Effects of remote ischaemic preconditioning on myocardial injury after major abdominal surgery in patients at high risk for cardiovascular adverse events in China (RIPC-MAS): protocol for a randomised, sham-controlled, observer-blinded trial

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ABSTRACT

Introduction Myocardial injury after non-cardiac surgery (MINS) caused by an ischaemic mechanism is common and is associated with adverse short-term and long-term prognoses. However, MINS is a recent concept, and few studies have prospectively used it as a primary outcome. Remote ischaemic preconditioning (RIPC) is a non-invasive procedure that induces innate cardioprotection and may reduce MINS.

Methods and analysis This is a multicentre, randomised, sham-controlled, observer-blinded trial. Patients with a high clinical risk of cardiovascular events who are scheduled to undergo major abdominal surgery will be enrolled. A total of 766 participants will be randomised (1:1 ratio) to receive RIPC or control treatment before anaesthesia. RIPC will comprise four cycles of cuff inflation for 5 min to 200 mm Hg and deflation for 5 min. In the controls, an identical-looking cuff will be placed around the arm but will not be actually inflated.

The primary outcome will be MINS, defined as at least one postoperative cardiac troponin (cTn) concentration above the 99th percentile upper reference limit of the cTn assay as a result of a presumed ischaemic mechanism. This trial will test the concentration of high-sensitivity cardiac troponin T (hs-cTnT). The secondary outcomes will be hs-cTnT levels reaching/above the prognostically important thresholds, peak hs-cTnT and total hs-cTnT release during the initial 3 days after surgery, length of hospital stay after surgery, length of stay in the intensive care unit, myocardial infarction, major adverse cardiovascular events, cardiac-related death, all-cause death within 30 days, 6 months, 1 year and 2 years after surgery, and postoperative complications and adverse events within 30 days after surgery.

Ethics and dissemination This study protocol (version 5.0 on 7 April 2023) was approved by the Ethics Committee of Sixth Affiliated Hospital of Sun Yat-sen University. The findings will be published in peer-reviewed journals.

Trial registration number NCT05733208.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, randomised, sham-controlled, observer-blinded trial with 766 participants.
⇒ Remote ischaemic preconditioning will be performed before anaesthesia.
⇒ A sham control instead of a blank control will be implemented.
⇒ The participants are awake and may be aware of the intervention.

INTRODUCTION

Over 300 million surgeries are performed annually in the world, and this number is steadily increasing.1 Although the level of surgical technology and anaesthesia management has continuously improved in recent decades,2 postoperative mortality remains far higher than the expectations of patients and doctors, accounting for 7.7% of global mortality.3 Adverse cardiovascular events are the main cause of postoperative mortality. Demographic changes have resulted in an increasing number of older patients with cardiovascular risk factors undergoing surgery who are susceptible to adverse cardiovascular events. Managing these patients is becoming a common challenge in the perioperative period.

Myocardial injury after non-cardiac surgery (MINS) is defined as at least one postoperative cardiac troponin (cTn) concentration above the 99th percentile upper reference limit of the cTn assay as a result of a presumed ischaemic mechanism during or within 30 days after non-cardiac surgery in 2021.4
Historically, these biomarker abnormalities have been ignored, but recent large prospective cohort studies have shown that silent cardiac biomarker elevations after non-cardiac surgery are common and associated with adverse short-term and long-term prognoses. Therefore, strategies to improve prevention, treatment, and outcomes of patients with MINS may provide major medical benefits.

As the diagnostic criteria for MINS were recently established by the American Heart Association in 2021, few studies have prospectively diagnosed MINS using these criteria as a primary outcome to evaluate prevention and management strategies in high-risk population. Remote ischaemic preconditioning (RIPC) is a phenomenon in which transient non-lethal ischaemia and reperfusion on an organ or tissue remote from the heart protects the myocardium from a lethal ischaemia. RIPC can be induced by inflating and deflating the blood pressure cuff placed on the upper arm. RIPC has been shown to be non-invasive and beneficial in reducing myocardial injury in the settings of cardiac bypass surgery, primary percutaneous coronary intervention and abdominal aortic aneurysm surgery. RIPC has also been shown to have anti-inflammatory and antithrombotic effects as well as endothelial protection. By definition, MINS is caused by ischaemia. Moreover, the pathophysiology of MINS has been demonstrated to involve endothelial dysfunction and increased platelet activation and hypercoagulability which are caused by a surge in inflammatory cytokines during surgery. In addition, perioperative haemodynamic fluctuations may provoke pre-existing plaque disruption or lead to an imbalance between oxygen supply and demand, finally causing myocardial injury. Considering the effects and mechanisms of RIPC and the pathophysiology of MINS, RIPC may potentially reduce the incidence of MINS.

