

Rationale and design of the AUGUST-AHF Study

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Abstract

Aims We aim to assess the effect of a lyophilized herbal injection on 90 day mortality and readmission rates in patients with acute heart failure (AHF).

Methods and results The AUGUST-AHF study is a multicentre, randomized, double-blind, placebo-controlled trial enrolling 1270 hospitalized patients for AHF. Patients are randomized to receive *YiqiFumai* lyophilized injection (5.2 g/day) or placebo for 10 days, in addition to standard therapy, using a 1:1 ratio via an interactive web response system. The primary endpoint is the 90 day all-cause mortality or AHF readmission rates. Secondary endpoints include 180 day all-cause mortality or heart failure readmission rates, length of hospital stay for the indexed AHF, 90 day cardiac-specific mortality rate, occurrence of worsening heart failure through Day 10, changes in the Minnesota Living with Heart Failure Quality of Life scale score through Day 180, and 90 day major adverse cardiac events. Additional secondary endpoints include change in dyspnoea via visual analogue scale (VAS) and Likert 7-point comparator scale, N terminal pro-B-type natriuretic peptide value and New York Heart Association functional class, and the total amount of diuretics for the indexed AHF hospitalization. Study recruitment is expected to be completed by March 2021, and follow-up will end in September 2021. In an optional sub-study, patients will be followed up for 3 years.

Conclusions To our best knowledge, AUGUST-AHF is the first study assessing the efficacy of a Chinese herbal injection in patients with AHF. The results will be valuable to guide clinicians in using *YiqiFumai* lyophilized injection, which was included in the latest Chinese Health Insurance Catalog.

Keywords Acute heart failure; *YiqiFumai* lyophilized injection; Mortality; Readmission; Chinese medicine injection

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Introduction

Heart failure (HF) is a group of complex clinical symptoms caused by abnormal changes in cardiac structure and/or function, resulting in abnormal ventricular systolic contraction and/or diastolic relaxation. Acute HF (AHF) refers to the rapid onset or deterioration of symptoms and/or signs of HF. It is a life-threatening condition that requires urgent assessment and treatment, usually leading to emergent hospitalization, especially among people aged 65 or older. AHF can present as a first occurrence of HF or as acute decompensation of chronic HF, which is more common and accounts for about 70–80% of all AHF hospitalizations.^{1–3} Patients admitted for AHF have a high risk of mortality and readmission, especially

in the first 90 days post discharge. The re-hospitalization rate in patients with AHF in 3–6 months after discharge was 10% to 20%, and the mortality rate was 20–30% in the same period.⁴ More specifically, depending on presentations, the 1 year mortality rate of patients admitted with AHF was 28.1% in pulmonary oedema, 54.0% in cardiogenic shock, 27.2% in decompensated HF, 12.8% in hypertensive HF, 34.0% in right HF and 20.6% in HF complicated with acute coronary syndrome, or 8.8% with reduced ejection fraction (<40%), 7.6% with mid-range ejection fraction (40–50%), and 6.3% with preserved ejection fraction (>50%).^{5,6} At present, treatment of AHF mainly includes intravenous diuretics with adjunctive vasodilators and inotropes, when necessary. However, in the past decade, studies on AHF treated with

new treatments or drugs have failed to prove long-term mortality benefits.^{7,8}

YiqiFumai lyophilized injection is an injection form herbal medicine extraction processed by modern technology from the ancient formula *Shengmai* powder, which is mainly composed of *Panax ginseng*, *Ophiopogon japonicus*, and *Schisandra chinensis*. Some studies have shown that *YiqiFumai* lyophilized injection can protect the myocardium by inhibiting oxidative injury, improving vascular endothelial function, and maintaining the functional integrity of myocardial tissue.^{9,10} At a molecular level, *YiqiFumai* lyophilized injection can inhibit mitogen-activated protein kinase, nuclear factor kappa-B, and other signal pathways and thus reduce the inflammation of myocardium, myocardial fibrosis, and ligation-induced ventricular remodelling, leading to improved cardiac function^{11–14} (Figure 1).

