Novel oral anticoagulants for the secondary prevention of cerebral ischemia: a network meta-analysis

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Abstract

Background: Novel oral anticoagulants (NOACs) have shown to be both safe and effective for ischemic stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). We conducted a network meta-analysis (NMA) using published data from secondary prevention subgroups of different phase III randomized clinical trials (RCTs) comparing individual NOACs with warfarin.

Methods: Eligible studies were identified by searching MEDLINE and SCOPUS and the Cochrane Central Register of Controlled Trials databases. First, we conducted a pairwise meta-analysis for each pairwise comparison, and then we performed NMA to combine direct and indirect evidence for any given pair of treatments. The comparative effects of all NOACs against warfarin were ranked with the surface under the cumulative ranking (SUCRA) curve for each outcome.

Results: We identified four RCTs (including 15,240 patients) comparing individual NOACs (apixaban, dabigatran, rivaroxaban) with warfarin. Using indirect evidence, dabigatran was related to a significantly lower risk of hemorrhagic stroke compared with rivaroxaban [risk ratio (RR) 0.28; 95% confidence interval (CI) 0.11–0.75], while rivaroxaban was associated with a significantly lower risk of major gastrointestinal bleeding compared with dabigatran (RR 0.14; 95% CI 0.03–0.74). We also performed clustered ranking plot for the primary efficacy and safety endpoints to identify the treatment with the probably best benefit-to-risk ratio profile.

Conclusions: The three NOACs showed differences in terms of safety and efficacy for secondary stroke prevention in NVAF. Our findings can serve only as hypothesis generation and require independent confirmation in head-to-head RCTs, owing to the sparse available evidence and increased uncertainty in both indirect effect estimates and ranking of treatments.

Keywords: apixaban, dabigatran, ischemic stroke, novel oral anticoagulant, rivaroxaban, transient ischemic attack

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Introduction

Oral direct inhibitors of both thrombin and factor Xa have now been developed and shown to be both safe and effective for the primary and secondary prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011]. Current guidelines from the American Heart Association/American Stroke Association (AHA/ASA) suggest that the use of vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs) is indicated for the

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prevention of recurrent ischemic stroke (IS) or transient ischemic attack (TIA) in patients with NVAF, whether paroxysmal or permanent, with an individualized agent selection based on risk factors, cost, tolerability, patient preference, potential drug interactions and other clinical characteristics [Kernan *et al.* 2014]. Until now available NOACs have not been directly compared in any head-to-head randomized clinical trial (RCT) [Skjøth *et al.* 2012], and such direct comparisons are unlikely in the near future due to the extreme cost and the large number of patients required for such comparisons [Harenberg *et al.* 2012].

In view of the former considerations we sought to conduct a systematic review and network meta-analysis (NMA) to indirectly compare the efficacy and safety of available NOACs in the secondary prevention of patients with previous IS/TIA and NVAF.

Methods

Study design

We performed a NMA using a frequentist model in Stata (Stata Statistical Software: Release 13; StataCorp. LP, College Station, TX). We followed a prespecified study protocol that has been published in the International Register PROSPERO (International Prospective Register of Ongoing Systematic Reviews) [Katsanos *et al.* 2015] and reported the meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement [Liberati *et al.* 2009].

Participants and interventions

We included patients with atrial fibrillation on electrocardiogram at screening or within the past 6 months and a history of previous stroke or TIA (duration of neurological symptoms $<$24 h) [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011]. We excluded patients with: severe heart valve disorder; stroke within 7–14 days from symptom onset or severe, disabling stroke within 3–6 months; increased risk of hemorrhage; creatinine clearance less than 30 ml/min; active liver disease; and pregnancy [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011].

We included therapies with NOACs or VKAs for the secondary prevention of NVAF, and excluded NOACs or VKAs that were not used for the secondary prevention of patients with IS and NVAF.

Search strategy and selection criteria

We searched studies of NOACs on secondary IS/TIA prevention in MEDLINE, SCOPUS and the Cochrane Central Register of Controlled Trials (CENTRAL), using the following terms in combination with individual drug names: *'ischemic stroke', 'cerebral ischemia', 'novel oral anticoagulant', 'NOAC', 'apixaban', 'dabigatran', 'rivaroxaban', 'edoxaban'* (supplementary online appendix p. 1). References to trials were also sourced from international trials registers via the World Health Organization's trials portal (http://apps.who.int/trialsearch/), regulatory agencies, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. No language or other database search restriction was applied.

