

Effect of alpha-lipoic acid on atrial fibrillation and biomarkers of myocardial injury in patients undergoing coronary artery bypass surgery: Study protocol of a randomized, double-blind, placebo-controlled clinical trial

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Title {1a}

Effect of alpha-lipoic acid on atrial fibrillation and biomarkers of myocardial injury in patients undergoing coronary artery bypass surgery: Study protocol of a randomized, double-blind, placebo-controlled clinical trial

Names of protocol contributors {3a}

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Abstract

Background: Coronary artery bypass grafting (CABG) is associated with several postoperative complications, notably atrial fibrillation (AF), which may arise due to myocardial reperfusion following ischemia and the resulting inflammatory response. Alpha-lipoic acid (ALA) is a potent antioxidant compound known for its ability to reduce oxidative stress and regenerate endogenous antioxidant defenses. The aim of this study is to investigate the effects of ALA supplementation on the incidence of AF and biomarkers of myocardial injury in patients undergoing CABG.

Methods: In this randomized, placebo-controlled, parallel-design clinical trial, 50 eligible patients scheduled for CABG, will be randomly assigned into two groups to receive either 1200 mg/day ALA (ALA group, n=25) or placebo (control group, n=25), starting 10 days prior to surgery and continuing for five days after CABG. The occurrence of AF will be monitored using Holter monitoring during the first 72 hours after surgery and electrocardiography (EKG) performed three times daily on postoperative days four and five. Changes in complete blood count (CBC), troponin I, creatine kinase, muscle brain subunits (CK-MB), albumin, total protein, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) concentrations will be assessed at baseline, 24hr and five days after surgery. The length of hospital and intensive care unit (ICU) stay will be recorded. Echocardiography will be performed at baseline and on postoperative day five. Dietary intake will be assessed throughout the study period.

Discussion: This trial is expected to provide valuable preliminary data on the effects of ALA supplementation in reducing post-CABG AF and myocardial injury. The findings may lay the groundwork for future research into the adjunctive use of ALA, alone or in combination with other antioxidants, to mitigate complications following CABG.

Trial registration: The research protocol has been approved by the Bioethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.THC.REC.1403.052). The trial protocol has also been registered with the Iranian Registry of Clinical Trials (IRCT20131125015536N16).

Keywords

Alpha-lipoic acid; Atrial fibrillation; Coronary artery bypass grafting; Creatine kinase-MB, Troponin

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Structured summary {1b}

Item	Description
Primary Registry and Trial Identifying Number {4}	The Bioethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.THC.REC.1403.052)
Secondary Identifying Numbers	The Iranian Registry of Clinical Trials (IRCT20131125015536N16).
Source(s) of Monetary or Material Support	This study is supported by Tehran University of Medical Sciences and Health Services with the grant number of 1403-4-212-75254.
Primary Sponsor and contact information {3b}	Tehran University of Medical Sciences Phone Number: (+98 21) 8889 6690-93 Email: Gsia@tums.ac.ir Fax: (+98 21) 8889 8532
Role of sponsor and funder {3c}	Providing appropriate grant for conducting the trial
Contact for Public Queries	Soheil Mansourian, MD Assistant Professor, Department of Surgery, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran Postal address: North Kargar St. Jalal-al-Ahmad Highway, Tehran, Iran Phone: +982188029600 E-mail: mansouriansoheil@gmail.com Mohammad Javad Hosseinzadeh-Attar, MD, PhD

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Public Title	The Effect of ALA on AF in patients with CABG
Scientific title	The Effect of ALA on atrial fibrillation and biomarkers of myocardial injury in patients undergoing coronary artery bypass surgery: Study protocol of a randomized, double-blind, placebo-controlled clinical trial

Countries of Recruitment	Iran
Health Condition(s) or Problem(s) Studied	Coronary artery bypass surgery
Intervention(s)	ALA
Key Inclusion and Exclusion Criteria	Inclusion criteria: age 40-70 years and being scheduled for on-pump CABG Exclusion criteria: a documented history of advanced renal failure (glomerular filtration rate <15 mL/min); cancer; liver failure or cirrhosis; uncontrolled hypothyroidism or hyperthyroidism; heart failure with reduced ejection fraction (EF < 30%); congenital heart disease, evidence of active gastrointestinal bleeding, uncontrolled diabetes defined as HbA1c > 8%, those currently using omega-3 fatty acid supplements or any form of antioxidant supplements, using corticosteroids during the past month
Study Type	Randomized, double-blind, parallel-design clinical trial
Date of First Enrollment (planned)	1th of August 2025
Sample Size	Fifty eligible patients will be randomly assigned to ALA (ALA group, n=25) or placebo (control group, n=25)
Primary outcome(s)	The occurrence of AF, troponin I, creatine kinase, muscle brain subunits (CK-MB), the length of hospital and intensive care unit (ICU) stay
Key Secondary outcome(s)	Erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) concentrations
Ethics Review	The Bioethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.TH.C.REC.1403.052) The Iranian Registry of Clinical Trials (IRCT20131125015536N16).
Individual Trial Participant Data sharing statement	All participants will read the terms and conditions written in informed consent and optionally they can accept to participate in

