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Comparison of short- and medium-term clinical outcomes of ST elevation myocardial infarction patients with spontaneous reperfusion: Early vs. late dual antiplatelet

Comparación de los resultados clínicos a corto y mediano plazo en pacientes con infarto agudo de miocardio con elevación del ST y reperfusión espontánea: Iniciación temprana versus tardía de la terapia antiplaquetaria dual

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SUMMARY

Background: *Cardiovascular disease remains the leading cause of mortality worldwide, and its global burden continues to rise. Previous studies have shown that the incidence of spontaneous reperfusion in STEMI patients can reach up to 30 %, and the timing of antiplatelet administration is associated with increased stable spontaneous perfusion and better prognosis and clinical outcomes.* **Objective:** *This study aims to compare the short- and medium-term clinical outcomes of STEMI patients who underwent spontaneous reperfusion and received early versus late dual antiplatelet treatment at the Integrated Heart Center of Dr. Wahidin Sudirohusodo Hospital, Makassar.* **Methods:** *We enrolled 49 STEMI patients with spontaneous reperfusion, consisting of 29 subjects who received DAPT ≤ 3 hours (Early DAPT) and 20 received DAPT >3 hours (Late DAPT) from onset.* **Results:** *There were significant differences between Early vs. Late DAPT in the incidence of composite MACCE (3.4 % vs. 35.0 %; p=0.003), MACCE within 30 days (3.4 % vs. 20.0 %; p=0.006), and within 6 months (0.0 % vs. 27.8 %; p=0.003). In addition, there was a significantly higher rate of heart failure and rehospitalization in the Late DAPT group (16.7 %; p=0.023; 22.2 %; p=0.008) compared to the Early DAPT group, who did not experience these events at all.* **Conclusions:** *This study demonstrates that early administration of DAPT is associated with a reduction in composite major adverse cardiovascular events.*

Keyword: *STEMI, spontaneous reperfusion, dual antiplatelet, MACCE.*

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RESUMEN

Antecedentes: *Las enfermedades cardiovasculares son la causa más común de muerte en todo el mundo, y su frecuencia va en aumento. Estudios previos han demostrado que la incidencia de reperfusión espontánea en pacientes con IAMCEST puede alcanzar hasta el 30 % y que el momento de administración de antiagregantes plaquetarios se asocia con un aumento de la perfusión espontánea estable y con un mejor pronóstico y resultados clínicos.* **Objetivo:** *Este estudio pretende comparar los resultados clínicos a corto y medio plazo de los pacientes con IAMCEST sometidos a reperfusión espontánea y que recibieron tratamiento antiagregante plaquetario dual, tanto precoz como tardío, en el Centro Cardiológico Integrado del Hospital Dr. Wahidin Sudirohusodo de Makassar.* **Métodos:** *Participaron 49 sujetos de estudio con diagnóstico de IAMCEST con reperfusión espontánea, de los cuales 29 sujetos recibieron DAPT 3 horas (DAPT Temprano) y 20 sujetos recibieron DAPT >3 horas (DAPT Tardío) desde el inicio.* **Resultados:** *Hubo diferencias significativas entre el DAPT precoz y el tardío en la incidencia de All-MACCE en general (3,4 % frente a 35,0 %; p=0,003), All-MACCE a los 30 días (3,4 % frente a 20,0 %; p=0,006) y a los 6 meses (0,0 % frente a 27,8 %; p=0,003). Además, hubo una tasa significativamente mayor de insuficiencia cardíaca y rehospitalización en el grupo de DAPT Tardío (16,7 %; p=0,023; 22,2 %; p=0,008) en comparación con el grupo de DAPT Temprano que no experimentó estos eventos en absoluto.* **Conclusiones**: *Este estudio demuestra que la administración precoz de DAPT se asocia a una reducción global de los eventos cardiovasculares adversos mayores.*

Palabras clave: *IAMCEST, reperfusión espontánea, doble antiagregación plaquetaria, MACCE.*

INTRODUCTION

Cardiovascular disease is the most common cause of death worldwide, and its frequency is increasing. Acute Coronary Syndrome is often the first clinical manifestation of cardiovascular disease (1). Based on data from the European Society of Cardiology (ESC), in 2019, there were an estimated 5.8 million new cases of Coronary Heart Disease in 57 ESC member countries, with an estimated average of 293.3 per 100 000 people (by age), <2.2 million deaths in the female sex, and >1.9 million deaths in the male sex (2). In the United States in 2013, it is estimated that around 38 % of 116 793 patients with Sudden cardiac arrest (SCA) who came to the hospital with acute ST-segment elevation myocardial infarction (STEMI) had a ratio of 57 % in men and 43 % in women (3).

