Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment–Elevation Myocardial Infarction

EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction)

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BACKGROUND: Timely primary percutaneous coronary intervention (PPCI) cannot be offered to all patients with ST-segment–elevation myocardial infarction (STEMI). Pharmaco-invasive (PhI) strategy has been proposed as a valuable alternative for eligible patients with STEMI. We conducted a randomized study to compare the efficacy and safety of a PhI strategy with half-dose fibrinolytic regimen versus PPCI in patients with STEMI.

METHODS: The EARLY-MYO trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction) was an investigator-initiated, prospective, multicenter, randomized, noninferiority trial comparing a PhI strategy with half-dose alteplase versus PPCI in patients with STEMI 18 to 75 years of age presenting ≤6 hours after symptom onset but with an expected PCI-related delay. The primary end point of the study was complete epicardial and myocardial reperfusion after PCI, defined as thrombolysis in myocardial infarction flow grade 3, thrombolysis in myocardial infarction myocardial perfusion grade 3, and ST-segment resolution ≥70%. We also measured infarct size and left ventricular ejection fraction with cardiac magnetic resonance and recorded 30-day clinical and safety outcomes.

RESULTS: A total of 344 patients from 7 centers were randomized to PhI (n=171) or PPCI (n=173). PhI was noninferior (and even superior) to PPCI for the primary end point (34.2% versus 22.8%, $P_{noninferiority}<0.05$, $P_{superiority}=0.022$), with no significant differences in the frequency of the individual components of the combined end point: thrombolysis in myocardial infarction flow 3 (91.3% versus 89.2%, $P=0.580$), thrombolysis in myocardial infarction myocardial perfusion grade 3 (65.8% versus 62.9%, $P=0.730$), and ST-segment resolution ≥70% (50.9% versus 45.5%, $P=0.377$). Infarct size (23.3%±11.3% versus 25.8%±13.7%, $P=0.101$) and left ventricular ejection fraction (52.2%±11.0% versus 51.4%±12.0%, $P=0.562$) were similar in both groups. No significant differences occurred in 30-day rates of total death (0.6% versus 1.2%, $P=1.0$), reinfarction (0.6% versus 0.6%, $P=1.0$), heart failure (13.5% versus 16.2%, $P=0.545$), major bleeding events (0.6% versus 0%, $P=0.497$), or intracranial hemorrhage (0% versus 0%), but minor bleeding (26.9% versus 11.0%, $P<0.001$) was observed more often in the PhI group.

CONCLUSIONS: For patients with STEMI presenting ≤6 hours after symptom onset and with an expected PCI-related delay, a PhI strategy with half-dose alteplase and timely PCI offers more complete epicardial and myocardial reperfusion when compared with PPCI. Adequately powered trials with this reperfusion strategy to assess clinical and safety outcomes are warranted.

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Clinical Perspective

What Is New?

- The EARLY-MYO trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction) is the first randomized trial comparing the efficacy and safety of a pharmaco-invasive strategy with half-dose fibrinolytic regimen versus primary percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction.
- In low-risk patients with ST-segment–elevation myocardial infarction presenting ≤6 hours after symptom onset and with an expected PCI-related delay, a pharmaco-invasive strategy with half-dose alteplase is noninferior (and even superior) to primary percutaneous coronary intervention for incidence of complete epicardial and myocardial reperfusion.
- Infarct size, left ventricular function, and 30-day clinical outcomes were similar, with minor bleeding seen more often in the pharmaco-invasive group versus the primary percutaneous coronary intervention group.

What Are the Clinical Implications?

- The results of our study suggest that a pharmaco-invasive approach with reduced-dose alteplase seems to offer effective and safe reperfusion in low-risk patients with ST-segment–elevation myocardial infarction with an expected PCI-related delay.
- Further larger randomized trials are necessary to draw secure conclusions, especially considering that the present study was not powered to assess clinical end points.

Primary percutaneous coronary intervention (PPCI) is considered to be the best reperfusion option in ST-segment–elevation myocardial infarction (STEMI) when it can be performed in a timely fashion and by an expert team[1,2] However, PPCI is not universally available, and delays in performing PPCI are common in real-world practice.[1] Even in some large cities, patients have a high chance of presenting to hospitals not providing around-the-clock PPCI service.

Pharmaco-invasive (PhI) strategy, an early reperfusion strategy encompassing initial prompt fibrinolysis with subsequent early catheterization, has been proposed as a therapeutic option for STEMI patients when timely PPCI is not feasible.[1,3,4] However, current evidence on the efficacy and safety of a PhI strategy in patients with STEMI remains limited, and its role is a matter of debate.[5] The recent STREAM trial (Strategic Reperfusion Early After Myocardial Infarction) showed that a PhI strategy could be a reasonable alternative to PPCI in STEMI patients presenting ≤3 hours of symptom onset and with an expected time delay from first-medical-contact (FMC) to PPCI >1 hour.[6] The only downside of the PhI arm was that its rate of intracranial hemorrhage with full-dose tenecteplase was 5 times higher than that of the PPCI group. However, the difference was not significant after a trial protocol amendment reducing tenecteplase dose by 50% in the elderly.[6] The latter observation suggested that a half-dose fibrinolytic regimen might be a safe and effective option for PhI treatment in eligible patients with STEMI. Interestingly, in an observational registry study in the United States in patients with STEMI with long PCI-related delays, a PhI strategy utilizing half-dose fibrinolysis (97% tenecteplase, 3% reteplase) combined with transfer for PCI achieved similar efficacy outcomes as PPCI without increased bleeding risk.[7] Consistent with these findings, in our pilot study in the Chinese population, early routine PCI after half-dose alteplase fibrinolysis appeared promising in the treatment of patients with STEMI who could not undergo timely PPCI.[8] Because no randomized clinical trials compared the efficacy and safety of a PhI strategy with reduced-dose fibrinolytic regimen versus PPCI in patients with STEMI, we designed the EARLY-MYO trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction) to evaluate the efficacy and safety of a PhI strategy with half-dose alteplase versus routine PPCI in patients with STEMI presenting ≤6 hours after symptom onset and with an expected PCI-related delay.

METHODS

Trial Oversight

The EARLY-MYO was a prospective, multicenter, randomized, parallel-group, open-label, noninferiority trial comparing a PhI strategy with half-dose fibrinolysis versus PPCI in patients with STEMI presenting ≤6 hours after symptom onset and with an expected PCI-related delay of ≥60 minutes (the study protocol is available in the online-only Data Supplement).

The EARLY-MYO investigators conceived, designed, and conducted the trial. They received funding and study drug from Boehringer Ingelheim. Data management and statistical analysis were performed by a third party independent from Boehringer Ingelheim. The first and last authors had full access to the study data, wrote the first draft of the manuscript, and had full responsibility for the decision to submit the report for publication. Boehringer Ingelheim had no role in the design, conduct, analysis, interpretation of data, or reporting of the EARLY-MYO trial. The study was performed in accordance with the Declaration of Helsinki of Good Clinical Practice. The study protocol was approved by an institutional review committee at each clinical center, and all subjects gave informed consent prior to randomization.

Enrollment Criteria

The study enrolled patients between 18 and 75 years of age who presented ≤6 hours after the onset of symptoms with

specific electrocardiographic criteria for acute STEMI (≥2 mm in 2 contiguous precordial leads or ≥1 mm in 2 peripheral leads) and with an expected PCI-related delay (expected time delay from FMC to first balloon dilation ≥90 minutes and difference between the time of FMC to balloon dilation minus the time from FMC to start of fibrinolysis ≥60 minutes).

Key exclusion criteria were any contraindication for fibrinolysis, left bundle-branch block in the presenting electrocardiogram (ECG), cardiogenic shock, and PCI or bypass surgery within the previous month. A complete list of the exclusion criteria is available in the online-only Data Supplement.

Randomization and Treatment

Patients who satisfied the inclusion and exclusion criteria were randomly assigned in a 1:1 fashion to either a PhI strategy with half-dose alteplase (PhI group) or routine PCI (PPCI group), using an interactive web-based response system with a permuted block randomization scheme stratified by time to randomization (<3 hours versus 3–6 hours).

All patients received 300 mg of aspirin and a loading dose of adenosine diphosphate receptor antagonists (300–600 mg clopidogrel or 180 mg ticagrelor) in the emergency room. Patients who had already taken aspirin or adenosine diphosphate receptor antagonists ≤12 hours before screening were given these agents the following day. Patients randomly assigned to the PhI group received half-dose alteplase (8-mg bolus followed by 42 mg in 90 minutes) and an unfractionated heparin bolus (60 U/kg to ≤4000 U followed by 12 U/kg/h to ≤1000 U/h). Eighteen-lead ECG was repeated every 30 minutes after start of fibrinolysis. Patients with persistent ST-segment elevation (ie, <50% resolution of ST-segment elevation) 90 minutes after start of alteplase with or without chest pain were considered as fibrinolysis failures and were referred for immediate rescue PCI. Other patients were recommended to undergo early routine catheterization within 3 to 24 hours after fibrinolysis and further undergo PCI of the presumed culprit lesion if the residual stenosis was ≥50%. Patients randomly assigned to PPCI received unfractionated heparin to achieve an activated clotting time of 350 to 450 seconds during the invasive procedure. PPCI was performed according to standard practice. Stents were implanted whenever technically possible, and the use of drug-eluting stents was encouraged. Glycoprotein IIb/IIIa inhibitor use was not allowed in any patient before PCI but was permitted during or after catheterization at the investigator's discretion. The decision to use thrombus aspiration also was at the discretion of the interventional cardiologist. Beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, statins, and postinterventional antithrombotic therapy were given to all patients as recommended in current guidelines.[3,4] All study participants were scheduled for follow-up at 30 days after enrollment.