We included RCTs comparing NOACs with each other or with warfarin (or any other VKA) in the secondary prevention of patients with IS/TIA and NVAF, while we excluded all retrieved observational studies (either prospective or retrospective). Reference lists of all articles that met the criteria and of relevant review articles were examined to identify studies that may have been missed by the database search. All retrieved studies were scanned independently by two reviewers (AHK and GT). In the case of disagreement regarding the literature search results between the two coauthors, the remaining coauthors were consulted and disagreement was resolved with consensus.

Risk of bias was assessed for each included study using the Cochrane Collaboration 'risk of bias' tool [Higgins *et al.* 2011] by two independent review authors (AHK and GT) and all emerging conflicts were resolved with consensus. The quality of evidence derived from the NMA were evaluated using a recently proposed approach by Salanti and colleagues [Salanti *et al.* 2014], which is based on the methodology developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for pairwise meta-analyses [Guyatt *et al.* 2011].

Outcomes

Primary outcomes included recurrent stroke or systemic embolism (treatment efficacy) and major bleeding events (treatment safety) [Connolly

et al. 2009; Granger *et al.* 2011; Patel *et al.* 2011]. Stroke was defined as a sudden, focal neurological deficit due to cerebrovascular ischemia that was neither reversible within 24 h nor due to another readily identified cause, such as tumor, trauma, or seizure [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011]. Systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion in the absence of another likely mechanism (e.g. atherosclerosis, trauma, or arterial catheterization) [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011]. Major bleeding was defined as clinically overt bleeding associated with fatality or involving a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), a decrease in hemoglobin concentrations of at least 2 g/dL, or transfusion of at least 2 units of whole blood or packed red blood cells [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011].

Secondary outcomes included: ISs; hemorrhagic strokes; all strokes (ISs and hemorrhagic strokes); intracranial bleedings; disabling or fatal strokes; deaths from any cause; cardiovascular deaths; and gastrointestinal major bleedings [Connolly *et al.* 2009; Granger *et al.* 2011; Patel *et al.* 2011].

Statistical analysis

First, we conducted a standard, pairwise meta-analysis for each pairwise comparison of treatments using a random-effects model (DerSimonian and Laird) to obtain estimates for all primary and secondary outcomes as risk ratios (RRs) with corresponding 95% confidence intervals (CIs) [DerSimonian and Laird, 1986]. Heterogeneity between studies was assessed with the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity, as per the Cochrane Handbook [Deeks *et al.* 2011].

Then we performed NMA to combine direct and indirect evidence for any given pair of treatments, and take into account the correlation induced by multi-arm trials [Salanti and Schmid, 2012]. The underlying assumption of transitivity suggests that all pairwise comparisons in the network do not differ with respect to the distribution of effect modifiers [Turner *et al.* 2012]. We presented the results for the comparative efficacy and tolerability by RR estimates and 95% CI. We assumed that heterogeneity is the same for all treatment comparisons and the assessment of statistical heterogeneity in the entire network was evaluated in light of its estimated empirical distribution. We considered values from 0.1 to 0.5 to be reasonable, while values 0.5 to 1.0 were considered to represent fairly high and above 1.0 fairly extreme heterogeneity [Turner *et al.* 2012]. We also evaluated the ranking of all primary and secondary outcomes using ranking probabilities; which treatment is the most efficacious regimen, the second best, the third best, and so on [Turner *et al.* 2012]. To rank the treatments we used the surface under the cumulative ranking (SUCRA) curve. SUCRAs expressed as percentages compare each intervention to an imaginary intervention that is always the best without uncertainty. A SUCRA of x% means that the drug achieves x% of the effectiveness of this imaginary drug, thus larger SUCRAs denote more effective interventions [Mavridis *et al.* 2015].

Pairwise analyses were conducted using Review Manager (RevMan) Version 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). NMA was performed with the Stata Statistical Software Release 13 for Windows (StataCorp.), using the function mvmeta [White *et al.* 2011] and also the codes developed by Chaimani and colleagues [Chaimani *et al.* 2013] which are available at http://mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis.

