original article

Cost-effectiveness of apixaban for stroke prevention in non-valvular atrial fibrillation in Saudi Arabia

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BACKGROUND: Apixaban, an oral anticoagulant for stroke and systemic embolism prevention in non-valvular atrial fibrillation (NVAF), was superior to warfarin in prevention of stroke and systemic embolism, bleeding outcomes and mortality (ARISTOTLE trial), and substantially reduced stroke risk, with no significant increase in major or intracranial bleeding risk versus aspirin (AVERROES trial).

OBJECTIVE: Estimate cost-effectiveness of apixaban versus other anticoagulants for NVAF treatment in Saudi Arabia.

DESIGN: Lifetime Markov model.

SETTING: A published model was adapted from the United Kingdom (UK) to the Saudi Arabia setting.

PATIENTS AND METHODS: The model enabled pairwise comparisons of apixaban against other anticoagulants, aspirin, and aspirin+clopidogrel. Apart from warfarin and aspirin, comparisons were indirect. Subpopulations included vitamin K antagonist (VKA) suitable and unsuitable patients. Medication and physician visit costs were from published lists. A cost ratio (0.533), from comparison of UK and Saudi physician visit costs, was applied to UK model inputs to estimate local event costs. Background life expectancy was from Saudi life tables. Model structure, treatment comparators, patient characteristics, event rates, and utilities were unchanged. Costs and health benefits were discounted by 3.5% annually.

MAIN OUTCOME MEASURE: Incremental cost-effectiveness ratio of cost per quality-adjusted life-year (QALY) gained.

SAMPLE SIZE: Model cohort of 1000 NVAF patients, for VKA suitable and VKA unsuitable populations.

RESULTS: Apixaban was dominant versus warfarin (VKA suitable) and rivaroxaban (VKA suitable and unsuitable). Compared against dabigatran (110mg, 150 mg, 110/150mg), the cost/QALY gained for apixaban was $5166, $11 143, $10 849 (VKA suitable) and $5 157, $14 424, $14 134 (VKA unsuitable), respectively. Cost/QALY for apixaban versus aspirin and aspirin+clopidogrel was $14 805 and $5784 (VKA suitable); and $10 564 and $4203 (VKA unsuitable), respectively. Sensitivity analyses demonstrated consistency of findings across varying inputs.

CONCLUSIONS: Apixaban was found to be cost-effective for stroke prevention among Saudi NVAF patients, when assessed using a US$20 000 willingness-to-pay threshold.

LIMITATIONS: Lack of robust local clinical, cost and utility data for model inputs. Lack of head-to-head clinical trial data for rivaroxaban, dabigatran, and clopidogrel plus aspirin comparators.

CONFLICT OF INTEREST: Study was funded by Pfizer Inc. and Bristol Myers-Squibb. KO, RS, SAK and AAA received salaries from their respective employers, but did not receive direct financial compensation for participation in or authorship of this study.

Atrial fibrillation (AF) is associated with considerable morbidity, mortality and healthcare costs worldwide, and accounts for one-third of hospitalizations for cardiac rhythm.[1] Individuals with non-valvular atrial fibrillation (NVAF) have an increased risk of stroke, heart failure, and thromboembolism, which contributes to the economic and clinical burden of the condition.[1-3]

Prevalence of AF in the United States (US), the United Kingdom (UK), and Europe is estimated to be 1-2%,[2-5] with global prevalence estimated at 0.1-4% in community-based studies.[6] While a large registry study of AF patients in Saudi Arabia has recently been conducted,[7] the prevalence of AF among the Saudi Arabia population is unclear. The burden of illness associated with AF in Saudi Arabia is high, with overall mean annual AF-related public sector medical costs estimated to be approximately USD$3000 (2013) per patient.[8] Assuming similar prevalence of AF in Saudi Arabia as in the United States, UK, and Europe,[2,4,5] and a population of 30.2 million in the year 2013,[9] the burden of illness for AF in Saudi Arabia was calculated to be between approximately USD$906 million and USD$1812 million in 2013.[2,4,5,8] The 2016 European Society of Cardiology guidelines for the management of atrial fibrillation, developed in collaboration with the European Association for Cardio-Thoracic Surgery, recommend that oral anticoagulation therapy be used for stroke prevention among AF patients with a CHA2DS2-VASc score of 2 or greater, and be considered for treatment of male patients with a CHA2DS2-VASc of 1.[10] Vitamin K antagonists (VKAs), including warfarin, have been the mainstay of anticoagulation therapy in AF patients for decades, while aspirin has been used in patients for whom VKA treatment is not suitable. Although VKAs are effective for stroke prevention, their use is limited by the requirement for frequent monitoring and dose adjustments, as well as multiple interactions with food and other drugs. Non-vitamin K antagonist oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, are relatively new treatment options for stroke prevention in NVAF patients that are being used with increasing frequency in clinical practice. When oral anticoagulation is initiated in a patient with AF who is eligible for treatment with an NOAC, an NOAC is recommended in preference to a Vitamin K antagonist. VKA treatment is still indicated in AF patients with mechanical heart valves or moderate or severe mitral stenosis.[10]

Apixaban has been evaluated in two large multinational clinical trials, the AVERROES and ARISTOTLE trials,[11,12] and was found to significantly reduce the risk of stroke and systemic embolism without significantly increasing the risk of major bleeding compared to aspirin.[11] Apixaban significantly reduced the risk of stroke and systemic embolism, major bleeding and all-cause mortality compared to warfarin.[12] Apixaban was approved in the US and Europe in 2012 and is recommended, along with other NOACs, by the Saudi Arabia Ministry of Health (MOH) clinical practice guidelines for anti-thrombotic treatment of NVAF in patients with a CHA2DS2-VASc score of 2 or greater.[13]

The availability of NOACs, of which apixaban, dabigatran, and rivaroxaban are approved by the Saudi Arabia MOH, has increased the treatment options available to physicians treating NVAF patients, and it is important to compare the clinical benefits and costs among all the available treatment options. The objective of this analysis was to estimate the cost-effectiveness of apixaban, compared to other anticoagulant therapies, aspirin and aspirin plus clopidogrel for stroke prevention among individuals with NVAF in Saudi Arabia.

