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Economic Evaluation

Cost-Effectiveness of Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation in Hong Kong

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ABSTRACT

Objectives: The emergence of direct oral anticoagulants (DOACs) has revolutionized the prevention of stroke related to nonvalvular atrial fibrillation (NVAF). Several DOACs are available on the market, while the cost-effectiveness comparison among DOACs and vitamin K antagonist (warfarin) in NVAF management in Hong Kong market remains scarce. The objective of this study was to assess the cost-effectiveness of DOACs and warfarin from a Hong Kong public institutional perspective to inform formulary listing decisions.

Methods: A previously developed Markov model was adapted to simulate the lifetime disease progression of a hypothetical cohort of 1000 patients. Net monetary costs, quality-adjusted life-year (QALY), and incremental cost-effectiveness ratio were computed for the following competing alternatives: warfarin, apixaban (5 mg twice daily), dabigatran (110 mg or 150 mg twice daily), and rivaroxaban (20 mg once daily). Probabilistic sensitivity analyses were conducted to address study uncertainties.

Results: In base-case results, all DOACs were associated with greater QALYs improvements and lower costs than warfarin. Rivaroxaban, apixaban, dabigatran 150 mg, dabigatran 110 mg, and warfarin resulted in net costs US dollar (USD) 8088, USD 8240, USD 8566, USD 8653, and USD 16 363 and net QALY 5.87, 6.017, 6.022, 5.98, and 5.829, respectively. In probabilistic sensitivity analysis, the probabilities of warfarin, rivaroxaban 20 mg, dabigatran 110 mg, dabigatran 150 mg, and apixaban 5 mg being cost-effective of 2000 iterations were 0%, 0%, 29.4%, 33.2%, and 37.4%, respectively.

Conclusion: Apixaban was the most cost-effective option compared with other DOACs and warfarin in the management of NVAF; this conclusion is consistent under all the tested uncertainty scenarios.

Keywords: anticoagulation, atrial fibrillation, cost-effectiveness analysis, Markov model.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice and associated with an increased risk of stroke.[1,2] Prevalence of AF in the Chinese population was estimated to be 0.7% to 1%.[3,4] Healthcare costs incurred by AF-associated ischemic stroke were estimated to be international dollars (I$) 41 420, I$12 895, and I$8184 for high-income, upper middle-income, and lower middle-income economies, respectively.[5] For > 50 years, warfarin has been the drug of choice in preventing AF-related strokes. Nevertheless, it requires frequent monitoring to maintain suitable dose due to its narrow therapeutic range and potential drug-drug and drug-food interactions.[6] The emergence of direct oral anticoagulants (DOACs) provides an additional treatment option for stroke prevention. All the pivotal trials involving DOACs enrolled patients with nonvalvular AF (NVAF) as the study population, defined as AF without mitral stenosis or valvular prostheses, to control the effect of thromboembolism.[7] DOACs have demonstrated at least clinically comparative efficacy and safety compared with warfarin in patients with NVAF[8,9] and are recommended in several clinical guidelines.[10,11] Moreover, DOACs were usually given in fixed dosing without the requirements for regular monitoring, thus associated with better drug compliance and adherence.[12]

Apart from clinical safety, efficacy, and adherence, cost-effectiveness is also vital to account for novel drugs regarding rapidly increasing healthcare expenditure. Valid economic evaluations can inform the prescribing and formulary listing of the most optimal therapy. The cost-effectiveness of DOACs against warfarin has been well documented globally.[13-16] Nevertheless, it is unclear which DOAC is the most cost-effective option. Previous studies[13,17] concluded that dabigatran was the most cost-effective option among DOACs, whereas Pink et al[18] claimed superior cost-effectiveness of apixaban versus other DOACs. Nevertheless, due to inconsistencies in market price, population utility, and differing healthcare systems, those findings cannot be extrapolated to other settings.[19] Hospital Authority (HA) is a constitutional agency managing all the government hospitals and institutes in Hong

Kong; it provided government subsided public healthcare services to > 7 million Hong Kong citizens since 1990.[20] We aimed to evaluate the cost-effectiveness of DOACs for stroke prevention among individuals with NVAF in Hong Kong to provide economic evidence for HA to inform treatment decision making and drug reimbursement plan.

