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Rationale and Design of the RESTORE Trial: A Multicenter, Randomized, Double-Blinded, Parallel-Group, Placebo-Controlled Trial to Evaluate the Effect of Shenfu Injection on Myocardial Injury in STEMI Patients After Primary PCI

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Abstract

Background The mortality following ST-segment elevation myocardial infarction (STEMI) remains substantial in the reperfusion era. Shenfu injection, as a traditional Chinese herbal formula, can alleviate ischemia-reperfusion injury through multiple pharmacologic effects. However, no robust data are available regarding the role of Shenfu injection in reducing infarct size for patients with STEMI undergoing primary percutaneous coronary intervention (PPCI).

Methods/Design This RESTORE trial is a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (NCT04493840). A total of 326 eligible patients with first-time anterior STEMI undergoing PPCI within 12 h of symptom onset will be enrolled from 10 centers in mainland China. Patients are randomized in a 1:1 fashion to receive either intravenous Shenfu injection (80mL Shenfu injection + 70mL 5% glucose injection) or placebo group (150mL 5% glucose injection) before reperfusion and followed by once a day until 5 days after PPCI. The primary end point is infarct size assessed by cardiac magnetic resonance (CMR) imaging 5±2 days after PPCI. The major secondary end points include enzymatic infarct size, microvascular obstruction, intramyocardial hemorrhage, left ventricular volume and ejection fraction assessed by CMR, as well as cardiovascular events at 30 days.

Conclusions The RESTORE trial is sufficiently powered to demonstrate the clinical effects of Shenfu injection on myocardial injury in STEMI patients undergoing PPCI in the contemporary era. (Am Heart J 2023;260:9–17.)

Despite therapeutic advances including greater use of reperfusion therapy and modern antithrombotic therapy, mortality following acute ST-segment elevation myocardial infarction (STEMI) remains substantial.[1,2] Reperfusion not only salvages ischemic myocardium from infarction but is paradoxically associated with irreversible myocardial and microvascular injury.[3,4] Many cardioprotective therapies with mechanical and pharmacological interventions have been proved to reduce infarct size in animal models.[5-8] However, translation of cardioprotection to clinical practice with better outcomes has been disappointing. This may be partly due to differences between preclinical models of transient myocar-

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Abbreviations: STEMI, ST-segment elevation myocardial infarction; CMR, cardiac magnetic resonance; PPCI, primary percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events; LAD, left anterior descending branch; TIMI, thrombolysis in myocardial infarction; IWRS, Interactive Web Response System; AE, adverse event; SAE, serious adverse event; LV, left ventricular; AUC, area under the curve; CK-MB, creatine kinase-myocardial band; CTFC, corrected TIMI frame count; TMPG, TIMI myocardial perfusion grade; SUSARS, suspicious unexpected serious adverse reactions; SSARS, suspicious serious adverse reactions; CEC, Clinical Events Committee; SD, standard deviation; FAS, full analysis set; RIC, remote ischemic conditioning.

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dial ischemia and STEMI patients with advanced age, comorbidities, and co-medications.[9,10] The lack of robust preclinical data, and incorrect design of studies in terms of patient selection and inappropriate timing and mode of delivery of the cardioprotective agent may also be responsible.[11-13] More importantly, the mechanisms involved in myocardial reperfusion injury are multifactorial, with multiple pathophysiological factors (calcium overload, oxidative stress, inflammation, and mitochondrial dysfunction), making it a complex phenomenon to target effectively.[3,4,14] Thus, ideal cardioprotection may require the combination of synergistic multitarget therapies.[15]

