Clinical Study of Lipoic Acid on Ischemic Heart Failure

Study Protocol

Research initiating unit: Zhongshan Hospital, Fudan University

Research units:

Zhongshan Hospital, Fudan University

Affiliated Zhongshan Hospital of Dalian University

the First Affiliated Hospital of Sun Yat-sen University

Shanxi Cardiovascular Hospital

Type of study: Multicenter, double-blind, randomized, placebo-controlled, parallel-group, exploratory

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一、Background

Heart failure is the common endpoint of various structural or functional heart diseases and represents the leading cause of death from cardiovascular diseases, with a 5-year mortality rate exceeding 50% [1-3]. Ischemic heart disease most frequently manifests as the clinical syndrome of heart failure, which is associated with high rates of morbidity and mortality, thereby garnering significant clinical attention. Current clinical treatments for ischemic heart failure primarily include pharmacological therapy, revascularization, therapeutic angiogenesis, and heart transplantation. Despite advancements in interventional techniques and the establishment of treatment strategies based on the "neuroendocrine," "hemodynamic disorders," and "immune-inflammatory" theories, which have partially improved clinical outcomes in patients with ischemic heart failure, these improvements fall far short of clinical needs. There is an urgent necessity to explore new therapeutic targets for heart failure from innovative perspectives.

Abnormalities in myocardial energy metabolism constitute a crucial pathological basis for heart failure, with mitochondria playing a pivotal role as the primary site for ATP production. Elucidating the role of mitochondrial energy metabolic remodeling in the pathogenesis of different types of heart failure and its potential for therapeutic intervention could facilitate the early identification of risk factors for heart failure and lead to more effective improvements in prognosis. Our previous research has focused on mitochondria in failing myocardium, and through proteomic analysis, we have identified nearly a hundred differentially expressed mitochondrial proteins, including aldehyde dehydrogenase 2 (ALDH2). ALDH2 is a key enzyme involved in mitochondrial glycolipid metabolism[4], possessing a redox-sensitive

thiol group at its active site. An increase in endogenous oxygen free radicals promotes the formation of disulfide bonds at the ALDH2 active site, leading to its inactivation [5]. Given the abundant distribution of this enzyme in the myocardium, we have conducted a series of studies on the role of ALDH2 in myocardial injury and protection. Our findings indicate that ALDH2 exerts cardioprotective effects by maintaining mitochondrial metabolic homeostasis under cardiovascular pathological stimuli such as ischemia, hypoxia, and alcohol exposure [6-12]. Furthermore, we have demonstrated that ALDH2 is a prerequisite for enhancing the therapeutic efficacy of stem cell transplantation in the treatment of heart failure [13-14]. Our research has pioneered international efforts in confirming the significant advantages of ALDH2 in preventing cardiovascular diseases and diabetes, sparking a global research fervor into the protective effects of ALDH2 in various disease contexts. Additionally, our findings have garnered international attention regarding ALDH2 as a potential target for drug development. The significance of ALDH2 in numerous human diseases is gradually being elucidated, with substantial evidence from domestic and international peers indicating its irreplaceable role in preventing other cardiovascular diseases, cerebrovascular diseases, hematological disorders, and malignant tumors, among others [15-18]. Autologous bone marrow-derived aldehyde dehydrogenase-bright (ALDH^br) cells, which express highly active ALDH2, have been proven safe and effective in patients with chronic myocardial ischemia [19]. Given its pivotal role in cellular protection and its significance in various human diseases, ALDH2 may represent a novel therapeutic target for the treatment of multiple diseases [20-21].

Lipoic acid (LA), a vitamin B-class compound, features a closed cyclic structure composed of sulfur and carbon atoms, conferring relatively high electron density and thus strong antioxidant properties. LA

