Cost-effectiveness of NOACs in patients with atrial fibrillation: using real-world data for external validation

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Introduction

- Atrial fibrillation (AF) is the most common cardiac arrhythmia and is a major cause of ischaemic stroke, heart failure and cardiovascular morbidity[1], with a prevalence of 2-3%[2] in the total Dutch population.
- Anticoagulant therapy with vitamin K antagonists (VKAs) has been the most commonly prescribed treatment for the prevention of ischaemic stroke in AF over the last few decades. However, on the basis of randomised clinical trial (RCT) results, European guidelines have adopted non-vitamin K antagonist oral anticoagulants (NOACs) as the preferred treatment since 2012[1,3].
- A network meta-analysis (NMA) on pivotal RCTs in 72,000 patients with AF[4] showed that NOACs were at least as effective in the prevention of ischaemic stroke compared to VKA, while there was a 50% decrease in the incidence of haemorrhagic stroke.
- Multiple cost-effectiveness analyses have been published on the different NOACs versus VKA on the basis of the RCTs results, using different models and cost assumptions.
- Recent availability of real-world data (RWD) of the NOACs offers possibilities for the external validation of the previous cost-effectiveness analysis findings based on the NMA of RCTs results[4].

Objectives

- To evaluate the cost-effectiveness of the apixaban versus VKA and other NOACs (dabigatran, edoxaban and rivaroxaban) for stroke prevention in patients with AF in the Dutch setting.
- To explore integrating RWD on clinical event risks into the cost-effectiveness model for the purposes of external validation of the NMA-based cost-effectiveness results.

Methods

COST-EFFECTIVENESS MODEL

- An existing Markov model[5] was updated based on the most recent literature to evaluate the cost-effectiveness of apixaban compared to dabigatran, edoxaban and rivaroxaban and VKA in Dutch patients with AF.
- Over a lifetime, a hypothetical cohort of 1,000 patients with AF could remain in or move through different health states (Figure 1). A cycle length of six weeks was used to capture all events within such a short time frame.
- In the NMA-based analysis (base-case), transition probabilities were based on the clinical event risks in patients receiving apixaban and VKA (warfarin) in the ARISTOTLE trial[7]. Hazard ratios (HRs) compared to apixaban for dabigatran (110 and 150 mg), rivaroxaban and edoxaban were obtained from the NMA by Lip et al[4], who made pairwise indirect comparisons between the ARISTOTLE[7], RE-LY[8], ROCKET-AF[9] and ENGAGE-AF[10] trials.
- Direct and indirect costs in- and outside the healthcare sector were considered, since the incremental cost-effectiveness ratios (ICERs) were calculated from a societal perspective[6]. Costs and QALYs were discounted at a rate of respectively 4% and 1.5% per year[6].
- The primary outcome of our analysis is the ICER. The ICER was compared to a willingness-to-pay (WTP) threshold of €20,000/QALY, based on the disease burden calculation (proportional shortfall of 0.14) as recommended by the Dutch guidelines for pharmacoeconomic evaluation[6].
- To evaluate the influence of uncertainty in input parameters on the ICER we conducted a probabilistic sensitivity analysis (PSA) by varying costs, utilities, transition probabilities simultaneously over their 95% confidence intervals while calculating the ICERs during 2,000 simulations.

