Prophylactic Intra-Aortic Balloon Counterpulsation for Delayed-Presentation Anterior ST-Segment Elevation Myocardial Infarction: A Prospective, Multicentre, Randomised Controlled Trial (PROACTIVE-AMI)

Study Protocol

Study type: Investigator-initiated

Sponsoring institution: Qilu Hospital of Shandong University

Version: 1.6

Version date: 17 July 2026

1. Background and Rationale

The cornerstone of care in acute ST-segment elevation myocardial infarction (STEMI) is the earliest possible restoration of flow in the infarct-related artery (IRA), so as to salvage the greatest possible amount of myocardium.[1] With continued refinement of the techniques and workflows of primary percutaneous coronary intervention (PPCI), in-hospital treatment delays have been substantially shortened; however, pre-hospital delay—which accounts for a larger proportion of total ischaemic time—remains unresolved, such that delayed reperfusion is still commonplace in routine practice.

Pre-hospital delay is a globally shared and long-standing challenge. The Swedish SWEDEHEART registry (1998–2017, n=89,155) showed that the median pre-hospital delay in patients with STEMI was as long as 2.5 hours (150 minutes) and had not improved appreciably over the preceding two decades.[2–3] United States data from 2018–2021 likewise showed that, among patients with STEMI transported by emergency medical services (EMS), the median symptom-onset-to-balloon time remained 148 minutes (approximately 2.5 hours); it was longer among self-presenting patients (195 minutes) and reached 240 minutes (4 hours) among those transferred from another hospital.[4] In China the problem is even more pronounced: the CAMI registry reported a median total ischaemic time of 5.5 hours in patients with STEMI, of which pre-hospital delay accounted for approximately 4 hours.[5–6]

Why is pre-hospital delay so critical? Beyond 120 minutes of myocardial ischaemia, the proportion of salvageable myocardium declines steeply, with necrosis extending from the subendocardium towards the epicardium in a "wavefront" pattern.[7–8] A subgroup analysis of the HORIZONS-AMI trial directly confirmed this time-dependent relationship: among patients with a symptom-to-balloon time (SBT) exceeding 4 hours, the risk of microvascular obstruction was increased 2.08-fold (OR 2.08; $P<0.0001$), and 3-year mortality rose from 2.6% in those with SBT ≤2 h to 7.2% in those with SBT >4 h ($P=0.007$).[9] In patients presenting late with anterior STEMI, myocardial necrosis is more extensive, reperfusion injury more marked, and the risk

of no-reflow higher; the risks of cardiogenic shock, heart failure and mechanical complications rise sharply, and both short- and long-term mortality remain high.[10]

Existing mechanical circulatory support (MCS) strategies face an evidentiary impasse of "rescue after the event." MCS devices are currently used chiefly as salvage therapy after cardiogenic shock has already developed; yet large randomised controlled trials such as IABP-SHOCK II (2012)[11] and ECLS-SHOCK (2023)[12] have failed to demonstrate a survival benefit in patients with established shock. The DanGer Shock trial (2024) was the first to show that the Impella CP reduced 180-day mortality in patients with STEMI complicated by cardiogenic shock (45.8% vs 58.5%; HR 0.74; P=0.04), but at the cost of a marked excess of severe bleeding (24.0% vs 6.2%) and limb-ischaemia complications, alongside a high device cost that limits broad adoption.[13] Taken together, this evidence suggests that once cardiogenic shock has developed, even MCS can seldom reverse the lethal pathophysiological cascade already set in motion. There is therefore a pressing need to shift clinical strategy from "rescue after the event" to "early prevention."

The pathophysiological rationale for IABP provides a theoretical foundation for early prevention. Unlike patients reperfused early, those presenting late with STEMI have often progressed to irreversible necrosis, such that the moment of reperfusion readily provokes severe reperfusion injury, accompanied by marked myocardial oedema and microvascular structural disruption, with restoration of tissue-level perfusion frequently precluded by no-reflow.[14–15] By augmenting coronary perfusion pressure during diastole and reducing left ventricular afterload through systolic deflation, IABP can stabilise peri-procedural haemodynamics, improve collateral perfusion of the infarct border zone, maintain perfusion of peripheral organs, and lower myocardial oxygen demand and wall tension—thereby attenuating adverse ventricular remodelling. Against the backdrop of an unresolved "benefit-versus-risk/cost" dilemma in the broader MCS field, IABP—by virtue of its procedural simplicity, comparatively low complication risk and manageable cost—represents the most suitable tool for early intervention within the emergency-care systems of developing

countries.

The CRISP-AMI trial provides an important "signal of benefit" for prophylactic IABP. That trial was the first to explore the value of prophylactic IABP insertion in patients with anterior STEMI without shock presenting within 6 hours of onset. Although the primary endpoint (infarct size) did not differ significantly (42.1% vs 37.5%; P=0.06), an exploratory composite endpoint (death, shock, or new/worsening heart failure) was significantly reduced (5.0% vs 12.0%; P=0.03), driven primarily by the complete prevention of cardiogenic shock (0 events in the IABP group vs 5 in the control group).[16] A subsequent substudy showed that, in the very-high-risk subgroup with large anterior infarction complicated by persistent ischaemia, 6-month mortality was 0% in the IABP group versus 24% in controls (P=0.046), further suggesting that higher-risk patients derive greater benefit from IABP;[17] moreover, patients who underwent unplanned crossover IABP insertion because of clinical deterioration had a markedly worse prognosis than those receiving early prophylactic insertion, corroborating the logic that "early prophylactic support" is superior to "late rescue therapy."[18]

However, the CRISP-AMI trial enrolled only early-reperfusion patients presenting within 6 hours of onset and thus cannot address the clinical question posed by delayed presenters (4–12 hours), a group with a substantially worse prognosis; furthermore, its substudy was a small-sample subgroup analysis and is insufficient to constitute high-level evidence.

