Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation

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Summary

Background: Vit-K antagonists are the therapy of choice to prevent thromboembolic events due to atrial fibrillation since many years. New oral anticoagulants (NOA) showed encouraging results vs. warfarin but there are no data directly comparing different NOA. We performed an adjusted indirect meta-analysis.

Methods: Randomized controlled trials (RCTs) were searched. Efficacy end points were the cumulative rate of thromboembolic stroke (TES) and systemic embolism (SE). Main safety end point was the rate of hemorrhagic stroke (HS).

Results: Three RCTs (50578 patients) were included. Overall, NOA were comparable to warfarin according to the cumulative risk of TES and SE, as well as for TES alone. NOA were associated with a reduced rate of SE [OR 0.64 (0.44, 0.94), P=0.02]. Compared to warfarin, NOA were associated with a significantly reduced risk of HS [OR 0.43 (0.34, 0.55), P<0.001, NNT to avoid a HS 153] and all cause death [OR 0.90 [0.84, 0.96], P=0.03, NNT to save one fatality 43]. Head to head comparison showed that in terms of cumulative rate of TES/SE, as well as of TES, none of the NOA was significantly superior to the others (all Ps>0.05). Rivaroxaban showed superiority in the prevention of SE. Dabigatran 150 mg/twice daily was associated with the largest reduction in the risk of HS vs. warfarin and vs. other NOA. Overall mortality was quite comparable across NOA.

Conclusions: Overall superiority of NOA over warfarin is largely influenced by the reduction of HS. Dabigatran 150 mg/twice daily seems to have the best risk/benefit profile.

Introduction

Atrial fibrillation (AF) is associated with a 4- to 5-fold increased risk of thromboembolic stroke (TES).1 It accounts for up to 15% of strokes regardless the age. This percentage reaches 30% in people >75 years.2 For more than 50 years, Vitamin K antagonists have been the primary medication to reduce the risk of thromboembolic events in patients with AF. Nevertheless, along with proven clinical efficacy, they have several limitations, including a number of interactions with other drugs and food, and
need for regular blood monitoring for dose adjustments. These drawbacks led to several attempts to find reliable alternative approaches, however, none eventually fulfilled the promise.

The scenario has dramatically changed in the last few years. As compared to Warfarin, Dabigatran, Rivaroxaban and Apixaban showed encouraging results.

Of note, a ‘head-to-head’ comparison of these new drugs has never been done and is unlikely in the future.

Indirect comparison meta-analyses, adjusted by a common control, enable head-to-head comparisons of two treatments originally compared in controlled trials to a common reference treatment. While obviously second to direct comparisons in the hierarchy of clinical evidence, their use has been recommended and their validity scientifically established. Building upon previous similar works from our group, we thus aimed to perform an adjusted indirect comparison meta-analysis of new oral anticoagulants (NOA) for stroke prevention in AF.

## Methods

### Design

The present review was performed according to the Cochrane Collaboration and PRISMA statements.

### Search strategy

PubMed was searched with established methods for randomized phase-III trials comparing warfarin with NOA in patients with non valvular AF without language restrictions (updated on 1 March 2012; see the Appendix A for further details). In addition, Google Scholar, The Cochrane Library and Scopus were also searched for pertinent citations. References of retrieved studies were checked for additional studies (backward snowballing) and 2008–11 conference proceedings of the American College of Cardiology, American Heart Association and European Society of Cardiology scientific sessions were also manually searched. No language restriction was enforced.

### Study selection

Citations were first scanned at the title/abstract level. Shortlisted studies were then retrieved in full text.

Specifically, inclusion criteria were randomized allocation, controlled comparisons against a vitamin K antagonist, patients with AF, follow-up of at least 1 year and intention-to-treat analysis.

### Abstraction and appraisal

The primary efficacy end-point was the cumulative rate of TES and systemic embolisms (SE) at the longest available follow-up. The primary safety end-point was the rate of hemorrhagic stroke (HS) at the longest follow up. Rates of extracraniar major bleeding (EMB), all cause mortality and myocardial infarction (MI) were also computed.

In addition, study validity was appraised according to the risk of bias tool recommended by The Cochrane Collaboration.

