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SHORT COMMUNICATION

Comparing the Cost Effectiveness of Non-vitamin K Antagonist Oral Anticoagulants with Well-Managed Warfarin for Stroke Prevention in Atrial Fibrillation Patients at High Risk of Bleeding

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Abstract

Background Several studies have compared the cost effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin using results from clinical trials evaluating NOACs. However, the time in therapeutic range (TTR) of warfarin groups ranged across clinical trials, and all were below the therapeutic goal of 70%. We compared the cost effectiveness of edoxaban 60 mg, apixaban 5 mg, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban 20 mg, and well-managed warfarin with a TTR of 70% in preventing stroke among patients with atrial fibrillation at high risk of bleeding.

Methods For the six treatments, we used a Markov state-transition model to quantify lifetime costs in $US and effectiveness in quality-adjusted life-years (QALYs). We simulated relative risk ratios of clinical events with each NOAC versus warfarin with a TTR of 70% using published regression models that predict how the incidence of thrombotic or hemorrhagic events changes for each unit change in TTR. We re-ran our analysis for two other estimates of TTR: 65 and 75%.

Results Treatment with edoxaban 60 mg cost $US127,520/QALY gained compared with warfarin with a TTR of 70% and cost $US41,860/QALY gained compared with warfarin with a TTR of 65%. However, warfarin with a TTR of 75% was more effective and less expensive than all NOACs. For three levels of TTR, apixaban 5 mg, dabigatran 150 mg, dabigatran 110 mg, and rivaroxaban 20 mg were dominated strategies.

Conclusions The comparative cost effectiveness of edoxaban and warfarin is highly sensitive to TTR. At the $US100,000/QALY willingness-to-pay threshold, our results suggest that warfarin is the most cost-effective treatment for patients who can achieve a TTR of 70%.

Key Points

We constructed a Markov model to investigate the cost effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin with a time in therapeutic range (TTR) of 65, 70, and 75%.

We found that treatment with edoxaban 60 mg cost $US127,520/QALY gained compared with warfarin with a TTR of 70% and cost $US41,860/QALY gained compared with warfarin with a TTR of 65%. Warfarin with a TTR of 75% was more effective and less expensive than NOACs.

Our results suggest that warfarin is the preferred strategy for patients who can achieve a TTR of 70%; nevertheless, further studies comparing NOACs and warfarin with a TTR of 70% are necessary to validate our findings.

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1 Introduction

Atrial fibrillation (AF) is a common arrhythmia and the most common cause of ischemic stroke in older patients [1]. The use of oral anticoagulants in AF can reduce stroke risk by around 60% and all-cause mortality by 26% [2]. However, the use of oral anticoagulation also increases the risk of bleeding. The HAS-BLED score is a tool commonly used in the prediction of bleeding risk with anticoagulation, with a HAS-BLED score ≥ 3 indicating an increased risk of bleeding [3]. In patients at low risk of stroke, commonly defined as having CHA2DS2-Vasc score < 2, bleeding risk may outweigh the benefit of stroke prevention [4]. However, evidence supports the benefit of anticoagulation for patients with a CHA2DS2-Vasc score ≥ 2, regardless of bleeding risk [2, 5, 6].

For decades, warfarin was the only oral anticoagulant available for stroke prevention in AF. Since 2010, four non-vitamin K antagonist oral anticoagulants (NOACs) have been approved by the US FDA to prevent stroke in AF: dabigatran, rivaroxaban, apixaban, and edoxaban. NOACs have become a focus of many cost-effectiveness analyses, because—although they cost more than warfarin [7]—NOACs have a more stable pharmacokinetic profile than warfarin and do not require routine laboratory monitoring [8–11]. Specifically, warfarin therapy requires international normalized ratio (INR) monitoring for dose adjustment [12]. The time that INR levels are within the recommended INR range is referred to as time in therapeutic range (TTR) and is negatively correlated with the risk of stroke and bleeding [13]. TTR $\geq 70\%$ is recommended for warfarin users [14]; whereas previous international studies have shown that a TTR $\geq 70\%$ is achievable in real-world clinical practice [14–16], this therapeutic goal is rarely achieved in the USA [17].