A dedicated randomised controlled trial in patients presenting late with acute anterior STEMI is therefore urgently needed to determine whether prophylactic IABP insertion before PPCI can improve clinical outcomes in this high-risk population. We accordingly hypothesise that, in such patients, prophylactic IABP insertion before PPCI significantly reduces the incidence of major adverse cardiovascular events (all-cause death, cardiogenic shock, and heart failure) at 180 days.

2. Objective

To evaluate whether, in patients presenting late (4–12 hours after onset) with acute anterior STEMI, prophylactic IABP insertion before PPCI reduces the incidence of MACE at 180 days compared with PPCI alone.

3. Study Design

This is a multicentre, randomised, open-label, blinded-endpoint (PROBE) trial. Because the IABP is an invasive haemodynamic-support device whose insertion entails femoral arterial puncture, fluoroscopic positioning of the balloon and continuous operation of the extracorporeal counterpulsation console, blinding at the level of the participant and the operator is not feasible. To minimise detection and information bias, however, a rigorous blinding mechanism has been instituted at the endpoint-assessment stage: all primary endpoint events will be centrally adjudicated by an independent Clinical Events Committee (CEC) under complete blinding to treatment allocation, and imaging endpoints will be analysed in a standardised fashion by an independent imaging core laboratory blinded to allocation. This design ensures that, within the real-world constraint of open-label treatment, the objectivity and internal validity of endpoint assessment are effectively preserved.

4. Study Population

This trial will enrol patients presenting late (4–12 hours after onset) with acute anterior STEMI. This population has prolonged ischaemic time and extensive myocardial involvement, and remains at substantial risk of cardiogenic shock, heart failure and death after PPCI; it therefore represents a population that may benefit from haemodynamic support.

4.1 Inclusion criteria (all must be met)

1) Age ≥18 years;

2) First electrocardiogram on arrival at the emergency department showing ST-segment elevation ≥2 mm in at least two contiguous anterior leads, or a

summed ST-segment elevation ≥4 mm across the anterior leads;

3) Onset of ischaemic symptoms consistent with acute myocardial infarction (e.g., chest pain, chest tightness, epigastric discomfort, or pain radiating to the left shoulder) to presentation ≥4 hours and ≤12 hours, with PPCI planned;

4) Coronary angiography confirming the IRA to be the left anterior descending artery, with complete occlusion (TIMI grade 0 flow) in a proximal segment (before the origin of the first septal or first diagonal branch);

5) Written informed consent provided by the patient or his/her legal representative.

4.2 Exclusion criteria (any one excludes)

1) Established cardiogenic shock (defined as systolic blood pressure <90 mmHg without pressor support, or a requirement for vasoactive agents to maintain blood pressure, together with blood lactate >2.0 mmol/L);

2) Established severe heart failure: Killip class III or higher before enrolment, or a requirement for non-invasive or invasive positive-pressure ventilation;

3) Established malignant arrhythmia, including cardiac arrest, ventricular fibrillation, ventricular flutter, pulseless ventricular tachycardia, or high-degree atrioventricular block;

4) Established serious mechanical complication (e.g., free-wall rupture, ventricular septal rupture, or acute severe mitral regurgitation);

5) Contraindication to IABP insertion (e.g., severe peripheral arterial disease precluding cannulation, aortic dissection, known aortic aneurysm, or known moderate-to-severe aortic regurgitation);

6) Prior myocardial infarction or known chronic heart failure (LVEF <50%);

7) Prior coronary artery bypass grafting (CABG);

8) Stroke within the preceding month, or known haemorrhagic stroke at any time;

9) Active gastrointestinal bleeding within the preceding 3 months, or any gastrointestinal condition associated with increased bleeding risk (e.g., severe oesophageal varices, active peptic ulcer);

10) Thrombolytic therapy already administered for the index event;

11) Any mechanical circulatory support device (IABP, Impella, extracorporeal membrane oxygenation [ECMO]) already initiated before coronary angiography;

12) Severe hepatic impairment (Child-Pugh class C, or ALT >5×ULN with total bilirubin >3×ULN), renal impairment (eGFR <15 mL/min/1.73 m² or long-term dialysis), or any end-stage condition with a life expectancy of less than 1 year;

13) Pregnancy or lactation;

14) Current participation in another interventional clinical trial.

5. Randomisation and Intervention

After the decision to proceed with PPCI has been made, patients will be informed of the study protocol and will provide written informed consent. Following angiography in the catheterisation laboratory, patients meeting the eligibility criteria will be allocated in a 1:1 ratio, via a central randomisation system, to the IABP group (intervention) or the standard-PCI group (control).

