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Management of Acute Coronary Syndrome in Indonesia: Insight from One ACS Multicenter Registry

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Abstract

Background: Acute coronary syndrome (ACS) is a life-threatening disorder that contributes to high morbidity and mortality in the world. Registry of ACS offers great guidance for improvement and research. We collated a multicenter registry to gain information about the demographic, management, and outcomes of ACS in Indonesia.

Methods: *IndONEsia Acute Coronary Syndrome Registry* (*One ACS Registry*) was a prospective nationwide multicenter registry with 14 hospitals participating in submitting data of ACS via standardized electronic case report form (eCRF). Between July 2018 and June 2019, 7634 patients with ACS were registered. This registry recorded baseline characteristics; onset, awareness, and transfer time; physical examination and additional test; diagnosis; in-hospital medications and intervention; complications; and in-hospital outcomes.

Results: Nearly half of the patients (48.8%) were diagnosed with STE-ACS. The most prevalent risk factors were male gender, smoking, and hypertension. Patients with NSTE-ACS tended to have more concomitant diseases including diabetes mellitus, dyslipidemia, prior AMI, HF, PCI, and CABG. The majority of ACS patients in our registry (89.4%) were funded by national health coverage. Antiplatelet, anticoagulants, antihypertensive, and statins were prescribed as 24-hours therapy and discharge therapy; however, the prescription of a potent P2Y12 inhibitor was low. More STE-ACS patients underwent reperfusion therapy than non-reperfusion (65.2% vs. 34.8%), and primary PCI was the most common method (45.7%). Only 21.8% of STE-ACS patients underwent reperfusion strategy within 0-3 hours of onset. The invasive strategy was performed in 17.6% of NSTE-ACS patients, and only 6.7% performed it early (within <24 hours). Patients who underwent the early invasive strategy had a shorter median LoS than the late invasive strategy ($P<0.001$). A shorter median LoS also found in intermediate and low-risk patients. The mortality rate in our ACS patients was 8.9%; STE-ACS patients showed higher mortality than NSTE-ACS (11.7 vs. 6.2%).

Conclusion: Our registry showed a comparable proportion between STE- and NSTE-ACS patients, with the male gender predominant in middle age. Both STE- and NSTE-ACS share the same risk factors. We need an improvement in referral time, especially in patients with STE-ACS. Evidence from our registry showed that two issues need to be addressed to improve ACS outcomes: optimal and adequate medical treatment and invasive strategy.

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Keywords: Acute coronary syndromes; Asia; Acute myocardial infarction; South East Asia; Indonesia; Medical management; Primary PCI; Early invasive strategy

Introduction

Acute coronary syndrome (ACS) is a life-threatening disorder that contributes to high morbidity and mortality in the world.[1] About one-third of all deaths in the world are caused by cardiovascular disease. ACS and sudden death cause around 1.8 million deaths per year.[2] Based on 2013 data, 0.5% of the Indonesian population was diagnosed with coronary artery disease (CAD). Furthermore, 1.5% of the population had CAD symptoms or were diagnosed with CAD.[3]

The ACS consisted of non-ST-segment elevation (NSTE-ACS) and ST-segment elevation (STE-ACS), which need immediate treatment in emergency settings. In STE-ACS patients, primary percutaneous coronary intervention (PPCI) should be performed within 90 minutes of first medical contact (FMC).[4,5] In NSTE-ACS patients, the timing of invasive strategy applied based on risk stratification: very high-risk patients (need an immediate invasive strategy in less than 2 hours), high-risk patients (need an early invasive strategy in less than <24 hours), and intermediate-risk patients (need an invasive strategy in less than <72 hours).[4]

Time is essential in the management of ACS. Delay in treatment may be caused by patient and/or system delay. In a previous study, nearly one-half of the patients in the study experienced a delay of≥120 minutes from onset to FMC. Thus, patient delay became a major contributor to prehospital delay.4 Nevertheless, system delay is more modifiable than patient delay in organizational measures.[5] Minimizing delays, therefore, should be one of the objectives in improving the clinical outcomes of ACS patients.

By far, there is very limited data related to the management and outcomes of ACS in Indonesia. Whereas in other countries, particularly in developed countries, they provide exemplary data including demographic, treatment, and outcomes of ACS. For example, Sweden has the SWEDEHEART registry which is a nationwide registry with 75 centers and 8800 patients in 2020 and included a high proportion of the national MI population.[6] Korea has the *Korea Acute Myocardial Infarction Registry* (KAMIR), a multicenter and nationwide data of patients with all stages of acute MI in 55 community and teaching hospitals.[7] Existing registries are great guidance for improvement and research. We collated a multicentre registry to gain information about the demographic, management, and outcomes of ACS in Indonesia.

Methods

Study design and data collection

Indonesia Acute Coronary Syndrome Registry (One ACS Registry) was a retrospective nationwide multicenter registry in Indonesia, which was initiated by *the Acute and Critical Cardiovascular Care Working Group of the Indonesian Heart Association*. 14 hospitals were participating in collecting the data of ACS. The principal investigator and local investigators from each center had the responsibility to supervise the progress of this study.

Participating centers should submit standardized electronic case report form (eCRF) consisting data of from all patients diagnosed with ACS in each center for 12 consecutive months. Submitted data then will be reviewed and approved by local investigators to maintain the quality of the data in each center. This registry recorded baseline characteristics; onset, awareness, and transfer time; physical examination and additional test; diagnosis; in-hospital medications and intervention; complications; and in-hospital outcomes.

