THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Pharmaco-Invasive Strategy with Half-Dose Recombinant Human Prourokinase Versus Primary Percutaneous Coronary Intervention

ORIGINAL INVESTIGATION

ABSTRACT

Background: Primary percutaneous coronary intervention (PPCI) is preferred as the reperfusion option for patients with ST-segment elevation myocardial infarction (STEMI).

Methods: This study conducted the pharmaco-invasive strategy with half-dose recombinant human prourokinase (PHDP) trial to evaluate whether the PHPD encompassing early fibrinolysis coupled with timely catheterization, provides efficacy and safety similar to that of PPCI in STEMI patients. We randomly assigned patients with STEMI aged 18-80 years who presented within 24 h of their symptoms to receive either PHDP or PPCI.

Results: There was no significant difference in the 2 arms for the primary endpoints, which were defined as thrombolysis in myocardial infarction (TIMI) flow grade 3, TIMI myocardial perfusion grade 3, and ST-segment resolution ≥70% 1 hour after percutaneous coronary intervention. The secondary endpoints, including slow flow/no-reflow ($P < .001$), malignant arrhythmia ($P < .001$), and hypotension ($P < .001$), occurred more frequently in the PPCI arm than in the PHDP arm. The combined 30-day follow-up outcomes occurred more often in the PPCI group than in the PHDP group ($P = .032$). There were no reported cases of in-hospital intracranial hemorrhage or major bleeding events; the rates of minor bleeding events were similar ($P = .157$).

Conclusion: Among patients with STEMI presenting ≤24 hours after symptom onset who received the PHDP, the efficacy of complete epicardial and myocardial reperfusion was similar to that among patients who received the PPCI. In addition, PHDP was associated with a decreased risk of procedure-related complications. Conducting clinical efficacy and safety trials with the pharmaco-invasive strategy and the half-dose of fibrinolytic drug is warranted.

Keywords: Complicationsfibrinolysis, percutaneous coronary intervention, recombinant human prourokinase, ST-segment elevation myocardial infarction

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Received: September 30, 2024
Accepted: December 4, 2024
Available Online Date: February 17, 2025

Cite this article as: Jiang C, Dou J, Yang H, et al. Pharmaco-invasive strategy with half-dose recombinant human prourokinase versus primary percutaneous coronary intervention. *Anatol J Cardiol.* 2025;29(4):164-172.

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DOI:10.14744/AnatolJCardiol.2025.4879

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion option for patients with ST-segment elevation myocardial infarction (STEMI) because it reduces the risk of death associated with cardiac causes and prevents major adverse cardiovascular events.[1] Previous studies have suggested that PPCI is superior to intravenous thrombolysis alone in patients with STEMI.[2,3] However, more recent clinical trials have shown that this approach cannot be performed in a timely manner in many regions, and percutaneous coronary intervention (PCI)-related delays from symptom onset to coronary intervention are common in clinical practice.[1,4-6] This factor leads to an increased risk of morbidity and mortality.[1,5]

The pharmaco-invasive (PhI) strategy includes timely fibrinolysis coupled with routine catheterization; this approach is recommended as an effective alternative by current guidelines and has shown favorable effects on epicardial and myocardial reperfusion in randomized clinical studies involving patients with acute STEMI who cannot undergo PPCI within the guideline-recommended time window.[1] However, the discrepancy between current guideline recommendations and real-world use is likely connected with the belief that the PhI strategy has a greater risk of major bleeding effects.[5,7] The results from the Strategic

Reperfusion Early after Myocardial Infarction (STREAM) study demonstrated that a disadvantage of the PhI strategy was its incidence of intracranial hemorrhage, with the total dosage of the fibrinolytic agents being five-fold greater than that of the PPCI.[7] It is interesting to compare the rate of bleeding events in the STREAM study with that in analogous intervention arms in the Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST Segment Elevation Myocardial Infarction (EARLY-MYO) trial, which favored the PhI strategy with a half dose of fibrinolytic drug over the PPCI.[7,8] However, whether the clinical efficacy and safety of these various treatment regimens change with the different pharmaceutical classes is uncertain.

We conducted the pharmaco-invasive strategy with half-dose recombinant human prourokinase (PHDP) trial to evaluate whether the PHPD encompassing early fibrinolysis coupled with timely catheterization, provides efficacy and safety similar to that of PPCI in STEMI patients who presented to our hospital ≤24 hours after symptom onset. Previous studies have reported on the efficacy and in-hospital safety of PHDP in patients with STEMI.[9] This study aims to further elucidate the complications during PCI and short-term follow-up outcomes of that research.

METHODS

Study Design and Eligibility

This is a prospective, open-label, randomized, single-center trial. All the subjects provided informed written consent, and the PHDP trial conformed to the Declaration of Helsinki. Patients who visited our hospital within 0-24 hours after symptom onset and had evidence of STEMI according to specific electrocardiogram criteria (ST-segment elevation of at least 2 mm in 2 or more contiguous precordial leads; ST-segment elevation of at least 1 mm in at least 2 peripheral leads; or left bundle-branch block), regardless of whether PCI-related delay was present, were eligible for participation (aged 18-80 years). The exclusion criteria for patients were as follows: (1) >80 years of age, (2) evidence of cardiac rupture, (3) cardiogenic shock, (4) fibrinolysis contraindication, (5) severe hepatic or renal insufficiency, (6) hypersensitivity reactions to contrast agents, (7) other diseases with a life expectancy ≤12 months, (8) patients who refused coronary angiography (CAG).

