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Cost-effectiveness analysis of anticoagulation options for non-valvular atrial fibrillation in Iran

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Abstract

Background Atrial fibrillation (AF) imposes a substantial economic and clinical burden, particularly in developing countries like Iran. This study aimed to evaluate the cost-effectiveness of anticoagulation options for non-valvular atrial fibrillation (NVAF) in Iran.

Methods We conducted a cost-effectiveness analysis comparing warfarin, apixaban, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban for NVAF patients from the Iranian payer's perspective. A Markov model with a lifetime horizon was used to estimate costs and quality-adjusted life years (QALYs). The model incorporated clinical event rates, case-fatality rates, and utility values. Uncertainty was assessed using deterministic sensitivity analysis and probabilistic sensitivity analysis.

Results Among the interventions, warfarin had the lowest cost ($1,755) but apixaban resulted in the highest QALYs (7.33). Apixaban was the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of $2,026 per QALY gained compared to warfarin. Apixaban dominated other treatments, with lower costs and higher QALYs. Probabilistic sensitivity analysis indicated that at Iran's willingness-to-pay threshold of $4,387 per QALY gained, apixaban had a high probability of being cost-effective (88.2%).

Conclusion Our study provides strong evidence for healthcare decision-makers in Iran, showing that apixaban is a cost-effective treatment for NVAF, potentially enhancing patient outcomes and optimizing healthcare expenditures.

Keywords Markov model, Cost-effectiveness, QALYs, Anticoagulation, Atrial fibrillation

Introduction

Atrial fibrillation (AF) significantly contributes to morbidity, mortality, and healthcare costs, being a leading cause of ischemic stroke, heart failure, and cardiovascular disease [1–4]. This burden is particularly severe in developing countries like Iran, where limited healthcare resources exacerbate the situation. A systematic review [5] estimated healthcare costs for AF-related ischemic strokes at $41,420 in high-income countries, $12,895 in upper middle-income countries, and $8,184 in lower middle-income nations. Stroke patients with AF incur higher direct medical costs than those without [6]. In

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2019, Iran had 339.1 thousand AF/AFL patients, with 48 thousand DALYs reported [7]. In a unpublished study, The economic burden of atrial fibrillation (AF) in Iran was 1,326,045,072,463 million Iranian Rial (IRR) [8]. AF prevalence varies globally due to demographic and lifestyle factors. For example, Sweden reports a 3.2% prevalence among adults aged 20 and older, increasing to over 10% for those aged 75–90 [9]. Greece has an estimated overall prevalence of 3.9% [10]. By 2050, global AF prevalence is expected to double to 4%, with 5 million new cases annually [11]. A local study in Iran found a 2.8% prevalence among individuals aged 50–79, with higher rates in women [12]. As Iran's population ages, the number of AF patients is projected to rise sharply. The financial burden of AF-related illnesses underscores the need for effective management in resource-constrained settings like Iran. Treatment options include vitamin K antagonists (VKAs) such as warfarin and direct oral anticoagulants (DOACs) like dabigatran and rivaroxaban [13, 14]. While newer medications demonstrate improved effectiveness and safety compared to warfarin, they are also more expensive [15, 16]. A study conducted in Fars province found that rivaroxaban is both cheaper and more effective than warfarin. However, it is important to note that this previous study only compared these two medications and did not evaluate other options, such as apixaban and other direct oral anticoagulants [17]. Therefore, to fill this gap in the literature, this study aims to evaluate the costs and effectiveness of warfarin, dabigatran (110 mg and 150 mg), rivaroxaban, and apixaban among patients with non-valvular atrial fibrillation (NVAF) in Iran.

Methods

Study design and perspective

We conducted a cost-effectiveness analysis to compare different anticoagulant options for non-valvular atrial fibrillation (NVAF) from the Iranian payer's perspective, considering direct medical costs. The effectiveness outcomes were measured in quality-adjusted life years (QALYs).

Target population and interventions

The target population for this study was NVAF patients aged 60 years, based on data from the Iranian Registry of Atrial Fibrillation (IRAF) [18]. Five anticoagulant drugs were included in the analysis: warfarin, apixaban, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban. These interventions were compared in terms of their clinical outcomes, costs, and QALYs gained.

