Preoperative Roxadustat and Myocardial Injury after Off-Pump Coronary Artery Bypass Graft Surgery
A Pilot Randomized Trial

STUDY PROTOCOL

Document information	Details
Study intervention	Roxadustat
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Statistical methods are included in Section 13. Appendices 1-4 and the original reference list are included.

1 Background

Myocardial injury and myocardial infarction are relatively common complications after cardiac surgery. Cardiac biomarker concentrations increase in almost all patients after cardiac surgery. Potential mechanisms include inadequately treated preoperative ischemia, insufficient intraoperative myocardial protection, and adverse surgical events such as incomplete revascularization, graft failure, or embolism [1,2]. A meta-analysis showed that high-sensitivity cardiac troponin I (hs-cTnI) peaks 6-8 hours after coronary artery bypass grafting (CABG), at a mean of 126 times the upper reference limit (URL); after off-pump CABG, the corresponding value was 61 times the URL [3]. Thus, postoperative troponin concentrations after CABG substantially exceed the thresholds in the Fourth Universal Definition of Myocardial Infarction (at least 10 times the URL) [4] and the Academic Research Consortium-2 consensus (at least 35 times the URL with new evidence of ischemia, or at least 70 times the URL) [5].

Myocardial injury and infarction after cardiac surgery are associated with increased risks of major adverse events, including malignant arrhythmias, heart failure, and death. Studies have demonstrated associations between postoperative hs-cTnI elevation and 30-day and longer-term mortality after different cardiac procedures [6,7]. Several studies have examined biomarker thresholds for perioperative myocardial injury and/or infarction in relation to patient outcomes. In the large multicenter VISION Cardiac Surgery study reported by Devereaux and colleagues in 2022, hs-cTnI greater than 5,670 ng/L (greater than 218 times the URL) on postoperative day 1, or greater than 1,522 ng/L (greater than 59 times the URL) on postoperative days 2-3, was associated with increased 30-day mortality after CABG or aortic valve replacement or repair. After other cardiac procedures, corresponding thresholds associated with increased 30-day mortality were greater than 12,981 ng/L (greater than 499 times the URL) on postoperative day 1 and greater than 2,503 ng/L (greater than 96 times the URL) on postoperative days 2-3 [6,8].

In 2024, the European Association for Cardio-Thoracic Surgery (EACTS) convened multidisciplinary experts to develop a new diagnostic algorithm (Figure 1 and Appendix 1) to improve the definition of perioperative myocardial infarction after cardiac surgery and the prediction of outcomes [2]. A prospective two-center cohort study demonstrated that, compared with the Fourth Universal Definition of Myocardial Infarction, the EACTS algorithm identified myocardial infarction at a similar rate while reducing overdiagnosis of myocardial injury and maintaining its ability to predict 1-year mortality [9]. Monitoring hs-cTnI changes during the first 3 postoperative days according to the EACTS algorithm may therefore be more suitable for identifying myocardial injury after CABG and may help predict postoperative outcomes.

Figure 1. EACTS algorithm for myocardial injury and infarction after cardiac surgery. The figure is reproduced in Appendix 1.

Hypoxia-inducible factor (HIF) has multiple roles in cardiac development, metabolic regulation, ischemic protection, and atherosclerosis [10]. HIF-1alpha is a central regulator of acute protection against ischemia. First, it promotes glycolysis to maintain energy supply: stabilization of HIF-1 after acute hypoxic injury upregulates glycolysis-related genes, including GLUT1, HK2, and LDHA, increases anaerobic metabolism, reduces reliance on oxidative phosphorylation, and maintains cardiomyocyte ATP production under hypoxia. This metabolic reprogramming is a core mechanism of HIF-mediated cardioprotection [11]. Second, HIF-1alpha suppresses oxidative metabolism and reduces reactive oxygen species (ROS). HIF-1 inhibits mitochondrial function, for example by downregulating pyruvate dehydrogenase activity and inducing pyruvate dehydrogenase kinase 1 expression, thereby reducing oxygen consumption and excessive ROS production and attenuating oxidative stress during ischemia-reperfusion injury [10].

Studies of ischemic and remote ischemic preconditioning have shown that brief hypoxic stimuli stabilize HIF-1alpha, activate downstream protective gene expression, and increase myocardial tolerance to subsequent severe ischemia [12]. HIF-regulated humoral factors, including erythropoietin, adenosine, and nitric oxide, are also upregulated and exert antiapoptotic, anti-inflammatory, and microcirculatory effects [13]. During later hypoxia, HIF-2alpha expression increases and gradually replaces HIF-1alpha

as a major regulator of oxygen homeostasis [14]. Several basic studies have shown that HIF-2alpha can enhance myocardial tolerance to acute ischemia by inducing cardiomyocyte amphiregulin, an epidermal growth factor family member [15,16]. Pharmacological targeting of HIF signaling with more precise control of pathway activation and timing may therefore enhance cardioprotection.

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that stabilizes HIF signaling, activates hypoxia-related protective pathways, and promotes erythropoiesis. Peak plasma concentrations occur 1-3 hours after oral administration. Roxadustat is generally administered two or three times weekly, with a half-life of 9.6-16 hours, allowing regular intermittent drug exposure. Under the approval of the National Medical Products Administration of China, its sole approved indication is anemia associated with chronic kidney disease (CKD), in both dialysis and nondialysis patients. Recent systematic reviews and meta-analyses have not generally identified a clear additional risk of adverse events with roxadustat [17]. Provenzano and colleagues reported that it effectively increased hemoglobin and reduced transfusion risk in patients with nondialysis-dependent CKD and CKD-associated anemia, without a significant increase in major adverse cardiovascular events (MACE) compared with placebo [18]. Another study suggested a lower risk of MACE with roxadustat than with erythropoietin (hazard ratio 0.78, 95% confidence interval [CI] 0.62-0.98) in patients with CKD-associated anemia [19].

In basic research, roxadustat promotes expression of HIF target genes, shifts metabolism from aerobic to anaerobic pathways, and increases tolerance to ischemia. In a mouse myocardial ischemia-reperfusion model, a single pretreatment dose significantly reduced infarct size and plasma creatine kinase activity, cardiomyocyte apoptosis, remodeling, and injury [20]. In a diabetic myocardial injury model, it activated antioxidant pathways through HIF-1alpha/UCP2 and exerted protective effects [21]. Zaruba and colleagues found that nuclear HIF-1alpha protein expression increased significantly 6 hours after intraperitoneal administration and peaked at 24 hours. In myocardial infarction, HIF-1alpha pathway activation and downstream gene transcription increased markedly after 1 week of intermittent dosing twice weekly, with enhanced reparative inflammation and a trend toward reduced cardiomyocyte apoptosis [22]. Animal and translational research provide a rationale for perioperative pharmacological preconditioning. Evidence syntheses suggest potential cardiovascular protective mechanisms, including reduced fibrosis, inflammation, and oxidative stress and increased angiogenesis [23].

