Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jul 29; 10(A):1211-1217.
https://doi.org/10.3889/oamjms.2022.9671
eISSN: 1857-9655
Category: *A - Basic Sciences*
Section: *Pharmacology*

Cost-Effectiveness of Ticagrelor for Acute Coronary Disease to Prevent Cardiovascular Events in Three Hospitals in Indonesia

Jarir At Thobari[1,2]*, Lucia Krisdinarti[3], Dhite Nugroho[2,4], Jonathan Haposan[2], Isman Firdaus[5], Rr. Arum Ramadhyan Suryandani[5], Muhammad Munawar[6], Jimmy Agung[6]

[1]Department of Pharmacology and Therapy, Division of Pharmacoepidemiology and Pharmacoeconomics, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [2]Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [3]Department of Cardiology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Dr. Sardjito Hospital, Yogyakarta, Indonesia; [4]Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Dr. Sardjito Hospital, Yogyakarta, Indonesia; [5]Department of Cardiology and Vascular Medicine, Harapan Kita Hospital, Jakarta, Indonesia; [6]Cardiac Center, Bina Waluya Hospital, Jakarta, Indonesia

Edited by: Sinisa Stojanoski
Citation: Thobari JA, Krisdinarti L, Nugroho D, Haposan J, Firdaus I, Suryandani RAR, Munawar M, Agung J. Cost-Effectiveness of Ticagrelor for Acute Coronary Disease to Prevent Cardiovascular Events in Three Hospitals in Indonesia. Open-Access Maced J Med Sci. 2022 Jul 29; 10(A):1211-1217.https://doi.org/10.3889/oamjms.2022.9621
Keywords: Ticagrelor; Cost-effectiveness; Acute coronary disease; Cost
***Correspondence:** Jarir At Thobari, Department of Pharmacology and Therapy, at the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Radiopoetro Building 2nd Floor, Sekip, Yogyakarta, Indonesia. E-mail: j.atthobari@ugm.ac.id
Received: 05-Apr-2022
Revised: 30-Jun-2022
Accepted: 19-Jul-2022

Funding: This research received a grant from AstraZeneca Pharmaceutical Company
Competing Interest: The authors have declared that no competing interest exists.

Abstract

BACKGROUND: Acute coronary syndromes (ACSs) are life-threatening cardiovascular (CV) disease associated with Indonesia's significant health and economic burdens.

AIM: The study objective was to evaluate the cost-effectiveness of ticagrelor in reducing CV endpoint in the Indonesia setting.

MATERIALS AND METHODS: Markov model was used as a decision analysis to compare ticagrelor with clopidogrel. We constructed decision tree model included four health conditions (no additional events, non-fatal myocardial infarction, non-fatal stroke, and any cause death). The probability of each state and quality-adjusted life years (QALYs) was derived from the PLATelet Inhibition and Patient Outcomes trial and Indonesia Life Table. The outcome's resource consumption and associated costs were collected from three hospitals (public, national referral, and private hospitals) in Indonesia. The study used 5 years and lifetime horizon and discounting rate of 3%.

RESULTS: The incremental QALYs and life-year gained (LYG) of ticagrelor in 5 years were 0.0410 and 0.0462, respectively; in a lifetime was 0.0828, and 0.0947, respectively. The ICER per QALY of ticagrelor versus clopidogrel in private, national referral, and public hospitals was USD 2390.276, USD 3813.638, and USD 1278.361, respectively, for 5 years; and USD 2471.392, USD 5453.987, and USD 2343.269, respectively, for a lifetime. The probability of ticagrelor to be cost effective was about 66.6% on a 5-year and 99.7% on a lifetime with willingness to pay USD 3634.

CONCLUSION: Compared to the clopidogrel, QALYs and LYG of use ticagrelor higher. The incremental cost-effectiveness ratio in 5 years and lifetime model showed under 1 time GDP, it means that the use of ticagrelor was vastly cost effective and acceptable to apply in the Indonesian clinical setting.

Introduction

Ischemic heart disease, including acute coronary syndromes (ACS), is life-threatening cardiovascular (CV) disorders associated with Indonesia's significant health and economic burdens. The combination of aspirin (acetylsalicylic acid) plus clopidogrel (a second-generation thienopyridine P2Y12 receptor antagonist) is suggested by international practice guidelines. At present, these agents are the most widely prescribed antiplatelet to prevent secondary atherothrombotic events among ACS patients [1].

Ticagrelor is a P2Y12 platelet adenosine diphosphate receptor antagonist, and it has been shown faster, more significant, and more P2Y12 inhibition than clopidogrel [2], [3], [4]. In the study of PLATelet Inhibition and Patient Outcomes (PLATO), it has been shown that in ACS patients who were randomized to receive 12 months of ticagrelor had reduced greatly in the combined endpoint of CV death, acute myocardial infarction (MI), or stroke, compared to those with clopidogrel. The study also showed a significant decrease in CV death but no significant difference in overall major bleeding [5]. Indonesia Drug Regulatory (BPOM) has been approved for ticagrelor to treat patients with ACS.