Study population

The population of this study consisted of patients above 18 years old admitted with ACS from July 2018 to June 2019. Patients diagnosed with ACS within hospitalization were also included. The diagnosis of ACS should be decided by a cardiologist through history taking, physical examination, initial electrocardiography (ECG), and cardiac markers according to the following criteria:

a) ST-ACS: symptoms consistent with myocardial ischemia with at least two continuous leads with ST-segment elevation ≥ 2.5 mm in men < 40 years, ≥ 2 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V2-V3 and/or ≥ 1 mm in other leads [in the absence of left ventricular hypertrophy (LVH) or left bundle branch block (LBBB)].[5]

b) NST-ACS: clinical presentation compatible with myocardial ischemia with normal ECG or abnormalities including ST-segment depression, transient ST-segment elevation, and T-wave changes in addition to dynamic elevation of cardiac markers.[7]

There were 14 healthcare facilities that met the requirements to participate in this study: 1 national cardiovascular center hospital (*Pusat Jantung Nasional Harapan Kita*/National Cardiovascular Center Harapan Kita/NCC Harapan Kita, Jakarta), 6 type A hospitals (Dr. Wahidin Sudirohusodo General Hospital, Makassar; Dr. M. Djamil General Hospital, Padang; Dr. Sardjito General Hospital, Yogyakarta; Sanglah General Hospital, Denpasar; Dr. Hasan Sadikin General Hospital, Bandung; and Dr. Saiful Anwar General Hospital, Malang) and 7 type B hospitals (Dr. Iskak General Hospital, Tulungagung; Cengkareng General Hospital, Jakarta; Otorita Hospital-Batam, Awal Bros Hospital, Batam; Santa Elizabeth Hospital, Batam; Dr. M. Yunus General Hospital, Bengkulu; and Rafflesia Hospital, Bengkulu). The national cardiovascular center (NCC) is a specialty hospital for cardiovascular disease national reference centers. Type A hospital serves at least 4 basic specialty medicine, 5 supporting specialty medicine, 12 other specialty medicine, and 13 sub-specialty medicine, with a minimum of 400 beds. Type B hospital serves at least 4 basic specialty medicine, 4 supporting specialty medicine, 8 other specialty medicine, and 2 basic subspecialty medicine, with at least 200 beds.

First medical contact (FMC) was the time when a patient was initially assessed and received the initial intervention (by a physician/paramedic/nurse/other trained emergency medical service personnel). FMC could occur in a prehospital setting or at hospital arrival. Ischemic time meant the time interval between symptom onset and reperfusion therapy. Eligible patients were patients with the onset of ACS less than 12 hours before reperfusion. Door-to-device (DTD) was the time interval from hospital arrival to the device deployment, while the door-to-needle (DTN) was defined as the time interval from hospital arrival to the start of the pharmacological infusion.

Sample recruitment

Patients who met the inclusion criteria were asked for informed consent to participate in this study. Informed consent was asked of the patient's guardian in case the patients were unable to give their consent. Patients who agreed to participate in this study were followed up until discharged from the hospital.

Data Analysis

Demographic data and clinical presentations will be shown in a descriptive form. Numerical data will be presented as mean (standard deviation/SD) or median (range). The association between categorical variables was analyzed using the Chi-square test, while differences in numerical variables based on subgroups were analyzed using an unpaired T-test or Mann-Whitney test. The risk assessment was conducted by calculating the odds ratio (OR) and 95% confidence interval (95%CI). Data analyses were processed using statistical software *SPSS version 24.0* for Windows MAC (SPSS Inc., Chicago, Illinois, US). Analytical tests and multivariate analysis will be performed as needed. A P value of <0.05 was considered as significant.

Ethical Approval

This study was approved by the National Institute of Health Research and Development, Ministry of Health Republic of Indonesia (Registry No. LB.02.01/2/KE.319/2020).

Results

Between July 2018 and June 2019, 7634 patients with ACS were admitted to the emergency departments of 14 participating health centers. Nearly half of the patients (48.8%) were diagnosed with STE-ACS. Male gender was predominant in both STE-ACS (83.5%) and NSTE-ACS (70.5%) groups, with a mean age of 57 (SD 11.1) years and 60 (SD 10.8) years, respectively. The majority of ACS patients in our registry (89.4%) were funded by national health coverage. Most of both STE-ACS and NSTE-ACS patients presented with typical ischaemic chest pain when admitted to the emergency room (92.7% and 84.6%, respectively). Smoking was the most common risk factor in STE-ACS patients (65.7%), while in NSTE-ACS patients, a history of hypertension was the highest risk factor (67.3%). However, patients with NSTE-ACS/UAP

tended to have more concomitant diseases including hypertension, diabetes mellitus, dyslipidemia, prior AMI, HF, PCI, and CABG than patients with STE-ACS. Heart failure and myocardial infarction in NSTE-ACS were 4 times higher than in STE-ACS (20.2 vs.5.1% and 34.5 vs, 8.3%, respectively). STE-ACS patients had a lower median ejection fraction than NSTE-ACS [46.8 (range 13.0-88.4) vs. 50.0 (18.0-88.4)], and more STE-ACS patients had a cardiac arrest (11.4% vs. 5%). Both STE- and NSTE-ACS showed a <40 mg/dL HDL level; however, we found that NSTE-ACS patients had a lower median eGFR [64.0 (range 3.0-177.8) mL/min/1.73m^2] **(Table 1)**. The majority of STE-ACS patients (86.7%) were identified as Killip I-II, whereas 40.3% of NSTE-ACS patients were classified as high risk and very high risk. Only 21.8% of STE-ACS patients underwent reperfusion strategy within 0-3 hours of onset.

The majority of ACS patients received antiplatelet as 24-hour therapy (97.9%) and discharge therapy (97.1%). However, the prescription of potent P2Y12 inhibitors was low (16.6% as 24-hour therapy and 17.8% as discharge therapy). In NSTE-ACS patients, anticoagulant as 24-hour therapy was administered more frequently (88.3%). Only 54% of ACS patients received high-intensity statin as medical treatment in ACS; about 35% had low to moderate-intensity patients and less than 10% did not receive any statin at all **(Table2)**.