### Table 1 Main clinical features of patients treated with NOA

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg/bid</th>
<th>Dabigatran 150 mg/bid</th>
<th>Rivaroxaban 20 mg/die⁴</th>
<th>Apixaban 5 mg/bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>71.4 ± 8.6</td>
<td>71.5 ± 8.8</td>
<td>73 (65–78)</td>
<td>70 (63–76)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64.3</td>
<td>63.2</td>
<td>39.7</td>
<td>35.5</td>
</tr>
<tr>
<td>Type of AF (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent/permanent</td>
<td>67.8</td>
<td>67.4</td>
<td>81.1</td>
<td>84.9</td>
</tr>
<tr>
<td>Paroxysmal/new onset</td>
<td>32.1</td>
<td>32.6</td>
<td>18.9</td>
<td>15.1</td>
</tr>
<tr>
<td>CHADS2-score (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>32.6</td>
<td>32.2</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>34.7</td>
<td>35.2</td>
<td>13</td>
<td>35.8</td>
</tr>
<tr>
<td>3–6</td>
<td>32.7</td>
<td>32.6</td>
<td>87</td>
<td>30.2</td>
</tr>
<tr>
<td>Previous stroke/TIA/SE (%)</td>
<td>19.9</td>
<td>20.3</td>
<td>54.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>16.8</td>
<td>16.9</td>
<td>16.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23.4</td>
<td>23.1</td>
<td>40.4</td>
<td>25</td>
</tr>
<tr>
<td>Previous use of VKA (%)</td>
<td>50.1</td>
<td>50.2</td>
<td>62.3</td>
<td>57.1</td>
</tr>
<tr>
<td>Previous use of Aspirin (%)</td>
<td>40</td>
<td>38.7</td>
<td>36.37</td>
<td>31.3</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; TIA: transient ischemic attack; VKA: vitamin K antagonists. In patients with creatinine clearance of 30–49 ml/min, the dose of Rivaroxaban was 15 mg/die.
Analysis

Review Manager 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark, http://ims.cochrane.org/revman) and Indirect Meta-analysis Tool (METCARDIO, Turin, Italy, http://www.metcardio.org/) were used for analysis. Outcomes were initially pooled using fixed-effect odds ratios (OR) with 95% confidence intervals (CI) and verified, in the presence of significant heterogeneity, by means of random effect in order to reduce possible sources of bias.

Adjusted indirect comparison of pooled estimates were then performed according to Song et al. Specifically, we generated, from fixed-effect ORs comparing dabigatran, apixaban and rivaroxaban vs. warfarin, interaction ORs for: (i) dabigatran vs. apixaban; (ii) dabigatran vs. rivaroxaban and; (iii) apixaban vs. rivaroxaban with pertinent 95% CI and Z scores for two-tailed hypothesis testing (P-significant if \( P < 0.05 \)). Specifically, these interaction ORs are calculated according to the formulas reported in Appendix B, where ‘ln’ is the natural logarithm, and ‘var’ is the variance. Both doses of dabigatran have been considered. Trial inconsistency was assessed with \( I^2 \). Given the few shortlisted studies, publication bias was not appraised. We also calculated the number needed to treat (NNT) or to harm (NNH) as the inverse of the absolute risk reduction (ARR), i.e. 1/ARR.

Results

From 117 citations we finally retrieve three randomized controlled trials (RCTs) totaling 50578 patients allocated to warfarin or NOA. Table 1 lists main features of included studies while Table 2 reports the quality assessment according to Cochrane/PRISMA statements.11,12

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation?</th>
<th>Allocation concealment used?</th>
<th>Blinding?</th>
<th>Risk of bias assessment of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE</td>
<td>Yes</td>
<td>(computed generated sequence)</td>
<td>Double blind, double dummy</td>
<td>Yes (interactive voice response system)</td>
</tr>
<tr>
<td>RELY</td>
<td>Yes</td>
<td>(computed generated sequence)</td>
<td>Double blind</td>
<td>Yes (interactive voice response system)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Yes</td>
<td>(computed generated sequence)</td>
<td>Double blind, double dummy</td>
<td>Yes (interactive voice response system)</td>
</tr>
</tbody>
</table>

Pair-wise overall comparison of NOA vs. warfarin

As for efficacy end-points, overall meta-analytic pooling showed that NOA were comparable to warfarin according to the cumulative risk of TES and SE \([OR 0.92 (0.83, 1.02) P=0.1]\) as well as for TES alone \([OR 0.93 (0.83, 1.05), P=0.24]\).

NOA were associated with a reduced rate of SE \([OR 0.64 (0.44, 0.94), P=0.02]\), although this analysis is affected by moderate inconsistency, \( I^2 50\% \). (Figure 1). Exact number of events/patients is shown in the figures.

