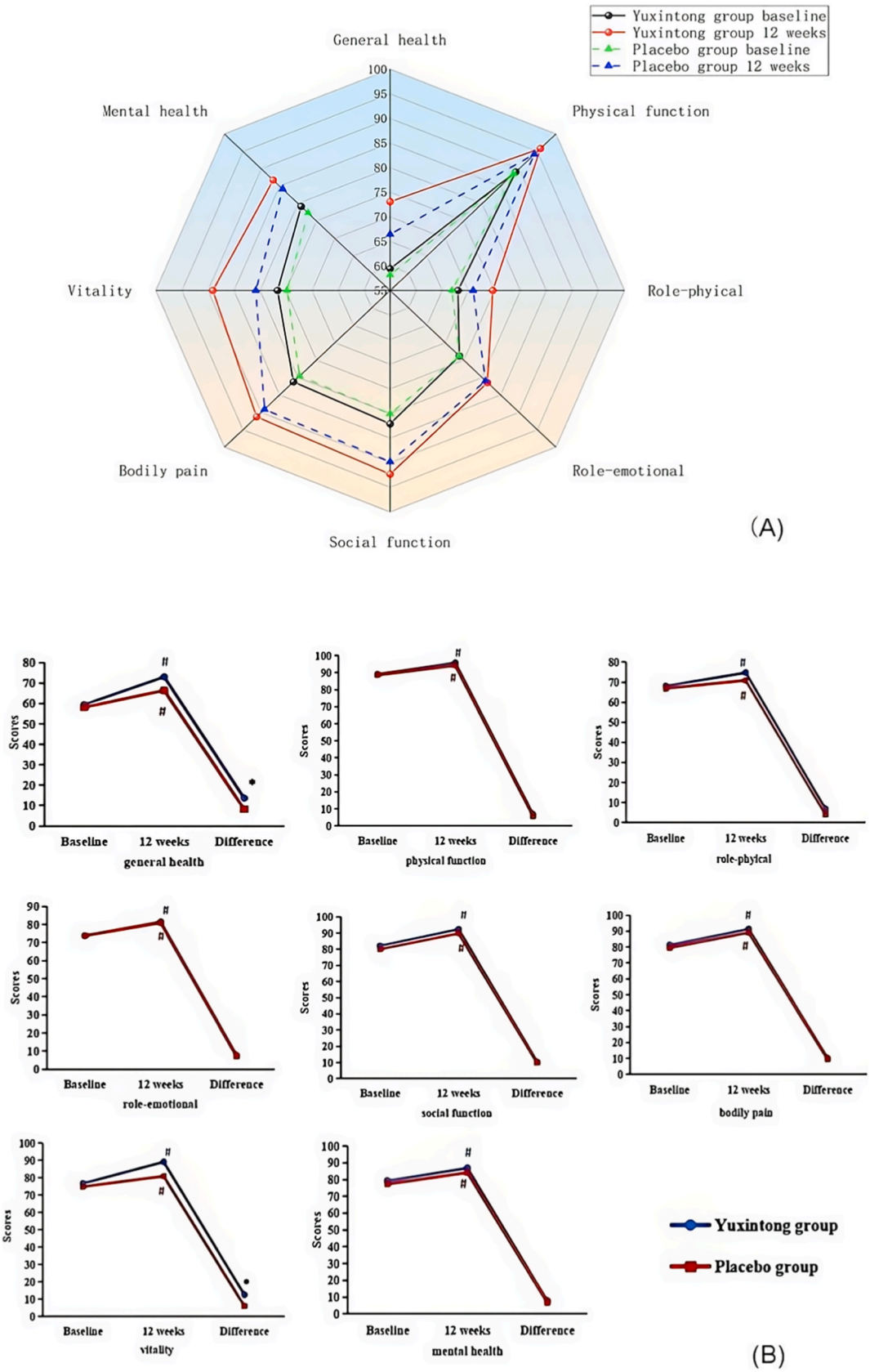

Fig. 4. SF-36 scores of the two groups.
(A) Radar chart; (B) line chart. # baseline vs 12 weeks, $P < 0.05$; * Yuxintong group vs placebo group, $P < 0.05$.

