

# Prospective randomized controlled trial study of Luofengning granule in the treatment of unstable angina

Kai Wang, PhD<sup>a</sup>, Jun-Jun Cai, PhD<sup>b</sup>, Yang Wu, MM<sup>a</sup>, Yu Wang, MD<sup>a</sup>, Lei-Lei Liu, PhD<sup>c</sup>, Lei Shi, PhD<sup>d</sup>, Xian Wang, MD<sup>a,e,\*</sup>

## Abstract

**Introduction:** Although the current western treatment plans for unstable angina (UA) has been optimized in past decades, UA still is a common phenotype of acute coronary syndrome and significantly influence the quality of life and endanger lives. In China, the clinical application of Chinese herb medicine is considered as an effective approach to treating UA and widely recognized by patients. In clinical practices, we found Luofengning granule (LFN-G) could improve clinical manifestations of patients with UA, but there is lack of rigorous proof of evidence-based medicine. This trial aims to further evaluate the efficacy of LFN-G in the treatment of UA.

**Methods:** A prospective, open-label, randomized, placebo-controlled clinical will be performed. A total of 60 patients diagnosed with UA will be randomly allocated to either the treatment group or the control group with a 1:1 ratio. The participants in the treatment group will receive LFN-G treatment and the participants in the control group will receive placebo. Meanwhile, both groups continue to undergo standard western medicine treatments. The duration of interventions is 4 weeks. The primary endpoint is the incidence of major cardiac adverse events, defined as a composite of recurrent angina, acute myocardial infarction (AMI), severe arrhythmia, heart failure, and cardiac death. Secondary outcomes include Seattle angina scale score, Chinese medicine syndromes and electrocardiograph (at weeks 0, 1, 2, 4), myocardial nuclides perfusion, measurement of wall motion score index and left ventricular ejection fraction, serum inflammation factors such as C-reactive protein, high sensitive-C-reactive protein, interleukin-6, matrix metalloproteinase-9, and so on (at weeks 0, 4). In addition, some biochemical indexes of blood and hematological indexes will be used to assess the safety of treatments. Any adverse effects of the treatment will be recorded.

**Discussion:** The results of this trial will provide compelling evidence of the efficacy and safety of LFN-G for treatment of UA and preliminarily reveal the potential mechanism of how LFN-G acts. Finally, it will widen treatment options for patients with UA.

**Abbreviations:** ACS = acute coronary syndrome, AEs = adverse events, CHM = Chinese herb medicine, CRFs = case report forms, LFN-G = Luofengning granule, NSTEMI = non-ST-elevation myocardial infarction, RCT = randomized controlled trial, STEMI = ST-elevation myocardial infarction, UA = unstable angina.

**Keywords:** Chinese herbal medicine, Luofengning granule, randomized controlled trial, unstable angina

*This trial is the clinical part of "the study of the efficacy and mechanism of Luofengning granule for treating unstable angina Based on the concept of endogenous wind due to collateral deficiency" (Project has been approved, number: No.2020-JYB-ZDGG-113).*

*This protocol of the trial has been approved by the Research Ethical Committee of Dongzhimen Hospital affiliated to the Beijing University of Chinese Medicine. The full data set will be available after the trial is published.*

*Trial registration number: ChiCTR2000030533, registered March 4, 2020.*

*Research Ethical Committee of Dongzhimen Hospital affiliated to the Beijing University of Chinese Medicine (The ethical application has been approved).*

*The full data set will be available when this trial is completed and published. Demand of data release should be made by contacting Xian Wang (the principle investigator).*

*The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.*

*The financial funding of this trial is from the Basic Scientific Research Operating Expenses Project of the Beijing University of Chinese Medicine (2020).*

*The funder will not participate in the study design, data collection and analysis, or the preparation of the manuscript. The funder just provides financial support for the study.*