Methods

Overview

This is a Markov model–based cost-effectiveness analysis comparing apixaban with warfarin, rivaroxaban, dabigatran 110 mg, and dabigatran 150 mg in the prevention of stroke in the Chinese population with NVAF. Patient profile, costs, and part of transition probabilities were sourced from a retrospective cohort analysis of incident patients with NVAF in the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic medical records database covering public healthcare services provided to 7 million Hong Kong residences.[20] Prescriptions, inpatient visits, laboratory test results, and diagnosis records are collected routinely for auditing and research purposes. For parameters not available from CDARS, landmark clinical trials, systematic literature review, expert opinion, and assumption were applied, wherever appropriate. Drug purchasing costs and dosages are listed in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003. Input parameters are summarized in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003. Reporting of the study is in line with the Consolidated Health Economic Evaluation Reporting Standards 2022 statement (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003).[21]

Model

We adapted a previously developed Markov model based on Microsoft Excel (Microsoft, Redmond, WA)[22,23] to assess the costs and clinical outcomes of 5 treatment strategies: warfarin (adjusted by target international normalized ratio [INR]), apixaban (5 mg twice daily), dabigatran (110 mg twice daily), dabigatran (150 mg twice daily), and rivaroxaban (20 mg once daily). Markov health state transition diagrams are illustrated in Figure 1. Taking public institutional perspectives (HA) into account, lifetime diseases progression was simulated for 1000 hypothetical patients with NVAF, whereas health state transitions, outcome of interests (quality-adjusted life-years [QALYs]), and direct healthcare cost were cumulated every 6 weeks until death. All costs and utilities were discounted at an annual rate 3.5%.

Source of demographic and clinical profiles

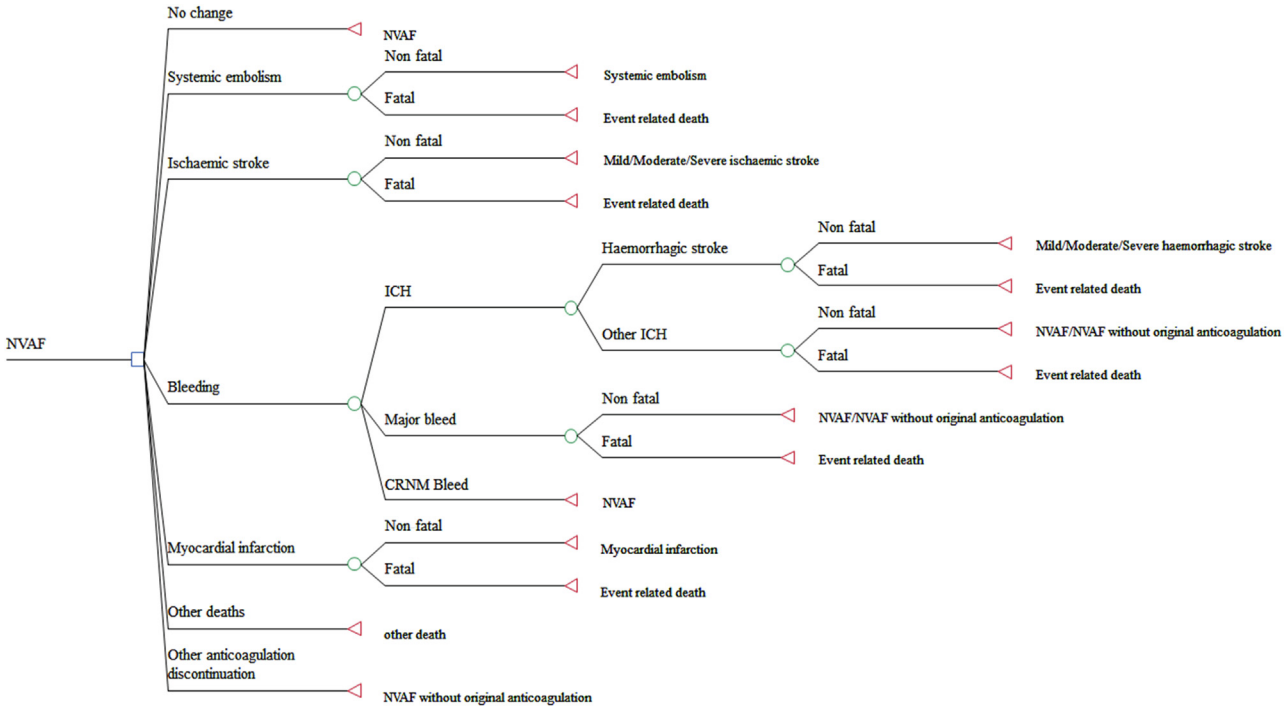
We identified patients with NVAF from CDARS during 2010 to 2016 as the study population. Cohort identification flowchart and the International Classification of Diseases ninth revision code used are presented in Appendix Figure 1 and Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003. Time in therapeutic range (TTR) and CHA2DS2-VASc score were calculated to adjust the risk of stroke among local patients with NVAF. The corresponding hazard ratio was presented in Table 1.[24]