Most existing cost-effectiveness studies used the results of the non-inferiority trials that compared NOACs and warfarin as input parameters in their calculations [18–23]. However, the TTR of warfarin treatment groups in these clinical trials was below the 70% recommended target and differed substantially across clinical trials, with a TTR of 64% in RE-LY (evaluating dabigatran) [9], 55% in ROCKET-AF (rivaroxaban) [11], 62% in ARISTOTLE (apixaban) [8], and 68% in ENGAGE AF-TIMI (edoxaban) [10]. To the best of our knowledge, only two studies have adjusted for these differences in TTR across trials when comparing the cost effectiveness of warfarin therapy and NOACs [24, 25], but these studies did not compare the cost effectiveness of each individual NOAC. Moreover, some argue that the efficacy of well-managed warfarin is similar or superior to that of NOACs for stroke prevention in patients with AF [13, 16, 26], so how the cost effectiveness of NOACs will compare to that of warfarin when the therapeutic goal of TTR of 70% is achieved remains unclear.

In the present study, we compared the cost effectiveness of edoxaban 60 mg, apixaban 5 mg, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban 20 mg, and well-managed, dose-adjusted warfarin, which was defined as a TTR of 70%.

2 Methods

2.1 Overview of Markov Model and Simulated Population

We used a previously published Markov state-transition model [7] to compare the cost effectiveness of edoxaban 60 mg, apixaban 5 mg, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban 20 mg, and well-managed warfarin with a TTR of 70% in the prevention of stroke and systemic embolism in patients with AF at high risk of bleeding. The AF population entered the model at 65 years of age, had moderate to high risk of stroke, defined as CHADS2 score ≥ 1, high risk of bleeding, defined as HAS-BLED ≥ 3, and did not use medications interacting with NOACs. The Markov model included the following states: AF on oral anticoagulation, AF on aspirin, severe stroke, other thromboembolic events, intracranial bleeding, extracranial bleeding, and death (Fig. 1). Other thromboembolic events included minor ischemic stroke, transient ischemic attack, and systemic embolism. The length of each cycle was 1 year, and patients were followed until they reached 90 years of age or died.

The model had the following major assumptions [7]: first, patients entered the model in the 'AF on oral anticoagulation' state, where they were treated with aspirin and

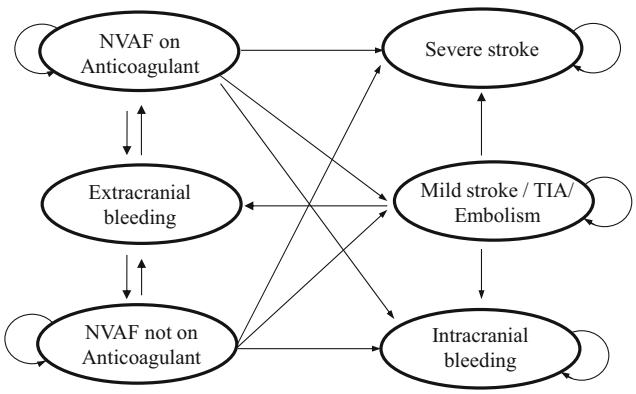

Fig. 1 Markov Model. *NVAF* nonvalvular atrial fibrillation, *TIA* transient ischemic attack. Dead state not shown to simplify the representation. Patients can transition to the dead state from all states. Reproduced from Hernandez et al. [7] with permission

one of the oral anticoagulant agents. Second, rates of adherence were assumed to be similar for all oral anticoagulant treatments [20]. Third, when patients experienced a stroke or other thromboembolic event, they resumed aspirin and anticoagulation therapy with the oral anticoagulant agent used before the event. All patients who survived an intracranial hemorrhage were assumed to discontinue oral anticoagulation therapy [27], but only 10% of those who experienced an extracranial bleeding were assumed to discontinue anticoagulation [28]. Fourth, acute costs of events were assumed to be the same for all treatments. Fifth, experiencing a major stroke, other thromboembolic event, or intracranial hemorrhage increased the risk of death in following cycles but not the risk of other events.

