Trials

STUDY PROTOCOL

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Intracoronary administration of tenecteplase to prevent PCI-related myocardial infarction in patients with echo-attenuated coronary plaques: study protocol for a multicenter, prospective, randomized controlled trial

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Abstract

Background Percutaneous coronary intervention (PCI)-related myocardial infarction (MI), especially the distal type associated with microvascular dysfunction, is not an uncommon complication of the procedure. Specific lesion features, the echo-attenuated plaques (EA) in particular, are well-established contributors to the pathogenesis of distal-type MI. These plaques are prone to disruption during PCI, leading to microvascular thrombosis and distal embolism. Tenecteplase (TNK), a 3rd-generation thrombolytic drug, has demonstrated effective thrombolytic capacity without significantly increasing the bleeding risk. Our study aims to evaluate whether a low-dose intracoronary TNK administration prior to PCI in patients with intravascular ultrasound (IVUS)-detected EA can reduce the occurrence of PCI-related MI and improve clinical outcomes.

Methods This trial is designed as a multicenter, prospective randomized controlled trial with a 1-month follow-up. The primary outcome of the study is the incidence of PCI-related myocardial infarction (MI) occurring within 48 h after PCI, which serves as a valid surrogate endpoint for assessing the efficacy of tenecteplase-based PCI in preventing future major adverse cardiovascular events (MACE) in patients with EA (Bulluck, et. al, Eur Heart J 42:2630–42, 2021) {1b.1}. Secondary outcomes include the proportion of patients with elevated postoperative high-sensitivity cTnI exceeding 5, 10, 35, and 70 times of the normal baseline, incidence of coronary slow flow after stent implantation and post-dilation, frame count of angiographic flow after stent implantation and post-dilation, as well as the incidence of MACE during hospitalization and at the 1-month follow-up.

Discussion This trial may demonstrate that an immediate intracoronary administration of low-dose TNK following PCI can effectively lower the incidence of PMI in patients with EA, while confirming the safety of this therapeutic approach.

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Trial registration Chinese Clinical Trial Registry (ChiCTR2400084840). Registered on May 27, 2024.

Keywords Peri-procedural myocardial infarction, Coronary artery disease, Echo-attenuated plaque, Percutaneous coronary intervention, Tenecteplase, Major adverse cardiovascular events

Introduction

Background and rationale {6a}

Percutaneous coronary intervention (PCI) is currently the main revascularization strategy for obstructive coronary artery disease (CAD). However, periprocedural myocardial infarction (PMI), which is defined as a significant elevation of troponin within 48 h after PCI accompanied by clinical features of myocardial ischemia (MI) [1], is not uncommon. PMI has emerged as a frequent and severe complication of PCI, with incidences ranging from 5 to 50%, varying by different criteria and definition [2, 3]. Clinically, PMI draws attention as it significantly increases the risk of major adverse cardiovascular events (MACE) [4].

PCI-related MI can be categorized into proximal and distal types. The proximal type occurs adjacent to the stent-implanted segment, typically due to dissection and side branch occlusion. The distal type, whereas, is more common, affecting 50% to 75% of cases. Its underlying pathophysiology is associated with microvascular dysfunction, including microembolism and vasospasm [5]. Notably, lesion characteristics are the main factors contributing to the development of distal-type PMI. Previous intravascular ultrasound (IVUS) studies have demonstrated a strong association between high plaque burden, echo-attenuated plaque (EA), or necrotic plaque and PCI-related MI [6, 7]. These plaques are prone to disruption during PCI, potentially leading to lipid leakage and the release of thrombogenic components into the coronary circulation, eventually causing microvascular thrombosis and distal embolism.

Low-dose intracoronary administration of thrombolytics has shown potential in inducing fibrinolysis and rapid dissolution of thrombi without significant adverse events [8–10]. Among these agents, TNK exhibits high specificity and efficient thrombolysis capacity without increasing the risk of systemic bleeding. Its intracoronary administration during PCI has been linked to significantly improved perfusion of the coronary arteries and microcirculation system [11–13]. Therefore, this study hypothesizes that the preventive use of low-dose TNK during elective PCI in CAD patients with EA, as identified by IVUS, may inhibit local thrombus activation, improve distal microcirculation perfusion, reduce the occurrence of distal type PMI, and potentially improve clinical prognosis.