Results

Our literature search highlighted four studies, including 15,240 patients, that were eligible for the systematic review and meta-analysis [Easton *et al.* 2012; Diener *et al.* 2010; Hankey *et al.* 2012; Tanahashi *et al.* 2013]. The PRISMA flowchart showing electronic searching processes is shown in the online supplementary appendix (Supplemental Figure S1). Studies excluded after retrieving the full text articles are reported in Supplemental Table I of the appendix. The mean age of participants was 70 years and 63% were men. Characteristics of included studies are briefly summarized in Table 1. No significant heterogeneity was found in most baseline characteristics, except for the proportion of VKA-naïve patients which was very low in one study protocol [Hankey *et al.* 2012] compared with the others [Easton *et al.* 2012; Diener *et al.* 2010] and the

Table 1. Characteristics of included studies.

Reference	Study name	Place	Total patients (*n*)	Prior Event	Index Tx (*n*)	Other Tx (*n*)	Reduced dose	Mean age	Males	Previous MI	CHF	DM	HTN	VKA naïve	CrCl<50 ml/min	Aspirin	Individual median TTR	Median follow up (years)	Discontinuation
Easton *et al.* [2012]	ARISTOTLE	Worldwide	3436	IS:28%, TIA:53%, IS+TIA: 9% Unknown: 10%	APX 5 mg (1694)	WRF (1742)	7% **(APX 2.5 mg)**	70.1	63%	17.0%	27%	26%	83%	39%	22%	31%	65% [51–76%]	1.8	APX: 22.6% WRF: 26.6%
Diener *et al.* [2010]	RE-LY	Worldwide	3623	IS:54.1% TIA: 37.3% IS+TIA: 8.6%	DBG 150 mg (1233) DBG 110 mg (1195)	WRF (1195)	N/A	70.5	62.9%	N/A	N/A	22.5%	76.8%	44.5%	N/A	39.8%	N/A	2.0	N/A
Hankey *et al.* [2012]	ROCKET AF	Worldwide	7468	IS: 65.7% TIA: 34.3%	RVX 20 mg (3754)	WRF (3714)	N/A	71.0	61%	15.1%	51%	24.2%	85%	41%	N/A	38%	57.1% [42.6-70.1%]	1.8	N/A
Tanahashi *et al.* [2013]	J-ROCKET AF	Japan	813	N/A	RVX 15 mg (408)	WRF (405)	19.9% **(RVX 10 mg)**	70.3	82.6%	6.4%	20.5%	25.2%	70.7%	9.3%	19.9%	36.2%	N/A	2.5	N/A

n: number of patients; Tx, treatment; MI, myocardial infarction; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; VKA, vitamin K antagonist; CrCl, creatinine clearance; TTR, time in therapeutic range; IS, ischemic stroke; TIA, transient ischemic attack; N/A, not available; APX, apixaban; DBG, dabigatran; RVX, rivaroxaban; WRF, warfarin.

racially different study population (only Japanese patients) in J-ROCKET AF [Tanahashi *et al.* 2013].

Risk of bias is presented for each study in Supplemental Figure S2 and all domains are summarized in Supplemental Figure S3. Risk of bias was generally low in all studies. Two of the studies did not provide missing data or losses to follow up [Easton *et al.* 2012; Hankey *et al.* 2012], while the method of random sequence allocation was not clearly presented in one study [Tanahashi *et al.* 2013]. One study was considered to have high risk of bias, due to the discovery of new adverse events after the publication of the original study [Connolly *et al.* 2010, 2014]. As for the sponsorship bias, all study protocols reported funding and interference in multiple domains (study design, data collection/analysis, results interpretation, manuscript writing) from the manufacturing companies that produced the corresponding drug under investigation. The quality assessment for all direct analyses using the GRADE Working Group grades of evidence is available in Supplemental Table II (supplementary online appendix p. 3).