Perioperative anemia and acute blood loss can substantially reduce oxygen transport and exacerbate myocardial oxygen supply-demand imbalance. Preoperative anemia has been reported in approximately 16%-54% of patients scheduled for cardiac surgery; approximately 5.5% have hemoglobin below 10 g/dL [24]. Postoperative anemia is more frequent, occurring in 29%-94%, and is often moderate to severe [25]. The 2018 Frankfurt Consensus reported associations between preoperative anemia and increased 30-day mortality (odds ratio [OR] 2.20, 95% CI 1.68-2.88) and acute myocardial infarction (OR 1.39, 95% CI 0.99-1.96) [26]. The ERAS Cardiac Society expert group recommended in 2023 that patients scheduled for cardiac surgery be screened for anemia and that treatment be started sufficiently early, generally 2-4 weeks before surgery, to increase hemoglobin and reduce transfusion requirements [27].

Roxadustat is effective in correcting anemia. First, a single oral dose of 1.0 mg/kg in patients with CKD-associated anemia produces an erythropoietin peak at approximately 8 hours, although the response is relatively short-lived and depends on fluctuations in drug concentration. Intermittent administration two or three times weekly produces transient endogenous erythropoietin elevations approaching the normal physiological range [28,29]. Compared with erythropoiesis-stimulating agents (ESAs), roxadustat produces similar increases in hemoglobin without a significant increase in cardiovascular events [30]. Second, perioperative stress induces inflammation, which suppresses responsiveness to ESAs; the hemoglobin response to roxadustat is not affected by inflammatory status [31]. Third, roxadustat substantially reduces hepcidin [32], enhancing iron absorption, mobilization, and utilization and improving functional iron deficiency. Intermittent preoperative administration may therefore reduce perioperative anemia.

Although off-pump CABG avoids cardiopulmonary bypass-related stress, surgical stress and ischemia-reperfusion injury remain. Incomplete revascularization, inadequate collateral perfusion, temporary intraoperative occlusion, and blood loss-related oxygen supply-demand imbalance may all cause

troponin release and myocardial injury. We hypothesize that intermittent oral roxadustat during the week before off-pump CABG may reduce postoperative high-sensitivity troponin concentrations and early myocardial injury. This approach has biological plausibility and clinical feasibility.

2 Study Objectives

The primary objective is to assess the feasibility of a clinical trial evaluating the effects of intermittent oral roxadustat for 2 weeks before off-pump CABG on postoperative myocardial injury and the incidence of MACE. Secondary objectives are to evaluate effects on peak troponin concentration within 7 days after surgery, the maximum change in serum creatinine from the preoperative value within 7 days after surgery, hemoglobin within 24 hours before surgery, and hemoglobin on the morning of postoperative day 1.

3 Participant Selection

3.1 Inclusion criteria

3.1.1 Age at least 45 years.

3.1.2 Scheduled for off-pump CABG.

3.1.3 Preoperative anemia: hemoglobin below 130 g/L in men or below 120 g/L in women.

3.2 Exclusion criteria

Patients meeting any of the following criteria will not be enrolled.

3.2.1 Diagnosed cancer.

3.2.2 Current treatment with erythropoietin.

3.2.3 New-onset myocardial injury: hs-cTnI is still rising or has not decreased to below 10 times the URL.

3.2.4 Severe hepatic dysfunction, defined as Child-Pugh class C (Appendix 2); preoperative stage V CKD requiring dialysis; or American Society of Anesthesiologists (ASA) physical status greater than IV.

3.2.5 Allergy to roxadustat.

3.2.6 Any other condition considered unsuitable for participation by the investigator or treating physician.

3.3 Criteria for withdrawal after starting the intervention

3.3.1 The patient requests withdrawal and revokes informed consent after the study intervention has begun.

3.3.2 The investigator withdraws the patient because of poor adherence, serious complications, or serious adverse events.

Reasons for withdrawal will be documented in detail in the case report form (CRF), which will be retained for inspection. Follow-up will be completed whenever possible. For patients lost to follow-up for any reason, the last assessed outcome value will be used as the final outcome in the intention-to-treat dataset.

3.4 Criteria for exclusion from the study

3.4.1 The patient requests withdrawal and revokes informed consent before the study intervention begins.

3.4.2 Surgery is canceled.

Reasons for exclusion will be recorded in detail. These patients will not be included in the intention-to-treat dataset but will be included in the safety analysis set.

3.5 Criteria for suspending or terminating the trial

3.5.1 The investigator identifies a serious safety problem.

3.5.2 A major safety problem occurs.

3.5.3 The sponsor suspends or terminates the trial for financial or administrative reasons.

3.5.4 The competent administrative authority revokes authorization for the trial.

Suspension or termination may be temporary or permanent. All trial records will be retained.

4 Overall Study Design

4.1 Study design

This is a randomized, double-blind, placebo-controlled pilot trial. The study intervention is preoperative oral roxadustat.

4.2 Sample size calculation

This pilot trial will assess intervention safety, feasibility, and trends in treatment effects. Based on similar studies and statistical principles, and balancing robust estimation against feasibility, 40 patients will be enrolled in each group, for a total of 80 patients.

5 Randomization and Blinding

5.1 Randomization

5.1.1 A biostatistician who is independent of trial conduct, data management, and statistical analysis will generate a computer-based, 1:1 block randomization sequence using R version 3.6, with block sizes of 4 or 6. The allocation list will be placed in sequentially numbered sealed randomization envelopes held by the study coordinator.

5.1.2 During enrollment, the coordinator will select the envelope corresponding to the patient's order of entry and provide the assigned study medication or matching placebo to study personnel. The coordinator will then reseal the randomization envelope until the end of the trial.

5.1.3 Study personnel will directly observe patients taking the study medication.

5.2 Blinding

5.2.1 Investigators and medical personnel

5.2.1.1 A designated coordinator will dispense study medication and coordinate investigators and medical personnel. This coordinator will not participate in preoperative preparation, intraoperative anesthesia management, postoperative treatment, or postoperative study follow-up.

