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Cost Effectiveness Analysis of Rivaroxaban Compared to Warfarin and Aspirin for Stroke Prevention Atrial Fibrillation (SPAF) in the Indonesian healthcare setting

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ABSTRACT

Main drugs used in the prevention of stroke among atrial fibrillation (AF) patients are antiplatelets (aspirin) and oral anticoagulants (OAC). OAC therapy can be difficult to administer due to drug and food interactions, adds the burden of required blood monitoring, narrow therapeutic window, and requirements for dose titration. Rivaroxaban is a single-dose oral anticoagulant which does not require blood monitoring, dose titration or has dietary interactions. Phase III clinical data from the ROCKET trial have recently been reported the non-inferiority of rivaroxaban over warfarin for the prevention of strokes in AF patients. To develop an economic model evaluating the clinical and cost-effectiveness of rivaroxaban for the prevention of stroke in non-valvular AF patients in the Indonesian health care settings. We conducted cost effectiveness analysis from the perspective of payer (national health insurance). Effectiveness data used the international data from previous RCT and network metaanalysis studies. Costs data used local data of Indonesia from national health insurance's reimbursement tariffs. Markov model was used, comprised of health and treatment states describing the management and consequences of AF. The main analysis was based on data from the phase III trials. Three months was used as cycle length. The time horizon was set at patients' lifetime (20 years). Costs and outcomes were discounted at a 3% annual rate. Subgroup analysis and extensive sensitivity analysis was conducted. Willingness to pay (WTP) threshold in Indonesia was set as 3 times GDP of Indonesia in 2015, equal about IDR 133,375,000 per quality-adjusted life year (QALY). Base case rivaroxaban vs warfarin has ICER of IDR 141,835,063per QALY at the current cost of rivaroxaban IDR 23,500 and ICER of 130,214,687 per QALY at the proposed cost of rivaroxaban IDR 22,000. One-way sensitivity analysis showed that the key drivers of cost-effectiveness were the utility decrement applied to stable warfarin patients, discontinuation/subsequent discontinuation rates for rivaroxaban, and discontinuation/subsequent discontinuation rates for warfarin. The probabilistic sensitivity analysis suggested that rivaroxaban was cost-effective compared to warfarin in about 45% of cases at the WTP per QALY. Rivaroxaban with the proposed price of IDR 22,000 was considered to be cost-effective when compared to warfarin.

Keyword: Rivaroxaban, warfarin, stroke, patient

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and associated with an increased risk of ischemic stroke by four to five folds (Reiffeld, 2014). Stroke caused by AF has higher morbidity and mortality than a stroke caused by another factor, possibly due to older age and more comorbidities in patients with AF-associated stroke. The risk of stroke in AF patients increases progressively with age, ranging from 1.5% in 50-59 year group to 23.5% in 80-89 year group (Alberts *et al*., 2012).

Scoring system is used to assess stroke risk in a patient with AF. The most widely used model is $CHADS_2$ stratification scheme, consist of five independent predictors of stroke risk in patients with nonvalvular AF (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, and prior Stroke or TIA). The maximum score is 6 points, with 1 point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus; and 2 points for prior stroke or TIA (Furie *et al.,* 2012). This scoring system categorizes nonvalvular AF patient to low risk ($CHADS_2$ score = 0), moderate risk ($CHADS_2$ score = 1), and high risk ($CHADS_2$ score ≥ 2) (Cartman *et al.,* 2013). Low-risk patients receive no treatment or aspirin, while high-risk patients should receive oral anticoagulation. Moderate risk patients can either treated by aspirin or oral anticoagulation (Cartman *et al.,* 2013; Lane *et al.,* 2012).

