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STUDY DESIGN

Efficacy of early initiation of ivabradine treatment in patients with acute heart failure: rationale and design of SHIFT-AHF trial

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Abstract

Aims Elevated heart rate (HR) in heart failure (HF) is associated with worse outcomes, particularly in acute HF (AHF). HR reduction with ivabradine reduces cardiovascular events in HF patients with reduced ejection fraction. The present trial aimed to test the hypothesis that the early HR reduction using ivabradine improves clinical outcomes in patients with AHF.

Methods and results SHIFT-AHF is a prospective, multi-centre, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of ivabradine when adding to standard therapy in AHF patients (SHIFT-AHF). The trial will include 674 AHF patients with left ventricular ejection fraction $< 45\%$ and New York Heart Association functional classes III–IV. Participants were enrolled from March 2020 and will be followed up until December 2022. Patients are randomized to treatment with ivabradine or placebo (randomization 1:1). After allocation, the dose of ivabradine is titrated according to HR. Six months' follow-up and three control visits (7, 90, and 180 days after enrolment) are required for every participant. Assessment involves clinical examination, laboratory tests, echocardiography, electrocardiography, heart rhythm, cardiac function, and quality of life. The primary endpoint is a composite of all-cause mortality or re-admission due to worsening HF. Secondary endpoints include the assessments of cardiac remodelling, cardiac functional capacity, and quality of life.

Conclusions The SHIFT-AHF trial will shed further light on the role of early HR reduction using ivabradine in patients with AHF.

Keywords Acute heart failure; Ivabradine; Randomized controlled trial; Outcomes

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Trial registration: Chinese Clinical Trial Register (ChiCTR2000029836)

Introduction

Heart failure (HF) is a global pandemic with an estimated worldwide prevalence of 38 million patients.[1,2] Acute HF (AHF) is a complex clinical syndrome associated with high morbidity, mortality, and health care expenditures, which are characteristic with rapid deterioration of symptoms and signs.[3] It is associated with an autonomic imbalance, specifically increased sympathetic activity, and reduced vagal activity, resulting in an increase in heart rate (HR) with reduced HR variability (HRV).[4] An inverse relationship exists between HR and prognosis in patients with poor left ventricular (LV) systolic function.[5]

HR higher than 70 b.p.m. was associated with more all-cause death and re-hospitalization during the HF

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vulnerable period, namely 3–6 months after AHF onsets, which was considered as the most concentrated period of adverse events.[6] However, the deficiency of HR control commonly appears in large-scale trials on HF, such as the HF-ACTION,[7] SHIFT,[8] and CIBIS-ELD trials.[9] During the period of AHF, there is an increase in HR concurrent with worsening symptoms, while the treatment becomes more difficult, leading to an overall increase in in-hospital mortality. Furthermore, the increasing HR from the onset of AHF to discharge remains unresolved.

Beta-blockers have been recommended to be useful in stabilizing HR in stable periods of HF because of its negative conduction action. Yet beta-blockers have negative inotropic effect. Conversely, ivabradine has no inotropic and conduction effect, which renders ivabradine administration a more effective treatment regimen during AHF period. The ETHIC-AHF trial documented that ivabradine treatment is feasible and safe during a decompensation episode of HF with reduced ejection fraction (HFrEF), but the sample size was too small, and there was no difference in mortality at 28 days' follow-up after discharge.[10] Until now, there is no evidence to support the efficacy and safety of ivabradine as early as admission in AHF patients regarding the reduction of long-term events.

Ivabradine, a specific HR-slowing drug, which inhibits the If current in the sinoatrial node, unlike beta-blockers, has no known cardiovascular effects other than HR reduction and was recently approved by the Food and Drug Administration for chronic HFrEF. The drug has also antianginal and anti-ischaemic properties in patients with stable angina.[11] SHIFT trail documented that isolated HR reduction with ivabradine improves the composite endpoint of HF re-hospitalizations and cardiovascular death in patients with systolic HF in sinus rhythm who have a resting HR (RHR) $\geq$ 70 b.p.m. before therapy,[8] as well as improvement in quality of life.[12] However, its effects on HR reduction are not known in AHF.

This SHIFT-AHF study was designed to evaluate whether the early HR reduction by ivabradine when added to standard therapy could improve the prognosis of AHF patients.