	the current trial and none of the personal information will be shared.
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Protocol version {2}

This is the first version of the protocol submitted for publication.

Introduction

Background and rationale {9a}

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide, affecting nearly half of adults over 20 years old (1). Coronary heart disease (CHD) remains the most common form of CVD and the leading cause of death globally, despite a 25% decline in CHD-related mortality over the past decade (2). Since the 1960s, coronary artery bypass graft (CABG) surgery has been a cornerstone in the management of coronary artery disease, with a reported mortality rate of just 2% (3).

Most CABG procedures involve cardiopulmonary bypass (CPB), which alters the patient's physiology and can lead to complications such as postoperative atrial fibrillation (POAF) (4). Ischemia-reperfusion injury during cardiopulmonary bypass generates reactive oxygen species (ROS), disrupts ATP production, and depletes mitochondrial glutathione—culminating in oxidative stress, intracellular calcium overload, and cellular damage (5, 6). POAF is associated with adverse outcomes, including hemodynamic instability, increased stroke risk, prolonged hospitalization, and higher healthcare costs (7).

Additionally, oxidative stress from CABG can trigger inflammation, myocyte dysfunction, and left ventricular hypertrophy, thereby increasing cardiac injury markers such as creatine kinase, muscle-brain isoform (CK-MB) and troponin (8, 9). To mitigate these complications, antioxidant therapies have been incorporated into treatment protocols.

Antioxidants such as N-acetylcysteine (NAC), polyunsaturated fatty acids (PUFA), and vitamin C reduce POAF by neutralizing ROS generated during cardiac surgery due to ischemia-reperfusion injury and inflammation. Antioxidants prevent oxidative damage to cardiac cells, especially atrial tissue, which is highly susceptible to oxidative stress, by scavenging free radicals (10). They also modulate inflammatory pathways and reduce cytokine release and leukocyte activation, which are involved in atrial electrical remodeling (11). In addition, antioxidants improve mitochondrial function and calcium handling in cardiomyocytes, stabilize electrical activity, and reduce the risk of arrhythmia (12). Finally, PUFAs and vitamin C may enhance endothelial function and reduce fibrosis, thereby further protecting against POAF and contributing to shorter hospital stay (13).

Alpha-lipoic acid (ALA), an organosulfur compound synthesized in mitochondria, was first isolated from bovine liver in the 1950s and initially misclassified as a vitamin (14). Beyond its role as a cofactor for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase in glucose/lipid metabolism, ALA acts as a potent antioxidant. It scavenges ROS, regenerates endogenous antioxidants (e.g., vitamins E, C, and glutathione), and mitigates oxidative damage to lipids and proteins (15, 16).

In 2014, a systematic review and meta-analysis of 23 randomized controlled trials involving 4,278 patients found that antioxidants—NAC, PUFAs, and vitamin C—significantly reduced POAF after cardiac surgery, with NAC (OR: 0.56), PUFAs (OR: 0.84), and vitamin C (OR: 0.50) all showing protective effects (17).

Few studies have been conducted on the effects of ALA supplementation on cardiac function and atrial fibrillation after surgery. A 2019 animal study on myocardial injury in rats showed that administration of 80 mg/kg ALA, two hours before heat exposure, significantly reduced troponin (18). In contrast, a 2021 experimental study on rats with myocardial infarction showed that administration of 50 mg/kg ALA for 10 days failed to significantly reduce troponin (19). In 2020, Al-Afaqi et al. investigated the effect of ALA on postoperative atrial fibrillation in patients undergoing

heart valve surgery and coronary artery bypass grafting. Ninety patients were equally and randomly divided into control and ALA groups. ALA was administered at a dose of 600 mg twice daily from five to 10 days before surgery and continued until discharge. The results of this study showed that the incidence of POAF was significantly reduced in the ALA group (11%) compared to the control group (33%) (20).

