

## Comparison of TIMI Flow in STEMI Patients With and Without Resolution on Reciprocal ST Segment Depression Obtaining Fibrinolytic Alteplase Therapy

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### ABSTRACT

**Background:** STEMI patients need revascularization to improve blood flow and myocardial reperfusion. Further information can be obtained from the ECG including infarct size and prognosis of STEMI patients. ST segment depression (STSD) in reciprocal leads is associated with poorer prognosis. STEMI patients with STSD resolution have a better TIMI flow compared with no STSD resolution. The aim of this study was to look for TIMI flow for STEMI subjects who received fibrinolytic therapy with and without resolution of STSD shortly after fibrinolytic.

**Methods:** This study is a prospective cohort study, in which 60 STEMI subjects, patients performed coronary angiography diagnostics to assess TIMI flow. The resolution on reciprocal STSD is defined as a decrease of 50% in the amount of reciprocal STSD in 90-minute after fibrinolytic therapy started.

**Results:** Bivariate analysis showed that ejection fraction <40% with  $p = <0.001$ ; QRS duration,  $p = <0.001$ ; anterior STEMI with  $p = <0.001$ ; are significant factors for STSD resolution. QRS Fragmentation with  $p = <0.001$ ; STSD resolution with  $p = <0.001$ ; ST elevation resolution with  $p = <0.001$ ; are significant factors for TIMI Flow. In the TIMI Flow comparison with reciprocal STSD resolution; the resolution of reciprocal STSD has a better TIMI flow with OR 28 [(5.5-141.9),  $p = <0.001$ ].

**Conclusion:** There were differences in TIMI Flow in STEMI patients with reciprocal STSD resolution and without reciprocal STSD resolution who received fibrinolytic alteplase therapy, where STEMI patients with reciprocal STSD resolution had a better TIMI Flow compared with STEMI patients without reciprocal STSD resolution.

**Keywords:** resolution; reciprocal ST segment depression; TIMI flow; STEMI; fibrinolytic

## INTISARI

**Latar Belakang:** Penderita infark miokard akut dengan elevasi segmen ST (IMAEST) memerlukan tindakan revaskularisasi untuk mengembalikan aliran darah dan reperfusi miokard. Lebih banyak informasi bisa didapatkan dari EKG meliputi ukuran infark dan prognosis penderita IMAEST. Depresi Segment ST (DSST) di sadapan resiprokal pada EKG pasien IMAEST yang di terapi dengan fibrinolitik secara klinis dikaitkan dengan prognosis yang lebih jelek. Pasien IMAEST dengan resolusi DSST memiliki TIMI *flow* yang lebih baik dibandingkan dengan tanpa resolusi DSST. Tujuan dari penelitian ini adalah untuk mencari perbandingan TIMI *flow* untuk subjek IMAEST yang mendapat terapi fibrinolitik dengan dan tanpa adanya resolusi DSST sesaat setelah fibrinolitik.

**Metode:** Penelitian ini merupakan studi kohort prospektif, dimana 60 orang subjek IMAEST, pasien dilakukan diagnostik angiografi koroner untuk menilai TIMI *flow*. Nilai resolusi DSST resiprokal adalah penurunan  $\geq 50\%$  besaran DSST resiprokal pada pasien IMAEST 90 menit sejak awal dimulai terapi fibrinolitik.

**Hasil:** Analisis bivariat menunjukkan bahwa fraksi ejeksi  $<40\%$  dengan  $p=<0,001$ ; durasi QRS,  $p=<0,001$ ; anterior IMAEST dengan  $p=<0,001$ ; merupakan faktor-faktor yang bermakna terhadap resolusi DSST. Fragmentasi QRS dengan  $p=<0,001$ ; resolusi DSST dengan  $p=<0,001$ ; resolusi ST elevasi dengan  $p=<0,001$ ; merupakan faktor-faktor yang bermakna terhadap TIMI *flow*. Pada perbandingan TIMI *flow* dengan resolusi DSST resiprokal; adanya resolusi DSST resiprokal memiliki TIMI *flow* yang lebih baik dengan [OR 28 (5.5-141.9),  $p=<0,001$ ].

