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Research Article

Cost-Effectiveness of Antithrombotic Agents for STEMI

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ABSTRACT

In Indonesia, the prevalence of Acute Coronary Syndrome (ACS) continues to rise annually and remains high. Aspirin and adenosine diphosphate receptor inhibitors are recommended as part of the dual antiplatelet therapy that is recommended by the standard guidelines for managing ACS. Ticagrelor, a new treatment option for ACS, has been made available during the current period of Indonesia's National Health Insurance. Ticagrelor is more effective, but it costs more. Objective: In patients with ST-Elevation Myocardial Infarction (STEMI), the goal of this study was to compare how much ticagrelor and clopidogrel cost when compared to one another with relative ratio (RR) analysis and 95% confidence interval (CI) with $p<0.05$ considered significant. This study was a decision tree-based retrospective cohort study with a one-year follow-up following the STEMI event. In 2017-2018, 496 patients, 92 of whom had taken ticagrelor and 404 of whom had taken clopidogrel, participated in the study at Dr. Sardjito General Hospital Yogyakarta. An incremental cost-effectiveness ratio (ICER) was used to present a cost-effectiveness analysis. In comparison to clopidogrel, the ticagrelor group's annual average total cost is higher. In the ticagrelor group, cardiovascular disease (CVD) event rates were 7.6%, while in the clopidogrel group, they were 21% (RR: 0.362, CI 95%: 0.173–0.755, p=0.005. Ticagrelor's ICER was IDR885.584 per CVD prevented compared to clopidogrel's. The yield of ticagrelor was lower (ICER <3 Gross Domestic Product/GDP) when compared to the WHO threshold ratio of willingness to pay (GDP per capita Indonesian = USD3.927, based on 2018). Ticagrelor is an antithrombotic that prevents CVD events in STEMI patients at the lowest cost.

INTRODUCTION

Worldwide, cardiovascular diseases account for the majority of human deaths. In 2015, the World Health Organization (WHO) estimated that 17.7 million people died from cardiovascular disease, accounting for 31% of all non-communicable disease deaths. There were 7.4 million of these deaths associated with ischemic heart disease (Garcia *et al.*, 2018). Additionally, cardiovascular disease is a significant financial burden on the healthcare system, with direct costs associated with hospitalization (Boisclair *et al.*, 2018).

Coronary heart disease (CHD), rheumatic heart disease, heart failure, ventricular arrhythmias, abdominal artery aneurysms, congenital heart disease, peripheral arterial disease, and congenital heart disease are all types of cardiovascular disease. Ischemic heart disease and coronary artery disease are other names for CHD, which is one of the leading causes of death globally, according to estimates provided by the WHO (Tumade *et al.*, 2016). CHD is another major disease in Indonesia, causing over 470,000 (17.05%) deaths annually (Hussain *et al.*, 2016; Iskandar *et al.*, 2017).

Acute coronary syndrome (ACS), which includes ST-Elevation Myocardial Infarction (STEMI), Non-ST-Elevation Myocardial Infarction (NSTEMI), and Unstable Angina (UA),

and is the most common cause of hospital emergency room visits, is one manifestation of CHD. ACS is the leading cause of death in the Asia-Pacific region, accounting for half of the global burden (Chan *et al*., 2016). The prevalence of ACS remains the highest in Indonesia, at 7.2%, and it continues to rise annually (Aurellia & Pujiyanti, 2015).

As per the rules for the administration of treatment for ACS according to the Indonesian Cardiovascular Expert Affiliation, ACS patients who will go through essential percutaneous coronary mediation ought to get double antiplatelet treatment such as ibuprofen and adenosine diphosphate (ADP) receptor inhibitors. Regardless of the approach taken to treat the condition, aspirin should be administered as soon as possible after the diagnosis of STEMI is made. A higher daily aspirin dose of 162-325 mg is the standard for treating STEMI, followed by a lower daily dose of 75-100 mg. Ticagrelor (loading dose 180 mg, followed by maintenance doses of 90 mg twice a day) or clopidogrel (higher doses recommended by loading 600 mg, followed by 150 mg per day) are two options for ADP receptor inhibitors that can be used in the event that ticagrelor is unavailable or contra-indicated (PERKI, 2015; Levine *et al*., 2016).

