Decision Model to Evaluate the Cost of Clinical Events Associated with Switching from Apixaban to Rivaroxaban among Patients with Non-Valvular Atrial Fibrillation in Germany

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Background

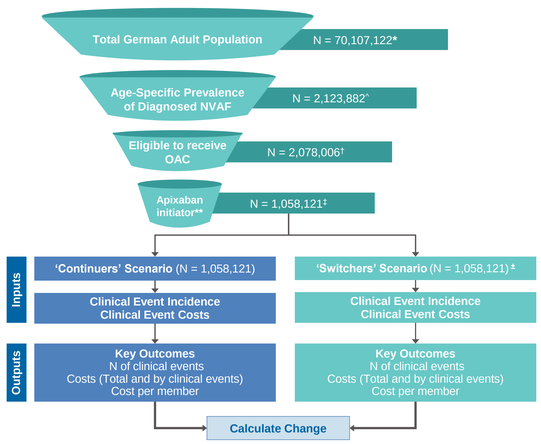
- A recent observational study among patients with non-valvular atrial fibrillation (NVAF) in the United States (US) demonstrated that patients who switched from apixaban to rivaroxaban experienced a higher risk of clinical events compared with patients who continued apixaban.[1]
  - Stroke/systemic embolism (SE) occurred in more patients who switched from apixaban to rivaroxaban (1.53 per 100 patient-years) compared with patients who continued apixaban (0.75 per 100 patient-years) [hazard ratio (HR): 1.99, 95% CI: 1.38–2.88].[1]
  - Major bleeding also occurred in more patients in the 'switcher' group (4.59 per 100 patient-years) compared with the 'continuer' group (2.44 per 100 patient-years) (HR:1.80, 95% CI: 1.46–2.23).[1]
  - The study provided real-world evidence of clinical outcomes associated with treatment switching in patients with NVAF. However, there is limited evidence on the economic outcomes of switching from apixaban to rivaroxaban.
- The objective of this study was to develop a decision model to evaluate the cost of clinical events associated with switching from apixaban to rivaroxaban among patients with NVAF in Germany.

Methods

Decision Model Overview

- The framework of the decision model is presented in **Figure 1**. The model evaluated the incidence and cost of stroke/SE (composite of ischemic stroke, hemorrhagic stroke, and SE) and major bleeding (composite of gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding) for the following two scenarios:
  - Patients with NVAF receiving apixaban to continue apixaban (the 'continuers').
  - Patients with NVAF receiving apixaban who switched to rivaroxaban (the 'switchers').
- The model analysis was conducted over a 1-year time horizon from a German public healthcare payer perspective.
- Incidence and cost of clinical events (stroke/SE and major bleeding) under the two scenarios were compared and the difference between the 'switchers' and 'continuers' scenarios outcomes were calculated to estimate the incremental cost of clinical events.

Figure 1. Decision Model Framework



Abbreviations: N = number; NVAF = non-valvular atrial fibrillation; OAC = oral anticoagulant
*Total German adult population sourced from the German Federal Statistical Office[2]; ^Calculated based on the German age distribution of people aged 65 years and above[2] and age-specific prevalence of diagnosed NVAF reported by Wilke et al, 2013[3]; †97.84% of the diagnosed NVAF patients are estimated to receive OAC therapy (Steinberg et al, 2015)[4]; ‡Apixaban market share estimate at 50.92% among patients receiving OAC[5]; ±100% of the patients with NVAF receiving apixaban were assumed to switch to rivaroxaban under the 'Switchers' scenario

Model Inputs

- The model inputs were informed using a real-world study (incidence and HR of clinical events),[1] clinical trial data (proportion of fatal events and distribution of severity of clinical events),[6-8] published epidemiology estimates,[2-5,9] and, publicly available cost databases and literature to estimate the clinical event costs.[10,11] An overview of key model inputs and sources is provided in **Table 1**.

Methods (continued)

Target Population

- The target population for the analysis was adult (≥18 years) patients with NVAF who initiated apixaban treatment.
- The size of the target population in Germany for the 'continuers' scenario was calculated using the German population age distribution, age-specific prevalence of NVAF reported in the published literature, the proportion eligible to receive oral anticoagulants (OACs), and the market share of apixaban in patients receiving OACs in Germany.[2-5,9]
- For the 'switchers' scenario, the size of the target population was calculated by assuming 100% of the 'continuers' scenario patients switched to rivaroxaban.

