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Differences in Coronary Grade Flow in Diagnostic Coronary Angiography Between Half Dose and Full Dose Pharmacoinvasive Strategy in Patients with ST-Elevation Myocardial Infarction (STEMI)

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ABSTRACT

Background: The time for managing patient with STEMI undergoing primary PCI strategy in indonesia has not yet achieved the ideal target < 90 minutes. Considering the risk of bleeding from fibrinolysis strategy, despite being part of the pharmacoinvasive strategy. Half dose pharmacoinvasive strategy was developed to address these limitations and its expected to give the same result as full dose pharmacoinvasive strategy

Objectives: To determine the diferences in coronary grade flow in diagnostic coronary angiography procedure between half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy in patients with STEMI

Methods: This study is an observational study with retrospective cohort design to determine the differences in coronary flow grade in diagnostic coronary angiography procedure between half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy in patients with STEMI using secondary data from SHERIVE study between February 2021 until march 2025. Coronary flow grade was assessed based on diagnostic coronary angiography and grouped into TIMI grade 3 flow as coronary flow patency and TIMI grade 0-2 flow (not TIMI grade 3 flow)

Result: There were 151 subjects who met the inclusion and exclusion criteria: 75 subjects in the half dose pharmacoinvasive strategy and 76 subjects in full dose pharmacoinvasive strategy. Bivariate analysis showed a significant difference in the degree of TIMI grade 3 flow between the half dose pharmacoinvasive strategy and the full dose pharmacoinvasive strategy, 33.33 % vs 52.63 % respectively (RR 0,633; IK 95 % 0,431-0,930;p=0,017). Multivariate analysis also found that the halfdose pharmacoinvasive strategy was an independent predictor of TIMI grade 3 flow (RR 0.377; 95% CI 0.185-0.765; p=0.007). Other independent predictors of achieving TIMI grade 3 flow included administration of ACE inhibitors/ARBs (RR 0.303; 95% CI 0.141-0.654; p=0.002)

Conclusion: There is a significant difference in TIMI grade 3 flow in diagnostic coronary angiography procedure between patients with STEMI undergoing half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy.

INTISARI

Latar Belakang: Waktu manajemen pasien IMA-EST yang menjalani Intervensi koroner perkutan (IKP) primer di Indonesia saat ini masih belum

mencapai target < 90 menit, dan dengan mempertimbangkan adanya risiko perdarahan dari terapi fibrinolisis, dan menjadi bagian dari strategi farmako-invasif. Strategi farmako-invasif dosis setengah diharapkan dapat memberikan luaran hasil yang sama dengan strategi farmako-invasif dosis penuh.

Tujuan Penelitian: Mengetahui perbedaan derajat aliran koroner TIMI 3 pada prosedur diagnostik invasif pada pasien IMA-EST yang dilakukan strategi farmako-invasif dosis setengah dengan strategi farmako-invasif dosis penuh

Metode Penelitian: Penelitian ini merupakan studi observasional analitik dengan desain kohort retrospektif untuk menilai perbedaan aliran derajat koroner pada prosedur diagnostik invasif yang dilakukan strategi farmako-invasif dosis setengah dan dosis penuh pada pasien IMA-EST, menggunakan data sekunder selama periode februari 2021 hingga Maret 2025 yang termasuk dalam penelitian SHERIVE Study. Aliran derajat koroner dinilai berdasarkan angiografi koroner sebagai prosedur diagnostik invasif, dan dikelompokan menjadi pasien dengan aliran derajat koroner TIMI 3 dan TIMI 0-2 (tidak TIMI 3)

Hasil: Terdapat 151 subjek yang memenuhi kriteria inklusi dan eksklusi : 75 subjek pada kelompok strategi farmako-invasif dosis setengah, 76 subjek pada kelompok strategi farmako-invasif dosis penuh. Analisis bivariat menunjukan adanya perbedaan yang bermakna derajat aliran koroner TIMI 3 antara strategi farmako-invasif dosis setengah dengan strategi farmako-invasif dosis penuh yaitu 33.33 % vs 52.63 % (RR 0,633; IK 95 % 0,431-0,930;p=0,017). Analisis multivariat juga mendapati bahwa stretegi farmako-invasif dosis setengah merupakan prediktor independen untuk aliran derajat koroner TIMI 3 (RR 0,377; IK 95 % 0,185-0,765;p=0,007). Prediktor independen lain tercapainya derajat aliran koroner TIMI 3 antara lain pemberian penghambat ACE/ARB (RR 0,303; IK 95 % 0,141-0,654;p=0,002)

Kesimpulan: Terdapat perbedaan derajat aliran koroner TIMI 3 yang bermakna pada prosedur diagnosis invasif antara pasien IMA-EST yang menjalani strategi farmako-invasif dosis setengah dengan strategi farmako-invasif dosis penuh.

INTRODUCTION

Heart disease remains the leading cause of death worldwide. According to the World Health Organization (WHO) in 2016, heart disease caused 17.9 million deaths, accounting for 31% of all deaths worldwide, and is estimated to increase to 23.6 million deaths by 2030. Epidemiological data shows that acute coronary syndrome (ACS) caused 10 million deaths and 120 million people suffered disabilities in the Asia-Pacific region between 1990 and 2010. In 2013, the prevalence of acute coronary syndrome in Indonesia was known to be 1.5% and is estimated to increase annually [1]

Acute Coronary Syndrome (ACS) consists of ST elevation Myocardial Infacrtion (STEMI), Non-ST elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP). ACS is an emergency or life-threatening condition that requires immediate treatment. Patients with ST elevation myocardial infarction (STEMI) should undergo reperfusion therapy as soon as possible, either with primary percutaneous coronary intervention (PCI) or with fibrinolysis therapy. Fibrinolysis therapy management is an important reperfusion strategy and is an option in patients with ST elevation Myocardial Infarction (STEMI) within 12 hours of onset when the patient is in a healthcare facility/hospital that does not have the facilities to perform primary percutaneous coronary intervention (PCI) with an estimated time from the first medical contact to primary PCI of more than 120 minutes [2].