5.1 Intervention group (prophylactic IABP)

The IABP will be inserted and activated before opening of the IRA, at a 1:1 augmentation ratio. Peri- and post-procedural anticoagulation will follow guideline-directed standard pharmacotherapy at the investigator's discretion. IABP support is recommended to be maintained for at least 24 hours and for no longer than 72 hours. In patients with haemodynamic instability, the investigator may extend the duration of counterpulsation as clinically judged. Weaning requires satisfaction of the predefined criterion of haemodynamic stability for ≥6 hours and will employ a stepwise reduction in the augmentation ratio.

5.2 Control group (standard primary PCI)

Patients will receive guideline-recommended standard primary PCI. In patients with multivessel coronary disease, only the IRA will be treated in the acute phase; staged revascularisation of non-IRA lesions is recommended before discharge or electively thereafter, with the precise timing determined by the operator on clinical grounds.

In principle, control-group patients will not receive prophylactic IABP or other MCS during the study. IABP support may be initiated under the crossover-rescue protocol only if one of the following occurs during or after PCI: (1) sustained hypotension or cardiogenic shock during or after the procedure; (2) haemodynamically unstable sustained ventricular tachycardia or ventricular fibrillation; (3) an acute mechanical complication (e.g., mitral regurgitation or ventricular septal defect); (4) no-reflow during PCI with haemodynamic deterioration; or (5) any other situation requiring IABP insertion. In the statistical analysis, patients who cross over to rescue therapy will nonetheless be analysed strictly according to their randomised allocation in the control group, in accordance with the intention-to-treat (ITT) principle.

Patients in both groups will receive standardised pharmacotherapy in accordance with current STEMI secondary-prevention guidelines, including dual antiplatelet therapy and the titrated use of β-blockers, ACE inhibitors/ARBs, statins and mineralocorticoid receptor antagonists (MRAs), particularly in patients with LVEF ≤40%.

6. Outcomes

6.1 Primary endpoint

The primary endpoint is the first occurrence of a major adverse cardiovascular event (MACE) within 180 days after randomisation. The pre-specified MACE composite comprises three event types: all-cause death, cardiogenic shock, and new or worsening heart failure.

All-cause death is defined as death from any cause within 180 days after randomisation. Death will be confirmed by inpatient records, discharge summaries,

death certificates, emergency-department records, follow-up records, death registries, or other verifiable medical sources. Provided that death during the specified follow-up period can be confirmed, it will be counted towards the all-cause-death component regardless of whether the cause is established. The date and, where available, the cause of death will be recorded by the investigator; classification of the cause as cardiac, non-cardiac, or undetermined will be adjudicated by the independent CEC under blinding to treatment allocation. An undetermined cause of death does not preclude counting the event towards the all-cause-death component.

Cardiogenic shock is defined as sustained failure of myocardial pump function occurring after randomisation, together with concurrent sustained hypotension and end-organ hypoperfusion. Patients must meet both of the following: first, systolic blood pressure persistently below 90 mmHg for at least 30 minutes, or a requirement for vasoactive or inotropic agents to maintain systolic blood pressure at ≥90 mmHg; and second, evidence of end-organ hypoperfusion, including elevated blood lactate, oliguria, altered mental status, cold and clammy skin, poor peripheral perfusion, or other manifestations of hypoperfusion accepted by the CEC. Blood lactate may serve as an important objective indicator of end-organ hypoperfusion, with a level >2.0 mmol/L supporting the adjudication of cardiogenic shock; however, a lactate measurement is not mandatory in every case.

New or worsening heart failure is defined as the appearance of new or markedly worsened symptoms or signs of heart failure within 180 days after randomisation, supported by corresponding objective evidence, together with the receipt of intensified therapy for heart failure or an unplanned hospitalisation, emergency-department visit or other unplanned healthcare encounter for heart failure. Symptoms or signs of heart failure include dyspnoea, orthopnoea, pulmonary rales, pulmonary oedema, jugular venous distension and peripheral oedema; objective evidence includes imaging showing pulmonary congestion or oedema, echocardiographic or haemodynamic findings indicating worsening cardiac function or elevated filling pressures, and a supportive rise in BNP/NT-proBNP. Intensified

therapy for heart failure includes intravenous loop diuretics, intravenous vasodilators, inotropic agents, vasoactive agents, non-invasive or invasive mechanical ventilation, or mechanical circulatory support for heart failure. An isolated fall in LVEF, an isolated rise in BNP/NT-proBNP, or an adjustment of oral medication alone does not constitute sufficient grounds for a heart-failure event; all suspected heart-failure events will be adjudicated by the independent CEC under blinded conditions on the basis of the relevant clinical data.

The primary endpoint will be analysed using time-to-event methods. The origin of time is the moment of randomisation, and the event time is defined as the first time at which the criteria for any MACE component are met. Where a single participant experiences more than one MACE component within 180 days, only the earliest event will be counted towards the primary composite endpoint; the individual occurrence of each MACE component will be reported separately among the secondary endpoints. Where a single clinical course simultaneously meets the criteria for more than one MACE component, the primary composite endpoint will be counted only once, with the CEC classifying the component according to the timing and predominant clinical presentation of the event.

6.2 Secondary endpoints

The following secondary endpoints are all pre-specified analyses without adjustment for multiplicity; their results are to be regarded as hypothesis-generating and should not serve as the basis for confirmatory conclusions. All secondary endpoints will be reported with point estimates, 95% confidence intervals and nominal P values.

