ORIGINAL ARTICLE

Streptokinase-Based Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention: A Propensity Score Matching Analysis from the Siriraj STEMI Network

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Objective: To investigate the efficacy and safety of pharmacoinvasive (PI) strategy compared to primary percutaneous coronary intervention (PPCI) in the setting of a real-world ST-elevation myocardial infarction (STEMI) network where streptokinase (SK) is predominantly prescribed.

Materials and Methods: The authors analyzed 325 STEMI patients who participated in The Siriraj STEMI network between July 2015 and October 2020. The primary efficacy endpoint was the incidence of cumulative major adverse cardiovascular and cerebrovascular events (MACCE) at one month, which were the composite of death, myocardial infarction, stroke, and non-coronary artery bypass graft (CABG)-related thrombolysis in myocardial infarction (TIMI) major or minor bleeding. The safety endpoint was non-CABG-related TIMI major or minor bleeding during the index hospitalization. Cox regression was performed for survival analysis. The authors applied propensity score matching to reduce the bias of the confounding variables.

Results: Two hundred four patients received fibrinolytic therapy, 191 (93.6%) obtained SK, and 121 participants underwent PPCI. After propensity score matching analysis, the incidence of cumulative MACCE at one-month follow-up was not significantly different between the PI and the PPCI group (p=0.726) as well as the incidence of bleeding endpoint (p=0.446). In the subgroup analysis of the 191 patients who received SK (SK-PI), there was no statistical difference in the occurrence of cumulative MACCE compared to PPCI (p=0.136). Killip classification class III (hazard ratio [HR] 7.50, 95% confidence interval [CI] 3.25 to 17.31, p<0.001), and class IV (HR 9.78, 95% CI 4.31 to 22.21, p<0.001) were independent risk factors for developing MACCE.

Conclusion: The streptokinase-based pharmacoinvasive strategy is non-statistically different in terms of efficacy and safety compared to PPCI. This evidence supports the utilization of the SK-PI approach in low- to middle-income countries where the availability of fibrin-specific fibrinolytic agents is often limited.

Keywords: Revascularization strategy; Acute coronary syndrome; Fibrinolytic therapy

Received 11 July 2022 | Revised 11 October 2022 | Accepted 11 October 2022

J Med Assoc Thai 2023;106(2):180-92

Website: http://www.jmatonline.com

Timely primary percutaneous coronary intervention (PPCI) is the mainstay of reperfusion therapy for patients presenting with ST-segment elevation myocardial infarction (STEMI)[1-3]. When PPCI is not feasible or not able to be conducted in time, immediate fibrinolytic therapy at the first medical contact (FMC) hospital and then urgent transfer for subsequent percutaneous coronary intervention (PCI) at the PCI center[4], referred to as the pharmacoinvasive (PI) strategy, serves as an alternative reperfusion approach.

The current STEMI guidelines recommend the fibrin-specific fibrinolytic agents such as tenecteplase (TNK) or recombinant tissue plasminogen activator (rt-PA), for use in the PI strategy[1]. These agents offer more efficacy to recanalize the infarct-related artery (IRA) with less antigenicity compared to the non-

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How to cite this article:

Towashiraporn K, Krittayaphong R, Tresukosol D, Phankingthongkum R, Tungsubutra W, Wongpraparut N, et al. Streptokinase-Based Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention: A Propensity Score Matching Analysis from the Siriraj STEMI Network. J Med Assoc Thai 2023;106:180-92.

DOI: 10.35755/jmedassocthai.2023.02.13782

fibrin-specific agent streptokinase (SK)[5]. However, because it is more affordable, SK is more widely used than the fibrin-specific fibrinolytic agents in low- to middle-income countries. Because SK is no longer used in wealthier countries it is seldom studied in clinical trials, resulting in a paucity of evidence for its use in the PI strategy. Therefore, the authors aimed to investigate the safety and efficacy of the PI strategy compared to PPCI in a real-world STEMI network in a middle-income country where SK is predominantly prescribed.

Materials and Methods

Patient selection

The authors enrolled consecutive patients from The Siriraj STEMI network between July 2015 and October 2020 who presented within 12 hours after STEMI onset to the first medical contact (FMC) hospital and were suitable for revascularization by either PPCI or PI strategy. Patients were excluded if 1) they received facilitated percutaneous coronary intervention such as pretreatment with any fibrinolytic drug and immediate transfer to PCI, regardless of fibrinolytic therapy[6], 2) coronary angiography after successful fibrinolysis was not performed within 72 hours after the initiation of fibrinolytic agents, or 3) if they had angina for more than 12 hours without evidence of ongoing ischemia. The Siriraj Institutional Ethical Review Board approved the present study [Protocol Number 1022/2563 (IRB3)].

The diagnosis of STEMI was made at the FMC hospital based on the 12-lead electrocardiography (ECG) criteria[1]. After a brief consultation with the attending cardiac interventionist at Siriraj Hospital, the appropriate reperfusion strategy was planned. Patients in the PPCI strategy were directly transferred to the authors' catheterization laboratory to undergo PPCI as soon as possible. Patients in the PI strategy received a fibrinolytic agent such as SK, weight-adjusted intravenous TNK, or t-PA, that was available at the FMC hospital. After receiving fibrinolysis therapy, the patients were transferred to the author' hospital. For patients who failed thrombolysis, urgent rescue PCI was initiated. If fibrinolytic therapy was successful, routine early coronary angiography was scheduled, and subsequent PCI was performed if indicated. Decisions regarding reperfusion strategy, procedural techniques during cardiac catheterization, and any medications prescribed at the FMC hospital or during index hospitalization with fibrinolytic agent, antiplatelet therapy, antithrombotic drugs, inotropic drugs if needed, or other medications, were made at the treating physician's discretion. All STEMI patients had follow-up visits at the dedicated STEMI clinic at the authors' cardiac center. The duration of the follow-up period depended on the treating physician's discretion, health coverage service, and the patient's willingness. Once the follow-up period was completed, STEMI patients were referred back to their primary hospital.