5.2.1.2 Personnel administering study medication will be unaware of allocation and will not participate in postoperative follow-up.

5.2.1.3 Anesthesiologists providing anesthesia and intraoperative management will be unaware of allocation and will not participate in postoperative follow-up.

5.2.1.4 Surgeons and other personnel providing surgical and ward care will be unaware of allocation and will not participate in postoperative follow-up.

5.2.1.5 Personnel collecting data and performing follow-up will be unaware of allocation and will not participate in anesthesia or perioperative management.

5.2.2 Participants

5.2.2.1 Both groups will receive study medication of the same appearance and at the same frequency.

5.2.2.2 Participants will be unaware of allocation.

6 Study Interventions

6.1 Study groups

6.1.1 Roxadustat group (ROX): oral roxadustat for 2 weeks before surgery, three times weekly, on alternate days. No dose will be administered on the day of surgery. The dose is 70 mg for body weight of at least 40 kg but below 60 kg, and 100 mg for body weight of at least 60 kg.

6.1.2 Placebo group (PBO): oral placebo matching roxadustat in appearance for 2 weeks before surgery, using the same administration frequency and method. The corresponding dose presentations are 70 mg for body weight of at least 40 kg but below 60 kg and 100 mg for body weight of at least 60 kg.

6.2 Preoperative preparation

6.2.1 All patients will undergo routine preoperative complete blood count and iron-status testing. Intravenous iron will be actively administered to patients with iron-deficiency anemia meeting any of the following: ferritin below 30 micrograms/L; ferritin 30-100 micrograms/L with transferrin saturation below 20%; or reticulocyte hemoglobin content below 29 pg.

6.2.2 Follow-up during medication administration: daily telephone follow-up will confirm study medication ingestion and any adverse symptoms or signs. Additional examinations will be performed when necessary.

6.3 Anesthesia and intraoperative management

6.3.1 Monitoring will follow clinical practice and include electrocardiography, pulse oxygen saturation, end-tidal carbon dioxide, inspired and expired anesthetic gas concentrations, noninvasive and/or invasive blood pressure, central venous pressure, nasopharyngeal temperature, and urine output. Pulmonary artery pressure and cerebral oxygen saturation will be monitored when clinically indicated.

6.3.2 Anesthesia will be induced with midazolam, ciprofol, sufentanil, and cisatracurium and maintained with intravenous ciprofol, sufentanil, and cisatracurium combined with inhaled sevoflurane. The bispectral index (BIS) will be maintained at 40-60.

6.3.3 Vasoactive agents, including ephedrine, atropine, dopamine, dobutamine, phenylephrine, epinephrine, and norepinephrine, may be administered according to clinical need, targeting blood pressure within 20% of baseline.

6.3.4 All patients will receive prophylactic intraoperative tranexamic acid 1 g. A cell-salvage device will be used routinely. Under the routine transfusion strategy, allogeneic red blood cells will be transfused for hemoglobin below 10 g/dL or clear evidence of tissue hypoxia caused by bleeding.

6.3.5 Postoperative analgesia: a patient-controlled intravenous analgesia pump will be connected at the end of surgery, containing sufentanil 150 micrograms in a total volume of 100 mL. The background infusion will be 1 mL/hour, with a 2-mL demand dose and an 8-minute lockout interval.

6.4 Postoperative management

6.4.1 Patients will remain intubated and be transferred to the cardiac surgical intensive care unit (ICU) with continuous electrocardiography, pulse oximetry, and invasive blood pressure monitoring.

6.4.2 ICU monitoring will include invasive blood pressure, heart rate, electrocardiography, pulse oxygen saturation, central venous pressure, nasopharyngeal temperature, and urine output. Arterial blood gases, complete blood count, biochemical tests, and coagulation tests will be obtained according to routine practice. Pulmonary artery pressure and cerebral oxygen saturation will be monitored when clinically indicated.

6.4.3 Myocardial injury biomarkers, including hs-cTnI, will be measured within 0-2 hours after ICU admission and on postoperative days 1, 2, and 3. Additional measurements may be obtained if myocardial injury is suspected. Postoperative myocardial injury/infarction will be diagnosed according to the 2024 EACTS algorithm (Figure 1).

6.4.4 Twelve-lead electrocardiography will be performed routinely at ICU admission and on postoperative day 1, with additional testing for chest pain, hemodynamic instability, arrhythmia, or a marked troponin increase.

6.4.5 Bedside echocardiography will be performed routinely on postoperative day 1, with additional examinations for hemodynamic instability, arrhythmia, or a marked troponin increase.

6.4.6 Postoperative care will follow routine practice, including mechanical ventilation and extubation; circulatory and vasoactive support; correction of anemia, electrolyte disturbances, and acid-base disorders; antiarrhythmic treatment; treatment of myocardial ischemia/infarction; and secondary prevention.

7 Observations and Data Collection

7.1 Preoperative data

After written informed consent, the preoperative assessor will collect the following baseline information.

7.1.1 Demographics, including initials, sex, date of birth, educational attainment, years of education, and body mass index.

7.1.2 Diagnoses and history, including the surgical diagnosis, comorbidities, medications, smoking and alcohol history, food and drug allergies, and previous surgery and anesthesia.

7.1.3 Major laboratory results, including complete blood count, biochemistry (including hs-cTnI and B-type natriuretic peptide [BNP]), and coagulation, and investigation results, including electrocardiography, echocardiography, peripheral vascular ultrasonography, and coronary angiography.

7.1.4 Disease severity and physical status, including New York Heart Association (NYHA) functional class, Charlson Comorbidity Index (Appendix 3), ASA physical status, and EuroSCORE (Appendix 4).

7.1.5 Preoperative hemoglobin and iron stores, including complete blood count, iron-status tests, and erythropoietin at baseline and before surgery on the day of surgery.

7.1.6 During the intervention period, from initiation of study medication until surgery, a wearable mobile monitoring device will monitor noninvasive blood pressure, heart rate, electrocardiography, and pulse oxygen saturation.

7.2 Intraoperative data

7.2.1 Blood will be collected after induction of anesthesia and before surgery to measure mechanistic biomarkers: vascular endothelial growth factor (VEGF), microRNA-210 (miR-210), and interleukin-6 (IL-6).

7.2.2 Anesthetic technique and duration, and medication types and doses.

7.2.3 Types and volumes of intravenous fluids, blood products and antifibrinolytic agents and their amounts, and intraoperative urine output.