Evidence before this study

To address vasospasm and the no-reflow phenomenon in distal type PMI, the use of coronary vasodilators (e.g., calcium channel blockers, nitroglycerin, sodium nitroprusside, or adenosine) might be beneficial, although the superiority of any specific agent remains unclear. Glycoprotein IIb/IIIA (GP IIb/IIIa) receptor inhibitors are recommended (ESC IIa Class C) for specific salvage therapies, including cases with high thrombus burden and instances of slow or no-reflow during the procedure [14]. However, GP IIb/IIIa receptor inhibitors may not be beneficial for AMI patients with high thrombus burden, as fibrin-rich fresh thrombi are less responsive to GPI therapy. The Chinese Expert Consensus on Microvascular Protection Strategy during Emergency PCI Therapy in Patients with ST-Elevation Myocardial Infarction (STEMI) recommends the use of intracoronary urokinase or TNK for targeted thrombolysis in cases with high coronary thrombus burden [15]. Kelly et al. also found that intracoronary TNK is safe and well-tolerated in patients experiencing thrombotic complications during complex PCI, showing consistent efficacy regardless of GP IIb/IIIa inhibitor use [16].

Added value of this study

Despite existing knowledge of PMI pathophysiology, current research has only focused on STEMI patients, with no investigations into the preventive use of low-dose intracoronary thrombolytics in routine elective PCI patients conducted. Consequently, current practice guidelines available lack specific preventive measures for PCI-related MI. Data from our study could help inform the clinical efficacy of low-dose thrombolytic agents, providing insights that could refine clinical guidelines and improve patient care.

Objectives {7}

To determine the effectiveness of low-dose intracoronary TNK administration in preventing PCI-related MI in CAD patients with EA.

Trial design {8}

This study is a multicenter, prospective, randomized, controlled, open-label parallel-group superiority trial. Patients will be randomly allocated at a 1:1 ratio to evaluate the effectiveness of low-dose intracoronary TNK

administration in preventing PCI-related MI in CAD patients with EA. Since the primary outcome, PCI-related MI, is a surrogate endpoint to MACE and mortality, we have adhered to the SPIRIT-Surrogate reporting guidelines in our protocol [17] {8.1}. The associated checklists are submitted as Additional file 1 for reference. For additional trial registration information and the expected timeline of this study, see Table 1 and Fig. 1.

Methods: participants, interventions, and outcomes

Study set-up {9}

This study aims to enroll coronary artery disease (CAD) patients with EA confirmed by IVUS at multiple centers, including Sir Run Run Shaw Hospital affiliated with Zhejiang University School of Medicine (lead unit), The First People's Hospital of Hangzhou Lin An District, Zhejiang Greentown Cardiovascular Hospital, The Fifth People's Hospital of Hangzhou Yuhang District and Ningbo Ninth Hospital.

Eligibility criteria {10}

Inclusion criteria

Patients' inclusion criteria will be: (1) age ≥ 18 years; (2) CAD patients tolerating dual antiplatelet therapy, and clinically indicated for elective PCI; (3) IVUS confirms lesion length ≥ 20 mm and meets the characteristics of EA: plaque showing ultrasound signal attenuation (longitudinal attenuation length ≥ 5 mm), excluding calcified and dense fibrous plaques; (4) acceptance of terms and conditions of the study and signature of the informed consent form, with a full understanding of the trial content, process, and potential adverse reactions; (5) willing to adhere to medical follow-up.

Exclusion criteria

Patients' exclusion criteria include (1) positive cardiac troponin I (cTnI) prior to percutaneous coronary angiography; (2) coronary artery bypass graft (CABG) lesion; (3) chronic total occlusion (CTO); (4) in-stent restenosis; (5) severe calcification; (6) left main coronary artery disease (LMCAD); (7) intervention of > 1 major coronary artery branch in a single PCI procedure; (8) side branch occlusion or blood flow-affecting dissection during PCI; (9) cardiogenic shock during PCI; (10) vulnerable populations, such as individuals with mental disorders, cognitive impairment, critical illness, pregnancy, lactation, genetic or acquired bleeding disorders with anticoagulation factor deficiency, or current use of oral anticoagulants.

Informed consent {26a.1}

Each subject will be fully informed in writing about the purpose, nature, procedures, and potential benefits and risks of the study. Subjects should be informed that they have the right to withdraw from the study at any time. Before enrollment, each subject should be given sufficient time to consider participation. Only subjects who voluntarily sign the informed consent form after being fully informed will be included in the study. If a subject is unable to read the informed consent form (e.g., illiterate subject), a witness must observe the informed consent process and sign the informed consent form.

Who will take informed consent? {26a}

Researchers will perform an initial eligibility screening and collect written informed consent. Written informed consent will be collected prior to baseline assessment.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

If there is collection of any data that is not included in the initial informed consent process for the main clinical trial, each participant must sign an additional consent form for the ancillary study.

Interventions

Explanation for the choice of comparators {6b}

In this randomized controlled trial, participants will be randomly divided into the intervention group (intracoronary administration of 4 mL of 0.9% NaCl solution containing 4mg of TNK) and the control group (intracoronary administration of 4 mL of 0.9% NaCl solution). The control intervention allows the evaluation of TNK effects in preventing PCI-related MI. Patient education encompassing disease-related knowledge, lifestyle guidance, complication prevention, rational drug use, and other pertinent contents will also be delivered to the control group. Both the intervention group and the control group will receive standard pharmacological treatments.