The current problem is that not all health facilities / hospitals can provide primary percutaneous coronary intervention (PCI) services 24 hours a day, 7 days a week, due to limitations in resources, facilities and clinical delays, and the golden time for primary PCI has not been achieved. Based on studies conducted in Indonesia, the current median door to balloon time is in the range of 70-288 minutes [3]. Pharmacoinvasive strategy is one options of the revascularization treatment where patients receive pharmacological revascularization with fibrinolysis therapy followed by routine coronary angiography performed 2-24 hours after successful fibrinolysis, or rescue PCI if fibrinolysis fails [2, 4].

In 1980s were a historic decade for cardiology, marked by the dawn of the fibrinolysis era. After DeWood demonstrated coronary thrombosis during Acute Myocardial Infarction (AMI) in an in vivo study. physicians and scientists at the time conducted the first large-scale randomized trials of fibrinolytic therapy. In 1986, GISSI-1 (Gruppo Italiano per lo studio della strepochinasi ell'infarto Miocardio) became the first randomized trial to definitively demonstrate that intravenous fibrinolytic therapy with

streptokinase improved survival, and GISSI-1 demonstrated that thrombolytic therapy was most effective when administered early after the onset of Acute Myocardial Infarction (AMI). Then in 1989 the GUSTO-1 (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) trial, a megatrial, confirmed the open artery hypothesis by showing that greater vessel patency at 90 minutes after treatment with intravenous t-PA (vs. streptokinase) and resulted in a 15% reduction in mortality. Since this landmark trial, the concept of door-to-needle time has become a priority in the treatment of acute coronary syndromes in hospitals nationwide [5, 6, 7].

The degree of coronary blood flow can be assessed qualitatively using the TIMI grade flow classification which is assessed directly using angiography. The assessment of coronary flow measurement using the Thrombolysis in Myocardial Infarction (TIMI) grade flow was first introduced in the TIMI 1 study in the 1980s, which was a study to assess the efficacy of intravenous streptokinase administration in patients with STEMI [8]. TIMI grade 3 flow, which indicates full revascularization in patients with STEMI, is associated with smaller infarction size and transmurality, while TIMI grade 0 flow indicates total occlusion of the epicardial coronary vessels. TIMI grade flow is a strong predictor of several outcome indices in patients with STEMI, including death, reinfarction, mechanical complications, arrhythmias, and left ventricular function after revascularization [8, 9, 10].

Considering the current golden time for primary PCI that has not been achieved and the risk of bleeding from fibrinolysis therapy, half dose pharmacoinvasive strategy is expected to provide the same outcome as full dose pharmacoinvasive strategy and also reduce the risk of bleeding. Currently, there are no data on comparing Thrombolysis in Myocardial Infarction (TIMI) grade flow between the half dose pharmacoinvasive strategy and the full dose pharmacoinvasive strategy in patients with STEMI at Sardjito General Hospital Yogyakarta.

METHODS

Design and Subject

This study was conducted as an analytical observational study. The study design was a retrospective cohort comparing TIMI grade flow in patients with STEMI undergoing half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy from the SHERIVE Study: Sardjito Hospital Revascularization Initiative Study. This study data were obtained from secondary data from patients with STEMI recorded in the SHERIVE study and medical records at Sardjito General Hospital Yogyakarta for the period February 2021 - March 2025. The study subjects were patients with STEMI at Sardjito Hospital who underwent reperfusion procedures with a half dose pharmacoinvasive strategy and a full dose pharmacoinvasive strategy included in the SHERIVE study, and met the inclusion criteria and did not meet the exclusion criteria. The study subjects were selected sequentially according to the SHERIVE study protocol.

The inclusion criteria for this study are: (1) Patients aged 18-70 years, (2) Patients diagnosed with STEMI who are registered in the SHERIVE Study: Sardjito Hospital Revascularization Initiative, (3) Onset of STEMI < 12 hours, (4) Received revascularization strategy with a half dose pharmacoinvasive strategy or a fulldose pharmacoinvasive strategy, (5) TIMI grade flow assessment was performed during an invasive diagnostic procedure based on the results of coronary arteriography and prior to coronary angioplasty. The exclusion criteria for the this study include: (1) Coronary angiography data was lost or not found in the IT data storage system of Sardjito General Hospital Yogyakarta, (2) Patients did not undergo coronary angiography, (3) Incomplete data from SHERIVE Study : Sardjito Hospital Revascularization Initiative and medical records at Sardjito General Hospital Yogyakarta.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 25 (International Business Machine Corp) for the Windows operating system. Data on the basic characteristics of research subjects for categorical data are presented in the form of frequency (n) and percentage (%), while numerical data are presented in the form of mean and standard deviation. as the mean value (standard deviation) using the unpaired T test for data with normal distribution, while for data with abnormal distribution using The Mann-Whitney test as an alternative and displayed in median. The non-inferiority hypothesis test foe unpaired categorical data was performed using the Chi-Square test if the requirements are met, and the Fisher's Exact test if the requirements are not met with the expected frequency <5. Furthermore, an analysis was conducted with a 5% confidence interval to determine non-inferiority. Bivariate and multivariate analyses were used to analyze confounding variables using multivariate linear regression test (backward elimination) on the dependent variable ($p < 0.25$).