Randomization and Trial Intervention

Patients who met the inclusion criteria were randomized at a 1 : 1 ratio to undergo PHDP or PPCI based on a random number table.

All the patients were assigned to undergo 1 of 2 treatment plans: half-dose recombinant human prourokinase (rhPro-UK) (10-mg bolus, followed by 15 mg in 30 minutes) or unfractionated heparin (60 U/kg bolus followed by 12 U/kg/h). The PPCI was performed according to current guidelines, with early use of unfractionated heparin to maintain an activated partial thromboplastin time of 50-70 seconds during the procedure. Antiplatelet therapy consisted of oral aspirin (300 mg loading dose, followed by 100 mg once daily) combined with a P2Y12 receptor antagonist (clopidogrel [loading dose 180 mg, followed by 75 mg once daily] or ticagrelor [loading dose 180 mg, followed by 90 mg twice daily]). Rescue PCI in the PHDP group was permitted in the presence of hemodynamic instability or ST-segment resolution (STR) <50% 90 minutes after fibrinolysis, according to 18-lead electrocardiography and the cardiologist's judgment; the remaining patients received angiography within 3-24 hours after thrombolysis and underwent further PCI if the residual stenosis was >50%. Thrombus aspiration, stent implantation, tirofiban, dopamine, sodium nitroprusside, atropine, and norepinephrine were offered in the catheterization room according to the condition of patients with STEMI, as decided upon by cardiologists.

Primary Endpoint

The primary endpoints of this trial were full epicardial and myocardial reperfusion, defined as thrombolysis in myocardial infarction (TIMI) flow grade (TFG) 3, TIMI myocardial perfusion (TMPG) grade 3, and STR ≥ 70% 1 hour after PCI. The participants had to satisfy all three criteria to reach the primary endpoint.[10-12] Coronary angiograms and the incidence of the individual components of the primary endpoint were carefully recorded and judged at the angiographic core laboratory by 2 experienced interventional cardiologists who were not involved in our study. All disputes were resolved by discussion.

Secondary Endpoint

The secondary endpoint was a combination of slow flow/no-reflow (defined as a TFG of 0-2), hypotension (≤90/60 mm Hg), or malignant arrhythmia during the procedure.[13,14] The malignant arrhythmia included ventricular fibrillation, ventricular tachycardia, cardiac arrest, pulseless electrical activity, second-degree atrioventricular Mobitz type 2 block, or third-degree atrioventricular block.

30-Day Follow-Up Outcomes and Bleeding Events

The 30-day follow-up outcomes of this trial were a composite of stroke, death from any cause, death from a cardiac cause, cardiac arrest, hospitalization for heart failure, hospitalization for unstable angina, revascularization with PCI or coronary artery bypass graft (CABG), and nonfatal myocardial infarction. The bleeding consisted of intracranial hemorrhage and major and minor bleeding events. Major bleeding

HIGHLIGHTS

- Among patients with ST-segment elevation myocardial infarction (STEMI) presenting within 24 hours after the onset of symptoms, the pharmaco-invasive strategy with half-dose recombinant human prourokinase (PHDP) was non-inferior to primary percutaneous coronary intervention (PPCI).
- The incidence of slow flow/no-reflow, malignant arrhythmia, or hypotension during the procedure was greater among the patients who received PPCI than among those who received a PHDP.
- Patients with STEMI who were assigned to receive the PHDP had a lower risk of combined 30-day follow-up outcomes than those who received PPCI.

is any clinically visible bleeding accompanied by a hemoglobin drop of ≥5 g/dL. Minor bleeding events were divided by location into epistaxis, gingival, bloody sputum, gastrointestinal bleeding, microscopic hematuria, macroscopic hematuria, fecal occult blood test positive or weekly positive, and subcutaneous hematoma.

Statistical Analysis

Using the Student's *t*-test or the Wilcoxon rank sum test, continuous variables were compared as the means, medians, and interquartile ranges; the Shapiro-Wilk test was used to determine the normality of the distribution. In the case of categorical variables, the Chi-square and Fisher's exact test were used to calculate the number of values and percentages. The primary endpoint was compared using the Cochran–Mantel–Haenszel test adjusted for stratification factors (i.e., time delay from symptom onset to randomization).

We also conducted a prespecified subgroup analysis for the primary endpoint according to age, sex, hypertension, diabetes, previous angina pectoris, Killip class, and symptom to reperfusion time. The incidence of the secondary endpoint and its components are reported as numbers and percentages in the column graphs. Two-sided *P* values less than .05 were considered to indicate statistical significance.

IBM Corporation's SPSS software (Armonk, NY, USA), version 26.0, was used for data analysis. To draw graphs, we used Prism software (GraphPad Software, Inc., San Diego, CA, USA), version 8, and R statistical software (R Foundation for Statistical Computing, Vienna, Austria), version 4.2.1.

