

# Cost-Effectiveness Analysis of Apixaban, Dabigatran, Rivaroxaban, and Warfarin for Stroke Prevention in Atrial Fibrillation in Taiwan

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## Abstract

**Background and Objectives** The aim of this study was to evaluate the cost effectiveness of novel oral anticoagulants (NOACs) for stroke prevention among atrial fibrillation (AF) patients by incorporating Taiwanese demographic information derived from a population-based database, the National Health Insurance Research Database (NHIRD), into cost-effectiveness analysis.

**Methods** From 1 January to 31 December 2012, 98,213 AF patients were selected from the NHIRD database. A Markov model was constructed that combined published secondary data with the Taiwan NHIRD to compare the cost and incremental cost effectiveness of apixaban 5 mg twice daily, dabigatran 110 or 150 mg twice daily, rivaroxaban 20 mg once daily, and warfarin.

**Results** The lifetime costs of warfarin, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban 20 mg, and apixaban 5 mg were US\$10,660, US\$13,693, US\$13,426, US\$13,455, US\$15,965, respectively. Apixaban resulted in an incremental cost effectiveness of US\$39,351, US\$27,039, US\$41,298, and US\$48,896 per quality-adjusted life-year (QALY) compared with warfarin, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban 20 mg, respectively. In Monte-Carlo analyses, apixaban 5 mg, rivaroxaban 20 mg, warfarin, and dabigatran 110 mg were cost effective in 83, 10.4, 7, and 0.8%, respectively, of the simulations using a willingness-to-pay (WTP) threshold of US\$50,000 per QALY.

**Conclusions** Apixaban was more cost effective than warfarin, dabigatran, and rivaroxaban for stroke prevention in patients with AF. Among the anticoagulant therapies, the WTP threshold of apixaban was about US\$50,000 per QALY gained. These cost-effectiveness estimations provide useful information to aid clinical decision making in stroke prevention for AF patients.

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## Key Points

In comparison with the published literature, the sex distribution, mean age for males and females, prevalence rate, incidence rate and distributions of CHADS<sub>2</sub> (congestive heart failure history, hypertension history, age  $\geq$  75 years, diabetes mellitus, ischemic stroke or TIA history [double]) scores, and some cost information for this study were calculated using the population-based National Health Insurance Research Database in Taiwan.

This cost-effectiveness analysis provided evidence that apixaban 5 mg was a more cost-effective alternative than warfarin, dabigatran 110 or 150 mg, and rivaroxaban 20 mg for stroke prevention in patients with atrial fibrillation (AF).

This study incorporated the demographic information into the cost-effectiveness analysis of novel oral anticoagulants (NOACs) in Taiwan, and thus its findings can provide a more precise estimation for the clinical decision making of the NOACs uses in Taiwan.

## 1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, which is highly prevalent with advancing age, associated with a substantial morbidity, and has an increased risk of all-cause mortality [1–5]. A nationwide study in Taiwan involving hospitalized patients reported a mean annual frequency of 127 hospitalization-based AF cases per 100,000 persons and a 1.65-fold increase in frequency from 1997 to 2002 [6]. A community-based cohort study estimated the prevalence of AF to be 1.4% in men and 0.7% in women, consistent with data in Caucasians [1, 4, 7]. Incidence rates of AF were 1.68 per 1000 person-years for men and 0.76 per 1000 person-years for women [1]. However, data from both studies were collected before 2002, and the updated true prevalence and incidence of AF from a nationwide population-based in Taiwan are currently unavailable.

A noticeable risk factor for ischemic stroke, AF is independently associated with a two- to seven-fold increase in the risk of ischemic stroke occurrence [8, 9]. In Taiwan, the prevalence of ischemic stroke was reported to be 21,000 per 100,000 persons among those aged 60–85 years and the mortality rate was 2300 per 100,000 among individuals aged 50–90 years in 2005 [10]. In 2007 alone, the total medical cost for stroke in Taiwan was up to US\$375 million. Vitamin K antagonists such as warfarin are superior to antiplatelet agents for secondary stroke