The STEMI network

Her Majesty Cardiac Center (HMCC), Faculty of Medicine Siriraj Hospital, Mahidol University, is a tertiary heart center located in Bangkok, Thailand. The facility has more than 15 years of 24/7 primary PCI service experience and performs more than one thousand PCI procedures annually. To systematically maximize the ability to manage STEMI, in July 2015 the Siriraj STEMI network has been established and became the referral center for two STEMI networks, the West-Bangkok STEMI network and the Ministry of Public Health's service plan zone Fifth STEMI network. The networks have more than 10 regional hospitals involved in the STEMI networks. The median distance from the network FMCs to the HMCC is 120 kilometers (km) with a maximum of 173 km. The HMCC is also the hub for two affiliated hospitals located nearby. Overall, the present study STEMI network covers several million people.

Data collection

The authors reviewed the electronic medical records and then manually extracted data to a dedicated case record form. Two investigators collected the baseline characteristics, procedural details, event data, and clinical endpoints. The patients who received fibrinolytic agents were included in the PI strategy group, while patients who initially underwent PPCI were allocated to the PPCI group.

Outcomes

The primary endpoint was cumulative major adverse cardiovascular and cerebrovascular events (MACCE) during a 1-month follow-up period. MACCE is a composite of death, stroke, myocardial infarction (MI), and non-coronary artery bypass graft (CABG)-related thrombolysis in myocardial infarction (TIMI), major or minor. The primary safety endpoint was a combination of non-CABG-related TIMI major or minor bleeding during the index hospitalization.

Definitions

STEMI was defined as persistent chest discomfort or other symptoms suggestive of ischemia with significant ST-segment elevation in at least two contiguous ECG leads. Heart failure symptoms at the time of presentation were classified using the Killip classification system[7]. The Global Registry of Acute Coronary Events (GRACE) risk score was calculated to assess the risk of death[8]. PPCI was defined as emergent PCI with coronary stent, balloon, or other approved device performed on an IRA without previous fibrinolytic treatment. PPCI must be done within 12 hours of symptom onset or up to 48 hours in specific clinical settings with any presence of ongoing symptoms suggestive of ischemia, hemodynamic instability, or life-threatening arrhythmia. Rescue PCI was defined as emergent PCI performed as soon as possible after failed fibrinolytic treatment. Facilitated PCI was defined as pretreatment with any fibrinolytic drug with transfer to the PCI within three hours after fibrinolysis, regardless of the result of fibrinolytic therapy. Routine early PCI strategy after fibrinolysis was defined as coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis. Pharmacoinvasive strategy was defined as fibrinolysis combined with rescue PCI in case of failed fibrinolysis, or routine early PCI strategy in case of successful fibrinolysis. Failed fibrinolysis was defined as failure to achieve more than 50% of ECG resolution of the highest elevation of the ECG lead 90 minutes after administration of fibrinolysis, or any symptoms suggestive of ongoing ischemia such as hemodynamic or electrical instability, worsening ischemia, or persistent chest pain. Successful fibrinolysis was defined as more than 50% ECG resolution 90 minutes after administration of fibrinolysis without any symptoms suggestive of ongoing ischemia. Time from onset to needle was the time from onset of symptoms to the initiation of fibrinolysis. The door-to-needle time was defined as the time from patient arrival at the FMC hospital to initiation of the fibrinolytic agent. The wire crossing time was defined as the time the coronary guidewire crossed the culprit lesion. Transfer time was defined as the duration from the FMC hospital to arrival at the authors' catheterization laboratory. Pre- and post-procedural coronary blood flow were classified using the TIMI classification[9]. Stroke was defined as the presence of new neurological deficits lasting longer than 24 hours with evidence of ischemia or hemorrhage from any imaging modality such as computed tomography or magnetic resonance imaging. MI was defined as any acute coronary syndrome, including STEMI and non-ST elevation acute coronary syndrome, diagnosed during the follow-up period. Major bleeding complications were classified using non-CABG-related TIMI major or minor bleeding criteria[10].

Statistical analysis and sample size calculation

Qualitative variables were presented as frequency and percentage and compared by the chi-square test. Continuous data with normal distribution were represented by mean and standard deviation and compared with the student's t-test. If the data were not normally distributed, then the median and minimum-maximum values are presented. The authors performed univariate and multivariate Cox regression analyses to assess independent predictors of clinical outcomes and presented them as hazard ratio (HR) and 95% confidence interval (CI). Cox regression was performed for survival analysis and presented with the Kaplan-Meier hazard graph. To calculate the sample size, the authors estimated the mortality rate at 30 days in the PPCI group to be 7% and in the PI group to be 3%[11]. The authors applied a statistical power (1-β) of 80% and an α level of 0.05 to arrive at a sample size of 120 patients in each group.

The authors used propensity score-matched analysis to reduce bias due to confounding variables[12]. Baseline variables were analyzed to identify differences between the PI and PPCI groups. The binary logistic regression statistics was used to find a variable with a p-value less than 0.2 as a model to detect the probability for matching. Then, by matching 1 to 1 the PI and PPCI groups with probabilities differed by not more than 0.2. After the propensity score was matched, there were 102 patients for each group. The C statistic for the propensity model was 0.69. However, the role of the C statistic for propensity score was still debated. Moreover, there was no exact cut point of the level of C statistic to identify the correct propensity score-match[13]. Data before and after propensity score-matching were presented. All p-values less than 0.05 were considered statistically significant. The authors used PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA) for data analyses.