Acute STEMI is a life-threatening medical emergency caused by a complete blockage of a coronary artery, leading to heart muscle damage (necrosis) which causes damage to cardiomyocytes, impaired heart function such as myocardial contractility, and serious complications like dysrhythmias and ventricular remodeling, as well as other serious complications and reperfusion with Percutaneous coronary intervention (PCI) is the current management recommendation to restore coronary blood flow immediately to save the maximum number of threatened cardiomyocytes damage (4).

The benefit of myocardial reperfusion is time-dependent, and the sooner coronary flow is restored, the better the patient's clinical outcome. As primary percutaneous coronary intervention (PPCI) has been widely used in patients with STEMI, coronary angiography data show that up to 30 % of patients with acute STEMI experience transient STEMI or spontaneous reperfusion, which has a smaller myocardial infarction area and a better prognosis and clinical outcome than patients without spontaneous reperfusion (5).

Most spontaneous reperfusion does not actually occur independently, but as a result of the administration of antithrombotic treatment (such as aspilet, clopidogrel, and low molecular weight heparins (LMWH) anticoagulants, Unfractionated Heparin (UFH) and GPIIb/IIIa inhibitors) and vasodilators before PPCI (5). Antiplatelet therapy is an important component in the management of patients with acute coronary syndrome, especially in the acute treatment phase of STEMI patients (6). Platelet inhibition with aspirin and P2Y12 receptor inhibitors is associated with reduced ischemic events, and an increased bleeding risk (7). The choice of antiplatelet regimen and timing of administration is very important and should consider the patient's bleeding risk (1).

Although spontaneous reperfusion is associated with better outcomes, its pathophysiology remains unclear (8). Several determinants

affect spontaneous reperfusion, such as endogenous thrombolysis activity, thrombus size, atherosclerotic condition, and vasomotor tone, which are believed to be associated with early spontaneous reperfusion (9,10). In general, coronary occlusion due to ruptured atherosclerotic plaque followed by thrombosis is considered the main cause of acute STEMI. In addition, plaque erosion and calcified nodules contribute to thrombus formation in acute STEMI without plaque rupture (4).

Patients with transient STEMI or spontaneous reperfusion (SR) have faster and more efficient endogenous fibrinolysis and reduced platelet reactivity (11). Clinically, SR patients have less extensive coronary artery disease, better coronary flow on angiography, lower peak of creatine kinase levels, and higher LV ejection fraction. Therefore, a better understanding of spontaneous reperfusion in STEMI patients would be highly clinically significant (4).

Early administration of Dual Antiplatelet Therapy (DAPT) is the administration of dual antiplatelet therapy within ≤3 hours of chest pain onset, while late DAPT administration is the administration of antiplatelet therapy >3 hours after chest pain onset. Early administration of DAPT is associated with several benefits compared to late administration, because reduces risks of major adverse cardiac events (MACE), stroke, and postoperative complications such as chest reoperation and dialysis in patients with acute coronary syndrome (ACS) and stroke, though it may increase transfusion rates. This is consistent with a meta-analysis study that found significant benefits of early administration (less than 3 hours from onset) of glycoprotein IIb/IIIa inhibitor antiplatelet compared to late administration (more than 3 hours from onset) of GP IIb/IIIa inhibitor in terms of spontaneous reperfusion with complete resolution of ST-segment, benefits of preprocedural epicardial recanalization, and also postprocedural benefits with improved TIMI 3 flow (12). Thus, this study aimed to assess and compare short and medium-term clinical outcomes of STEMI patients with spontaneous reperfusion receiving Early vs. Late dual antiplatelet therapy.

METHODS

This is an observational, single-center, retrospective cohort study.

Population and Sample

The study population comprised all STEMI patients with spontaneous reperfusion recorded in the Hospital Information System (SIRS) at the Integrated Heart Center of Dr. Wahidin Sudirohusodo General Hospital, Makassar, between June 2021 and June 2024. Consecutive sampling was employed, enrolling all eligible patients meeting inclusion criteria (age >18 years, STEMI onset <12 hours with spontaneous reperfusion, documented DAPT loading, and coronary angiography within <12 hours of admission) until the minimum sample size was achieved. Exclusion criteria included COVID-19 diagnosis, thrombolytic therapy, prior CAD/PCI/CABG, structural or moderate-severe valvular heart disease, prior anticoagulant/antiplatelet use, bleeding disorders, malignancies, severe CKD (eGFR <30 mL/min), or severe infections (sepsis/SIRS). Data was collected sequentially to ensure representative sampling.

