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Budget and health impact of switching eligible patients with atrial fibrillation to lower- dose dabigatran

Tanja Fens [a,b], Lisa de Jong [a,b], Bregt Kappelhoff [c], Cornelis Boersma [a,b,d] and Maarten J. Postma [a,b,d,e,f,g]

[a]Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [b]Health-Ecore Ltd, Groningen/Zeist, The Netherlands; [c]Department of Market Access & Healthcare Affaires, Boehringer Ingelheim bv, Amsterdam, The Netherlands; [d]Department of Management Sciences, Open University, Heerlen, The Netherlands; [e]Department of Economics, Econometrics & Finance, Faculty of Economics & Business, University of Groningen, Groningen, The Netherlands; [f]Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [g]Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia

ABSTRACT

Objectives: To assess the comparative budget and health impact of lower-dose dabigatran versus reduced doses of apixaban and rivaroxaban in atrial fibrillation (AF) patients eligible for a lower-/reduced-dose due to individual patient characteristics in the Netherlands.

Methods: A budget impact model was developed in accordance with ISPOR guidelines. A 3-year-time horizon was considered, and analyses were conducted from a Dutch healthcare payer's perspective. The model applies published data to local AF-epidemiology, allowing calculations to estimate clinical events (strokes and haemorrhages) and costs. The analyses were based on real-world outcomes from patients with AF receiving a first direct oral anticoagulant (DOAC) prescription for low-dose dabigatran (110 mg) and a reduced dose of apixaban (2.5 mg) or rivaroxaban (15 mg). Two situations of switching treatments from one to another DOAC were modelled: switching from apixaban to dabigatran and from rivaroxaban to dabigatran. Base case results were given as savings per 100 patient-year, per total Dutch population, and events avoided. A univariate sensitivity analysis was conducted to explore the uncertainty around epidemiological and event costs input data. Scenario analyses were performed to estimate the effect of different market shares and potential price reductions due to future patent expiry for the total real-world population from the Netherlands.

Results: The 3-years outcomes of switching patients eligible for a lower-/reduced-dose due to individual patient characteristics from apixaban or rivaroxaban to dabigatran resulted in cost savings estimated at €157 or €72 thousand per 100 patient-years, respectively, or €146 million per total Dutch population. Looking into the clinical events, dabigatran reflected the lowest number of mortalities, ischemic strokes, major bleeding, non-major bleeding, and haemorrhagic stroke compared to apixaban and rivaroxaban. The sensitivity analysis consistently reflected cost savings, with the ischeamic stroke events having the biggest impact. Accounting for the Dutch situation, both scenarios showed total savings ranging from €45 to €229 million over 3 years.

Conclusions: Switching eligible AF-patients from reduced-dose apixaban or rivaroxaban to lower-dose dabigatran has the potential to reduce healthcare payer's budget expenditures and provide health gains. Cost savings can potentially be further enhanced by market share adjustments and further price reductions.

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Introduction

Atrial fibrillation (AF) is 'a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction, which Electro cardiographic characteristics include irregular R-R intervals (when atrioventricular conduction is not impaired), absence of distinct repeating P waves, and irregular atrial activations' [1]. AF is the most common cardiac arrhythmia in adults, affecting up to 1% of the population worldwide [2,3], with North America and Europe as leading regions concerning numbers patients [4]. In Europe, a growing trend exists in AF patients, indicating that from 2000 to 2060, AF-cases among adults above 55-years-old will be doubled [5]. In the Netherlands, this corresponds to an increase of AF-prevalence among the Dutch population from 1.6% to 3.2%, particularly among populations over 75-years-old [5].

The available treatments for stroke prevention in AF patients include the well-established *vitamin K anta*

CONTACT Tanja Fens t.fens@rug.nl Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen 9713 GZ, The Netherlands

gonists (VKA) (i.e., warfarin, phenprocoumon, or acenocoumarol), the *direct oral anticoagulants* (DOAC) (i.e., dabigatran etexilate, rivaroxaban, apixaban, and edoxaban) or combinations [1]. The first are used for decades, relevantly reducing the stroke risk [6], while requiring continuous INR monitoring. As warfarin is a mixture of *R*- and S-warfarin enantiomers, metabolized by different CYP P450 cytochromes, interaction with other medications may easily alter warfarin metabolism and influence its efficacy as well as potential interactions with food may emerge [7]. The DOACs were introduced to overcome these limitations of warfarin, as well as further enhance efficacy and safety. Dabigatran etexilate [8] acts as direct thrombin inhibitor, while rivaroxaban [9], apixaban [10] and edoxaban [11] are direct factor Xa inhibitors. DOACs are less likely to interact with other medications and food, are more convenient for patients to use in the absence of requiring continuous monitoring and report potential enhanced efficacy, and safety [12]. Available lower-/reduced-dose regimens for DOACs provide dosing flexibility. Dose reduction criteria for dabigatran (110 mg twice a day) include elderly patients (>80 years), concomitant use of verapamil or increased bleeding risk; for apixaban (2.5 mg twice a day), at least two of these criteria, elderly patients (>80 years), body weight ≤60 kg or serum creatinine ≥1.5 mg/dL; for rivaroxaban (15 mg once a day), when the estimated glomerular filtration rate (eGFR) is 15–49 ml/min or for edoxaban (30 mg once a day) if any of these criteria is fulfilled, 15–50 ml/min eGFR, body weight ≤60 kg, or concomitant use of dronedarone, ciclosporin, erythromycin or ketoconazole [1]. Particularly, lower-dose dabigatran 110 mg has been thoroughly studied in prospective clinical trials on the use of DOACs in patients with AF [13,14].

The current European Society of Cardiology (ESC) guidelines for the diagnosis and management of atrial fibrillation endorse DOACs as the preferred option in the treatment of AF-patients based on their efficacy, safety, and ease of use [1]. Besides the recommendations of the existing guidelines, an inappropriate dosing of DOACs in treating AF patients is not uncommon, highlighting the need for proper dosing [1,15]. Underdosing with DOACs may lead to an increased risk of stroke while overdosing potentially leads to major bleeding [15]. The availability of DOACs in lower-/reduced-doses was shown to be more suitable for patients with increased risk of bleeding [16]. An observational cohort study showed that the lower-dose dabigatran has lower rates of bleeding compared to the reduced doses of apixaban and rivaroxaban [17]. Such safety advantages might be embraced with a potential switch within the DOACs class and lead to possible cost savings. Moreover, comparing the DOACs with each other can provide information for making the right treatment choice. Existing economic analyses [18–21] show favourable cost-effectiveness or cost savings by switching from VKA to DOAC-treatments or from one DOAC to another (e.g., rivaroxaban to dabigatran) [22,23] for AF-patients using standard (higher) doses. While the standard (higher) doses of AF-treatments with DOACs are well studied [18], the costs and health effects of lower-/reduced-dose DOACs still largely remain unknown.

The objective of this study was to assess the comparative budget and health impact of lower-dose dabigatran versus reduced doses of apixaban and rivaroxaban in AF patients eligible for a lower-/reduced-dose due to individual patient characteristics in the Netherlands.

Methods

Study design

An Excel-based cost-calculator model was designed to perform a budget impact analysis (BIA) in accordance with the Dutch budget impact calculation recommendation in the guideline for economic evaluations in healthcare and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force report Budget Impact Analysis-Principles of good Practice [24,25]. In brief, the items involve information about objectives, epidemiology and management of health problem, clinical impact, economic impact, study design, patient population, intervention mix, time horizon, perspective, analytic framework, input data, data sources, analyses, uncertainty, budget period resource use, cost and clinical impact, uncertainty and scenario analyses, main conclusion and limitations. Items within these ISPOR guidelines are given as supplemental material. The model allows calculations based on clinical event rates and costs, as well as medication costs when switching treatments from one DOAC to another (i.e., from apixaban or rivaroxaban to dabigatran) per 100 patients year and further per Dutch population as a whole.

