



Cost–effectiveness and budget impact analysis of switching from apixaban to rivaroxaban treatment among patients with nonvalvular atrial fibrillation in a German healthcare setting

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Aim: Direct oral anticoagulant (DOAC) switching often occurs in patients with nonvalvular atrial fibrillation (NVAF) for medical and nonmedical reasons. Limited data describe the economic consequences of DOAC switching in patients with NVAF. This study evaluates the cost–effectiveness and budget impact of initiating apixaban and switching to rivaroxaban versus initiating and continuing apixaban for patients with NVAF, from a German payer perspective. **Materials & methods:** Built on an existing model, a cohort-level lifetime Markov model was developed, including dynamic pricing assumptions to account for anticipated generic entry of DOACs. The modeled population ($n = 1000$) included German patients with NVAF, eligible for oral anticoagulation, who initiated on apixaban. The primary model outcome was the incremental cost–effectiveness ratio, assessed using cost per quality-adjusted life year (QALY) gained and a willingness-to-pay threshold of €48,750/QALY. A secondary model outcome was a 5-year budget impact analysis. **Results:** Switching patients from apixaban to rivaroxaban led to 285 additional events per 1000 patient years, resulting in 0.079 fewer QALYs and higher total costs per patient (€21,357 vs €16,390 for apixaban continuers). In the base case analysis (with generic pricing assumptions), switching from apixaban to rivaroxaban was dominated (i.e., less effective and more costly) by continuing apixaban. In the budget impact analysis (with generic pricing assumptions), switching from apixaban to rivaroxaban led to additional cumulative costs of €490 per patient over 5 years. **Conclusion:** Despite the introduction of generic discounting, switching patients with NVAF from apixaban to rivaroxaban led to higher total costs and fewer QALYs under base case assumptions, meaning apixaban switchers were dominated by apixaban continuers from a German payer perspective. Switching patients from apixaban to rivaroxaban also led to greater budget impact over 5 years.

Plain language summary: Cost impact of switching patients with nonvalvular atrial fibrillation from apixaban to rivaroxaban compared with remaining on apixaban in Germany

What is this article about? Atrial fibrillation (AF) is a heart rhythm disorder increasing the risk of blood clots and therefore stroke. Patients with nonvalvular AF (NVAF) are commonly prescribed direct-acting oral anticoagulants (DOACs), such as apixaban and rivaroxaban, to reduce this risk. DOAC switching is common in clinical settings for medical and nonmedical reasons, but few studies describe the economic implications of DOAC-to-DOAC switching in patients with NVAF. This study evaluates the cost–effectiveness and budget impact of switching patients with NVAF from apixaban to rivaroxaban versus continuing apixaban in Germany.

How was the research carried out? A cost–effectiveness and budget impact analysis was conducted using a mathematical model that assessed clinical event incidence, quality-adjusted life years (QALYs, a metric combining quantity and quality of life) and costs in patients switching from apixaban to rivaroxaban versus continuing apixaban. The model used dynamic pricing to account for ongoing loss of exclusivity of DOACs and generic entry.

What were the results? Cost–effectiveness analysis indicated that switching patients from apixaban to rivaroxaban led to more clinical events, fewer QALYs, and higher total costs versus continuing apixaban over a lifetime horizon, meaning apixaban switchers were dominated (less effective and more costly) by apixaban continuers. Switching from apixaban to rivaroxaban also led to greater budget impact over 5 years.

Why is the study important? Switching patients with NVAF from apixaban to rivaroxaban increased healthcare costs and reduced QALYs due to higher clinical event incidence.

Despite generic rivaroxaban being available before generic apixaban, the lower price savings during this period do not offset the higher medical costs from increased clinical event management in apixaban switchers.

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Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide, projected to affect 17.9 million people in Europe by 2060 [1–3]. AF increases the risk of stroke occurrence fivefold when compared with patients without AF [4] and increases stroke severity, resulting in higher morbidity and mortality [5–7]. Furthermore, patients with AF have reduced health-related quality of life compared with the general population or patients with other heart diseases [8]. Overall, the comorbidities and complications associated with AF accrue significant costs, which alongside the growing prevalence of AF, poses considerable burden to healthcare systems across Europe. In Germany alone it is estimated that the total direct costs of AF exceed €660 million each year [9].

Historically, vitamin K antagonists (VKAs), such as warfarin or phenprocoumon, were the mainstay treatments used for the prevention of stroke and systemic embolism (SE) in patients diagnosed with nonvalvular AF (NVAF). However, it is now well documented that direct oral anticoagulants (DOACs) offer several advantages over VKAs, including their ease of administration, rapid onset of action, fewer drug–drug interactions, reduced need for intense monitoring, and have an equal or superior efficacy and safety compared with warfarin [10–15]. The European Society of Cardiology recommends a range of DOACs, including apixaban, rivaroxaban, dabigatran and edoxaban, in preference to VKAs for stroke prevention in patients with NVAF [4]. Despite having similar mechanisms of action, data indicate there are differences in the clinical effectiveness and safety between DOAC treatments [4,10]. However, European Society of Cardiology guidelines do not specify which DOAC should be used as a first-line treatment for patients with NVAF. The availability of multiple DOACs, coupled with a lack of consensus as to which DOAC should be used first-line, means DOAC switching often occurs in clinical practice for several reasons [16,17]. These reasons include medical factors, such as lack of effectiveness or adverse events, and nonmedical factors, such as formulary restrictions due to increasing costs [16,17].