Model structure

A validated Markov model was employed with a lifetime horizon and a 1-year cycle length, encompassing various mutually exclusive health states: NVAF, ischemic stroke (IS), systemic embolism (SE), bleeding, myocardial infarction (MI), other unrelated deaths, and event-unrelated anticoagulant discontinuation [19]. Bleeding events are classified into intracranial hemorrhage (ICH), other major bleeding, and clinically relevant non-major bleeding (CRNMB). The model also accounts for varying levels of ischemic and hemorrhagic stroke severity: mild, moderate, and severe. Patients enter the model at age 60 in the NVAF state without complications. During each annual cycle, patients may remain in their current state or transition to another due to clinical events. A half-cycle adjustment was applied to prevent overestimation or underestimation of costs and utilities. The state transition diagram is illustrated in Supplementary Figures S1.

Model parameters

Transition probabilities

The transition probabilities used in the model, along with their sources, are detailed in Supplementary Table S1. Clinical event rates for patients treated with warfarin were derived from Dorian et al. [19], which analyzed data from the ARISTOTLE trials—a landmark study comparing apixaban with warfarin in patients with non-valvular atrial fibrillation (NVAF) [20]. We also included probabilities of transitioning to different health states after event-unrelated treatment discontinuation, sourced from Dorian et al. and Jong et al. [19, 21]. Additionally, we recognized the impact of stroke severity on costs and outcomes by incorporating distributions of patients across various severity levels [21]. Case-fatality rates following each event were integrated into the model to account for the increased mortality risk associated with specific clinical events. Furthermore, we adjusted for additional mortality risk factors per event, acknowledging that conditions like AF, stroke, and myocardial infarction (MI) significantly affect long-term survival [19, 21]. Mortality data due to other causes at different ages was obtained from Iran's life Table (22). We also accounted for the probability of unrelated anticoagulant discontinuation since adherence can vary among patients, using data from de Jong et al. [21]. Relative risks for each anticoagulant compared to warfarin were included to reflect their varying effectiveness, sourced from meta-analyses and network meta-analyses [23–25].

Costs

This study focused solely on direct medical costs (see Supplementary Table S2). The costs of the five anticoagulant drugs were obtained using dosage information from Iran's Food and Drug Administration (FDA) website [26]. Costs associated with various health states, such as myocardial infarction and ischemic stroke, were derived from a previous Iranian study [27]. However, average costs by disease severity were not reported in that study; thus, we calculated average costs for each disease state using cost ratios from studies conducted in other countries (see Supplementary Table S2). We estimated the cost of clinically relevant non-major bleeding as 18% of a mild hemorrhagic stroke and major bleeding as 55% of a mild hemorrhagic stroke based on averages from five studies [19, 21, 28–30]. All cost data were adjusted for consumer price inflation in Iran for 2022.

Utilities

As part of this economic evaluation, quality-adjusted life years (QALYs) were used as the outcome measure. QALYs combine length and quality of life into a single metric to assess health intervention effectiveness [31, 32]. For this study, QALYs were calculated by multiplying the estimated time spent in each health state by the corresponding utility weight. Utility weights range from zero (for death) to one (for perfect health). Data on utility and disutility values were extracted from international studies (see Supplementary Table S2). Future costs and health benefits were discounted at an annual rate of 5% [33, 34].

Analysis

To assess the cost-effectiveness of the five anticoagulants, we calculated incremental cost-effectiveness ratios (ICERs) using the formula:

$$ICER = \frac{C_1 - C_2}{E_1 - E_2}$$

We interpreted ICERs according to World Health Organization guideline [35] for low- and middle-income countries like Iran. A drug is considered very cost-effective if its ICER is below Iran's GDP per capita ($4,387 in 2022) [36]; it remains cost-effective if the ICER is one to three times this threshold.

Sensitivity analysis

We performed deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) to evaluate model robustness. DSA involved one-way sensitivity analysis and Tornado diagrams, adjusting parameters based on 95% confidence intervals or assuming a standard deviation of 10–20% of the mean when unavailable. For PSA, we conducted 1,000 Monte Carlo simulations using parameter distributions, applying beta distributions for utility values and probabilities, Gamma distributions for costs, and log-normal distributions for relative risks. Findings were summarized with a cost-effectiveness acceptability curve (CEAC) and Monte Carlo acceptability at the $4,387 WTP level. We used TreeAge Pro 2020 for model development and analysis while following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [37].

