Farmeconomia. Health economics and therapeutic pathways 2018; 19(1): 11-20
https://doi.org/10.7175/fe.v19i1.1346

ORIGINAL RESEARCH

Estimating the cost-effectiveness of treatment for prevention of thromboembolic events in at-risk adults with non-valvular atrial fibrillation

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ABSTRACT

INTRODUCTION: The direct oral anticoagulants (DOACs) have demonstrated a more predictable effect and a more favorable risk-benefit ratio compared to the standard oral anticoagulant treatment for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF).
AIM: To estimate the efficiency of DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban vs. warfarin), in the prevention of clinical events in adult patients with NVAF.
METHODS: A deterministic incremental cost-effectiveness analysis was performed to evaluate the avoidance of a clinical event and the incremental cost per avoided clinical event, in a hypothetical population of 100,000 adult patients with NVAF, over 1-year period. In the absence of head-to-head comparison trials between DOACs, relative risks were derived from a network meta-analysis. Clinical events considered include stroke/systemic embolism (SE) and major bleeding. Only direct health costs related to the management of clinical events and drug acquisition costs were considered. Clinical event management costs were derived from literature and from the Diagnosis Related Group (DRG) tariffs. Net annual treatment costs were calculated based on the daily dose reported in the Summary of Product Characteristics (SPCs) and the ex-factory price of each drug.
RESULTS: Among DOACs, apixaban was associated with the highest net clinical benefit with 1,064 avoided events over 1 year, compared to warfarin (728 major bleeding events and 336 strokes/SE). Furthermore, apixaban is the most efficient DOAC, with a cost per avoided event equal to € 16,672 vs. warfarin (€ 24,120 for edoxaban 60 mg, € 36,777 for dabigatran 150 mg).
CONCLUSION: Apixaban has the highest potential net clinical benefit among DOACs for patients with NVAF and the least incremental cost per avoided event for the Italian National Health Service.

Keywords

Direct oral anticoagulants; Thromboembolic events; Non-valvular atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) represents the most prevalent form of cardiac arrhythmia. In Europe and the US 1 in 4 middle-aged adults will develop AF and it is estimated that by 2030 in Europe there will be 14-17 million of AF patients with 120,000-215,000 new cases per year [1]. In Italy, a recent observational study estimated a prevalence of AF equal to 1.7% for a total of 1,036,448 cases [2]. AF is independently associated with a higher risk of all-cause and cardiovascular mortality, the latter due to sudden death, heart failure, and stroke. Compared to subjects without AF, stroke, which is the main complication of AF, is nearly five times more frequent in subjects with AF [3]. Ischemic stroke due to AF is associated with higher mortality and worse functional outcomes than non AF-associated ischemic stroke, and AF is responsible for 20-30% of ischemic stroke [1].

In this context, the prevention of stroke represents a primary goal in the management of patients with AF and a high thromboembolic risk. The current European guidelines recommend to evaluate the annual incidence of cerebral stroke using the CHA2DS-VASc score

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Received: 12 January 2018
Accepted: 22 February 2018