The European Society of Cardiology guidelines recommends the use of Vitamin K Antagonist (VKA) such as warfarin, or non-VKA such as rivaroxaban as oral anticoagulation for moderate and high-risk patients (Lip *et al.,* 2014). Although warfarin has been standard therapy for high-risk AF patients for decades, it has a narrow therapeutic profile, multiple medications and food interactions, and requires frequent blood coagulation monitoring for controlling INR between 2.0-3.0 (Reddy *et al.,* 2012). Phase III ROCKET-AF trial showed rivaroxaban was non-inferior to warfarin for prevention of all stroke and systemic embolism, and superior to warfarin in safety considering its similar rate of overall bleeding and lower rates of intracranial bleeding, fatal bleeding, and bleeding at critical sites (Fox *et al.,* 2011; Morais *et al.,* 2014).

The objective of this project was to develop an economic model evaluating the cost-effectiveness of rivaroxaban for the prevention of stroke in nonvalvular AF patients in the Indonesian healthcare setting. The secondary objective was to explore the impact on the efficacy of alternative interventions in real-life clinical practice based on findings from a network meta-analysis. As Indonesia is moving towards universal health coverage since 2014, such economic evaluation studies are gaining important as part of health technology assessment for healthcare decision-making.

MATERIAL AND METHODS

Model Structures

The analysis was performed to project the long-term cost-effectiveness of treating AF patients with rivaroxaban compared to warfarin and aspirin for the prevention of stroke in an Indonesian setting. The main analysis was based on data from the phase III trials. The developed model was, therefore, a Markov model, comprised of health and treatment states describing the management and consequences of AF. Costs and outcomes were assigned to each state and used to give an output of cost per quality-adjusted-life-year (QALY). This model was developed in MS Excel to ensure transparency and flexibility.

The population evaluated in the base case scenario was similar to the patient population of the ROCKET clinical trial. They were patients with non-valvular AF and at moderate (CHADS2 risk score of 2) to high risk (CHADS2 risk score of 3 or higher) of stroke. Patients entered the model starting at 60 years of age.

The following subgroups were considered in this model: Current warfarin patients: for this subgroup, the payoffs of the therapy initiation step could be adjusted so that they do not require frequent monitoring; Warfarin-naïve patients; Non-warfarin patients (high-risk patients who have failed warfarin or never received warfarin and received aspirin or no treatment). In addition, modules could be set up so that sequence of active treatment could be considered, such that a patient starting on warfarin might fail and proceeded to either receiving aspirin or no treatment; Patients managed in different settings (e.g. specialist anticoagulation clinic vs. generalist care); Patients at high risk of stroke, including those with a previous stroke: these can be analyzed by adjusting the baseline risk, but the relative treatment effects are currently from ROCKET as a whole population.

Patients entered the model with stable uncomplicated AF and being treated with one of the following interventions: (a) rivaroxaban 20mg, once daily (100% patients on 20mg o.d.), followed

by aspirin once discontinued, (b) rivaroxaban 20mg, once daily (100% patients on 20mg o.d.), followed by no treatment once discontinued, (c) warfarin, target INR of 2.5, 4.5mg, once daily, followed by aspirin once discontinued, (d) warfarin, target INR of 2.5, 4.5mg, once daily, followed by no treatment once discontinued, (e) aspirin, recommended dose 75-325mg, one dose of 160 mg was given in Indonesian practice, or (f) no treatment. Warfarin could also be evaluated using an adjusted effectiveness according to INR control status.

Stroke was categorized into minor if it resulted in minimum residual sequelae and patients were capable of returning to independent living, and major, if it required inpatient rehabilitation after stabilization with residual sequelae which prevented patients from returning to independent living. Another way to determine stroke severity was by using Rankin scores from the ROCKET trial, breaking down the major stroke category into moderate and severe strokes, where the moderate stroke was defined as Rankin score of 3-4, and severe stroke was defined as Rankin score of 5. This breakdown was applied to costs only, and the utility of a major stroke was applied to both moderate and severe strokes.