7.2.4 Surgical procedure, duration of coronary manipulation, and duration of mechanical circulatory support, including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and cardiopulmonary bypass.

7.2.5 Blood pressure, heart rate, BIS, and temperature from induction of anesthesia until departure from the operating room, retrieved from the anesthesia information system at 5-minute intervals.

7.2.6 Arterial blood gases after induction of anesthesia and after completion of coronary manipulation.

7.2.7 Intraoperative adverse events, as described in Section 9.

7.3 Postoperative observations

7.3.1 Myocardial injury and heart failure biomarkers: hs-cTnI and BNP/N-terminal pro-B-type natriuretic peptide (NT-proBNP) at ICU admission (0-2 hours), on postoperative days 1 and 2, and the highest values before discharge or within 30 postoperative days.

7.3.2 Anemia: hemoglobin at ICU admission (0-2 hours) and on postoperative days 1 and 2; the lowest hemoglobin before discharge or within 30 postoperative days; and treatment, including blood products, iron, and erythropoietin.

7.3.3 Mechanistic serum biomarkers in selected participants: blood sampling on postoperative day 1 for VEGF, miR-210, and IL-6.

7.3.4 Major adverse cardiovascular events (MACE): myocardial infarction diagnosed using the EACTS algorithm (Appendix 1 and Figure 1); stroke, including ischemic and hemorrhagic stroke; and cardiovascular death, including death from myocardial infarction, heart failure, arrhythmia, stroke, or other cardiovascular causes.

7.3.5 Other adverse events

7.3.5.1 Serious arrhythmia: new-onset arrhythmia requiring treatment, including antiarrhythmic medication, pacemaker implantation, electrical cardioversion or defibrillation, or radiofrequency ablation.

7.3.5.2 Congestive heart failure: new dyspnea with bilateral pulmonary crackles; cardiomegaly or pulmonary edema-related infiltrates on chest radiography, or systolic or diastolic dysfunction on echocardiography; BNP/NT-proBNP above the upper limit of normal; and a requirement for inotropic agents and diuretics.

7.3.5.3 Postoperative pneumonia: suspected pulmonary infection treated with antibiotics, together with at least one of the following: new or changed sputum; new or increased pulmonary infiltrates; temperature above 38.3 degrees Celsius; or white blood cell count above 12,000/mm3.

7.3.5.4 Respiratory failure: arterial oxygen tension (PaO2) below 60 mmHg on room air; a PaO2/fraction of inspired oxygen ratio below 300 during oxygen therapy or mechanical ventilation; or a requirement for ventilatory support for at least 48 hours.

7.3.5.5 Acute kidney injury

7.3.5.5.1 Acute kidney injury (AKI) is defined using the KDIGO-AKI creatinine criteria [33], with the preoperative serum creatinine as baseline. Either of the following qualifies: an increase of at least 0.3 mg/dL (26.5 micromol/L) within 48 hours; or an increase to at least 1.5 times baseline within 7 days.

7.3.5.5.2 Staging of acute kidney injury

Stage	Serum creatinine	Urine output
1	Increase to 1.5-1.9 times baseline within 7 days, or increase by at least 0.3 mg/dL (26.5 micromol/L) within 48 hours.	Below 0.5 mL/kg/hour for 6-12 hours.
2	Increase to 2.0-2.9 times baseline within 7 days.	Below 0.5 mL/kg/hour for at least 12 hours.
3	Increase to at least 3.0 times baseline within 7 days; serum creatinine at least 4.0 mg/dL (353.6 micromol/L); or initiation of renal replacement therapy.	Below 0.3 mL/kg/hour for at least 24 hours, or anuria for at least 12 hours.

7.3.5.6 Sepsis: life-threatening organ dysfunction caused by infection, with a Sequential Organ Failure Assessment (SOFA) score of at least 2.

7.3.5.7 Gastrointestinal bleeding: clear clinical evidence such as hematemesis, bloody stool, or decreased hemoglobin, or confirmation at surgical exploration or endoscopy, requiring transfusion, hemostatic treatment, or other therapy.

7.3.5.8 Unplanned repeat cardiac surgery: an unplanned second operation within 30 postoperative days.

7.3.5.9 Noncardiac death: death from a noncardiac cause within 30 postoperative days.

7.3.6 Other measurements

7.3.6.1 Pain: assessed twice daily on postoperative days 1-3, at 06:00-08:00 and 18:00-20:00, at rest and during coughing using a visual analogue scale from 0 (no pain) to 10 (worst pain).

7.3.6.2 ICU and postoperative hospital length of stay: patients remaining hospitalized beyond postoperative day 30 will be recorded as not discharged by day 30 and censored in the analysis.

8 Outcome Measures

8.1 Primary outcome

The primary outcome is trial feasibility, expressed as the protocol completion rate, defined as the proportion of randomized participants meeting all of the following:

(1) Receipt of study medication according to the assigned treatment regimen.

(2) Completion of key perioperative myocardial injury biomarker measurements (hs-cTnI) at ICU admission (0-2 hours) and on postoperative days 1, 2, and 3.

(3) Completion of postoperative day 30 follow-up.

8.2 Secondary outcomes

8.2.1 Recruitment rate: the number of eligible patients who sign informed consent and undergo randomization divided by the total number of eligible patients.

8.2.2 Highest hs-cTnI concentration within 3 days after surgery.

8.2.3 Percentage of patients with AKI stage 2 or higher.

8.3 Other outcomes

8.3.1 Treatment adherence: the number of patients completing all planned doses divided by the number randomized.

8.3.2 Hemoglobin before surgery and on the morning of postoperative day 1.

8.3.3 Amount of allogeneic blood transfused during and after surgery.

8.3.4 ICU and postoperative hospital length of stay.

8.3.5 Incidence of myocardial injury and MACE within 30 postoperative days. MACE comprises myocardial infarction, stroke, ventricular arrhythmia requiring treatment, new-onset heart failure, repeat surgery, and cardiovascular death. Myocardial injury/infarction will be diagnosed using the EACTS algorithm (Appendix 1 and Figure 1).

8.3.6 Incidence of other major complications within 30 postoperative days.

8.3.7 Changes in serum VEGF, miR-210, and IL-6 from baseline to postoperative day 1 in selected participants.

8.4 Safety outcomes

8.4.1 Incidence of adverse events during the study.

8.4.2 Incidence of serious adverse events related to study medication.

8.4.3 Incidence of other major complications within 30 postoperative days.

9 Adverse Events

9.1 Definition

An adverse event is an unexpected, unfavorable medical occurrence associated with any medical measure during the study, irrespective of its relationship to study medication. It may be an unexpected or undesirable symptom, sign (including an abnormal laboratory finding), or temporary illness associated with product use.