	Dabigatran (RE-LY) [6]			Apixaban (ARISTOTLE) [7]		Rivaroxaban (ROCKET-AF) [8]		Edoxaban (ENGAGE AF-TIMI 48) [9]		
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind		Randomized, double-blind		
Patients (n.)	18,113			18,201		14,264		21,105		
Follow-up (years)	2			1.8		1.9		2.8		
Age	71.5 ± 8.7 (mean ± SD)			70 (63–76) [median (interquartile range)]		73 (65–78) [median (interquartile range)]		72 (64–78) [median (interquartile range)]		
CHADS2 score (mean)	2.1			2.1		3.5		2.8		
	Warfarin (n. = 6022)	Dabigatran 150 BID (n. = 6076)	Dabigatran 110 BID (n. = 6015)	Warfarin (n. = 9081)	Apixaban 5 mg BID (n. = 9120)	Warfarin (n. = 7133)	Rivaroxaban 20 mg QD (n. = 7131)	Warfarin (n. = 7036)	Edoxaban 60 mg QD (n. = 7035)	Edoxaban 30 mg QD (n. = 7034)
	Event/year (%)	Event rate/ year,% (RR vs. warfarin)	Event rate/ year,% (RR vs. warfarin)	Event rate/ year,% (RR vs. warfarin)	Event rate/year,% (RR vs. warfarin)	Event/year (%)	Event rate/year,% (RR vs. warfarin)	Event/year (%)	Event rate/year,% (RR vs. warfarin)	Event rate/year,% (RR vs. warfarin)
Stroke/SE	1.72	1.12 (0.65, 0.52-0.81; p <0.001[1])	1.54 (0.89, 0.73-1.09; p <0.001[2])	1.60	1.27 (0.79, 0.66-0.95; p <0.001[2], p = 0.01[3])	2.4	2.1 (0.88, 0.75-1.03; p <0.001[2], p = 0.12[3])	1.80	1.57 (0.87, 0.73-1.04; p <0.001[2], p = 0.08[3])	2.04 (1.13, 0.96-1.34; p = 0.005[2], p = 0.10[3])
Ischaemic stroke	1.22	0.93 (0.76, 0.59-0.97; p = 0.03)	1.34 (1.10, 0.88-1.37; p = 0.42)	1.05	0.97 (0.92, 0.74-1.13; p = 0.42)	1.42	1.34 (0.94; 0.75-1.17; p = 0.581)	1.25	1.25 (1.00, 0.83-1.19; p = 0.97)	1.77 (1.41, 1.19-1.67; p <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14-0.49; p <0.001)	0.12 (0.31, 0.17-0.56; p <0.001)	0.47	0.24 (0.51, 0.35-0.75; p <0.001)	0.44	0.26 (0.59; 0.37-0.93; p = 0.024)	0.47	0.26 (0.54, 0.38-0.77; p <0.001)	0.16 (0.33, 0.22-0.50; p <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82-1.08; p = 0.41)	2.92 (0.80, 0.70-0.93; p = 0.003)	3.09	2.13 (0.69, 0.60-0.80; p <0.001)	3.45	3.60 (1.04; 0.90-2.30; p = 0.58)	3.43	2.75 (0.80, 0.71-0.91; p <0.001)	1.61 (0.47, 0.41-0.55; p <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29-0.61; p <0.001)	0.23 (0.29 0.19-0.45; p <0.001)	0.80	0.33 (0.42, 0.30-0.58; p <0.001)	0.74	0.49 (0.67; 0.47-0.93; p = 0.02)	0.85	0.39 (0.47, 0.34-0.63; p <0.001)	0.26 (0.30, 0.21-0.43; p <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19-1.86; p <0.001)	1.13 (1.04, 0.82-1.33; p = 0.74)	0.86	0.76 (0.89, 0.70-1.15; p = 0.37)	1.24	2.00 (1.61; 1.30-1.99; p < 0.001)	1.23	1.51 (1.23, 1.02-1.50; p = 0.03)	0.82 (0.67, 0.53-0.83; p <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; p = 0.12)	0.82 (1.29, 0.96-1.75; p = 0.09)	0.61	0.53 (0.88, 0.66-1.17; p = 0.37)	1.12	0.91 (0.81; 0.63-1.06; p = 0.12)	0.75	0.70 (0.94, 0.74-1.19; p = 0.60)	0.89 (1.19, 0.95-1.49; p = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77-1.00; p = 0.051)	3.75 (0.91, 0.80-1.03; p = 0.13)	3.94	3.52 (0.89, 0.80-0.99; p = 0.047)	2.21	1.87 (0.85; 0.70-1.02; p = 0.07)	4.35	3.99 (0.92, 0.83-1.01; p = 0.08)	3.80 (0.87, 0.79-0.96; p = 0.006)

Table I. *Summary of the phase III RCTs. Modified from [1]*

[1] For non-inferiority and superiority

[2] For non-inferiority

[3] For superiority

which stratifies patients with thromboembolic risk based on gender (female have a higher risk) and the presence of congestive heart failure, hypertension, age ≥ 65 years, diabetes, previous stroke or transient ischemic attack (TIA) or thromboembolism, and vascular disease [1]. Oral anticoagulation (OAC) is not indicated in absence of clinical risk factors (CHA2DS2-VASc = 0 – includes women without other stroke risk factors), while is highly recommended in subjects with AF and CHA2DS2-VASC ≥ 2 (if men) or ≥ 3 (if women). OAC has potential clinical net benefit also in patients with one risk factor, therefore it should be considered in men with CHA2DS2-VASC = 1 and women with CHA2DS2-VASC = 2 [1].

The traditional standard oral anticoagulant treatment is represented by warfarin and other vitamin K antagonists (VKAs) which have demonstrated to reduce the risk of stroke by 64% compared with placebo [4]. However, VKA therapy presents some limitations, such as interactions with drugs and food, the need for regular dosage adjustment based on periodic INR (International Normalized Ratio) monitoring, and the risk of major bleeds, which could reduce patient compliance [5]. During the last years new direct anticoagulant drugs which overcome some of these limitations have been developed.

