Acta Cardiologia Indonesiana

pISSN:2460-5700
eISSN:2579-4345

Web page: jurnal.ugm.ac.id/v3/jaci

Association of Resolution of Sum ST-Segment Deviation with Major Adverse Cardiovascular Events in Patients with ST-Elevation Myocardial Infarction after Reperfusion

Shelarosa Arumdita*, Nahar Taufiq, Lucia Kris Dinarti

Departemen Kardiologi dan Kedokteran Vaskular, Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan, Universitas Gadjah Mada

ARTICLE INFO

*Corresponding author

email:
dr.shelarosaarumdita@gmail.com

Address:
Jalan Griya Taman Asri, Ngaglik, Sleman, DIY

Keywords:
resolution of sum ST-segment deviation; major adverse cardiovascular events; STEMI

Manuscript submitted:
Revised and accepted:

ABSTRACT

Background: The incidence of acute myocardial infarction with ST-segment elevation (STEMI) causes an infarct area which expansion can be reduced by reperfusion strategies. The infarct size can predict major cardiovascular events (MACE). The changes of ST-segment on electrocardiography (ECG) are one of the modalities for assessing infarct size. Resolution of sum ST-segment deviations occurring in STEMI has been associated with worse clinical outcome although the mechanism is uncertain.

Objective: To determine the relationship between the resolution of the number of ST-segment deviations with major cardiovascular events in STEMI patients undergoing reperfusion.

Research Methods: Analytical observational study with ambi-directional cohort using secondary data at RSUP Dr. Sardjito were conducted in July 2019-June 2022. The STEMI patient undergoing reperfusion were enlisted, either primary PCI or pharmacoinvasive. The data was including basic characteristics, ECG, reperfusion data, and clinical outcomes. Resolution of sum ST-segment deviations were obtained from the percentage of diagnostic ECG and post-reperfusion ECG to the sdiagnostic ECG. Resolution is significant if ≥50% and not significant if <50%.

Results: Of a total 140 subjects, 92 subjects experienced MACE and 48 subjects did not. In subjects with significant resolution, there was no significant in MACE (70.5% vs. 70.8%, p=0.774). In multivariate analysis, left ventricular ejection fraction (OR 0.73; 95% CI 0.65-0.82; p=0.001) and TIMI flow after PCI (OR 0.28; 95% CI 0.09-0.9; p=0.033) significantly affect MACE. In the sub-analysis of the resolution of sum ST-segment deviations to the MACE components, the results obtained a significant relationship between arrhythmias (p=0.018) and reinfarction (p=0.011).

Conclusions: The significant resolution of sum ST-segment deviations in STEMI patients undergoing reperfusion did not have a significant relationship with MACE.

INTISARI

Latar Belakang: Kejadian infark miokard akut dengan elevasi segmen-ST (IMA-EST) menyebabkan adanya area infark yang perluasannya dapat dikurangi dengan adanya tindakan reperfusi. Luas area infark dapat memprediksi kejadian kardiovaskular mayor (KKM). Perubahan segmen-ST pada elektrokardiografi (EKG) merupakan salah satu modalitas penilaian

luas area infark. Resolusi jumlah deviasi segmen-ST yang terjadi pada IMA-EST telah dikaitkan dengan luaran klinis yang lebih buruk mesikpun mekanismenya masih belum pasti.

Tujuan: Mengetahui hubungan resolusi jumlah deviasi segmen-ST dengan kejadian kardiovaskular mayor pada pasien IMA-EST yang dilakukan reperfusi.

Metode Penelitian: Observasi analisis ini dilakukan secara kohort ambi-directional menggunakan data sekunder di RSUP Dr. Sardjito sejak periode Juli 2019-Juni 2022 pada populasi pasien IMA-EST yang dilakukan reperfusi, baik IKP primer ataupun farmakoinvasif. Dilakukan penelusuran terhadap karakteristik dasar, EKG, data reperfusi, dan luaran klinis. Data resolusi jumlah deviasi segmen-ST didapatkan dari persentase selisih EKG diagnostik dan EKG pasca reperfusi terhadap EKG diagnostik. Resolusi signifikan bila ≥ 50% dan tidak signifikan bila <50%.

Hasil: Dari total 140 subjek penelitian, didapatkan 92 subjek mengalami KKM dan 48 subjek tidak mengalami KKM. Pada subjek dengan resolusi signifikan, tidak didapatkan penurunan KKM yang bermakna (70,5% vs 70,8%, p=0,774). Pada analisa multivariat didapatkan fraksi ejeksi ventrikel kiri (OR 0,73; 95%IK 0,65-0,82; p=0,001) dan aliran TIMI pasca IKP (OR 0,28; 95%IK 0,09-0,9; p=0,033) mempengaruhi KKM secara signifikan. Pada subanalisis resolusi jumlah deviasi segmen-ST terhadap komponen KKM, didapatkan hasil hubungan yang bermakna pada aritmia (p=0,018) dan reinfark (p=0,011).

Simpulan: Resolusi jumlah deviasi segmen-ST yang signifikan pada pasien IMA-EST yang dilakukan reperfusi tidak memiliki hubungan yang bermakna terhadap penurunan KKM.

Introduction

Cardiovascular disease (CVD) is still the most cause of death in the world.[1] An estimated 17.9 million people worldwide died from heart disease, this number is equivalent to 31% of all deaths in the world. Meanwhile the data in Indonesia, estimates coronary artery disease (CAD) incidence range from 0.1% to 2%.[2] Data at RSUP dr. Sardjito in 2017 showed that from 633 of acute coronary syndromes (ACS), 449 (70%) were acute myocardial infarction with ST elevation (STEMI)[3].