Results

Table 1; Fig. 1 present the base-case results of the cost-effectiveness analysis comparing warfarin with other anticoagulants. Warfarin had the lowest cost at $1,755 per patient. Apixaban, with an incremental cost of $358 and an additional 0.18 QALYs gained, resulted in an incremental cost-effectiveness ratio (ICER) of $2,026 per QALY. Rivaroxaban and both doses of dabigatran had higher costs and lower QALYs, indicating they are dominated strategies. Apixaban is the most cost-effective option, with an ICER below the willingness-to-pay threshold of $4,387 per QALY, and it also yielded the highest net monetary benefit among the anticoagulants.

The one-way sensitivity analysis evaluated how changes in key model parameters affected cost-effectiveness results. The tornado diagram (Supplementary Figure S2) displays the ten variables with the greatest influence on the ICER, showing their low and high values. The probability of unrelated anticoagulant discontinuation for apixaban had the most significant impact, raising the ICER to $2,995. Other influential factors included the relative risk of IS with apixaban versus warfarin, treatment costs, and utilities associated with atrial fibrillation. This analysis confirms that apixaban is the most cost-effective anticoagulant strategy for managing NVAF.

A PSA with 1,000 Monte Carlo simulations was performed to assess uncertainty in all model parameters. The CEAC (Fig. 2) shows that at a WTP threshold of $2,200 or less, warfarin is more likely to be cost-effective than apixaban. However, as the WTP threshold increases, the probability of apixaban being cost-effective rises while that of warfarin decreases.

Table 1 Base-case results comparing Warfarin with other anticoagulants

Strategy	Cost ($US)	Incremental cost ($US)	QALYs	Incremental QALYs	ICER ($US/QALY)	Category	NMB ($US)
Warfarin	1,755	-	7.16	0.00	-	Undominated	29,646
Apixaban	2,113	358	7.33	0.18	2,026	Undominated	30,064
Rivaroxaban	2,207	94	7.23	-0.11	-886	AD	29,502
Dabigatran 150 mg	2,310	197	7.21	-0.12	-1,587	AD	29,322
Dabigatran 110 mg	3,462	1,350	7.18	-0.15	-8,920	AD	28,050

Note: QALYs: quality-adjusted life-years; ICER: incremental cost-effectiveness ratio; Abs. dominated: Absolutely dominated NMB is net monetary benefit and it is calculated as (incremental benefit * WTP threshold) – incremental cost

