

Research Article

Cost-Effectiveness of Rivaroxaban Compared with Other Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation in Public Sector of Malaysia

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Abstract

Despite the amount of research performed, the cost-effectiveness of direct oral anticoagulants (DOACs) in subpopulations with different risk factors for stroke has been very little studied. This study aims to explore the cost-effectiveness of the DOACs available in Malaysia in preventing stroke in different subpopulations from a government perspective. An existing Markov model was adapted to assess the cost-effectiveness of the DOACs that are available in Malaysia namely, apixaban (AP), dabigatran (DA) and rivaroxaban (RV). Each was compared with vitamin K antagonists (VKA) in stroke prevention in different patient subpopulations including chronic kidney disease (CKD), high-age, diabetes (DM), and prolonged hospital stay. Cost-effectiveness was assessed by the incremental cost-effectiveness ratio (ICER) benchmarked against the local threshold for cost-effectiveness. The total cost of VKA, AP, DA and RV was Malaysian Ringit (RM) RM9,811 (1USD=RM4.76), RM16,858, RM18,318 and RM20,161 respectively. The quality adjusted life-years (QALYs) gained compared with VKA were 6.11, 6.09 and 6.15 respectively. The ICER when compared with VKA at base case was 57,539, -90,682 and 68,156 respectively. AP had the most favourable ICER at base case. RV had the best ICER compared to AP and DA in patients with CKD and DM at a willingness-to-pay threshold of 1-GDP. Probabilistic sensitivity analysis showed that RV was consistently the most favourable DOAC under a threshold of 2-GDP for all subpopulations. These findings suggested that rivaroxaban has the most favourable ICER in the CKD and DM patient subgroups for stroke prevention among the DOACs available in Malaysia at a threshold of 2-GDP.

Keywords

Stroke Prevention, Direct Oral Anticoagulants, Cost-Effectiveness, Diabetes, Chronic Kidney Disease, Threshold, QALY

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1. Introduction

Stroke has been identified as the major cause of disability and death worldwide which is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage [1, 2]. In most Asian countries, the prevalence rate of atrial fibrillation (AF) in the adult population is ~1%. Although lower in prevalence than western countries (estimated ~2%) [3], the prevalence of stroke was expected to increase by 3.4 million people between 2012 and 2030 due to the aging of the population, together with the decrease in case fatality after stroke [4]. Recent data from the Institute for Health Metrics and Evaluation in 2019 indicate a notable increase in stroke cases in Malaysia, ranking it as the third leading cause of mortality and contributing significantly to the nation's disability rate [5]. Hence the economic burden and subsequent impact on the healthcare budget and society is enormous. However, the cost-effectiveness of therapeutic options available for non-valvular atrial fibrillation (NVAF) for stroke prevention in Malaysia has not been systematically evaluated.

Direct oral anticoagulants (DOACs) are relatively new agents demonstrating superiority or noninferiority to prior standards of care which includes anticoagulation with vitamin K antagonists (VKA; ie, warfarin), or low-molecular-weight heparins (LMWHs). DOACs present several advantages over VKAs, including reduced monitoring requirements, less frequent follow-up visits, immediate onset and offset effects of the drug (particularly crucial for periprocedural and acute bleeding management), and fewer interactions with both drugs and food [6].

The cost-effectiveness of DOACs has been well studied on a global and regional basis. Their clinical benefits in stroke prevention have been previously reported by both local and overseas countries. For cost-effectiveness studies of DOACs, the common approaches for evaluation include the use of real-world evidence (RWE) and economic projection models. In South Korea, a study investigated the cost-effectiveness of DOACs and warfarin specifically among AF patients with intermediate stroke as the risk factor by using national representative data. The study showed that both apixaban and rivaroxaban could be considered as cost-effective [7]. Similarly, in Malaysia, an earlier study suggested that DOACs were cost effective compared to warfarin in the treatment of AF-related stroke in a patient cohort from a local medical centre [8]. In another study performed at a similar setting, results suggested that sub-group of AF-related stroke patients, variables such as the severity of stroke, sub-types of strokes (ischemia, haemorrhagic, and unspecified), and patients' discharge disposition status were the factors that significantly affect the cost of stroke treatment [8]. In a Spanish study, DOACs were compared with VKA for stroke prevention in patients with NVAF using a Markov model with input from

real-world data. The results suggested that rivaroxaban and dabigatran were cost-effective compared with VKA [9]. A recent Chinese study utilised a Markov model constructed to compare patients' quality-adjusted life years (QALYs) using drug cost, cost of the examination, and incremental cost of other treatments. Based on a willingness-to-pay threshold of China, rivaroxaban was the most cost-effective choice and warfarin was the least [10]. A recent systematic review showed that NOACs were more cost-effective than VKA but this conclusion probably applies to high-income countries more [11]. Despite the wide research that was performed in stroke prevention, the effect of DOACs in subpopulations with different risk factors for stroke have been very little studied.