The proportion of STE-ACS patients who underwent reperfusion therapy was higher than non-reperfusion (65.2% vs. 34.8%), and primary PCI (PPCI) was the most common method of reperfusion (45.7%). A total of 2644 (71.0%) patients were eligible for reperfusion, and 81.2% of them underwent reperfusion. Median patient awareness in STE-ACS was 150 (range 5-699) minutes, with a long median ischemic time of 405 (range 36-2020) minutes. Our STE-ACS patients also had a system delay in median transfer time [165 (range 5-660) minutes **(Table 3)**, hence we had as high as 78.1% of patients receiving a definitive therapy beyond 3 hours after onset.

The mortality rate in our ACS patients was 8.9%, with a median length of stay (LoS) of 5 (range 0-74) days. STE-ACS patients showed higher mortality than NSTE-ACS (11.7 vs. 6.2%). In ST-ACS, the lowest mortality rate was found in the PPCI strategy (8.3%), compared to fibrinolysis (10.9%) and no revascularization (16.9%) **(Figure 1)**. The mortality rate in late presenters (>12 hours) was higher than in early presenters (14.1% vs. 10.8%). Patients who underwent fibrinolysis within 3 hours of onset had a comparatively low mortality rate with patients who underwent PPCI (7.3% and 7.6%, respectively) **(Table 4)**.

Most of the NSTE-ACS patients in our registry are classified as intermediate risk (38.1%), followed by very high risk (27.0%) and low risk (21.6%). However, the invasive strategy was performed in 17.6% of NSTE-ACS patients, and only 6.7% performed it early (within <24 hours). The highest rate of revascularization was found in intermediate risk (38.2%). The mortality rate in NSTE-ACS patients was 6.2%, with a median LoS of 5 (range 0-45) days. In very high-risk patients, the mortality rate in the invasive strategy was lower than in the conservative strategy (12.9% vs. 19.2%, P=0.046). In very high-risk patients, an early invasive strategy is followed with a higher mortality rate than a late invasive strategy (19.5% vs. 8.8%, P=0.009) **(Table 5)**. Patients who underwent the early invasive strategy had a shorter median than the late invasive strategy [4 (range 0-30) days vs. 5 (range 0-36) days, P<0.001). A shorter median LoS also found in intermediate and low-risk patients ([5 (range 0-37) days and 4 (range 0-27) days, respectively] **(Table 6)**.

Discussion

Our registry showed 48.8% of ACS was STE-ACS and 51.2% was NSTE-ACS. This was similar to a report from ACCESS Investigator that found 46% STE-ACS and 54% NSTE-ACS in developing countries.[8] The proportion of NSTE-ACS in our registry was also similar to a registry in South Korea (56.6%).[9] Compared to other established registries in South Korea, Europa, and the US,[10,11,12,13,14] in which the mean or median age was over 60 years, our patients had younger age. A previous study showed that insurance types had a role in the outcome of patients admitted with ACS.[15] Furthermore, a study in the US showed that less evidence-based therapy and worse outcomes were found in NSTE-ACS patients whose primary payer for their treatment was a federal system health insurance, compared to those whose treatment was insured by health maintenance organizations or other private payers.[16] Those findings

Table 1. Characteristics of ACS patients.

Characteristics	Total (N=7.634)	STE-ACS (n=3.275)	NSTE-ACS (n=3.909)	P value
Male gender, n(%)	5.867 (76.9)	3.110 (83.5)	2.757 (70.5)	< 0.001
Median age (range), years	59 (18-95)	57 (20-95)	60 (18-95)	< 0.001
Insurance status, n(%)				< 0.001
National health coverage	6822 (89.4)	3.232 (86.8)	3.590 (91.9)	
Personal	736 (9.6)	469 (12.6)	267 (6.8)	
Company insurance	69 (0.9)	21 (0.6)	48 (1.2)	
Symptoms, n(%)				
Chest pain	6.759 (88.5)	3.453 (92.7)	3.306 (84.6)	< 0.001
Autonomic symptoms	5.427 (71.1)	2.972 (79.8)	2.455 (62.8)	< 0.001
Lasting >20 minutes	6.053 (79.3)	3.080 (82.7)	2.973 (76.1)	< 0.001
New onset of angina	2.996 (39.2)	970 (26.0)	2.026 (51.8)	< 0.001
Referred pain	3.664 (48.0)	1.993 (53.5)	1.671 (42.7)	< 0.001
Dyspnea	2.635 (34.5)	994 (26.7)	1.641 (42.0)	< 0.001
Risk factors, n(%)				
Smoking	4.340 (56.9)	2.448 (65.7)	1.892 (48.4)	< 0.001
Hypertension	4.548 (59.6)	1.918 (51.5)	2.630 (67.3)	< 0.001
Diabetes mellitus	2.466 (32.3)	1.034 (27.8)	1.432 (36.6)	< 0.001
Dyslipidemia	1.301 (17.0)	512 (13.7)	789 (20.2)	< 0.001
Family history	484 (6.3)	212 (5.7)	272 (7.0)	0.031
Comorbidities, n(%)				
Prior asthma/COPD	151 (2.0)	62 (1.7)	89 (2.3)	0.061
Prior CABG	151 (2.0)	4 (0.1)	147 (3.8)	< 0.001
Prior AMI	1.660 (21.7)	310 (8.3)	1.350 (34.5)	< 0.001
Prior heart failure	980 (12.8)	191 (5.1)	789 (20.2)	< 0.001
Prior peripheral vascular disease	55 (0.7)	16 (0.4)	39 (1.0)	0.005
Prior cerebrovascular disease	326 (4.3)	169 (4.5)	157 (4.0)	0.315
Prior PCI	866 (11.3)	142 (3.8)	724 (18.5)	< 0.001
Clinical presentation				
Median systolic BP (range), mmHg	129 (40-255)	123 (40-255)	130 (60-255)	< 0.001
Median diastolic BP (range), mmHg	78 (20-180)	76 (20-180)	79 (20-170)	0.001
Median heart rate (range), bpm	80 (18-252)	80 (18-206)	81 (18-252)	< 0.001
Median ejection fraction (range), %	48.0 (13.0-88.4)	46.8 (13.0-88.4)	50.0 (13.0-88.4)	< 0.001
Anterior location of infarction, n (%)	2.171 (28.4)	1988 (53.4)	183 (4.7)	< 0.001
Cardiac arrest, n (%)	622 (8.1)	425 (11.4)	197 (5)	< 0.001
Laboratory examination				
Median total cholesterol level (range),	172.0 (53.0-509.0)	175.0 (55.0-509.0)	170.0 (53.0-432.0)	< 0.001
mg/dL	115.0 (23.0-335.0)	118.0 (23.0-335.0)	112.0 (26.0-335.0)	0.454
Median LDL level (range), mg/dL	38.0 (10.0-161.0)	38.0 (10.0-161.0)	38.0 (10.0-123.0)	< 0.001
Median HDL level (range), mg/dL	124.0 (51.0-848.0)	124.0 (51.0-848.0)	124.0 (51.0-841.0)	0.366
Median triglyceride level (range), mg/dL	30.0 (1.3-460.0)	28.0 (1.3-336.0)	32.0 (8.0-460.0)	< 0.001
Media urea level (range), mg/dL	1.1 (0.1-17.7)	1.1 (0.1-15.3)	1.1 (0.2-17.7)	< 0.001
Median creatinine level (range), mg/dL	67.0 (3.0-182.8)	70.6 (3.2-182.8)	64.0 (3.0-177.8)	< 0.001
Median eGFR (range), mL/min/1.73m^2				

