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Does X(a) mark the spot? An indirect mixed treatment comparison of Xa inhibitors compared to warfarin for patients with atrial fibrillation

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ABSTRACT

The study sets out to compare the safety and efficacy of oral Non-vitamin K antagonists and warfarin in patients with atrial fibrillation.

Background: Patients with atrial fibrillation carry a higher than normal risk for stroke, thus making them dependent on long-term anticoagulation treatment. While warfarin is considered to be the gold standard, several of its attributes, hinder adherence of patients to the therapeutic regimen. A new therapeutic category, the oral Non-vitamin K antagonist oral anticoagulants, aims to provide better and safer care to patients presenting with atrial fibrillation.

Method: An indirect mixed treatment comparison using data from published randomised controlled trials.

Results: Looking at the primary efficacy endpoint of stroke or systematic embolism, apixaban, rivaroxaban and dabigatran, demonstrated significant superiority compared to warfarin, while a trend exists for edoxaban [OR: 0.84 (95% CI 0.74–1.02)]. At the primary safety endpoint of major bleeding, evidence suggest that apixaban and edoxaban are superior to warfarin. Warfarin proved to be safer regarding gastrointestinal bleeding, compared to rivaroxaban, dabigatran and edoxaban. At the secondary efficacy endpoints of hemorrhagic and intracranial stroke, all Non-vitamin K antagonists oral anticoagulants were related to reduced risk versus warfarin.

Conclusions: The Non-vitamin K antagonist oral anticoagulants constitute a new and promising category in the field of atrial fibrillation, even in the context of uncertainty, which an indirect comparison yields.

Introduction

As life expectancy continues to rise, the prevalence of certain chronic conditions rises alongside and they impose a significant burden on health systems [1]. Among the array of chronic health conditions, heart conditions stand-out. At a granular level among the multitude of heart conditions, atrial fibrillation (AF) prevails. AF comprises the most common sustained abnormal heart rhythm and it is defined by the rapid and unpredictable contractions of the atria of the heart. Its incidence is estimated to rise more than double by 2030 a finding which is imputed to an ageing population [2]. A causal relationship between AF and stroke has been established and if AF is left untreated the risk of stroke increases five-fold. With this seen more often than none, a substantial burden is held by health systems worldwide, both for medical care and rehabilitation costs [3]. Therefore, AF patients require long-term anticoagulation treatment for stroke prevention [4]. The selection of an anticoagulation agent reaches a stand-off between efficacy and potential adverse events, especially major bleeding, with the latter being one of the major reasons why anticoagulation treatment is underutilised.

The current benchmark in the stroke prevention in AF patients is warfarin, the only anticoagulant that was granted an official indication for stroke prevention in AF before 2010. Warfarin is a vitamin k antagonist (VKA) with a proven efficacy in reducing stroke and death. Its efficacy is compromised by an increased risk of bleeding [5] while its use is further restrained due to its several interactions with food and other drugs. These ensue to the need for frequent coagulation monitoring [6]. Consequently, the risk of interaction, coupled with the requirement for frequent laboratory monitoring has culminated to high discontinuation rates of warfarin [7].

As a result, approximately only half of AF patients receive the indicated anticoagulation treatment [8]. This accentuates the imperative and clear need for safer and easier to administer and monitor agents, whose pharmacokinetic properties should largely

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be unscathed by dietary habits and/or concomitant administration of other products [6–9].

The advances in pharmacology and the better understanding of the molecular origin of the coagulation pathways have facilitated and enhanced the research for targeted and selective anticoagulation agents.

The new pharmaceutical category of Non-vitamin K oral anticoagulants (NOACs) has raised hopes to this direction of providing safe, convenient and efficacious stroke prevention pathway [10]. NOACs can be classified into two broad categories: The direct factor Xa inhibitors, which include apixaban, rivaroxaban and edoxaban and the direct thrombin inhibitors, such as dabigatran. Factor Xa is a single enzyme in the coagulating process and it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways [11]. Specifically, factor Xa is the first factor to be activated after the activation of the tissue factor, whose trigger signals the initiation of the thrombin generation and fibrin formation sequence. In this biological activity cascade, factor Xa catalyses the formation of more than 100 thrombin molecules. These findings have shifted the focus of research in this therapeutic field towards the development of more effective and safer agents.

Currently, 4 agents were granted a regulatory approval (rivaroxaban, dabigatran, edoxaban, apixaban). No comparative studies have been performed yet as these would require huge number of patients in high quality randomised controlled trials (RCT); foremost such studies may fall outside the strategic scope of marketing authorization holders.

Methodology

What is more, even if RCT are frequently compared to placebo or an older technology method, they usually cannot be compared to all potentially comparative products. This creates a gap which can be spanned through the use of indirect mixed treatment comparisons (MTC), and generate a treatment network. MTC has emerged as the pinnacle in synthesising evidence from direct and indirect comparisons and it can help estimate the relative effects for treatments that are not directly compared. The latter is achieved by pooling both direct and indirect evidence, to strengthen inferences.

To this direction, the aim of this study is to perform a MTC of all commercially available Xa inhibitors and enable informed decision making in this field.

A systematic review was conducted for randomised controlled trials (RCT) comparing new Xa inhibitors to warfarin in patients with AF. We searched the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, Scopus, as well as referring papers. Major cardiological congress abstracts were also searched. We used the mesh terms “new oral anticoagulants,” “oral thrombin inhibitors,” “oral factor Xa inhibitors,” “dabigatran,” “rivaroxaban,”, “dabigatran” “edoxaban,” “betrixaban”. The quality of the studies was assessed with the Cochrane risk of bias tool.

According to the PICO structure, the following inclusion criteria were defined as below:

1. Population: Adults aged 18 years and older with nonvalvular AF.
2. Interventions: Randomised controlled trials that compared NOACs, including dabigatran, rivaroxaban, edoxaban and apixaban. (We did not restrict this to blinded studies, since warfarin needs monitoring which impedes the blinding process)
3. Comparators: warfarin and NOAC
4. Outcomes: Stroke or systemic embolism, stroke myocardial infarction (MI), all-cause, major bleeding, gastrointestinal bleeding, hemorrhagic stroke, ischemic stroke and intracranial bleeding.