Patient population

This study considered non-valvular AF-patients eligible for lower-dose treatment of DOACs. Patients with prescriptions for standard-dose oral anticoagulants were not considered. The population data was taken from nationally published data [26–28], and a Danish real-world study on patients (nationwide population) with non-valvular atrial fibrillation receiving a first prescription for a lower-/reduced-dose of dabigatran, apixaban, or rivaroxaban [17]. In the study [17], inverse

probability treatment weighting was applied by calculating propensity scores for the treatment alternatives across the study population. Estimations of the patient population in Dutch settings are given in Figure 1. We identified the users of the anticoagulants given with the following ATC codes: B01AA, B01AE, and B01AF in 3 years (2023, 2024, and 2025), accounting for population growth through the years [29]. 80% of this population were with AF-indication, of which 72% (mean value estimate over 10 years from 2017 to 2026) were DOACs users [28,30]. From those, 13% were B01AE07 (dabigatran), 36% B01AF02 (apixaban), 40% B01AF01 (rivaroxaban), and 11% B01AF03 (edoxaban), based on the same average over 10 years, and assumed to be stable over the years [30]. Finally, we accounted for the proportion of lower-/reduced-dose users for each DOAC: 52% of dabigatran users, 30% of apixaban users, and 25% of rivaroxaban users [31]. Highest percentage of lower-dose users of dabigatran in the clinical practice in the Netherlands might be owed to various factors such as 1) individual patient characteristics, 2) having officially registered lower-dose form, 3) availability of a specific antidot (idarucizumab) and 4) better evidence for its use delivered from the existing clinical trials [8,32].

Intervention mix

The model concerns interventions with DOACs given for the treatment of stroke prophylaxis for AF. We considered specifically indicated lower or reduced dose DOAC formulations such as dabigatran 110 mg, twice-a-day, apixaban 2.5 mg twice-a-day, or rivaroxaban 15 mg once-a-day.

In the base case, where we present outcomes per 100 patient-year, two situations were observed as a new intervention mix. First, switching 100% of the patients on treatment with reduced-dose apixaban to lower-dose dabigatran, and second, switching 100% of treatment with reduced-dose rivaroxaban to lower-dose dabigatran. When expressing the results per total Dutch population, the new intervention mix accounted for switching 100% of the patients on treatment with reduced-dose apixaban and rivaroxaban to lower-dose dabigatran.

In scenario analyses, we present outcomes per Dutch population. As edoxaban was registered later than the other three DOACs, real-world data about the clinical events on this DOAC are still scarce, and edoxaban was excluded from our current analysis. The new intervention mix reflected low uptake (15%, 30%, 45%) and high uptake (30%, 60%, 90%), switching scenarios in years one, two, and three accordingly. The number of patients for the current and new intervention mix in scenario analyses is given in the Appendix (Table A1).

Time horizon and perspective

A 3-year-time horizon was applied, in line with the Dutch budget impact calculation recommendation in the guideline for economic evaluations in healthcare

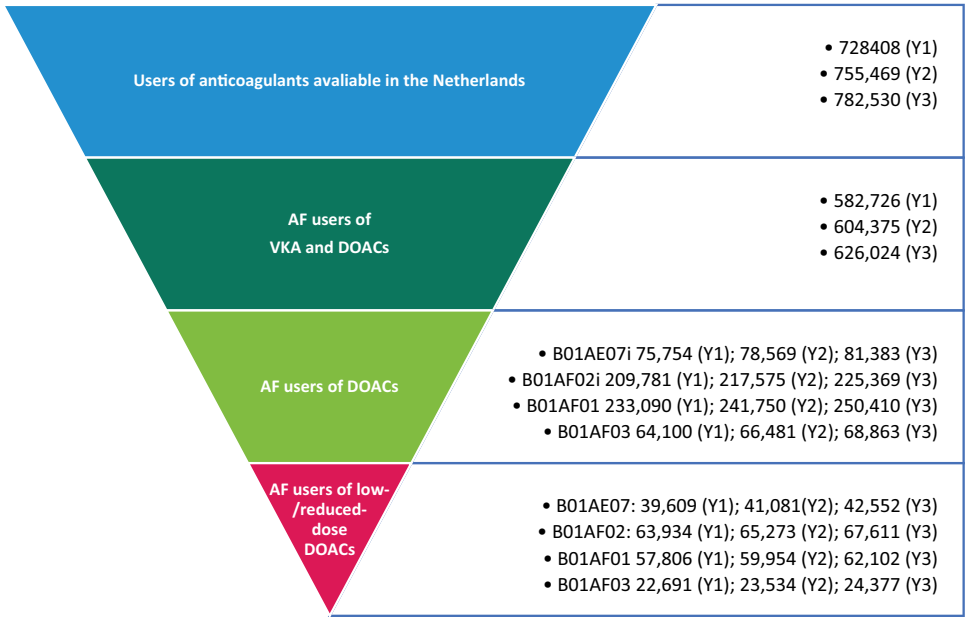

Figure 1. Patient population estimations in Dutch settings.

Note: DOAC – direct oral anticoagulant; VKA – Vitamin K-antagonists; ATC code – Anatomical Therapeutic Chemical code; B01AE07 (dabigatran); B01AF02 (apixaban); B01AF01 (rivaroxaban); B01AF03 (edoxaban).

*edoxaban is not included in this analysis.

[33] and the ISPOR Task Force report Budget Impact Analysis-Principles of good Practice [24,25]. Results were given per year (2023, 2024, and 2025) and aggregated after the 3 years of intervention, with no discounting applied [24,25].

The analyses were conducted from a Dutch healthcare payer's perspective. Only direct healthcare costs were included (notably, clinical event and medication costs), as recommended by the guidelines [24,25,33].

Analytic framework description

The analytic framework is explained through a model flow diagram (Figure 2). The eligible population for entering the model included the lower-/reduced-dose DOAC users based on individual patient characteristics. These populations were accounted for in a situation of switching all reduced-dose apixaban users to lower-dose dabigatran users or a situation of switching all reduced-dose rivaroxaban users to lower-dose dabigatran users. These situations could (partly) occur simultaneously and therefore results of both situations can potentially be (partly) aggregated, as explored in a scenario analysis.

Clinical events included in the model were ischaemic strokes, haemorrhagic stroke, major bleeding, non-major bleeding, and systemic embolism. The event risks in the first year differ from the event risks in the second and third year (generally decreasing from first to subsequent years) [17]. Mortality differences between DOACs were not included as

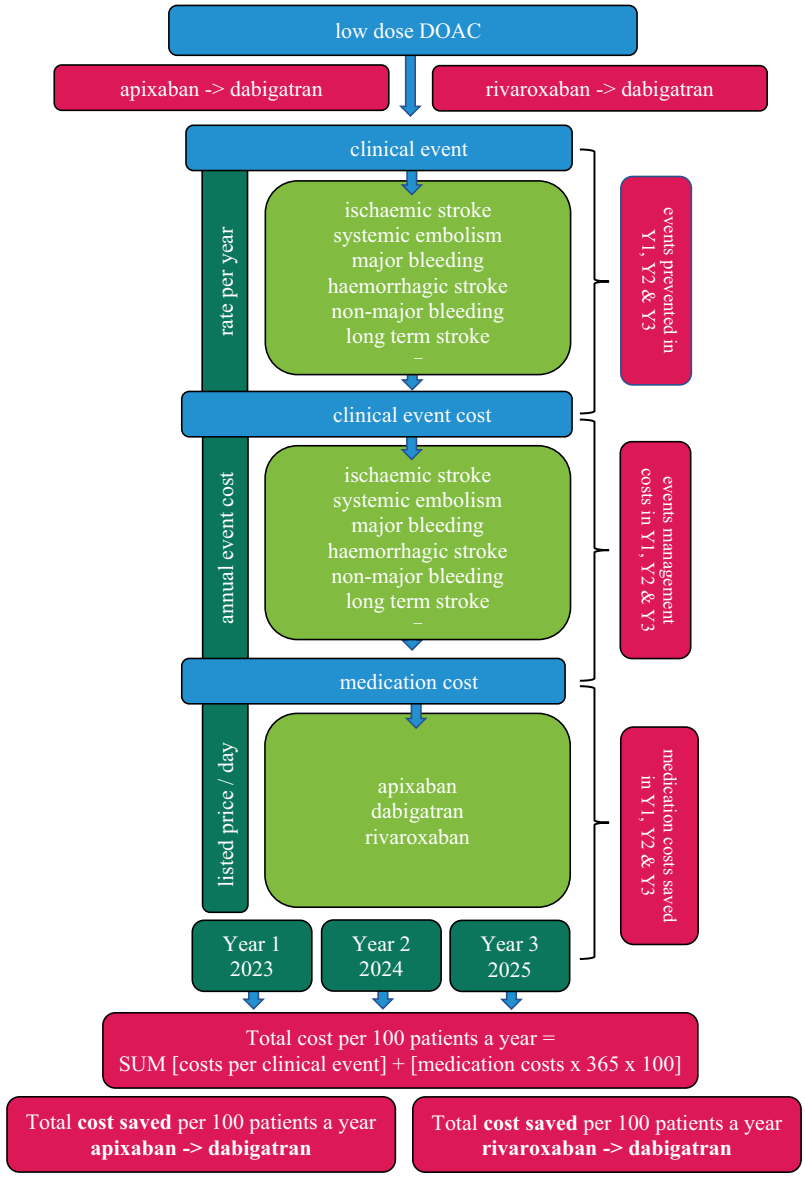

Figure 2. Model flow diagram.