has demonstrated favorable preventive and therapeutic effects on diabetes and its complications, various brain and neurodegenerative diseases, and aging [22-24]. The role of LA in cardiovascular diseases has increasingly attracted attention, with studies confirming that LA can restore ALDH2 activity by reducing disulfide bonds at its active site in mitochondria, thereby enhancing nitrate tolerance [25]. Subsequently, scholars have discovered that lipoic acid (LA) also exerts protective effects on diabetic cardiomyopathy and acute ischemia-reperfusion injury by restoring the activity of ALDH2 [26-28]. Given the protective role of ALDH2 in ischemic heart failure and the ability of LA to reduce ALDH2 activity, we propose the following scientific hypothesis: during the recovery phase of post-ischemic heart failure, lipoic acid can improve myocardial mitochondrial energy metabolism and inhibit oxidative stress by reducing the activity of ALDH2 in myocardial mitochondria, thereby protecting against post-ischemic heart failure. Currently, due to its potent antioxidant properties and rare adverse effects, lipoic acid has been widely promoted for clinical use. Clinically available forms of lipoic acid include intravenous injections and oral capsules, with indications for sensory abnormalities caused by diabetic peripheral neuropathy. Adverse reactions are extremely rare, with an incidence rate of <1/10,000, primarily manifesting as gastrointestinal symptoms such as nausea and vomiting, cutaneous allergic reactions, abnormal taste perception, or hypoglycemia.

This study employs a prospective, multicenter, randomized, and controlled research design to assess the clinical outcomes of patients with heart failure following myocardial infarction (MI) who are treated with a combination of lipoic acid capsules and standard pharmacological therapy. The evaluation will be conducted using a range of indicators, including primary endpoint events, secondary endpoint events, control of risk

factors, and surveys on medication adherence. The primary objective is to elucidate the significant role of lipoic acid capsules in managing post-MI heart failure, thereby paving the way for innovative approaches in heart failure treatment.

This structured approach ensures a rigorous and comprehensive assessment, allowing us to draw meaningful conclusions about the efficacy and safety of lipoic acid capsules in this patient population. By integrating multiple evaluation metrics, we aim to provide a holistic view of the treatment's impact on patient outcomes, ultimately contributing to the advancement of evidence-based practices in heart failure management.

二、Objectives

The clinical outcomes of lipoic acid capsules combined with standard pharmacological therapy in patients with heart failure following myocardial infarction are evaluated through indicators such as primary endpoint events, secondary endpoint events, control of risk factors, and surveys on medication adherence.

三、Protocol

3.1 Design

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group, exploratory trial.

3.2 Population

Inclusion criteria: 1. Patients aged 18 years or older who had been diagnosed with acute myocardial infarction (AMI) for more than 30 days. The diagnosis of AMI was based on the Fourth Universal Definition of Myocardial Infarction, which encompassed clinical evidence of acute

myocardial ischemia and with detection of a rise and/or fall of cardiac troponin (cTn) values, with at least 1 value above the 99th percentile upper reference limit (URL) and at least 1 of the following: symptoms of myocardial ischemia; new ischemic electrocardiogram changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography; 2. Patients were diagnosed with chronic heart failure (NYHA class II-IV) with a documented LVEF≤50%. The diagnosis of chronic heart failure was based on the global definition[16]: Symptoms and signs of HF with elevated natriuretic peptides (BNP) (NTproBNP＞600pg/ml or BNP≥150pg/ml; NT-proBNP≥400 pg/mL or BNP≥100 pg/mL, if patients were hospitalized for heart failure within 12 months; 3. The patients were clinically stable and had received optimal medical treatment with a fixed dosage for at least 4 weeks; 4. Patients were fully informed about this study and provided written informed consent.

Exclusion criteria: patients who were allergic to drugs of similar chemical classes (Vitamin B) as well as known or suspected contraindications to the study drugs; already used other investigational drugs at the time of enrollment, or within 30 days or over 5 half-lives of the drug prior to enrollment; with a history of intolerance to recommended target doses of ALA; have been diagnosed with acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy); with systolic blood pressure < 100 mmHg; severe liver function abnormalities (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 3 times the upper limit of normal); an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2, as measured by the simplified MDRD

formula; a serum potassium > 5.2 mmol/L; were pregnant or planning to become pregnant.

Withdrawal criteria: 1. The participant themselves requests to withdraw from the trial; 2. The participant experiences an intolerable adverse event, or an adverse event that, in the investigator's opinion, necessitates withdrawal from the study; 3. The participant is unable to adhere to the study protocol for treatment, demonstrates poor compliance, or is deemed by the physician to be unsuitable for continued participation in the study group.

3.3 Number of Cases and Grouping Method

The overall trial plans to enroll 300 patients who meet the inclusion criteria, and they will be randomly assigned to either the treatment group or the control group, with 150 patients in each group. This study is a prospective, multicenter, randomized, and controlled trial. It is planned to include 100 cases from our hospital, 100 cases from Affiliated Zhongshan Hospital of Dalian University, 50 cases from the First Affiliated Hospital of Sun Yat-sen University and 50 cases from Shanxi Cardiovascular Hospital.