As for safety end-points, NOA showed large superiority in terms of HS \([OR 0.43 (0.34, 0.55), P<0.001, NNT to save one HS 153]\) but not in
Figure 1. Overall meta-analytic comparison: efficacy endpoints. Single study fixed-effect odds ratios and 95% CI are shown by squares and horizontal lines. Overall and group pooled odds ratios with 95% CI are shown by diamonds. SE: systemic embolism, TES: thromboembolic stroke, VKA: vitamin K antagonist.

Figure 2. Overall meta-analytic comparison: safety endpoints. Single study fixed-effect odds ratios and 95% CI are shown by squares and horizontal lines. Overall and group pooled odds ratios with 95% CI are shown by diamonds. EMB: extracranial major bleeding; HS: hemorrhagic stroke. VKA: vitamin K antagonist.
terms of EMB [OR 0.98 (0.91, 1.07), \( P=0.69 \)] (Figure 2).

NOA were superior to warfarin for the risk of all cause death [OR 0.90 [0.84, 0.96], \( P=0.03 \), NNT to save one fatality 43] while being comparable for the risk of MI (Figure 3).

Analyses of EMB and MI showed significant inconsistency, \( I^2 \) 73%, thus a further computation has been performed applying random effect model in order to reduce the potential impact of bias. On the other hand, results obtained with both fixed effect model and random effect model were quite consistent: OR with Random effect model for EMB: 0.98 (0.84–1.14), \( P=0.82 \); OR with random effect model for MI: 1.04 (0.8–1.42), \( P=0.67 \).

**Adjusted indirect meta-analysis of NOA**

Head to head comparisons for efficacy end points (Table 3) showed that in terms of cumulative rate of TES/SE, as well as of TES, none of the NOA was significantly superior to the others. Rivaroxaban showed superiority in the prevention of SE compared to all the other NOA.

Head to head comparisons for safety end points showed that Dabigatran 150 mg/twice daily was associated with a further reduced risk of HS compared to Rivaroxaban. On the other hand Apixaban showed a reduced risk of EMB compared to Dabigatran 150 mg/twice daily as well as to Rivaroxaban.

Overall mortality was quite comparable across NOA.

Risk of MI was higher with both doses of Dabigatran compared to other NOA.

**Discussion**

Robust evidences of efficacy entitiled warfarin and other vitamin K antagonists as the drugs of choice to prevent thromboembolic events in patients with AF since decades,\(^1\) despite the well known limitations. The latter drove the need for valid alternative drugs which should ideally be at least as effective as warfarin but also easier to manage.

Recent publication of RE-LY,\(^4\) ARISTOTLE\(^5\) and ROCKET-AF\(^6\) trials built up the basis for an epochal change.

These trials share somewhat similar conclusions. Primary efficacy end-point at 1 year was consistently the cumulative rate of any stroke and SE and all the trials reached statistically significance for the primary hypothesis. Specifically, RE-LY and ARISTOTLE trials showed ‘superiority’ while ROCKET-AF reached the expected ‘non-inferiority’ compared to warfarin. These results were substantially conditioned by a large and consistent reduction of HS rate, although inclusion of HS in the efficacy evaluation could be questioned considering that HS is a side-effect of anticoagulants, perhaps an ominous complication. Notably, only Dabigatran
150 mg/twice daily significantly reduced the risk of TES compared to warfarin.

The aforementioned trials however differ in several ways, thus interpretation must use much caution. Dabigatran is a direct Thrombin inhibitor that is administered twice daily, while apixaban and rivaroxaban are direct Factor Xa inhibitors, the former administered twice daily, the latter once daily.

In the RE-LY trial, allocation to either drugs was not concealed, while in ARISTOTLE and ROCKET-AF a double blind fashion was achieved. Study populations were also different as in the ROCKET-AF trial patients with 0–1 CHADS score were not included (Table 1).

Notably, although ROCKET-AF trial enrolled a higher risk population, mean percentage of time in which INR was in the therapeutic range was the lowest, i.e. 55% vs. 62% in the ARISTOTLE trial and 65% in the RE-LY trial. Time into therapeutic range is strongly associated with the risk of adverse events.14

Dabigatran and Rivaroxaban has already received approval for the prevention of thromboembolic events in patients with AF.15–17

In a recent analysis, despite the much higher cost of the drug itself, Dabigatran showed even cost-effectiveness compared to warfarin when accounting for costs of regular monitoring.18 On the other hand, generic warfarin is expected to be far less expensive. Practitioners and patients will be soon facing the question of which is the right medication, perhaps without any direct comparison (see Table 4 for Pharmacokinetics of the novel oral anticoagulants and use in specific metabolic conditions).