The direct oral anticoagulants (DOACs) have been approved for the prevention of stroke in patients with NVAF (non-valvular AF) thereby excluding AF patients with mechanical heart valves or moderate to severe mitral stenosis. The DOACs currently indicated are factor Xa inhibitors apixaban, edoxaban, and rivaroxaban; and the direct thrombin inhibitor dabigatran; they have demonstrated a more predictable effect and a more favorable risk-benefit ratio, without the need for INR monitoring, compared to standard therapy. In phase III trials (Table I), and in several indirect comparisons, both the individual DOACs and the entire class were considered non-inferior, or superior, to warfarin in the reduction of stroke, systemic embolism (SE), intracranial bleeding, and mortality [6-14] and are recommended in the first-line treatment of patient with AF in preference to VKAs [1].

When selecting a DOAC for stroke prevention in AF, several factors must be considered, including the evaluation of the net clinical benefit, since the anticoagulant activity, which allows reducing ischemic stroke and systemic embolism, must be balanced against an increased risk of hemorrhagic events.

Despite the overall clinical net benefit of DOACs compared with VKAs, mainly due to reduced incidence of intracranial bleeding, there are important differences in the safety and efficacy profile among DOACs. A recent systematic review and meta-analysis of RCT aimed to identify the most effective, safe, and cost-effective anticoagulant for stroke prevention in AF, demonstrated that apixaban seems to have the best risk benefit ratio [12,15].

The results, obtained from 23 RCTs, confirmed that apixaban 5 mg *bis in die* (BID – twice daily), dabigatran 150 mg BID, edoxaban 60 mg *quaque die* (QD – once daily), and rivaroxaban 20 mg QD all reduce the risk of stroke or systemic embolism, major bleeding, intracranial bleeding, and all-cause mortality compared with warfarin. Of the available DOACs, apixaban offers the best balance between efficacy and safety since it was ranked the best intervention for many of the outcomes evaluated, including stroke or SE, myocardial infarction, major bleeding, and all-cause mortality [12].

Another network meta-analysis, which included seven trials (for a total of 52,701 patients), showed that, while apixaban 5 mg BID and dabigatran 150 mg BID proved to be equally superior to warfarin in preventing stroke + SE, apixaban was associated with fewer major bleeding events than dabigatran 150 mg BID (OR = 0.73; CI95%: 0.57-0.93) and rivaroxaban 20 mg QD (OR = 0.66; CI95%: 0.52-0.84) and fewer drug discontinuations than dabigatran 150 mg BID (OR = 0.64; CI95%: 0.52-0.78) and 110 mg BID (OR = 0.66; CI95%: 0.54-0. 81). Since the ENGAGE AF-TIMI was ongoing, data for edoxaban were inconclusive [9].

Edoxaban was included in a network meta-analysis of the four phase III RCTs with the aim to assess the relative efficacy and safety of DOACs [11]. The results show that apixaban has a better safety profile in comparison to the other DOACs. Indeed it was associated with fewer bleeding events of any type (OR = 0.81; CI95%: 0.89-0.74) than edoxaban 60 mg QD and less major and GI bleeds than dabigatran 150 mg (major: OR = 0.75; CI95%: 0.61-0.90; GI: OR = 0.59; CI95%: 0.41-0.82) and rivaroxaban (major: OR = 0.67; CI95%: 0.82-0.55; GI: OR = 0.58; CI95%: 0.86-0.43) [11]. Finally, an indirect comparison analysis based on the phase III clinical trials found that there were no significant efficacy differences between edoxaban 60 mg QD and apixaban 5 mg BID, but apixaban was associated with lower clinically relevant non-major bleeding (HR = 0.79; CI95%: 0.70-0.90) and gastrointestinal bleeding (HR = 0.72; CI95%: 0.55-0.96) [14]. Regarding gastrointestinal bleeding, the meta-analysis from Ruff et al., which compared DOACs as a class with warfarin, showed that DOACs are associated with significant reductions in stroke, intracranial hemorrhage and mortality, a simi-

lar risk of major bleeding, and a higher risk of GI bleeding. However, individual comparisons show that, unlike dabigatran 150 mg, rivaroxaban and edoxaban 60 mg, apixaban is associated with a decreased risk of gastrointestinal bleeding [13].