We adhered to the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews (Fig. 1). PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses [12].

The titles and abstracts were screened by the lead reviewer and two reviewers independently to exclude clearly irrelevant references. If the abstract did not provide sufficient data to enable selection, full papers were reviewed. Secondly, full-text manuscripts were screened for compliance with inclusion criteria of the review by two independent reviewers. Disagreements were resolved by discussion or by consulting with the lead reviewer in order to reach a consensus [12]. We identified 2988 papers through database searching and an additional of 126 from other sources. Having performed all the steps dictated by the PRISMA guidelines, including removal of duplication and records excluded on title, 2833 papers were excluded and we fully we fully assessed 65 papers. Sixty-one were finally excluded and the indirect comparison was conducted using 4 eligible RCTs [13–16].

Two independent reviewers extracted data from the RCTs and the lead reviewer assessed their correctness. The primary efficacy outcome of this study was the stroke or systemic embolism. Secondary efficacy endpoints such as stroke, ischemic or uncertain type of stroke, hemorrhagic stroke and death from any cause and myocardial infarction were also assessed. The primary safety outcome was major bleeding and secondary safety endpoints such as gastrointestinal bleeding, were also cited as part of the assessment. The quality of the included trials was investigated by the Cochrane Collaboration's tool for assessing risk for bias, which evaluates allocation concealment, sequence generation, blinding of patients, blinding of personnel and blinding of investigators, incomplete data, selective reporting and other validity flaws [17]. The risk for bias in each domain was classified as high, low, or unclear for each RCT.

Data synthesis and analysis outcome measures

The statistical analysis was performed using a MTC model, based on the Bayesian methodology (Fig. 2). The model assumes that the number of specified events (primary and secondary safety and efficacy endpoints) follow a binomial likehood, while the probability of each event is modelled on a logit scale [18]. The relative treatment effects are reported as the posterior median odds ratio (OR), using a 95% credible interval (CI).

The MTC offers two major advantages: Primarily, it allows estimation of relative treatment effects among products that were not tested head-to-head, without disrupting the randomisation -a major bias in this kind of tests. In addition to this, the ability to include both direct and indirect comparisons can further combat uncertainty.

Based on the methodology, the agents were classified according to the probability of each one being the best in each corresponding endpoint. Each treatment was ranked on generated probabilities for all treatment being at every possible rank, for which a mean distribution was calculated. These not integer-valued ranks can display the probability that each agent is best at a given indication [19]. The model was synthesised on winbugs software [20], with a code first introduced by Dias et al [21]. Studies that reported zero or 100% events in all arms were excluded since they contributed no evidence to the relative effect. The model reports both random and fixed effects on the basis of model fit. Since there was only one study per product, a random effect analysis was used to achieve this. The goodness of fit was assessed with the posterior mean of the residual deviance and the deviance information criteria (DIC). Heterogeneity was reported as the posterior median between trial standard deviation with 95% CI.