The ACS treatment places a heavy burden on Indonesian population. Whenever a novel treatment is available, especially one that is more costly but more beneficial than conventional treatments, the cost-effectiveness of the new medicine must be evaluated to determine whether it makes economic sense to improve outcomes, especially in the era of Indonesia's universal insurance system.

Therefore, the primary objective of this study was to evaluate the cost-effectiveness of ticagrelor in reducing CV death, MI, or stroke in Indonesian patients with the ACS. The secondary objective of this study was to assess the disease cost of MI and stroke.

Materials and Methods

Decision tree and Markov model

A Markov model was used as a decision analysis to compare ticagrelor with alternative therapy strategy (clopidogrel) and outcome. The two-component model consists of a simple decision tree corresponding to the 1-year PLATO study period. To simulate the short-term cost-effectiveness of ticagrelor, we constructed a 1-year decision tree that included four mutually exclusive health conditions (no additional events, non-fatal MI, non-fatal stroke, and any cause death), as shown in Figure 1. The beginning of the tree revealed that the treatment was given for ACS. There was a probability of developing a healthy state on receiving treatment, resulting in four health states. It was assumed that the treatment duration was only 1 year and that the remaining treatment in the Markov cycle had no rebound effect. At the end of 1 year, patients were assigned to one of six mutually exclusive Markov model health states: No further events, non-fatal MI, post-MI, non-fatal stroke, post-stroke, and death. The probabilities of treatment efficacy and health states were derived from PLATO clinical trials for ticagrelor and clopidogrel [6].

Subsequent events are modeled as a Markov structure with the potential for a recurring CV event that could be lethal from other causes. Model parameters corresponding to the 1st year following treatment (ticagrelor vs. clopidogrel) included the probability of each state (all-cause of death, non-fatal stroke, non-fatal MI, and no event), annual costs (IDR) for all-cause of death, stroke, MI, and no event, including costs of ticagrelor and clopidogrel per day.

The probability of each state and quality-adjusted life years (QALYs) was derived from the PLATO trial. We model the outcomes as transitions from one Markov health state to another (Figure 1). Each year, the cohort accumulates the costs and QALYs, based on their health status. The health state based on PLATO trial was death from CV causes, non-fatal MI, and non-fatal stroke.

We estimated the annual mortality rate (MR) in the no event state using age- and gender-specific MR from Indonesia Life Tables. The PLATO trial data were used to estimate mortality risks of non-fatal MI, post-MI, and post-stroke. The mortality risks of non-fatal stroke are derived from the literature or data from the study hospitals.

Costs associated with outcomes

The outcome's resource consumption and associated costs were collected from three hospitals