A recent retrospective observational study from Deitelzweig *et al.* [18] investigated the impact of DOAC switching (initial apixaban therapy to rivaroxaban or from initial rivaroxaban therapy to apixaban) on the risk of stroke/SE and major bleeding (MB) in patients with NVAF in US clinical practice. When compared with continuing apixaban treatment, results indicated that switching from apixaban to rivaroxaban increased the risk of stroke/SE (hazard ratio [HR]: 1.99, 95% CI: 1.38–2.88) and MB (HR: 1.80, 95% CI: 1.46–2.23) [18]. While this data may provide insight to clinicians and patients considering a DOAC switch between apixaban and rivaroxaban, it is necessary to understand the health economic implications of DOAC switching to aid decision-making at the healthcare system level, particularly with the ongoing loss of exclusivity (LOE) across DOACs and the growing availability of generics.

Most cost–effectiveness analyses (CEAs) apply a constant treatment price that does not account for cost changes over a patient's lifetime, nor make any assumptions about drug genericization, thus fail to consider the significant price erosions which may occur following LOE [19]. By omitting future changes in treatment price, CEAs may misrepresent real-world conditions in terms of treatment costs, which may cause healthcare decision makers to undervalue interventions [20]. To yield more comprehensive and reflective cost–effectiveness projections, CEAs

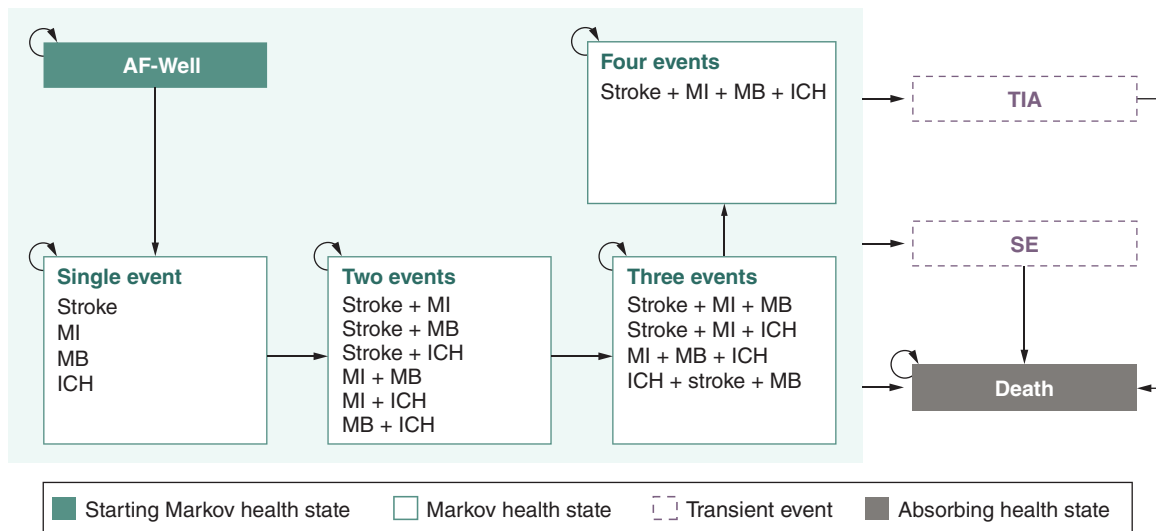


Figure 1. Markov model.

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

should account for drug genericization and incorporate dynamic pricing with appropriate assumptions regarding the date of LOE and the percentage of patients changing to generics [19]. This is particularly important in treatment landscapes where generic options are becoming increasingly available, such as DOACs for patients with NVAf.

A previous economic analysis investigated the cost of clinical events associated with switching patients with prevalent NVAf from apixaban to rivaroxaban using a decision model from a German healthcare payer perspective [21]. However, given this was a budgetary analysis that evaluated event related costs over a short time horizon, it does not consider the effects of disease progression, patients' QoL or patient survival in the long-term, nor the impact of generic pricing over time. To address these gaps in knowledge and build upon the current evidence base, this study aims to evaluate the cost-effectiveness and budget impact of two different treatment scenarios for patients with NVAf from the German payer perspective. Specifically, this study will compare initiating treatment with apixaban and then switching to rivaroxaban versus initiating and continuing treatment with apixaban, based on a previously published cohort-level Markov model [10] with an additional budget impact calculator, adapted to reflect the findings of the Deitelzweig *et al.* [18] publication and to a German setting, while further incorporating generic pricing assumptions.

Materials & methods

Patient population

The modeled population included German patients with NVAf, eligible for oral anticoagulation, who were receiving apixaban. The cohort size considered within the cost-effectiveness model was 1000 patients, with a mean age of 75 years and 49% male, based on demographic data published by Deitelzweig *et al.* [18].

Model overview

To assess the cost-effectiveness of receiving apixaban and then switching to rivaroxaban versus continuing with apixaban in patients with NVAf from a German healthcare perspective, a cohort-level Markov model was developed in Microsoft Excel®. The consolidated health economic evaluation reporting standard (CHEERS 2022) checklist was followed throughout this study [22].

The Markov model included 17 health states (Figure 1), based on a structure published by Lopez-Lopez *et al.* [10] and Sterne *et al.* [23]. Patients with NVAf entered the model in an initial 'AF-Well' state, defined as those without the existence of comorbidities. Using predefined probabilities, patients either remained in the 'AF-Well' state or experienced one of the following events: stroke, myocardial infarction (MI), MB or intracranial hemorrhage (ICH). Per cycle, patients could experience up to four events (including the initial event) in any sequence. Two transient

event states for SE and transient ischemic attack (TIA) were included in the model, which incurred one-off costs and utility decrements. Transient events were assumed to have no long-term effect on risk of events, costs or health-related quality of life. In any health state, patients were at risk of death.

To capture the chronic and progressive nature of NVAf, a lifetime (up to 100 years) model horizon with a 3-monthly cycle was employed to align with published literature [10,24]. The model applied an annual discounting rate of 3% to costs and benefits over the modeled horizon, in line with the Institute for Quality and Efficiency in Health Care guidelines [25]. The primary model outcome was the incremental cost–effectiveness ratio (ICER), expressed as the cost per quality-adjusted life year (QALY) gained. As Germany does not have a pre-specified willingness-to-pay (WTP) threshold, a threshold of one-times the per capita gross domestic product for Germany, i.e., €48,750 in 2023 [26], was used to align with WHO guidance for cost–effectiveness evaluation [27]. Other model outcomes included total and incremental clinical event rates, costs, QALYs, life years (LYs) and time on treatment.