Rivaroxaban (RV), apixaban (AP) and dabigatran (DA) are the DOACs currently available in the public sector of Malaysia. This study aims to investigate the cost-effectiveness of the DOACs available in Malaysia in preventing stroke in different subpopulations from a government's perspective. It is hoped that the results will offer insight into this aspect thus bridging existing gaps in knowledge.

2. Materials and Methods

An existing Markov model was adapted to assess the cost-effectiveness of the DOACs that are available in Malaysia namely, RV, AP and DA. Each was compared with VKA in stroke prevention in different patient subpopulations including chronic kidney disease (CKD), high-age, diabetes mellitus (DM), and prolonged hospital stay.

2.1. Model Overview

This analysis was adapted from an existing Markov model assessing the comparative costs and outcomes of RV, DA and AP, each compared with VKA, for the first-line treatment of adult patients with NVAF and with more than one risk factor for stroke [12]. This model was chosen because patient subgroups with different risk factors of strokes, including CKD and DM, were not studied before in Asian populations.

This analysis was from the Malaysian healthcare provider's perspective, with a 30-year time span to fully incorporate the costs and consequences of AF. The cycle length was set to three months which was considered short enough to sufficiently capture the frequency of major events and to allow adequate granularity of events and costs. Both future costs and future quality-adjusted life years (QALYs) are discounted at 3.5% per annum.

This model comprises a series of health states based on potential complications of NVAF (stable AF, acute and post-major ischaemic stroke (IS), acute and post-minor IS, acute and post-myocardial infarction (MI), acute and post-intracranial haemorrhage (ICH) and gastrointestinal (GI) bleed), and the absorbing state of death (Figure 1). Patients on

VKA and each of the studied DOACs were to transit through the model in cycles of 3 months, accumulating QALYs associated with each health state, together with the costs of

treatment, events, and subsequent monitoring. All model inputs are presented in Table 1.

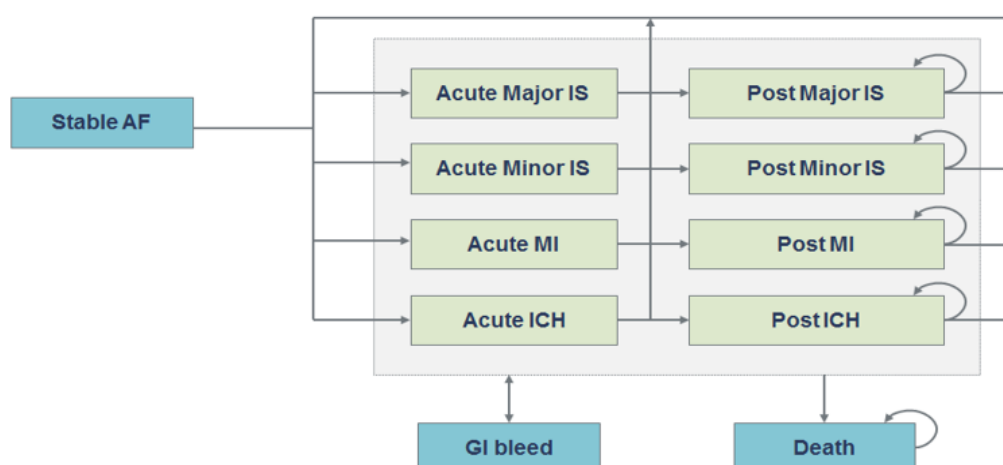


Figure 1. Schematic illustration of model. The model comprises a series of health states based on potential complications of NVAf (stable AF, acute and post-major IS, acute and post-minor IS, acute and post-MI, acute and post-ICH and GI bleed), and the absorbing state of death. Patients on VKA and each of the studied DOACs were transit through the model in cycles of 3 months, accumulating QALYs associated with each health state, together with the costs of treatment, events, and subsequent monitoring.

Table 1. Summary of model inputs.

