VALUE IN HEALTH 21 (2018) 1365–1372

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Utility Analysis of Apixaban versus Warfarin in Atrial Fibrillation Patients with Chronic Kidney Disease

Shoroq M. Altawalbeh, PharmD, PhD [1,*], *Osama Y. Alshogran, MS, PhD* [1], *Kenneth J. Smith, MD, MS* [2]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan;* [2]*Section of Decision Sciences, Center for Research on Health Care, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

ABSTRACT

Background: Warfarin use for stroke prevention in atrial fibrillation (AF) patients with chronic kidney disease is debated. Apixaban was shown to be safer than warfarin, with superior reduction in the risk of stroke, systemic embolism, mortality, and major bleeding irrespective of kidney function. **Objectives:** To evaluate the cost-utility of apixaban compared with warfarin in AF patients at different levels of kidney function. **Methods:** A Markov model was used to estimate the cost effectiveness of apixaban compared with warfarin in AF patients at three levels of kidney function: estimated glomerular filtration rate (eGFR) of more than 80 ml/min, 50 to 80 ml/min, and 50 ml/min or less. Event rates and associated utilities were obtained from previous literature. The model adopted the US health care system perspective, with hospitalization costs extracted from the Healthcare and Utilization Project. Treatment costs were obtained from official price lists. Univariate and probabilistic sensitivity analyses were performed to evaluate the robustness of results. **Results:** Apixaban was a dominant treatment strategy compared with warfarin in AF patients with eGFR levels of 50 ml/min or less and 50 to 80 ml/min. In patients with an eGFR of more than 80 ml/min, apixaban was cost-effective compared with warfarin, costing $6307 per quality-adjusted life-year gained. Results were consistent assuming anticoagulant discontinuation after major bleeding events. Compared with dabigatran and rivaroxaban, apixaban was the only cost-effective anticoagulant strategy relative to warfarin in both mild and moderate renal impairment settings. **Conclusions:** Apixaban is a favorably cost-effective alternative to warfarin in AF patients with normal kidney function and potentially cost-saving in those with renal impairment.

Keywords: apixaban, atrial fibrillation, cost-utility, kidney disease, warfarin

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a fivefold increase in the risk of stroke [1]. Oral anticoagulation with vitamin K antagonists such as warfarin reduces the risk of thromboembolism and stroke in patients with AF [2]. Nevertheless, warfarin clinical use is challenging. Novel oral anticoagulants (NOACs) have been shown to be at least as effective as or superior to warfarin in the reduction of stroke and intracranial bleeding in patients with AF [3]. In addition, these agents provide consistent anticoagulation without the need for routine monitoring and are associated with less drug and food interaction [4,5]. Even though NOACs are substantially more expensive as compared with warfarin, economic evaluations have shown that these agents could be cost-effective options [6–9].

Patients with chronic kidney disease (CKD) have a higher prevalence of AF than the general population [10]. It was estimated that AF is present in about 18% of patients with advanced CKD [11]. In addition, patients with CKD are at higher risk for treatment complications, especially thromboembolic and major bleeding events [12,13]. Conflicting findings regarding stroke and major bleeding risks were reported in AF patients with CKD treated with warfarin [14,15]. Warfarin has been shown to carry extra risk in patients with CKD compared with AF patients without CKD [15]. Recent observational studies suggested that warfarin use may be associated with increased rates of bleeding and mortality, especially in patients with end-stage renal disease (ESRD) [16]. NOACs are increasingly being prescribed for patients with impaired renal function as an alternative to warfarin [17]. They have been shown to be at least as effective and safe as standard warfarin therapy in AF patients with renal impairment [18,19]. The optimal anticoagulation strategy in this patient population is, however, unclear and requires further assessment.

Apixaban is an NOAC that acts by the direct inhibition of factor Xa and can be safely used in patients with ESRD [20]. Apixaban may be a preferable choice in patients with moderate to severe

* *Address correspondence to:* Shoroq M. Altawalbeh, Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan.

E-mail: smaltawalbeh@just.edu.jo

1098-3015/$36.00 - see front matter

https://doi.org/10.1016/j.jval.2018.06.009

CKD because it has less renal elimination (27%) compared with other NOACs such as dabigatran (80%), rivaroxaban (36%), or edoxaban (50%) [17,21,22]. Extensive renal elimination is a drawback in the use of anticoagulant agents in patients with kidney impairment because of increased risk of accumulation and consequently bleeding. Even in patients with renal impairment in whom dose adjustment might be appropriate, increased sensitivity to renal impairment is problematic because renal function can decline quickly and suddenly because of acute renal injury [23].