METHODS

Model

A previously published Markov cohort model[14,15] was adapted from the United Kingdom (UK) setting to the Saudi Arabia MOH perspective. The model structure, treatment comparators, patient characteristics, clinical model inputs, and utility values remained consistent with the original UK model. Drug and clinical event costs and mortality estimates were updated to reflect Saudi Arabia setting. The model conceptualizes the outcomes of NVAF in terms of discrete health states, the transition

probabilities of patients between those states, and associated healthcare costs, life years (LYs), and quality-adjusted life years (QALYs). The model was developed in Microsoft® Excel with the following characteristics: a lifetime time horizon, six-week cycle length, and seventeen discrete health states that are identical in structure for each treatment option (**Figure 1**). The health states considered were: NVAF, ischemic stroke (mild, moderate, severe), recurrent ischemic stroke (mild, moderate, severe), hemorrhagic stroke (mild, moderate, severe), recurrent hemorrhagic stroke (mild, moderate, severe), myocardial infarction (MI), systemic embolism, NVAF without original anticoagulation, and death.

The model was structured to allow for pairwise comparisons of apixaban (5 mg BID) against each of the following seven other treatments for AF: warfarin (base-case; VKA suitable population only); aspirin; aspirin plus clopidogrel; dabigatran (110 mg BID); dabigatran (150 mg BID); a combination of dabigatran starting with 150 mg BID and switching to 110 mg BID at the age of 80 years (as per the summary of product characteristics); and rivaroxaban (20 mg QD). These treatment comparators and doses from the original UK model,[14,15] as well as monitoring practices for warfarin treatment, were summarized in a brief survey that was completed by a local experienced cardiologist, who confirmed that all treatment assumptions were consistent with clinical practice in Saudi Arabia. Additionally, local drug price lists published by the Saudi Food and Drug Authority (SFDA),[16] were checked to confirm the availability and dosages of the treatment comparators in Saudi Arabia.

In the absence of local health technology assessment (HTA) guidelines, the model retained all original assumptions (e.g. time horizon, discount rate), which followed a UK perspective, and were based on the recommendations set forth by the National Institute for Health and Care Excellence (NICE).[14,15] A detailed description of the UK model, including supplementary online information, has previously been published.[14,15]

Patient population

The characteristics of the patient population in the Saudi Arabia adaptation remained consistent with the original model: AF patients with differing risks of stroke,

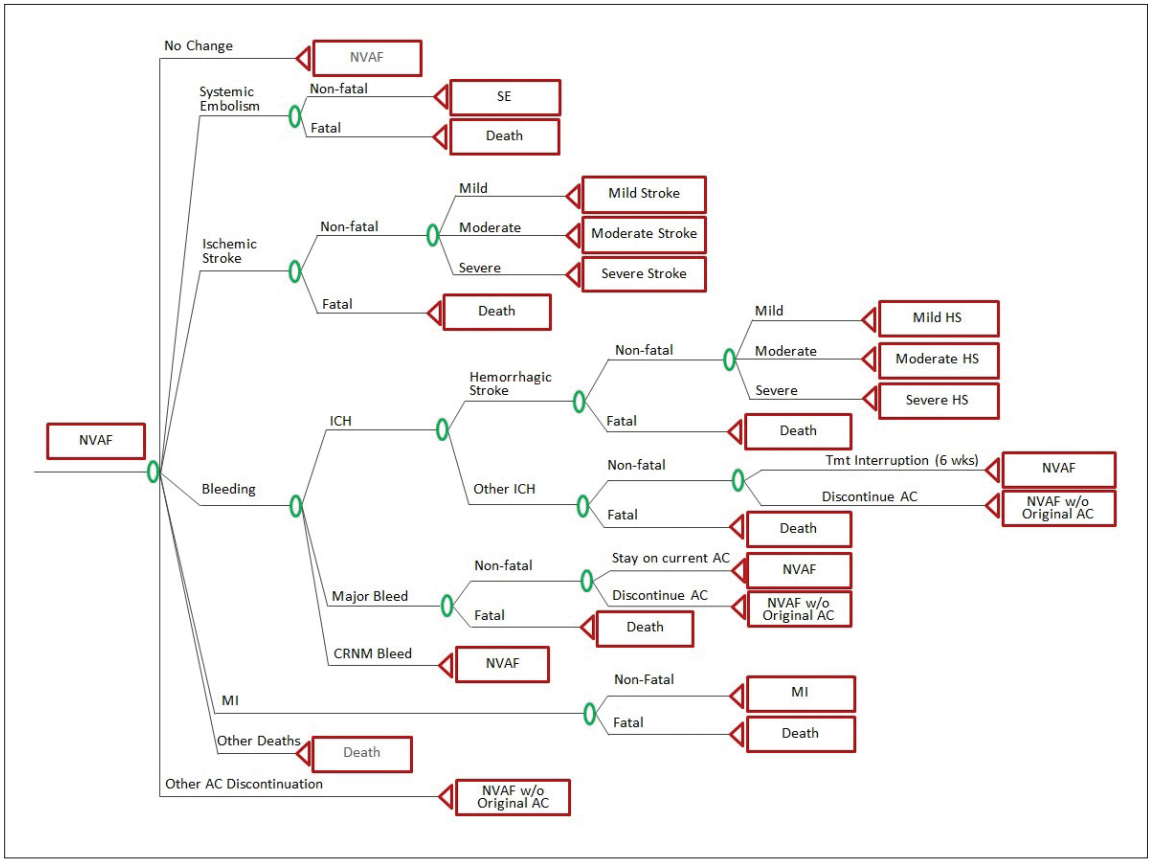


Figure 1. Markov model structure overview.

requiring anticoagulation for stroke prevention.[14,15] Two subpopulations were included: patients who failed on VKAs and/or were expected to be unsuitable for VKAs ("VKA unsuitable"); and patients who were suitable for VKAs ("VKA suitable"). Model inputs for patient characteristics for the base-case scenario (**Table 1**), were based on the characteristics of the subjects enrolled in the AVERROES and ARISTOTLE[11,12] clinical trials for VKA unsuitable and VKA suitable populations, respectively. Patient characteristics included in the model included mean age, sex (i.e. % female), and distribution of CHADS2 score for the cohort. Age and sex distributions were used to inform life expectancy, while CHADS2 score were used to inform risk of thrombotic events.

Treatment efficacy and safety data were taken from the apixaban clinical trials AVERROES and ARISTOTLE,[11,12] which compared apixaban to aspirin and warfarin, respectively. Clinical event rates for all events except bleeds were based on the intention-to-treat (ITT) subjects, while rates for bleeds were based on modified ITT subjects from first dose to two days following final dose (**Table 2**). For all other comparators, treatment comparisons were indirect, as no head-to-head clinical trial data were available. Hazard ratios (HRs) relative to apixaban were estimated using data from the following trials: ROCKET-AF (rivaroxaban 20 mg every day vs. warfarin),[17] RELY (dabigatran 110 mg twice daily vs. warfarin; dabigatran 150 mg twice daily vs. warfarin),[18] and ACTIVE-A (clopidogrel 75 mg every day + aspirin 75-100 mg/day vs. aspirin 75-100 mg/day).[19] Detailed methodology for the indirect treatment comparison has been presented in the original UK model publication and its corresponding Supplemental Appendix A.[15] Event rates and HRs for the indirect treatment comparisons have previously been published[15] and are presented in the supplementary material online (**Supplemental Table 1**).