Despite emerging evidence supporting antioxidants in cardiac surgery, few studies have investigated the effects of ALA on POAF and myocardial injury markers in CABG patients. This trial aims to evaluate the efficacy of ALA supplementation in reducing POAF incidence and cardiac biomarker elevation.

Explanation for the choice of comparator {9b}

As a randomized placebo-controlled clinical trial, patients in the control group (n=25) will receive a placebo containing lactose, magnesium stearate and starch, prepared by the School of Pharmacy, as two 600 mg capsules (total dose of 1200 mg) with identical identical shape, smell, taste, and packaging using at 6 AM and 6 PM.

Objectives {10}

We aimed to assess the effects of ALA supplementation on improving POAF incidence, modulating myocardial injury indicated by CK-MB and troponin I, and decreasing inflammation after CABG. Furthermore, we will also assess the efficacy of ALA on length of hospital and ICU stays compared to control group.

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

In this randomized, double-blind, parallel-design clinical trial, 50 eligible patients scheduled for CABG will be included if they meet the defined inclusion and exclusion criteria. The inclusion criteria are age 40-70 years, and being scheduled for on-pump CABG. The exclusion criteria are: a documented history of advanced renal failure (glomerular filtration rate <15 mL/min); cancer; liver failure or cirrhosis; uncontrolled hypothyroidism or hyperthyroidism; heart failure with reduced ejection fraction (EF< 30%); congenital heart disease or evidence of active gastrointestinal bleeding. Patients with uncontrolled diabetes, defined as HbA1c > 8%; those currently using omega-3 supplements, any form of antioxidant supplements, or corticosteroids used during the past month; and those unwilling to participate in the study or unable to adhere to the intervention protocol will not be enrolled.

Informed consent will be obtained from the participants prior to initial assessments and randomization. The research protocol has been approved by the Bioethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.THC.REC.1403.052). The trial protocol has also been registered with the Iranian Registry of Clinical Trials (IRCT20131125015536N16).

Trial design {12}

In this randomized, double-blind, parallel-design clinical trial, 50 eligible patients scheduled for CABG will be included if they meet the defined inclusion and exclusion criteria. The enrollment process is illustrated in **Figure 1**. The study protocol was designed based on the Recommendations for Interventional Trials (SPIRIT) 2025 guideline.

Methods: Participants, interventions and outcomes

Trial setting {13}

This study will be conducted on 50 On-Pump CABG candidate patients with cardiac arrest at Tehran Heart Center, Tehran, Iran. Patients will be provided with a comprehensive explanation of the study objectives after meeting the inclusion and exclusion criteria.

Table 1. Characteristics of the patients who will be included in the trial

Characteristic	The people we would expect to see included
Age	40-70 years old
Sex	Both sex
Gender	Both gender
Race, ethnicity and ancestry	We will not have any limitation
Socioeconomic status	We will not have any limitation
Geographic location	We will not have any limitation
Other characteristics relevant to the trial	-

Eligibility criteria for participants {14a}

The inclusion criteria are age 40-70 years, and being scheduled for on-pump CABG. The exclusion criteria are: a documented history of advanced renal failure (glomerular filtration rate <15 mL/min); cancer; liver failure or cirrhosis; uncontrolled hypothyroidism or hyperthyroidism; heart failure with reduced ejection fraction ($EF < 30\%$); congenital heart disease or evidence of active gastrointestinal bleeding. Patients with uncontrolled diabetes, defined as $HbA1c > 8\%$; those currently using omega-3 supplements, any form of antioxidant supplements, or corticosteroids used during the past month.

Eligibility criteria for sites and those delivering interventions {14b}

This study is a double-blind trial conducting in a tertiary center of excellence in cardiovascular diseases affiliated to the Tehran University of Medical Sciences. Principal investigators, cardiologists, surgeons, nurses and patients will be unaware of the treatment allocation to the study.

Who will take informed consent? {32a}

After meeting the inclusion and exclusion criteria, eligible patients will receive a comprehensive explanation of the study objectives and subsequently be asked to complete an informed consent form. This process will be conducted by a blinded member of the research team.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

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Intervention and comparator

Intervention and comparator description {15a}

Patients in the ALA group (n=25) will receive 1200 mg/day ALA (Alarich, Arvand Pharmed), administered as two 600 mg capsules daily (at 6 AM and 6 PM), starting 10 days prior to surgery and continuing for five days after CABG, for a total duration of 15 days.