RESULT

Basic Characteristics of Research Subjects

This study was conducted by collecting research samples from STEMI patients at Sardjito General Hospital Yogyakarta who underwent reperfusion procedures with half dose and full dose pharmacoinvasive strategies included in the SHERIVE study. This study included a total of 151 subjects, consisting of 76 subjects undergoing full dose pharmacoinvasive strategies and 75 subjects undergoing half dose pharmacoinvasive strategies. The description of the basic characteristics of the study subjects is shown in Table 1, which consists of demographic data such as subject age, gender, risk factors for acute coronary heart disease such as hypertension, diabetes mellitus, dyslipidemia, and smoking, as well as clinical data of STEMI patients which includes heart rate, blood pressure in the emergency department, onset, Killip class, ST-segment location, premedications given including beta blockers, sublingual nitrates, NTG iv and ACE inhibitors/ARBs, fibrinolysis agents used, angiographic data such as coronary lesions, infarct-related arteries, TIMI grade flow

in invasive diagnostic procedures before angioplasty, and after angioplasty (with or without stent placement).

Table 1. Basic Characteristics of Research Subjects

Variables		Half dose pharmacc invasive (n : 75)	Full dose pharmacc invasive (n : 76)	P
Age (Years)	≤60	56(74.66%)	56(73.68%)	0.890
	>60	19(25.33%)	20(26.32%)	
Gender	Man	68 (90.66%)	64 (84.21%)	0.232
	Woman	7(9.33%)	12(15.76%)	
Risk Factors (n, %)	Smoke	43(57.33%)	44(57.89%)	0.944
	Hypertension	43(57.33%)	37(48.68%)	0.287
	Diabetes mellitus	16(21.05%)	24(31.57%)	0.154
	Dyslipidemia	39(52.00%)	47(61.84%)	0.222
ST Segment Elevation Location	Anterior	34(45.33%)	50(65.78%)	0.011*
	Inferior	43(57.33%)	24(31.57%)	0.001*
	Posterior	29(38.66%)	11(14.47%)	0.001*
	Lateral	18(24.00%)	27(35.52%)	0.109
	Right	13(17.33%)	8(10.52%)	0.227
Killip Class	I	69 (92%)	73(96.05%)	0.327
	II	6 (8.00%)	3 (3.94%)	
Pulse Rate (beats per minute)	<100	58(77.33%)	68(89.47%)	0.045*
	≥ 100	17(22.67%)	8(10.53%)	
Blood Pressure (mmHg)	Systole	131.77 (96.00-206.00	132.30 (98.00 205.00)	0.994
	Diastole	81.86 +-14.40	81.02 +-13.22	0.709
Onset (Hour)	< 3	11(14.66%)	5(6.57%)	0.106
	≥ 3	64(85.34%)	71(93.43%)	
Door to Needle (Minutes)	≤ 30	23(30.66%)	35(46.05%)	0.052
	>30	52(69.34%	41(53.95%)	
Premedications therapy	ACE inhibitors/ARBs	26(34.66%)	40(52.63%)	0.026*
	Beta Blocker	1(1.33%)	7(9.21%)	0.063
	Sublingual nitrate	37(49.33%)	47(61.84%)	0.122
	NTG iv	13(17.33%)	9(11.84%)	0.339
Fibrinolytic Agent	Alteplase	72(96.00%)	72(94.73%)	1,000
	Streptokinase	3(4.00%)	4(5.26%)	
Coronary Lesion, n (%)	non-significant CAD	3(4.00%)	4(5.26%)	1,000
	CAD1VD	31 (41.33%)	35 (46.05%)	0.559
	CAD2VD	22 (29.33%)	22 (28.94%)	0.958
	CAD3VD	18 (24%)	15(19.73%)	0.526
Angiography Data of Infarction-Relate Arteries, n (%)	LM	1(1.33%)	1(1.31%)	1,000
	LAD	33(44.00%)	48(63.15%)	0.018*
	LCx	5(6.66%)	3(3.94%)	0.494
	RCA	37 (49.33%)	24(31.57%)	0.026*
TIMI Final Coronary Flow	TIMI 0-2	10 (13.33%)	8 (10.52%)	0.595
	TIMI 3	65(86.64%)	68 (89.48%)	

Note: *p value < 0.05 with Chi square test, or Fisher's exact test, and unpaired T test; ACE=Angiotensin-Converting Enzyme, ARB=Angiotensin II Receptor Antagonist, NTG iv = Intravenous Nitroglycerin

The basic characteristics of the study subjects showed that the age of <60 years between the two groups showed a fairly high value, namely 73.33% in the half dose pharmacoinvasive group and 69.73% in the full dose pharmacoinvasive group. Most of the study subjects were male with a total of 68 subjects (90.66%) in the half dose pharmacoinvasive group and 64 subjects (84.21%) in the full dose pharmacoinvasive group (p = 0.232).