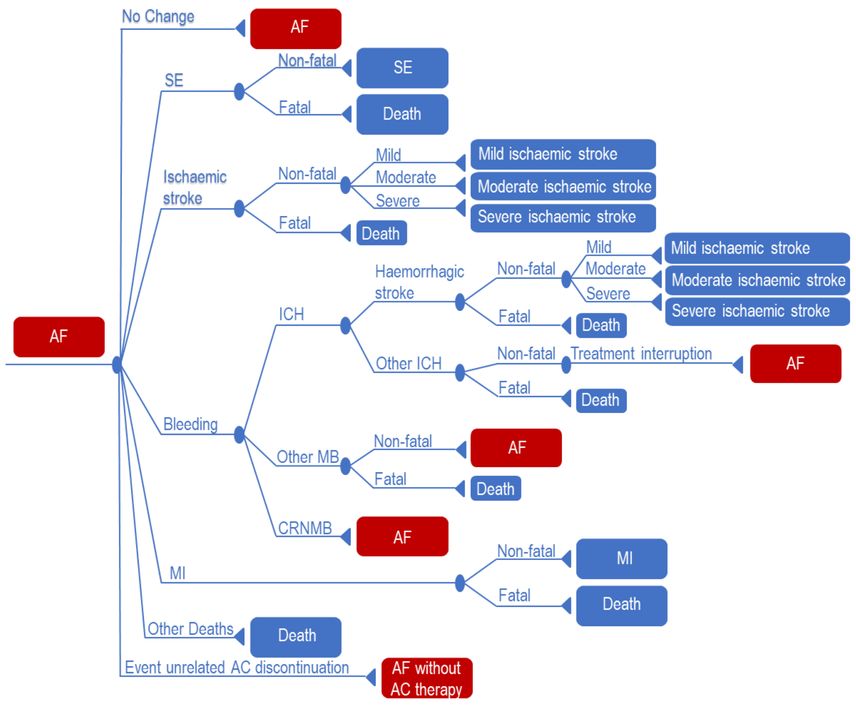

Figure 1. Representation of the Markov model. *All patients entered the model in the AF state, from where they could move to another health state upon the occurrence of one of the following events: 'ischaemic stroke', 'haemorrhagic stroke', 'other ICH', 'other MB', 'CRNMB', 'SE', 'MI', 'other deaths' or 'event unrelated AC discontinuation'. The triangles show the state a patient enters after an event. These states can be transient (red squares) or absorbing (blue squares). Abbreviations: AC, anticoagulant; AF, atrial fibrillation; CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; MI, myocardial infarction; SE, systemic embolism.*

SYSTEMATIC LITERATURE SEARCH TO IDENTIFY RWD ON CLINICAL EVENT RATES

- We conducted a systematic literature search to identify eligible publications to inform the RWD-based analysis.
- We used combinations of the following MESH terms for our PRISMA statement[11] based systematic literature search through PubMed: "real world" OR "observational" OR "registry" AND "atrial fibrillation" AND "apixaban".
- The study considered most appropriate by satisfying all eligibility criteria (Table 1) for the RWD-analysis was implemented in the model.

Table 1. Eligibility criteria for real-world studies to inform the RWD-based analysis

Eligibility criteria
Language: English
Time frame: January 1 2012 to December 1 2018
Study type: Real-world observational studies (e.g. prospective and retrospective cohort studies and database or registry studies) as well as meta-analyses combining different real-world observational studies
Indirect comparative real-world studies had to make use of propensity score matching of subgroups
Reporting outcomes for all the primary endpoints of the ARISTOTLE trial (ischaemic stroke, SE, MB, ICH, haemorrhagic stroke)[8]
Reported hazard ratios comparing apixaban to other NOACs (at least dabigatran and rivaroxaban*) or VKA.
Publications reporting data for the same patients were evaluated and only the publication with the most representative population was included

ICH, intracranial haemorrhage; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; VKA, vitamin K antagonist.
**Edoxaban received European Medicines Agency approval in 2015, and is therefore often not yet included in real-world studies.*

- Clinical event rates (other than the primary endpoints) that were not reported in a RWD study were assumed to remain the same as the ones considered in the NMA-based analysis.
- Outcomes of the NMA-based deterministic analysis and PSA were presented, and compared to the outcomes of the RWD-based analysis for the purpose of external validation.

Results

SYSTEMATIC LITERATURE SEARCH

- Multiple RWD studies were identified in the systematic search (266 records, of which 46 screened on full-text; Figure 2).
- Forty-five of the full-text screened articles did not meet eligibility criteria: 15 studies did not include all relevant comparators and 25 studies did not report all outcomes of interest. One study reported odds ratios and three studies did not report HRs of comparing the NOACs to each other. Two studies did meet all the inclusion criteria but had possible overlap in included patients[12,13]. Of these two, the article of Lip et al.[12] was considered the most appropriate for use in the RWD-based analysis, since they included the largest population size (321,182 patients) using different databases, among which the same database as used by Deitelzweig et al.[13].