End Points and Definitions

The primary end point of the study was complete epicardial and myocardial reperfusion after PCI, defined as thrombolysis in myocardial infarction (TIMI) flow grade (TFG) 3 for epicardial reperfusion and TIMI myocardial perfusion (TMPG) grade 3 for myocardial reperfusion and complete (≥70%) ST-segment resolution of the initial sum of ST-segment elevation (STR) 60 minutes after PCI.

The key secondary end points were frequency of the individual components of the primary end point: TFG 3 for complete epicardial perfusion, TMPG 3 for complete myocardial perfusion, and STR ≥70% at 60 minutes after PCI. Other secondary end points included: left ventricular (LV) function and infarct size assessed by cardiac magnetic resonance (CMR) on days 4 to 7, wall motion score index assessment by echocardiography on days 4 to 7 and 30 days, and clinical events through day 30.

The key safety end point was the incidence of major bleeding and intracranial hemorrhage.

Epicardial and Myocardial Reperfusion

Coronary angiograms were anonymized and centrally assessed at an independent core laboratory by experienced readers without knowledge of treatment assignment or clinical outcomes. Flow in the epicardial arteries was assessed for TFG and corrected TIMI frame count using previously described methods.[9,10] TMPG and TIMI myocardial perfusion frame count were used to assess myocardial tissue level perfusion.[11,12] TIMI myocardial perfusion frame count is a novel method recently described by our group to standardize and quantify myocardial perfusion.[12,13]

Additional assessment of myocardial reperfusion was carried out using ST-segment analysis. Eighteen-lead ECGs were obtained on admission and 60 minutes after the procedure. At an independent core laboratory, the sum of ST-segment elevation 20 ms after the J point was measured and compared with the baseline ECG. The percent resolution was categorized based on Schroder's method as complete (≥70%), partial (30% to <70%), or none (<30%).[14]

LV Function

Contrast-enhanced CMR was performed using a 1.5-T, or 3-T scanner using dedicated cardiac surface coils.[15] Infarct size was expressed as a percentage of the LV mass (% LV). The incidence of microvascular obstruction and intramyocardial hemorrhage also were recorded. The scans were reviewed by 2 expert observers at an independent core laboratory. Echocardiography examination was done in hospital on the same day as magnetic resonance imaging examination and at 30-day follow-up. Quantitative echocardiographic analysis of wall motion score index was assessed by the 16-segment model as recommended.[16] All echocardiographic data were stored digitally in digital imaging and communications in medicine format for subsequent offline analysis. Observers of CMR and echocardiography were blinded to the treatment strategy and all other clinical data.

Clinical and Safety Outcomes

Clinical follow-up was performed at 30 days. All-cause death, nonfatal reinfarction, heart failure, and stroke after randomization constituted the clinical end points. The main safety end point was the incidence of major bleeding and other adverse events. All bleeding complications were classified using GUSTO severity criteria (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries).[17] Independent study monitors reviewed all source documents onsite for accuracy and completeness. Clinical and safety end points were verified by a blinded adjudication committee.

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Sample Size and Statistical Analysis

The sample size was estimated assuming that the incidence of the primary end point (complete epicardial and myocardial reperfusion after PCI) in the PhI group was 25% and 20% in the PPCI group based on data from the GRACIA-2 trial (Groupo de Análisis de Cardiopatía Isquémica Aguda) and our pilot study.[8,18] With this assumption, the trial was designed to enter 326 patients to conclude the noninferiority of PhI to PPCI at a 1-sided α=0.025 level based on the prespecified noninferiority margin of 0.7 with 80% power. Assuming a 7% withdrawal rate, a total patient number of 350 (ie, 175 patients per arm) would be needed.

Final Analysis

The primary analysis was performed on the full analysis set on an intention-to-treat basis. The data are presented as numbers and percentages for categorical variables, which were compared using the Fisher exact test; continuous variables are reported as mean±SD or medians with interquartile ranges and were compared using a Student's *t* test or the Wilcoxon rank sum test as appropriate. The Shapiro-Wilk test was used to examine normality of distribution. The analysis for the primary end point was conducted using the Cochran-Mantel-Haenszel test controlling for stratification factor (ie, time interval between disease onset and enrollment). The relative risk and its 95% confidence limit were estimated for the primary end point to test for noninferiority between PhI and PPCI. PhI would be claimed as noninferior if the lower bound of the 95% confidence limit lied entirely to the right of the noninferiority margin (δ),which was set as 0.7. If a noninferiority claim was established, then the superiority test would be performed. For the primary end point, we also performed prespecified subgroup analyses according to time to randomization, sex, weight, systolic blood pressure, infarct location, Killip class, and a history of diabetes mellitus or hypertension. For event-free survival, we compared Kaplan-Meier curves using a log-rank test. A 2-sided alpha level of 0.05 was considered to indicate statistical significance. All data analyses were conducted using SAS software (SAS Institute), version 9.2 or higher.

RESULTS

Patients Characteristics

A flowchart of the trial is shown in Figure 1. A total of 344 patients with STEMI were enrolled from January 13, 2014, to September 25, 2016, at 7 Chinese centers: 171 were allocated to a PhI strategy and 173 to PPCI. The primary end point (ie, full reperfusion after PCI) could not be calculated in 16 patients (10 in PhI group and 6 in PPCI group; *P*=0.200). Of the 16 patients with a missing primary end point, 1 died before catheterization could be performed, 3 refused coronary angiography, 1 refused PCI, and 11 did not require PCI. Thus, the primary end point was available in 328 patients (161 in the PhI group and 167 in the PPCI group).

Baseline demographic and clinical characteristics were well balanced and are summarized in Table 1. The median age of the study population was 58 (interquartile range [IQR]: 51.0–64.0) years, and 88.9% were men. In all, 51.1% had hypertension, 24.4% had diabetes mellitus, and 40.1% presented with an anterior STEMI. The 2 groups had a similar hemodynamic status, depicted by blood pressure, heart rate, and Killip class.

Angiographic data are shown in Table 2. Distribution of the culprit artery and stent use was similar in both groups. A high rate of radial access was observed in both the PhI (98.1%) and PPCI (97.6%) groups. However, the thrombus burden at first angiography in PPCI group was significantly higher than in the PhI group (*P*=0.008). Thrombus aspiration (*P*<0.001) and use of glycoprotein IIb/IIIa inhibitors (*P*<0.001) were more frequent in the PPCI group.

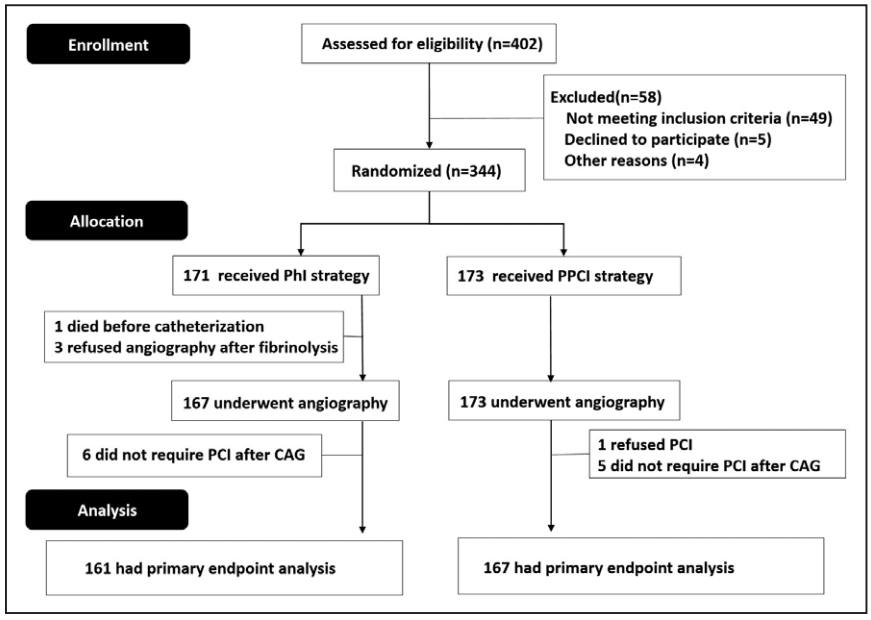

Figure 1. Flowchart of the trial. CAG indicates coronary angiogram; PhI, pharmaco-invasive; and PPCI, primary percutaneous coronary intervention.