Intervention description {11a}

- Experimental group: Immediate intracoronary injection of 4 mL of 0.9% NaCl solution containing 4mg of TNK following balloon angioplasty (dilation).
- Control group: Immediate intracoronary injection of 4 mL of 0.9% NaCl solution following balloon angioplasty (dilation).
- The use of other devices during PCI will be decided based on the operator's experience.

Criteria for discontinuing or modifying allocated interventions {11b}

Discontinuation from the treatment program will be considered in the following conditions:

Table 1 WHO trial registration data set

Data category	Information
Primary registry and trial identifying number	ChiCTR2400084840
Date of registration in primary registry	2024/05/27
Secondary identifying numbers	-
Source (s) of monetary or material support	Self-funded
Primary sponsor	The study received no specific sponsor
Secondary sponsor(s)	The study received no specific sponsor
Contact for public queries	Wenbin Zhang
Contact for scientific queries	Wenbin Zhang
Public title	Intracoronary administration of tenecteplase to prevent PCI-related myocardial infarction in patients enriched with attenuated signal coronary plaques
Scientific title	Intracoronary administration of tenecteplase to prevent PCI-related myocardial infarction in patients enriched with attenuated signal coronary plaques
Countries of recruitment	China
Health condition(s) or problem(s) studied	Coronary heart disease
Intervention(s)	Immediate intracoronary injection of 4 mL of 0.9% NaCl solution containing 4mg of TNK following balloon angioplasty (dilation)
(Control)	Immediate intracoronary injection of 4 mL of 0.9% NaCl solution following balloon angioplasty (dilation)
Key inclusion and exclusion criteria	-
(Inclusion criteria)	1. Age ≥ 18 years; 2. CAD patients tolerating dual antiplatelet therapy, and clinically indicated for elective PCI; 3. IVUS confirms lesion length ≥ 20 mm and meets the characteristics of EA: plaque showing ultrasound signal attenuation (longitudinal attenuation length ≥ 5 mm), excluding calcified and dense fibrous plaques; 4. Acceptance of terms and conditions of the study and signature of the informed consent form, with a full understanding of the trial content, process, and potential adverse reactions; 5. Willing to adhere to medical follow-up
(Exclusion criteria)	1. Positive cardiac troponin I (cTnI) prior to percutaneous coronary angiography; 2. Coronary artery bypass graft (CABG) lesion; 3. Chronic total occlusion (CTO); 4. In-stent restenosis; 5. Severe calcification; 6. Left main coronary artery disease (LMCAD); 7. Intervention of > 1 major coronary artery branch in a single PCI procedure; 8. Side branch occlusion or blood flow-affecting dissection during PCI; 9. Cardiogenic shock during PCI; 10. Vulnerable populations, including individuals with mental disorders, cognitive impairment, critical illness, pregnancy, lactation, genetic or acquired bleeding disorders with anticoagulation factor deficiency, or current use of anticoagulants
Study type	Interventional study
	Multicenter, prospective, randomized controlled, open-label trial
	Primary purpose: To determine the effectiveness of low-dose intracoronary TNK administration in preventing PCI-related MI in CAD patients with EA
Date of first enrolment	August 1, 2024
Target sample size	432 (Both control and experimental group)
Recruitment status	Pending
Primary outcome(s)	Incidence of PCI-related MI
Key secondary outcomes	Proportion of patients with elevated postoperative high-sensitivity cTnI exceeding 5, 10, 35, and 70 times of the normal baseline; Incidence of slow-flow after stent implantation and post-dilation; Frame count of angiographic flow after stent implantation and post-dilation; Incidence of MACE during hospitalization and post-operative 1-month follow-up

STUDY PERIOD					
	Study approvals	**Inclusion**	**Hospitalization**	**1-month follow-up**	**Close-out**
TIMEPOINT	***15/5/2024***	***August 2024 - August 2025***	***August 2024 - August 2025***	***August 2024 - August 2025***	***August 2025-***
Approvals (Ethics Committee)	X				
ENROLMENT:					
Eligibility screen		X			
Informed consent		X			
Randomization		X			
INTERVENTIONS:					
Control: 4mL 0.9%NaCl			X		
Experimental: 4mg TNK			X		
ASSESSMENTS:					
Incidence of PCI-related MI			X		
Elevation of postoperative cTnI			X		
Slow-flow incidence after stent implantation and post-dilation			X		
Angiographic flow frame count after stent implantation and post-dilation			X		
MACE incidence during hospitalization and post-operative 1-month follow-up			X	X	
DATA ANALYSIS:					
Data analyses					X
Publication					X

Fig. 1 Illustration of the research phases

(1) Participants voluntarily withdraw from the study;
(2) If the participant is unable to continue the protocol treatment due to adverse events;
(3) The researcher(s) deem continued participation to be inappropriate or detrimental to the participant.