As a well-known traditional Chinese medicine, Shenfu injection is an extracted solution prepared from ginseng (Panax; family: Araliaceae) and aconite (Radix aconiti lateralis preparata, Aconitum carmichaeli Debx; family: Ranunculaceae) with ginsenosides and aconite alkaloids as the main active ingredients,[16,17] which contains 1 mg/mL Panax ginseng C.A. Mey and 2 mg/mL Aconitum Carmichaeli Debeaux.[18,19] Shenfu injection is used for restoring "Yang" from collapse and tonifying "Qi" for relieving desertion and has been proposed as a therapeutic approach for cardiac arrest and shock.[18,20] Mechanistically, Shenfu injection has the potential to target different signaling pathways within the cardiomyocyte or different proponents of myocardial reperfusion injury (cardiomyocyte, platelets, inflammation, and microvasculature).[21] Thus, it may provide more effective cardioprotection than a single targeted approach. We firstly conducted a pilot study and found that the use of Shenfu injection was safe but was not associated with a significant reduction of infarct size by cardiac magnetic resonance (CMR) in reperfused patients with STEMI.[22] Therefore, we designed the multicenter randomized evaluation of Shenfu injection to reduce myocardial injury (RESTORE) trial to provide solid evidence regarding the role of Shenfu injection in limiting myocardial injury in STEMI patients undergoing primary percutaneous coronary intervention (PPCI).

Methods

Study design

This study is an investigator initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial comparing Shenfu injection with placebo in STEMI patients undergoing PPCI (Figure). This trial was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University approved this study (2019013). This trial has been registered at ClinicalTrials.gov (NCT04493840).

Study objectives

The primary objective is to evaluate whether the administration of intravenous Shenfu injection, as compared to placebo, could reduce infarct size assessed by CMR in patients with acute anterior STEMI after PPCI.

The secondary objective is to evaluate the effects of Shenfu injection as compared with placebo on enzymatic infarct size, microvascular obstruction, intramyocardial hemorrhage, myocardial perfusion, cardiac function, and major adverse cardiovascular and cerebrovascular events (MACCE) after PPCI for STEMI.

Study population

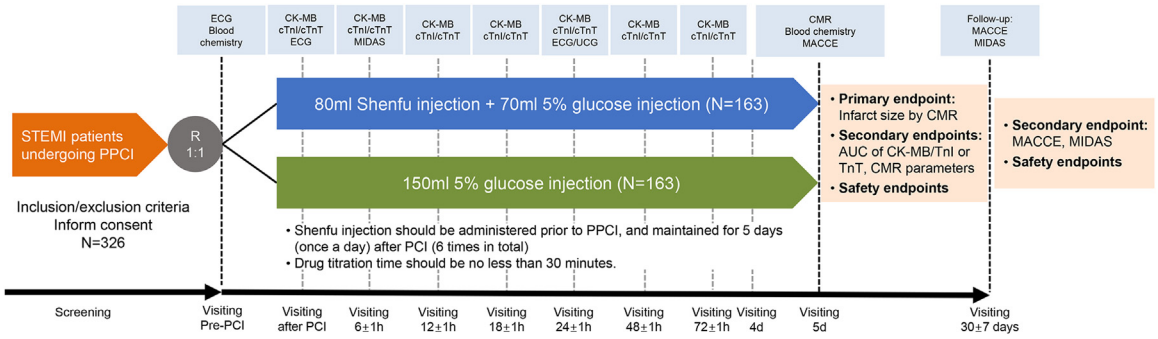
All patients enrolled should be first-time acute anterior STEMI who are scheduled for PPCI with the time from onset of ischemic symptom to the time of initial balloon inflation ≤12 hours. All subjects will provide written informed consent. Patients will be enrolled in the trial according to baseline clinical criteria, but only those meeting the angiographic criteria (the presence of left anterior descending branch [LAD] occlusion in proximal or middle segment with pre-PCI thrombolysis in myocardial infarction [TIMI] flow 0 or 1 according to baseline coronary angiogram) will be included in the primary analysis. A total of 326 patients from about 10 centers are expected to be recruited in the present study. The eligibility criteria including inclusion and exclusion criteria are listed in the Table I. Patients meeting all the inclusion criteria and none of the exclusion criteria are eligible for randomization.