prevention in AF, but warfarin has significant limitations that result in its underuse [11]. A Taiwanese study showed that while 89% of the AF patients were considered to be at the highest or high risk for thromboembolism, only 24.7% of the total number of AF patients received appropriate antithrombotic therapy [12]. A cost-effectiveness analysis, using hypothetical data assumption, has compared the use of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in AF in the USA and showed that apixaban, dabigatran, and rivaroxaban were all cost-effective alternatives to warfarin [13–17]. However, a cost-effectiveness analysis was considered to use the local countries' demographic information. It would be more convincing if the important parameters, including the sex distribution, mean age for males and females, prevalence rate, incidence rate and distributions of CHADS<sub>2</sub> (congestive heart failure, hypertension, age = 75 years, diabetes mellitus, stroke [doubled]) score, and some cost information were estimated using a population-based database. Therefore, our study aimed to incorporate these same important parameters, estimated using a population-representative database, the Taiwan National Health Insurance Research Database (NHIRD) database, into the cost-effectiveness analysis in Taiwan, and to compare the costs and incremental cost effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in AF patients in Taiwan.

## 2 Methods

### 2.1 Data

This study used two types of data resources. The demographic data were retrieved from the NHIRD in Taiwan. Taiwan launched the NHI program in 1995 and now enrolls more than 99.6% of the population in Taiwan [18]. The database is one of the largest and most comprehensive population-based databases in the world, and has been confirmed by the National Health Insurance Administration (NHIA) to be representative of the Taiwan population [18]. The database used in this study consisted of de-identified secondary data released for research purposes; this principle complies with the Personal Information Protection Act in Taiwan, and this study was exempt from full review by the National Taiwan University Hospital Research Ethics Committee. The data in this study were retrieved from the NHIRD for patients who had a primary or secondary diagnosis of AF based on the *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM) codes (ICD-9-CM 427.13) between January 2005 and December 2012 and did not have AF in 2004. Patients were included if they were aged 18 years or over, continuously

enrolled in the NHI program, and had two or more diagnoses of AF in outpatient visits or one or more inpatient admission with AF. Patients who had evidence of congenital cardiac diseases were excluded.

Among the three novel anticoagulants (NOACs) in this study, dabigatran was approved by the NHIA on 13 July 2011, rivaroxaban on 1 January 2012, and apixaban on 14 August 2013. Due to the 2-year time lag of database release, and the 1–2 years required to be able to observe stable use of the newly approved drug in Taiwan, complete effectiveness data cannot be obtained from the NHIRD; therefore, we still needed to use related information taken from published studies. The adverse events and clinical data were taken from three trials: (1) the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial for apixaban; (2) the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial for dabigatran 110 and 150 mg; and (3) ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism) for rivaroxaban. The adverse events and clinical data for warfarin were pooled from ARISTOTLE, RE-LY, and ROCKET-AF. Data on transition probabilities and increases in death risk were taken from other published economic evaluations. Multiple classifications of ischemic stroke, intracranial hemorrhage, and myocardial infarction (MI) were used, with probabilities derived from the literature.

### 2.2 Decision Model

A Markov model was constructed to estimate the state-transition probabilities of disease states and pathways among patients after non-valvular AF (NVAF), including NVAF,

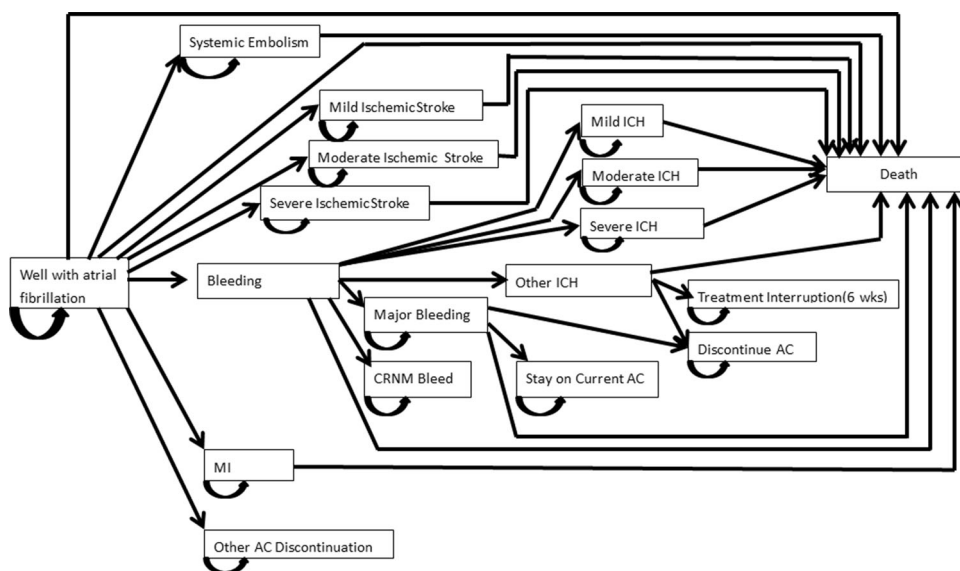
mild ischemic stroke (mild stroke), moderate ischemic stroke (moderate stroke), severe ischemic stroke (severe stroke), mild hemorrhagic stroke (HS), moderate HS, severe HS, MI, systemic embolism, NVAF without original anticoagulation, and death, which is shown in Fig. 1. After taking into account the estimated state-transition probabilities of the above-mentioned disease states and pathways, we estimated the expected cost-related values of five anticoagulation treatment strategies, including apixaban 5 mg twice daily, dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and adjusted-dose warfarin with a target international normalized ratio (INR) of 2–3. The base-case patient population was derived from demographic information from the Taiwan NHIRD in 2012. The base case included the following health states: well, MI, major or minor intracranial hemorrhage (ICH), major or minor ischemic stroke, and death, which are shown in the Markov model diagram in Fig. 1.