*The authors have no conflicts of interest to disclose.*

*<sup>a</sup> Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, <sup>b</sup> Department of Hepatology, Tianjin Third Central Hospital, Tianjin, <sup>c</sup> School of Traditional Chinese Medicine, <sup>d</sup> School of Life Science, <sup>e</sup> Institute for Cardiovascular Disease, Beijing University of Chinese Medicine, Beijing 100029, People's Republic of China.*

*\* Correspondence: Xian Wang, Institute for Cardiovascular Disease, Dongzhimen Hospital, Beijing University of Chinese Medicine, No.5 Haiyuncang, Dongcheng District, Beijing 100029, People's Republic of China (e-mail: dzmyywx@163.com).*

*Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.*

*This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

*How to cite this article: Wang K, Cai JJ, Wu Y, Wang Y, Liu LL, Shi L, Wang X. Prospective randomized controlled trial study of Luofengning granule in the treatment of unstable angina. *Medicine* 2020;99:20(e20025).*

*Received: 18 March 2020 / Accepted: 27 March 2020*

*<http://dx.doi.org/10.1097/MD.00000000000020025>*

## 1. Introduction

Unstable angina (UA) is a phenotype of acute coronary syndrome (ACS), defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis. Recent study indicated that the overall prevalence for angina is 3.4% in US adults  $\geq 20$  years of age.<sup>[1]</sup> Approximately 10% of patients with acute chest pain present to the emergency department will be diagnosed with UA.<sup>[2]</sup> Compared with the other 2 phenotypes of ACS, ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), UA exhibits a lower risk of in-hospital death.<sup>[2,3]</sup> However, The Global Registry of Acute Coronary Events (GRACE) study showed there was no significant difference of 5-year total mortality among patients with 3 types of ACS (STEMI vs NSTEMI vs UA was 19% vs 22% vs 18%).<sup>[4]</sup>

Based on the pathogenesis of 3 types of ACS, the treatment of ACS exists differences. With vascular total occlusion caused by plaque rupture, coronary revascularization is the core of treatment of STEMI. In recent year, UA and NSTEMI were considered to present a similar clinical and electrocardiograph (ECG) features (ST-segment depressions and T-wave inversion). Clinical guidelines recommended rename the both referred to as the NSTEMI-ACS together and distinguishment based on high-sensitivity cardiac troponin measurements.<sup>[2,5,6]</sup> In absence of coronary artery total occlusion, the treatment plans of NSTEMI-ACS based on the comprehensive evaluation based on clinical and ECG manifestations and myocardial biomarkers, including anti-myocardial ischemia therapy, antiplatelet or anticoagulation therapy, statin therapy, and revascularization therapy, and so on.

Although current treatment options of UA have been demonstrated for definite improvement of long-term prognosis, there still are some deficiencies. GRACE study showed post-ACS 5-year deaths most occurred after initial hospital discharge, post-discharge deaths occupied up to 97% of 5-year total deaths in UA and this figure was much higher than in STEMI (68%) and NSTEMI (86%).<sup>[4]</sup> The cardiovascular prevention treatments after acute coronary syndrome (CPACS) study found only 31% of UA patients received revascularization therapy in China, which was lower than STEMI patients.<sup>[7]</sup> Besides, some patients with UA manifest refractory angina, current treatments have shown some promise in angina reduction but not yet achieved the goal such as objective data like myocardial blood flow, survival, and re-hospitalization.<sup>[8]</sup> These results may reflect insufficient attention were pay to the treatment of UA and current treatments for UA needs further optimization. Thus, complementary treatments for UA are urgently needed to further improve the prognosis and quality of life of patients with UA.