Note: DOACs – direct oral anticoagulants; Y – year.

*To be noted that long-term stroke is a post-stroke state that we account for costs effects.

basis in the event-cost calculations per 100 patient-year to avoid the artefact of differences in budget requirements (less patients = less costs) [17]. The impact on mortality was, however, included when reflecting calculations per Dutch population and the clinical/health impact. The model accounts for two types of cost: cost per clinical event and medication cost. The costs per clinical event and medication cost were assumed to be the same through the 3-year-time horizon. The final model outcomes reflect budget impact per 100 patient-year after one, after two, and after 3 years (2023–2025) in total. In addition to this, we present the cost and health impact per Dutch population.

Input data and data sources

The model input data was taken from published national sources identified through a literature search in PubMed using the key words 'Dutch OR Netherlands' and 'DOAC OR NOAC' (see the search results in the supplemental material), related citations, as well as Dutch health-related sources available online (Table 1). Clinical event costs were taken from published economic analyses on DOACs [19,39,40], and the medication costs were based on official list prices [36–38]. All the costs were inflated (using the CCEMG – EPPI-Centre Cost Converter v.1.4.) to the 2023 cost year [41]. As no published data from real-world evidence (RWE) study on DOACs for the Netherlands is available (although there are ongoing RWE studies) [42], as mentioned, annual rates for clinical events were taken from a Danish national study [17]. The market shares per DOAC were taken from national sources reflecting real-world utilisation of the DOACs in the Netherlands [43].

Analyses

The BIA-model was used to calculate the cost and health impact of future treatment mix with increased use of lower-dose dabigatran. Base case-, scenario and sensitivity- and analyses were performed, reflecting the relation between annual event rates, event costs, and medication costs. The clinical outcomes occurrence from each product and the potential number of events prevented were given for the Dutch situation. Here, we also accounted for the effect of mortality. Comparison analyses (difference of two proportions) were used to show statistical significance comparing avoided mortality cases when using the treatments.

Sensitivity and scenario analyses

Univariate sensitivity analyses were performed to identify which epidemiological and event costs input parameter will

Table 1. BIA-model input data.

Dutch population	Population size and market *shares*						Ref.
-Population with AF	80% = 582,726 (Y1); = 604,375 (Y2); = 626,024 (Y3);						[30]
-population using DOACs*	72% = 495228						[28]
	Rate per 100 patient/year						
	dabigatran		apixaban		rivaroxaban		
Clinical events	Y1	NY	Y1	NY	Y1	NY	[17]
IS	3.17	2.19	4.42[§]	3.27	3.38	2.11	
SE	0.14	0.16	0.36	0.18	0.15	0.07	
MB	3.31	2.43	4.14	3.74	4.59	3.56	
HS	0.28	0.31	0.38	0.33	0.43	0.65	
LTS	0.78	0.58	0.98	0.78	1.36	1.26	
NMB	10.50	8.22	15.53	14.40	15.81	11.8	
Costs							
Clinical event cost	Costs per event (€, 2023)						
IS	€ 20,983						[34]
SE	€ 6,100						[35]
MB	€ 5,640						[35]
HS	€ 20,983						[34]
LTS	€ 4,406						[34]
NMB	€ 35						[35]
Medication costs	Costs per day (€, 2023)						
apixaban 2.5 mg	€ 2.24						[36]
dabigatran 110 mg	€ 1.88						[37]
rivaroxaban 15 mg	€ 2.15						[38]

Note: AF – atrial fibrillation; DOACs – direct oral anticoagulants; IS – ischaemic stroke; SE – systemic embolism; MB – major bleeding; HS – haemorrhagic stroke; LTS – long-term stroke; NMB – non-major bleeding; S – scenario; Y – year.
*Mean value estimate over 10 years from 2017–2026, based on the same average over 10 years, and assumed to be stable over the years.
annual rate in year 2 or 3 = (risk after 2.5 years − 0.4 x risk after 1 year)/0.6.
SLTS costs in Y2&Y3= LTS costs x [(event rate IS in Y1+event rate HS in Y1) + (event rate IS in NY + event rate HS in NY)].

have the biggest impact on the budget impact for the two situations given in the base case per 100 patient-year. The effect of each individual event rate and event costs on the total budget impact was explored while holding the remaining parameters constant. Parameters were varied one by one for ±25% of their base case value [44]. Outcomes were presented in tornado diagrams.

The economic impact was explored in two scenario analyses, given per Dutch population. The first scenario looked into the effect of the market share of DOACs used in the Netherlands in the years 2023, 2024, and 2025. Low- and high-market share uptake switches were explored. Unlike the base case scenario, where we switch 100% of one treatment to another, here we switch simultaneously from two treatments to one, with a gradually increasing percentage each successive year. The second scenario looked into the effect of price changes when using prices after patent expiration for all three products analysed. The price adjustments were accounting for estimate/factor in the first (0.54), second (0.39), and third (0.30) year after patent expiry [45].

Results

Economic impact

The cost-savings per 100 patient years were estimated at €157 or €72 thousand for 3 years for the switch of reduced dose apixaban and rivaroxaban to lower-dose dabigatran, respectively. The budget impact is mostly driven by event costs. Disintegrated costs per year for each treatment are given in Figure 3. The potential total savings for the Dutch population (in total 498,924 eligible patients for lower-/reduced-dose apixaban, rivaroxaban, and dabigatran in 3 years) if all reduced doses of apixaban and rivaroxaban are brought to 0, in each of the three observed years, can lead to total cost-savings of €146 million in 3 years.

Health/Clinical impact

The clinical events included in the model (ischemic stroke, systemic embolism, major bleeding, haemorrhagic stroke, non-major bleeding) were mainly avoided when using lower-dose dabigatran instead of reduced doses apixaban or rivaroxaban (Table 2 and Figure A1). In the case of apixaban patients switching to dabigatran, the major bleedings and the ischemic strokes contributed the most to the prevented parameters. When switching rivaroxaban patients to dabigatran, the majority of the avoided events were major bleeding in the first year and systemic embolism in the second and third year. The test for mortality impact showed statistical significance, confirming that switching patients on reduced-dose apixaban or rivaroxaban to lower-dose dabigatran significantly reduces mortality.

Sensitivity analyses

The variations around event costs and -ratio parameters, explored in sensitivity analyses, show consistent cost-savings. Results are presented in Figures 4(a) and Figure 4(b) for switching 100% of the patients from treatment with reduced-dose apixaban to lower-dose

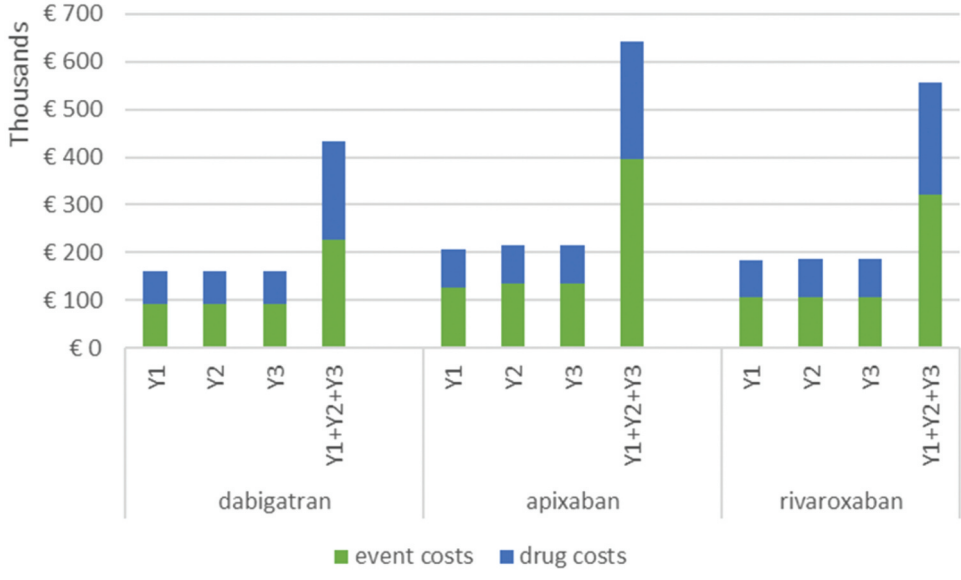

Figure 3. Annual and total treatment costs per 100 patient year in the Netherlands.
Note: Y – year.