In a recent consensus document, published on the European Heart Journal [16,17], the Authors give suggestions, based on the results of phase III trials or, if unavailable, on expert opinion, for chosing the drug and/or dose for particular subgroups of patients. In particular, apixaban 5 mg twice daily is recommended as first choice for patients with AF and high risk of gastrointestinal bleeding, chronic kidney failure (creatinine clearance 30-49 ml/min) or older than 75 years .

Aim of this paper is to estimate the efficiency of DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban vs. warfarin) in the prevention of clinical events in adult patients with NVAF from the perspective of the Italian NHS.

METHODS

A deterministic incremental cost-effectiveness analysis was performed in Microsoft Excel®. The effectiveness side is defined as the avoidance of a clinical event, which may be either a stroke/SE (primary efficacy indicator) or a major bleed (primary safety indicator). The overall cost-effectiveness indicator is the incremental cost per avoided clinical event, evaluated in a hypothetical population of 100,000 adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II), (Figure 1). Time horizon is one year.

Clinical input

Clinical events considered in the analysis include the primary efficacy outcome of stroke/SE and the primary safety outcome of major bleeding. In the absence of RCTs that directly compare apixaban with other DOACs, relative risks were derived from the network meta-analysis (NMA) by Lip et al. [18]. NMA is a type of analysis widely used in pharmacoeconomics for overcoming the lack of head-to-head trials, as reported by the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices [19] and the NICE guide to the methods of technology appraisal [20].

Lip et al. conducted a network meta-analysis including data from phase III RCTs on full dose apixaban, edoxaban, dabigatran, and rivaroxaban (Table I) vs. warfarin, to assess the relative efficacy and safety in stroke prevention of apixaban vs. other DOACs [18], both on the overall evaluated population and in three subgroups: i) patients with CHADS2 score ≥ 2; ii) use in secondary prevention (patients with previous stroke or TIA); iii) patients with high quality anticoagulation control with warfarin [18]. The results of the comparison of DOACs with warfarin were consistent with the results from the RCTs and broadly similar in the overall and subgroup results, with apixaban showing the most favorable efficacy and safety profile.

The current analysis is conducted as a series of pairwise comparisons between DOACs and warfarin, using the HRs of the annual risk of stroke/SE and major bleeding (Table II) [18].

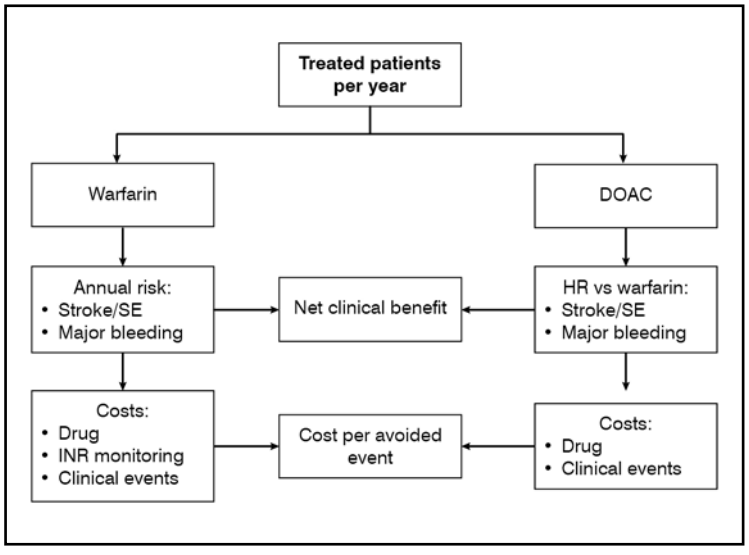

Figure 1. *Structure of the cost calculation*

In RCTs and NMA analyses, data on hemorrhagic strokes are included as part of stroke/SE and major bleeding. In order to avoid double-counting these events in the calculation of the net clinical benefit, the number of hemorrhagic strokes was subtracted from major bleeding events counts (Table II). Similarly, gastrointestinal bleeds, included in major bleeding counts, were not considered as separate clinical events.

Cost input

Since the analysis was conducted from the perspective of the Italian NHS, only direct health costs related to acquisition and monitoring of drugs and to management of episodes of stroke/SE and major bleeding events were considered.

