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ORIGINAL RESEARCH ARTICLE

Integrating Real-World Evidence in Economic Evaluation of Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation in a Developing Country

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Abstract

Objective This study aimed to estimate the cost effectiveness of non-vitamin K oral anticoagulants (NOACs) compared with warfarin for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) in Thailand where suboptimal anticoagulation control is common.

Materials and Methods A hypothetical cohort of 65-year-old patients with NVAF and their disease progression was simulated in the Markov model. The following anticoagulant agents were used: warfarin, dabigatran, rivaroxaban, and apixaban. Warfarin with high, intermediate, and low time in therapeutic ranges (TTR) was used as the three different reference treatments. Baseline clinical events were obtained from a recently published real-world study in Thailand. A lifetime horizon was utilized in this model, and all analyses were performed from societal and healthcare perspectives. The results were reported as incremental cost-effectiveness ratios (ICERs) in 2021 US dollars per quality-adjusted life-year (QALY) gained. The sensitivity analyses were performed to assess the influence of parameter uncertainty.

Results Apixaban was a cost-effective intervention compared with warfarin with low and intermediate TTR groups. In the low TTR group, the ICERs were $779 and $816 per QALY gained from the societal and healthcare perspectives, respectively, and in the intermediate TTR group, the ICERs were $2038 and $3159 per QALY gained from the societal and healthcare perspectives, respectively. Both ICERs were below the accepted willingness-to-pay threshold ($4806) in the context of Thailand's healthcare.

Conclusions In a developing country where suboptimal anticoagulation control is common, apixaban was the cost-effective alternative to warfarin for patients with both low and intermediate TTR control.

1 Introduction

Stroke is one of the most significant causes of mortality and morbidity in patients with non-valvular atrial fibrillation (NVAF) [1, 2]. The NVAF population are at a fivefold increased risk of stroke compared with the general population [3]. Vitamin K antagonists (e.g. warfarin) have long been the mainstay in stroke prevention for NVAF patients; however, maintaining optimal anticoagulation

Key Points

Previous cost-effectiveness studies using mostly input parameters from a developed health system showed that non-vitamin K oral anticoagulants (NOACs) were not cost effective compared with an old drug, i.e. warfarin. However, when using effectiveness and safety parameters that derived from a real-world study in a developing country, NOACs were found to be a cost-effective alternative to warfarin, particularly among patients with poor anticoagulation control.

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control with warfarin presents a major challenge [4]. The common quality indicator of anticoagulation control among warfarin users is the percentage of time in therapeutic range (TTR) [5]. Various guidelines suggest that maintaining TTR ≥ 65% is required to achieve optimal clinical outcomes [6, 7]. On the other hand, studies have shown that suboptimal warfarin control (TTR < 65%) was associated with increased risks of stroke, major bleeding, or even death [8–11]. Suboptimal anticoagulation control is a global problem but this issue is more pronounced and more common in resource-restraint countries [4, 12–14]. A recent nationwide registry in Thailand showed that 64% of warfarin users had suboptimal TTR control (TTR < 65%) [11]. Furthermore, a recent multicenter cohort study in Thailand showed that 30.7, 18.6, and 50.7% of Thai warfarin users had high TTR (TTR ≥ 65%), intermediate TTR (TTR 51–64%) and poor TTR (TTR ≤ 50%), respectively [15]. Studies from other developing countries and emerging economies showed a similar pattern [12–14, 16]. The currently preferred anticoagulants recommended by most international guidelines are the non-vitamin K oral anticoagulants (NOACs) due to their favorable efficacy and safety profile and ease of use compared with warfarin [1, 2, 17]; however, NOACs were found to be cost effective compared with warfarin, mostly in high-income countries [18]. Recent cost-effectiveness studies conducted in the context of Thailand's healthcare showed that NOACs were not cost effective compared with warfarin [19–21]. The two main reasons for these findings were (1) efficacy and safety parameters applied in the model were derived from trials conducted in developed countries; and (2) the willingness-to-pay (WTP) threshold in Thailand (Thai Baht [THB] 160,000 or US dollars (US$) 4806, with a conversion rate of THB33.29 to US$1) is significantly less than developed countries. Recently, a multicenter, real-world study compared the effectiveness and safety of NOACs with warfarin in Thailand. Results showed that NOACs were associated with a 54% reduction in the risk of major bleeding. In addition, among warfarin users with poor TTR (TTR ≤ 50%), NOACs were associated with a 42% reduction in the risk of thromboembolism. This magnitude of benefits appeared much larger than findings reported from trials conducted mostly in developed countries [15]. With a large difference in the magnitude of benefits, the cost-effectiveness equation may subsequently be affected or altered. As a result, this study was conducted to assess the cost effectiveness of NOACs compared with different levels of warfarin control for stroke prevention in NVAF patients. The results from this study may provide useful information for developing countries where warfarin treatment is commonly suboptimal.

2 Methods

2.1 Overall Description

A cost-effectiveness analysis was performed to compare NOACs versus warfarin for stroke prevention in NVAF patients in the context of Thailand's healthcare. A decision tree and Markov model were adopted to capture total cost and health outcomes through a patient's lifespan using societal and healthcare perspectives. Our results were presented as incremental cost-effectiveness ratios (ICERs) in 2021 US$ per quality-adjusted life-year (QALY) gained. The WTP threshold of US$4806 per QALY (THB160,000/QALY) was used to determine whether the option was cost effective. A lifetime horizon was utilized in this model, and all analyses were performed from the societal and healthcare perspectives. The cycle length was 3 months and a 3% annual discount rate was applied to all costs and outcomes.