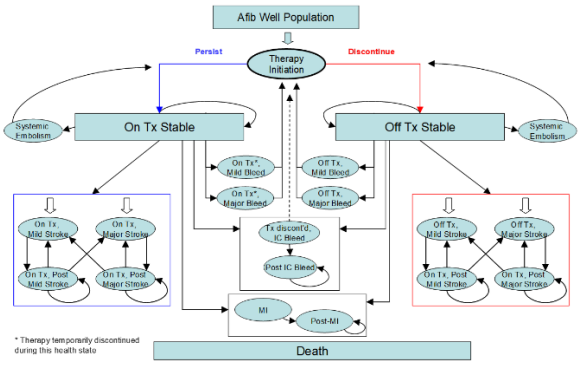

Figure 1. Overall model structure

Patients were always at risk of major complications in the model unless they already experienced an acute event; patients could not experience two acute major complications in the same cycle. The major complications under consideration in this model were an ischemic stroke, systemic embolism, myocardial infarction, and bleeding. Death was included as payoffs of these complications and as background mortality rates. The major events were classified as transient events (non-boxed, see Figure 1) or events with permanent after-effects (boxed). The intracranial (IC) bleeding event might be transient or permanent, depends on the stroke risk of the population. A high-risk population followed the dotted line after experiencing an IC bleed and re-initiating therapy, while low/medium risk patients stayed off anticoagulation in the post- IC bleeding state.

Each health state has a cost and a utility weight which describes quality-of-life associated as a pay-off. These will be summed with the cohort progression and used to calculate the model outputs. The cycle length should be short enough to sufficiently capture the frequency of major events. We used 3 months for the cycle length, as it would allow adequate granularity of events and costs. Published studies used cycle lengths ranging from 30 days to one year. The model's time horizon was set to describe the lifetime of the patients (in the model, it was set to 20 years), in order to fully incorporate the costs and consequences of AF in line with the National Institute for Health and Care Excellence (NICE) guidelines. Costs and outcomes were discounted at a 3% annual rate. Costs were presented in Indonesian currency (IDR) in the year 2012.

The model was constructed for Indonesian healthcare setting and captured anticoagulation management in a secondary care setting. In Indonesia, AF patients are primarily managed by specialists in hospitals. Thus the model was designed to reflect this approach.

Baseline epidemiology data applied in the model were taken from a range of sources, although much of the published data were from Europe. However, resource use and costs reflected the treatment patterns specific to Indonesian healthcare sector. For the present analyses, a payer perspective was adopted, however, the model is capable of considering a wider societal perspective. Productivity loss functionality uses the human capital approach. Other parameters required for the calculation of indirect costs were the average number of days of productivity loss (paid) for each type of event and average labor cost per day.

Clinical effectiveness and treatment discontinuation

The clinical data inputs were obtained from two main sources: the Phase III ROCKET trial or the network meta-analysis (NMA) conducted to allow comparison of rivaroxaban to non-warfarin compa-rators, which were not included in the ROCKET trial. Baseline event rates were set as

Table I. Drug acquisition cost and unit costs for warfarin administration

Drug	Cost per tab (IDR)	Dose	Cost per Day	Reference
Warfarin (2mg)	979	2mg/day	979	E-catalogue (Presidential Regulation, 2014; MoH Regulation, 2014)
Aspirin (80mg)	116	160mg/day	232	E-catalogue (Presidential Regulation, 2014; MoH Regulation, 2014)
Clopidogrel (75mg)	3,400	75mg/day	3,400	E-catalogue (Presidential Regulation, 2014; MoH Regulation, 2014)
Rivaroxaban (20mg)	23,500	20mg/day	23,500	E-catalogue (Presidential Regulation, 2014; MoH Regulation, 2014)
Dabigatran	**12,936**		**25,872**	E-catalogue (Presidential Regulation, 2014; MoH Regulation, 2014)

Table II. Costs for warfarin administration

Item	Unit Cost	Low	High	Reference
Warfarin Monitoring Visit (first ever)	140,850	121,288	167,977	Hospital records (high)
Warfarin Monitoring Visit (subsequent)	121,288	-	-	Hospital records (high)
GP based warfarin monitoring	-	-	-	N/A
Check-ups for other therapy	-	-	-	N/A
Patient Transport Service	-	-	-	N/A
% of patients using transport (payer perspective)	**-**	**-**	**-**	Not reimbursed

Table III. Resource use for warfarin administration

Item	Frequency over three months	Reference
Therapy Initiation Period	12	KOL
Warfarin Monitoring Visit (maintenance phase)	3	BPJS Health insurance
Therapy Re-initiation	4	BPJS Health insurance
Monitoring visits for novel OAC and aspirin users	0	Assumption

either the warfarin arm rates from the ROCKET trial or the placebo arms of clinical trials used in the NMA. Relative risk reductions (RRR) were then applied, using either treatment effects from ROCKET or NMA.