Statement

We never used artificial intelligence-assisted technologies (such as Large Language Models, chatbots, or image creators) in the production of the submitted work.

RESULTS

Patient Characteristics

The study population flow chart is shown in Figure 1. From September 1, 2019, to October 31, 2021, we enrolled 149 patients with acute STEMI who provided written informed consent. In the PHDP group, 2 patients refused CAG after fibrinolysis. In the PPCI group, 3 patients died before meeting the primary endpoint. As a result, 144 patients (71 in the PHDP group and 73 in the PPCI group) met the primary efficacy endpoint.

The baseline and clinical characteristics of the 2 arms were balanced (Table 1). Ages ranged from 32 to 80 years, with a mean age of 57 years, and 81.9% were men.

In Table 2, angiographic and procedural characteristics are presented. The distributions of infarct-related arteries, radial artery access, and stent implantation were similar between the 2 groups. The prevalence of pre-PCI TFG 3 (63.4% vs. 17.8%, $P < .001$) and pre-PCI TMPG 3 (40.8% vs. 17.8%, $P < .001$) was greater in the PHDP group than in the PPCI group. The use of tirofiban ($P < .001$) and dopamine ($P = .001$) was more common in the PPCI arm. In the PHDP

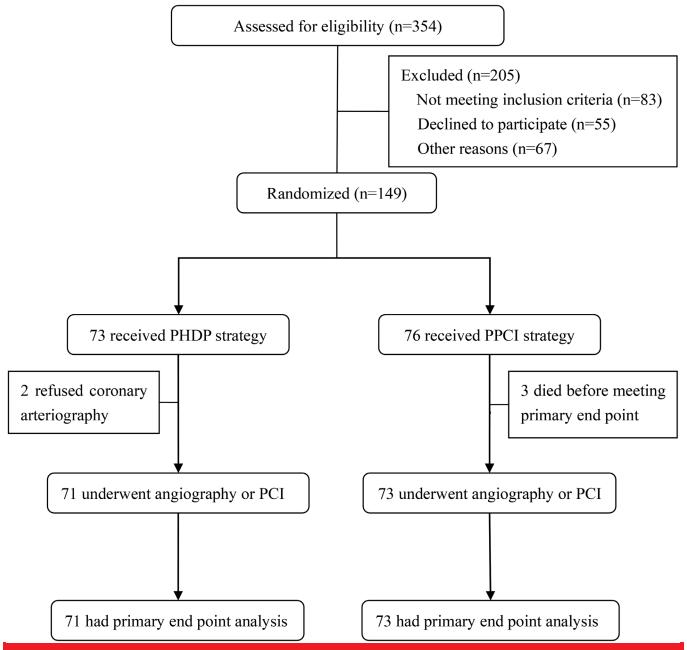

Figure 1. CONSORT flow diagram.

group, 62 (87.3%) patients achieved the clinical criterion of successful fibrinolytic reperfusion (i.e., STR ≥ 70%). Of these patients, 60 (84.5%) achieved the angiographic criterion of successful fibrinolytic reperfusion (i.e., post-PCI TFG 3). Nine patients (12.7%) immediately received rescue PCI.

In Table 3, the time intervals are detailed. The time from symptom onset to first medical contact (FMC) was similar between the 2 groups, and a high rate of time between symptom onset and reperfusion (rhPro-UK injection or arterial sheath insertion) 0-6 h was observed in both the PHDP (90.1%) and PPCI (79.5%) arms. The time from FMC to reperfusion >120 minutes occurred more frequently in the PPCI arm than in the PHDP arm (0% vs. 35.6%, $P < .001$).

Primary Endpoint

The primary endpoint was 57.7% in the PHDP group and 54.8% in the PPCI group (risk ratio [RR], 1.063; 95% CI, 0.759-1.488) (Figure 2, Table 4). An analysis of prespecified subgroups showed consistent results (Figure 3).

Secondary Endpoint

The secondary endpoint was 12.7% in the PHDP group vs. 60.3% in the PPCI group (RR, 4.012; 95% CI, 2.176-7.396). Figure 4 and Table 4 show each component of the secondary endpoint. Slow flow/no-reflow (5.6% vs. 34.2%, $P < .001$), malignant arrhythmia (4.2% vs. 27.4%, $P < .001$), and hypotension (11.3% vs. 45.2%, $P < .001$) occurred more frequently in the PPCI arm than in the PHDP arm.

