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ORIGINAL RESEARCH

Long-term health benefits of stroke prevention with apixaban versus vitamin K antagonist warfarin in patients with non-valvular atrial fibrillation in Germany: a population-based modelling study

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ABSTRACT

Background: Patients with non-valvular atrial fibrillation (NVAF) have a five times higher stroke risk. For more than 50 years, vitamin K antagonists (VKAs) have been the primary medication for stroke prevention. Apixaban, a non-vitamin K oral anticoagulant (NOAC), has demonstrated better efficacy and safety characteristics than the VKA warfarin in the ARISTOTLE trial. This study aims to quantify the potential societal effects of using apixaban instead of VKA in the German NVAF population from 2017 to 2030.

Methods: Using an existing Markov model and a dynamic population approach, we modelled the health benefits of apixaban in patients with NVAF compared to VKA therapy in the German population from 2017 to 2030.

Results: The results represent the extrapolated direct long-term health benefits of apixaban over VKA therapy for the German NVAF population. From 2017 until 2030, the use of apixaban instead of a VKA could avoid 52,185 major clinical events. This includes 15,383 non-fatal strokes or SEs, 22,483 non-fatal major bleeds, and 14,319 all-cause deaths, which correspond to 109,887 life years gained.

Conclusion: This study demonstrated that using apixaban instead of VKA for stroke prevention can lead to considerable reduction in cardiovascular events.

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KEYWORDS
Non-valvular atrial fibrillation; non-vitamin K antagonist; oral anticoagulants; stroke prevention

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice with an overall prevalence of around 2% in the general population [1]. Patients with AF are five times more likely to experience a stroke and have an increased risk of premature death [2]. AF causes at least 15–20% of all ischemic strokes, resulting in enormous personal, social, and economic cost [3]. This underlines the need for effective stroke prevention in patients with AF. For more than half a century, vitamin K antagonists (VKAs) like warfarin and phenprocoumon have been the primary medication for stroke prevention. Nevertheless, VKA therapy requires frequent monitoring, is limited by a narrow therapeutic range, and is associated with an increased risk of bleeding [2]. In light of such drawbacks, an alternative class of anticoagulant was sought, resulting in the development of non-vitamin K dependent oral anticoagulants (NOACs). The NOAC apixaban received EU-wide approval in November 2012 for stroke prevention in non-valvular AF (NVAF) patients with one or more risk factors for stroke [4].

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, which included 18,021 non-valvular atrial fibrillation (NVAF) patients, showed that apixaban was superior to warfarin in preventing stroke or systemic embolism (SE) and was associated with significant reduction in the risk of major bleeding and all-cause mortality compared to warfarin [5]. With respect to the primary efficacy endpoint (hemorrhagic or ischemic stroke or SE), apixaban demonstrated significant superiority over warfarin. The event rate was 1.27% per year in the apixaban group, as compared to 1.60% per year in the warfarin group (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.66–0.95, $p = 0.01$). The rate of major bleeding was 2.13% per year in the apixaban group compared to 3.09% per year in the warfarin group (HR 0.69, 95% CI 0.60–0.80, $p < 0.001$), and the rates of all-cause death were 3.52% and 3.94% per year, respectively (HR 0.89, 95% CI 0.80–0.99, $p = 0.047$). Similar results were observed in recently published real-world data studies comparing the VKAs warfarin and phenprocoumon to apixaban [6,7].

The present study extrapolates findings from the ARISTOTLE trial to NVAF patients in Germany for the years 2017 to 2030, with the aim of predicting the long-term clinical benefits of apixaban.

2. Methods and data

2.1. Target population

The determination of the AF target population was based on a study that examined the incidence and prevalence of AF using information from about 8.3 million statutory health-insured subjects in Germany, representing approximately 14% of the total Statutory Health Insurance (SHI) population [1]. This enables a

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reliable extrapolation of the age-specific prevalence and incidence rates to the entire SHI population. The proportion of the NVAF patients among the AF population was derived from German Competence Network on Atrial Fibrillation (AFNET) registry data [8]. The NVAF patient's need for anticoagulation therapy was defined by the presence of one or more risk factors for stroke as previously outlined by the Institute for Quality and Efficiency in Health Care's (IQWiG) benefit assessment of apixaban [9]. The detailed process of identifying the relevant population is shown in Figure 1.