Clinical Parameters

- Incidence of clinical events in the 'continuers' and 'switchers' scenarios was sourced from the analysis of a retrospective observational study using Optum Clinformatics® Data Mart, which contains data from around 75 million privately insured individuals and includes medical and pharmacy claims data covered by commercial and Medicare Advantage insurance.
- Adult patients diagnosed with atrial fibrillation (AF) and treated with apixaban or rivaroxaban in the US between January 2012 and June 2022 were selected for the analysis.[1] US clinical parameters are assumed to be applicable for Germany.
  - The study-reported incidence rates of stroke/SE and major bleeding per 100 person-years among those who continued apixaban treatment and those who switched to rivaroxaban from apixaban were used to inform clinical event incidence under the 'continuers' scenario and the 'switchers' scenario, respectively.
  - Monthly probabilities of clinical events were calculated for each scenario and were assumed to be constant throughout the time horizon. These probabilities were then applied each month to the target population to derive the incidence of clinical events.
- The distribution of severity of clinical events was treatment-specific and data were sourced from the pivotal clinical trials of apixaban and rivaroxaban.[6-8]
  - Fatal event rates for ischemic stroke and hemorrhagic stroke were calculated as one minus the sum of mild, moderate, and severe event rates.
  - Fatality of intracranial hemorrhage and other major bleeding on rivaroxaban were assumed the same as apixaban, while no fatality was assumed for gastrointestinal bleeding and SE.

Table 1. Summary of Key Model Inputs and Sources

Input	Value		
Target population, n*	1,058,121*		
Clinical Event Incidence and HR**			
	Incidence per 100 PY in 'Continuers'	**Incidence per 100 PY in 'Switchers'**	**HR for 'Switchers' vs. 'Continuers' (95% CI)**
Ischemic stroke	0.53	1.05	1.89 (1.21–2.94)
Hemorrhagic Stroke	0.19	0.40	2.12 (1.03–4.35)
Systemic Embolism	0.03	0.08	3.38 (0.60–18.89)
Gastrointestinal Bleeding	1.13	2.54	2.15 (1.61–2.88)
Intracranial Hemorrhage	0.57	0.78	1.36 (0.83–2.24)
Other Major Bleeding	0.87	1.39	1.50 (1.03–2.19)
Clinical Event Costs (2023 Euro)			
	Acute^ (one-off)	**Long-term‡ (per month)**	**Fatal event costs±**
Ischemic stroke Mild Moderate Severe	 €4,320.94 €4,639.91 €7,672.90	€1,205.74	€7,672.90
Hemorrhagic Stroke Mild Moderate Severe	 €4,320.94 €4,639.91 €7,672.90	€1,205.74	€7,672.90
Systemic Embolism	€1,753.93	€264.90	-
Gastrointestinal Bleeding	€2,740.32	-	-
Intracranial Hemorrhage	€7,672.90	-	-
Other Major Bleeding	€2,740.32	-	-

Abbreviations: CI = confidence interval; HR = hazard ratio; PY = person year.
*Calculated using Destatis Statistisches Bundesamt,[2,9] Wilke et al 2013,[3] Steinberg et al 2015,[4] IQVIA Diagnosis Monitor[5]; **Sources: Deitelzweig et al, 2024[1]; ^Sources: Krejczy et al 2014,[10]; ‡Sources: InEK aG-DRG-System 2023[11]; ± Assumption: Assumed the same as severe acute costs.

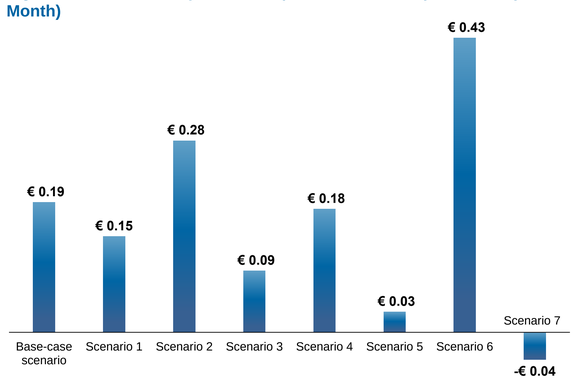
Clinical Event Costs

- The model accounts for clinical event costs (acute and long-term) and fatal event costs. All cost inputs (**Table 1**) reflect euros for the 2023 cost year.
- Acute and long-term management costs are accounted for in the clinical events included in the model and are derived from the published literature and database in Germany.[10,11]
  - Acute costs were applied as one-off costs to patients experiencing clinical events and assumed an inpatient admission associated with it.
  - Acute costs of ischemic stroke and hemorrhagic stroke were calculated through the weighted average across mild, moderate, and severe events.
  - Long-term management costs were applied monthly for the remainder of the model time horizon for the cohort experiencing these events.
- Fatal event costs were applied as one-off costs to the proportion of the cohort experiencing fatality due to clinical events.
  - Fatal ischemic stroke and hemorrhagic stroke were assumed to have the same costs as their severe acute events.
  - Costs of fatal gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding were assumed to be zero.