Thus, we planned this multicentre, parallel-group, randomised, sham-controlled, observer-blinded trial to evaluate the efficacy and safety of RIPC for the prevention of MINS after major abdominal surgery.

METHODS AND ANALYSIS

Objective

This study aimed to evaluate the efficacy and safety of RIPC in preventing MINS in patients undergoing major abdominal surgery. This study protocol (version 5.0 on 7 April 2023) was approved by the institutional review board. The trial flow diagram is presented in figure 1.

Study setting

This is a multicentre, parallel-group, randomised, sham-controlled, observer-blinded trial conducted at three centres in China.

Outcomes

Primary outcomes

We will choose the MINS as the primary outcome.

According to the diagnostic criteria established by the American Heart Association, the diagnostic criteria for MINS are the following: (a) elevated postoperative cTn with ≥1 cTn measurement above the 99th percentile of the upper reference limit for the cTn assay, with a rise/fall pattern indicative of acute myocardial injury; (b) occurs in the first 30 days (and typically within 72 hours) after surgery; (c) myocardial injury is caused by a presumed ischaemic mechanism in the absence of an overt precipitating non-ischaemic cause; (d) an ischaemic feature is not required.

Contemporary cTn assays (cardiac troponin T (cTnT) or cardiac troponin I (cTnI)) or high-sensitivity cTn (hs-cTnT or hs-cTnI) assays are all useful for MINS diagnosis. We plan to test the level of hs-cTnT before the first implementation of RIPC or control treatment which is performed approximately 24 hours before anaesthesia, and once a day on postoperative day 1, day 2 and day 3. The level of hs-cTnT will be measured by an Elecsys System using the Cobas e801 (Roche Diagnostics) assay. The lower limit of detection is 3 ng/L and the upper limit of detection is 10 000 ng/L. The upper reference limit of the 99th percentile is 14 ng/L.

In case of patients with normal baseline troponin values, myocardial injury is considered if the level of postoperative hs-cTnT level is above 14 ng/L. In case of patients with abnormal baseline troponin values, myocardial injury is considered acute if there is a ≥20% rise of cTnT after non-cardiac surgery, an absolute increase in hs-cTnT ≥14 ng/L above preoperative values or an increase in hs-cTnT ≥5 ng/L above the prior concentration and with a peak hs-cTnT ≥20 ng/L.

MINS will be centrally adjudicated by two independent blinded reviewers in the endpoint adjudication committee (EAC) based on all clinical information obtained during the index hospitalisation, and non-ischaemic causes of elevated troponin levels such as sepsis or pulmonary emboli or stroke, will be excluded. In cases of disagreement between the two reviewers, the EAC adjudicator will provide the authoritative assessment endpoint.

In the document of the Fourth Universal Definition of Myocardial Infarction, non-ischaemic myocardial injury included cardiac conditions such as heart failure, myocarditis, cardiomyopathy (any type), Takotsubo syndrome, coronary revascularisation procedure, cardiac procedure other than revascularisation, catheter ablation, defibrillator shocks, cardiac contusion and systemic conditions such as sepsis, infectious disease, chronic kidney disease, stroke, subarachnoid haemorrhage, pulmonary embolism, pulmonary hypertension, infiltrative diseases (eg, amyloidosis, sarcoidosis), chemotherapeutic agents, critically ill patients and strenuous exercise.