Thirty-Day Follow-Up Outcomes

As shown in Table 5, the rate of combined 30-day follow-up outcomes was greater in the PPCI group than in the PHDP group (2.8% vs. 12.3%, respectively; $P < .032$). No all-cause death, cardiac death, hospitalization for heart failure, or cardiac arrest was observed; the rates of nonfatal reinfarction

Table 1. Baseline Characteristics of Patients

Characteristic	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Age, years (mean ± SD)	57.48 ± 9.76	58.22 ± 11.66	−0.413	.680
Male sex, n (%)	62 (87.3)	56 (76.7)	2.739	.098
Body mass index, kg/m^2 [median (IQR)]	26.23 (23.57, 28.37)	25.78 (23.41, 28.40)	−0.178	.859
Weight, kg [median (IQR)]	79.00 (65.00, 84.00)	74.00 (65.00, 82.50)	−0.640	.522
Smoking (previous or active), n (%)	57 (80.3)	50 (68.5)	2.620	.106
Drinking (previous or active), n (%)	27 (38.0)	35 (47.9)	1.444	.230
Hypertension, n (%)	35 (49.3)	35 (47.9)	0.026	.871
Diabetes, n (%)	18 (25.4)	24 (32.9)	0.986	.321
Hypercholesterolemia, n (%)	13 (18.3)	20 (27.4)	1.683	.195
Hypertriglyceridemia, n (%)	25 (35.2)	32 (43.8)	1.119	.290
Peripheral artery disease, n (%)	8 (11.4)	16 (22.2)	2.944	.086
Previous angina pectoris, n (%)	29 (40.8)	27 (37.0)	0.226	.635
Previous coronary intervention, n (%)	5 (7.0)	6 (8.2)	0.071	.790
History of ischemic stroke, n (%)*	2 (13.3)	9 (7.0)	–	.321
History of hemorrhagic stroke, n (%)*	0 (0)	11 (7.7)	–	1.000
Family history of coronary disease, n (%)*	1 (12.5)	10 (7.4)	–	.479
Respiratory rate, breaths/min (mean ± SD)	18.00 (17.00, 20.00)	18.00 (17.50, 20.00)	−0.763	.445
Heart rate, beats/min (mean ± SD)	77.24 ± 17.234	73.89 ± 16.22	1.201	.232
Pulse rata, beats/min (mean ± SD)	77.13 ± 17.321	73.89 ± 16.22	1.158	.249
Systolic blood pressure, mm Hg (mean ± SD)	137.37 ± 26.21	134.59 ± 22.68	0.681	.497
Diastolic blood pressure, mm Hg (mean ± SD)	85.35 ± 15.97	83.62 ± 13.99	0.694	.489
Infarct location, n (%)			0.250	.617
Anterior	37 (52.1)	35 (47.9)		
Not anterior	34 (47.9)	38 (52.1)		
Killip class, n (%)			3.473	.062
I	55 (77.5)	65 (89.0)		
II-IV	16 (22.5)	8 (11.0)		
Laboratory tests				
White blood cell counting, 10^{12}/L [median (IQR)]	9.30 (8.20, 11.90)	9.70 (7.35, 11.80)	−0.244	.807
Red blood cell counting, 10^{12}/L (mean ± SD)	4.70 ± 0.56	4.72 ± 0.52	−0.240	.811
Platelet, 10^9/L [median (IQR)]	217.00 (178.00, 267.00)	222.00 (194.00, 252.50)	−0.741	.459
Hemoglobin, g/L (mean ± SD)	147.89 ± 17.97	148.59 ± 18.49	−0.231	.818
Scr, μmol/L [median (IQR)]	62.00(54.00, 78.00)	64.00 (50.50, 76.50)	−0.240	.810
Glucose, mmol/L [median (IQR)]	5.70 (5.00, 8.30)	6.00 (5.15, 8.50)	−1.023	.306
Triglyceride, mmol/L [median (IQR)]	1.39 (0.94, 2.21)	1.65 (0.99, 2.56)	−0.907	.364
Total cholesterol, mmol/L (median (IQR))	4.4 (4.00, 5.10)	4.4 (3.70, 5.05)	−0.394	.694
HDL-C, mmol/L (mean ± SD)	1.17 ± 0.27	1.15 ± 0.21	0.491	.624
LDL-C, mmol/L [median (IQR)]	2.53 (1.99, 2.90)	2.39 (1.99, 2.94)	−0.476	.634
Cys-C, mmol/L [median (IQR)]	1.03 (0.91, 1.14)	0.99 (0.89, 1.20)	−0.280	.780
Echocardiography				
LVEF, % [median (IQR)]	54.00 (45.00, 55.00)	55.00 (45.00, 55.00)	−1.385	.166
LVEDD, mm [median (IQR)]	48.00 (46.00, 53.00)	47.00 (45.00, 50.00)	−1.650	.099

The data are presented as the median (interquartile range), n (%), or mean ± SD. *Fisher exact probability method.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PHDP, pharmaco-invasive with half-dose recombinant human prourokinase; PPCI, primary percutaneous coronary intervention; SCr, serum creatinine.

(*P* = .617), PCI or CABG revascularization (*P* = .366), or stroke (*P* = 1.000) were similar between the arms. The incidence of hospitalization for angina pectoris was significantly greater in the PPCI group than in the PHDP group (0.0% vs. 8.2%, *P* = .028).

In-Hospital Bleeding Events

As shown in Table 6, there were no reported cases of in-hospital intracranial hemorrhage or major bleeding events. The rates of minor bleeding events were similar (*P* = .157). Table 6 describes the minor bleeding events classified by location.