Research Procedures

Electronic medical records (SIRS) of STEMI patients treated at the Integrated Heart Center of Dr. Wahidin Sudirohusodo General Hospital, Makassar, were analyzed, including those meeting predefined inclusion/exclusion criteria. Collected data encompassed demographic characteristics (sex, age), risk factors (hypertension, diabetes mellitus, smoking), clinical parameters (Killip class, creatinine levels, ejection fraction, troponin), and DAPT timing (early ≤3 hours vs. late >3 hours from pain onset). It was evaluated 6-month clinical outcomes (heart failure, recurrent infarction, stroke, and mortality), with all procedures adhering to hospital medical service standards.

Data Analysis

Data analysis was performed using SPSS software version 24. Categorical variables were expressed as frequencies and percentages (n, %), while numerical variables were presented as mean±SD for normally distributed data or median (interquartile range) for non-normally distributed data. Normality testing was conducted using the Shapiro-Wilk test. Bivariate analysis employed independent T-tests (normal distribution) or Mann-Whitney U tests (non-normal distribution) for numerical variables, and Chi-square or Fisher's exact tests for categorical variables. Clinical outcome differences between early and late DAPT groups were analyzed using Kaplan-Meier curves with log-rank testing (significance set at $p<0.05$). All analyses were conducted with a 95 % confidence level.

Ethical Approval

This study received ethical approval from the Health Research Ethics Committee of Hasanuddin University's Faculty of Medicine and Dr. Wahidin Sudirohusodo General Hospital (Approval No. 265/UN4.6.4.5.31/PP36/2025). All participants provided written informed consent after receiving complete explanations regarding the study's purpose, benefits, and procedures. The research protocol was conducted in strict accordance with health research ethical guidelines.

RESULTS

The baseline characteristics of the study participants are presented in Table 1. The subjects were divided into two groups based on DAPT administration timing: early group (n=29) and late group (n=20). The mean age was 53.34±10.39 years in the early group compared to 54.80±10.28 years in the late group (p=0.631). Regarding sex distribution, both groups showed a male predominance, with 86.2 % in the early group and 95.0 % in the late group (p = 0.318). Smoking was more prevalent in the late group (90.0 %) compared to the early group (75.9 %), although this difference was not statistically significant (p=0.209). The prevalence of hypertension was 55.2 % in the early group and 45.0 % in the late group (p = 0.484). Diabetes mellitus was more common in the late group (40.0 %) than in the early group (20.7 %), with a p-value of 0.141.

The clinical characteristics and treatments received by the study participants are ilustrated in Table 2. The average onset time in the early group was 7.38 ± 4.78 hours, whereas in the late group, it was 9.18 ± 4.69 hours, with a p-value of 0.201. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed no significant differences between the two groups, with p-values of 0.922 and 0.949, respectively.

The distribution of the Killip score showed that most of our patients in both groups were in class 1, 93.1 % in the early group and 90.0 % in the late group. Class 4 was found in 3.4 % of subjects in the early group and 10.0 % in the late group (p = 0.465). The average TIMI Score in the early group was 3.52 ± 1.41, while in the late group it was 3.25 ± 1.83 (p = 0.566).

In terms of treatments received, all subjects in both groups received aspirin (100.0 %). Clopidogrel use was nearly similar, at 82.8 % in the early group and 80.0 % in the late group (p = 0.806). Similarly, ticagrelor use showed no significant difference (p = 0.953). Anticoagulant use was higher in the late group (45.0 %) compared to the early group (27.6 %), but the difference was not statistically significant (p = 0.208). The DAPT administration time in the early group averaged 1.62 ± 0.86 hours, while in the late group it was 6.55 ± 3.73 hours (p < 0.001).

Table 3 demonstrates that administering dual antiplatelet therapy (DAPT) at different timepoints resulted in variations in laboratory parameters, though not all differences were statistically significant. In this study, hemoglobin levels tended to be higher in the early group (13.70 ± 2.72 g/dL) compared to the late group (12.70 ± 2.78 g/dL), though this difference was not statistically significant (p = 0.219). Similarly, leukocyte and platelet count showed no significant differences between groups.

Notably, random blood glucose (RBG) was significantly higher in the late group (165.84 ± 71.72 mg/dL vs. 129.68 ± 39.51 mg/dL; p = 0.031), suggesting a potential influence of DAPT timing on glucose metabolism. Additionally,

Table 1. Baseline characteristics of the study participants.