CAD=coronary artery disease, COPD=chronic obstructive pulmonary disease, AMI=acute myocardial infarct, HF=heart failure, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, CVA=cerebrovascular accident, PAD=peripheral vascular disease.

Table 2. Medical treatment in ACS.

Pharmacotherapy	First 24 hours			P value	At discharged			P value
	Total (N=7.634)	STE-ACS (n=3.725)	NSTE-ACS (n=3.909)		Total (N=6.953)	STE-ACS (n=3.288)	NSTE-ACS (n=3.665)	
Antiplatelet, n (%)	7.477 (97.9)	3.665 (98.4)	3.812 (97.5)	0.005	6.754 (97.1)	3.224 (98.1)	3.530 (96.3)	< 0.001
Aspirin	7.409 (97.1)	3.642 (97.8)	3.767 (96.4)	< 0.001	6.599 (94.9)	3.193 (97.1)	3.406 (92.9)	< 0.001
P2Y12 inhibitor								
Clopidogrel	6.240 (81.7)	2.984 (80.1)	3.256 (83.3)	< 0.001	5.367 (77.2)	2.505 (76.2)	2.862 (78.1)	0.003
Ticagrelor	1.268 (16.6)	737 (19.8)	531 (13.6)	< 0.001	1.235 (17.8)	692 (21.0)	543 (14.8)	< 0.001
RAS blocker	5.568 (72.9)	2.571 (69.0)	2.997 (76.7)	< 0.001	5.583 (80.3)	=2.610 (79.4)	2.973 (81.1)	0.004
Beta blocker	4.012 (52.6)	1.599 (42.9)	2.413 (61.7)	< 0.001	4.914 (70.7)	2.253 (68.5)	2.661 (72.6)	< 0.001
Ca channel blocker	756 (9.9)	121 (3.2)	635 (16.2)	< 0.001	915 (13.2)	192 (5.8)	723 (19.7)	< 0.001
Aldosterone antagonist	374 (4.9)	72 (1.9)	302 (7.7)	< 0.001	522 (7.5)	168 (5.1)	354 (9.7)	< 0.001
Diuretic	2.160 (28.3)	903 (24.2)	1.257 (32.2)	< 0.001	1.803 (25.9)	675 (20.5)	1.128 (30.8)	< 0.001
Nitrate	4.125 (54.0)	1.673 (44.9)	2.452 (62.7)	< 0.001	3.330 (47.9)	1.294 (39.4)	2.036 (55.6)	< 0.001
Anticoagulants, n (%)	6.233 (81.6)	2.783 (74.7)	3.450 (88.3)	< 0.001	199 (2.9)	76 (2.3)	123 (3.4)	0.004
UFH	1.340 (17.6)	848 (22.8)	492 (12.6)	< 0.001	-	-	-	-
Fondaparinux	1.936 (25.4)	608 (16.3)	1.328 (34.0)	< 0.001	-	-	-	-
Enoxaparin	3.039 (39.8)	1.386 (37.2)	1.653 (42.3)	< 0.001	-	-	-	-
Warfarin	-	-	-	-	199 (2.9)	76 (2.3)	123 (3.4)	0.004
Statins, n (%)	6.868 (90.0)	3.433 (92.2)	3.435 (87.9)	< 0.001	6262 (90.1)	3.061 (93.1)	3.201 (87.3)	< 0.001
High intensity statin	4.172 (54.7)	2.283 (61.3)	1.889 (48.3)	< 0.001	3746 (53.9)	2.045 (62.2)	1.701 (46.4)	< 0.001
Low to moderate intensity statin	2.731 (35.8)	1.166 (31.3)	1.565 (40.0)	< 0.001	2532 (36.4)	1.021 (31.1)	1.511 (41.2)	< 0.001

Table 3. Healthcare performance in STE-ACS (n=2.519).

Variables	Median (range), mins
Onset to FMC	150 (5-699)
Transfer time	165 (5-660)
Door to device	91 (18-1851)
Door to needle	60 (10-645)
Ischemic time	405 (36-2020)

were in adherence with the finding in our registry, in which most of the patients received national health coverage for their ACS treatment and had less optimal outcomes in terms of in-hospital mortality.