In addition to western medicine treatment, many Chinese patients with UA would like to seek help of Chinese herb medicine (CHM). CHM has been demonstrated to have a good clinical effect. Some meta-analysis has demonstrated the efficacy and safety of CHM.<sup>[9-11]</sup> Luofengning granule (LFN-G) is a Chinese herbal formula based on the the theory of “endogenous wind due to collateral deficiency,” includes 6 herbs: Lumbricus (Di long), Radix Clematidis (Wei lingxian), Radix Cynanchi Paniculati (Xu changqing), Panax notoginseng (San qi), Astragalus (Huang qi), and Borneol (Bing pian). Previous observational study demonstrated that LFN-G has definite effectiveness in the treatment of UA<sup>[12]</sup> associated with its’ multiple pharmacologic effects include anti-inflammatory,<sup>[13]</sup> immune regulation,<sup>[14]</sup> improving endothelial function,<sup>[15]</sup> and coagulation regulation.<sup>[16]</sup> However, there is no rigorous

randomized controlled trial (RCT) that verify above conclusions. Thus, we design this prospective, open-label, randomized, placebo-controlled clinical to further evaluate the efficacy and safety of LFN-G for treating UA. This trial will provide a more compelling evidence of LFN-G and expand therapeutic options for UA.

## 2. Materials and methods

### 2.1. Ethical aspects

The study is conducted in accordance with the Declaration of Helsinki (Edinburgh 2000 version). The final protocol (version: November 31, 2019) of this trial has been approved by the Research Ethical Committee of Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine (the ethical application has been approved). In addition, this trial has been registered in the Chinese Clinical Trial Registry (No. ChiCTR2000030533, registered March 4, 2020). Before the enrollment, all participants should sign written informed consents. If there will be any significant modification of the protocol, it should be reviewed by the research ethical committee and updated on the registry web (<http://www.chictr.org.cn>) timely.

### 2.2. Study design

This present study is a prospective, open-label, randomized, placebo-controlled clinical trial. A total of 60 patients diagnosed with UA are eligible for enrolment and they will be randomly allocated to the treatment group or the control group in a 1:1 ratio. The study flowchart is showed in Figure 1.