In China, *YiqiFumai* lyophilized injection is mainly used in the treatment of cardiovascular diseases including AHF. It was recently included in China’s new National Medical Insurance Catalog,¹⁵ although evidence supporting its use for such conditions including AHF is largely indeterminate owing to the poor quality of previous studies.¹⁶

The objective of this study is to assess the effect of *YiqiFumai* lyophilized injection on the 90 day death or readmission rate in patients with AHF.

Study design

This multicentre, double-blind, randomized, placebo-controlled trial will be conducted at 50 hospitals in China. The study flow chart is presented in Figure 2. Study recruitment is expected to be completed by March 2021, and follow-up will end in September 2021. The trial was registered on www.Chictr.org.cn: ChiCTR2000029117.

The AUGUST-AHF Executive Committee (Appendix) designed the trial in collaboration with the corresponding author of this article. The trial is being conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. Written approval from the appropriate ethics committees is required, and each patient must provide written informed consent prior to participation.

Study population

To participate in AUGUST-AHF, patients must be ≥18 years of age, fulfilling the 2017 American College of Cardiology Foundation/American Heart Association (ACC/AHA) guidelines² for the diagnosis of AHF regardless of left ventricular ejection fraction or New York Heart Association

Figure 1 Potential mechanisms of the beneficial effects of *YiqiFumai* lyophilized injection in patients with acute heart failure. ECM, extracellular matrix; IL, interleukin; CK, creatine kinase; LDH, lactate dehydrogenase; MAPKs, mitogen-activated protein kinases; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa-B; TIMPs, tissue inhibitor of matrix metalloproteinases; TNF-α, tumour necrosis factor-α

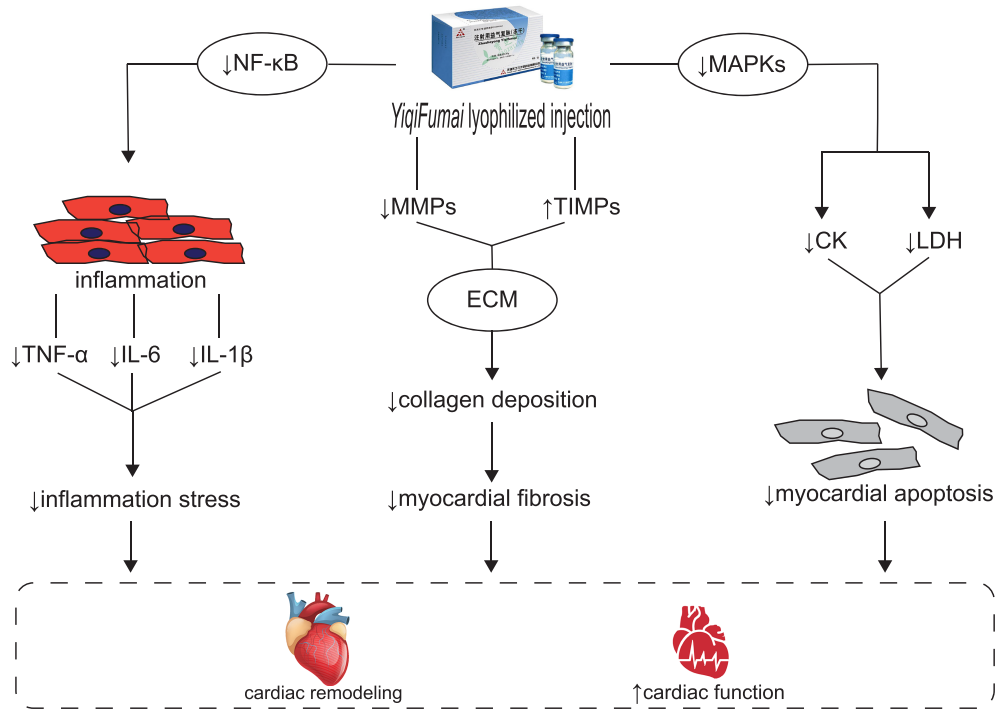
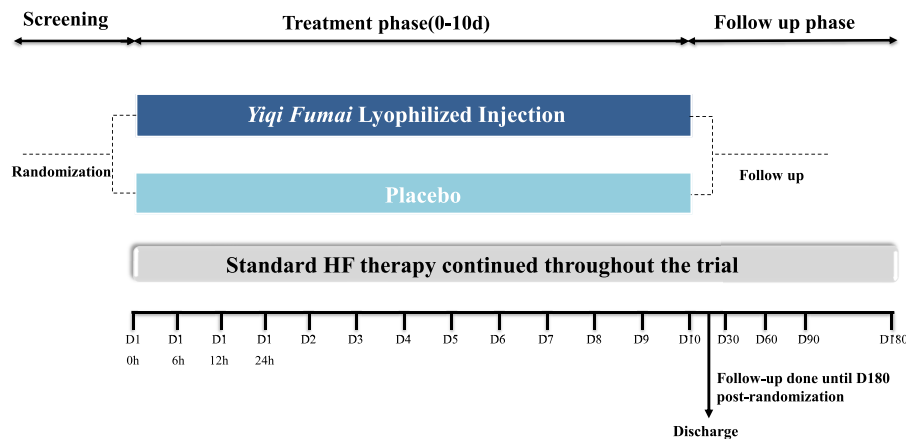