Secondary outcomes

1. Participants with the concentration of hs-cTnT reaching/above the prognostically important thresholds.
   - Prognostically important thresholds are defined as hs-cTnT ≥20 to <65 ng/L with an absolute change
of ≥5 ng/L, any elevation ≥65 ng/L, or any absolute change ≥14 ng/L.  
2. Peak concentration of hs-cTnT within the initial 3 days after surgery.  
3. Total hs-cTnT release within the initial 3 days after surgery (area under the curve).  
4. Length of postoperative stay.  
5. Length of stay in the intensive care unit (ICU).  
6. Myocardial infarction within 30 days, 6 months, 1 year and 2 years after surgery.  
   - Myocardial infarction is diagnosed according to the Fourth Universal Definition of Myocardial Infarction.18  
7. Major adverse cardiovascular events (MACEs) within 30 days, 6 months, 1 year and 2 years after surgery.  
   - MACEs are defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.19  
8. Cardiac-related deaths within 30 days, 6 months, 1 year and 2 years after surgery.  
   - Cardiac-related deaths are defined as all deaths for which there was no clinical or postmortem evidence of non-cardiac aetiology.  
9. All deaths within 30 days, 6 months, 1 year or 2 years after surgery.  
10. Major postoperative complications within 30 days after surgery.
- Major postoperative complications include cardiovascular complications (severe arrhythmia, acute heart failure or myocardial infarction), pulmonary complications (hypoxaemia, need for non-invasive or invasive mechanical ventilation, acute respiratory distress syndrome, pneumonia), neurological complications (stroke or altered consciousness), gastrointestinal complications (liver failure, gastrointestinal bleeding or perforation), urological complications (acute kidney dysfunction), haematological complications (platelets <100×10⁹/L), thromboembolic complications (deep venous thrombosis, pulmonary embolism), infectious complications (anaesthetic leak, surgical site infection, urinary tract infection, sepsis, and septic shock) and death. ²⁰ The detailed diagnostic criteria are provided in online supplemental materials.

11. Adverse events within 30 days after surgery.

Adverse events refer to all adverse medical events that occur after a subject receives the intervention, which can manifest as symptoms, signs, diseases or laboratory abnormalities, including occurrences which are not necessarily caused by or related to the intervention. The detailed definitions are provided in online supplemental materials.

### Eligibility criteria

#### Inclusion criteria

1. Patients with a high clinical risk of cardiovascular events.
   - A high clinical risk of cardiovascular events is defined as ≥65 years of age or ≥45 years of age with a history of coronary artery disease, peripheral arterial disease or stroke. ⁴ ²¹
   - A history of coronary artery disease includes a history of acute myocardial infarction, finding of stenosis on coronary angiogram or positive stress testing. A history of peripheral artery disease encompasses all arterial diseases other than coronary arteries and the aorta, including lower extremity artery disease, the carotid and vertebral, upper extremities, mesenteric and renal arteries. ²² A history of stroke is defined as history of acute new focal neurologic deficit judged by treating physicians to be of vascular cause lasting more than 24 hours.

2. Patients scheduled to undergo major abdominal surgery.
   - Major abdominal surgery is defined as a skin incision, expected operative duration of at least 2 hours, and expected hospital stay of at least 3 days. ²³ The operation types of surgery mainly included gastric or small intestinal surgery, hiatal hernia repair, hepatobiliary surgery, pancreatic, colorectal, urological or renal, gynaecological and other surgery performed on multiple abdominal organs.

#### Exclusion criteria

1. Immediate or urgent surgery or surgery where there is insufficient time to perform RIPC.
2. Abdominal vascular surgery, such as surgery for abdominal aortic aneurysm.
3. Experience of conditions precluding the use of RIPC in both arms.
4. Patients who are being treated with drugs, such as sulphonamide or nicorandil.
5. With contraindications for anaesthetic regime required in this trial.

### Recruitment

Participants will be recruited by trained investigators in each participating hospital. Eligible patients will obtain all relevant information about the study in form of oral explanation but also in form of an information sheet. After they give written consent to take part in the study, they will be screened to complete a questionnaire comprising contact details, demographics, detailed medical history and medication listing. The participant has the right to withdraw from the study at any time of the study process without prejudice to their future care.

### Randomisation and treatment groups

Eligible patients will randomly (1:1 ratio) be assigned to receive RIPC or no RIPC (control). The random sequence will be generated by an independent statistician using the SAS software (V.9.4), with stratification by participating centre and type of anaesthesia using permuted blocks. Then, the sequence will be implemented securely into the web-based secure electronic module for central randomisation incorporated in the electronic data capture system (Zhejiang Taimei Medical Technology, China). Access to this module and results of randomisation will be strictly controlled and limited to unmasked trained implementer of the RIPC or control. The members involved in participant recruitment, data collection and outcome assessment, and participant care in the perioperative period will be blinded.