Previous studies showed male sex, hypertension, smoking, age, dyslipidemia, and diabetes, as the most prevalent risk factors.[10-14,17-18] Our registry also found that male gender, smoking, and hypertension were the most common risk factors. Patients with NSTE-ACS tended to have more concomitant diseases including hypertension, diabetes mellitus, dyslipidemia, prior AMI, HF, PCI, and CABG than patients with STE-ACS. This finding was similar to a study in Egypt[18] and other registries.[9] However, the proportion of NSTE-ACS with prior HF and prior AMI in our registry was higher than in other registries.

Plasma levels of HDL-cholesterol were described for decades as having an inverse relationship to the incidence of CAD. The anti-atherosclerotic effects of HDL have been related to their role in stimulating cholesterol efflux, as their anti-inflammatory, antioxidant, anti-aggregating, anti-coagulant, and pro-fibrinolytic properties. HDL-C was an important parameter for predicting the risk and the clinical outcomes of AMI in young male patients. Smoking has also been described as one of the causes of low HDL[19] The high proportion of smoking and low HDL may explain the median younger age in our registry as compared to the registry in US, Europe, and even South Korea.[10-14]

In our NSTE-ACS patients, no significant difference was found between conservative ys. invasive strategy. The mortality benefit was seen only in very high

risk group. Invasive strategy in the very high risk

Table 4. Mortality rate based on onset presentation among reperfusion strategy in STE-ACS.

Variables	Total (n=2.409)	Fibrinolysis (n=706)		PPCI (n=1,703)		P value
		Survived	Died	Survived	Died	
0-3 hours	524 (21.8)	204 (92.7)	16 (7.3)	281 (92.4)	23 (7.6)	1.000
3-6 hours	866 (35.9)	228 (88)	31 (12)	565 (93.1)	42 (6.9)	0.021
6-12 hours	755 (31.3)	166 (86.9)	25 (13.1)	519 (92)	45 (8)	0.05
>12 hours	264 (10.9)	31 (86.1)	5 (13.9)	197 (86.4)	31 (13.6)	1.000

Table 5. Management and outcomes in NSTE-ACS patients.

Variables	Conservative (n=3.220)		Invasive strategy (n=689)		P < 0.005	Early invasive strategy (n=262)		Late invasive strategy (n=427)		P value
	Survived	Died	Survived	Died		Survived	Died	Survived	Died	
Total (n=3.909)	3.009 (93.4)	211 (6.6)	656 (95.2)	33 (4.8)	0.099	244 (93.1)	18 (6.9)	412 (96.5)	15 (3.5)	0.029
Very high risk (n=1.057)	691 (80.8)	164 (19.2)	176 (87.1)	26 (12.9)	0.046	62 (80.5)	15 (19.5)	114 (91.2)	11 (8.8)	0.009
High risk (n=518)	393 (93.6)	27 (6.4)	95 (96.9)	3 (3.1)	0.296	41 (97.6)	1 (2.4)	54 (96.4)	2 (3.6)	0.193
Intermediate risk (n=1.488)	1.214 (99.1)	11 (0.9)	260 (98.9)	3 (1.1)	0.724	84 (97.7)	2 (2.3)	176 (99.4)	1 (0.6)	0.621
Low risk (n=846)	711 (98.7)	9 (1.3)	125 (99.2)	1 (0.8)	1.000	57 (100.0)	0	68 (98.6)	1 (1.4)	0.620

Table 6. Length of stay according to risk stratification and reperfusion strategy in NSTE-ACS patients.

Risk stratification	Total (n=3.909)	Conservative (n=3.220)	Invasive strategy (n=689)	P value	Early invasive strategy (n=262)	Late invasive strategy (n=427)	P value
All	5 (0-45)	5 (0-45)	5 (0-36)	0.001	4 (0-30)	5 (0-36)	< 0.001
Very high risk	5 (0-45)	5 (0-45)	5 (0-30)	0.293	5 (1-30)	5 (0-25)	0.805
High risk	5 (0-38)	5 (0-38)	5 (1-19)	0.211	5 (2-17)	5 (1-19)	0.495
Intermediate risk	5 (0-37)	5 (0-37)	5 (0-36)	0.001	4 (0-22)	5 (2-36)	< 0.001
Low risk	4 (0-27)	4 (0-17)	4 (1-27)	0.030	4 (1-17)	5 (2-27)	0.001

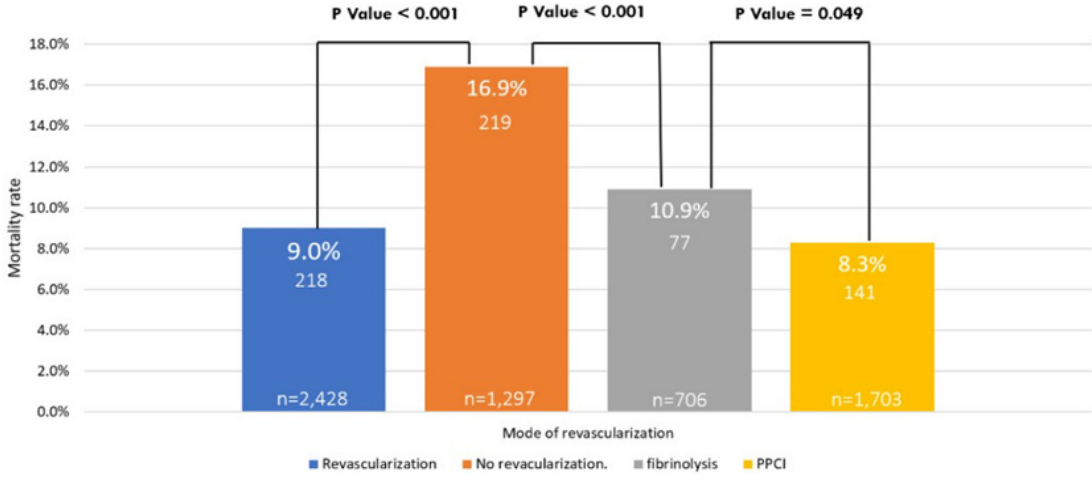

Figure 1. Hospital mortality rate in ST-ACS based on reperfusion strategies.