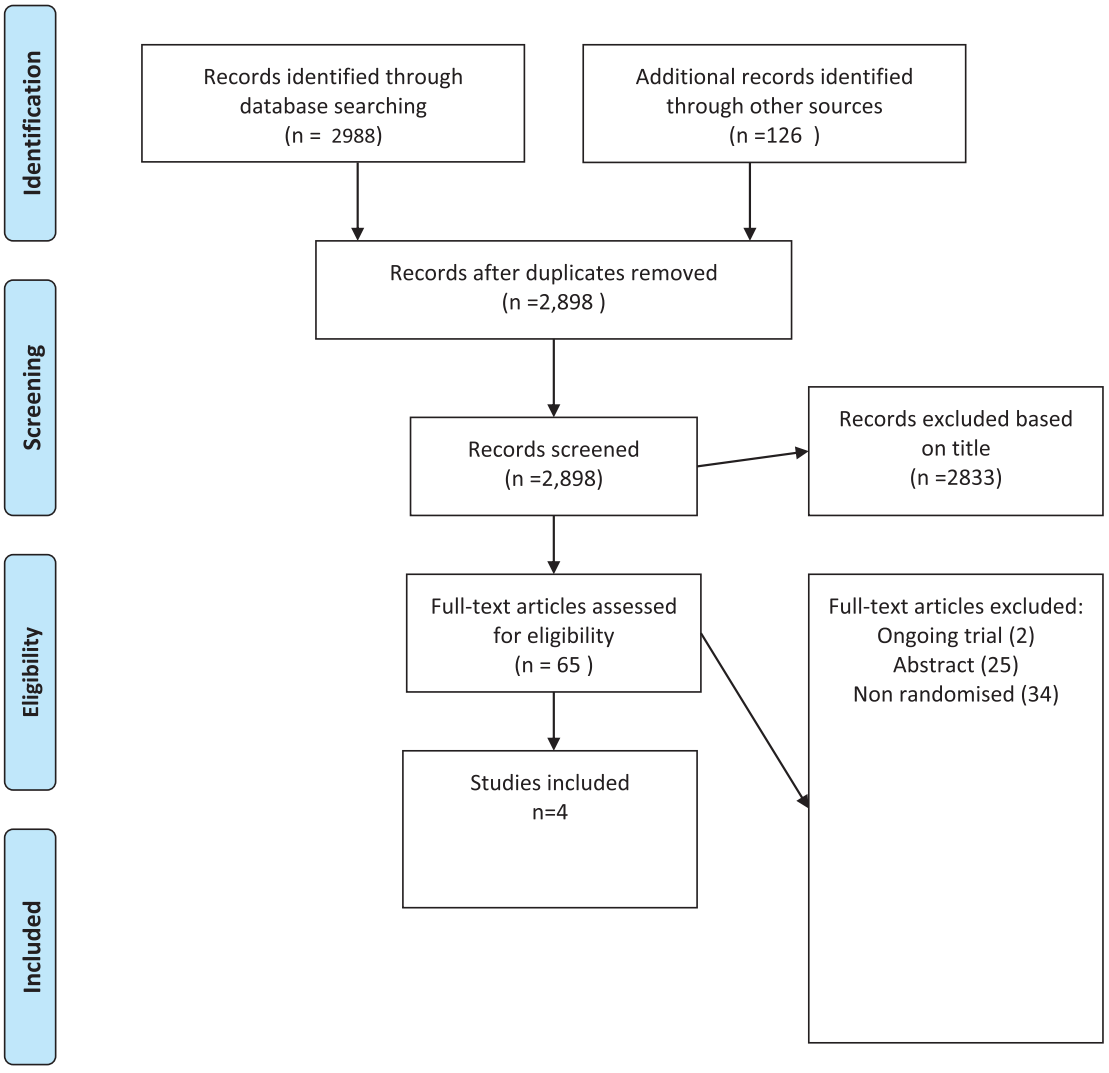

Fig. 1. Flow diagram of literature review.

The comparison between direct and indirect evidence was performed through a Bayesian p-value, which provides an evidence of a significant effect. The Bayesian methodology capitalizes on the use of priors. Therefore, vague normal priors with mean zero and variance 10,000 were used for all trial baselines and relative effect parameters.

The convergence of the model, which defines the model's credibility, was assessed through visual inspection of trace plots and through Brooks–Gelman–Rubon plots. This was achieved after 50,000 burn-in iterations and an additional 100,000 iterations were performed to confirm the stability and accuracy of the model. The assessment of the consistency of both the direct and indirect evidence was not feasible, as no network loops seemed to exist in the studies.

Literature review

Our search yielded four trials which met our criteria and were included in this study. ROCKET AF is a multicentre, randomised double-blind, double dummy study which recruited 14,264 patients and compared rivaroxaban 20 mg to dose-adjusted warfarin [13]. ROCKET AF study had a non-inferiority endpoint pertaining to the prevention of stroke or systemic embolism, which was prespecified to be performed in the per-protocol population. ARISTOTLE trial, also a non-inferiority randomized controlled, double-blind, parallel arm trial utilised an intention-to-treat analysis (ITT) only for the efficacy outcomes, but not for safety endpoints, which included patients who have received at least one dosage of the medicine [14]. ARISTOTLE compared warfarin (target international normalized ratio (INR): 2.0 to 3.0) with apixaban 5 mg bd in patients with AF.

RE-LY is a prospective randomized open-label study. Contrary to the study being non-blinded, the investigators, the steering committee and the sponsor were blinded, thus reducing the risk for bias. RE-LY recruited 18,113 patients which were randomised in three arms: dabigatran 110 mg, dabigatran 150 mg and adjusted-dose warfarin [15].

ENGAGE AF-TIMI was a double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with dose-adjusted warfarin (target INR: 2.0 to 3.0) in 21,105 patients with moderate to-high-risk atrial fibrillation (median follow-up, 2.8 years) [16]. The primary efficacy end-point was stroke or systemic embolism. This analysis used the modified intention-to-treat population.

Results

Primary endpoints

Stroke or systemic embolism

At the primary efficacy endpoint, all Xa inhibitors demonstrated superiority to warfarin except both doses of edoxaban and dabigatran of 110 mg. The results for edoxaban 60 mg should be treated