**Kesimpulan:** Terdapat perbedaan TIMI *flow* pada penderita IMAEST dengan resolusi DSST resiprokal dan tanpa resolusi DSST resiprokal yang mendapatkan terapi fibrinolitik alteplase, dimana penderita IMAEST dengan resolusi DSST resiprokal memiliki nilai TIMI *flow* yang lebih baik dibandingkan dengan penderita IMAEST tanpa resolusi DSST resiprokal.

## INTRODUCTION

Acute myocardial infarction ST segment elevation (STEMI) is a part of acute coronary syndrome that occurs due to a total blockage of coronary arteries by thrombus formed or released as the body's response to arterosclerotic plaque rupture. STEMI can result in sudden death even before being taken to hospital, after and during treatment. Even though the mortality rate has declined in the past two decades, about one in 25 patients who survive during the initial treatment period will die within the first year after STEMI.<sup>1</sup> Decrease in mortality rates associated with the progress of early reperfusion action, both mechanically (Primary Percutaneous Coronary Intervention - Primary PCI), and pharmacologically / fibrinolytic.<sup>2,3</sup>

STEMI features a typical picture of ST segment elevation in the infarct area and accompanied by ST segment depression (STSD) on reciprocal or noninfarct area with a prevalence of 54% to 82%.<sup>4,5</sup> Initially STSD in the reciprocal

lead was considered a benign electrical phenomenon.<sup>6,7</sup> Subsequent studies provide an alternative opinion that STSD in reciprocal leads shows extensive infarction by culprit lesions, as evidenced by higher cardiac enzyme levels, larger left ventricular regional wall abnormalities and lower ejection fractions (EF) compared to patients without STSD. Patients with STSD tend to experience short-term (in hospital) and long-term complications and higher mortality compared to patients without STSD.<sup>8,9,10,11</sup>

Research conducted by Tjandrawidjaja *et al.* evaluated the impact of STSD resolution on STEMI patients treated with primary PCI, including comparing angiographic reperfusion assessments. STEMI patients with STSD resolution have better TIMI flow than without STSD resolution.<sup>12</sup> Research conducted by de Lemoss *et al.* compared the assessment of reperfusion by angiography in STEMI patients treated with streptokinase and with alteplase with the results of alteplase having TIMI flow

better than streptokinase.<sup>13</sup> In developing countries the choice of fibrinolytic therapy with streptokinase is more widely used, but with the development of pharmacotherapy, alteplase tends to be superior to streptokinase.

The purpose of this study was to assess and compare TIMI flow between STEMI patients who received alteplase fibrinolytic therapy with or without DSST resolution. This fibrinolytic agent is often used as the initial line of therapy given if the primary PCI cannot be performed.

**METHODS**

This study was a prospective cohort study to assess TIMI flow comparisons with and without STSD resolution in STEMI patients receiving fibrinolytic therapy. STSD was assessed at the beginning of the patient's arrival and STSD resolution was assessed 90 minutes from the start of fibrinolytic administration by the cardiology resident who was on duty at the emergency unit. Fibrinolytic therapy was carried out with alteplase, which prior to fibrinolytic action was given the same dual antiplatelet (160 mg aspirin and clopidogrel 300 mg), followed by administration of anticoagulants for 3-8 days. After that the initial PCI will be conducted to assess TIMI flow.

TIMI flow is assessed when a coronary angiography diagnostic is performed. This TIMI flow assessment was carried out by interventional