Table 2. Events prevented by switching eligible patients for reduced doses of apixaban and rivaroxaban to lower-dose dabigatran.

	Apixaban to dabigatran				Rivaroxaban to dabigatran			
Event	Y1	Y2	Y3	Y1+Y2+Y3	Y1	Y2	Y3	Y1+Y2+Y3
IS	1,526	1,236	1,280	4,043	698	369	382	1,449
SE	171	51	53	275	31	−24	−25	−18
MB	1,294	1,444	1,496	4,235	1,342	1,135	1,176	3,654
HS	128	87	90	305	138	259	268	665
NMB	308	271	281	859	477	517	536	1,530
Mortality	5,615	6,022	6,237	17,874	4,980	3,755	3,890	12,625
TOTAL	**9,042**	**9,110**	**9,437**	**27,590**	**7,667**	**6,011**	**6,226**	**19,904**

Note: IS – ischaemic stroke; SE – systemic embolism; MB – major bleeding; HS – haemorrhagic stroke; NMB – non-major bleeding; Y – year.

dabigatran and switching 100% of treatment with reduced-dose rivaroxaban to lower-dose dabigatran, respectively. These variations were made around the base case cost savings of €157 or €72 thousand per 100 patient-year for both situations. The biggest impact is owed to ischemic stroke and major bleeding rates. The ranges per input are given in the Appendix (Table A2).

Scenario analyses

The market share effect variations indicate potential savings up to €90 and €45 million when accounting for high – and lower uptake scenario switches of the lower-/reduced-dose DOACs. Looking into the effect of medicine price reductions due to patent expiry, cost savings can go up to €229 million in 3 years (Figure 5).

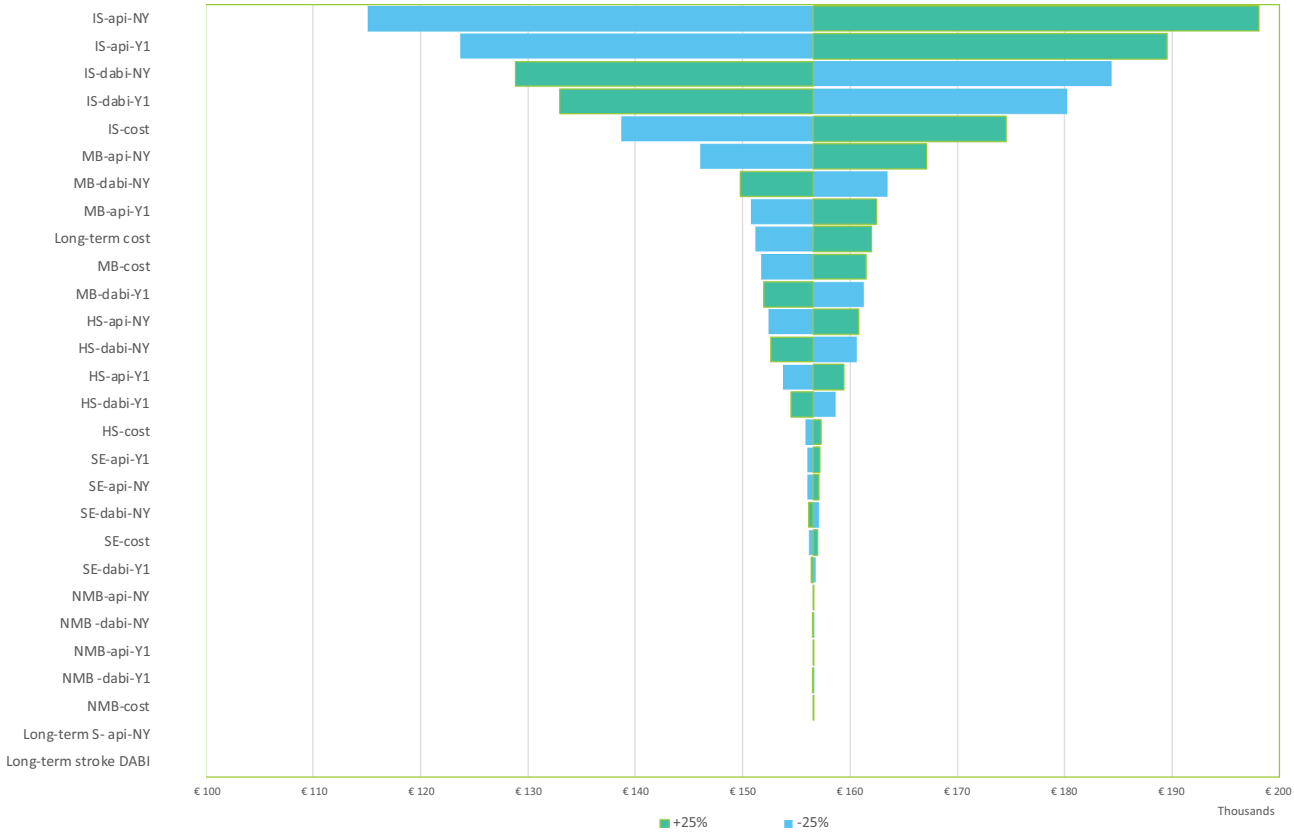

Figure 4. (a) Tornado diagram from univariate sensitivity analysis for switching 100% of the patients from treatment with reduced-dose apixaban to lower-dose dabigatran with base case costs savings €152, varying for ± 25% around the base case values. (b) Tornado diagram from univariate sensitivity analysis for switching 100% of treatment with reduced-dose rivaroxaban to lower-dose dabigatran with base case costs savings €71, varying for ± 25% around the base case values.

Note: Y – year; NY – next year; riva – rivaroxaban; api – apixaban, dabi – dabigatran, AF – atrial fibrillation; IS – ischaemic stroke; SE – systemic embolism; MB – major bleeding; HS – haemorrhagic stroke; LTS – long-term stroke; NMB – non-major bleeding.