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was shown to be safer than warfarin with superior reduction in the risk of stroke, systemic embolism, mortality, and major bleeding irrespective of kidney function [24,25]. Various analyses assessed the cost effectiveness of apixaban versus other anticoagulants in nonvalvular AF in multiple countries and showed that apixaban is the most cost-effective therapeutic option for stroke prevention [26–33]. In the general AF population, apixaban was the most cost-effective NOAC agent, costing less than $50,000 per quality-adjusted life-year (QALY) gained [34]. Nevertheless, the cost effectiveness of apixaban was not investigated in AF patients with renal impairment.

With higher AF risk in patients with CKD and the high cost of illness in this patient population, use of a cost-effective anticoagulant agent is essential. Furthermore, the higher acquisition cost of apixaban makes full economic evaluation more helpful in guiding clinical practice decisions. To our knowledge, this is the first study evaluating the cost-utility of apixaban versus warfarin specifically in AF patients at varying kidney function levels.

Methods

The Primary Decision Model Structure and Analysis

A Markov model was constructed using TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA) to estimate the incremental costs and quality-adjusted life expectancy associated with apixaban (5 mg twice a day) compared with warfarin (with standard clinic monitoring) in the AF patient population at three levels of kidney function. Treatment alternatives were compared among subgroups of patients with an estimated glomerular filtration rate (eGFR) of more than 80 ml/min (no renal impairment), 50 to 80 ml/min (mild renal impairment), and 50 ml/min or less (moderate renal impairment); patients with calculated creatinine clearance of less than 25 ml/min were excluded from the ARISTOTLE study. The incremental cost-effectiveness ratio (ICER), the final outcome of the decision model, was computed for each eGFR subgroup to determine costs per QALY gained for apixaban compared with warfarin. The model adopted the US health care system perspective, with all costs in 2014 US dollars. Future costs and QALYs were discounted by 3% according to the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine [35,36].

Cohorts were simulated in base-case analyses and transitioned in 1-month cycles through five distinct health states including AF without complications (without cerebrovascular or systemic embolism events), postischemic stroke, posthemorrhagic stroke, postsystemic embolism, and death (Fig. 1). Parameter mean values used in base-case analyses are presented in Table 1. Each cohort was followed over a 45-year time horizon (with a starting age of 40 years and up to 85 years) to evaluate long-term effects and costs. During each 1-month cycle, patients could survive or die from ischemic stroke, hemorrhagic stroke, systemic embolism, or major bleeding. Additional risk of age-based mortality was incorporated using US life tables.

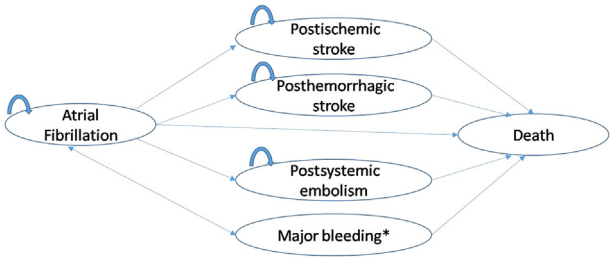

Fig. 1 – Schematic presentation of the Markov model. Patients transitioned through five clinical health states: atrial fibrillation (without cerebrovascular or systemic embolism events), postischemic stroke, posthemorrhagic stroke, postsystemic embolism, and death. *Major bleeding is assumed to be a transient health state.

Primary Model Sensitivity Analyses

Univariate sensitivity analyses were conducted to test the robustness of our base-case results and to identify the most influential parameters affecting the decision. Each parameter was varied over its plausible range while keeping all other parameters constant at their base-case values. Parameter ranges were assigned either on the basis of reported 95% confidence intervals or otherwise by using the 95% confidence intervals produced from integer parameter distributions.

In addition, the robustness of base-case results was evaluated by conducting a probabilistic sensitivity analysis (PSA) using Monte-Carlo simulation with 5000 iterations. In PSA, uncertainty was evaluated by simultaneously varying all model parameters through random sampling from their respective distributions (Table 1). Beta, uniform, and gamma distributions were assigned to event probabilities, utilities, and cost estimates, respectively. PSA results are presented in terms of probabilities of being favored at various willingness-to-pay (WTP) levels in cost-effectiveness acceptability curves.

Primary Model Assumptions

Certain assumptions were made in the decision model. First, patients surviving modeled events including stroke, thromboembolic, or bleeding events were assumed to stay on the same assigned anticoagulant medication. Second, a maximum of one event could occur in each monthly cycle. Third, we assumed 100% adherence to anticoagulant medications without discontinuation or medication switch. Fourth, persons in the postevent states can still have other events occur because previous events do not prevent subsequent events from occurring. Finally, only acute event costs were included in the analyses. Long-term costs were not included because of the lack of reliable recent data that are specific for events modeled in this study, which would bias the analysis against an intervention with fewer negative events.

Primary Model Event Rates and Mortality

Event probabilities in both treatment arms were derived from event rates reported in the ARISTOTLE trial for each eGFR level [24]. Mortality associated with ischemic stroke, hemorrhagic stroke, systemic embolism, and major bleeding was obtained from previous literature [31,37,38].