2.2. Size of prevalent population

The derived target population was adjusted according to the expected market share of NOACs within the NVAF patient population (72%) in 2017 [10]. The market share of apixaban within NOACs is expected to reach 41% in 2017 [11]. The resulting number of prevalent NVAF patients receiving apixaban in 2017 is 314,638.

2.3. Size of incident population 2018 until 2030

The size of the incident cohorts from 2018 until 2030 is based on the age-specific incidence rates from Wilke et al. (2013) [1]. As the incidence rates of NVAF increase with age, the changes in the age structure of Germany's population were accounted for using demographic forecasts from the German Federal Statistical Office [12]. This resulted in increased sizes of incident NVAF cohorts over time. In addition, the size of the population was adjusted according to the market share of NOACs and of apixaban within the share of NOACs. Both are predicted to slightly increase from 72% to 75% and 41% to 50%, respectively, and stay constant afterward until 2030 [11]. These calculations led to an incidence model population ranging from 60,000 to 90,000 patients per year up to 2030.

2.4. Markov model

To model the long-term health benefits of apixaban over VKA therapy in Germany for the target NVAF population with regard to strokes or SEs, major bleeding, and all-cause mortality, we used a published Markov cohort simulation model and an open cohort model. The Markov model, which was developed with UK-specific input parameters, and its general assumptions have previously been presented in detail [13]. The Markov model was developed to compare clinical outcomes for an average NVAF patient in a scenario where apixaban is available versus another scenario where the anticoagulant treatment is limited to the VKA warfarin in the United Kingdom. The model simulates various health states that the patients can enter, remain in, or move ('transition') between as an approximation to the potential real-life patient journey. A patient cohort can enter the model or change the health state every six weeks.

It is assumed that during each cycle, patients may remain in their current health status or experience an event that would cause them to move to one subsequent state. The likelihood of each of these outcomes is known as its transition probability. These probabilities are built into the model and applied to the