2.2 Input Probabilities

To estimate the relative risks of stroke, thromboembolic events, intracranial bleeding, and extracranial bleeding with NOACs when compared with warfarin at a TTR of 70%, we first estimated the incidence rates for these events that would have been observed for the warfarin group in the four clinical trials if the TTR had been 70%. To do so, we used the regression models estimated by Wan et al. [13], which predict how the incidence of thrombotic or hemorrhagic events changes for each unit change in TTR [13]. Then, we took the ratio between event rates actually observed in the clinical trials and our simulated estimates for event incidence with warfarin at a TTR of 70%. This ratio represented how many times the event frequency observed in clinical trials was larger than what it would have been had the TTR been 70%. Finally, we calculated the relative risks for events for each NOAC versus warfarin with a TTR of 70% as the product of this ratio and the relative risks observed in each of the four trials [8–11]. We repeated the same process to estimate the relative risks of events for NOAC versus warfarin with a TTR of 65% and TTR of 75% (Table 1).

The remaining inputs for the model are shown in Table 1 in the Electronic Supplementary Material (ESM) [7]. The baseline cost of warfarin therapy was estimated as the upper bound cost of a previous publication to account for more frequent INR testing [7]. Mortality estimates were derived from the US National Vital Statistics Reports [29], drug costs were obtained from http://www.goodrx.com, and estimates for costs of acute care provided for clinical events were obtained from the Healthcare and Utilization Project [30]. Estimates for follow-up costs after events, and for utilities were based on previous publications [27, 31–35]. All costs were inflated to $US, year 2015 values, using the Consumer Price Index for medical care [36].

2.3 Analysis

We adopted a US third-party payer perspective and quantified costs with each treatment strategy in year 2015 $US and effectiveness in quality-adjusted life-years (QALYs), and we calculated incremental cost-effectiveness ratios (ICERs). In one-way sensitivity analyses, we varied each parameter over the range shown in Table 1 and Table 1 in the ESM and identified the thresholds of variables at which the preferred treatment changed. Additionally, we performed a Monte Carlo probabilistic sensitivity analysis to test the robustness of our results to the simultaneous change of all input parameters. Specifically, we generated 10,000 random draws from the distribution of each of the input parameters and constructed a cost-effectiveness acceptability curve. Event probabilities and utilities were modelled as Beta distributions, relative risks as log-normal distributions, and costs as Gamma distributions. We defined cost-effective strategies based on the $US100,000/QALY gained willingness-to-pay (WTP) threshold, a commonly cited benchmark in the USA [37]. We repeated all analyses for a TTR of 65 and of 75% and after excluding edoxaban from the list of compared strategies, because this agent is not indicated in patients with creatinine clearance >95 ml/min [38].

3 Results

In the base-case analysis, edoxaban 60 mg had the highest effectiveness (8.14 QALYs), followed by dabigatran 150 mg (8.02), dabigatran 110 mg (8.01), warfarin with a TTR of 70% (7.96), apixaban 5 mg (7.95), and rivaroxaban 20 mg (7.38) (Table 2). Dabigatran 110 mg was the most expensive treatment ($US242,878) followed by dabigatran 150 mg ($US238,388), rivaroxaban 20 mg ($US237,483), apixaban 5 mg ($US235,933), edoxaban 60 mg ($US221,930) and warfarin with a TTR of 70% ($US199,393). Treatment with edoxaban 60 mg cost $US127,520/QALY gained compared with treatment with warfarin with a TTR of 70%. All other NOACs were dominated strategies since they were more expensive and less effective than edoxaban.