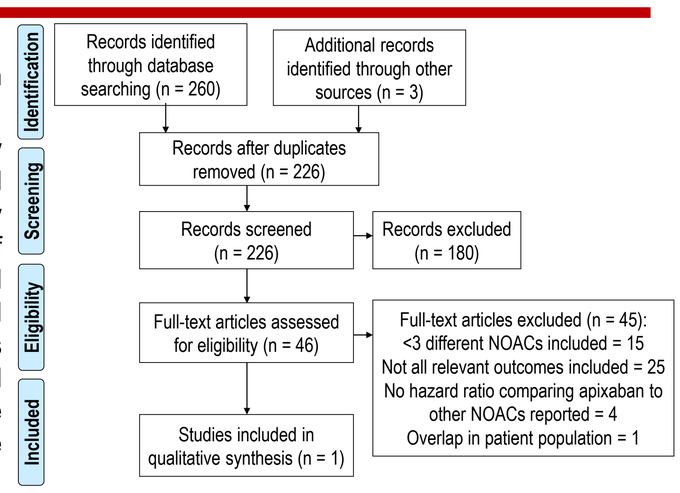

Figure 2. PRISMA flow diagram for systematic literature search used to identify RWD on clinical event rates. *NOACs, non-vitamin K antagonist oral anticoagulants*

BASE-CASE: NMA-BASED ANALYSIS

- In the NMA-based analysis, apixaban appeared to be cost-effective compared to VKA (€3,506 per QALY) and dominant (cost-saving and more effective) over dabigatran, edoxaban and rivaroxaban (Table 2).
- Apixaban is the most cost-effective treatment option at the €20,000/QALY WTP threshold with 50% (Figure 3A).

EXTERNAL VALIDATION: RWD-BASED ANALYSIS

- In the RWD-based analysis, apixaban was dominant over all other anticoagulants (Table 2).
- At the €20,000/QALY WTP threshold, apixaban is the most cost-effective treatment option with 90% (Figure 3B).

Table 2. Base-case results of the NMA-based and RWD-based analyses comparing apixaban to VKA and other NOACs.

Comparator	Incremental costs	Incremental QALYs	ICER
	NMA-based analysis		
VKA	€920	0.262	€3,506/QALY
Dabigatran (110mg)	- €2,692	0.177	Dominant
Dabigatran (150 mg)	- €819	0.131	Dominant
Rivaroxaban	- €1,027	0.101	Dominant
Edoxaban	- €197	0.065	Dominant
	RWD-based analysis		
VKA	- €1,358	0.330	Dominant
Dabigatran	- €3,612	0.310	Dominant
Rivaroxaban	- €1,625	0.124	Dominant

ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis, QALY, quality adjusted life-year; RWD, real-world data, VKA, vitamin K antagonist.