Methods

Study design

This study is a prospective, multi-centre, double-blind, randomized, placebo-controlled trial in patients with AHF. The present trial has been registered on web of Chinese Clinical Trial Registry (ChiCTR2000029836) on 15 February 2020. The study is designed to compare the efficacy of ivabradine with placebo in addition to standard therapy of AHF.[13,14] The investigation conforms with the principles outlined in the Declaration of Helsinki. Written informed consent will be obtained by physician prior to allocation. The overall trial design for SHIFT-AHF is shown on *Figure 1*. Eligible patients are randomly assigned via a computed random permuted block design method to either ivabradine or placebo, balancing on ages ($\geq$65 vs. $<$65 years) and sex. Patients and physicians are masked to the treatments. The enrolment started from March 2020 and will end in December 2021, while follow-up will be performed until December 2022. The outline of the study is illustrated in *Figure 2*.

Study patients

Patients aged $>$ 18 years with New York Heart Association (NYHA) functional classes III–IV who are admitted to each centre due to AHF by worsening HF symptoms or signs and requiring urgent medical therapy are eligible to enrol. The main inclusion and exclusion criteria are listed in *Table 1*.

Interventions

The two treatment arms will be as follows:

- Standard therapy in AHF (STAHF) + ivabradine
- Standard therapy in AHF (STAHF) + placebo

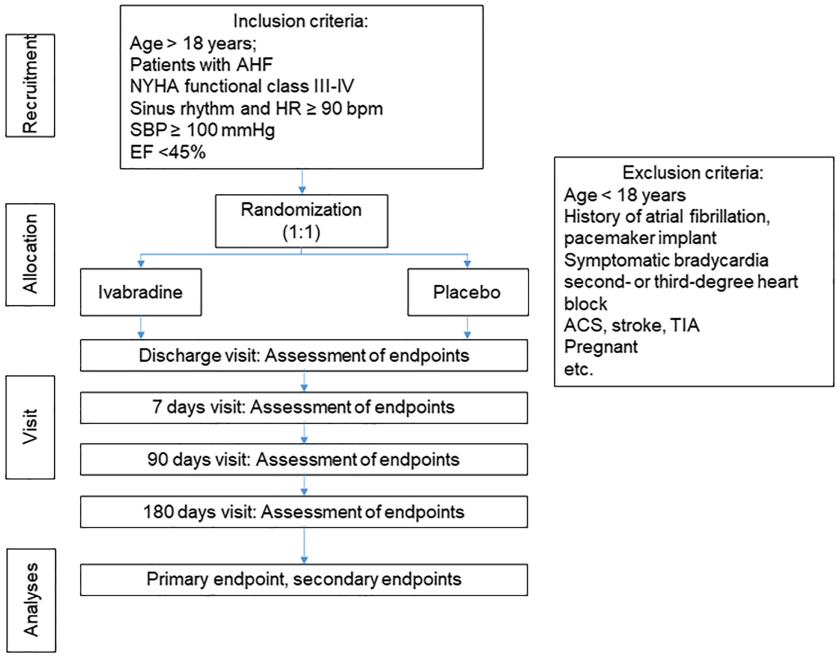
Ivabradine

Ivabradine, a specific HR-slowing drug, has been proved to be safe in the treatment of acute decompensated HF in two small sample clinical studies.[10,15] Ivabradine or placebo will be given to patients on the basis of STAHF from D0 after the initial assessment on admission. The starting dose is 5 mg twice daily. RHR of participants should be re-evaluated after 24 h (D2). If the RHR is more than 70 b.p.m., the dose should be maintained. The dose will be decreased to 2.5 mg twice daily if RHR is $<$70 b.p.m.. Once the RHR is $<$60 b.p.m. or the symptoms related with bradycardia appear, ivabradine or placebo should be stopped. The dose titration and time points of assessments are shown in *Figure 2*.

Standard therapy in acute heart failure

All patients will receive standard therapy including oral or intravenous diuretics, vasodilators, inotropic agents, vasopressors, and vasopressin antagonists as determined by the investigator and local standards.[13,14] Nitroglycerin, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitor, beta-blockers, or aldosterone antagonists will be used according

FIGURE 1 Flow chart of SHIFT-AHF trial. ACS, acute coronary syndrome; TIA, transient ischaemic attack.



to the status of the participants. Monitoring of STAHF will be done throughout the trial by the Executive and Steering Committees. Investigators and study coordinators will be provided with feedback reports indicating the percentage of patients at their local sites that received guideline-based care and potential ways to deliver optimal care based on AHF management guidelines.[3,16,17]

Other heart rate-lowering drugs

Except for beta-blockers, other HR-lowering drugs will be stopped, including digoxin, non-dihydropyridine calcium blockers and class I anti-arrhythmics. Amiodarone and sotalol are not recommended in the period of the study. Beta-blockers such as carvedilol, bisoprolol, and metoprolol