### 2.3. Recruitment

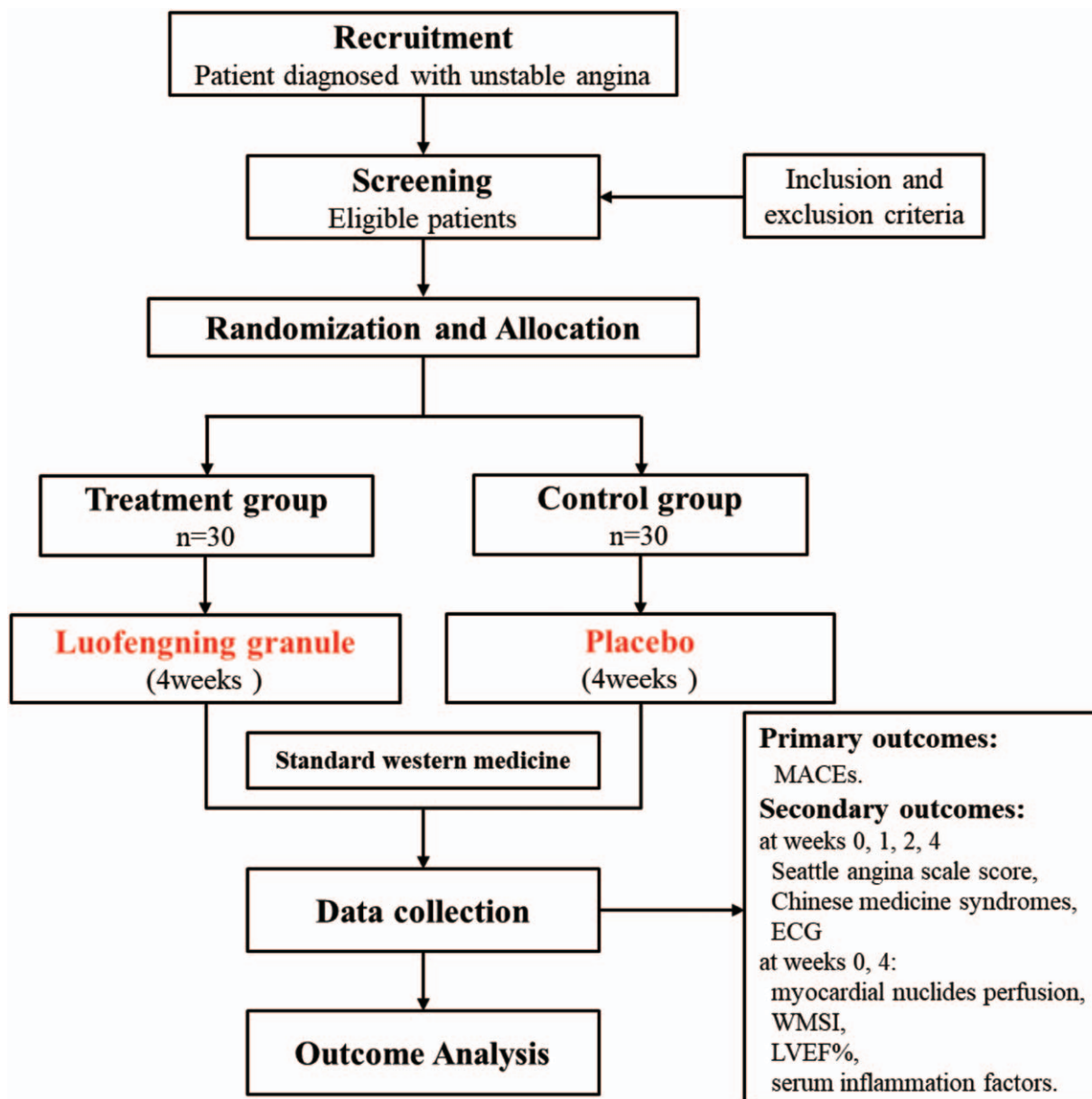
Two trained investigators will perform this procedure. A total 60 patients will be recruited from cardiac out-patient and ward of the Dongzhimen hospital affiliated to Beijing University of Chinese Medicine, from June 2020 until December 2022. Before the enrollment, all patients will receive a comprehensive view of informed consent, including objective, therapeutic interventions, scheduling, trial benefits, and possible risks of this trial. Only after signing a written informed consent, patients could be enrolled in this trial.

### 2.4. Randomization and masking

A designated investigator of our team will use an interactive Web response system to randomly allocate participants to receive either LFN-G or placebo after enrollment in a 1:1 ratio. Randomization will be stratified by age, sex, morbid status, and comorbidities. Due to this trial is an open-label trial, so neither participants nor investigators is not masked to the treatment option.

### 2.5. Diagnostic criteria

Western medicine diagnostic criteria for UA were determined by referring to related guidelines for the management of NSTEMI-ACS.<sup>[2,5,6]</sup> Traditional Chinese medicine (TCM) syndrome diagnostic criteria evaluation of UA is based on Standards for TCM industry of the People’s Republic of China (ZY/T001.1-94).<sup>[17]</sup> In the process of diagnosis and syndrome differentiation, 2 cardiac physicians of TCM will make the diagnosis respectively.



**Figure 1.** Flow chart of the study design. ECG = electrocardiograph, LVEF% = left ventricular ejection fraction, MACEs = major adverse cardiac events, WMSI = wall motion score index.

If there exists diagnostic controversy, a consensus would be reached through further discussing or third-party advice.

## 2.6. Eligibility criteria

Inclusion criteria:

- Diagnosed with UA by a cardiac physician.
- 18 to 80 years old.
- No gender restriction.
- Voluntary to participate and providing written informed consents, as required by Good Clinical Practice (GCP).

Exclusion criteria:

- Angina pectoris caused by noncoronary stenosis such as abnormal thyroid function, cardiomyopathy, high adrenergic

state, mental stress, left ventricular load increased (hypertension, aortic stenosis), tachycardia, violent activities, and so on.