1) The individual incidence of each MACE component at 180 days (all-cause death, cardiogenic shock, heart failure);

2) Cardiac death at 180 days;

3) Length of hospital stay;

4) NT-proBNP at 90 and 180 days;

5) Left ventricular ejection fraction (LVEF) at 90 and 180 days;

6) Left ventricular end-diastolic volume (LVEDV) at 90 and 180 days.

6.3 Safety endpoints

The safety endpoints encompass the following, all assessed within a 30-day follow-up window:

1) Major bleeding: BARC type 3–5 bleeding events, including access-site and non-access-site bleeding;

2) Major vascular complications: ischaemia of the access limb, pseudoaneurysm (diameter >2 cm or requiring intervention) or arterial dissection requiring surgical or endovascular repair;

3) Thrombocytopenia (platelet count $<100\times10^9$/L or a >50% decline from baseline);

4) Stroke: including ischaemic and haemorrhagic stroke, adjudicated by the CEC on the basis of imaging and neurology consultation.

6.4 Follow-up

All participants will undergo daily clinical assessment during hospitalisation, including vital signs, laboratory tests, electrocardiographic monitoring and recording of clinical events. After discharge, follow-up will be conducted at 30 days (±7 days), 90 days (±14 days) and 180 days (±14 days); in-person clinic visits are preferred, supplemented by structured telephone follow-up for those unable to attend. Imaging assessments are scheduled at three time points: baseline (3–10 days after the procedure), 90 days and 180 days. For participants lost to follow-up, the study team will make at least three telephone contact attempts within each follow-up window (≥48 hours apart); if these fail, confirmation will be sought through the participant's designated emergency contact, and vital status will ultimately be verified through the medical-insurance database and the household-registration system, so as to ensure completeness of the primary endpoint.

7. Sample-Size Estimation

The primary endpoint is the first occurrence within 180 days after randomisation of a major clinical composite comprising all-cause death, cardiogenic shock, and new or worsening heart failure.

The estimated 180-day primary-endpoint event rate in the control group is derived from our institution's historical EAST-STEMI cohort. Screened according to inclusion criteria similar to those of the present trial—delayed-presentation anterior STEMI, symptom-onset-to-presentation of 4–12 hours, complete proximal LAD occlusion, and standard PPCI—this cohort comprised 314 patients, among whom the 180-day primary composite endpoint occurred in 61, an event rate of 19.4%.

In the CRISP-AMI trial, the composite of death, cardiogenic shock or heart failure occurred in 5.0% versus 12.0% of patients with anterior STEMI without cardiogenic shock, a relative risk of approximately 0.42. Given the differences between CRISP-AMI and the present trial in symptom-to-presentation time, patient-selection characteristics and endpoint definitions, we have not adopted its observed effect size directly, but have instead pre-specified that IABP will reduce the risk of the first primary composite event by 50% relative to standard PPCI (HR 0.50).

Calculations were performed using the Logrank Tests (Freedman) procedure in PASS 15.0.5. At a two-sided significance level of α=0.05, 80% power and 1:1 randomisation, an estimated 71 primary-endpoint events are required, corresponding to a base total sample size of 477. Allowing for approximately 5% loss to follow-up or unevaluable primary endpoints, the final planned enrolment is 504 patients—252 in the intervention group and 252 in the control group.

8. Statistical Analysis

8.1 Analysis populations

Five analysis populations are pre-specified:

The intention-to-treat (ITT) population is the primary analysis population and

comprises all randomised patients, irrespective of the treatment actually received; patients are analysed strictly according to their randomised allocation, so as to preserve the baseline comparability conferred by randomisation and to avoid attrition bias.

The modified intention-to-treat (mITT) population excludes, from the ITT population, patients found after randomisation not to meet key eligibility criteria.

The per-protocol (PP) population further excludes, from the mITT population, patients with a major protocol violation, including intervention-group patients in whom the IABP was not inserted and activated before opening of the IRA; control-group patients who received IABP or other MCS without meeting the pre-specified rescue-crossover criteria; serious violation of the eligibility criteria; and patients with a missing and unadjudicable primary endpoint. Protocol-permitted rescue IABP crossover in the control group is not defined as a protocol violation but will be handled in the PP analysis as pre-specified in the statistical analysis plan; the primary analysis will remain a strictly randomised ITT analysis.

The as-treated population regroups patients according to the treatment actually received and is used to assess the influence of treatment crossover on the effect estimate.

The safety population comprises all patients who underwent any study-related procedure (puncture, coronary angiography, PCI or IABP insertion).

The primary analysis of the primary endpoint is based on the ITT population, with the PP and as-treated analyses serving as sensitivity analyses.

8.2 Primary analysis

The primary endpoint is the first occurrence of MACE within 180 days after randomisation. The primary analysis follows the intention-to-treat principle, with all randomised participants analysed according to their randomised allocation. MACE-free survival curves will be estimated for the two groups using the

Kaplan–Meier method, and the 180-day cumulative MACE incidence derived therefrom as one minus the 180-day MACE-free survival probability. Between-group differences will be compared using a log-rank test stratified by the pre-specified randomisation stratification factors. A stratified Cox proportional-hazards model will be used to estimate the hazard ratio (HR) for the IABP group relative to the control group and its two-sided 95% confidence interval, with the stratification factors consistent with those of the log-rank test.

The event time is defined as the interval from randomisation to the first occurrence of any MACE component. Participants without MACE will be censored at 180 days after randomisation; participants lost to follow-up before 180 days without prior MACE will be censored at the date of last confirmed MACE-free status. The primary analysis will use a two-sided significance level of $\alpha=0.05$. Per-protocol analysis and any necessary covariate-adjusted analysis will serve as sensitivity analyses; the principal conclusions rest on the pre-specified primary analysis in the ITT population.