STEMI is a transmural myocardial death caused by an occlusion in coronary flow. The occlusion is caused by the rupture of an atherosclerotic plaque in the coronary artery which triggers a thrombosis. Management of STEMI should be as fast as possible in terms of diagnosis and therapy in order to minimize the myocardial cell damage and complications. The presence of a total thrombus requires an immediate reperfusion therapy both pharmacologically and mechanically. Referring to the latest STEMI guidelines, primary PCI is still the strategy of choice. However, timely access to primary PCI remains a challenge. Thus, pharmacoinvasive strategies have been developed ever since[4,5,6].

The infarct size caused by STEMI can be reduced by up to 50% with reperfusion strategies[7]. The extent of the infarct size can predict major cardiovascular events (MACE) including death, reinfarction, arrhythmias, heart failure, and cardiogenic shock. Bulluck et al., (2015) explained that 1 month mortality after myocardial infarction was 2.5-5%, and myocardial dysfunction and heart failure after infarction were still the main contributors to morbidity and mortality worldwide.[8] Meanwhile, Arso et al., (2014) studied STEMI patients at Dr. Sardjito Hospital Yogyakarta. There were 10.3% MACE in post-fibrinolysis patients and 9.4% MACE in post-primary PCI patients where the comparison between the two is not statistically significant (RR 1.09, 0.33 – 3.55 (95% CI), p=0.87)[9].

The processes affecting the extent of myocardial infarction are ischemic cascade, microvascular obstruction, reperfusion injury, and no-reflow phenomenon. Therefore, in addition to reperfusion strategies (mechanical or pharmacological), drug therapy also has a role in reducing infarct size, by administering anticoagulant (Unfractionated Heparin, Enoxaparin, Fondaparinux, Bivalirudin), antiplatelet (Aspirin, Clopidogrel, Ticagrelor, Cangrelor, Prasugrel), anti-angina (beta blockers, calcium channel blockers, nitrates), statins, and antiremodelling (Angiotensin Converting Enzyme Inhibitors (ACE-I)/ Angiotensin Receptor Blockers (ARBs))[7,8,10].

The extent of the infarction can be assessed with several modalities including Cardiovascular Magnetic Resonance (CMR), Single Photon Emission Computed Tomoraphy (SPECT), echocardiography, biomarkers, and electrocardiography (ECG). The CMR is currently considered the gold standard for visualization and quantification of myocardial infarction. In clinical practice, ECG is still the first diagnostic test for the evaluation of patients with ischemic heart disease

because it is safe, low cost, and generally available. Several ECG abnormalities can be considered as markers of myocardial infarction and their relationship independently to the infarct area has not been widely studied[11].

ST-segment deviation is one of the diagnostic signs of acute myocardial infarction. Several studies have shown that resolution of ST-segment elevation (STE-R) after PCI in STEMI patients has been shown to correlate with reperfusion success and prognosis[12]. The ST-segment resolution is an important predictor of infarct-related artery (IRA) patency and effective microcirculatory perfusion[13]. The occurrence of ST-segment resolution within the first 60-120 minutes after pharmacological and mechanical reperfusion therapy is an accurate predictor of infarct-associated arterial patency and the degree of effective microvascular perfusion[14]. Although several studies in STEMI patients have reported ST-segment depression, only a few have assessed the prognostic value of resolution of ST-segment depression after reperfusion[15].

Concomitant of ST-segment depression in STEMI has been associated with poorer clinical outcome although the mechanism remains uncertain. It has been described previously in the study of Schroder et al., (1994) and other studies that sum of ST-segment deviations (elevation and depression) represents the area of at risk and its resolution is a relevant prognostic value[16]. The ECG assessment in STEMI used 12 leads to assess the presence of ST depression and elevation as quantitative variables. It is called ST-segment deviations, that can predict the infarct size and mortality in patients with ACS. Previous studies on the resolution of depression or ST-segment elevation of the infarct size became the basis of this study. Until now, there has been no study that uses the resolution of sum ST-segment deviations as an ECG parameter to predict MACE of STEMI after reperfusion[12-15,17].

Methods

This study is an analytical observational with a cohort ambi-directional method conducted in RSUP Dr. Sardjito after receiving permission from FKKMK UGM medical ethical committee. The study subjects were STEMI patients underwent reperfusion strategy in RSUP Dr. Sardjito Yogyakarta. Study subject data was taken secondarily from RSUP Dr. Sardjito and medical records that have fulfilled inclusion and exclusion criteria from July 2019-June 2022.

Inclusion criteria in this study consist of 1) Patient diagnosed with STEMI, ≤24 hour onset, Killip I, and underwent reperfusion strategy (primary PCI or pharmacoinvasive), 2) Patients with two 12 leads ECG (diagnostic ECG and post-reperfusion ECG), 3) Age ≥18 years old. The exclusion criteria are: 1) ECG cannot be analyzed properly (incomplete or inadequate), 2) Confounding of ECG recording (artefact, left bundle branch block (LBBB), fascicular block, pre-excitation, early repolarization pattern, and pacing rhythm).