Transition Probability

Risk of clinical events

Event rates for the comparators were based on a systematic review,[25] which is intent to permit indirect comparisons between apixaban and other anticoagulants (ACs) currently on the market for use in stroke prevention among patients with NVAF.

Figure 1. Markov health state transition diagram.



CRNM indicates clinically relevant non-major; ICH, intracerebral hemorrhage; NVAF, nonvalvular atrial fibrillation.

Table 1. Demographic and clinical profiles of patients with NVAF in CDARS 2010-2016.

Characteristics	Value	Stroke hazard ratio stratification for Warfarin	Stroke hazard ratio stratification for Apixaban
Sample size	71 705		
Demographic			
Male, n (%)	35 669 (49.7)		
Female, n (%)	36 036 (50.3)		
Mean age (males), years	73.2		
Mean age (females), years	78.9		
TTR distribution, n (%)*			
0%-52.38%	1596 (61.5)	1.542	0.92
52.38%-66.02%	474 (18.3)	1.000	1.00
66.02%-76.51%	275 (10.6)	0.836	0.69
76.51%-100%	250 (9.6)	0.717	0.56
CHA2DS2-VASc score distribution, n (%)†			
0-1	15 363 (21.4)	0.205	0.444
2	13 913 (19.4)	0.222	0.621
≥ 3	42 429 (59.2)	1.426	1.145

Note. Stroke hazard ratio was sourced from ARISTOTLE trial.[24]
CDARS indicates Clinical Data Analysis and Reporting System; NVAF, nonvalvular atrial fibrillation; TTR, time in therapeutic range.
*TTR was estimated using the Rosendaal method.
†CHA2DS2-VASc comprise of C: congestive heart failure; H: hypertension; A2: age ≥ 75; D: diabetes Mellitus; S: previous stroke/transient ischemic attack; V: vascular disease; A: age 65–74 years; Sc: sex category.

Landmark clinical trials included were the ARISTOTLE[24] (apixaban 5 mg vs warfarin, INR 2.0-3.0), the ROCKET–AF[26] (rivaroxaban 20 mg vs warfarin, INR 2.0-3.0), and the RELY[27] (dabigatran 110 mg vs dabigatran, 150 mg vs warfarin, INR 2.0-3.0). Indirect comparisons were made via warfarin as the common comparator and hazard ratios for each pairwise comparison were derived.