RIPC will consist of four cycles of 5 min inflation of a blood pressure cuff on the upper arm to 200 mm Hg, followed by 5 min deflation. For patients with systolic blood pressure (SBP) ≥175 mm Hg, the cuff will be inflated to at least 25 mm Hg above the SBP.²⁴ In the controls, an identical-looking cuff will be placed around the upper arm. However, unlike in RIPC, the valve of inflation pump is unlocked, such that the cuff cannot be inflated. The operation of the control including cycling number and cycling time are identical to those of the RIPC procedure, except that the blood pressure cuff does not inflate. RIPC or control treatment will be performed two times, one at approximately 24 hours before anaesthesia and the other at approximately 1 hour before anaesthesia.

The anaesthesia regimes will be restricted to either total intravenous anaesthesia containing propofol or volatile anaesthesia without propofol and the anaesthesia regime will be one of the stratification factors. The same goal of
## Pain regimes will be set, which is a pain score no more than 3 after surgery, to balance the increment of oxygen demand caused by pain. The choice of pain regimes will be left to anesthesiologist and the patients’ requirement to maintain the generalisability of the results.

### Follow-up
**Figure 2** provides details of the schedule of enrolment, interventions and assessments. Blood will be collected to test the hs-cTnT concentration before the first implementation of RIPC or control treatment, and once a day on postoperative day 1, day 2 and day 3. The participants will be followed-up at the bedside by investigators every day to record postoperative complications, adverse events, and the length of ICU stay and hospital stay and followed up by telephone at 30 days to investigate the adverse events and the events of myocardial infarction, death and the cause of death. Moreover, they will be followed up by telephone at 6 months, 1 year and 2 years to investigate the events of myocardial infarction, MACEs, death and the cause of death.

### Sample size calculation
Based on the results of PIXIE trial in 2019⁵ and the VISION study in 2017,³ 30%–35% of the patients developed MINS according to the diagnostic criteria established by the American Heart Association. We estimated that RIPC would reduce the incidence to 20%. Therefore, assuming an incidence of 31% in the control group and 20% in the RIPC group, we calculated that 650 participants would be required to detect this difference using R software (V.4.2.1), with a 5% type I error and a power of 90% in a two-sided test. The planned number of patients for enrolment was finally set at 766 (383 participants

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Figure 2 The schedule of enrolment, interventions and assessments. hs-cTnT, high-sensitivity cardiac troponin T; ICU, intensive care unit; MACE, major adverse cardiovascular event; RIPC, remote ischaemic preconditioning.
in each group), considering a 15% dropout rate and non-compliance.

**Statistical analysis**

A detailed statistical analysis plan will be produced prior to unblinding of any data. All continuous, normally distributed or approximately normally distributed variables will be expressed as mean (SD). All continuous, non-normally distributed variables will be expressed as median (IQR). Differences between groups will be investigated using the Student’s t-test for normally distributed or approximately normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and Pearson’s $\chi^2$ test or Fisher’s exact test for categorical variables. Two-tailed tests will be performed. Risk ratios with 95% CIs will be calculated using log-binomial regression or Poisson regression. HRs and CIs will be calculated using Cox proportional hazards modelling and Kaplan-Meier curves will be produced. Risk difference with 95% CIs will be calculated using binomial regression or Poisson regression. Differences in means (continuous variables) together with 95% CIs will be calculated using linear regression models or generalised estimation equation. Both adjusted analyses and unadjusted analyses will be performed. $P<0.05$ will be considered statistically significant. Analyses will be performed both in the full analysis set and in the per-protocol set. In the intention to treat analysis, the missing data will be imputed by the method of multiple imputation. In the per-protocol analysis, the missing data will not be imputed. Subgroup analyses will be stratified by sex, type of anaesthesia, age group, trial centre, revised cardiac risk index and Duke activity status index. Statistical analyses will be performed using R software (V.4.2.1).