Table 1. Baseline Characteristics of Patients

Characteristic	Total (n=344)	PhI (n=171)	PPCI (n=173)	*P* Value
Age, y	58 (51–64)	59 (52–65)	58 (50–64)	0.277
Men	306 (89.0)	153 (89.4)	153 (88.6)	0.864
Body mass index, kg/m^2	24.5±0.2	24.6±0.2	24.5±0.3	0.620
Weight, kg	70.0 (63.5–76.0)	70.0 (64.0–78.3)	69.8 (63.3–75.0)	0.232
Hypertension	176 (51.1)	91 (53.4)	85 (49.7)	0.453
Diabetes mellitus	84 (24.4)	42 (24.8)	42 (25.6)	1.000
Hypercholesterolemia	75 (21.8)	33 (19.3)	42 (25.6)	0.297
Peripheral artery disease	1 (0.3)	1 (0.6)	0 (0)	0.497
Previous angina pectoris	90 (26.1)	38 (22.4)	52 (29.9)	0.111
Previous coronary intervention	6 (1.7)	6 (3.7)	0 (0)	0.014
Previous stroke				
Ischemic stroke	13 (3.8)	7 (4.1)	6 (3.6)	0.786
Hemorrhagic stroke	1 (0.3)	1 (0.6)	0 (0)	0.497
Family history of coronary disease	27 (7.8)	14 (8.1)	13 (7.8)	0.844
Heart rate, beats/min	77.5±13.8	76.6±12.6	78.5±14.9	0.219
Blood pressure, mm Hg				
Systolic blood pressure	132±19.8	117.0±142.0	119.0±149.0	0.128
Diastolic blood pressure	81.3±12.5	80.4±13.1	82.2±11.9	0.181
Infarct location				0.590
Anterior	175 (50.9)	84 (49.1)	91 (52.7)	
Not anterior	169 (40.1)	87 (50.9)	82 (47.3)	
Killip class				0.510
I	322 (93.6)	162 (94.7)	160 (92.2)	
II–IV	22 (6.4)	9 (5.3)	13 (7.8)	
TIMI risk score				0.365
Low risk (0–3)	260 (75.6)	129 (75.4)	131 (75.7)	
Moderate risk (4–6)	76 (22.1)	40 (23.4)	36 (20.8)	
High risk (7–14)	8 (2.3)	2 (1.2)	6 (3.5)	
Laboratory tests				
Hemoglobin, g/L	151 (142–161)	150 (142–161)	152 (141–160)	0.824
Red blood cell counting, 10^{12}/L	4.9 (4.6–5.2)	4.8 (4.6–5.2)	4.91 (4.5–5.3)	0.503
Platelet, 10^9/L	213 (179–244)	214 (176–246)	212 (181–241)	0.442
Mean platelet volume, fL	10.1 (9.2–10.9)	10.1 (9.2–10.8)	10.1 (9.3–11)	0.701
Scr, μmol/L	75 (66–87.5)	76 (67–87.9)	74 (65–87)	0.639
Glucose, mmol/L	7.4 (6.2–9.8)	7.36 (6.0–9.8)	7.4 (6.3–9.8)	0.433
Total cholesterol, mmol/L	5.1 (4.4– 5.8)	5.1 (4.3–5.8)	5.1 (4.5–5.8)	0.595
Triglyceride, mmol/L	1.7 (1.2–2.8)	1.7 (1.2–2.8)	1.8 (1.2–2.9)	0.890
HDL-C, mmol/L	1.1 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	0.493
LDL-C, mmol/L	3.3 (2.6–3.7)	3.3 (2.6–3.8)	3.3 (2.7–3.7)	0.599
CRP, mg/L	2.0 (1.0–4.6)	2.2 (1.0–5.4)	1.7 (1.0–3.8)	0.578

CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PhI, pharmaco-invasive; PPCI, primary percutaneous coronary intervention; SCr, serum creatinine; and TIMI, thrombolysis in myocardial infarction. Data are presented as median (interquartile range), n (%), or mean±SD.

In the PhI group, 120 (74.5%) patients achieved ECG criteria of successful fibrinolytic reperfusion (ie, STR ≥50%) and underwent early routine catheterization. Of these patients, 104 (64.6%) showed TFG 2/3 of the infarct vessel on initial angiography. Forty-one patients (25.5%) were considered as fibrinolysis failures

Table 2. Procedural Characteristics of Patients

Characteristics	Total (n=328)	PhI (n=161)	PPCI (n=167)	*P* Value
Radial artery access	321 (97.9)	158 (98.1)	163 (97.6)	1.000
Coronary artery disease				0.572
Single vessel disease	127 (38.7)	60 (37.3)	67 (40.1)	
Multivessel disease	201 (61.3)	102 (63.4)	99 (59.3)	
Infarct related artery				0.679
LAD	164 (50.0)	77 (47.8)	87 (52.1)	
LCX	24 (7.3)	11 (6.8)	13 (7.8)	
RCA	137 (41.8)	71 (44.1)	66 (39.5)	
LM	3 (0.9)	2 (1.2)	1 (0.6)	
Target vessel diameter	3 (3–3.5)	3 (3–3.5)	3 (3–3.5)	0.360
Stent implantation				1.000
Drug-eluting stent	307 (93.3)	148 (91.9)	159 (95.2%)	
Bare-metal stent	2 (0.6)	1 (0.6)	1 (0.6)	
TIMI flow pre-PCI				<0.001
0	165 (50.3)	40 (24.8)	125 (74.9)	
1	12 (3.7)	8 (5.0)	4 (2.4)	
2	40 (12.2)	30 (18.6)	10 (6.0)	
3	111 (33.8)	83 (51.6)	28 (16.8)	
TMPG flow pre-PCI				<0.001
0	171 (52.1)	41 (25.5)	130 (77.8)	
1	25 (7.6)	19 (11.8)	6 (3.6)	
2	58 (17.7)	46 (28.6)	12 (7.2)	
3	74 (22.6)	55 (34.2)	19 (11.4)	
Thrombus grade				0.008
0	81 (24.7)	64 (39.8)	17 (10.2)	
1	34 (10.4)	26 (16.2)	8 (4.8)	
2	10 (3.0)	6 (3.7)	4 (2.4)	
3	21 (6.4)	15 (9.3)	6 (3.6)	
4	16 (4.9)	9 (5.6)	7 (4.2)	
5	166 (50.6)	41 (25.5)	125 (74.9)	
Thrombus aspiration	111 (33.8)	29 (18.0)	82 (49.1)	<0.001
GPI use				
During intervention	94 (28.7%)	18 (11.20)	76 (45.50)	<0.001
After intervention	81 (24.7%)	14 (8.70)	67 (40.10)	<0.001
Contrast volume, mL	130 (100–160)	120 (100–150)	150 (100–160)	0.605

GPI indicates GP IIb/IIIa inhibitor; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; PhI, pharmaco-invasive; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; and TMPG, TIMI myocardial perfusion grade. Data are presented as median (interquartile range) or n (%).

(ie, STR <50%) and underwent urgent angiography. Of these patients, 17 (10.6%) showed TFG 2/3 of the infarct vessel on initial angiography.

A detailed breakdown of time intervals is shown in Table 3. Symptom onset to FMC and randomization intervals was similar between the 2 groups. The median time between symptom onset and start of reperfusion therapy (alteplase injection or arterial sheath insertion) was 210 (IQR: 166–270) minutes and 280 (IQR: 214–340) minutes, respectively (*P*<0.001). The median time from randomization to PCI was longer in the fibrinolysis group than in the PPCI group, with a delay of 2.1 hours for rescue PCI and 10.2 hours for routine early PCI.

Epicardial and Myocardial Reperfusion

The primary end point (full reperfusion, defined as TFG 3 and TMPG 3, and complete STR; the patient had to meet all 3 criteria to achieve the primary end point) amounted to 34.2% in the PhI arm versus 22.8% in

Table 3. Time Intervals of EARLY-MYO Trial

Time Delay (Min)	PhI (n=171)	PPCI (n=173)	*P* Value
Symptom onset to first medical contact	148 (108–204)	155 (114–210)	0.559
Symptom onset to randomization	190 (136–251)	185 (137–242)	0.971
Symptom onset to arterial sheath insertion	695 (451–1115)	280 (214–340)	<0.001
Symptom onset to reperfusion treatment	210 (166–270)	280 (214–340)	<0.001
Randomization to arterial sheath insertion	521 (303–957)	110 (50–160)	<0.001
Randomization to reperfusion treatment	57 (7–88)	110 (50–160)	<0.001

EARLY-MYO indicates Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction; PhI, pharmaco-invasive; and PPCI, primary percutaneous coronary intervention. Data are presented as median (interquartile range).

the PPCI arm (risk ratio [RR], 1.48; 95% confidence interval [CI], 1.04–2.10; $P_{noninferiority}$ <0.05), reaching the prespecified noninferiority criterion. Subsequent superiority testing resulted in favor of the PhI arm ($P_{superiority}$ = 0.022). Further prespecified subgroup analyses showed consistent results (Figure 2).

No significant differences by study treatment were found in the frequency of the individual components of the primary end point (Figure 3), namely, TFG 3 after PCI (91.3% versus 89.2%, *P*=0.580), TMPG 3 (65.8% versus 62.9%, *P*=0.730), and STR ≥70% (50.9% versus 45.5%, *P*=0.377). Consistent with the latter findings, corrected TIMI frame count (as a continuous measurement for epicardial reperfusion) and TIMI myocardial perfusion frame count (as a continuous measurement for myocardial reperfusion) after PCI showed no significant difference between the 2 treatments (Figure 4).

Infarct Size and LV Function

CMR was performed at the hospital at a median of 5 (IQR: 4–7) days, with 5.5 (IQR: 4–7) days in the PhI group and 5 (IQR: 4–6) days in the PPCI group (*P*=0.220). CMR-defined infarct size (23.3%±11.3% versus 25.8%±13.7%, *P*=0.101), LV ejection fraction (52.2%±11.0% versus 51.4%±12.0%, *P*=0.562), and incidence of microvascular obstruction (70.7% versus 73.3%, *P*=0.652) were similar in the 2 groups (Figure 5A–D). Of interest is the similar incidence of intramyocardial hemorrhage between the PhI and PPCI groups (51.7% in PhI versus 55.7% in PPCI, *P*=0.531). Echocardiography-defined wall motion score index was also similar between groups in-hospital (1.46±0.03 versus 1.48±0.04, *P*=0.663) and at 30-day (1.41±0.04 versus 1.42±0.04, *P*=0.875) follow-up (Figure 5E and F). Analysis of plasma B-type natriuretic peptide level agreed with these findings, with no significant difference between groups in-hospital (*P*=0.236) and at 30-day (*P*=0.545) follow-up (Figure 5G and H).