Table 2. Angiographic Characteristics of Patients

Characteristic	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Radial artery access, n (%)*	70 (98.6)	73 (100)	–	.493
Coronary artery disease, n (%)			4.541	.103
Single-vessel disease	25 (35.2)	34 (46.6)		
Two-vessel disease	19 (26.8)	23 (31.5)		
Three-vessel disease	27 (38.0)	16 (21.9)		
Infarct-related artery, n (%)			1.994	.369
LAD	39 (54.9)	40 (54.8)		
LCX	13 (18.3)	8 (11.0)		
RCA	19 (26.8)	25 (34.2)		
PTCA, n (%)	55 (77.5)	67 (91.8)	5.699	.017
Stent implantation, n (%)			4.770	.092
0	22 (0.31)	14 (0.192)		
1	48 (0.676)	54 (0.74)		
≥2	1 (0.014)	5 (0.068)		
Thrombus aspiration, n (%)	0 (0)	2 (2.7)	–	.497
TFC pre-PCI, n (%)			39.663	<.001
0	9 (12.7)	37 (50.7)		
1	2 (2.8)	8 (11.0)		
2	15 (21.1)	15 (20.5)		
3	45 (63.4)	13 (17.8)		
TMPG flow pre-PCI, n (%)			33.096	<.001
0	9 (12.7)	38 (52.1)		
1	2 (2.8)	7 (9.6)		
2	31 (43.7)	15 (20.5)		
3	29 (40.8)	13 (17.8)		
Syntax score [median (IQR)]	12.00 (7.00, 20.00)	15.00 (9.00, 20.50)	−0.880	.379
Medication use, n (%)				
Tirofiban	15 (21.1)	39 (53.4)	16.020	<.001
Dopamine	10 (14.1)	28 (38.4)	10.916	.001
Sodium nitroprusside	0 (0)	1 (1.4)	–	1.000
Atropine	1 (1.4)	3 (4.1)	–	.620
Norepinephrine	2 (2.8)	1 (1.4)	–	.617
Rate of successful fibrinolysis, n (%)				
Electrocardiographic criteria	62 (87.3)	–	–	–
Angiographic criteria	60 (84.5)	–	–	–

The data are presented as the median (interquartile range), n (%), or mean ± SD. *Fisher exact probability method.
LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TFG, thrombolysis in myocardial infarction flow grade; TMPG, thrombolysis in myocardial infarction myocardial perfusion.

Table 3. Time Intervals of the PHDP Trial

Time Delay	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Visit type, n (%)			3.330	.189
Call 120	14 (19.7)	17 (23.3)		
Clinic visit	53 (74.6)	46 (63.0)		
Referral	4 (5.6)	10 (13.7)		
Symptom to FMC, minutes [median (IQR)]	72.00 (38.00, 158.00)	89.00 (37.50, 178.50)	−0.713	.476
FMC to reperfusion, n (%)			89.057	<.001
0-60 minutes	55 (77.5)	2 (2.7)		
60-120 minutes	16 (22.5)	45 (61.6)		
>120 minutes	0 (0)	26 (35.6)		
Symptom to reperfusion, n (%)*			4.115	.130
0-6 hours	64 (90.1)	58 (79.5)		
6-12 hours	3 (4.2)	10 (13.7)		
12-24 hours	4 (5.6)	5 (6.8)		
FMC to sheath, minutes [median (IQR)]	706.00 (444.00, 965.00)	95.00 (76.00, 150.00)	−8.869	<.001
Door to sheath, minutes [median (IQR)]	724.00 (448.00, 966.00)	83.00 (73.00, 105.50)	−8.913	<.001
Operation time, minutes [median (IQR)]	28.00 (20.00, 35.00)	27.00 (20.00, 35.50)	−0.070	.944
Fibrinolysis to PCI, n (%)			–	–
Rescue PCI	9 (12.7)	–	–	–
3-6 hours	10 (14.1)	–	–	–
6-12 hours	22 (31.0)	–	–	–
12-24 hours	30 (42.3)	–	–	–

Data are presented as the median (interquartile range), n (%), or mean ± SD. *Fisher exact probability method.
FMC, first medical contact.

DISCUSSION

This study showed that among STEMI patients presenting within 24 hours after the onset of symptoms, PHDP was non-inferior to PPCI, regardless of PCI-related delay. The incidence of the secondary composite endpoint of slow flow/no-reflow, malignant arrhythmia, or hypotension during the procedure was greater among the patients who received PPCI than among those who received PHDP. This difference may be mainly related to the greater percentage of patients with a TFG 3 before the first angiography in the PHDP group. In our study, patients with STEMI who were assigned to receive PHDP had a lower risk of combined 30-day follow-up outcomes than those who received PPCI. No intracranial hemorrhages or major bleeding events occurred in either group.

