Original Article

Impact of intracoronary reteplase during primary percutaneous coronary intervention on infarct size in large anterior myocardial infarction: rationale and design of the RECOVER II trial

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Background: Thrombus embolization and microvascular obstruction during percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) is commonly detected, which causes inadequate myocardial perfusion and elevated infarct size. An approach with low-dose intracoronary fibrinolytic treatment for reducing distal embolization and improving myocardial reperfusion in high-risk STEMI cases remains controversial.

Methods: The RECOVER II study represents a multicenter, randomized, double-blind, parallel-group trial assessing low-dose adjunctive intracoronary reteplase during primary PCI in individuals with large anterior myocardial infarction and thrombus determined by angiography. The trial will enroll 306 cases who present within 12 h following STEMI for proximal or mid left anterior descending artery occlusion undergoing primary PCI. Cases will be randomized to receive a bolus intracoronary reteplase at 9 mg or 18 mg *vs*. placebo. The drug will be delivered over 2 minutes proximal to culprit lesions with an intracoronary catheter early after wire-crossing and before thrombus aspiration or balloon dilation.

Results: The primary outcome will be infarct size assessed by late gadolinium-enhanced magnetic resonance imaging (MRI) (% of left ventricular mass) on day 7 after enrollment. Secondary outcomes will include the amount of microvascular obstruction and myocardial salvage index examined via MRI on day 7, angiographic measures of reperfusion [Thrombolysis in Myocardial Infarction (TIMI) coronary flow grade, TIMI frames count and myocardial blush grade], incidence of complete ST-segment resolution at 2 hours after reperfusion, area under the curve for troponin T, and rates of major adverse cardiovascular events at 30 days.

Conclusions: RECOVER II will determine whether the addition of low-dose intracoronary reteplase early after wire-crossing as an adjunct to reperfusion treatment reduces infarct size in individuals with large anterior myocardial infarction.

Trial Registration: ClinicalTrials.gov Identifier: NCT04571580.

Keywords: Myocardial infarction; reteplase; percutaneous coronary intervention (PCI); infarct size

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Introduction

ST-segment elevation myocardial infarction (STEMI) mainly results from the acute thrombus occlusion of the coronary artery due to rupture or erosion of atherosclerotic plaque (1). Timely reperfusion treatment to decrease infarct size and ameliorate ventricular function is considered the standard of care in acute STEMI (1). Primary percutaneous coronary intervention (PCI) for emergency reopening of the occluded coronary artery is preferentially utilized for reperfusion in STEMI cases within 12 h of symptom onset (2). Nevertheless, myocardial reperfusion after primary PCI is generally inadequate because of distal thrombus embolization impairing microvascular reperfusion and increasing infarct size (3,4).

Thrombolytic therapy can replace or jointly utilized with PCI for STEMI management (5). However, PCI supplemented with adjunctive intravenous fibrinolytic treatment provided before PCI induces paradoxical thrombin activation, clotting and bleeding. Since Sezer and collaborators reported that the modified approach applying intracoronary low-dose thrombolytic treatment with streptokinase at 250 kU upon primary PCI could ameliorate myocardial reperfusion and reduce infarct size, the possible effectiveness of combined intracoronary fibrinolytic treatment in primary PCI attracts increasing attention (5-8). Our recently published ERUPTION trial also showed that adjunctive intracoronary pro-urokinase (pro-UK) administered prior to stent implantation during primary PCI could ameliorate myocardial reperfusion and reduce infarct size estimated from creatine kinase with no additional major bleeding events (7). However, the T-TIME study found no benefit of low intracoronary alteplase dose in decreasing microvascular obstruction (MVO) and infarct size determined by contrast-enhanced cardiac magnetic resonance imaging (CMR) in acute STEMI cases who presented within 6 h of symptom onset (8).