Table 4
Adverse events in the SS.

	Yuxintong group (n = 198)		Placebo group (n = 195)		P value
	Number of patients	Incidence (95 %CI) (%)	Number of patients	Incidence (95 %CI) (%)	
Adverse events	32	16.16 (11.05–21.27)	24	12.31 (7.44–16.56)	0.27
Mild adverse events	31	15.66 (11.13–21.41)	19	10.77 (7.0–16.2)	–
Moderate adverse events	1	0.51 (0.01–2.78)	3	1.54 (0.32–4.43)	–
Serious adverse events	0	0.00	2	1.03(−0.4,-2.4)	–
Adverse reactions	4	2.02 (0.55–5.10)	2	1.0 (0.12–3.67)	0.68
Mild adverse reactions	3	1.52 (0.31–4.36)	2	1.0 (0.12–3.67)	–
Moderate adverse reactions	1	0.51 (0.01–2.78)	0	–	–
Serious adverse reactions	0	–	0	–	–
Relationship between the study drug and AE					
Definitely related	0	–	0	–	–
Probably related	0	–	0	–	–
Possibly related	0	–	0	–	–
Unlikely related	8	4.04 (1.75–7.79)	6	3.08 (1.13–6.59)	–
Unrelated	24	12.12 (8.15–17.38)	18	7.69 (4.58–12.45)	–
AE-related discontinuation	2	1.01 (0.12–3.62)	2	1.0 (0.12–3.67)	1

the AT for middle-aged nonmanual workers aged 34–74 years should exceed 40 % of maximal oxygen uptake. Patients with CHD often experience angina pectoris during excessive exercise, leading to limited daily activities and reduced skeletal muscle activity. And the CPET was often terminated prematurely due to symptom limitation. The AT excludes subjective factors and is therefore more sensitive than VO_2peak in quantifying CRF (Fletcher et al., 2013). The results of the present study indicated that compared with placebo, Yuxintong capsule in addition to conventional Western medications for 12 weeks significantly increased AT, suggesting that the effective oxygen uptake was improved during the transition from aerobic to anaerobic metabolism.

The body's aerobic capacity is closely related to mitochondrial function (Chance et al., 1955). A study showed that the ginsenosides in red ginseng reduced myocardial oxygen consumption, increased ischaemic myocardial tolerance, eliminated free radicals, inhibited lipid peroxidation, and minimized oxidative stress-induced mitochondrial damage (Piao et al., 2019). Ginsenosides regulated mitochondrial oxidative phosphorylation, energy metabolism, biosynthesis, apoptosis, mitophagy, and the status of membrane channels, thereby improving the mitochondrial oxidative energy supply capacity (Jiang et al., 2021; Wang et al., 2020). These findings provide a potential mechanistic rationale for the observed improvement in AT following Yuxintong capsule treatment in patients with stable CHD.

In our study, the total scores of the SF-36 improved significantly after treatment in both the Yuxintong and placebo groups. Furthermore, compared with the placebo group, the Yuxintong group showed greater improvements in the general health and vitality scores of the SF-36. Previous studies have shown that the saponins of *Panax notoginseng*, a component of Yuxintong capsule, improved glucose uptake and absorption by skeletal muscle, increased the blood oxygen content in the myocardium, and decreased myocardial oxygen consumption (Yuan et al., 2012; Kitamura et al., 2017). *Corydalis yanhusuo* protected the myocardium by resisting myocardial ischemia and reducing apoptosis of cardiomyocytes (Li et al., 2017). Red ginseng can increase the antioxidant capacity of skeletal muscle and the myocardium in rats, while its extracts can improve the contractility and strength of skeletal muscle during exercise (Shin et al., 2020). These findings indicated the potential mechanisms by which Yuxintong capsule improved the general health and vitality scores on the SF-36 for patients with stable CHD.