Drug and event cost

We calculated cost by normative-cost approach using the unit cost mostly from national health insurance's reimbursement tariffs and few from hospital records. The daily dose of warfarin was 2mg, based on KOL opinion. The daily dose of aspirin (ASA) for prevention of AF was 160mg. Table I and II shows the drug acquisition costs and the warfarin monitoring costs used in the model, Table III shows the resource use for warfarin administration, and Table IV shows the summary of the costs and references used for the model.Rivaroxaban, aspirin, and dabigatran are all fixed-dose oral therapies that do not require any additional blood monitoring. Thus, any visits related to these therapies were assumed to be included in routine care check-ups. Warfarin requires dose-titration and monitoring visits over the duration of therapy. It is recommended for patients initiated with warfarin for the first time, or after a period of therapy interruption, to see a physician regularly and frequently to adjust the dose of warfarin until the INR is stable, which has a target therapeutic range between 2.0 to 3.0. Once the INR is stabilized, the number of visits may be decreased, but are still

Table IV. A summary of the costs and references used for the model

Event	Base case cost (IDR)	Low (IDR)	High (IDR)	Source
Stroke Treatment Costs				
Acute Treatment – minor	9,026,200	7,521,800	10,530,500	INA CBG 2016 Java-Bali region (MoH Regulation,2016)
Acute Treatment – major	15,145,900	12,621,600	17,670,200	INA CBG 2016 Java-Bali region (MoH Regulation, 2016)
Acute Treatment – excess days	N/A			
Follow-on Care (per quarter) – major stroke	336,085	74,338	757,071	Hospital records
Rehabilitation Costs per day	58,204	29,344	195,626	BPJS Health insurance
Bleed Treatment Costs				
Acute Treatment – minor	9,254,263	7,711,886	10,796,640	INA CBG 2016, Java-Bali region (MoH Regulation, 2016)
Acute Treatment – major	39,512,583	32,927,153	46,098,014	INA CBG 2016, Java-Bali region (MoH Regulation, 2016)
Acute Treatment – IC bleed	8,763,300	7,302,700	12,254,000	INA CBG 2016, Java-Bali region (MoH Regulation, 2016)
Follow-on Care (per quarter) – IC bleeds	336,085	74,338	757,071	Hospital records
Rehabilitation Costs (per quarter)	465,631	29,344	195,626	Assumption [Eight days of rehabilitation (similar with major stroke) at the same cost as post-ischaemic stroke rehabilitation]
SE treatment costs				
Acute treatment	5,902,700	4,919,000	13,020,100	INA CBG 2016 Java-Bali, TIA as a proxy for systemic embolism (MoH Regulation, 2016)
MI treatment costs				
Acute treatment	12,241,100	5,712,800	20,577,400	INA CBG 2016 Region 1, average of inpatient hospital class and severity (MoH Regulation, 2016)
Follow-on care (per quarter)	673,000	641,000	973,300	INA CBG 2016 Region 1, average of outpatient hospital class (1 visit/ quarter) (MoH Regulation, 2016)

required due to the fact that warfarin efficacy is influenced by many factors, including concomitant medication and diet. When patients were re-initiated on therapy, it was assumed that there were some records of the last dose at which the patient remained stable, and thus re-titration would require less frequent visits. The assumption for the number of visits required for re-initiation was based on KOL opinion. The cost per visit differs according to the setting of care where monitoring takes place, whether in general practitioner (GP) office or in the specialised anticoagulation clinic. In the present model, 100% patients were assumed to be treated in anticoagulation clinics in addition, the model has the option of incorporating a cost for using patient transport services to attend anticoagulation clinics. This was not applied for Indonesia as travel costs are not reimbursed.