Figure 2 Design for the AUGUST-AHF trial

functional class. Eligible patients are randomized within 16 h after presentation to the hospital into the two study arms. Detailed inclusion and exclusion criteria are listed in *Table 1*.

Randomization and blinding

Randomization will be performed using simple randomization with an allocation ratio of 1:1, as recommended for large

Table 1 Key inclusion and exclusion criteria in AUGUST-AHF

Key inclusion and exclusion criteria in AUGUST-AHF
<p>Key inclusion criteria</p> <ol style="list-style-type: none"> 1. Diagnosis of AHF 2. Age \geq 18 years 3. Voluntarily participate in and sign the informed consent form 4. Randomization will have to be completed within 16 h of presentation^a <p>Key exclusion criteria</p> <ol style="list-style-type: none"> 1. SBP \leq 90 mmHg during baseline screening; patients who are known to be non-compliant, or those with uncontrolled hypertension (SBP \geq 180 mmHg or DBP $>$ 110 mmHg after treatment) 2. Haematocrit $<$ 25% prior to enrolment, haemoglobin $<$ 8.0 g/dL, or a history of transfusion within 14 days prior to screening, or active life-threatening gastrointestinal bleed 3. Major neurological events, including cerebrovascular events, occurred within 60 days prior to enrolment 4. Known liver damage or potentially severe liver disease (ALT or AST $>$ 10 times normal) 5. Known severe renal insufficiency (eGFR $<$ 25 mL/min/1.73 m²) or planned or under dialysis, or apparent acute contrast nephropathy during screening period 6. AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with ventricular rate $<$ 45 b.p.m., or atrial fibrillation/flutter with sustained ventricular response of $>$120 b.p.m. 7. Known to have acute myocarditis, obstructive hypertrophic cardiomyopathy, complex congenital heart disease, constrictive or restrictive pericarditis, cardiac tamponade, severe aortic stenosis, or severe mitral stenosis 8. Severe aortic regurgitation or mitral regurgitation requiring surgery or percutaneous intervention 9. Dyspnoea due to obvious non-cardiac causes, such as acute or chronic respiratory disease or infection 10. Patients who have received any organ transplant or is currently on the list to receive an organ transplant 11. Current mechanical ventilation or circulation support (including within 2 h prior to screening) or planned to provide mechanical ventilation or circulation support (tracheal intubation, mechanical ventilation; intra-aortic balloon pump or any ventricular assist device; haemofiltration or dialysis) 12. Those who have used the study medication 3 months before screening, or who have participated in other studies within 30 days before enrolment 13. Pregnant or lactating women or those who want to become pregnant during the trial or within 3 months after treatment 14. Patients with a history of YiqiFumai lyophilized injection allergy 15. Patients with major psychiatric disorders, including but not limited to major depression, alcohol dependent; patients with a history of drug abuse, and those with active sexually transmitted infections (syphilis, genital warts, etc.) 16. Patients with a history of any organ malignancy with or without treatment in the past year, or with a cancer diagnosis with known estimated life expectancy of $<$1 year 17. Those who are unable to follow the doctor's advice or complete follow-up assessments or unsuitable for the trial as judged by the researchers at baseline assessment

AHF, acute heart failure; ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetate transaminase; DBP, diastolic blood pressure; GI, gastrointestinal; eGFR, estimated glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure.