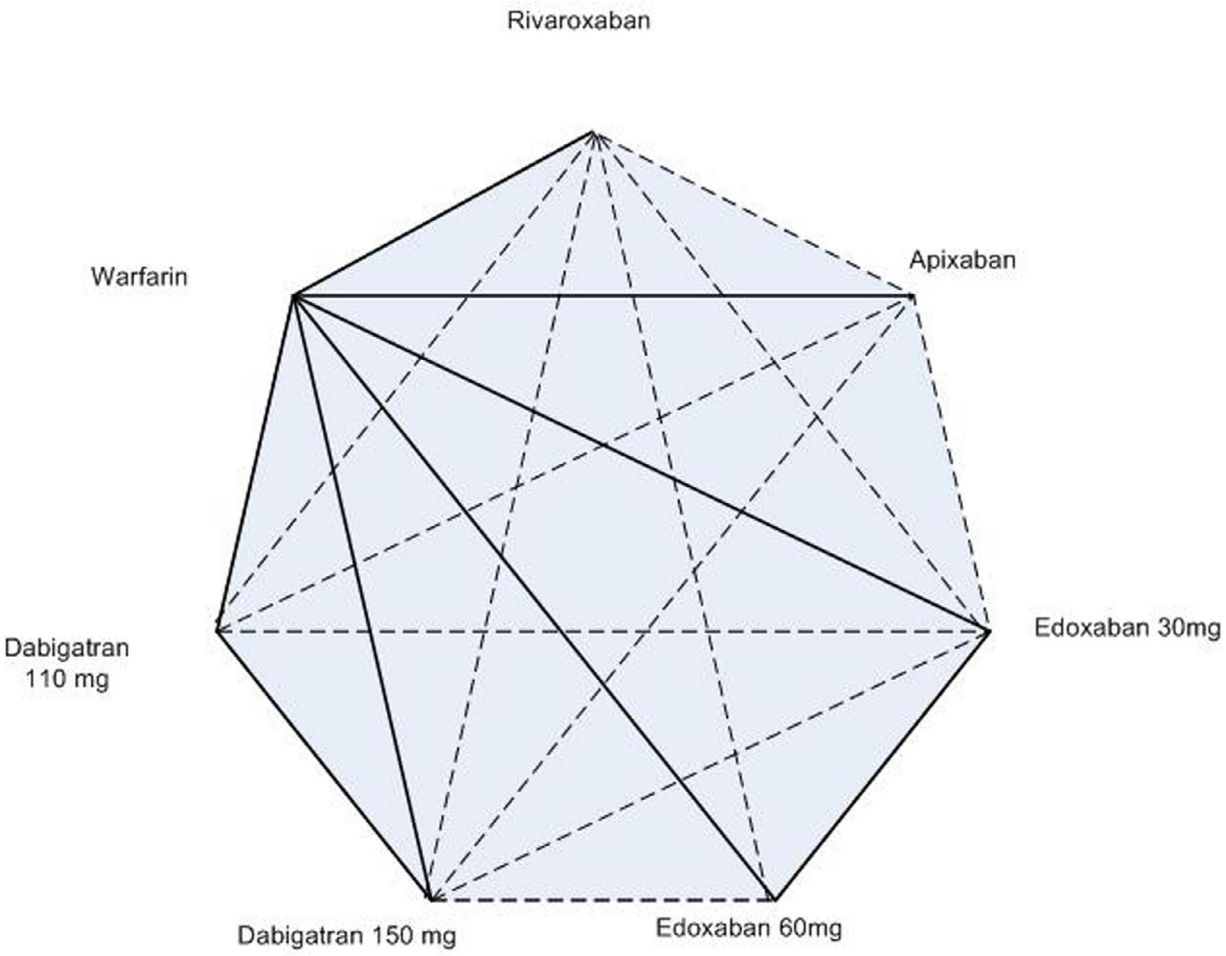

Fig. 2. Indirect network meta-analysis/mixed treatment comparison of Xa inhibitors vs warfarin. (Dotted line implies indirect evidence-solid line represents direct evidence).

with caution : OR 0.87; 95% CI 0.74–1.02 (Table 1). Dabigatran 150 mg was superior to rivaroxaban and apixaban and carried the highest probability of being the most effective in this endpoint (79.6%) (Table 2) (Fig. 3).

Major bleeding

Major bleeding constitutes the primary safety endpoint. Except for rivaroxaban and dabigatran 150 mg, all other agents were associated to significant superiority to warfarin (Table 3). Indirect comparison indicated that apixaban, both doses of edoxaban and dabigatran 110 mg showed superiority to Rivaroxaban. Edoxaban 30 mg was superior to edoxaban 60 mg, both doses of dabigatran, apixaban and rivaroxaban, while it conveyed a 99% probability to be the best (Table 4). Apixaban was found superior to rivaroxaban and dabigatran 150 mg (Fig. 4).

Secondary endpoints

All-cause mortality

Rivaroxaban and apixaban were associated to lower risk versus warfarin, dabigatran 150 mg and edoxaban 30 mg. Edoxaban 60 mg was superior to edoxaban 30 mg. Rivaroxaban demonstrated the highest probability (77%) of being the best agent pertinent to the all-cause mortality (Tables 3 and 4).

Stroke only

Apixaban and dabigatran 150 mg were related to significantly lower risk in comparison to warfarin. Apixaban and rivaroxaban were associated with lower risk versus edoxaban 30 mg. Dabigatran 150 mg was superior to dabigatran 110 mg and to both doses of edoxaban, also reflected in its 86% probability to be the best agent (Tables 1 and 2).

Myocardial infarction (MI)

With a 60% probability of being the best in terms of MI prevention, Rivaroxaban surpassed apixaban which demonstrated a commensurate 27% probabilitiy and edoxaban 60 mg which carried a 10% probability respectively (Table 4).

Warfarin was associated with lower risk than dabigatran 150 mg. Rivaroxaban demonstrated significant superiority to both dosages of dabigatran and edoxaban 30 mg. Apixaban was also superior to both doses of dabigatran, while edoxaban 60 mg was superior to low dose of edoxaban (Table 3).

Hemorrhagic stroke

All Xa inhibitors proved significant superiority to warfarin. Amongst the Xa category, dabigatran 150 mg was superior to rivaroxaban and edoxaban 60 mg, strongly demonstrating the highest probability of being the best. Edoxaban 60 mg was inferior to its counterpart lower dose (Tables 1 and 2).

Intracranial stroke

All Xa inhibitors were associated to significant risk reduction versus warfarin. The low dose of dabigatran and edoxaban were

Table 1
Odds ratio of efficacy endpoints.