Strategies to improve adherence to interventions {11c}

Routine follow-up is necessary for every patient who underwent PCI. Therefore, no extra measures will be taken to improve the adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

Both the intervention group and the control group will receive standard pharmacological treatments and hospital care.

Provisions for post-trial care {30}

The administration of TNK aims to prevent the occurrence of PCI-related MI. The dosage of TNK used in our trial is reported safe in other studies. If any risk of harm is identified, the principal investigator will intervene to

minimize the potential harm. Besides, the research team will provide appropriate compensation if necessary.

Outcomes {12}

Outcomes will be collected during hospitalization and again at 1-month follow-up after PCI.

Primary outcome measure

Incidence of PCI-related MI

PCI-related MI is defined as the increase of high-sensitivity cTnI to more than 5 times the 99th percentile upper reference limit (>5×99th percentile URL) within 48 h post-PCI in patients with normal baseline cTnI values. Notably, PCI-related MI is a valid surrogate endpoint for subsequent MACE [1]. The rationale for employing a surrogate endpoint, rather than a clinical endpoint, includes (a) the significantly higher incidence rates of PMI compared to MACE in post-PCI conditions, which facilitates more straightforward and efficient observation of outcomes; and (b) the primary focus of this research on PMI, which is strongly associated with increased cardiac mortality and heightened risk of future MACE [1, 18] {12.1}.

Secondary outcome measures

1. Proportion of patients with elevated postoperative high-sensitivity cTnI exceeding 5, 10, 35, and 70 times of the normal baseline.
2. Incidence of slow-flow after stent implantation and post-dilation.
3. Frame count of angiographic flow after stent implantation and post-dilation.
4. Incidence of MACE during hospitalization and postoperative 1-month follow-up.

Safety endpoints

Proportion of major bleeding (BARC bleeding classification type 2 or type 3) occurring within 24 h post-PMI.

Participant timeline {13}

The participant timeline is shown in Fig. 2.

Sample size {14}

This study is a RCT with an experimental group and a control group. The allocation ratio between the groups is 1:1. Based on previous literature and clinical data from our center, the assumed incidence rate of PCI-related MI in the control group is 20% [1, 3]. The experimental group is assumed to have a 35% lower incidence rate of PCI-related MI compared to the control group. Using a two-sided alpha of 0.05 and a power of 80%, a total sample size (*N*) of 720 patients was calculated using PASS 2023 software. Considering a 20% dropout rate due to loss to follow-up or refusal to follow-up, at least 864 subjects are required for the studies, with at least 432 subjects in each group.

Recruitment {15}

Participant recruitment will begin in August 2024 and is expected to continue until August 2025. We will recruit participants from the other four sub-centers, including The First People's Hospital of Hangzhou Lin An District, Zhejiang Greentown Cardiovascular Hospital, The Fifth People's Hospital of Hangzhou Yuhang District, and Ningbo Ninth Hospital.

Assignment of interventions: allocation

Sequence generation {16a}

This randomized controlled trial will employ a 1:1 allocation ratio on the participants. The allocation process will be managed using Electronic Data Capture (EDC), a clinical trial centralized randomization system. Researchers will access the system with unique account credentials. Upon entering a participant's information, participants will be randomly assigned following simple randomization procedures, and a randomized number generated by the system will be used to track each patient.

Concealment mechanism {16b}

Allocation concealment will be guaranteed through the following mechanisms: Staff will log in to the EDC Trial Data cloud and enter the information for the participants. The EDC system will randomly assign participants to either group in a 1:1 ratio. A unique patient profile will be generated once all necessary baseline information is entered. Access to these data requires authorized account credentials.

Implementation {16c}

The allocation sequence will be generated by EDC centralized randomization system. XH will be in charge of enrolling the patients. The Trial Management Committee (TMC) will assign participants to interventions.

Assignment of interventions blinding

Who will be blinded {17a}

Participants and investigators will be aware of the intervention that has been assigned to them in this open-label trial. Because of the nature of the patient-reported outcome measures, not all outcome evaluations will be blinded. During the analysis, the statistician will be blinded to the allocation.