2.2 Interventions

The following anticoagulant agents were considered: warfarin, dabigatran, rivaroxaban and apixaban. We did not perform separate analyses for each dose of NOAC because there was only a small to no difference in the pricing of full and reduced doses of NOAC in Thailand; hence we used the average price of both doses. In addition, the effectiveness and safety data that we obtained were from a real-world study where both full and reduced doses were used based on the discretion of physicians. Warfarin treatment was further subdivided into three categories based on TTR—warfarin ≥ 65% (high TTR), warfarin 51–64% (intermediate TTR), and warfarin ≤ 50% (low TTR)—and used as reference treatments.

2.3 Economic Model

A hypothetical cohort of 65-year-old NVAF patients and their disease progression was simulated in the Markov model (Fig. 1). Patients entered this model in an NVAF 'well' state without any contraindications to anticoagulant therapy. From the initial 'well' NVAF health state, patients can experience one of the following key clinical events: ischemic stroke (IS), myocardial infarction (MI), intracranial hemorrhage (ICH), major extracranial hemorrhage (ECH), and death. According to the severity of attack, IS and ICH were subdivided into minor and major, and hemorrhagic stroke was included in ICH. IS, ICH, and MI were modeled as closed health states. Once patients experience one of these three events, they cannot transit into other health states. Patients can experience recurrent events with or without severity in a closed state, or

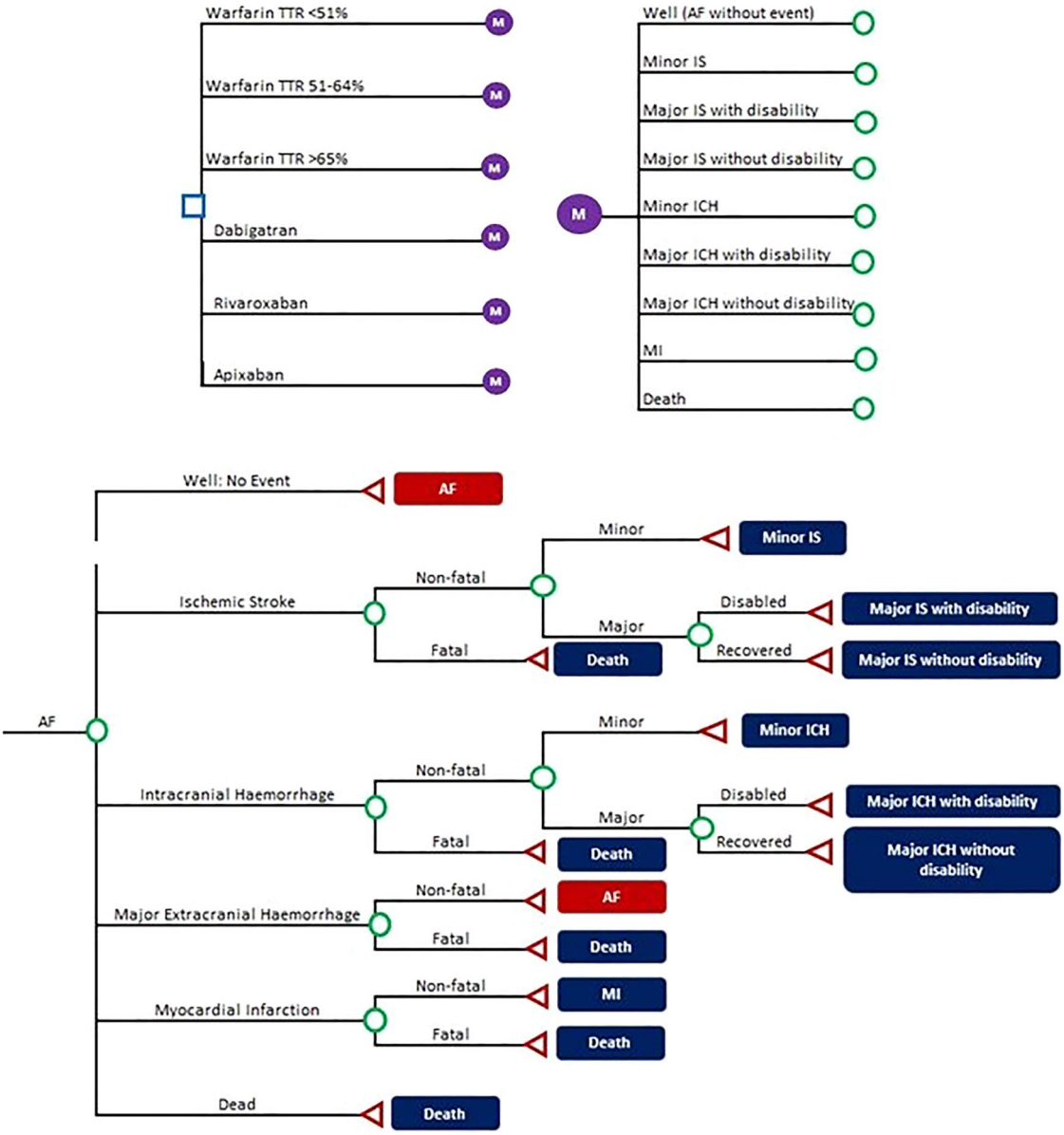

Fig. 1 Schematic of the Markov model. M represented a Markov model with ten health states. Health states highlighted in blue are permanent health states, while the remainder are transient health states. *AF* atrial fibrillation, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *TTR* time in therapeutic range

exit the model as death. However, major ECH was modeled as a transition health state. Patients undergoing major ECH were allowed to return into the 'well' NVAF state.