	Value	Range in DSA	Distribution in PSA	Refer-ences
Clinical values				
Pr major stroke - Rivaroxaban	0.227%	(0.21%, 0.24%)	Beta (819, 360,359)	16
Pr minor stroke - Rivaroxaban	0.072%	(0.07%, 0.08%)	Beta (821, 1,138,660)	16
Pr Myocardial infarction - Rivaroxaban	0.225%	(0.2%, 0.25%)	Beta (280, 124,175)	16
Pr GI Bleed - Rivaroxaban	0.687%	(0.64%, 0.74%)	Beta (694, 100,280)	16
Pr ICH - Rivaroxaban	0.333%	(0.3%, 0.37%)	Beta (444, 132,953)	16
Pr major stroke - Dabigatran	0.221%	(0.2%, 0.24%)	Beta (538, 243,383)	16
Pr minor stroke - Dabigatran	0.070%	(0.06%, 0.08%)	Beta (539, 768,976)	16
Pr Myocardial infarction - Dabigatran	0.254%	(0.22%, 0.3%)	Beta (192, 75,285)	16
Pr GI Bleed - Dabigatran	0.636%	(0.57%, 0.7%)	Beta (398, 62,145)	16
Pr ICH - Dabigatran	0.313%	(0.19%, 0.22%)	Beta (252, 80,144)	16
Pr major stroke - Apixaban	0.202%	(0.06%, 0.07%)	Beta (650, 320,870)	16
Pr minor stroke - Apixaban	0.064%	(0.23%, 0.25%)	Beta (650, 1,013,536)	16
Pr Myocardial infarction - Apixaban	0.240%	(0%, 0%)	Beta (1600, 665,788)	16
Pr GI Bleed - Apixaban	0.489%	(0.25%, 0.32%)	Beta (444, 90,300)	16
Pr ICH - Apixaban	0.279%	(0.19%, 0.22%)	Beta (311, 111,339)	16
Pr major stroke - VKA	0.311%	(0.3%, 0.32%)	Beta (5613, 1,801,672)	16
Pr minor stroke - VKA	0.099%	(0.1%, 0.1%)	Beta (5625, 5,699,430)	16
Pr Myocardial infarction - VKA	0.240%	(0.23%, 0.25%)	Beta (1600, 665,788)	16

	Value	Range in DSA	Distribution in PSA	Refer-ences
Pr GI Bleed - VKA	0.568%	(0.56%, 0.58%)	Beta (10739, 1,878,734)	16
Pr ICH - VKA	0.387%	(0.38%, 0.4%)	Beta (6725, 1,732,154)	16
Probability of mortality from major stroke	25.57%	(25.09%, 26.05%)	Beta (7996, 23,276)	16
Probability of mortality from GI bleed	14.63%	(13.74%, 15.52%)	Beta (882, 5,147)	16
Probability of mortality from Post-major stroke	8.12%	(7.35%, 8.92%)	Beta (390, 4,410)	16
Probability of mortality from Post IC bleed	14.11%	(11.85%, 16.57%)	Beta (128, 781)	16
Probability of mortality from ICH	28.50%	(24.23%, 32.78%)	Beta (122, 306)	16
Probability of mortality from MI	24.67%	(23.79%, 25.55%)	Beta (2257, 6,893)	16
Probability of mortality from Post-MI	8.24%	(7.17%, 9.34%)	Beta (211, 2,347)	16
Utility values				
Stable AF	0.80	(0.78, 0.82)	Beta (1425, 361)	17
Minor IS	0.67	(0.57, 0.77)	Beta (56, 28)	18
Major IS	0.38	(0.32, 0.44)	Beta (56, 28)	18
Post minor IS	0.67	(0.57, 0.77)	Beta (105, 172)	18
Post major IS	0.56	(0.48, 0.64)	Beta (75, 59)	18
GI bleeding	0.70	(0.60, 0.81)	Beta (51, 22)	20
IC bleeding	0.56	(0.48, 0.64)	Beta (75, 59)	18
Post IC bleeding	0.67	(0.57, 0.77)	Beta (56, 27)	18
MI	0.72	(0.61, 0.83)	Beta (46, 18)	19
Post MI	0.80	(0.68, 0.92)	Beta (34, 9)	19
Cost (RM)				
Rivaroxaban daily cost	6.74	(5.06, 8.43)	Gamma (61, 0.11)	MI*
Dabigatran daily cost	6.84	(5.13, 8.55)	Gamma (61, 0.11)	MI*
Apixaban daily cost	6.54	(4.91, 8.18)	Gamma (61, 0.11)	MI*
VKA daily cost	0.39	(0.29, 0.49)	Gamma (61, 0.01)	24
Acute Treatment - minor	3,224	(2,418, 4,030)	Gamma (61, 52)	8
Acute Treatment - major	4,571	(3,428, 5,714)	Gamma (61, 74)	8
Follow up costs - Minor (per cycle)	534	(336, 777)	Gamma (200, 3)	8
Follow up costs - Major (per cycle)	1,134	(572, 1,884)	Gamma (102, 11)	8
Rehabilitation Costs	418	(314, 523)	Gamma (61, 7)	22
Acute Treatment	19,381	(14,536, 24,227)	Gamma (61, 315)	21
Follow up costs - MI (per cycle)	474	(391, 564)	Gamma (8, 60)	21
Acute Treatment - GI bleed	5,876	(4,407, 7,345)	Gamma (61, 96)	22
Acute Treatment - IC bleed	10,749	(8,062, 13,436)	Gamma (61, 175)	22
Follow up costs - Bleeds	1,469	(572, 1,884)	Gamma (1138, 1)	22
Rehabilitation Costs	261	(196, 326)	Gamma (61, 4)	23

* Abbreviation: DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; Pr, probability; GI, gastrointestinal; ICH, intracranial haemorrhage; VKA, vitamin K antagonists; IC, intracranial; MI, myocardial infarction; AF, atrial fibrillation; IS, ischaemic stroke; MI*, market intelligence.