Several limitations of this study should be noted. First, this study was conducted during the COVID-19 pandemic, and patients quarantine measures hindered normal follow-up, which was a primary reason for the 15 % dropout rate. Second, the follow-up period was only three months, which may explain why the improvements in efficacy indicators did not reach statistical significance. Finally, our trial included only patients from mainland China, and further studies are needed to determine whether the findings are applicable to patients of different races.

5. Conclusion

Yuxintong capsule, as an adjunctive therapy to conventional treatment, improved AT, and general health and vitality scores on the SF-36 scale in patients with stable CHD.

CRediT authorship contribution statement

Liying Zheng: Writing – original draft, Investigation. **Changgeng Fu:** Writing – original draft, Investigation. **Lei Song:** Writing – original draft, Investigation. **Xiaoyan Lu:** Investigation. **Hongyan Jiang:** Investigation. **Meili Yu:** Investigation. **Ao Geng:** Investigation. **Lijing Zhang:** Investigation. **Zhigeng Hu:** Investigation. **Li Wang:** Investigation. **Jinghui Zheng:** Investigation. **Deyu Fan:** Investigation. **Zhenyu Wang:** Investigation. **Zhen Wu:** Investigation. **Yue Deng:** Investigation. **Shangquan Xiong:** Investigation. **Ping Zhan:** Investigation. **Ming Zhang:** Investigation. **Zhaoqi Huang:** Investigation. **Ling Feng:** Investigation. **Yixin Wang:** Investigation. **Yan Feng:** Investigation. **Jie Zhang:** Investigation. **Mei Xue:** Writing – review & editing, Funding acquisition, Formal analysis. **Hao Xu:** Project administration, Investigation. **Dazhuo Shi:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Keji Chen:** Writing – review & editing, Investigation.

Author agreement

All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2026.121169.

Data availability

Data will be made available on request.

References

Al-Lamee, R., Thompson, D., Dehbi, H.M., Sen, S., Tang, K., Davies, J., Keeble, T., Mielewczik, M., Kaprielian, R., Malik, I.S., Nijjer, S.S., Petraco, R., Cook, C., Ahmad, Y., Howard, J., Baker, C., Sharp, A., Gerber, R., Talwar, S., Assomull, R., Mayet, J., Wensel, R., Collier, D., Shun-Shin, M., Thom, S.A., Davies, J.E., Francis, D. P., 2018. Percutaneous coronary intervention in stable angina (ORBITA): a doubleblind, randomised controlled trial. Lancet 391 (10115), 31–40. https://doi.org/10.1016/S0140-6736(17)32714-9.

Boden, W.E., O'Rourke, R.A., Teo, K.K., Hartigan, P.M., Maron, D.J., Kostuk, W.J., Knudtson, M., Dada, M., Casperson, P., Harris, C.L., Chaitman, B.R., Shaw, L., Gosselin, G., Nawaz, S., Title, L.M., Gau, G., Blaustein, A.S., Booth, D.C., Bates, E.R., Spertus, J.A., Berman, D.S., Mancini, G.B., Weintraub, W.S., COURAGE Trial Research Group, 2007. Optimal medical therapy with or without PCI for stable coronary disease. N. Engl. J. Med. 356 (15), 1503–1516. https://doi.org/10.1056/NEJMoa070829.

Chang, X., Liu, J., Wang, Y., Guan, X., Liu, R., 2023. Mitochondrial disorder and treatment of ischemic cardiomyopathy: potential and advantages of Chinese herbal medicine. Biomed. Pharmacother. 159, 114171. https://doi.org/10.1016/j.biopha.2022.114171.

Chance, B., Williams, G.R., 1955. Respiratory enzymes in oxidative phosphorylation. I. Kinetics of oxygen utilization. J. Biol. Chem. 217 (1), 383–393.