2.4 Model Assumptions

Consistent with previous studies, this model included several important assumptions. First, similar adherence was observed among all treatment strategies; second, therapeutic effects occurred shortly after treatment start and remained persistent over time; and third, no switching or stopping of treatment was allowed after patients encountered any clinical events. In other words, patients stayed in the same treatment category for the duration of the model. We adapted this model from a previously published study [19], which was originally developed in another published study [20] and was validated by specialist physicians in internal medicine and neurosurgery.

2.5 Input Parameters

Baseline clinical events for warfarin interventions (low, intermediate, and high TTR) were obtained from a recently published real-world study from Thailand [15]. We applied relative risks of NOACs to compare with the reference treatments by constructing a parametric survival model using Weibull regression. Consistent with previous studies, we assumed warfarin does not affect the MI outcome in AF patients. To account for the increased risk of event associated with aging, we adjusted the risk by a factor of 1.46, 1.97, and 1.30 per decade of life for stroke, bleeding, and MI, respectively. These adjustment factors were used in a previous cost effectiveness of NOAC in the Thai context [19]. The relative risk of recurrence of clinical events was assumed to be independent of interventions and was estimated to be 2.2 for IS, 2.72 for bleedings, and 2.04 for MI [20, 22, 23]. Disease-specific severity distribution and case fatality of each health state were also adopted from previous studies. Parameters used in our model are presented in electronic supplementary Table 1.

2.6 Probability Data

A life table of the general Thai population provided age-specific all-cause mortality inflated by an excess risk of 1.5 for patients with well-state NVAF [24]. Patients could die from both disease-specific events and other causes within 3 months. Higher mortality was applied to survivors of major clinical events depending on the disease severity levels, using standardized mortality ratios from the literature.

2.7 Costs and Utilities

Both direct and indirect costs were included in the total cost. All cost values were extracted from a published work and converted to 2021 US$ [19]. The baseline utility was 0.84, adopted from published literature [19]. The baseline utility was then adjusted to account for the disutility associated with aging and the occurrence of clinical events. The analysis considered no variation in utility values among interventions.

2.8 Statistical Analyses

The parametric model was applied by fitting the Weibull regression. All analyses were performed using STATA MP 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). One-way sensitivity analysis was undertaken to determine how sensitive the base-analysis result was to fluctuations in the input parameters. The results of one-way sensitivity analyses were presented in Tornado diagrams. We also performed a scenario analysis to assess the impact of a price reduction of NOACs, which may occur with the introduction of generic products. A price reduction of 20 and 50% was chosen based on findings from a previous study suggesting that such a reduction may be adequate to meet the Thai WTP threshold [19]. In addition, multivariate probabilistic sensitivity analyses (PSAs) were conducted with 1000 Monte Carlo simulations using Microsoft Excel 2022 (Microsoft Corporation Redmond, WA, USA) to explore the uncertainties of parameters. Transition probabilities were drawn from a parametric survival model based on a Weibull regression, using the method of Cholesky matrix decomposition [25]. Utilities were assigned using a beta distribution, while costs were assigned using a gamma distribution. Relative risks were assigned by log-normal distribution. The results of PSA were presented as cost-effectiveness acceptability curves (CEAC) to show the probability of NOACs being cost effective compared with warfarin.

3 Results

3.1 Base-Case Analysis

We performed base-case analyses of warfarin compared with NOACs from the societal and healthcare perspectives. We considered warfarin with varying TTR control degrees as three different populations and calculated three ICERs compared with NOACs. Apixaban was found to be cost effective compared with both the low and intermediate TTR groups (electronic supplementary Table 2). Compared with the low TTR group, the ICER was $779 and $816 per QALY gained from the societal and healthcare perspectives, respectively, and compared with the intermediate TTR group, the ICER was $2038 and $3159 per QALY gained from the societal and healthcare perspectives, respectively (Figs. 2a–c, 3a–c). All ICERs were below the accepted WTP threshold in the Thai healthcare setting.

3.2 Sensitivity Analyses

The ten largest influential variables were presented in tornado diagrams in a decreasing hierarchy of influence (Fig. 4a–c for the low TTR group; Fig. 5a–c for the intermediate TTR group; and electronic supplementary Fig. 1 for the high TTR group). The events of IS, ICH, and major ECH, the prices of NOACs, and the discount rates were found to influence the ICERs throughout all interventions. In the PSA, apixaban's probability of being cost effective was around 60, 57, and 35% compared with the low, intermediate, and high TTR groups, respectively, at a WTP