Randomization and blindness

All eligible patients are randomized via Interactive Web Response System (IWRS) in a 1:1 fashion in blocks of 4, to 1 of the 2 study arms (Shenfu injection or placebo) before PPCI. This system is maintained by a third-party of the Institute of Clinical Research, Peking University. The randomization number assigned by IWRS is automatically linked to a unique medication number of research drugs (Shenfu injection or placebo).

The drugs used in the study are provided by the collaborator, China Resources Sanjiu Medical & Pharmaceutical Co, Ltd, and packaged according to the randomization allocation list and the blinded principle. Shenfu injection is a colored transparent liquid, and the matched drug 5% glucose injection is a colorless transparent liquid. In order to reduce the bias, a disposable lucifugal infusion bag and apparatus will be used during the infusion to effectively cover the study drug and matched placebo. To maintain the double-blind design, only the designated unblinded medical professional knows the group information. The injection is prepared by the medical professional according to the dosage of the study drug in a separate room. All the medical professionals will follow the blind and mask standard operating procedure and be

Figure



Flowchart of RESTORE study. AUC, area under the curve; CK-MB, creatine kinase-myocardial band; CMR, cardiac magnetic resonance; ECG, electrocardiograph; MACCE, major adverse cardiovascular and cerebrovascular events; MIDAS, myocardial infarction dimensional assessment scale; PPCI, primary percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UCG, Ultrasonic Cardiography.

Table I. Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥18 and <75 y
2. First-time acute anterior STEMI scheduled for PPCI
3. ST segment elevation in at least two contiguous precordial leads according to electrocardiogram
4. Symptoms onset ≤12 h
5. The presence of proximal or middle left anterior descending branch occlusion with pre-PCI TIMI flow 0 or 1 according to baseline coronary angiogram
6. Written informed consent

Exclusion criteria

1. Cardiogenic shock, serious heart failure (Killip class III or above), malignant ventricular arrhythmia, or mechanical complications
2. Post cardiopulmonary resuscitation (including cardioversion)
3. Patients who have received thrombolytic therapy or upstream GPIIb/IIIa inhibitors
4. Uncontrolled hypertension (systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg)
5. Prior myocardial infarction, PCI or CABG
6. Known severe hepatic insufficiency (AST/ALT >3-fold the upper limit of normal value) or known renal insufficiency
7. Malignant tumor, lymphoma, HIV-positive, or cirrhosis with life expectancy <1 y
8. Patients with active bleeding, intracranial hemorrhage, major surgery or trauma within 1 mo, or ischemic stroke or transient ischemic attack within 6 mo
9. History of anemia (hemoglobin <90g/L) or thrombocytopenia (thrombocyte $<100 \times 10^9$/L)
10. Patients who require simultaneous intervention of left main disease during PPCI or those with multivessel disease who plan to treat non-culprit vessels within 7 d (simultaneous or staged)
11. Scheduled for CABG within one month after randomization
12. Pregnancy, lactation, or potentially fertile women
13. Patients who have known to be allergic to Shenfu injection or its components or patients with serious adverse effect
14. Patients with contraindication to CMR (metal foreign body in the body, claustrophobia, etc.)
15. Participation in other clinical trial in recent 3 mo
16. Patients who cannot complete this trial or comply with the protocol

BP, blood pressure; CABG, coronary artery bypass graft; CMR, cardiac magnetic resonance; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

required to sign a confidentiality agreement. During the process above, the study investigator (doctors), subjects, data managers, statisticians, and clinical research associate are all blinded to the allocated treatment. Only medical professionals know the drugs used. All relevant personnel must strictly abide by the blind regulations and prohibit information leakage.