The PhI strategy is recommended as a reasonable alternative by current guidelines for patients with STEMI when PPCI

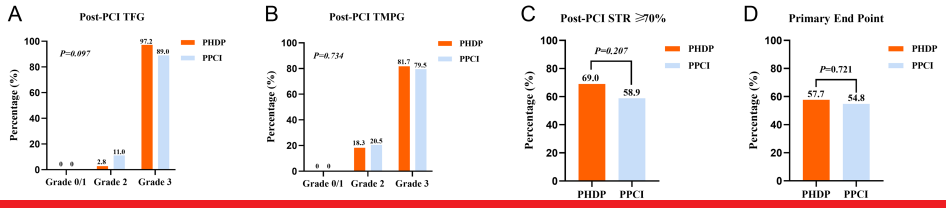

Figure 2. Primary endpoint and individual components of the primary endpoint in the 2 groups. HDP, pharmaco-invasive with half-dose recombinant human prourokinase; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; RR, risk ratio; STR, ST-segment resolution; TFG, thrombolysis in myocardial infarction flow grade; TMPG, thrombolysis in myocardial infarction myocardial perfusion.

Table 4. Primary and Secondary Endpoints of the PHDP Trial

Endpoint	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Primary endpoint, n (%)	40 (54.8)	41 (57.7)	0.127	.721
Post-PCI TFG, n (%)			3.692	.055
0/1	0 (0)	0 (0)		
2	2 (2.8)	8 (11.0)		
3	69 (97.2)	65 (89.0)		
Post-PCI TMPG, n (%)			0.115	.734
0/1	0 (0)	0 (0)		
2	13 (18.3)	15 (20.5)		
3	58 (81.7)	58 (79.5)		
Post-PCI STR ≥ 70%, n (%)	49 (69.0)	43 (58.9)	1.595	.270
Secondary endpoint, n (%)	9 (12.7)	44 (60.3)	35.059	<.001
Slow flow/no-reflow, n (%)	4 (5.6)	25 (34.2)	18.322	<.001
Malignant arrhythmia, n (%)	3 (4.2)	20 (27.4)	14.400	<.001
Hypotension, n (%)	8 (11.3)	33 (45.2)	20.356	<.001

The data are presented as the median (interquartile range), n (%).
PCI, percutaneous coronary intervention; STR, ST-segment resolution; TFG, thrombolysis in myocardial infarction frame count grade; TMPG, thrombolysis in myocardial infarction myocardial perfusion grade.

cannot be performed within evidence-based timeframes.[1,4] This approach involves early fibrinolysis coupled with routine catheterization. Rapid prehospital fibrinolysis would overcome the PCI-related delay from symptom onset to reperfusion, which would result in a greater incidence of major adverse cardiac events when patients with STEMI cannot present to PCI-capable hospitals promptly.[5,8,15] Despite previous randomized trials indicating that a half-dose fibrinolytic strategy is not inferior to PPCI regarding myocardial and epicardial reperfusion while reducing life-threatening consequences,[7,8,16] these benefits may not be applicable to real-world practice due to insufficient evidence.

This study with half-dose rhPro-UK can be compared with the efficacy of half-dose alteplase in the EARLY-MYO trial. As in the EARLY-MYO trial, the primary endpoint was defined for complete epicardial and myocardial reperfusion.[8] However, this study extends the benefits to patients who present 6 to 24 hours after symptom onset. Finally, a total of 57.7% of the PHDP participants and 54.8% of the PPCI participants met the primary endpoint (RR 1.063; 95% CI, 0.759-1.488). The rate of complete epicardial and myocardial reperfusion was 11.4% greater with the PhI strategy than with the PPCI in the EARLY-MYO trial (RR 1.48; 95% CI

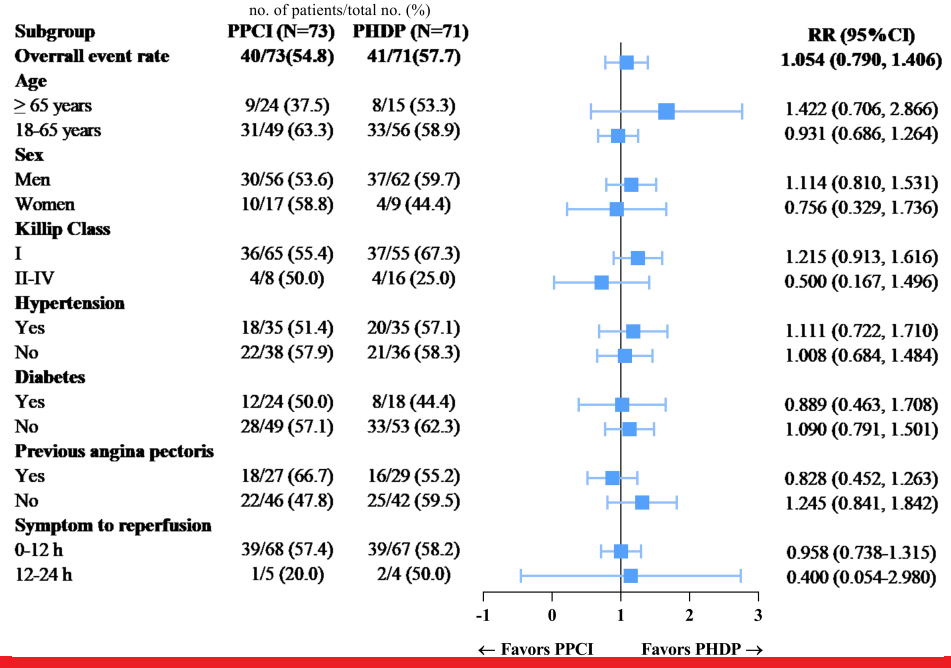

Figure 3. Prespecified subgroup analyses of the primary endpoint among the 2 groups.

