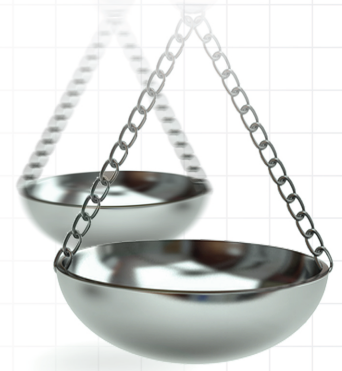




US cost–effectiveness analysis of apixaban compared with warfarin, dabigatran and rivaroxaban for nonvalvular atrial fibrillation, focusing on equal value of life years and health years in total

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Aim: Warfarin and direct-acting oral anticoagulants (DOACs) are widely prescribed to patients with nonvalvular atrial fibrillation (NVAF) to reduce risk of stroke and systemic embolism (SE). This study aimed to assess the cost–effectiveness of apixaban compared with warfarin, dabigatran and rivaroxaban, for patients with NVAF from a US healthcare payer (Medicare) perspective. **Methods:** A cohort-level Markov model was developed based on a previously published model, for the US setting, factoring in anticipated price decreases due to market entry of generic drugs. Two retrospective cohort studies in US Medicare patients provided inputs to quantify clinical events in the base case setting and in a scenario analysis. For this study, equal value of life-years (evLYs) and health years in total (HYT) were used. Cost–effectiveness was assessed based on a willingness-to-pay threshold of \$100,000 per evLY gained (evLYG) or HYT gained (HYTG). **Results:** Apixaban treatment was associated with gains of 2.23, 1.08 and 1.72 evLYs and 2.26, 1.08 and 1.73 HYTs, compared with warfarin, dabigatran and rivaroxaban, respectively. In the base case analysis from a Medicare perspective, apixaban was cost-effective (i.e., value for money) compared with warfarin, dabigatran and rivaroxaban, with corresponding incremental cost–effectiveness ratio (ICER) per evLYG (and HYTG) of \$10,501 (\$10,350), \$7809 (\$7769) and \$758 (\$768), respectively. When a societal perspective was included, and in a scenario analysis using US Medicare data from the Ray *et al.* study to quantify treatment effects, apixaban dominated rivaroxaban (i.e., less expensive and more effective) in terms of ICER per evLYG (and HYTG). **Conclusion:** Using dynamic pricing assumptions, treatment with apixaban compared with warfarin, dabigatran and rivaroxaban was associated with incremental evLYs and HYT and represents a cost-effective treatment option in patients with NVAF, from a US healthcare payer (Medicare) perspective.

Plain language summary: What is this article about?: Atrial fibrillation (AF) is the most common heart rhythm disorder and is a major cause of stroke, which may lead to disability or death. Warfarin and direct-acting oral anticoagulants (DOACs; medicines that help prevent blood clots from forming) are widely used to treat people with nonvalvular atrial fibrillation (NVAF) to lower their risk of stroke and systemic embolism (SE), conditions where clots cause blockages in blood vessels in the brain or elsewhere in the arterial system, respectively. This research aimed to evaluate whether apixaban, a DOAC, is a cost-effective treatment option compared with warfarin, and other DOACs (dabigatran and rivaroxaban) for people with NVAF covered under the Medicare fee-for-service program in the US.

How was the research carried out?: A cost–effectiveness analysis was undertaken using a specially designed mathematical model that analyzed the health benefits (e.g., clinical events such as stroke and

major bleeds averted, and years of life gained) and costs of apixaban compared with warfarin, dabigatran and rivaroxaban.

What were the results?: The study showed that apixaban reduced stroke and major bleeding events and was the most cost-effective compared with warfarin, dabigatran and rivaroxaban.

What do the results of the study mean?: The results indicate that for the US Medicare population, using apixaban to treat people with NVAf is a cost-effective treatment option.

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Keywords: apixaban • cost-effectiveness • equal value of life years • health years in total • Medicare • nonvalvular atrial fibrillation

Atrial fibrillation (AF) is the most common of the sustained heart arrhythmias. It is projected that 16 million people will suffer from this condition in the US by 2050, due to an ageing population [1]. It is associated with a fivefold increase in stroke occurrence and an increase in stroke severity compared with patients without AF, resulting in higher morbidity and mortality [2–4]. Prior to 2010, warfarin was the only available anticoagulant for the prevention of stroke in patients diagnosed with AF in the US. Since 2010, a range of direct-acting oral anticoagulants (DOACs) including apixaban, dabigatran, rivaroxaban and edoxaban have been approved by the Food and Drug Administration as alternatives to warfarin for the prevention of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAf) [5–8]. The DOACs have more predictable pharmacokinetics, do not require monitoring, are easier to use, have fewer interactions with other drugs and are at least equally efficacious or have better clinical outcomes than warfarin [9–13].

Since their approval, there have been several analyses comparing DOACs to warfarin [9]. In 2017, Lopez-Lopez *et al.* [9] and Sterne *et al.* [14] conducted a systematic review and network meta-analysis (NMA) of the randomized controlled trials (RCTs) and a subsequent cost-effectiveness analysis with the aim of comparing DOACs for the prevention of stroke in AF and for the primary prevention, treatment and secondary prevention of venous thromboembolism (VTE). They concluded that all DOACs appear to have equal or superior efficacy compared with warfarin, and that apixaban was associated with the highest net benefit and quality-adjusted life years (QALY) [9,14]. In addition, apixaban had the highest probability of being the most cost-effective treatment for the prevention of stroke in patients with AF [9,14]. While there are no RCTs that have directly compared different DOACs with each other, differences in the reported clinical efficacy and safety of the DOAC treatments concluded from NMAs, indicate it is also important to compare the cost-effectiveness of DOAC treatments against each other.

Traditional cost-effectiveness analyses focus on cost per QALY gained. QALY is an international standard of health outcome measure that combines both the quantity and quality of life (QoL) by multiplying the time spent in a particular health state by a QoL score associated with that state [15]. To complement the use of QALY, this study used two additional metrics; equal value of life years (evLYs) and health years in total (HYT), which can be used to evaluate the cost-effectiveness of pharmaceutical treatments. The evLY methodology was designed to apply the full value of a healthy life year to all gains in life-years, irrespective of age, disability, or illness [16,17]. This approach reduces the risk of discrimination against any patient group. The HYT measure separates life expectancy effects from QoL impacts and is the total of life expectancy combined with adjusted QALYs, which are estimated over a duration corresponding to the maximum survival period of the respective alternative [18]. This metric overcomes the limitations of QALYs which does not account for the quality-of-life impacts during the added years of life [18].

A US-based cost-effectiveness assessment of DOACs is of importance for stakeholders to identify effective interventions, however the assessment should be comprehensive and multifactorial. Furthermore, the pricing of branded DOACs is subject to change upon the expiration of exclusive selling rights in the US, leading to the introduction of generic DOACs to the market. Incorporating dynamic drug pricing into cost-effectiveness analysis, representing the expected future prices following loss of exclusivity (LOE), provides a more comprehensive and realistic assessment of a drug's value, thereby informing more effective and efficient healthcare decisions, as recommended by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and health technology assessment (HTA) guidelines [19–21]. This study aimed to assess the cost-effectiveness of apixaban compared with warfarin, dabigatran, and rivaroxaban using the dynamic drug pricing assumptions for patients with NVAf from the US Medicare Fee for Service payer perspective, with a focus on evLYs and HYTs.