Study treatment

Subjects who fulfill with all the clinical inclusion/exclusion criteria and sign the informed consent forms will be assigned a randomization number with corresponding package number of the study drugs. The drug administrator distributes the corresponding study

drugs to the designated unblinded medical professional. Medical professional prepares the injection according to the dosage of Shenfu injection (80mL Shenfu injection + 70mL 5% glucose injection) or matched placebo (150mL 5% glucose injection) in a separate room. The professional identifies the study drug number on the lucifugal infusion bag and delivers the drug to the subject. The study drug intravenous infusion will be started no more than 60 minutes before the anticipated PCI and continue for at least 30 minutes after restoration of blood flow in the culprit vessel. Then, study drug should be maintained for 5 days (once a day) after PCI (6 times in total). After the infusion is completed, the drug bottle and infusion bag are handed over to the drug administrator for storage.

Each center will allocate a specific drug administrator to manage the storage, delivery, recording, and recycling of the study drug. The study drug is stored in a special pharmacy at room temperature and locked in a counter. The remaining study drugs are stored separately and recorded on the "Study Drug Delivery Form" and returned to the sponsor for destruction after the clinical trial.

All patients receive the standard treatments of STEMI according to current guidelines and local standard of care, including reperfusion therapy (PPCI) and medical therapies. The use of thrombus aspiration and type of stents are left to the discretion of the operator. In patients with STEMI without complete revascularization, selective revascularization is recommended to be performed more than 30 days after PPCI if the patient condition permits. After PPCI, dual antiplatelet therapy, lipid-lowering therapy, angiotensin-converting enzyme inhibitors, beta-receptor blocker, and/or antihypertensive therapy are prescribed according to current guidelines. It is not allowed to use other Chinese medicine injections and oral medicines that may affect the observation of efficacy according to the judgment of researcher.

Follow-up

All randomized subjects will have a follow-up telephone contact or office visit (preferred) at 30 days after randomization. The follow-up data including vital signs, laboratory tests, echocardiography, MACCE, questionnaire of quality of life, adverse event (AE), serious adverse event (SAE) and concomitant medications will be collected.

End points

The primary end point is infarct size assessed by CMR imaging (percent infarcted myocardium relative to left ventricular [LV] mass) at 5±2 days after PPCI. The secondary points as following: microvascular obstruction and intramyocardial hemorrhage by CMR, enzymatic infarct size by measuring the area under the curve (AUC) of creatine kinase-myocardial band (CK-MB) within 72 hours after PPCI, the AUC of cardiac troponin I (cTnI/cTnT), peak value of CK-MB and peak value of cTnI/cTnT, ST segment resolution (%) according to electrocardiograph, TIMI flow grade, corrected TIMI frame count (CTFC), TIMI myocardial perfusion grade (TMPG), myocardial salvage index, myocardial edema, LV end-diastolic volume, LV end-systolic volume, left ventricular ejection fraction assessed by CMR, MACCE (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergency revascularization) and individual end point events at discharge and 30 days after PPCI. For complete details of end point definitions, see Table II.

Assessment of AE, SAE, suspicious unexpected serious adverse reactions (SUSARS), and suspicious serious adverse reactions (SSARS) are necessary. All AEs and SAEs will be assessed about their relation with the research drug and be followed up until recovery or stabilized. Clinical Events Committee (CEC) will oversee and adjudicate all end point events occurring at 30 days in a blind manner. CEC consist of physicians not participating in the study. The committee members and the CEC management team will be kept completely in the dark about the randomized treatment and any patient identifying information.

The definitions of adverse event, drug preparation process, CMR imaging protocol, and the schedule of assessment (Supplementary Table I) are provided in Supplementary Materials.

Statistical consideration

The sample size calculation of the study was based on the results of our pilot randomized clinical trial,[22] using PASS 16 software (NCSS, Kaysville, UT). According to the pilot trial, the mean values of infarct size in the Shenfu injection group and placebo group were 24.0% and 28.0%, respectively (responding median values are 24.1% and 29.1%, respectively), and standard deviation (SD) was 11.33.[22] A sample size of 260 patients randomized to Shenfu injection group and placebo group will have 80% statistical power to detect a significant difference at a single-sided alpha level of 2.5%. Accounting for a 20% dropout rate, a total of 326 cases will be enrolled, with each group responsible for 163 cases.