Inadequate trial design might be responsible for such discrepancy, e.g., sample size, inclusion criteria, dosage and schedule of intracoronary fibrinolytic treatment, and the definition of the primary endpoint. In theory, fibrinolytic treatment should effectively alleviate thrombi abundant in fibrins that are responsible for distal embolization and MVO. Therefore, added intracoronary fibrinolytic treatment in primary PCI should be examined for its therapeutic effects in high-risk STEMI cases as examined by angiography and/or infarction location. We present the following article in accordance with the SPIRIT reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-756/rc).

Methods

Study design

The RECOVER II study represents an investigator-initiated, multi-center, randomized, double-blind, parallel-group clinical study assessing intracoronary reteplase as adjunct to reperfusion treatment in primary PCI in individuals with anterior myocardial infarction, planning to enroll 306 cases in 15 centers in China. The trial primarily aims to show that in individuals with large myocardium at risk (anterior STEMI), an intracoronary bolus of reteplase prior to coronary reperfusion decreases CMR-detected infarct size at 7 days. The recruitment started in July 2021, and is expected to end in October 2022.

Eligibility

Inclusion criteria

- Age of 18–75 years;
- Symptom onset <12 h;
- Acute myocardial infarction with prolonged chest pain and persistent ST-segment elevation in ≥2 contiguous leads;
- Coronary artery occlusion at the proximal-mid location in the left anterior descending (LAD) coronary artery [Thrombolysis in Myocardial Infarction (TIMI) coronary flow grade 0 or 1], or abnormal coronary flow (TIMI flow grade 2) with overt thrombus determined by angiography (TIMI grade 2+).

The TIMI thrombus grading scale (9) was utilized for thrombus burden quantitation, with grades from 0 (no thrombus) to 5 (complete occlusion).

Exclusion criteria

- Previous myocardial infarction;
- Previous hemorrhagic stroke or current stroke of undefined cause, or ischemic stroke or transient ischemic attack within the last 180 days;
- Major surgery or substantial trauma within the last 30 days;
- Suspected aortic dissection;
- Non-medically controlled severe hypertension (blood pressure >180/110 mmHg);
- Diagnosed kidney impairment (estimated glomerular filtration rate below 30 mL/min) or severe hepatic dysfunction;