Health-related outcomes

We used health utility data from previous studies in other settings. These studies used various methods to elicit preference including single measurement using standard gamble and multi-attribute measurement using EQ5D.

Table V. Summary of base case utilities

Health State	Utility	Source
Utility: Stable AF – not on treatment	0.78	Berg *et al*. 2010
Utility: Stable AF – on warfarin treatment	0.94	Robinson *et al.*2001
Utility: Stable AF – on other therapy	0.78	Berg *et al.* 2010
Utility Decrement: Initiating Warfarin treatment	0.94	Robinson *et al*. 2001
Utility: Minor Stroke	0.64	Robinson *et al.*2001
Utility: Post Minor Stroke	0.72	Berg *et al* 2010
Utility: Major Stroke	0.19	Robinson *et al*. 2001
Utility: Post Major Stroke	0.48	Berg *et al* 2010
Utility: Systemic Embolism	0.66	
Utility: Minor Bleed	0.78	Sullivan *et al.* 2006
Utility: Major Bleed	0.60	
Utility: Intracranial Bleed	0.60	Lenert *et al.* 1997
Utility: Post IC Bleed	0.74	Haacke *et al*. 2006
Myocardial Infarction	0.68	Lacey *et al*. 2003
Post Myocardial Infarction	0.69	Sanders *et al*. 2001

A systematic search was performed to identify health state utility values in stable AF, stroke, post-stroke, embolism, myocardial infarction, and bleeding events in a non-valvular AF population. Utility value for stable untreated AF represents the baseline untreated state of an AF patient who is 73 years old (Table V).

Analysis

Subgroup analysis

The model has the capability of incorporating analyses for various subgroups. The potential subgroups described in the sub-headings below have been identified and incorporated into the model: (a) VKA-difficult – high resource use, (b) VKA-difficult – poor INR control, (c) VKA-difficult – high resource use and poor INR control, (d) non-VKA users, (e) high risk of stroke, (f) prior stroke, (g) VKA-naïve, and (h) "user defined".

For the high risk of stroke, prior stroke, and VKA-naïve sub-groups, relative risks were taken from the ROCKET trial (Table VI). The model was set up to use the relative risks from either the safety on-treatment or the intent-to-treat ROCKET populations, depending on which was selected. For the three VKA difficult sub-groups and the non-VKA use sub-group, the relative risks used were based on assumptions (Table V). The ones below are based on SoT data.

The distribution of patient INR status for patients receiving warfarin treatment in an anticoagulation clinic setting was based on Yousef *et al*., (2004) study and those receiving warfarin monitoring via a general practice settings was based on Dolan *et al*. (2008) study.

Sensitivity analysis

Extensive sensitivity analyses were carried out in order to evaluate the findings of the model. One-way sensitivity analyses were carried out to test the impact of varying key parameters on the model outcomes to a worst/best case scenario. Key parameters were varied to low and high values within plausible ranges. For parameters such as clinical efficacy values which are based on robust studies or reviews, the reported 95% CI was used. For parameters for which there are still uncertainties surrounding the source data, ranges reported in the literature were used, in order to ascertain the potential outcome a different data source should be selected. For cost and resource inputs, ranges provided by Bayer were applied.

The probabilistic sensitivity analysis (PSA) is a stochastic analysis conducted to test second-order uncertainty in the model and evaluates the model for overall robustness. For this purpose, random values are simulated in 500 iterations. Random values for each of the key parameters of the model were extracted from a probability distribution characterizing the range of expected values of each variable.