Fan, Q., Jia, J., 2020. Translating research into clinical practice: importance of improving cardiorespiratory fitness in stroke population. Stroke. 51 (1), 361–367. https://doi.org/10.1161/STROKEAHA.119.027345.

Fletcher, G.F., Ades, P.A., Kligfield, P., Arena, R., Balady, G.J., Bittner, V.A., Coke, L.A., Fleg, J.L., Forman, D.E., Gerber, T.C., Gulati, M., Madan, K., Rhodes, J., Thompson, P.D., Williams, M.A., American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention, 2013. Exercise standards for testing and training: a scientific statement from the American Heart association. Circulation 128 (8), 873–934. https://doi.org/10.1161/CIR.0b013e31829b5b44.

Guazzi, M., Adams, V., Conraads, V., Halle, M., Mezzani, A., Vanhees, L., Arena, R., Fletcher, G.F., Forman, D.E., Kitzman, D.W., Lavie, C.J., Myers, J., 2012. EACPR/AHA Scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 126 (18), 2261–2274. https://doi.org/10.1161/CIR.0b013e31826fb946.

Guazzi, M., Bandera, F., Ozemek, C., Systrom, D., Arena, R., 2017. Cardiopulmonary exercise testing: what is its value? J. Am. Coll. Cardiol. 70 (13), 1618–1636. https://doi.org/10.1016/j.jacc.2017.08.012.

Gibbons, E.S., 1987. The significance of anaerobic threshold in exercise prescription. J Sports Med Phys Fitness. 27 (3), 357–361.

Huang, Q., Lou, T., Lu, J., Wang, M., Chen, X., Xue, L., Tang, X., Qi, W., Zhang, Z., Su, H., Jin, W., Jing, C., Zhao, D., Sun, L., Li, X., 2022. Major ginsenosides from Panax ginseng promote aerobic cellular respiration and SIRT1-mediated mitochondrial biosynthesis in cardiomyocytes and neurons. J Ginseng Res 46 (6), 759–770. https://doi.org/10.1016/j.jgr.2022.02.002.

Interventional Cardiology Group of Cardiovascular Branch of Chinese Medical Association, Atherosclerosis and Coronary Heart Disease Group of Cardiovascular Branch of Chinese Medical Association, Thrombosis Prevention Committee of Cardiovascular Physicians Branch of Chinese Medical Association, 2018. Guidelines for the diagnosis and treatment of stable coronary heart disease. Chinese Journal of Cardiovascular Disease 46 (9), 680–694.

Jiang, L., Yin, X., Chen, Y.H., Chen, Y., Jiang, W., Zheng, H., Huang, F.Q., Liu, B., Zhou, W., Qi, L.W., Li, J., 2021. Proteomic analysis reveals ginsenoside Rb1 attenuates myocardial ischemia/reperfusion injury through inhibiting ROS production from mitochondrial complex I. Theranostics 11 (4), 1703–1720. https://doi.org/10.7150/thno.43895.

Kavanagh, T., Mertens, D.J., Hamm, L.F., Beyene, J., Kennedy, J., Corey, P., Shephard, R. J., 2002. Prediction of long-term prognosis in 12169 men referred for cardiac rehabilitation. Circulation 106 (6), 666–671. https://doi.org/10.1161/01.cir.0000024413.15949.

Kitamura, K., Takamura, Y., Iwamoto, T., Nomura, M., Iwasaki, H., Ohdera, M., Murakoshi, M., Sugiyama, K., Matsuyama, K., Manabe, Y., Fujii, N.L., Fushiki, T., 2017. Dammarane-type triterpene extracts of Panax notoginseng root ameliorates hyperglycemia and insulin sensitivity by enhancing glucose uptake in skeletal muscle. Biosci. Biotechnol. Biochem. 81 (2), 335–342. https://doi.org/10.1080/09168451.2016.1246173.