^aPresentation starts as the earliest of time of presentation at the emergency room/department, intensive/cardiac care unit, or ward (excludes emergency medical service or other pre-hospital care).

clinical trials.¹⁷ The study is double-blinded. Independent drug administrators will log into the randomization system to obtain the group information with the random number, and then they will assign the research drug to the nurse who will be responsible for drug infusion. Opaque infusion bags together with infusion devices for both groups will be visually inspected by the hospital pharmacist to ensure identical appearances. Participants and all members of the study including the whole health care team are blinded to study drug assignment.

Study intervention

YiqiFumai lyophilized injection or placebo is administered as an intravenous infusion beginning within 4 h after

randomization, ideally for 10 days. It has to be pointed out that unlike many developed countries, the length of stay for AHF hospitalizations is currently around 10 days in China.^{18,19} Patients in the treatment group will receive *YiqiFumai* lyophilized injection (eight bottles at once, 0.65 g/bottle, 5.2 g in total) diluted with 5% glucose or 0.9% normal saline injection, 250 mL once daily, at 40 drops per minute or 160 mL/h. The placebo group will receive 5% glucose or 0.9% normal saline injection 250 mL daily at the same infusion rate. Because patients with AHF are usually fluid overloaded, all patients will be monitored closely for tolerance during and after fluid infusions. Adverse events including worsening of symptoms will be documented and are allowed to justify the premature cessation of treatment or initiation of additional interventions if needed. Additionally, the steering committee (Appendix) of AUGUST-AHF will assess these adverse

Table 2 Assessment schedule

Time points	Screen	Baseline		Study drug infusion (10 days)										Follow-up				
	16 h	D0	6h	12h	24h	D2	D3	D4	D5	D6	D7	D8	D9	D10	D30	D60	D90	D180
Screening procedures	X																	
Basic information ^a		X																
Physical examination with vital signs ^b		X			X	X	X	X	X	X	X	X	X	X				
Body weight		X			X	X	X	X	X	X	X	X	X	X				
Laboratory inspection ^c	X													X				
ECG ^d	X													X				
Myocardial injury biomarker ^e	X																	
BNP/NT-proBNP ^f	X																	
NT-proBNP ^g		X												X				
NYHA cardiac function classification		X												X			X	
Echocardiogram	X																	
HF signs and symptoms symptoms ^h		X	X	X	X	X	X	X	X	X	X	X	X	X				
Total intravenous diuretics		X			X	X	X	X	X	X	X	X	X	X				
MLHFQ scale		X												X	X	X	X	X
Hospitalization days ⁱ														X				
Assessment of readmission															X	X	X	X
Assessment of death															X	X	X	X
Major adverse cardiac events ^j															X	X	X	X
Adverse and serious adverse events ^k		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ^l		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; MLHFQ, Minnesota Living with Heart Failure Quality of Life; NT-proBNP, N terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WHF, worsening heart failure; X, assessment.

^aBasic information include patient's demographic information, disease history, alcohol and tobacco history, allergy history, and influenza vaccination history.

^bA complete physical examination will be performed at screening; an abbreviated physical examination will be performed at all other specified time points.

^cLaboratory inspection include biochemistry, haematology, urine routine, will be measured locally at baseline and Day 10.

^dECGs will be performed and interpreted locally at screening and at Day 10 or discharge, whichever occurs first.

^eMyocardial injury biomarkers include creatine kinase isoenzyme, lactate dehydrogenase (LDH), and troponin, which will be measured locally at baseline.

^fPatients will be tested for BNP or NT-proBNP locally during screening.

^g300 patients will be selected for NT-proBNP testing at Day 10.

^hHF signs and symptoms, and WHF are assessed through Day 10; and visual analogue scale is used to measure the dyspnoea at baseline, 6 h, 12 h, 24 h, and approximately the same time daily while hospitalized up to Day 10. Likert 7-point comparator scale is used for patients to compare the difference of his/her dyspnoea from the time of presentation to the hospital; the record time is the same as the visual analogue scale (VAS) except for the baseline.