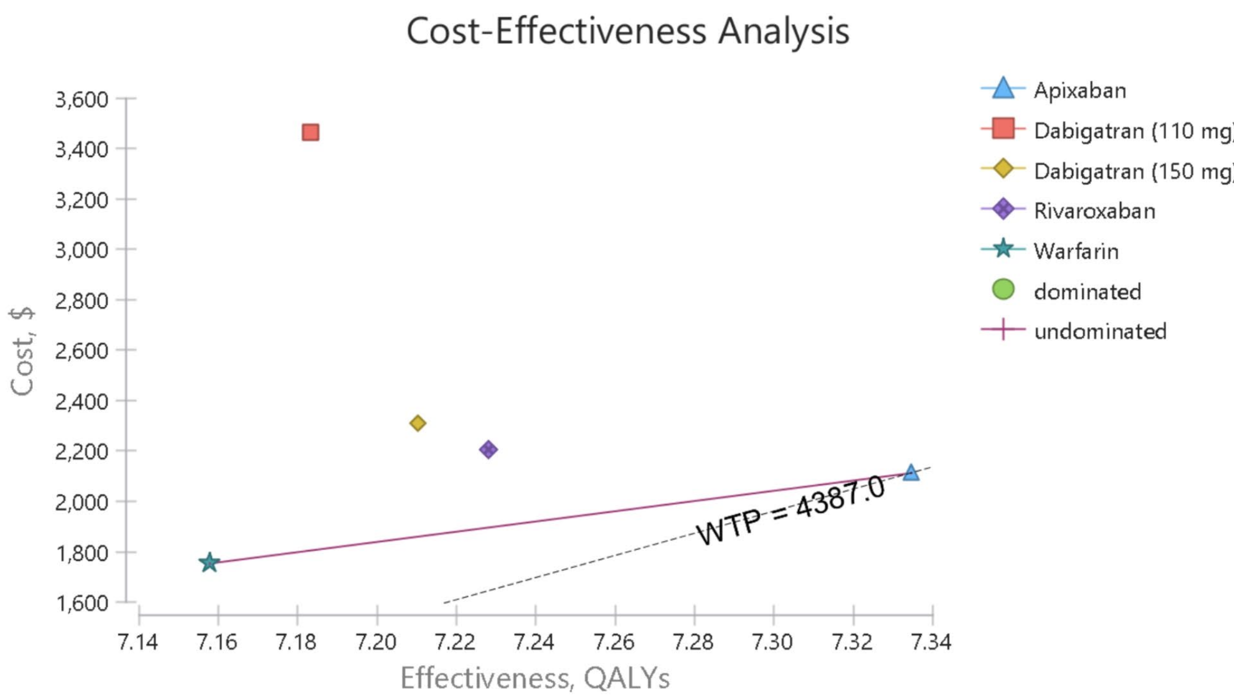

Fig. 1 Cost- effectiveness analysis of comparing warfarin, rivaroxaban, dabigatran 110 mg, dabigatran 150 mg, and apixaban

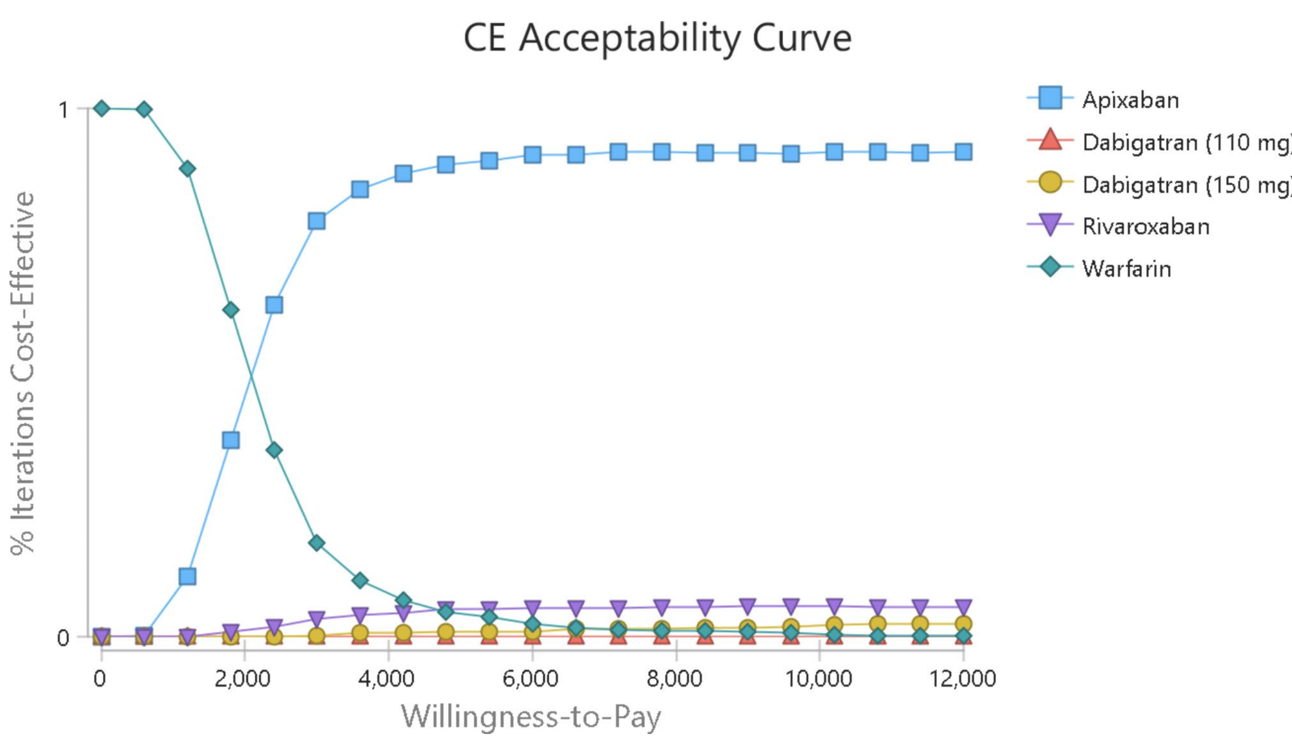

Fig. 2 Cost-effectiveness (CE) acceptability curve at a varying willingness-to-pay threshold

Supplementary Figures S3A and S3B show the Monte Carlo acceptability at Iran's GDP per capita ($4,387) and three times that amount ($13,161) for all treatment options. At a WTP threshold of $4,387, apixaban has an 88.2% probability of being cost-effective, compared to warfarin's 6.3%. At three times the GDP, apixaban probability increases to 91.3%, while warfarin drops to 0.2%, confirming apixaban as the most cost-effective option.