cardiologists through coronary angiography recordings. The sample collection uses the quota (consecutive) method where each subject that meets the inclusion criteria is used as a sample of the study with a minimum number of samples based on the sample calculation formula as many as 27 people for each group. Baseline data, subject identity, history, physical examination, ECG (pre fibrinolytic and 90 minutes from the start, fibrinolytic / post fibrinolytic therapy), chest radiograph, cardiac enzyme examination (CKMB and troponin I), echocardiography, coronary angiography and drug use were recorded complete. All of this data will be recorded carefully. From all the data possessed by the subjects, the initial important data evaluated were 12 lead ECG at the time of entry into the Haji Adam Malik General Hospital emergency unit and 90 minutes from the start of fibrinolytic therapy with a recording speed of 25 mm/s and a scale of 10 mm/mv. Pre fibrinolytic STSD was assessed by calculating the number of deep ST segment depression in the reciprocal leads measured at 80 ms after the j point against the isoelectric line as shown in the figure 1. STSD measurements on the ECG will be done manually using a 150 mm Krisbow dial caliper (KW0600352) and a magnifying glass. The measurement results are reported in units of mm. Reciprocal STSD resolution is done using the formula:

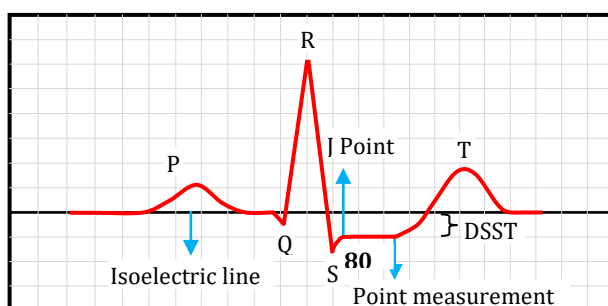


Figure.1 How to measure depth of ST depression

$$\text{Resolution } \sum \text{STSD (\%)} = \frac{\sum \text{STSD pre fibrinolytic} - \sum \text{STSD post fibrinolytic}}{\sum \text{STSD pre fibrinolytic}} \times 100$$

After that, the two groups that were treated with alteplase will be given anticoagulants for 3-8 days. After that the initial PCI was conducted to assess TIMI flow. TIMI flow was assessed when diagnostic coronary angiography was performed, TIMI flow assessment was performed by interventional cardiologists through coronary angiography recordings and compared angiography results based on TIMI flow (TIMI flow 0, TIMI flow 1, TIMI flow 2, TIMI flow 3), then the results analyzed statistically.

Categorical variables are presented by number or frequency (n) and percentage (%). Numerical variables are presented with mean (average) and standard deviations for data that are normally distributed, while numerical data that are not normally distributed use the median (middle value), which is then compared with Student's t-test or Mann Whitney U. Normality test on numerical variables on all study subjects using one sample Kolmogorov Smirnov ( $n > 50$ ) or Shapiro Wilk ( $n < 50$ ). For samples that were found to be significant in the bivariate analysis test, they were included in the multivariate test. Analysis of statistical data using computer statistical devices, the value of  $p < 0.05$  was said to be statistically significant.

## RESULTS

The research subjects were divided into two groups, namely the STEMI group with reciprocal STSD resolution (30 people, 50%) and the STEMI group without reciprocal STSD resolution (30 people, 50%). The results of this study showed a statistically significant difference between the STEMI group and reciprocal STSD resolution and the STEMI group without reciprocal STSD resolution in terms of left ventricular ejection fraction, anterior STEMI and duration of QRS.

In terms of left ventricular ejection fraction, it was seen that the STEMI group with reciprocal STSD resolution had a higher left ventricular ejection fraction value than the STEMI group without reciprocal STSD resolution of 52% versus 43% ( $p = < 0.001$ ). The STEMI group with reciprocal STSD resolution rarely occurs in the STEMI anterior compared to the STEMI group without reciprocal STSD resolution of 10 people (33.3%) versus 25 people (83.3%) ( $p = < 0.001$ ). Whereas the QRS duration of the STEMI group with reciprocal STSD resolution has a better QRS duration of 70 ms versus 80 ms ( $p = < 0.001$ ). Each variable proportion value can be seen in table 1.