The Onset <3 hours in the half dose pharmacoinvasive group was 14.66% while in the full dose pharmacoinvasive group it was 6.57% (p=0.106). The Door to Needle time ≤ 30 minutes in the half dose pharmacoinvasive group was 30.66% while in the full dose pharmacoinvasive group was

46.05% with a p value of 0.052. These data indicate that most subjects did not achieve the target of Door to Needle time ≤ 30 minutes, which is the target time for fibrinolysis from the first medical contact according to the acute coronary syndrome management guidelines established by PERKI in 2024 [11].

The proportion of several risk factors in the study subjects showed fairly similar values in both groups. There were 43 subjects (57.33%) in the half-dose group and 44 subjects (57.89%) in the full-dose group who smoked (p=0.944). Subjects with hypertension were 57.33% in the half dose group and 48.66% in the full dose group (p=0.278). Subjects with diabetes were 21.05% in the half dose group and 31.57% in the full dose group (p=0.154). The proportion of subjects with dyslipidemia was 52% in the half-dose group and 61.84% in the full dose group.

The Proportion of premedications therapy administered, such as sublingual nitrates, NTG iv, and Beta blockers, did not differ significantly. In contrast, The proportion of ACE inhibitor/ARB administration was 34.66% in the half dose group compared to 52.63% in the full dose group (p = 0.026). Most subjects received the fibrinolytic agent with alteplase (96% vs. 94.73%), and some used streptokinase (4% vs. 5.26%) (p = 1.00).

The data on the proportion of the final TIMI grade flow or post-angioplasty showed that there was not significantly different in TIMI grade 3 flow results between the half dose pharmacoinvasive strategy and the full dose pharmacoinvasive strategy, with TIMI 3 grade flow value of 86.64% vs. 89.48% with p value of 0.595.

The characteristic data in this study showed that the patients with STEMI who underwent full dose and half dose pharmacoinvasive strategies were mostly men and aged <60 years (74.66% vs 73.68%). This is consistent with epidemiological data from the Jakarta Acute Coronary Syndrome registry in 2016 which stated that 86% of patients with STEMI in Jakarta, Indonesia were male, with an average age of 55 years [12]. Then based on epidemiological data from the One ACS Registry in Indonesia in 2022 explains that patients with STEMI in Indonesia are predominantly male (83.5%) with a median age of 57 years [13]. This data differs from a 2020 metaanalysis study from 5 Asia Pacific countries including Australia, Japan, Korea, Malaysia and Singapore which showed that 78.7% of patients with STEMI were male with a combined average age of 61 years. However, the data also shows that the average age range of patients with STEMI varied greatly,Which patients in Malaysia having the youngest combined average age of 56 years, in contrast to Japan which had the oldest combined average age of 67.1 years [14].

Several risk factors for coronary heart disease (CHD) include hypertension, diabetes mellitus, dyslipidemia, and smoking, which are modifiable risk factors included in this study. Based on a multicenter cross-sectional survey study from the Indonesia-INTERASPIRE study in 2025 involving 402 research subjects, the proportion of studysubjects had a risk factor for hypertension of 61% and 74.4 % had history of smoking. Other risk factors included dyslipidemia at 35.4% and diabetes mellitus at 30.2% [15]. A population-based case-control study conducted in 2023 in Sleman Regency, Yogyakarta, explained that hypertension, diabetes mellitus, hypercholesterolemia, and smoking were independent risk factors for the occurrence of acute coronary heart disease [16]. From the One ACS Registry study, it was found that hypertension and smoking were still the most common risk factors in patients with STEMI with a proportion of 51.5% and 65.75%, followed by diabetes mellitus at 27.8% and dyslipidemia at 13.7%. In this study, 57% of the study subjects smoked with similar proportion in both the half dose and full dose groups. Hypertension was found to be comparable between the half dose and full dose groups (57.33% vs. 48.68%; p: 0.287), the risk factor for diabetes mellitus also had comparable proportion between the two groups (21.05% vs. 31.57%, p: 0.154), and in this study, dyslipidemia had a fairly high proportion with 52% in the half dose group and 61.84% in the full dose group. This is different from the One ACS Registry study which found only 13.7% of cases of patients with STEMI [13].

The onset time in the half dose and full dose pharmacoinvasive groups mostly had an onset time ≥ 3 hours proportion, namely 85.34% vs 93.43% with a p-value of 0.106. Although not directly comparable, this is different from previous study in the EARLY-MYO study, which showed a median onset time at first medical contact of 148 minutes (108-204 minutes), and a median onset to reperfusion therapy with a half dose pharmacoinvasive strategy of 210 minutes (166-270 minutes), and the time from randomization to the half dose pharmacoinvasive strategy obtained a median time of 57 minutes (7-88 minutes) [17]. In a pooled analysis study for patients aged ≥75 years in the STREAM-1 and 2 studies, the median onset time of the half-dose pharmaco-invasive group was 120 minutes (90-162 minutes) and the full dose pharmacoinvasive group was 105 minutes (80-155 minutes) and the median of a quality ECG to the pharmaco-invasive strategy in the half-dose group was 27 minutes (17-41 minutes) vs. 26 minutes (19-40 minutes) in the full dose group [18]. In this study, the time from symptom onset to diagnosis of STEMI at Sardjito General Hospital Yogyakarta was longer than in previous studies, possibly due to differences in operational definitions from previous studies that assessed onset to first medical contact, but in this study assessed the duration of onset to medical contact at Sardjito General Hospital Yogyakarta, resulting in differences results. This study also found that the door to needle time for both the half dose and full dose groups was mostly more than 30 minutes, with a proportion of 69.34% in the half dose group vs 53.63% in the full dose group; p 0.052. The door to needle time target according to the guidelines for managing patients with STEMI should be ≤ 30 minutes [2, 11].