Mortality and fatality

All-cause mortality rate by age was derived from the Hong Kong life table.[28] Additional mortality risk for patients with NVAF over the general population was adapted from Friberg et al.[29] Baseline mortality rates after ischemic stroke and hemorrhagic stroke were sourced from Lip et al's[23] work and further adjusted by stroke severity (grouped as mild, moderate, and severe).[30-32] Additional mortality rates after myocardial infarction and system embolism (SE) were based on study of Bronnum-Hansen et al[33] and model assumption, respectively. No risk adjustment factor was applied to other clinical events. Case fatality rates for SE and bleeding were derived from the ARISTOTLE[24] secondary analysis and were assumed consistent across treatments. Case fatality rate for ischemic stroke and hemorrhagic stroke was obtained from the synthesis evidence of clinical trials.[24,26,27]

Medication adherence based on real-world evidence

Upon the occurrence of stroke, other major bleeds (gastrointestinal bleeds and nonintracerebral hemorrhage [non-ICH] and nongastrointestinal bleeds), and SE, patients may stay on the initially assigned ACs or get second line treatment (aspirin). While upon the occurrence of a hemorrhagic stroke and myocardial infarction, it is assumed that all patients discontinue AC completely. A proportion of patients who stuck to initial treatment after occurrence of clinical events were estimated by dividing the number of patients who reinitiated the treatment within 90 days after the event with the number of patients taking the treatment within 90 days before event and survive. Details of medication adherence after clinical events were reported in Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003. Particularly, treatment switch for the occurrence of other ICH was not assessed because hemorrhagic stroke was considered as all ICH in the International Classification of Diseases Ninth Revision coding system.

Utility

The baseline utility for patients with NVAF was sourced from a local study by Ho et al.[34] Disutilities associated with averse events and AC utilization were adapted from a UK-based utility catalog in the absence of local evidence.[35]

Costs

Costs comprised the following parameters: (1) treatment cost based on local retail prices (per internal communication with industry partners), (2) management costs for INR and renal monitoring (sourced from the HA Ordinance[36]), and (3) acute care costs associated with clinical events. Event cost per episode was calculated by multiplying daily inpatient charges in public hospitals[37] by the median hospital length of stay estimated from the CDARS cohort (Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003). All costs were converted to 2020 US dollar (USD) (1 USD = 7.76 Hong Kong dollars[38]).

Base-Case Analysis

In light of the lack of local economic evaluation guidelines, we used one time gross domestic product per capita of Hong Kong in 2020[39] (USD 46 091) as the cost-effectiveness threshold according to the World Health Organization CHOosing Interventions that are Cost-Effective (WHO-CHOICE)[40] recommendation. Treatments with incremental cost-effectiveness ratio (ICER) below the

threshold will be considered cost-effective. Alternatives were ordered from lowest cost to highest cost to calculate incremental costs and effectiveness.

Sensitivity Analyses

Deterministic sensitivity analysis was performed for apixaban versus warfarin using up to 109 parameters, where each parameter was varied according to the 95% confidence intervals and SDs where applicable while holding all other parameters constant. In the Monte Carlo simulation-based probabilistic sensitivity analysis (PSA), all tested variables were varied concurrently with a predefined distribution and simulated for 2000 iterations. ICER was calculated for each iteration and plotted on a cost-effective plane. Cost-effective acceptability curve displayed the probability of each comparator being the most cost-effective strategy under the willingness to pay (WTP) threshold (USD 46 091/QALY).

Result

Population

We included 71 705 patients with NVAF (male, 49.7%; mean age, 73.2 years; female, 50.3%; mean age, 78.9 years) to estimate the Hong Kong population-specific parameters (Table 1[24]). Notably, 61.5% of patients with NVAF had a suboptimal INR control, defined as TTR ≤ 52.38%. These patients do not benefit from warfarin and are exposed to higher risk of stroke.