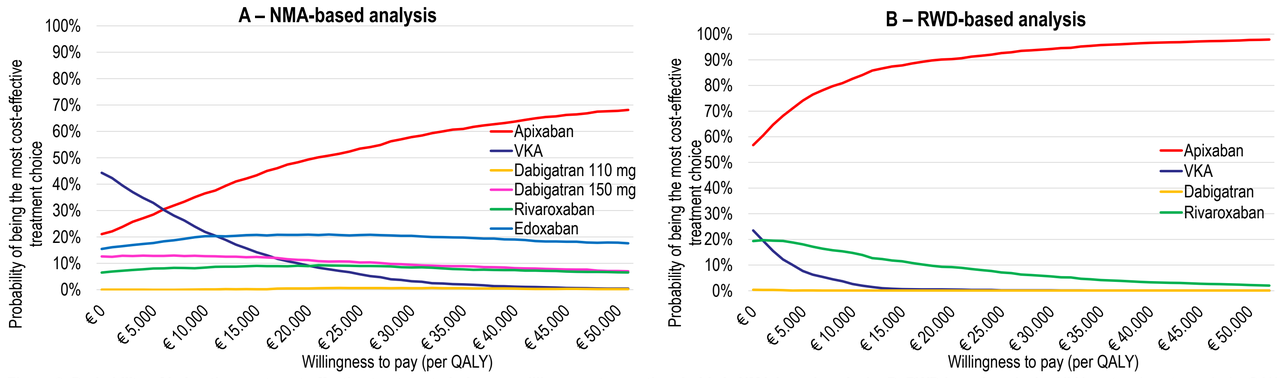

Figure 3. Probability of being the most cost-effective treatment choice per willingness-to-pay threshold. A. NMA-based analysis; B. RWD-based analysis. *NMA, network meta-analysis, QALY, quality adjusted life-year; RWD, real-world data, VKA, vitamin K antagonist.*

Discussion

KEY STRENGTHS OF THIS STUDY

- This cost-effectiveness study compared apixaban to VKA as well as other NOACs dabigatran, edoxaban and rivaroxaban in a single model. Since NOACs have been the preferred treatment for the prevention of stroke in patients with AF since 2012, it has become more relevant to compare NOACs to each other instead of comparing to VKA.
- The major advantage of this study is that both an NMA and RWD were used for cost-effectiveness evaluation. Including RWD in an existing RCT(NMA)-based model can be used as external validation of the initial results.
- The clinical event rates were based on studies containing data on more than 72,000 (NMA) and 320,000 patients (RWD), respectively. These high numbers of patients increase the reliability and robustness of the analyses.

LIMITATIONS OF USING RWD FOR EXTERNAL VALIDATION

- Most studies were not eligible for external validation due the fact that not all relevant endpoints were included, or they were only presented as combined outcomes (e.g. ischaemic stroke/SE). The real-world study by Lip et al.[12] included all the relevant endpoints, however, data on CRNMB, MI, treatment discontinuation and other cardiovascular hospitalisation were not reported.
- Not all comparators in the NMA[4] were included in our selected RWD[12]. The NMA presented results on both doses of dabigatran registered in Europe, while the real-world study[12] reported the combined results of different dabigatran doses. Moreover, edoxaban was not included in the RWD, because it received relatively late market access compared to the other three NOACs.
- Real-world studies include heterogeneous populations from different countries. As a result, differences in clinical outcomes can be expected, which can potentially lead to differences in economic outcomes. Therefore, results depend strongly on the choice of RWD used for external validation.
- RWD on clinical event rates in Dutch patients treated with NOACs is currently lacking. In the coming years, the recently launched project "DUTCH-AF registry"[14] aims to include 6,000 Dutch patients with AF to collect data on effectiveness, adherence and bleeding risk of NOACs and VKAs. It will be interesting to have this data of Dutch patients, since the patient characteristics, such as $CHADS_2/CHA_2DS_2$-VASc scores and age, can obviously differ among populations.

Conclusions

- **Based on both the NMA-based and RWD-based analyses, apixaban is generally cost-effective or even cost-saving (less costly and more effective) compared to VKA and other NOACs in the overall population of patients with AF.**
- **To validate the results of an RCT-based cost-effectiveness analysis, RWD can be integrated in the same model. This remains a challenge for many reasons, among them being the difference in the assessed endpoints and underlying populations in RCTs and RWD, which limits robust comparisons and implementation in the cost-effectiveness models.**

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This study was financially supported by Bristol-Myers Squibb and Pfizer. M.J. Postma has received educational and research grants from Boehringer Ingelheim, Pfizer, Bayer, and Bristol-Myers Squibb. M.V. Huisman reports grants and personal fees from Pfizer-BMS, Bayer Health Care, Boehringer-Ingelheim, and Daiichi-Sankyo during the conduct of the study. H. Rila and J. Stevanovic are employees of Bristol-Myers Squibb and were involved with the start of the research but did not influence the results and discussion. L.A. de Jong, J. Groeneveld and M. van Hulst have no conflicts of interest with relation to the subject.

The manuscript describing the full results of this project was published (Sept 18th, 2019) in PLOS ONE.

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