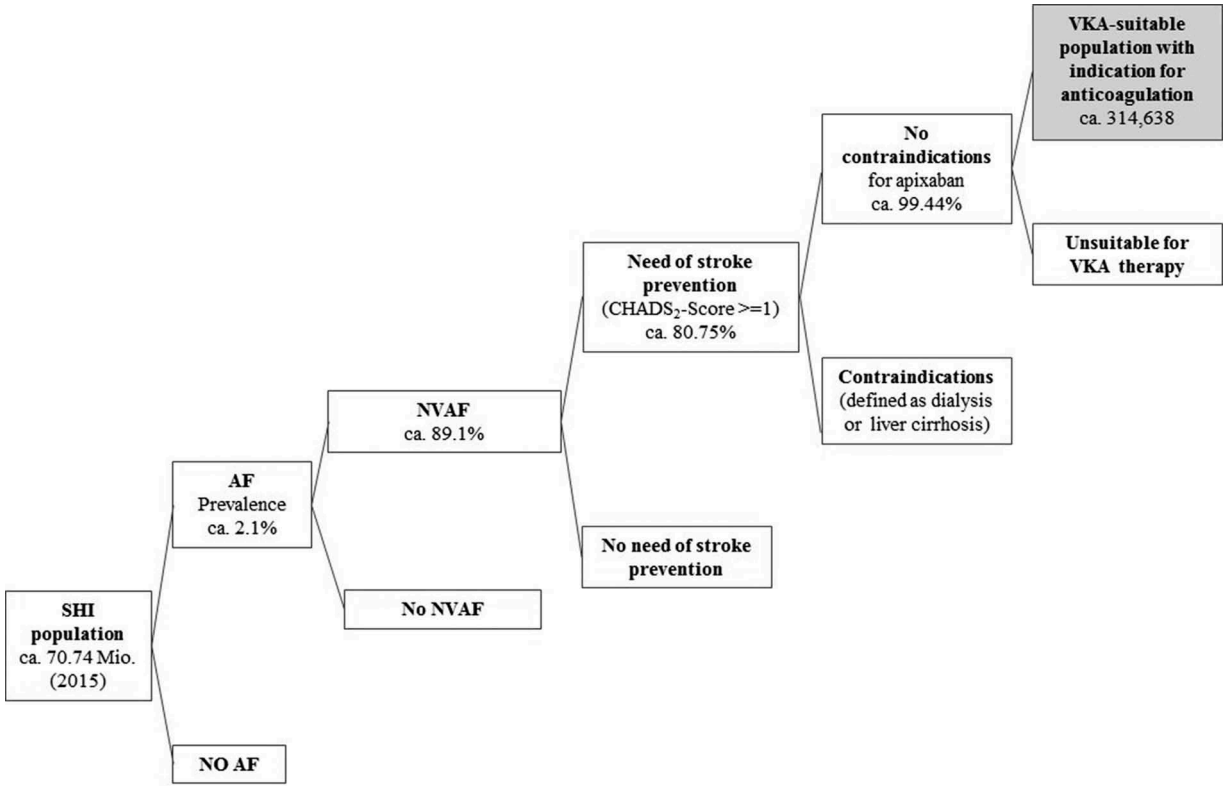

Figure 1. **Procedure for identifying the target population**.
Information about the relevant proportions derived from: AF Prevalence: [1]; NVAF [26]; Need for stroke prevention: weighted average from [27] and [28]; No contraindications for apixaban: [1, 28, 29]; VKA-suitable population: [26, 28, 30]. SHI = Statutory Health Insured; AF = Atrial Fibrillation; NVAF = Non-valvular Atrial Fibrillation; VKA = vitamin K antagonist.

defined population during each cycle to calculate how the patients would be distributed between different health states at the end of the cycle. This method allows the model to calculate the related health benefits that will have accumulated for the defined population as time has elapsed in the model. An abbreviated structure of the Markov model is depicted in Figure 2.

Structure of underlying Markov model transition probabilities and clinical event rates for the Markov model were mainly derived from the ARISTOTLE trial, which compared the quality of anticoagulation between apixaban and the VKA warfarin [5]. However, to ensure the validity of the results for the German setting and to account for the analysis time frame, several adjustments to the original model and patient's baseline characteristics were made. These adjustments are summarized in Table 1. Most importantly, we replaced the underlying baseline mortality risk from UK data with Germany-specific mortality rates and the time in therapeutic range (TTR) from ARISTOTLE with German-specific TTR data [14,15]. The TTR describes the quality of anticoagulation control by quantifying the percentage of time a patient spends at a suitable level of anticoagulation (international normalized ratio of 2–3). Only a high TTR has been associated with a positive benefit-risk-ratio of the VKA therapy [16]. Population mortality risks were adjusted for the increased mortality in AF patients [17]. It was assumed that the relative mortality risks and the risks for relevant clinical events used in the existing UK model would also apply to the German population. The categorization of relevant clinical endpoints followed the major efficacy and safety outcomes of the ARISTOTLE trial [5]. Furthermore, baseline mortality was assumed to be equal between both treatments, while mortality due to a reduction in clinical events is not. This means that only deaths directly related to both treatments were considered when estimating the long-term health benefits.

A list of the most relevant clinical input parameters for our analysis used in the underlying Markov model can be found in Appendix A.

Phenprocoumon represents the most commonly prescribed VKA in Germany [18,19], while all clinical studies are conducted with the VKA warfarin. German authorities considered phenprocoumon to be equivalent to warfarin with respect to the observed anticoagulant effects in phase III trials [9]. Therefore, it was assumed that the results of the warfarin controlled ARISTOTLE trial would also apply to the comparison of apixaban and phenprocoumon [31].