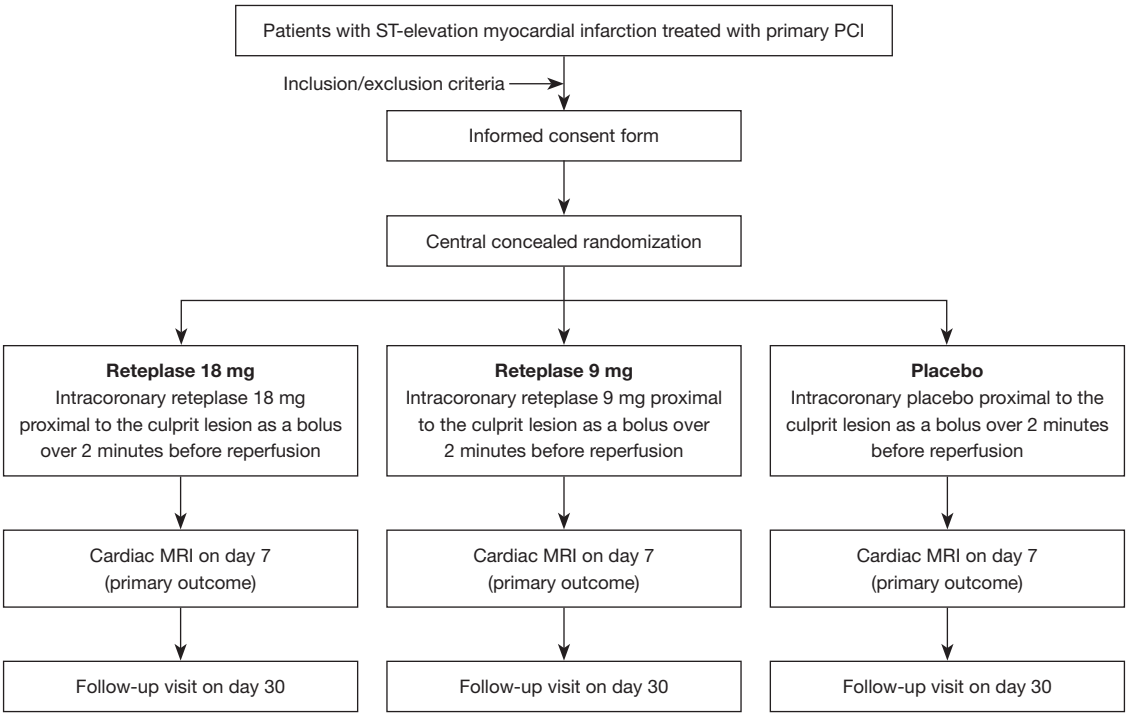

Figure 1 Flowchart of RECOVER II. PCI, percutaneous coronary intervention; MRI, magnetic resonance imaging.

- Pregnancy or lactation;
- No informed consent;
- Involvement in a different trial within the past month;
- Any other condition that may put the patient at risk or influence the study results in the investigators' opinion.

Screening and informed consent

Only patients who clearly understood the information regarding the trial were eligible for enrolment. Cardiologists in the emergency room were responsible for screening patients for inclusion. The trial's information sheet was given to all participants, who provided signed informed consent in the emergency room.

Randomization and blinding

A web-based tool was utilized for randomizing cases and collecting electronic case report forms (CRFs). Patients underwent randomization in the catheter laboratory (*Figure 1*), at 1:1:1 for the placebo and both reteplase (9 and 18 mg) groups; the sequence was concealed electronically. The cardiologists performing PCI and treating patients were unaware of grouping. Participants and independent data reviewers were also blinded to patient grouping.

Interventions

Right after wire crossing, participants received intervention based on grouping in the catheter laboratory. Study drugs (placebo, reteplase 9 mg and reteplase 18 mg) were manually infused, respectively, over 2 min directly into infarct-associated arteries, proximal to culprit lesions, with a thrombus-aspiration catheter or a selective intracoronary microcatheter. To minimize thrombus embolization, each drug was infused before balloon angioplasty or manual thrombus aspiration.

Concomitant therapies

The patients were administered a loading dose of ticagrelor (180 mg) or clopidogrel (600 mg) prior to PCI. Aspirin was administered at 300 mg (loading dose) in individuals with no previous aspirin therapy. Primary PCI was recommended according to contemporary practice guidelines (1). PCI's approach and device were selected by physicians blinded to grouping. During the PCI, the patients received unfractionated heparin (70–100 U/kg) for anticoagulation.

All other evidence-based therapeutics, including statin, ACE inhibitors and beta-blockers, were provided to all cases during hospitalization and follow-up.

Follow-up

The baseline information of the patients was collected, including demographic and patient indexes, cardiovascular risk factors, medical histories with relevance and laboratory findings. Visits for endpoint assessment were scheduled at 24 h, 7 and 30 days following the index PCI (*Figure 1*).

Funding and trial management

This trial had funding from National Key Research and Development Program of China (No. 2016YFC1301203), National Natural Science Foundation (No. 82170458) and Key Clinical Research Projects of National Clinical Research Center for Interventional Medicine (No. 2021-003). ANGDE BioPharm (Shandong, China) provided the study drugs, including reteplase (9 mg, 18 mg) and placebo.

The study steering committee comprised a chairman, principal investigators, and sponsor and Clinical Research Organization (CRO) representatives. These individuals were responsible for reviewing and approving the trial protocol, reviewing the study progression and interacting with sponsors and the CRO to discuss study progression.

Ethical statement

The study had approval from the Ethics Committee of Zhongshan Hospital, Shanghai [No. B2020-134(2)], and had approval from independent ethics committees or institutional review boards at various sites. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Conference of Harmonization and Good Clinical Practice. The clinical trial registration number is NCT04571580. Informed consent and study information were provided to all patients prior to randomization. All data will be encrypted and stored in an online database accessible only to the main researchers and administrators. The patients primarily enrolled in this trial have the right to withdraw at any time point, and the reasons will be documented.