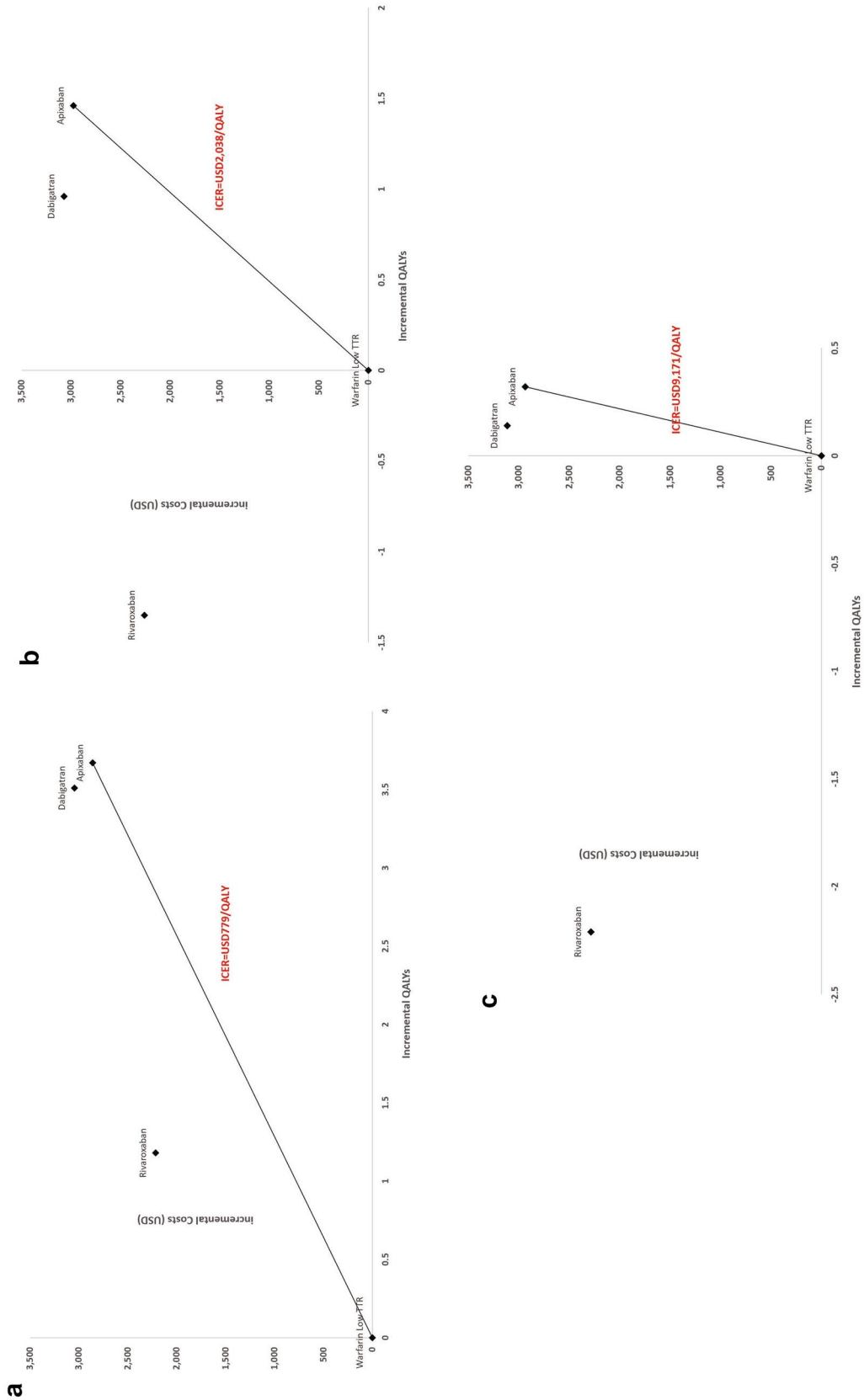

Fig. 2 Incremental costs and effects (measured in QALYs) of NOACs relative to warfarin from a societal perspective. **a** Low TTR; **b** intermediate TTR; **c** high TTR. *QALYs* quality-adjusted life-years, *NOACs* non-vitamin K oral anticoagulants, *TTR* time in therapeutic range, *USD* US dollars, *ICER* incremental cost-effectiveness ratio