Cost-effectiveness of a health technology is generally based on the incremental cost-effectiveness ratio (ICER) defined as the difference in cost between two possible interventions, divided by the difference in their effect, and the unit is usually dollar per QALY gained. In Malaysia, the national threshold for cost-effectiveness is based on an earlier recommendation by the World Health Organisation (WHO) which suggests any technology that is less than 1 to 3 times gross domestic product (GDP) per capita per QALY gained is considered to be cost-effective [13]. The GDP per capita of Malaysia in 2022 was USD11,972 (1USD=RM4.74) (RM56,028 est.) [14] and hence any intervention with an ICER less than RM56,028 should be considered as very cost-effective. If the ICER exceeds 3 times GDP i.e. RM168,084, the intervention will be deemed as not cost-effective. There is also an alternative approach used by some previous local studies. This is the willingness-to-pay (WTP) approach which was reported in an earlier study that the Malaysian WTP threshold ranges between RM 19,929 and RM 28,470 [15]. An intervention is considered cost-effective if its ICER lies within this range. However, this latter approach may not be so update as the range values will change in the real-world environment after a certain period. In such circumstances, the GDP approach may be a better reflection of the affordability of Malaysia.

2.2. Clinical Data and Transition Probabilities

RWE was used to inform clinical event rates for VKA, while rates for DOACs, including RV, AP and DA; were estimated by applying relevant RWE hazard ratios (HRs) to the VKA transition probabilities [16] (Table 1). All estimated annual rates were converted to 3-month probabilities before implementation in the model.

2.3. Utility

Utility values were derived from various publications. For stable AF, the source of EuroQol- 5 Dimension (EQ-5D) utility was a local study with subjects recruited from within two public hospitals in Penang, Malaysia, approximately 0.80 [16]. For utility values of stroke, GI and IC bleedings, and myocardial infarction, the research group used United Kingdom population results instead, as no local population-based studies were found [17-20].

2.4. Cost Data

Three relevant cost categories were identified: drug acquisition costs, administration costs (including monitoring and other costs), and clinical event-related costs [8, 21-24]. All costs have been adjusted to 2023 and the details of the data

sources are summarised in Table 1. Local cost data was adopted from local sources.

2.5. Sensitivity Analysis

2.5.1. Deterministic Sensitivity Analysis (DSA)

A series of one-way sensitivity analyses were run for the base case in order to determine the significant drivers of cost-effectiveness. All parameters were included in the variation. Unless otherwise specified, the confidence interval was used as lower and upper bound of the DSA. When not available, a $\pm 25\%$ variation for costs and a $\pm 15\%$ variation for event risks and utilities of the base value were applied for low and high values.

2.5.2. Scenario Analysis

Analysis on the cost-effectiveness of sub-populations, including patients with moderate to severe CKD stage 3-5, patients with age > 85 years old, and patients with diabetes, were conducted. In details, the transition probabilities for these sub-population, were estimated based on various publications [25-27]. Additional analysis on the outcome of length of stay was conducted based on United Arab Emirates population data [28].

2.5.3. Probabilistic Sensitivity Analysis (PSA)

In addition, a stochastic component was included in the model allowing for PSA. All parameters with second order uncertainty were included in the PSA. Parameters that did not carry second order uncertainty were excluded. These included discount rates and time horizon, unit costs from published reference lists, and patient characteristics such as age and co-morbidities. A beta distribution was used for probabilities, utility values and proportion whereas gamma was used for cost. The variation used in the DSA was used as the confidence interval to estimate the distribution parameters.

3. Results

3.1. Base-Case Analysis

In the base-case analysis, the cost of VKA, AP, DA and RV was RM9,811, 16,858, 18,318 and 20,161 respectively (1USD=RM4.74). The total QALYs gained were 5.98, 6.11, 6.09 and 6.15 respectively. The ICER of AP was comparable to RV with DA dominated as compared with VKA. Hence the results here suggest that both AP and RV were cost-effective in stroke prevention compared with VKA (Table 2, Figure 2 & Figure 3).