2.5. Open cohort model

The adjusted Markov model estimates the occurrence of clinical events for *one* average German NVAF patient over time. To extrapolate the results of ARISTOTLE to the *entire* German NVAF population, an open cohort model for simulation of the number of clinical events with and without the availability of apixaban from 2017 until 2030 was developed. In contrast to the Markov model,

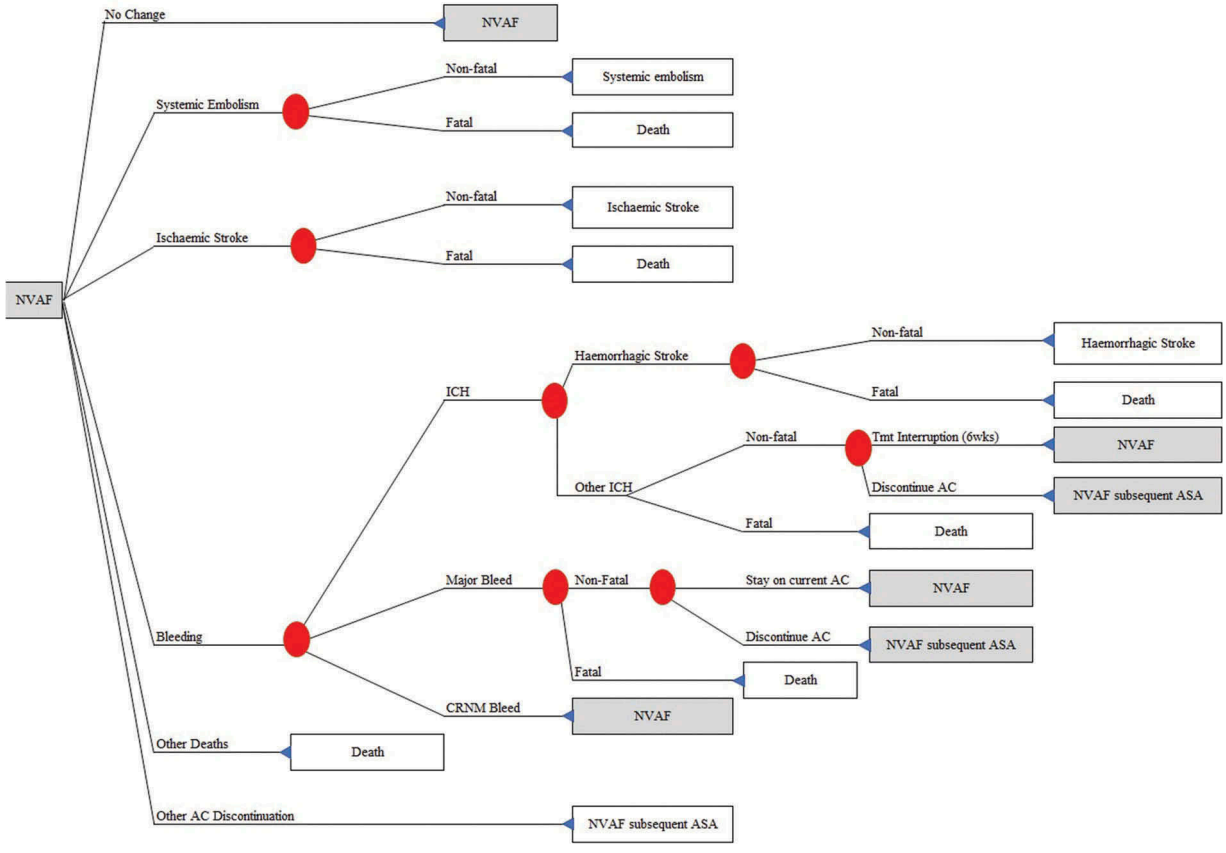

Figure 2. Structure of underlying Markov model.
All patients remain in the 'NVAF' state until stroke, bleed, SE, MI, treatment discontinuation, or death occurs, whereby the transition probabilities of these events depend on the treatment. Triangles show the health state the patient enters after an event. Health states not colored are permanent health states, the grey colored health states are temporary health states for a maximum period of 6 weeks before the patients return to the prior or subsequent health state. [13]

Table 1. Cost-effectiveness model for UK and adjustments for the German setting.