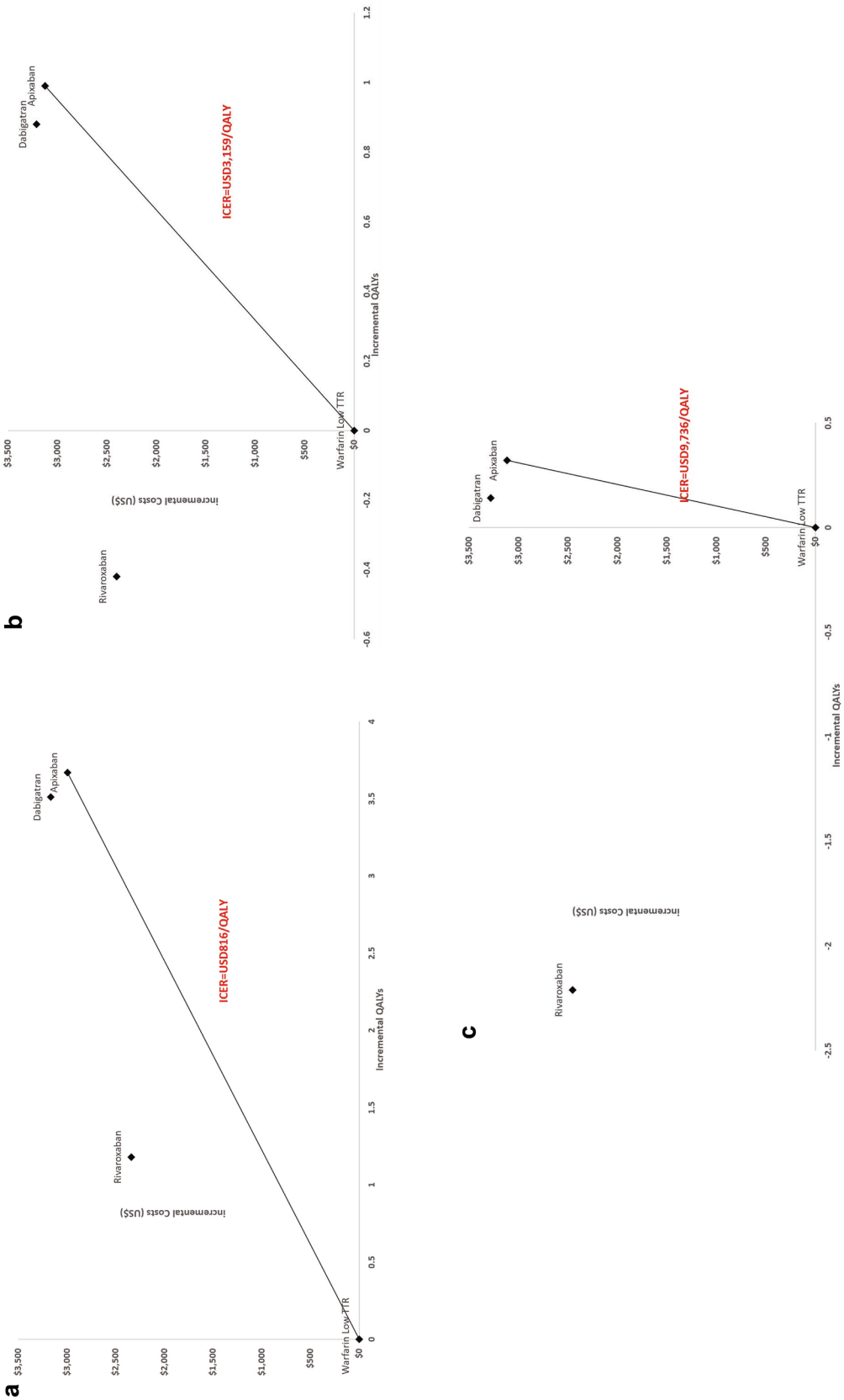

Fig. 3 Incremental costs and effects (measured in QALYs) of NOACs relative to warfarin from a healthcare perspective. **a** Low TTR; **b** intermediate TTR; **c** high TTR. *QALYs* quality-adjusted life-years, *NOACs* non-vitamin K oral anticoagulants, *TTR* time in therapeutic range, *USD* US dollars, *ICER* incremental cost-effectiveness ratio