Statistical analysis

The trial required 306 cases, i.e., 102 in each group, administered CMR at day 7 following enrollment, estimating about 10% missing data. The study targeted an 80% power at a one-sided alpha level of 2.5%, to detect a difference of 5% between the reteplase and placebo groups, assuming a standard deviation of 12% for the degree of infarct size in the control group, accosting to Bulluck and collaborators (10), who provided recommendations to standardize the evaluation of infarct size by CMR based on published randomized trials with inclusion criteria similar to those of this study.

The primary analysis was to comparatively assess the 18 mg reteplase and placebo groups; in case of significance at a 2.5% level, the 9 mg reteplase and placebo groups would be comparatively assessed instead as primary analysis. Such hierarchical strategy was utilized for preserving an overall type I error rate of 2.5%. In case of non-significant difference between the 18 mg and placebo groups, the 9 mg and placebo groups were also compared as secondary analysis. All outcome analyses were carried out by linear regression (continuous variables), logistic regression (binary variables), or proportional odds logistic regression (ordinal variables).

The primary outcome will undergo a post hoc analysis by multiple imputation for missing data. Therapeutic effects on the primary outcome in various subgroups, on the basis of age, sex, body mass index, diabetes mellitus status, hypertension, smoking, history of myocardial infarction, ischemic time (≤6 *vs.* >6 h), TIMI coronary flow grade at first angiography and TIMI-based thrombus grade, will be compared. Regression models will be utilized for assessing therapeutic effects in various subgroups via treatment-by-subgroup interactions.

Results

A blinded Clinical Event Committee independently will adjudicate discrepant outcome data. Outcome definitions are provided in detail in *Tables 1*,*2*.

Primary outcome

Infarct size [% of left ventricular mass (LVM)] based on late gadolinium-enhanced magnetic resonance imaging (MRI) at 7 days following enrollment was considered the primary outcome.

Secondary outcomes

MRI-based secondary outcomes comprised MVO (% of

Table 1 Definitions of MRI outcomes (8)

Infarct size
Acute infarction was detected on the basis of abnormal wall motion, rest first-pass myocardial perfusion and late gadolinium enhancement findings in 2 imaging planes. Myocardial mass of late gadolinium (g) was determined by computer-based planimetry. The infarction territory was drawn with the 5 standard deviations technique, and assessed as % of LVM
Microvascular obstruction
Microvascular obstruction was reflected by a dark region on early gadolinium enhancement images obtained 1, 3, 5 and 7 minutes after contrast agent administration, which persisted until the 15-minute time point. Myocardial mass (g) for this dark region was determined via manual drawing, as % of LVM
Myocardial salvage
Myocardial salvage was determined by subtracting percent infarct size from percent area-at-risk, defined as the area of edema. The myocardial salvage index was determined as myocardial salvage area by the initial area-at-risk
Myocardial hemorrhage
On T2* parametric maps, 20 ms was utilized as a threshold. A region with signal intensity reduction in the infarcted area and T2* <20 ms indicated myocardial hemorrhage. Manual delineation was performed, with the area quantitated as % of LVM

LVM, left ventricular mass; MRI, magnetic resonance imaging.

Table 2 Definitions of secondary outcomes (9)

TIMI coronary flow grading
Grades were 0 to 3 for no flow, reduced flow through the obstruction, slow but complete filling with slow clearance and normal flow and clearance, respectively
TIMI frame counting
Corrected TFC, encompassing the definitions of the first and last frames, was obtained as proposed by Gibson and collaborators (9). TFC was 100 for occluded vessels. TFC for the left anterior descending artery underwent correction for the longer dimension via division by 1.7
Myocardial blush grading
Grading was performed as follows: grade 0, absence of myocardial blush/contrast density; grade 1, limited myocardial blush; grade 2, some myocardial blush but reduced in comparison with that found by angiography in a contralateral/ipsilateral non-infarcted coronary artery; grade 3, intact myocardial blush as detected by angiography in a contralateral/ipsilateral non-infarcted coronary artery
ST-segment resolution
ST-segment resolution was assessed as the % resolution of total ST-segment elevation in the infarct leads from paired electrocardiograms performed prior to PCI and 2-h post-PCI. It was graded as complete, partial and none with values of >70%, 30–70% and <30%, respectively

PCI, percutaneous coronary intervention; TFC, TIMI frame count; TIMI, Thrombolysis in Myocardial Infarction.