Treatment for ACS certainly puts a physical and financial strain on society, especially in Indonesia, where the disease is becoming more common every year. In the current era of Indonesia's National Health Insurance (JKN), alternative treatments for the incidence of ACS (ticagrelor) are available; however, these treatments have a higher therapeutic efficacy but come at a higher cost. As a result, evaluations related to effectiveness and costs are required for new treatment alternatives in order to establish a level of effectiveness that is proportional to the costs that must be incurred. Ticagrelor's effectiveness and price are still the subjects of little research in Indonesia. As a result, the goal of this study was to compare ticagrelor's effectiveness and cost to clopidogrel, which is considered an outdated treatment for ACS, in terms of lowering the risk of heart attacks, strokes, and cardiovascular deaths.

METHODS

Study Design

This observational research was a retrospective cohort study with an economic evaluation of patients treated at Dr. Sardjito General Hospital Yogyakarta who had a new STEMI and received ticagrelor and clopidogrel therapy between 2017 and 2018. From the patient's medical record, the data were retrieved retrospectively. The pharmacoeconomic analysis is based on the perspective of Dr. Sardjito Hospital Yogyakarta as a health service provider. It involves calculating direct medical costs using a decision-tree design model with a year of observation since the patient was hospitalized with a diagnosis of a new STEMI. This method of analyzing the effectiveness of therapy refers to the patient's clinical outcome.

Participants

Patients who were diagnosed with a new ACS STEMI in 2017-2018 period at Dr. Sardjito Hospital Yogyakarta were eligible for the study. Patients with ACS who had a diagnosis other than STEMI were excluded.

Outcomes

Assessment of effectiveness in both groups therapy was based on the incidence of cardiovascular disease (CVD) events such as non-fatal myocardial infarction, stroke, and cardiovascular death during observation time points at 1 year.

Statistical Considerations

The participants in this study were individuals who had recently been diagnosed with a STEMI and had received antithrombotic therapy in the form of ticagrelor and/or clopidogrel at Dr. Sardjito Hospital Yogyakarta. The sample size was determined using the formula for unpaired categorical analysis. The following equation was used to calculate the minimum sample size used in this study (**Figure 1**).

P1 = 0.8, P2 = 0.9 (Wallentin *et al*., 2009)

$$n1=n2 = \frac{(Z\alpha \sqrt{2PQ} + Z\beta\sqrt{P_1Q_1+P_2Q_2})^2}{(P_1-P_2)^2}$$

$$\mathbf{n1 = n2 = \frac{(1{,}64\ \sqrt{2x0{,}85x0{,}15} + 0{,}842\ \sqrt{0{,}8x0{,}2+0{,}9x0{,}1})^2}{(0{,}8 - 0{,}9)^2}}$$

$$\mathbf{n1 = n2 = 127{,}2 \approx 127}$$

Figure 1. The Equation of Minimum Sample

Cost-Effectiveness Analysis

Incremental Cost-Effectiveness Ratio was obtained by looking at the cost differences in the two types of therapy regimen groups, compared to the differences in the effectiveness of each group of treatment regimens which were the number of CVD events.

RESULTS AND DISCUSSION

General Description

The number of samples reached as many as 495 people who met the inclusion criteria for the study and were used as research subjects. Based on how the therapeutic regimens were administered, the subjects were further divided into two groups: a ticagrelor therapy group with 91 subjects and a clopidogrel therapy group with 404 subjects. Observations were made in both groups within a year of the patient's initial STEMI diagnosis.

Basic Characteristics of Research Subjects

Table 1 displays the fundamental characteristics of the subjects: age, sex, comorbidities, payment methods, medication, invasive procedures, and the difference in length of stay (LoS) between the two groups of antithrombotic therapy regimens.

Based on the data in Table 1, it generally shows that the two groups of antithrombotic therapy regimens were not significantly different. This can be seen in the homogeneity of the variables of age, sex, comorbidities, comedication and length of stay, which was $p>0.05$. The non-homogeneous variable of the two groups of antithrombotic therapy regimens was the payment method (insurance) with a $p<0.001$