Apixaban (Eliquis, Princeton, NJ USA and Pfizer, Inc., New York, NY USA) is an NOAC developed, manufactured and marketed by Bristol-Myers Squibb and Pfizer, Inc Alliance. For this study, all efficacy and safety data were taken from previously published clinical trials, and no drug was supplied by the manufacturer for this study.

Table 1. Characteristics of patients in the apixaban cost-effectiveness model.

	VKA unsuitable[a,c]	VKA suitable[b,c,d]
Sex (%)		
Male	58.5	64.7
Female	41.5	35.3
Starting age (years)		
Male	70	70
Female	70	70
CHADS2 distribution (%)		
CHADS2=0-1	38.2	34.0
CHADS2=2	35.2	35.8
CHADS2≥3	26.6	30.2
Mean CHADS2 score	2.0	2.1

VKA = vitamin K antagonist. Source: [a]AVERROES trial[11]; [b]ARISTOTLE trial[12]; [c]Dorian et al[14]; [d]Lip et al[15]

Costs and utilities

Costs used in the model are presented in **Table 3** and **Table 4** (2013 US Dollars [USD]). Unit costs for medications were obtained from publicly available price lists for the region, published by the SFDA,[16] and were converted to USD.

Due to a lack of available local data for the costs of managing clinical events related to AF, the costs used in this adaptation were informed by the event costs in the UK model. This methodology assumed that the event costs were proportionate to those estimated for the UK. A ratio of Saudi physician visit costs to UK National Health Service (NHS) physician visit costs was calculated, to inform a mean cost ratio to be applied to the UK event costs. Cost ratios were averaged across nine types of outpatient visits (family physician, medical cardiologist, diabetologist, hematologist, neurologist, endocrinologist, pulmonologist, echocardiogram, electrocardiogram), yielding a mean cost ratio of 0.533 for Saudi costs compared to UK costs. The estimated average cost ratio was applied to the UK model costs for managing clinical events, after the latter had been inflated from 2010 to 2013 Great Britain pounds (£) using an inflation factor of 1.13. The inflation factor was estimated from the health component of the consumer price index.[20]

Due to the lack of utility data available for Saudi Arabia, utility estimates were taken from a published catalogue of EQ-5D scores for the United Kingdom,[21] and are presented in **Table 5**. An annual discount rate of 3.5% was applied to both costs and health benefits occurring beyond the first year.

Mortality

Background life expectancy by age and sex, for the estimation of deaths from other causes for the cohort, was estimated by fitting a Gompertz survival function to the 2011 Saudi life tables,[22] following the same methodology applied in the original UK model.[14] Applying the Gompertz function, which corresponds to exponential mortality rate increases over time, allowed for the estimation of mortality risk by 6-week cycle length, rather than yearly based on annual life table data. Deaths due to strokes, myocardial infarction, systemic embolism, and bleeds were explicitly modelled as events and were excluded from the background mortality data to avoid double counting. As mortality data from Saudi Arabia for these clinical events were unavailable, information from the UK was used to estimate the proportion of cardiovascular deaths out of deaths from any cause, that are expected to be observed in Saudi Arabia.

A technical validation was conducted on the model, and was specific to the sections that were adapted to reflect the perspective of Saudi Arabia. All issues arising from the validation process were assessed and corrected as necessary. The validation process was conducted through review of the adapted components by a second analyst not involved in the original model adaptation.

Analysis

For both the VKA suitable and VKA unsuitable populations, clinical and economic outcomes were predicted for a cohort of 1000 NVAF patients over their lifetime. Costs included in the model were those relating to medications, administration, monitoring tests, and other direct medical services. Health effects were expressed in terms of LYs and QALYs. Life years gained reflects the estimated additional number of years of life obtained by using the treatment. Total LYs were summed for each comparator, for time spent by all patients in each non-death health state across all cycles over the lifetime duration of the model, based on the risks of experiencing different events (transition probabilities; **Table 2** and **Supplemental Table 1**). For QALYs, both morbidity and mortality are incorporated and the utility weight (0-1) associated with each health state (**Table 5**) was multiplied by the time spent in each health state, then summed for all patients over the model lifetime. The specific outputs from the cost-effectiveness model, for each comparator, were: mean total costs per patient over the lifetime duration of the model; and mean total LYs and QALYs per patient over

Table 2. Clinical event rates in the apixaban cost-effectiveness model (per 100 person-years).

Rate of Ischemic Stroke by CHADS2 score	**VKA Unsuitable**		**VKA Suitable**	
CHADS2 Score	**Apixaban**	**Aspirin**	**Apixaban**	**Warfarin**
0-1	0.83	1.41	0.52	0.46
2	1.53	3.36	0.95	0.93
3-6	1.96	5.19	1.53	1.94
Average stroke rate	1.37	3.10	0.98	1.08
Stroke Severity Distribution (%)	**VKA Unsuitable**		**VKA Suitable**	
Severity (Modified Rankin Scale)	**Apixaban**	**Aspirin**	**Apixaban**	**Warfarin**
Mild (mRS 0-2)	40%	36%	53%	45%
Moderate (mRS 3-4)	28%	38%	21%	30%
Severe (mRS 5)	12%	15%	8%	10%
Fatal (mRS 6)	20%	11%	18%	15%
Hemorrhagic Stroke Severity Distribution (%)	**VKA Unsuitable**		**VKA Suitable**	
Severity (Modified Rankin Scale)	**Apixaban**	**Aspirin**	**Apixaban**	**Warfarin**
Mild (mRS 0-2)	7%	7%	23%	20%
Moderate (mRS 3-4)	20%	20%	32%	15%
Severe (mRS 5)	27%	27%	10%	12%
Fatal (mRS 6)	46%	46%	35%	53%
Rate of clinical events	**VKA Unsuitable**		**VKA Suitable**	
	Apixaban	**Aspirin**	**Apixaban**	**Warfarin**
Intracranial hemorrhage	0.34	0.35	0.33	0.80
Other major bleed	1.07	0.57	1.79	2.27
Clinically relevant non-major bleed	3.11	2.37	2.08	3.00
Myocardial infarction	0.76	0.89	0.53	0.61
Systemic embolism	0.06	0.41	0.09	0.10
Other CV hospitalization	10.46	12.09	10.46	10.46
Other treatment discontinuation	17.31	19.01	13.18	14.41

Abbreviations: CV=cardiovascular; mRS=modified Rankin Scale; VKA=vitamin K antagonist. Source: Dorian et al[14]; Lip et al[15]

Table 3. Unit costs and average daily dosages of treatment comparators in the Saudi Arabia apixaban cost-effectiveness model.