LVM) and myocardial salvage index at 7 days. Angiographic secondary outcomes included TIMI coronary flow grade, number of TIMI frames and myocardial blush grade. The incidence of complete ST-segment resolution on electrocardiogram (ECG) obtained 2-h post-PCI was also determined. The area under the curve (AUC) for troponin T based on blood specimens collected immediately prior to reperfusion and at 6, 12, 18 and 24 h will be assessed. Left ventricular ejection fraction values were determined on echocardiograms at 7 and 30 days. Cardiovascular death, myocardial reinfarction and target vessel revascularization at 30 days were considered major adverse cardiovascular events (MACEs).

Safety outcomes were myocardial hemorrhage amount (% of LVM) based on MRI at 7 days and the rate of in-hospital major bleeding events based on the TIMI bleeding

Table 3 Primary PCI with adjunctive intracoronary fibrinolytics therapy (11)

Study, year	Enrollment	Study design	Primary endpoint	Outcome
Sezer *et al.*, 2007, (5)	N=41. Inclusion criteria: STEMI within 12 h of symptom onset, TIMI flow grade 0 or 1	2 groups: primary PCI with intracoronary streptokinase (250 kU) *vs.* placebo after stenting	Microvascular function assessed 2 days post-PCI, including CFR and IMR	Improvement in microvascular function with intracoronary streptokinase
ERUPTION, 2021, (7)	N=345. Inclusion criteria: STEMI within 12 h of symptom onset	3 groups: primary PCI with intracoronary placebo, recombinant pro-urokinase (20 mg), tirofiban (10 μg/kg), after balloon angioplasty and before stenting	CTFC post-PCI	Improved CTFC and infarct size determined from creatine kinase with intracoronary pro-urokinase and tirofiban
T-TIME, 2019, (8)	N=440. Inclusion criteria: STEMI within 6 h of symptom onset, angiographic thrombus	3 groups: primary PCI with intracoronary placebo, 10 or 20 mg alteplase after balloon angioplasty and before stenting	Microvascular obstruction by CMR at 2–7 days after PCI	No improvement in microvascular obstruction or infarct size with intracoronary alteplase
RECOVER II (in progress)	N=306. Inclusion criteria: anterior STEMI within 12 h of symptom onset, angiographic thrombus (TIMI thrombus grade >2)	3 groups: primary PCI with intracoronary placebo, 9 or 18 mg reteplase before balloon angioplasty	Infarct size by CMR at 7 days after PCI	Pending
STRIVE (in progress), (8)	N=200. Inclusion criteria: STEMI within 6 to 12 h of symptom onset with a large thrombus burden by angiography (TIMI thrombus grade >3)	3 groups: primary PCI with intracoronary placebo, 10 or 20 mg alteplase before stenting	Post-procedural MBG 0/1 or distal embolization	Pending
RESTORE-MI (in progress) (11)	N=800. Inclusion criteria: STEMI within 6 h of symptom onset, IMR >32 after primary PCI	3 groups: primary PCI with intracoronary placebo, 1/3 or 1/6 systemic weight-based dose tenecteplase	Cardiovascular mortality and rehospitalization for heart failure at 24 months	Pending

CFR, coronary flow reserve; CMR, cardiac magnetic resonance; CTFC, corrected thrombolysis in myocardial infarction frame count; IMR, index of microvascular resistance; MGB, myocardial blush grade; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

classification.