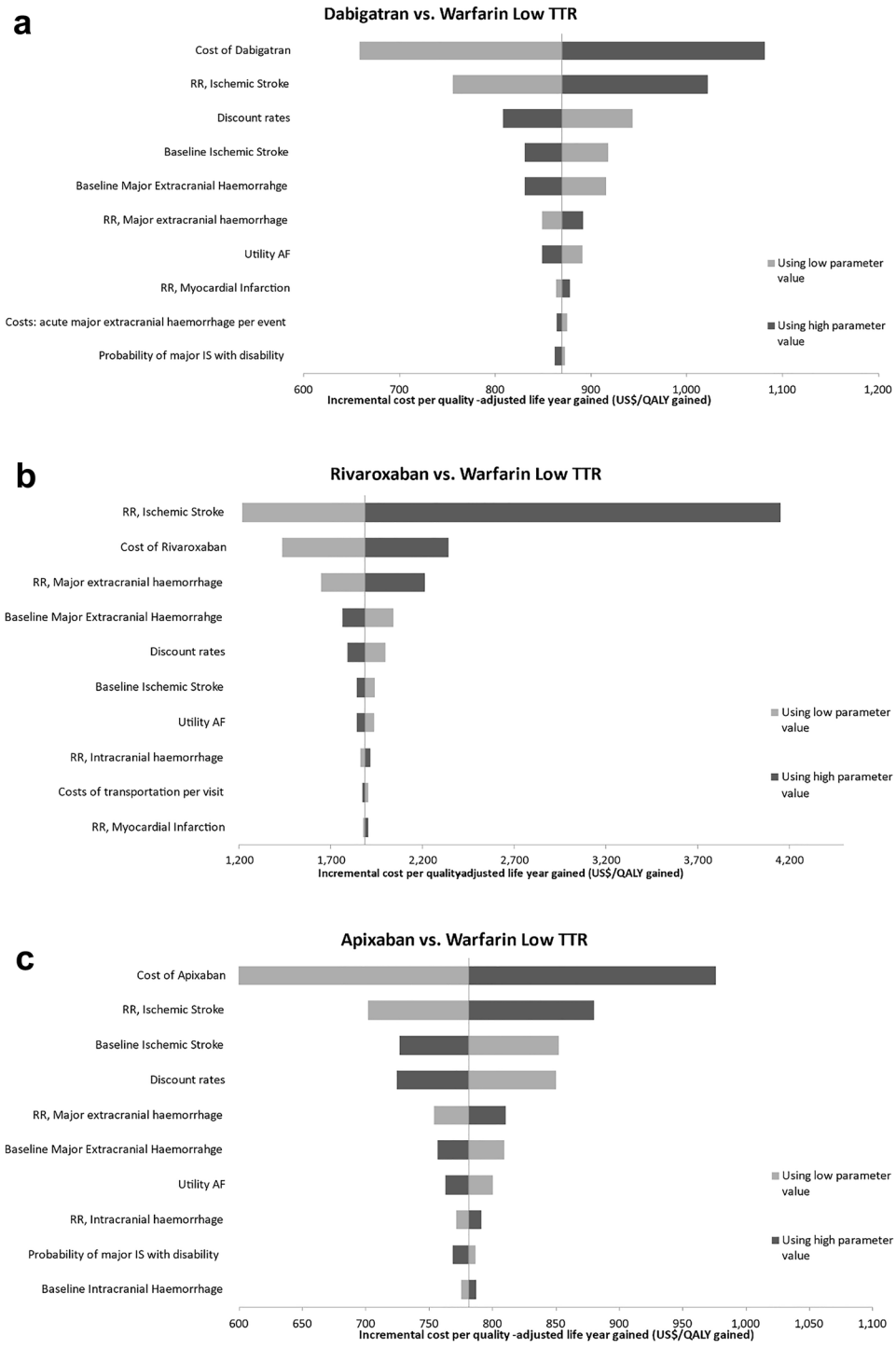

Fig. 4 Results of one-way sensitivity analysis (Tornado diagram) for base-case analysis comparing each NOAC with low TTR warfarin. **a** Dabigatran; **b** rivaroxaban; **c** apixaban. *NOAC* non-vitamin K oral anticoagulant, *TTR* time in therapeutic range, *QALY* quality-adjusted life-year, *AF* atrial fibrillation, *IS* ischemic stroke, *USD* US dollars, *RR* relative risk

threshold of $4806 (Fig. 6a–c and electronic supplementary Fig. 2a–c). Scenario analysis suggests that a 50% reduction in apixaban price would make it cost effective in all TTR groups (electronic supplementary Table 3)

4 Discussion

Cost-effectiveness analysis has become a standard measurement on the value of health intervention with policy implication [26]; however, accurate analysis relies partly