Intervention & comparators

The model included one treatment arm (apixaban [5 mg twice daily (bd)] pre-switch and rivaroxaban [20 mg once daily (od)] post-switch) and one control arm (apixaban [5 mg bd] pre- and post-switch), as shown in [Supplementary Figure 1](#). All patients initiated treatment with apixaban in both the treatment and control arm as the pre-switch therapy. The model assumed all patients (100%) in the treatment arm switched from apixaban to rivaroxaban at the end of cycle 2 (6 months), based on the mean time to switch from the Deitelzweig *et al.* [18] publication, while patients in the control arm continued treatment with apixaban. At any cycle, patients were at risk of discontinuing to no treatment following a clinical event (stroke, MB, MI, ICH, SE or TIA) based on event-based discontinuation probabilities ([Supplementary Table 1](#)).

Disease progression

A Markov process was used to capture the movement of patients across each health state, using event probabilities ([Supplementary Table 2](#)), treatment discontinuation ([Supplementary Table 3](#)) and history of prior clinical events ([Supplementary Table 4](#)) [10]. For apixaban continuers, event incidence rates were sourced from Deitelzweig *et al.* [18], a US claims database (Optum's Clinformatics® Data Mart Database) study which assessed clinical outcomes in patients with NVAf continuing or switching DOAC (apixaban and rivaroxaban) treatment, and converted to 3-month baseline event probabilities to align with cycle length. For apixaban switchers, baseline event probabilities were transformed using hazard ratios (HRs) primarily derived from Deitelzweig *et al.* [18] ([Supplementary Table 2](#)). As Deitelzweig *et al.* [18] did not report HRs or incidence rates for all events, some were derived from Sterne *et al.* [23], a network meta-analysis of randomized controlled trial data which studied AF outcomes ([Supplementary Table 2](#)). To consider the impact of prior events, the probability of event occurrence was changed dependent on which events a patient had previously experienced, based on HRs derived from the Lopez-Lopez *et al.* [10] and Sterne *et al.* [23] network meta-analyses ([Supplementary Table 4](#)). Event probabilities for no treatment were used to account for the impact of discontinuing treatment, which were derived by applying HRs for no treatment versus apixaban treatment from the Sterne *et al.* [23] study to the baseline event probabilities for apixaban continuers ([Supplementary Table 3](#)). The model assumed that the transition probabilities remained unchanged over time. However, to account for the increasing age and thus increasing mortality risk of the cohort each cycle, German-specific general population life tables were employed from GENESIS-Online [28].

Health-related quality of life

Baseline utility was based on the health state a patient resided in, with a specific health utility value applied to each health state ([Supplementary Table 1](#)). For the AF-well health state baseline utility was 0.779, based on a publication from Berg *et al.* [29]. Upon the occurrence of an acute event (stroke, MB, MI, ICH, SE, TIA) a one-off disutility was applied in the incident cycle ([Supplementary Table 1](#)), sourced from a published systematic review and network meta-analysis [10]. The long-term impact of stroke, MI and ICH events on QoL was included by applying event-specific utilities to all subsequent cycles once an event occurred, based on Lopez-Lopez *et al.* [10] and Haacke *et al.* [30] data. Death was assigned a utility value of zero. Where multiple comorbidities occurred, the revised health state utility was based on the multiplicative product of the relevant comorbidity utility values. Utility values were adjusted for age by multiplying the age-related utility adjustment based on the current cohort age [31].

Costs

The model assessed cost benefits from the perspective of the German public healthcare payer. Cost inputs for the model were German-specific and were obtained from published literature [32,33] and national databases [34,35] (Supplementary Table 1). Costs were inflated to 2023 using the consumer price index where necessary [36]. Where a clinical event occurred, a one-off clinical event cost was applied to the cycle in which the event took place. Following the occurrence of stroke, MB, MI or ICH, annual event-specific maintenance costs (adjusted to reflect the 3-month cycle length) were applied to all subsequent cycles. Treatment acquisition costs, calculated as the cost of 3 months of therapy, were applied per cycle while on treatment [35]. To account for the anticipated price erosions of DOACs following LOE and the increased availability of generic options, dynamic pricing of apixaban and rivaroxaban was enabled in the model. For base case analysis, generic prices were set as 10% of list prices, assuming a discount of 90% following LOE to ensure cost estimates are conservative. Based on anticipated patent expiry dates in Europe at the time of model development (January 2024) [37,38], generic rivaroxaban was introduced from the start of cycle 1, where it was assumed all patients (100%) received generic rivaroxaban. Meanwhile, generic apixaban was introduced from the start of cycle 9, where it was also assumed all patients (100%) received generic apixaban. Generic pricing remained available for the duration of the time horizon. Monitoring costs, calculated as the cost of monitoring for 3 months of therapy, were applied per cycle while on treatment [32].

Sensitivity & scenario analyses

A deterministic one-way sensitivity analysis was used to determine the impact of changing individual parameters on the modeled analysis outcomes. The mean value for key model parameters were independently varied by reported 95% CIs; where 95% CIs were not reported, parameters were varied by $\pm 10\%$ of their mean value. By adjusting each parameter (costs and clinical parameters) individually, the sensitivity of the results to that parameter was assessed. A probabilistic sensitivity analysis (PSA) was also conducted over 1000 iterations to quantify the joint impact of parameters' uncertainty on model results by assigning a distribution to each parameter. A gamma distribution was assigned for costs, while a normal distribution was assigned for certain inputs relating to baseline patient characteristics, such as age or height. Inputs describing utilities or disutilities were assigned either normal, beta or gamma distributions. Baseline event rates were assigned beta distributions, while a log-normal distribution was assigned for HRs. Cost-effectiveness acceptability curves were generated using the results of the PSA to assess the cost-effectiveness of apixaban switchers versus apixaban continuers over a range of WTP thresholds from €0 to €100,000.