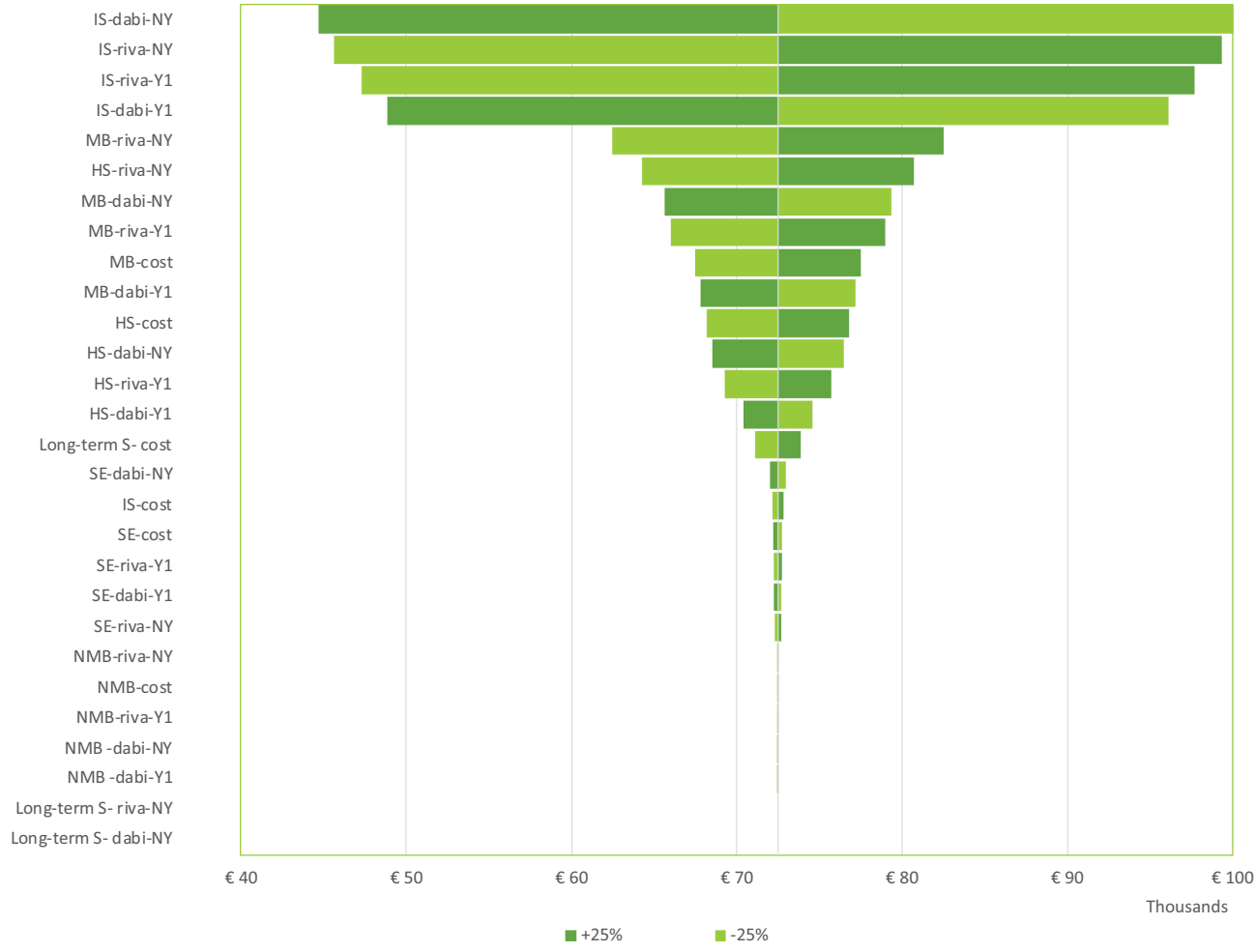

Figure 4. (Continued).

Discussion

Main findings

Assessing the comparative budget and health impact of lower-dose dabigatran versus reduced-dose apixaban and rivaroxaban in patients with AF eligible for lower-/reduced-dose in the Netherlands reflected costs savings and clinical event avoidance. The base case analysis indicated a saving of €72 thousand per 100 patients over 3 years when all patients using reduced-dose rivaroxaban switch to lower-dose dabigatran. These savings were twice as high (€157 thousand) when switching from reduced-dose apixaban to lower-dose dabigatran. In addition to this base-case cost savings, the avoidance of undesired events proved beneficial in most cases for lower-dose dabigatran. This is reflected mainly by ischemic stroke and major bleeding events avoided. Over 3 years' time that equals to more than 4000 for both events when switching from apixaban to dabigatran or 1,449 ischemic strokes and 3,654 major bleedings when switching from rivaroxaban to dabigatran. The significant reduction in the number of deaths is an additional benefit demonstrated in this study.

The total cost of €952 million over 3 years for the treatment of patients with AF who are eligible for lower-/reduced-dose DOACs in the Netherlands was mainly driven by the events cost. Considering more conservative scenarios, where patients gradually switch from reduced doses apixaban and rivaroxaban to lower-dose dabigatran, show slightly lower budget savings. For example, a low uptake scenario would lower the total costs to €907 million and a high uptake to €862 million over 3 years, but both still reflecting potential savings. In the coming years, it is expected that the DOACs registered in the Netherlands would go out of patent. It has been shown that medicine prices drop substantially after patent expiry in the Netherlands. In particular, for medicines with relatively high annual revenues, for example, DOACs, this would account for substantial price drop ratios [45]. The scenario exploring the effect of patent expiry resulted in a decrease in the DOACs budget from €952 million to €723 million over 3 years.

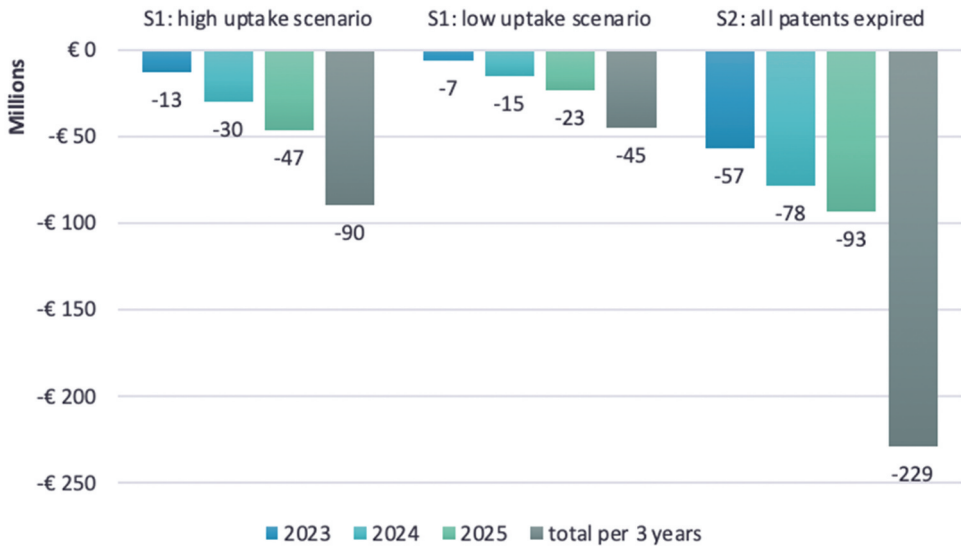

Figure 5. Scenario analyses.

Note: S1: market share effect with high and lower uptake scenario per Dutch population; S2: medicine prices effect when all patents are expired; Y – year.

Interpretation

The national reports evaluating the experiences and costs around the use of DOACs imply a need for reducing the costs in the future [46]. In fact, in 2020, rivaroxaban and apixaban took the top place on the list of medicines with the highest expenditures [47,48]. Moreover, as the DOACs use increases through the years, expenditures for these medicines become a bigger burden for the Dutch health budget [49]. Therefore, looking into the budget impact was the logical direction for these analyses. The budget and health impact of DOACs in patients with AF were a research interest in several previous publications reflecting the Dutch situation, but all focused on the effect of standard dosing [19,35,50–52]. Most of these studies considered comparisons of individual DOACs compared to VKAs. For example, Jacobs et al. [52] and Stevanovic et al. [19], respectively, showed a favourable cost-effectiveness for rivaroxaban and apixaban compared to VKAs. Moreover, the cost-effectiveness and monetary benefits of dabigatran standard dose in AF were previously demonstrated compared to VKAs, showing a favourable cost-effectiveness ratio [51,53]. While all these studies made comparisons to VKAs, another study [35] showed apixaban to be the one with most favourable clinical events when comparing to other standard dosing DOACs. Yet, there are no cost data available showing the comparisons of lower-/reduced-dose DOACs for eligible patients with AF in the Dutch settings.

A recent observational study from Norway comparing stroke (systemic embolism) and major bleedings for patients using reduced dose DOACs showed favourable outcomes for dabigatran compared to apixaban and rivaroxaban [54]. This is in line with the clinical inputs we used for our analysis, reflecting less stokes and haemorrhages associated with patients receiving lower-dose dabigatran than the ones receiving reduced doses of apixaban or rivaroxaban [17]. However, the risks of these studies are not directly comparable as Nielsen et al. [17] looked into the risks of lower-/reduced-dose of DOACs compared to warfarin, and not to another DOAC medicine, as Rutherford et al. [54] did. Another recent patient-level network meta-analysis exploring standard and lower-/reduced-dose DOACs use in AF compared to warfarin also showed better outcomes for preventing haemorrhagic-related events and deaths [55]. However, that study accounted for four pivotal randomized clinical trials and not for a RWE. Furthermore, in a Canadian retrospective cohort study that looked into the dose-specific outcomes, it was shown that only the lower-dose dabigatran had lower mortality risk compared to warfarin, while other DOACs did not show this effect [56].