Research Protocol

Study data collected were the subjects with both diagnostic ECG and post-reperfusion ECG (right and posterior lead are as indicated). The diagnostic ECG is the first ECG recorded for diagnosing STEMI at admission. Meanwhile post-reperfusion ECG is ECG evaluation at 60-90 minutes after reperfusion. The sum of ST-segment deviation calculated by sum up of total elevation and depression of ST-segment in one ECG recorded, in millimeter (mm) unit. Resolution of sum STD was obtained by calculating the percentage difference between the sum STD on the diagnostic ECG and post-reperfusion ECG (Image 1-2).

$$Resolution\ of\ \Sigma\ STD\ (\%) = \frac{\Sigma\ STD\ diagnostic - \Sigma\ STD\ post\ reperfusion}{\Sigma\ STD\ diagnostic} \times 100\%$$

Image 1. Formulation of resolution of sum STD

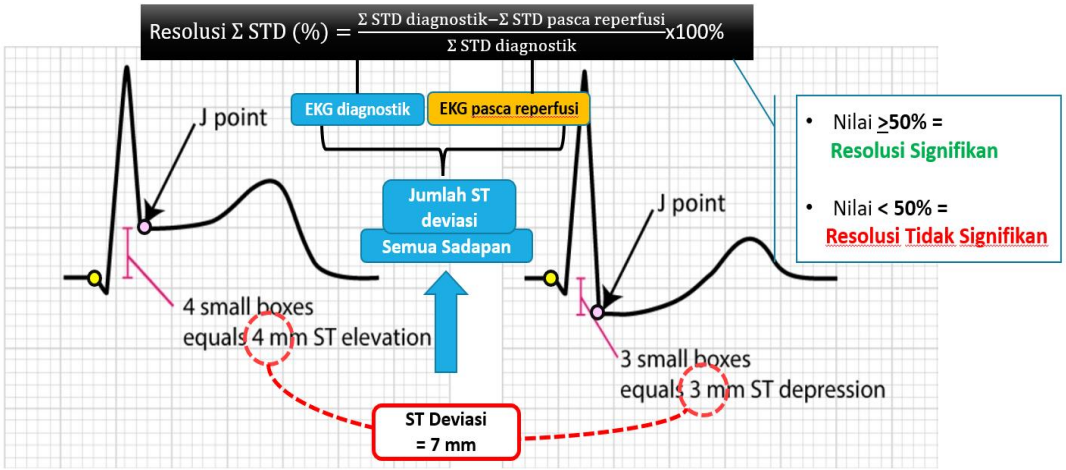

Image 2. Resolution of sum ST-segment

The ECG is scanned for imaging analysis and magnified using ImageJ software on a high-resolution computer screen. Assessment of the consistency of the ST segment deviation measurement was read by two experts (cardiologists) who were blind to studies that had previously measured Cohen's kappa (K) values, if > 0.6 with p < 0.05 when the measurement, the results were considered good (same) and can be used as an appraiser. The parameters that will be analyzed are patient's clinical characteristics consist of; age, sex, risk factors, comorbidities, drug therapy, total ischemic time, left ventricle ejection fraction (LVEF), reperfusion strategy, IRA, multivessel disease (MVD), TIMI flow post-PCI, resolution of sum STD, and MACE (heart failure, arrythmia, cardiogenic shock, reinfarction, and cardiac death).

Statistical Analysis

Data were analyzed with Statistical Package for the Social Science (SPSS) International Business Machine (IBM) software version 25. Univariate analysis numeric variable using Kolmogorov-Smirnov test where p > 0.05 showed normally distributed data. Numeric variables will be shown as mean/median + standard deviation (SD). The resolution of sum STD was expressed as significant and non-significant categorical data. The hypothesis was analyzed using Chi-Square test if the data is normally distributed, and using Fisher Exact test if not normally distributed. Confounding variables were analyzed using multivariate analysis with logistic regression.

Result

Baseline Characteristics of Study Subjects

This study recruited 140 subjects of STEMI patients after reperfusion who met the inclusion and exclusion criteria. Baseline characteristic data are shown in Table 1. The mean age in MACE was not significantly higher than without MACE (57.2 ± 10.5 vs. 56.0 ± 9.8; p=0.504). The proportion of male was higher than female, both in MACE and without MACE (85.9% vs. 83.3%; p=0.690). Hypertension was at the most of all risk factors (86 subjects). There were 55 subjects of hypertension with MACE and 31 subjects without MACE (59.7% vs. 64.5%; p=0.580). Drug therapy in MACE group included the use of anticoagulation in 40 subjects (43.4%), antiplatelet in 92 subjects (100%), antiangina in 69 subjects (75%), anti-remodelling in 64 subjects (69.6%), and statins in 90 subjects (97.8%). There was no significant difference of drug therapy between MACE and without MACE.

The median total ischemia time was not significantly different between MACE and without MACE (460.5 minutes vs. 527 minutes; p=0.374). Meanwhile, on echocardiographic data, the median LVEF subjects with MACE was significantly lower than without MACE (41% vs 55.5%; p=0.001). A total of 47 subjects (51%) with MACE were multivessel disease. In subjects with MACE, 41 subjects (44.5%) underwent primary PCI, 11 subjects (12%) underwent routine PCI, and 40 subjects (43.5) underwent rescue PCI. There was a significant difference on the reperfusion strategy between MACE and without MACE (p=0.013). In subjects with IRA in the LAD, there were 56 subjects with MACE and 22 subjects without MACE (60.8% vs 45.8%; p=0.089). Subjects with TIMI 3 flow after PCI was significantly less in MACE than without MACE (80.5% vs. 95.8%; p=0.014). Assessment of the resolution sum ST-segment deviations on the ECG was carried out by two cardiologists with the interrater reliability test (Cohen's Kappa) to find the suitability of the categorical calculation results between observers. The Kappa value of observer 2 against observer 1 was 1.00 (K> 0.8).