	Warfarin Annual Risk (%) [6]	HR vs. warfarin (CI95%) [18]			
		Apixaban 5 mg BID	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Edoxaban 60 mg QD
Stroke/SE	1.60	0.79 (0.66-0.95)	0.65 (0.52-0.81)	0.87 (0.74-1.03)	0.87 (0.75-1.02)
Major bleeding	3.09	0.69 (0.60-0.80)	0.93 (0.81-1.07)	1.05 (0.91-1.2)	0.80 (0.71-0.91)
Hemorragic stroke	0.47	0.51 (0.35-0.74)	0.26 (0.13-0.48)	0.59 (0.39-0.89)	0.55 (0.39-0.78)

Table II. *HR vs. warfarin used in the analyses*

	Daily dose	Package	Ex-factory price (€/day)	Acquisition legal price discount (-5%)	Legal price discount (-5%)	Confidential discount	Price volume agreement
Apixaban	5 mg BID	60 tablets 5 mg	2.23	Yes	P	Yes	Yes
Dabigatran	150 mg BID	60 tablets 150 mg	2.23	Yes	P	Yes	Yes
Rivaroxaban	20 mg QD	28 tablets 20 mg	2.20	Yes	P	Yes	No
Edoxaban	60 mg QD	28 tablets 60 mg	2.09	Yes	A	Yes	No
Warfarin	5 mg QD	30 tablets 5 mg	0.07[1]	-	-	-	-

Table III. *Drug acquisition costs (prices refer to 2016)*
[1] Retail price
A = At the time of the acquisition; P = Returned as payback

Event management costs

Clinical event management costs over 1 year include all costs incurring during the acute period and any long-term maintenance costs. The annual cost attributed to a major bleed is approximated with the corresponding DRG-based tariff paid to hospitals by the National Health Service [21], in particular DRG 174 – GI major bleed was used (€ 3,317 per event). Stroke/SE management cost derive from data reported in an observational study conducted on 411 Italian stroke survivors, followed up for 12 months [22]. In this study, the total direct healthcare costs amounted to an average € 11,747 per stroke survivor, considering both ischemic and hemorrhagic stroke.

Drug costs

Drug acquisition costs were taken from the Italian Official Gazette [23,24] and according with the current legislation apixaban (Eliquis®, Pfizer/Bristol-Myers Squibb), dabigatran (Pradaxa®, Boehringer Ingelheim), rivaroxaban (Xarelto®, Bayer Pharma/Janssen Pharmaceuticals) and edoxaban (Lixiana®, Daiichi-Sankyo) are valued using ex-factory prices, while retail price was considered for warfarin (Coumadin®, Bristol-Myers Squibb). Net annual treatment costs were calculated based on the daily dose reported in the SPCs of each drug (Table III).

For warfarin treated patients an annual INR monitoring cost of € 380 was considered, as reported by Pradelli et al. [25] in which the annual cost reported by Mennini et al. [26] was actualized to 2013 values.

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to take into account uncertainties in the input parameters. This was obtained by a Montecarlo simulation: the simulation was repeated 1,000 times sampling all the key parameters from appropriate distributions fitted on the available mean and standard error (SE). The PSA was conducted on the hazard ratios (HRs) for each event considered (i.e. stroke/SE, major bleeding, hemorrhagic stroke). For the PSA, the natural logarithm was sampled from a normal distribution fitted on the confidence intervals reported. The parameters and the distributions used for the PSA are reported in Appendix A.

RESULTS

Figure 2 shows the number of stroke/SE and major bleeding events avoided and the net clinical benefit achieved with each DOAC compared to warfarin for the treatment of a hypothetical cohort of 100,000 patients with NVAF, with one or more risk factors over 1-year pe-