8.3 Secondary-endpoint analysis

All secondary endpoints will be reported with effect sizes, two-sided 95% confidence intervals and nominal P values, without adjustment for multiplicity; the results are intended chiefly for effect-size estimation and hypothesis generation and do not serve as the basis for confirmatory conclusions. The individual 180-day MACE components—all-cause death, cardiogenic shock, and new or worsening heart failure—will be analysed using the Kaplan–Meier method and Cox proportional-hazards models, reporting cumulative event incidence, HR and 95% confidence interval. Other time-to-event endpoints, such as cardiac death, will undergo similar exploratory analysis. Other binary endpoints will be analysed using the chi-square or Fisher exact test, reporting event rates, relative risk (RR) and risk difference (RD) with 95% confidence intervals. Length of hospital stay will be analysed using an independent-samples t test or the Wilcoxon rank-sum test according to the data distribution. LVEF and LVEDV will be compared using analysis of covariance (ANCOVA) with the corresponding baseline value as covariate;

NT-proBNP will be natural-log-transformed before analysis by ANCOVA.

The safety endpoints will be analysed in the safety population; categorical variables will be analysed using the chi-square or Fisher exact test, reporting event rates with 95% confidence intervals. The analyses of individual MACE components and other secondary endpoints do not carry independent confirmatory statistical power and serve chiefly to assess the direction and magnitude of the treatment effect.

8.4 Pre-specified subgroup analyses

The following subgroups are pre-specified for stratified analysis: symptom-onset-to-door time (4–8 h vs 8–12 h), age (<65 vs ≥65 years), sex (male vs female), diabetes (present vs absent) and coronary-lesion complexity (SYNTAX score ≤22 vs >22). Each subgroup analysis will incorporate a subgroup-by-treatment interaction term in the Cox model, with $P<0.10$ as the threshold for an interaction effect. All subgroup results will be displayed as forest plots showing the HR and 95% CI for each subgroup. It must be emphasised that all subgroup analyses are hypothesis-generating, are not adjusted for multiplicity, and should not serve as the basis for confirmatory conclusions.

8.5 Handling of missing data

Vital status for the primary endpoint (MACE) will be ascertained through multiple channels—clinic follow-up, telephone follow-up, emergency-contact tracing, medical-insurance database queries and household-registration verification—with an anticipated missing rate of <3%. For patients with remaining missingness, the following sensitivity analyses will be performed: (i) a worst-case analysis, assuming all missing patients in the IABP group died and all missing patients in the control group survived; (ii) a best-case analysis, assuming the converse; and (iii) a tipping-point analysis, systematically increasing the proportion of deaths among missing IABP-group patients to determine the minimum missing-to-death proportion required to reverse the primary conclusion, so as to assess the robustness of the result to assumptions about missing data. Missing continuous variables will be handled

under the missing-at-random (MAR) assumption using a mixed model for repeated measures (MMRM), with multiple imputation (m=50) as a sensitivity analysis.

8.6 Interim analysis

One formal interim analysis is planned at approximately 50% of the planned information, operationally when approximately 50% of randomised participants have completed 180-day follow-up and the corresponding primary-endpoint events have been adjudicated. Alpha spending will follow the Lan-DeMets α-spending function approximating an O'Brien-Fleming boundary. At 50% information, the efficacy-stopping boundary is approximately $P<0.003$ ($Z\approx2.96$), and the significance boundary at the final analysis is approximately $P<0.047$. Futility stopping will use a conditional-power rule: if, under the currently observed data and assuming the true effect equals the alternative hypothesis, the calculated conditional power is <10%, the independent Data and Safety Monitoring Board (DSMB) may recommend stopping the trial for futility. Safety stopping is not bound by a pre-specified boundary; the DSMB may, at any time and on the basis of accumulating safety data (in particular, a rate of severe bleeding or vascular complications in the IABP group markedly higher than anticipated), recommend suspending enrolment or terminating the trial. The interim analysis will be performed unblinded by an independent statistician, with results submitted only to the DSMB; investigators and the CEC will remain blinded.

All statistical analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) or R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The statistical analysis plan (SAP) will be finalised and publicly registered before database lock.

9. Risk–Benefit Assessment

9.1 Risk analysis

This trial involves intra-aortic balloon insertion and percutaneous coronary intervention, with potential risks including:

1) Risks related to IABP insertion: access-site bleeding, haematoma, pseudoaneurysm, retroperitoneal haemorrhage, limb ischaemia, aortic dissection, balloon rupture and thrombocytopenia;

2) Risks related to PPCI: coronary dissection, perforation, no-reflow, stent thrombosis and arrhythmia;

3) Risks related to antiplatelet/anticoagulant therapy: bleeding events (including gastrointestinal and intracranial haemorrhage);

4) Risks related to the underlying disease of the study population: cardiogenic shock, worsening heart failure, malignant arrhythmia and cardiac death.

These risks have well-established management protocols in current clinical practice. All members of the study team have undergone standardised IABP training, and vital-sign monitoring, bleeding-risk assessment and vascular-complication screening will be rigorously undertaken during and after the procedure. Clear management pathways and a crossover-rescue protocol have been established for anticipated serious adverse events.