**Data management**

The data will be entered into the electronic data capture database, which has data entry and validation rules to reduce data entry errors, and the management functions to facilitate auditing. Participants’ data will be held securely in line with data protection legislation. Anonymous datasets will be stored in the Research Data storage facility at Sun Yat-sen University. The data management team will be responsible for establishing the module in the electronic data capturing system, designing the case report form, reviewing data blindly, locking database, exporting data and so on.

**Monitoring, safety and audit**

The coordinating centre will be responsible for coordinating the three participating centres, and collecting data from each centre, laboratory and EAC. The Trial Steering Committee (TSC) will be responsible for the protocol design and implementation, drafting the final report and submission for publication. The EAC will be responsible for validating and adjudicating the endpoints independently.

This trial will be overseen and audited by the Clinical Research Centre, Ethics Committee and Data Safety Monitoring Committee (DSMC). The DSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, determining whether there are any unforeseen effects of RIPC, recommending to the TSC whether the trial needs to be changed or terminated based on analysis. The DSMC will first convene prior to trial initiation and will then define frequency of subsequent meetings (at least two a year). The Clinical Research Centre and Ethics Committee will monitor the trials annually. The investigators at each centre will be responsible for registering and reacting in case of serious adverse event (SAE) and suspected unexpected serious adverse reaction (SUSAR) happened. The investigators at each centre will report the related SAE and SUSAR to the chief investigator, the ethics committees and the DSMC.

**Public and patient involvement**

Public and patient involvement (PPI) representatives have been actively involved in the study design stage, including the development of an intervention protocol and adding outcomes that PPI representatives care about, such as participants with the concentration of hs-cTnT above the prognostically important thresholds. PPI will advise on the communication with participants and report of the findings of this study with a wider audience.

**ETHICS AND DISSEMINATION**

This study was reviewed and approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University. Potential participants are required to provide written informed consent before participating in the trial. The results of this study will be presented at national and international meetings and published in peer-reviewed journals. We will work with our PPI contributors to produce study summaries for the patients.

**Trial status**

This trial has started on 6 May 2023. We planned to complete this trial in December 2027.

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**Contributors**

The corresponding author Y2 and the co-corresponding author S-QJ conceived the study and obtained funding; FW and C-JL contributed equally to design the study and prepare the first draft of this manuscript; J-KS, Q-SH, BMN
and XW contributed to design the study and revise the manuscript. All the authors have read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**REFERENCES**


The definition of adverse events and major postoperative complications

**Adverse Event (AE)** refers to all adverse medical events that occur after a subject receives the intervention, which can manifest as symptoms, signs, diseases, or laboratory abnormalities, including occurrences which are not necessarily caused by or related to the intervention.

**Severe adverse event (SAE)** refers to any adverse event that 1) results in death; 2) is life-threatening (subject at immediate risk of death)*; 3) requires in-patient hospitalisation or prolongation of existing hospitalisation**; 4) results in persistent or significant disability or incapacity; 5) consists of a congenital anomaly or birth defect; 6) other important medical events.

*‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Unexpected adverse events** that have not been defined as endpoints, expected complications of the RIPC stimulus or expected complications of usual clinical care should be also reported as either an SAE or AE, depending on their severity.

**Expected adverse events related to the RIPC procedure**

The benign nature of the RIC stimulus excludes there being any expected serious adverse events (PMID:31500849). There is a small possibility of having skin petechiae caused by cuff inflation. Since the patient is awake, the patient may experience numbness and discomfort during the preconditioning procedure.

**Expected adverse events related to usual clinical care**
Adverse events such as hypothermia (core temperature <36 °C), hypotension (systolic blood pressure < 90 mmHg, or mean arterial pressure < 65 mmHg), allergic reaction, postoperative nausea and vomiting, postoperative bleeding and other adverse events will be recorded.

Allergic reaction

The clinical suspicion of a perioperative allergic reaction is based on a pattern of symptoms suggestive of allergy and their onset in relation to the administration of potential triggers (PMID: 31130272). According to the Ring and Messmer scale (PMID: 65572), there are four grades: 1) Grade I—Skin, mucosal signs, or both: generalised erythema, extensive urticaria, or both with or without angioedema; 2) Grade II—Moderate multi-organ involvement: skin, mucosal signs, or both with or without moderate hypotension, tachycardia, moderate bronchospasm or gastrointestinal symptoms; 3) Grade III—Life-threatening mono- or multi-organ involvement: life-threatening hypotension, tachycardia, or bradycardia with or without cardiac arrhythmia, severe bronchospasm, skin, mucosal signs, or both, or gastrointestinal symptoms; 4) Grade IV—Cardiac or respiratory arrest.