9.2 Monitoring and recording

9.2.1 During preoperative study medication administration, telephone follow-up will be conducted every other day, with routine perioperative testing.

9.2.2 Adverse events will be monitored from the first study medication dose until 24 hours after surgery. Events that occur will be followed until complete resolution or completion of treatment.

9.2.3 Follow-up personnel will ask patients about symptoms and review monitoring records and monitor playback data. The onset, duration, and clinical treatment of abnormalities will be documented in detail. The occurrence, type, timing, severity, duration, and outcome of adverse events will be observed and recorded promptly.

9.3 Assessment and management of expected adverse events

9.3.1 Hypertension: systolic blood pressure above 180 mmHg or more than 30% above baseline. Intravenous vasodilator injection or infusion may be administered.

9.3.2 Hypotension: systolic blood pressure below 90 mmHg or more than 30% below baseline. Intravenous vasopressor injection or infusion may be administered.

9.3.3 Arrhythmia: new-onset arrhythmia requiring intervention or treatment.

9.3.4 Hypoxemia: arterial oxygen saturation (SaO2) below 90% or PaO2 below 60 mmHg. Treatment may include increasing inspired oxygen concentration or blood pressure.

9.3.5 Cardiac dysfunction: a requirement for mechanical circulatory support, including IABP, ECMO, or a ventricular assist device, or unanticipated CABG using cardiopulmonary bypass.

9.3.6 Thromboembolism: lower-extremity deep vein thrombosis diagnosed by ultrasonography or computed tomography (CT) venography; pulmonary embolism confirmed by CT pulmonary angiography or ventilation-perfusion scanning; or imaging evidence of arterial embolism meeting diagnostic criteria for stroke, myocardial infarction, or acute limb ischemia. Suspected thromboembolism will trigger immediate diagnostic evaluation and anticoagulation, intervention, or thrombolysis according to guidelines and local pathways.

9.3.7 If a potentially study drug-related adverse event occurs, ward physicians may initially manage it according to the above principles. Study medication may be stopped and study personnel notified when necessary.

9.3.8 Adverse events will be followed until complete resolution or completion of treatment.

10 Serious Adverse Events

10.1 Definition

A serious adverse event is an unexpected medical occurrence resulting in death, a life-threatening condition, prolonged hospitalization, persistent or significant disability or functional impairment, or another serious event. Serious adverse events will be monitored from the first study medication dose until 12 hours after surgery. Events that occur will be followed until complete resolution or completion of treatment.

10.2 Reporting and management

10.2.1 Study medication will be stopped immediately if a serious adverse event occurs, and prompt symptomatic treatment will be provided.

10.2.2 In addition to active treatment or resuscitation, the principal investigator and ethics committee will be notified by telephone and in writing within 24 hours of awareness.

10.2.3 If a treatment-related death occurs, the trial will be stopped immediately, the ethics committee notified as soon as possible, and relevant information documented and retained.

10.2.4 All serious adverse events will be followed until adequately resolved or the patient's condition is stable.

11 Unblinding and Emergency Unblinding

11.1 After all participants have completed the study and CRFs have been entered and checked, the database will be locked. The first unblinding will then occur and data will be provided to statisticians for analysis. A second unblinding will occur after statistical analysis is complete.

11.2 In an emergency, such as a serious adverse event, the randomization envelope may be opened to guide treatment according to allocation.

12 Data Management

12.1 Investigators will enter original observations promptly, completely, and accurately into the CRF.

12.2 Monitors will assess compliance with the protocol. After investigator signature, CRFs will be transferred promptly to the clinical trial data custodian.

12.3 Entered and checked CRFs will be filed and retained in numerical order.

13 Statistical Analysis

13.1 Analysis populations

13.1.1 Full analysis set: all randomized patients who undergo surgery, with minimal exclusions according to the intention-to-treat principle.

13.1.2 Per-protocol set: the full analysis set excluding patients with major protocol violations.

13.1.3 Safety analysis set: all randomized patients who receive at least one dose of study medication.

13.2 General principles

13.2.1 As this is a pilot trial, analyses will primarily estimate feasibility, effect sizes, and 95% CIs. Hypothesis tests will be exploratory rather than confirmatory.

13.2.2 Continuous variables will be summarized as mean (standard deviation) or median (interquartile range), as appropriate. Categorical variables will be summarized as numbers and percentages.

13.2.3 All tests will be two-sided.

13.2.4 Missing primary outcome data will not be imputed. Sensitivity analyses may be performed for secondary and other outcomes as appropriate.

13.2.5 No multiplicity adjustment will be made for key secondary or exploratory outcomes. These analyses will estimate the direction and magnitude of effects and inform a future confirmatory trial.

13.3 Baseline and perioperative characteristics

13.3.1 Baseline and perioperative data will be summarized descriptively by randomized group.

13.3.2 Continuous variables will be compared using an independent-samples t test or Wilcoxon rank-sum test, as appropriate. Categorical variables will be compared using the chi-square test or Fisher's exact test.

13.3.3 Standardized differences will be calculated for important baseline variables to assess balance. Covariate-adjusted sensitivity analyses may be performed if meaningful imbalance is observed.

13.4 Primary outcome

13.4.1 Protocol completion rate will be analyzed in the full analysis set.

13.4.2 Between-group differences will be expressed as risk differences (RDs), risk ratios (RRs), and corresponding 95% CIs.

13.4.3 Fisher's exact test will be used because of the small sample size.

13.5 Secondary and other outcomes

13.5.1 Other feasibility outcomes, including recruitment rate, treatment adherence, completeness of key outcome data, and completion of 30-day follow-up, will be compared using the chi-square test or Fisher's exact test. Differences will be expressed as RRs with 95% CIs.

13.5.2 The composite incidence of myocardial injury and MACE within 30 days after surgery will be compared using the chi-square test. Differences will be expressed as RRs with 95% CIs.

13.5.3 Other categorical outcomes, including AKI stage 2 or higher and other major complications within 30 days, will be compared using the chi-square test, with RRs and 95% CIs reported.

13.5.4 Continuous outcomes, including highest hs-cTnI within 72 hours, changes in other serum biomarkers from baseline, and amount of allogeneic blood transfused, will be compared using an independent-samples t test or Wilcoxon rank-sum test. Repeated measurements will be analyzed using linear mixed-effects models. Differences will be reported as mean or median differences with 95% CIs.