Results

Patient characteristics

Between July 2015 and October 2020, 335

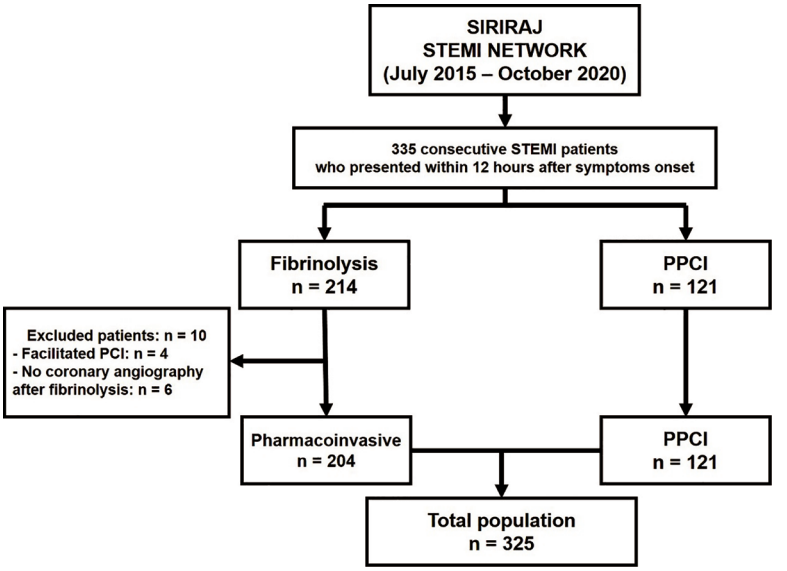

Figure 1. Study flow chart.

PCI=percutaneous coronary intervention; PPCI=primary percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction

consecutive STEMI patients received care in the present study STEMI network and 325 STEMI patients were enrolled in the present analysis. Ten patients were excluded (Figure 1). One hundred twenty-one patients underwent PPCI, and 204 patients received fibrinolytic agents (PI group), of which 93.6% received SK for reperfusion therapy. The median age of the PPCI and PCI groups were 66 (IQR 63.8 to 68.3) and 61 (IQR 58.8 to 62) years old, respectively. Patients in the PPCI group were more likely to be at least 65 years of age (PPCI with 52.1% versus PI with 38.7%, p=0.019), more likely to be female (PPCI with 38.8% versus PI with 21.6%, p=0.001), and more likely to have hypertension (p=0.026). Patients in the PPCI group were at higher risk for morbidity and mortality after index events since they had a significantly higher incidence of cardiogenic shock at presentation (p=0.021), higher Killip classification (p=0.044), higher rate of the atrioventricular block at arrival (p=0.004), and higher GRACE risk score (p<0.001). Patients in the PPCI group were more likely to receive ticagrelor at hospital discharge (p<0.001). Systolic blood pressure at presentation, LVEF during hospitalization, and cardiac arrest rates at arrival were similar between groups. After propensity score matching, there were no significant differences in baseline characteristics (Table 1).

Sixteen variables were used for propensity-matched analysis, age (years), female gender, body mass index, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease requiring hemodialysis, history of previous PCI, anterior STEMI, inferior STEMI, cardiogenic shock at presentation, cardiac arrest at arrival, atrioventricular block at presentation, Killip classification, and GRACE risk score.

Time delays

The median time from angina onset to the administration of a fibrinolytic drug was 165 (IQR 107 to 260) minutes. The median door-to-needle time was 56 (IQR 40 to 88) minutes. Of the 204 patients in the PI group, 155 (76%) achieved successful fibrinolytic therapy and underwent routine early invasive coronary angiography. The median time to PCI after successful fibrinolysis was 15.13 (IQR 8.4 to 22) hours. Forty-nine patients who failed fibrinolytic therapy were immediately treated with rescue PCI.

For the PPCI group, the median total ischemic time was 319 (IQR 229 to 467) minutes, and the median transfer time from FMC hospital to HMCC was 76.5 (IQR 36.3 to 100) minutes.

Procedural details

Patients in the PI group had a significantly higher incidence of initial TIMI flow grade 3 (70.1% versus 14.9%, p<0.001) with a similar incidence of post-PCI TIMI flow grade 3 (95.6% versus 91.7%,