Results from one-way sensitivity analyses showed that warfarin at a TTR of 70% was the preferred strategy at the $US100,000/QALY WTP threshold, unless the cost of edoxaban was $<$$US3024 (88% of baseline cost), the quality of life with intracranial hemorrhage was <0.13, the relative risk of stroke with edoxaban versus warfarin at a TTR of 70% was <0.93, the relative risk of other thromboembolic events with edoxaban versus warfarin at a TTR of 70% was <0.79, or the relative risk of intracranial

Table 1 Input event probabilities, by time in therapeutic range

Input variable	RR, base case (range)			References
	Warfarin at TTR 65%	Warfarin at TTR 70%	Warfarin at TTR 75%	
Severe stroke				
RR dabigatran 150 mg versus warfarin	0.80 (0.63–1.03)	1.07 (0.84–1.38)	1.61 (1.27–2.08)	[9]
RR dabigatran 110 mg versus warfarin	1.17 (0.93–1.47)	1.56 (1.25–1.97)	2.35 (1.87–2.97)	[9]
RR rivaroxaban 20 mg versus warfarin	1.34 (0.98–1.81)	2.01 (1.31–2.43)	2.70 (1.98–3.66)	[40]
RR apixaban 5 mg versus warfarin	0.91 (0.75–1.09)	1.22 (1.00–1.46)	1.84 (1.51–2.21)	[8]
RR edoxaban 60 mg versus warfarin	0.82 (0.651.04)	1.10 (0.86–1.40)	1.66 (1.30–2.11)	[10]
Other thromboembolic event				
RR dabigatran 150 mg versus warfarin	0.75 (0.49–1.14)	1.00 (0.66–1.53)	1.50 (1.00–2.31)	[9, 41]
RR dabigatran 110 mg versus warfarin	0.71 (0.48–1.06)	0.96 (0.65–1.42)	1.44 (0.97–2.14)	[9, 41]
RR rivaroxaban 20 mg versus warfarin	1.19 (0.99–1.44)	1.59 (1.33–1.93)	2.40 (2.00–2.91)	[11]
RR apixaban 5 mg versus warfarin	0.92 (0.74–1.19)	1.23 (0.99–1.59)	1.86 (1.49–2.39)	[8]
RR edoxaban 60 mg versus warfarin	0.66 (0.53–0.87)	0.89 (0.70–1.16)	1.34 (1.06–1.75)	[10]
Intracranial hemorrhage				
RR dabigatran 150 mg versus warfarin	0.42 (0.28–0.63)	0.57 (0.38–0.85)	0.88 (0.59–1.32)	[9]
RR dabigatran 110 mg versus warfarin	0.33 (0.21–0.49)	0.44 (0.28–0.67)	0.68 (0.44–1.03)	[9]
RR rivaroxaban 20 mg versus warfarin	1.02 (0.71–1.41)	1.38 (0.97–1.91)	2.13 (1.49–2.95)	[28]
RR apixaban 5 mg versus warfarin	0.49 (0.35–0.67)	0.66 (0.47–0.91)	1.01 (0.72–1.40)	[8]
RR edoxaban 60 mg versus warfarin	0.40 (0.29–0.53)	0.54 (0.39–0.72)	0.83 (0.60–1.11)	[10]
Extracranial hemorrhage				
RR dabigatran 150 mg versus warfarin	1.13 (0.97–1.32)	1.52 (1.31–1.78)	2.35 (2.02–2.74)	[9]
RR dabigatran 110 mg versus warfarin	0.99 (0.84–1.16)	1.34 (1.14–1.56)	2.06 (1.76–2.42)	[9]
RR rivaroxaban 20 mg versus warfarin	1.75 (1.38–2.14)	2.36 (1.87–2.90)	3.65 (2.89–4.48)	[40]
RR apixaban 5 mg versus warfarin	0.91 (0.79–1.08)	1.24 (1.06–1.45)	1.91 (1.64–2.24)	[8]
RR edoxaban 60 mg versus warfarin	0.77 (0.68–0.89)	1.04 (0.91–1.20)	1.60 (1.41–1.85)	[10]