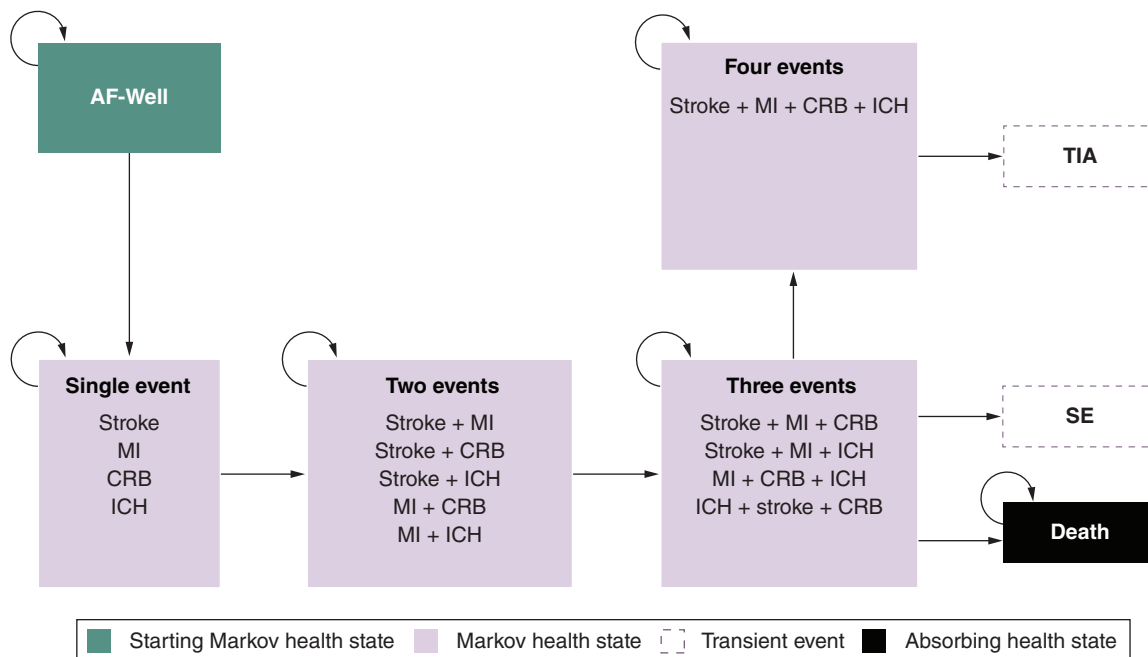


Figure 1. Markov model illustrating the health states and events experienced by patients with non-valvular atrial fibrillation.

AF: Atrial fibrillation; CRB: Clinically relevant bleeding; ICH: Intracranial hemorrhage; MI: Myocardial infarction; SE: Systemic embolism; TIA: Transient ischemic attack.

Methods

Patient population

The modelled population was US Medicare patients with NVAf, eligible for oral anticoagulation. The cohort size analyzed within the cost–effectiveness model was 1000 patients, with a mean age of 70 and 60% male, based on the demographics of patients in RCTs identified by the systematic review conducted by Lopez-Lopez *et al.* [9].

Model structure & overview

A cohort-level Markov model was built in Microsoft Excel[®] to conduct a cost–effectiveness analysis of apixaban compared with warfarin, dabigatran, and rivaroxaban for the treatment of NVAf from the US Medicare Fee for Service payer perspective. In addition, a societal perspective was also incorporated (Supplementary material). The consolidated health economic evaluation reporting standard (CHEERS 2022) checklist [22] was followed throughout this cost–effectiveness analysis.

The model comprised 17 health states following the structure from Lopez-Lopez *et al.* [9] and Sterne *et al.* [14] (Figure 1). All patients entered the model with NVAf without the previous experience of a stroke, myocardial infarction (MI) or other bleeding related events. Based on predefined probabilities, patients then stayed in the NVAf state or experienced a clinically relevant event: stroke, clinically relevant bleeding (CRB; consisting of major gastrointestinal bleed, major non-gastrointestinal extracranial hemorrhage, clinically relevant nonmajor extracranial hemorrhage), MI or intracranial hemorrhage (ICH). Following the initial event, a patient could experience up to three other events (including the same event), in any order per model cycle. Transient ischemic attack (TIA) and SE were transient event states that incurred one-time (acute) costs and utility decrements during the cycle when event occurred. These events had no long-term impact on event risk, costs, or health-related quality of life (HRQoL). Patients were at risk of dying in any health state they resided in.

As NVAf is a chronic illness, a lifetime model horizon with a three-monthly cycle length was adopted to reflect the progressive and chronic pathology of NVAf in line with published literature [9,23]. The model incorporated a default rate of 3% in the annual discounting of costs and benefits over the modelled horizon, in line with US recommendations [24].

Table 1. Input parameters for clinical event hazard ratios following prior clinical events.						
Clinical event	Prior stroke	Prior CRB	Prior MI	Prior ICH	No prior MI	No prior stroke
	Mean HR (SE)	Mean HR (SE)	Mean HR (SE)	Mean HR (SE)	Mean HR (SE)	Mean HR (SE)
Stroke	4.02 (0.06)	1.32 (0.04)	1.25 (0.03)	1.79 (0.07)	1.0	-
CRB	1.39 (0.09)	3.32 (0.04)	1.25 (0.04)	2.95 (0.21)	1.0	-
MI	1.00 (0.10)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.0	-
ICH	1.63 (0.17)	3.53 (0.08)	0.94 (0.09)	10.18 (0.09)	-	-
Systemic embolism	3.60 (0.05)	1.36 (0.04)	1.28 (0.03)	1.82 (0.06)	-	-
TIA	3.60 (0.05)	1.36 (0.04)	1.28 (0.03)	1.82 (0.06)	-	-
ACM	1.32 (0.13)	1.32 (0.15)	1.03 (0.18)	1.32 (0.15)	0.97 (0.18)	0.76 (0.12)
Clinical event hazard ratios were sourced from Lopez-Lopez <i>et al.</i> [9]. ACM: All-cause mortality; CRB: Clinically relevant bleeding; HR: Hazard ratio; ICH: Intracranial hemorrhage; MI: Myocardial infarction; SE: Standard error; TIA: Transient ischemic attack.						