13.5.5 Time-to-event outcomes, including ICU and hospital length of stay, will be analyzed using Kaplan-Meier methods and log-rank tests. Univariate Cox models will estimate hazard ratios with 95% CIs.

13.6 Safety outcomes

13.6.1 Adverse and serious adverse events will be described.

13.6.2 Management of adverse events will be described.

13.6.3 Incidences of adverse events, their management, and postoperative complications will be compared using the chi-square test, continuity-corrected chi-square test, or Fisher's exact test.

14 Quality Control and Quality Assurance

14.1 Training of investigators and medical personnel

14.1.1 Before study initiation, the protocol will be explained to investigators and medical personnel, who must comply strictly throughout the trial.

14.1.2 All participating personnel must complete training concerning study participants before taking part in the study.

14.1.3 Personnel must implement the trial strictly according to the protocol and complete CRFs fully, accurately, and in detail. All observed findings and abnormalities will be verified and recorded promptly to ensure reliable data.

14.1.4 All instruments and equipment used for study examinations must meet strict quality standards and function properly.

14.1.5 Standard statistical methods will be used to summarize and analyze results, with participation by personnel familiar with biostatistics.

14.1.6 All trial conclusions must be derived from source data.

14.2 Monitoring during the trial

14.2.1 The principal investigator will designate a person with a public health educational background to monitor study conduct.

14.2.2 Monitoring will ensure that implementation, data recording, and analysis comply with the protocol and relevant regulations.

14.2.3 Initial, periodic, and closeout monitoring will be performed before and during the study. Monitoring will occur after enrollment of the first three patients and at least every 12 weeks during the study.

14.2.4 Monitoring will include the following.

14.2.4.1 Confirm that designated investigators have completed training.

14.2.4.2 Confirm that enrolled patients satisfy inclusion and exclusion criteria.

14.2.4.3 Confirm that randomization and interventions follow the protocol.

14.2.4.4 Confirm that follow-up and outcome assessments follow the protocol.

14.2.4.5 Review source records for at least 5% of enrolled patients, primary outcome source records for 100% of patients, and informed consent forms for 10%-20% of patients. These proportions may be adjusted according to monitoring findings.

14.2.4.6 Confirm that all serious adverse events have been reported to the ethics committee according to the protocol, and review source records for every serious adverse event.

14.2.4.7 Confirm submission and approval by the ethics committee of protocol amendments, participant-related documents, serious adverse event reports, annual reports, and related documents.

14.2.5 A written report will follow each monitoring visit, documenting the date, monitor, and findings. The monitor will report identified problems to the principal investigator and discuss corrective measures.

15 Ethical Requirements

15.1 The trial will comply with the Declaration of Helsinki and relevant Chinese regulations governing clinical trials. The protocol must be approved by the clinical research ethics committee before implementation.

15.2 Before enrollment, the study physician must provide each patient with a complete written explanation of the study purpose, procedures, and potential risks, including the right to withdraw at any time. Each patient will receive an informed consent form, and the physician must obtain informed consent before study entry. Consent documents will be retained with the trial records. For this trial, the patient and the person authorized to act as the patient's representative while the patient is anesthetized must receive this information before surgery and document consent and authorization by signing the informed consent form and authorization form. The hospital's standard authorization form will be used.

15.3 Study results will be published in scientific articles. All participants' personal information will remain confidential.

16 Trial Termination

16.1 The trial will be terminated early if a study medication-related death occurs and will be reported promptly to the ethics committee. Restarting requires ethics committee approval.

16.2 Under normal circumstances, the trial may end after enrollment and data collection are complete and the principal investigator agrees.

17 Document Retention

CRFs will be retained for 5 years in accordance with Good Clinical Practice requirements.

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Appendix 1 Diagnosis and Management of Perioperative Myocardial Injury and Infarction After Cardiac Surgery Based on High Sensitivity Troponin

EACTS 2024 expert consensus

Step 1 Routine postoperative monitoring and hs-cTn testing

1. Biomarkers: high-sensitivity cardiac troponin I or T (hs-cTnI or hs-cTnT).

2. Measurement times: 0-2, 24, and 48 hours after surgery, and 72 hours if necessary.

3. Record the peak hs-cTn within 48-72 hours after surgery and calculate its multiple of the URL.

Step 2 Diagnostic pathways based on peak hs-cTn

1 Pathway A Peak hs-cTn below 10 times the URL

1.1 Assessment: the diagnostic threshold for perioperative myocardial infarction (PMI) has not been reached.

1.2 Clinical significance: the elevation represents routine postoperative myocardial biomarker release and is unrelated to PMI.

1.3 Management

1.3.1 Continue routine postoperative monitoring.

1.3.2 No additional ischemia-related investigations are required.

1.3.3 Continue care according to the clinical pathway.

2 Pathway B Peak hs-cTn at least 10 but below 35 times the URL

2.1 Assessment: a gray zone requiring additional supporting evidence.

2.2 Clinical significance: this concentration alone is insufficient to diagnose PMI but reaches the threshold of some earlier definitions, such as the Fourth Universal Definition of Myocardial Infarction (UDMI), and warrants vigilance.

2.3 Management

2.3.1 Initiate further evaluation.

2.3.1.1 Electrocardiography (ECG): assess for new pathological Q waves, new persistent left bundle branch block (LBBB), or new ST-T changes.

2.3.1.2 Imaging: consider transthoracic or transesophageal echocardiography (TTE/TEE) for new regional wall motion abnormalities (RWMA) or new loss of viable myocardium.

2.3.2 Decision branches

2.3.2.1 Positive ECG or imaging findings: diagnose PMI.

2.3.2.2 Negative ECG and imaging findings: diagnose myocardial injury without infarction; continue observation and manage contributing factors such as anemia, hypoxemia, or arrhythmia.

3 Pathway C Peak hs-cTn at least 35 but below 500 times the URL

3.1 Assessment: strongly suggestive of PMI; immediate confirmatory investigations are required.

3.2 Clinical significance: concentrations meet or exceed PMI thresholds used in major definitions, such as ARC-2 and the Society for Cardiovascular Angiography and Interventions (SCAI), and are associated with adverse postoperative outcomes.

3.3 Management

3.3.1 Mandatory confirmatory investigations

3.3.1.1 ECG: obtain an urgent tracing and compare serially.

3.3.1.2 Imaging investigations

3.3.1.3 TTE/TEE is preferred to assess new RWMA or loss of myocardium.

3.3.1.4 Consider cardiac magnetic resonance imaging (CMR) or CT angiography (CTA) if available or clinical suspicion is high.