Primary Model Costs

The study was conducted from the US health care system perspective, where only direct medical costs in US dollars were considered. Costs of apixaban (5 mg twice daily) and warfarin were obtained from an official price list (www.goodrx.com) and were $404 and $10/

Table 1 – Base-case model variables and ranges: event probabilities, mortality estimates, costs, and utilities

Model parameters	Estimate	Range	Assumed distribution
Event probabilities (annual %)			
eGFR of ≤50 ml/min			
Ischemic stroke, warfarin [24]	1.6	1.2–2.2	Beta
Ischemic stroke, apixaban [24]	1.7	1.3–2.3	Beta
Hemorrhagic stroke, warfarin [24]	0.88	0.56–1.3	Beta
Hemorrhagic stroke, apixaban [24]	0.27	0.11–0.5	Beta
Systemic embolism, warfarin [24]	0.12	0.02–0.29	Beta
Systemic embolism, apixaban [24]	0.08	0.01–0.22	Beta
Major bleeding, warfarin [24]	6.2	5.4–7.5	Beta
Major bleeding, apixaban [24]	3.2	2.5–4.0	Beta
eGFR of 50–80 ml/min			
Ischemic stroke, warfarin [24]	1.08	0.85–1.35	Beta
Ischemic stroke, apixaban [24]	0.93	0.71–1.15	Beta
Hemorrhagic stroke, warfarin [24]	0.52	0.37–0.71	Beta
Hemorrhagic stroke, apixaban [24]	0.23	0.13–0.35	Beta
Systemic embolism, warfarin [24]	0.07	0.023–0.14	Beta
Systemic embolism, apixaban [24]	0.09	0.032–0.16	Beta
Major bleeding, warfarin [24]	3.16	2.8–3.65	Beta
Major bleeding, apixaban [24]	2.42	2.08–2.83	Beta
eGFR of >80 ml/min			
Ischemic stroke, warfarin [24]	0.79	0.59–1.01	Beta
Ischemic stroke, apixaban [24]	0.73	0.55–0.94	Beta
Hemorrhagic stroke, warfarin [24]	0.27	0.16–0.40	Beta
Hemorrhagic stroke, apixaban [24]	0.22	0.13–0.33	Beta
Systemic embolism, warfarin [24]	0.06	0.02–0.12	Beta
Systemic embolism, apixaban [24]	0.03	0.003–0.08	Beta
Major bleeding, warfarin [24]	1.82	1.51–2.17	Beta
Major bleeding, apixaban [24]	1.45	1.18–1.76	Beta
Probability of death after event (%)			
Ischemic stroke [38]	8.0	7.1–9.6	Beta
Hemorrhagic stroke [37]	16.4	9.14–24.7	Beta
Systemic embolism [31]	9.0	5.0–13.7	Beta
Major bleeding [31]	2.0	1.13–3.0	Beta
Costs ($)			
Treatment cost warfarin (per month) [54]	15.35*	7.68–23.03	Gamma
Treatment cost apixaban (per month) [54]	404	202–606	Gamma
Ischemic stroke hospitalization [40]	15,790	15,320–16,260	Gamma
Hemorrhagic stroke hospitalization [40]	21,623	20,761–22,485	Gamma
Systemic embolism hospitalization [40]	15,976	13,942–18,010	Gamma
Major bleeding hospitalization [40]	9,818	4,909–14,727	Gamma
Status utilities (0–1)			
AF and CKD without complications [42]	0.81	0.678–0.914	Uniform
Postischemic stroke [41]	0.443	0.426–0.460	Uniform
Posthemorrhagic stroke [41]	0.431	0.414–0.448	Uniform
Postsystemic embolism [41]	0.627	0.589–0.664	Uniform
Acute utility decrements (0–1)			
Ischemic stroke [42]	0.139	0.118–0.160	Uniform
Hemorrhagic stroke [42]	0.139	0.118–0.160	Uniform
Systemic embolism [42]	0.12	0.102–0.139	Uniform
Major bleeding [42]	0.18	0.155–0.209	Uniform

AF, atrial fibrillation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio.
* Treatment cost includes $5.35 for monthly INR monitoring test.

month for apixaban and warfarin, respectively. The cost of one international normalized ratio test was obtained from the *Medicare Reimbursement Handbook* 2015 and included in the monthly warfarin cost ($5.35) [39]. All event hospitalization costs were obtained from the Healthcare and Utilization Project for 2014 [40].

Primary Model Utilities

Health state utilities for patients with AF were obtained from previous literature and applied to the model baseline states (Table 1) [41,42]. Chronic state utilities were adjusted with acute utility decrements associated with the occurrence of stroke, systemic embolism, and major bleeding events (Table 1) [42].