The key model outcomes were total and incremental clinical events, costs, evLYs and HYT, in addition to the incremental cost–effectiveness ratio (ICER) per outcome (evLYs and HYT). To calculate evLYs for the intervention in each cycle, the following formula was used:

$$evLY_A = \frac{QALY_A}{LY_A} \times LY_B + 0.851 \times (LY_A - LY_B)$$

Where A represents the intervention (i.e., apixaban [5 mg twice daily (bd)]) while B represents the specific comparator treatment. The evLY for the intervention is contingent on the choice of the comparator treatment, as it directly influenced by the value of LY_B. The variability in LY_B for different comparator treatments contributes to the differences observed in the evLY for the intervention. To note, it is assumed that LY_A is greater than LY_B. The total evLYs were calculated by summing up the evLYs gained in each model cycle until the model time horizon. This calculation was based on methodology [25] which utilizes a value of 0.851 for the value of a healthy life year based on the age- and gender-adjusted utility of the healthy US population. The HYTs were calculated for the intervention arm using this formula:

$$HYT = evLY_A + \left(\frac{QALY_A}{LY_A} - \frac{QALY_B}{LY_B} \right) \times (LY_A - LY_B)$$

Where A represents the intervention (i.e., apixaban [5 mg bd]) and B represents the comparator. It is assumed that LY_A is greater than LY_B. This calculation was based on methodology reported in Basu *et al.* [18] The evLYs and HYT were reported as yearly values and assumed to be discounted at the current 3% per year. The equations for evLY and HYT are used for the intervention (apixaban) arm only; for the comparator arms evLY and HYT were equal to QALY [18,26]. The incremental evLY or HYT was the difference between evLY (or HYT) for the intervention and the comparator arm. Cost–effectiveness was assessed based on a willingness-to-pay threshold (WTP) of \$100,000 per evLY gained (evLYG) or HYT gained (HYTG).

Intervention & comparators

The model incorporated one intervention arm (apixaban [5 mg bd]) and three comparator arms (warfarin, dabigatran [150 mg bd] and rivaroxaban [20 mg once-daily (od)]) as the first-line of treatment. As there is no consensus on the recommendation regarding further lines of treatment and no clinical data for treatments used in further lines of treatment, only one line of treatment was included. Within any cycle, there was a probability for patients to discontinue treatment following a clinical event (stroke, CRB, MI, ICH, SE or TIA) and transition to no treatment, where they remained for the rest of the time horizon (Supplementary Table 1). After experiencing an initial clinical event, there was an increased risk of experiencing further clinical events which was accounted for in the model (Table 1).

Disease progression & treatment efficacy

The model utilizes a Markov process to capture the progression of patients through each health state, using baseline event probabilities [9] that are transformed using relative measures of efficacy for different treatments (Table 2) and

Table 2. Input parameters for baseline clinical event probabilities and clinical event rate hazard ratios for DOACs compared with warfarin.

Clinical event	Annual baseline event probabilities	Warfarin		Apixaban (5 mg bd)		Dabigatran (150 mg bd)		Rivaroxaban (20 mg od)		No treatment	
	Mean, % (SE)	Mean HR	SE	Mean HR	SE	Mean HR	SE	Mean HR	SE	Mean HR	SE
Stroke	1.20 (0.08)	1.00	0.00	0.71	0.08	0.80	0.07	0.72	0.07	2.79	0.28
CRB [†]	6.60 (2.53)	1.00	0.00	0.51	0.07	1.04	0.04	1.38	0.04	0.44	0.04
MI	0.79 (0.09)	1.00	0.00	0.86	0.13	1.27	0.15	0.79	0.13	1.00	0.10
ICH	0.94 (0.29)	1.00	0.00	0.54	0.12	0.38	0.11	0.65	0.08	0.44	0.04
Systemic embolism	1.70 (0.90)	1.00	0.00	0.65	0.33	0.65	0.11	0.95	0.09	0.31	0.03
TIA	2.50 (2.12)	1.00	0.00	0.74	1.12	2.68	1.42	2.68	1.41	0.21	0.02
ACM	3.80 (0.61)	1.00	0.00	0.66	0.05	0.73	0.05	0.81	0.04	1.18	0.12

Baseline event probabilities were sourced from Lopez-Lopez *et al.* [9]. Clinical event rate hazard ratios were informed by Graham *et al.* [27], except for MI, systemic embolism, TIA and no treatment which were informed by Lopez-Lopez *et al.* [9].

[†] Graham *et al.* [27] reported CRB as major extracranial bleeding.

ACM: All-cause mortality; bd: Twice-daily; CRB: Clinically relevant bleeding; DOAC: Direct oral anticoagulant; HR: Hazard ratio; ICH: Intracranial hemorrhage; MI: Myocardial infarction; od: Once-daily; SE: Standard error; TIA: Transient ischemic attack.

history of prior clinical events [9] (Table 1). Two retrospective cohort studies in US Medicare patients provided inputs to quantify clinical events in the base case setting and in a scenario analysis. In the base case, hazard ratios (HRs) of clinical events (stroke, CRB, ICH and all-cause mortality [ACM]) by treatment were derived from Graham *et al.* [27], a retrospective cohort study of US Medicare patients with NVAf initiated on warfarin, dabigatran, rivaroxaban or apixaban. Hazard ratios were calculated for thromboembolic stroke, ICH, major extracranial bleeding, and ACM, comparing each DOAC (apixaban [5 mg bd], dabigatran [150 mg bd], rivaroxaban [20 mg od]) with warfarin. As Graham *et al.* [27] did not report HRs for MI, SE and TIA by treatment, these were derived from Lopez-Lopez *et al.* [9]. General population life tables were used to account for the changing mortality risk as the cohort ages through the model [28,29].

Health-related quality of life

Health state utility values were derived from a published cost–effectiveness analysis [30], a systematic review and network meta-analysis (NMA) [31] and a study that calculated community-based EuroQol-5D (EQ-5D) index scores [32]. A specific health utility value was applied to each health state; US-specific utility values were used for all health states except for stroke and ICH (Supplementary Table 1). In states with multiple events, the revised utility of the health state was the multiplicative of the relevant clinical event utility values. Patients were at risk for the following events: stroke, CRB, MI, ICH, SE and TIA. When patients experienced one of these events, a one-off disutility (was subtracted from the utility value in the cycle in which the event occurred [Supplementary Table 1]). Age-adjustment of utilities was also taken into account, as the utility value was multiplied by the age-related utility adjustment for the general US population based on the current simulated age [33].

Costs

Relevant costs were US-specific and inflated to 2022 prices using the Consumer Price Index factor (Supplementary Table 1). Clinical event costs were applied in the cycle of the event's occurrence as a one-off cost and derived from various published economic analyses [34–38]. For 'clinically relevant bleeding' a weighted average of major gastrointestinal bleed, major non-gastrointestinal extracranial hemorrhage, clinically relevant nonmajor extracranial hemorrhage was used, in alignment with the definition of 'clinically relevant bleeding' from Lopez-Lopez *et al.* [9] and Sterne *et al.* [14]. Maintenance costs are costs incurred over a lifetime following a clinical event (applied to stroke, MI, and ICH) and were applied as per cyclic (three-monthly) cost. The cost of ICH was calculated as the weighted average of mild, moderate and severe stroke. Clinical event and maintenance costs were derived from various published economic analyses [34–38].