Postoperative nausea and vomiting (PONV)

PONV is defined as nausea, retching or vomiting. Nausea is defined as a feeling of the urge to vomit. Retching is defined as an attempt to vomit that is not productive of stomach contents. Vomiting is defined as episodes of expulsion of gastric content. (PMID: 15190136)

Postoperative bleeding

Blood loss that: 1) is fatal; 2) leads to significant hypotension requiring inotrope therapy; 3) leads to urgent (within 24 hours) intervention (other than superficial vascular or wound repair); 4) intracranial haemorrhage; 5) results in post-operative haemoglobin ≤ 70g/L AND that requires a transfusion of ≥ 2 units of red blood cells; 6) results in a haemoglobin drop of ≥ 50g/L AND that requires a transfusion of ≥ 2 units of red blood cells; 7) requires a transfusion of ≥ 4 units of red blood cells within a 24 hour period; 8) leads to any other intervention (eg, embolization, superficial vascular repair); 9) is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

Major postoperative complications are reported in the outcome of major postoperative complications within 30 days after surgery, including cardiovascular complications (severe arrhythmia, acute heart failure or myocardial infarction), pulmonary complications (hypoxemia, need for non-invasive or invasive mechanical ventilation, acute respiratory distress syndrome, pneumonia), neurologic complications (stroke or altered consciousness), gastrointestinal complications (liver
failure, gastrointestinal bleeding or perforation), urological complications (acute kidney dysfunction), hematological complications (sequential organ failure assessment score (SOFA) sub-score of 2 points or more in the coagulation component (platelets <100 x 10^9/L), thromboembolic complications (deep venous thrombosis, pulmonary embolism), infectious complications (anastomotic leak, surgical site infection, urinary tract infection, sepsis, and septic shock), and death. (PMID: 35947398)\textsuperscript{5}

The criteria for cardiovascular complications (severe arrhythmia, acute heart failure or myocardial infarction)

1. **Severe arrhythmia** such as supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, and ventricular fibrillation is diagnosed by electrocardiogram.

2. **Acute heart failure** is ascertained by appropriate clinical history and examination with consistent cardiac ultrasonography.

3. **Myocardial infarction** is diagnosed according to the Fourth Universal Definition of Myocardial Infarction (PMID: 30571511)\textsuperscript{6}. The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following: 1) Symptoms of myocardial ischemia; 2) New ischemic ECG changes; 3) Development of pathological Q waves; 4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; 5) Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

The criteria for pulmonary complications (hypoxemia, need for non-invasive or invasive mechanical ventilation, acute respiratory distress syndrome, pneumonia).

1. **Hypoxemia** is defined as a PaO2 <60 mmHg or SpO2 <90% on room air.

2. **Noninvasive ventilation**: Noninvasive ventilation is considered in case of presence and persistence for more than 30 minutes of hypoxemia (as defined above) and at least one of the following: a) Respiratory rate higher than 30/min; b) Clinical signs suggestive of intense respiratory muscle work
and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction.

3. **Acute respiratory distress syndrome (ARDS)** is defined according to the new global definition of ARDS in 2023 including a) intubation not required; high flow nasal oxygen ≥ 30 L/min; b) hypoxemia levels of PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 315 mmHg with SPO2 ≤ 97%; c) bilateral opacities confirmed by one of the following: chest radiograph, computed tomography, or ultrasound with a well-trained operator; d) in resource limited settings the following are not required: PEEP, oxygen flow, or specific respiratory support devices.

4. **Pneumonia**: There are 3 specific types of pneumonia: clinically defined pneumonia (PNU1), and pneumonia with specific laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3). PNU 3 is not a possible event in this trial and will not be discussed.