Table 1. Baseline characteristics of STEMI patient after reperfusion

Variables	MACE		p
	Yes (n: 92)	No (n: 48)	
Age, mean ± SD	57.2 ± 10.5	56.0 ± 9.8	0.504
Sex			
Male, n (%)	79 (85.9%)	40 (83.3%)	0.690
Female, n (%)	13 (14.1%)	8 (16.7%)	
Risk Factors			
Hypertension, n (%)	55 (59.7)	31 (64.5)	0.580
Smoking, n (%)	45 (48.9)	26 (54.1)	0.555
Diabetes Melitus, n (%)	26 (28.2)	15 (31.2)	0.712
Dyslipidemia, n (%)	57 (62.9)	23 (47.9)	0.111#
Drug therapy			
Anticoagulant, n (%)	40 (43.4)	24 (50.0)	0.462
Antiplatelet, n (%)	92 (100)	47 (97.9)	0.343
Antiangina, n (%)	69 (75)	40 (83.3)	0.260
Anti-remodelling, n (%)	64 (69.5)	37 (77.0)	0.346
Statin, n (%)	90 (97.8)	48 (100)	0.546
Total ischemic time, median (IQR) (minutes)	460.5 (327.5-682.5)	527 (329-910)	0.374
LVEF, median (IQR) (%)	41 (37-46)	55.5 (50-61)	0.001*#
MVD, n (%)	47 (51.0)	28 (58.3)	0.414
IRA			
LAD, n (%)	56 (60.8)	22 (45.8)	0.089#
Non-LAD, n (%)	36 (39.2)	26 (54.2)	
Reperfusion Strategy			
Primary PCI, n (%)	41 (44.5)	20 (41.7)	0.013*#
Pharmacoinvasive			
Rescue PCI, n (%)	40 (43.5)	13 (27.1)	
Routine PCI, n (%)	11 (12.0)	15 (31.2)	
TIMI flow post-PCI			
TIMI 0-1, n (%)	10 (10,8)	1 (2,1)	0.014*#
TIMI 2, n (%)	8 (8,7)	1 (2,1)	
TIMI 3, n (%)	74 (80,5)	46 (95,8)	
Sum STD (mm)			
Diagnostic ECG, median (IQR)	15,2 (0,7-57,1)	13,5 (4,3-33,1)	0.134
Post-reperfusion ECG, median (IQR)	5,5 (0-16,5)	4,8 (0,7-16,7)	0.298
Resolution of sum STD, median (IQR) (%)	62,4 (0-79,0)	61,3 (5,8-86,9)	0.764

Information: SD, standard deviation; MACE, major adverse cardiac events; IQR, interquartile range; mm, milimeter; n, number of subjects; LVEF, left ventricular ejection fraction; MCD, multivessel disease; IRA, infarct-related artery
*p <0.05 is significant result
#Variables analyzed in multivariate (p<0.25)

Association Between Resolution of Sum ST-Segment Deviation and MACE

The hypothesis test in this study was to see the relationship between resolution of sum ST-segment deviation and MACE. The data presented in a 2x2 table with independent variables (significant resolution and non-significant resolution) are placed in rows and MACE (yes and no) are placed in columns (Table 2). The association was analyzed using the Chi Square test. Subjects with significant resolution have fewer MACE (63 subjects (65.0%)), compared to non-significant resolution (29 subjects (67.5%)). However, this did not show a significant difference (p=0.774). So that significant resolution of sum ST-segment deviation didn't have significant association with less MACE.

Table 2. Analysis of association between Resolution of Sum ST-Segment Deviation and MACE

Resolution of Sum ST-Segment Deviation, n (%)	MACE		p	RR	95% CI
	Yes	No			
Significant resolution	63 (65.0)	34 (35.0)	0.77	0.89	0.42-1.92
Non-significant resolution	29 (67.5)	14 (32.5)			

Information: n, number of subjects; RR, relative risk; CI, confidence interval

Multivariate Analysis of Confounding Factors to MACE

Based on the results of the previous bivariate analysis, there was a significant relationship between LVEF (p=0.001) and TIMI flow post-PCI (p=0.014) on MACE. Variables with p > 0.25 analyzed in multivariate are dyslipidemia, LVEF, IRA, and TIMI flow post-PCI. In multivariate analysis using logistic regression (Table 3), the significant variables were dyslipidemia (OR 3.43; 95% CI 1.00-11.69; p=0.049), LVEF (OR 0.73; 95% CI 0.65-0.81; p=0.001), and TIMI flow post-PCI (OR 0.25; 95% CI 0.07-0.82; p=0.023).

Table 3. Multivariate Analysis of Confounding Factors to MACE

Variables	p	OR	95% CI	
			Lower	Upper
Resolution of Sum ST segment Deviation	0.392	1.75	0.48	6.39
Dyslipidemia	0.057	3.44	0.96	12.32
LVEF	0.001*	0.73	0.65	0.82
Reperfusion strategy	0.300	2.22	0.49	10.13
IRA LAD Non-LAD	0.967	0.97	0.28	3.40
TIMI flow post-PCI TIMI 0-1 TIMI 2 TIMI 3	0.033*	0.28	0,09	0.90

Information: LVEF, left ventricular ejection fraction; IRA, infarct-related artery; OR, Odd Ratio; CI, confidence interval
*p <0.05 is significant result

Sub-analysis of MACE components

The five components of the KKM were analyzed using Chi Square test with a 2x2 table. The incidence of arrhythmias was significantly more (p=0.018) in patients with a significant resolution (≥50%), while the incidence of reinfarction was significantly lower (p=0.011). Meanwhile, the incidence of heart failure, cardiogenic shock and death did not have a significant relationship with the resolution of sum ST-segment deviations (Table 4).

Tabel 4. Association between resolution of sum ST-segment deviation and cardiac death, heart failure, arrythmia, reinfarction dan cardiogenic shock.