Table 1. Baseline characteristics

Variables	Before propensity matching			After propensity matching		
	PI (n=204)	PPCI (n=121)	p-value	PI (n=102)	PPCI (n=102)	p-value
Age ≥65 years; n (%)	79 (38.7)	63 (52.1)	0.019*	46 (45.1)	47 (46.1)	0.888
Female; n (%)	44 (21.6)	47 (38.8)	0.001*	30 (29.4)	33 (32.4)	0.649
BMI; mean±SD	24.87±5.85	23.79±3.56	0.068	23.90±3.19	24.18±3.43	0.550
Systolic BP (mmHg); mean±SD	132.54±29.54	131.62±31.79	0.798	128.80±33.58	136.09±31.07	0.128
Diastolic BP (mmHg); mean±SD	80.97±19.24	79.27±20.53	0.465	76.58±19.50	81.72±20.15	0.079
Pulse (beats per minute); mean±SD	74.80±17.79	75.28±20.96	0.839	71.15±20.04	76.99±20.63	0.052
Hypertension; n (%)	111 (54.4)	81 (66.9)	0.026*	58 (56.9)	66 (64.7)	0.251
Diabetes mellitus; n (%)	56 (27.5)	45 (37.2)	0.067	33 (32.4)	34 (33.3)	0.881
Dyslipidemia; n (%)	96 (47.1)	69 (57.0)	0.082	55 (53.9)	56 (54.9)	0.888
Hemodialysis; n (%)	1 (0.5)	0 (0.0)	0.441	0 (0.0)	0 (0.0)	-
History of previous PCI; n (%)	1 (0.5)	4 (3.3)	0.066	1 (1.0)	1 (1.0)	1.000
Anterior STEMI; n (%)	97 (47.5)	57 (47.1)	0.939	45 (44.1)	49 (48.0)	0.574
Inferior STEMI; n (%)	105 (51.5)	63 (52.1)	0.917	57 (55.9)	52 (51.0)	0.483
Cardiogenic shock; n (%)	13 (6.4)	17 (14.0)	0.021*	11 (10.8)	9 (8.8)	0.638
Cardiac arrest at arrival; n (%)	7 (3.4)	9 (7.4)	0.107	7 (6.9)	6 (5.9)	0.774
Atrioventricular block; n (%)	11 (5.4)	18 (14.9)	0.004*	11 (10.8)	8 (7.8)	0.470
Killip classification; n (%)			0.044*			0.408
Class I	147 (72.1)	72 (59.5)		72 (70.6)	65 (63.7)	
Class II	27 (13.2)	19 (15.7)		10 (9.8)	18 (17.6)	
Class III	18 (8.8)	13 (10.7)		9 (8.8)	10 (9.8)	
Class IV	12 (5.9)	17 (14.0)		11 (10.8)	9 (8.8)	
GRACE risk score; mean±SD	116.37±28.46	133.85±35.71	<0.001*	125.10±30.10	126.39±30.42	0.761
LVEF (%); mean±SD	51.20±11.96	49.47±12.84	0.222	51.82±12.53	50.10±12.73	0.332
Fibrinolytic treatment; n (%)			<0.001*			<0.001*
SK	191 (93.6)	0 (0.0)		95 (93.1)	0 (0.0)	
TNK	8 (3.9)	0 (0.0)		4 (3.9)	0 (0.0)	
rt-PA	5 (2.5)	0 (0.0)		3 (2.9)	0 (0.0)	
Aspirin; n (%)	194 (95.1)	114 (94.2)	0.895	94 (92.2)	97 (95.1)	0.549
Clopidogrel; n (%)	177 (86.8)	78 (64.5)	<0.001*	84 (82.4)	63 (61.8)	<0.001*
Ticagrelor; n (%)	13 (6.4)	34 (28.1)	<0.001*	8 (7.8)	32 (31.4)	<0.001*
Prasugrel; n (%)	4 (2.0)	1 (0.8)	0.655	2 (2.0)	1 (1.0)	0.549
ACEI; n (%)	97 (47.5)	69 (57.0)	0.073	53 (52.0)	64 (62.7)	0.151
Beta-blocker; n (%)	126 (61.8)	68 (56.2)	0.365	56 (54.9)	58 (56.9)	0.904
Statin; n (%)	190 (93.1)	115 (95.0)	0.088	93 (91.2)	98 (96.1)	0.119
Diuretic; n (%)	10 (4.9)	9 (7.4)	0.333	7 (6.9)	8 (7.8)	0.820

ACEI=angiotensin-converting-enzyme inhibitors; BMI=body mass index; BP=blood pressure; GRACE=The Global Registry of Acute Coronary Events; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; PI=pharmacoinvasive; PPCI=primary percutaneous coronary intervention; SD=standard deviation; rt-PA=recombinant tissue plasminogen activator; SK=streptokinase; STEMI=ST-segment elevation myocardial infarction; TNK=tenecteplase

* Statistically significant variables

p=0.152) (Table 2). Patients underwent PPCI were more likely to receive balloon angioplasty only (9.1% versus 3.4%, p=0.031). The use of drug-eluting stents during PCI was similar in both groups (p=0.293). After propensity score matching, the PI group still had a significant higher incidence of pre-PCI TIMI flow grade 3 (71.6% versus 16.7%, p<0.001) with a similar rate of balloon angioplasty alone (p=0.06). The rate of urgent CABG (p=0.621), the maximum stent size (p=0.094), and the maximum stent length (p=0.968) were similar between groups.

Efficacy and safety outcomes

There was no significant difference in the

Table 2. Procedural details

Variables	All patients cohort			After propensity score matching		
	PI (n=204)	PPCI (n=121)	p-value	PI (n=102)	PPCI (n=102)	p-value
Infarct related artery; n (%)						
LM	0 (0.0)	1 (0.8)	0.372	0 (0.0)	1 (0.8)	0.316
LAD	96 (47.1)	54 (44.6)	0.671	43 (42.2)	46 (45.1)	0.672
LCX	14 (6.9)	4 (3.3)	0.175	9 (8.8)	4 (3.9)	0.152
RCA	93 (45.6)	61 (50.4)	0.400	49 (48.0)	50 (49.0)	0.889
Graft	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Other	1 (0.5)	1 (0.8)	0.708	1 (1.0)	1 (1.0)	1.000
Number of disease vessel; n (%)						
0	5 (2.5)	0 (0.0)	0.162	2 (2.0)	0 (0.0)	0.498
1	87 (42.6)	54 (44.6)	0.728	37 (36.3)	47 (46.1)	0.155
2	66 (32.4)	34 (28.1)	0.422	38 (37.3)	27 (26.5)	0.098
3	46 (22.5)	33 (27.3)	0.337	25 (24.5)	28 (27.5)	0.632
Pre-PCI TIMI flow; n (%)						
0	24 (11.8)	79 (65.3)	<0.001*	13 (12.7)	64 (62.7)	<0.001*
1	4 (2.0)	5 (4.1)	0.301	1 (1.0)	5 (4.9)	0.212
2	33 (16.2)	19 (15.7)	0.910	15 (14.7)	16 (15.7)	0.845
3	143 (70.1)	18 (14.9)	<0.001*	73 (71.6)	17 (16.7)	<0.001*
Stent deployment: Yes; n (%)	177 (86.8)	109 (90.1)	0.374	88 (86.3)	91 (89.2)	0.522
Number of stents; n (%)			0.835			0.832
0	27 (13.2)	12 (9.9)		14 (13.7)	11 (10.8)	
1	129 (63.2)	79 (65.3)		64 (62.7)	70 (68.6)	
2	41 (20.1)	25 (20.7)		20 (19.6)	17 (16.7)	
3	7 (3.4)	5 (4.1)		4 (3.9)	4 (3.9)	
Balloon only: Yes; n (%)	7 (3.4)	11 (9.1)	0.031*	4 (3.9)	11 (10.8)	0.060
CAG only: Yes; n (%)	20 (9.8)	0 (0.0)	<0.001*	10 (9.8)	0 (0.0)	0.001*
Use of DES: Yes; n (%)	168 (82.4)	105 (86.8)	0.293	84 (82.4)	87 (85.3)	0.568
Urgent CABG: Yes; n (%)	3 (1.5)	3 (2.5)	0.674	1 (1.0)	3 (2.9)	0.621
Maximum stent size (mm); mean±SD	3.36±0.55	3.22±0.47	0.029*	3.39±0.58	3.26±0.46	0.094
Maximum stent length (mm); mean±SD	31.32±14.14	32.16±14.76	0.632	31.33±14.75	31.42±14.71	0.968
Post-PCI TIMI flow; n (%)						
0	1 (0.5)	1 (0.8)	0.708	0 (0.0)	0 (0.0)	
1	0 (0.0)	3 (2.5)	0.051	0 (0.0)	3 (2.9)	0.081
2	8 (3.9)	6 (5.0)	0.656	3 (2.9)	6 (5.9)	0.498
3	195 (95.6)	111 (91.7)	0.152	99 (97.1)	93 (91.2)	0.074