Base-Case Analyses

In the base case, dabigatran 150 mg has the greatest efficacy with 6.022 QALY gained, followed by apixaban (6.017 QALYs). Rivaroxaban has both the lowest costs USD 8088 and also the least 5.870 QALYs gained (Fig. 2), ordering alternative treatments from lowest cost to highest cost. Comparing with rivaroxaban that had the lowest cost, apixaban associated with improved QALY gained (0.147 QALYs) at the cost of USD 152, leading to an ICER USD 1034/QALY below the threshold of WTP. The subsequent dabigatran 150 mg provided a marginally higher improved QALY gained (0.005 QALYs) while being associated with a considerable increased cost (USD 326), leading to an ICER (USD 67 633/QALY) greater than the WTP threshold; hence not being cost-effective. Comparing with dabigatran 150 mg, both dabigatran 110 mg (incremental cost, USD 87; incremental effectiveness, −0.042) and warfarin (incremental cost, USD 7797; incremental effectiveness, −0.193) resulted in less QALY but increased lifetime costs, therefore being dominated (Table 2). Apixaban was found to be the cost-effective alternative compared with warfarin and other DOACs.

Sensitivity Analysis

Deterministic sensitivity analysis

The top 15 parameters with the greatest influence on the ICER comparing apixaban with warfarin were presented in tornado diagrams in descending order (Fig. 3). Warfarin monitoring costs, risk of ischemic stroke for warfarin, and risk of ICH for apixaban contributed most to the variation of ICER. Varying all of these variables over predefined ranges, apixaban remains the cost-effective alternative to warfarin under the WTP USD 46091/QALY.

Cost-effective acceptability curve

Using a WTP threshold of USD 46 091 per QALY, in the PSA including 2000 iterations in the Monte Carlo simulation, the probability of warfarin, rivaroxaban 20 mg, dabigatran 110 mg, dabigatran 150 mg, and apixaban 5 mg being cost-effective were 0%, 0%, 29.4%, 33.2%, and 37.4%, respectively (Fig. 4).

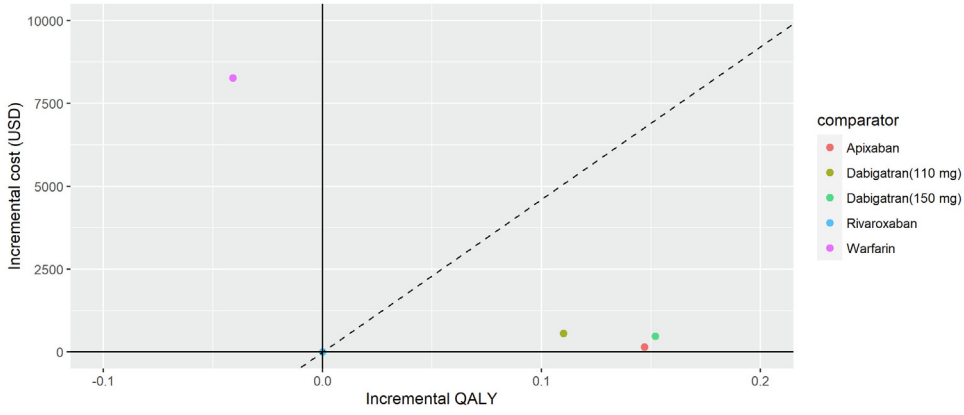
Discussion

Summary of Study Finding

Using the territory-wide database and local market evidence, we adapted a validated Markov cohort model[22,23] to evaluate the cost-effectiveness of apixaban against other ACs in treating patients with NVAF in Hong Kong. Given that there are no established WTP threshold guidelines for Hong Kong, the WTP threshold was set to one gross domestic product per capita in 2020 (USD 46 091). Both base-case and sensitivity analyses indicate that apixaban is a cost-effective alternative to rivaroxaban, dabigatran 110 mg, and dabigatran 150 mg in stroke prevention from the perspective of the public payer. Our findings are in line with studies in other settings.[15,23,41-43]

Although the base-case analysis of the QALY improvements for dabigatran 150 mg is slightly higher than apixaban, PSA results suggested that apixaban was associated with the greatest mean QALY as 5.11 of 2000 iterations, against 4.92 QALY for warfarin, 4.95 QALY for rivaroxaban, 5.04 QALY for dabigatran 110 mg, and 5.08 QALY for dabigatran 150 mg (Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.02.003). Therefore, apixaban remains the most cost-effective

Figure 2. Cost-effectiveness plane.