Resolution of Sum ST-Segment Deviation, n (%)	Cardiac Death		p	RR	95% CI
	Yes (n : 7)	No (n : 133)			
Significant resolution	5 (71.4)	92 (69.2)	1.000	1.11	0.21-5.98
Non-significant resolution	2 (28.6)	41 (30.8)			
	Heart Failure		p	RR	95% CI
	Yes (n : 88)	No (n : 52)			
Significant resolution	61 (69.3)	36 (69.2)	0.991	1.00	0.48-2.11
Non-significant resolution	27 (30.7)	16 (30.8)			
	Arrythmia		p	RR	95% CI
	Yes (n : 12)	No (n : 128)			
Significant resolution	12 (100)	85 (66.4)	0.018*	-	-
Non-significant resolution	0 (0)	43 (33.6)			
	Reinfarction		p	RR	95% CI
	Yes (n : 6)	No (n : 134)			
Significant resolution	1 (16.7)	96 (71.6)	0.011*	0.08	0.01-0.70
Non-significant resolution	5 (83.3)	38 (28.4)			
	Cardiogenic shock		p	RR	95% CI
	Yes (n : 17)	No (n : 123)			
Significant resolution	13 (76.4)	84 (68.3)	0.493	1.51	0.46-4.93
Non-significant resolution	4 (23.6)	39 (31.7)			

Information: n, number of subjects; RR, relative risk; CI, confidence interval
* p <0.05 is significant result

Discussion

Clinical Characteristics

In our study, the mean age of subjects with MACE was 57 years and without MACE was 56 years. This is comparable to the mean age of STEMI patients undergoing reperfusion in previous studies conducted on the population at Dr. RSUP. Sardjito from 2008-2010, which was 55-58 years9. In another study which studied the relationship between ST-segment depression and MACE in 179 STEMI patients undergoing primary PCI, the mean age of the subjects was not much different18. Male sex was more prevalent in the study sample population, 85.9% with MACE and 83.3% without MACE. This is the

same as the previous study conducted on STEMI patients at Dr. RSUP. Sardjito, which is 85-86%. In addition, the proportion of sex is also the same as data in the Jakarta Acute Coronary Syndrome Registry, which is 85-86%. The results of the proportion of sexes are in accordance with the epidemiological data which states that the male sex has a higher incidence of STEMI than the female. Subjects with hypertension in this study was 86 subjects (61.4%) which is more than other risk factors. Previous study found that hypertension was less in the STEMI patients who had primary PCI or fibrinolysis, as many as 56 subjects (42.7%)9. Therefore, strict control of hypertension risk factors should be carried out in STEMI as a secondary prevention.

The median of total ischemia time in subject with MACE was 460.5 minutes, with an interquartile range of 327.5-682.5 minutes. Meanwhile, Tjandrawidjaja et al., (2010) found the mean total ischemia time was about 200 minutes15. In the study by Redfors et al., (2021), which included 3115 STEMI patients undergoing primary PCI, the median total ischemia time was 185 minutes with an interquartile range of 130-269 minutes19. The total ischemia time in this study was 2 times longer than the two studies.

Total ischemia time includes time from onset until the patient is having PCI. Factors that affect longer total ischemia time are the lack of public awareness of the symptoms of STEMI to the activation of the early medical system and wire crossing time which is not in accordance to the guidelines for managing STEMI. A cross-sectional study in Iran in 2019, as many as 2103 STEMI patients undergoing primary PCI showed a mean onset of 279 (120-630) minutes. Uneducated patient, use of private transportation or referral from another hospital, and description of atypical chest pain symptoms were associated with a longer duration of onset. A study in Portugal also found that primary care facility referral patients significantly (Beta 1.75; 95% CI 1.41-2.16; p<0.001) prolong the time of onset20,21. So the length of time total ischemia in this study is influenced by many things that need to be investigated further.

Multivessel disease was found more in both of MACE (51%) and without MACE (58.3%) (p=0.414). However, this number is less than in Ghaffari et al., (2020), which was 84 (86.9%) subjects18. In Shah et al., (2016) it was stated that patients with multivessel disease had higher risk factors than single vessel disease, as many as 38.1% of subjects had hypertension22. The same study also mentions a higher median age for multivessel disease, which is 59 years. Infarct related artery (IRA) in our study subjects was dominated by LAD as many as 56 subjects (60.8%) with MACE and 22 subjects (45.8%) without MACE (p=0.089). Stone et al., (2016) studied relationship between infarct area and clinical outcome in 2632 STEMI patients who underwent primary PCI, and there were 1631 subjects (62.1%) with IRA LAD, while 1001 subjects (37.9%) with IRA Non-LAD23. This is comparable to that obtained in this study.

There was a significant difference of MACE in reperfusion strategy in our study (p = 0.013). Rescue PCI were more in patient with MACE than those without (43.5% vs 27.2%; p=0.013). Meanwhile, routine PCI was the opposite, less in patient with MACE (12% vs 31.2%; p=0.013). The reperfusion strategy has a association with MACE, where the incidence of MACE is lower in routine PCI and higher in rescue PCI, while primary PCI is relatively the same. This suggests that patients with fibrinolysis will have a beneficial effect on clinical outcome when continued with routine PCI24.

Resolution of Sum ST-Segment Deviation and MACE

The aim of this study was to see the association between the resolution of sum ST-segment deviations and MACE in STEMI after reperfusion. In the 2x2 table showed MACE in significant resolution is lower than non-significant resolution (65% vs 67.5%; p = 0.774). In the era of primary PCI and fibrinolysis, STE-R is associated with a smaller infarct size. The presence of resolution of ST-segment depression (STD-R) is also of prognostic importance because it reflects ischemia in other areas of the myocardium or is reciprocal of areas with ST-segment elevation. Thus, resolution of sum ST-segment deviations is associated with larger infarct size and poorer prognosis25. There are other factors that affect the infarct area, which can also affect the outcome of the resolution of sum ST-segment deviations26. In this study, through the previous bivariate test, it was found that the LVEF, reperfusion strategy and TIMI flow post-PCI affected MACE. The relationship between these three variables on the resolution of sum ST-segment deviations may affect the results of this study.