RR relative risk, *TTR* time in therapeutic range

Table 2 Base-case analysis results: total and incremental costs and quality-adjusted life-years per patient

Comparator	Cost	Effectiveness	Incremental costs	Incremental effectiveness	ICERs ($/QALY)
Warfarin with a TTR of 70%	199,393	7.9615	–	–	–
Edoxaban 60 mg	221,930	8.1382	22,538	0.17674	127,520
Apixaban 5 mg	235,933	7.9451	14,003	− 0.19308	Dominated
Rivaroxaban 20 mg	237,483	7.3806	15,553	− 0.75757	Dominated
Dabigatran 150 mg	238,388	8.0165	16,458	− 0.1217	Dominated
Dabigatran 110 mg	242,878	8.0131	43,486	− 0.12515	Dominated

Costs are presented as $US, year 2015 values, and effectiveness as QALYs

ICER incremental cost-effectiveness ratio, *QALY*s quality-adjusted life-years, *TTR* time in therapeutic range

bleeding with edoxaban versus warfarin at a TTR of 70% was <0.41 (Table 2 in the ESM).

Figure 2 shows the results of the Monte Carlo probabilistic sensitivity analyses. Warfarin with a TTR of 70% had the highest likelihood of being the most cost-effective strategy (67%) at the $US100,000/QALY WTP threshold, followed by edoxaban 60 mg (32%), dabigatran 150 mg (0.2%), dabigatran 110 mg (0.1%), apixaban 5 mg (0.02%), and rivaroxaban 20 mg (0%). Edoxaban 60 mg had the highest likelihood of being the most cost-effective alternative for WTP thresholds $>$$US130,000/QALY.

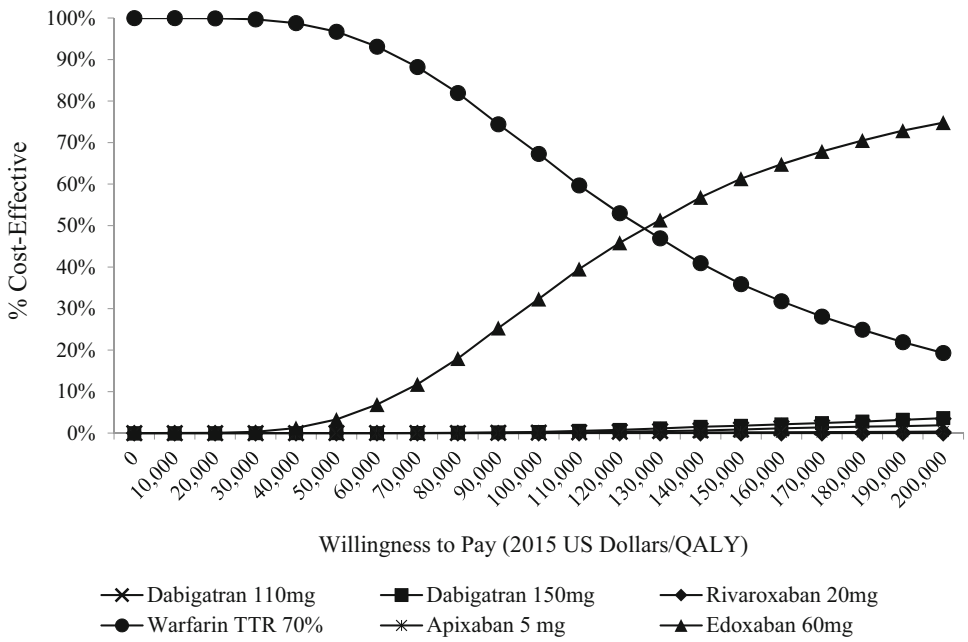

Fig. 2 Cost-effectiveness acceptability curve when time in therapeutic range with warfarin was 70%. Results from Monte Carlo probabilistic sensitivity analysis, when edoxaban was included in the analysis. *QALY* quality-adjusted life year, *TTR* time in therapeutic range