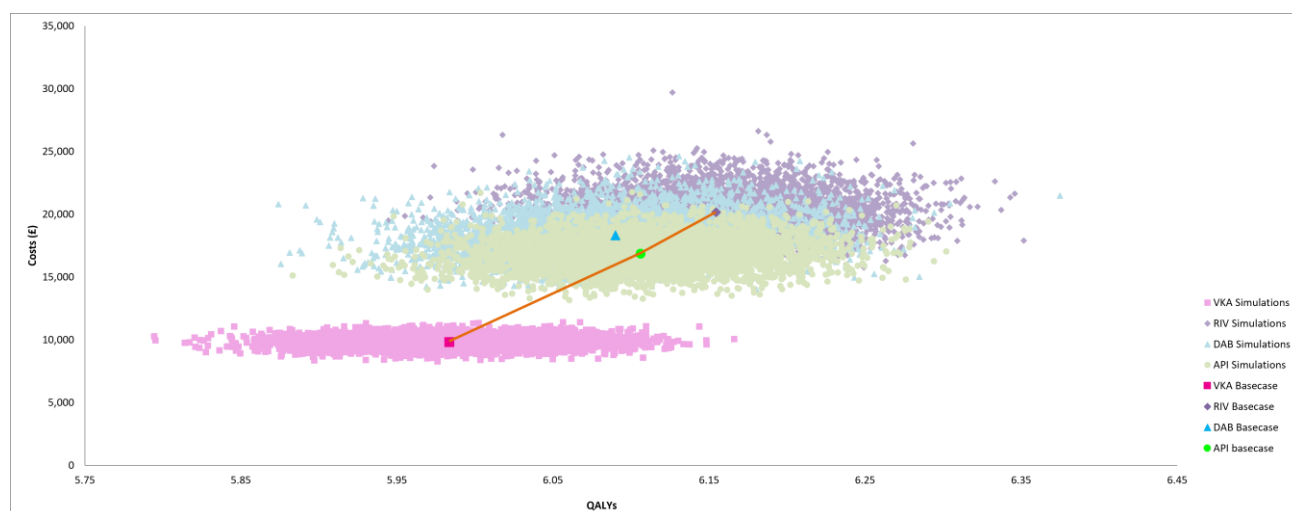


Figure 2. Cost Effectiveness (CE) plane for base-case population. The cost of VKA, AP, DA and RV was RM9,811, 16,858, 18,318 and 20,161 respectively (1USD=RM4.74).