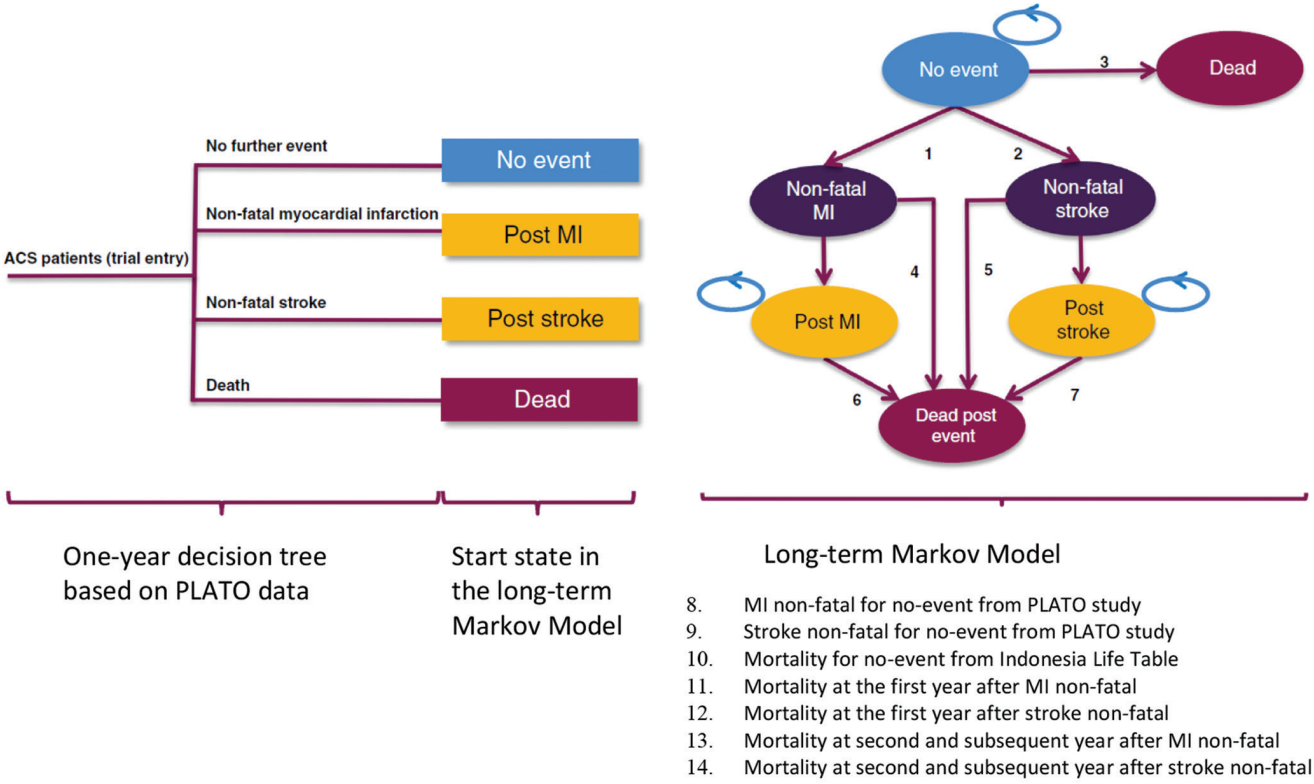

Figure 1: Representation of the decision model. A Markov process had four health states (based on the PLATO trial) and 1 year of cycle length. Patients remain in good condition until an event occurs (e.g., a stroke). The event probabilities depend on the treatment. The next model was a model parameter for subsequent years

in Indonesia. The analysis included costs of ticagrelor and clopidogrel, both generic and branded products, fee charges for medicines, bleeding associated costs, diagnosis, treatment, hospitalization, and costs of visit for stroke non-fatal both hemorrhagic and non-hemorrhagic, MI non-fatal, and death of any CV disease causes. The data-related costs were collected from the payment unit at the hospital per patient visit or hospitalization. The time horizon of data-related costs was 1 year ago since patients were diagnosed.

In this study, to estimate the cost of illness, three hospitals were selected as representatives as three types of referral hospitals in Indonesia, which were a national cardiac center hospital (NCCH) and a cardiac private hospital (CPH) in Jakarta, and a public general hospital in Yogyakarta. These three hospitals were also academic and certified as the national and international quality standards.

Study outcome

The QALYs and life-years gained (LYG) were measured as the study outcomes. These utilities were taken from Indonesia Life Table and standardized Indonesia mortality to associate with outcomes from PLATO trial. Outcome and costs were discounted at 3.0% per year.

Study model analysis

An ICER was calculated by incremental cost and QALY's of ticagrelor versus clopidogrel for 5 years and lifetime. The ICER was calculated as mean total costs from a combination of the three hospitals site and ICER per hospital.

Two forms of sensitivity analysis were used to address input model's uncertainty and evaluate base-case result's robustness. First, input of each parameter was varied within reasonable range (low and high), and the each ICER was calculated. It was included for the low and high value of ticagrelor and clopidogrel per day, discount rate, annual risk of MI of no event, increased risk of death for each event, annual costs (IDR) for each event, annual QALY for non-fatal MI, and annual QALY decrement of each event.

Second, bootstrap probabilistic analysis was performed with 10,000 repetitions. Each repetition, input values were generated from a regression model of PLATO trial and distributions for the Markov model. The results of 10,000 repetitions were plotted on ICER plane and CE acceptability curve. CE curve indicated the probability that given the uncertainty, cost effective of ticagrelor versus clopidogrel for increasing values of willingness to pay (WTP) for an additional QALY. The WHO recommendations for WTP could be linked to National GDP, with 1–3 times GDP/capita representing an acceptable ICER [7].

Model input parameter

A decision tree was used to see any condition caused by the effect of ticagrelor and clopidogrel regarding ACS with no event, non-fatal myocardial infarct, non-fatal stroke, and death due to all-cause. This study used the parametric value of the decision tree from Indonesian data as a baseline. Except for "no event," we used the PLATO trial as a baseline. The values and references of parameters are summarized in Table 1.

Table 1: Parameter included in 1-year decision tree

1-year of decision tree	Ticagrelor	Clopidogrel	Source
No event	0.8945	0.875	PLATO trial. Nikolic [8]
Myocardial infarction non-fatal	0.0634	0.0611	Indonesia hospital data
Stroke non-fatal	0.0178	0.0192	Indonesia hospital data
Any cause of death	0.1096	0.1385	Indonesian hospital data

This study also used the PLATO trial's value as a parameter for increased risk of death, QALY for no event, and annual QALY decrement. The parameters were used to see specific conditions such as ACS patients with no event, non-fatal MI, post-MI, non-fatal stroke, and post-stroke. The hazard ratio was used to count the increased risk of death in this study. That value and parameter are summarized in Table 2. The price of ticagrelor in Indonesia was IDR 15,000.00, and clopidogrel was IDR 1650.00, which then converted to USD. The Markov model uses a discount rate for outcomes and costs to maintain value in every cycle. We used a 3% discount rate based on Indonesian data.