	Original UK model	Source	Adjusted model for Germany	Source
Average Age	70.0	[5]	74.6	[1,9]
Gender distribution	64.7%	[5]	62.2%	[1]
% males	35.3%		37.3%	
% females				
Background Mortality	From ARISTOTLE	[5,25]	German life tables	[14]
until 1.8 years	UK life tables		German life tables	
Average TTR	62.0%	[5,13]	67.6%	[15]
Time frame	Lifetime		2017 until 2030 (up to 122 6-week cycles)	
Relevant clinical endpoints	Ischemic and hemorrhagic stroke, SEs, major bleeding, clinical relevant bleeds, myocardial infarction, all-cause death [5].		Stroke (ischemic and hemorrhagic) or SEs, major bleeding, all-cause death	

where one cohort is followed over the remaining lifetime, an open cohort model allows new patient cohorts to enter every model cycle. In cycle 1, the prevalent population defined above enters the model (n = 314,638). In each following cycle, a newly incident cohort of NVAF patients enters the population model (n = 7,500–11,000 per 6-week cycle).

Mapping the years from 2017 to 2030 using six-week cycles yields 122 model cycles. Annual incident cohorts were evenly distributed into the eight to nine model cycles per year, leading to 122 different cohorts entering the model over the predefined time frame.

The probabilities for stroke or SE, major bleeding, or all-cause death within one patient cohort over time were directly extracted from the Markov model. Because of the lack of robust estimates to define prospective development of patient characteristics and overall risk for clinical events, it was assumed that these probabilities remain constant between cohorts over time. In each cycle, the event probabilities are multiplied with the size of all included cohorts. This led to the total number of strokes or SEs, major bleeding and all-cause deaths for every 6-week period for the scenario with apixaban or the scenario with VKA. The graphical summary of the dynamic population model is presented in Figure 3.

For estimation of the number of life years gained due to the use of apixaban instead of VKA through to 2030, the difference in time spent in the model for the entire patient population between the two scenarios was calculated. Patients who died over the course of the simulation left the model, and therefore the difference in time spent in the model equals the number of predicted gained life years.