The study subjects were mostly with Killip I clinical condition, both in the half dose group (92%) and full dose (96.05%) (p: 0.327). This is also consistent with the EARLY-MYO study which showed that most of the study subjects clinical condition was Killip I (94.7%) [17]. From the pooled analysis study on patients aged ≥75 years in the STREAM 1

and 2 studies also showed that the number of study subjects was mostly with Killip I clinical condition where in the full dose group it was 92.9% and the half dose 89% [18]. Systolic blood pressure in both groups did not differ with the median value of systolic blood pressure in the half dose group being 131.77 mmHg (96-206 mmHg) and 132.30 mmHg (98-205 mmHg) in the full dose group (p: 0.994) and diastolic blood pressure in both groups was also not much different with the mean diastolic blood pressure in the half dose and full dose groups (81.86 ± 14.40 vs 81.02 ± 13.22, p: 0.709).

There was a difference in the location of ST segment elevation between two groups. The location of anterior segment elevation was more common in the full dose group (65.78%) than in the half dose group (45.33%) (p: 0.001), while Inferior and posterior ST segment elevation were more common in the half dose group (57.33% and 38.66%) than in the full dose group (31.57% and 14.47%) (p: 0.001). This is also consistent with the pooled analysis study for patients aged ≥75 years from the STREAM 1 and 2 studies where the location of anterior segment elevation was more common in the full dose group (59.5%) [18]. Data from the One ACS Registry shows that patients with STEMI in Indonesia are more likely to experience anterior infarctions, around 51% [13]. Premedication therapy administration such as ACE/ARB inhibitors was found to be more common in the full dose group (52.63%, p: 0.026) but the administration of Beta blockers, sublingual Nitrates, and IV NTG had the same proportion in both groups. Data from the One ACS Registry shows that patients with STEMI in Indonesia in the first 24 hours mostly received renin-angiotensin-aldosterone system (RAAS) blockers or ACE/ARB inhibitors at 69% followed by Nitrates at 44.9% and Beta blockers at 42.9% [13]. Most of the subjects in this study received fibrinolysis agents with alteplase in both half dose and full dose groups (96.00% vs 94.73%) and a small proportion received with streptokinase (4.00% vs 5.26%) (p: 1.00).

For coronary arteriography results, there were not significantly different coronary lesion between the two group, both the half dose and full dose groups. The most common findings were CAD1VD (41.33% vs 46.05%, p: 0.559), and CAD2VD (29.33% vs 28.94%, p 0.958), followed by CAD3VD (24% vs 19.73%, p: 0.526) and non-significant CAD (4% vs 5.26%, p: 1.0). Then from the angiography data, it was found that LAD as an infarction-related arteries were more common in the full dose group (63.15% vs 44%, p: 0.018), while RCA as an infarction-related arteries were more common in the half dose group (49.33% vs 31.57%, p 0.026). In other study such as EARLY-MYO showed that subjects given half dose pharmacoinvasive with alteplase had a single coronary lesion or CAD1VD of 37.3% with an infarct-related artery in the LAD of 47.8% and in the RCA of 44.1% [17]. Similarly, a study conducted in China showed that patients who received half-dose pharmaco-invasive with Prourokinase showed that subjects with a single coronary lesion or CAD1VD were found to be 35.2% with an infarct-related artery in the LAD of 54.9% which corresponds to a greater proportion of anterior segment elevation of 52.1% and an infarct-related artery in the RCA of 26.8% [19]. Currently, there are still not many studies comparing full dose pharmacoinvasive group with half dose group but from several studies it shows that the proportion of infarct-related arteries is comparable to the proportion of ST segment elevation.

This study found that 65 subjects (43.04%) achieved TIMI grade 3 flow, consisting of 25 subjects (33.33%) from the half dose pharmacoinvasive group and 40 subjects (52.60%) from the full dose pharmacoinvasive group. This is different from the pooled analysis study at age >75 years in the STREAM 1 and 2 studies using the fibrinolysis agent with Tenecteplase, which found no no significant difference between the half dose pharmacoinvasive group and the full dose pharmacoinvasive group (55.6% vs. 62.2%, p: 0.849) [18]. In other study using a half dose pharmacoinvasive strategy, higher TIMI 3 coronary flow rates of over 50% were achieved, such as in the EARLY-MYO study, which showed that subjects who received a pharmacoinvasive strategy with a half dose alteplase achieved TIMI grade 3 flow with the results of 51.6% [17]. Similarly, the results of the TIMI grade 3 flow in another study in China showed that TIMI grade 3 flow in invasive diagnostic procedure before percutaneous coronary intervention was 63.4% using the half dose fibrinolytic agent prourokinase [19].

Full dose pharmacoinvasive strategy is currently still the second-line alternative in patients with STEMI who are not eligible for primary percutaneous coronary intervention (PCI), with an odds ratio for mortality of 0.79 (95% confidence interval [CI], 0.59–1.08) compared with conventional fibrinolytic strategy [2]. However, current evidence regarding the safety and efficacy of current pharmacoinvasive strategy is still limited, in the 2014 STREAM-1 (Strategic Reperfusion Early After Myocardial Infarction-1) study which examined the full dose pharmacoinvasive strategy with Tenecteplase in those aged ≥75 years showed an increase in the incidence of intracranial bleeding, so an early amendment was made by changing the dose to half the dose in the cohort study and then no further intracranial bleeding occurred after the dose was reduced to half. This finding is considered to be a hypothesis worthy of confirmation and further research STREAM-2 (Strategic Reperfusion Early After Myocardial Infarction-2) in patients with STEMI ≥60 years with a pharmacoinvasive strategy with half dose tenecteplase provides similar clinical efficacy results and better resolution of ST segment elevation after coronary angiography compared with primary percutaneous coronary intervention (PPCI) [18].