QALY indicates quality-adjusted life-year; USD, US dollar.

Table 2. Base-case results comparing apixaban with other anticoagulants.

Comparator	Net cost, USD	Net QALY	Incremental cost, USD	Incremental QALY	ICER	Conclusion
Rivaroxaban	8088	5.87				
Apixaban	8240	6.017	152	0.147	1034	Cost-effective
Dabigatran (150 mg)	8566	6.022	326	0.005	65 200	Not cost-effective
Dabigatran (110 mg)	8653	5.98	87	−0.042	−2071	Dominated
Warfarin	16 363	5.829	7797	−0.193	−40 399	Dominated

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; USD, US dollar.

strategy as WTP rises (Fig. 4). Among all the published models that investigated the cost-effectiveness of ACs in Chinese population, a similar cost-effectiveness pattern was found in Taiwan, where PSA simulations generated the best health outcomes for apixaban, followed by dabigatran 15 0mg, dabigatran 110 mg, rivaroxaban, and warfarin.[43] In agreement with our findings, 2 systematic reviews on the efficacy and safety of DOACs for NVAF management also suggested that apixaban was consistently associated with the most favorable benefit-risk profile and should therefore be given priority in use.[44,45]

Local Evidence

The use of real-world evidence ascertains the relevance to the Hong Kong setting, as in clinical trial settings patients generally receive improved care and enhanced adherence to the drug and have stringent recruitment criteria, which may overestimate the effects in real practice. For example, compared with the population in ARISTOTLE[24] (mean age, 70 years; proportion of female, 35%), patients with NVAF in Hong Kong are considerably older (mean age for male, 73.2 years; mean age for female, 78.9 years) with a balanced sex ratio (proportion of female, 49.7%). In our study, patient demographic information and clinical profiles such as TTR range, CHA2DS2-VASc score distribution, and acute event costs were derived from CDARS. This would allow us to adjust the treatment effect and cost in accordance with local clinical practice and economic practice.

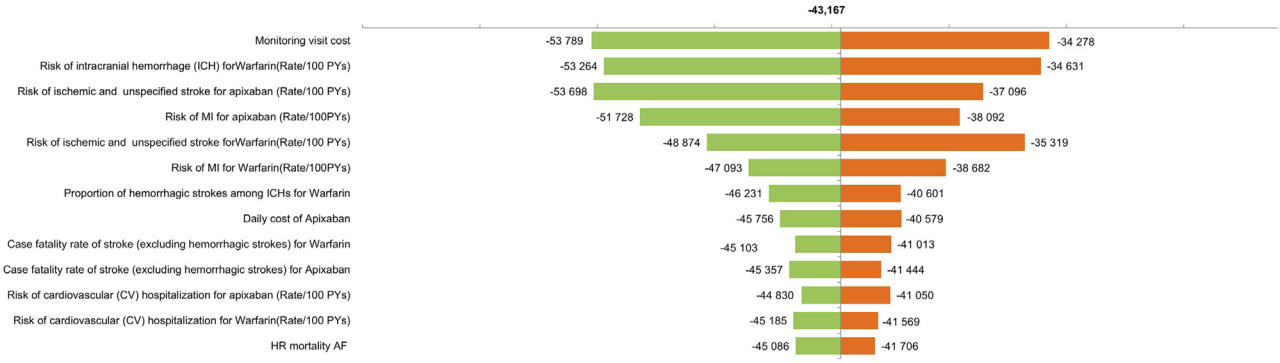
Clinical and Policy Implication

Consistent with the recommendation of DOACs in the treatment of NVAF from clinical practice guidelines, we found that the use of DOACs is a more efficient and cost-effective choice in managing NVAF-related stroke than warfarin, the primary reasons being that (1) DOACs require far less investment in drug surveillance, reflected as warfarin monitoring costs in the model, which explains the lower costs of DOACs than warfarin despite the more expensive prices, (2) DOACs tend to prolong lifespan and improve the quality of life of patients with NVAF. Therefore, health policy enforcers should give way to the therapeutic option to prevent stroke in patients with NVAF with better performance in clinical and financial environments. Furthermore, our findings suggest apixaban to be the most cost-effective strategy among DOACs and thus should be given priority when making relevant clinical decisions in stroke prevention for patients with NVAF.