To explore the impact of excluding dynamic pricing assumptions on the model outcomes, a scenario analysis was conducted with generic pricing disabled and static brand prices used until the end of the time horizon. Additional scenario analyses investigated the impact of the length of time horizon used in the model, employing both 5 and 10-year time horizons. Furthermore, as the current list price of rivaroxaban is higher than apixaban, threshold analyses were undertaken applying a range of discounts from 0 to 100% to the rivaroxaban list price to determine whether this is a key driver of cost-effectiveness outcomes. Notably, threshold analyses were conducted both with and without the generic pricing discounts applied on top of the discounts to rivaroxaban list price. A further scenario was conducted based on the assumption that all patients remain on lifelong treatment and do not discontinue treatment following a clinical event.

Budget impact analysis

An additional budget impact calculator was included in the model to estimate total costs (treatment costs, event costs, long-term management costs and monitoring costs) over a 5-year time horizon with and without generic pricing assumptions enabled. All inputs and assumptions aligned with those detailed in the cost-effectiveness analysis.

Results

When compared with continuing treatment with apixaban, switching existing patients with NVAF on apixaban to rivaroxaban was associated with an increased event rate for all clinical events, with the exception of MI (Figure 2). While switching patients to rivaroxaban treatment was estimated to avert two MIs, an additional 25 strokes, 68 MBs, 18 ICHs, 3 SEs and 173 TIAs (per 1000 patient years) were observed in the apixaban switchers arm versus the apixaban continuers arm over a lifetime horizon (Figure 2). Post-switch, the mean time on treatment

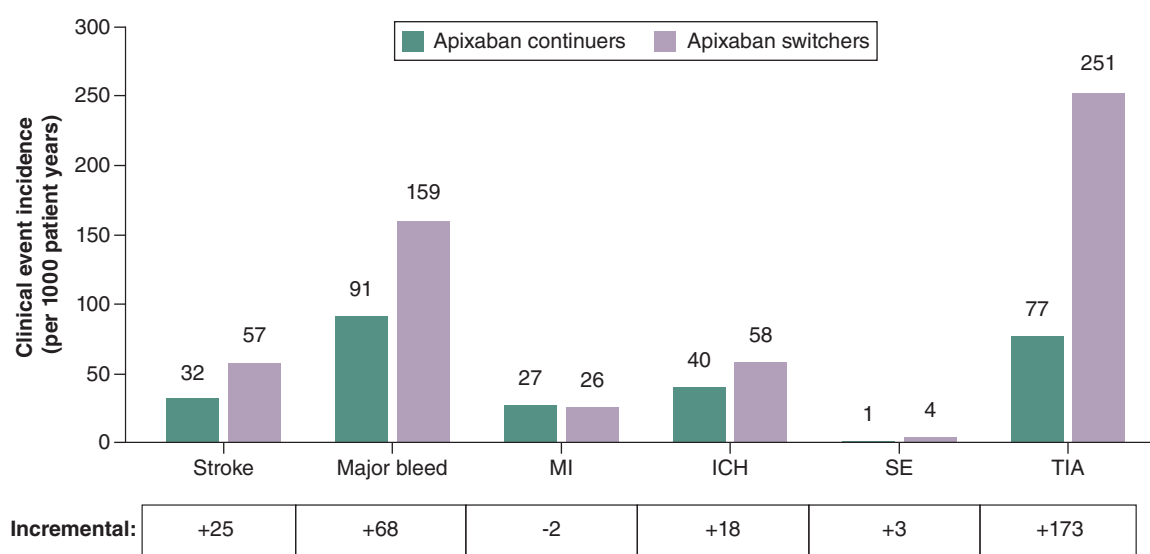


Figure 2. Base case: modeled clinical event rates per 1000 patient years. Incremental values may not correspond to the chart due to rounding.
ICH: Intracranial hemorrhage; MI: Myocardial infarction; SE: Systemic embolism; TIA: Transient ischemic attack.

Table 1. Summary of lifetime costs per patient associated with apixaban continuers and apixaban switchers.		
Costs	Apixaban continuers	Apixaban switchers (to rivaroxaban)
Event costs	€4285.10	€8286.59
Stroke	€744.50	€1317.85
MB	€606.10	€1042.99
MI	€806.59	€750.50
ICH	€921.47	€1324.97
SE	€8.43	€25.12
TIA	€1198.01	€3825.16
Long-term management costs	€6497.25	€8435.27
Monitoring costs	€956.84	€886.48
Drug costs	€4650.32	€3748.93
Total costs	€16,389.51	€21,357.27
Incremental costs	€4967.76	

ICH: Intracranial hemorrhage; MB: Major bleeding; MI: Myocardial infarction; SE: Systemic embolism; TIA: Transient ischemic attack.

for apixaban switchers was lower compared with apixaban continuers at 9.19 versus 10.09 years, respectively, as apixaban switchers had higher clinical event rates leading to treatment discontinuation.

Despite having lower monitoring and drug costs, switching from apixaban to rivaroxaban treatment was associated with higher one-off clinical event-related costs and long-term management costs, resulting in higher total healthcare costs for apixaban switchers (€21,357 per patient) versus apixaban continuers (€16,390 per patient) (Table 1). A substantial difference in costs were seen for one-off clinical event-related costs, where switching to rivaroxaban resulted in higher stroke (€1318 vs €745), MB (€1043 vs €606), ICH (€1325 vs €921), SE (€25 vs €8) and TIA (€3825 vs €1198) costs per patient over the lifetime horizon compared with continuing apixaban treatment (Table 1). The drug costs associated with apixaban switchers (€3749) were lower than those for apixaban continuers (€4650), reflecting the earlier introduction of generic discounting for rivaroxaban in the model (cycle 1 vs cycle 9, respectively) and the lower mean time on treatment for apixaban switchers.