Our model adopted the payer’s perspective and utilized a lifetime time horizon. Outcomes were modeled as the transition from one health state to another using 6-week cycles, and costs and utilities were applied to each outcome over the expected duration. Costs and benefits were discounted at 3.5% per year starting from the first year, and reported in 2012 US dollars. Cost effectiveness was determined as the cost per quality-adjusted life-year (QALY) gained and all analyses were performed using TreeAge Pro Suite 2012 (TreeAge Software, Williamstown, MA, USA) [19].

### 2.3 Probability of Adverse Outcomes in the Decision Model

The risks of adverse events were based on data from four clinical trials: the ARISTOTLE and AVERROES

**Fig. 1** Markov model and possible clinical non-valvular atrial fibrillation events in this study. AC anticoagulant, CRNM clinically relevant non-major, ICH intracranial hemorrhage, MI myocardial infarction



(Apixaban versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trials for apixaban 5 mg twice daily; the RE-LY trial for dabigatran 110 and 150 mg twice daily; and ROCKET-AF for rivaroxaban 20 mg once daily [20–23]. Because apixaban had not been approved by the Taiwan Department of Health at the time of study initiation, and dabigatran and rivaroxaban were approved in 2011 and 2012, the study database did not include data for apixaban, dabigatran, or rivaroxaban. However, the outcome variables for warfarin in this study were derived from the NHIRD.

We classified ischemic stroke into one of four categories—no residual neurological sequelae, minor, major, or fatal [24]—and assumed 28% of ischemic neurologic events would be transient ischemic attacks (TIAs) [25–27]. Additionally, we assumed that the risk of stroke would increase by 1.4-fold per 10 years of life [28], and that the risk of mortality increased by 3.7-fold after an ischemic stroke or ICH [29]. Hemorrhages were classified into four categories: minor, gastrointestinal, myocardial, or fatal [13, 18, 21, 28]. ICHs were further classified as minor, major, or fatal [24]. We assumed patients who had a major hemorrhage would discontinue anticoagulation therapy and switch to aspirin therapy alone. The risk of MI was increased by 1.3-fold per 10 years of life, compounded monthly [30]. Mortality rates were assumed to increase by 1.05-fold after an MI [7], and were adjusted for age (beginning at age 70 years), presence of AF and prior stroke or TIA, and type of antithrombotic therapy. We assumed that event rates for other conditions not included in our model were similar across all treatments.

## 2.4 Quality-Adjusted Life-Years Estimates

QALYs were calculated by multiplying the time spent in each health state by corresponding utility (quality-of-life) estimates derived from the medical literature [5, 31–34]. The measurement of quality of life used EQ-5D and was estimated based on a large-scale survey data from Taiwan [35]. The baseline utility value was adjusted for age, AF, and anticoagulation therapy [31].