Table 1. Patient Characteristics

	Ticagrelor (n=91)	Clopidogrel (n=404)	*p* value
Age, n (%)			
< 60 year	47 (51.6)	203 (50.2)	0.900
≥ 60 year	44 (48.4)	201 (49.8)	
Sex, n (%)			
Male	77 (84.8)	327 (80.9)	0.504
Female	14 (15.4)	77 (19.1)	
Comorbidities. n (%)			
Hypertension	85 (93.4)	388 (96)	0.412
Diabetes Mellitus	36 (39.6)	118 (29.2)	0.072
Dyslipidemia	91 (100)	404 (100)	1.000
Insurance, n (%)			
JKN	79 (86.8)	382 (94.6)	0.026
General/Individual	7 (7.6)	8 (2.0)	
Jamkesda/Jamkesos	4 (4.3)	11 (2.7)	
Others	1 (1.1)	3 (0.7)	
Comedication, n (%)			
Antihypertension	85 (93.4)	388 (96)	0.412
Antidiabetic	36 (39.6)	118 (29.2)	0.072
Antilipidemic	91 (100)	404 (100)	1.000
Invasive Actions			
PTCA	69 (75.8)	273 (67.6)	0.145
Non-PTCA	22 (24.1)	132 (32.7)	
LoS Inpatient			
Median (Min – Max)	5.00 (2 – 24)	5.00 (1 – 45)	0.622

JKN, *Jaminen Kesehatan Masyarakat;* LoS, Length of Stay: PTCA, percutaneous transluminal coronary angioplasty.

Table 2. Output of Antithrombotic Effectiveness

Therapy (n)	CVD (+) (%)	CVD (-) (%)	RR unadjusted (CI 95%)	RR adjusted (CI 95%)
Ticagrelor (91)	7 (7.7)	84 (92.3)	0.366	0.348
Clopidogrel (404)	85 (21.0)	319 (79.0)	(0.175-0.764)	(0.153-0.791)

*Relative Ratio (RR) adjusted = RR based on age, gender, comorbid, comedication variables; CI, confidence interval; CVD, cardiovascular disease.

Table 3. Overall Costs Based on Type of Care

Type of Care	Ticagrelor (n=91)		Clopidogrel (n=404)	
	Cost (IDR)	Mean ± SD (million)	Cost (IDR)	Mean ± SD (million)
Inpatient	4,903,982,574	53,890 ± 4,118	17,988,453,286	44,526 ± 3,931
Outpatient	170,272,643	4,426 ± 0,456	225,968,848	2,012 ± 0,333
Total	5,074,255,217	58,316 ± 4,574	18,214,422,134	46,537 ± 4,264

IDR, Indonesian Rupiah; SD, standard deviation.

Analysis by Type of Antithrombotic

Analysis of antithrombotic therapy was conducted to see the effectiveness of both therapies based on parameters such as CVD (-) and CVD (+). The results of the outcome analysis of antithrombotics in this study are presented in Table 2.

Based on the type of antithrombotic therapy used in STEMI patients presented in Table 2, it shows that the percentage of CVD events is lower in the antithrombotic ticagrelor group compared with the clopidogrel antithrombotic group. After bivariable (unadjusted) and multivariable (adjusted) analyses, results significantly showed that the ticagrelor antithrombotic group was better than the clopidogrel antithrombotic group in preventing CVD in patients diagnosed with STEMI.

Cost of STEMI Therapy

The cost calculation in this study in both groups of therapy regimens is seen from the perspective of hospital (provider) payments. The accumulation of patient therapy costs is calculated by adding up the various components of direct medical costs. Data related to total costs (inpatient and outpatient) are presented in Table 3.

Table 3 outlines the total combined cost of treatment status in each group of antithrombotic therapy regimens which significantly indicates that the total mean in the ticagrelor therapy regimen group is greater than in the clopidogrel therapy regimen group.

CEA Ticagrelor and Clopidogrel
Incremental Cost-Effectiveness Ratio

ICER is used to determine the number of additional costs for each change in one unit of cost-effectiveness. ICER value calculation is performed to see the magnitude of the additional cost of treatment using ticagrelor antithrombotic relative to clopidogrel (generic) given to patients with STEMI. Data from ICER calculation results are presented in Table 4.

Based on the information presented in Table 4, it shows that the antithrombotic therapy regimen on ticagrelor is more cost-effective relative to clopidogrel by spending IDR11,778,265 per 13 prevented CVDs or IDR885,584 per 1 prevented CVDs.

Cost-effectiveness planning.

Based on the calculation of the ICER value of ticagrelor antithrombotic relative to the clopidogrel antithrombotic, the ticagrelor cost-effectiveness planning graph is described in Figure 2.