FIGURE 2 Outline of SHIFT-AHF trial. After the enrolment is complete, patients are randomly allocated to either interventional group or control group. STAHF is given to both groups, while ivabradine or placebo is given on top of STAHF to patients according to allocation. Ivabradine or placebo treatment is started at D0 visit. The starting dose is 5 mg twice daily. Resting heart rate (RHR) of participants should be re-evaluated after 24 h (D2). If the RHR is more than 70 b.p.m., the dose should be maintained. The dose will be decreased to 2.5 mg twice daily if RHR is <70 b.p.m.. Once the RHR is <60 b.p.m. or the symptoms related with bradycardia appear, ivabradine or placebo should be stopped The third, fourth, and fifth heart rate assessments are arranged at D7 visit, D90 visit, and D180 visit, respectively. AHF, acute heart failure; RHR, resting heart rate; STAHF, standard therapy in acute heart failure.

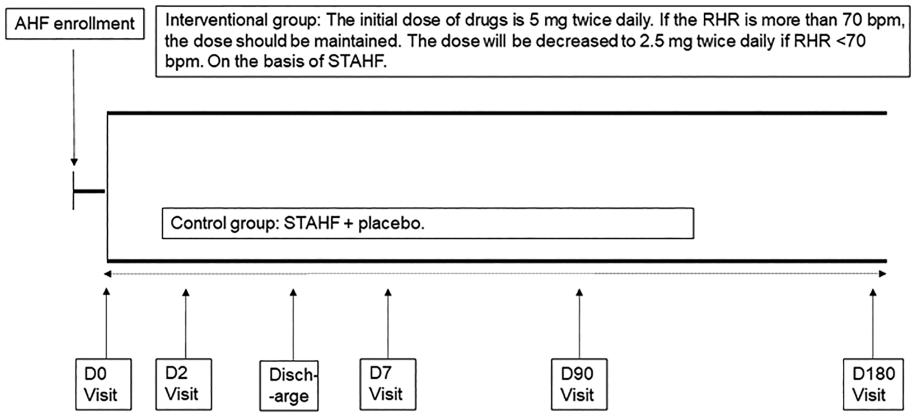


Table 1 Main inclusion and exclusion criteria of SHIFT-AHF

Main inclusion criteria
• Patients >18 years of age with the capacity to provide written informed consent
• LVEF < 45%
• Currently hospitalized for a diagnosis of AHF, including all of the following measured at any time between presentation and the end of screening:
(1) Persistent dyspnoea at rest or with minimal exertion
(2) Signs of fluid overload such as pulmonary congestion or oedema of lower extremity
• B-type natriuretic peptide (BNP) ≥ 300 pg/mL or N-terminal (NT)-proBNP ≥ 1200 pg/mL
• Sinus rhythm and heart rate ≥ 90 b.p.m.[a] at the start and at the end of screening
• Able to be randomized within 16 h from presentation to the hospital
• New York Heart Association functional classes III–IV
• SBP ≥ 100 mmHg
Main exclusion criteria
• Currently taking ivabradine or any use within the past 30 days
• Enrolment in any other clinical trial involving an investigational agent or device
• History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs including heart rate-slowing drugs such as beta-blockers
• History of atrial fibrillation, pacemaker implant, long QT syndrome
• Symptomatic bradycardia or second-degree or third-degree heart block
• ACS, active myocarditis, stroke, TIA, coronary or carotid revascularization, or major CV surgery within the past 3 months
• Primary cause of dyspnoea due to non-cardiac, non-HF causes such as acute or chronic respiratory disorders
• Planned coronary or carotid revascularization within the next 6 months
• Implantation of cardiac resynchronization therapy within the past 3 months or intent to place
• Patients with a history of heart transplant, currently on the transplant list, or with an left ventricular device
• Isolated right HF due to severe pulmonary disease
• Documented untreated ventricular arrhythmia with syncopal episodes within the past 3 months
• Presence of haemodynamically significant mitral, aortic, or hypertrophic obstructive cardiomyopathy
• History of malignancy or any organ system (other than localized and resectable skin cancers) within the past year with a life expectancy of <1 year
• Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL or increased ammonia levels) or history of cirrhosis with evidence of portal hypertension (e.g. presence of oesophageal varices)
• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin test result
• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using 2 birth control methods

ACS, acute coronary syndrome; AHF, acute heart failure; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TIA, transient ischaemic attacks.
[a]Heart rate should be measured consecutively twice on 12-lead electrocardiogram with 10 min interval after admission.

could be used without dosage adjustment in our study. The drug usage is decided by the physician.