CABG=coronary artery bypass graft; CAG=coronary angiography; DES=drug-eluting stent; LAD=left anterior descending artery; LCX=left circumflex artery; LM=left main coronary artery; PCI=percutaneous coronary artery intervention; PI=pharmacoinvasive; PPCI=primary percutaneous coronary intervention; RCA=right coronary artery; SD=standard deviation; TIMI=thrombolysis in myocardial infarction

* Statistically significant variables

occurrence of in-hospital MACCE; PI with 11.3% versus PPCI with 10.7% (p=0.262) and PI with 11.8% versus PPCI with 9.8% in the propensity-matched cohort (p=0.747) (Table 3). Cardiac death during index hospitalization in the PI and PPCI group was similar (PI with 3.4% versus PPCI with 1.7%, p=0.083). No incidence of MI was reported. At the 1-month follow-up, the occurrence of MACCE was also not significantly different after the propensity score matching (PI with 11.8% versus PPCI with 8.8%; adjusted HR 1.18, 95% CI 0.47 to 2.97, p=0.726) (Figure 2).

The primary safety outcome, combined non-CABG-related TIMI bleeding during the index hospitalization, was non-significant difference between the PI group at 15 events (7.4%) and the PPCI group at 7 events (5.8%) (p=0.286), and in the propensity score matched cohort (PI with 6.9%

Table 3. Events data

Data	All patients; n (%)				After propensity score matching; n (%)			
	PI (n=204)	PPCI (n=121)	Adjusted HR (95% CI)	p-value	PI (n=102)	PPCI (n=102)	Adjusted HR (95% CI)	p-value
In-hospital								
MACCE	23 (11.3)	13 (10.7)	1.57 (0.72 to 3.43)	0.262	12 (11.8)	10 (9.8)	1.22 (0.36 to 4.16)	0.747
Death	8 (3.9)	6 (5.0)	4.75 (0.67 to 33.57)	0.119	6 (5.9)	4 (3.9)	1.97 (0.01 to 345.5)	0.797
• Cardiac	7 (3.4)	2 (1.7)	58.4 (0.6 to 5763.7)	0.083	5 (4.9)	2 (2.0)	-	
• Non-cardiac	1 (0.5)	4 (3.3)	-		1 (1.0)	2 (2.0)	-	
MI	0 (0.0)	0 (0.0)	-		0 (0.0)	0 (0.0)	-	
Stroke	8 (3.9)	1 (0.8)	7.12 (0.62 to 82.15)	0.116	4 (3.9)	1 (1.0)	-	
• Ischemic	5 (2.5)	1 (0.8)	19.29 (0.4 to 1012.8)	0.143	3 (2.9)	1 (1.0)	-	
• ICH	3 (1.5)	0 (0.0)	-		1 (1.0)	0 (0.0)	-	
TIMI bleeding	15(7.4)	8 (6.6)	1.74 (0.63 to 4.84)	0.289	7 (6.9)	7 (6.9)	0.47 (0.09 to 2.43)	0.369
• Minor or major	15(7.4)	7 (5.8)	1.75 (0.63 to 4.85)	0.286	7 (6.9)	6 (5.9)	0.47 (0.09 to 2.43)	0.370
30-day MACCE								
MACCE	23 (11.3)	12 (9.9)	1.85 (0.89 to 3.87)	0.100	12 (11.8)	9 (8.8)	1.18 (0.47 to 2.97)	0.726
Death	8 (3.9)	6 (5.0)	1.75 (0.60 to 5.10)	0.309	6 (5.9)	4 (3.9)	1.19 (0.31 to 4.57)	0.797
• Cardiac	7 (3.4)	2 (1.7)	4.29 (0.89 to 20.61)	0.069	5 (4.9)	2 (2.0)	1.84 (0.33 to 10.29)	0.490
• Non-cardiac	1 (0.5)	4 (3.3)	0.36 (0.04 to 3.42)	0.373	1 (1.0)	2 (2.0)	0.60 (0.05 to 7.86)	0.697
MI	0 (0.0)	0 (0.0)	-	-	0 (0.0)	0 (0.0)	-	-
Stroke	8 (3.9)	1 (0.8)	6.14 (0.71 to 52.76)	0.098	4 (3.9)	1 (1.0)	4.36 (0.44 to 42.83)	0.206
• Ischemic	5 (2.5)	1 (0.8)	4.64 (0.50 to 4313)	0.177	3 (2.9)	1 (1.0)	3.09 (0.29 to 33.18)	0.351
• ICH	3 (1.5)	0 (0.0)	-	-	1 (1.0)	0 (0.0)	-	-
TIMI bleeding	15 (7.4)	8 (6.6)	1.74 (0.63 to 4.84)	0.289	7 (6.9)	7 (6.9)	0.47 (0.09 to 2.43)	0.369
• Minor or major	15 (7.4)	7 (5.8)	1.75 (0.63 to 4.85)	0.286	7 (6.9)	6 (5.9)	0.47 (0.09 to 2.43)	0.370

HR=hazard ratio; ICH=intracranial hemorrhage; MACCE=major adverse cardiovascular and cerebrovascular events; MI=myocardial infarction; PI=pharmacoinvasive strategy; PPCI=primary percutaneous coronary intervention; CI=confidence interval

versus PPCI with 5.9%; adjusted HR 0.47, 95% CI 0.09 to 2.97, p=0.370). Unfortunately, three cases of intracranial hemorrhage were reported in the PI group. In the multivariate analysis (Table 4), Killip classification class III (HR 7.50, 95% CI 3.25 to 17.31, p<0.001) and class IV (HR 9.78, 95% CI 4.31 to 22.21, p<0.001) were associated with adverse outcomes.