Treatment costs were applied per cycle as the cost of three months of treatment while on treatment and sourced from the IBM Micromedex[®] database [39]. The model enabled dynamic pricing of DOACs to account for the expected price trajectories of these treatments after loss of exclusivity (LOE) and entry of generic competition. Future price trajectories of DOACs were based on key assumptions on the timing of generic entry (Supplementary

Table 2), and the impact that generic entry has on price. Generic price was set as 65% of the brand price value, assuming a 35% price reduction post-LOE for all DOACs. The start date for calculating the number of cycles was September 2023. The proportion of patients using generics was 55% in the first cycle where generic DOACs were used. For subsequent cycles, an increased uptake of 2.5% was incorporated for DOAC treatments with discounted price. Once introduced to the market and stabilized, DOACs with generic pricing remained available for the rest of the time horizon (until cycle 328).

Monitoring costs were applied per cycle as the cost of 3 months of monitoring while on treatment. These costs were obtained from the relevant literature for warfarin [40,41] and Medicare [42] for the DOACs. Monitoring for warfarin was calculated based on 1.6 international normalized ratio (INR) tests per month and two GP visits per year. Cost of death was applied as a one-off cost to the number of individuals moving from any health state to the death health state based on the ACM-adjusted with event-specific (stroke, MI, ICH, CRB) mortalities described in Table 1 and derived from relevant published economic analyses [30,37,38,43].

Societal costs were applied in the model for the additional analysis from the societal perspective in line with a previous HTA submission [44] where indirect costs associated with a stroke event were applied as a combination of the following factors: informal care received from caregivers, productivity losses from morbidity and mortality, and social care costs. Indirect costs were applied to three events in the model: stroke, MI and TIA. Additionally, social care costs were applied per cycle for each individual with incident or prevalent stroke. Further detail on societal costs can be found in the [Supplementary material](#).

Sensitivity & scenario analyses

Parameter uncertainty was investigated through deterministic one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). For the deterministic OWSA, key model parameters were independently varied by either applying a 20% increase or decrease to the mean value or by predetermined values, including 95% confidence intervals. Both costs and clinical parameters were varied, and the impact of each on the ICER (per evLYG or HYTG) was evaluated. Results for the OWSA were presented for both ICER per evLYG and ICER per HYTG and ranked in order of the sensitivity of modelled results to changes in parameter values.

For the PSA, the parameters used in the deterministic OWSA were varied simultaneously; parameters were assigned a distribution based on the underlying data [45]. Normal or Gamma distributions were applied to model inputs which described baseline patient characteristics such as age or height, and costs. A log-normal distribution was used for HRs. Beta distributions were applied to model inputs describing health related utilities. The results of the PSA were employed to obtain the cost-effectiveness acceptability curves, showing the probability of each alternative intervention being cost-effective across a range of possible values of WTP for an additional evLY.

For a scenario analysis, an alternative US publication (Ray *et al.* [46], a retrospective cohort study of Medicare patients with AF initiated on apixaban or rivaroxaban) was explored as an alternative source for treatment effectiveness data, which reported HRs for clinical events for rivaroxaban compared with apixaban ([Supplementary Table 3](#)). In this scenario, baseline event probabilities [9] were used for apixaban as the reference treatment, and HRs derived from Graham *et al.* [27]. This analysis specifically focused on comparing the treatment effects of rivaroxaban and apixaban, given the focus on these two DOACs in Ray *et al.* [46]. In this scenario, patients that experienced an event were not switched to no treatment as there is a lack of head-to-head data of no treatment to apixaban for the Medicare population. As a result, this scenario exclusively presented analyses for first-line treatment only.

An additional alternative scenario explored was the exclusion of the dynamic pricing assumptions for DOACs that had not lost their exclusivity as of 2024. Thus, as dabigatran LOE was June 2022, its generic price was set as 65% of the brand price value in this scenario.

Results

Treatment with apixaban resulted in lower clinical event rates per 1000 patients for all clinical events, compared with warfarin during first-line treatment ([Figure 2](#)). When compared with dabigatran and rivaroxaban, clinical event rates for apixaban at first-line were lower, except for ICH (event rate higher for apixaban compared with dabigatran) and MI (event rate higher for apixaban compared with rivaroxaban). Treatment with apixaban was estimated to avert 17 strokes, 204 CRBs, 4 MIs, 28 ICHs, 29 SEs and 32 TIAs, per 1000 patients, compared with warfarin ([Figure 2](#)). Treatment with apixaban averted 6 and 0 stroke(s), 241 and 392 CRBs, 2 and 25 SEs, 231 and 226 TIAs, compared with dabigatran and rivaroxaban, respectively, per 1000 patients. Additionally, apixaban treatment was estimated to avert 13 MIs, yet resulted in an additional 6 ICHs compared with dabigatran. When