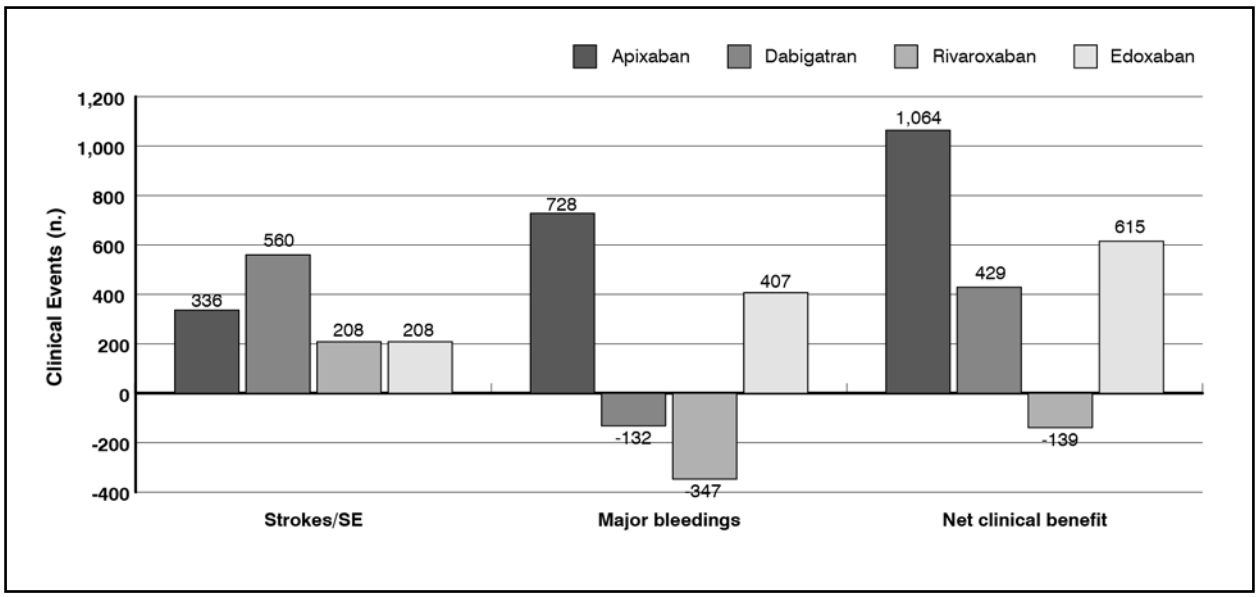

Figure 2. *Number of Clinical Events Avoided vs. warfarin (negative values indicate increased number of events with the treatment compared to warfarin)*

	Costs (€)[1]			Net clinical benefit	
	Event-related	Drug	Monitoring	Avoided events (n.)	Cost per avoided event (€)
Apixaban vs. warfarin	-6,360,441	62,092,500	-38,000,000	1,064	16,672
Dabigatran vs. warfarin	-6,142,135	59,535,750	-38,000,000	428	35,924
Edoxaban vs. warfarin	-3,791,737	56,613,750	-38,000,000	615	24,120
Rivaroxaban vs. warfarin	-1,291,714	56,613,750	-38,000,000	-139	N/A

Table IV. *Net costs and net clinical benefit of DOACs vs. warfarin*
[1] Negative values indicate savings with the treatment compared to warfarin

riod. Among DOACs, apixaban, with 336 stroke/SE and 728 major bleeding events avoided, showed the highest clinical benefit, followed by edoxaban 60 mg, and dabigatran 150 mg, while rivaroxaban, according to the methodology used and the outcomes considered, would not seem to have a net clinical benefit, as defined for the purpose of the present analysis, over warfarin.

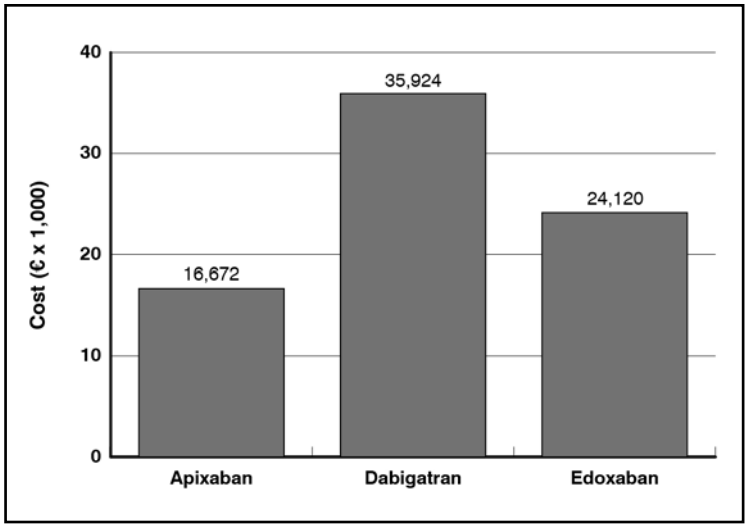

Figure 3. *Incremental cost per avoided event (vs. warfarin). The graph does not show the result for rivaroxaban, as its cost per avoided event resulted negative (dominated)*

Table IV reports the incremental costs associated with each DOAC vs. warfarin. The higher drug acquisition cost associated with apixaban, compared with other DOACs, is coupled with the lowest incidence of clinical events, resulting in the least cost per avoided event (Figure 3).

Sensitivity analysis

Figure 4 shows the results of the PSA in terms of cost-effectiveness acceptability curve (CEAC).