Sensitivity Analysis Model with Anticoagulant Discontinuation Assumed after Major Bleeding

In comparison with the primary analysis that assumes restarting the anticoagulants after major bleeding events as supported by

some of the literature [43,44], this sensitivity model assumes anticoagulant discontinuation after major bleeding because no definite evidence-based recommendations are available [43]. In this model, a new health status of "post major bleeding" was added. Event probabilities for patients entering this new health status were extracted from the literature. These are presented in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.009.

Sensitivity Analysis Model with Composite Stroke/Systemic Embolism Outcome, and with Dabigatran and Rivaroxaban Included in the Model

The primary analysis model was limited to warfarin and apixaban because apixaban is the preferred NOAC agent in patients with impaired renal function, and because of the limited data on the other available NOAC agents in the modeled scenario (by eGFR level and for stroke, systemic embolism, and major bleeding). In this sensitivity model, combined strokes and systemic embolism in addition to major bleeding event probabilities were extracted from the ARISTOTLE [24], the Randomized Evaluation of Long-term Anticoagulation Therapy [45], and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) [13] trials. The incremental costs and quality-adjusted life expectancy associated with the four anticoagulants were compared in the AF patient population within two patient groups of mild and moderate renal impairments. Anticoagulant discontinuation after major bleeding events was also assumed in this model. The parameters are presented in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.009.

Results

Base-Case Analysis (Primary Model)

Under base-case conditions, apixaban is a dominant treatment strategy compared with warfarin (was less expensive and more effective) in AF patients with eGFR levels of 50 ml/min or less and 50 to 80 ml/min. The incremental QALYs with apixaban compared with warfarin expectancy were 0.7 QALY with an eGFR of 50 ml/min or less and 0.54 QALY with an eGFR of 50 to 80 ml/min. In comparison with apixaban, warfarin was associated with higher total costs of $5,607 with an eGFR of 50 ml/min or less and $814 with an eGFR of 50 to 80 ml/min. Treatment with apixaban was more costly than with warfarin only in patients with normal kidney function (eGFR >80 ml/min); nevertheless, apixaban was very cost-effective compared with warfarin when considering the commonly cited benchmark WTP thresholds for US health care interventions, that is, $50,000 to $100,000/QALY gained [46]. Treatment with apixaban cost $6307/QALY gained compared with warfarin (Table 2).

Sensitivity Analysis (Primary Model)

Table 3 presents the effect of underlying parameter values and assumptions for which the base-case results were sensitive within each eGFR subgroup. Univariate sensitivity analyses showed that apixaban was robustly favored across all parameter ranges included in the model for patients with an eGFR of 50 ml/min or less. Apixaban was economically favored after varying of all input parameters in patients with an eGFR of 50 to 80 ml/min. Variation of some parameters, including probabilities of ischemic stroke, major bleeding, and treatment cost for apixaban-treated patients, were all associated with warfarin no longer being dominated. Nevertheless, apixaban remained favorably cost-effective (costlier, more effective) when a WTP threshold of $50,000/QALY was used. For example, a 15% increase in major bleeding probability for apixaban-treated patients (of $\geq$0.0278) results in warfarin no longer being dominated (i.e., makes it less expensive, but still less effective than apixaban). Apixaban was, however, still cost-effective when considering a WTP threshold of $50,000/QALY, with a cost of $3,872/QALY at the upper limit of its plausible probability range (3.63%).

Nevertheless, preference for apixaban was less robust in patients with normal kidney function (eGFR >80 ml/min). Apixaban was dominated with a 19% decrease in probabilities of ischemic stroke in warfarin-treated patients. Furthermore, apixaban was dominated with a 20% increase in probability of ischemic stroke for apixaban-treated patients. Results were also sensitive to increased probability of hemorrhagic stroke for apixaban; apixaban ICER was exceeding the WTP of $50,000/QALY at probabilities of 0.00319 or higher. All one-way sensitivity analysis thresholds for changing base-case decisions are presented in Table 3.

PSA (Primary Model)

Apixaban was a dominant strategy in 99% of the Monte-Carlo simulations and was cost-effective in 98% of the simulations at a WTP threshold of $50,000/QALY. Likewise, in patients with an eGFR of 50 to 80 ml/min, apixaban was the favored strategy in 76% of the simulations and cost-effective in 97% of the simulations at a WTP threshold of $50,000/QALY. Given an eGFR of more than 80 ml/min, apixaban was dominant only in 17% of the Monte-Carlo simulations, but apixaban was still cost-effective in 75% of the iterations at a WTP threshold of $50,000/QALY. Figure 2 displays the cost-effectiveness acceptability curves.

Sensitivity Analysis Model with Anticoagulant Discontinuation Assumed after Major Bleeding

Similar to the primary analysis results, in this model in which anticoagulant discontinuation after major bleeding events was assumed, apixaban was a dominant treatment strategy compared with warfarin in AF patients with eGFR levels of 50 ml/min or less and 50 to 80 ml/min. In patients with normal kidney function (eGFR >80 ml/min), apixaban treatment was a cost-effective alternative to warfarin with an ICER of $695/QALY gained. Detailed results are presented in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.009.