		Stroke or systemic embolism		Stroke		Hemorrhagic stroke		Intracranial stroke		Ischemic stroke	
		Median OR	95 CI%	Median	95 CI%	Median OR	95 CI%	Median OR	95 CI%	Median OR	95 CI%
Warfarin											
	Rivaroxaban	0.77*	0.63–0.93	0.82	0.67–1.01	0.57*	0.35–0.90	0.63*	0.45–0.89	0.90	0.72–1.12
	Apixaban	0.79*	0.66–0.95	0.78*	0.65–0.95	0.50*	0.34–0.73	0.41*	0.29–0.57	0.92	0.74–1.14
	Dabigatran 110 mg	0.91	0.74–1.12	0.92	0.74–1.14	0.30*	0.16–0.54	0.30*	0.19–0.46	1.12	0.89–1.41
	Dabigatran 150 mg	0.65*	0.52–0.82	0.64*	0.51–0.81	0.25*	0.12–0.47	0.40*	0.26–0.59	0.77*	0.59–0.98
	Edoxaban 60 mg	0.87	0.74–1.02	0.88	0.7476–1.03	0.53*	0.37–0.76	0.45*	0.33–0.61	1.00	0.83–1.2
	Edoxaban 30 mg	1.14	0.98–1.32	1.14	0.97–1.33	0.32*	0.21–0.49	0.30*	0.21–0.42	1.43*	1.21–1.70
Rivaroxaban											
	Apixaban	1.02	0.78–1.34	0.95	0.72–1.25	0.88	0.48–1.61	0.65	0.40–1.051	1.01	0.74–1.38
	Dabigatran 110 mg	1.18	0.89–1.56	1.11	0.83–1.48	0.52	0.24–1.12	0.47*	0.278–0.82	1.24	0.90–1.71
	Dabigatran 150 mg	0.85	0.63–1.14	0.78	0.57–1.05	0.44*	0.19–0.97	0.63	0.37–1.06	0.85	0.60–1.19
	Edoxaban 60 mg	1.11	0.87–1.43	1.06	0.82–1.37	0.93	0.52–1.68	0.71	0.45–1.13	1.11	0.83–1.48
	Edoxaban 30 mg	1.49*	1.16–1.9	1.38*	1.07–1.77	0.56	0.30–1.06	0.47*	0.29–0.77	1.59*	1.2–2.10
Apixaban											
	Dabigatran 110 mg	1.14	0.87–1.51	1.172	0.88–1.55	0.60	0.28–1.21	0.72	0.41–1.24	1.22	0.89–1.67
	Dabigatran 150 mg	0.83	0.622–1.1	0.82	0.60–1.10	0.50	0.23–1.05	0.96	0.57–1.60	0.83	0.59–1.16
	Edoxaban 60 mg	1.08	0.85–1.38	1.11	0.87–1.43	1.06	0.63–1.79	1.08	0.69–1.70	1.09	0.82–1.45
	Edoxaban 30 mg	1.44*	1.14–1.83	1.451*	1.13–1.85	0.64	0.36–1.13	0.72	0.44–1.17	1.56*	1.18–2.05
Dabigatran 110 mg											
	Dabigatran 150 mg	0.72*	0.57–0.9	0.7*	0.55–0.88	0.84	0.38–1.85	1.32	0.80–2.20	0.68*	0.53–0.87
	Edoxaban 60 mg	0.94	0.73–1.22	0.95	0.73–1.24	1.769	0.89–3.6	1.49	0.88–2.56	0.89	0.66–1.2
	Edoxaban 30 mg	1.261	0.97–1.62	1.23	0.95–1.60	1.075	0.52–2.30	0.99	0.57–1.76	1.27	0.96–1.70
Dabigatran 150 mg											
	Edoxaban 60 mg	1.30	0.99–1.72	1.36*	1.02–1.81	2.09*	1.03–4.51	1.12	0.68–0.86	1.30	0.95–1.78
	Edoxaban 30 mg	1.73*	1.32–2.26	1.76*	1.33–2.34	1.27	0.60–2.82	0.75	0.44–1.28	1.86*	1.38–2.53
Edoxaban 60 mg											
	Edoxaban 30 mg	1.31*	1.12–1.53	1.29*	1.10–1.52	0.6079*	0.37–0.95	0.66*	0.44–0.99	1.43*	1.20–1.69

* Evidence of a significant effect.

Table 2
Probability of each agent being the best for the efficacy endpoints.

Agent	Probability of being the best at reducing stroke or systemic embolism	Probability of being the best at reducing stroke	Probability of being the best at reducing haemorrhagic stroke	Probability of being the best at reducing intracranial stroke	Probability of being the best at reducing ischemic stroke
Warfarin	0%	0%	0	0%	0%
Rivaroxaban	12.2%	4%	0%	0%	13.6%
Apixaban	7.2%	8%	0%	2.8%	10.5%
Dabigatran 110 mg	0%	0%	26.5%	46%	0%
Dabigatran 150 mg	79.6%	86%	55.5%	4.6%	74%
Edoxaban 60 mg	0.7%	0.6%	0%	0.4%	1.6%
Edoxaban 30 mg	0%	0%	17%	45.9%	0%

superior to rivaroxaban and they both carried the highest probability of being the best agents. Additionally, edoxaban 30 mg was superior to the 60 mg (Tables 1 and 2).

Gastrointestinal bleeding

The edoxaban 30 mg carried the highest probability of being the most effective. Its clinical benefit was superior to all other Xa inhibitors-except apixaban- and also to warfarin. Warfarin was superior to all agents except the dabigatran 110 mg and apixaban (Tables 3 and 4).

Intracranial bleeding

All Xa inhibitors except apixaban, reduced the risk of intracranial bleeding compared to warfarin. Among the Xa inhibitors, both

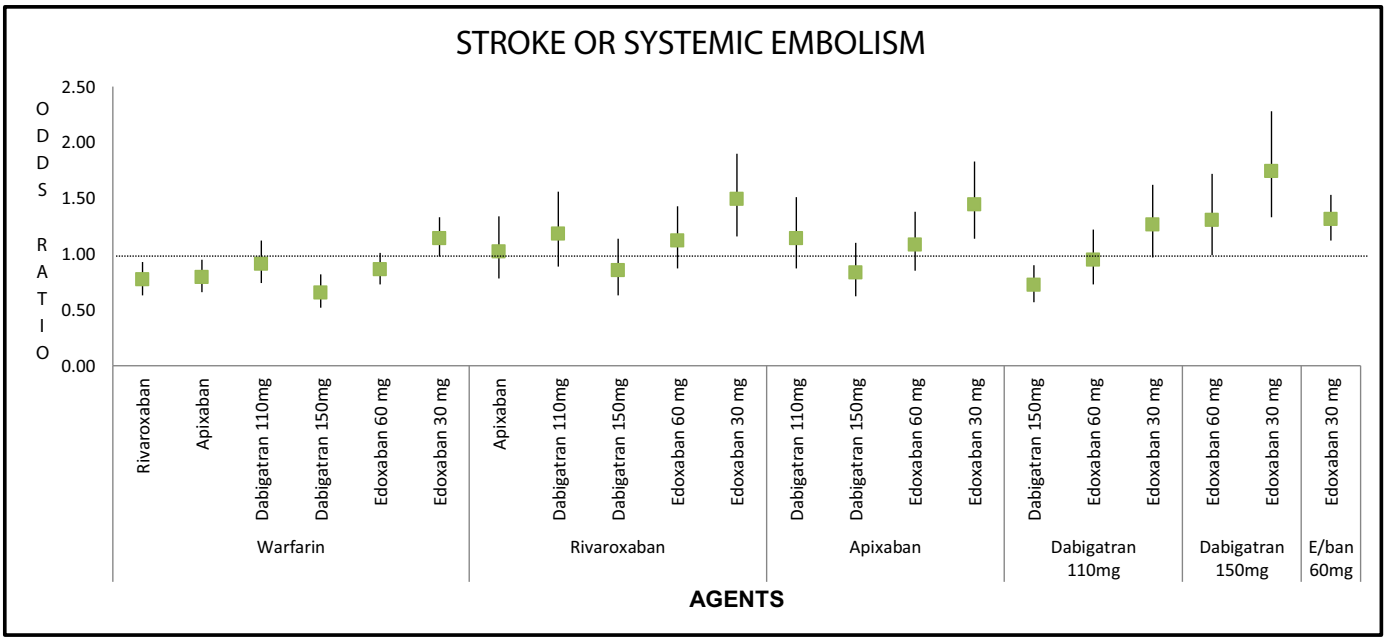

Fig. 3. Odds ratio for stroke or systemic embolism endpoint (95% credible interval).