Randomization: The randomization method employed in this study is block randomization. The statistician generated a random number table using computer software and conducted drug blinding based on it.

Blinding Procedure: Participants who are randomly assigned to the placebo group will also take capsules that are identical in appearance to those containing lipoic acid. Investigators at each center will be unaware of the difference between the two. Under normal circumstances, the blind will be maintained until all participants have completed the study and the database has been finally locked. Emergency unblinding may only occur when the participant's treatment status is required to determine special

emergency treatment. The date, time, and reason for unblinding will be recorded in the original documents and CRF (Case Report Form) tables.

3.4 Investigational Drugs

3.4.1 Investigational Medicinal Products:

Investigational Drug: Lipoic Acid Capsules

Placebo: Contains starch as the inert ingredient, with an identical appearance to the investigational drug

3.4.2 Dosage Form, Dose, Route of Administration, Administration Method, Frequency of Administration, and Treatment Duration

Dosage Form: 100mg capsules

Dose: 600mg per day

Route of Administration: Oral

Frequency of Administration: 200mg per dose, administered three times daily

Treatment Duration: 24 months

3.4.3 Packaging and Labeling

For research only Protocol ID：2018-120

Lipoic Acid Capsules for Clinical Trial Use

Drug ID: _____ **Name Abbreviation**:_____

Dispensing Date: _____

Dosage and Administration: Take 2 capsules at a time, three times daily.

Packaging: Each bottle contains xx capsules.

Storage: Keep the container tightly closed. **Expiration Date:** XXXX

All unused medication, along with its original packaging, must be returned to the investigator.

Keep out of reach of children

3.4.4 Drug Interactions

Lipoic acid acts as a metal chelator, hence particular caution should be exercised to avoid taking it concurrently with medications containing metal components (such as iron and magnesium preparations).

Additionally, it should not be taken simultaneously with milk due to its calcium content. If lipoic acid is administered half an hour before breakfast, iron and magnesium preparations can be taken during lunch or dinner.

Lipoic acid may potentiate the hypoglycemic effects of insulin and oral antidiabetic drugs. Therefore, it is recommended to monitor blood glucose levels regularly, especially when initiating treatment with this product. In some patients, to prevent the occurrence of hypoglycemic symptoms, it may even be necessary to reduce the dosage of insulin and oral antidiabetic medications.

3.5 Research Procedures

3.5.1 Screening and Enrollment Period

At the hospital's heart failure outpatient clinic and inpatient ward, consecutive patient screening was initiated based on inclusion and exclusion criteria. Detailed information about the study objectives, significance, and procedures was provided to patients. Their consent was obtained, and informed consent forms were signed.

Eligible patients were randomized in a 1:1 ratio to either the lipoic acid capsule group or the control group. Patients continued their current optimized medications and additionally received the study drug.

ALA Group:

Standard treatment for post-myocardial infarction heart failure + lipoic acid capsules (1 capsule/dose, 3 times/day for the first week, escalated to 2 capsules/dose, 3 times/day thereafter, swallowed with warm water).

Placebo Group:

Standard treatment for post-myocardial infarction heart failure + placebo (1 capsule/dose, 3 times/day for the first week, escalated to 2 capsules/dose, 3 times/day thereafter, swallowed with warm water).

Concomitant Standard Therapy (Medications and Devices):

Patients should adhere to current treatment guidelines[29], with therapies tailored by clinicians based on individual conditions. Risk factors such as blood glucose, blood pressure, and lipids should be controlled. Patients should receive dietary guidance for cardiac health (e.g., low-salt diet) and lifestyle modifications, including weight monitoring, physical exercise, smoking cessation, and alcohol restriction. Device-based therapies, including but not limited to stent implantation, may be administered according to current guidelines and patient conditions.

3.5.2 Follow-up Period

Patients underwent baseline visits on Day 0 post-randomization, followed by visits at Months 6, 12, and 24, totaling 4 on-site visits for efficacy, compliance, and safety assessments until study completion. The follow-up period lasted 24 months.

Visit 1 (Screening and Enrollment Period)

Inclusion and exclusion criteria

Informed consent signing

Past medical history and comorbidities

Comprehensive physical examination

Detailed documentation of medical history, comorbidities, treatment, concomitant medications, blood pressure, heart rate, weight measurement.