Univariate sensitivity analyses showed that apixaban was dominant across all parameter ranges included in the model for patients with eGFR levels of 50 ml/min or less and 50 to 80 ml/min. In patients with normal kidney function (eGFR >80 ml/min), apixaban was dominant in the following cases: probabilities of ischemic stroke in warfarin-treated patients exceeding 0.001; probabilities of ischemic stroke in apixaban-treated patients being less than 0.0058; probabilities of major bleeding in warfarin-treated patients exceeding 0.02; probabilities of major bleeding in apixaban-treated patients being less than 0.013; and when apixaban treatment costs per month are less than $299.

Sensitivity Analysis Model with Composite Stroke/Systemic Embolism Outcome, and with Dabigatran and Rivaroxaban Included in the Model

In this model, base-case results showed that apixaban was the only cost-effective anticoagulant strategy and was dominant in relative to warfarin, dabigatran, and rivaroxaban in both mild and moderate renal impairment settings. Detailed costs and effectiveness estimated for the four anticoagulants are presented in Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.009.

Table 2 – Base-case analysis results

Strategy	Cost	Incremental cost	QALYs	Incremental QALYs	ICER
			eGFR of ≤50 ml/min		
Apixaban	$17483	–	15.76	–	–
Warfarin	$23,090	$5,607	15.06	−0.7	Dominated
			eGFR of 50–80 ml/min		
Apixaban	$12,362	–	16.66	–	–
Warfarin	$13,176	$814	16.12	−0.54	Dominated
			eGFR of >80 ml/min		
Warfarin	$8,158	–	16.82	–	–
Apixaban	$9,168	$1,010	16.98	0.16	$6,307.25

eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

In patients with moderate renal impairment, univariate sensitivity analyses showed that apixaban was dominant across all plausible parameter ranges. In patients with mild renal impairment, warfarin and dabigatran were undominated with varying variables as detailed in Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.06.009. Nevertheless, apixaban was still cost-effective with ICERs less than $50,000/QALY in all cases.

Discussion

This study primarily evaluated the cost effectiveness of apixaban versus warfarin for prevention of stroke and other thromboembolic events in AF patients at different levels of kidney function. Overall, study results point toward the preference of apixaban in AF patients with renal impairment, which was supported by both deterministic analyses and PSAs. In addition, considering both the cost and effectiveness of available NOACs, dabigatran and rivaroxaban were also inferior to apixaban in patients with mild and moderate renal impairment.

Our analysis showed that in patients with an eGFR of less than 80 ml/min, warfarin was absolutely dominated, with modeled patients treated with warfarin incurring higher costs and achieving fewer QALYs. Results were robust when varying base-case parameter values over plausible ranges, particularly when eGFR was less than 50 ml/min. Apixaban was favored on the basis of event rates obtained from the ARISTOTLE trial, which found apixaban to be more effective in preventing stroke, systemic embolism, and major bleeding events compared with warfarin among all kidney function levels, with apixaban's superiority increasing as the eGFR decreased, primarily for major bleeding risk reduction [24]. Apixaban decreased bleeding risk by 50% with moderately decreased kidney function (eGFR 30–49 ml/min) [24], and may be even applicable to patients with ESRD [47]. In our study, the superiority of apixaban in alleviating economic burden related to hemorrhagic stroke, systemic embolism, and major bleeding events decreased total cost, despite the higher acquisition cost of apixaban. Similarly, mortality associated with these events and event-related disutility decreased, contributing to the production of more QALYs with apixaban in this population.

In AF patients with normal kidney function (eGFR >80 ml/min), apixaban was a very cost-effective alternative to warfarin. Apixaban, compared with warfarin, costs only $6307/QALY gained. In agreement with our results, previous investigations conducted on the basis of ARISTOTLE data have demonstrated the cost-effective nature of apixaban versus warfarin for stroke prevention in the general AF patient population [33,48,49]. This also has been clearly

Table 3 – Univariate sensitivity analyses results and thresholds for changing base-case decision

Sensitivity parameters	Base-case value	Threshold value	Decision change
		eGFR of 50–80 ml/min	
Probability of (%)			
Ischemic stroke, apixaban	0.93	≥1.123	Warfarin not dominated, but apixaban is cost-effective (ICER up to $20,350/QALY at probability of 1.39%)
Major bleeding, apixaban	2.42	≥2.781	Warfarin not dominated, but apixaban is cost-effective (ICER up to $3,872/QALY at probability of 3.63%)
Treatment cost, apixaban	404	≥529	Warfarin not dominated, but apixaban is cost-effective (ICER up to $944/QALY at monthly cost of $606)
		eGFR of >80 ml/min	
Probability of (%)			
Hemorrhagic stroke, apixaban	0.22	≥0.319	Apixaban ICER >$50,000/QALY
Ischemic stroke, warfarin	0.79	≤0.639	Apixaban-dominated
Ischemic stroke, apixaban	0.73	≥0.87	Apixaban-dominated

eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

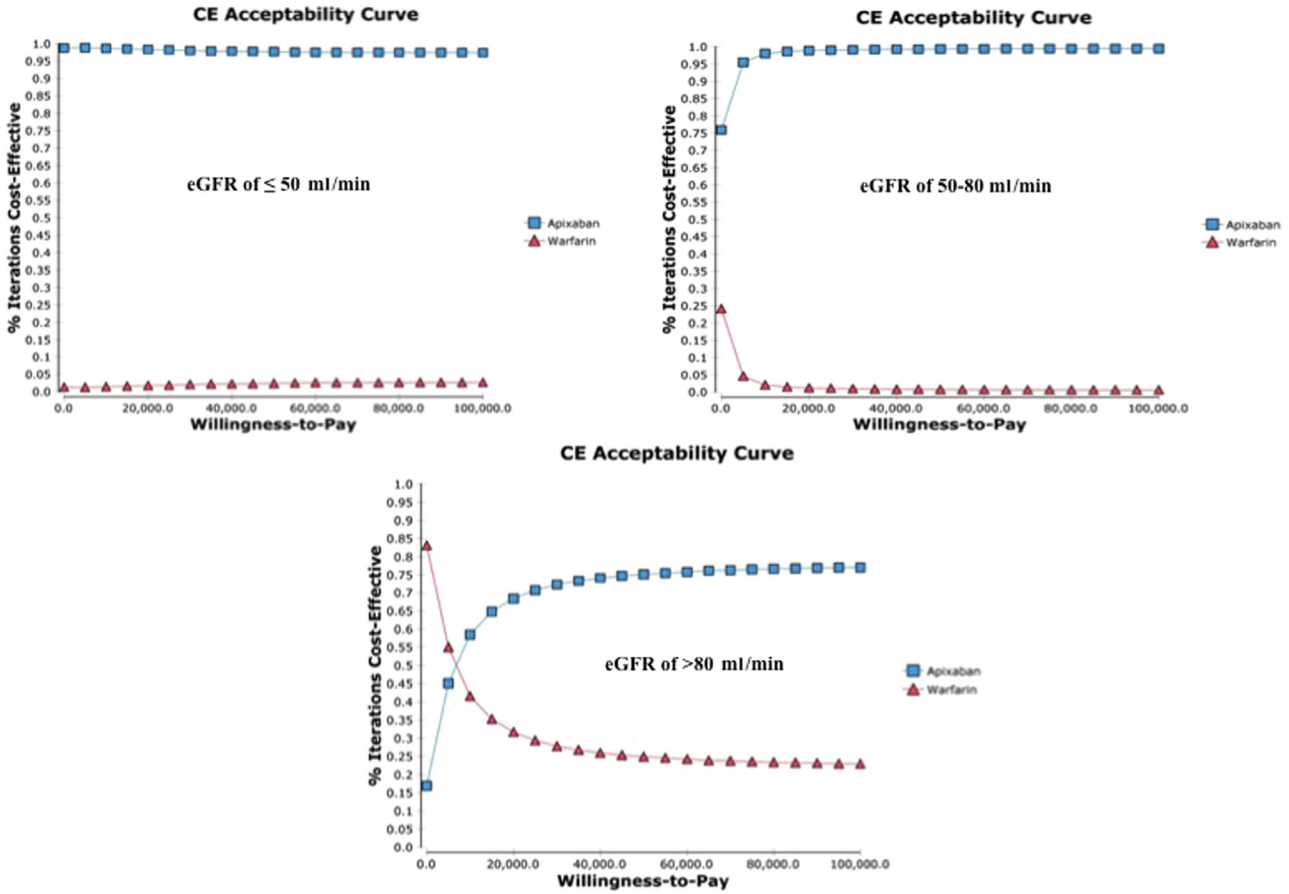

Fig. 2 – CE acceptability curves showing probabilities of treatments being cost-effective at a range of willingness-to-pay values. CE, cost effectiveness; eGFR, estimated glomerular filtration rate.

supported in a recent systematic review on the cost effectiveness of apixaban in AF, and suggested that apixaban is cost-effective compared with warfarin with ICERs ranging from €5,607 to €57,245/QALY ($6,663–$68,027/QALY gained) [50]. Nevertheless, in contrast with renal impaired subgroups in this study, results were quite sensitive to variation in persons with normal kidney function.

Irrespective of renal function, both dabigatran and rivaroxaban were associated with significantly higher risks of stroke, systemic embolism, and major bleeding and lower related medical costs compared with apixaban [51,52]. In comparison with dabigatran and rivaroxaban in the present study, apixaban was consistently the only cost-effective treatment strategy in patients with mild and moderate renal impairment.