Clinical and Safety Outcomes

No difference in outcomes was apparent for the rate of major clinical events over the 30-day follow-up (Table 4). In the 3 patients who died, 1 (0.6%) in the PhI group and 2 (1.2%) in the PPCI group, death was secondary to cardiovascular causes (1 cardiac rupture in PhI group, and 1 cardiac rupture and 1 subacute stent

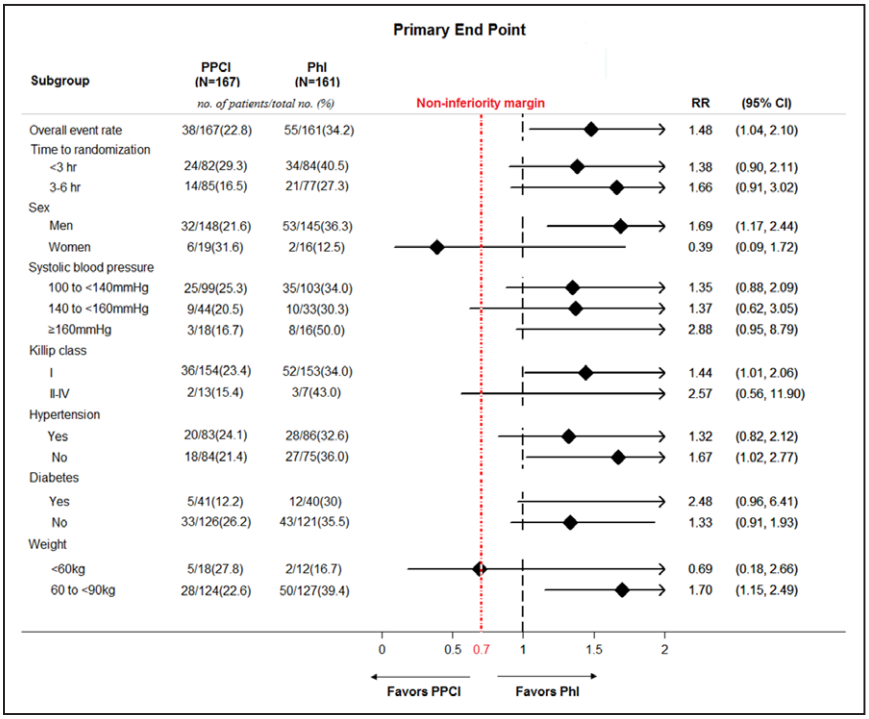

Figure 2. Prespecified subgroup analyses of the primary end point among the 2 treatment arms. PhI would be claimed as noninferior if the lower bound of the 95% confidence limit lied entirely to the right of the noninferiority margin (δ) that was set as 0.7 (indicated as red dash line). PhI indicates pharmaco-invasive; and PPCI, primary percutaneous coronary intervention.

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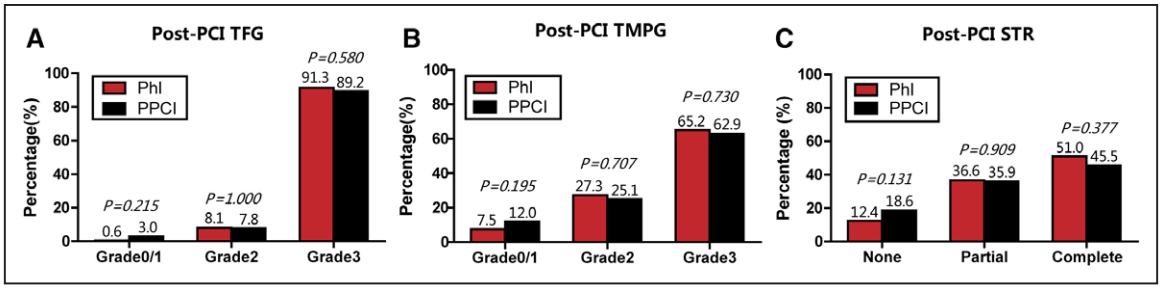

Figure 3. Individual components of the primary end point in the 2 treatment arms.
A, Postinterventional TFG. **B**, Postinterventional TMPG. **C**, Postinterventional STR. PCI indicates percutaneous coronary intervention; PI, pharmaco-invasive; PPCI, primary PCI; STR, ST-segment resolution; TFG, TIMI flow grade; and TMPG, TIMI myocardial perfusion grade.

thrombosis in the PPCI group). The incidences of nonfatal reinfarction (0.6% versus 0.6%, *P*=1.0), heart failure (13.5% versus 16.2%, *P*=0.545), and stroke (0% versus 0%) were similar between groups. The 30-day incidence of the combined outcomes was also similar: 14.6% in the PhI group and 17.9% in the PPCI group, respectively (*P*=0.466). Kaplan-Meier 30-day event-free survival curves comparing PhI-treated patients and PPCI-treated patients are shown in Figure 6 (*P*=0.313 by log-rank test).

The safety outcomes at 30-day follow-up are shown in Table 4. Rates of major bleeding events (0.6% versus 0%, *P*=0.497) and intracranial hemorrhage (0% versus 0%) were similar, but minor bleedings were observed more often in the PhI group compared with the PPCI group (26.9% versus 11.0%, respectively; *P*<0.001). Bleeding events classified by location are shown in Table 5.

DISCUSSION

EARLY-MYO was the first randomized clinical trial to compare the efficacy and safety of a PhI strategy with half-dose alteplase fibrinolysis versus PPCI in patients with STEMI. The EARLY-MYO results showed that, in patients with STEMI at low risk presenting ≤6 hours after symptom onset and with an expected PCI-related delay, a PhI strategy with half-dose alteplase and timely PCI was noninferior (and even superior) to PPCI in terms of incidence of complete epicardial and myocardial reperfusion. CMR-defined infarct size and LV function as well as the 30-day rate of clinical outcomes were similar. Rates of major bleeding events were similar, and no intracranial hemorrhages were observed in either group, with minor bleedings seen more often in the PhI group.

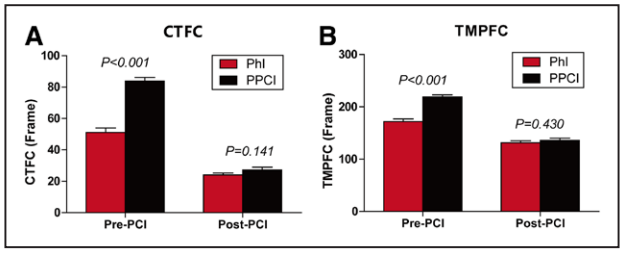

Figure 4. Continuous measurements of epicardial and myocardial perfusion in the 2 treatment arms.
A, Pre- and postinterventional CTFC. **B**, Pre- and postinterventional TMPFC. CTFC indicates corrected TIMI frame count; PCI, percutaneous coronary intervention; PhI, pharmaco-invasive; PPCI, primary PCI; TMPFC, TIMI myocardial perfusion frame count; and TIMI, thrombolysis in myocardial infarction.

Reperfusion for STEMI treatment in the modern era encompasses mechanical and pharmacological strategies.[1,2] It is generally well accepted that PPCI is the preferred reperfusion strategy for all patients with STEMI when it can be performed within the guideline-recommended timeframe at PPCI-capable facilities.[3,4] However, PPCI is not universally available, and large international registries continue to demonstrate persistent delays to PPCI in STEMI.[1] Thus, despite major efforts to develop STEMI networks in many counties, timely PPCI is still limited by challenges in distance, weather, and resources, and physicians are often faced with the decision to either accept PCI-related delays or administer fibrinolysis immediately.[1] It has been suggested that the combination of early reperfusion by initial fibrinolysis with subsequent early PCI, the so-called PhI strategy, could combine the widely available and rapid pharmacological reperfusion with the more complete and sustained reperfusion provided by PCI. Although PhI strategy has been proposed as a therapeutic option for patients with STEMI, current data on the safety and efficacy of such a PhI strategy compared with PPCI are limited.[6,18–20]

The recent STREAM trial enrolled patients with STEMI presenting ≤3 hours of symptom onset with an expected time delay from FMC to PPCI >1 hour. The trial showed no significant between-group difference in the primary end point of all-cause death, shock, congestive heart failure, or reinfarction at 30-day and 1-year follow-up.[6,21] Our EARLY-MYO trial enrolled patients with STEMI presenting ≤6 hours after symptom onset and for whom the expected PCI-related delay was ≥60 minutes. This trial compared the efficacy and safety of

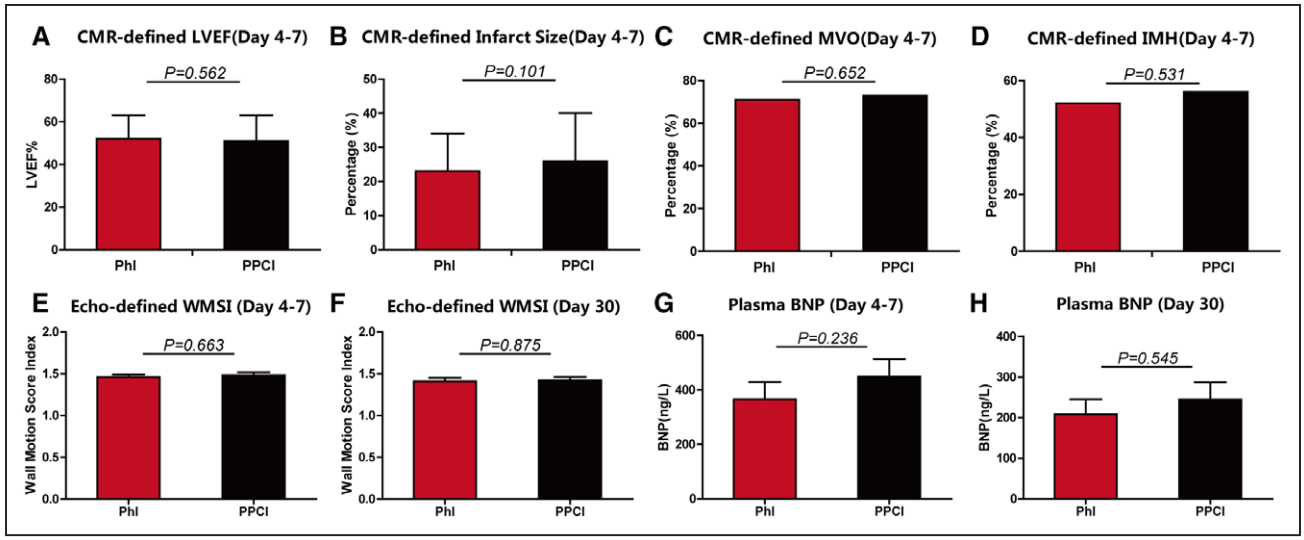

Figure 5. Infarct size and left ventricular function in the 2 treatment arms.
A, CMR-defined LVEF on days 4 to 7. **B**, CMR-defined infarct size on days 4 to 7. **C**, CMR-defined MVO on days 4 to 7. **D**, CMR-defined IMH on days 4 to 7. **E**, Echocardiography-defined WMSI on days 4 to 7. **F**, Echocardiography-defined WMSI on day 30. **G**, Plasma BNP on days 4 to 7. **H**, Plasma BNP on day 30. BNP indicates B-type natriuretic peptide; CMR, cardiac magnetic resonance; Echo, echocardiography; IMH, intramyocardial hemorrhage; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; PhI, pharmaco-invasive; PPCI, primary percutaneous coronary intervention; and WMSI, wall motion score index.