Cardiac function assessment (6-minute walk test: 6MWD)

Electrocardiogram (ECG)

Echocardiography

Laboratory tests: blood/urine/biochemical parameters, brain natriuretic peptide (BNP), coagulation function

Distribution of study medication

Instructions for the next follow-up visit date and brief physical examination

Visit 2 (Month 6 post-randomization), Visit 3 (Month 12 post-randomization), Visit 4 (Month 24 post-randomization)

Heart failure symptoms and signs

Comprehensive physical examination

Blood pressure, heart rate, weight measurement

Documentation of primary and secondary endpoint events

Adverse event recording

Cardiac function assessment (6MWD)

ECG

Echocardiography

Laboratory tests (blood/urine/biochemical parameters, BNP), coagulation function

Distribution/collection of study medication

Instructions for the next follow-up visit date or study termination

During months without on-site visits, researchers should contact patients via telephone to inquire about adverse events, endpoint events, and changes in concomitant medications, completing corresponding records.

3.6 Study Endpoint

3.6.1 Primary Endpoint:

A composite endpoint of all-cause death and rehospitalization due to heart failure during the 24-month follow-up period.

3.6.2 Secondary Endpoints:

The second endpoints included all-cause death and rehospitalization due to heart failure, non-fatal MI or non-fatal stroke during the 24-month follow-up period. The changes of LVEF and 6MWD were also assessed from baseline to 24 months.

3.6.3 Endpoint Definitions

All-cause death is defined as death due to any cause.

Rehospitalization due to heart failure is defined as nonelective repeat hospitalization in all patients alive at discharge for heart failure.

MI is defined based on the Fourth Universal Definition of Myocardial Infarction, which encompassed clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin (cTn) values, with at least 1 value above the 99th percentile upper reference limit (URL) and at least 1 of the following: symptoms of myocardial ischemia; new ischemic electrocardiogram changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography

Stroke is defined on the basis of the presence of acute infarction as demonstrated by imaging or based on the persistence of symptoms.

四、Adverse Event

4.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial subject following the administration of a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.

Serious Adverse Event (SAE): An event occurring during the clinical trial that results in hospitalization, prolongation of hospitalization, disability, impairment of work ability, life-threatening condition, death, congenital anomaly, or other significant medical events.

4.2 Severity

Mild: The event is tolerable to the subject, does not affect treatment, requires no special intervention, and has no impact on the subject's recovery.

Moderate: The event is intolerable to the subject, requires special intervention, and has a direct impact on the subject's recovery.

Severe: The event is life-threatening, leads to death or disability, and requires immediate emergency intervention.

4.3 Documentation and Reporting of Adverse Events

Clinical adverse events may occur during the subject's treatment. Once an adverse event (including significant adverse events) occurs, the following details should be recorded in detail on the Case Report Form (CRF): time of occurrence, clinical manifestations, management, duration, outcome, and relationship to the study drug. For subjects with abnormal laboratory test results, follow-up should be conducted until the results return to normal, to the pre-treatment level, or until it is confirmed that the abnormalities are unrelated to the study drug. In the case of a serious adverse event, a Serious Adverse Event Form should be completed and reported to the sponsor, ethics committee, CFDA Safety Monitoring Department, and health administrative department within 24 hours.

4.4 Risk Prevention and Management

The investigator should assess the clinical significance of abnormal laboratory results and provide possible explanations. Laboratory abnormalities resulting from previously reported adverse events should

also be recorded as adverse events in the Adverse Event Form. Laboratory abnormalities with clinical significance that meet one or more of the following criteria should be recorded as independent diagnoses in the Adverse Event section of the CRF (excluding abnormalities resulting from previously reported adverse events):1.Accompanied by clinical symptoms； 2.Leading to changes in clinical medication； 3.Requiring modification of concomitant therapy.

For unexplained abnormal laboratory values, repeat testing should be performed, and follow-up should continue until the value returns to the normal reference range or baseline, and/or a reasonable explanation is found. If a clear explanation is identified, it should be documented on the CRF.

During the clinical trial, investigators should closely monitor the occurrence of serious adverse events. Upon the occurrence of a serious adverse event, necessary measures should be taken first to ensure the safety of the subject, followed by reporting to the sponsor, contract research organization (CRO), and the ethics committee of the center within 24 hours.