3.1 Sensitivity Analyses Ranging Time in Therapeutic Range (TTR)

Our results changed considerably when we repeated our analyses using two other estimates of TTR (65 and 75%). The ICER of edoxaban 60 mg versus warfarin at a TTR of 65% was $US41,860/QALY, but warfarin with a TTR of 75% was more effective and cheaper than edoxaban 60 mg. In both cases, the remaining NOACs were dominated strategies. These results are consistent with the findings from the Monte Carlo sensitivity analyses (Fig. 3): warfarin with a TTR of 65% was preferred over edoxaban for WTP thresholds <$US45,000 (Fig. 3a). However, when warfarin therapy achieved a TTR of 75%, warfarin was the anticoagulant preferred for all values of WTP (Fig. 3b).

3.2 Sensitivity Analyses Excluding Edoxaban from the Analysis

When edoxaban was not included in the analysis, dabigatran 150 mg cost $US708,497/QALY gained compared with treatment with warfarin at a TTR of 70%. Dabigatran 110 mg, rivaroxaban 20 mg, and apixaban 5 mg were dominated strategies. Results from the Monte Carlo sensitivity analyses were consistent with the base-case results: at the $US100,000/QALY WTP threshold, warfarin was cost effective in 99% of the scenarios simulated (Fig. 1 in the ESM). At the $US200,000/QALY WTP threshold, warfarin was cost effective in 83% of the cases, followed by dabigatran 150 mg (10%), dabigatran 110 mg (6%), and apixaban 5 mg (1%). Dabigatran would only become cost effective at WTP thresholds >$US710,000/QALY.

4 Discussion

To our knowledge, to date, our study is the first to compare the cost effectiveness of warfarin and all NOACs approved for the prevention of stroke in patients with AF while accounting for the differences in TTR observed in the trials that evaluated each NOAC. Our results suggest that, for patients who can achieve a warfarin TTR of 70%, warfarin is the most cost-effective strategy at the $US100,000/QALY WTP threshold.

In a previous publication [7], we used the same Markov model to compare the cost effectiveness of warfarin with that of each individual NOAC without accounting for the differences in TTR of the warfarin group in the clinical trials that evaluated NOACs. With ICERs of $US77,565/QALY and $US108,631/QALY, we found that edoxaban and apixaban were the strategies most likely to be cost effective at the WTP thresholds commonly used in the USA [7]. These ICERs for NOACs are smaller than those from our present analysis because the TTR of the warfarin group in all clinical trials was <70% [8–11]. Yet, the TTR for the warfarin treatment group in the clinical trial that evaluated edoxaban was considerably close to this threshold (68%) [10], which likely explains why edoxaban is the second preferred strategy after warfarin in our current analysis.

Our findings are consistent with those of Janzic and Kos [24], who compared the cost effectiveness of NOACs and warfarin at a TTR of 70% from the Slovenian perspective and found that warfarin with a TTR of 70% was cost effective at the WTP threshold commonly used in this country. Adopting a US perspective, You [25] compared