Variable	DAPT administration		p-value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Age (years)	53.34 ± 10.39	54.80 ± 10.28	0.631
Sex			
Male	25 (86.2 %)	19 (95.0 %)	0.318
Female	4 (13.8 %)	1 (5.0 %)	
Smoking			
Yes	22 (75.9 %)	18 (90.0 %)	0.209
No	7 (24.1%)	2 (10.0 %)	
Hypertension			
Yes	16 (55.2 %)	9 (45.0 %)	0.484
No	13 (44.8 %)	11 (55.0 %)	
Diabetes Mellitus			
Yes	6 (20.7 %)	8 (40.0 %)	0.141
No	23 (79.3 %)	12 (60.0 %)	

Values are n (%) or mean ± SD, unless stated otherwise. Continuous variables were compared using an independent samples t-test, and categorical variables with the Pearson Chi-square test.

Table 2. Clinical Characteristics and Treatment Received by the study participants.

Variable	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Onset (Hours)	7.38 ± 4.78	9.18 ± 4.69	0.201
Systolic BP (mmHg)	126.00 ± 22.28	126.65 ± 23.03	0.922
Diastolic BP (mmHg)	76.34 ± 13.52	76.10 ± 12.63	0.949
KILLIP Score			
I	27 (93.1 %)	18 (90.0 %)	
II	1 (3.4 %)	0 (0.0 %)	0.465
III	0 (0.0 %)	0 (0.0 %)	
IV	1 (3.4 %)	2 (10.0 %)	
TIMI Score	3.52 ± 1.41	3.25 ± 1.83	0.566
Acute MI Location			
Anterior	13 (44.8 %)	8 (40.0 %)	0.737
Inferior	16 (55.2 %)	12 (60.0 %)	
Aspilet	29 (100.0 %)	20 (100.0 %)	-
Clopidogrel	24 (82.8 %)	16 (80.0 %)	0.806
Ticagrelor	6 (20.7 %)	4 (20.0 %)	0.953
Anticoagulants	8 (27.6 %)	9 (45.0 %)	0.208
Administration Time (Hours)	1.62 ± 0.86	6.55 ± 3.73	<0.001*

Values are n (%) or mean ± SD, unless stated otherwise. Continuous variables were compared using an independent samples t-test, and categorical variables with the Pearson Chi-square test. *p < 0.05

Table 3. Laboratory Characteristics of Study Subjects

Variable	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
HB (g/dL)	13.70 ± 2.72	12.70 ± 2.78	0.219
WBC ($10^3/\mu$L)	11.46 ± 3.47	12.04 ± 2.78	0.536
PLT ($10^3/\mu$L)	262 (114-565)	246 (154-468)	0.966
NEUT (%)	68.12 ± 12.77	73.70 ± 7.51	0.090
LYMPH (%)	22.5 (5-79)	17 (7-78)	0.223
CR (mg/dL)	1.24 ± 1.15	1.07 ± 0.66	0.552
RBG (mg/dL)	117 (68-258)	146 (66-350)	0.031*
Na (mmol/L)	137.44 ± 3.55	136.06 ± 4.42	0.269
K (mmol/L)	4.15 ± 0.39	4.31 ± 0.55	0.283
Cl (mmol/L)	107.28 ± 4.03	106.71 ± 2.82	0.614
Hs-Trop I (pg/mL)	14 460.15 (20.5-400.000)	23 997.82 (6.9-400.000)	0.105
Chol (mg/dL)	202.39 ± 56.72	196.06 ± 45.53	0.692
LDL (mg/dL)	127.25 ± 48.31	121.68 ± 35.37	0.670
HDL (mg/dL)	37.85 ± 12.20	46.47 ± 13.12	0.027*
TG (mg/dL)	161 (57-310)	135 (49-404)	0.331

Values are n (%) or mean ± SD, unless stated otherwise. Continuous variables were compared using an independent samples t-test, and categorical variables with the Pearson Chi-square test. Non-normally distributed data were analyzed with the Mann-Whitney U test and presented as median. *$p < 0.05$

HDL levels were significantly higher in the late group (46.47 ± 13.12 mg/dL vs. 37.85 ± 12.20 mg/dL; p = 0.027), while other lipid parameters (total cholesterol, LDL, and triglycerides) showed no significant differences. High-sensitivity troponin I (Hs-Trop I) levels also trended higher in the late group, although not stastistically significant (p = 0.105).

The comparison of hospitalization duration (Length of Stay/LOS) between patients receiving early dual antiplatelet therapy (DAPT) and those receiving late DAPT is presented in Table 4. The early DAPT group had an average LOS of 5.83 ± 1.53 days, while the late DAPT group showed an average of 6.37 ± 2.21 days. Although there was a numerical difference between the two groups, statistical analysis revealed that this difference was not statistically significant (p = 0.323).