Table 5. 30-Day Follow-Up Outcomes of the PHDP Trial

Outcome	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Combined follow-up outcomes, n (%)	2 (2.8)	9 (12.3)	4.616	.032
All-cause death, n (%)	0 (0)	0 (0)	–	–
Cardiac death, n (%)	0 (0)	0 (0)	–	–
Cardiac arrest, n (%)	0 (0)	0 (0)	–	–
Nonfatal myocardial infarction, n (%)*	2 (2.8)	1 (1.4)	–	.617
PCI or CABG revascularization, n (%)*	1 (1.4)	4 (5.5)	–	.366
Hospitalization for angina pectoris, n (%)*	0 (0)	6 (8.2)	–	.028
Hospitalization for heart failure, n (%)	0 (0)	0 (0)	–	–
Stroke, n (%)*	0 (0)	1 (1.4)	–	1.000

The data are presented as the median (interquartile range), n (%).
*Fisher exact probability method.

1.04-2.10; $P_{noninferiority} < .05$; $P_{superiority} = .022$), achieving the prespecified non-inferiority and superiority criterion.[8] The difference between the 2 trials was mainly related to sample size and patient characteristics.

In addition, PHDP was associated with a lower secondary endpoint rate (a composite clinical outcome of slow flow/no-reflow, malignant arrhythmia, or hypotension in the procedure): 12.7% in the PHDP group and 60.3% in the PPCI group (RR, 4.012; 95% CI, 2.176-7.396). The individual components of the secondary endpoint also tended to occur more often in the PPCI arm than in the PHDP arm. These observations have yet to be previously mentioned in clinical trials comparing a PhI strategy to PPCI in STEMI patients. PCI is effective for treating STEMI, and the smoothness of the process is closely linked to patient outcomes. Previous studies have shown that the incidence of slow flow or no reflow during PCI can reach 15.1%-19.5%. Both Yip et al[17] and Dong-bao et al[18] identified delayed reperfusion and heavy coronary artery thrombus load as independent risk factors for the occurrence of slow flow or no reflow during the procedure. In this study, the PHDP group demonstrated significantly higher TMPG 3 before PCI compared to the PPCI group (40.8% vs. 20.5%, *P* < .001), with no patients requiring thrombus aspiration during the procedure (0.0% vs. 2.7%, *P* = .497). Early thrombolysis effectively reduced the thrombus load in the coronary arteries, decreasing the incidence of slow flow or no reflow to 5.6%, thereby lowering the occurrence of intraoperative hypotension. Early opening of the infarct-related artery can salvage some myocardial cells in the ischemic border zone, reducing the infarct area. This, in turn, lessens the formation of malignant ventricular conduction pathways between the infarcted and non-infarcted myocardial cells, contributing to a reduced incidence of intraoperative malignant arrhythmias.[19] Additionally, it can also diminish hemodynamic instability caused by malignant arrhythmias, thereby lowering the risks associated with PCI.

Table 6. In-Hospital Bleeding Events

Bleeding Event	PHDP (n = 71)	PPCI (n = 73)	$t/\chi^2/z$	*P*
Intracranial hemorrhage, n (%)	0	0	–	–
Major bleeding events, n (%)	0	0	–	–
Minor bleeding events, n (%)	23 (32.4)	16 (21.9)	2.000	.157
Epistaxis, n (%)*	1 (1.4)	2 (2.7)	–	1.000
Gingival, n (%)	1 (1.4)	1 (1.4)	–	1.000
Bloody sputum, n (%)	1 (1.4)	1 (1.4)	–	1.000
Gastrointestinal bleeding, n (%)	0 (0)	1 (1.4)	–	1.000
Microscopic hematuria, n (%)	13 (18.3)	8 (11.0)	1.561	.211
Macroscopic hematuria, n (%)	0 (0)	1 (1.4)	–	1.000
Fecal occult blood test positive or weekly positive, n (%)	11 (15.5)	4 (5.5)	3.868	.050
Subcutaneous hematoma, n (%)*	1 (1.4)	0 (0)	–	.493

The data are presented as the median (interquartile range), n (%).
*Fisher exact probability method.

Previous studies have indicated that the PhI strategy is more likely to trigger bleeding events, which is particularly pronounced in elderly patients.[20,21] The STREAM trial showed that no intracranial hemorrhage was observed among patients ≥75 years of age who underwent the PhI strategy and subsequently had their fibrinolytic drug dose reduced by half, suggesting that the PhI strategy involving half-dose fibrinolytic agents might reduce the risk of bleeding events.[7] In our trial, similar to the EARLY-MYO trial,[8] intracranial hemorrhage was not observed, although there was a low number of minor bleeding events, no major bleeding events were reported in the PHDP trial. Besides, the PPCI group had a greater rate of combined 30-day follow-up outcomes than did the PHDP group (2.8% vs. 12.3%, respectively; *P* < .032); a benefit was observed with PHDP concerning the rate of the composite 30-day follow-up outcome of hospitalization for angina pectoris, which was lower than that with PPCI. However, the benefits were not reflected in the other major adverse cardiovascular events (MACEs). These results demonstrated the superiority of PHDP in safety and efficacy.