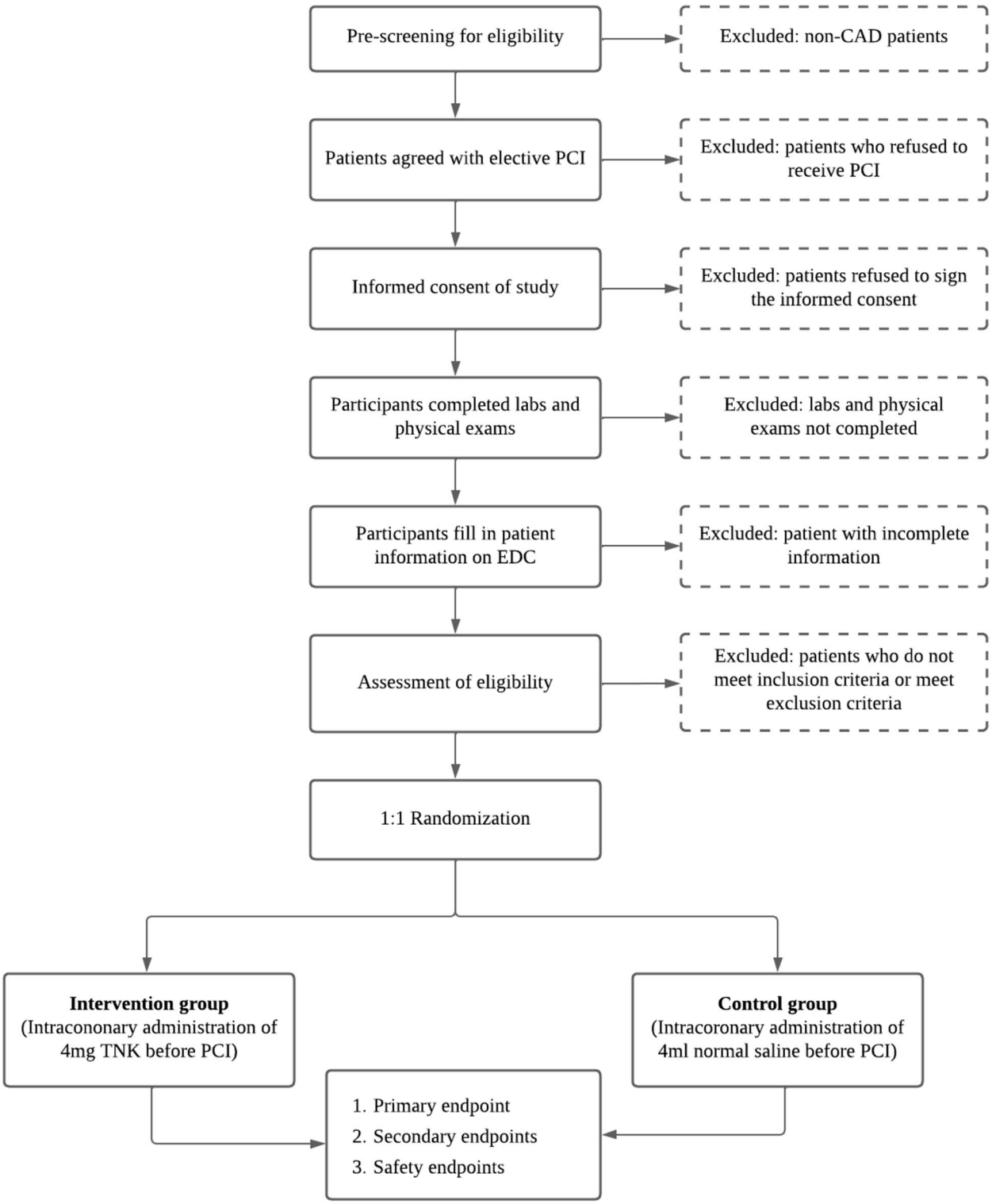

Fig. 2 Participant timeline

Procedure for unblinding if needed {17b}

Procedure for unblinding is not applicable as this is an open-label trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected utilizing EDC at each site. Data collection will commence 1 month post-PCI and will be stored in the form of an electronic case report form. The clinical research coordinator (CRC) will complete the electronic case report form. Investigators will be notified of any changes made by CRC and a system/edit check automatically be conducted by the system. Authorized investigators will be permitted to access the study computers and evaluate the data throughout the study.

Plans to promote participant retention and complete follow-up {18b}

If any missing data is detected via the EDC system, the researcher will contact the participants by telephone.

Data management {19}

Study teams are tasked with self-monitoring both study processes and data to ensure a well-run trial and to identify and mitigate issues before they are identified by external monitoring entities, potentially avoiding time-consuming corrections. Internal monitoring includes monitoring for proper informed consent documentation/records, eligibility criteria, and data quality.

Monitoring is usually conducted by stakeholders involved in the research to pinpoint issues and enhance processes. A unique identification code will be generated for data analysis to ensure security. Any errors or missing data information will be reported to data managers (DM) in Data Query Reports. DM receiving the inquiry will verify the original records to ascertain the necessary corrections. Original paperwork and signed informed consent forms will be stored in locked file cabinets.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

All data will be entered by two members of the research team independently, and analyzed once confirmed to be consistent. Statistical analysis will be conducted using SPSS 22.0.