Table 2: Parameters and values were used in the economic model for a 1-year decision tree

Parameter	Value	Sources
Yearly risk		
Myocardial infarction in no event	0.0189	PLATO, Nikolic [8]
Stroke in no event	0.0033	PLATO, Nikolic [8]
Increased risk of death		
No event	2.000	Indonesia Life Table, Allen, Taneja
Myocardial infarction non-fatal	6.000	PLATO, Nikolic [8]
Post-myocardial infarction	3.000	PLATO, Nikolic [8]
Stroke non-fatal	7.430	Dennis [9]
Post-stroke state	3.000	PLATO, Nikolic [8]
Yearly QALY for no event	0.875	PLATO
Yearly QALY decrement		
Myocardial infarction non-fatal MI	0.063	PLATO
Post-myocardial infarction	0.063	PLATO
Stroke non-fatal	0.138	PLATO
Post-stroke	0.138	PLATO

PLATO: PLATelet inhibition and patient outcomes, QALY: Quality-adjusted life years.

Results

The baseline characteristics of patients in the three hospitals are shown in Table 3. In general, the patients were male with an average age of 57 until 66 years old except for stroke hemorrhage, which starts

Table 3: Characteristic of sample in three hospital

Characteristic	STEMI	NSTEMI	Stroke hemorrhage	Stroke non-hemorrhage
Male (%)	82.6	73.9	58.4	57.7
Female (%)	17.4	26.1	41.6	42.3
Age (mean±SD)	57±11.072	59±10.444	57±16.262	62±13.274
National insurance (%)	78.7	82.2	89.4	90

from 40 years old. Furthermore, most of the patients have already used National Health Insurance (BPJS).

Cost of illness

The Markov model was used to see the cost of illness on MI and stroke cases. In each hospital, the costs were different. The cost of illness of MI in Harapan Kita Hospital was USD 1525.40, and costs after MI were USD 165.30, whereas the cost of illness in Binawaluya Hospital was USD 7189.22, and costs after MI were USD 1848.26. Meanwhile, the cost of illness of MI disease in Sardjito Hospital was USD 3546.80, and costs after MI were 1848.26 (Table 4).

The cost of stroke illness in Harapan Kita Hospital was USD 127.30, and after stroke was USD 147.90. The cost of illness in Binawaluya Hospital was USD 3733.52, and the cost after stroke was USD 1576.08. In comparison, the cost of illness of MI in Sardjito Hospital was USD 3733.52, and costs after MI were USD 1848.26 (Table 4).

Table 4: Costs of illness of ACS in three hospitals

Cost of illness (USD)	National cardiac center hospital	Cardiac private hospital	General public hospital
Myocardial infarction	1525.4	7189.22	3546.8
Post-myocardial infarction	165.3	1848.26	1848.26
Stroke	127.3	3733.52	3733.52
Post-stroke	147.9	1576.08	1576.08
No event	165.3	1848.26	1848.26

Currency 1 USD=13.759 IDR, ACS: Acute coronary syndrome.

Compared with no event's costs, it showed that the cost of illness of MI was the highest. Patients who had a stroke showed the cost was also high, but the cost was still less than those of MI, except in Harapan Kita, where the cost of the stroke was less than patients who did not get any event.

We calculated every cost based on the diagnosis from all patient data. The majority of the expenses were direct costs. We only calculated administration, accommodation, and ambulance costs for indirect costs. It showed that the cost of the procedure contributed most of the total cost in each hospital (USD 208.25). Costs of drugs used by patients were the second highest cost (USD 1013.61).

Based on the diagnosis, coronary artery disease (CAD) (USD 5902.09) had the highest cost compared to other diagnoses, and non-ST-elevation myocardial infarct (USD 3437.86) had the lowest cost. There was an elevated cost of CAD disease and stroke hemorrhagic, particularly with other drugs (>USD 1000). The overall expenses showed that in 1 year, patients spent $4138.88 on therapy (Table 5).

Case-base analysis

The results of the 5-year decision tree showed that the QALYs and life years in the three hospitals got the precisely same incremental point, the QALYs were gained 0.0410, and the life year was gained 0.0462. This result showed that ticagrelor has slight effects than clopidogrel. The cost of ticagrelor in every hospital was different and depended on the illness. Patients with ACS with no event and stroke showed the costs of ticagrelor higher than clopidogrel. Other findings consistently showed a negative incremental value for ACS patients with MI and death. The ICER in CPH was USD 2471.392, NCCH was USD 5453.987, and GPH was USD 2343.269 (Tables 6-8).