a PhI strategy with half-dose fibrinolytic regimen versus PPCI in patients with STEMI. The results showed that a PhI strategy with half-dose alteplase offered more complete epicardial and myocardial reperfusion after PCI when compared with PPCI. Moreover, CMR-defined infarct size and LV ejection fraction were comparable between PhI and PPCI strategies. Using echocardiography, the GRACIA-2 trial showed that 6-week LV ejection fraction was similar between PhI and PPCI groups (P=0.11),[18] whereas by left ventriculograms, the FAST-MI (French Registry on Acute ST-Elevation Myocardial Infarction) showed that in-hospital LV ejection fraction was significantly higher in the PhI arm than in the PPCI arm (P=0.003).[20] At 30-day follow-up, the rate of clinical outcomes including death, nonfatal reinfarction, heart failure, and stroke were equally distributed across the PhI and PPCI groups. Our results are of clinical importance because a PhI strategy with half-dose alteplase fibrinolytic regimen (8-mg bolus, followed by 42 mg in 90 minutes) achieved a reasonable rate of successful fibrinolysis: 74.5% based on clinical criteria (ie, STR ≥ 50% on ECG) and 75.2% based on angiographic criteria (ie, TFG 2/3 on angiography). Although 100 mg alteplase is recommended in a standard or an accelerated regimen in the guidelines, the TUCC trial (TPA/Urokinase Comparisons in China) showed that half-dose alteplase also is effective, with 79% patients achieving a TFG 2/3 on initial angiography after fibrinolysis.[22] Moreover, our pilot study showed that a PhI strategy with half-dose alteplase fibrinolytic regimen achieved

Table 4. Clinical and Safety Outcomes

Outcome	Total (n=344)	PhI (n=171)	PPCI (n=173)	*P* Value
Clinical outcomes				
Death	3 (0.9)	1 (0.6)	2 (1.2)	1.000
Reinfarction	2 (0.6)	1 (0.6)	1 (0.6)	1.000
Heart failure	51 (14.8)	23 (13.5)	28 (16.2)	0.545
Stroke	0 (0)	0 (0)	0 (0)	—
Combined clinical outcome	56 (16.3)	25 (14.6)	31 (17.9)	0.466
Safety outcomes				
Minor non-ICH bleeding	65 (18.9)	46 (26.9)	19 (11.0)	<0.001
Major non-ICH bleeding	1 (0.3)	1 (0.6)	0 (0)	0.497
ICH bleeding	0 (0)	0 (0)	0 (0)	—

ICH indicates intracranial hemorrhage; PhI, pharmaco-invasive; and PPCI, primary percutaneous coronary intervention. Data are presented as n (%).

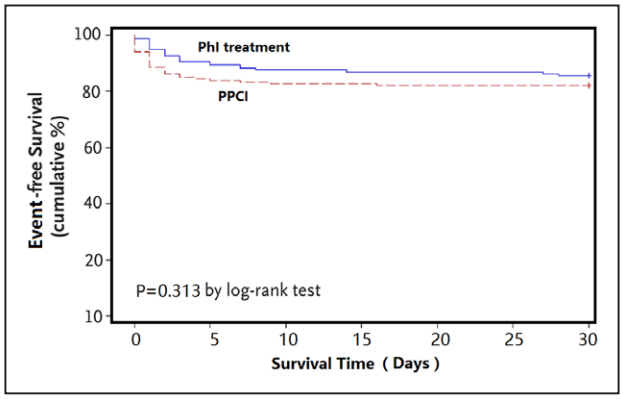

Figure 6. Kaplan–Meier analysis of freedom from the combined clinical outcomes.
Kaplan–Meier survival curve for freedom from the composite of all-cause mortality, nonfatal myocardial infarction, heart failure, and stroke ≤30 days. PhI indicates pharmaco-invasive; and PPCI, primary percutaneous coronary intervention.

a success fibrinolytic rate of 77% in STEMI.[8] Thus, the PhI strategy with half-dose alteplase fibrinolytic regimen appears to be an effective reperfusion strategy for eligible patients with STEMI.

In terms of safety, our study somewhat unexpectedly showed that no intracranial hemorrhages were observed in both the PhI (0 of 171 patients, 0%) and PPCI (0 of 173 patients, 0%) groups at the 30-day follow-up. Note that in the STREAM trial,[6,21] the overall rate of intracranial hemorrhage was significantly higher in the PhI versus PPCI group (0.96% versus 0.21%, respectively; *P*=0.04), but it was not significantly different after the trial protocol was amended to reduce the dose of tenecteplase by 50% (which was made after 20% of planned recruitment) in patients ≥75 years of age (0.54% versus 0.26%, respectively; *P*=0.45). After fibrinolytic dosage amendment, no cases of intracranial hemorrhage occurred (0 of 97 patients, 0%) among patients 75 years of age or older, compared with 3 of 37 patients (8.1%) in this age group before the amendment, suggesting that a half-dose fibrinolytic regimen in the elderly might reduce bleeding risk in the PhI therapy setting. Also considering the higher bleeding rate (5.0% versus 2.7%, *P*=0.03) reported by Henry[23] in patients who received full-dose lytics and early PCI, a half-dose fibrinolysis regimen was used in the present study. We observed low rates of major bleeding events in the PhI arm, suggesting that a half-dose fibrinolytic regimen could be an effective and a safe option for PhI therapy in eligible patients with STEMI. It should be noted that our enrolled patients were a low-risk group (ie, ≈75% had a low TIMI risk score of 0–3, patients >75 years of age were excluded, and >90% of the patients were in Killip class I), which could explain the low event rates observed in our study. Moreover, radial access has recently been associated with a 33% reduction in major bleeding, which drove a 28% reduction of mortality compared with femoral access.[24] Thus, a high rate of radial access (>97%) also would contribute to the low event rate observed in our study. Our CMR findings on intramyocardial hemorrhage were also interesting because one might posit that fibrinolytic therapy would increase the risk of intramyocardial hemorrhage in patients with STEMI. However, the incidence of intramyocardial hemorrhage was comparable between the 2 groups (52% in the PhI arm and 56% in the PPCI arm), indicating that the PhI strategy with a half-dose fibrinolytic regimen would not increase intramyocardial hemorrhage in STEMI. Consistent with our study, the registry investigation by Larson et al[7] in patients with STEMI with expected PCI-related delays showed that a strategy utilizing half-dose fibrinolysis combined with transfer for PCI achieved comparable efficacy outcomes as PPCI without increased bleeding risk.

Another important factor that influenced the efficacy and safety of the PhI strategy is the time window between fibrinolysis and angioplasty. In the ASSENT-4 trial (The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction),[25] patients who underwent PCI at 1 to 3 hours from randomization had higher rates of ischemic complications and mortality than patients undergoing PPCI, which indicates a prothrombotic effect of fibrinolysis followed by too early PCI. In the BRAVE trial (Bavarian Reperfusion Alternatives Evaluation),[26] the fibrinolytic group underwent PCI 2 hours after administration of half-

Table 5. Bleeding Events Classified by Location

Location	Total (n=344)	PhI (n=171)	PPCI (n=173)	*P* Value
Gingival	20 (5.8)	16 (9.4)	4 (2.3)	0.005
Hematuria	16 (4.7)	11 (6.4)	5 (2.9)	0.132
Hemoptysis	2 (0.6)	1 (0.6)	1 (0.6)	1.000
Gastrointestinal hemorrhage	5 (1.5)	4 (2.3)	1 (0.6)	0.213
Cath access site bleeding	8(2.3)	7 (4.1)	1 (0.6)	0.036
Intraocular hemorrhage	1(0.3)	0 (0)	1 (0.6)	1.000
Epistaxis	4 (1.2)	2 (1.2)	2 (1.2)	1.000
Others, n (%)	10 (2.9)	6 (3.5)	4 (2.3)	0.541

PhI indicates pharmaco-invasive; and PPCI, primary percutaneous coronary intervention. Data are presented as n (%).

dose of reteplase instead of a full-dose of fibrinolysis. Despite the higher percentage of preintervention TIMI 3, such an adjustment did not lead to a reduction in infarct size or a better outcome. In our EARLY-MYO trial, the time delay between fibrinolysis and PCI was in accordance with guideline recommendation (within 3–24 hours after fibrinolysis) and similar to the strategies that appeared favorable in the STREAM trial, the GRACIA-2 trial, and the Transfer-AMI trial (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction).[6,18,27]

Limitations

Several study limitations should be considered to place its findings in the proper context. First, the objective of this noninferiority trial was to evaluate the complete epicardial and myocardial reperfusion rate with 2 reperfusion strategies (PhI versus PPCI) aligned with current guidelines in patients with STEMI ≤6 hours and for whom immediate PCI was not possible. More clinical outcome data must be obtained to confirm the reperfusion benefit observed in this study. Second, the reperfusion drugs used in previous studies were tenecteplase or reteplase, which have slower plasma clearance and greater fibrin specificity and can be injected as a bolus.[7] However, alteplase is the only human tissue plasminogen activator available in China during the enrollment period. Third, the patients with STEMI enrolled in the present study were at low risk and not >75 years of age. Thus, the high rate of successful fibrinolysis with half-dose alteplase might not be applicable to all populations and needs to be tested further. Fourth, within the PhI strategy, the optimal timing for routine early PCI after fibrinolysis remains ill defined. Further studies are warranted to identify the best timing for routine PCI after fibrinolysis. Finally, caution is advised when extrapolating our findings to all patients with STEMI within the recommended time window for reperfusion. We should note that in our study, PhI therapy was only considered in patients with STEMI who had expected PCI-related time delay ≥1 hour and only included patients with STEMI presenting ≤6 hours of symptom onset.