To consider the time each person in the population is at risk for the outcomes of interest, we expressed the results per 100 patient-year. This allows for better comparisons between different populations and the generalizability of the outcomes. However, it does not account for the (growth of) the population size. Expressing the results on the population level provides insight into the impact on the national health budget (about €106 billion in 2023) [57], representing 0.1% of the total Dutch healthcare budget. Based on our estimations, approximately 31% of the total AF population using DOACs are eligible for lower-/reduced-dose of DOACs. Though within this percentage, propositions differ per DOAC, as they slightly differ in indication. A single-

centered prospective study included 86,4% of patients using standard dose, leaving 13,6% eligible for lower-/reduced-dose [58]. This study used observations made between 2013 and 2017, including 799 patients, of which 30% were ≥75 years old. We estimated number for the situation from 2023 to 2026, including between 580 and 626 thousand DOAC-users per year, accounting for the population growth. The timing and number of participants in the study, together with the inclusion criteria, might explain the lower proportion of eligible population for lower-/reduced-dose compared to our inputs [58]. Moreover, the proportion of the 75+ population was lower than in our study, which is the age group with the most patients eligible for lower-/reduced-dose DOACs. Considering our population data source [29] (from 2017 to 2021), the same age group (≥75 years old) accounts for 46% of the total AF population. As the population grows older, we can expect this percentage to grow further in the coming years, including the years considered in our model, and with that, to have a higher % of the population eligible to lower-/reduced-dose of DOACs.

Prescribing patterns for DOAC medication, market shares for dabigatran, apixaban, rivaroxaban, and edoxaban were evaluated in five regions of the Netherlands, showing that apixaban and rivaroxaban were most frequently prescribed [59]. That aligns with our inputs for market shares, which we based on public source using insurance data, as it better reflects real-word use and does not require adherence adjustments [29]. At the beginning of the introduction of the DOACs in the Netherlands, the uptake of the innovative DOACs was lower compared to other European countries, among others, due to a well-established network of thrombose-monitoring centers [60]. However, seeing the market share percentages now, this difference seems to have reduced.

The prices of DOACs used in our model are based on list prices, inclusive value-added tax (VAT), and exclusive pharmacists fee [36–38]. In the Netherlands, the DOACs have been available on the Dutch market for more than 10 years since 2008 (dabigatran, apixaban) and 2011 (rivaroxaban). On the one hand, one can argue that a price decrease can be expected in the short term due to patent expiration, loss of market exclusivity, and availability of generics. On the other hand, the Netherlands is a specific case where the Dutch system removed the incentive for price competition allowing generic manufacturers to set their prices close to the reimbursement prices, e.g., the generic form of apixaban [36,61]. Nevertheless, the literature indicates that the number of generic manufacturers entering the market may influence the speed of price fall [62]. Evidently, medication costs could fluctuate over time, potentially impacting its use in practice. We explored this effect of price change by following recommendations given in a Dutch study on how to decrease medication prices in the years after patent expiry. The study explored potential price drops based on annual revenues to distinguish between different medicine categories [45]. Another Dutch study that explored the price developments after patent expiry for three different medicines (enalapril, fluoxetine, and ranitidine) observed a decrease in prices indeed [63]. Nevertheless, the exact proportions of price decreases are not comparable as different medication groups are considered. Vondeling et al. [64], exploring the impact of patent expiry on medication prices in Europe, indicated variations in the price decrees between medications and emphasized the need to use country-specific data, as we did in our study. Lastly, while the price can contribute to the budget impact, the clinical events and corresponding related costs remain the same irrespective of DOACs being a generic or originator.

Strengths and limitations

To our knowledge, this is the first budget and health impact model considering DOACs in patients with AF that require a lower-/reduced-dose because of their patient characteristics (e.g., age or renal function). The study accounted for cost as well as for health outcomes on a population level (per 100 patient years and for the total population in the Netherlands). The effect of mortality was also shown for these users. Furthermore, it fills the gap for studies that compare DOACs with each other rather than DOACs with VKA. Moreover, it complements the existing literature by providing results based on real-world data instead of the commonly used clinical trials. Finally, it better reflects the AF population in relation to the individual patient characteristics, as a substantial proportion requires lower-/reduced-dose DOACs.

Several limitations need to be acknowledged. First, relative risk inputs were based on a single RWE study conducted in Denmark [17]. This potently alarms selective bias as the population characteristics may differ and impact the transferability to other settings. RWE studies include heterogeneous populations, and therefore differences in clinical outcomes can be expected. Moreover, differences in clinical outcomes may be owed to the different mechanisms of action of the DOACs, but also to the comorbidities affecting DOACs pharmacokinetics, mainly the renal or hepatic impairment and obesity [65]. The use of another study might lead to different outcomes. Second, the diagnosis for each DOAC slightly differs between lower-dose

dabigatran or reduced-dose apixaban and rivaroxaban. In fact, there are no lower-dose formations of apixaban and rivaroxaban, only reduced ones [66]. The reduced dose is indicated for patients with two of these three conditions, older than 80 years, weight under 60 kg or creatinine from 1.5 mg/dL up (apixaban), patients who develop acute renal failure (rivaroxaban), while the lower-dose of dabigatran is specifically indicated for patients in the age group of 75–80 with high bleeding- and low thrombotic risk, or patients older than 80 years. Nevertheless, all can be given to patients above 80 years or older with AF, as those have a generally increased risk of bleeding [13,67]. These variations in dose-reduction criteria, but also the possibility for misclassification [68], might impact the proportions eligible for a switch from one DOAC to another, which we explored in scenario analyses. Another limitation is the exclusion of the fourth DOAC edoxaban. Including edoxaban in the analyses might have had an impact on total expenditure. Nevertheless, we did account for its share on the market when determining market shares of DOACs in the Dutch market.

Implications for practice and policy

Given the evidence in this study, we recommend careful targeting of treatments for patients eligible for lower-/reduced-dose DOACs. In fact, a study evaluating data from the electronic hospital information system in a Dutch medical center showed that reduced-dose DOAC was a predictor for incorrect prescribing: 11% of the patients received an inappropriate dose, of which 4,5% received a standard dose while being eligible for lower-/reduced-dose [68]. More research is needed to fully understand the impact of different doses on patient outcomes. Furthermore, we should not underestimate the effect of AF screening, which also adds to the number of prevented strokes in the AF patient population [69]. Having this said, revising the diagnosis guidelines is needed to combine the effect of screening and eligibility of patients for lower-/reduced-dose DOAC for best clinical outcomes.

Conclusions

Switching patients with AF who are eligible for lower-/reduced-dose DOACs from reduced-dose rivaroxaban and apixaban to lower-dose dabigatran can potentially reduce the healthcare payer's budget expenditures and provide health gains. Cost savings might be further enhanced by increasing the lower-dose dabigatran market share and potential future price reductions due to, e.g., patent expiry.

Disclosure statement

CB and MJP reported receiving grants and honoraria from various pharmaceutical companies, including BI. They are both shareholders of Health-Ecore, the Netherlands. TF and LdJ are partly employed as consultants at Health – Ecore, the Netherlands. BK is employee at BI in the Netherlands. No other disclosures were reported.

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Compliance with ethical standards

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Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

TF, LdJ, CB and MJP developed the design and conceptualization this study. BK provided company-specific data. TF collected the data, performed the analysis, made the model and wrote the first draft of the manuscript. The data were analysed by TF and LdJ. LdJ, BK, MJP and CB did critical revision of the model and the paper. MJP and CB acted as supervision. All authors read and approved the final manuscript.

ORCID

Tanja Fens http://orcid.org/0000-0003-3995-447X
Lisa de Jong http://orcid.org/0000-0001-8814-0670
Bregt Kappelhoff http://orcid.org/0009-0006-9397-450X
Cornelis Boersma http://orcid.org/0000-0002-1190-2638
Maarten J. Postma http://orcid.org/0000-0002-6306-3653

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Appendix

Table A1. Current and new treatment mix in scenario analyses.

Patients on lower-/reduced dose DOACs	*Population/Dutch settings Number of patients*			Ref.
Scenario analyses				[28]
CTM	Y1 (2023)	Y2 (2024)	Y3 (2025)	
apixaban 2.5 mg	39609	41081	42552	
dabigatran 110 mg	62934	65273	67611	
rivaroxaban 15 mg	57806	59954	62102	
edoxaban 30 mg	22691	23534	24377	
NTM-Scenario low uptake				
apixaban 2.5 mg	57720	78649	100923	
dabigatran 110 mg	53494	45691	37186	
rivaroxaban 15 mg	49135	41968	34156	
edoxaban 30 mg	22691	23534	24377	
NTM-Scenario high uptake				
apixaban 2.5 mg	75832	116217	159293	
dabigatran 110 mg	44054	26109	6761	
rivaroxaban 15 mg	40464	23982	6210	
edoxaban 30 mg	22691	23534	24377	

Note: CTM – current treatment mix, NTM – new treatment mix; Y – year.