Treatment	Tablet size (mg)	Cost per tablet (USD)	Average daily dose (mg)	Number of tablets per day	Average cost per day (USD)
Apixaban[16]	5	1.40	10	2	2.80
Aspirin [BMS affiliate communication]	75	0.02	150	2	0.04
Warfarin[16]	5	0.32	5	1	0.32
Dabigatran (110 mg)[16]	110	1.40	220	2	2.80
Dabigatran (150 mg)[16]	150	1.40	300	2	2.80
Rivaroxaban[16]	20	3.00	20	1	3.00
Clopidogrel[16]	75	2.36	75	1	2.36

Abbreviations: mg=milligram; USD=United States dollars.

Table 4. Clinical episodes and associated costs considered in the Saudi Arabia apixaban cost-effectiveness economic model, Saudi Arabia Ministry of Health perspective.

Event	Cost[a] (2013 USD)	Unit	Duration
Monitoring visit (applicable to warfarin only)	71.99	per visit	N/A
Routine care	0.00	per visit	N/A
Stroke (excluding hemorrhagic stroke)			
Mild			
Acute care	6883.53	per episode	2 weeks
Long-term maintenance	146.70	per month	Lifetime
Moderate			
Acute care	6501.61	per episode	2 weeks
Long-term maintenance	159.90	per month	Lifetime
Severe			
Acute care	14 249.27	per episode	2 weeks
Long-term maintenance	450.30	per month	Lifetime
Fatal ischemic stroke	9154.37	per episode	N/A
Hemorrhagic stroke			
Mild			
Acute care	6883.53	per episode	2 weeks
Long-term maintenance	146.70	per month	Lifetime
Moderate			
Acute care	6501.61	per episode	2 weeks
Long-term maintenance	159.90	per month	Lifetime
Severe			
Acute care	14 249.27	per episode	2 weeks
Long-term maintenance	450.30	per month	Lifetime
Fatal hemorrhagic stroke	9154.37	per episode	N/A

Table 4 (cont.). Clinical episodes and associated costs considered in the Saudi Arabia apixaban cost-effectiveness economic model, Saudi Arabia Ministry of Health perspective.

Event	Cost[a] (2013 USD)	Unit	Duration
Systemic embolism			
Acute care	6883.53	per episode	2 weeks
Long-term maintenance	146.70	per month	Lifetime
Other ICH (excluding hemorrhagic stroke)	3040.27	per episode	N/A
Other major bleeds (excluding ICH)			
GI bleeds	1508.70	per episode	N/A
Non-ICH and non-GI related major bleeds	3987.62	per episode	N/A
Clinically relevant non-major bleeds	1145.33	per episode	N/A
Myocardial infarction			
Acute care	2039.14	per episode	N/A
Long-term maintenance	6.51	per month	Lifetime
Other cardiovascular hospitalization	1586.69	per episode	N/A
Anticoagulant management costs			
Dyspepsia	84.03	per month	
Renal monitoring	3.03	per year	

Abbreviations: GI=gastrointestinal; ICH=intracranial hemorrhage; N/A=not applicable; USD=United States dollars.

[a]Clinical event costs for the Saudi Arabia model were calculated by applying a cost ratio of 0.533 to clinical event costs from the UK model,[14] due to a lack of local Saudi Arabia cost data. The cost ratio was calculated through comparison of UK and Saudi Arabia physician visit costs.

the lifetime duration of the model. Total costs incurred and QALYs gained were recorded and used to check for dominance or to calculate incremental cost-effectiveness ratios (ICERs).

Given that no established willingness to pay (WTP) thresholds exist in Saudi Arabia, the analysis assessed the cost-effectiveness of apixaban versus each of the comparators using threshold values of $20 000 and $30 000 USD, which are lower than the commonly used WTP thresholds in the US ($50 000/QALY) and the UK (£20 000/QALY).[14,23-25]

The impacts of changes to various model inputs were evaluated through univariate sensitivity analyses, in which model parameters were varied using their 95% Confidence Intervals (CIs). Model results were regenerated with one model parameter varied at a time, while other parameters were kept constant. Probabilistic sensitivity analysis (PSA) was also conducted to account for variability in outcomes due to statistical uncertainty in inputs. Values of key input parameters, including event rates, costs, risks and utilities, were assigned a probability distribution and varied across 2000 simulations. Time horizon, population characteristics, and model settings were kept constant. One-way and probabilistic sensitivity analyses were performed for the apixaban vs. warfarin comparison in the VKA suitable population, and for the apixaban vs. aspirin comparison in the VKA unsuitable population. Probabilistic sensitivity analyses were also conducted for the apixaban vs. rivaroxaban comparison in both the VKA suitable and VKA unsuitable populations.

RESULTS

Base-case analysis

Incremental costs and outcomes for apixaban versus each model comparator are presented in **Table 6** (VKA suitable) and **Table 7** (VKA unsuitable), ranked by the cost-effectiveness of apixaban versus each comparator. In the VKA suitable population, apixaban was dominant (more effective and less costly) versus warfarin and rivaroxaban. Compared to dabigatran, the incremental cost per QALY gained for apixaban ranged from $5166 (vs. 110 mg BID) to $11 143 (vs. 150 mg BID). In comparison to aspirin or aspirin plus clopidogrel, the incremental costs per QALY for apixaban were $14 805 and $5784 respectively.

For the VKA unsuitable population, apixaban was

Table 5. Utility estimates used in the model.