(1) Quantitative data

Continuous data will be examined for normal distribution using Shapiro–Wilk method:

- Data with a normal distribution will be expressed as means ± SD and compared between groups using the *t*-test.
- Data with a non-normal distribution will be expressed as medians (interquartile range) and compared between groups using the Mann–Whitney *U* tests.

(2) Count data

Count data will be expressed as counts (percentages) and compared between groups using chi-square tests or Fisher's exact test.

(3) Dropout analysis

The number of actual enrolled participants and excluded participants will be statistically described to understand the underlying reasons for dropout.

(4) Baseline equivalence analysis

Analysis of variance (ANOVA) or Fisher exact test will be adopted to compare demographic data and other baseline characteristics to assess equivalence among groups.

Methods for additional analysis (e.g., subgroup analysis) {20b}

No additional analysis will be conducted.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

There will be no replacement or imputation of missing values. Patients who are lost to follow-up will be considered to have dropped out of therapy. Results will be reported using both the intention-to-treat approach and the per-protocol analysis, accounting for any missing data.

Composition of the data monitoring committee, its role and reporting structure {21a}

There will be no data monitoring committee as this is considered to be a low-risk intervention.

Interim analysis {21b}

There will be no interim analysis. However, if deemed necessary after careful consideration by all its members, an unplanned interim analysis concerning safety and efficacy may be initiated at any point during the trial. The

results from this analysis will provide guidance to the principal investigator on whether to continue, modify, or terminate the study.

Adverse event reporting {22}

The primary study-related adverse events are adverse reactions to TNK, which include intracranial hemorrhage and other minor bleeding events. Previous studies have shown that the use of small-dose TNK during surgery does not increase the risk of bleeding. However, the research team will closely monitor for bleeding events and provide timely treatment based on the severity of the bleeding, referring to the 2016 Acute Coronary Syndrome (ACS) Antithrombotic Therapy and Bleeding Prevention Multidisciplinary Expert Consensus. The types and frequencies of any adverse event will be reported to the Chinese National Adverse Reaction Monitoring Center. The adverse events monitored include: i) normal or abnormal laboratory test changes before and after the clinical trial; and ii) the relationship between the abnormal changes and management strategies employed.

Frequency and plans for auditing trial conduct {23}

Audit procedures will comply with the ICH GCP (Guideline for Good Clinical Practice of the International Conference on Harmonisation) and regulatory requirements. A project management-related meeting will be conducted both weekly and monthly. Weekly meetings will be held every Friday. Monthly meetings will be conducted at the last day of every month. The project management group will audit information on the research. The ethics committee will meet every 6 months.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

The steering committee (SC) will be responsible for assessing and approving any protocol revisions. The amended protocol will also be submitted to the Medical Ethics Committee of the Sir Run Run Shaw Hospital of Zhejiang University and reported to the participants as deemed necessary.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The results of the clinical trial will be published in the form of articles, but the specific scope and time of publication are yet to be determined. All relevant data and information will be disclosed when the article is published.

Confidentiality {27}

This study will adhere strictly to the ICH GCP guidelines for data collection, sharing, and maintenance. To ensure confidentiality, several measures will be implemented: (1) all participants must sign a detailed informed consent form before any data collection begins; (2) each participant will be assigned a unique, randomized identification number to protect their privacy in the tracking process; (3) access to the study dataset will be only granted to approved investigators and study nurses; (4) researchers only have access to the data collected by themselves and cannot review data collected by others. All data will be stored on a secure database (EDC) for confidentiality. No associated information will be disclosed beyond the scope permitted by relevant laws and/or regulations.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No genetic or molecular analysis will be conducted in this trial or for future use.

Composition of the coordinating center and trial steering committee {5d}

Design and conduct of the study: preparation of protocol and amendments; preparation of IB (investigators brochure) and CRFs (case report forms); reports on studies to be published; establishment of the composition of TMC's members.

SC (steering committee): final protocol agreement; patient recruitment and communication with the lead investigator; review of the trial's progress; consent for protocol and/or IB adjustments to ensure a smooth run of the study. The steering committee comprises all principal investigators, with a designated regional coordinator selected from among the principal investigators at each study site.

Trial Management Committee (TMC) (principal investigator, research physician, administrator): study planning; organization of steering committee meetings; report of adverse events to the Chinese National Adverse Reaction Monitoring Center; maintenance of the trial master file; budget management and contractual difficulties with individual centers; randomization; data verification.

Lead investigators: recruitment; data collection; CRF completion, as well as study patient follow-up and adherence to the study protocol and IB. Each participating center will be assigned a lead investigator who is responsible for patient identification and management.