Discussion

This study conducted a full economic evaluation of several anticoagulants—warfarin, dabigatran (110 mg and 150 mg), rivaroxaban, and apixaban—for patients with nonvalvular atrial fibrillation (NVAF) in Iran. As similar studies [19, 21, 38, 39], our study indicated that apixaban was the most cost-effective option, with an ICER below Iran's GDP per capita of $4,387 per QALY gained. Apixaban demonstrated lower costs and greater effectiveness compared to dabigatran and rivaroxaban. Sensitivity analyses showed low uncertainty regarding apixaban cost-effectiveness, as it was cost-effective in about 90% of PSA iterations, confirming the robustness of these results. A systematic review of economic models for newer anticoagulants found that apixaban was dominant (lower cost and more effective) compared to aspirin and cost-effective relative to warfarin [40]. However, some studies report different results [41, 42]. For example, a US study indicated that dabigatran was optimal with an ICER of $35,055 per QALY gained compared to warfarin [43]. Direct comparisons are challenging due to variations in patient populations, model structures, input parameters, perspectives, and currencies. Each study's specific context and methodology can significantly influence cost-effectiveness findings, making direct comparisons with our Iran-based analysis difficult.

A key factor in determining the cost-effectiveness of a health intervention is the cost-effectiveness threshold. Iran lacks an established threshold, so we followed the World Health Organization's guideline, which considers an intervention highly cost-effective if its cost-effectiveness ratio is below the GDP per capita. In 2022, Iran's GDP per capita was $4,387, significantly lower than the thresholds used in Saudi Arabia ($20,000-$30,000) [28], the United States ($50,000) [44], and the United Kingdom (£20,000) [45]. Our sensitivity analysis confirmed that the findings were robust; varying uncertain parameters did not significantly affect the outcomes, with apixaban remaining the most cost-effective option. The utility value for atrial fibrillation (AF) and the cost of apixaban were identified as the two most influential parameters [29]. Wang et al. [43] attributed inconsistent cost-effectiveness results for apixaban versus dabigatran to their relative costs, noting apixaban was nearly 5% higher in one study and 17% lower in another [46]. In our study, apixaban was $218 (72.3%) less than dabigatran 110 mg and $22 (20.1%) less than dabigatran 150 mg.

This analysis has limitations. A primary concern is that utility, relative risk, and transition probability data were extracted from studies in other countries. While the study offers valuable economic insights for local decision-makers, the lack of robust Iran-specific clinical and utility data necessitates cautious interpretation of the findings. Access to high-quality local data would enhance cost-effectiveness estimates for AF treatment strategies in Iran and similar contexts. Additionally, the analysis used a payer's perspective rather than a societal perspective, omitting direct non-medical costs and productivity losses.

Conclusion

This full economic evaluation is the first in Iran to compare the cost-effectiveness of five anticoagulants for atrial fibrillation (AF) patients. Our findings indicate that apixaban is the most cost-effective option at a WTP threshold of $4,387 per QALY gained. Deterministic and probabilistic sensitivity analyses confirmed these results. Future research quantifying healthcare resource utilization and quality of life in AF patients could provide more accurate cost-effectiveness estimates and valuable insights for decision-makers. The need for further studies on patient adherence to anticoagulant therapies and the exploration of the cost-effectiveness of these treatments across different Iranian subpopulations, particularly in urban versus rural settings, is essential. This focus will provide valuable insights for optimizing treatment strategies and improving healthcare outcomes in diverse populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-024-07004-2.

Supplementary Material 1

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Author contributions

SR and RD contributed to the study design and data analysis. RD, SR, MM, and MB contributed to the conceptualization, design of the study, interpretation, drafting, and critical revision of the intellectual content of the final manuscript. All authors read and approved the final version of the manuscript.

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Data availability

The data collected and examined for this study can be found in this published paper. The specific datasets used are available upon request by contacting the study's corresponding author.

Declarations

Ethics approval and consent to participate

The study has been approved by the Research Ethics Committee of the School of Public Health at Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1402.077). The required data were extracted from previous studies on this topic according to the study aims, and consequently, obtaining informed consent was not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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