In pairwise comparisons for the primary and secondary outcomes no evidence of statistical heterogeneity was seen in general, except for the pairwise analysis of total bleeding (I^2 = 92%) and gastrointestinal major bleeding (I^2 = 71%) (Supplemental Figures S4–S14). NOACs reduced the risk of stroke or systemic embolism (RR 0.85; 95% CI 0.74–0.97), hemorrhagic stroke (RR 0.40; 95% CI 0.23–0.72) and intracranial bleeding (RR 0.42; 95% CI 0.27–0.66) in comparison with warfarin. There was no reduction in the risk of major bleeding (RR 0.85; 95% CI 0.71–1.03), any bleeding (RR 0.86; 95% CI 0.68–1.09), gastrointestinal major bleeding (RR 0.94; 95% CI 0.53–1.66), IS (RR 1.00; 95% CI 0.84–1.19), disabling or fatal stroke (RR 0.86; 95% CI 0.71–1.03), death from any cause (RR 0.91; 95% CI 0.80–1.02) and cardiovascular death (RR 0.91; 95% CI 0.77–1.09).

Networks of eligible comparisons are presented in Figure 1, showing predominantly pairwise comparisons for dabigatran (one study, two arms) and rivaroxaban (two studies, two arms each) compared with apixaban (one study, two arms). It is clear from the network plots in Figure 1 that estimates for all comparisons are formed either directly or indirectly. More, specifically,

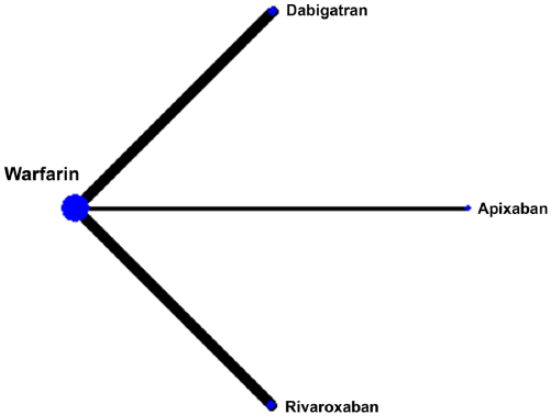

Figure 1. Network plot for the primary efficacy outcome (the size of nodes is proportional to the number of patients randomized to interventions. Thickness of lines is proportional to the number of studies contributing to the direct comparison).

for studies comparing a NOAC with warfarin there is only direct evidence whereas for studies comparing two NOACs there is only indirect evidence. Hence, the choice is between direct *versus* network estimates for warfarin comparisons and between indirect vs network estimates for NOAC comparisons. Since two out of three comparisons have one study, between-study variation cannot be estimated for these comparisons. By analyzing the entire network of trials simultaneously, assuming a common heterogeneity parameter for all comparisons, we allow borrowing information across the different comparisons which allow estimation of heterogeneity and portray this extra source of uncertainty in the network results. On the other hand, if the assumption that the underlying true effects vary in the same way in all treatment comparisons is not correct we may get a biased estimate for heterogeneity. In this occasion that we have a few number of trials and direct (and indirect) estimates are similar to the network estimates, the joint analysis of all trials seems justifiable.

Data for direct comparisons and network estimates for most primary and secondary outcomes are shown in Table 2 and, for other outcomes in the appendix (Supplemental Table IV). In indirect analyses dabigatran was found to be associated with a lower risk for hemorrhagic stroke (RR 0.28; 95% CI 0.11–0.75) compared with rivaroxaban, while rivaroxaban was associated with lower risk for major gastrointestinal bleeding compared with dabigatran (RR 0.14; 95% CI

Table 2. Relative effect of both indirect and network meta-analysis estimates for each pair of drugs accompanied by 95% confidence intervals according to the outcome under consideration.