The relationship between LVEF and the resolution of sum ST-segment deviations is still unknown, but the relationship with the STD-R is known to be significant from previous literature. According to Adithya et al., (2018), STEMI with STD-R had better LVEF than STEMI without resolution (52% vs 43%; p<0.001)25. Another study by Kim et al., (2019) stated the same result about STE-R. Patients with STE-R >50% had higher mean LVEF compared with STE-R <50% (54% vs 45%; p=0.011)27. In our study, the median LVEF in subjects with MACE was 41% and in subjects without MACE was 55.5% (p=0.001). Because of the relationship between the STE-R and STD-R to LVEF, it is possible that this could affect the clinical outcome of this study.

The relationship between of reperfusion strategy and resolution of sum ST-segment deviations has been investigated. Resolution of sum ST-segment deviations in STEMI with pharmacoinvasive strategy was significantly higher compared with primary PCI (84.40% vs. 57.77%; RR 1.46; 95% CI 1.10-1.93; p=0.005)6. In our study, the population including STEMI with primary and pharmacoinvasive strategy. It is possible that differences in reperfusion strategies affect the relationship between the resolution of sum ST-segment deviations to the MACE.

The relationship between TIMI flow and the resolution of sum ST-segment deviations has not been found in previous studies, but a relationship has been found on the STD-R in STEMI with fibrinolysis. In subjects with TIMI 3 flow, there were 28 subjects (93.3%) with resolution and 10 subjects (33.3%) without resolution. The subjects with STD-R had better TIMI flow post-fibrinolysis (OR 28 (5.5-141.9); p<0.001)28. A significant difference in TIMI flow on the resolution of ST-segment depression also allows for the influence of TIMI flow on MACE in our study.

Larger infarct size in the literatures has been described as being strongly associated with MACE in STEMI patients. The resolution of sum ST-segment deviations in this study may be more appropriate to describe the risk areas. So that another factor that affects the results of this study is the choice of resolution of sum ST-segment deviations as an ECG parameter, which includes elevation and depression. As previously noted, the Selvester score has been recognized as a prognostic tool for the STEMI, followed by the Aldrich and Wilkins scores. The three scores do not include only ST-segment changes. So maybe the resolution of sum ST-segment deviations alone is not suitable for measuring the infarct area, but area at risk (AAR) instead. The resolution of the number of ST-segment deviations in this study did not represent a significant prognostic value for MACE when compared with LVEF, reperfusion strategy and TIMI flow post-PCI. These three variables are strongly correlated with larger infarct size6,25,27,28, but their relationship with AAR has not been clearly elucidated. This might explain why the LVEF is significantly related to MACE, while the resolution of sum ST-segment deviations is not in line with LVEF to MACE.

The AAR makes some researchers want to see how significant the effect is on MACE, especially in STEMI with post-reperfusion residual ischemia or multivessel disease. Assessment of AAR post-reperfusion or in subjects with multivessel disease then provides insight into the complete or culprit-only revascularization decision. If the resolution of sum ST-segment deviations can estimate AAR, then the hope is that a significant resolution can be associated with a reduction in AAR, and it could predict MACE in patient with multivessel disease. In the CvLPRIT study, it was shown that MACE was significantly lower in patients after complete revascularization in primary PCI29. Several meta-analyses supporting the CvLPRIT study also confirmed that subjects with multivessel disease predominated among STEMI patients undergoing primary PCI and this had a negative effect on 30-day mortality30. The multivessel disease dominating the subjects in this study may affect the relationship between the resolution of sum ST-segment deviations and MACE. However, we did not elaborate complete or culprit-only revascularization in this study data. In a recent meta-analysis, who analyzed 9 large randomized trials including the CvLPRIT, PRAMI and DANAMI-3 PRIMULTI trials, found that STEMI with complete revascularization were associated with reduced risk of MACE and reinfarction31. This is in line with the idea that reducing AAR (one of which is complete revascularization) will reduce risk of MACE. The assessment of AAR, one of which can be done by measuring the resolution of sum ST-segment deviations, becomes important to do as a prognostic indicator7,32.

Analysis of association between the resolution of sum ST-segment deviations was also carried out on death, heart failure, arrhythmias, reinfarction, and cardiogenic shock (MACE components). From the results of this study, it was found that the association between the resolution of sum ST-segment deviations was significant to the incidence arrhythmias and reinfarction. Significant resolution was more in patients with arrythmia than those without (100% vs 66.4%; p=0.018). Meanwhile, significant resolution was less in patients with reinfarction than those without (16.7% vs 71.6%; p=0.011).

In the era of reperfusion, the phenomenon of ventricular arrhythmias began to be common. One such form of arrhythmia is the hemodynamically tolerable AIVR originating in the reperfused area of the myocardium. However, as the study progressed, in STEMI with TIMI 3 flow after primary PCI, >90% of whom had reperfusion arrhythmias associated with a larger infarct size33. At reperfusion, the coronary microcirculation is heavily infiltrated by neutrophils and platelets. Neutrophils cause tissue and endothelial damage and can aggregate with platelets, thereby clogging capillaries and impeding coronary flow. Ultimately, vasoconstrictor agents released by damaged endothelium, neutrophils, and platelets contribute to causing sustained vasoconstriction of the coronary microcirculation33. This is sufficient to explain the significant association between the significant resolution of sum ST-segment deviations and the incidence of arrhythmias. Several studies also have revealed that there is a significant relationship between ST-segment resolution and reinfarction. One of them is by Sejersten et al., (2009) who investigated the long-term prognostic value of ST-segment resolution in patients with fibrinolysis or primary PCI. The study was conducted in a cohort involving 1421 STEMI patients. One explanation for the relationship between ST-segment resolution and reinfarction is that there is impaired microcirculation in patients with non-significant resolution. So that there is an area of the myocardium exposed to the risk of reinfarction in the future. In addition, non-significant resolution may indicate that fragile atherosclerotic plaques remain at risk for reinfarction24.