ⁱThe hospitalization days and coronary care unit (CCU) hospitalization days were recorded when the patients were discharged.

^jMajor adverse cardiac events (MACEs), which were defined as the composite of total death; MI; stroke, hospitalization because of HF; and revascularization, including percutaneous coronary intervention, and coronary artery bypass graft.

^kNon-serious and serious adverse events will be reported from the signing of the informed consent form through Days 10 and 180, respectively.

^lConcomitant medication will be recorded at baseline and during hospitalization and follow-up period. In the follow-up phase, only those drugs currently being taken or that were taken within 24 h prior to the visit (Day 30, Day 60, Day 90, and Day 180) will be collected.

events throughout the trial and in case of an unexpectedly high event rate including premature cessation of fluid infusion may decide to unblind, pause, or stop the trial at any time, if deemed necessary. All patients will receive standard HF management during both the index hospitalization and the follow-up period for 180 days.

Study assessments

Patients will be assessed daily while hospitalized through Day 10. They will also be assessed at Days 30, 60, 90, and 180 (*Table 2*). At each of these assessment time point, HF signs and symptoms will be assessed and documented in the case report form, for example, dyspnoea evaluation via the visual analogue scale and the Likert 7-point comparator scale. Body weight is assessed through Day 10. Throughout this trial, especially during and right after study infusions, patients will be monitored closely for the occurrence of worsening HF, which is defined as worsening signs and/or symptoms of HF that require additional interventions, which may include increase in supplemental oxygen requirement, kidney or circulatory support, and mechanical ventilation. The daily total amount of diuretics, including intravenous and oral, will be recorded. Electrocardiograms and laboratory evaluation will be performed at baseline and Day 10 and as needed. N terminal pro-B-type natriuretic peptide will be checked in 300 patients at the selected sites at baseline and Day 10. The length of stay in the intensive care unit, if any, together with the length of stay in hospital will be recorded in the case report form. If patient is discharged prior to Day 10, necessary outcome lab tests and exams will be performed right before patient discharge. Patients will be observed 180 days after indexed hospital presentation for death, AHF re-hospitalization, and major adverse cardiac events, which were defined as the composite of total death, myocardial infarction, stroke, hospitalization because of AHF, and revascularization, including percutaneous coronary intervention and coronary artery bypass graft. Additionally, non-serious adverse events are reported through Day 10 or discharge, and serious adverse events are reported through Day 180. All medication use will be recorded until the end of the last assessment time point. In a further optional sub-study, patients will be followed up remotely for between 3 years or till death.

In the follow-up period, we will use a smartphone-based application (app) to improve patient compliance. The physician will fill in the necessary details of post-discharge instructions and follow-ups in the app before patient discharge. Within 7 days prior to each visit point (Days 30, 60, 90, and 180), the app will request inputs from patients regarding medication and lifestyle modification compliance together with information for the Morisky Medication Adherence Scale (MMAS)-8, the Chinese version of which was found to have a relatively high reliability and validity for patients with HF.²⁰

Study outcomes

The primary endpoint is a composite of 90 day all-cause mortality or AHF readmission rate. The secondary endpoints are shown in *Table 3*. Adverse events, serious adverse events, and laboratory abnormalities will be recorded and compared between the two groups. All potential study endpoints will be adjudicated by a central adjudication committee (*Appendix*).

Sample size calculation

A sample size of 1270 participants will provide the trial with 80% power for the log-rank test to detect about 34% lower relative risk of 90 day all-cause mortality or readmission rate in the treatment group than in the placebo group with a two-sided significance level of 0.05 and 20% dropouts, assuming that a 90 day event rate of 20% for death or readmission in the placebo group on the basis of previous studies.^{21–23}

Statistical analysis

For the primary outcome, the time from randomization to the first AHF readmission or all-cause death will be calculated in days through Day 90. Patients who withdraw consent or who are lost to follow-up without an event will be censored at the last date the patient was known to be alive. Kaplan–Meier estimates will be used, and the groups will be compared with a log-rank test. Relative risk reductions and