Patients in the control group (n=25) will receive a placebo containing 1200 mg lactose, magnesium stearate and starch, prepared by the School of Pharmacy, as two 600 mg capsules (at 6 AM and 6 PM). The supplement and placebo will have identical shape, smell, taste, and packaging. The capsule containers will be marked with labels A and B by an independent individual who is blinded to the study design and objectives.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

Participants who are unwilling to remain in the study or unable to comply to the intervention protocol will be excluded.

Strategies to improve adherence to intervention/comparator {15c}

To help participants stay engaged with the intervention, daily check-ins and follow-ups by the research team and healthcare providers will be done. These regular touchpoints are meant to offer support, answer questions, and help manage any side effects or concerns that may come up.

Concomitant care permitted or prohibited during the trial {15d}

Throughout the trial, participants will receive whatever care they need—whether it's medication, surgery, nutrition or extra support—alongside their regular treatments. The attending physician will be there to guide the process and make sure everything goes as smoothly and safely as possible.

Ancillary and post-trial care {34}

This study is classified as minimal risk and does not involve any medical intervention. Therefore, provisions for ancillary care, post-trial care, and compensation for harm are not applicable. Participants will not incur any medical expenses related to their involvement. Should any discomfort or distress arise, they are encouraged to speak with the researcher, who will offer appropriate support or referral as needed.

Outcomes {16}

Primary outcomes

1. Assessment of CK-MB and troponin I via blood samples 10 days before surgery, 24 hours and five days after surgery in the ALA and placebo groups.
2. Assessment of the incidence of POAF via holter monitoring for the first 72 hours after surgery and 12 leads EKG, three times a day, for the next two days in the ALA and placebo groups.

Secondary outcomes

1. Assessment of the length of hospital and ICU stays via medical record in the ALA and placebo groups.
2. Assessment of patients reported dietary intakes via 24 hour recalls, every three days during hospitalization in the ALA and placebo groups.
3. Assessment of echocardiographic indices and LVEF 10 days before and five days after surgery in the ALA and placebo groups.
4. Assessment of changes in CBC , albumin, total protein, ESR, CRP concentrations via blood samples in the ALA and placebo groups 10 days before surgery.

Harms {17}

1. Challenges in patient recruitment: Efforts will be made to overcome existing barriers through coordination with faculty members, formal correspondence via the research vice-chancellor, and in-person visits to explain and justify the study's objectives.
2. Potential patient non-cooperation: Patients will be reassured that all costs associated with the required tests will be fully covered. They will also be encouraged to participate through clear communication about the study's purpose and potential benefits.