CONCLUSIONS

For patients with STEMI at low risk presenting ≤6 hours after symptom onset and for whom the expected PCI-related delay was ≥60 minutes, a PhI strategy with half-dose alteplase and timely PCI offered more complete epicardial and myocardial reperfusion when compared with PPCI. Particularly relevant to emerging countries with limited health budgets and not well-organized STEMI networks for PPCI, the results of our study suggest PhI therapy as a viable strategy for patients with STEMI who cannot receive timely PPCI. Moreover, the present results also underscore the importance of conducting clinical trials that are adequately powered to assess clinical outcomes and comparative bleeding risks and to optimize treatment strategy for patients at different risk levels.

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DISCLOSURES

None.

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FOOTNOTES

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Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment–Elevation Myocardial Infarction: EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment–Elevation Myocardial Infarction)

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SUPPLEMENTAL MATERIAL

Supplementary Methods

EARLY routine catheterization after alteplase fibrinolysis vs. primary PCI in acute ST-segment–elevation MYOcardial infarct

EARLY-MYO Trial

Clinical Trials Register: NCT01930682

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1 Study design

1.1 Overview

Early, successful restoration of myocardial perfusion after a ST-elevation myocardial infarction (STEMI) is the most effective way to reduce final infarct size and improve clinical outcome[1, 2]. Reperfusion for STEMI treatment in the modern era encompasses mechanical and pharmacological strategies. It is generally well-accepted that primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy for all STEMI patients when it can be performed within the guideline-recommended timeframe at PPCI-capable facilities[3, 4]. However, PPCI is not universally available, and delays in performing percutaneous coronary intervention (PCI) are common in real-world practice[5,6]. Even in some large cities, patients have a high chance of presenting to hospitals not providing around-the-clock staffing. Given this background, in recent years there has been great interest and progress in creating triage strategies for STEMI patients who cannot receive timely PPCI.

Pharmaco-invasive (PhI) strategy, an early reperfusion strategy by initial prompt fibrinolysis with subsequent early catheterization (with either routine early PCI after successful fibrinolysis or rescue PCI as needed), has been proposed as a therapeutic option for STEMI patients when timely PPCI is not feasible[6-9]. However, current evidence on the efficacy and safety of PhI strategy in STEMI patients is limited, and the role of PhI strategy in STEMI continues to be debated. Given that no randomized clinical trial is available to compare a PhI strategy with half-dose fibrinolytic regimen versus PPCI in STEMI patients, investigators plan to perform a controlled, randomized trial to evaluate the efficacy and safety of a PhI strategy with half-dose alteplase fibrinolysis versus PPCI in STEMI patients.

1.2 Study Objective

The EARLY-MYO (EARLY routine catheterization after alteplase fibrinolysis vs. PPCI in acute ST-segment elevation MYOcardial infarction) is an investigator-initiated, prospective, multicenter, randomized (1:1), open-label, actively-controlled, parallel group, non-inferiority trial comparing the clinical efficacy and safety of a PhI strategy with half-dose fibrinolysis versus PPCI in STEMI patients presenting within 6 hours after symptom onset and with an expected PCI-related delay of ≥60 min.

1.3 Study Population

It is planned to randomize a total of 350 patients with acute STEMI presenting within 6 hours after symptom onset and with expected time delay from first-medical-contact (FMC) to first balloon inflation ≥90 min and an expected "PCI-related delay time" (defined as the time of FMC to balloon inflation minus the time from FMC to start of fibrinolytic therapy) ≥60 min. Patients will be identified by the inclusion and exclusion criteria. All the inclusion criteria will be fulfilled in eligible patients, and exclusion criteria will disqualify patients. Eligible patients will be randomized to one of the treatment regimens: 1) PhI group: receiving early routine catheterization within 3-24 hours or rescue coronary intervention as needed after half-dose alteplase fibrinolytic therapy; 2) PPCI group: receiving routine PPCI. Prior to randomization, all eligible subjects will be consented. Patients' participation will start once they have signed the informed consent form and will conclude when they have undergone the last extension phase visit. Duration of follow-up will be up to 30 days.

1.4 Use of Alteplase

The investigational drug alteplase powder and solvent for solution for injection and infusion (Actilyse®) is manufactured by Boehringer Ingelheim. Dosage form and packaging of the drug: 1 vial contains 50 mg alteplase, and 1 vial of solvent contains 50 mL sterilised water for injections.

● Drug substance: Alteplase, a recombinant human tissue-type plasminogen activator, a glycoprotein, which activates plasminogen directly to plasmin. When administered intravenously, alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin leading to dissolution of the fibrin clot.

● Toxicology: In subchronic toxicity studies in rats and marmosets no other unexpected side effects than increased bleeding tendency at higher doses were found. No indications of a mutagenic potential were found in mutagenic tests.

● Pharmacokinetics: Alteplase is cleared rapidly from circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 mL/min.). The relevant plasma half-life $T_{1/2}$ alpha is 4 - 5 minutes. This means that after 20 minutes less than 10% of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

In our trial, excluding the patients with contraindication, alteplase will be given as an intravenous bolus (8-mg) followed by 42-mg ivgtt in 90 min before PCI in PhI Group.

2 Selection Criteria

2.1 Inclusion Criteria

1. Age: 18 or over and less than 75 years old;
2. Patents with STEMI with symptom onset within 6 h before randomization;
3. ECG: ≥2 mm ST-segment elevation in 2 contiguous precordial leads or ≥1 mm ST-segment elevation in 2 contiguous extremity leads;
4. Patents with an expected PCI-related delay [expected time delay from FMC to first balloon dilation≥90 min, and difference between the time of FMC to balloon dilation minus the time from FMC to start of fibrinolysis ≥60 minutes)]
5. Signed informed consent form prior to trial participation.

2.2 Exclusion Criteria

1. Evidence of cardiac rupture;
2. ECG: new left bundle branch block;
3. "Diagnosis to balloon inflation" time over 3 hours;
4. Fibrinolysis contradictions:
    - Definite cerebral apoplexy history;
    - Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery) or recent trauma to the head or cranium (i.e. < 3 months);
    - Active bleeding or known bleeding disorder/diathesis;
    - Recent administration of any i.v. or s.c. anticoagulation within 12 hours including unfractionated heparin, enoxaparin and/or bivalirudin or current use of oral anticoagulation (warfarin or coumadin);

- Uncontrolled hypertension, defined as a single blood pressure measurement ≥ 180/110 mm Hg (systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg) prior to randomisation;
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current myocardial infarction); prolonged or traumatic cardiopulmonary resuscitation (> 10 minutes) within the past 2 weeks; major surgery pending in the following 30 days;

5. Severe complication
    - Other diseases with life expectancy ≤12 months;
    - Any history of severe renal or hepatic dysfunction (hepatic failure, cirrhosis, portal hypertension or active hepatitis); neutropenia, thrombocytopenia; known acute pancreatitis;
    - Known acute pericarditis and/or subacute bacterial endocarditis;
    - Arterial aneurysm, arterial/venous malformation and aorta dissection;
6. Complex heart condition
    - Cardiogenic shock (SBP <90mmHg after fluid infusion or SBP<100mmHg after vasoactive drugs);
    - PCI within previous 1 month or previous bypass surgery;
    - Previously known coronary artery disease not suitable for revascularization;
    - Hospitalisation for cardiac reason within past 48 hours;
7. Not suitable for clinical trial
    - Inclusion in another clinical trial;
    - Previous enrollment in this study or treatment with an investigational drug or device under another study protocol in the past 7 days;
    - Pregnant or lactating;
    - Body weight <40kg or >125kg;
    - Known hypersensitivity to any drug that may be used in the study;
    - Inability to follow the protocol and comply with follow-up requirements or any other reason the investigator feels would place the patient at increased risk.

2.3 Removal of Patients

2.3.1 Removal of Individual Patients

Patients have the right to withdraw from the study at any time without the need to justify the decision. The investigator has the right to remove patients from the study for noncompliance, administrative or other reasons. It is understood that an excessive rate of withdrawals can render the study results uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. The sponsor reserves the right to terminate a patient from the trial for non-adherence.

2.3.2 Criteria of Removal of Patients from the Trial

Patients should be withdrawn from the trial prior to completion if any of the following criteria are met: 1) inconsistency with the inclusion and exclusion criteria is detected after recruitment; 2) protocol violation (including poor compliance); 3) in light of safety issues, it is no longer proper for the patients to participate in the trial because of the occurrence of adverse events; 4) withdrawal required by the patients. Patients refuse to participate or continue to participate in the trial; and 5) pregnancy.

2.3.3 Discontinuation of the Trial by the Sponsor

Sponsor reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons: 1) failure to meet expected enrollment goals at a particular trial site; and 2) violation of GCP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

2.3.4 Removal of Individual Patient's Treatment

Every attempt will be made to detect the reason for withdrawal from the trial, e.g. adverse event, lack of efficacy, removal from the trial determined by the investigator, other reasons which should be documented in the case report form (CRF). Adverse event should be assessed, determined and followed up by the investigators.

3 Study Methodology

3.1 Screening and Enrollment

The ordered enrollment process consists of screening, treatment and follow-up period. All patients are referred to medical center in this clinical trial for reperfusion therapy. The trial will be explained to the individual patient for consideration. The potential participant will be given adequate time to have all their questions answered and to carefully consider participation. Written consent of participant is necessary.

3.2 Baseline Procedures

All patients will routinely receive guideline-directed medical therapy (GDMT), such as antiplatelet therapy, and testing to clarify diagnosis during the screening period. Randomization and administration of study medication will start in the Screening Period. Their participation is concluded when they have undergone the last extension phase visit (unless the patient is lost to follow up, informed consent is withdrawn or early discontinuation).