As a consequence of higher clinical event rates, switching from apixaban to rivaroxaban among patients with NVAF resulted in fewer QALYs and LYs (-0.079 and -0.086, respectively) compared with continuing apixaban

Table 2. Base case: cost-effectiveness analysis results comparing apixaban switchers (to rivaroxaban) versus apixaban continuers.

	Apixaban continuers	Apixaban switchers (to rivaroxaban)
Total costs	€16,389.51	€21,357.27
Total QALYs	5.44	5.36
Total LYs	9.67	9.58
Incremental costs and benefits vs apixaban continuers		
Incremental costs	–	€4967.76
Incremental QALYs	–	-0.079
Incremental LYs	–	-0.086
Cost-effectiveness vs apixaban continuers		
Cost per QALY gained	–	Dominated
Cost per LY gained	–	Dominated

LY: Life year; QALY: Quality-adjusted life year.

Table 3. Probabilistic sensitivity analysis (1000 iterations): cost-effectiveness analysis results comparing apixaban switchers (to rivaroxaban) versus apixaban continuers.

	Apixaban continuers	Apixaban switchers (to rivaroxaban)
Total costs	€16,755.49	€21,425.93
Total QALYs	5.45	5.37
Total LYs	9.73	9.63
Incremental costs and benefits vs apixaban continuers		
Incremental costs	–	€4670.44
Incremental QALYs	–	-0.088
Incremental LYs	–	-0.101
Cost-effectiveness vs apixaban continuers		
Cost per QALY gained	–	Dominated
Cost per LY gained	–	Dominated

LY: Life year; QALY: Quality-adjusted life year.

treatment. Consequently, apixaban switchers were dominated (had fewer QALYs and greater costs) by apixaban continuers (Table 2).

Sensitivity analysis

Deterministic one-way sensitivity analysis demonstrated that the most influential parameters of the model were the probability of discontinuing treatment upon TIA event incidence, the HR for impact of prior MB for ACM, and the HR for impact of no prior stroke for ACM (Supplementary Figure 2). Apixaban switchers remained dominated by apixaban continuers for majority of parameter changes, with the exception of varying the HR for impact of treatment switching for ACM, where switching to rivaroxaban resulted in positive incremental QALYs yielding an ICER of €28,875 per QALY gained, thus was considered cost-effective versus continuing treatment with apixaban as the ICER remained below the WTP threshold.

In line with the results of the base case, the PSA demonstrated that higher costs and fewer QALYs were observed for apixaban switchers versus apixaban continuers, meaning apixaban switchers were dominated by apixaban continuers (Table 3). Results of the PSA comparing the incremental costs and incremental QALYs of apixaban switchers versus apixaban continuers across 1000 simulations is shown in Supplementary Figure 3. Most iterations (71.0%) resided in the North-West quadrant, demonstrating that switching to rivaroxaban was more costly and less effective. While some iterations (28.2%) resided in the North-East quadrant (i.e., switching to rivaroxaban was more effective at a higher cost), most simulations were above the assumed WTP threshold of €48,750 thus not considered cost-effective. At the base case WTP threshold of €48,750 the probability of apixaban switchers being at least cost-effective was 11.30% when compared with apixaban continuers (Supplementary Figure 4).

Table 4. Scenario analysis with generic pricing excluded: cost–effectiveness analysis results comparing apixaban switchers (to rivaroxaban) versus apixaban continuers.

	Apixaban continuers	Apixaban switchers (to rivaroxaban)
Total costs	€20,146.80	€28,723.91
Total QALYs	5.44	5.36
Total LYs	9.67	9.58
Incremental costs and benefits vs apixaban continuers		
Incremental costs	–	€8577.10
Incremental QALYs	–	-0.079
Incremental LYs	–	-0.086
Cost–effectiveness vs apixaban continuers		
Cost per QALY gained	–	Dominated
Cost per LY gained	–	Dominated

LY: Life year; QALY: Quality-adjusted life year.

Table 5. Threshold analysis of the list price for rivaroxaban with and without generic pricing assumption: cost–effectiveness analysis results comparing apixaban switchers (to rivaroxaban) versus apixaban continuers.

Discount to rivaroxaban list price	Generic pricing enabled [†]			Generic pricing excluded		
	Incremental cost	Incremental QALYs	Cost per QALY	Incremental cost	Incremental QALYs	Cost per QALY
0%	€4967.76	-0.079	Dominated	€8577.10	-0.079	Dominated
10%	€4863.54		Dominated	€7534.90		Dominated
20%	€4759.32		Dominated	€6492.69		Dominated
30%	€4655.10		Dominated	€5450.48		Dominated
40%	€4550.87		Dominated	€4408.27		Dominated
50%	€4446.65		Dominated	€3366.06		Dominated
60%	€4342.43		Dominated	€2323.85		Dominated
70%	€4238.21		Dominated	€1281.64		Dominated
80%	€4133.99		Dominated	€239.43		Dominated
90%	€4029.77		Dominated	-€802.78		€10,152.08 (not cost-effective)
100%	€3925.55		Dominated	-€1844.99		€23,332.05 (not cost-effective)

[†] For the purpose of this threshold analysis, incremental discounts were applied to the rivaroxaban list price prior to loss of exclusivity, meaning any further discounts due to generic pricing were applied to this discounted list price.

QALY: Quality-adjusted life year.