**PNU 1 or PNU2 Diagnostic Criteria** (PMID:18538699)

Both diagnoses require (1) Two or more serial chest radiographs with at least one of the following: (a) new or progressive and persistent infiltrate; (b) consolidation; (c) cavitation. AND (2) Signs/Symptoms: (a) at least ONE of the following: (i) fever (>38°C) with no other recognized cause (ii) Leukopenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3) (iii) For adults >70 years old, altered mental status with no other recognized cause and (b) at least two (PNU1) or one (PNU2) of the following: (i) new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements; (ii) new onset or worsening cough, dyspnkea or tachypnoea; (iii) crackles or bronchial breath sounds; (iv) Worsening gas exchange.

PNU2 also requires at least ONE of the following: (1) Positive growth in blood culture not related to another source of infection (2) Positive growth in culture of pleural fluid (3) Positive quantitative culture from minimally contaminated low respiratory tract specimen (eg, brochoalveolar lavage or protected specimen brushing) (4) ≥5% brochoalveolar lavage-obtained cells contain intracellular bacteria on direct microscopic exam (eg, Gram stain) (5) Histopathologic exam shows at least ONE of the following evidences of pneumonia:(a) Abscess formation or foci of consolidation with intense polymorphonuclear(PMN) accumulation in bronchioles and alveoli (b) Positive quantitative culture of lung parenchyma.

The criteria for neurologic complications (stroke or altered consciousness):
1. **Stroke** is defined as acute new focal neurological deficit judged by treating physicians to be of vascular cause lasting >24 hours with confirmation by CT scan and/or MRI.

2. The presence of postoperative **altered consciousness** is determined clinically by the treating physician, defined as a Glasgow Coma Scale (GCS) score ≤ 14. Additionally, postoperative delirium is judged by 3D-CAM or CAM-ICU and delirium rating scale-revised-98 (DRS-R-98).

The criteria for gastrointestinal complications: liver failure, gastrointestinal bleeding or perforation:

1. **Acute liver failure** is defined as acute onset of hepatic encephalopathy of grade II or above within 2 weeks with the following manifestations: a) extreme fatigue, with severe gastrointestinal symptoms such as obvious anorexia, bloating, nausea, vomiting, etc; b) progressive exacerbation of jaundice in the short term (serum total bilirubin ≥ 171 µmol/L or daily increase ≥ 17.1µmol/L); c) The bleeding tendency is obvious, with plasma prothrombin activity (PTA) ≤ 40% (or INR ≥ 1.5), and other reasons are excluded; d) Progressive shrinkage of the liver (PMID: 30685919).

2. **Gastrointestinal bleeding** is diagnosed according to clinical symptoms such as tachycardia, hypotension, hematemesis and melena, and laboratory test such as the level of hemoglobin, or endoscopy, or angiography, or computed tomography or computed tomographic angiography, or magnetic resonance angiography (PMID: 16015555).

3. **Gastrointestinal perforation** is diagnosed according to clinical symptoms such as abdominal pain, signs such as plate shaped abdomen, total abdominal tenderness, rebound pain, and muscle tension, and X-ray or computed tomography.

The criteria for urological complications (acute kidney dysfunction)

**Acute kidney injury** is defined as one of the following: (1) an increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; (2) an increase in serum creatinine to ≥ 1.5 times baseline within the previous 7 days; (3) urine volume ≤ 0.5 ml/kg/h for 6 hours according to Based on the KDIGO clinical practice guidelines (PMID: 22890468).

The criteria for **hematological complications** is SOFA sub-score of 2 points or more in the coagulation component (platelets <100×10^9/L).

The criteria for **thromboembolic complications**

1. **Deep venous thrombosis** is diagnosed by D-dimer, color doppler ultrasonic examination, CT venography, MR venography, and phlebography.

2. **Pulmonary embolism** is diagnosed by D-dimer, and CT pulmonary angiography.
The criteria for infectious complications (anastomotic leak, surgical site infection, urinary tract infection, sepsis, and septic shock)

**Surgical site infection (SSI)** is classified as superficial incisional surgical site infection, deep surgical site infection or organ/space surgical site infection (PMID:18538699).

Superficial incisional SSI must meet the following criterion: (1) Infection occurs within 30 days after the operative procedure and (2) involves only skin and subcutaneous tissue of the incision and (3) patient has at least one of the following: (a) purulent drainage from the superficial incision; (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (c) at least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is cultured positive or not cultured. A culture-negative finding does not meet this criterion; (d) diagnosis of superficial incisional SSI by the surgeon or attending physician.