Limitations

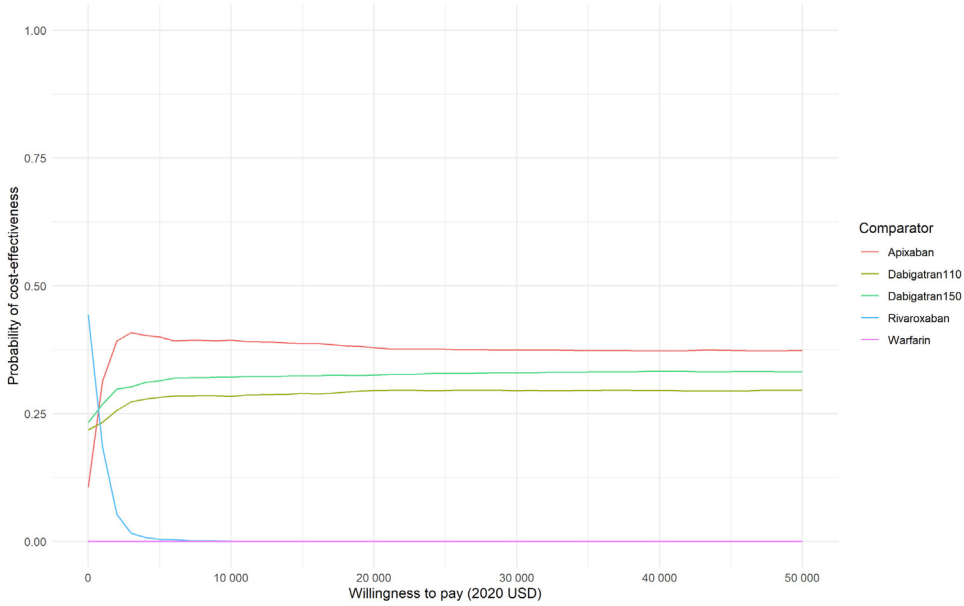
This model has several limitations. First, given the limitations of the data source, we were unable to estimate the event cost incurred in emergency and intensive care settings nor the healthcare costs stratified by stroke severity. Second, a common limitation for the Markov model is that we assumed the transition probabilities among health states were consistent with treatment

Figure 3. Deterministic sensitivity analysis comparing warfarin versus apixaban.



AF indicates atrial fibrillation; HR, heart rate; MI, myocardial infarction; PY, person-year.

Figure 4. Cost-effective acceptability curve comparing warfarin, rivaroxaban, dabigatran 110 mg, dabigatran 150 mg, and apixaban.



USD indicates US dollar.

efficacy from landmark trials and would remain constant over a lifetime period, which might not be the case given that clinical trials usually have short follow-up periods (1.8 years in ARISTOTLE[24] to 2.5 years in RELY[27]) but the time horizon of our model is lifetime. Finally, in the absence of local evidence, model input parameters were sourced from many heterogenous sources, future studies could focus on the update of suitable parameters.

Conclusions

By integrating real-world evidence and landmark clinical trial outcomes, we localized a previously verified Markov cohort model to the Hong Kong setting. The base-case results and sensitivity analyses are highly consistent, indicating that apixaban is the most cost-effective strategy in prevention of stroke for patients with NVAF compared with warfarin, rivaroxaban, and dabigatran. Our findings could serve to inform formulary drug list decisions and further expand the utilization of DOACs in Hong Kong.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2023.02.003.

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