Levraut, J., Iwase, H., Shao, Z.H., Vanden Hoek, T.L., Schumacker, P.T., 2003. Cell death during ischemia: relationship to mitochondrial depolarization and ROS generation. Am. J. Physiol. Heart Circ. Physiol. 284 (2), H549–H558. https://doi.org/10.1152/ajpheart.00708.2002.

Ling, H., Wu, L., Li, L., 2006. Corydalis yanhusuo rhizoma extract reduces infarct size and improves heart function during myocardial ischemia/reperfusion by inhibiting apoptosis in rats. Phytother Res. 20 (6), 448–453. https://doi.org/10.1002/ptr.1875.

Lewis, G.D., Malhotra, R., Hernandez, A.F., McNulty, S.E., Smith, A., Felker, G.M., Tang, W.H.W., LaRue, S.J., Redfield, M.M., Semigran, M.J., Givertz, M.M., Van Buren, P., Whellan, D., Anstrom, K.J., Shah, M.R., Desvigne-Nickens, P., Butler, J., Braunwald, E., NHLBI Heart Failure Clinical Research Network, 2017. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA 317 (19), 1958–1966. https://doi.org/10.1001/jama.2017.5427.

Lei, Y., Liu, J.X., Shang, X.H., Chen, K.J., 1996. Effects of yuxintong capsule on plasma endothelin and hemorheology in dogs with acute myocardial ischemia. Zhongguo Zhong Xi Yi Jie He Za Zhi (4), 23–25.

Lei, Y., Shi, D.Z., Zhong, B., Chen, K.J., 1997. The effect of yuxintong on the expression of ECE and NOS genes in acute ischemic myocardium of dogs and the immunohistochemical study of copper zinc SOD. Zhongguo Zhong Xi Yi Jie He Za Zhi 10, 607–610.

Li, R., Liu, S., Sun, Y., Wei, T., 1999. Clinical study on the treatment of coronary heart disease angina pectoris with Qi deficiency and blood stasis type by yuxintong capsule. Chinese J. Traditional Chinese Medicine Sci. Technol. 6 (5), 330–331.

Li, Q., Guan, H., Wang, X., He, Y., Sun, H., Tan, W., Luo, X., Su, M., Shi, Y., 2017. Fingerprint-efficacy study of the quaternary alkaloids in Corydalis yanhusuo. J. Ethnopharmacol. 207, 108–117. https://doi.org/10.1016/j.jep.2017.06.036.

Piao, M.J., Kang, K.A., Zhen, A.X., Fernando, P.D.S.M., Ahn, M.J., Koh, Y.S., Kang, H.K., Yi, J.M., Choi, Y.H., Hyun, J.W., 2019. Particulate matter 2.5 mediates cutaneous cellular injury by inducing Mitochondria-associated endoplasmic reticulum stress: protective effects of ginsenoside Rb1. Antioxidants. 8 (9), 383. https://doi.org/10.3390/antiox8090383.

Qi, J., Li, H., Yang, Y., Sun, X., Wang, J., Han, X., Chu, X., Sun, Z., Chu, L., 2024. Mechanistic insights into the ameliorative effects of hypoxia-induced myocardial injury by Corydalis yanhusuo total alkaloids: based on network pharmacology and experiment verification. Front. Pharmacol. 14, 1275558. https://doi.org/10.3389/fphar.2023.1275558.

Rezende, P.C., Hueb, W., Garzillo, C.L., Lima, E.G., Hueb, A.C., Ramires, J.A., Filho, K.R., 2013. Ten-year outcomes of patients randomized to surgery, angioplasty, or medical treatment for stable multivessel coronary disease: effect of age in the medicine, angioplasty, or Surgery study II trial. J. Thorac. Cardiovasc. Surg. 146 (5), 1105–1112. https://doi.org/10.1016/j.jtcvs.2012.08.015.