The lifetime result showed higher effects, both in terms of life-year gained (LYG) of 0.0947, and QALYs gained 0.0828 in each hospital. The costs of ticagrelor were higher than clopidogrel. The outcome was the same as the deterministic 5-year assessment. Patients with stroke disease had no event showed higher costs to spend than clopidogrel. Besides, patients with MI and those who died showed that the costs of ticagrelor were less than clopidogrel. The ICER incremental per QALY showed in CPH was USD 2390.276, NCCH was USD 3813.638, and GPH was USD 1278.361 (Tables 6-8).

Table 6: Summary of deterministic analysis discounted cost-effectiveness results for a lifetime and 5 years in General Public Hospital (GPH)

Cost (USD)	Ticagrelor	Clopidogrel	Incremental	ICER
Lifetime				
Study drug	299.48	33.32	266.16	
No event (ACS related)	6853.45	6823.17	30.28	
MI related	818.28	916.63	−98.35	
Stroke related	96.42	90.28	6.14	
Death related	339.65	438.09	−98.44	
Total cost	8407.28	8301.49	105.79	
Outcomes				
Life years	7.0751	6.9804	0.0947	1117.047
QALYs	6.0543	5.9716	0.0828	1278.361
Five years				
Study drug	299.48	33.32	266.16	
No event (ACS related)	6421.22	6400.31	20.91	
MI related	663.32	761.55	−98.24	
Stroke related	86.44	80.7	5.75	
Death related	339.65	438.09	−98.44	
Total cost	7810.11	7713.98	96.14	
Outcomes				
Life years	3.9354	3.8892	0.0462	2081.369
QALYs	3.4070	3.3660	0.0410	2343.269

ACS: Acute coronary syndrome, QALYs: Quality-adjusted life years.

Sensitivity analysis

The probabilistic sensitivity analysis performed 10.000 simulations and ran in the multiway analysis. For a lifetime, the ICER per QALY of probability sensitivity analysis was USD 0.204. The case-base results are

Table 5: Table of detail cost in three hospitals

Diagnosis	Number	Cost										Total cost
		Admin	Room	Ambulance	Gas	Laboratory	Drugs	Procedure	Facility of health	Physiotherapy	Radiology	
CAD	628	17.88	186.19	2.27	53.44	62.24	2744.53	2833.54	-	-	1.99	5902.09
STEMI	713	490.05	67.76	1.5	18.09	147.1	412.68	2193.22	0.01	2.46	181.06	3513.94
NSTEMI	560	594.93	59.91	0.8	13.4	195.3	297.6	2051.89	0.2	5.59	218.41	3437.86
SH	243	58.32	413.31	16.92	235.36	60.12	1228.54	2334.01	-	1.04	4.41	4352.04
SNH	745	236.2	414.81	11.23	106.12	128.66	597.73	2159.84	0	5.22	48.26	3708.09
Total	2889	305.96	210.54	5.34	65.84	125.93	1013.61	2308.25	0.01	3.13	100.27	4138.88

CAD: Coronary artery disease, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction.

Table 7: Summary of deterministic analysis discounted cost-effectiveness results for a lifetime and 5 years horizons in National Cardiac Centre Hospital (NCCH)

Cost	Ticagrelor	Clopidogrel	Incremental	ICER
Lifetime				
Study drug	299.48	33.32	266.16	
No event (ACS related)	13,039.1	12,833.31	205.79	
MI related	1804.29	1917.01	−112.72	
Stroke related	284.21	270.9	13.31	
Death related	194.39	251.36	−56.96	
Total cost	15,621.48	15,305.89	315.58	
Outcomes				
Life years	7.70751	6.9804	0.0947	3332.402
QALYs	6.0543	5.9716	0.0828	3813.638
Five years				
Study drug	299.48	33.32	266.16	
No event (ACS related)	8206.39	8105.39	101	
MI related	855.39	949.86	−94.47	
Stroke related	139.08	131.05	8.02	
Death related	194.39	251.36	−56.96	
Total cost	9694.73	94,970.97	223.76	
Outcomes				
Life years	3.9354	3.8892	0.0462	4844.411
QALYs	3.407	3.366	0.041	5453.987

ACS: Acute coronary syndrome, QALYs: Quality-adjusted life years.

robust for likely changes in input parameters. The sensitivity analysis results were plotted on the cost-effectiveness plane (Figure 2). The results in the plane showed that the increase of incremental QALYs followed increased incremental costs in most of the simulations. The plane showed only some results plotted under the horizontal line in cost-effectiveness.