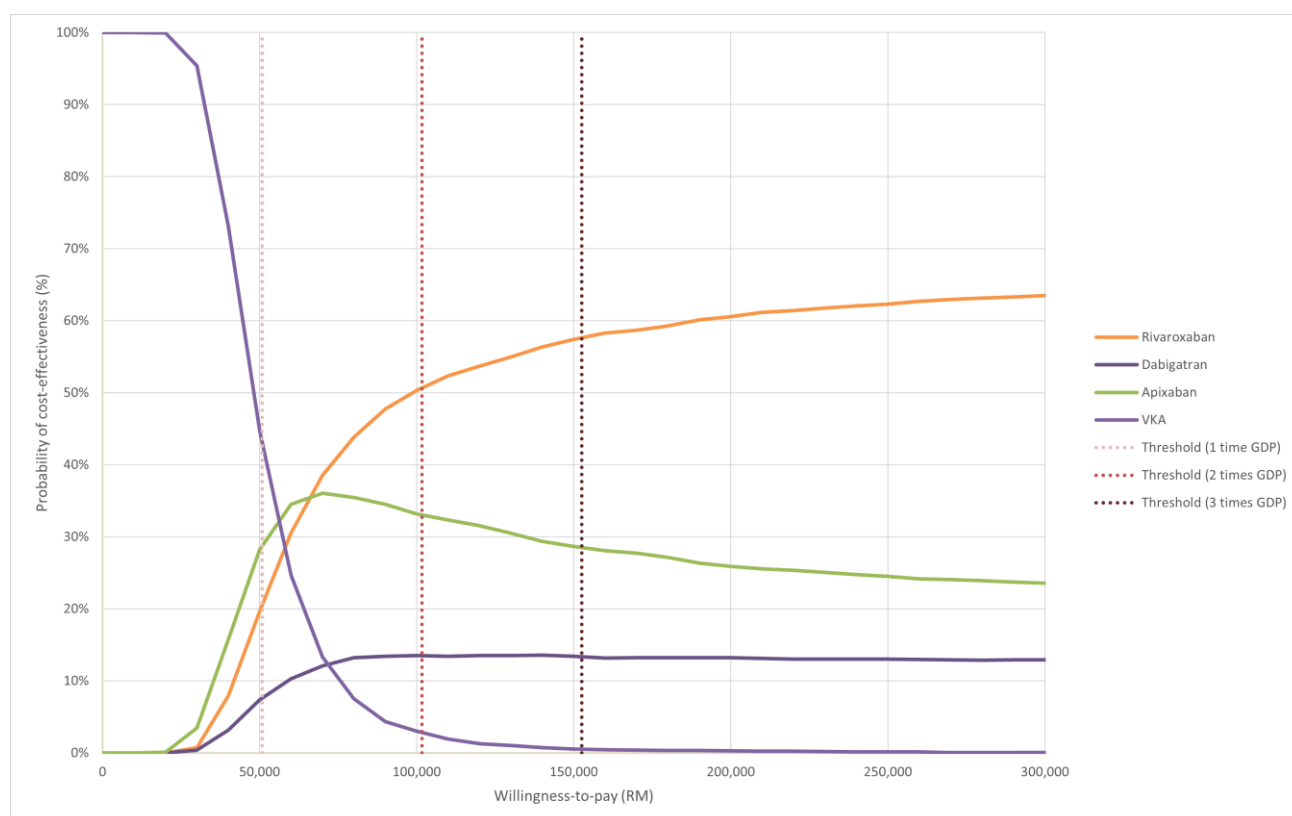


Figure 3. Cost-Effectiveness Acceptability Curve (CEAC) for base-case population. The ICER of AP was comparable to RV with DA dominated as compared with VKA with total QALYs gained for; AP=6.11; RV=6.15; DA=6.09 and VKA=5.98.

Table 2. Summary of model results.

Treatment	Total Costs (RM) (95% CI)	Total QALYs (95% CI)	ICERs vs VKA
Base-case scenario			
VKA	9,811 (8,973; 10,704)	5.98 (5.88; 6.08)	-
Apixaban	16,858 (14,582; 19,484)	6.11 (6.00; 6.22)	57,539

Treatment	Total Costs (RM) (95% CI)	Total QALYs (95% CI)	ICERs vs VKA
Dabigatran	18,318 (15,667; 21,665)	6.09 (5.97; 6.22)	(Dominated)
Rivaroxaban	20,161 (17,329; 23,453)	6.15 (6.05; 6.27)	68,156
Sub-population with moderate to severe CKD stage 3-5			
VKA	14,931 (9,471; 11,242)	4.46 (5.68; 5.9)	-
Apixaban	21,193 (15,254; 20,096)	4.84 (5.74; 6.02)	16,316 (Extendedly dominated)*
Dabigatran	21,774 (15,502; 21,618)	4.87 (5.71; 6.06)	16,474 (Extendedly dominated)
Rivaroxaban	23,564 (17,566; 23,839)	5.05 (5.90; 6.15)	14,433
Sub-population with age > 85 years old			
VKA	14,367 (13,218; 15,625)	4.68 (4.57; 4.79)	-
Apixaban	20,640 (18,374; 23,229)	5.01 (4.80; 5.21)	19,351
Dabigatran	21,984 (19,463; 25,055)	4.85 (4.69; 5.01)	(Dominated)
Rivaroxaban	23,284 (20,541; 26,388)	5.09 (4.94; 5.24)	31,739
Sub-population with diabetes			
VKA	10,318 (8,973; 10,704)	5.79 (5.88; 6.08)	-
Apixaban	17,538 (14,582; 19,484)	5.88 (6.00; 6.22)	78,880 (Extendedly dominated)
Dabigatran	18,170 (15,667; 21,665)	5.87 (5.97; 6.22)	(Dominated)
Rivaroxaban	20,544 (17,329; 23,453)	6.03 (6.05; 6.27)	42,948
Length of stay (LOS)		Average LOS	
VKA	9,811 (8,954; 10,692)	0.27 (0.27; 0.27)	
Apixaban	16,858 (14,597; 19,521)	0.17 (0.18; 0.15)	69,040
Dabigatran	18,318 (15,578; 21,600)	0.16 (0.18; 0.14)	243,022 (Extendedly dominated)
Rivaroxaban	20,161 (17,304; 23,423)	0.14 (0.14; 0.14)	112,981

* Extendedly dominated: The intervention is ruled out as it has an incremental cost-effectiveness ratio that is greater than that of a more effective intervention

Abbreviation: QALYs, quality-adjusted life-years; CI, confidence interval; ICER, incremental cost-effectiveness ratio; VKA, vitamin K antagonists; CKD, chronic kidney disease; LOS, length of stay

3.2. Scenario Analysis

3.2.1. Sub-population with Moderate to Severe CKD Stage 3-5

For moderate to severe CKD patients, both AP and DA were extendedly dominated by RV which showed an ICER of RM14,433/QALY vs 16,316 and 16,474 for AP and DA respectively as compared to VKA (Table 2, Supplementary Figures 1 & 2).

3.2.2. Sub-population with Diabetes

In patients with diabetes, both AP and DA were extendedly dominated by RV which showed an ICER of 42,948 vs 78,880 for AP and -73,469 (vs AP) for DA (Table 2, Supplementary Figures 3 & 4).

3.2.3. Sub-population with Age > 85 Years Old

For elderly patients, AP was shown to have the most favourable ICER initially but if the threshold increases, RV became more cost-effective and DA again appeared to be the least cost-effective DOAC (Table 2, Supplementary Figures 5 & 6).