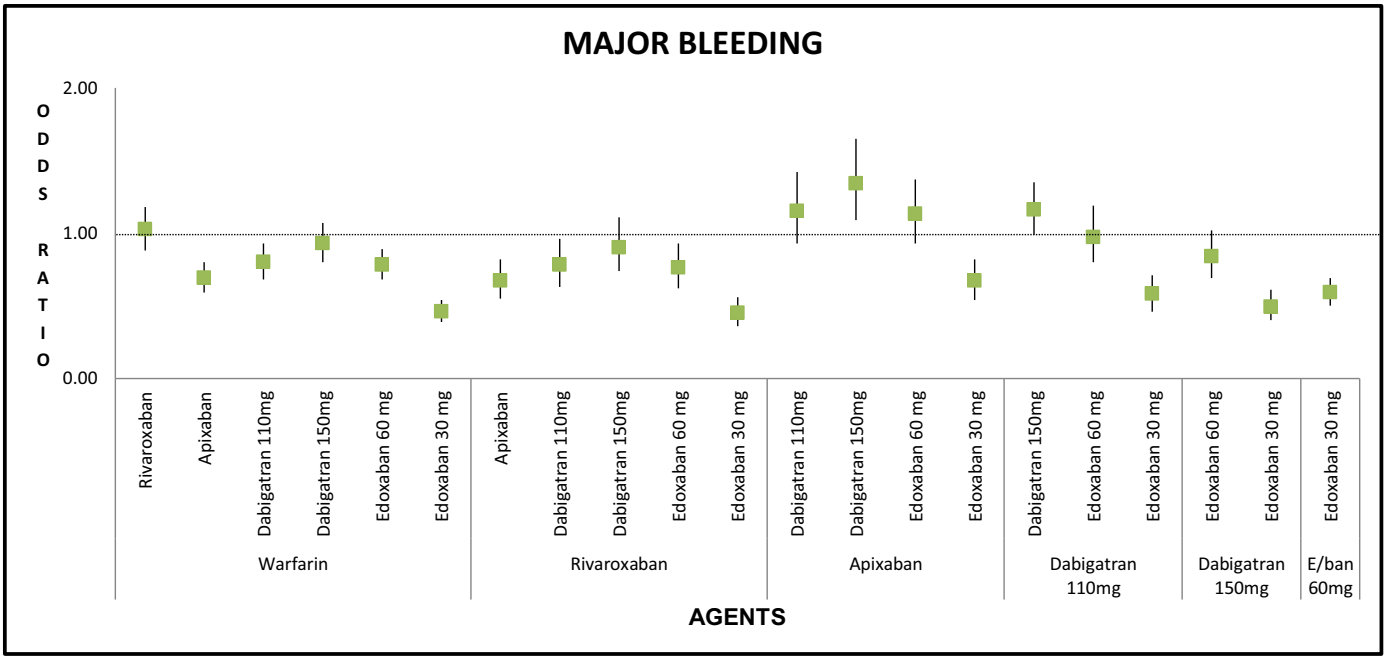

Fig. 4. Odds ratio for major bleeding endpoint (95% Credible interval).

doses of dabigatran and edoxaban demonstrated superiority to rivaroxaban and apixaban. Edoxaban 30 mg was also superior to its counterpart high dose, while along with dabigatran low dose, these two agents demonstrated the highest probabilities of being the best agents, pertinent to the intracranial bleeding (Tables 3 and 4).

Ischemic stroke

Dabigatran exhibited the highest probability of being the best Xa inhibitor, in terms of ischemic stroke reduction (Tables 1 and 2).

Model fit

The values of DIC were close to the number of data points, indicating a well-fitting model for all endpoints. We did not observe any differences of ≥5 points for residual deviance and the generated DIC values were considered meaningful. We verified the mode fit by inspection of individual data points' contributions to the residual deviance.

Discussion

In the primary composite efficacy endpoint, the prevention of stroke and systemic embolism, all Xa inhibitors (except edoxaban 30 mg-the credible interval of edoxaban 60 mg suggests a borderline significant effect and it should be interpreted with caution) demonstrated evidence of a significant effect compared to warfarin's corresponding one. Amongst the NOAC category, evidence of a significant difference was found only between the edoxaban 30 mg and that of rivaroxaban, apixaban, and dabigatran. Similar

Table 3
Odds ratio of safety endpoints, all cause mortality and myocardial infarction.