Stroke or systemic embolism			
Apixaban	0.96 (0.65–1.41)	0.95 (0.52–1.72)	0.77 (0.57–1.03)
0.95 (0.65–1.40)	Dabigatran	0.99 (0.56–1.75)	0.80 (0.63–1.03)
0.84 (0.59–1.19)	0.88 (0.64–1.20)	Rivaroxaban	0.81 (0.48–1.35)
0.77 (0.57–1.03)	0.80 (0.63–1.03)	0.92 (0.75–1.11)	Warfarin
Major bleeding			
Apixaban	0.90 (0.54–1.49)	0.78 (0.55–1.10)	**0.75 (0.56–0.99)**
0.90 (0.44–1.83)	Dabigatran	0.86 (0.54–1.36)	0.83 (0.55–1.25)
0.78 (0.35–1.72)	0.86 (0.44–1.71)	Rivaroxaban	0.96 (0.79–1.18)
0.75 (0.42–1.34)	0.83 (0.55–1.25)	0.96 (0.56–1.66)	Warfarin
Ischemic stroke			
Apixaban	1.09 (0.47–2.50)	0.86 (0.61–1.22)	0.75 (0.48–1.19)
0.90 (0.43–1.88)	Rivaroxaban	0.79 (0.37–1.68)	0.69 (0.31–1.56)
0.86 (0.57–1.30)	0.96 (0.52–1.78)	Warfarin	0.88 (0.66–1.17)
0.76 (0.44–1.29)	0.84 (0.42–1.68)	0.88 (0.63–1.22)	Dabigatran
Hemorrhagic stroke			
Dabigatran	0.50 (0.18–1.42)	**0.28 (0.11–0.73)**	**0.20 (0.09–0.46)**
0.51 (0.18–1.47)	Apixaban	0.55 (0.24–1.28)	**0.40 (0.21–0.77)**
0.28 (0.11–0.75)	0.55 (0.24–1.29)	Rivaroxaban	0.72 (0.43–1.22)
0.20 (0.09–0.46)	**0.40 (0.21–0.77)**	0.72 (0.43–1.22)	Warfarin
Intracranial bleeding			
Dabigatran	0.82 (0.32–2.06)	0.46 (0.20–1.05)	**0.31 (0.15–0.63)**
0.83 (0.29–2.34)	Apixaban	0.56 (0.27–1.15)	**0.38 (0.21–0.68)**
0.48 (0.19–1.21)	0.58 (0.20–1.68)	Rivaroxaban	0.68 (0.45–1.04)
0.31 (0.16–0.61)	**0.38 (0.17–0.83)**	0.64 (0.32,1.29)	Warfarin
Gastrointestinal major bleeding			
Rivaroxaban	0.21 (0.04–1.10)	**0.18 (0.04–0.81)**	**0.14 (0.03–0.67)**
0.21 (0.04–1.30)	Apixaban	0.84 (0.45–1.56)	0.64 (0.29–1.43)
0.18 (0.04–0.89)	0.84 (0.37–1.93)	Warfarin	0.76 (0.46–1.26)
0.14 (0.03–0.74)	0.64 (0.24–1.70)	0.76 (0.46–1.27)	Dabigatran

All relative effect estimates are presented as risk ratios (RRs). RRs smaller than one favor the row drug, whereas RR larger than one favor the column drug. RRs in the upper diagonal represent the indirect estimate for the three novel oral anticoagulants (NOACs) and the direct estimate for each NOAC *versus* warfarin, while RRs in the lower diagonal represent the network estimates for all comparisons. Significant differences in the relative effects between a pair of drugs are given in bold.

0.03–0.74). No significant associations between NOACs were identified in other primary or secondary outcomes.

The comparative effects of all NOACs were ranked using SUCRA values. We created hierarchies of effect size on the basis of SUCRA rankings for all outcomes (Supplemental Figures S15–S24). Finally, we created scatter plots of the SUCRA values for the primary efficacy (stroke or systemic embolism) and safety (major bleeding) outcomes (Figure 2), and for the SUCRA values of the IS plotted against the hemorrhagic stroke (Figure 3). In both clustered ranking plots Apixaban was highlighted as the treatment with the probably best benefit-to-risk ratio profile among NOACs. More specifically, apixaban was ranked as the most likely treatment option to reduce stroke/systemic embolism as well as major bleeding (Figure 2). Moreover, it was ranked as the most likely treatment option to reduce IS and the second most likely treatment option to reduce hemorrhagic stroke (Figure 3). However, our confidence in both indirect effect estimates and ranking of treatments was considered limited (Supplemental Table III).