Dissemination plans {31a}

The findings of the study will be presented to the public at academic conferences. The authorship will be determined by the steering group based on contributions.

Discussion

The most critical strategy in managing PMI management is prevention. However, current procedural and pharmacological strategies have shown limited effectiveness. To date, apart from antiplatelet drugs and statins, no other medications—including the widely prescribed calcium channel blocker (CCB) and Angiotensin-converting enzyme inhibitors/ Angiotensin receptor blockers (ACEIs/ARBs)—have demonstrated efficacy in reducing PMI incidence [3]. Consequently, this protocol presents a detailed description of a multicenter RCT, designed to evaluate the effectiveness of low-dose intracoronary TNK in preventing PMI in CAD patients with EA but do not have MI. Despite the controversial efficacy of TNK-facilitated PCI in STEMI patients, these cases were largely attributed to specific underlying issues, such as full-dose thrombolytic usage, insufficient anticoagulation/antiplatelet therapy, and treatment delays [19, 20]. Our study aims to minimize these factors while standardizing the extent of microvascular obstruction and ischemic times for optimal drug effectiveness and study results. Furthermore, TNK was chosen as the subject of our study due to its demonstrated advantages in both animal and clinical studies, including reduced systemic bleeding, higher fibrin specificity, and improved thrombolytic efficacy in cardiovascular and cerebrovascular events [21, 22]. The dosage of intracoronary TNK used in our study is a 4 mg bolus, primarily referencing to the safety dosage reported by Gibson CM et al. [11, 13, 20].

This study has several critical implications. Similar to previous studies involving other drugs, we will administer the thrombolytic agent directly and immediately into the culprit artery following PCI. This approach allows us to explore the therapeutic efficacy in CAD patients undergoing PCI to the optimal extent. Secondly, the presence of EA, which contributes to the pathogenesis of PMI, solidifies the clinical relevance of our findings.

There are some limitations of this study. Firstly, our study primarily focuses on PMI, which is considered an early periprocedural complication. Consequently, we just keep track of MACE for 1 month, rendering long-term outcomes unknown. Secondly, the optimal regimen and dosage of TNK in this setting, which may influence the trial results, are unknown.

Trial status

Protocol version {3}: original; version 1.1 20,240,606.

Recruitment start date: August 1, 2024.

Anticipated completion of recruitment: August 1, 2025.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ARB	Angiotensin receptor blockers
ANOVA	Analysis of variance
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blockers
cTnI	Cardiac troponin I
CTO	Chronic total occlusion
EA	Echo-attenuated plaque
EDC	Electronic data capture
ICH GCP	Guideline for Good Clinical Practice of the International Conference on Harmonisation
IVUS	Intravascular ultrasound
LMCAD	Left main coronary artery disease
MI	Myocardial infarction
NaCl	Sodium chloride
PCI	Percutaneous coronary intervention
MI	Peri-procedural myocardial infarction
SC	Steering Commitee
STEMI	ST-segment elevated myocardial infarction
TMC	Trial Management Committee
TNK	Tenecteplase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08605-9.

Additional file 1. The combined SPIRIT-Surrogate extension checklist.

Additional file 2. Model Consent Form.

Acknowledgements

We would like to thank Guangzhou Recomgen Biotech Co., Ltd for supporting this study.

Model consent form {32}

The model consent form is submitted as Additional file 2.

Authors' contributions {31b}

XH designed the overall project; DL designed the statistical methods and improved the practicality of the study; XH and Y(H)L were equally responsible for writing the protocol and manuscript; WZ and YL assisted in designing the project and reviewing the manuscript. All the authors read and approved the final manuscript.

Funding

None.

Data availability

The data generated by the study will eventually belong to the study team. If the subjects are infringed due to data disclosure in the trial, the research team will provide them with appropriate compensation if necessary.

Declarations

Ethics approval and consent to participate {24}

This trial protocol has been conducted in agreement with the ethics guidelines of the 1975 Declaration of Helsinki, and the Medical Ethics Committee of the Sir Run Run Shaw Hospital of Zhejiang University has approved the study design, protocols, information letters, and informed consent form.

Competing interests {28}
The authors declare that they have no competing interests.