Table 3 Outcomes

Outcomes
Primary outcome
90 day all-cause mortality or heart failure readmission rate
Secondary outcomes
1. 180 day all-cause mortality or heart failure readmission rate
2. 90 day cardiac-specific mortality rate
3. Length of hospital stay for the indexed acute heart failure event
4. 90 day major cardiovascular adverse event (MACE) incidence
5. Occurrence of worsening heart failure (WHF) conditions through Day 10
6. Changes in Minnesota Living with Heart Failure Quality of Life (MLHFQ) scale through Day 180
7. Total amount of intravenous diuretics for the indexed acute heart failure
8. Change in dyspnoea via visual analogue scale (VAS)
9. Change in dyspnoea via Likert 7-point comparator scale
10. Change in NT-proBNP value
11. Change in NYHA functional class

Major adverse cardiac events (MACE)s, which were defined as the composite of total death; MI; stroke, hospitalization because of HF; and revascularization, including percutaneous coronary intervention, and coronary artery bypass graft. NT-proBNP, N terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

associated 95% confidence intervals (CIs) will be estimated from the Cox proportional hazards model including the group variable.

For the secondary outcomes, time-to-event variables will be analysed using the same analysis described for the primary outcome. Continuous variables will be assessed using *t*-test or the Wilcoxon rank sum test as appropriate. Categorical variables will be compared between groups with the χ^2 test or Fisher exact test. Longitudinal continuous variables will be analysed by fitting a repeated-measures analysis model. Additionally, adverse events, serious adverse events, and laboratory abnormalities will also be compared using the χ^2 test or Fisher exact test, as appropriate.

All statistical analyses will be performed according to the intention-to-treat principle, using SAS version 9.4 (SAS Institute Inc) with a two-sided *P* value < 0.05 considered significant.

Discussion

In the past 20 years, with the application of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardiac defibrillators, substantial progress has been made in the treatment of chronic HF, especially in decreasing the mortality rates in patients with HF with reduced ejection fraction. However, the available acute interventions in AHF have been largely limited to diuretics with uncertain long-term benefits from adjunctive vasodilators and inotropes. Despite therapeutic advances for chronic HF, AHF has high mortality and readmission rates, especially in the first 90 days post discharge. Treatments that may provide long-term mortality benefits and decrease hospital readmissions in patients with AHF remain highly sought after.

Drug rationale

YiqiFumai lyophilized injection, a contemporary Chinese herbal medicine preparation, is mainly used for the treatment of cardiovascular diseases in China. In animal models, *YiqiFumai* lyophilized injection was found to increase left ventricular contraction, reduce left ventricular end-diastolic pressure, and thus increase cardiac output. At a pathophysiological level, *YiqiFumai* lyophilized injection improves coronary blood flow, reduces myocardial oxygen consumption, inhibits inflammatory mediators, and reduces myocardial injury.^{12,13,24} It also has been found to improve extracellular matrix remodelling by inhibiting the activity of myocardial matrix metalloproteinases.²⁴ In a meta-analysis that included a total of 20 randomized controlled trials, Xie and Dai¹⁶ reported that on top of an acceptable safety

profile, *YiqiFumai* lyophilized injection when combined with standard HF therapy may improve the performance of 6 min walk test and cardiac function via increasing left ventricular ejection fraction and reducing left ventricular end-diastolic dimension.

The dose used in the drug manual per the manufacturer is 5.2 g (eight bottles) once daily; it is also the dosage used in most previous clinical studies.¹⁶ In our trial, we will utilize the same dosing regimen. The dripping rate will be about 40 drops per minute or 160 mL/h as recommended in the instructions. The majority of the previous studies adopted a 7 or 10 day course of treatment and reached statistically significant clinical benefits as compared with control; as a result, the duration of treatment in this trial aims at maximal 10 days unless that the patient is discharged prior to that.