## 2.5 Costs

In this study, costs were projected over 30 years or until death, and future costs and life-years (LYs) were discounted at 3.5% per year. Because apixaban, dabigatran, and rivaroxaban were not available through the NHI before 2010, the medication costs of dabigatran and rivaroxaban were estimated based on those previously reported by Harrington and colleagues [13]. The warfarin medication cost was based on the dose and cost reimbursed by the

Taiwan NHI. The one-time event cost was estimated from costs published by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project under the relevant diagnosis-related group (DRG) [36]. Long-term costs for adverse events and warfarin- and non-warfarin-associated costs were calculated from the median value of published studies or the US Medicare reimbursement rates for the appropriate DRG.

## 2.6 Sensitivity Analyses

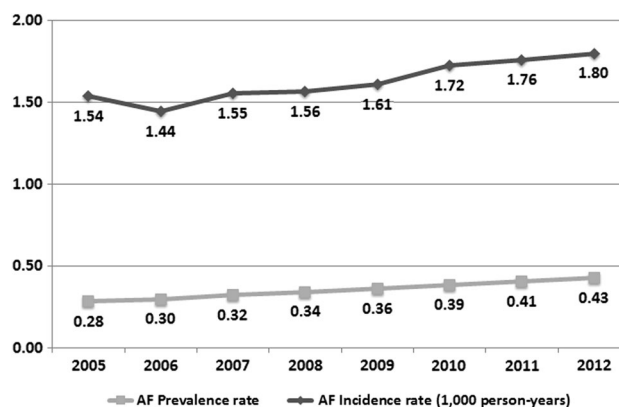
One-way sensitivity analyses of all variables included in the decision model were performed over their plausible ranges to identify influential model variables. Secondly, a probabilistic sensitivity analysis was performed using a first-order Monte-Carlo simulation for 2000 iterations. For each iteration, the values for all input variables were randomly sampled from their respective distributions. A normal distribution was assumed for continuous-type data, a log-normal distribution for hazard rates, beta distribution for stroke onset probabilities, and gamma distribution for costs.

All the parameters that were used for the base case for Markov model analysis, cost-effectiveness analysis, and sensitivity analysis are shown in the Electronic Supplementary Material.

## 3 Results

### 3.1 Prevalence and Incidence of Atrial Fibrillation

Using data from the nationally representative database (NHIRD), the prevalence rates of AF showed an increasing trend from 0.28% in 2005 to 0.43% in 2012. The incidence rates of AF also showed a slightly increasing trend from 1.54 per 1000 person-years in 2005 to 1.80 per 1000 person-years in 2012 (Fig. 2).



**Fig. 2** Incidence and prevalence of atrial fibrillation in Taiwan from 2005 to 2012. *AF* atrial fibrillation

**Table 1** Demographic information for atrial fibrillation patients in the 2012 study population

Variables	Value
Sex [ <i>n</i> (%)]	
Male	54,606 (55.6)
Female	43,607 (44.4)
Age (years) [mean ± SD]	
Male	75.1 ± 14.4
Female	77.1 ± 13.6
CHADS <sub>2</sub> score (%)	
0	16.1
1	39.6
2	33.8
3	9.9
4	0.4
5	0.1
6	0.1
Mean CHADS <sub>2</sub> score	1.4

CHADS<sub>2</sub> congestive heart failure history, hypertension history, age ≥ 75 years, diabetes mellitus, ischemic stroke or transient ischemic attack history (double), SD standard deviation

### 3.2 Base-Case Analysis

In this study, the incidence-based demographic information for AF patients in the 2012 study population were applied to the Markov model as the base-case patient population, including 55.6% male and 44.4% female, mean age 75.1 (male) and 77.1 (female) years, and mean CHADS<sub>2</sub> score of 1.4 (Table 1).

Under base-case conditions, apixaban 5 mg was associated with higher QALYs and LYs than warfarin, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban 20 mg (Table 2). The lifetime costs were US\$10,660, US\$13,693, US\$13,426, US\$13,455, and US\$15,965 for warfarin, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban 20 mg, and apixaban 5 mg, respectively. Apixaban resulted in incremental cost-effectiveness ratios (ICERs) of US\$39,351, US\$27,039, US\$41,298, and US\$58,991 per QALY gained compared with warfarin, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban 20 mg, respectively. The ICERs for apixaban per LY gained were US\$46,830

**Table 2** Costs, life-years, quality-adjusted life-years, and incremental cost-effectiveness ratios for each anticoagulant therapy in the base-case analysis