Scenario analyses

When using static brand prices throughout the whole time horizon to explore the exclusion of dynamic generic pricing in the model, results predicted that apixaban switchers were still dominated (had fewer QALYs and greater costs) by apixaban continuers (Table 4). Other scenario analyses explored the impact of employing shorter time horizons in the model, where results indicated that apixaban switchers continued to be dominated (had fewer QALYs and greater costs) by apixaban continuers when using both 5 and 10-year time horizons (Supplementary Table 5). Separate threshold analyses explored the impact of the drug acquisition price of rivaroxaban on model outcomes, applying a range of discounts to the list price of rivaroxaban. With generic pricing enabled, results of the threshold analyses indicated that apixaban switchers continued to be dominated (had fewer QALYs and greater costs) by apixaban continuers, despite discounts of up to 100% being applied to the list price of rivaroxaban (Table 5). With generic pricing excluded, threshold analyses indicated that apixaban switchers were still dominated (had fewer QALYs and greater costs) by apixaban continuers when discounts of up to 80% were applied to the list price of rivaroxaban (Table 5). When discounts of 90–100% were applied, apixaban switchers had fewer QALYs and less costs versus apixaban continuers, though were not considered cost-effective as the ICER remained below the WTP threshold (Table 5). Results of a further scenario analysis exploring the assumption that all patients

Table 6. Annual total budget impact of apixaban switchers (to rivaroxaban) versus apixaban continuers over 5 years.

	Apixaban continuers		Apixaban switchers		Incremental	
	Per patient	Per 1000 patients	Per patient	Per 1000 patients	Per patient	Per 1000 patients
Generic pricing assumptions enabled [†]						
Year 1	€1426.13	€1,426,126	€1248.51	€1,248,505	-€177.62	-€177,621
Year 2	€1334.92	€1,334,923	€1019.07	€1,019,069	-€315.85	-€315,855
Year 3	€593.65	€593,648	€963.10	€963,095	€369.45	€369,447
Year 4	€570.30	€570,297	€897.52	€897,517	€327.22	€327,220
Year 5	€539.81	€539,809	€826.91	€826,908	€287.10	€287,099
Cumulative	€4464.80	€4,464,804	€4955.09	€4,955,094	€490.29	€490,290
Generic pricing assumptions disabled						
Year 1	€1426.13	€1,426,126	€1834.22	€1,834,217	€408.09	€408,091
Year 2	€1334.92	€1,334,923	€2065.28	€2,065,283	€730.36	€730,360
Year 3	€1234.70	€1,234,700	€1862.20	€1,862,203	€627.50	€627,503
Year 4	€1130.59	€1,130,591	€1662.49	€1,662,490	€531.90	€531,899
Year 5	€1025.40	€1,025,401	€1471.35	€1,471,353	€445.95	€445,952
Cumulative	€6151.74	€6,151,742	€8895.55	€8,895,547	€2743.81	€2,743,805

[†] Generic prices are set as 10% of list price, assuming a discount of 90% following loss of exclusivity; generic rivaroxaban was introduced from the start of cycle 1, generic apixaban was introduced from the start of cycle 9.

Total budget impact includes event costs, long-term management costs, monitoring costs and drug costs.

continued with lifelong therapy indicated that apixaban switchers continued to be dominated (had fewer QALYs and greater costs) by apixaban continuers when treatment discontinuation was excluded ([Supplementary Table 6](#)).

Budget impact analysis

Switching existing patients with NVAf from apixaban to rivaroxaban was associated with higher incremental costs compared with continuing treatment on apixaban, irrespective of generic pricing assumptions. When considering base case generic pricing assumptions, switching existing patients from apixaban to rivaroxaban was associated with greater budget impact, with 5-year cumulative incremental total costs per patient (per 1000 patients) of €490 (€490,290) ([Table 6](#)). Notably, with generic pricing assumptions applied, the costs for apixaban switchers were lower compared with apixaban continuers during the first 2 years, due to the earlier introduction of generic discounting for rivaroxaban. In these first 2 years, switchers transitioned to generic rivaroxaban, while continuers remained on branded apixaban. Only after the 2nd year, when apixaban also became generic (in cycle 9), did the drug costs become comparable. The initial savings associated with switching to generic rivaroxaban were later offset by the higher costs from the increased incidence of clinical events among switchers ([Table 6](#)). With generic pricing assumptions disabled, switching existing patients from apixaban to rivaroxaban similarly had a greater budget impact, with 5-year cumulative incremental total costs per patient (per 1000 patients) of €2744 (€2,743,805) ([Table 6](#)). Furthermore, switching existing patients with NVAf from apixaban to rivaroxaban was associated with higher incremental event rates compared with continuing treatment on apixaban, with a 5-year cumulative incremental total of 288 events per 1000 patient years ([Supplementary Table 7](#)). This resulted in higher incremental event-related costs associated with switching to rivaroxaban, with 5-year cumulative incremental event costs per patient (per 1000 patients) of €1393 (€1,393,276) ([Supplementary Table 7](#)).

Discussion

Although switching between DOAC therapies often occurs when treating patients with NVAf in clinical practice [16], this topic is under investigated and there is limited understanding of the clinical and economic implications of DOAC switching for patients and healthcare systems. Furthermore, with DOACs continuing to lose exclusivity and more generic options coming to market, there is a need for cost-effectiveness analyses to utilize forecasted price trajectories to inform more accurate and representative results. To the authors' knowledge, this is the first cost-effectiveness and budget impact analysis to evaluate the clinical and economic outcomes of switching to rivaroxaban treatment versus continuing apixaban treatment in patients with NVAf, which incorporates dynamic pricing into the model to account for LOE and generic entry. Findings from this study indicate that switching patients with

NVAF from apixaban to rivaroxaban was dominated (had fewer QALYs and greater costs) by continuing apixaban treatment in a German public payer perspective over a lifetime horizon and had a greater budget impact over 5 years.