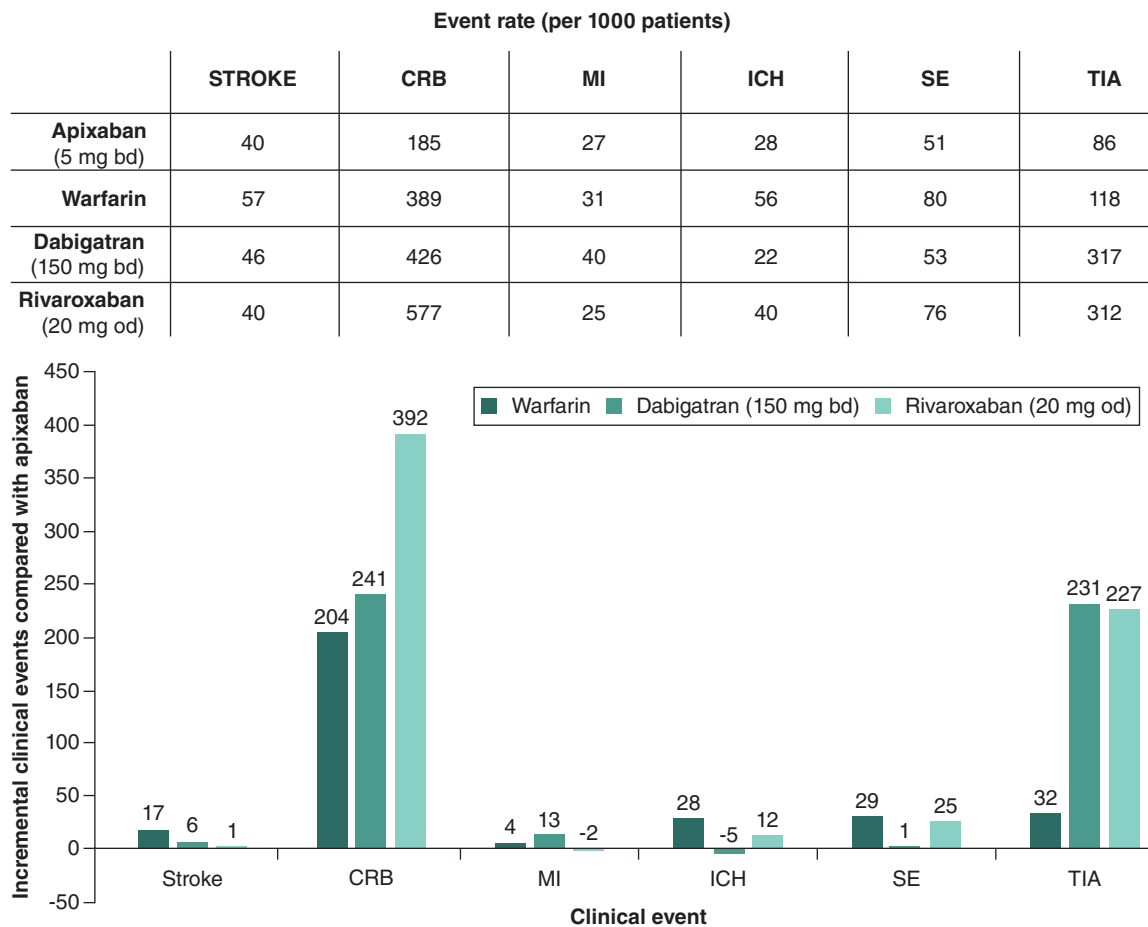


Figure 2. Modelled clinical event rates per 1000 patients for apixaban, warfarin, dabigatran, and rivaroxaban during first-line treatment. There are no adequate and well-controlled head-to-head clinical trials comparing the efficacy and safety of direct-acting oral anticoagulants.
bd: Twice-daily; CRB: Clinically relevant bleeding; ICH: Intracranial hemorrhage; MI: Myocardial infarction; od: Once-daily; SE: Systemic embolism; TIA: Transient ischemic attack.

compared with rivaroxaban, apixaban resulted in an additional 2 MIs, yet averted 12 ICHs. When considering clinical event rates over the full time horizon, for patients that switch to no treatment after first-line treatment, event rates were higher across all treatments ([Supplementary Figure 1](#)). Treatment with apixaban was estimated to avert 33 strokes, 304 CRBs, 5 MIs, 67 ICHs, 32 SEs and 35 TIAs, per 1000 patients, compared with warfarin ([Supplementary Figure 1](#)). Treatment with apixaban was estimated to avert 351 and 532 CRBs, 32 and 66 ICHs, 4 and 23 SEs, 233 and 225 TIAs, compared with dabigatran and rivaroxaban, respectively, per 1000 patients. Additionally, apixaban treatment was estimated to avert 18 strokes and 13 MIs compared with dabigatran. When compared with rivaroxaban, apixaban resulted in an additional 14 strokes and 2 MIs.

With the exception of monitoring costs, apixaban resulted in lower non-drug healthcare costs including event costs for acute events, health state costs for the long-term management of an event, societal costs and death costs ([Table 3](#)). A noticeable difference in costs were seen for event costs; apixaban treatment resulted in lower costs of \$15,446 compared with \$22,522, \$22,425 and \$25,948 for warfarin, dabigatran and rivaroxaban, respectively. Specifically, treatment with apixaban resulted in lower stroke (\$3661), CRB (\$5155) and TIA (\$1092) costs compared with warfarin (stroke: \$4975, CRB: \$8320 and TIA: \$1180), dabigatran (stroke: \$4555, CRB: \$9,306 and TIA: \$3214) and rivaroxaban (stroke: \$4805, CRB: \$11,360 and TIA: \$2859). Treatment with warfarin was associated with higher monitoring costs of \$18,149 compared with \$1707 for apixaban, \$1421 for dabigatran, and \$1260 for rivaroxaban. Apixaban resulted in highest total per patient costs when considering a Medicare only perspective. Rivaroxaban resulted in the highest total per patient costs when considering a Medicare and societal

Table 3. Summary of results or lifetime costs per patient associated with apixaban, warfarin, dabigatran and rivaroxaban.

	Apixaban (5 mg bd)	Warfarin	Dabigatran (150 mg bd)	Rivaroxaban (20 mg od)
Event costs	\$15,446	\$22,522	\$22,425	\$25,948
Stroke	\$3661	\$4975	\$4555	\$4805
CRB	\$5155	\$8320	\$9306	\$11,360
MI	\$643	\$623	\$826	\$550
ICH	\$3612	\$5841	\$3325	\$4858
SE	\$1283	\$1584	\$1199	\$1517
TIA	\$1092	\$1180	\$3214	\$2859
Health state costs	\$16,269	\$19,812	\$17,685	\$17,991
Monitoring costs	\$1707	\$18,149	\$1421	\$1260
Drug costs	\$51,923	\$459	\$35,187	\$38,032
Societal costs [†]	(\$13,947)	(\$15,664)	(\$16,085)	(\$14,416)
Social care costs [†]	(\$3418)	(\$4049)	(\$4722)	(\$4533)
Death costs	\$2180	\$3201	\$2399	\$2963
Stroke	\$216	\$197	\$178	\$138
CRB	\$153	\$202	\$233	\$267
MI	\$9	\$6	\$8	\$4
ICH	\$173	\$210	\$90	\$130
Comorbid event [‡]	\$1628	\$2587	\$1890	\$2424

[†] Societal costs and social care costs are set to zero in the base case analysis, but included as a scenario (societal perspective).

[‡] Comorbid events are death costs due to multiple events.

ACM: All-cause mortality; bd: Twice-daily; CRB: Clinically relevant bleeding; HR: Hazard ratio; ICH: Intracranial hemorrhage; MI: Myocardial infarction; od: Once-daily; SE: Systemic embolism; TIA: Transient ischemic attack.

perspective. For apixaban, the total costs for Medicare only (and Medicare and societal) were \$87,525 (\$104,890), compared with \$64,143 (\$83,856) for warfarin, \$79,117 (\$99,924) for dabigatran and \$86,194 (\$105,143) for rivaroxaban (Table 4). This was due to the higher drug costs associated with apixaban (\$51,923) per patient over the entire time horizon, reflecting the later projected LOE of apixaban compared with dabigatran and rivaroxaban (Table 3).

Patients treated with apixaban had more evLYs and HYT when compared with warfarin, dabigatran, and rivaroxaban (Table 4). Apixaban treatment was associated with gains of 1.08 and 1.72 evLYs and 1.08 and 1.73 HYTs, compared with dabigatran and rivaroxaban, respectively. When compared with warfarin, apixaban showed larger gains of 2.23 evLYs and 2.26 HYTs. In the base case analysis, apixaban was cost-effective compared with all comparators (warfarin, dabigatran and rivaroxaban) in terms of all outcome measures considered in the analysis, when a WTP threshold of \$100,000 per evLYG or HYTG was used (Table 4). The ICER for apixaban versus warfarin, dabigatran, and rivaroxaban, in terms of evLYG (or HYTG) was \$10,501 (\$10,350), \$7809 (\$7769) and \$775 (\$768), respectively. When the societal perspective was included, apixaban dominated rivaroxaban (i.e., less expensive and more effective) and remained cost-effective compared with warfarin and dabigatran. The ICER for apixaban versus warfarin, dabigatran, and rivaroxaban, in terms of evLYG (or HYTG) was \$9446 (\$9310), \$4612 (\$4589) and -\$147 (-\$146), respectively (Table 4).