Anticoagulant	Cost (US\$)	LYs	QALYs	ICER (US\$/QALY)	ICER (US\$/LY gained)
Warfarin	10,660	8.276	5.850	39,351	46,830
Dabigatran 110 mg	13,693	8.327	5.896	27,039	24,548
Dabigatran 150 mg	13,426	8.349	5.918	41,298	37,732
Rivaroxaban 10 mg	13,455	8.368	5.937	48,896	58,991
Apixaban 5 mg	15,965	8.386	5.985	(Reference group)	(Reference group)

ICER incremental cost-effectiveness ratio, LYs life-years, QALYs quality-adjusted life-years

versus warfarin, US\$24,548 versus dabigatran 110 mg, US\$37,732 versus dabigatran 150 mg, and US\$48,896 versus rivaroxaban 20 mg.

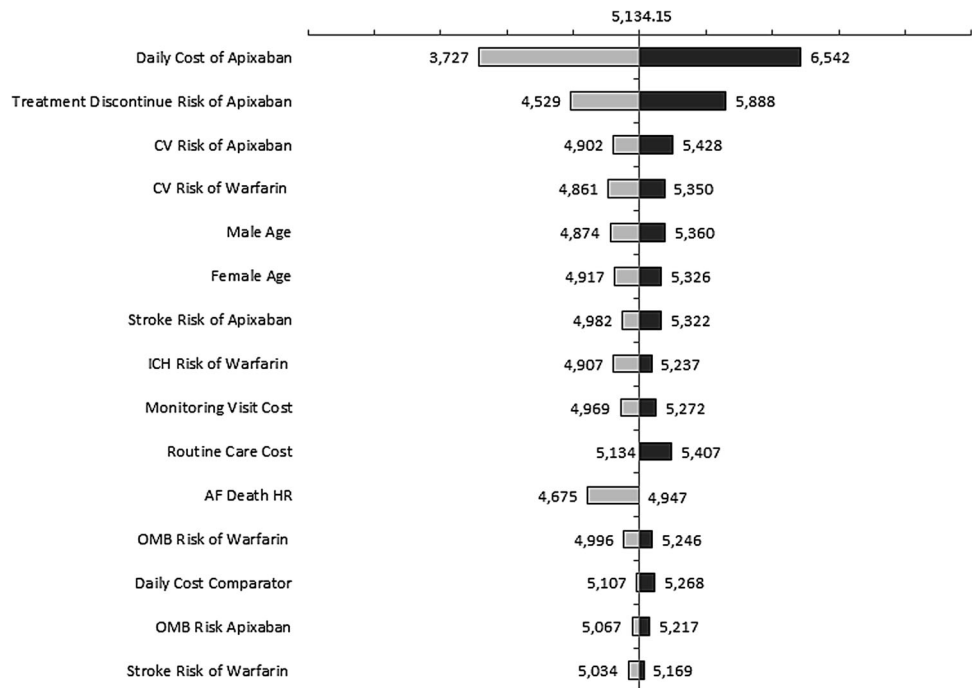
### 3.3 Probabilistic Sensitivity Analysis

Key variables with the most influence in total costs included the daily cost of apixaban, risk of treatment discontinuation of apixaban, cardiovascular risks of apixaban and warfarin, age, and the risk of stroke associated with apixaban (Fig. 3). The daily cost of apixaban had the greatest effect on incremental costs. Risk of treatment discontinuation associated with apixaban and cardiovascular risks associated with apixaban and warfarin were among the risks with most effect on incremental costs. Using a willingness-to-pay (WTP) threshold of US\$50,000 per QALY, apixaban 5 mg, warfarin, rivaroxaban 20 mg, dabigatran 110 mg, and dabigatran 150 mg were cost effective in 85, 5, 9, 1.1, and 0.2% of the Monte-Carlo simulations, respectively (Fig. 4). By taking into account two willingness-to-pay thresholds of US\$40,000 and US\$50,000, the probabilistic sensitivity analyses of apixaban 5 mg in comparison with warfarin, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban 20 mg is shown in Table 3.