In the subgroup analysis of the risk of developing MACCE (Figure 3), the revascularization approach by PPCI for STEMI patients aged at least 65 years decreased the risk of MACCE 5.72-fold compared to PI (HR 5.72, 95% CI 1.31 to 24.97, p=0.02). On the other hand, there was no statistical difference in patients less than 65 years (HR 1.39, 95% CI 0.31 to 4.20, p=0.846).

Discussion

Using propensity score matching analysis, the authors conclude that 1) the PI strategy was not statistically different in terms of efficacy and safety compared to PPCI in a real-world STEMI network setting where SK is predominantly prescribed, and 2) higher Killip classification was strongly associated with MACCE.

Timely PPCI is the reperfusion of choice for patients presenting with STEMI[1-3] because this approach reduces mortality, re-infarction, and stroke relative to fibrinolytic therapy[14]. However, geographical limitations, logistical problems, or reimbursement issues result in PPCI not being always feasible or able to be conducted in time. Therefore, the pharmacological revascularization using fibrinolytic agents is an alternative reperfusion strategy[1,15-17] that leads to either partial or complete recanalization of the IRA. Furthermore, fibrinolytic therapy can potentially reduce total ischemic time, the cornerstone of STEMI management. Unfortunately, re-infarction rates may be high after the initial successful reperfusion[18], and the efficacy of fibrinolytic agents declines over time compared to PPCI[19]. For these reasons, the PI strategy, which combines pharmacological and catheter-based approaches, plays a vital role in STEMI management when PPCI is not a viable option.

Theoretically, the PI approach consists of

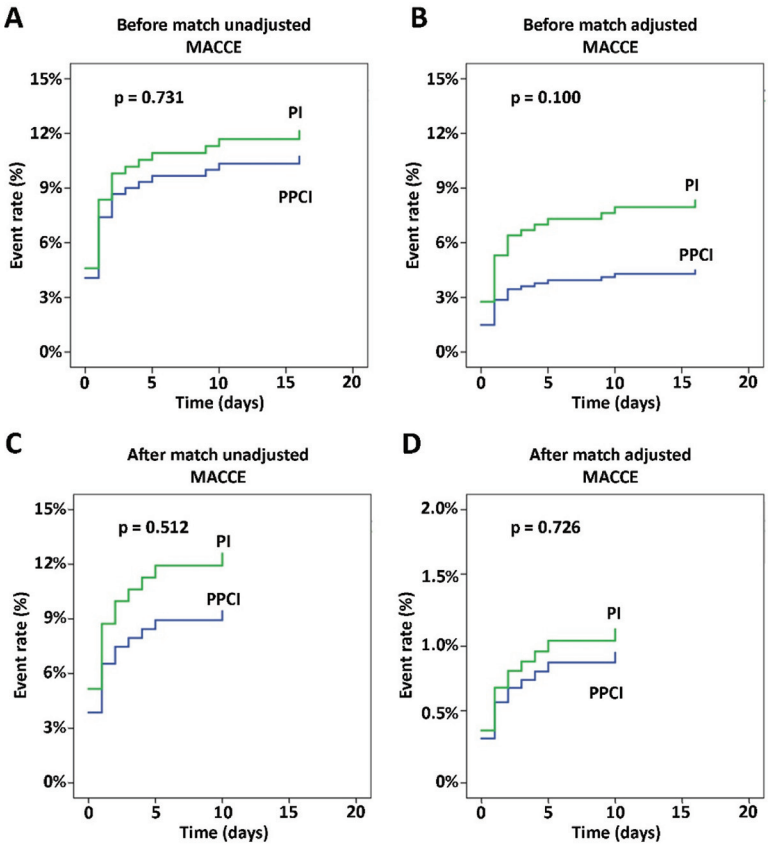

Figure 2. Kaplan-Meier curves of the primary composite endpoint. There was no significant difference in the primary composite endpoint between the pharmacoinvasive strategy (n=204) and primary PCI (n=121). (A) the result before propensity scored matched and unadjusted for confounding variables. (B) the result before propensity scored matched and adjusted for confounding variables. (C) the result after propensity scored matched and unadjusted for confounding variables. (D) the result after propensity scored matched and adjusted for confounding variables.

HR=hazard ratio; MACCE=major adverse cardiovascular and cerebrovascular events; PI=pharmacoinvasive strategy; PPCI=primary percutaneous coronary intervention; CI=confidence interval

initiating fibrinolytic therapy at the FMC hospital followed by immediate transfer to a PCI-capable center[20,21] where coronary angiography will be performed when either rescue PCI if fibrinolysis has failed or as routine early angiography within 2 to 24 hours after successful fibrinolysis. The PI strategy using fibrin-specific agents has proven efficacy and safety, which was demonstrated in landmark randomized controlled trials[22,23] and real-world studies[11,16,17,24-26]. Thus, the current STEMI guideline[1] recommends fibrin-specific agents, especially single-bolus weight-adjusted TNK, for the PI strategy.

Time delays due to logistical challenges or lack of essential emergency medical resources affect the reperfusion strategy in Thailand[27]. Consequently, the PI strategy has become the predominant reperfusion approach for STEMI patients nationwide. Regarding reimbursement issues, streptokinase is currently the principal fibrinolytic agent prescribed for STEMI in Thailand.