Sensitivity analysis

Deterministic OWSAs within the model demonstrated that when apixaban was compared with warfarin, the three most important drivers of the model were apixaban treatment costs, cost discount rate and the HR for apixaban treatment effect for ACM, leading to a range of ICERs (per evLYG [HYTG]) from \$5837 to \$15,164 (\$5753 to \$14,946) (Supplementary Figure 2A and Supplementary Figure 3A). When apixaban was compared with dabigatran and rivaroxaban, treatment costs (for apixaban, dabigatran and rivaroxaban), the HR for apixaban treatment effect for ACM and stroke were the key drivers of the model (Supplementary Figure 2B, Supplementary Figure 2C, Supplementary Figure 3B and Supplementary Figure 3C). In all scenarios, the ICERs (per evLYG or HYT) remained lower than the \$100,000 WTP making apixaban cost-effective in all scenarios.

The results of the probabilistic sensitivity analysis visualizing the incremental costs, incremental evLYs and incremental HYT of each of the 1000 simulations on the cost-effectiveness plane are shown in Supplementary

Table 4. Base case results: Costs, health outcomes and incremental cost–effectiveness ratio comparing apixaban versus warfarin, dabigatran and rivaroxaban from the Medicare perspective (and societal perspective).

Costs		Apixaban (5 mg bd)	Warfarin	Dabigatran (150 mg bd)	Rivaroxaban (20 mg od)
Total costs	Medicare perspective	\$87,525	\$64,143	\$79,117	\$86,194
	Medicare and societal perspective	\$104,890	\$83,856	\$99,924	\$105,143
Total costs (excluding drug costs)	Medicare perspective	\$35,602	\$63,684	\$43,930	\$48,161
	Medicare and societal perspective	\$52,967	\$83,396	\$64,737	\$67,110
Benefits					
QALYs		6.52	5.48	6.04	5.74
LYs		11.02	9.38	10.25	9.78
evLYs†		7.70 vs warfarin 7.12 vs dabigatran 7.46 vs rivaroxaban	5.48	6.04	5.74
HYT‡		7.74 vs warfarin 7.13 vs dabigatran 7.47 vs rivaroxaban	5.48	6.04	5.74
Incremental costs and benefits of apixaban vs comparators					
Incremental costs	Medicare perspective	-	\$23,382	\$8408	\$1331
	Medicare and societal perspective	-	\$21,034	\$4966	-\$252
Incremental costs (excluding drug costs)	Medicare perspective	-	-\$28,082	-\$8328	-\$12,559
	Medicare and societal perspective	-	-\$30,429	-\$11,770	-\$14,143
Incremental QALYs		-	1.04	0.48	0.78
Incremental LYs		-	1.64	0.77	1.24
Incremental evLYs		-	2.23	1.08	1.72
Incremental HYT		-	2.26	1.08	1.73
Cost–effectiveness of apixaban vs comparators					
ICER per QALYG	Medicare perspective	-	\$22,423 (cost-effective)	\$17,639 (cost-effective)	\$1706 (cost-effective)
	Medicare and societal perspective	-	\$20,171 (cost-effective)	\$10,418 (cost-effective)	Dominant
ICER per LYG	Medicare perspective	-	\$14,302 (cost-effective)	\$10,945 (cost-effective)	\$1075 (cost-effective)
	Medicare and societal perspective	-	\$12,866 (cost-effective)	\$6464 (cost-effective)	Dominant
ICER per evLYG	Medicare perspective	-	\$10,501 (cost-effective)	\$7809 (cost-effective)	\$775 (cost-effective)
	Medicare and societal perspective	-	\$9446 (cost-effective)	\$4612 (cost-effective)	Dominant
ICER per HYTG	Medicare perspective	-	\$10,350 (cost-effective)	\$7769 (cost-effective)	\$768 (cost-effective)
	Medicare and societal perspective	-	\$9310 (cost-effective)	\$7769 (cost-effective)	Dominant

Equal value of life-years (evLYs) assigns the complete value of a healthy life year to all gains in life-years, ensuring that irrespective of age, disability, or illness, all gains in life-years are regarded with equal worth [16,17].
The HYT measure is the total of life expectancy combined with adjusted QALYs, which are estimated over a duration corresponding to the maximum survival period of the respective alternative [18].
† The evLYs for the intervention (apixaban) is vs a specific comparator. The evLY or HYT for each comparator (warfarin, dabigatran and rivaroxaban) is equal to its QALYs.
bd: Twice-daily; evLY: Equal value life-years; evLYGs: Equal value life-years gained; HYT: Health year in total; HYTG: Health year in total gained; ICER: Incremental cost–effectiveness ratio; LY: Life-years; LYG: Life-years gained; od: Once-daily; QALY: Quality-adjusted life-year; QALYG: Quality-adjusted life-year gained.

Figure 4 and [Supplementary Figure 5](#). Most iterations resided in two quadrants; North- East (apixaban was more effective at a higher cost) and South-East (apixaban was more effective at a lower cost). Apixaban has a 95% probability of being the cost-effective treatment at WTP values $>\sim\$40,000$ per evLYG when compared with warfarin and dabigatran and $\sim\$20,000$ per evLYG when compared with rivaroxaban. At our base case WTP threshold of \$100,000, the probability of apixaban being cost-effective was 100%, 99.5% and 98.9% when compared with warfarin, dabigatran and rivaroxaban, respectively ([Supplementary Figure 6](#)).

Table 5. Cost-effectiveness results (scenario analysis: alternative treatment effects).

Costs		Apixaban (5 mg bd)	Rivaroxaban (20 mg od)
Total costs	Medicare perspective	\$99,015	\$114,576
	Medicare and societal perspective	\$116,184	\$132,934
Total costs (excluding drug costs)	Medicare perspective	\$38,514	\$59,309
	Medicare and societal perspective	\$55,683	\$77,667
Benefits			
QALYs		6.79	6.38
LYs		11.52	11
evLYs [†]		7.22 vs rivaroxaban	6.38
HYT [†]		7.23 vs rivaroxaban	6.38
Incremental costs and benefits of apixaban vs rivaroxaban			
Incremental costs	Medicare perspective	-	-\$15,561
	Medicare and societal perspective	-	-\$16,750
Incremental costs (excluding drug costs)	Medicare perspective	-	-\$20,795
	Medicare and societal perspective	-	-\$21,984
Incremental QALYs		-	0.41
Incremental LYs		-	0.53
Incremental evLYs		-	0.84
Incremental HYT		-	0.85
Cost-effectiveness of apixaban vs rivaroxaban			
ICER per QALYG	Medicare perspective	-	Dominant
	Medicare and societal perspective	-	Dominant
ICER per LYG	Medicare perspective	-	Dominant
	Medicare and societal perspective	-	Dominant
ICER per evLYG	Medicare perspective	-	Dominant
	Medicare and societal perspective	-	Dominant
ICER per HYTG	Medicare perspective	-	Dominant
	Medicare and societal perspective	-	Dominant

Alternative treatment effects were informed by Ray *et al.* [46].