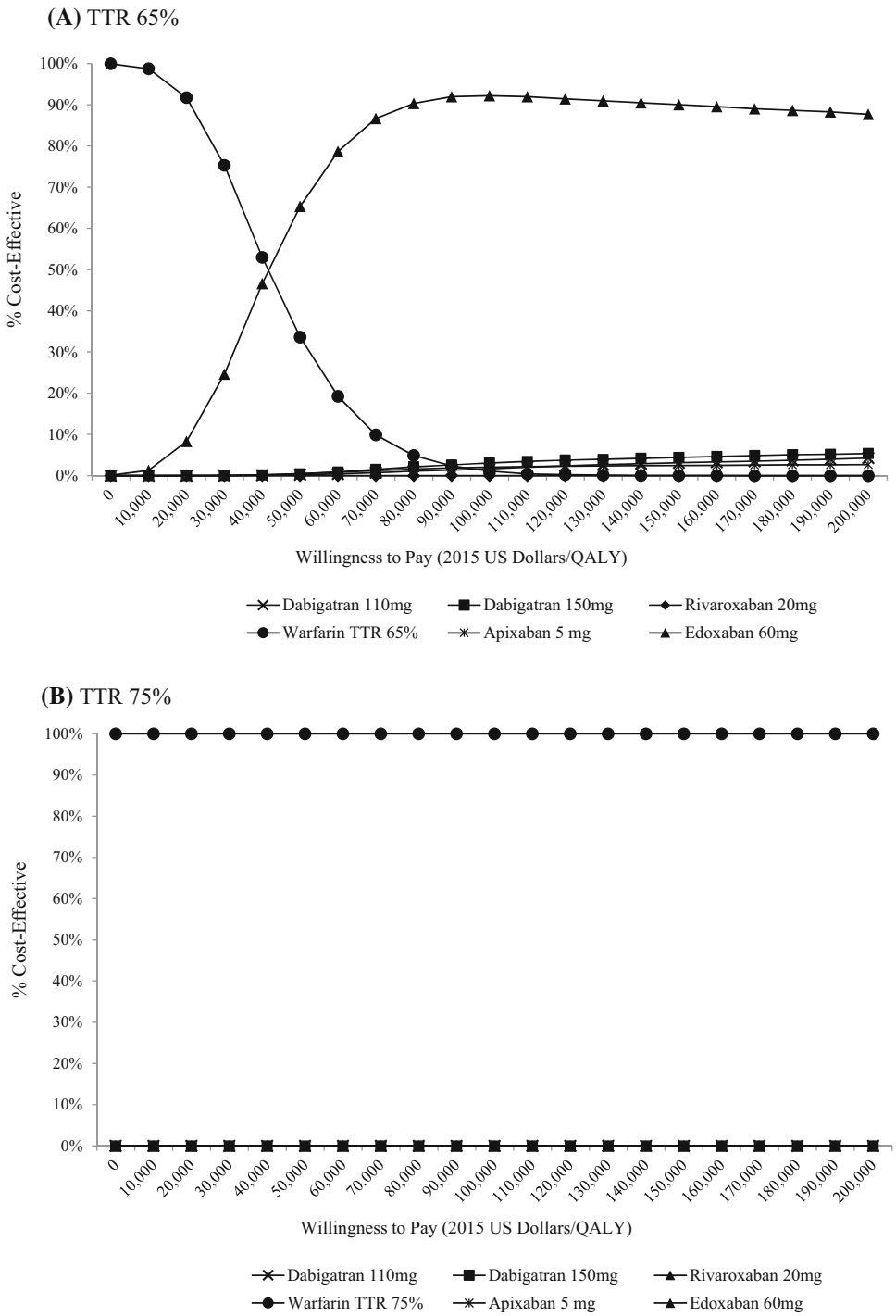

Fig. 3 Cost-effectiveness acceptability curve when time in therapeutic range with warfarin was **a** 65% and **b** 75%. Results from Monte Carlo probabilistic sensitivity analysis, when edoxaban was included in the analysis. *QALY* quality-adjusted life year, *TTR* time in therapeutic range

the cost effectiveness of NOACs and warfarin at a TTR of 70% and found that warfarin was the most cost-effective treatment at the $US50,000/QALY WTP threshold but that NOACs were preferred for WTP thresholds > $US100,000/QALY. However, this study grouped all NOACs together, and the estimates for the monthly costs of NOAC therapy were considerably smaller than ours, which may explain the different results.