Blinded treatment arms will be used in all the statistical analyses. A detailed statistical analysis plan will be finalized before database locking. The primary efficacy analysis will be performed on a full analysis set (FAS), which is defined as all subjects who are randomized, meet all inclusion criteria including proximal or middle LAD occlusion with pre-PCI TIMI flow 0 or 1, and have used the study drug (at least one dose). All randomized subjects who have received the study drug and have provided safety information, are included in the safety analysis.

Table II. End points definitions

Primary end points
Infarct size (% of left ventricular mass) assessed by CMR imaging at 5±2 d after PCI
Secondary end points
1. Microvascular obstruction (% of left ventricular mass) assessed by CMR imaging at 5±2 d after PCI
2. Intramyocardial hemorrhage (% of left ventricular mass) assessed by CMR imaging at 5±2 d after PCI
3. AUC of CK-MB within 72 h (immediately after admission [0 h], and 6 h, 12 h, 18 h, 24 h, 48 h and 72 h after PCI) after PCI
4. AUC of cardiac troponin I (cTnI/cTnT) immediately after admission (0 h), and 6 h, 12 h, 18 h, 24 h, 48 h and 72 h after PCI
5. Peak value of CK-MB and cTnI (within 72 h after PCI)
6. ST segment resolution (%) according to ECG (before PCI, immediately after PCI and 24 h after PCI)
7. TIMI flow grade, corrected TIMI frame count, TIMI myocardial perfusion grade (before and after PCI)
8. AAR assessed by CMR imaging at 5±2 d after PCI
9. Myocardial salvage index assessed by CMR imaging at 5±2 d after PCI: ([AAR – infarct size])/AAR]x100%
10. Left ventricular end-diastolic volume assessed by CMR imaging at 5±2 d after PCI
11. Left ventricular end-systolic volume assessed by CMR imaging at 5±2 d after PCI
12. Left ventricular ejection fraction assessed by CMR imaging at 5±2 d after PCI
13. MACCE, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergency revascularization, rehospitalization for heart failure (at discharge and 30 d after PCI)
Other parameters
14. Slow flow, no flow during procedure
15. Malignant arrhythmia (ventricular fibrillation, ventricular tachycardia, etc.) during PCI
16. High-sensitivity C-reactive protein immediately after admission (0 h), and 24, 72 h and 5 d after PCI
17. Brain natriuretic peptide immediately after admission (0 h), and 24, 72 h and 5 d after PCI
18. Questionnaire of quality of life: Myocardial Infarction Dimensional Assessment Scale (MIDAS) score (6 h and 30 d after PCI)

AAR, area at risk; AUC, area under the curve; CK-MB, creatine kinase-myocardial band; CMR, cardiac magnetic resonance; ECG, electrocardiograph; MACCE, major adverse cardiovascular and cerebrovascular events PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Generally, continuous variables are summarized using mean, SD, median, and quartiles, whereas categorical variables are summarized using frequencies and percentages, as appropriate. The primary end point will be compared between Shenfu injection and placebo by student *t* test or Wilcoxon rank test. A covariance analysis model will also be used, which would estimate the LSmean and 95% confidence interval of CMR infarct size between groups, taking into account the center effect and the baseline characteristics that could be related to the infarct size. Secondary end points will be analyzed using $\chi 2$ test or Fisher exact test for categorical data and student *t* test or Wilcoxon rank test for continuous variables, as appropriate. Multiple linear regression analysis will be performed to identify the association between variables and infarct size. For MACCE and individual end point events, the Kaplan-Meier method will be used to calculate the 30-day events rate, and the log-rank test will be used to compare the 30-day events rate between the groups. Subgroup analysis will be performed to evaluate the effect of Shenfu injection on primary and secondary end points. The prespecified subgroups are shown in Table III. No interim analysis will be performed. Missing data at baseline will not be imputed. Missing data for the primary end point will be censored at the last follow-up visit. All missing patient will be searched for alive or dead status. All the analyses will be performed using SAS 9.4 (or higher version, SAS Institute Inc, Cary, North Carolina). All statistical tests are two-sided with $P < .05$ considered statistically significant.