Multivariate Analysis

In this study, a multivariate test was conducted on confounding variables with p value <0.25 (dyslipidemia, LVEF, IRA, reperfusion strategy and TIMI flow post-PCI). The LVEF (OR 0.73; 95% CI 0.65-0.82; p=0.001) and TIMI flow post-PCI (OR 0.28; 95% CI 0.09-0.90; p=0.033) were significantly affecting resolution of sum ST-segment deviations to MACE.

According to Kosmidou et al., (2017), LVEF is a strong independent predictor of death or heart failure in STEMI

after primary PCI. The risk of death and heart failure in patients with normal ejection fraction (HR 2.08, 95% CI 1.14–3.78) was the same as that of low ejection fraction (HR 1.83, 95% CI 0.61–5.47) (p=0.81)34. In our study, the median ejection fraction was 41% in subjects with MACE and 55.5% in subjects without MACE (p=0.001). So that it is possible in the next study to divide the two groups or research with one particular ejection fraction group to see a stronger relationship between the resolution of sum ST-segment deviations and MACE.

The optimal TIMI flow post-PCI is TIMI 3 flow where blood flow reaches the distal coronary circulation. The TIMI 2 flow is suboptimal which does not indicate effective restoration of myocardial perfusion (Adhitya et al., 2019). This study shows that the better the TIMI flow post-PCI, the lower MACE, and vice versa. The TIMI flow 0-1 in subject with MACE were 10 subjects (10.8%), while without MACE was 1 subject (2.1%). The TIMI flow 3 in in subjects with MACE were 74 subjects (80.5%), while without MACE were 46 subjects (95.8%). Statistically, there was significant difference between TIMI flow post-PCI degree and MACE (p=0.014).

Conclusions

Significant resolution of sum ST-segment deviation in STEMI after reperfusion did not have significant association with less MACE.

Acknowledgements

The authors would like to thank all staff and residents of the Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, for the discussion and suggestions regarding this research.

Funding Sources

This research receives no specific grant from any funding agency.

Disclosures and Ethics

The authors have no conflicts of interest to declare. This study has been approved by medical ethics committee of Faculty of Medicine, Nursing, and Public Health, Gadjah Mada University number KE/FK/0895/EC/2022.

References

1. World Health Organization. 2011. Global Atlas on cardiovascular disease prevention and control, Geneva.
2. Badan Penelitian dan Pengembangan Kesehatan. 2013. Riset Kesehatan Dasar, Jakarta.
3. Hidayati, F., Huda, R., Bagaswoto, H.P., Setianto, B.Y. and Taufiq, N. 2018. Patient's Profile Accross Our Intensive Cardiac Care Unit: A Single Center Study at Sardjito Hospital. Acta Cardiologia Indonesiana, 4(1).
4. Rhee, J.W., Sabatine, M.S. and Lilly, L.S. 2011. Acute Coronary Syndromes. In L. S. Lilly, ed. Patophysiology of Heart Disease. Philadelphia: Wolter Kluwer, pp. 161–90.
5. Ibanez, B., James, S., Agewall, S., Antunes, M.J., Bucciarelli-Ducci, C., et al. 2017. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal, 39, pp.119–177.
6. Bainey, K.R., Armstrong, P.W., Zheng, Y., Brass, N., Tyrrell, B.D., et al. 2019. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction in Clinical Practice: Insights from the Vital Heart Response Registry. American heart journal, (October), pp.1–12.
7. McAlindon E, Bucciarelli-Ducci C, Suleiman MS, and Baumbach A. 2014. Infarct size reduction in acute myocardial infarction. Heart Journal, pp. 1-6
8. Bulluck, H., Yellon, D.M., and Hausenloy, D.J. 2016. Reducing myocardial infarct size: challenges and future opportunities. Heart, 102, pp.341-348.
9. Arso, I.A., Setianto, B.Y., Taufiq, N., Hartopo, A.B. 2014. In-hospital Major Cardiovascular Events between STEMI Receiving Thrombolysis Therapy and Primary PCI. Acta Medica Indonesiana-The Indonesian Journal of Internal Medicine Vol 46 (No.2), pp.124-130.
10. Yasir, P., Vijayan, P., and Shahar, L. 2017. A Review of Strategies for infarct size reduction during acute myocardial infarction. Cardiovascular Revascularization Medicine.
11. Lee, D.C., Albert, C.M., Narula, D., Kadish, A.H., Panicker, G.P., et al. 2020. Estimating Myocardial Infarction Size with a Simple Electrocardiographic Marker Score. J Am Heart Assoc ;9:e014205.
12. Andrade, P.B., Rinaldi, F.S., Bergonso, M.H., Tebet, M.A., Nogueira, E.F., et al. 2013. ST-Segment Resolution after Primary Percutaneous Coronary Intervention: Characteristics, Predictors of Failure, and Impact on Mortality. Revista Brasileira de Cardiologia Invasiva (English Edition), 21(3), pp.227–233.
13. Farkouh, M.E., Reiffel, J., Dressler, O., Nikolsky, E., Parise, H., et al. 2013. Relationship between ST-segment recovery and clinical outcomes after primary percutaneous coronary intervention: The HORIZONS-AMI ECG substudy report. Circulation: Cardiovascular Interventions, 6(3), pp.216–223.
14. Dizon, J.M., Brener, S.J., Maehara, A., Witzenbichler, B., Biviano, A., et al. 2014. Relationship between ST-segment resolution and anterior infarct size after primary percutaneous coronary intervention: Analysis from the INFUSE-AMI trial. European Heart Journal: Acute Cardiovascular Care, 3(1), pp.78–83.
15. Tjandrawidjaja, M.C., Fu, Y., Westerhout, C.M., White, H.D., Todaro, T.G., et al. 2010. Resolution of ST-segment depression: A new prognostic marker in ST-segment elevation myocardial infarction. European Heart Journal, 31(5), pp.573–581.
16. Schroder, R., Dissman, R., Bruggemann, T., Wegscheider, K., Linderer, T., et al. 1994. Extent of Early ST Segment Elevation Resolution: A Simple but Strong Predictor of Outcome in Patients With