		Major bleeding		Gastrointestinal bleeding		Intracranial Bleeding		All cause mortality		MI	
Warfarin		Median OR	95 CI%	Median	95 CI%	Median OR	95 CI%	Median OR	95 CI%	Median OR	95 CI%
	Rivaroxaban	1.02	0.88–1.18	1.46*	1.19–1.812	0.71*	0.55–0.91	0.82*	0.68–0.99	0.79	0.61–1.03
	Apixaban	0.69*	0.59–0.80	0.87	0.67–1.14	0.87	0.67–1.14	0.89*	0.79–0.99	0.87	0.65–1.16
	Dabigatran 110 mg	0.80*	0.68–0.93	1.113	0.86–1.43	0.30*	0.19–0.46	0.98	0.85–1.12	1.37	0.99–1.9
	Dabigatran 150 mg	0.93	0.80–1.07	1.461*	1.15–1.851	0.40*	0.27–0.59	1.08	0.95–1.2	1.4	1.01–1.96
	Edoxaban 60 mg	0.78*	0.68–0.89	1.23*	1.01–1.495	0.45*	0.33–0.61	0.94	0.85–1.05	0.94	0.74–1.19
	Edoxaban 30 mg	0.46*	0.39–0.54	0.67*	0.53–0.84*	0.3*	0.21–0.43	1.09	0.98–1.21	1.2	0.96–1.51
Rivaroxaban											
	Apixaban	0.67*	0.55–0.82	0.59*	0.42–0.83	1.22	0.85–1.76	1.07	0.86–1.34	1.09	0.74–1.62
	Dabigatran 110 mg	0.78*	0.63–0.96	0.75	0.54–1.05	0.42*	0.25–0.69	1.18	0.94–1.49	1.72*	1.13–2.62
	Dabigatran 150 mg	0.90	0.74–1.11	0.99	0.72–1.36	0.56*	0.35–0.89	1.31*	1.04–1.65	1.76*	1.16–2.69
	Edoxaban 60 mg	0.76*	0.62–0.93	0.83	0.62–1.11	0.63*	0.42–0.94	1.14	0.92–1.42	1.17	0.82–1.68
	Edoxaban 30 mg	0.45*	0.36–0.56	0.45*	0.33–0.62	0.42*	0.27–0.65	1.32*	1.07–1.64	1.50*	1.06–2.14
Apixaban											
	Dabigatran 110 mg	1.15	0.93–1.42	1.26	0.88–1.82	0.34*	0.2–0.57	1.1	0.92–1.31	1.56*	1.01–2.42
	Dabigatran 150 mg	1.34*	1.09–1.65	1.66*	1.16–2.37	0.46*	0.28–0.73	1.22*	1.02–1.45	1.60*	1.04–2.48
	Edoxaban 60 mg	1.13	0.93–1.37	1.4*	1.00–1.94	0.51*	0.34–0.78	1.06	0.91–1.24	1.07	0.73–1.56
	Edoxaban 30 mg	0.67*	0.54–0.82	0.76	0.54–1.08	0.34*	0.22–0.53	1.23*	1.05–1.43	1.37	0.95–1.98
Dabigatran 110 mg											
	Dabigatran 150 mg	1.16*	0.99–1.35	1.31*	1.04–1.65	1.32	0.8–2.21	1.11	0.97–1.27	1.02	0.76–1.38
	Edoxaban 60 mg	0.97	0.80–1.19	1.10	0.80–1.51	1.49	0.88–2.5	0.96	0.81–1.15	0.68	0.45–1.03
	Edoxaban 30 mg	0.58*	0.46–0.71	0.60*	0.43–0.84	1	0.5–1.7	1.11	0.94–1.32	0.87	0.58–1.3
Dabigatran 150 mg											
	Edoxaban 60 mg	0.84	0.69–1.02	0.84	0.61–1.13	1.12	0.6–1.86	0.87	0.73–1.03	0.66	0.44–1.00
	Edoxaban 30 mg	0.49*	0.40–0.61	0.46*	0.33–0.63	0.75	0.44–1.28	1	0.85–1.19	0.85	0.57–1.26
Edoxaban 60 mg											
	Edoxaban 30 mg	0.59*	0.50–0.69	0.54*	0.43–0.67	0.66*	0.33–0.99	1.15	1.04–1.28	1.27*	1.01–1.61

* Evidence of significant effect.

Table 4
Probability of each agent of being the best in safety, MI and all-cause mortality endpoints.

Agent	Probability of being the best in reducing major bleeding	Probability of being the best at reducing gastrointestinal bleeding	Probability of being the best at reducing intracranial bleeding	Probability of being the best in reducing MI	Probability of being the best in reducing all-cause mortality
Warfarin	0%	0%	0%	2%	0
Rivaroxaban	0%	0%	0%	60%	71%
Apixaban	0%	6.8%	0%	27%	22%
Dabigatran 110 mg	0%	0.1%	47%	1%	2%
Dabigatran 150 mg	0%	0%	4.6%	0%	0%
Edoxaban 60 mg	0%	0%	0%	10%	3%
Edoxaban 30 mg	99%	93%	47%	0%	0%

evidence of significant difference effect was also found between dabigatran 110 and dabigatran 150 mg. In the primary safety endpoint, major bleeding, all Xa inhibitors except rivaroxaban and dabigatran 150 mg, demonstrated evidence of a significant effect compared to warfarin, an observation that aligns with previous findings [22,23]. Bleeding comprises a major concern in AF treatment and has largely impeded warfarin's uptake, therefore these findings cast light on this topic. Amongst the Xa inhibitors, all Xa inhibitors (except dabigatran 150 mg) demonstrated evidence of significant effect compared to that of rivaroxaban, while the low doses of dabigatran (110 mg) and edoxaban (30 mg) evinced superior safety profile further documented by the 99% probabilities of edoxaban 30 mg being the safest agent.

This was further corrobrated by the superior performance of edoxaban 30 mg in the rates of gastrointestinal bleeding (GI), showing a 93% probability of being the best agent. Although data

Table 5
Cochrane risk of bias tool.

	Selection bias		Reporting bias	Performance bias	Detection bias	Attrition bias	Other bias
	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Other sources of bias
ARISTOTLE, 2011	+	+	+	+	+	?	+
ENGAGE AF-TIMI, 2013	+	+	+	+	+	+	+
RE-LY, 2009	+	+	+	?	?	+	+
ROCKET AF, 2011	+	+	+	+	+	+	?