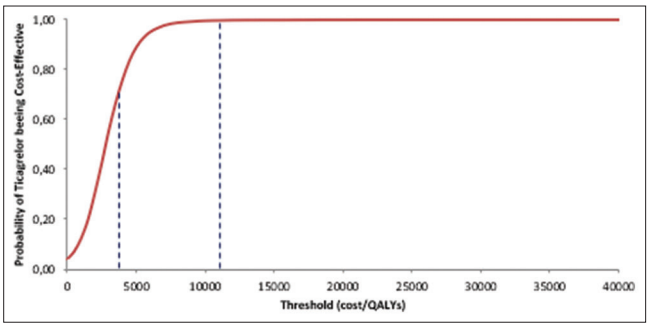

Figure 2: Cost-effectiveness acceptability curve of ticagrelor in three hospitals

For the acceptability of sensitivity analysis shown in Figure 2, we used Indonesian GDP as an acceptability baseline. One GDP was USD 3900, and

Table 8: Summary of deterministic analysis discounted cost-effectiveness results for a lifetime and 5 years horizons in cardiac private hospital

Cost	Ticagrelor	Clopidogrel	Incremental	ICER
Lifetime				
Study drug	299.48	33.32	266.16	
No event (ACS related)	17,705.03	174,797.79	207.24	
MI related	2600.87	2776.83	−175.95	
Stroke related	323.81	308.27	15.54	
Death related	387.84	503.03	−115.19	
total cost	21,317.03	21,119.24	197.8	
Outcomes				
Life years	7.0751	6.9804	0.0947	2088.652
QALYs	6.0543	5.9716	0.0828	2390.276
Five years				
Study drug	299.48	33.32	266.16	
No event (ACS related)	12,872.32	12,769.87	102.46	
MI related	1440.64	1602.92	−162.28	
Stroke related	178.68	168.43	10.25	
Death related	387.84	503.03	−115.19	
Total cost	15,178.96	15,077.57	101.39	
Outcomes				
Life years	3.9354	3.8892	0.0462	2195.172
QALYs	3.407	3.366	0.041	2471.392

ACS: Acute coronary syndrome, QALYs: Quality-adjusted life years.

ICER of GPH (2343.269) and CPH (2471.392) was shown under one GDP in a 5-year trial. Only the ICER of NCCH is above the one GDP [10]. All ICERs from three hospitals were under one GDP for the lifetime analysis. The probability of ticagrelor is cost effective was 66.6% on a 5-year and 99.7% on lifetime with WTP USD 3634. It means ticagrelor considered highly cost effective compared to clopidogrel.

Long-term Markov trial was used to calculate the costs and QALYs of the patients for 5 years and lifetime horizon [11]. About 3% is used as a discount rate to maintain the value of the result each cycle in the Markov model. We used the hazard ratio to predict the risk of death in the Markov cycle. The higher hazard ratio was 7.43 in non-fatal stroke. The result of 5 years and lifetime trials showed QALYs and life years slightly higher than using clopidogrel. Besides, the total cost spent on ticagrelor is higher than clopidogrel. It assumed that clopidogrel dominated by ticagrelor for the effects.

Discussion

This study is an economic analysis of ticagrelor in the Indonesian setting. We use Indonesian data and the PLATO trial to make a 1-year decision tree and compare clopidogrel on ACS patients. Markov model was run to calculate the results in every model time horizon (5 years and lifetime). We use 3% as the discount rate on the Markov trial based on Indonesian data to maintain the value from each cycle.

The result showed QALYs and life years slightly higher in ticagrelor than those in clopidogrel. Compared from each horizon time, QALYs and life year had a higher value in lifetime trial (life year 0.0947 and QALYs 0.0828) than in 5-year trial (QALYs 0.0410 and life year 0.0462). It is assumed that using ticagrelor can increase the patients' quality of life for a long time. However, this study found that the costs of ticagrelor are higher than clopidogrel. This study result also corresponds with a modeling study using the Markov model in Hong Kong that 0.046 QALY per patient was gained by ticagrelor over 5 years compared to clopidogrel [12]. Furthermore, the modeling study in Hong Kong suggests that ticagrelor can save direct medical treatment cost up to USD 369 per patient over a lifetime [12].

To see the acceptability of ticagrelor in Indonesia, we calculate the ICER in three hospitals as representative private and public hospitals in Indonesia. Using Indonesia GDP1 as a threshold, we compare the ICER value of each hospital.Within 5-year horizon, the ICER of Binawaluya Hospital and Sardjito Hospital were under the value of 1 GDP. Besides, the ICER of Harapan Kita Hospital was higher than one value of

GDP value but still under of 3 times GPD. The tree showed that 66% of using ticagrelor was highly cost effective in the 5-year decision.

Furthermore, for the lifetime horizon, all ICER values from each hospital got under the GDP1. It showed that 99.7% for a lifetime was highly cost effective than clopidogrel. This finding corresponds with the study result in Hong Kong, where the ICER of the therapy is below 1 GDP per capita with a 90% probability of being cost effective [12].

This study finding, and other previous studies in Asia, agreed that ticagrelor would be more cost effective for a longer period of use [12], [13], [14]. The initially higher cost of ticagrelor is counterbalanced by the higher efficacy and safety of ticagrelor, resulting in higher cost-effectiveness over a longer period [12]. However, based on a study in five Asian countries showing no cost-effectiveness at 12-month use of ticagrelor, it seemed likely that the ticagrelor to be cost effective later than 12 months [12], [15].