9.2 Benefit analysis

For patients presenting late (4–12 hours after onset) with acute anterior STEMI, there is at present no evidence base for prophylactic mechanical circulatory support specific to this population. This trial seeks to determine whether prophylactic IABP insertion before PPCI reduces the 180-day incidence of MACE. Should the study hypothesis hold, participants may derive direct benefits including a reduced risk of cardiogenic shock, improved cardiac function, fewer heart-failure events and lower mortality. In addition, participants will receive closer follow-up and monitoring than in routine practice, facilitating the timely detection and management of potential complications.

On balance, the risks of this trial fall within a controllable range, and the anticipated scientific value and societal benefit outweigh the risks that participants may bear.

10. Safety Monitoring and Data Management

10.1 Independent Data and Safety Monitoring Board

An independent DSMB will be established before the trial begins. The Board will comprise five independent experts with no conflict of interest with the study (planned to include two interventional cardiologists, one biostatistician, one methodologist and one ethicist). The DSMB is responsible for periodically reviewing the accumulating safety data and interim-analysis results during the study, and for advising the Steering Committee on whether to amend the protocol or terminate the trial early.

Operating procedures: review meetings are planned before enrolment of the first patient (at which point a detailed charter will be drafted and confidentiality agreements signed) and every 6 months thereafter, or every 50 patients enrolled, whichever comes first. To avoid introducing bias, only DSMB members and the designated independent statistician may access unblinded allocation data. The DSMB's membership and formal charter will be finalised before enrolment of the first patient and filed with the ethics committee.

10.2 Clinical Events Committee

To ensure objectivity of endpoint assessment, an independent CEC will be established before database lock and unblinding. The Committee is planned to comprise at least three independent cardiovascular specialists with extensive clinical-trial experience who are not involved in the study. The CEC is responsible for the centralised, blinded adjudication of all primary and key secondary endpoint events, in complete ignorance of patients' allocation, in accordance with a pre-specified unified adjudication charter.

Operating procedures: adjudication will employ an independent, back-to-back, two-reviewer system; where the two reviewers disagree, the matter will be referred to a third senior member of the Committee for final arbitration. The CEC's membership and detailed adjudication charter will be finalised during the start-up phase and formally endorsed by all members before the first endpoint adjudication.

10.3 Data management

Clinical data will be collected and managed using a validated electronic data capture (EDC) system. Preset logical validation rules (range, consistency and completeness checks) will automatically generate queries for outliers and missing data. Key variables will undergo independent double data entry with consistency checking, and discrepancies will be resolved by reference back to source documents.

10.4 Quality control

Site eligibility requirements: participating sites must be tertiary hospitals with an annual emergency-PCI volume of ≥200 cases, with investigators proficient in the use of IABP. All candidate sites will undergo qualification review and feasibility assessment before trial initiation.

Investigator training: all study personnel must complete GCP training and obtain the corresponding certificate. Study-specific training includes protocol training (covering interpretation of inclusion/exclusion criteria and the randomisation workflow), standardised IABP training (device selection, timing of insertion, weaning procedures and complication management), and EDC-system training.

10.5 Ethics statement

The study protocol and informed-consent form will be submitted for review and approval to the ethics committee/institutional review board (IRB/IEC) of each participating site before initiation; other sites may commence ethics submission only after the sponsoring institution's ethics committee has granted initial approval. The design and conduct of the study will strictly comply with the Declaration of Helsinki (2013 revision), ICH-GCP E6(R2), and all requirements of China's Good Clinical Practice for Drug Clinical Trials (2020 edition). All participants or their legal representatives must provide written informed consent before any study-related procedure.

This study does not represent a generalisation of the clinical indications for IABP. The

conventional indications for IABP are acute myocardial infarction complicated by cardiogenic shock, mechanical complications, or haemodynamic support for high-risk PCI. The focus of this study is a specific subpopulation with an exceptionally poor prognosis but for which no dedicated evidence base yet exists—large anterior STEMI with delayed reperfusion. Because of prolonged ischaemic time, large infarct size and severe microvascular injury, this population is highly prone to haemodynamic collapse during and after PPCI. From a pathophysiological standpoint, prophylactic IABP is intended to provide "pre-emptive circulatory protection" and constitutes a "forward shift" of therapeutic strategy rather than an "expansion" of indications. Through rigorous inclusion criteria (anterior STEMI, complete proximal LAD occlusion, TIMI grade 0, symptom onset 4–12 hours), the study precisely delineates the target population; the exclusion criteria simultaneously specify contraindications to IABP insertion (severe peripheral arterial disease, aortic dissection/aneurysm, moderate-to-severe aortic regurgitation) and patients already requiring therapeutic MCS, ensuring that the intervention is confined to the high-risk subgroup most likely to benefit—in keeping with the ethical principles of risk minimisation and a reasonable expectation of benefit.

The IABP balloon catheters and associated consumables used in the intervention group will be funded by the project's research budget, and participants will bear no cost for these consumables. Clinical-trial liability insurance will be purchased for all participants, providing free treatment and reasonable financial compensation for any injury sustained through participation in the study. Enrolment will commence only after registration of the study on ClinicalTrials.gov.

11. Adverse Events and Contingency Plans

11.1 Definition of adverse events

An adverse event (AE) is any untoward medical occurrence in a participant during the study (from signing of informed consent to the end of 180-day follow-up), manifesting as a symptom, sign, laboratory abnormality or device-related abnormality,

whether or not causally related to the study procedures (IABP insertion, PPCI) or study workflow.