Health state	Utility		Source
Non-valvular atrial fibrillation (baseline)	0.7270	-	21
Stroke			
Mild	0.6151	-	21
Moderate	0.5646	-	21
Severe	0.5142	-	21
Hemorrhagic stroke			
Mild	0.6151	-	21
Moderate	0.5646	-	21
Severe	0.5142	-	21
Systemic embolism	0.6265	-	21
Myocardial infarction	0.6098	-	21
Transient health states	**Utility decrement**	**Duration**	**Source**
Clinical events			
Other intracranial hemorrhage	0.1511	6 weeks[a]	21
Other major bleeds	0.1511	2 weeks[a]	21
Clinically relevant non-major bleeds	0.0582	2 days[a]	21
Other cardiovascular hospitalization	0.1276	6 days[a]	21
Use of anticoagulant	**Utility decrement**	**Duration**	
Aspirin	0.0020	While on aspirin	29
Warfarin	0.0120	While on warfarin	29
NOACs	0.000[b]	---	

Abbreviations: NOACs = non-vitamin K antagonist oral anticoagulants. [a]Assumption based on clinical expert opinion.[14,15] [b]Assumption.

dominant versus rivaroxaban. Compared to dabigatran, the incremental cost per QALY gained for apixaban ranged from $5157 (vs. 110 mg BID) to $14 424 (vs. 150 mg BID). The incremental costs per QALY for apixaban versus aspirin or aspirin plus clopidogrel were $10 564 and $4203, respectively

Sensitivity analyses

Model inputs with the most influence on the ICER values for the VKA suitable population were data on stroke and bleeding risks, disease-specific mortality adjustment factors, the utility decrement assigned to patients treated with warfarin, the risk of treatment discontinuations for both apixaban and warfarin, and cost of monitoring visits associated with warfarin (**Figure 2A**). The model inputs with the most influence on the ICER values for the VKA unsuitable population were cost of apixaban, disease-specific mortality adjustment factors, and data on stroke risks (**Figure 2B**). There was more uncertainty around the ICER values for apixaban in the VKA suitable population as evidenced by the wider bars of the associated tornado diagram (**Figure 2A**).

The scatterplot of the PSA for the apixaban versus warfarin comparison in the VKA suitable population lies below the $0 cost line on the cost-effectiveness plane, and the majority of data points are to the right of the effectiveness line, meaning that apixaban is very likely to be more effective and cheaper than warfarin (**Figure 3A**). The probability that apixaban is cost-effective compared to warfarin at various WTP thresholds is shown in **Figure 4A**. At both the $20 000 and $30 000 thresholds apixaban was cost-effective in 98% of the PSA simulations.

The cost-effectiveness plane in **Figure 3B** shows the results of the PSA for the apixaban vs. aspirin comparison in the VKA unsuitable population. The majority of the scatterplot lies above the $0 cost line and to the

Table 6. Incremental costs and outcomes for apixaban versus other comparators in VKA suitable atrial fibrillation patients in Saudi Arabia.

Comparator Apixaban versus:	Incremental cost (USD)	Incremental QALY	Cost per QALY gained (USD)	Incremental LY	Cost per LY gained (USD)
Warfarin	-$1137	0.133	Dominant	0.12	Dominant
Rivaroxaban	-$149	0.029	Dominant	0.04	Dominant
Dabigatran (110 mg)	$373	0.072	$5166	0.09	$4157
Aspirin + Clopidogrel	$507	0.088	$5784	0.112	$4540
Dabigatran (150 mg) & Dabigatran (110 mg)	$463	0.043	$10 849	0.05	$9096
Dabigatran (150 mg)	$467	0.042	$11 143	0.05	$9342
Aspirin	$2932	0.198	$14 805	0.25	$11 686

Abbreviations: LY=life year; mg=milligram; QALY=quality-adjusted life year; USD=United States dollars.

Table 7. Incremental costs and outcomes for apixaban versus other comparators in VKA unsuitable atrial fibrillation patients in Saudi Arabia.

Comparator Apixaban versus:	Incremental cost (USD)	Incremental QALY	Cost per QALY gained (USD)	Incremental LY	Cost per LY gained (USD)
Rivaroxaban	-$115	0.018	Dominant	0.02	Dominant
Aspirin + Clopidogrel	$339	0.081	$4203	0.102	$3322
Dabigatran (110 mg)	$332	0.064	$5157	0.08	$4185
Aspirin	$2001	0.189	$10564	0.23	$8621
Dabigatran (150 mg) & Dabigatran (110 mg)	$431	0.031	$14134	0.03	$12388
Dabigatran (150 mg)	$434	0.030	$14424	0.03	$12653

Abbreviations: LY=life year; mg=milligram; QALY=quality-adjusted life year; USD=United States dollars.

right of the effectiveness line meaning that apixaban is very likely to be more effective and more expensive than aspirin. At the $20000 WTP threshold apixaban was cost-effective compared to aspirin in 94% of the PSA simulations, and at the $30000 threshold apixaban was cost-effective in 97% of the PSA simulations (**Figure 4B**).

In both the VKA suitable and VKA unsuitable populations, the majority of the PSA scatterplots for the apixaban vs. rivaroxaban comparison are below the $0 cost line on the cost-effectiveness plane and to the right of the effectiveness line, indicating that apixaban was more effective and cheaper than rivaroxaban in the majority of simulations (**Figure 3C and Figure 3D**). However, a portion of each scatterplot was below the $0 cost line and to the left of the effectiveness line, indicating lower cost and lower effectiveness of apixaban compared to rivaroxaban in both the VKA suitable and VKA unsuitable populations. In the VKA suitable population, apixaban was cost-effective compared to rivaroxaban in 94% of the PSA simulations at the $20000 WTP threshold, and in 96% of the PSA simulations at the $30000 WTP threshold (**Figure 4C**); corresponding numbers in the VKA unsuitable population were 90% and 92%, respectively (**Figure 4D**).

DISCUSSION

There is a lack of published information available on the cost-effectiveness of therapies for stroke prevention among individuals with NVAF in Saudi Arabia or surrounding regions. To our knowledge, this analysis provides the first pharmacoeconomic evidence for NVAF treatment in Saudi Arabia. A previously published model[14,15] was adapted to Saudi Arabia setting through updates to medication and clinical event costs and mortality estimates. The underlying model structure, treatment comparators, patient characteristics, clinical model

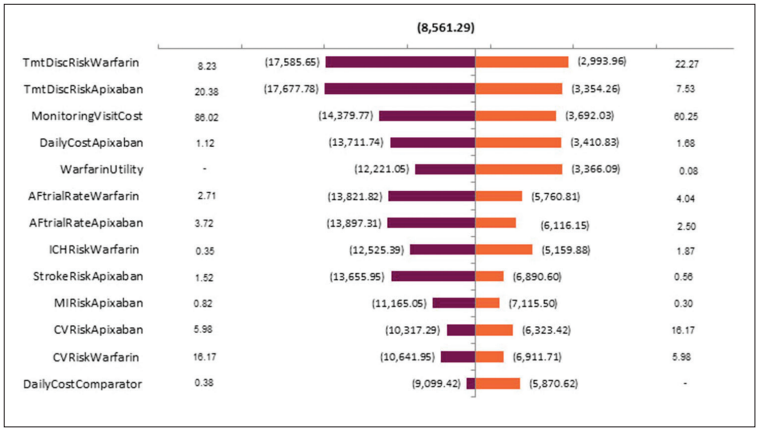


Figure 2A. One-way sensitivity analysis of apixaban vs. warfarin (VKA suitable).