DISCUSSION

In the last years warfarin was progressively substituted by DOACs as anticoagulant therapy for the prevention of stroke in patients with NVAF. In pivotal RCTs, DOACs have demonstrated net clinical benefit compared with warfarin, mainly driven by

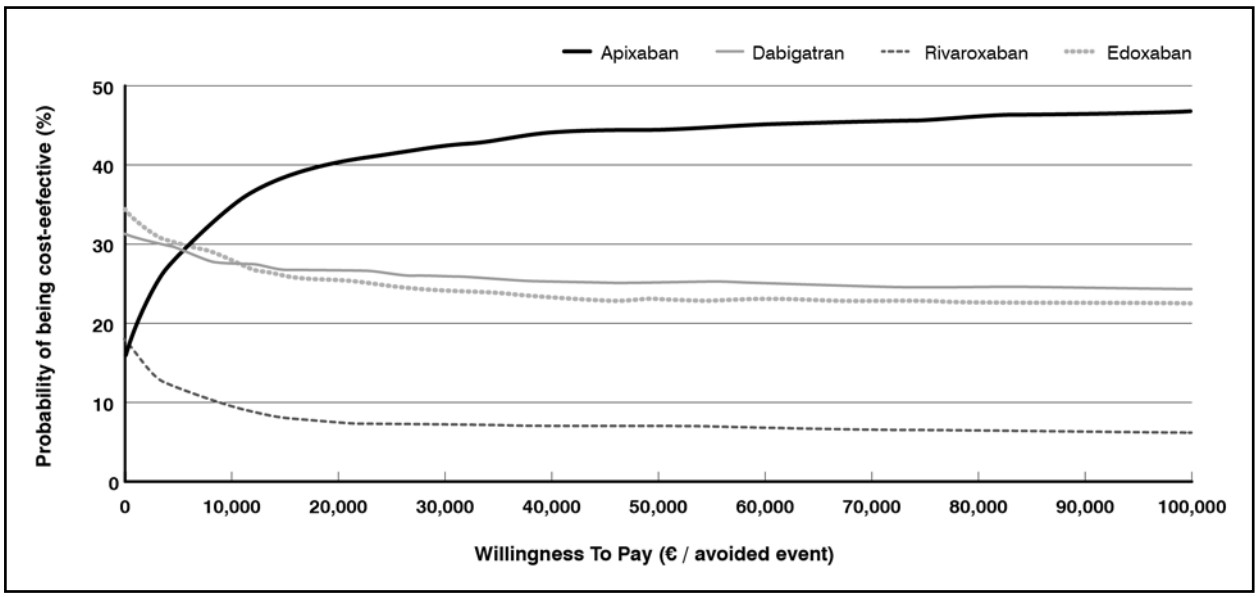

Figure 4. *Cost-effectiveness acceptability curve*

a significant reduction of intracranial bleedings [6-9]. However, relevant differences in the incidence of major and gastrointestinal bleeding have been observed among DOACs, and apixaban seems to have the best safety profile, with a lower incidence of major bleeding [10-12] including gastrointestinal bleeding [13,14].

The economic value of apixaban has been demonstrated in an independent cost-effectiveness analysis conducted in UK and based on the data from a network meta-analysis of 23 RCTs [12], which showed that apixaban has a slightly higher expected quality-adjusted life expectancy (QALYs: 5.49 vs. 5.45 of rivaroxaban, 5.42 of dabigatran 150 mg, and 5.41 of edoxaban 60 mg) and the highest probability of being the most cost-effective first-line therapy for AF (close to 60% for willingness to pay thresholds of £ 20,000-30,000). In a systematic review on the cost-effectiveness of apixaban for stroke prevention, which included 23 cost-effectiveness studies from 14 countries, apixaban appears to be more cost-effective than warfarin and other DOACs [27].

In particular, apixaban was cost-effective compared to warfarin according to the cost-effectiveness thresholds used in various countries, furthermore all the studies indicated that apixaban was cost-effective, or dominant, with ICERs below the WTP thresholds. The economic evaluations showed a mean ICER equal to 16,502 €/QALY (7,212-57,245 €/QALY) and the probability of apixaban to be cost-effective equal to 73.4%.

The evaluation of the net clinical benefit allows balancing efficacy (in terms of reduction of ischemic stroke and systemic embolism) and risk (in terms of hemorrhagic events) of the anticoagulant therapy with DOACs vs. warfarin and, in the absence of direct comparisons, may help clinical decisions.

In the present analysis, which aimed to evaluate the costs associated with the prevention of stroke/SE and major bleeding in adult patients with NVAF, apixaban was associated with 1,064 avoided events over 1 year (728 major bleeding events and 336 strokes/SE), the highest net clinical benefit compared to warfarin among considered DOACs. Furthermore, apixaban was found to be the most efficient DOAC, with the lower incremental cost per avoided event equal to € 16,672 vs. warfarin. Finally, the results of the PSA shown that apixaban had the highest chances to be the most cost-effective treatment for any WTP thresholds higher than € 5,000 per avoided event.