- Patients with stroke or undergone PCI or coronary artery bypass grafting within 1 month before enrollment.
- Poorly controlled hypertension (systolic pressure  $\geq 160$  mm Hg or diastolic blood pressure  $\geq 100$  mm Hg).
- Patients with coexistent severe heart failure (New York heart association (NYHA), Class IV) and severe arrhythmia (atrial fibrillation, atrial flutter, paroxysmal ventricular tachycardia, sinus bradycardia [heart rate  $< 55$ ], complete left bundle branch block).
- Combined liver dysfunction (defined as Alanine transaminase (ALT) and/or Aspartate aminotransferase (AST) 3 times higher than the upper limit of normal) and kidney dysfunction (defined as creatinine clearance rate less than  $30\text{ mL/min/1.73 m}^2$ ).

- The terminal phase cachexia of malignant tumors.
- High bleeding risk, such as hemorrhagic constitution, history of hemorrhage of vital organs (brain or upper gastrointestinal tract) within 6 months, low platelet counts, abnormal coagulation function, recent active hemorrhage, and so on.
- Underwent surgery within 1 month.
- Women who are under breastfeeding, pregnancy or preparing for pregnancy.
- Poor compliance.
- Known or suspected to be allergic to experimental drugs or allergic constitution.
- Patients who participate in any other clinical study or take any of its investigational drugs within the last 3 months.

### 2.7. Termination and withdrawal criteria

All participants have right to withdraw from the trial depends on their own will. The reason will be recorded in the case report forms (CRFs) and the patient will continue standard western medicine treatment after withdrawing. The criteria of termination and withdrawal including:

- The participant who has serious adverse events (AEs) may caused by experimental drug is considered to be inappropriate to continue the trial based on the cardiologist's judgment.
- The participant's condition becomes deteriorated or develops other diseases that may affect the study.
- Important deviations occur in the process of the clinical trial, such as poor compliance.
- The participant is not willing to continue the clinical trial.

### 2.8. Test drugs

Drugs for clinical trials are LFN-G and placebo (LFN-G mimics), provided by the Guangdong E-Fong Pharmaceutical Technology Development Co, Ltd (Guangdong, China). Formula ingredients of LFN-G includes: Lumbricus (Di long) 10g, Radix Clematidis (Wei lingxian) 15g, Radix Cynanchi Paniculati (Xu changqing) 12g, Panax notoginseng (San qi) 3g, Astragalus (Huang qi) 10g, and Borneol (Bing pian) 0.1g. All ingredients are herbal granules. These granules are mixed and packaged into 2 single-dose sachets, each weighing 25.05g. The placebo consists of medical starch dextrin without active ingredients. Through adding a variety of food colorings and flavouring agents, the placebo will present a similar weight, appearance and taste as close as possible to the real LFN-G.

## 3. Treatment

### 3.1. Treatment plan

All participants will receive a standard western medicine treatment in accordance with guidelines<sup>[2,5,6]</sup> judged by a senior cardiology physician, including but not limited to anti-myocardial ischemia therapy, antiplatelet or anticoagulation therapy, statin therapy. Meanwhile, all participants will accept lifestyle adjustments.

**Experimental group:** Participants will receive LFN-Gs (divided into 2 equally- weight in separate packages, each 25.05g), dissolving each package in 100mL warm boiled water after breakfast and supper for 4 weeks.

**Control group:** Patients will be given placebo granules (divided into 2 equally- weight in separate packages, each 25.05g). The administration is in accordance with the experimental group.

### 3.2. Collection of serum

The subject blood samples will be collected by a designated nurse before and after intervention and designated investigator will centrifuge blood samples in the laboratory. After centrifugation, the supernatant was transferred in frozen pipe and stored at  $-80^{\circ}\text{C}$  for preservation in the biological sample bank of the Dongzhimen hospital. All samples will be destructed when the trial end.

### 3.3. Outcome measures

Primary outcome is the incidence of major cardiac adverse events, defined as a composite of recurrent angina, acute myocardial infarction, severe arrhythmia, heart failure, and cardiac death. This outcome will be compared with the baseline and the 4th week.