3.3 Randomization

After providing informed consent, patients who meet inclusion and exclusion criteria will be randomly assigned to one of the two following open-label treatment regimens at a ratio of 1:1 ("PhI" group or "PPCI" group) and will be stratified according to the time interval between disease onset and enrollment (less than 3 hours and 3-6 hours). Doctors who informed the patient will take care of allocation by means of third-party randomization. This will involve the use of an Interactive Web-based Response System (IWRS) which will be implemented to assign a medication number to an eligible patient as well as to track enrollment across all centres.

3.4 Standard Care Procedures

All patients with STEMI will receive guideline recommended treatment. At the emergency room, all patients will receive upfront 300 mg of aspirin and a loading dose of ADP receptor antagonists. For patients who have already taken aspirin or ADP receptor antagonists within 12 hours before screening, aspirin or ADP receptor antagonists will be given the following day. Beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, and

post-interventional antithrombotic therapy will be administered to patients as outlined in the ESC guidelines for myocardial infarction.[2] All study participants will be scheduled for follow-up at 30 days after enrollment.

3.5 PhI Group Procedures

All patients randomly assigned to PhI group will receive an intravenous bolus of unfractionated heparin (60 U/kg up to a maximum of 4000 U) followed by alteplase administration. Alteplase will be given as an intravenous bolus (8-mg) followed by 42-mg ivgtt in 90 min. After alteplase administration, unfractionated heparin (12 U/kg/h up to a maximum of 1000 U/h) will be given continuously until the catheterization. Eighteen-lead ECG will be repeated every 30 minutes after start of fibrinolysis. Early routine catheterization within 3 - 24 hours after fibrinolytic therapy will be performed, if required, PCI or, in case of insufficient ST resolution at 90 min, rescue PCI. The decision on rescue PCI will be taken 90 min (or earlier if clinically indicated) after injection of alteplase according to ST-segment resolution (less than 50% reduction in ST-segment elevation). PCI of the presumed culprit lesion in the infarct-related artery will be performed if the residual stenosis was at least 50%, regardless of the flow and patency status.

3.6 PPCI Group Procedures

Patients randomly assigned to PPCI group will receive unfractionated heparin to achieve an activated clotting time of 350-450 seconds during the invasive procedure. PPCI will be performed according to standard practice. A stent will be implanted whenever technically possible, and the use of drug-eluting stents is encouraged.

The use of thrombus aspiration device is at investigator's discretion during percutaneous coronary intervention if thrombus grade is ≥ 3 degrees. Glycoprotein IIb/IIIa inhibitor use is not allowed before PCI. The use of Glycoprotein IIb/IIIa in the catheter lab or post-catheterization is at investigator's discretion in accordance with ESC guidelines[2].

3.7 Rescue medication and additional treatment

Bleeding is a major complication of thrombolytic therapy. For minor bleeding, the patient will be monitored continuously, and symptomatic treatment will be given. If patients develop neurological symptoms within the initial 72 hours post thrombolysis, intracranial hemorrhage (ICH) should be ruled out. Any thrombolysis, antiplatelet and anti-coagulation therapy should be stopped and a cranial CT should be obtained to rule out ICH. A neurologist and hematologist should be consulted. According to the clinical situation, freeze-dried plasma, protamine, platelets or cryoprecipitate should be given. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the CRFs.

3.8 Study Endpoints and Definitions

3.8.1 Endpoints of Efficacy

3.8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is complete epicardial and myocardial reperfusion following angioplasty, defined as: TIMI flow grade (TFG) 3 for epicardial reperfusion, TIMI myocardial perfusion grade (TMPG) 3 for myocardial reperfusion, and resolution of the initial sum of ST-segment elevation (STR) ≥ 70% in 60 min post catheterization.

3.8.1.2 Secondary Efficacy Endpoint

The key secondary endpoints are the frequency of the individual components of the primary endpoint: TFG 3 for complete epicardial perfusion, TMPG 3 for complete myocardial perfusion, and STR≥70% in 60 min post catheterization. Other secondary endpoints include: 1) left

ventricular (LV) function and infarct size assessment by cardiac magnetic resonance (CMR) on day 4-7; 2) wall motion score index (WMSI) assessment by echocardiography on day 4-7 and 30 days; and 3) clinical events (all cause death, reinfarction, heart failure, and stroke) through 30-day follow-up.

3.8.2 Assessment of efficacy

3.8.2.1 Epicardial and Myocardial Reperfusion

Coronary angiograms will be centrally assessed at an independent core laboratory by experienced readers without knowledge of treatment assignment or clinical outcome. Flow in the epicardial arteries will be assessed by TFG[10], and corrected TIMI frame count (CTFC) will be used to assess epicardial perfusion[11]. Myocardial tissue-level perfusion will be assessed by TMPG and TIMI myocardial perfusion frame count (TMPFC) [12,13]. TMPFC is a novel method described by our group recently to standardize and quantify myocardial perfusion[13]. Additional assessment of myocardial reperfusion will be carried out using ST-segment analysis[14].

- **TFG and CTFC**: TFG is assessed as previously defined[10]: TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion; TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory; and TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely. The CTFC will be measured with a frame counter to objectively evaluate an index of coronary flow as a continuous quantitative variable, i.e., the number of cineframes required for contrast to first reach standardized distal coronary landmarks in the infarct-related artery[11]. The first frame used for TIMI frame counting is the first frame in which dye fully enters the artery. The last frame is counted or included as one of the frames and is defined as the frame when dye first enters the distal landmark branch. These frame counts are corrected for the longer length of the LAD by dividing by 1.7 to arrive at the CTFC.
- **TMPG and TMPFC**: The TMPG is assessed as previously defined[12]: 1) TMPG 0: Failure of dye to enter the microvasculature. Either minimal or no ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion; 2) TMPG1: Dye slowly enters but fails to exit the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (~30 seconds between injections); 3) TMPG2: Delayed entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase; and 4) TMPG3: Normal entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of the washout phase, similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3. The TMPFC was developed to standardize and quantify myocardial perfusion by timing the filling and clearance of contrast in the myocardium using cine-angiographic frame-counting[13]. The first frame of TMPFC is defined as the frame that clearly demonstrates the first appearance of myocardial blush beyond the IRA (F1). The last frame of TMPFC is then defined as the frame where contrast or myocardial blush disappears (F2). TMPFC is therefore F2-F1 frame counts at filming rate of 15 frames/sec.

- **STR**: Eighteen-lead ECGs will be obtained before and 60 minutes after the procedure. At an independent core laboratory blinded to treatment assignment and clinical outcome, the sum of ST-segment elevation 20 ms after the J point will be measured and compared with the baseline ECG. ST-segment elevation resolution will be calculated as the initial sum of ST-segment elevation minus the sum of ST-segment elevation on the post-PCI ECG divided by the initial sum of ST-segment elevation and expressed as a percentage, and stratified into three categories based on Schroder's method[14]: Complete resolution is defined as a resolution of ≥70% of the sum of the initial ST-segment elevation; partial resolution is defined as ST-segment resolution<70% to 30%; and absent resolution is defined as ST-segment resolution <30%.

3.8.2.2 Left Ventricular Function

LV function will be assessed by contrast-enhanced CMR, echocardiography, and blood B-type natriuretic peptide (BNP).

- Contrast-enhanced CMR will be performed 3 to 7 days after STEMI using a 1.5-T or 3-T scanner with dedicated cardiac surface coils. For LV function, cine steady-state free-precession sequences will be used in standard orientations. Infarct size will be determined in short axis late enhancement images using semiautomatic contouring, and expressed as a percentage of the LV mass (% LV). The incidence of microvascular obstruction and intramyocardial haemorrhage also will be recorded. The scans will be reviewed, and a consensus reached, by 2 expert observers at an independent core laboratory.

- Echocardiography examination will be done in hospital on the same day as MRI examination and also at 30-day follow-up. Quantitative echocardiographic studies of wall motion will be done with the 16-segment model as recommended. The WMSI will be calculated as the sum of the scores in each segment divided by 16. Each segment will be given a score based on its systolic function (normal = 1, hypokinesis = 2, akinesis = 3). All echocardiographic data will be stored digitally in DICOM format for subsequent offline analysis. Observers of CMR and echocardiography will be blinded to the treatment strategy and all other clinical data.

- Blood BNP will be tested at randomization, in-hospital and day 30.

3.8.2.3 Clinical Outcomes

Clinical follow-up will be performed at 30 days. All cause death, non-fatal reinfarction, heart failure, and stroke after randomization constitute the clinical endpoints, defined as follows:

- **Death**: Death will be classified as cardiovascular or non-cardiovascular. All cause deaths will be considered cardiac unless a definite noncardiac cause can be established.

- **Reinfarction**: 1) Reinfarction within 18 hours of onset of the index myocardial infarction: new ST elevation of ≥1 mm in at least 2 contiguous leads and recurrent cardiac ischemic symptoms ≥20 min at rest. 2) Reinfarction after 18 h of onset of the index myocardial infarction but before myocardial necrosis biomarkers have returned to normal: myocardial necrosis biomarker re-elevation (troponin) defined as an increase of ≥50% over a previous value that was decreasing, and at least one of the following: recurrent cardiac ischemic symptoms ≥20 min at rest, or one of the following ECG changes: new ST-segment elevation ≥1 mm in at least 2 contiguous leads, or development of new pathological Q waves on the ECG, or new left bundle branch block. 3) Reinfarction after myocardial necrosis biomarkers have returned to normal (excluding myocardial infarction in patients undergoing PCI in the previous 24 h): elevation of myocardial necrosis biomarkers typical of acute MI, with at least one of the following: recurrent cardiac ischemic symptoms ≥20 min at rest, or development

of new pathological Q waves on the ECG, or ECG changes indicative of ischemia, or pathological findings of an acute myocardial infarction. 4) Reinfarction within 24 h after PCI: Troponin ≥3 times the upper limit of normal and, if the pre-PCI troponin was >ULN, both an increase by ≥50% over the previous value, and documentation that troponin was decreasing prior to the suspected recurrent MI (no symptoms are required), or development of new pathological Q waves on the ECG (no symptoms are required).