was mostly performed late beyond 48 hours, not in adherence with the recommended time within 2 hours of presentation.[20] However, the late invasive strategy had lower 8.8% mortality compared to 19.5% in the early invasive. This finding is consistent with recent metanalysis findings. These data confirm that blanket use of early invasive management of all NSTE-ACS patients is not required.[21] The risk-benefit of invasive procedure in very high-risk stratification of NSTE-ACS must be weight beyond the recommended guidelines, especially in a patient with poor perfusion and severe acidosis invasive strategy may do more harm than good.[22]

As a 24-hour and discharge therapy, antihypertensive was prescribed in addition to antiplatelets, anticoagulants, and statins. A previous study found that complete optimal medical treatment is associated with substantially lower 1-year mortality.[23] Early administration of beta-blocker gave benefits in survival hence oral beta-blocker should be prescribed within the first 24 hours in hemodynamically stable patients. Routine prescription of beta-blocker at discharge also should be considered in STE-ACS since it resulted in mortality reduction at 2.1 years follow-up, Especially in ACS with reduced left ventricular ejection fraction.[5] In high-risk NSTE-ACS, optimal care resulted in mortality benefits that persisted up to 8 years from hospital discharge.[24]

Potent P2Y12 inhibitor shows benefit in reducing the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding.[25] Therefore, the current European and local guidelines prioritize the use of potent P2Y12 inhibitors over the less potent one.[5,26,27] However, the prescription of potent P2Y12 inhibitors in our registry was low despite its superiority in thrombotic risk reduction as shown in large-scale randomized trials.[28] A meta-analysis of randomized controlled trials (RCTs) found that high-intensity statin is possibly beneficial in ACS regarding major adverse cardiovascular events (MACE), with a relative ratio (RR) less than 1 in both Asian and non-Asian patients. However, the administration of this intensive statin should be closely monitored for any possible adverse events.[29] In our registry, only half of the patients received high-intensity statin. National insurance coverage has certainly a role in the proportion of patients receiving medical treatment. National insurance coverage has limited resources to adhere to current recommendations regarding the usage of potent antiplatelets and high-intensity statins.

In patients with the acute coronary syndrome, lipid management aims to reduce LDL-C by >_50% from baseline and to achieve LDL-C <1.4 mmol/L (<55 mg/ dL) to further reduce the incidence of heart attack, revascularisation, and of ischaemic stroke, as recommended in European Guidelines.[5,20,30] In our registry the median LDL was 115 (23-335) mg/dL and the use of high-intensity statin is mandatory to reach the 55 mg/dL level of LDL. A reduction of LDL by 50% is needed to gain the benefit of reduced future incidence of heart attack, revascularisation, and ischaemic stroke. There is arguably no benefit in in-hospital mortality but the evidence for cardiovascular secondary prevention is in abundance.[30]

To maximize efficiency, a regional reperfusion strategy is recommended.[5] In STE-ACS, the preferred reperfusion therapy is primary PCI (PPCI), which is performed within 12 hours of symptom onset.[5,27] In our registry, nearly two thirds of STE-ACS patients underwent reperfusion therapy and the most common method was PPCI. A retrospective cohort study showed that PCI during hospitalization is concomitant with optimal medical treatment related to a lower 1-year mortality rate. Noticeably, PCI treatment within 4 days (OR 0.42; 95%CI 0.37 to 0.48) is associated with substantially lower 1-year mortality.[20] More than three-quarters of eligible patients in our registry had PPCI and the lowest mortality rate was found in the PPCI strategy, compared to fibrinolysis and no revascularization.

The timing of thrombolytic therapy plays a crucial role in ACS outcomes. Delayed reperfusion beyond 3 hours of onset is associated with larger infarct size and higher 1-year mortality. In our registry, the proportion of early invasive strategy was very low and the mortality rate in both STE- and NSTE-ACS was higher than in previous registries.[9] Time delay between the onset of ACS and reperfusion achievement is affected by 4 (four) components: patient delay (in seeking medical attention), transport delays, door-to-needle time, and thrombolytic reperfusion time. Despite the high number of patients having PPCI, our registry showed an extended patient awareness (possibly due to patient

and EMS delays) as well as system delays. A system delay might be due to poor performance and quality of healthcare.

Studies showed that post-fibrinolysis STE-ACS patients were safely discharged after 3 days of presentation,[31] while current guidelines recommend an early invasive risk-based approach and early discharge for NSTE-ACS, especially the low-risk patient.[32] Another study found that longer LoS accompanied by more comorbidities and in-hospital complications.[33] Early discharge is considered safe, and feasible, and results in similar outcomes with patients who stay for 4-5 days in the hospital.[34,35] Our registry showed an overall median LoS of 5 (range 0-74) days, and early invasive strategy followed by shorter LoS. We found that the benefit of the invasive strategy in NSTE-ACS patients was more related to LoS, not in-hospital mortality. Interestingly, there was no benefit of an early invasive strategy in the high- and very high-risk groups. The early invasive strategy has a higher mortality than the late invasive strategy (19.2% vs. 8.8%; P=0.009).

Our registry showed a comparable proportion between STE- and NSTE-ACS patients, with the male gender predominant in middle age. Both STE- and NSTE-ACS share the same risk factors. We need an improvement in referral time, especially in patients with STE-ACS. Despite the high mortality in patients with NSTE-ACS, the invasive strategy in this group was not statistically different from the conservative strategy. Evidence from our registry showed that two issues need to be addressed to improve ACS outcomes: optimal and adequate medical treatment and invasive strategy.