The cumulative MACCE rate was high in both the PI and PPCI groups at 23 events (11.3%), and 12 events (9.9%), respectively. This reflects the high burden of STEMI morbidity and mortality in the national healthcare system, similar to other countries around the world[28]. The incidence of combined in-hospital, non-CABG-related TIMI major or minor bleeding was numerically higher in the pharmacoinvasive group at 15 events (7.4%) versus 7 events (5.8%), respectively, but this was not statistically significant after propensity score matched (p=0.370). This finding encourages the treating physician to cautiously consider the contraindications of fibrinolytic agents before prescribing them. In addition, the risk of bleeding

Table 4. Univariate and Multivariate Analysis for Predicting Primary Outcomes

Data	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age ≥65 years	1.09 (0.56 to 2.13)	0.793		
Female gender	2.27 (1.17 to 4.41)	0.016*		
BMI ≥25 kg/m^2	1.52 (0.78 to 2.96)	0.217		
Systolic BP ≥100 mmHg	0.28 (0.13 to 0.63)	0.002*		
Diastolic BP ≥80 mmHg	0.51 (0.23 to 1.10)	0.084		
Pulse ≥80 beats per minute	2.03 (0.96 to 4.28)	0.064		
Hypertension	1.19 (0.60 to 2.35)	0.627		
Diabetes mellitus	1.49 (0.76 to 2.92)	0.251		
Dyslipidemia	0.64 (0.33 to 1.27)	0.202		
History of previous PCI	2.05 (0.28 to 14.94)	0.481		
Anterior STEMI	1.89 (0.95 to 3.75)	0.069		
Inferior STEMI	0.48 (0.24 to 0.96)	0.038*		
Cardiogenic shock	5.11 (2.50 to 10.44)	<0.001*		
Cardiac arrest at arrival	7.04 (3.19 to 15.54)	<0.001*		
Killip classification		<0.001*		<0.001*
Class I	Reference		Reference	
Class II	0.43 (0.06 to 3.32)	0.418	0.43 (0.06 to 3.32)	0.418
Class III	7.50 (3.25 to 17.31)	<0.001*	7.50 (3.25 to 17.31)	<0.001*
Class IV	9.78 (4.31 to 22.21)	<0.001*	9.78 (4.31 to 22.21)	<0.001*
GRACE risk score ≥140	5.44 (2.71 to 10.94)	<0.001*		
LVEF <40%[1]	4.29 (2.21 to 8.32)	<0.001*		
Pharmacoinvasive	1.13 (0.56 to 2.27)	0.731		

BP=blood pressure; GRACE=the Global Registry of Acute Coronary Events; HR=hazard ratio; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; STEMI=ST-elevation myocardial infarction; CI=confidence interval

* Statistically significant variables

[1] Missing data regarding LVEF were imputed for 32 patients.

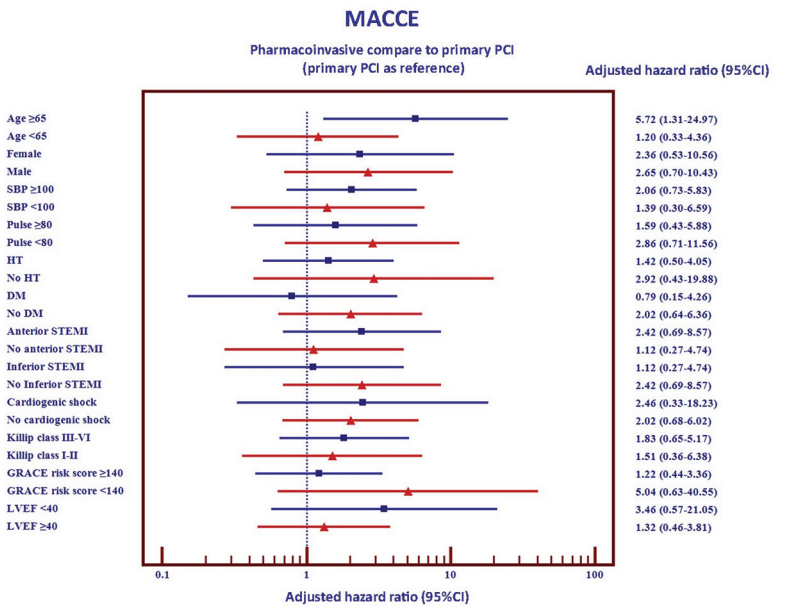

Figure 3. Forrest plot presented as adjusted HR and 95% CI for the risk-developing major adverse cardiovascular and cerebrovascular events (MACCE).

DM=diabetes mellitus; GRACE=the Global Registry of Acute Coronary Events; HR=hazard ratio; HT=hypertension; LVEF=left ventricular ejection fraction; MACCE=major adverse cardiovascular and cerebrovascular events; PCI=percutaneous coronary intervention; SBP=systolic blood pressure; STEMI=ST-elevation myocardial infarction; CI=confidence interval

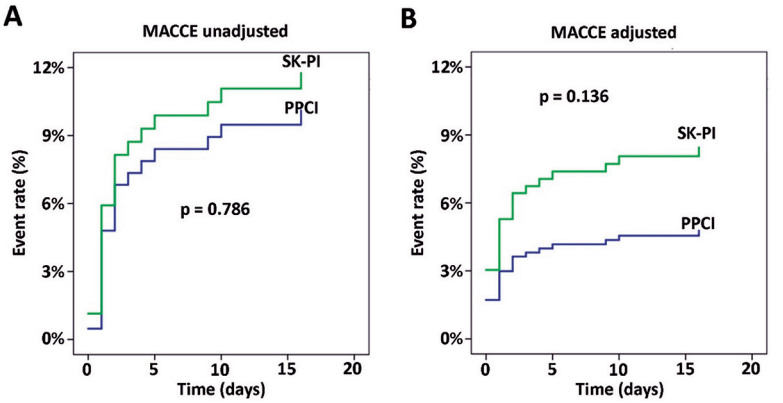

Figure 4. Kaplan-Meier curves of the major adverse cardiovascular and cerebrovascular events (MACCE) of streptokinase-based pharmacoinvasive strategy (SK-PI) (n=191) versus primary PCI (n=121). There was no significant difference in the primary composite endpoint between the SK-PI strategy and primary PCI. (A) the results before adjusted for confounding variables. (B) the result after adjusting for confounding variables.