Acute Myocardial Infarction. JACC Vol.24, No.2 : 384-91
17. Reinstadler, S. J., Baum, A., Rommel, K. P., Eitel, C., Desch, S., et al. 2015. ST-segment depression resolution predicts infarct size and reperfusion injury in ST-elevation myocardial infarction. British medical journal, 101(22), 1819–1825.
18. Ghaffari, S., Kolahdouzan, K., Rahimi, M., and Tajlil, A. 2020. Predictors of ST Depression Resolution in STEMI Patients Undergoing Primary PCI and Its Clinical Significance. International Journal of General Medicine:13 271 –279
19. Redfors B., Mohebi R., Giustino G., Chen S., Selker H.P., et al. 2021. Time Delay, Infarct Size and Microvascular Obstruction After Primary Percutaneous Coronary Intervention for ST-Segment–Elevation Myocardial Infarction. Circulation: Cardiovascular Interventions ;14:e009879
20. Pereiraa, H., Caléa, R., Pintob, F. J., Pereiraa, E., Caldeiraa, D., Melloc, S., Vitorinoa, S., Almeidad, M. de S., & Mimosoe, J. (2018). Cardiologia. Portuguese Journal of Cardiology, 37(5).
21. Poorhosseini, H., Saadat, M., Salarifar, M., Mortazavi, S. H., & Geraiely, B. (2019). Pre-Hospital Delay and Its Contributing Factors in Patients with ST-Elevation Myocardial Infarction; a Cross sectional Study. Archives of Academic Emergency Medicine, 7(1)
22. Shah, R., Clare, R.M., Chiswell, K., Jones, S., Kumar, S., et al. 2016. Impact of Non-Infarct-Related Artery Disease on Infarct Size and Outcomes (from the CRISP-AMI Trial). The American Journal of Medicine
23. Stone, G.W, Selker, H.P., Thiele, H., Patel, M.R., Udelson, J.E., et al. 2016. Relationship Between Infarct Size and Outcomes Following Primary PCI. JACC vol 67 no14: 1674-83
24. Sejersten, M., Valeur, N., Grande, P., Nielsen, T.T., and Clemmensen, P. 2009. Long-Term Prognostic Value of ST-Segment Resolution in Patients Treated With Fibrinolysis or Primary Percutaneous Coronary Intervention. JACC Vol.54, No.19: 1763-1769
25. Adhitya, A.S., Hasan, H., Sitepu, A., dan Mukhtar, Z. 2018. Resolution of ST-Segment Depression in Reciprocal Leads as Predictor Mayor Adverse Cardiac Event for ST-Segment Elevation Myocardial Infarction with Fibrinolytic Therapy. Indonesian J Cardiol; 39 : 68-78
26. Schroder, R. 2004. Prognostic Impact of Early ST-Segment Resolution in Acute ST-Elevation Myocardial Infarction. Circulation ;110:e506-e510.
27. Kim, J.S., Lee, H.J., Yu, C.W., Kim, Y.M., Hong, S.J., et al. 2016. INNOVATION Study (Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment-Elevation Myocardial Infarction). Circ Cardiovasc Interv;9:e004101
28. Adhitya, A.S., Hasan, H., Hasan, R., Siregar, A.A., Mukhtar, Z., dan Nasution, A.N. 2019. Comparison of TIMI Flow in STEMI Patients With and Without Resolution on Reciprocal ST Segment Depression Obtaining Fibrinolytic Alteplase Therapy. Acta Cardiologia Indonesiana (Vol.5 No.2): 129-135
29. Gershlick, A.H., Khan, J.N., Kelly, D.J., Greenwood, J.P., Sasikaran, T., et al. 2015. Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease. The CvLPRIT Trial. Journal of The American College of Cardiology Vol.65, No.10; 963-972
30. Park, D.W., Clare, R.M., Schulte P.J., Pieper, K.S., Shaw, L.K., et al. 2014. Extent, location, and clinical significance of non-infarctrelated coronary artery disease among patients with ST-elevation myocardial infarction. JAMA ;312:2019–27
31. Ahmad, Y., Howard, J.P., Arnold, A., Prasad, M., Seligman, H., et al. 2020. Complete Revascularization by Percutaneous Coronary Intervention for Patients With ST-Segment–Elevation Myocardial Infarction and Multivessel Coronary Artery Disease: An Updated Meta-Analysis of Randomized Trials. Journal of the American Heart Association. 2020;9:e015263
32. Schou, A., Grove, U.S.L., Worbech, T.H., Andersen, M.P., Terkelsen, C.J., et al. 2011. ECG-based Estimation of Area at Risk in Acute Myocardial Infarction. Computing in Cardiology; 38:413-416.
33. Niccoli, G., Burzotta, F., Galiuto, L., dan Crea, F.2009. Myocardial No-Reflow in Humans. JACC Vol.54, No.4: 281-292
34. Kosmidou, I., Redfors, B., Selker, H.P., Thiele, H., Patel, M.R., et al. 2017. Infarct size, left ventricular function, and prognosis in women compared to men after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: results from an individual patient-level pooled analysis of 10 randomized trials. European Heart Journal; 38, 1656–1663