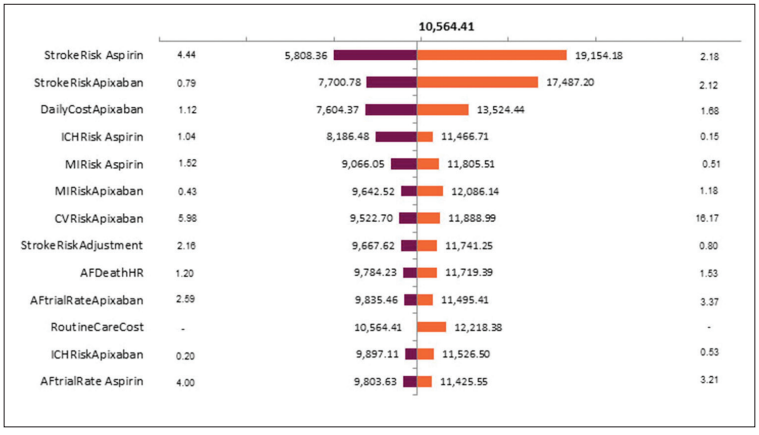


Figure 2B. One-way sensitivity analysis of apixaban vs. aspirin (VKA unsuitable).

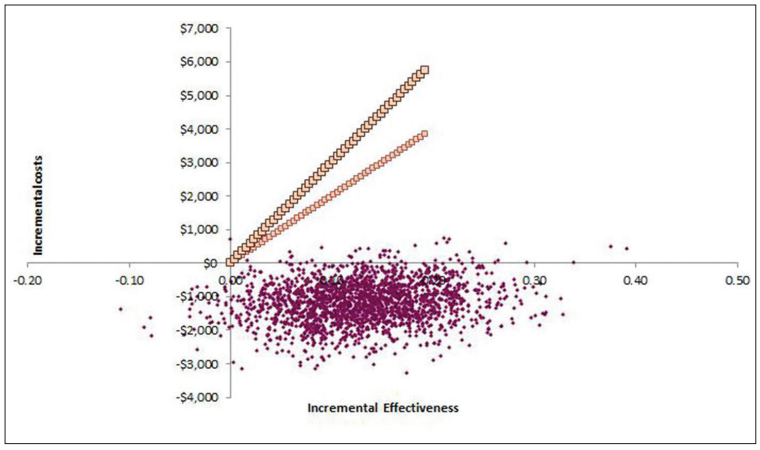


Figure 3A. Probabilistic sensitivity analysis of apixaban vs. warfarin (VKA suitable).

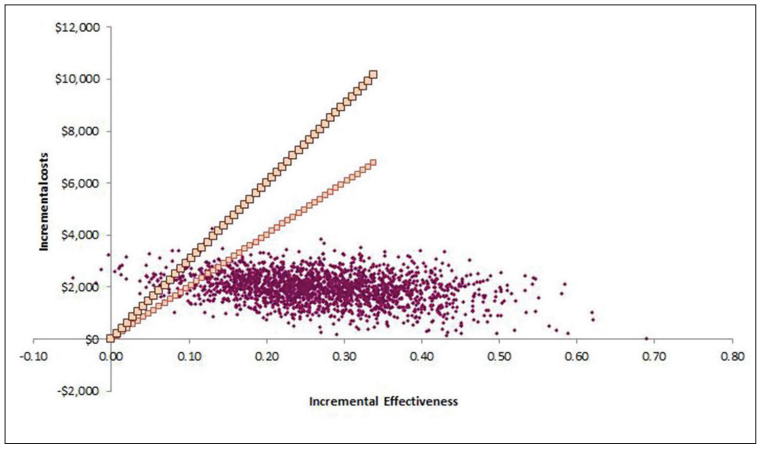


Figure 3B. Probabilistic sensitivity analysis of apixaban vs. aspirin (VKA unsuitable).

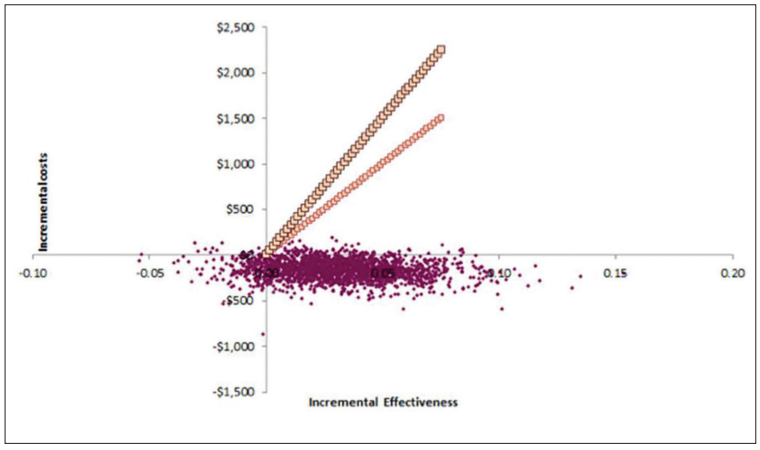


Figure 3C. Probabilistic sensitivity analysis of apixaban vs. rivaroxaban (VKA suitable).

inputs, and utility values remained consistent with the original UK model.[14,15]

In the present analysis, apixaban demonstrated dominance against warfarin in the VKA suitable population, and against rivaroxaban in both VKA suitable and VKA unsuitable populations. Apixaban was also found to be a cost-effective treatment strategy for stroke prevention among NVAF patients in Saudi Arabia, with ICERs for both VKA suitable and VKA unsuitable populations that fell within the WTP threshold of $20 000 USD. Since no established WTP thresholds exist for Saudi Arabia, WTP thresholds of $20 000 and $30 000 USD were used in this analysis. These conservative WTP thresholds are lower than those widely accepted in the US ($50 000/QALY) and the UK (£20 000/QALY),[14,23-25] and are considerably lower than the $100 000 USD threshold increasingly being used in the US[23] and that was recently used in a published Saudi cost-effectiveness study.[26]

Given the lack of published cost-effectiveness analyses for anticoagulant use in the management of NVAF in Saudi Arabia, there are no local data against which to contrast the findings of the present study. The ICERs estimated for Saudi Arabia were consistent with the published results of the original UK apixaban model[14,15] in demonstrating cost-effectiveness of apixaban. While apixaban treatment was associated with lower incremental LYs and QALYs in this adaptation, the incremental costs were also lower in Saudi Arabia which resulted in ICERs that were well below acceptable cost-effectiveness thresholds for other jurisdictions, such as the US and the UK.