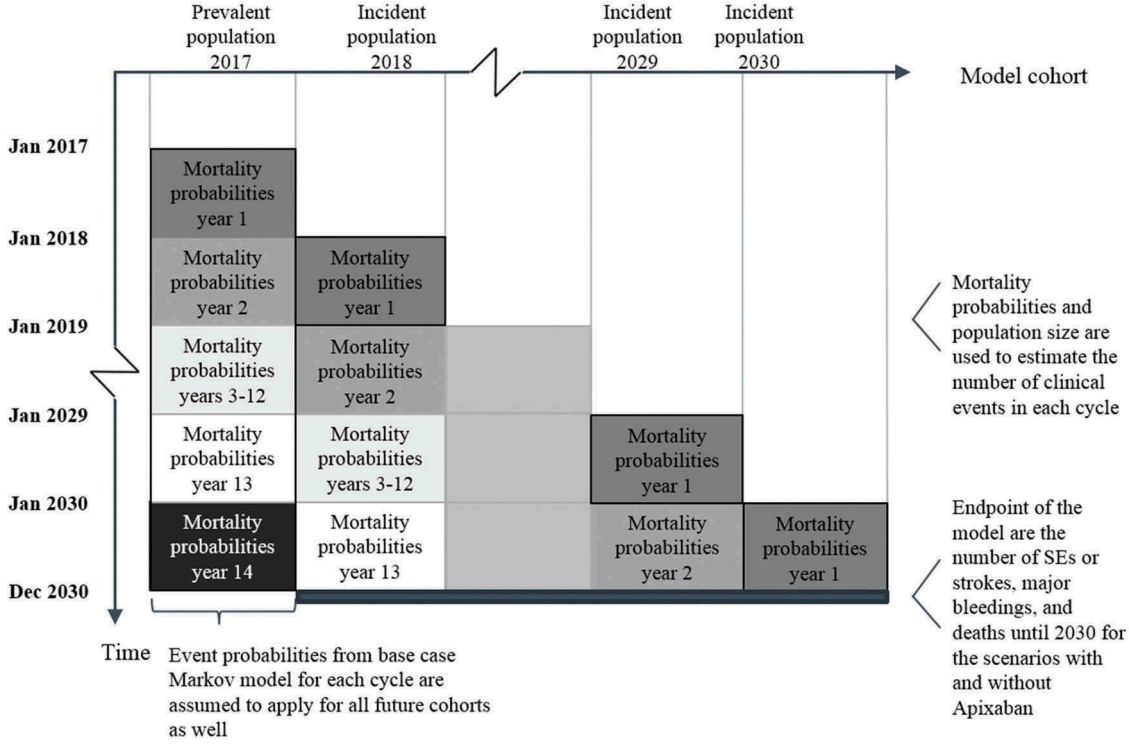

Figure 3. **Conceptual approach of the dynamic population model for the years 2017 to 2030.**
Event and transition probabilities are stacked on to the different cohorts. Each color represents the entire unique set of probabilities used for a specific cycle in the underlying Markov model for each of the incident cohorts entering the model. The probability of an event (e.g. stroke) for a patient of the prevalent cohort entering the model in 2017 in cycle 1 (or year 1 in figure 3) is the same as for a patient in the incident cohort entering the model in 2030. Source: Illustration based on [31]. * To increase the clarity of the figure for the dynamic population model, annual cycles instead of 6-week cycles are presented.

3. Results

3.1. Population size

The size of the modelled apixaban population steadily increases from 314,638 patients in early 2017 to 780,583 patients in 2030. The population increases due to the high incidence rate of NVAF in older age groups, the demographic change in Germany, and the rising use of NOACs including apixaban for anticoagulation.

3.2. Predicted differences in clinical events

Compared to anticoagulation with VKA, the Markov model and dynamic population approach predicted that apixaban would prevent an additional 52,185 major clinical events from 2017 until 2030, which equals 4,349 major clinical events per year. This included 15,383 non-fatal strokes or SEs, 22,483 non-fatal major bleeds, and 14,319 all-cause deaths. In this analysis, hemorrhagic strokes were not considered as major bleeding to avoid over estimating the clinical benefit of apixaban over VKA. The predicted deaths mainly originated from the differing probabilities of suffering from fatal strokes or SEs and major bleeds. The prevented all-cause deaths correspond to an estimated 109,887 gained life years in the German NVAF population. This corresponds to 0.7 years of life per patient treated in the model. However, the number of gained life years might be underestimated as confined time frames were used and patients were not followed beyond the year 2030. The predicted differences in development of clinical events between apixaban and VKA therapy between 2017 and 2030 are depicted in Figure 4.

The shape of the curves shown in Figure 4 is heavily affected by the large cohort of prevalent patients entering the model in 2017. In later years, fewer events in this population are prevented, as most of patients either already discontinued apixaban and switched to VKA therapy, discontinued anticoagulation altogether, or died. In the first years of the model, a similar trend is predicted for the number of deaths. However, in later years of the model, the number of predicted prevented deaths declines. This is a result of the difference in size between the prevalent cohort and the incident cohorts: for patients taking apixaban more event-related deaths are prevented in the prevalent population prolonging survival in a larger cohort compared to VKA therapy. In later years, due to the high age of the once prevalent population of 2017, the background mortality of these surviving patients is 0.02 per 6-week cyle, leading to the diminishing trend of avoided deaths.

4. Discussion

We demonstrated that in the years 2017 until 2030, apixaban therapy compared to VKA therapy may prevent 15,383 non-fatal strokes or SEs, 22,483 non-fatal major bleeds, and 14,319 deaths, which may translate into 109,887 gained life years for the German NVAF patient population.

Although direct comparisons are not possible due to the differences in the models and modelling assumptions, our calculation is in general agreement with a previously reported modelling analysis [20]. Pisters et al. utilized data from the