Switching between DOAC therapies may occur for various reasons, including treatment-related factors (e.g., lack of effectiveness, ease of administration or adverse events), patient-centered factors (e.g., a lack of adherence) or nonmedical factors (e.g., healthcare expenditure) [39]. Until recently there has been a lack of data assessing the clinical outcomes between patients continuing their initial DOAC therapy versus those who switch to a different DOAC. As previously noted, the results from the Deitelzweig *et al.* [18] study indicated that switching from apixaban to rivaroxaban increased the risk of stroke/SE and MB versus continuing apixaban. Building upon these findings, this cost-effectiveness analysis demonstrated that switching patients to rivaroxaban treatment resulted in higher clinical event rates for all clinical events, with the exception of MI, when compared with continuing treatment with apixaban. Furthermore, apixaban switchers had a lower mean time on treatment compared with continuers, due to higher rates of event-based discontinuation. Together these results indicate that greater clinical benefits may be achieved by retaining patients with NVAF on apixaban treatment where they can remain on treatment for longer periods of time, where clinically appropriate.

At the time of conducting this study, it is anticipated that rivaroxaban will lose exclusivity prior to apixaban in Germany, meaning the price of rivaroxaban will likely reduce significantly in the near future due to the market entry of generics. While a lower acquisition price may encourage healthcare providers to favour rivaroxaban treatment, it is necessary to consider the potential clinical and economic impact of switching to rivaroxaban in patients with NVAF. As a result, this model incorporated generic rivaroxaban acquisition pricing in cycle 1, applying a 90% discount to the brand price to reflect the expected price erosions associated with generic entries into the market. Despite having lower drug acquisition and monitoring costs, switching to rivaroxaban was associated with higher one-off clinical event-related costs and long-term management costs, resulting in apixaban continuers yielding the lowest total healthcare costs. This was largely driven by the lower clinical event rates for strokes, TIAs and MBs observed in patients continuing treatment with apixaban, which subsequently resulted in cost savings. A separate scenario analysis using static brand prices throughout the lifetime horizon similarly concluded that apixaban switchers remained dominated by apixaban continuers. Together these findings indicate that continuing treatment with apixaban may result in considerable cost savings at the German healthcare system level compared with switching to rivaroxaban, even when significant price erosions occur due to LOE.

It is important to note that the current list price of rivaroxaban is higher than apixaban, and so it is necessary to determine whether this influences the favourable economic outcomes observed here for apixaban continuers. To explore this, a threshold analysis applying a range of discounts to the list price for rivaroxaban was conducted and concluded that apixaban switchers were still dominated (had fewer QALYs and greater costs) by apixaban continuers despite a discount of 100% being applied, with generic pricing enabled. These findings consolidate that the main driver of the results of this cost-effectiveness analysis is likely due to the incremental difference in clinical event rates for apixaban continuers compared with apixaban switchers.

Few studies have investigated the economic implications of DOAC switching in patients with NVAF [40,41]. Prior analyses from Subash *et al.* [40,41] used decision models to evaluate the cost of clinical events associated with switching from apixaban to rivaroxaban treatment in patients with NVAF from the US and German perspective. Results concluded that switching patients with prevalent NVAF from apixaban to rivaroxaban was associated with an increase of €158.9 million ($n = 1.05$ million patients; incremental cost per patient per month: €19.59) and \$17.9 million ($n = 48,838$ patients; incremental cost per patient per month: \$30.58) in clinical event-related costs from the perspective of German and US healthcare payers, respectively. These results support the observations from this study, that switching to rivaroxaban is dominated by continuing apixaban treatment in patients with NVAF. Other economic analyses comparing the cost-effectiveness of apixaban versus other DOACs in patients with NVAF similarly conclude that apixaban is a cost-effective treatment option compared with rivaroxaban [42–44]. While these analyses do not assess the impact of DOAC switching directly, these findings are consistent with the conclusions of this study and further demonstrate the potential economic and clinical benefit of apixaban treatment.

In the additional budget impact analysis with generic pricing assumptions enabled, switching patients from apixaban to rivaroxaban resulted in cost savings in years 1 and 2, but incurred additional costs in years 3 to 5. Absolute costs for apixaban (to rivaroxaban) switchers were highest in year 1 as the model assumed all patients switched from apixaban to rivaroxaban at the end of cycle 2 (6 months), meaning the introduction of generic

rivaroxaban in cycle 1 had no impact on costs until post-switch. Following treatment switch to generic rivaroxaban (at the end of cycle 2), the absolute costs for apixaban (to rivaroxaban) switchers started to decrease for the remainder of year 1. Absolute costs for apixaban continuers were highest in years 1 and 2, prior to the introduction of generic apixaban in cycle 9; but by year 3, costs for apixaban continuers were lower than for switchers, reflecting the higher incidence of events in the switching cohort. Overall, these results indicate that while short-term drug acquisition savings can be made by switching existing patients with NVAf from apixaban to rivaroxaban, larger cumulative costs were incurred over 5 years in these patients compared with patients who remained on apixaban, despite later generic entry.

As previously noted, this is the first cost-effectiveness and budget impact analysis assessing the clinical and economic outcomes of DOAC-to-DOAC switching in patients with NVAf, to the authors' current knowledge. The modelling approach used for this cost-effectiveness analysis aligns with methodologies described in prior health technology assessments of DOACs in this indication and has several other strengths. For example, the inclusion of dynamic pricing in this model to account for LOE and generic entry allows for more comprehensive and accurate cost-effectiveness projections. Additionally, the clinical inputs utilized in the model were sourced from a real-world evidence study, thus results may be more reflective of real-world clinical practice.