3.2.4. Length of Stay (LOS)

When replacing the outcomes with LOS, DA once again was shown to be the least cost-effective one in terms of cost/hospital day avoided (RM243,022). It was extendedly dominated by AP and RV (ICER of RM69,040/day avoided and RM112,981/day avoided respectively) (Table 2, Supplementary Figures 7 & 8).

3.3. Sensitivity Analysis

For PSA, VKA was considered as cost-effective among all the comparators in the base-case population, under a threshold of 1-GDP per capita (Figures 2-3). RV was consistently the most cost-effective option under a threshold of 2-time GDP per capita across all subpopulations (Supplementary Figures 1-8).

4. Discussion

Globally, stroke poses a very high economic burden on the public budget due to its prevalence and the associated cost of care and rehabilitation [23]. This burden is further exacerbated if the patient has other co-morbidities such as CKD and DM. Hence a therapy capable of reducing the risk of stroke in any of these high-risk populations will offer both clinical and economic benefits. Stroke is the third leading cause of mortality in Malaysia with 5.9% increase in premature death from 2005 to 2015. Local ischemic stroke incidence increases annually by 29.5% and haemorrhagic stroke by 18.7%. With increasing number of stroke patients, the cost of stroke management is most likely to rise [23].

CKD and DM are recognised as risk factors of stroke. In particular, the CKD risk factor is considered to be an independent factor [29]. Healthcare resource utilisation associated with these 2 conditions is heavy due to their chronic nature and the requirement for specialty services such as renal dialysis. Hence any therapeutic benefit offered by interventions to improve the outcomes will have a significant impact on the healthcare budget.

Healthcare in Malaysia is provided via a 2-tiered system – a public and a private sector. The public system is funded from taxation and the private system is mainly through out-of-pocket payments or from insurance coverage. Over the years, the public system has been able to provide a universal healthcare coverage to all citizens although the quality of service has much room for improvement. This is mainly due to the ever-increasing healthcare cost while the competition for budget is also rising. Under this constraint, the Ministry of Health of Malaysia is therefore very cautious in drug reimbursement policy. In recent years, long-term cost-effectiveness is often taken into consideration on top of acute budget impact by frontline clinicians. Hence a drug with long-term benefits will be preferred among other factors.

In this study, the daily cost of RV lies between that of AP and DA (RM6.54 vs RM6.74 vs RM6.84). In the base-case scenario, in terms of cost-effectiveness expressed as ICER compared with VKA, RV and AP are both more preferred than DA but with RV slightly exceeded the 1-GDP threshold but less than 2-GDP. This finding is consistent with overseas studies [9] and in complete agreement with 2 other recent regional studies [7, 10]. This is of pivotal importance as clinical and economic impacts may differ in different jurisdictions. To the best of the research group's knowledge, this is the first study in Malaysia using the WHO recommended

approach as the threshold for cost-effectiveness in assessing DOACs. Hence the results and subsequent conclusion should be the most reliable ones.

In addition of the base-case scenario, this study also examined the cost-effectiveness of different DOACs in different subpopulations which are also considered as high-risk groups in Malaysia. These subpopulations include patients with severe CKD (stage 3-5), age above 85, DM, and prolonged hospital stay.

Prevalence of CKD in Malaysia is 9.07% of the total population, of which 0.36% are at stage 5 CKD or end-stage renal disease (ESRD). In the current study, it was shown that for moderate to severe CKD patients, the ICER of both AP and DA, when compared with VKA, were dominated by RV which showed an improvement in QALYs (0.09, 95%CI: [0.02; 0.23]) and cost (RM7220, 95%CI: [4863; 9554]) compared with VKAs, yielding an ICER of RM14,433/QALY (Table 2 and Supplementary Figures 1 and 2). In another sub-population of patients with age > 85 years old, the current results suggested that RV can also be considered as cost-effective with an ICER of RM68,156/QALY (Table 2 and Supplementary Figures 5 and 6).

Another subpopulation in which RV was shown to have the most favourable ICER among all the DOACs was the diabetic group in which both AP and DA were dominated by RV (Table 2 and Supplementary Figures 3 and 4). This is another important finding due to the ever-increasing prevalence of DM in Malaysia. This is projected to increase from 20% in 2019 to 31.3% of the 36.02 million population by 2025 [30]. In 2010 alone, an estimated USD 600 million was spent on diabetes-related healthcare in the country, accounting for approximately 16% of the overall national healthcare budget [31]. It is therefore of high priority that cost-effective interventions should be adopted to avoid adding further burden to this already costly disease.