- **Heart failure:** Patients presenting with at least one of the following conditions and requiring treatment with diuretics: 1) Pulmonary oedema/congestion on chest x-ray without suspicion of a non-cardiac cause; 2) Rales >1/3 up from the lung base; 3) Pulmonary capillary wedge pressure (PCWP) >25 mmHg; 4) Dyspnoea with pO_2 < 80 mmHg or O_2 sat < 90 % (no supplemental O2) in the absence of known lung disease.
- **Stroke**: Any stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as a computerized tomography (CT) or magnetic resonance imaging (MRI) be performed.

3.8.3 Safety Endpoints

The main safety endpoint is the incidence of major bleeding and other adverse event. All bleeding complication will be classified by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severity criteria[15]. Adverse event is defined as any event which constitutes a hazard or a handicap to a participant irrespective of a connection with the pharmaceutical product. Independent study monitors will review all source documents onsite for accuracy and completeness. Clinical and safety endpoints will be verified by a blinded adjudication committee.

3.8.4 Assessment of Safety Endpoints

Incidence of bleeding events will be classified by the GUSTO severity criteria[15]. GUSTO criteria for classifying the severity of bleeding complications:

- **Severe or life-threatening bleeding**: Intracranial bleeding or bleeding that causes substantial hemodynamic compromise requiring treatment;
- **Moderate bleeding**: Bleeding which needs blood transfusion;
- **Minor bleeding**: Other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

3.9 Safety Assessment

3.9.1 Assessment of Adverse Events

3.9.1.1 Definitions of Adverse Events

Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Adverse events will be monitored throughout the study and reported in the CRF.

Accompanying the widespread and increasing use of radiographic contrast media in diagnostic and interventional procedure, contrast-induced nephropathy (CIN) is the leading complication

after angiography. CIN is defined as a 25% or 0.5mg/dL increase in serum creatinine from baseline. Thus, CIN will be considered as adverse event.

Serious adverse event (SAE)

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment, which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Adverse Events of Special Interest (AESI)

In accordance with China GCP and related regulations, AESI includes symptomatic intracranial hemorrhage or known bleeding disorder, and the serum concentration of ALT is over thrice the upper limit of normal.

AESIs are usually not reported immediately to HAs, Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), and investigators. However, they will be reported instantly if they meet the criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) or if expedited reporting was requested by investigators.

All AESIs are entered into Boehringer Ingelheim global Adverse Reaction Information System (ARISg) and will be processed in the same manner and within the same timelines as an SAE.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event:

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, and confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.
- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

If a SAE is reported, the causal relationship must be provided by the investigator for study medication and study design, trial drug and for any relevant past or concomitant medications provided on the SAE form.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the CRF.

Changes in vital signs, physical examination, and laboratory tests will be only then recorded as AEs if they are not associated with an already reported AE, symptom or diagnosis, and the

investigational drug is either discontinued, reduced or increased, or additional treatment is required, i.e. concomitant medication is added or changed.

During the clinical trial, patients will be required to report spontaneously any AEs as well as the time of onset, duration and intensity of these events.

3.9.1.2 Adverse Event and Serious Adverse Event Reporting

All adverse events, serious and non-serious, occurring during clinical trial (i.e., from signing the informed consent onwards through the observational period) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRFs / SAE reporting forms regardless of whether the investigational product has been administered or not and irrespective of causal relationship.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs.

Reporting AEs occurring up to 30 days after all treatment discontinuation:

The investigator also has the responsibility to report AEs occurring up to 30 days after all treatment discontinuation. Any AEs reported to the sponsor during this phase must be documented in the safety database/CRF as is applicable. This information also must be reported immediately to the head of the trial site. With receipt of any further information to these events, a follow-up SAE report must be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

With receipt of any further information to these events, a follow-up SAE report must be provided immediately within 24 hours or the next business day; whichever is shorter. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

Investigators must file the serious adverse event in the report form immediately after its occurrence and send the report to SFDA, relevant government department, Boehringer Ingelheim Int. Trading (Shanghai) Co. Ltd. (BI), relevant contract research organization (CRO) and ethics committee with signature and date indicated on the report by the investigator.

This immediate report is required regardless of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified significant events defined as Adverse Events of Special interest in this protocol becomes available.

Pregnancy:

In rare cases, pregnancy might occur in clinical trials. Once a woman has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor and stop trial medication. Drug exposure during pregnancy must be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of Boehringer Ingelheim Int. Trading (Shanghai) Co. Ltd. (BI). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials. If the female patient does experience a SAE after exposure, both a Pregnancy Monitoring Form and a SAE report form should be filled out.

3.9.2 Assessment of Safety Laboratory Parameters

The laboratory tests will be performed at the central laboratory service provider. Instructions on collection, handling/ processing, and shipping of the samples will be provided in the investigator site file by the central laboratory.

Laboratory results of the patients will be available to the respective investigator within 24 hours.

Clinically relevant laboratory values should be commented on lab report printouts. A clinically relevant value may be either within or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit lab kit and should be repeated until normalization or stabilization or until an alternative explanation has been found.

Renal function (SCr) is tested at baseline and 24-72h after PCI. BNP is tested at randomization, in-hospital and at day 30.

4 Follow-Up Procedures

All study participants were scheduled for follow-up at 30 days after enrollment. All patients are to adhere to the visit schedule. If any visit must be rescheduled, subsequent visits should follow the original visit date schedule. In some instances, such as holidays, it may not be possible to schedule a patient visit at the specified interval. For those situations some flexibility will be allowed: 30±5 days.

5 Data Management

5.1 Data Collection

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

For CRFs all data must be derived from source documents.

5.2 Data Monitoring

An independent Data and Safety Monitoring Board (DSMB) will monitor the accruing safety and outcome data. The DSMB will be composed of independent cardiologists, independent interventionists and one independent biostatistician. The DSMB will review safety data regularly, and provide and conduct analyses of the data at the request of the Steering Committee and/or Executive Committee. The DSMB analyses and operations will be formally separated from the sponsor, the investigators and the Steering/Executive Committee. The DSMB will advise the Study Chairman by giving recommendations on trial continuation or aspects of study conduct.

6. Statistical Analysis Plan Summary

This is an investigator-initiated, prospective, multicenter, randomized, open-label, actively controlled, parallel-group, non-inferiority designed trial, comparing a PhI strategy with half-dose alteplase fibrinolysis versus PPCI in STEMI patients. The primary endpoint is complete epicardial and myocardial reperfusion, defined as TFG3 for epicardial reperfusion, TMPG 3 for myocardial reperfusion, and resolution of initial sum of ST-segment elevation ≥ 70% following angioplasty.

The null hypothesis is that the relative risk ($\theta_{PhI/PPCI}$) of complete epicardial and myocardial reperfusion rate for the PhI group vs. PPCI group is lower than the specified non-inferiority margin δ=0.7. The alternative hypothesis is that the relative risk of PhI vs. PPCI is higher than or equal to 0.7, i.e., H_0: $\theta_{PhI/PPCI} < 0.7$ vs. H_a: $\theta_{PhI/PPCI} \geq 0.7$. The relative risk and its 95% confidence limit will be estimated for the primary endpoint to test for non-inferiority of PhI over PPCI. The lower bound of the confidence interval (CI) of relative risk of PhI vs. PPCI will be compared to the non-inferiority margin for non-inferiority testing. PhI would be claimed as non-inferior if the 95% confidence limit lied entirely to the right of the non-inferiority margin (δ) which was set as 0.7. The null hypothesis will be tested at the one-sided $\alpha = 0.025$ significance level. If and only if the non-inferiority claim is established, the superiority testing will be performed to compare the response rate of PhI (P_{PhI}) to PPCI (P_{PPCI}) with the hypotheses stated as: H_0: $P_{PhI} \leq P_{PPCI}$ vs. H_a: $P_{PhI} > P_{PPCI}$. The primary analysis for the primary endpoint will be conducted using the CMH test.

6.1 Sample Size Calculation

The sample size is estimated assuming that the incidence of the primary endpoint (i.e., complete epicardial and myocardial reperfusion post-PCI) is 25% in PhI group and 20% in the PPCI group based on data from the GRACIA-2 trial [9]. With the latter assumption, the trial is designed to include a total of 326 patients to prove non-inferiority of PhI to PPCI at a one-sided α=0.025 level based on the prespecified non-inferiority margin of 0.7 with 80% power. Considering an approximate 7% withdrawal rate, total patient number is estimated at 350, i.e., 175 patients per arm.

6.2 Planned Analysis

The primary analysis will be performed on the full analysis set (FAS). Patients will be analyzed as randomized using the intention-to-treat (ITT) principle. The data will be presented as numbers and percentages for categorical variables and compared using the Chi-square test or Fisher exact test; continuous variables will be reported as mean ± SD or medians with interquartile ranges and compared using a Student t test or the Wilcoxon rank sum test, as appropriate. The primary analysis for the primary endpoint will be conducted using the CMH test controlling for stratification factor (i.e., time interval between disease onset and enrollment). The relative risk and its 95% confidence limit will be estimated for the primary endpoint to test for non-inferiority between the PhI group and the PPCI group. PhI will be claimed as non-inferior if the 95% confidence limit lied entirely to the right of the non-inferiority margin (δ) which was set as 0.7. If and only if the non-inferiority claim is established, the superiority test will be performed. For the primary endpoint, we also will perform prespecified subgroup analyses according to time to randomization, sex, weight, systolic blood pressure, infarct location, Killip class, and a history of diabetes or hypertension. For event-free survival, wewill compare Kaplan–Meier curves using a log-rank test.

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