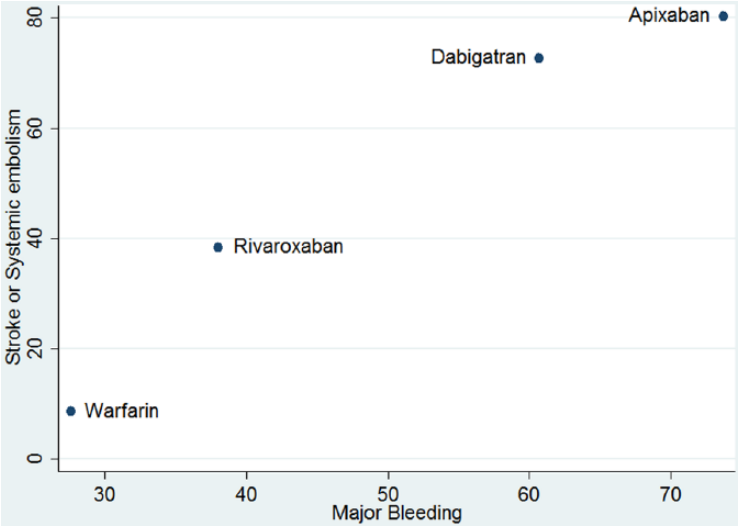

Figure 2. Clustered ranking plot for efficacy (stroke or systemic embolism) and safety (major bleeding).

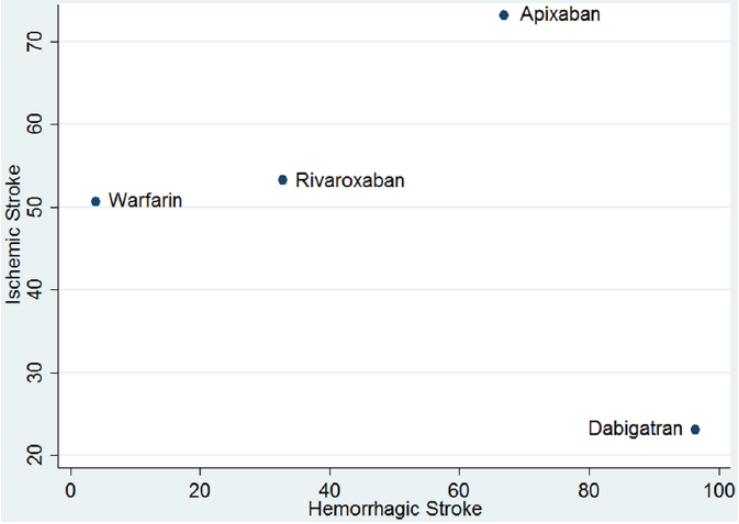

Figure 3. Clustered ranking plot for ischemic stroke and hemorrhagic stroke risks.

Discussion

Our NMA, overcoming the major limitation of conventional pairwise meta-analyses, provides evidence-based hierarchies for the efficacy and safety of available oral anticoagulants for the secondary prevention of IS/TIA recurrence in patients with NVAF. Another major finding of our NMA is that all NOACs are beneficial compared with warfarin, a finding which is not directly visible from the individual studies due to the rare probability of events and the resulting low statistical power of the studies. Based on current evidence apixaban was highlighted as having the probably best benefit-to-risk ratio, while significant differences on the risk of hemorrhagic stroke and gastrointestinal bleeding between dabigatran and rivaroxaban emerged in the indirect analysis.

Our findings lend support to current AHA/ASA recommendations that classify apixaban as the NOAC with the highest level of evidence (Class I; Level of Evidence A) for the prevention of recurrent stroke in patients with history of stroke or TIA in comparison with dabigatran (Class I; Level of Evidence B) and rivaroxaban (Class IIa; Level of Evidence B) [Kernan *et al.* 2014].

Moreover, in subgroup analysis of AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment), apixaban 5 mg twice daily was found to be an efficacious alternative to aspirin for secondary stroke prevention of NVAF patients who are unsuitable for VKA therapy [Diener *et al.* 2012]. Interestingly, apixaban exhibited a similar profile to aspirin in terms of safety (hemorrhagic events), while it was shown to be more effective in terms of efficacy (reduction of ischemic events). Even though economic evaluation studies performed in different health systems suggest that all NOACs (apixaban [Stevanović *et al.* 2014], dabigatran [Wouters *et al.* 2013], rivaroxaban [Kleintjens *et al.* 2013]) are cost-effective alternatives to VKAs, apixaban was highlighted as the most economically efficient alternative to warfarin in a French study that compared together warfarin, all NOACs and aspirin for stroke prevention in NVAF patients [Lanitis *et al.* 2014].