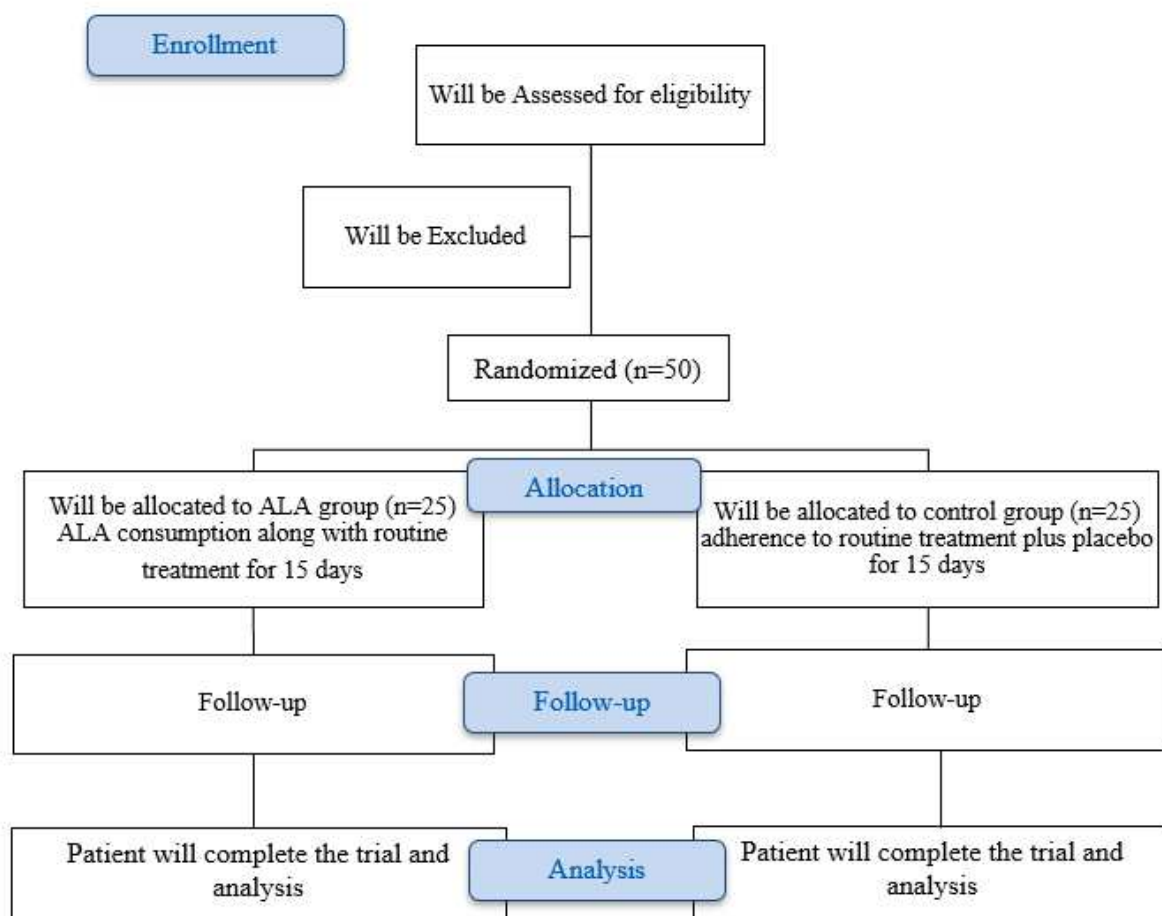


Figure1. CONSORT Flow Diagram Illustrating the Anticipated Steps of the Study

Participant timeline {18}

The important time points in this study include baseline (10 days before surgery), 24h after surgery (T_{24h}), three days (T_{72h}), and five days after surgery (T₅). **Table 2** demonstrates more details about the study and participant timeline.

Table 2. Schedule of enrolment, interventions and assessments during the study

Timepoint	T _{Base} (10 days before surgery)	T _{OR} (Surgery day)	T _{24h} (24 hr after surgery)	T _{72h} (Three days after surgery)	T ₅ (Five days after surgery)
Eligibility screening	✓				
Obtaining informed consent	✓				
Study randomization and allocation	✓				
Anthropometric assessment	✓				
Ordering intervention	✓				
Echocardiography	✓				✓
Check CK-MB, Troponin I, CBC, Creatinine, urea, FBS, LFT, Bil, CRP, ESR, Albumin, Total protein, Na, K, Ca, P, Mg serum levels	✓		✓		✓
Holter monitoring for the first 72h after surgery			✓		
EKG, TDS for days 4 and 5 after surgery				✓	

Sample size {19}

The sample size was determined using a formula designed for clinical trials to compare two independent groups, with CK-MB levels selected as the primary outcome variable. Based on preliminary estimates, the standard deviation was assumed to be 0.6 in the ALA group and 1.0 in the placebo group, with a minimum clinically meaningful difference of 1.0. To account for an anticipated 30% dropout rate during follow-up, the final calculation indicated that at least 25 participants per group would be necessary to achieve sufficient statistical power for detecting the intended treatment effect.

Recruitment {20}

Patients undergoing on-pump CABG represent a common population in cardiac care settings. To facilitate efficient enrollment, eligible patients admitted to Tehran Heart Center will be selected according to predefined inclusion and exclusion criteria. The research team, comprising clinicians and research coordinators, will identify potential participants from the surgical waiting lists. During hospitalization, these patients will be assessed and provided with comprehensive information about the study including its potential benefits and risks. Informed consent will be obtained prior to randomization.

Assignment of interventions: randomization

Sequence generation: who will generate the sequence {21a}

The allocation sequence will be generated by an independent statistician who is not involved in recruitment and patient management.

Sequence generation: type of randomization {21b}

A computer-based random number generator will be used for creating the allocation sequence in permuted blocks of four. To maintain the blinding, the generated sequence will be secured by health providers, clinicians, and patients.

Allocation concealment mechanism {22}

Eligible patients will be randomly assigned to either the ALA group or the control group, using an online randomization service with a 1:1 allocation ratio. During the trial, only the statistician and data manager will have access to the allocation sequence. To minimize allocation bias, healthcare providers and clinicians will remain blinded to group assignments.

Implementation {23}

An independent researcher will generate the random allocation sequence. Participants will be

enrolled and assigned to intervention or placebo groups by a clinical investigator using the concealed sequence. Only the pharmacy and data manager will be unblinded for labeling and dispensing; all other staff and participants will remain blinded.

Assignment of interventions: blinding

Who will be blinded {24a}

This study is a double-blind clinical trial. All participants, directly involved in patient care or study implementation including principal investigators, cardiologists, surgeons, and nurses will remain blinded to treatment allocation. Patients will also be unaware of their assigned group throughout the study.