Based on Figure 2, it shows that antithrombotic therapy in the ticagrelor therapy regimen requires more additional costs than in the clopidogrel therapy regimen but has better

effectiveness in preventing the occurrence of CVD (+) in STEMI patients.

DISCUSSION

This pharmacoeconomic study was conducted with a retrospective cohort research design. The economic design method used is a cost-effectiveness analysis approach with a decision-tree model design that is used to observe the cost-effectiveness of antithrombotic use in new STEMI patients in Dr. Sardjito General Hospital Yogyakarta 2017-2018 period. Obtained subjects included 1,626 patients diagnosed with ACS. Of these, there were 495 subjects who met the study inclusion criteria and were then used as research subjects. The subjects were further grouped into two types of groups based on the administration of the therapeutic regimen, namely the ticagrelor therapy group with 91 subjects and the clopidogrel therapy group with 404 subjects. The measurement parameter for clinical outcomes in this study is the level of effectiveness of the antithrombotic therapy regimen given to new STEMI patients. Information on the results of the research analysis referred to in Table 2 shows that the level of effectiveness in the ticagrelor therapy regimen was better than the clopidogrel therapy regimen (p=0.005). This was reflected in the percentage of STEMI patients in the ticagrelor therapy regimen group who experienced fewer CVD (+) events compared to the clopidogrel therapy regimen group with RR: 0.366, 95% CI: 0.175-0.764, p=0.005.

The cumulative calculation of the total average cost for 1 year in STEMI patients intervened with ticagrelor or clopidogrel antithrombotic therapy presented in Table 3 shows that, the total average cost paid by STEMI patients with ticagrelor therapy regimens is relatively greater compared to the therapeutic regimens of ticagrelor or clopidogrel presented in Table 4 shows that the total average costs paid by STEMI patients with ticagrelor therapy regimens are relatively greater than clopidogrel and statistical analysis with Mann Whitney tests showed significant results (p=0.001).

Table 4. ICER Ticagrelor Relative to Clopidogrel

Antithrombotic	Average cost/patient (million)	Effectiveness (%) CVD (-)	ICER ($\Delta C/\Delta E$) (million)
Ticagrelor	58,316	92.3	
Clopidogrel	46,537	79	
Incremental	11,778 (ΔC)	13.3 (ΔE)	0.886

CVD, cardiovascular disease.

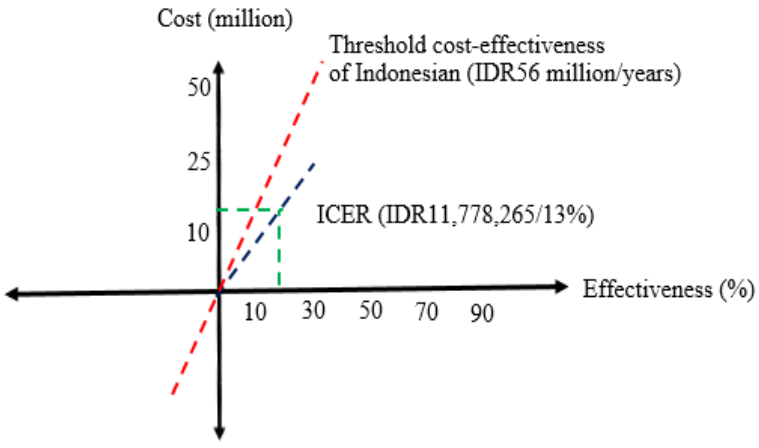


Figure 2. Cost-effectiveness Plan for Ticagrelor Therapy

The ICER calculation value obtained based on the ΔC/ΔE formula was IDR885,584. The results of the ICER calculation show that the ticagrelor therapy regimen group requires a higher cost to prevent CVD (+) events, so it can be said that antithrombotic therapy with ticagrelor does require a higher cost but is commensurate with the effectiveness of better treatment. When compared with the WHO willingness-to-pay threshold ratio (Indonesian GDP per capita = USD3,927), the ICER value in this study is very far below Indonesian GDP per capita which is IDR56,000,000 (USD1=IDR14,260). Based on these calculations, the ICER <3GDP is considered cost-effective.

CONCLUSIONS

The ticagrelor antithrombotic group was more cost-effective relative to the clopidogrel antithrombotic group with an ICER value of IDR885,584 per CVD prevented (ICER <3GDP).

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CONFLICT OF INTEREST

No conflict of interest between all authors

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