Table 2 Endpoints

Primary endpoint
The composite of all-cause mortality or readmission due to worsening HF
First secondary endpoints
All-cause death
Cardiovascular death
Readmission due to HF
The cardiac remodelling measured by echocardiography
The changes of NYHA functional classes or 6 min walk test
The changes of quality of life assessed by MLHFQ or KCCQ
Other secondary endpoints
All-cause mortality from randomization through day 180
CV mortality (HF, myocardial infarction, sudden cardiac death, or other CV) from randomization through Day 180
Bradycardia or second-degree or third-degree heart block
No. of subjects with hypotensive episodes
Incidence rate of new atrial fibrillation

KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

Endpoints

The primary endpoint is a composite of all-cause death or re-admission due to worsening HF. The secondary endpoints are the cardiac remodelling measured by echocardiography, the changes of cardiac functional capacity assessed by 6 min walk test (6MWT) and NYHA functional classes, the changes of quality of life assessed by Minnesota Living with Heart Failure Questionnaire (MLHFQ) score or Kansas City Cardiomyopathy Questionnaire (KCCQ), and incidence rate of new atrial fibrillation (*Table 2*).

Assessments and definitions

All participants should be assessed on scheduled profiles (shown in *Table 3*). HF-related symptoms and signs including dyspnoea, oedema, fatigue, and vital signs should be assessed. Cardiac remodelling is evaluated via echocardiography, including measurement of LVEF, the ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue

Table 3 Timeline of assessments

		D0	D2	Discharge	D7	D90	D180
Symptoms and signs	BP, RHR, RR, dyspnoea, oedema, weakness, etc.	X	X	X	X	X	X
Cardiac remodelling	LVESVI, LVEDVI, LVMI, LVeDD, LVeSD, LVEF		X	X	X	X	X
Heart rate and rhythm	RHR, average HR, HRV, AF, etc.	X	X	X	X	X	X
Laboratory tests	Blood cell count, troponin T, NT-proBNP, creatinine, ALT, etc.	X	X	X	X	X	X
Safety	Bradycardia, etc.		X	X	X	X	X
Cardiac functional capacity	NYHA, 6MWT			X	X	X	X
Quality of life	MLHFQ/KCCQ			X	X	X	X

AF, atrial fibrillation; ALT, alanine aminotransferase; HR, heart rate; HRV, heart rate variability; LVeDD, LV end-diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVeSD, LV end-systolic diameter; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; RHR, resting heart rate.

relaxation velocity (E/e′ ratio), LV end-systolic and end-diastolic volume, LV end-systolic and end-diastolic diameter, LV mass index, and LV fractional shortening (%). HR and rhythm are monitored using 24 h electrocardiogram (Holter). Arrhythmic events and indexes like average HR, RHR, and HRV are recorded. Laboratory tests are performed using whole peripheral blood, with blood cell count, troponin T and N-terminal pro-brain natriuretic peptide, urea nitrogen, creatinine, electrolytes (sodium, potassium, and chloride), bilirubin, glucose, albumin, aspartate aminotransferase, and alanine aminotransferase are measured.

Adverse events are evaluated and recorded. An adverse event refers to any medical event related to the use of intervention in human clinical trials, whether or not it is considered intervention related. Cardiac functional capacity is assessed through the NYHA Functional Classification and 6MWT. Quality of life is evaluated by MLHFQ or KCCQ.

Statistical consideration

Sample size calculation

We assumed that the calculative event rate of primary endpoints (all-cause death or re-hospitalization for HF) within 6 months from their discharge is ~0.6 in control group, based on the result of previous studies. Estimated HR of primary endpoint of interventional group to the control group would be 0.85. This trial is designed to have 80% power to detect a 15% relative reduction in the risk of the primary outcome in the ivabradine group within 6 months, as compared with the control group, based on an expected composite incidence at 6 months of 60% in the control group using a log-rank test with a two-sided α of 0.05. A total sample size of 642 patients is planned according to the Schoenfel and Richter method, with a 1 year period for patient enrolment and follow-up periods of 6 months. Assuming the missing rate for 6 months is 5%, the overall sample size is expected to be ~674.