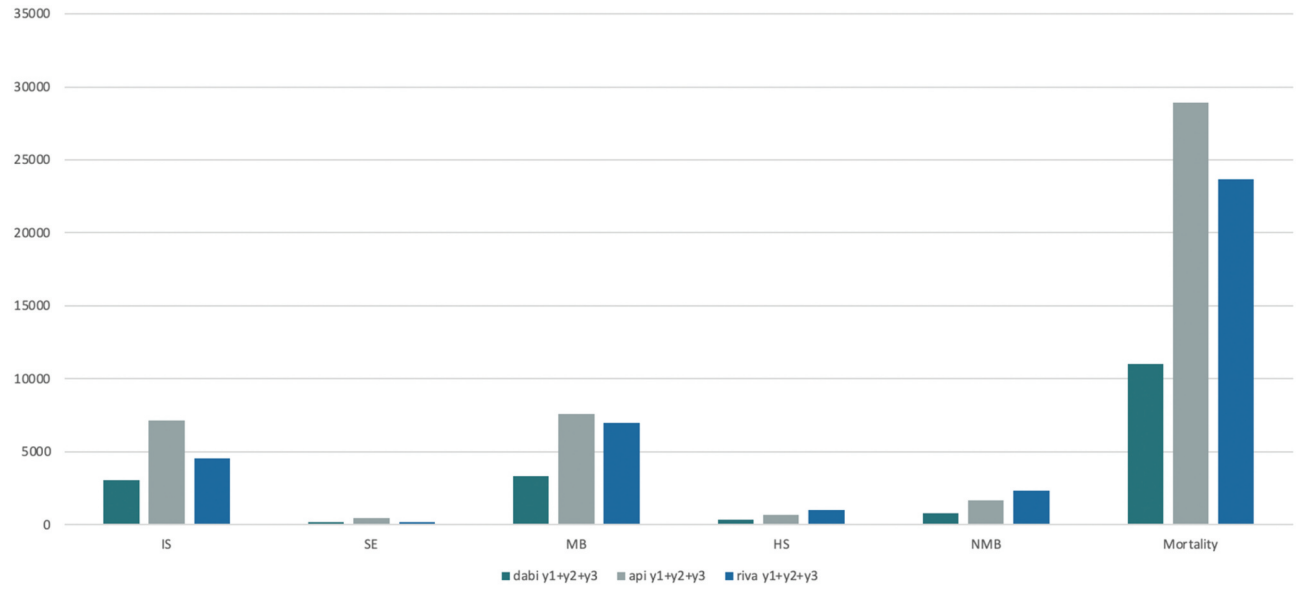
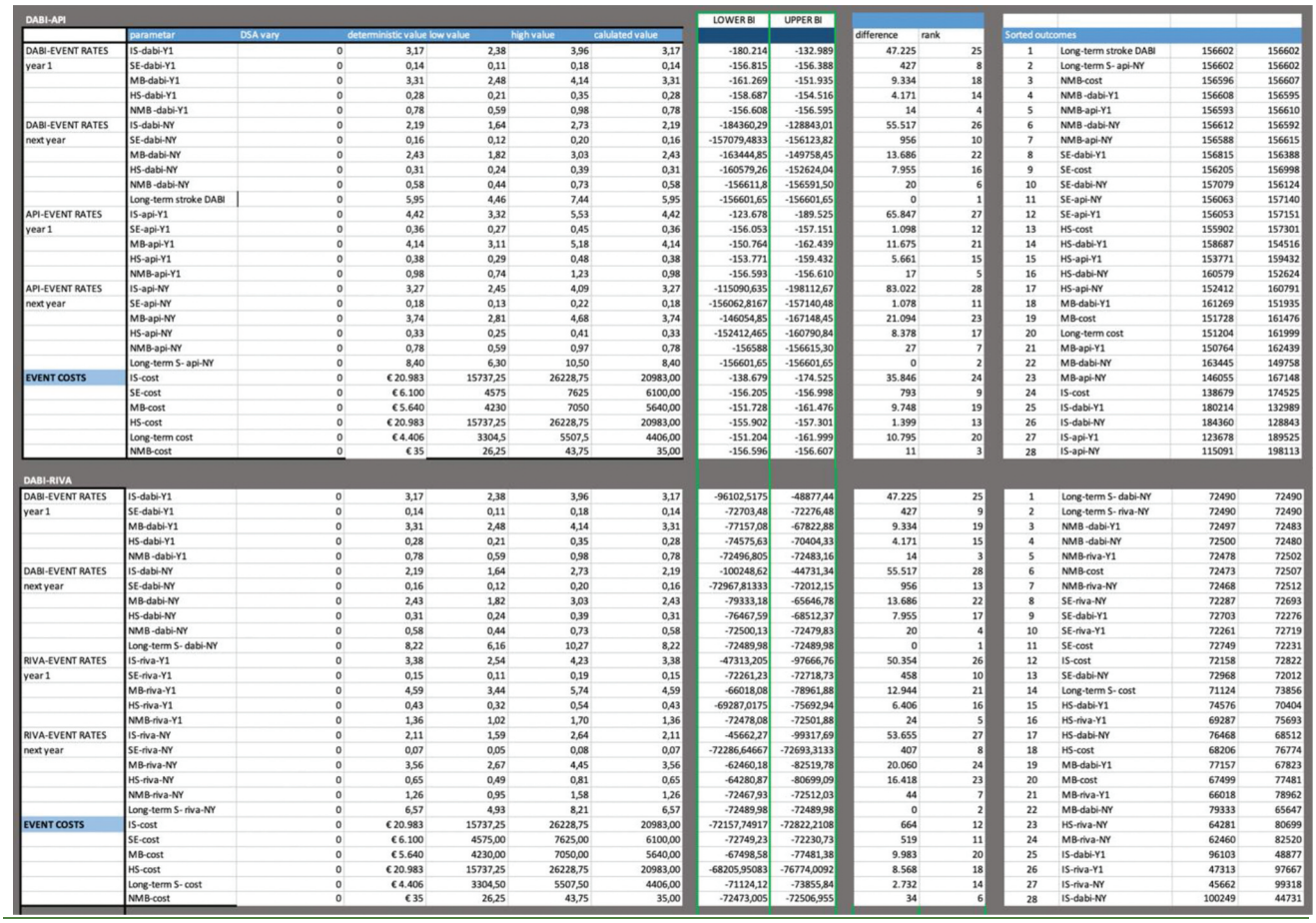


Figure A1. Number of events per medicine given in the Dutch population with atrial fibrillation eligible for lower-/reduced dose of direct oral anticoagulant.

Note: IS – ischaemic stroke; SE – systemic embolism; MB – major bleeding; HS – haemorrhagic stroke; NMB – non-major bleeding; Y – year.

Table A2. Input parameters for sensitivity analyses.