Anticipated adverse events (potentially common in this study):

1) IABP-related: access-site bleeding/haematoma, pseudoaneurysm, retroperitoneal haemorrhage, limb ischaemia, aortic dissection, balloon rupture, thrombocytopenia, haemolysis;

2) PPCI-related: coronary dissection, perforation, no-reflow, stent thrombosis, arrhythmia (VF, VT), contrast-induced nephropathy;

3) Antiplatelet/anticoagulant-related: gastrointestinal bleeding, gingival bleeding, cutaneous ecchymosis, intracranial haemorrhage;

4) Underlying-disease-related: worsening heart failure, cardiogenic shock, recurrent myocardial infarction, cardiac death.

Unanticipated adverse events: adverse events not clearly listed in the existing literature or the IABP product labelling and judged by the investigator to be possibly related to the study procedures.

11.2 Definition of serious adverse events

A serious adverse event (SAE) is any medical occurrence at any dose or during any procedure that meets one or more of the following: death; life-threatening; requiring hospitalisation or prolongation of hospitalisation; resulting in permanent or significant disability/incapacity; or requiring intervention to prevent permanent impairment. This study focuses particularly on cardiac death, major bleeding (BARC 3–5), vascular complications requiring surgical intervention, cardiac mechanical complications, stroke, and acute renal failure requiring dialysis.

11.3 Recording and reporting of adverse events

Every adverse event, whether or not serious and whether or not related to the study intervention or procedures, must be recorded on the case report form. For participants

who withdraw because of an adverse event, the investigator should continue to visit them until recovery, or until the principal investigator/investigator judges that further follow-up is unnecessary, and record accordingly. The dates of onset and resolution of the adverse event should be noted on the case report form. For serious adverse events (SAEs), the investigator must report to the sponsoring institution, the principal investigator and the site's ethics committee within 24 hours of becoming aware, and complete subsequent written reporting in accordance with each site's ethics-committee and applicable regulatory requirements. All SAEs must be followed until the event has resolved, stabilised, reached a clear outcome, or the investigator judges that further follow-up is unnecessary. SAEs suspected of being related to the IABP device or to study procedures must additionally be reported in accordance with medical-device clinical-research and hospital management requirements.

12. Study Organisation

12.1 Sponsoring institution

Institution: Qilu Hospital of Shandong University

Principal investigators: Yuguo Chen, Chuanbao Li

Address: 107 Wenhua West Road, Lixia District, Jinan, Shandong Province

Responsibilities: study protocol design, initial ethics approval, management of the central randomisation system, data management and statistical analysis, establishment and coordination of the DSMB and CEC, training and quality control of the participating sites, and overall study coordination and progress management.

12.2 Participating sites

1) Fuwai Hospital, Chinese Academy of Medical Sciences — Principal investigator: Qing Gu
2) Jining No. 1 People's Hospital — Principal investigator: Daqing Song
3) The Affiliated Hospital of Qingdao University — Principal investigator: Peng Li

Note: additional participating sites will be added according to enrolment progress, with separate ethics submissions made at that time.

The shared responsibilities of each participating site include: screening and enrolment of participants according to the protocol, obtaining informed consent, randomisation, IABP insertion or standard PCI, in-hospital management, post-discharge follow-up at 30/90/180 days, entry of clinical data into the EDC system, and adverse-event reporting.

13. Funding and Materials

13.1 Funding source

This is an investigator-initiated clinical study with no external commercial sponsor. The operational funding required (including but not limited to participant insurance, subsidies for study-related investigations, data management, statistical analysis, and meeting and travel expenses) is provided as an unrestricted research grant by Teleflex Medical Trading (Shanghai) Co., Ltd. The funder plays no part in the design or conduct of the study, in data collection or analysis, in interpretation of the results, or in manuscript preparation. The investigators retain full ownership of all study data and of the published findings.

13.2 Conflict-of-interest statement

The members of the study team declare no employment relationship, equity holding or consultancy relationship with Teleflex Medical Trading (Shanghai) Co., Ltd. The company provides only funding and study consumables and has imposed no restrictive conditions on the study design or results.

14. Participant Withdrawal and Study Termination

Participants may withdraw their informed consent and voluntarily leave the study at any time, without any effect on their subsequent routine medical care. At withdrawal, the investigator should clearly record whether the participant is withdrawing only from further follow-up or is completely revoking permission to use all data already

collected. Unless the participant explicitly requests deletion of their data, data already collected will be included in the final analysis; for the primary endpoint, the study team will make every effort to ascertain vital status through public databases. If IABP is removed early in the intervention group because of complications, or the control group crosses over to IABP because of clinical deterioration, participants should nonetheless complete all follow-up according to their original randomised allocation, and their data will be analysed on the intention-to-treat (ITT) principle. Any early termination of the trial requires a recommendation from the independent DSMB and the approval of the Steering Committee and ethics committee before it may be enacted.

15. Protocol Deviations and Amendments

15.1 Protocol deviations

A protocol deviation is any intentional or unintentional act or record that departs from the ethics-committee-approved protocol. Protocol deviations are classified as:

Minor deviations: those with no substantive impact on participants' rights, safety or the integrity of the study results, such as a minor breach of a follow-up window or the omission of individual secondary data. Minor deviations are recorded after assessment by the principal investigator (PI) and need not be reported separately to the ethics committee.