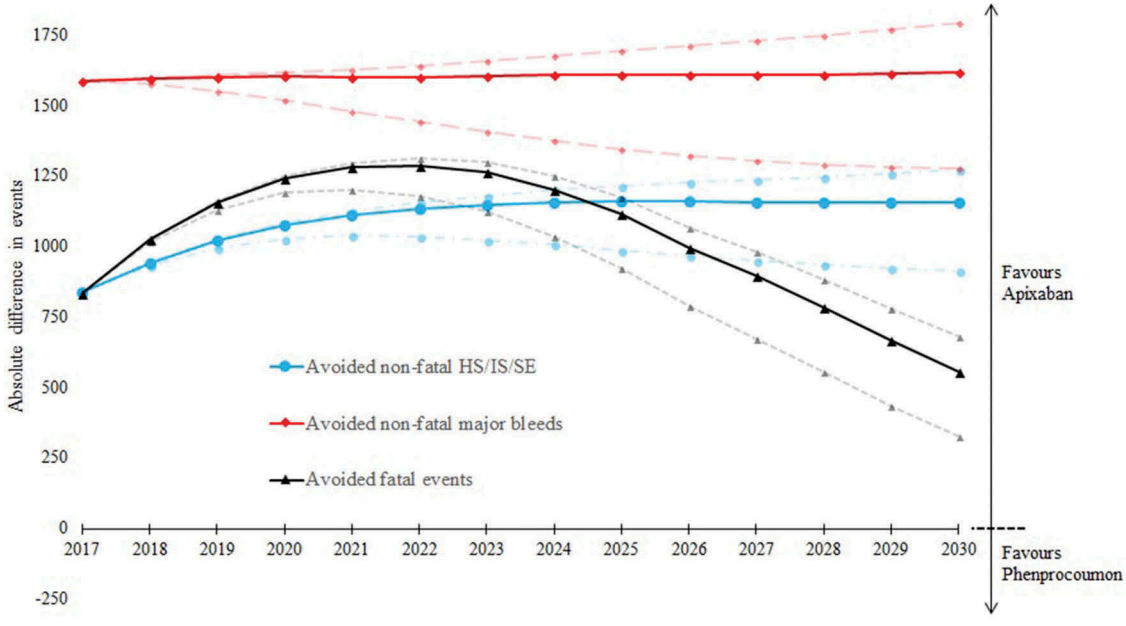

Figure 4. Difference in clinical events for the apixaban scenario compared to the VKA scenario.
Similar to the steady increase of the population size, the number of strokes or SEs as well as major bleeds per year would slightly increase over time. Dashed lines represent the upper and lower boundaries of the predicted market share of apixaban and VKA therapy. Bold line depicts the base case scenario. Positive values mean that fewer events occurred in the scenario with apixaban then with VKA. The upper boundary depicts a scenario in which the share of NOACs in NVAF patients would rise to 90% whereby the share of apixaban within the NOACs increases from 41% in 2017 up to 50% until 2022. The total number of predicted avoided clinical events in this scenario would be 16,027 non-fatal strokes or SEs, 23,483 major bleeds, and 15,012 deaths. In the lower boundary, the share of NOACs in NVAF patients and the share of apixaban within NOACs remain on their 2017 values (72% and 41%, respectively) until 2030. This would lead to 13,597 avoided strokes or SEs, 19,779 prevented major bleeds, and 12,429 avoided deaths.

EuroHeart Survey on AF and event rates from apixaban trials to model the potential net clinical benefit per year for apixaban in the European population. The authors predicted that the use of apixaban instead of VKA therapy for the NVAF population in Europe could result in the prevention of 64,573 clinical events (major bleeds and thromboembolisms) and deaths per year [20]. With Germany accounting for roughly 10% of Europe's population, our calculation of 4,349 prevented clinical events and all-cause deaths per year are generally in line with the computed results from Pisters et al. [20].

With 50% of stroke patients experiencing significant functional deficits, 50% of the intracranial bleeds causing at least minor disability, and anticoagulation-related bleeding events reducing significantly the quality of life of the patient, our model helps to illustrate the potential medical impact of the utilization of apixaban compared to VKA over time [21–23].

Considering the functional impairment and long-term consequences associated with the estimated number of avoided events in Germany, the findings implicate that apixaban has a significant clinical impact on the German NVAF population.

5. Limitations

Although this study was conducted using robust and widely used data as well as established methods, the results have to be interpreted in light of the following limitations.