As shown in Table 5, the late DAPT group demonstrated poor 30-day clinical outcomes compared to the early DAPT group, with a significantly higher incidence of all-cause major adverse cardio-cerebro-vascular events (MACCE) (20.0 % vs. 3.4 %; p = 0.006). Although not statistically significant, the late DAPT group also showed higher rates of heart failure (10.0 % vs. 0.0 %; p=0.082) and rehospitalization (15.0 % vs. 3.4 %; p=0.147), while no cases of recurrent infarction or stroke were observed in either group during the observation period.

According to Table 6, during the 3 months, the late DAPT group showed an incidence of heart failure, rehospitalization, and All-MACCE of 11.1 %, while no such events occurred in the early DAPT group. Although this difference was not statistically significant (p=0.067), the findings suggest a more favorable trend with early DAPT administration. No cases of recurrent infarction, stroke, or mortality were recorded in either group during this observation period.

Table 7 shows the comparison of 6-month clinical outcomes between patients receiving early and late DAPT therapy. The results show that the late DAPT group had significantly higher rates of heart failure (16.7 %; p=0.023), rehospitalization (22.2 %; p=0.008), and All-MACCE (27.8 %; p=0.003) compared to the early DAPT group which experienced none of

Table 4. Comparison of Hospital Length of Stay (LOS) Between Early DAPT and Late DAPT Patients

Variable	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Length of Stay (LOS)(days)	5.83 ± 1.53	6.37 ± 2.21	0.323

Values are n (%) or mean ± SD, unless stated otherwise. Continuous variables were compared using an independent samples t-test. *p < 0.05.

Table 5. Comparison of 30-Day Clinical Outcomes between Early DAPT and Late DAPT Patients

Adverse Outcomes	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Heart Failure	0 (0.0 %)	2 (10.0 %)	0.082
Re-Infark	0 (0.0 %)	0 (0.0 %)	-
Stroke	0 (0.0 %)	0 (0.0 %)	-
Rehospitalization	1 (3.4 %)	3 (15.0 %)	0.147
Mortality	0 (0.0 %)	2 (10.0 %)	0.082
All-MACCE	1 (3.4 %)	4 (20.0 %)	0.006*

Values are n (%). Comparison was performed using Pearson's Chi-Square. MACCE = Major Adverse of Cardio Cerebrovascular Events. *p < 0.05.

Table 6. Comparison of 3-Month Clinical Outcomes between Early DAPT and Late DAPT Patients

Adverse Outcomes	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Heart Failure	0 (0.0 %)	2 (11.1 %)	0.067
Re-Infark	0 (0.0 %)	0 (0.0 %)	-
Stroke	0 (0.0 %)	0 (0.0 %)	-
Rehospitalization	0 (0.0 %)	2 (11.1 %)	0.067
Mortality	0 (0.0 %)	0 (0.0 %)	-
All-MACCE	0 (0.0 %)	2 (11.1 %)	0.067

Values are n (%). Comparison was performed using Pearson's Chi-Square. MACCE = Major Adverse o Cardio Cerebro Vascular Events. *p < 0.05.

these events. Meanwhile, no cases of recurrent infarction or stroke were found in either group, and mortality only occurred in one patient in the late DAPT group (5.6 %; p=0.199). These findings further strengthen the potential clinical benefits of early DAPT administration in reducing major cardiovascular events in the medium term.

Table 7. Comparison of 6-Month Clinical Outcomes Between Early DAPT and Late DAPT Patients

Adverse Outcomes	DAPT Administration		P-Value
	Early (≤3 H) (n=29)	Late (>3 H) (n=20)	
Heart Failure	0 (0.0 %)	3 (16.7 %)	0.023*
Re-Infark	0 (0.0 %)	0 (0.0 %)	-
Stroke	0 (0.0 %)	0 (0.0 %)	-
Rehospitalization	0 (0.0 %)	4 (22.2 %)	0.008*
Mortality	0 (0.0 %)	1 (5.6 %)	0.199
All-MACCE 30 Days	0 (0.0 %)	5 (27.8 %)	0.003*

Values are n (%). Comparison was performed using Pearson's Chi-Square. MACCE = Major Adverse of Cardio Cerebro Vascular Events. *p < 0.05.

Figure 1 shows the comparison of overall All-MACCE occurrences, whether due to mortality, heart failure, or rehospitalization from any cause (cardiac or non-cardiac), between patients receiving early and late DAPT therapy. All-MACCE events were significantly higher in the late DAPT group (35.0 %) compared to the early DAPT group (3.4 %), with a p-value of 0.003. These results suggest that early administration of DAPT may offer greater protection against major cardiovascular events.