3.3.1.5 Consider coronary angiography, particularly in patients with hemodynamic instability, persistent ischemic ECG changes, or extensive new RWMA. Invasive angiography should be actively considered to identify graft failure, which accounts for approximately two thirds of PMI.

3.4 Diagnostic conclusions

3.4.1 Diagnose PMI when ECG or imaging evidence of ischemia is present.

3.4.2 Even without definite ischemic evidence, elevations in this range should be recorded as severe myocardial injury and included in prognostic analyses.

4 Pathway D Peak hs-cTn at least 500 times the URL

4.1 Assessment: confirmed PMI.

4.2 Clinical significance

4.2.1 The literature states that large postoperative biomarker elevations have prognostic significance even without additional supporting evidence of ischemia. At concentrations at least 500 times the URL, PMI can be diagnosed directly without ECG or imaging evidence.

4.2.2 These concentrations are strongly associated with substantially increased postoperative mortality.

4.3 Management

4.3.1 Diagnose PMI immediately.

4.3.2 Coronary angiography is strongly recommended to establish the cause, particularly to exclude graft failure, and guide potential emergency revascularization such as percutaneous coronary intervention (PCI).

4.3.3 Obtain ECG and echocardiography concurrently to assess the extent of injury and functional effects.

4.3.4 Intensify monitoring and treatment, providing circulatory support according to cardiac function and hemodynamic status.

Part 3 Integrated diagnostic classification

hs-cTn	Confirmatory evidence required	Evidence and diagnosis
Below 10 x URL	No	No PMI; routine postoperative release.
10-35 x URL	Yes	Positive ECG or imaging evidence required. With evidence: PMI. Without evidence: myocardial injury.
35-500 x URL	Yes	Positive ECG or imaging evidence required. With evidence: PMI. Without evidence: severe myocardial injury.
At least 500 x URL	No	No additional evidence required; direct diagnosis of confirmed PMI.

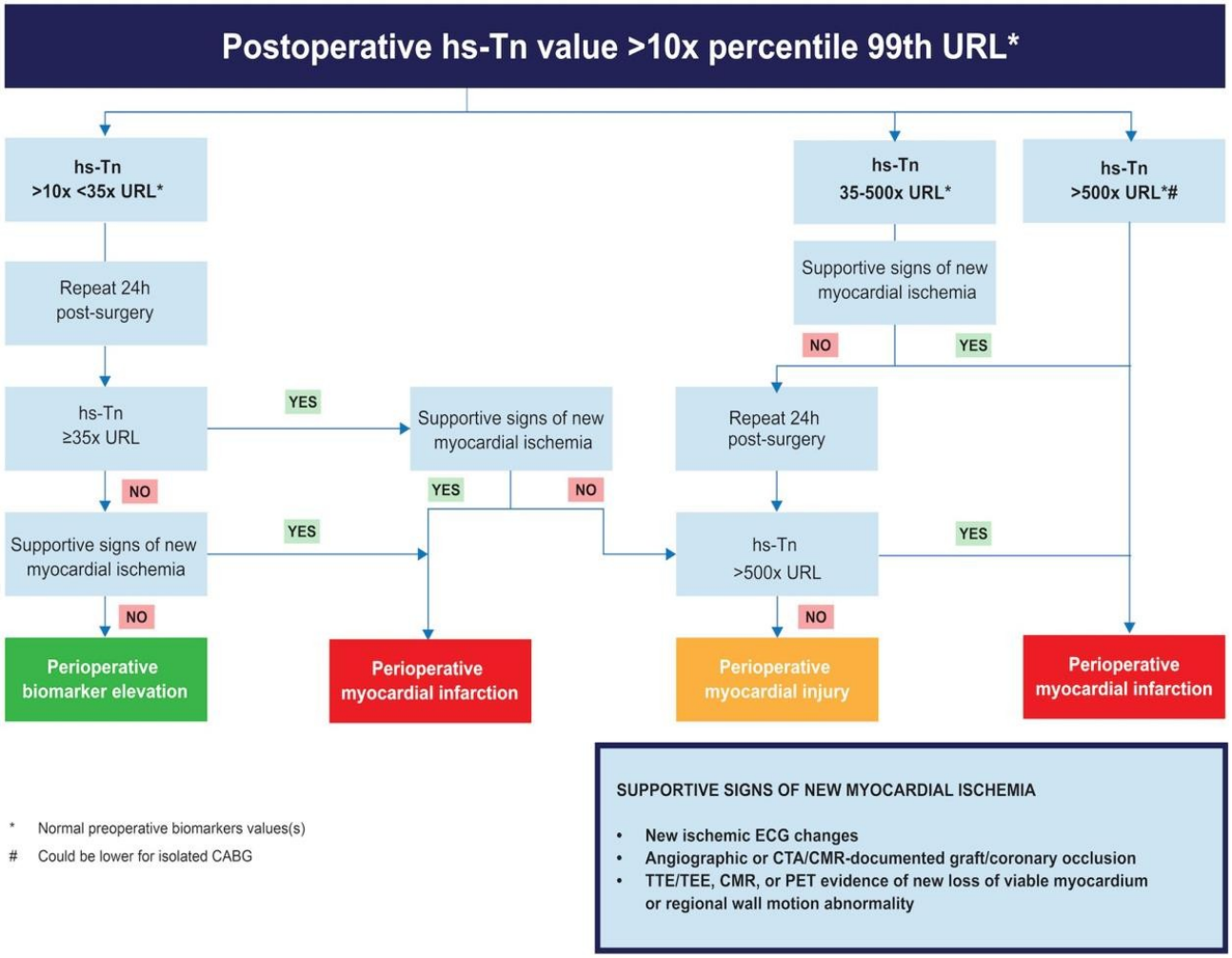


Figure 1. EACTS diagnostic algorithm for myocardial injury and infarction after cardiac surgery. Original English figure reproduced from the source protocol.

Appendix 2 Child Pugh Classification

The modified Child-Pugh classification has three classes: A, 5-6 points; B, 7-9 points; and C, 10-15 points.

Variable	1 point	2 points	3 points
Hepatic encephalopathy	None	Stages 1-2	Stages 3-4
Ascites	None	Mild	Moderate or greater
Serum bilirubin (micromol/L)	Below 34.2	34.2-51.3	Above 51.3
Serum albumin (g/L)	At least 35	28-34	Below 28
Prothrombin time (seconds)	14 or less	15-17	18 or more

Hepatic encephalopathy stages: stage 1, prodromal; stage 2, precoma; stage 3, somnolence; stage 4, coma.