Our study has limitations. Event rates derived from the ARISTOTLE clinical trial, with highly monitored protocols, may not be representative of real-world practice. Furthermore, event rates based on a 1.8-year average follow-up period in the ARISTOTLE trial may not be accurately applied to a 45-year time horizon. In addition, the results cannot be extrapolated to patients with severe CKD (creatinine clearance <25 ml/min) or with ESRD, because they were excluded from the ARISTOTLE trial. Assumptions such as those of 100% compliance to medication, maintaining the same efficacy of apixaban over the 45-year follow-up, and similar costs of apixaban over the time period might not be completely valid. Finally, because we did not include long-term costs of adverse events, our results would tend to bias against the intervention associated with fewer events, in this case apixaban, making the case favoring apixaban even stronger.

Overall, treatment with anticoagulants is of paramount importance in patients with CKD who are at a higher risk of stroke and mortality because of prevalent AF [10]. Increased bleeding and thromboembolic risks associated with decreased kidney function make appropriate oral anticoagulant selection challenging [20]. The optimal choice for preventing stroke in this population should consider efficacy, safety, and cost. In particular, apixaban has shown preferable outcomes over warfarin regarding reduced major hemorrhagic events [24,53]. Building on this evidence, the present study demonstrates that apixaban is an economically favorable alternative to warfarin in AF patients with normal kidney function and potentially cost-saving in those with renal impairment. This study reinforces previous evidence of the favorable cost effectiveness of apixaban in populations with normal kidney function and provides new evidence to consider guideline revision to acknowledge apixaban as a first-line treatment in patients with CKD.

Conclusions

This study demonstrates that apixaban is a cost-effective alternative anticoagulant to warfarin in patients with AF irrespective of kidney function. The cost effectiveness of apixaban is most

evident in patients with lower eGFR levels in whom warfarin is not economically favorable.

Source of financial support: This project was supported by the Deanship of Scientific Research at Jordan University of Science and Technology (grant no. 87/2017).

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.06.009.

REFERENCES

[1] Wolf PA, Dawber TR, Thomas Jr HE, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–7.

[2] Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.

[3] Ntaios G, Papavasileiou V, Diener HC, et al. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized controlled trials. Int J Stroke 2017;12:589–96.

[4] Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood 2010;115:15–20.

[5] Schirmer SH, Baumhakel M, Neuberger HR, et al. Novel anticoagulants for stroke prevention in atrial fibrillation: current clinical evidence and future developments. J Am Coll Cardiol 2010;56:2067–76.

[6] Kansal AR, Zheng Y, Pokora T, et al. Cost-effectiveness of new oral anticoagulants in the prevention of stroke in patients with atrial fibrillation. Best Pract Res Clin Haematol 2013;26:225–37.

[7] Wisloff T, Hagen G, Klemp M. Economic evaluation of warfarin, dabigatran, rivaroxaban, and apixaban for stroke prevention in atrial fibrillation. Pharmacoeconomics 2014;32:601–12.

[8] Hernandez I, Smith KJ, Zhang Y. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation at high risk of bleeding and normal kidney function. Thromb Res 2017;150:123–30.

[9] Hallinen T, Soini EJ, Linna M, et al. Cost-effectiveness of apixaban and warfarin in the prevention of thromboembolic complications among atrial fibrillation patients. Springerplus 2016;5:1354.

[10] Lau YC, Proietti M, Guiducci E, et al. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. J Am Coll Cardiol 2016;68:1452–64.

[11] Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J 2010;159:1102–7.

[12] Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009;119:1363–9.

[13] Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32:2387–94.

[14] Harel Z, Chertow GM, Shah PS, et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis: a systematic review and meta-analysis. Can J Cardiol 2017;33:737–46.

[15] Qamar A, Bhatt DL. Stroke prevention in atrial fibrillation in patients with chronic kidney disease. Circulation 2016;133:1512–5.

[16] Granger CB, Chertow GM. A pint of sweat will save a gallon of blood: a call for randomized trials of anticoagulation in end-stage renal disease. Circulation 2014;129:1190–2.

[17] Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol 2016;67:2888–99.

[18] Harel Z, Sholzberg M, Shah PS, et al. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. J Am Soc Nephrol 2014;25:431–42.

[19] Sardar P, Chatterjee S, Herzog E, et al. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Can J Cardiol 2014;30:888–97.

[20] Pelliccia F, Rosanio S, Marazzi G, et al. Efficacy and safety of novel anticoagulants versus vitamin K antagonists in patients with mild and moderate to severe renal insufficiency: focus on apixaban. Int J Cardiol 2016;225:77–81.

[21] Buckley LF, Rybak E, Fanikos J, et al. Direct oral anticoagulants in patients with atrial fibrillation and renal impairment, extremes in weight, or advanced age. Clin Cardiol 2017;40:46–52.

[22] Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. Int J Nephrol Renovasc Dis 2017;10:135–43.