This analysis has several important limitations. First, the lack of Saudi-specific cost estimates for managing clinical events, such as MI, stroke, and bleeds, limited our ability to incorporate local estimates of costs associated with these events, both in the acute phase and long-term, in the model. While available costs from the UK were used to estimate the cost of these events in Saudi Arabia, based on a cost ratio of UK to Saudi physician costs, they may not be reflective of the actual costs associated with the management of these events in Saudi Arabia. The impact of these assumptions on the estimated ICERs is uncertain, as the magnitude of errors between the estimated costs and true costs of these clinical events in Saudi Arabia are unknown. However, findings from the one-way sensitivity analyses indicated that variations in clinical event costs did not have a high impact on the cost-effectiveness of apixaban relative to the other comparators. Additionally, local medication costs were available through published sources, and local clinician input was obtained to validate the treatment comparators and assumptions in the model.

Second, clinical event rates in the model for rivaroxaban, dabigatran, and clopidogrel plus aspirin were estimated using indirect treatment comparison, as no head-to-head clinical trial data were available for these comparators and apixaban. Methods for the indirect comparison have been described previously, and its key limitations were that the analysis did not control for differences in study design, patient baseline characteristics, CHADS2 score, or time in therapeutic range.[15] However, based on the specific variations that were not controlled for between included studies, the authors concluded that the differences were more likely to have favored the other comparators, rather than apixaban.[15] The authors also reported that their results were consistent with results from other indirect comparisons of these treatments.[15] In the absence of head-to-head clinical trial data, the estimates from this indirect comparison provide reasonable estimates of comparative treatment effects for use in the economic model.

Further, this analysis was conducted from the Saudi Arabia MOH perspective and costs were updated from MOH sources, where available. Findings from this analysis may not be generalizable to other healthcare settings in Saudi Arabia, such as private payer or institutions. Additionally, this analysis used utilities based on a UK EQ-5D catalogue,[21] given the absence of local utility estimates. Although Saudi-specific utility estimates were not available, since those used were taken from a European population, it is plausible to assume that they would be similar for the Saudi population. The same assumption has been applied in other prior studies.[27,28]

While background mortality estimates in the adaptation were based on Saudi life tables, the proportion of patients expected to die from cardiovascular causes in the model (to be excluded from the life tables) used UK-specific detail due to a lack of local data, and may not be representative of cardiovascular mortality rates in Saudi Arabia. Further, efficacy and safety data for apixaban and other model comparators were taken from large clinical trials that were conducted outside Saudi Arabia and may not reflect the efficacy and safety of the AF treatments in Saudi Arabia population. However, these were all large multi-national trials that included patients from a variety of backgrounds, and it was assumed that efficacy and safety would be similar in Saudi Arabia population.

Future research to quantify the resource utilization, costs, and health-related quality of life impacts of AF, particularly those associated with AF-related clinical events, would enable the more thorough estimation of cost-effectiveness of treatments to prevent stroke among the population with AF.

In the present economic model adaptation, apixa-

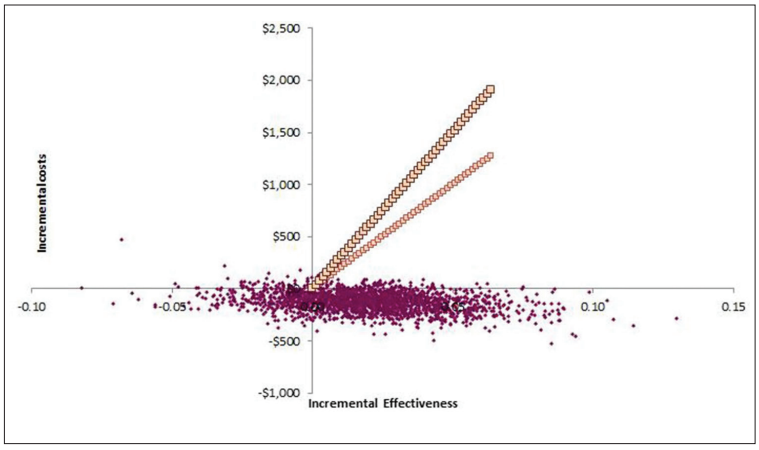


Figure 3D. Probabilistic sensitivity analysis of apixaban vs. rivaroxaban (VKA unsuitable).

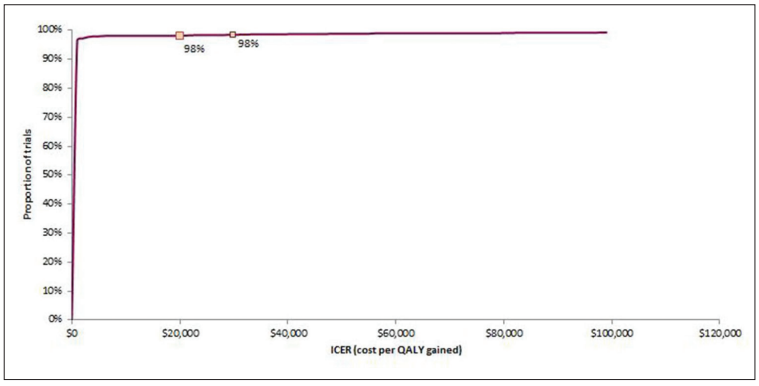


Figure 4A. Probability of apixaban being cost-effective at willingness to pay thresholds of $20 000 and $30 000 per QALY, based on 2000 replications. Apixaban compared to warfarin (VKA suitable).