We used a previously published Markov model for our analysis [13]. In addition to the already published limitations, we had to make the following assumptions in order to adapt the model for our purpose: Because of the lack of predictive data, we assumed that the transition probabilities or event risks in the Markov model remain constant for all cohorts entering the model from 2017 until 2030. This may not necessarily be the case since the general stroke risk or the risk for major bleeds could be reduced in the future by factors such as general changes in lifestyle or improved TTR for VKA patients. Furthermore, we may have underestimated the number of gained life years as we used a confined time frame and did not follow patients over the course of their lifetime beyond the year 2030.

The predicted numbers of prevented clinical events are highly depending on the size of the model population. For our analysis, the size of the NVAF population in Germany was calculated based on AF prevalence and incidence data from 2009 [1]. However, these data may have underestimated the size of the current and future AF patient population due to narrow inclusion criteria and the rapidly evolving technologies for detection of AF [24].

6. Conclusion

Effective stroke prevention in NVAF patients has the potential to not only reduce stroke-related deaths but also prevent stroke-related disability, which imposes an enormous burden on patients, their social environment, and the SHI system.

Therefore, using an existing Markov model and a dynamic population approach, we modelled the potential health benefits of apixaban in patients with NVAF compared to VKA therapy in the German population from 2017 to 2030. We determined the population size according to a German survey, specific inclusion and exclusion criteria, and the predicted market share of apixaban. The results represent the extrapolated direct long-term health benefits of apixaban over VKA therapy based on the results of the ARISTOTLE trial and an existing Markov model. From 2017 until 2030, the use of apixaban instead of a VKA could prevent 52,185 major clinical events. This includes 15,383 non-fatal strokes or SEs, 22,483 non-fatal major bleeds, and 14,319 deaths, which correspond to 109,887 gained life years. The presented findings illustrate the potential health benefit of apixaban over VKA for an increasing NVAF population in Germany. By providing these more tangible figures of the potential benefit of apixaban, our analysis may help physicians to make informed decisions in clinical practice.

Key issues

- This modelling approach demonstrated that using apixaban instead of VKA for stroke prevention in non-valvular atrial fibrillation can lead to considerable reduction of cardiovascular events in the German population for the years 2017 to 2030.
- The results of the clinical trial ARISTOTLE, an existing cost-effectiveness model of apixaban, and a dynamic population model were combined to model these effects.
- More specifically, the use of apixaban instead of a VKA could avoid 52,185 major clinical events. This includes 15,383 non-fatal strokes or SEs, 22,483 non-fatal major bleeds, and 14,319 all-cause deaths, which correspond to 109,887 life years gained.

Author Contributions

Sebastian Himmler and Malina Mueller contributed equally to the study design, data analysis and interpretation, to the manuscript writing and to final manuscript review. Dennis Ostwald contributed to the study design and revising it critically for intellectual content. Ahmed Seddik was involved in revising it critically for intellectual content. Eva Hradetzky and Edin Basic have supervised data collection and statistical analyses and participated in drafting the article, revising it critically and for intellectual content. All authors read and approved the final manuscript.

Declaration of Interest

S Himmler, M Müller, A Seddik, are employees of WifOR, an independent economic research institute in Darmstadt. D Ostwald is the CEO and founder of WifOR. Dr. Hradetzky and Dr. Basic are employees of Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

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Appendix A

CHADS2 distribution and clinical event rates per 100 patient years as used by Dorian et al. (2014) [13]:

	VKA suitable	VKA unsuitable	
CHADS2 distribution in population			
CHADS2: 0–1	34.0%	38.2%	
CHADS2: 2	35.8%	35.2%	
CHADS2: 3–6	30.2%	26.6%	
	Apixaban	Warfarin	Hazard ratio
Clinical event rates			
Average stroke rate*	0.98	1.09	1.09
% of fatal stroke	18%	15%	
Intracranial hemorrhage rate	0.33	0.80	2.38
% of hemorrhagic strokes among intracranial hemorrhage	77%	64%	
% of fatal hemorrhagic stroke	35%	53%	
Other major bleed rate	1.79	2.27	1.27
Systemic embolism rate	0.09	0.10	1.11
Case-fatality rates after event			
Other intracranial hemorrhage	13.0%		
Other major bleed	2.0%		
Systemic embolism	9.4%		

*Stroke rate depends on CHADS2-score; For sources and more details, please refer to Dorian et al. (2014) [13].