Deep incisional SSI must meet the following criterion: (1) Infection involving the deep soft tissues (eg, fascial and muscle layers) of the incision occurring within 30 or 90 days after the operative procedure and (2) the infection meets at least one of the following: (a) purulent drainage from the deep incision but not from the organ/space component of the surgical site (b) a deep incision spontaneously dehisces or is deliberately opened by a surgeon AND is culture-positive or not cultured AND the patient has at least one of the following signs or symptoms: (i) fever (>38°C) (ii) localized pain or tenderness. A culture-negative finding does not meet this criterion (c) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

Organ/space surgical site infection must meet the following criterion: (1) Infection occurs within 30 or 90 days after the operative procedure (2) infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure (3) patient has at least one of the following: (a) purulent drainage from a drain that is placed through a stab wound into the organ/space (b) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space (c) an abscess or other evidence involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
Urinary tract infection: Symptomatic urinary tract infection—A symptomatic urinary tract infection must meet both of the following criteria and did not have a urinary catheter in place on the date of event nor the day before the event: (1) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), suprapubic tenderness, costovertebral angle pain or tenderness, urgency, frequency or dysuria AND (2) Patient has a positive urine culture, that is, >10^5 microorganisms per ml of urine with no more than 2 species of microorganisms. Catheter-Associated Urinary Tract Infection—The patient must have had and indwelling catheter that has been in place for > 2 days on the date of the event and was either still present at the time of event or removed the day before the event. A catheter associated urinary tract infection must meet both of the following criteria: (1) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38°C), suprapubic tenderness, costovertebral angle pain or tenderness, urgency, frequency or dysuria. AND (2) Patient has a positive urine culture, that is, >10^9 microorganisms per ml of urine with no more than 2 species of microorganisms. Other infections of the urinary tract (kidney, ureter, bladder, urethra, or tissue surrounding the retroperitoneal or perinephric space) must meet at least one of the following criteria: (1) Patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site. AND (2) patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination. AND (3) Patient has one of the following signs or symptoms with no other recognized cause: (a) fever (>38°C). (b) localized pain or localized tenderness at the involved site with at least one of the following: (i) purulent drainage from affected site; (ii) organisms cultured from blood that are compatible with suspected site of infection; (iii) radiographic evidence of infection. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection (PMID: 26903338). Septic shock is identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation (PMID: 26903338).
## Sequential [Sepsis-Related] Organ Failure Assessment Score (PMID: 8844239)

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
</tr>
<tr>
<td>PaO2/FIO2, mm Hg</td>
<td>0</td>
</tr>
<tr>
<td>≥400</td>
<td>1</td>
</tr>
<tr>
<td>&lt;400</td>
<td>2</td>
</tr>
<tr>
<td>&lt;300</td>
<td>3</td>
</tr>
<tr>
<td>&lt;200 with respiratory support</td>
<td>4</td>
</tr>
<tr>
<td>&lt;100 with respiratory support</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
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<tr>
<td>Platelets, ×10^9/L</td>
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<tr>
<td>≥150</td>
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<td>&lt;150</td>
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<td>&lt;50</td>
<td>4</td>
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<tr>
<td>&lt;20</td>
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<tr>
<td><strong>Liver</strong></td>
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<tr>
<td>Bilirubin, µmol/L</td>
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<td>102–204</td>
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<td><strong>Cardiovascular</strong></td>
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<td>MAP ≥70 mm Hg</td>
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<tr>
<td>MAP &lt;70 mm Hg</td>
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<tr>
<td>Dopamine &lt;5 or dobutamine (any dose)*</td>
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<tr>
<td>Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1*</td>
<td>3</td>
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<tr>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1*</td>
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<tr>
<td><strong>Central nervous system</strong></td>
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<td>Glasgow Coma Scale score</td>
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<td>6–9</td>
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<td>&lt;6</td>
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<td><strong>Renal</strong></td>
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<td>300–440</td>
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<td>Urine output, mL/d</td>
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<td>&lt;200</td>
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* Catecholamine doses are given as µg/kg/min for at least 1 hour.

## References