References

1. Kolansky, D. M. (2009). Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. The American Journal of Managed Care, 15(2 Suppl), S36-41. http://www.ncbi.nlm.nih.gov/ Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry pubmed/19355807.
2. Bueno, H. (2018). Epidemiology of acute coronary syndromes. In A. J. Camm, T. F. Lüscher, G. Maurer, & P. W. Serruys (Eds.), ESC CardioMed. Oxford University Press. https://doi.org/10.1093/med/9780198784906.001.0001.
3. Balitbang Kemenkes RI. (2013). Riset Kesehatan Dasar 2013. https://pusdatin.kemkes.go.id/resources/download/general/Hasil%20Riskesdas%202013.pdf. p. 83–99. Accessed 5 June 2022.
4. Viana, M., Laszczyńska, O., Araújo, C., Borges, A., Barros, V., Ribeiro, A. I., Dias, P., Maciel, M. J., Moreira, I., Lunet, N., & Azevedo, A. (2020). Patient and system delays in the treatment of acute coronary syndrome. Revista Portuguesa de Cardiologia (English Edition), 39(3), 123–131. https://doi.org/10.1016/j.repce.2019.07.007.
5. Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., Caforio, A. L. P., Crea, F., Goudevenos, J. A., Halvorsen, S., Hindricks, G., Kastrati, A., Lenzen, M. J., Prescott, E., Roffi, M., Valgimigli, M., Varenhorst, C., Vranckx, P., Widimský, P., … Gale, C. P. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal, 39(2), 119–177. https://doi.org/10.1093/eurheartj/ehx393.
6. Bäck, M., Leosdottir, M., Hagström, E., Norhammar, A., Hag, E., Jernberg, T., Wallentin, L., Lindahl, B., & Hambraeus, K. (2021). The SWEDEHEART secondary prevention and cardiac rehabilitation registry (SWEDEHEART CR registry). European Heart Journal - Quality of Care and Clinical Outcomes, 7(5), 431–437. https://doi.org/10.1093/ehjqcco/qcab039.
7. Sim, D. S., & Jeong, M. H. (2017). Differences in the Korea Acute Myocardial Infarction Registry Compared with Western Registries. *Korean Circulation Journal*, 47(6), 811. https://doi.org/10.4070/kcj.2017.0027.
8. ACCESS Investigators. (2011). Management of acute coronary syndromes in developing countries: ACute Coronary Events—a multinational Survey of current management Strategies. *American Heart Journal*, 162(5), 852-859.e22. https://doi.org/10.1016/j.ahj.2011.07.029.
9. Kim, J. H., Chae, S.-C., Oh, D. J., Kim, H.-S., Kim, Y. J., Ahn, Y., Cho, M. C., Kim, C. J., Yoon, J.-H., Park, H.-Y., & Jeong, M. H. (2016). Multicenter Cohort Study of Acute Myocardial Infarction in Korea – Interim Analysis of the Korea

Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circulation Journal*, 80(6), 1427–1436. https://doi.org/10.1253/circj.CJ-16-0061.

10. Lee, S. H., Kim, J. H., Jeong, M. H., Park, H., Jeong, Y. A., Ahn, Y., Kim, J. H., Chae, S. C., Kim, Y. J., Hur, S. H., Seong, I. W., Hong, T. J., Choi, D., Cho, M. C., Kim, C. J., Seung, K. B., Chung, W. S., Jang, Y. S., Cho, J. G., … Park, S. J. (2015). Clinical Characteristics and Outcomes of Acute ST-Segment Elevation Myocardial Infarction in Younger Korean Adults. *Korean Circulation Journal*, 45(4), 275. https://doi.org/10.4070/kcj.2015.45.4.275.
11. Zhang, S., Ge, J., Yao, K., & Qian, J. (2011). Meta-Analysis of Early Versus Deferred Revascularization for Non–ST-Segment Elevation Acute Coronary Syndrome. *The American Journal of Cardiology*, 108(9), 1207–1213. https://doi.org/10.1016/j.amjcard.2011.06.035.
12. Lagerqvist, B., James, S. K., Stenestrand, U., Lindbäck, J., Nilsson, T., & Wallentin, L. (2007). Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. *New England Journal of Medicine*, 356(10), 1009–1019. https://doi.org/10.1056/NEJMoa067722.
13. Canto, J. G. et al. (2012) 'Atherosclerotic Risk Factors and Their Association With Hospital Mortality Among Patients With First Myocardial Infarction (from the National Registry of Myocardial Infarction)', *The American Journal of Cardiology*, 110(9), pp. 1256–1261. doi: 10.1016/j.amjcard.2012.06.025.
14. Chung, S.-C., Gedeborg, R., Nicholas, O., James, S., Jeppsson, A., Wolfe, C., Heuschmann, P., Wallentin, L., Deanfield, J., Timmis, A., Jernberg, T., & Hemingway, H. (2014). Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *The Lancet, 383*(9925), 1305–1312. https://doi.org/10.1016/S0140-6736(13)62070-X.
15. Chakraborty, S., Bandyopadhyay, D., Amgai, B., Sidhu, J. S., Paudel, R., Koirala, S., Hajra, A., Ghosh, R. K., & Lavie, C. J. (2021). Does Insurance Effect the Outcome in Patients With Acute Coronary Syndrome?: An Insight from the Most Recent National Inpatient Sample. Current *Problems in Cardiology, 46(1),* 100411. https://doi.org/10.1016/j.cpcardiol.2019.02.003.
16. Calvin, J. E., Roe, M. T., Chen, A. Y., Mehta, R. H., Brogan, G. X., DeLong, E. R., Fintel, D. J., Gibler, W. B., Ohman, E. M., Smith, S. C., & Peterson, E. D. (2006). Insurance Coverage and Care of Patients with Non–ST-Segment Elevation Acute Coronary Syndromes. *Annals of Internal Medicine, 145*(10), 739. https://doi.org/10.7326/0003-4819-145-10-200611210-00006.
17. Lin, C.-C., Lee, P.-Y., Chen, K.-C., Liao, P.-C., Hsu, J.-C., & Li, A.-H. (2020). Clinical, Demographic, and Biochemical Characteristics of Patients with Acute ST-Segment Elevation Myocardial Infarction: An Analysis of Acute Coronary Syndrome Registry Data of a Single Medical Center from 2005 to 2016. *Acta Cardiologica Sinica, 36*(1), 1–7. https://doi.org/10.6515/ACS.202001_36(1).20190704D.
18. Abdelmoneim, H. M., Hasan-Ali, H., & Abdulkader, S. S. (2014). Demographics of Acute Coronary Syndrome (ACS) Egyptian patients admitted to Assiut University Hospital: Validation of TIMI and GRACE scores. *The Egyptian Journal of Critical Care Medicine, 2*(1), 3–11. https://doi.org/10.1016/j.ejccm.2014.07.001.
19. Ramirez, A. and Hu, P. P. (2015) 'Low High-Density Lipoprotein and Risk of Myocardial Infarction', Clinical Medicine Insights: Cardiology, 9, p. CMC.S26624. doi: 10.4137/CMC.S26624.
20. Collet, J.-P. et al. (2021) '2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation', *European Heart Journal, 42*(14), pp. 1289–1367. doi: 10.1093/eurheartj/ehaa575.
21. Kite, T. A. et al. (2022) 'Timing of invasive strategy in non-ST-elevation acute coronary syndrome: a meta-analysis of randomized controlled trials', *European Heart Journal*. doi: 10.1093/eurheartj/ehac213.
22. Jentzer, J. C. et al. (2019) 'Utility and Challenges of an Early Invasive Strategy in Patients Resuscitated From Out-of-Hospital Cardiac Arrest', JACC: *Cardiovascular Interventions, 12*(8), pp. 697–708. doi: 10.1016/j.jcin.2019.01.245.
23. Ten Have, P., Hilt, A. D., Paalvast, H., Eindhoven, D. C., Schalij, M. J., & Beeres, S. L. M. A. (2020). Non-ST-elevation myocardial infarction in the Netherlands: room for improvement! Netherlands