Population rationale

For patient recruitment, there is no limitation on left ventricular ejection fraction in patients with AHF in this trial. Rationales include the following: (i) potential variations in clinical effects of *YiqiFumai* lyophilized injection remain unclear in patients with different left ventricular ejection fraction, and (ii) restriction on patient selection will limit the applicability of the intervention in the AHF population. Included patients' plasma natriuretic peptide levels will be in line with the diagnostic criteria of the 2017 ACC/AHA guidelines for AHF.²

Assessment time point rationale

There are two important time points in our trial: 90 days and 16 h. The former indicates that the primary outcome evaluation time point is 90 days after hospital presentation. The early stage after hospitalization of AHF, also known as 'the vulnerable stage', has a particularly high risk for adverse clinical outcomes; it is the period when most cardiovascular events occur. The exact time when the vulnerable period extends to is not clear, but limited evidence shows that it can last as long as 60–90 days.^{25,26} As a result, many studies use 90 days as one of the cut point for outcome assessments in patients with AHF. Similarly, we utilize 90 days after initial evaluation as the major outcome assessment time point for this trial, assessing the efficacy of *YiqiFumai* lyophilized injection in AHF.

In this trial, eligible patients are randomized within 16 h after hospital presentation. Patients were randomized within 48 h of hospitalization in the ASCEND-HF trial and within 16 h from presentation in the RELAX-AHF trial; the results from these trials revealed that the actual median time elapsed till receiving treatment was 15.5 and 7.9 h, respectively.^{23,27} Although neither ASCEND-HF nor RELAX-AHF demonstrated benefits of the studied medication

in cardiovascular death or hospital readmission for HF, the RELAX-AHF trial did find that serelaxin (30 µg/kg per day) was associated with dyspnoea relief and decreased deaths at Day 180.²³ On the other hand, nesiritide was not associated with the rate of death, and its effects on dyspnoea were small and nonsignificant in the ASCEND-HF trial.²⁷

Early intervention may play a role in the positive benefits of serelaxin in the RELAX-AHF trial. Does it mean the sooner the better? Not really. One study showed that only two-thirds of patients suspected of AHF within 1 h of presentation were finally confirmed to have AHF at 6 h after presentation, suggesting that an early intervention for susceptible AHF may lead to inclusions of patients with a false diagnosis of AHF.²⁸ No information was provided in previous studies on the timing of initiating *YiqiFumai* lyophilized injection for AHF,¹⁶ and the effects of early versus late initiation of *YiqiFumai* lyophilized injection for the treatment of AHF remain to be explored. Taking into consideration all the available information, we chose 16 h after hospital presentation to maximize the potential benefits of

YiqiFumai lyophilized injection while also providing reasonable time frame for the correct diagnosis of AHF.

Study design rationale

In this trial, we use opaque dark colour infusion bags and for the double-blind design because the mixture injection solution with herbal extracts has a distinct colour, and blinding can be difficult without similar appearances.²⁹ This is also the possible reason that most previous herbal injection clinical trials were not double-blind. Our design thus can minimize selection and evaluation bias caused by unblinding, providing fair, objective, and reliable results.

During the follow-up period of this trial, the highlight is that we designed a smartphone app to improve patient compliance. Patients will enter a follow-up period after discharge from the hospital till Day 180. Patient compliance is known to be very important in the management of HF.^{1–3} Patients should follow physicians' instructions after hospital discharge,

Table 4 Comparison of AUGUST-AHF and ACT-ADIHF designs

	AUGUST-AHF	ACT-ADIHF
Design	Multicentre	Multicentre
Sample size	1270 (ongoing)	666 (ongoing)
Random method	IWRS	IWRS
Blind method	Double blind	Single blind
Inclusion criteria		
Population	Acute HF	Acute decompensated ischaemic HF
Age	≥18 years	40–79 years
Randomized time	Within 16 h of presentation	Unclear
Diagnosed with coronary heart disease	No	Yes
NYHA classification	No limitation	III–IV
BNP/NT-proBNP	No limitation	BNP > 200 pg/mL
LVEF	No limitation	No limitation
Intervention		
Treatment group	<i>YiqiFumai</i> lyophilized injection + standardized western medications	<i>YiqiFumai</i> lyophilized injection + standardized western medications
Control group	Placebo (5% glucose or 0.9% normal saline injection 250 mL) + standardized western medications	Standardized western medications
Administration time of study drug	No more than 4 h after randomization	Unclear
Intervention phase	10 days	7 days
Follow-up phase	180 days	60 days
Ways to improve compliance	Customized follow-up APP	Unclear
No. of visits planned	18	4
Outcomes		
Primary outcome	90 day all-cause mortality or HF readmission 180 day all-cause mortality or HF readmission rate, length of hospital stay, 90 day cardiovascular death rate, 90 day MACE incidence, WHF through Day 10, MLHFQ scale, dyspnoea VAS score, Likert 7-point comparator scale, NYHA functional class, total amount of intravenous diuretics, NT-proBNP	BNP level Composite endpoint (all-cause death, HF emergency/readmission, acute coronary syndrome, revascularization, malignant arrhythmia, cardiogenic shock, stroke, and pulmonary embolism), LVEF, TNT/TNI, cardiothoracic ratio, life quality scale, scores of the four TCM diagnostic methods
Secondary outcomes		