There were very few previous studies which had examined the cost-effectiveness of DOACs in the above-mentioned subpopulations. In the current study, due to the lack of relevant data, the research group had to adopt overseas data and supported by local data wherever necessary. Examples of local data used include utility data and the acquisition and AE management costs of all the DOACs. The transition probabilities between the different states of diabetes were from an Asian study [25]. To the best of the research group's knowledge, this is the first study on the cost-effectiveness DOACs on these populations in Malaysia and will therefore contribute significantly in helping decision makers to make informed policy decisions.

This report has closely followed the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement by meeting 24 of the 28 requirements [32].

This study has several limitations. Firstly, not all data were from local sources due to the ongoing scarcity of relevant data in Malaysia for making projections. Nonetheless, the research group made efforts to maximize the use of local data whenever possible, particularly relying on local sources for all

cost-related and epidemiological data. Secondly, the results were projected using a Markov model, which may benefit from additional RWE for further substantiation. Lastly, the analysis did not encompass all available DOACs in the market; rather, it was focused solely on those listed on the formulary of the Malaysia Ministry of Health, aligning with the government's perspective in our study.

5. Conclusions

The analysis of DOACs in Malaysia reveals that rivaroxaban demonstrates the most favourable ICER across several high-risk subgroups, including patients with CKD, elderly patients, individuals with extended hospital stays, and those with DM at a threshold of 2-GDP. While these findings are promising, it is crucial to substantiate them with further research grounded in real-world evidence which provides insights into patient adherence, long-term outcomes, and healthcare resource utilization.

Abbreviations

AF	Atrial Fibrillation
NVAF	Non-Valvular Atrial Fibrillation
DOAC	Direct Oral Anticoagulant
VKA	Vitamin K Antagonists
LMWHs	Low Molecular-weight Heparins
RWE	Real-World Evidence
RV	Rivaroxaban
AP	Apixaban
DA	Dabigatran
CKD	Chronic Kidney Disease
DM	Diabetes Mellitus
QALYs	Quality Adjusted life Years
IS	Ischemic Stroke
MI	Myocardial Infarction
ICH	Intracranial Haemorrhage
GI	Gastrointestinal
DSA	Deterministic Sensitivity Analysis
PSA	Probabilistic Sensitivity Analysis
Pr	Probability
ICER	Incremental Cost-Effectiveness Ratio
WHO	World Health Organisation
GDP	Gross Domestic Product
WTP	Willingness-to-Pay
HRs	Hazard Ratios
EQ-5D	EuroQol-5 Dimension
LOS	Length of Stay
CE	Cost Effectiveness
CEAC	Cost-Effectiveness Acceptability Curve
ESRD	End-Stage Renal Disease
CHEERS 2022	Consolidated Health Economic Evaluation Reporting Standards 2022

Supplementary Material

The supplementary material can be accessed at <https://doi.org/10.11648/j.xxxx.2024xxxx.xx>

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Author Contributions

Kenneth Kwing-Chin Lee: Conceptualisation, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review and editing

Charles Zheng: Data curation, Formal analysis, Software, Validation

Jing-Sheng Lim: Data curation, Formal analysis, Writing – review and editing

June Wai-Yee Choon: Methodology, Visualization, Writing – original draft, Writing – review and editing

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography



Kenneth Kwong-Chin Lee is Professor of Health Economics at School of Medicine, Monash University Malaysia. He obtained his undergraduate degree in pharmacy from the University of Washington in Seattle, USA. His subsequent higher qualifications were from the Chinese University of Hong Kong and the University of Oxford, UK. Prof Lee is widely recognized as one of the pioneers in health economics and outcomes research in Asia. He has been Editor-in-chief of Journal of Medical Economics since 2006 and Topic Editor of “Increasing Importance of Patients-generated Real-World Data for Healthcare Policy Decisions about Medicinal Products” of Frontiers in Pharmacology since 2020. His areas of specialty include both micro and macro health economics. He had worked on individual drug therapies and surgical procedures as well as healthcare policy. He had been advisor of several Malaysia government committees including the Pharmacoeconomics Guideline Advisory Committee and Drug Pricing Control Committee.



Charles Zheng is a Staff Member of Cochrane Singapore. He acquired his degree in Preventive Medicine from Shanghai Jiao Tong University in 2012, and his Master of Philosophy in Public Health from The University of Hong Kong and Master of Science in Health Technology Assessment from University of York in 2014 and 2019, respectively. His major research interests lie in health economic modelling, real-world study and systematic reviews.



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Research Field

Kenneth Kwong-Chin Lee: Health technology assessment, Health policy research, Cost-effectiveness analysis of pharmaceuticals, Indirect cost of cancer patients, Equity to access healthcare

Charles Zheng: Health economics, Health technology assessment, Epidemiology, Biostatistics, Real-World Evidence

Jing-Sheng Lim: Health technology assessment, Economic burden of disease (direct and indirect cost), Oncology, Health policy research, Equity to access healthcare

June Wai-Yee Choon: Health Economics, Healthcare Financing, Healthcare Policy, Real-World Evidence