Secondary outcomes including:

- (1) Seattle angina scale score: This score includes 4 aspects (physical activity limitation, angina frequency, treatment satisfaction, and disease cognition) and it can provide information of participants' subjective assessment of therapy. This outcome will be compared the baseline with the 1st, 2nd, 3rd, and 4th week.
- (2) Chinese medicine syndromes: This outcome will be compared the baseline with the 1st, 2nd, 3rd, and 4th week.
- (3) ECG: The change of St-segment and T wave of baseline and the 1st, 2nd, 3rd, and 4th week.
- (4) Myocardial nuclides perfusion: It will be used to evaluate myocardial perfusion under endocardium and epicardium of the baseline and the 4th week.
- (5) Echocardiography: Measurement of wall motion score index and left ventricular ejection fraction of the baseline and the 4th week.
- (6) Vitro measurement: Measurement of serum inflammation factors such as C-reactive protein, high sensitive-C-reactive protein, interleukin-6, matrix metalloproteinase-9, and so on.

### 3.4. Safety assessment

The dosage of experimental herbs used in this trial is all within the recommended range based on the People's Republic of China Pharmacopeia (2015 edition). At the process of trial, we also utilize laboratory tests to evaluate liver and kidney function to ensure the safety of participants from the time of enrollment through the follow-up period.

### 3.5. AEs

Any AEs will be requested to record in CRFs regardless of their relationship to the intervention. If serious AEs occur, the intervention should be stopped immediately and a detailed description of the time, severity, relationship with the drug, and the treatment measurement will be recorded. Serious AEs will be reported to the Steering Committee and Ethics Committee within 24 hours. In addition, a follow-up will be conducted until the AEs disappeared.

### 3.6. Data management and quality control

All information related with this trial will be recorded in CRFs by a trained and qualified investigator. No correction of completed CRFs is allowed once completed. The record of CRFs will be reviewed by the clinical inspector. To ensure the accuracy of the data, 2 investigators will input and proofread the data respectively. In addition, all papery documents and electronic versions of the CRF will be preserved in the secure research archives for 5 years after trial completing at the Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine and only can be viewed by the research team.

### 3.7. Statistical analysis

The data will be analyzed using the Statistical Package for the Social Sciences version 22.0 (SPSS 22.0, Chicago, IL). The qualitative data is analyzed by descriptive statistics, expressed by frequency and percentage; the measurement data is expressed as mean  $\pm$  standard deviation and tested by *t* test or *q* test. Chi-square test is used for counting data. Spearman correlation analysis is used for single factors and logistic regression analysis is used for multiple factors. The composition ratio data is tested by  $\chi^2$  test. Unidirectional ordered data were tested by rank sum test. All statistical tests will be bilateral tests and *P*-values  $< .05$  is considered to indicate statistical significance.

## 4. Discussion

UA is a common manifestation of coronary artery disease that seriously affects the quality of life and causes deaths and potential years of life lost. Current treatments for UA are still not satisfy all clinical conditions. There is a wide acceptance of CHM for treating coronary artery disease in China and it has obvious curative effect indeed. In a long-term clinical work of our team, we have found the efficacy and safety of LFN-G in treatment of UA. But we need a compelling RCT evidence to further demonstrate the benefits and risks of adding LFN-G to the standard western medicine treatment for patients with UA.

In order to evaluate the efficacy and safety of LFN-G, we design this prospective, open-label, randomized, placebo-controlled trial. In this trial, we focus on the incidence of major cardiac adverse events, angina score, quality of life, and utilize some objective physical and chemical indicators to ensure the reliability and generality of the results.

There exist some limitations to this study. First, this is a single-center, small scale RCT. Second, the follow-up duration is relatively short. Third, this trial will be performed in Beijing, China, there may be regional and ethnic deviations. Thus, if we finally get a promising result from this current, we consider conducting a multicenter, randomized, large scale, and long follow-up trial in order to provide more significant information to guide clinical treatment.