Table VI. Clinical effectiveness

Event	Risk relative to	RR	CI	Source
Relative risk data inputs for High-Risk Stroke sub-group				
Ischemic stroke	Warfarin	0.93	0.74 – 1.18	ROCKET
Systemic embolism	Warfarin	0.21	0.07 – 0.62	ROCKET
Major Bleed	Warfarin	1.11	0.94 – 1.32	ROCKET
Intracranial bleed	Warfarin	0.65	0.45 – 0.93	ROCKET
Relative risk data inputs for Prior Stroke sub-group				
Ischemic stroke	Warfarin	1.0	0.73 – 1.37	ROCKET
Systemic embolism	Warfarin	0.36	0.23 – 0.46	ROCKET
Major Bleed	Warfarin	1.66	0.82 – 3.35	ROCKET
Intracranial bleed	Warfarin	2.28	1.04 – 4.99	ROCKET
Relative risk data inputs for VKA Naïve sub-group				
Ischemic stroke	Warfarin	0.91	0.63 – 1.30	ROCKET
Systemic embolism	Warfarin	0.14	0.02 – 1.15	ROCKET
Major Bleed	Warfarin	1.02	0.77 – 1.34	ROCKET
Intracranial bleed	Warfarin	0.57	0.34 – 0.96	ROCKET
Relative risk data inputs for VKA difficult – High Resource Use sub-group				
Ischemic stroke	Warfarin	0.94	0.75 – 1.17	Assumption
Systemic embolism	Warfarin	0.23	0.09 – 0.61	Assumption
Major Bleed	Warfarin	1.14	0.98 – 1.33	Assumption
Intracranial bleed	Warfarin	0.67	0.47 – 0.93	Assumption
Relative risk data inputs for VKA difficult – poor INR control sub-group				
Ischemic stroke	Warfarin	0.94	0.75 – 1.17	Assumption
Systemic embolism	Warfarin	0.23	0.09 – 0.61	Assumption
Major Bleed	Warfarin	1.14	0.98 – 1.33	Assumption
Intracranial bleed	Warfarin	0.67	0.47 – 0.93	Assumption
Relative risk data inputs for VKA difficult – high resource use and poor INR control sub-group				
Ischemic stroke	Warfarin	0.94	0.75 – 1.17	Assumption
Systemic embolism	Warfarin	0.23	0.09 – 0.61	Assumption
Major Bleed	Warfarin	1.14	0.98 – 1.33	Assumption
Intracranial bleed	Warfarin	0.67	0.47 – 0.93	Assumption
Relative risk data inputs for Non-VKA users sub-group				
Ischemic stroke	Placebo	0.32	0.10 – 0.74	Assumption
Systemic embolism	Placebo	0.41	0.03 – 3.79	Assumption
Major Bleed	Placebo	3.83	0.84 – 17.04	Assumption
Intracranial bleed	Placebo	3.09	0.25 – 26.54	Assumption

RESULT AND DISCUSSION

One-way sensitivity analysis (Figure 2) shows that the key drivers of cost-effectiveness between rivaroxaban vs warfarin based on cost per QALY were the utility decrement applied to stable warfarin patients, discontinuation/ subsequent discontinuation rates for rivaroxaban, and discontinuation/subsequent discontinuation rates for warfarin. PSA results are showed as cost-effectiveness acceptability curves (CEACs) (Figure 3). The willingness-to-pay (WTP) threshold in Indonesia, which is three times the gross domestic product (GDP) per capita, is IDR 133.375.000 per QALY. Indonesia per capita GDP used in this study referred to the World Bank data in the year 2015, which was USD 3,347). The WTP threshold used at the time the study was conducted with the currency rate of 1 USD = IDR 13,285. The CEAC curve shows that, based on 1000 iterations, rivaroxaban was cost-effective compared to warfarin in about 45% of cases at the WTP per QALY of IDR 133.375.000.

This cost-effectiveness study in Indonesian setting using the payer's perspective showed that, when compared with warfarin, treatment with rivaroxaban led to an ICER lower than the

Table VII. Cost-effectiveness ratio

Scenario	Price of Rivaroxaban at the time of analysis (IDR 23,500)		Proposed price of Rivaroxaban (IDR 22,000)	
	Rivaroxaban 15/20mg	Warfarin 2mg	Rivaroxaban 15/20mg	Warfarin 2mg
Total cost (IDR)	47,789,630	21,689,839	45,651,306	21,689,839
Total QALY	4.79	4.61	4.79	4.61
Incremental cost (IDR)	26,099,792		23,961,467	
Incremental QALY	0.18		0.18	
ICER (IDR per QALY)	NA	Rivaroxaban vs Warfarin 141,835,063		Rivaroxaban vs Warfarin 130,214,687