Results

- In the German population, 1,058,121 patients with prevalent NVAF were identified to be currently receiving apixaban after applying the eligibility criteria.
- Over a one-year horizon, switching all of the 1,058,121 patients from apixaban to rivaroxaban results in 33,691 additional clinical events (8,249 stroke/SE, 22,615 major bleeding, and 2,827 deaths) compared with continuing with apixaban. The additional clinical events incurred an incremental cost of €158.9 million in the 'switchers' scenario vs. the 'continuers' scenarios (**Table 2** and **Table 3**).
- At a per-member level, this incremental clinical event costs translates to € 2.27 per person per year and € 0.19 per person per month.
- Scenario analysis was conducted to test the impact of alternative input values and assumptions. The scenarios and results are demonstrated in **Figure 2**.
  - Continuation of apixaban was the favorable strategy over the strategy of switching these patients to rivaroxaban across all scenarios tested.
  - We also assessed the outcomes in patients who continued rivaroxaban vs. patients who were switched to apixaban from rivaroxaban (scenario 7 in **Figure 2**). Relevant clinical data were also based on the same study[1] as the base-case analysis. The findings of this scenario demonstrated cost savings (in terms of clinical event costs) associated with switching rivaroxaban patients to apixaban due to a reduction in the incidence of clinical events.

Figure 2. Scenario Analysis Result (Incremental Cost per Person per Month)



Scenario 1: Clinical event costs based on German DRG codes (base-case – based on literature); **Scenario 2**: Time horizon-3-year (base-case – 1 year); **Scenario 3**: 50% switches to rivaroxaban (base-case – 100%); **Scenario 4**: 'switcher' cohort event rates using hazard ratio (base-case – using incidence rate); **Scenario 5**: 'switcher' cohort event rates using hazard ratio lower bound (base-case – using incidence rate); **Scenario 6**: 'switcher' cohort event rates using hazard ratio upper bound (base-case – using incidence rate); **Scenario 7**: Rivaroxaban 'continuer' vs 'switcher' to apixaban (base-case – apixaban 'continuer' vs 'switcher').

Conclusions

- Modelling data from a US claims study, results suggest switching from apixaban to rivaroxaban could translate to a substantial increase in clinical event-related costs for German payers, driven by an increased incidence of stroke/SE and major bleeding.
- This conclusion was consistent across different scenarios for apixaban 'continuers' vs. 'switchers' tested.

Table 2. Clinical model results over 1-year timeframe

	'Continuers' Scenario	'Switchers' Scenario	Difference ('Switchers' minus 'Continuers')†
Number of Eligible Patients	**1,058,121**	**1,058,121**	**0**
Total Number of Clinical Events	**37,798**	**71,489**	**33,691**
Stroke/SE	7,935	16,184	**8,249**
Ischemic Stroke	5,607	11,105	**5,499**
Hemorrhagic Stroke	2,010	4,232	**2,222**
SE	317	846	**529**
Major Bleeding	27,183	49,798	**22,615**
Gastrointestinal Bleeding	11,951	26,848	**14,897**
Intracranial Hemorrhage	6,030	8,251	**2,221**
Other Major Bleeding	9,202	14,699	**5,497**
Deaths	2,681	5,508	**2,827**
Numbers Needed to Continue on Apixaban to Avoid One Event			
Ischemic Stroke		193	
Hemorrhagic Stroke		477	
SE		2,001	
Gastrointestinal Bleeding		72	
Intracranial Hemorrhage		477	
Other Major Bleeding		193	

Abbreviations: SE=Systemic embolism
†Positive values favor the strategy of apixaban continuation over switching these patients to rivaroxaban.

Table 3. Model Results Over 1-Year Timeframe

Total Clinical Event Costs	**€ 193,022,808**	**€ 351,965,777**	**€ 158,942,970**
Stroke/SE Cost	€ 75,646,823	€ 143,032,872	€ 67,386,050
Major Bleeding Cost	€ 104,233,701	€ 177,159,128	€ 72,925,427
Fatal Event Costs	€ 13,142,284	€ 31,773,777	€ 18,631,493
Incremental Outcomes			
Total Cost per Person per Year*		€ 2.27	
Total Cost per Person per Month*		€ 0.19	
Total Cost per Patient per Year**		€ 150.21	
Total Cost per Patient per Month**		€ 12.52	

Abbreviations: SE=Stroke/systemic embolism
*Calculated by dividing the total incremental clinical event costs per year (or month) by population size
**Calculated by dividing the total incremental clinical event costs per year (or month) by the number of NVAF patient eligible for treatment.

Limitations

- The model results should be interpreted in the context of the analysis limitations that the clinical event history of patients was not tracked over the time horizon and the general mortality was not modeled.
- Data that provided clinical inputs in the model was collected in the US, highlighting a potential limitation in generalisability when used to inform analysis in Germany.

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Disclosure

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RS and **DMH** are employees and shareholders of Pfizer. **MH** and **MZ** are employees of Bristol Myers Squibb. **MZ** is also an employee of the University of Southern California. **AS** and **CD** are employees of Evidera, a business unit of PPD, part of Thermo Fisher Scientific, which was contracted by the Bristol Myers Squibb-Pfizer Alliance to conduct this study.

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