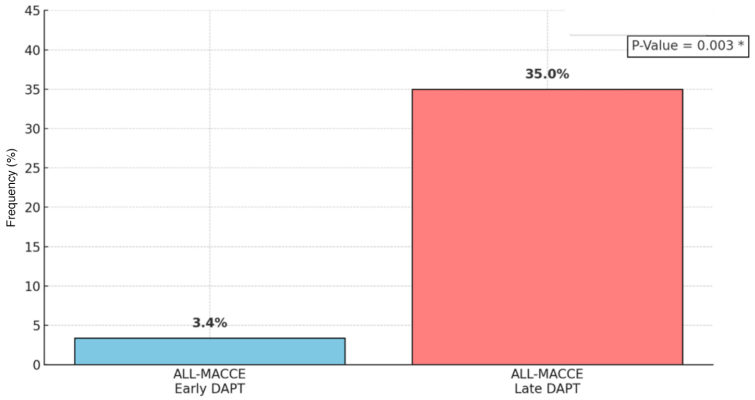

Figure 1. Comparison of Clinical Outcomes between Early DAPT and Late DAPT Groups. On the ordinate axis, the quantity of cases is expressed as a percentage.

Figure 2 displays Kaplan-Meier curves comparing survival between patients receiving Early DAPT and Late DAPT therapy throughout follow-up from hospital admission. The results demonstrate that the Early DAPT group (blue line) maintained a higher survival probability compared to the Late DAPT group (red line) across the observation period. The "+" symbols represent censored data - patients who did not experience events by the monitoring endpoint. This graphic indicates that Early DAPT administration is associated with superior clinical outcomes compared to delayed (Late DAPT) treatment.

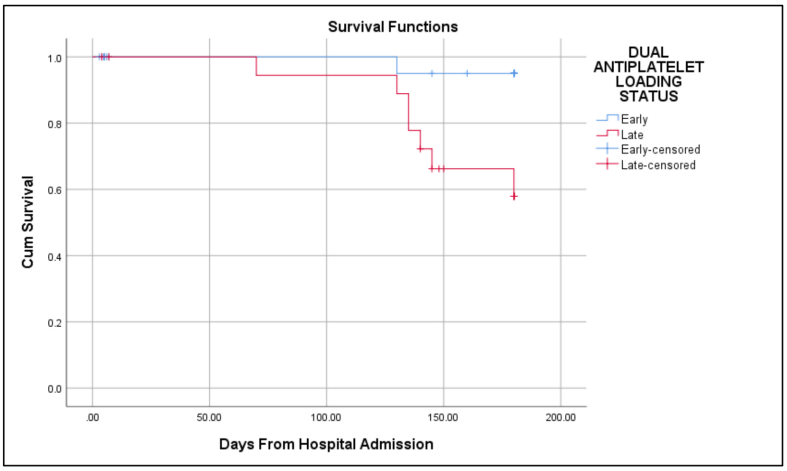

Figure 2. Kaplan-Meier Survival Analysis by DAPT Timing Status.

DISCUSSION

Acute STEMI is a life-threatening condition. Current guidelines recommend immediate reperfusion using techniques such as PPCI to promptly restore coronary blood flow and salvage as much jeopardized myocardium as possible (13). Interestingly, up to 30 % of patients with STEMI exhibit TIMI grade 3 flow at emergent angiography, even without prior invasive intervention or fibrinolytic therapy. This condition is known as spontaneous reperfusion (SR). SR is associated with smaller infarct size, fewer stents used, and better short-term outcomes. Although endogenous thrombus lysis or release of coronary spasm can lead to SR, the pathological and pathophysiological mechanisms remain unclear (4,14).

In the present study, 49 patients who received DAPT experienced SR. This is in line with the findings of Şeker et al. (15), who stated that early administration of glycoprotein IIb/IIIa inhibitors before PPCI is associated with an increased incidence of SR, with incidence rates reaching approximately 40 % in various studies. These findings suggest that aggressive pharmacological interventions in the early phase, such as DAPT in our study, may contribute to the occurrence of SR before invasive measures are taken.

In the present study, spontaneous reperfusion occurred in 49 patients receiving DAPT therapy, with the majority of patients being male (early: 86.2 %; late: 95 %) and a mean age of approximately 53-54 years. When compared with data from Rimar et al. (16), the group of patients who experienced spontaneous reperfusion (n = 98) had a higher mean age of 63 years, with a proportion of women of 30 %. This suggests that patients in our study tended to be younger and more male-dominated.