The EARLY-MYO (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST Elevation Myocardial Infarction) study is the first randomized trial comparing the efficacy and safety of a half dose pharmacoinvasive strategy using the fibrinolysis agent with alteplase compared to primary percutaneous coronary intervention (PPCI) in patients with STEMI had a fairly good conclusion where the half dose pharmacoinvasive strategy provided more complete epicardial and myocardial reperfusion results compared to

PPCI (34.2% vs 22.8%, Risk Ratio (RR) 1.48; 95% Confidence Interval [CI]: 1.04-2.10; p non-inferiority < 0.05) [17]. Therefore, adequate clinical trials with this reperfusion strategy to evaluate clinical outcomes and safety are still needed.

Differences in Coronary Grade Flow in Invasive Diagnostic Procedures Between Half Dose Pharmacoinvasive Strategy and Full Dose Pharmacoinvasive Strategy in Patients with STEMI

To know the differences of Coronary grade flow in Invasive Diagnostic Procedures Between Half dose pharmacoinvasive strategy and Full dose pharmacoinvasive strategy in patients with STEMI, a bivariate analysis was performed using Chi-Square test if the requirements are met, and Fisher's Exact test if the requirements are not met with the expected frequency <5, which we show in Table 2.

Bivariate analysis was performed by analyzing the difference in the proportion of TIMI grade 3 flow and non-TIMI grade 3 flow or TIMI grade 0-2 flow between the half dose pharmacoinvasive group compared to the full dose using a 2 x 2 table with a Chi-square analysis test to determine the relative risk ratio (RR) value. The results of this study showed that total of 65 subjects produced TIMI grade 3 flow, consisting of 25 subjects (33.33%) from the half dose pharmacoinvasive group and 40 subjects (52.63%) from the full dose pharmacoinvasive group.

Table 2. Hypothesis Analysis test of differences in TIMI 3 Grade Flow in invasive diagnostic procedures between Half Dose Pharmacoinvasive and Full Dose Pharmacoinvasive strategy.

		TIMI Grade 3 Flow						
		Yes (n = 65)		No (n = 86)		RR	IK 95%	P
		n	%	N	%			
Revascularization Strategy	Half Dose Pharmacoinvasive Strategy	25	33.33	50	66.67	0.633	0.431-0.930	0.017
	Full Dose Pharmacoinvasive Strategy	40	52.63	36	47.37			

Description: n= number of samples; IK=confidence interval; RR= relative risk;

The results of the bivariate analysis showed that there was a significant difference in the proportion of TIMI grade 3 flow between half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy with Relative Risk (RR) value of 0.633 (p=0.017; 95% CI 0.431-0.930). The difference in the proportion of TIMI grade 3 flow between the half dose pharmacoinvasive strategy group compared to the full dose pharmacoinvasive strategy group was 19.30% (Table 2).

Variables considered as confounding variables include Age, Gender, Coronary risk factors, killip class, heart rate, blood pressure, door to needle, onset and premedications therapy. Bivariate analysis was also performed on the TIMI grade 3 flow (Table 3). The results of the bivariate analysis showed that the administration of ACE inhibitors/ARBs was significantly associated with TIMI 3 coronary flow (p< 0.05).

Table 3. Bivariate Analysis of Confounding Variables on TIMI Grade 3 Flow

Variables			TIME 3 (n : 65)	TIMI 0-2 (n : 86)	RR	IK95%	P
Age (Years)	≤60		46 (70.76%)	66 (76.74%)	0.84	0.570-1.246	0.406
	>60		19 (29.24%)	20 (23.26%)			
Gender	Man		57 (87.69%)	75 (87.20%)	1,01	0.675-1.537	0.929
	Woman		8 (12.31%)	11 (12.80%)			
Risk Factors (n, %)	Smoke	Yes	41 (63.07%)	46 (53.48%)	1,18	0.898-1.556	0.238*
		No	24 (36.93%)	40 (46.52%)			
	Hypertension	Yes	31 (47.69%)	49 (56.97%)	0.85	0.641-1.129	0.258
		No	34 (52.31%)	37 (43.03%)			
	Diabetes mellitus	Yes	16 (24.61%)	24 (27.90%)	0.93	0.688-1.259	0.650
		No	49 (75.39%)	62 (72.10%)			
	Dyslipidemia	Yes	35 (53.84%)	51 (59.30%)	0.90	0.683-1.208	0.503
		No	30 (46.16%)	35 (40.70%)			
Killip Class	I		62 (95.38%)	80 (93.02%)	1,31	0.510-3.362	0.733
	II		3 (4.62%)	6 (6.98%)			
Heart Rate (beats pe minute)	<100		56(86.15%)	70(81.39%)	1,23	0.707-2.157	0.436
	≥ 100		9(13.85%)	16 (18.61%)			
Blood Pressur (mmHg)	Systole		125.00(97.00-206.00)	131.00(96.00-205.00)			0.192*
	Diastole		80.52 +-13.78	82.13 +-13.82			0.477
Onset (Hours)	< 3		4(6.15%)	12(13.95%)	0.55	0.232-1.319	0.123*
	≥ 3		61(93.85%)	74(87.05%)			
Door to Needl (Minutes)	≤ 30		26(40%)	32(37.20%)	1,06	0.737-1.551	0.727
	> 30		39(60%)	54(62.80%)			
Premedications therapy	ACE inhibitors/ARB	Yes	22(33.84%)	44(51.16%)	0.74	0.563-0.975	0.034*
		No	43(66.16%)	42(48.84%)			
	Beta Blocker	Yes	3(4.61%)	5(5.81%)	0.90	0.520-1.580	1,000
		No	62(95.39%)	81(94.19%)			
	Sublingual nitrate	Yes	40(61.53%)	44(51.16%)	1,19	0.909-1.576	0.204*
		No	25(38.47%)	42(48.83%)			
	NTG iv	Yes	8(12.30%)	14(16.27%)	0.87	0.617-1.246	0.493
		No	57(87.70%)	72(83.72%)			