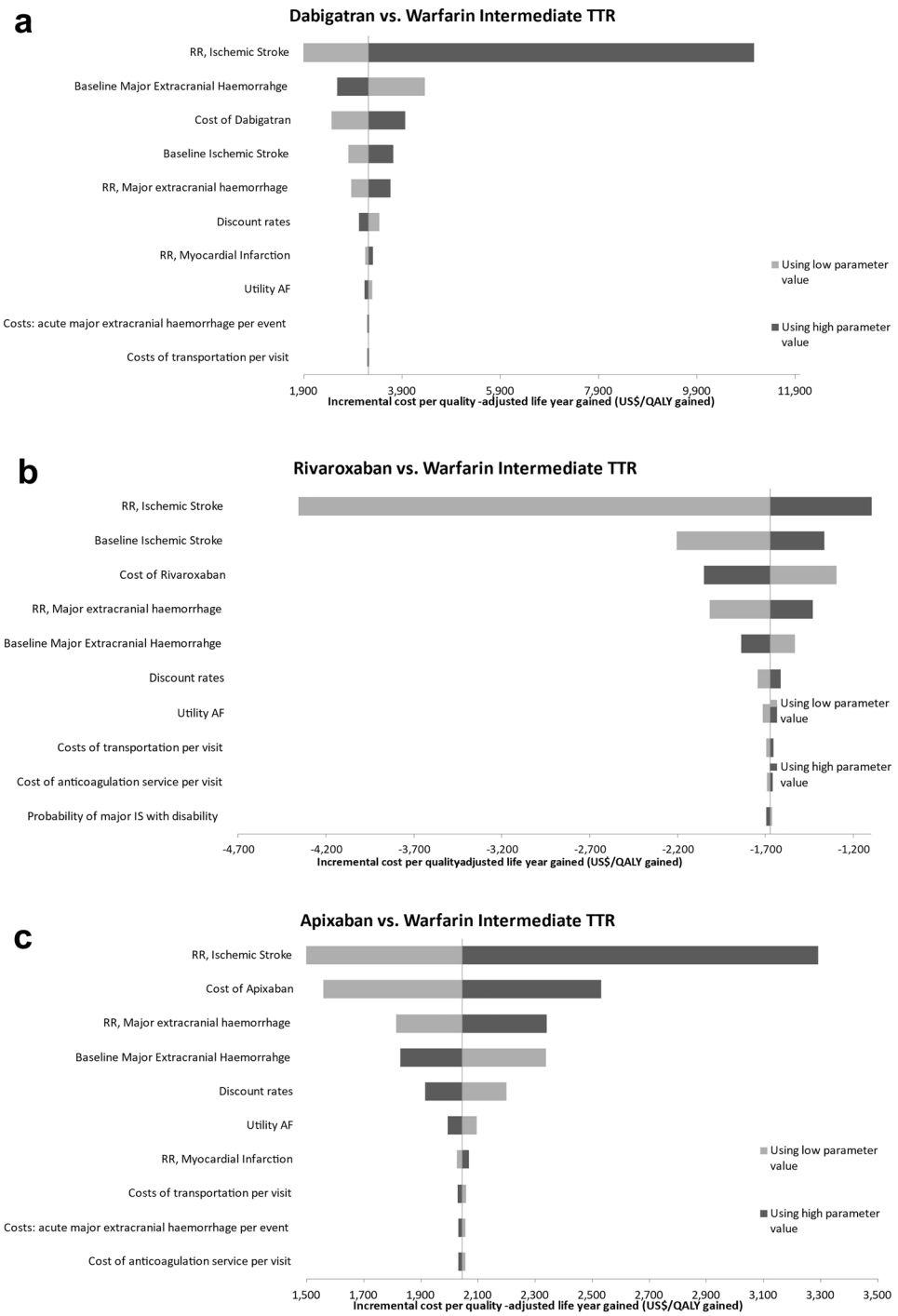

Fig. 5 Results of one-way sensitivity analysis (Tornado diagram) for base-case analysis comparing each NOAC with intermediate TTR warfarin. **a** Dabigatran; **b** rivaroxaban; **c** apixaban. *NOAC* non-vitamin K oral anticoagulant, *TTR* time in therapeutic range, *QALY* quality-adjusted life-year, *AF* atrial fibrillation, *USD* US dollars, *RR* relative risk

on the availability of data from a local context. Directly applying efficacy and safety data from randomized controlled trials conducted in advanced health systems into a cost-effectiveness analysis model of a developing country may not accurately represent the true value of a health intervention in such a healthcare context. Unfortunately, data from randomized controlled trials or real-world data from developing countries are extremely limited. As a result, most cost-effectiveness studies in developing countries have been conducted using data from developed countries, despite this limitation.

Recently, the first multicenter, real-world study in Thailand was conducted in 2055 patients, comparing the effectiveness and safety of NOACs with warfarin at varying TTR levels, with an average follow-up time of > 2 years. Results of the study showed that NOACs provided a much larger

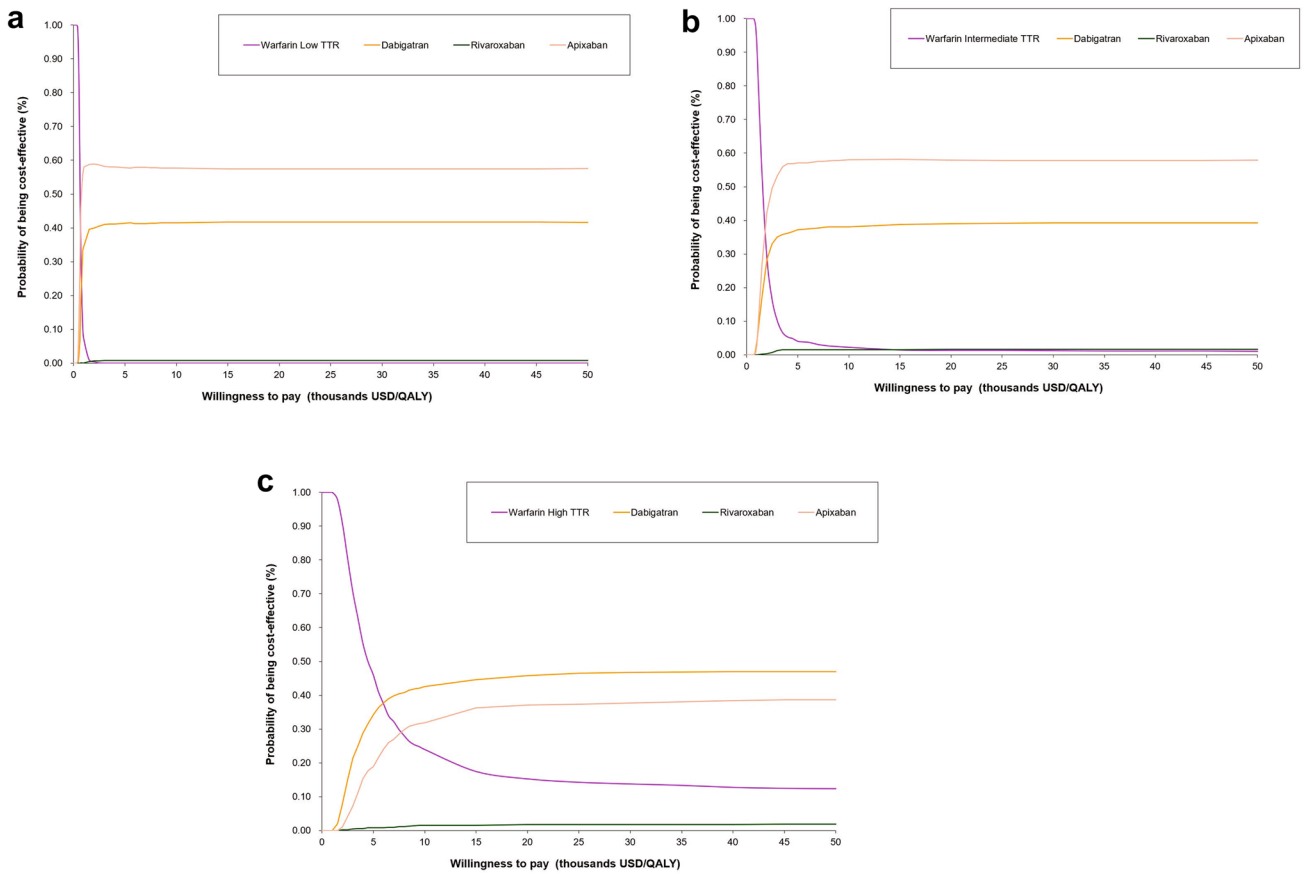

Fig. 6 Cost-effectiveness acceptability curves comparing NOACs with warfarin. **a** low TTR; **b** intermediate TTR; **c** high TTR. *NOACs* non-vitamin K oral anticoagulants, *TTR* time in therapeutic range, *USD* US dollars, *QALY* quality-adjusted life-year

magnitude of benefits compared with warfarin, especially when TTR is less than optimal [15]. The main reason for this is because warfarin performance relies heavily on the quality of anticoagulation control [27]. With poor TTR, the incidence of thromboembolism and bleeding increase exponentially [27]. Poor anticoagulation control is a global problem that puts large numbers of patients around the world at risk for adverse outcomes [4]. While NOACs are an attractive alternative to warfarin, access to these agents remain limited in developing countries, mainly due to cost issue [28].