In terms of risk factors, the prevalence of diabetes mellitus in patients with spontaneous reperfusion in the study Rimar et al. was 21 % (16), similar to the early DAPT group in our study (20.7 %), but lower than the late DAPT group (40.0 %). A smoking habit was found in 49 % of patients with spontaneous reperfusion in the study Rimar et al. (16), whereas in our study, smokers were more prevalent in the late group (90 %) than in the early group (75.9 %). Although this difference was not statistically significant in our study, this finding indicates that smoking remains an important factor related to the thrombotic process and the likelihood of spontaneous reperfusion (15). Hypertension was also found in 45 % of patients with spontaneous reperfusion in the Rimar et al (16) study, a rate similar to our early DAPT group (55.2 %) and late group (45.0 %). This suggests that the

hypertension factor may not make a big difference in the chance of spontaneous reperfusion.

In subjects with spontaneous reperfusion, mean laboratory parameters included hemoglobin 13.29 ± 2.76 g/dL, leukocytes 11.70 ± 3.17 x10^3/μL, platelets 254 (134-516) x10^3/μL, creatinine 1.17 ± 0.94 mg/dL, and glucose 131.5 (67- 304) mg/dL. Mean electrolyte levels and lipid profile were also within normal ranges, with Hs-Trop I levels reaching 19 228.98 pg/mL. Based on these laboratory parameters —specifically, age, hemoglobin, leukocytes, creatinine, and platelets —the PRECISE-DAPT score can be calculated. This score was originally developed to estimate bleeding risk in patients with acute coronary syndrome who are receiving long-term antiplatelet therapy. However, recent studies have shown that the PRECISE-DAPT score may also correlate with the likelihood of spontaneous reperfusion in patients with STEMI (15).

Spontaneous reperfusion can be assessed either by clinical, ECG, and/or coronary angiography. Where if based on clinical or ECG refers to a condition where the occluded coronary artery reopens naturally identified through ECG in the form of improvement with spontaneous, complete or partial resolution (≥70 %) of ST segment elevation spontaneously before definitive reperfusion therapy and or significantly reduced chest pain ≥70 % assessed using a visual analog score of 0-10 (where scale 0 is no pain, while scale 10 is maximum pain experienced), or on angiography the achievement of TIMI grade 2-3 flow in the infarct-related artery (IRA) before interventions such as PCI (14).

The present showed that patients with STEMI who had lower PRECISE-DAPT scores were more likely to have infarct artery patency (IRA) before primary PCI. The median score in the group with spontaneously open arteries was lower than the group with complete occlusion (PRECISE-DAPT score 10 (3-46) vs. 14 (3-50); $p < 0.01$). This suggests that a low score not only reflects minimal bleeding risk but may also be associated with a lighter thrombus burden or a more effective endogenous thrombolysis process (14,15).

These findings were reinforced by a study by Şaylık and Akbulut (17), which analyzed 204 STEMI patients undergoing primary PCI. The results showed that a higher PRECISE-DAPT score was related to a greater intracoronary thrombus burden, thus reducing the likelihood of spontaneous reperfusion. Conversely, a lower score indicates a more stable vascular condition and a faster likelihood of the artery opening spontaneously.

Our results indicate that the mean length of hospitalization of patients with early DAPT was slightly shorter than that of late DAPT (5.83 ± 1.53 vs. 6.37 ± 2.21 days). Still, this difference was not statistically significant ($p = 0.323$). Within 30 days, there was no significant difference between the two groups in clinical outcomes such as heart failure, reinfarction, stroke, rehospitalization, death, or all-MACCE (rehospitalization and all-MACCE 3.4 % vs. 5.0 %, respectively; $p = 0.787$). During the 3 months, there were no major clinical events in either group. However, at 6 months, the rehospitalization and all-MACCE rates were significantly higher in the late DAPT group (20.0 % vs. 0.0 %; $p = 0.012$). There was also one case of heart failure in the late group, although not significant ($p = 0.224$). These results are in line with the findings of Yang et al. (18), who examined 938 patients with NSTEMI who underwent PCI and were divided based on the timing of DAPT administration (<6 hours vs. >6 hours after arrival at the ED) (18). The study showed that the group receiving DAPT for more than 6 hours had a significantly higher rate of MACE during hospitalization (8.37 % vs. 3.52 %; $p = 0.009$). Components of MACE in the >6 hour group included increased rates of stroke (0.88 % vs. 0.42 %), death (7.05 % vs. 2.95 %), as well as one case of reinfarction. In addition, although not statistically significant, the >6-hour group also showed higher trends in 14-day readmission rates (4.85 % vs. 2.53 %; $p = 0.144$) and return to the emergency department within 72 hours (2.20 % vs. 0.84 %; $p = 0.095$). Meanwhile, revascularization measures (PCI and CABG) within 30 days tended to be performed more in the <6-hour group, with PCI reaching 12.66 % vs. 7.93 % ($p = 0.052$) (18).