Statistical methodology

All statistical analyses will be independently performed at the Tongji University epidemiological research lab. The analyses of the adjudicated primary and secondary outcomes will be conducted using data for all patients who had undergone randomization, according to the intention-to-treat principle. For the baseline variables, summary statistics will be constructed employing frequencies and proportions for categorical data and means and SD for continuous variables. The patient characteristics will be compared using Fisher's exact test for categorical outcomes and *t*-tests for continuous variables, as appropriate. The primary endpoint of a composite of all-cause death and readmission for worsening HF will be analysed using the stratified log-rank test for eligible patients with age ($\geq$65 vs. $<$65 years) and sex as stratification factors. Time to events will be estimated using the Kaplan–Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors. Sensitivity analyses will also be performed by means of the unadjusted Cox models.

All comparisons are planned, and all *P* values will be two-sided. A *P* value of $<$0.05 will be considered to be statistically significant. All statistical analyses will be performed using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA).

Study management

An independent executive committee chaired by the main principal investigators (PIs) has been established before March 2020, which was composed of PIs of each centre, coordinators, statisticians, clinical investigators. The PIs are responsible for conducting research and deliberating over the protocol correction. The coordinators are responsible for randomizing, connecting the multi-centres, and inspecting the process of investigation. The statisticians are responsible for data management and statistics. The physicians are responsible for patients' management and modifying medicine prescription according on their specific condition. The clinical investigators are responsible for implementing enrolment, collecting medical records, and follow-up patients. Events validation committee composed of cardiovascular specialists will adjudicate all endpoint events and drug adverse events.

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Data management

All data are coded and stored on hospital password-protected computers. Any physical copies of the case report forms and all study-related documents are archived at the hospital. All data are checked monthly by investigators (D. X. and J. Z.) to ensure that all protocols and ethical guidelines for data collection and analysis are followed. Study participants are closely monitored by the investigators. Case report forms are used to record any suspected harms of the study treatments. Study participants may be withdrawn from the study if there is suspicion of treatment harms (e.g. hypotension, bradycardia, and second-degree or third-degree heart block). Monitoring of the data and quality of the study are performed by the senior investigators (D. X. and J. Z.) who comprise a data monitoring committee.

Ethical considerations

The SHIFT-AHF trial complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. The institutional review board at each participating centre independently approved the protocol, and written informed consent was obtained from all study participants prior to enrolment. SHIFT-AHF is registered at Chinese Clinical Trial Register (ChiCTR2000029836).

End of trial

The trial will end once 674 patients have been enrolled.

Dissemination

Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations relating to the study will be authorized by the Chinese Clinical Trial Center and Tongji University. Authorship will be determined according to the internationally agreed criteria for authorship. In addition, a lay summary will be available on the websites of Chinese Clinical Trial Register. Investigators who would like access to the trial data set are encouraged to submit a brief application, outlining rationale and analytical plan, to the trial management group for approval for additional studies.

Trial status

Recruitment is ongoing. The first patient was recruited in March 2020, and we expect recruitment to be complete in December 2021.

Discussion

The SHIFT-AHF trial will try to document if early HR reduction by ivabradine will improve the composite endpoints in patients with AHF.

SHIFT-AHF is a prospective, multi-centre, double-blind, randomized controlled trial designed to assess the efficacy and safety of early HR reduction by ivabradine when added to standard therapy in patients hospitalized for AHF. Despite the conclusive results of SHIFT, expedited Food and Drug Administration approval, and a strong recommendation in the USA and European guidelines for HFrEF, there is a more limited experience with ivabradine in patients hospitalized for acute decompensated HF and patients with severe signs and symptoms of HF. In addition, it is well established that in-hospital initiation of evidence-based medications results in greater long-term adherence. Given the burden of hospitalizations for worsening HF and the unacceptably high postdischarge event rate, the safe initiation of ivabradine in the acute setting may fulfil an important unmet clinical need.

HRV reflects autonomic nervous system status. As sympathetic dominance is an important pathophysiology of HF, HRV is a known important prognostic factor of HF. Ivabradine, a specific HR-slowing drug, should be assessed for HRV. A Holter monitoring device will measure 24 h HRV. The changes in value from baseline between the two groups will be compared. The trial will try to demonstrate if ivabradine will have the advantages of HRV reduction in AHF patients.

The present design has a few limitations. As ivabradine reveals a significant effect on slowing HR compared with placebo, it is unlikely that drug administration is performed in a completely blind way to physician, especially when the baseline HR is $>$90 b.p.m. This may not avoid selection bias. This is a short-term follow-up study that covers only 6 months. We speculate that the lack of effective approach to evaluate the occurrence of some secondary endpoints in such a short period may not avoid information bias.

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Conflict of Interest

None declared.

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