Probability analysis was run using multiway and plotted in the plane. The probability showed that increased incremental QALYs followed with increased incremental costs. Some plots showed that using ticagrelor can gain more QALYs and cost savings. The result of the probabilistic analysis was robust after being done in 10,000 simulations.

A study of ticagrelor compared to clopidogrel in ACS patient was done in many countries [3], [13], [16], [17], [18]. The same result was obtained in a Canadian study that showed ticagrelor was more cost effective than clopidogrel [19]. In addition, a study in Thailand [14] using the Markov model and Plato as baseline showed the same result where ticagrelor was more cost effective than clopidogrel and acceptable because the cost was still below the threshold in Indonesia. A THEMIS study in Swedish suggested that ticagrelor is also cost effective in coronary artery patients with type-2 diabetes comorbidity [20]. It shows that ticagrelor cost-effectiveness is potentially studied further for varied clinical characteristics of complications (CV death, MI, stroke, etc.), combination with other treatments, and comorbidities (diabetes, hypertension, etc.).

The TREAT study (Ticagrelor in Patients with ST-Elevation MI Treated with Pharmacological Thrombolysis) indicates that ticagrelor administration after fibrinolytic treatment did not substantially decrease the frequency of CV events compared to clopidogrel [21]. Nevertheless, we demonstrated a solid 5-year and lifetime trial multiway sensitivity assessment showing that ticagrelor was more cost efficient than clopidogrel.

In a Markov model, an individual's health is classified as a discrete state, and individuals change from state to state at a fixed time interval with dynamical probabilities [22], [23]. Due to the nature of human physiology, which is complicated and time varying, the characterization of a person's health with a limited amount of discrete conditions is a rough estimation of the real-world condition. The extension of the Markov model structure with tracker variables during the simulation and submodels for a disease that captures a more vibrant representation of comorbidities could address these limits [24].

Conclusion

Quality-adjusted Life Years (QALYs) and Life Years Gained (LYG) are higher in the ticagrelor compared to those in clopidogrel. The incremental of cost-effectiveness ratio in 5 years and lifetime model showed under of 1 time GDP, it means that the use of ticagrelor was vastly cost effective and acceptable to apply in the Indonesian clinical setting.

Authors' Contributions

All authors have fulfilled the criteria of authorship. Authors contributed to the study conception/design. The first draft of the manuscript was written by Jarir At Thobari, and all authors commented on previous versions of the manuscript. This manuscript has been read and approved for submission by all the named authors.

References

1. Kowalczyk M, Banach M, Mikhailidis DP, Hannam S, Rysz J. Ticagrelor--a new platelet aggregation inhibitor in patients with acute coronary syndromes. An improvement of other inhibitors? Med Sci Monit. 2009;15(12):Ms24-30.
   PMid:19946242
2. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, *et al*. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The ONSET/OFFSET study. Circulation. 2009;120(25):2577-85. https://doi.org/10.1161/circulationaha.109.912550
   PMid:19923168
3. Henriksson M, Nikolic E, Ohna A, Wallentin L, Janzon M. Ticagrelor treatment in acute coronary syndrome is cost-effective in Sweden and Denmark. Scand Cardiovasc J. 2014;48(3):138-47. https://doi.org/10.3109/14017431.2014.902494
   PMid:24650118
4. Henriksson M, Janzon M. Cost-effectiveness of ticagrelor in acute coronary syndromes. J Expert Rev Pharmacoeconomics Outcomes Res. 2013;13(1):9-18. https://doi.org/10.1586/erp.12.89
5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H,

Held C, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. J N Engl J Med. 2009;361(11):1045-57. https://doi.org/10.1056/nejmoa0904327
PMid:19717846