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References

1. Bulluck H, Paradies V, Barbato E, Baumbach A, Bøtker HE, Capodanno D, et al. Prognostically relevant periprocedural myocardial injury and infarction associated with percutaneous coronary interventions: a Consensus Document of the ESC Working Group on Cellular Biology of the Heart and European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2021;42(27):2630–42.
2. Pervaiz MH, Sood P, Sudhir K, Hermiller JB, Hou L, Hattori K, et al. Periprocedural myocardial infarction in a randomized trial of everolimus-eluting and Paclitaxel-eluting coronary stents: frequency and impact on mortality according to historic versus universal definitions. Circ Cardiovasc Interv. 2012;5(2):150–6.
3. Herrmann J. Peri-procedural myocardial injury: 2005 update. Eur Heart J. 2005;26(23):2493–519.
4. Testa L, Van Gaal WJ, Biondi Zoccai GGL, Agostoni P, Latini RA, Bedogni F, et al. Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. QJM. 2009;102(6):369–78.
5. Babu GG, Walker JM, Yellon DM, Hausenloy DJ. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. Eur Heart J. 2011;32(1):23–31.
6. Sahashi Y, Kawasaki M, Okubo M, Kawamura I, Kawase Y, Yoshida A, et al. Development of 60 MHz integrated backscatter intravascular ultrasound and tissue characterization of attenuated signal coronary plaques that cause myocardial injury after percutaneous coronary intervention. Heart Vessels. 2022;37(10):1689–700.
7. Hoshi T, Sato A, Akiyama D, Hiraya D, Sakai S, Shindo M, et al. Coronary high-intensity plaque on T1-weighted magnetic resonance imaging and its association with myocardial injury after percutaneous coronary intervention. Eur Heart J. 2015;36(29):1913–22.
8. Boscarelli D, Vaquerizo B, Miranda-Guardiola F, Arzamendi D, Tizon H, Sierra G, et al. Intracoronary thrombolysis in patients with ST-segment elevation myocardial infarction presenting with massive intraluminal thrombus and failed aspiration. Eur Heart J Acute Cardiovasc Care. 2014;3(3):229–36.
9. Jayagopal PB, Sarjun Basha KM. Intracoronary tenecteplase in STEMI with massive thrombus. Indian Heart J. 2018;70(3):446–9.
10. Dibra A, Mehilli J, Dirschinger J, Pache J, Neverve J, Schwaiger M, et al. Thrombolysis in myocardial infarction myocardial perfusion grade in angiography correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis. J Am Coll Cardiol. 2003;41(6):925–9.
11. Alyamani M, Campbell S, Navarese E, Welsh RC, Bainey KR. Safety and Efficacy of Intracoronary Thrombolysis as Adjunctive Therapy to Primary PCI in STEMI: A Systematic Review and Meta-analysis. Can J Cardiol. 2021;37(2):339–46.
12. Sezer M, Oflaz H, Gören T, Okçular I, Umman B, Nişanci Y, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med. 2007;356(18):1823–34.
13. Gibson CM, Kumar V, Gopalakrishnan L, Singh P, Guo J, Kazziha S, et al. Feasibility and Safety of Low-Dose Intra-Coronary Tenecteplase During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction (ICE T-TIMI 49). Am J Cardiol. 2020;125(4):485–90.
14. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87–165.
15. Chinese Society of Cardiology, Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Chinese expert consensus on microvascular protection strategy during emergency PCI therapy in patients with ST-elevation myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi. 2022;50(3):221–30.
16. Kelly RV, Crouch E, Krumnacher H, Cohen MG, Stouffer GA. Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. Catheter Cardiovasc Interv. 2005;66(3):327–32.
17. Manyara AM, Davies P, Stewart D, Weir CJ, Young AE, Blazeby J, et al. Reporting of surrogate endpoints in randomised controlled trial reports (CONSORT-Surrogate): extension checklist with explanation and elaboration. BMJ. 2024;9(386): e078524.
18. Gaudino M, Di Franco A, Dimagli A, Biondi-Zoccai G, Rahouma M, PerezgrovasOlaria R, et al. Correlation Between Periprocedural Myocardial Infarction, Mortality, and Quality of Life in Coronary Revascularization Trials: A Meta-analysis. Journal of the Society for Cardiovascular Angiography & Interventions. 2023;2(3):100591.
19. Thiele H, Eitel I, Meinberg C, Desch S, Leuschner A, Pfeiffer D, et al. Randomized Comparison of Pre-Hospital–Initiated Facilitated Percutaneous Coronary Intervention Versus Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction Very Early After Symptom Onset: The LIPSIA-STEMI Trial (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction). JACC Cardiovasc Interv. 2011;4(6):605–14.
20. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet. 2006;367(9510):569–78.
21. Warach SJ, Ranta A, Kim J, Song SS, Wallace A, Beharry J, et al. Symptomatic Intracranial Hemorrhage With Tenecteplase vs Alteplase in Patients With Acute Ischemic Stroke: The Comparative Effectiveness of Routine Tenecteplase vs Alteplase in Acute Ischemic Stroke (CERTAIN) Collaboration. JAMA Neurol. 2023;80(7):732–8.
22. Wang L, Hao M, Wu N, Wu S, Fisher M, Xiong Y. Comprehensive Review of Tenecteplase for Thrombolysis in Acute Ischemic Stroke. J Am Heart Assoc. 2024;13(9):e031692.

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