Description: *p < 0.25, $) Fisher exact test; OR = odds ratio, IK = confidence interval, ACE = Angiotensin-Converting Enzyme, ARB = Angiotensin II Receptor Antagonist, NTG iv = Intravenous Nitroglycerin.

Variables in this study that had a p value <0.25 (Table 3) in the bivariate analysis test were continued in the multivariate analysis using logistic regression test to determine variables that independently influenced the TIMI 3 grade flow significantly. These variables include smoking as a risk factor (p: 0.238), systolic blood pressure (p: 0.192), administration of ACE inhibitors / ARB (p: 0.034), administration of sublingual Nitrate (p: 0.204) and Onset (p: 0.123). There were two variables, namely systolic blood pressure and administration of ACE inhibitors / ARB which may have a linear correlation relationship, so the Pearson analysis test was performed, yielding a value of r : 0.42 with p <0.001 which positively has a moderate linear correlation, then the systolic blood pressure variable was not included in the multivariate analysis. Multivariate analysis was then performed on 5 variables, namely half

dose pharmacoinvasive strategy, smoking as a risk factors, administration of ACE/ARB inhibitors, administration of sublingual nitrates and onset time, using binomial logistic regression with the backward elimination method to determine variables that were independently associated with TIMI grade 3 flow (Table 4).

Table 4. Multivariate Analysis of TIMI Grade 3 Flow

	Stage 1	Stage 2	Stage 3			
				OR	IK 95%	
	P	p	P		Lower	On
Half Dose Pharmaco-invasive	0.011	0.011	0.007*	0.377	0.185	0.765
Onset ≥ 3 hours	0.202	0.236				
Smoke	0.209					
ACE inhibitors/ARBs	0.003	0.003	0.002*	0.303	0.141	0.654
Sublingual nitrate	0.058	0.059	0.056			

Description: *p value < 0.05; OR = odds ratio, IK = confidence interval, ACE = Angiotensin-Converting Enzyme, ARB = Angiotensin II Receptor Antagonist

Based on the multivariate analysis, it was found that the half dose pharmacoinvasive strategy was an independent predictor of achieving TIMI grade 3 flow with an odds ratio (OR) of 0.377 (95% CI 0.185-0.765; p = 0.006). Then, other independent predictors of TIMI grade 3 flow included the administration of ACE inhibitors/ARBs (OR 0.303; 95% CI 0.141-0.654; p = 0.002).

Half dose pharmacoinvasive strategy and administration of ACE inhibitors/ARBs were predictive factors for achieving lower TIMI grade flow (TIMI 0-2), while the other three variables, namely sublingual nitrate administration, onset ≥3 hours, and smoking as a risk factor, did not show a significant relationship as predictive factors for achieving TIMI grades 3 flow in multivariate analysis.

DISCUSSION

From previous studies that have been published, there are currently no studies discussing the differences between half dose pharmacoinvasive and full dose pharmacoinvasive in assessing TIMI grade 3 flow in invasive diagnostic procedure as a result of complete reperfusion, so this study is important as a basis for further studies. The results of this study based on bivariate analysis showed that the TIMI grade 3 flow in invasive diagnostic procedure in the half dose pharmaco invasive group was lower than in the full dose pharmacoinvasive group (33.33% vs. 52.60%, p: 0.017). In contrast to other studies from a pooled analysis of studies with patients aged ≥75 years in the STREAM-1 and 2 studies, the results of the degree of TIMI 3 grade flow in invasive diagnostic precedure in both groups between the half dose and full dose pharmacoinvasive strategies were not significantly different (55.6% vs. 62.2%, p: 0.849) [18]. This can be influenced by the type of fibrinolysis agent used, where Tenecteplase has a higher percentage of TIMI grade 3 flow after fibrinolysis compared to Alteplase and Streptokinase (63% vs 54% and 34%) [20, 21].

This study shows that the full dose pharmacoinvasive strategy is still better than the half dose pharmacoinvasive strategy with the outcome of TIMI grade 3 flow in invasive diagnostic procedure or preintervention diagnosis, however, the final TIMI grade 3 flow or post intervention TIMI grade 3 flow results showed no significantly different in two groups between the half dose group and the full dose group (86.64% vs 89.48%, p: 0.595). Based on the EARLY-MYO study, it was shown that although the percentage of TIMI grade 3 flow in invasive diagnostic procedure in the half-dose pharmacoinvasive group had a higher percentage value compared to pre-Primary PCI (51.6% vs. 16.8%, p<0.001), this did not cause a reduction in the size of the cardiac infarction based on Magnetic Resonance Imaging (MRI) of the Heart or give better clinical outcomes, and the final TIMI 3 results post-PCI showed no significant difference between the half-dose pharmacoinvasive strategy and PPCI (91.3% vs. 89.2%, p: 0.580) [17].