Current status

Currently, ten medical centers are recruiting patients. The RESTORE trial started enrolling patients on July 30, 2020, and 236 patients have been enrolled on July 31, 2022. It is expected that recruitment will be completed by January 2023 (Supplementary Figure 1). The last patient's 30-day follow-up data are expected to be completed by February 2023. The main results will be reported by June 2023.

Study organization

The RESTORE trial is led by the Academic Research Organization REACTION (Research and Education Allies in CAD Trials, Initiatives and Organized Networks) Groups, the coordinating center being the China National Clinical Research Center for Cardiovascular Disease, Beijing Anzhen Hospital. The study is overseen by an executive steering committee that is chaired by Shaoping Nie, Chairman of the REACTION Group. The core laboratories of Beijing Anzhen Hospital, Capital Medical University are responsible for off-line analyses of CMR data blinded to the patients' clinical data and treatment allocation. Data management and analyses are under the responsibility of Institute of Clinical Research, Peking University.

Table III. Subgroups of interest

1. Age (< 65 y vs. ≥ 65 y)
2. Female
3. Hypertension
4. Diabetes
5. Smoking
6. Left ventricular ejection fraction (≤ 50% vs. > 50%)
7. The time from onset of ischemic symptom to the time of initial PCI balloon inflation (≤ 6 h vs. > 6 h)
8. Killip class (Killip class I vs. Killip class > I)
9. Pre-PCI TIMI flow (TIMI 0 flow or TIMI 1 flow)
10. Patients on ticagrelor vs. clopidogrel
11. Anticoagulation agents (bivalirudin vs. heparin)
12. Glycoprotein IIb/IIIa antagonists

PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

The trial is sponsored by China Resources Sanjiu Medical & Pharmaceuticals. The funders have no role in study design and conduct, data management, interpretation of the results, or decisions for publication. The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the paper, and its final contents.

Discussion

Timely reperfusion therapy by PPCI has contributed to a decline in mortality rates after STEMI over past decades,[23] but the 1-year cardiac mortality remains high (≈8%).[24] Several cardioprotective therapies have been proposed to be effective at reducing infarct size, but failed to improve clinical outcomes in STEMI patients.[25,26] One major reason might be that myocardial infarction is multifactorial, affecting cardiomyocyte as well as other cell types, including platelets, fibroblasts, endothelial and smooth muscle cells, and immune cells, via multiple mechanisms.[15] A single-targeted approach may be insufficient to produce a robust effect on reperfusion injury. In this regard, an emerging concept has been to adopt a multitargeted strategy with additive or synergistic therapies.

Current multitargeted therapies include a combination of different ischemia conditioning strategies, a combination of pharmacological and conditioning strategies, and a combination of pharmacological treatments.[15] Although the results of studies investigating the effects of remote ischemic conditioning (RIC) alone on clinical outcomes in STEMI patients are conflicting,[27-29] combined RIC and ischemic postconditioning showed improved myocardial salvage after STEMI.[28] The ongoing CARIOCA (Combined Application of Remote and IntraCoronary Ischemic Conditioning in Acute Myocardial Infarction) trial (NCT03155022) is testing this approach with clinical events as end points. As a single agent targeting multiple pathways, metoprolol has been used intravenously in STEMI before reperfusion, but results have been conflicting.[30,31] Also, recent studies showed intravenous administration of atorvastatin with multiple cardioprotective mechanisms early after the onset of ischemia reduced the markers of acute cardiac damage in animal models,[32] which needs to be verified in humans. However, some agents with new therapeutic targets did not show reduction in infarct size in well-designed trials.[33,34] N-acetylcysteine (NAC) was used to scavenge reactive oxygen species and potentiates the effects of nitroglycerine. The NACIAM (N-acetylcysteine in Acute Myocardial Infarction) trial combined these 2 agents and showed reduced CMR-assessed infarct size by >30% relative to nitroglycerin infusion alone.[35] Taken together, these studies provide a new direction for research into multitarget cardioprotective therapy.