How will be blinding be achieved {24b}

The supplement and placebo will be identical shape, color, smell, taste, and packaging to ensure indistinguishability. Capsule containers will be labeled as "A" and "B" by an independent third party who is blinded to the study design, objectives and group allocation. Neither participants nor healthcare providers will be aware of the treatment assignment, maintaining double-blind conditions throughout the trial.

Procedure for unblinding if needed {24c}

Unblinding will only occur in exceptional circumstances where knowledge of the allocated intervention is essential for the clinical management of a participant in a medical emergency (e.g., severe allergic reaction or other life-threatening event). In such cases, the treating physician may request unblinding through the principal investigator, who will contact the unblinded data manager to disclose the participant's allocation. Any unblinding event will be documented, including the reason and individuals involved. Decisions regarding withdrawal of unblinded participants from further intervention will be made on a case-by-case basis, taking into account participant safety and trial integrity.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Assessments

Prior to group allocation, participants' height, weight, and body mass index (BMI) will be measured and documented. Subsequently, one of the researchers will collect data on personal characteristics, including age, current medications and supplements, used within the past two months, underlying medical conditions, surgical history, and smoking status.

Biochemical measurements

Blood samples will be collected at baseline, 24 hours and five days postoperatively to assess serum concentrations of CBC, troponin I, CK-MB, albumin, total protein, CRP, and ESR, in accordance with laboratory protocols and kit instructions. Extra serum, separated by centrifugation at 3500 rpm for 10–15 minutes, will be aliquoted and stored at -80°C until analysis.

Dietary intake

Patients will be assessed every three days and a 24-hour dietary recall will be conducted. If the patient is conscious at the time of assessment, the recall will be obtained directly from the patient; otherwise, information will be gathered through interviews with the patient's companion and nurse supplemented by a review of medical records. The collected dietary data will be translated into food items, and total energy and nutrient intake will be analyzed using NUTRITIONIST IV software (version 7.0; N-Squared Computing, Salem, OR, USA).

Echocardiography

Cardiac function will be evaluated using echocardiography. Both left and right ventricular function will be documented, with left ventricular function specifically assessed by calculating EF. Echocardiographic assessments will be conducted preoperatively and on postoperative day five to monitor perioperative changes in cardiac function and identify any signs of myocardial dysfunction or remodeling.

POAF

POAF will be monitored using a combination of continuous 72-hours holter monitoring and standard 12-lead EKG. A portable holter device equipped with 12 electrodes will be applied within the first 24 hours after

surgery to continuously record electrocardiographic data for 72 hours. This device captures timing and voltage data at each PQRS complex and is capable of detecting arrhythmic events, including AF. Holter data will be analyzed using automated rhythm detection algorithms, followed by manual verification by trained cardiologists to confirm arrhythmia episodes. Upon completion of holter monitoring, standard 12-lead EKG recordings will be performed three times daily on postoperative days four and five, providing a static snapshot of cardiac electrical activity across multiple anatomical vectors. All EKGs will be interpreted by cardiologists blinded to group allocation. POAF will be defined as AF occurring after surgery, characterized by the absence of discrete P waves and the presence of irregular QRS complexes lasting longer than 30 seconds. The timing, duration, and frequency of POAF episodes will be documented.

Length of stay

Length of hospital and ICU stay will be documented using hospital records.

Plans to promote participant retention and complete follow-up {25b}

During the trial, nursing staff will administer the intervention capsules twice daily at scheduled times (6 AM and 6 PM), with each dose documented in the medical chart to ensure adherence. Throughout hospitalization, patients will be closely monitored by the research team to maintain engagement and address any concerns promptly. Any missed data will be actively pursued through medical record review or follow-up communication with the patient or their designated contact.

Data management {26}

Data management will follow the guidelines of the Iranian Registry of Clinical Trials (IRCT). Study data will be collected using standardized paper CRFs at baseline (10 days pre-operative), 24 hours post-surgery, and on day five post-surgery. Each patient will be followed until discharge. Data will be independently entered into a version-controlled Excel master workbook in long format. Discrepancies will be reconciled against source CRFs, with resolutions documented in a query log. The cleaned and frozen dataset will then be exported to STATA for analysis. A comprehensive data dictionary—including variable names, types, units, and missing-value codes—will be maintained. A STATA do-file documenting all importation and cleaning steps will be archived. File versions,

editors, and timestamps will be tracked via an audit log. The linkage file (containing study IDs and personal identifiers) will be stored separately in an encrypted, access-restricted location. Encrypted daily incremental backups and weekly full backups will be performed. After resolving all data queries, the database will be formally locked. The final de-identified STATA dataset, codebook, and do-file will be archived and made available under appropriate data-sharing agreements.