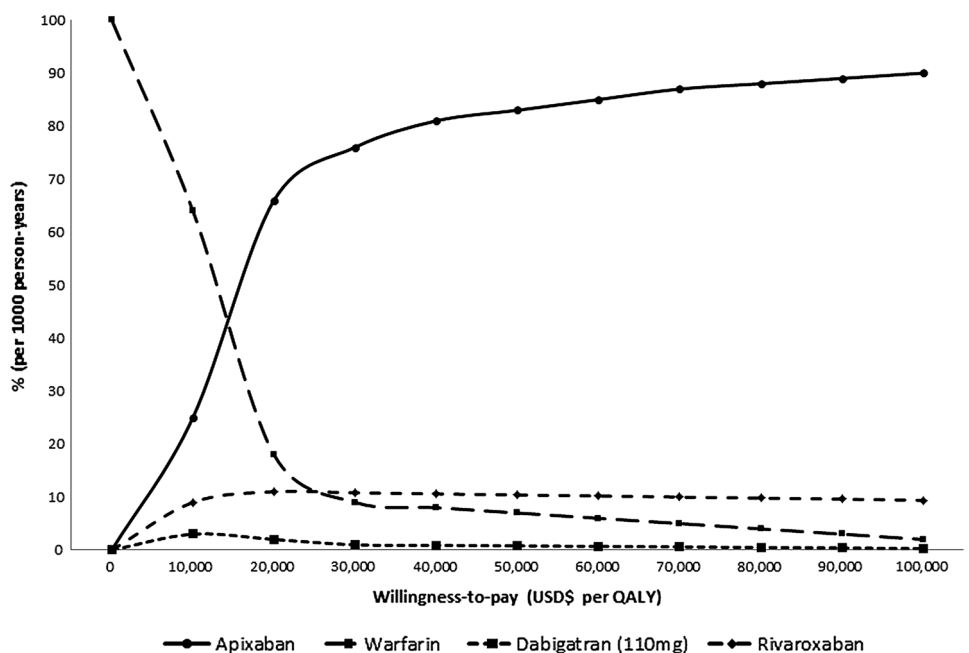
## 4 Discussion

This study incorporated demographic information derived from a population-based database in Taiwan into the cost-effectiveness study to investigate the cost effectiveness of apixaban for stroke prevention among AF patients. The data showed increasing trends in both prevalence and incidence rates of AF from 2005 to 2012. The prevalence rates in this study were lower than estimates from a community-based cohort study in Taiwan, which reported 0.7% prevalence in men and 1.4% in women [1]. Data from a cross-sectional survey in the USA also showed a higher overall prevalence of 0.95%, estimated based on age-specific prevalence from 1996 to 1997 [4]. Other Asian studies reported prevalence rates of 0.61% among a randomly recruited Chinese sample of 2000 adults and 0.64% in a Japanese study [32, 37]. The incidence of AF reported

**Fig. 3** Tornado diagram: each horizontal bar represents the net monetary benefit (in US dollars) expected from a possible range based on simulation analysis. AF atrial fibrillation, CV cardiovascular, HR hazard ratio, ICH intracranial hemorrhage, OMB other major bleeds



**Fig. 4** Cost-effectiveness acceptability curves showing the probability that each treatment strategy is cost effective for a given maximum willingness-to-pay threshold per quality-adjusted life-year gained. QALY quality-adjusted life-year



in this study were consistent with the estimates of 1.68 per 1000 person-years for men and 0.76 per 1000 person-years for women from Chien et al. [1], but were lower than the report of 2–3 cases per 1000 person-years among adults aged 55–64 years in the Framingham Heart Study [5].

The results indicated that apixaban was more cost effective than warfarin, dabigatran 100 or 150 mg, and rivaroxaban 20 mg for stroke prevention in patients with AF. The base-case analysis estimated an incremental cost of US\$39,351 per QALY gained for apixaban 5 mg compared

with warfarin, which was well within the range considered to be cost effective [32]. Apixaban 5 mg was also associated with ICERs of US\$39,351, US\$27,039, US\$41,298, and US\$58,991 per QALY gained compared with warfarin, dabigatran 110 mg, dabigatran 150 mg, and rivaroxaban 20 mg, respectively. Based on the simulation results, 83% of the simulations would accept the WTP threshold of US\$50,000 per QALY; and the WTP was estimated to be US\$50,000, was a percentage of acceptance of almost over 90%. In comparison with published studies, this was similar