BNP, brain natriuretic peptide; HF, heart failure; IWRS, interactive web response system; LVEF, left ventricle ejection fraction; MACE, major cardiovascular adverse event; MLHFQ, Minnesota Living with Heart Failure Quality of Life; NT-proBNP, N terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TCM, traditional Chinese medicine TNT/TNI, troponin T/I; VAS, visual analogue scale; WHF, worsening heart failure.

including medication compliance, lifestyle modification, diet, and exercises. Patients' non-compliance with physician instructions can result in worsening HF symptoms, leading to re-hospitalizations or even more serious cardiovascular events.³⁰ Nowadays, the increase in the complexity of treatment plans for HF has further reduced the compliance of patients, especially in elderly people. In HF trials, patients' compliance during the follow-up period likely also plays a role in the credibility of trial results. To address this problem, we designed a smartphone-based app to improve patient adherence. This app mainly reminds patients to fill in the data regarding treatments and the MMAS-8 within 7 days prior to each assessment time points (Day 30, Day 60, Day 90, and Day 180).

Primary outcome rationale

We selected the primary outcome as the composite endpoint of 90 day all-cause mortality or HF readmission rate for the following three reasons. Firstly, reducing mortality and re-hospitalization rates of HF are a goal of important clinical significance for patients, physicians, and health policy decision makers.³¹ The 2018 Chinese HF guidelines clearly advocate that clinical studies of Chinese herbal therapies should emphasize and include their mortality impacts as the primary endpoint.³ Secondly, the composite endpoints may improve trial efficiency by increasing the event incidence rate and reducing the required sample size and allowing adequate accrual of events over a shorter follow-up period.³² Thirdly, in previous clinical studies on *YiqiFumai* lyophilized injection, the mortality and readmission rates were not primary endpoints.¹⁶ For example, the trial of ACT-ADIHF³³ published in 2018 assessed the efficacy of *YiqiFumai* lyophilized injection on acute decompensated ischaemic HF; the primary outcome of this trial was the change in BNP concentrations. As the ACT-ADIHF is the only relatively well-designed trial for *YiqiFumai* lyophilized injection so far, we compared the differences in the study design between this trial and the ACT-ADIHF trial (*Table 4*).

Conclusion

To our best knowledge, AUGUST-AHF is the first multicentre, large sample, randomized, double-blind, placebo-controlled

trial to assess the efficacy of a Chinese herbal medicine injection for patients with AHF. The results will be valuable to answer the question regarding the efficacy of this medication and guide clinicians in using *YiqiFumai* lyophilized injection, which was included in the latest National Medical Insurance Catalog of China.

Conflict of interest

None declared.

Author Contributions

Hongcai Shang and Yan Liu drew up the research design. Jingjing Zhang and Yang Sun drafted the protocol. Jingjing Zhang, Kehua Zhou, and Yan Liu wrote the manuscript in English. Ying Chen, Jiayuan Hu, and Changming Zhong participated in the design amendment and helped with the project coordination. Hongcai Shang, Yan Liu, Xiaoyu Zhang, and Ying Chen contributed to protocol ethics and trial registration. Kehua Zhou revised the details and the language. Yan Liu made the statistical plan. Hongcai Shang is the principal investigators of the whole project. All authors reviewed the manuscript content and approved the final version for submission.

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Appendix

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Data and Safety Monitoring Committee: Xin Sun, Zhangsheng Yu, Xiaohua Zhou, Hao Xu, Xinfeng Guo.

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