? Indicates unclear risk of bias.
+Indicates low risk of bias.
-Indicates high risk of bias.

are rather inconclusive, results from this meta-analysis suggest that Xa inhibitors are associated with higher rates of gastrointestinal bleeding, for which evidence of statistical difference exist between warfarin and rivaroxaban, dabigatran 150 mg and edoxaban 60 mg. Nevertheless, this finding must be weighted against their superior effect in the intracranial bleeding endpoint, in which all NOAC demonstrated a significant positive effect compared to warfarin. These differences between NOAC and warfarin are expected to be augmented in real life since in these studies the older patients, who carry a higher risk for major bleeding are not sufficiently presented. Also, it was proved that patients in clinical studies demonstrated better levels of warfarin-owing to stricter protocol-defined monitoring-compared to patients in the community [24]. Indicatively, the mean percentage of time spent in the therapeutic range for warfarin patients was 63.6% (95% CI: 61.6%-65.6%), while in community settings the corresponding percentage further plummeted, a finding that illustrates the unmet clinical need in this sector [24]. Real life data from the Danish registry [25,26] indicate a lower risk of GI bleeding for apixaban and dabigatran compared to warfarin, while, on the contrary, rivaroxaban demonstrated increased risk of GI bleeding [27].

Given that warfarin's downside, which has emerged as a barrier in its wider market penetration and adherence of patients, is the interaction with both medicines and food, along with the frequent need to monitor, we anticipate that in real life, Xa inhibitors will demonstrate superior efficacy and safety compared to the published data.

Scrutinizing the Xa category, some intra-category disparities were identified. It was observed that all the Xa inhibitors demonstrated evidence of significant effect compared to warfarin in the endpoints of haemorrhagic and intracranial stroke, except rivaroxaban. Regardless of the latter, the low performance of rivaroxaban in the foresaid endpoints has to be weighed against its superior performance at the all-cause mortality and at the MI endpoints (evidence of superior performance compared to Dabigatran 110 mg and Dabigatran 150 mg and edoxaban low dose, while apixaban is superior to dabigatran 150 mg).

Conclusion

The current study affirms that Xa inhibitor category is superior to the gold standard treatment warfarin, a finding that streamligns with other authors [28]. The data also indicate that some endpoints are still engulfed by uncertainty, since the results are rather inconclusive and more research could elucidate the effect of this new category. Further to this, data from this study also point out some divergences among NOACs, pertinent to the selected endpoints. Using this information, a physician would be able to choose a product, based on the particularities of the individual patient.

It is imperative, that despite the efforts to address heterogeneity in the MTC, the included trials feature some differences that cannot be adequately construed in a meta-analysis. The open-label design of the RE-LY study is a potential bias source cascading to the overestimation of dabigatran effects [29]. Some authors delineate that corrections stemming out of the open-label bias study design, could minimise the reported differences between apixaban and dabigatran [29]. This controversy was further expounded by a review which included three of the four agents of our network and concluded that the study design was not responsible for the reported differences. Rather, the blinding of the studies was of major importance [30]. Nevertheless, our comprehensive assesment regarding bias suggests that the included studies carry a low bias risk, as assessed by the Cochrane risk of bias tool (Table 5).

The differences in the study design of the four included studies further perpetuate to the defined inclusion criteria, for which significant heterogeneity has been observed. ROCKET-AF and ENGAGE AF-TIMI enrolled patients with moderate to high risk of stroke, and in particular 90% of patients in the ROCKET-AF study had a CHADS2 score of $\geq$3. On the contrary ARISTOTLE and RE-LY studies enrolled patients with CHADS2 score of $>$2. ROCKET-AF recruited an older population. Common and yet distinct characteristics were noted across trials, such as a better mean time in the therapeutic range in the RE-LY, ENGAGE and ARISTOTLE trials. The mean time was slower in the ROCKET-AF trial, albeit only for the non-North Americans recruited patients, which correspond to 50% of the study size. Some of the findings can be attributed to the aforementioned issues.

The RE-LY study publication based all efficacy and safety analyses on the ITT population. The efficacy analysis of the ARISTOTLE and ENGAGE AF-TIMI 48 was performed on the ITT population, while the safety endpoints were assessed with the per-protocol population. In THE ROCKET trial, the primary analysis was performed in the per-protocol population, which may cascade to potential confounding and selection bias.

The use of Bayesian methodology can be of value in the evidence synthesis field. One of its attribute is the ability to present, in addition to the OR, the probability for each agent to be the best at a given endpoint. This may enhance the comprehension of clinical data by non-experts, such as political persons, who are usually involved in the decision-making process. But even for experts, this acts as a snapshot enabling the transcend to the multilayer context of clinical reporting and thus assemble a holistic view of effectiveness and safety. In this therapeutic domain, which is designated by an array of products with several endpoints, each one assigned a varying weight, the probability feature may elucidate in a more cogent and legible way, the effects of each product and facilitate a meaningful conclusion, diverting dubious analysis, even in the face of-inherent-uncertainty.

The MTC approach emerges as pivotal in the health technology assessment era, since it gives answers in cases where the individual or pair-wise meta-analyses of trials, travail to deliver comprehensible estimates of all the effectiveness parameters. The use of MTC can extenuate this shortage, and its utilisation can spell-out a multifaceted perspective of a therapeutic field, pertinent to the efficacy and safety of products.

Age structure is transforming and it is anticipated that by 2050, the size of the population pool aged 65 years and above, will double [31]. This forecast implies that cardiovascular conditions, as an age-related causality, will constitute a significant morbidity, mortality and cost-driver factor. Therefore, the assessment of medicines based on reliable and qualitative data must reach the stand-off of increasing functional life-years in the elderly, without jeopardising the financial capacity of health systems worldwide.

Limitations of the study

This study features several limitations. Firstly, the RCTs which were cited in this study had different designs, to which a certain percentage of the differences could be attributed such as statistical analysis approaches. Secondly, differences which are attributed to patient demographics cannot be ignored. Adding to these, the variance between warfarin and NOAC may be even wider in real life, since in general patients in studies monitored by community physicians, 12.2% less time was spent in the therapeutic range compared to treatment time in patients in randomized trials. Some reasoning for the latter could be attributed to warfarin's unpredictable pharmacokinetic and pharmacodynamic properties [24].

This study sheds light to the comparative assessment of an interesting new pharmacological category. Given that comparative studies are rather unlikely to be conducted due to costs and strategic planning of involved companies, indirect comparison constitutes the best alternative option.

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