**Table 3** Percentages of acceptance of willingness-to-pay thresholds of US\$40,000 and US\$50,000

Anticoagulant	Acceptance (%)			
	WTP/QALY		WTP/Life Year	
	US\$40,000	US\$50,000	US\$40,000	US\$50,000
Apixaban vs. warfarin	81	90	71	81
Apixaban vs. dabigatran 110 mg	99	99	99	99
Apixaban vs. dabigatran 150 mg	91	95	92	95
Apixaban vs. rivaroxaban	89	92	90	92

QALY quality-adjusted life-year, WTP willingness to pay

to the USA (US\$50,000) [13] and Japan (US\$50,000) [38] but less than Germany (€50,000 ≈ US\$54,415) [39]. In Taiwan, once a new drug is approved by the NHIA, the NHI program will fully or partly reimburse the drug costs. Therefore, the WTP threshold of US\$50,000 is not only similar to that of a near Asian country (Japan), but is also acceptable by Taiwanese people due to coverage in the NHI program.

In another published study, a model established by Dorian et al. compared apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg with warfarin from the US perspective and showed that all three oral anticoagulants were cost-effective alternatives to warfarin [15]. In agreement with our findings, apixaban was considered the optimal anticoagulant with an ICER of US\$15,026 compared with warfarin and it was cost effective in 45% of the Monte-Carlo simulations. Another model comparing new oral anticoagulants with warfarin showed that apixaban or dabigatran 150 mg were optimal for different patient characteristics, while dabigatran 110 mg and rivaroxaban were reported to be unlikely to be cost effective [16].

Of the models that directly compared apixaban 5 mg with warfarin, Kamel et al. estimated an ICER of US\$11,400 per QALY for apixaban compared with warfarin based on a subgroup of patients with AF and prior stroke or TIA from the ARISTOTLE trial [36]. In the Monte-Carlo analysis, apixaban was cost effective in 62% of simulations using a threshold of US\$50,000 per QALY. A similar study by Lee et al. [21] also demonstrated apixaban to be a dominant economic strategy compared with warfarin and the Monte-Carlo analysis deemed apixaban to be cost effective in 98% of the simulations.

The demographic parameters used are a strength of this study; for example, the gender distribution, mean age of males and females, prevalence rate, incidence rate and distribution of CHADS<sub>2</sub> scores, and some cost information were estimated using the population-based database, NHIRD. In addition, the Markov model was created using a base-case population derived from the NHIRD to avoid

heterogeneity of patient populations from clinical trials and ensure relevance to the Taiwan setting. However, there are limitations to our study that should be considered when interpreting the results. First, this study adapted the ICD-9-CM codes to identify AF diagnoses from the NHIRD and the coding accuracy of the relevant ICD-9-CM codes has not been properly evaluated. Second, the costs of dabigatran and rivaroxaban were estimated using US costs and apixaban was estimated to be 125% of the dabigatran 150 mg cost, since apixaban and rivaroxaban were not available before 2012 for inclusion in the cost-effectiveness analysis. The results of this study might be different if they were based on the costs of the same novel oral anticoagulants in different countries. The conclusions of our analyses may be interpreted differently if decision makers do not prescribe based on the US\$50,000 per QALY threshold.

## 5 Conclusion

By incorporating demographic information from a population-based database into the cost-effectiveness analysis, apixaban 5 mg was found to be a cost-effective alternative to warfarin, dabigatran 110 and 150 mg, and rivaroxaban 20 mg for stroke prevention in patients with AF. Apixaban 5 mg was the more cost-effective treatment of the three new oral anticoagulants and the most likely to be cost effective at a WTP threshold above US\$50,000 per QALY gained. These cost-effectiveness estimations provide useful information to aid clinical decision making in stroke prevention for AF patients.

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## Compliance with Ethical Standards

**Funding** This study was sponsored by Pfizer (Taiwan), grant number DN-PC-100-015.

**Conflict of interest** Neither of the authors is an employee of Pfizer (Taiwan). Chieh-Yu Liu is a full-time associate professor in the Department of Midwifery and Women Health Care, National Taipei University of Nursing and Health Sciences, and has received research grants from Pfizer Taiwan Inc. Hui-Chun Chen is a graduate student in the Department of Nursing, National Taipei University of Nursing and Health Sciences.

**Ethical approval** Due to the nature of secondary data analysis and using previously collected and anonymous data, all data analysis procedures conducted in this paper were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and this study was classified as being in the Exempt Review category.

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