Equal value of life-years (evLYs) assigns the complete value of a healthy life year to all gains in life-years, ensuring that irrespective of age, disability, or illness, all gains in life-years are regarded with equal worth [16,17].

The HYT measure is the total of life expectancy combined with adjusted QALYs, which are estimated over a duration corresponding to the maximum survival period of the respective alternative [18].

[†]The evLYs for the intervention (apixaban) is vs a specific comparator. The evLY or HYT for each comparator (rivaroxaban) is equal to its QALYs.

bd: Twice-daily; evLY: Equal value life-year; evLYG: Equal value life-year gained; HYT: Health year in total; HYTG: Health year in total gained; ICER: Incremental cost-effectiveness ratio; LY: Life-year; LYG: Life-year gained; od: Once-daily; QALY: Quality-adjusted life-year; QALYG: Quality-adjusted life-year gained.

Scenario analysis

When using alternative effectiveness estimates for apixaban in comparison with rivaroxaban from Ray *et al.* [46], the model predicted that apixaban treatment was estimated to avert 12 strokes, 454 CRBs, 3 MIs, 82 ICHs, 10 SEs and 25 TIAs, compared with rivaroxaban per 1000 patients during first-line treatment (Supplementary Figure 7).

Apixaban resulted in lower total per patient costs (\$99,015 and \$116,184) when compared with rivaroxaban (\$114,576 and \$132,934), when considering a Medicare only and Medicare and societal perspective, respectively. This was largely due to the lower event costs related to apixaban treatment (Supplementary Table 4). Apixaban treatment was associated with gains of 0.84 evLYs and 0.85 HYTs, compared with rivaroxaban (Table 5). Thus, apixaban dominated rivaroxaban (i.e., less expensive and more effective) across all outcome measures and across both perspectives (Table 5).

Another scenario explored the exclusion of the introduction of dynamic pricing in the model, using static brand prices for all DOACs except for dabigatran (as it lost exclusivity in June 2022). Apixaban was still cost-effective compared with warfarin, dabigatran and rivaroxaban. The ICER for apixaban versus warfarin, dabigatran and rivaroxaban in terms of evLYs (or HYT) gained was \$15,683 (\$15,457), \$4322 (\$4300) and \$2714 (\$2687), respectively (Table 6).

Table 6. Scenario analysis with generic pricing excluded: cost–effectiveness results (Medicare perspective).

Costs	Apixaban (5 mg bd)	Warfarin	Dabigatran (150 mg bd)	Rivaroxaban (20 mg od)
Total costs	\$99,064	\$64,143	\$94,410	\$94,403
Total costs (excluding drug costs)	\$35,602	\$63,684	\$43,930	\$48,161
Incremental costs and benefits of apixaban vs comparators				
Incremental costs	-	\$34,921	\$4654	\$4661
Incremental costs (excluding drug costs)	-	-\$28,082	-\$8,328	-\$12,559
Incremental QALYs	-	1.04	0.48	0.78
Incremental LYs	-	1.64	0.77	1.24
Incremental evLYs	-	2.23	1.08	1.72
Incremental HYT	-	2.26	1.08	1.73
Cost–effectiveness of apixaban vs comparators				
ICER per QALYG	-	\$33,488 (cost-effective)	\$9763 (cost-effective)	\$5973 (cost-effective)
ICER per LYG	-	\$21,360 (cost-effective)	\$6058 (cost-effective)	\$3765 (cost-effective)
ICER per evLYG	-	\$15,683 (cost-effective)	\$4322 (cost-effective)	\$2714 (cost-effective)
ICER per HYTG	-	\$15,457 (cost-effective)	\$4300 (cost-effective)	\$2687 (cost-effective)

Treatment effects were informed by Graham *et al.* [27].
bd: Twice-daily; evLYs: Equal value life-year; evLYG: Equal value life-year gained; HYT: Health year in total; HYTG: Health year in total gained; ICER: Incremental cost–effectiveness ratio; LY: Life-year, LYG: Life-year gained; od: Once-daily; QALY: Quality-adjusted life-year; QALYG: Quality-adjusted life-year gained.

Discussion

The purpose of this study was to assess the cost–effectiveness of apixaban compared with warfarin, dabigatran and rivaroxaban, for patients with NVAF from the US Medicare Fee for Service payer perspective. It is widely reported that DOACs are cost-effective compared with warfarin for the prevention of stroke and SE in patients with NVAF; however, differences in the clinical effectiveness concluded from NMAs, and safety of treatments within the DOAC class [9] indicate that their wider value may vary by treatment. It is important for the cost–effectiveness of DOACs to be evaluated to ensure optimal value for payers and healthcare systems. Findings from this study indicate apixaban is cost-effective compared with dabigatran, rivaroxaban and warfarin in patients with NVAF based on both current and expected future prices of apixaban and its comparators, representing value for US payers. Despite having higher drug acquisition costs, apixaban yielded greater incremental health outcomes than other DOACs. The favorable cost–effectiveness outcomes were driven by reductions in clinical events (primarily bleeding events) and their associated cost savings. Results of sensitivity analyses indicated that the cost–effectiveness of apixaban was robust to changes in key model parameters.

Numerous studies have evaluated the cost–effectiveness of DOAC treatments with warfarin, yet few have compared the cost–effectiveness of DOACs with other DOACs in patients with NVAF [47,48]. Walter *et al.* [47] evaluated the cost–effectiveness of apixaban compared with other DOACs from an Austrian perspective in patients with AF and concluded that apixaban was highly cost-effective compared with dabigatran, edoxaban, rivaroxaban, and warfarin. Similarly, Lip *et al.* [48] evaluated the cost–effectiveness of apixaban versus dabigatran and rivaroxaban from the UK perspective and concluded that apixaban may be a cost-effective alternative compared with dabigatran and rivaroxaban. The results of these analyses are closely aligned with observations from our study, that apixaban is cost-effective compared with dabigatran and rivaroxaban (based on Graham *et al.* [27] clinical effectiveness inputs) and dominates (i.e., was less expensive and more effective) rivaroxaban (based on Ray *et al.* [46] clinical effectiveness inputs). Further, inclusion of a societal perspective alongside the Medicare base case, resulted in apixaban dominating rivaroxaban and remaining cost-effective compared with warfarin and dabigatran.

Furthermore, other cost–effectiveness analyses have sought to ‘rank’ DOAC treatments based on outcomes compared with warfarin. Lopez-Lopez *et al.* [9] concluded that all DOAC treatment had a positive incremental net benefit compared with warfarin, with apixaban ranking highest (of all DOACs) on the balance of efficacy, safety and cost. Similarly, Canestaro *et al.* [49] undertook a US cost–effectiveness analysis of apixaban, dabigatran, and rivaroxaban compared with warfarin and concluded that apixaban provided the greatest value for money and was cost-effective at a WTP threshold of \$100,000. Harrington *et al.* [30] conducted a similar analysis and concluded that apixaban was the preferred anticoagulant for patients with NVAF as it was most likely to be the cost–effectiveness

treatment option at all WTP thresholds above \$40,000 per QALY gained. In addition, a recent systematic review of cost–effectiveness analyses found apixaban to have the lowest median ICER and highest cost–effectiveness of all oral anticoagulant treatments [50].