Discussion

The possible effectiveness of supplemental intracoronary fibrinolytic treatment in primary PCI currently attracts increasing attention. Besides the ERUPTION and T-TIME trials, two phase 3 studies are currently assessing low doses of alteplase (STRIVE, NCT03335839) and tenecteplase (RESTORE-MI, NCT03998319), respectively, as shown in *Table 3*. In the ERUPTION, T-TIME and STRIVE trials, the scheduled intervention involved intracoronary infusion of fibrinolytics after balloon angioplasty or aspiration thrombectomy and before stent implantation. In our trial, intracoronary fibrinolytic therapy was infused after wire crossing and before thrombus aspiration or balloon dilation for reducing mechanical distal embolization of the thrombus, which results in increased rate of coronary reperfusion as reported by Erbel *et al.* (12). Another strategy applied by Sezer *et al.* (5) and the RESTORE-MI trial (11) is to perform adjunctive intracoronary fibrinolytic treatment after balloon dilation and stenting during PCI, suggesting a possible role in delivering fibrinolytic treatment only to the microcirculatory system.

In the RECOVER trial (13), intracoronary infusion of diltiazem or verapamil through a selective microcatheter in the culprit vessel could reverse no-reflow with elevated efficacy compared with nitroglycerin during primary PCI.

In this study, intracoronary infusion of the fibrinolytic drug was also targeted upstream of the culprit lesion through a selective microcatheter rather than a guiding catheter, with the intent of decreasing the fibrinolytic impact on the high-grade luminal thrombus, reducing systemic effects and minimizing bleeding events. The fibrin-specific fibrinolytic drug should be selected because of an elevated patency rate and a reduced rate of bleeding complications compared with streptokinase (5).

The pro-UK dose (20 mg) utilized for intracoronary infusion in the ERUPTION trial approximated two-fifths of the common entire dose administered intravenously in fibrinolytic treatment of myocardial infarction, which could ameliorate myocardial reperfusion and decrease infarct size with no additional major bleeding events (7). Streptokinase dose (250 kU) in Sezer *et al.* was 25% of the total dose usually given intravenously due to elevated bleeding risk (5). The T-TIME study applied a low dose of alteplase (10–20 mg) for intracoronary treatment, reporting no benefit in reducing infarct size and no increase in major bleeding events (8). The dose of reteplase (9 or 18 mg) used in this trial, around 25–50% of the commonly administered total dose applied in intravenous fibrinolytic treatment, was based on data reported by the FINESSE trial, suggesting intravenous half-dose reteplase plus abciximab could improve early ST-segment resolution in comparison with abciximab-facilitated PCI or primary PCI (14). The befitting dose and the optimal time (pre- or post-arterial patency) for intracoronary fibrinolytic treatment deserve further investigation.

Post-MI CMR was used to evaluate myocardial infarct size and MVO (10). CMR-based infarct size shows tight associations with overall mortality and hospitalization due to heart failure within 1 year (10,15). On this point, 3 top baseline determining factors of infarct size in primary PCI are anterior infarct location, pre-PCI TIMI 0/1 flow and time from symptom onset to first device use (15). Most of the mechanisms used to reduce infarct size, e.g., intracoronary antioxidant treatment, vasodilator administration and use of potent antiplatelet agents, show no overt superiority over common primary PCI (11). Our trial examined only infarcts in the proximal or mid-LAD coronary artery with TIMI 0, 1 or 2 grade flow when the first angiography (prior to wire passage). Careful selection of those high-risk patients, who most likely would benefit from a new cardioprotective treatment to reduce infarct size, could reduce sample size.

The study by Sezer *et al.* (5) utilized invasive wire-based tools to assess myocardial reperfusion instead of CMR. The primary outcome of the STRIVE trial is also a composite endpoint comprising post-procedural myocardial blush grade (0 or 1) and distal embolization. When unfavorable intramyocardial hemorrhage is found in T-TIME trial, CMR must be included in the safety evaluation of intracoronary fibrinolytic therapy in STEMI cases with an important amount of at-risk myocardium undergoing primary PCI (16).

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-756/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-756/dss

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-756/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-756/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study had approval from the Ethics Committee of Zhongshan Hospital, Shanghai [No. B2020-134(2)], and had approval from independent ethics committees or institutional review boards at various sites. The study was conducted in accordance with the Declaration of Helsinki (as revised in

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