Major deviations: those that may affect participant safety, rights, or the scientific integrity of the study results—for example, enrolment of a patient not meeting the inclusion criteria or meeting an exclusion criterion, performance of a study procedure without informed consent, use of a prohibited medication, or failure to report a serious adverse event (SAE) as required. Major deviations must be reported to the ethics committee within 5 working days of becoming aware, with an explanation of the cause and corrective measures.

All protocol deviations must be recorded in the EDC and summarised descriptively in the statistical analysis plan.

15.2 Protocol amendments

Should a substantive amendment to the protocol be required during the study (including but not limited to changes to the inclusion/exclusion criteria, the primary endpoint, the intervention, or the sample size), the investigator must submit an amendment application to the ethics committee and may implement it only after written approval. Non-substantive changes (such as typographical corrections or updates to contact details) may be implemented after filing. All protocol amendments must be updated promptly on ClinicalTrials.gov.

16. Confidentiality

Participants' personal information will be kept strictly confidential in accordance with the Personal Information Protection Law of the People's Republic of China and related laws and regulations. Each participant will be assigned a unique study number, and all electronic data and biological samples will be identified by this number, without directly displaying the participant's name, identity-card number, or other identifying information.

Information that could identify a participant (e.g., original informed-consent forms, screening records) will be stored in locked filing cabinets at the study institution, accessible only to authorised members of the study team.

Publications and academic presentations of the study data will present only aggregate statistical results and will not disclose any content that could identify a specific participant. When discharging their monitoring, audit or inspection duties, the sponsoring institution, project management, monitors and regulatory authorities may access participants' coded data without breaching the principle of confidentiality, but may not remove identifying information from the study institution.

17. Study Timeline

The total planned duration of the study is 24 months, with enrolment expected to commence after ethics approval and completion of ClinicalTrials.gov registration. Study preparation and conduct are anticipated to run from August 2026 to July 2028,

with the precise date of enrolment commencement contingent on the timing of ethics approval and registration.

18. References

[1]2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes. *Circulation.* 2025.

[2]Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J.* 2017;38(41):3056-3065.

[3]Ericsson M, Alfredsson J, Strömberg A, Thylén I, Sederholm Lawesson S. Temporal trends and prognostic impact of pre-hospital delay in ST-elevation myocardial infarction—20-year observational study from the SWEDEHEART registry. *Eur Heart J Acute Cardiovasc Care.* 2025;zuaf165.

[4]Jollis JG, Granger CB, Zègre-Hemsey JK, et al. Treatment Time and In-Hospital Mortality Among Patients With ST-Segment Elevation Myocardial Infarction, 2018-2021. *JAMA.* 2022;328(20):2033-2040.

[5]Song F, Yu M, Yang J, et al. Symptom-Onset-To-Balloon Time, ST-Segment Resolution and In-Hospital Mortality in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention in China: From China Acute Myocardial Infarction Registry. *Am J Cardiol.* 2016;118(9):1334-1339.

[6]Yang J, Zhao Y, Wang J, et al. Current status of emergency medical service use in ST-segment elevation myocardial infarction in China: Findings from China Acute Myocardial Infarction (CAMI) Registry. *Int J Cardiol.* 2024;406:132040.

[7]Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. *Circulation.* 1977;56(5):786-794.

[8]Redfors B, Mohebi R, Giustino G, et al. Time delay, infarct size, and microvascular obstruction after primary percutaneous coronary intervention for

ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv.* 2021;14(1):e009879.

[9]Prasad A, Gersh BJ, Mehran R, et al. Effect of Ischemia Duration and Door-to-Balloon Time on Myocardial Perfusion in ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv.* 2015;8(15):1966-1974.

[10]Elbadawi A, Elgendy IY, Mahmoud K, et al. Temporal Trends and Outcomes of Mechanical Complications in Patients With Acute Myocardial Infarction. *JACC Cardiovasc Interv.* 2019;12(18):1825-1836.

[11]Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. *N Engl J Med.* 2012;367(14):1287-1296.

[12]Thiele H, Zeymer U, Akin I, et al. Extracorporeal Life Support in Infarct-Related Cardiogenic Shock. *N Engl J Med.* 2023;389(14):1286-1297.

[13]Møller JE, Engstrøm T, Jensen LO, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. *N Engl J Med.* 2024;390(15):1382-1393.

[14]Targeting an Ischemic Time <120 Minutes in ST-Segment–Elevation Myocardial Infarction. *J Am Heart Assoc.* 2019.

[15]Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2009;54(23):2145-2153.

[16]Patel MR, Smalling RW, Thiele H, et al. Intra-aortic Balloon Counterpulsation and Infarct Size in Patients With Acute Anterior Myocardial Infarction Without Shock: The CRISP AMI Randomized Trial. *JAMA.* 2011;306(12):1329-1337.

[17]van Nunen LX, van 't Veer M, Schampaert S, et al. Intra-aortic balloon counterpulsation reduces mortality in large anterior myocardial infarction complicated by persistent ischaemia: a CRISP-AMI substudy. *EuroIntervention.* 2015;11(3):286-292.

[18]Kohl LP, Leimberger JD, Chiswell K, et al. Clinical characteristics and outcomes after unplanned intraaortic balloon counterpulsation in the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction trial. *Am Heart J.* 2016;174:7-13.