**Table 1. Baseline Characteristics of research subjects classified based on reciprocal STSD resolution**

	Subjects n= 60	Resolution in ST Segment depression		p
		Presence, n=30	Absence, n=30	
Age (year old)	54 ± 8	54 ± 8	53 ± 9	0.526
Male (n, %)	46 (76)	22 (73)	24 (80)	0.542
Body weight (kg)	68 ± 8	69 ± 9	67 ± 8	0.480
Systolic BP (mmHg)	126 ± 22	128 ± 21	125 ± 24	0.594
Heart rate (x/min)	77 ± 15	77 ± 12	76 ± 17	0.815
Smoker (n, %)	39 (65)	18 (60)	21 (70)	0.417
Diabetes mellitus (n, %)	24 (40)	11 (36.7)	13 (54)	0.598
Hypertension (n, %)	35 (58)	16 (53.3)	19 (63.3)	0.432
Dyslipidemia (n, %)	45 (75)	25 (83.3)	20 (66.7)	0.136
Obesity (n, %)	11 (18)	6 (20)	5 (16.7)	0.739
Anterior STEMI (n, %)	35(58)	10 (33.3)	25 (83.3)	<0.001
Ejection fraction (%)	45 (25-60)	52 (25-60)	43 (26-54)	<0.001
Leukocyte (mm <sup>3</sup> )	12.647±3.778	13.231±2.980	12.063±4.411	0.234
Ureum (mg/dl)	23.2 (9-105)	21.0 (9-105)	25.5 (13-90)	0.426
Creatinine (mg/dl)	0.9 (0.6-6.6)	0.9 (0.6-6.6)	0.89 (0.6-3.6)	0.827
Onset (hour)	5 ( 1-11)	4 (1-11)	5 ( 1-10)	0.761
QRS duration (ms)	70 (60-120)	70 (60-80)	80 (60-120)	<0.001

The total number of research subjects was 60 people consisting of 38 people (62%) with TIMI flow 3, 19 people (31%) with TIMI flow 2, 2 people (5%) with TIMI flow 1, 1 person (2 %) with TIMI flow 0, as shown in figure 2. While the optimal and suboptimal TIMI flow proportion consists of 38 optimal TIMI flow and 22 people with suboptimal TIMI flow (figure 3).

The TIMI flow assessment is based on coronary angiography results by assessing coronary artery blood flow. The TIMI flow assessment was carried out by two blind observers without knowing the patient's diagnosis. If there is a difference between the observers, the highest value is taken from TIMI Flow. In this study the value of inter-observer variability was tested using the Kappa test (Cohen's Kappa Coefficient). TIMI flow assessment is carried out by two assessment

observers who are interventionist. The Kappa ( $\kappa$ ) value of inter-observer variability is 0.623 which is included in good categorization with a value of  $p = 0.000$ .

The subjects in the optimal TIMI flow group have more resolution on reciprocal STSD compared to the suboptimal TIMI flow group which was 28 people (93.3%) versus 2 people (6.7%) and this was statistically significant with a P value =  $< 0.001$ . In contrast, the optimal TIMI flow group of about 10 people (33.3%) did not have a reciprocal STSD resolution compared to 20 people (66.7%) in the suboptimal TIMI Flow group. Furthermore, it can be concluded that STEMI patients without reciprocal STSD resolution have a 28 times chance of suboptimal TIMI Flow compared with STEMI patients with reciprocal STSD resolution (table 2).