6. Kang HJ, Clare RM, Gao R, Held C, Himmelmann A, James SK, *et al*. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: A retrospective analysis from the platelet inhibition and patient outcomes (PLATO) trial. Am Heart J. 2015;169(6):899-905.e1. https://doi.org/10.1016/j.ahj.2015.03.015
PMid:26027629
7. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: Alternative approaches. J Bull World Health Organ. 2014;93(2):118-24. https://doi.org/10.2471/blt.14.138206
PMid:25883405
8. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: Results from the PLATO study. Eur Heart J. 2013;34(3):220-8. https://doi.org/10.1093/eurheartj/ehs149
PMid:22719022
9. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: The oxfordshire community stroke project. J Stroke. 1993;24(6):796-800. https://doi.org/10.1161/01.str.24.6.796
10. Cowper PA, Pan W, Anstrom KJ, Kaul P, Wallentin L, Davidson-Ray L, *et al*. Economic analysis of ticagrelor therapy from a US perspective: Results from the PLATO study. J Am Coll Cardiol. 2015;65(5):465-76. https://doi.org/10.1016/j.jacc.2014.11.034
PMid:25660925
11. Liew D, Lourenço RD, Adena M, Chim L, Aylward P. Cost-effectiveness of 12-month treatment with ticagrelor compared with clopidogrel in managing acute coronary syndromes. J Clin Ther. 2013;35(8):1110-7.e9. https://doi.org/10.1016/j.clinthera.2013.06.015
PMid:23891361
12. Wu DB, Choon JW, Chong CW, Lee BS, Lee KK. Economic evaluation of ticagrelor in treating patients with acute coronary syndrome in Hong Kong: A Cost-Utility analysis. Int J Health Econ Policy. 2020;5(3):63-71. https://doi.org/10.11648/j.hep.20200503.13
13. Chin CT, Mellstrom C, Chua T, Matchar DB. Lifetime cost-effectiveness analysis of ticagrelor in patients with acute coronary syndromes based on the PLATO trial: A Singapore healthcare perspective. Singapore Med J. 2013;54(3):169-75. https://doi.org/10.11622/smedj.2013045
PMid:23546032
14. Wu B, Tobe RG, Liu Y, He B. Health economic analysis of antiplatelet therapy for acute coronary syndromes in the context of five eastern Asian countries. Clin Drug Invest. 2018;38(7):621-30. https://doi.org/10.1007/s40261-018-0649-x
PMid:29713921
15. Yamwong S, Permsuwan U, Tinmanee S, Sitara P. Long-term cost-effectiveness of ticagrelor in patients with acute coronary syndromes in Thailand. Health Econ Rev. 2014;4(1):17. https://doi.org/10.1186/s13561-014-0017-3
PMid:26208920
16. Fanari Z, Weiss S, Weintraub WS. Cost-effectiveness of antiplatelet and antithrombotic therapy in the setting of the acute coronary syndrome: Current perspective and literature review. Am J Cardiovasc Drugs. 2015;15(6):415-27. https://doi.org/10.1007/s40256-015-0131-6
PMid:26068886
17. Gasche D, Ulle T, Meier B, Greiner RA. Cost-effectiveness of ticagrelor and generic clopidogrel in patients with the acute coronary syndrome in Switzerland. Swiss Med Wkly. 2013;143:w13851. https://doi.org/10.4414/smw.2013.13851
PMid:24089294
18. Theidel U, Asseburg C, Giannitsis E, Katus H. Cost-effectiveness of ticagrelor versus clopidogrel for preventing atherothrombotic events in adult patients with the acute coronary syndrome in Germany. Clin Res Cardiol. 2013;102(6):447-58. https://doi.org/10.1007/s00392-013-0552-7
PMid:23474908
19. Grima DT, Brown ST, Kamboj L, Bainey KR, Goeree R, Oh P, *et al*. Cost-effectiveness of ticagrelor versus clopidogrel in patients with acute coronary syndromes in Canada. Clinicoecon Outcomes Res. 2014;6:49-62. https://doi.org/10.2147/ceor.s51052
PMid:24493930
20. Steg P, Bhatt DL, James SK, Darlington O, Hoskin L, Simon T, *et al*. Cost-effectiveness of ticagrelor in patients with type 2 diabetes and coronary artery disease with a history of PCI: An economic evaluation of THEMIS-PCI using a Swedish healthcare perspective. Eur Heart J. 2020;41(Suppl_2):ehaa946-3538. https://doi.org/10.1093/ehjci/ehaa946.3538
21. Berwanger O, Lopes RD, Moia DDF, Fonseca FA, Jiang L, Goodman SG, *et al*. Ticagrelor versus clopidogrel in patients with stemi treated with fibrinolysis: TREAT trial. J Am Coll Cardiol. 2019;73(22):2819-28. https://doi.org/10.1016/j.jacc.2019.03.011
PMid:30898608
22. Schuetz CA, Ong SH, Bluher M. Clinical trial simulation methods for estimating the impact of DPP-4 inhibitors on cardiovascular disease. Clinicoecon Outcomes Res. 2015;7:313-23. https://doi.org/10.2147/ceor.s75935
PMid:26089691
23. Coleman CI, Limone BL. Cost-effectiveness of universal and platelet reactivity assay-driven antiplatelet therapy in acute coronary syndrome. Am J Cardiol. 2013;112(3):355-62. https://doi.org/10.1016/j.amjcard.2013.03.036
PMid:23631863
24. Capodanno D, Buccheri S, Romano S, Capranzano P, Francaviglia B, Tamburino C. Decision analytic markov model weighting expected benefits and current limitations of first-generation bioresorbable vascular scaffolds: Implications for manufacturers and next device iterations. Circ Cardiovasc Interv. 2018;11(1):e005768. https://doi.org/10.1161/circinterventions.117.005768