Confidentiality {33}

Each participant will be assigned a unique study identification code, which will be used on all study-related forms and databases to de-identify personal information. Identifiable data (e.g., names, contact details, medical records) will be stored separately from coded research data and accessed only by authorized personnel. Personal information will not be disclosed without explicit written consent, and all data will be handled in accordance with institutional ethical regulations.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

The parametric or non-parametric distribution of variables will be assessed using appropriate statistical tests and plots. Descriptive statistics including mean, standard deviation (SD), median, range, frequency, and percentage will be used to summarize the data as appropriate. Statistical comparisons between the two groups will be performed using the independent samples t-test and Mann–Whitney U test, depending on data distribution. Within-group comparisons relative to baseline values will be conducted using the linear mixed model (LMM) or Wilcoxon signed-rank test.

Another LMM, will be applied to adjust for potential confounding variables. All statistical analyses will be performed using STATA software, version 18.0 (StataCorp. 2025. *Stata 18 Base Reference Manual*. College Station, TX: Stata Press).

Who will be included in each analysis {27b}

All randomized participants in both groups of ALA and control will be included in each analysis.

How missing data will be handled in the analysis {27c}

To minimize missing data, the trial will be conducted precisely based on the protocol. To handle missing data in our analysis we would use Inverse Probability Weighting (IIPW) method. In addition, we will use linear mixed model this model could be consider as a Intention To Treat (ITT) method a 30% dropout rate during follow up will be calculated. The primary statistical analyses (independent samples t-test, Mann-Whitney U test, paired t-test, Wilcoxon signed-rank test, and regression models) will be conducted using a complete-case analysis approach.

Methods for additional analyses (e.g. subgroup analyses) {27d}

Pre-specified subgroup analyses will be conducted based on age, sex, and EF subgroups, if appropriate. AnLMM will be used to control for potential confounding variables and adjust the imbalances at baseline as well as considering the possible correlation of measurements in repeated (three or two times) evaluations. Sensitivity analyses will be performed to evaluate the robustness of results to model assumptions and missing data.

Interim analyses {28b}

No interim analyses for efficacy are planned for this trial.

Protocol and statistical analysis plan {5}

The full trial protocol including the detailed statistical analysis plan will be made publicly accessible as a journal supplementary material, if necessary.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The coordinating centre will be based at the Cardiovascular Diseases Research Institute at Tehran Heart Center and will be responsible for day-to-day trial management, data coordination, and communication across study sites. The coordinating centre team, led by the chief investigator and

supported by clinical research coordinators, will monitor participant recruitment, assessments, and data collection on a daily basis. A multidisciplinary team, comprising representatives from Tehran University of Medical Sciences, senior investigators, and experts in cardiology, biostatistics, and clinical research, will provide independent oversight of the trial. This team will meet when necessary to review trial progress, protocol adherence, participant safety, and any adverse events to support decision-making and ensure ethical and scientific integrity throughout the study.

Composition of the data monitoring committee, its role and reporting structure {28a}

As this is a single-center trial investigating a dietary antioxidant supplement with a well-documented safety profile, a formal external Data Monitoring Committee (DMC) will not be established. Safety oversight will instead be conducted by an internal Data and Safety Monitoring Board (DSMB) consisting of a cardiologist, a clinical nutritionist, and a surgeon. The DSMB will review reported adverse events and study conduction at predefined intervals. Any recommendations will be communicated to the Trial Steering Committee at the Tehran Heart Center.

Frequency and plans for auditing trial conduct {29}

Data entry and trial conduct will be routinely checked by the research team for accuracy and protocol compliance. The trial status will be monitored every six months through progress reports and scheduled inspections conducted by the committee.

Protocol amendments {31}

No major changes have been made to the protocol since the trial began. Any future modification will be reported on the IRCT website.

Dissemination policy {8}

Following completion data collection and final statistical analysis, the primary results will be disseminated to both the scientific community and the public. A manuscript prepared in accordance

with CONSORT guidelines will be submitted for publication in a peer-reviewed journal and made available through scientific databases. A lay summary of the findings will also be prepared and made available to participants upon request.