The limitations associated with the assumptions of our Markov model have been discussed elsewhere [7]. Our approach to investigating the cost effectiveness of NOACs compared with that of warfarin at a TTR of 70% made our study subject to two additional weaknesses. First, to estimate rates of events with warfarin at a TTR of 70%, we used estimates from published regressions [13], assuming the relationship between the incidence of thromboembolic

and bleeding events follows a linear relationship with TTR. Real-life rates of thromboembolic or hemorrhagic events with warfarin at a TTR of 70% may differ from our estimates. Future studies should compare the effectiveness and safety outcomes of NOACs with well-managed warfarin, defined as a TTR of at least 70%, in either a randomized setting or in real-world clinical practice. Then, it will be important to conduct cost-effectiveness analyses similar to ours but with updated estimates for the hazard ratio (HR) of clinical events for NOACs compared with warfarin. Second, our results are only generalizable to patients with good anticoagulation control while receiving warfarin and who can achieve a TTR of 70% and not to those with difficulties maintaining a therapeutic INR. Third, because the objective of our study was to investigate the cost effectiveness of NOACs compared with that of well-managed warfarin, we did not conduct analyses for estimates of TTR $<65\%$. This is not especially concerning since, in those cases, edoxaban would also have been the preferred anticoagulant treatment.

Although our estimates based on the assumption that the incidence of thromboembolic and bleeding events follows a linear relationship with TTR should be interpreted with caution, our results suggest that, for patients who can achieve a TTR of 70%, warfarin should be the treatment of choice. One may argue that this information is not actionable when prescribing oral anticoagulants to warfarin-naïve patients, who do not have a record of INR monitoring. However, clinicians could identify patients who are more likely to achieve this therapeutic goal by assessing patient characteristics associated with a higher likelihood of TTR, including male sex, presence of family support, good medication management capacity, and no alcohol use [39], and initiate them on warfarin. Warfarin-experienced users who are well-managed on warfarin and have a TTR of 70% should not be switched to NOACs. NOACs, and preferably the most cost-effective—edoxaban, should then be reserved for warfarin-naïve patients who are unlikely to achieve a TTR of 70%, indicated by a record of medication non-adherence, and for warfarin-experienced users whose INR monitoring record shows a TTR $\leq 65\%$. Nevertheless, further studies directly comparing effectiveness and stay outcomes of NOACs and well-managed warfarin are needed to validate our findings and clarify the place of NOACs and warfarin in the anticoagulation of patients with AF who can achieve a TTR of 70% on warfarin.

Our findings have two additional implications. First, our findings reinforce the importance of anticoagulation management, particularly its cost-saving potential. Previous research estimated that the cost of anticoagulation monitoring to achieve a TTR of 70% was half the difference in cost between NOACs and warfarin [16]. In our study, we found that lifelong treatment with warfarin at a TTR of 75% was more effective than NOACs but cost around $US20,000 less per patient than treatment with edoxaban and between $US35,000 and 40,000 less than treatment with the remaining NOACs. Finally, the differences in results we noted after accounting for the TTR across clinical trials emphasizes the need to account for the heterogeneity of data sources while searching for input parameters in cost-effectiveness analyses.

5 Conclusion

Our results suggest that warfarin is the most cost-effective oral anticoagulation treatment in the prevention of stroke and systemic embolism in patients with AF with a high risk of bleeding and who can achieve a TTR of 70% with warfarin. Future analyses directly comparing clinical outcomes of NOACS versus warfarin with a TTR of at least 70% are needed to clarify the most optimal anticoagulation treatment in patients who can be well-managed with warfarin.

Compliance with Ethical Standards

Conflicts of interest Alexa R. Hospodar, Kenneth J. Smith, Yuting Zhang, and Inmaculada Hernandez have no conflicts of interest that are directly relevant to the content of this manuscript.

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