The main driver of the results of these cost–effectiveness analyses is the incremental difference in efficacy and safety outcomes for apixaban and other DOACs compared with warfarin. This model was predicated on the model developed by Lopez-Lopez *et al.* [9] and Sterne *et al.* [14] which was developed for the evaluation of DOAC treatments undertaken by the National Institute for Health and Care Excellence (NICE) in the UK. Within the study, a systematic literature review was undertaken and subsequent NMA of trials, comparing DOACs with warfarin to provide event rates to inform their model. Compared with warfarin, treatment with apixaban was associated with significant reductions in the risk of key outcomes such as stroke or SE, major bleeding, and ACM [9]. To enhance relevance and generalizability of the adapted model to the US Medicare setting, US event rate data was sourced from two recent real-world US registry-based studies evaluating the relative effectiveness of DOACs in US clinical practice [27,46]. These real-world studies reported favorable results for apixaban across many outcomes, driving the model conclusion that apixaban is a cost-effective or dominant treatment (when compared with rivaroxaban only) for US Medicare patients with NVAf. Overall, the consistent conclusions across different models, despite varying inputs, validates these findings and highlights the value of apixaban for payers and healthcare systems.

The Institute for Clinical and Economic Review developed a cost–effectiveness model to inform Centers for Medicare & Medicaid Services (CMS) drug price negotiations, comparing both apixaban and rivaroxaban to warfarin and dabigatran [51]. Their analysis concluded that both apixaban and rivaroxaban have a high certainty of a small net benefit (B rating) versus warfarin.

Utilizing evLY and HYT metrics for evaluating cost–effectiveness ensures less discrimination against the elderly, disabled and terminally ill, because all life years gained are valued the same as that of a healthy life. Removing this source of discrimination is especially pertinent among Medicare populations to ensure fairer access to effective treatments. The ICERs per evLYG and HYTG from our analysis were below commonly referenced WTP thresholds of \$100,000 indicating that apixaban is a cost-effective (or dominant) treatment option for patients with NVAf regardless of the health benefit metric evaluated.

With DOAC treatments due to lose exclusivity in the coming years, it is important to evaluate cost–effectiveness from the US payer perspective based on expected price trajectories. While generic pricing was a core element of the base case, a scenario analysis was also conducted with branded prices for DOACs. ICER per evLYG and ICER per HYTG varied little in the scenario where generic pricing was excluded, and apixaban remained cost-effective compared with warfarin, dabigatran and rivaroxaban, supporting that it is a cost-effective treatment for patients with NVAf in the US.

There are a number of limitations associated with this modelling approach. First, no distinction was made between the severity of ischemic stroke due to an absence of data. Therefore, a weighted average of costs available for different stroke severity was applied to correspond with a single measure of risk. Second, in the absence of data to indicate otherwise, event rates were assumed to be consistent over time and not vary with age. Third, the model assumed that patients switch to no treatment after experiencing an event when receiving a first-line treatment. This assumption was made due to a lack of efficacy data for further lines of treatment, the absence of an agreed treatment sequence after the failure of a treatment, and to enable comparisons between treatments rather than between treatment sequences. If further lines of treatment were added, where regardless of the choice of the first-line of treatment, patients were switched to the same subsequent treatment, the effect on the ICER would most likely be minimal because most patients remain on first-line therapy the longest and when patients do eventually switch to second-line, the subsequent treatments are non-differential across arms. Fourth, maintenance costs for multiple event states utilize the maximum cost for constituent events and thus may overestimate total costs. Fifth, for the scenario analysis using alternative US data from Ray *et al.* [46] for treatment effects, patients that experienced an event were not switched to no treatment. This assumption was made due to the lack of head-to-head data of no treatment to apixaban for the Medicare population. Additionally, due to the absence of available data, not all utility values were US-specific and therefore may not accurately reflect QoL of patients in the US following an event. Finally, the focus of this study was the US Medicare population, and results may not be generalizable to other populations. Due to the lack of data availability specific for a US population, we utilized data from multiple sources. However, clinical event rates were key drivers of the ICER identified in the deterministic OWSA and were

based on data from a retrospective cohort study of US Medicare patients [27], which is aligned with our modelled population and demonstrates robustness of our findings.

Further strengths of this study is the utilization of the same modelling approach as past HTA assessments (i.e., NICE) and the basing clinical event rates and effectiveness estimates on large and recent US real-world studies. A further strength is the use of dynamic generic pricing, as it allows for more accurate cost–effectiveness results, as it is reflective of pricing changes associated with impending DOAC generic entries into the market. In conclusion, treatment with apixaban has the potential to avert clinical events in patients with NVAf, resulting in accompanying gains in incremental evLYs and HYT and is a cost-effective treatment option compared with dabigatran, rivaroxaban, and warfarin in this patient population.

Summary points

- A cost–effectiveness model was developed based on the structure from Lopez-Lopez *et al.* [9] and Sterne *et al.* [14] to evaluate the lifetime cost and health outcomes for apixaban compared with warfarin, dabigatran and rivaroxaban for patients with nonvalvular atrial fibrillation (NVAf) from the US Medicare Fee for Service payer perspective.
- The model factored in anticipated price decreases due to market entry of generic drugs based on the anticipated timing for loss of exclusivity.
- This study focused on equal value of life years (evLYs) and health years in total (HYT). cost–effectiveness was assessed based on a willingness-to-pay threshold (WTP) of \$100,000 per evLY gained (evLYG) or HYT gained (HYTG).
- In the base case analysis, using US data from Graham *et al.* [27] results indicate apixaban was cost-effective compared with warfarin, dabigatran and rivaroxaban, with corresponding incremental cost–effectiveness ratios (ICER) per evLYG (or HYTG) of \$10,501 (\$10,350), \$7809 (\$7769) and \$758 (\$768), respectively.
- When a societal perspective was included, and in a scenario analysis using alternative US data from Ray *et al.* [46] for treatment effects, apixaban dominated rivaroxaban (i.e., less expensive and more effective) in terms ICER per evLYG (and HYTG).
- Apixaban, compared with warfarin, dabigatran and rivaroxaban was a cost-effective treatment option for patients with NVAf based on both current and expected future price of apixaban and its comparators, representing value for US payers.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0163>

Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. N Atreja, K Johannesen, R Subash, M Hagan and D Hines inputted on the economic model and interpreted the data/results. C Bektur, I Dunnett and E Stawowczyk adapted an existing economic model and interpreted the data/results. All authors reviewed and approved the final version of the manuscript.

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Competing interest disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data sharing statement

Upon request, and subject to review, the Pfizer/BMS Alliance will provide the data that supports the findings of this study.

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