Previously, there were three studies that evaluated the cost effectiveness of NOACs compared with warfarin in the Thai healthcare setting, all of which showed that NOACs were not cost effective. However, these previous studies were performed with input parameters derived mostly from published literature in the developed countries, especially the efficacy and safety data. With the availability of real-world effectiveness and safety data from Thailand, we were able to re-examine this issue by conducting a new cost-effectiveness analysis using key input parameters of effectiveness and safety that represent the actual performance of NOACs in the Thai health system. We were also able to assess the value of an NOAC compared with varying degrees of TTR control among warfarin users, making our analysis unique compared with other studies. As for other key input parameters, we adopted the best available parameters at the time of conducting this work. Since the studies by Rattanachotphanit et al. [20] and Ng et al. [19] were conducted in a local Thai context, a number of input parameters from these studies were also adopted in our study. When local data were not available, input parameters were taken from literature reviews, particularly the most recent systematic review and network meta-analysis.

The results of our study showed that an NOAC, apixaban in this case, was found to be cost effective when compared with warfarin with low and intermediate TTR, which contradicts the conclusion from previous cost-effectiveness studies in Thailand. However, none of the NOACs are shown to be cost effective compared with the high TTR group. This finding may help streamline the potential use of an NOAC to patients whose TTR remains poor despite their best attempts with warfarin. Overall, this strategy seems more logical compared with a complete substitution of an NOAC for warfarin, which may present a challenge in terms

of the budget impact to a resource-limited health system. In addition, a price reduction of 50% will make apixaban cost effective in all TTR groups and may represent an attractive replacement for warfarin in this indication. This is possible with either price negotiation with the branded product or the introduction of generic product with at least 50% lower cost. Although NOACs are available in Thailand's market, these drugs are currently not reimbursed fully in the universal coverage scheme. Results of our analysis may serve as useful information for relevant healthcare agencies when a reimbursement policy is made.

Our study has several limitations. First, since the data input into our model were derived from a retrospective real-world study, the confounding factors of residual effects and unmeasured confounders, which are a non-randomized measure of treatment effect from not using a randomized treatment allocation, along with missing events and lack of adjudication, may remain despite statistical adjustment.

Additionally, the data were from tertiary-level hospitals, which may not limit the generalizability. Second, our model did not incorporate the issue of anticoagulant interruption after major bleeding or switching to aspirin, which can occur in real clinical practice. Third, our model assumed that clinical events were mutually exclusive, which may not reflect the actual clinical scenario where patients may simultaneously encounter more than one event. Fourth, our findings may be affected if there are changes in several factors, mainly the event rates of adverse clinical outcomes and the pricing of NOACs. Since the patents of some NOACs have expired, a drastic change in pricing may occur with the introduction of generic products. Such a change will mostly change the cost-effectiveness equation seen in our study, as in our scenario analysis. Fifth, although different disutility values, including the acute and maintenance phases, should be considered to distinguish and better reflect different health states, we applied the same disutility values for the acute and maintenance phases similar to a previous study [20], due to the unavailability of separate disutility data from a local context. Lastly, we were unable to include edoxaban in our analysis, despite it being shown to have a favorable safety and efficacy profile, especially in the elderly [29, 30], because we did not have real-world effectiveness and safety data of edoxaban in the Thai population. At the time when the real-world study by Mitsuntisuk et al was conducted, edoxaban was still unavailable in most study sites [15].

5 Conclusions

In a developing country where anticoagulation control with warfarin is suboptimal, apixaban was found to be a cost-effective alternative to warfarin, particularly among patients with poor (TTR ≤ 50%) to intermediate (51–64%) TTR levels. This finding can be useful to inform policy makers and health authorities to consider the inclusion of NOACs in a reimbursement scheme to provide access to this life-saving drug for the population, particularly for those whose TTR remains suboptimal despite best attempts with warfarin. From a larger perspective, since poor anticoagulation control is a global issue, our finding may be applied or utilized in other developing countries with a similar healthcare context. Moreover, the results of our study highlight the importance and value of using real-world data from a local healthcare context as essential parameters to ensure that the true value of a health intervention can be accurately assessed. As a result, attempts to create and utilize real-world data in health policy decision making is urgently needed among all developing countries around the world.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40256-023-00570-z.

Declarations

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Conflict of interest M. Sakil Syeed, Teerawat Nonthasawadsri, Richard E. Nelson, Nathorn Chaiyakunapruk and Surakit Nathisuwan declare they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Data availability statement All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Code availability Not applicable.

Consent for publication Not applicable.

Author contributions All authors have made substantial contributions to this study. All authors were involved in the conception and design of the study. SS, TN, and SN were responsible for acquisition of the data. All authors were responsible for data analysis and data interpretation, drafting of the manuscript, and approved the final version.

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