In other NMAs assessing the efficacy and safety of NOACs in the prevention of thromboembolic events in NVAF patients apixaban was found to be associated with fewer bleeding events compared with edoxaban, dabigatran and rivaroxaban [Fu *et al.* 2014; Mantha and Ansell, 2012; Lip *et al.* 2012]. In a previously published indirect comparison analysis of NOACs on secondary IS prevention in patients with NVAF, dabigatran 110 mg was associated with a lower risk for hemorrhagic stroke (HR 0.15; 95% CI 0.03–0.66) and intracranial bleeding (HR 0.27; 95% CI 0.10–0.73) compared with rivaroxaban. No significant differences were found for the aforementioned outcomes between rivaroxaban and the higher dose of dabigatran (150 mg) [Rasmussen *et al.* 2012]. However, it should be noted that this indirect comparison analysis [Rasmussen *et al.* 2012] included a smaller number of RCTs (three *versus* four in the present study) and patients (14,427 *versus* 15,240 in the present study), while SUCRA probabilities were not used to rank the different NOACs in terms of safety and efficacy endpoints. Last but not least, GRADE methodology was not employed in this indirect comparison analysis [Rasmussen *et al.* 2012] to critically evaluate the quality of evidence derived from this NMA.

Our study has several limitations. First, no direct comparisons (head-to-head RCTs) among NOACs were available and thus a formal statistical method could not be used to test the network consistency [Salanti, 2012]. We considered the transitivity assumption to hold true for the network as possible effect modifiers were balanced among included trials. The majority of patients (>90%) in the included trials had a $CHADS_2$ score of more than 3, due to the history of prior cerebral ischemic event, and thus the imbalances in $CHADS_2$ score noticed in meta-analyses of the entire studies population [Pengo *et al.* 2012; Cope *et al.* 2015] were not found in the subgroups of patients with prior IS/TIA and NVAF. However, it should be noted that the individual TTR was not mentioned in two out of four study protocols [Diener *et al.* 2010; Tanahashi *et al.* 2013], while the other two trials reported relatively similar individual median TTR values of 65% (51–76%) [Easton *et al.* 2012] and 57.1% (42.6–70.1%) [Hankey *et al.* 2012], respectively. In a recent meta-analysis of RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials, comparing the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation, a significant interaction of TTR on the treatment effect of NOACs was found [Ruff *et al.* 2014]. More specifically, no association was detected between NOACs (in comparison with warfarin) and reduced risk of stroke or systemic embolism in the subgroup of patients with TTR ⩾66% (RR 0.93; 95% CI 0.76–1.13). In contrast, there was a significant reduction of 31% in the risk of stroke or systemic embolism in patients randomized to NOACs (in comparison with warfarin) in patients with TTR <66% (RR 0.69; 95% CI 0.59–0.81) [Ruff *et al.* 2014]. Also, in contrast to the fact that women suffer more frequently cardioembolic strokes, it should be noted that the trials included predominantly male patients (Table 1).

Second, in NMA we decided to pool together both dabigatran doses (110 and 150 mg) and both rivaroxaban doses (15 and 20 mg). This decision was made to increase the statistical power of the analysis, and after reassurance from pairwise analyses that no heterogeneity was detected in all comparisons between the aforementioned doses. Third, even though the risk of bias was considered to be generally low in all study protocols, the discovery of new adverse events after the publication of the original study in the RE-LY trial [Connolly *et al.* 2010 2014] had a substantial impact in the evaluation of this study and consequently on the validity of all network findings. Finally, as both RE-LY [Connolly *et al.* 2009] and ROCKET AF trials [Patel *et al.*

2011] excluded per study protocol patients with severe stroke within 6 and 3 months before screening, respectively, there is uncertainty as to whether the results of this meta-analysis can also be valid for patients with severe stroke.

In conclusion, our NMA detected differences among NOACs in terms of safety and efficacy for secondary stroke prevention. Dabigatran and rivaroxaban differ in terms of prevention of major bleeding and hemorrhagic stroke, while apixaban appears to present with the optimal benefit/risk profile among the three NOACs. Even though the findings of the present meta-analysis could be considered in the appropriate NOAC selection for patients with a high risk for intracerebral or gastrointestinal hemorrhage, they may serve only for hypothesis generation and require independent confirmation in future head-to-head RCTs. A large three arm trial with all NOACs may be the most appropriate setting to delineate the differences between them.

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