Our findings about the PhI strategy are of medical importance because this approach involving half-dose rhPro-UK (25 mg) reached a surprising rate of successful fibrinolysis: 84.5% based on angiographic criteria (i.e., TFG 2/3 on angiography). Notably, our rate of successful fibrinolysis was similar to the rate of 85.4% reported in phase IV clinical trials of the prourokinase phase.[22] Indeed, the rate of successful fibrinolysis in this trial was higher than that reported in the EARLY-MYO trial[8] (74.5% based on clinical criteria and 75.2% based on angiographic data), which performed to compare the PhI strategy with half-dose alteplase to PPCI alone. Half-dose alteplase also proved effective in the Tissue Plasminogen Activators/Urokinase Comparisons in China (TUCC) trial.[23] Thus, as noted by previous clinical trials, the

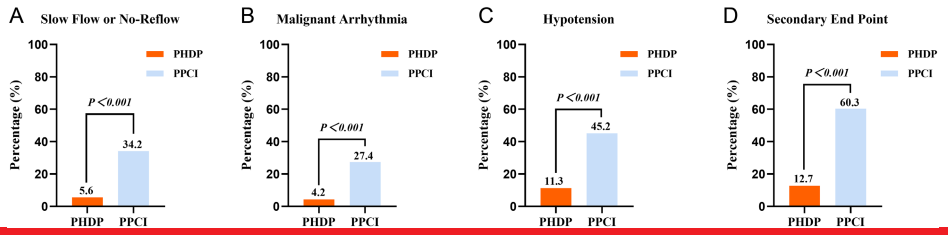

Figure 4. Secondary endpoints and individual components of the secondary endpoints in the 2 groups.

effect of a half-dose of fibrinolytic drug on the rate of successful fibrinolysis appears to be homogeneous, with no consistent evidence that 1 member of the drug class is superior to another for efficacy and safety.

Another critical factor that influences the clinical outcome of the PhI strategy is the timeframe from thrombolysis to catheterization. According to the ASSENT-4 trial, ischemic complications and mortality were greater in patients who received PCI at 1-3 hours after randomization than in those who received PPCI, implying that early catheterization caused the prothrombotic effect of thrombolytic therapy.[24] However, in the Bavarian Reperfusion Alternatives Evaluation (BRAVE) trial, patients who underwent PCI 2 hours after fibrinolysis with half-dose reteplase had a higher rate of preintervention TIMI 3; such treatment did not improve infarct size or clinical outcome.[25] In our trial, the timeframe from fibrinolysis to angiography complied with contemporary treatment guideline standards (3-24 hours after thrombolysis) and was similar to the therapies that appeared favorable in the Transfer-AMI trial, GRACIA-2 trial, STREAM trial, and EARLY-MYO trial.[7,8,16,26] However, further clinical trials are warranted to determine the optimum timeframe between fibrinolysis and PCI.

We summarize the strengths and limitations of this trial. Among its strengths, a key innovation of this trial was the use of half the dosage of rhPro-UK in the PhI strategy. The rate of total bleeding events in the PHDP group was low, and there were no reported cases of in-hospital intracranial hemorrhage or major bleeding events. Concurrently, this strategy achieved reasonable successful fibrinolysis rates, with only 12.7% of STEMI patients being referred for timely rescue coronary intervention. However, the subsequent superiority test did not favor any therapeutic strategy due to the insufficient sample size. Additionally, the results of this trial are not generalizable to patients ≥ 80 years of age who were not enrolled.

In conclusion, among patients with STEMI presenting ≤ 24 h after symptom onset who were assigned to receive the PHDP strategy, the efficacy of complete epicardial and myocardial reperfusion was similar to that among patients assigned to receive PPCI alone. In addition, PHDP was associated with a decreased risk of procedure-related complications. Conducting clinical efficacy and safety trials with the PhI strategy and a half-dose of fibrinolytic drug is warranted.

Availability of data and materials: The data adopted in this study are available from the corresponding author upon request.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Chengde Central Hospital (approval no.: 20181113001).

Informed Consent: We enrolled 149 patients with acute STEMI who provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: C.J. and J.D. contributed to the data curation, formal analysis, software, visualization, writing – original draft, and writing – review and editing; D.L. and J.G. contributed to the conceptualization, data curation, formal analysis, funding acquisition, project administration, resources, and writing – review and editing; H.Y., R.G., and J.G. contributed to the data curation, investigation, supervision, validation, and writing – review and editing; B.L., H.S., Y.H., and L.Z. contributed to the project administration, supervision, and writing – review and editing. D.L. takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Acknowledgements: The PHDP investigators thank Jiang Zhou, MD, Shuliang Zhang, MD, Zhiguo Chen, MD, all the medical staff in the cardiology and emergency departments, and the patients, ethics committee members, and staff who participated in this study.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This work was supported by the S&T Program of Chengde (nos. 201804A013 and 202109A019), and the Medical Science Research Project of Hebei Province (no. 20200348).

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