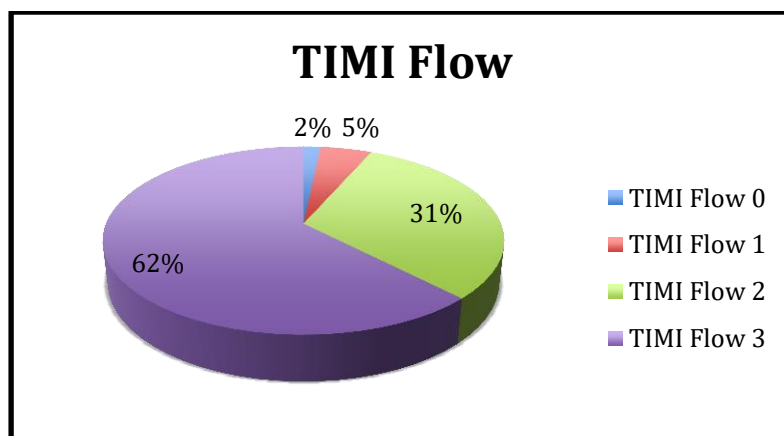


Figure 2. TIMI flow proportion diagram

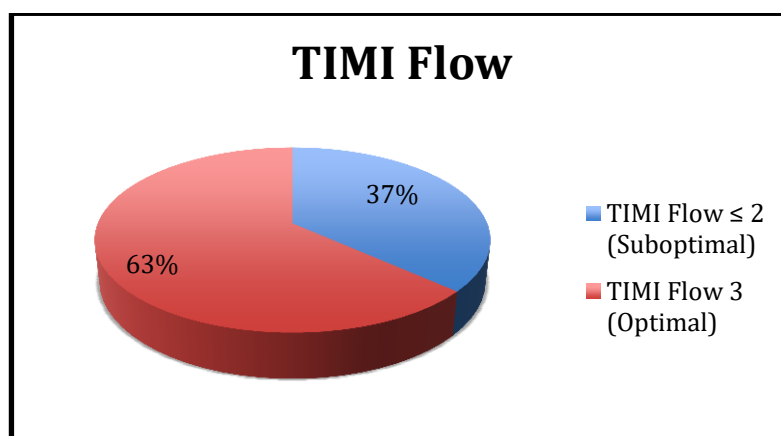


Figure 3. The optimal and suboptimal TIMI flow proportion diagram

**Table 2. Bivariate TIMI flow analysis research subjects to reciprocal STSD resolution**

Variable	STSD Resolution		Total	P value	OR	95% CI
	Presence n=30	Absence n=30				
TIMI flow 0,1,2	2 (6.7)	20 (66.7)	22 (36.7)	<0.001	28.0	5.5 -141.9
TIMI flow 3	28 (93.3)	10 (33.3)	38 (63.3)			

## DISCUSSION

In this study after fibrinolytic action with alteplase, patients were given additional anticoagulant therapy for 3-8 days. After that, the patient underwent coronary angiography, and TIMI flow was assessed. From the results of this study, TIMI flow 0, 1, 2 and 3. Of the total 60 study samples, 38 patients (62%) with TIMI flow 3 were obtained, 19 patients (31%) found TIMI flow 2, 2 patients (5%) found TIMI flow 1, 1 patient (2%) found TIMI flow 0. The optimal TIMI flow is TIMI flow 3 where normal blood flow reaches the distal coronary circulation, while the suboptimal TIMI flow is TIMI flow  $\leq 2$  which has no effective restoration in myocardial perfusion.<sup>14,15</sup> The results of this study are in accordance with Kostic *et al.* study where patients with STEMI after administration of alteplase had statically higher coronary blood flow (TIMI flow 3) of 72.5%.<sup>16</sup>

Comparative results of TIMI Flow for STEMI patients who received fibrinolytic therapy with alteplase in STEMI with reciprocal STSD resolution and without reciprocal STSD resolution showed different findings on TIMI Flow. STEMI patients with reciprocal STSD resolution after receiving fibrinolytic therapy alteplase had more TIMI Flow 3 values than STEMI patients without reciprocal STSD resolution after receiving alteplasefibrinolytic therapy which was 28 people (93.3%) compared with 10 people (33.3%) and this is statistically significant with a value of  $p < 0.001$ . The results of this study resemble previous studies comparing TIMI Flow with reciprocal DSST resolution by Tjandrawidjaja *et al.* but in populations with primary PCI therapy.

TIMI flow assessment is subjective, so an interventionist is needed as observer. To assess the amount of difference between observers, the Kappa test was used to see the differences between the agreements observed. From this study, the Kappa (K) value was 0.623, meaning that the inter-observer agreement was good.

## CONCLUSION

Based on the results of data analysis obtained in this study it was concluded that there were differences in TIMI Flow in STEMI patients with reciprocal STSD resolution and without reciprocal STSD resolution receiving fibrinolytic alteplase therapy, where STEMI patients with reciprocal STSD resolution had a better TIMI Flow compared to those without reciprocal STSD resolution.

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