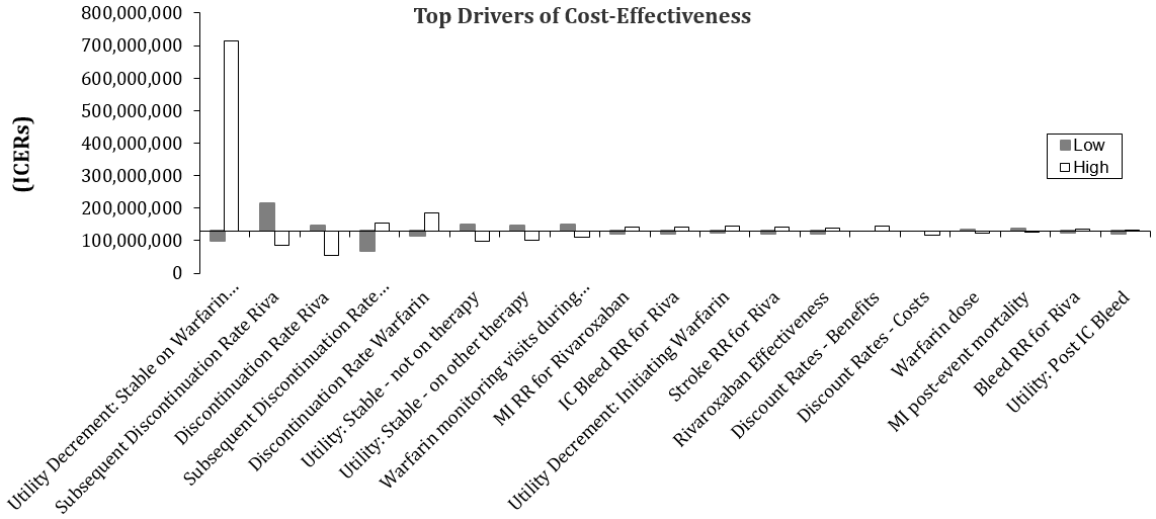

Figure 2. Tornado diagram – ICER vs warfarin

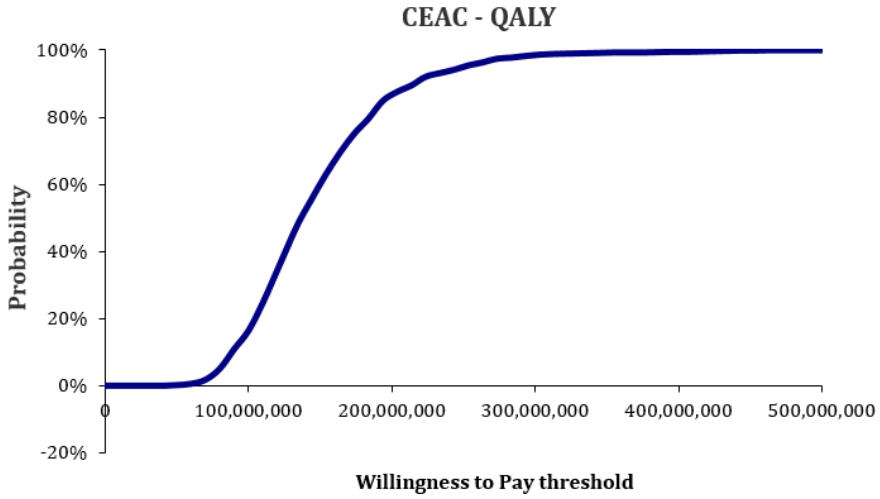

Figure 3. Cost-effectiveness acceptability curve of rivaroxaban vs warfarin

Indonesian WTP of IDR 133.375.000 per QALY.Given the economic variation across Indonesia, it is likely that in some regions rivaroxaban will represent a cost-effective treatment for SPAF.