All safety follow-up visits will be conducted 15 days after the end of the study visit. For subjects who withdraw prematurely, safety follow-up will also be conducted 15 days after the end of the study visit, unless the investigator deems it necessary for the subject to return to the hospital for follow-up measurements due to persistent adverse events at the end of treatment or clinically significant abnormalities in laboratory tests or vital signs. Safety follow-up may be conducted via telephone.

五、Statistic Method

5.1 Sample Size Calculation

This pilot and feasibility study was designed to evaluate the efficacy and safety of ALA in IHF patients and get the reference data on outcomes related to clinical events for the future RCT with large sample size. As a feasibility trial, 300 patients were expected to be enrolled during the study period. Assumptions for sample size calculation included the following: the event rate for primary outcomes was 35% at 24 months in the control group[30]; the HR for the ALA group was estimated to be 0.60 and a withdrawal rate of 5% at 24 months in both groups. A total of 300 (150 per group) subjects followed up for a fixed period of 24 months provides 80% power to reject the null hypothesis at the two-sided 0.1 significance level.

5.2 Statistical Analysis of Research Data

5.2.1 Analysis Variables

The analysis variables include subject characteristics at baseline, laboratory indicators, auxiliary examination indicators (electrocardiogram; echocardiogram), and endpoint event indicators.

5.2.2 Analysis Populations

All patients who meet the screening criteria and commence treatment with lipoic acid capsules should be included in the Safety Population (SP). The analysis of the primary endpoint and other endpoint was based on the FAS dataset (Full Analysis Set). The FAS set is defined as the set that adheres to the ITT (Intent-to-Treat) principle with the additional condition that the investigational drug has been used for at least one month, allowing for reasonable exclusions and enabling the reflection of the investigational drug's efficacy and safety to the greatest extent possible. Per-protocol analysis (PP set):Refers to subjects who do not have serious protocol violations in terms of inclusion and exclusion

criteria, treatment, and measurement of main indicators. The analysis was performed after the population withdrew from the study.

5.2.3 Statistical Methods

All statistical analyses were performed with R version 4.0.2. Normally distributed continuous variables were reported as the mean±SD, and non-normally distributed continuous variables were expressed as the median and interquartile range. Categorical data were expressed as absolute values and percentages and analyzed using the chi-square or Fisher's exact test. The Student's t-test or Wilcoxon rank-sum test was performed to determine differences between groups. Survival analyses were based on the time to the first event. The cumulative incidence of the time-to-event end points is expressed as Kaplan-Meier curves over 24 months after randomization. Cox proportional hazard models were used to estimate HR and 2-sided 95% CI. A linear mixed-effects model was used to analyze the differences in changes of LVEF and 6MWD between the ALA group and the placebo group, with study centers included as random effects. Subgroup analysis was performed for age (whether≤65 years old), sex, smoking status, past medical history (hypertension, diabetes mellitus, atrial fibrillation), NYHA functional class, NT-proBNP levels, LVEF(whether≤30%), and whether the patient received triple therapy.

The analysis of safety and efficacy was performed in full analysis set (FAS) adhering to the intention-to-treat principle. The type I error rate (2-sided α) was set at 0.05.

六、Ethics

6.1 Ethical Committee Review

This protocol, the written informed consent form, and materials directly related to the subjects must be submitted to the ethical committee for review. Formal initiation of the study may proceed only upon obtaining written approval from the ethical committee. Investigators must submit periodic (if applicable) progress reports to the ethical committee. Upon termination and/or completion of the study, investigators must notify the ethical committee in writing. Investigators must promptly report all changes occurring during the study (such as revisions to the protocol and/or informed consent form) to the ethical committee and must not implement these changes without prior approval from the ethical committee, unless the changes are made to eliminate obvious and immediate risks to the subjects. In such cases, the ethical committee will be notified.

6.2 Informed Consent

Investigators must provide subjects or their legal representatives with an easily understandable informed consent form that has been approved by the ethical committee. Subjects or their legal representatives must be given sufficient time to consider participation in the study. No subject may be enrolled until a signed written informed consent form has been obtained. During the subject's participation, all updated versions of the informed consent form and written information will be provided to the subjects. The informed consent form shall be retained as an important document of the clinical trial for future reference.

七、Confidentiality Measures

The results of this study may be published in medical journals. However, we will ensure the confidentiality of patient information in

compliance with legal requirements. Patient personal information will not be disclosed unless required by relevant laws. When necessary, government regulatory authorities, the hospital's ethics committee, and relevant personnel may access patient data in accordance with regulations.

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