Ascites grading: shifting dullness below the midaxillary line is grade 1; between the midclavicular and midaxillary lines, grade 2; and beyond the midclavicular line, grade 3.

Appendix 3 Charlson Comorbidity Index

Comorbidity	Definition	Points
Myocardial infarction	Definite or probable history of infarction, with ECG changes and/or cardiac enzyme changes.	1
Congestive heart failure	Exertional or paroxysmal nocturnal dyspnea with symptomatic or clinical response to digitalis, diuretics, or afterload-reducing drugs. Patients taking medication without symptomatic or clinical improvement are not included.	1
Peripheral vascular disease	Intermittent claudication, previous arterial bypass, gangrene, acute arterial insufficiency, or an untreated thoracic or abdominal aortic aneurysm at least 6 cm in diameter.	1
Cerebrovascular disease	History of cerebrovascular disease with no or minor residual deficits, or a history of transient ischemic attack.	1
Dementia	Chronic cognitive impairment.	1
Chronic pulmonary disease	Dyspnea on mild exertion regardless of treatment; dyspnea on moderate exertion despite treatment; or dyspnea at rest despite treatment, oxygen dependence, carbon dioxide retention, or baseline PaO2 below 50 mmHg.	1
Connective tissue disease	Systemic lupus erythematosus, polymyositis, mixed connective tissue disease, polymyalgia rheumatica, or moderate to severe rheumatoid arthritis.	1
Peptic ulcer disease	Peptic ulcer requiring treatment, including ulcer-related gastrointestinal bleeding.	1
Mild liver disease	Chronic hepatitis or cirrhosis without portal hypertension.	1
Diabetes without chronic complications	Previous hospitalization for ketoacidosis, hyperosmolar coma, or glycemic control; juvenile-onset or brittle diabetes; and other diabetes treated with insulin or oral medication, excluding diet-only treatment.	1
Diabetes with chronic complications	Retinopathy, neuropathy, or nephropathy.	2
Hemiplegia or paraplegia	Severe hemiplegia or paraplegia due to stroke or another cause.	2
Renal disease	Serum creatinine above 3 mg/dL (270.0 micromol/L), uremia, dialysis, or previous kidney transplantation.	2
Nonmetastatic solid tumor	Nonmetastatic solid malignancy first treated within the past 5 years, including breast, colon, lung, and other cancers.	2
Leukemia	Acute or chronic myeloid leukemia, acute or chronic lymphocytic leukemia, or polycythemia vera.	2
Lymphoma	Hodgkin lymphoma, Waldenstrom macroglobulinemia, myeloma, or other lymphoma.	2
Moderate or severe liver disease	Cirrhosis with portal hypertension, with or without previous variceal bleeding.	3
Metastatic solid tumor	Metastatic solid malignancy, including breast, lung, colon, and other cancers.	6
AIDS	Definite or probable AIDS. Asymptomatic HIV infection alone is not classified as AIDS.	6

Note: age points are not included in the Charlson Comorbidity Index in this protocol.

Appendix 4 EuroSCORE II Preoperative Risk Assessment Form

1 Patient related factors

Variable	Options and source item codes
Age	Measured age: _____ years
Sex	[ ] Male (0) [ ] Female (1)
Renal impairment Creatinine clearance (CrCl), calculated using Cockcroft-Gault	[ ] CrCl >85 mL/min (0) [ ] CrCl 50-85 mL/min (1) [ ] CrCl <50 mL/min, not on dialysis (2) [ ] Dialysis (3)
Extracardiac arteriopathy	[ ] No (0) [ ] Yes (1) Intermittent claudication; carotid occlusion or stenosis >50%; amputation for arterial disease; or previous or planned intervention on the abdominal aorta, limb arteries, or carotids.
Poor mobility	[ ] No (0) [ ] Yes (1) Severely impaired mobility secondary to musculoskeletal or neurological disease.
Previous cardiac surgery	[ ] No (0) [ ] Yes (1) At least one previous major cardiac operation requiring opening of the pericardium.
Chronic lung disease	[ ] No (0) [ ] Yes (1) Long-term bronchodilator or corticosteroid treatment.
Active endocarditis	[ ] No (0) [ ] Yes (1) Still receiving antibiotic treatment for endocarditis at surgery.
Critical preoperative state	[ ] No (0) [ ] Yes (1) Ventricular tachycardia/fibrillation or resuscitated sudden death; preoperative chest compressions; mechanical ventilation before anesthesia; inotropic support; IABP or ventricular assist device before entry to the operating room; or preoperative acute renal failure.
Insulin-dependent diabetes	[ ] No (0) [ ] Yes (1)

2 Cardiac related factors

Variable	Options and source item codes
NYHA class	[ ] I (0) [ ] II (1) [ ] III (2) [ ] IV (3)
CCS class IV angina	[ ] No (0) [ ] Yes (1) Angina at rest and inability to undertake any activity.
Left ventricular function (LVEF)	[ ] LVEF at least 51% (0) [ ] LVEF 31%-50% (1) [ ] LVEF 21%-30% (2) [ ] LVEF 20% or less (3)
Recent myocardial infarction	[ ] No (0) [ ] Yes (1) Within 90 days before surgery.
Pulmonary hypertension	[ ] None: systolic pressure <31 mmHg (0) [ ] Moderate: 31-55 mmHg (1) [ ] Severe: >55 mmHg (2)

3 Procedure related factors

Variable	Options and source item codes
Urgency	[ ] Elective (0) [ ] Urgent (1) [ ] Emergency (2) [ ] Salvage (3)
Weight of intervention	[ ] Isolated CABG (0) [ ] One major non-CABG procedure (1) [ ] Two major procedures (2) [ ] Three or more major procedures (3)
Thoracic aortic surgery	[ ] No (0) [ ] Yes (1) Involvement of the thoracic aorta, aortic root, or aortic arch.

4 Risk classification

Predicted mortality	Source risk category	Select
0%-2.99%	Low	[ ]
3%-5.99%	Intermediate	[ ]
At least 6%	High	[ ]

Final predicted mortality using EuroSCORE II: _____ %

Risk category: _____

Note: enter the variables into the calculator at http://www.euroscore.org/calc.html to obtain predicted mortality (%). The item codes in this form must not be added directly to calculate mortality. EuroSCORE II uses a logistic regression model rather than a simple additive score.