MACCE=major adverse cardiovascular and cerebrovascular events; PPCI=primary percutaneous coronary intervention; SK-PI=streptokinase-based pharmacoinvasive strategy

from fibrinolytic agents and the risks of delayed myocardial salvage by transferring patients to the PCI-capable center should also be carefully considered.

The present study findings regarding the efficacy of the PI strategy, which predominately uses SK, are compatible with the data from earlier clinical trials of the fibrin-specific PI strategies[16,17,24,25]. However, Rashid et al.[29] stated that the PI strategy is associated with higher bleeding complications after propensity score matching analysis, a conclusion that contrasts with the present study data. In the present study subgroup analysis of patients received SK (SK-PI), there was no significant difference in cumulative MACCE compared to PPCI (p=0.136) (Figure 4).

The authors used the following parameters for adjusted HR and 95% CI, female gender, systolic blood pressure more than or equal to 100 mmHg, diastolic blood pressure greater than 80 mmHg, pulse more than 80 beats per minute, history of dyslipidemia, anterior STEMI, inferior STEMI, cardiogenic shock during presentation, cardiac arrest at arrival, Killip classification Class III and IV, GRACE risk score more than or equal to 140, left ventricular ejection fraction (LVEF) less than 40%, Pre-PCI TIMI grade 3-4, and PI strategy.

The present study STEMI network aimed to deliver prompt reperfusion therapy for STEMI patients[2]. The authors measured an acceptable median transfer time from the regional hospital to PPCI of 76.5 (IQR 36.3 to 100) minutes, which is shorter than the previous report of the Thailand National PCI Registry[30], and the median time to routine coronary angiography after successful fibrinolysis was 15.13 (IQR 8.4 to 22) hours. Both metrics complying with standard STEMI guidelines[1]. However, the door-to-needle time was 56 (IQR 40 to 88) minutes, beyond the guideline's time frame, which may be explained by local logistical challenges, or the lack of experienced physicians to interpret the ECG and initiate the fibrinolytic agents. Nevertheless, the present door-to-needle time is better than the previous report[31].

Initial pre-PCI TIMI flow in the PI group was significantly better than in the PPCI group both before and after propensity score matching, and the median time from symptom onset to reperfusion therapy in the PI group was shorter than in the PPCI group at 165 (IQR 17 to 260) minutes versus 319 (IQR 229 to 467) minutes. These findings suggest that the PI strategy recanalizes the occluded IRA, thus enhancing the probability of salvaging the myocardium. Nevertheless, the post-PCI TIMI flow was similar in both groups.

When comparing the present study total ischemic time, which is strongly correlated to STEMI prognosis[32], with the Korea Acute Myocardial Infarction Registry (KAMIR) registry, there are several intriguing findings. The total ischemic time of the present study PI strategy was 165 (IQR 107 to 260) minutes, which was the same as the KAMIR registry at 165 (IQR 92 to 281) minutes. However, the present study total ischemic time in the PPCI group was higher at 319 (IQR 229 to 467) minutes versus

255 (IQR 158 to 464) minutes[26]. This may reflect the inherent challenges in the organization and operation of STEMI networks in a middle-income country and suggests that the use of the PI strategy is justified when PPCI service is not widely available.

The present study registry data indicate that the patients at the highest risk for morbidity and mortality such as cardiogenic shock, higher GRACE risk scores, and presence of atrioventricular block, are more likely to receive PPCI for coronary reperfusion. In other words, the severity of the disease influences the decisions of the treating physician, and PPCI may be the preferred mode of revascularization in high-risk patients.

Advanced age is a strong predictor of adverse events among STEMI patients[33,34]. PPCI is the most promising revascularization strategy in these patients as it has been shown to improve clinical outcomes during index admission and long-term follow-up compared to fibrinolytic treatment[35,36]. The present study also confirms that PPCI is the optimal revascularization therapy as it markedly decreased the incidence of MACCE in a population with advanced age (Figure 3). Therefore, the administration of fibrinolytic therapy must be performed cautiously in elderly patients.

The present study has limitations. First, although using a propensity score matching analysis, residual confounding factors, biases may persist. Second, this present study only reported the short-time follow-up of the clinical outcomes. In addition, it should be noted that as the mortality rate was lower than expected, the authors changed the primary endpoint to the occurrence of MACCE at one month. This may underpower the result of this present study. Finally, the present study findings reflect the conditions of the STEMI Network and may not be generalizable to other settings.

Conclusion

The pharmacoinvasive strategy with the predominant use of SK is not statistically different from PPCI in terms of efficacy and safety. This evidence supports the use of the SK-PI approach in the context of low and middle-income countries where the availability of fibrin-specific agents may be limited.

What is already known on this topic?

The PI strategy using fibrin-specific fibrinolytic agents such as TNK or rtPA, is an alternative approach for STEMI when PPCI is not feasible or cannot be conducted in a timely fashion. The PI strategy has proven efficacy and safety in STEMI management.

What this study adds?

The study confirms the efficacy and safety of the SK-based PI strategy, which has not been widely investigated because SK is rarely used in the wealthier countries. The findings support the SK-based PI approach in the context of low- to middle-income countries where fibrin-specific fibrinolytic agents recommended in current STEMI guidelines are often not available.

Acknowledgment

The authors appreciate the support and dedication of the medical staff and all coordinators at HMCC, and that of all of the regional hospitals within the authors' STEMI network. The authors would like to express their appreciation to Dr. Mark Simmerman for professionally editing this manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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