The relationship between confounding variables and the TIMI grade 3 flow was also analyzed in this study. The results of the bivariate analysis showed that the administration of ACE inhibitors / ARBs was significantly associated with the TIMI grade 3 flow (p: 0.034). Multivariate analysis was performed with those with a p value <0.25 in the bivariate analysis test including Smoking, Onset ≥ 3 hours, Systolic blood pressure, administration of ACE inhibitors / ARBs and administration of sublingual Nitrates, but systolic blood pressure and administration of ACE inhibitors / ARBs had a significant linear correlation relationship, so the multivariate analysis was continued with 4 confounding variables, namely Smoking, Onset ≥ 3 hours, administration of ACE inhibitors / ARBs and administration of Sublingual Nitrates and the independent variable of the half dose pharmacoinvasive group. From the multivariate analysis, there are two statistically significant variables, including the half dose pharmacoinvasive strategy group and the administration of ACE/ARB inhibitors. In multivariate analysis, the half-dose pharmacoinvasive strategy was independently associated with a lower likelihood of achieving TIMI grade 3 flow (OR 0.377; 95% CI 0.185–0.765; p = 0.007). Similarly, administration of ACE inhibitors or angiotensin receptor blockers (ACE-I/ARB) was independently associated with a lower likelihood of achieving TIMI grade 3 flow (OR 0.303; 95% CI 0.141–0.654; p = 0.002).

Based on the 2023 guidelines for the management of acute coronary heart disease from the European Society of Cardiology (ESC), it is explained that the administration of ACE inhibitors is recommended for patients with acute coronary heart disease with symptoms of heart failure, LVEF ≤40%, diabetes mellitus, hypertension and/or chronic renal failure, with recommendation class of IA. The routine use of ACE inhibitors in all patients with acute

coronary heart disease can be considered regardless of the LVEF value in patients even though the recommendation class is lower, with recommendation class of IIA [2]. In this study, the use of ACE/ARB inhibitors was found to be more common in the full dose pharmacoinvasive group in addition to other indications due to hypertension, this proportion is comparable to the location of ST segment elevation in the Anterior which is also more common, this is consistent with the guidelines for the management of Acute Coronary Heart Disease (CHD) from the American Heart Association (AHA) in 2025 which explains the administration of Renin-Angiotensin-Aldosterone System inhibitors, namely oral ACE inhibitors or ARBs in Acute CHD patients with high risk (LVEF ≤ 40%, hypertension, diabetes, or anterior AMI-EST) can reduce the incidence of death due to all causes and death due to cardiovascular causes with recommendations class of IA [22]. However, the guidelines do not specifically explain when the medication should be administered during hospitalization/in the hospital.

Zhao et al (2022) explained from previous experimental studies that the expression levels of Angiotensin-converting enzyme (ACE), angiotensin (Ang) II, Ang II type 1 receptor, and Ang II type 2 receptor increased significantly within a few hours in areas of myocardial ischemia with reperfusion. This suggests that activation of the renin-angiotensin system in the heart may play an important role in regulating reperfusion injury or myocardial ischemia. Zhao et al., (2022) also explained that administering ACE/ARB inhibitors can significantly and rapidly reduce infarct size and inflammatory responses and provide earlier benefits. Thus, the administration of ACE/ARB inhibitors has a cardioprotective effect with a potential mechanism that caused by the initial effects of reducing neurohormonal activation, increasing collateral coronary artery flow, and increasing regional heart muscle movement [23].

On observational study conducted by Chen et al (2022) showed that the administration of ACE inhibitors/ARBs to patients with acute coronary syndrome without heart failure undergoing PCI did not significantly reduce the risk of death from all causes, death from cardiovascular causes, and/or recurrent myocardial infarction. However, patients who were not given ACE inhibitors/ARBs had worse TIMI grade flow scores before percutaneous coronary intervention and longer door-to-balloon times [24].

Inhibition of angiotensin converting enzyme (ACE) is known to increase coronary artery blood flow through partial inhibition of angiotensin II and increased bradykinin activity, from the results of a study conducted in 1995 showed that the increase in coronary blood flow after administration of ACE inhibitors is not entirely caused by the mechanism of angiotensin II inhibition and is partly mediated through the pathway of increasing endogenous bradykinin, which provides preferential vasodilatory effect on the subendocardial myocardium [25]. However, in this study it was found that the administration of ACE/ARB inhibitors caused the lower possibility result of TIMI grade 3 flow in invasive diagnostic procedures, and in this study no data was collected regarding the dose of the drug given and when and how long the ACE/ARB inhibitor drug was given in both the half-dose and full-dose pharmaco-invasive strategy groups so that this is one of the weakness in this study.

CONCLUSION

There is a significant difference in TIMI grade 3 flow in diagnostic coronary angiography procedure between patients with STEMI undergoing half dose pharmacoinvasive strategy and full dose pharmacoinvasive strategy.

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DISCLOSURES AND ETHICS

This research was conducted based on the approval of the Biomedical and Clinical Research Ethics Committee, FK-KMK Universitas Gadjah Mada with an ethical approval letter issued with letter number KE/FK/1627/EC/2025 and permission from the Director of Sardjito General Hospital Yogyakarta with a research permit letter at Sardjito General Hospital Yogyakarta with letter number DP.04.03/D.XI.2.31975/202.

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