### Author contributions

**Conceptualization:** Xian Wang.

**Investigation:** Kai Wang, Yang Wu, Yu Wang.

**Project administration:** Xian Wang.

**Methodology:** Lei-Lei Liu, Lei Shi.

**Project administration:** Xian Wang.

**Trial design:** Kai Wang, Xian Wang.

**Writing – original draft:** Kai Wang, Jun-Jun Cai.

**Writing – review and editing:** Lei-Lei Liu, Lei Shi, Xian Wang.

## References

- [1] Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67–492.
- [2] Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267–315.
- [3] Puelacher C, Gugala M, Adamson PD, et al. Incidence and outcomes of unstable angina compared with non-ST-elevation myocardial infarction. *Heart* 2019;105:1423–31.
- [4] Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian study). *Eur Heart J* 2010;31:2755–64.
- [5] Chinese Society of Cardiology, Editorial Board of Chinese Journal of Cardiology Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndrome. *Chin J Cardiol* 2017; 45:359–76.
- [6] Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2014;64:e139–228.
- [7] Gao R, Patel A, Gao W, et al. Prospective observational study of acute coronary syndromes in China: practice patterns and outcomes. *Heart* 2008;94:554–60.
- [8] Amritphale A, Amritphale N. Refractory angina: the current state of mechanical therapies. *Curr Cardiol Rep* 2019;21:46.
- [9] Tan D, Wu JR, Zhang XM, et al. Sodium tanshinone II A sulfonate injection as adjuvant treatment for unstable angina pectoris: a meta-analysis of 17 randomized controlled trials. *Chin J Integr Med* 2018; 24:156–60.
- [10] Yang X, Xiong X, Yang G, et al. Chinese patent medicine Xuefu Zhuyu capsule for the treatment of unstable angina pectoris: a systematic review of randomized controlled trials. *Complement Ther Med* 2014;22:391–9.
- [11] Zhang JH, Shang HC, Gao XM, et al. Compound salvia droplet pill, a traditional Chinese medicine, for the treatment of unstable angina pectoris: a systematic review. *Med Sci Monit* 2008;14:RA1–7.
- [12] Jing GJ, Yang R, Liu DW, et al. The study of the clinical effect and mechanism of Luofengning I prescription in the treatment of unstable angina pectoris of coronary heart disease. *Beijing J Tradit Chin Med* 2017;36:82–4.
- [13] Yang R. Clinical Observation on the Treatment of Unstable Angina Pectoris with Luofengning I Prescription and the Effect on Inflammatory Factors of Macrophages. Beijing, China: Beijing University of Chinese Medicine; 2013.
- [14] Yang R, Zhu HY, Zhao MJ, et al. Primary study on the anti-inflammatory mechanism of Luofengning I based on mononuclear-macrophage inflammatory model. *Chin J Integr Med Cardio-Cerebrovasc Dis* 2014;12:1240–3.
- [15] Sun T. The Effect of Luofengning I Prescription on Coronary Vascular Endothelial Function in Myocardial Infarction Rats Based on the Theory of Pathogenesis of “Endogenous Collateral Wind”. Beijing, China: Beijing University of Chinese Medicine; 2015.
- [16] Sun T, Wang X. Regulative effect of Luofengning I on system of thrombomodulin-activated protein C-endothelial protein C receptor in rats with myocardial infarction. *Chin J Evid Based Cardiovasc Med* 2017;9:1342–5.
- [17] National Administration of Traditional Chinese Medicine. The diagnosis basis, syndrome classification and curative effect evaluation of chest arthralgia and cardiodynia—standards of traditional Chinese medicine of the People’s Republic of China (Criteria for the diagnosis and curative effect of internal diseases of Traditional Chinese Medicine) (ZY/T0011-94). *J Liaoning Univ Tradit Chin Med* 2016;18:32.