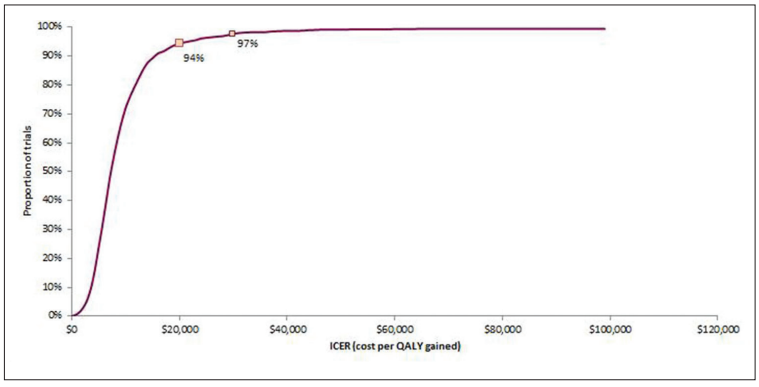
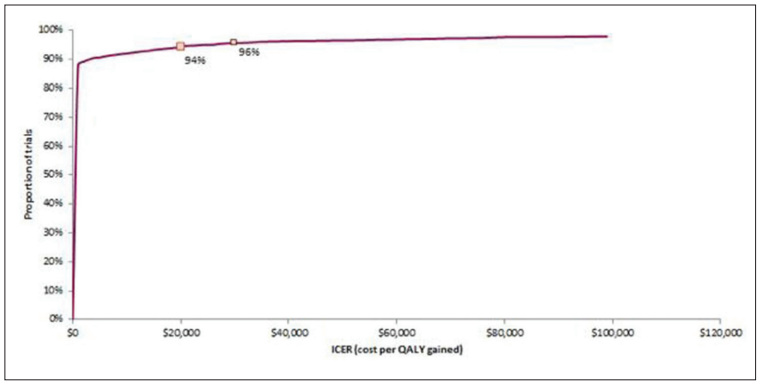


Figure 4B. Apixaban compared to aspirin (VKA unsuitable).



Figrue 4C. Apixaban compared to rivaroxaban (VKA suitable).

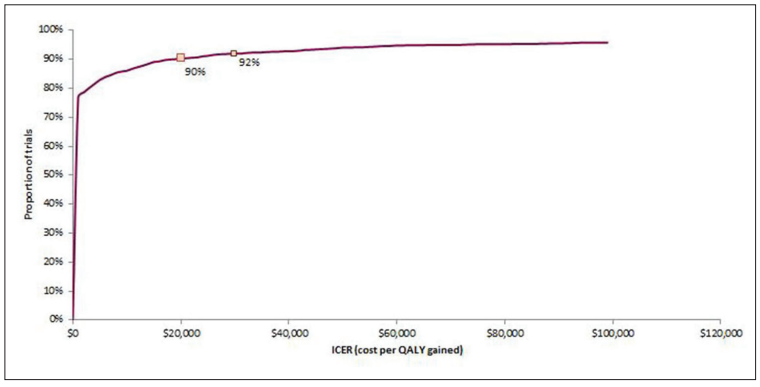


Figure 4D. Apixaban compared to rivaroxaban (VKA unsuitable).

ban was shown to be a cost-effective treatment for stroke prevention among individuals with NVAF in Saudi Arabia, particularly when compared to warfarin and rivaroxaban. Incremental cost-effectiveness ratios of apixaban versus all comparators were within the $20 000 WTP threshold, which is considerably lower than the typically accepted WTP thresholds for the UK and US. These results provide informative economic evidence that can aid local decision-makers; however, given the lack of local clinical, cost and utility data, results should be interpreted with caution. Availability of robust local data inputs, particularly for the cost of clinical event management, would enable refinement of apixaban cost-effectiveness estimates for NVAF treatment in Saudi Arabia.

Conflcit of interest disclosure

Katherine Osenenko and Robert Sambrook are employees of ICON plc, who were paid consultants to Bristol-Myers Squibb and Pfizer, Inc. in connection with the adaptation of the economic model and the development of this manuscript. Sid Ahmed Kherraf is an employee of Pfizer, Inc. Ayman Abdel Aziz was an employee of Pfizer Inc., at the time of study conduct and manuscript preparation. Ahmad Hersi has received honoraria from Pfizer Inc. for giving talks and workshops.

Financial disclosures

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Supplemental Table 1. Risk of clinical events in the apixaban cost-effectiveness model.

Risk of Ischemic Stroke	**VKA Unsuitable/VKA Suitable**			
Hazard Ratio – Apixaban as reference	Dabigatran 110[a,d]	Dabigatran 150[b,d]	Rivaroxaban[b,d]	Aspirin + Clopidogrel[c]
Ischemic Stroke	1.198	0.823	0.980	1.521
Ischemic Stroke Severity Rate	**VKA Unsuitable/VKA Suitable**			
Severity (Modified Rankin Scale)	Dabigatran 110[a,d]	Dabigatran 150[b,d]	Rivaroxaban[b,d]	Aspirin + Clopidogrel[c]
Mild (mRS 0-2)	35%	35%	49%	35%
Moderate (mRS 3-4)	28%	22%	18%	31%
Severe (mRS 5)	10%	8%	6%	11%
Fatal (mRS 6)	27%	35%	27%	23%
Hemorrhagic Stroke Severity Rate	**VKA Unsuitable/VKA Suitable**			
Severity (Modified Rankin Scale)	Dabigatran 110[a,d]	Dabigatran 150[b,d]	Rivaroxaban[b,d]	Aspirin + Clopidogrel[c]
Mild (mRS 0-2)	35%	35%	49%	35%
Moderate (mRS 3-4)	28%	22%	18%	31%
Severe (mRS 5)	10%	8%	6%	11%
Fatal (mRS 6)	27%	35%	27%	23%
Risk of Clinical Events	**VKA Unsuitable/VKA Suitable**			
Hazard Ratio – Apixaban as reference	Dabigatran 110[a,d]	Dabigatran 150[b,d]	Rivaroxaban[b,d]	Aspirin + Clopidogrel[c]
Intracranial Hemorrhage	0.733	1.020	1.731	2.058
Other major bleed	1.205	1.371	1.436	0.798
Clinically relevant non-major bleed	1.155	1.303	1.488	1.908
Myocardial Infarction	1.474	1.456	0.935	0.875
Systemic Embolism	1.00	1.00	1.00	1.00
Other CV hospitalization	1.00	1.00	1.00	1.00
Other treatment discontinuation	1.452	1.505	1.184	1.290

Abbreviations: CV=cardiovascular; mRS=modified Rankin Scale; VKA=vitamin K antagonist.

Source: [a]RELY trial (dabigatran 110 mg twice daily vs. warfarin; dabigatran 150 mg twice daily vs. warfarin);[18] [b]ROCKET-AF (rivaroxaban 20 mg OD vs. warfarin);[17] [c]ACTIVE-A (clopidogrel 75 mg once daily + aspirin 75-100 mg/day vs. aspirin 75-100 mg/day);[19] Lip et al[15]