DABI-API							LOWER BI	UPPER BI						
	parametar	DSA vary	deterministic value	low value	high value	calulated value			difference	rank	Sorted outcomes			
DABI-EVENT RATES	IS-dabi-Y1	0	3,17	2,38	3,96	3,17	-180.214	-132.989	47.225	25	1	Long-term stroke DABI	156602	156602
year 1	SE-dabi-Y1	0	0,14	0,11	0,18	0,14	-156.815	-156.388	427	8	2	Long-term S- api-NY	156602	156602
	MB-dabi-Y1	0	3,31	2,48	4,14	3,31	-161.269	-151.935	9.334	18	3	NMB-cost	156596	156607
	HS-dabi-Y1	0	0,28	0,21	0,35	0,28	-158.687	-154.516	4.171	14	4	NMB -dabi-Y1	156608	156595
	NMB -dabi-Y1	0	0,78	0,59	0,98	0,78	-156.608	-156.595	14	4	5	NMB-api-Y1	156593	156610
DABI-EVENT RATES	IS-dabi-NY	0	2,19	1,64	2,73	2,19	-184360,29	-128843,01	55.517	26	6	NMB -dabi-NY	156612	156592
next year	SE-dabi-NY	0	0,16	0,12	0,20	0,16	-157079,4833	-156123,82	956	10	7	NMB-api-NY	156588	156615
	MB-dabi-NY	0	2,43	1,82	3,03	2,43	-163444,85	-149758,45	13.686	22	8	SE-dabi-Y1	156815	156388
	HS-dabi-NY	0	0,31	0,24	0,39	0,31	-160579,26	-152624,04	7.955	16	9	SE-cost	156205	156998
	NMB -dabi-NY	0	0,58	0,44	0,73	0,58	-156611,8	-156591,50	20	6	10	SE-dabi-NY	157079	156124
	Long-term stroke DABI	0	5,95	4,46	7,44	5,95	-156601,65	-156601,65	0	1	11	SE-api-NY	156063	157140
API-EVENT RATES	IS-api-Y1	0	4,42	3,32	5,53	4,42	-123.678	-189.525	65.847	27	12	SE-api-Y1	156053	157151
year 1	SE-api-Y1	0	0,36	0,27	0,45	0,36	-156.053	-157.151	1.098	12	13	HS-cost	155902	157301
	MB-api-Y1	0	4,14	3,11	5,18	4,14	-150.764	-162.439	11.675	21	14	HS-dabi-Y1	158687	154516
	HS-api-Y1	0	0,38	0,29	0,48	0,38	-153.771	-159.432	5.661	15	15	HS-api-Y1	153771	159432
	NMB-api-Y1	0	0,98	0,74	1,23	0,98	-156.593	-156.610	17	5	16	HS-dabi-NY	160579	152624
API-EVENT RATES	IS-api-NY	0	3,27	2,45	4,09	3,27	-115090,635	-198112,67	83.022	28	17	HS-api-NY	152412	160791
next year	SE-api-NY	0	0,18	0,13	0,22	0,18	-156062,8167	-157140,48	1.078	11	18	MB-dabi-Y1	161269	151935
	MB-api-NY	0	3,74	2,81	4,68	3,74	-146054,85	-167148,45	21.094	23	19	MB-cost	151728	161476
	HS-api-NY	0	0,33	0,25	0,41	0,33	-152412,465	-160790,84	8.378	17	20	Long-term cost	151204	161999
	NMB-api-NY	0	0,78	0,59	0,97	0,78	-156588	-156615,30	27	7	21	MB-api-Y1	150764	162439
	Long-term S- api-NY	0	8,40	6,30	10,50	8,40	-156601,65	-156601,65	0	2	22	MB-dabi-NY	163445	149758
EVENT COSTS	IS-cost	0	€ 20.983	15737,25	26228,75	20983,00	-138.679	-174.525	35.846	24	23	MB-api-NY	146055	167148
	SE-cost	0	€ 6.100	4575	7625	6100,00	-156.205	-156.998	793	9	24	IS-cost	138679	174525
	MB-cost	0	€ 5.640	4230	7050	5640,00	-151.728	-161.476	9.748	19	25	IS-dabi-Y1	180214	132989
	HS-cost	0	€ 20.983	15737,25	26228,75	20983,00	-155.902	-157.301	1.399	13	26	IS-dabi-NY	184360	128843
	Long-term cost	0	€ 4.406	3304,5	5507,5	4406,00	-151.204	-161.999	10.795	20	27	IS-api-Y1	123678	189525
	NMB-cost	0	€ 35	26,25	43,75	35,00	-156.596	-156.607	11	3	28	IS-api-NY	115091	198113
DABI-RIVA														
DABI-EVENT RATES	IS-dabi-Y1	0	3,17	2,38	3,96	3,17	-96102,5175	-48877,44	47.225	25	1	Long-term S- dabi-NY	72490	72490
year 1	SE-dabi-Y1	0	0,14	0,11	0,18	0,14	-72703,48	-72276,48	427	9	2	Long-term S- riva-NY	72490	72490
	MB-dabi-Y1	0	3,31	2,48	4,14	3,31	-77157,08	-67822,88	9.334	19	3	NMB -dabi-Y1	72497	72483
	HS-dabi-Y1	0	0,28	0,21	0,35	0,28	-74575,63	-70404,33	4.171	15	4	NMB -dabi-NY	72500	72480
	NMB -dabi-Y1	0	0,78	0,59	0,98	0,78	-72496,805	-72483,16	14	3	5	NMB-riva-Y1	72478	72502
DABI-EVENT RATES	IS-dabi-NY	0	2,19	1,64	2,73	2,19	-100248,62	-44731,34	55.517	28	6	NMB-cost	72473	72507
next year	SE-dabi-NY	0	0,16	0,12	0,20	0,16	-72967,81333	-72012,15	956	13	7	NMB-riva-NY	72468	72512
	MB-dabi-NY	0	2,43	1,82	3,03	2,43	-79333,18	-65646,78	13.686	22	8	SE-riva-NY	72287	72693
	HS-dabi-NY	0	0,31	0,24	0,39	0,31	-76467,59	-68512,37	7.955	17	9	SE-dabi-Y1	72703	72276
	NMB -dabi-NY	0	0,58	0,44	0,73	0,58	-72500,13	-72479,83	20	4	10	SE-riva-Y1	72261	72719
	Long-term S- dabi-NY	0	8,22	6,16	10,27	8,22	-72489,98	-72489,98	0	1	11	SE-cost	72749	72231
RIVA-EVENT RATES	IS-riva-Y1	0	3,38	2,54	4,23	3,38	-47313,205	-97666,76	50.354	26	12	IS-cost	72158	72822
year 1	SE-riva-Y1	0	0,15	0,11	0,19	0,15	-72261,23	-72718,73	458	10	13	SE-dabi-NY	72968	72012
	MB-riva-Y1	0	4,59	3,44	5,74	4,59	-66018,08	-78961,88	12.944	21	14	Long-term S- cost	71124	73856
	HS-riva-Y1	0	0,43	0,32	0,54	0,43	-69287,0175	-75692,94	6.406	16	15	HS-dabi-Y1	74576	70404
	NMB-riva-Y1	0	1,36	1,02	1,70	1,36	-72478,08	-72501,88	24	5	16	HS-riva-Y1	69287	75693
RIVA-EVENT RATES	IS-riva-NY	0	2,11	1,59	2,64	2,11	-45662,27	-99317,69	53.655	27	17	HS-dabi-NY	76468	68512
next year	SE-riva-NY	0	0,07	0,05	0,08	0,07	-72286,64667	-72693,3133	407	8	18	HS-cost	68206	76774
	MB-riva-NY	0	3,56	2,67	4,45	3,56	-62460,18	-82519,78	20.060	24	19	MB-dabi-Y1	77157	67823
	HS-riva-NY	0	0,65	0,49	0,81	0,65	-64280,87	-80699,09	16.418	23	20	MB-cost	67499	77481
	NMB-riva-NY	0	1,26	0,95	1,58	1,26	-72467,93	-72512,03	44	7	21	MB-riva-Y1	66018	78962
	Long-term S- riva-NY	0	6,57	4,93	8,21	6,57	-72489,98	-72489,98	0	2	22	MB-dabi-NY	79333	65647
EVENT COSTS	IS-cost	0	€ 20.983	15737,25	26228,75	20983,00	-72157,74917	-72822,2108	664	12	23	HS-riva-NY	64281	80699
	SE-cost	0	€ 6.100	4575,00	7625,00	6100,00	-72749,23	-72230,73	519	11	24	MB-riva-NY	62460	82520
	MB-cost	0	€ 5.640	4230,00	7050,00	5640,00	-67498,58	-77481,38	9.983	20	25	IS-dabi-Y1	96103	48877
	HS-cost	0	€ 20.983	15737,25	26228,75	20983,00	-68205,95083	-76774,0092	8.568	18	26	IS-riva-Y1	47313	97667
	Long-term S- cost	0	€ 4.406	3304,50	5507,50	4406,00	-71124,12	-73855,84	2.732	14	27	IS-riva-NY	45662	99318
	NMB-cost	0	€ 35	26,25	43,75	35,00	-72473,005	-72506,955	34	6	28	IS-dabi-NY	100249	44731

Note: Y – year; riva – rivaroxaban; api – apixaban, dabi – dabigatran, AF – atrial fibrillation; IS – ischaemic stroke; SE – systemic embolism; MB – major bleeding; HS – haemorrhagic stroke; LTS – long-term stroke; NMB – non-major bleeding; Y – year, NY – next year.