Furthermore, although there is no evidence specifically exploring the relationship between the timing of DAPT administration and spontaneous reperfusion in STEMI cases, Luca et al. (12) in their meta-analysis of 1 662 patients from 11 studies found that early intravenous

administration of antiplatelet glycoprotein IIb/IIIa inhibitors was associated with increased spontaneous reperfusion rates and better ST-segment resolution on ECG. This provides theoretical support for our findings, where early DAPT administration may contribute to improved stable spontaneous perfusion and better clinical outcomes.

Our findings are also relevant when linked to Alkatiri et al. (19), who examined the effect of the timing of eptifibatide administration on TIMI flow in STEMI patients undergoing primary PCI (19). Although the focus of the intervention differed (eptifibatide as a glycoprotein IIb/IIIa inhibitor), this study highlights the importance of timing in pharmacological intervention. They found that eptifibatide administration more than 90 minutes before the first angiography resulted in better TIMI flow compared to administration less than 90 minutes, characterized by a lower proportion of TIMI flow 2 (5.1 % vs. 18.9 %; $p = 0.036$) and a decreasing trend in TIMI flow 0. This suggests that, in addition to the timing of DAPT, the timing of administration of other antiplatelets, such as eptifibatide, may also affect coronary perfusion outcomes (19).

The study by Rodriguez et al. (20) offers an important perspective on the delayed initial presentation of STEMI patients, which is a key upstream factor contributing to delayed therapy. In an analysis of 1,297 patients, it was found that nearly a quarter of patients were presented late (>6 hours from chest pain onset), and this group had a significantly higher mortality rate. Factors such as black ethnicity, low income, and diabetes mellitus were identified as independent predictors of late presentation. In contrast, a previous history of heart disease played a protective role. This study suggests that social factors and comorbidities influence the timing of therapy delivery, which in turn may impact clinical outcomes (20). In particular, in the context of patients with spontaneous reperfusion, the study of Rimar et al. provides a relevant clinical basis (16). They showed that patients with spontaneous reperfusion had a lower degree of myocardial damage (indicated by a higher percentage of non-Q wave AMI and lower peak creatine kinase levels), as well as significantly lower 30-day and one-year mortality rates than patients who received thrombolytics, primary angioplasty, or no reperfusion. However, they also found that patients with spontaneous reperfusion were more prone to re-ischemia (35 %) and required further interventions such as angiography or bypass surgery. This suggests that despite a favorable initial prognosis, this group still requires close attention (16).

In line with Wang and He (5), who also evaluated the clinical and angiographic characteristics of STEMI patients with spontaneous reperfusion (defined as TIMI flow grade 3 before PCI). The study found that patients with spontaneous reperfusion were generally younger, had lower peak troponin I values, and higher thrombus burden, with the main lesion often being in the distal part of the LAD. Interestingly, although these patients tended to have milder initial clinical conditions, they exhibited significant thrombotic characteristics, which may increase the risk of re-ischemia if not treated optimally. This finding aligns with our results, showing rehospitalization rates in the late DAPT group after 6 months post-discharge.

The limitation of this study is that the study sample is limited to the PCI era, in PCI center hospitals with cardiac catheterization laboratories, where STEMI patients with onset < 12 hours will be activated by the cardiac catheterization laboratory team for primary PCI revascularization, and STEMI patients with onset < 12 hours in non-PCI center hospitals will be treated with fibrinolytic measures with drugs first.

CONCLUSION

Early initiation of dual antiplatelet therapy was associated with clinical benefits in reducing the short- and medium-term. These findings suggest that while early DAPT does not influence certain outcomes, it may play a critical role in improving overall cardiovascular prognosis in this patient population.

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Authors' contribution

Conceptualization: AHA, AFM, ZD, NB; Methodology: AAZ and AQ; formal analysis and investigation: NB and AQ; writing- original draft: NB and AQ; writing—review and editing: AQ; resources and supervision: AHA, AFM, ZD; Validation: AHA, AFM, ZD. The authors read and approved the final manuscript.

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Availability of data and materials

Applicable upon request

Declarations

Ethics approval and consent to participate

This clinical study was approved by the Health Research Ethics Committee of Hasanuddin University's Faculty of Medicine, Makassar, and Dr. Wahidin Sudirohusodo Central Hospital (Protocol No. 265/UN4.6.4.5.31/PP36/2025). All participants provided written informed consent prior to enrollment.

Consent for publication

Not Applicable

Competing interest

The authors declare that they have no competing interests

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