Ross, R., Blair, S.N., Arena, R., Church, T.S., Després, J.P., Franklin, B.A., Haskell, W.L., Kaminsky, L.A., Levine, B.D., Lavie, C.J., Myers, J., Niebauer, J., Sallis, R., Sawada, S.S., Sui, X., Wisløff, U., 2016. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart association. Circulation 134 (24), e653–e699. https://doi.org/10.1161/CIR.0000000000000461.

Schulz, K.F., Altman, D.G., Moher, D., CONSORT Group, 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Br. Med. J. 340, c332. https://doi.org/10.4103/0976-500X.72352.

Stefanos, R., Graziella, D., Giovanni, T., 2020. Methodological aspects of superiority, equivalence, and non-inferiority trials. Intern. Emerg. Med. 15 (6), 1085–1091. https://doi.org/10.1007/s11739-020-02450-9.

Shin, E.J., Jo, S., Choi, S., Cho, C.W., Lim, W.C., Hong, H.D., Lim, T.G., Jang, Y.J., Jang, M., Byun, S., Rhee, Y., 2020. Red ginseng improves exercise endurance by promoting mitochondrial biogenesis and myoblast differentiation. Molecules 25 (4), 865. https://doi.org/10.3390/molecules25040865.

Sun, X.G., Hansen, J.E., Beshai, J.F., Wasserman, K., 2010. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J. Am. Coll. Cardiol. 55 (17), 1814–1823. https://doi.org/10.1016/j.jacc.2009.10.075.

Wu, Y.H., Li, N., Xu, B.H., 2018. Clinical study of yuxintong capsule combined with nicorandil in the treatment of microvascular angina. Modern Medicine and Clinical 33 (11), 2787–2790.

Wei, L.L., 2009. Clinical observation of yuxintong capsule in the treatment of unstable angina. Chinese Journal of Traditional Chinese Medicine 24 (11), 1532–1533.

World Medical Association, 2013. World medical association declaration of helsinki: ethical principles for medical research involving human subjects. JAMA 310 (20), 2191–2194. https://doi.org/10.1001/jama.2013.281053.

Wang, F., Roh, Y.S., 2020. Mitochondrial connection to ginsenosides. Arch Pharm. Res. (Seoul) 43 (10), 1031–1045. https://doi.org/10.1007/s12272-020-01279-2.

Yang, Y., Wang, H., Zhang, M., Shi, M., Yang, C., Ni, Q., Wang, Q., Li, J., Wang, X., Zhang, C., Li, Z., 2022. Safety and antifatigue effect of Korean red ginseng capsule: a randomized, double-blind and placebo-controlled clinical trial. J Ginseng Res 46 (4), 543–549. https://doi.org/10.1016/j.jgr.2021.09.001.

Yuan, H.D., Kim, J.T., Kim, S.H., Chung, S.H., 2012. Ginseng and diabetes: the evidences from in vitro, animal and human studies. J. Ginseng. Res. 36 (1), 27–39. https://doi.org/10.5142/jgr.2012.36.1.27.

Zhang, H., Zhao, C., Hou, J., Su, P., Yang, Y., Xia, B., Zhao, X., He, R., Wang, L., Cao, C., Liu, T., Tian, J., 2022a. Red ginseng extract improves skeletal muscle energy metabolism and mitochondrial function in chronic fatigue mice. Front. Pharmacol. 13, 1077249. https://doi.org/10.3389/fphar.2022.1077249.

Zhou, Z., Wang, J., Song, Y., He, Y., Zhang, C., Liu, C., Zhao, H., Dun, Y., Yuan, D., Wang, T., 2018. Panax notoginseng saponins attenuate cardiomyocyte apoptosis through mitochondrial pathway in natural aging rats. Phytother Res. 32 (2), 243–250. https://doi.org/10.1002/ptr.5961.

Zhang, C., Zhang, B., Zhang, X., Wang, M., Sun, X., Sun, G., 2022b. Panax notoginseng saponin protects against diabetic cardiomyopathy through lipid metabolism modulation. J. Am. Heart Assoc. 11 (4), e023540. https://doi.org/10.1161/JAHA.121.023540.