Heart Journal : *Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, 28*(10), 537–545. https://doi.org/10.1007/s12471-020-01433-x.

24. Hall, M., Bebb, O. J., Dondo, T. B., Yan, A. T., Goodman, S. G., Bueno, H., Chew, D. P., Brieger, D., Batin, P. D., Farkouh, M. E., Hemingway, H., Timmis, A., Fox, K. A. A., & Gale, C. P. (2018). Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. *European Heart Journal, 39*(42), 3798–3806. https://doi.org/10.1093/eurheartj/ehy517.
25. Lindholm, D. et al. (2014) 'Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial', *European Heart Journal, 35*(31), pp. 2083–2093. doi: 10.1093/eurheartj/ehu160.
26. Valgimigli, M. et al. (2018) '2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS', *European Journal of Cardio-Thoracic Surgery, 53*(1), pp. 34–78. doi: 10.1093/ejcts/ezx334.
27. PERKI (2018) Pedoman tata laksana sindroma koronerakut. 4th edn. Edited by D. A. Juzar et al. Jakarta.
28. Sibbing, D., Orban, M. and Massberg, S. (2013) 'Potent P2Y12 receptor inhibitors in patients with acute coronary syndrome', Hämostaseologie, 33(01), pp. 9–15. doi: 10.5482/HAMO-12-12-0022.
29. Yu, S., Jin, J., Chen, Z., & Luo, X. (2020). High-intensity statin therapy yields better outcomes in acute coronary syndrome patients: a meta-analysis involving 26,497 patients. *Lipids in Health and Disease, 19*(1), 194. https://doi.org/10.1186/s12944-020-01369-6.
30. Baigent, C. et al. (2010) 'Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials', *The Lancet, 376*(9753), pp. 1670–1681. doi: 10.1016/S0140-6736(10)61350-5.
31. Newby, L. K., Eisenstein, E. L., Califf, R. M., Thompson, T. D., Nelson, C. L., Peterson, E. D., Armstrong, P. W., van de Werf, F., White, H. D., Topol, E. J., & Mark, D. B. (2000). Cost Effectiveness of Early Discharge after Uncomplicated Acute Myocardial Infarction. *New England Journal of Medicine, 342*(11), 749–755. https://doi.org/10.1056/NEJM200003163421101.
32. Anderson, J. L., Adams, C. D., Antman, E. M., Bridges, C. R., Califf, R. M., Casey, D. E., Chavey, W. E., Fesmire, F. M., Hochman, J. S., Levin, T. N., Lincoff, A. M., Peterson, E. D., Theroux, P., Wenger, N. K., Wright, R. S., Smith, S. C., Jacobs, A. K., Adams, C. D., Anderson, J. L., … Riegel, B. (2007). ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction. *Journal of the American College of Cardiology, 50*(7), e1–e157. https://doi.org/10.1016/j.jacc.2007.02.013.
33. Vavalle, J. P., Lopes, R. D., Chen, A. Y., Newby, L. K., Wang, T. Y., Shah, B. R., Ho, P. M., Wiviott, S. D., Peterson, E. D., Roe, M. T., & Granger, C. B. (2012). Hospital Length of Stay in Patients with Non-ST-segment Elevation Myocardial Infarction. *The American Journal of Medicine, 125*(11), 1085–1094. https://doi.org/10.1016/j.amjmed.2012.04.038.
34. Karabulut, A., Cakmak, M., Uzunlar, B., & Bilici, A. (2011). What is the optimal length of stay in hospital for ST elevation myocardial infarction treated with primary percutaneous coronary intervention? *Cardiology Journal, 18*(4), 378–384. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21769818.
35. Swaminathan, R. v., Rao, S. v., McCoy, L. A., Kim, L. K., Minutello, R. M., Wong, S. C., Yang, D. C., Saha-Chaudhuri, P., Singh, H. S., Bergman, G., & Feldman, D. N. (2015). Hospital Length of Stay and Clinical Outcomes in Older STEMI Patients After Primary PCI. *Journal of the American College of Cardiology, 65*(12), 1161–1171. https://doi.org/10.1016/j.jacc.2015.01.028