A study in Belgian setting, which also took the payer perspective and based on the results of the ROCKET trial, showed almost similar results. The incremental QALY was lower in the Belgian setting, but the incremental cost was higher in the Indonesian setting, due to significant different in drug acquisition cost. In Belgian setting, rivaroxaban was cost-effective compared to warfarin to prevent stroke in AF patients. The ICER of rivaroxaban compared to warfarin was quite similar with that in the Indonesian setting (EUR 8,809 per QALY, or around IDR 131.1 million per QALY). However, the Belgian WTP is higher; and even the lowest WTP, EUR 10,000 (= IDR 149 million) in the sensitivity analysis gave 66% cases in which rivaroxaban will be more cost-effective than warfarin (Kleintjens *et al.,* 2013). Another study in the United States of America (USA) with similar perspective showed that rivaroxaban is cost-effective compared to warfarin in preventing stroke in AF patients. The ICER for rivaroxaban vs warfarin was USD 27,498 per QALY (= IDR 365.3 million), but the USA WTP was considerably higher than the Indonesian WTP, resulting in the cost-effectiveness of rivaroxaban over warfarin (Lee *et al.,* 2012). A study in Singaporean setting, with a slightly different perspective from health care system, showed a higher ICER (USD 26,727 per QALY or IDR 355.1 million) compared to this study, with a higher WTP of USD 58,500 (IDR 777.1 million), leads to the cost-effectiveness of rivaroxaban compared to warfarin (Wang *et al.,* 2014).

One-way sensitivity analysis in this study showed the key drivers of the high ICER. When compared with warfarin, the drivers were the utility decrement applied to stable warfarin patients, discontinuation/subsequent discontinuation rates for rivaroxaban, and discontinuation/subsequent discontinuation rates for warfarin.Meanwhile, the PSA showed that, with the current WTP, rivaroxaban with the lower offered price was cost-effective compared to warfarin.

The results of the sensitivity analyses conducted in the base case model settings and other scenarios indicated that model findings were sensitive to a range of parameters in the model. Notably, many sensitivity analyses returned ICERs below the WTP for Indonesia. Nonetheless, it should be considered that uncertainty in cost and resource inputs had a limited impact on findings. During model development, it was also noted that a high rate of background mortality limited opportunities to benefit from stroke prevention in AF patients. As progress is made to reduce background mortality in Indonesia, it is likely that the treatment with rivaroxaban will become more cost-effective.

It should be considered that base case comparisons against warfarin were made using the SOT data set. The safety of treatment is more representative of efficacy in clinical practice but is less conservative. A scenario analysis using ITT data led to a small increase in the base case ICER.

Rivaroxaban is a new oral anticoagulant that offers physicians and patients an opportunity to bridge the treatment gap in AF due to suboptimal warfarin use. Rivaroxaban successfully demonstrated non-inferiority compared to warfarin for the prevention of stroke and systemic embolism and was similar to warfarin on the principal safety outcome of major and non-major clinically relevant bleeding. Patients in the rivaroxaban arm of the ROCKET AF study also had favorable cardiovascular outcomes relative to warfarin, with a statistically significant 15% relative risk reduction in the pre-specified composite secondary endpoint of stroke, non-CNS systemic embolism, myocardial infarction and vascular death. In addition, rivaroxaban showed a trend to lower rates of MI, vascular death, and all-cause mortality compared with warfarin (Patel, 2011).

This study have some limitations. First, this study used health utility parameters from other settings, not from Indonesian measurement. This might influence the result of study since the health utility is influenced by socio-demographic of population. Second, this economic evaluation study used modelling approach to evaluate the cost effectiveness of rivaroxaban compared to warfarin, in which some uncertainties are possible. However, we also presented sensitivity analysis results of the study.

CONCLUSION

The cost-effectiveness analysis showed that rivaroxaban with the offered price is cost-effective compared to warfarin in Indonesian healthcare setting. This study was run with a price per day of rivaroxaban of IDR 23,500. Under consideration of an EJP of IDR 22,000 per day, the cost-effectiveness will be improved.

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