Alongside the strengths of this study, there are some limitations which should be acknowledged. First, only apixaban and rivaroxaban were included in this study partly due to availability of data in Deitelzweig *et al.* [18], the US claims database study used to provide event incidence rates in our model. While future researchers may wish to explore other switching combinations, it is important to note that apixaban and rivaroxaban are the most commonly used DOACs in Europe. Second, minor bleeds were not captured by the model, aligning with the assumption from the Lopez-Lopez *et al.* [10] model that minor non-clinically relevant bleeds were not included as transient events. As nonmajor bleeding events (including minor bleeding) have been reported in patients with AF receiving anticoagulation therapy [45,46], this cost-effectiveness model may underestimate the burden of bleeding events in clinical practice, thus may provide a conservative evaluation. Third, the baseline population profile and the time to treatment switch (6 months) was based on data reported in the Deitelzweig *et al.* [18] study which was informed by a US database, thus may not be fully reflective of a German population. Similarly, an assumption was made that the clinical event rate probabilities and HRs obtained from US-based studies were representative of a German population. Fourth, due to a lack of German QoL data, utility inputs were not derived from German-specific sources and so may not be fully representative of the real-world population. Nevertheless, sensitivity analyses indicated that utility inputs were not key drivers of the model outcomes, so this is unlikely to have significant impact on the conclusions drawn from this study. Fifth, as with any economic model, outcomes will be dependent on the inputs selected to populate the model and different inputs may give different results. Finally, the model did not differentiate patients based on whether DOAC-to-DOAC switches were due to medical reasons, such as a lack of efficacy, or nonmedical reasons, such as formulary restrictions due to increasing costs or patient preferences. It is important to acknowledge that the reasoning behind DOAC switches may effect clinical and economic outcomes differently, though due to an absence of data to inform clinical event rates by reasons of switching, this study utilised aggregated data to reflect the overall patient population. Future research should investigate the rationale for DOAC switching in patients with NVAf to identify whether there are patient subgroups which may be at higher risk of treatment changes over time.

In conclusion, switching from apixaban to rivaroxaban in patients with NVAf was associated with an increase in total costs and a reduction in QALYs, primarily driven by an increased rate of strokes, TIA and MB events. As a result, switching patients with NVAf from apixaban to rivaroxaban was dominated by continuing treatment with apixaban from the German payer perspective. Meanwhile, switching existing patients from apixaban to rivaroxaban was also associated with greater budget impact over a 5 year time horizon. These findings provide further insight into the clinical and economic implications of DOAC switching in patients with NVAf, potentially facilitating more informed decision making.

Summary points

- Switching between direct oral anticoagulant (DOAC) therapies is common in clinical settings; however, there is limited research into the economic implications of DOAC-to-DOAC switching in patients with nonvalvular atrial fibrillation (NVAf) at the healthcare system level.
- Based on a previously published model, a cohort-level Markov model was built to assess the cost-effectiveness and budget impact of switching patients with NVAf from apixaban to rivaroxaban compared with continuing patients on apixaban, from the German healthcare payer perspective over a lifetime horizon.
- Due to the anticipated price erosions of DOACs following loss of exclusivity and more generic options coming to market, dynamic pricing of apixaban and rivaroxaban was enabled in the model based on forecasted loss of exclusivity timings in Germany at the time of model development in January 2024.
- The study primarily focused on the incremental cost-effectiveness ratio, measured using cost per quality-adjusted life year (QALY) gained, and a willingness-to-pay threshold of €48,750 was used to assess cost-effectiveness based on WHO guidance.
- Switching patients with NVAf from apixaban to rivaroxaban was associated with an increased event rate for all clinical events modeled (stroke, major bleeding, intracranial hemorrhage, systemic embolism and transient ischemic attack), with the exception of myocardial infarction, when compared with continuing apixaban treatment.
- Over a lifetime horizon, apixaban switchers accrued higher total costs (€4968) and fewer QALYs (-0.079) compared with continuing apixaban treatment.
- In the base case analysis, with generic pricing assumptions enabled, results indicated that switching patients with NVAf from apixaban to rivaroxaban was dominated (i.e., had fewer QALYs and greater costs) by continuing treatment with apixaban, from the German healthcare payer perspective.
- A scenario analysis using static brand prices throughout the time horizon to explore the exclusion of generic pricing assumptions in the model predicted that apixaban switchers remained dominated by apixaban continuers.
- In the budget impact analysis using generic pricing assumptions, switching patients from apixaban to rivaroxaban incurred €490 in additional cumulative costs per patient over 5 years.
- Switching from apixaban to rivaroxaban among patients with NVAf was associated with a substantial increase in direct healthcare costs and a reduction in QALYs, mostly driven by an increased rate of strokes, transient ischemic attacks and major bleeding events.

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-2025-0008>

Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors participated in the concept and design of the paper. R Subash, V Vasilopoulos and E Stawowczyk conducted the data acquisition/analysis and performed the modelling. C Dickerson and C Salter drafted the manuscript. T Strakosch, M Zhang, M Hagan, E Dworatzek and A Kisser provided critical feedback and supervision throughout the research process. All authors participated in data interpretation and critical revision of the paper. Final approval of the manuscript was given by all authors.

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Competing interests disclosure

R Subash, E Dworatzek and A Kisser are employees and shareholders of Pfizer. M Zhang is an employee of Bristol Myers Squibb and the University of Southern California. M Hagan was an employee of Bristol Myers Squibb at the time of writing this study. T Strakosch was an employee of FIECON at the time of writing this study; FIECON received funding from the Pfizer/Bristol Myers Squibb Alliance in connection with the conduct of this study. C Salter, C Dickerson and E Stawowczyk are employees of Health Economics and Outcomes Research Ltd., HEOR Ltd. received funding from the Pfizer/Bristol Myers Squibb Alliance in connection with the development of this manuscript and conduct of the study. V Vasilopoulos was an employee of HEOR Ltd. at the time of writing this study. The authors have no other competing interests or relevant affiliations with any organization/entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No editorial/medical writing support was provided in relation to this study.

Data sharing statement

Upon request, and subject to review, Pfizer/Bristol Myers Squibb Alliance will provide data that support the findings of this study.

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