[23] Belmar Vega L, de Francisco ÁLM, Bada da Silva J, et al. New oral anticoagulants in patients with chronic kidney disease. Nefrología 2017;37:244–52.

[24] Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012;33:2821–30.

[25] Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE randomized clinical trial. JAMA Cardiol 2016;1:451–60.

[26] Giorgi MA, Caroli C, Giglio ND, et al. Estimation of the cost-effectiveness of apixaban versus vitamin K antagonists in the management of atrial fibrillation in Argentina. Health Econ Rev 2015;5:52.

[27] Stevanovic J, Pompen M, Le HH, et al. Economic evaluation of apixaban for the prevention of stroke in non-valvular atrial fibrillation in the Netherlands. PLoS One 2014;9:e103974.

[28] Ademi Z, Pasupathi K, Liew D. Cost-effectiveness of apixaban compared to warfarin in the management of atrial fibrillation in Australia. Eur J Prev Cardiol 2015;22:344–53.

[29] Athanasakis K, Boubouchairopoulou N, Karampli E, et al. Cost effectiveness of apixaban versus warfarin or aspirin for stroke prevention in patients with atrial fibrillation: a Greek perspective. Am J Cardiovasc Drugs 2017;17:123–33.

[30] Li X, Tse VC, Lau WC, et al. Cost-effectiveness of apixaban versus warfarin in Chinese patients with non-valvular atrial fibrillation: a real-life and modelling analyses. PLoS One 2016;11:e0157129.

[31] Dorian P, Kongnakorn T, Phatak H, et al. Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. Eur Heart J 2014;35:1897–906.

[32] Lanitis T, Kongnakorn T, Jacobson L, et al. Cost-effectiveness of apixaban versus warfarin and aspirin in Sweden for stroke prevention in patients with atrial fibrillation. Thromb Res 2014;134:278–87.

[33] Lee S, Mullin R, Blazawski J, et al. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLoS One 2012;7:e47473.

[34] Shah A, Shewale A, Hayes CJ, et al. Cost-effectiveness of oral anticoagulants for ischemic stroke prophylaxis among nonvalvular atrial fibrillation patients. Stroke 2016;47:1555–61.

[35] Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. New York, NY: Oxford University Press; 2005.

[36] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996.

[37] Krumholz HM, Merrill AR, Schone EM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes 2009;2:407–13.

[38] Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690–8.

[39] Roche Diagnostics and American Medical Association. Medicare reimbursement handbook for healthcare professionals. 2015. Available from: http://www.coaguchek-usa.com/content/dam/internet/dia/coaguchek/coaguchek-usa_com/coaguchek_hcp/pdf/CoaguChek-Medical-Reimbursement-Handbook-for-HCP.pdf. [Accessed August 21, 2017].

[40] Agency for Healthcare Research and Quality. National and regional estimates on hospital use for all patients from the HCUP nationwide inpatient sample (NIS). Healthcare Cost and Utilization Project Online (HCUPnet). Available from: http://hcupnet.ahrq.gov/. [Accessed July 2017].

[41] Hattori N, Hirayama T, Katayama Y. Medical care for chronic-phase stroke in Japan. Neurol Med Chir (Tokyo) 2012;52:175–80.

[42] Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care 2005;43:736–49.

[43] Smit MD, Van Gelder IC. Resumption of anticoagulation after major bleeding decreases the risk of stroke in patients with atrial fibrillation. Evid Based Med 2017;22:107–8.

[44] Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. Am J Cardiol 2014;113:662–8.
[45] Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation 2014;129:961–70.
[46] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.
[47] McCullough PA, Ball T, Cox KM, et al. Use of oral anticoagulation in the management of atrial fibrillation in patients with ESRD: Pro. Clin J Am Soc Nephrol 2016;11:2079–84.
[48] Kamel H, Easton JD, Johnston SC, et al. Cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in atrial fibrillation. Neurology 2012;79:1428–34.
[49] Hernandez I, Smith KJ, Zhang Y. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation at high risk of bleeding and normal kidney function. Thromb Res 2017;150:123–30.
[50] Pinyol C, Cepeda JM, Roldan I, et al. A systematic literature review on the cost-effectiveness of apixaban for stroke prevention in non-valvular atrial fibrillation. Cardiol Ther 2016;5:171–86.
[51] Deitelzweig S, Luo X, Trocio J, et al. All-cause, stroke/systemic embolism-, and major bleeding-related health-care costs among elderly patients with nonvalvular atrial fibrillation treated with oral anticoagulants. Clin Appl Thromb Hemost 2018;24:602–11.
[52] Amin A, Keshishian A, Trocio J, et al. Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Curr Med Res Opin 2017;33:1595–604.
[53] Hart RG, Eikelboom JW, Brimble KS, et al. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol 2013;29:S71–8.
[54] Webpage GR. Available from: http://www.goodrx.com/. [Accessed June 9, 2017].