Discussion

Myocardial ischemia–reperfusion injury remains a significant challenge in cardiovascular surgery, particularly following procedures (21). The restoration of blood flow after a period of ischemia initiates a cascade of deleterious effects, characterized by elevated oxidative stress markers, including xanthine oxidase, nuclear factor kappa B (NF- κ B), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (22). These mediators play a critical role in the pathogenesis of POAF and cardiac dysfunction (23).

The enhanced generation of ROS such as superoxide anion, hydroperoxyl radical, hydroxyl radical, and hydrogen peroxide during CABG contributes to oxidative damage and myocardial injury. This oxidative stress leads to elevated levels of cardiac biomarkers, including CK-MB and troponin I, which reflect myocyte necrosis. Higher concentrations of these enzymes are associated with adverse postoperative outcomes and increased risk of complications (24, 25).c

Numerous studies have demonstrated that antioxidant-mediated myocardial protection exerts beneficial effects in reducing complications associated with CABG procedures (26–28). Among these agents, ALA has emerged as a promising therapeutic candidate, showing significant cardioprotective properties against ischemia–reperfusion injury (29). ALA has been shown to attenuate infarct size, reduce cardiomyocyte apoptosis, and suppress inflammatory responses, thereby contributing to the preservation of overall cardiac function (30).

The molecular mechanisms underlying these benefits primarily involve activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling cascade, which facilitates the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) and subsequent upregulation of cytoprotective genes, most notably heme oxygenase-1 (HO-1) (31). HO-1, a key antioxidant

enzyme, plays a central role in mediating the anti-inflammatory and anti-apoptotic actions of ALA by degrading pro-oxidant heme into biliverdin, carbon monoxide, and free iron, thereby reducing oxidative stress and cellular injury (32).

Clinical evidence increasingly supports the therapeutic potential of ALA in cardiovascular settings. One study demonstrated that long-term administration of 600 mg/day of ALA over a 12-month period significantly reduced key inflammatory biomarkers, including tumor necrosis factor-alpha (TNF- α), C-reactive protein (CRP), and interleukin-6 (IL-6) (33). These pro-inflammatory cytokines are well-established contributors to cardiac hypertrophy, myocardial injury, endothelial dysfunction, and adverse ventricular remodeling. These findings suggest that ALA supplementation may enhance cardiac resilience, reduce inflammation-mediated damage, and improve postoperative functional outcomes (34, 35).

Despite these promising findings, critical gaps remain in our understanding of ALA and its clinical effects in patients undergoing CABG. If ALA supplementation is shown to significantly reduce postoperative complications such as AF and improve cardiac function, it may serve as a valuable adjunctive therapy in the perioperative management of patients undergoing cardiac surgery.

Trial status

This is the first version of the protocol submitted for publication. The study has been registered with the Iranian Registry of Clinical Trials (IRCT20131125015536N16) and has received ethics approval (IR.TUMS.TH.C.REC.1403.052). Recruitment began on August 1, 2025, at Tehran Heart Center and is expected to be completed by early 2026.

Abbreviations

CABG, Coronary artery bypass grafting; AF, atrial fibrillation; ALA, alpha-lipoic acid, CK-MB, creatine kinase, muscle brain subunits ; CRP, C-reactive protein; CVD, cardiovascular disease; CHD,

coronary heart disease; CPB, cardiopulmonary bypass; NAC, N-acetylcysteine; PUFA, polyunsaturated fatty acids; EF, ejection fraction; BMI, body mass index; ESR, erythrocyte sedimentation rate; EKG, electrocardiography; ICU, intensive care unit; I/R, ischemia-reperfusion; NADPH, nicotinamide adenine dinucleotide phosphate; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha

Declarations

Acknowledgements

Not applicable

Authors' contributions {3a}

RS, SM, EA, MH, AJ, MY, MAB, and MJH contributed to the design and developed methodology. RS contributed to the manuscript writing. MJH has reviewed the manuscript and validated the methodology. All authors read and approved the final manuscript.

Sources of funding and other support {7a}

This study will be supported by Tehran University of Medical Sciences and Health Services with the grant number of 1403-4-212-75254.

Availability of data and materials {6}

No datasets were generated or analyzed during the current study.

Ethics approval and consent to participate {30}

This study will be conducted according to the principles of the Declaration of Helsinki. This study was confirmed by the ethics committee of Tehran University of Medical Sciences with the code of IR.TUMS.TH.C.REC.1403.052. Moreover, it was registered in the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the code number IRCT20131125015536N16.

Consent for publication

All participants will read the terms and conditions written in informed consent and optionally they can accept to participate in the current trial.

Competing interests {7b}

The authors have no competing interest in declaring.

Authors' information (optional)

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