However, equaling the relevance of all clinical events may be a limitation of the methodology we used to estimate the net clinical benefit: as previously pointed out, an approach weighting the number of events by event-specific clinical relevance tariffs may be more accurate in reflecting the global clinical balance among avoided ischemic events and potential excess bleeds [28-31].

A recent Italian research aimed to estimate the net clinical benefit of DOACs vs. warfarin based on data from phase III clinical trials [31] applied this weighing approach to assess the net clinical benefit of the DOACs, as compared to warfarin, in AF patients. The results of this analysis are in agreement with our unadjusted approach in terms of ranking among DOACS,

with apixaban showing the highest net clinical benefit, followed by edoxaban, dabigatran, and rivaroxaban [31]. However, a notable difference refers to rivaroxaban, that also outperforms warfarin when the net clinical benefit is estimated using the weighed approach. When we repeated our analysis using as input the net clinical benefit reported by Renda et al. [31], our conclusions were unaffected: apixaban is the most efficient DOAC, with a cost per avoided event equal to € 13,038 vs. warfarin (€ 14,252 for edoxaban 60 mg, € 15,092 for dabigatran 150 mg, and € 23,408 for rivaroxaban).

Another possible limitation of our analysis is the deterministic use of the central estimate of the HRs calculated by Lip et al. [18]; however, the consistence of the results obtained using two different sources as clinical input strengthens our confidence in the main conclusion of the analyses.

A caveat needed in interpreting our results is inherent to the type of comparison feeding the clinical side of the analyses, i.e. indirect comparison – full validity can be claimed for the comparisons of the single DOACs vs. warfarin, in the specific population of AF patients evaluated in the pivotal RCTs, while the comparisons among the former are valid to the extent to which these populations can be regarded as comparable.

Two more limitations to be kept in mind are common to all model-based economic evaluations, and relate to the need to combine different sources in one single conceptual framework, and to the limited transferability of the economic result from one setting to others – these results are Italy specific.

CONCLUSIONS

Several studies and meta-analyses suggest that apixaban has the highest potential net clinical benefit among DOACs for patients with NVAF. Our findings demonstrate that the higher drug acquisition cost associated with apixaban is coupled with the lowest incidence of clinical events, resulting in the least incremental cost per avoided event from the perspective of the Italian health service.

Funding

The conduct of the analysis and the publication of this article were sponsored by Pfizer Italy and Bristol-Myers Squibb Italy. Medical writing support and journal styling services were provided by SE*Ed* Medical Publishers and funded by Pfizer Italy and Bristol-Myers Squibb Italy.

Conflict of interest

M. Bellone is employee of AdRes, which has received project funding by Pfizer Italy and Bristol-Myers Squibb Italy for the conduct of the analysis.
LP is co-owner and employee of AdRes, which has received project funding by Pfizer Italy and Bristol-Myers Squibb Italy for the conduct of the analysis. LP is an editorial member of Farmeconomia. Health Economics and Therapeutic Pathways.
M. Bo has received honoraria from Pfizer Italy and Bristol-Myers Squibb Italy, Boehringer Italy, and Bayer Italy for scientific collaborations.

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APPENDIX A

Event	Expected value[1]	Distribution type	Mean	SE[2]
Apixaban vs. warfarin				
Stroke/SE	-0,236	Normal	-0,236	0,357
Major bleeding	-0,371	Normal	-0,371	0,282
Hemorragic stroke	-0,673	Normal	-0,673	0,734
Dabigatran vs. warfarin				
Stroke/SE	-0,431	Normal	-0,431	0,434
Major bleeding	-0,073	Normal	-0,073	0,273
Hemorragic stroke	-1,347	Normal	-1,347	1,280
Rivaroxaban vs. warfarin				
Stroke/SE	-0,139	Normal	-0,139	0,324
Major bleeding	0,049	Normal	0,049	0,271
Hemorragic stroke	-0,528	Normal	-0,528	0,809
Edoxaban vs. warfarin				
Stroke/SE	-0,139	Normal	-0,139	0,301
Major bleeding	-0,223	Normal	-0,223	0,243
Hemorragic stroke	-0,598	Normal	-0,598	0,679

Table IA. *Parameters and distributions used for the PSA*
[1] These values represent the natural logarithm of reported HRs
[2] Obtained from reported CI95%