As a Chinese herbal formula, Shenfu injection is characterized by multicomponents and multiple pharmacologic effects.[21] Its quality is strictly controlled in compliance with the standard of the China Ministry of Public Health (official approval code: certification number Z20043117; No. 110804, Ya'an, China).[16] It has been widely used in the treatment of acute disorders such as shock, cardiac arrest, and heart failure,[18,20,36-38] probably by scavenging reactive oxygen species and inhibiting calcium overload and cardiomyocyte apoptosis.[21] Previous animal studies have also showed that Shenfu injection confers cardioprotection against ischemia-reperfusion injury through broad pharmacological functions, including inhibiting oxidative stress, suppressing cell apoptosis, inhibiting calcium overload.[39-41] Additionally, Shenfu injection could improve myocardial injury and cardiac function by improving microcirculatory dysfunction, ameliorating myocardial blood supply, and reducing inflammation reaction.[42] However, there are no data regarding its efficacy in patients with STEMI.

To observe the effect of Shenfu injection on myocardial infarction, we firstly enrolled 40 patients with first-time anterior STEMI undergoing PPCI in a single-center pilot study (NCT02709798). Although the infarct size assessed by CMR and CK-MB release kinetics did not statistically differ between Shenfu injection and placebo groups, there was a trend towards reduction in CMR infarct size in the Shenfu injec-

tion group, especially among patients with extensive infarct.[22]

To further confirm this finding, we designed the multicenter RESTORE trial with a sample size of 326 patients in about 10 participating centers across China. We only enrolled patients with large anterior STEMI with occlusion of the proximal/mid LAD, thereby representing a high-risk subset most likely to benefit from an adjunct therapy. This trial is placebo-controlled and the primary end point is infarct size on late gadolinium enhancement CMR imaging, which is a main determinant of post-STEMI adverse outcome.[43] The drug infusion covered all the reperfusion phase before and 5 days after PPCI to ensure adequate therapeutic levels. To our knowledge, this is the largest trial focusing on a traditional Chinese medicine with multiple effects and will provide consistent and robust evidence on the protective effects of Shenfu injection against reperfusion injury.

Limitations

First, this study will only enroll anterior STEMI patients with occlusion of the proximal/mid LAD, a subtype most likely to benefit from cardioprotective therapy. The study results may thus not be readily generalizable to other sites of myocardial infarction. Second, this study will exclude subjects with severe heart failure (Killip class III or above), which means that the results of this study cannot apply to the critically ill patients. Third, only a single dose of Shenfu injection is evaluated in this study, which cannot exclude different results with varying dose regimens.

Conclusions

The RESTORE trial is a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial with sufficient power to provide data regarding the clinical efficacy of Shenfu injection in STEMI patients undergoing PPCI in the contemporary era.

Author Contributions

XW and SN contributed to the trial design. XW, XY, XM, SN contributed to protocol development. XW, RG, YG, QG, YY, WG, WZ, HW, LX, HA, BQ contributed to acquisition, analysis, or interpretation of data; XW and SN contributed to writing of the manuscript; XY contributed to the statistical analysis and actively participated in the writing of the statistical sections of the manuscript; all authors critically reviewed the manuscript and approved the final version. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.02.005.

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