From a practical point of view, it is conceivable that the individual patient in which INR value has been adequate for long time does not really need to switch to NOA. This consideration is corroborated by data from a recent meta-analysis showing that the annual rate of stroke in patients treated with warfarin has decreased from 2.09% in earlier studies to 1.66% in RCTs performed in the last 6 years, as a result of an improved quality of anticoagulation and a greater proportion of time spent in therapeutic range.19

In our overall analysis NOA were equivalent to warfarin according to the cumulative risk of TES and SE as well as for TES alone. On the other hand, NOA were associated with 36% reduced rate of SE and an impressive 57% reduction in HS. Consistently, NOA were associated with a reduced risk of all-cause mortality.

From the adjusted comparisons across different NOA, we observed that none of them was superior to the others in terms of the cumulative rate of TES/SE as well as of TES alone. Among others, Rivaroxaban appeared particularly protective against SE.

EMB: extracranial major bleeding; HS: hemorrhagic stroke; MI: myocardial infarction; OR: odds ratio; SE: systemic embolism; TES: thromboembolic stroke.
The latter showed the lowest risk of EMB. Mortality rate showed no significant differences across NOA. Both in absolute terms compared to warfarin and according to head to head adjusted comparisons, Dabigatran 150 mg/twice daily could be reasonably entitled as having the best risk/benefit profile as the higher risk of MI initially observed in the first publication of the RE-LY trial did not offset the significantly lower risk of all-cause mortality compared to warfarin. Moreover, a detailed post hoc analysis of the RE-LY trial including the assessment of silent MI showed no significant difference between Dabigatran 150 mg/twice daily and warfarin. Availability of possible antidotes will also be an issue. Prothrombin complex concentrate has been shown able to immediately and completely reverse the anticoagulant effect of rivaroxaban in healthy subjects, while having no influence on the anticoagulant action of dabigatran, that is, on the other hand, dialyzable.

Note worthy, the near future will see further complexity as newer agents such as Edoxaban and Betrixaban, both oral Factor Xa Inhibitors, are still under investigation. The latter, as being the only new anticoagulant excreted almost unchanged through bile (renal excretion <5%), appears particularly promising for patients with advanced renal failure.

### Limitations

Limitations of meta-analyses are well known. Adjusted indirect comparison meta-analysis is an established statistical technique which, together with network meta-analysis, belongs to the wider family of multiple treatment meta-analyses. Despite being usually consistent with results of direct comparisons, they are occasionally conflicting with head-to-head randomized trials. In particular, substantial differences between direct and indirect comparisons may be anticipated in the absence of comparability of patients and/or interventions, and when similarity,

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Pharmacokinetics of the novel oral anticoagulants and use in specific metabolic conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Dose for AF</td>
<td>Factor IIa</td>
</tr>
<tr>
<td>Effect of food</td>
<td>75–150 mg/twice daily</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>May delay (but not limit) absorption</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>1 h</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Activation by esterases—renal</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Use 75 mg twice daily if CrCl = 15–30 ml/min*m$^2$</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-glycoprotein inhibitors or inducers</td>
</tr>
<tr>
<td>Overdose management</td>
<td>Unknown (can be dialyzed)</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; CY = cytochrome; N/A = not applicable or available; SCR = serum creatinine; $T_{1/2}$: half-life; $T_{max}$: assumption to peak plasmatic concentration time.
consistency and homogeneity assumptions are not met. This is not the case of our analysis as the only true difference across studies was the inclusion of a slightly higher risk population in the ROCKET-AF trial.

Moreover, there is evidence that, at least in selected cases, adjusted indirect comparison meta-analyses may be less biased than direct comparisons for evaluating new interventions.  

## Conclusions

A randomized head to head direct comparison of NOA is unlikely to be done. Present data, while providing numbers and figures of practical utility, contribute to clarify the complex scenario that is progressively emerging from recent literature. However, literature has always a difficult translation into real world. Only the long-term use of these new agents in a real-world clinical setting will demonstrate how they compare with vitamin K antagonists in terms of efficacy, safety and cost.

Nonetheless, the new era of oral anticoagulation for stroke prevention in AF has clearly begun.

## Acknowledgements

We would like to thank Ms Giulia D’ Agostino for her irreplaceable support.

## Conflict of interest

None declared.

## References


**Appendix A**


**Appendix B**

1. ln (ORdabigatran vs. apixaban) = ln (ORdabigatran vs. warfarin) − ln (ORapixaban vs. warfarin), and var [ln (ORdabigatran vs. apixaban)] = var [ln (ORdabigatran vs. warfarin)] + var [ln (ORapixaban vs. warfarin)]

2. ln (ORdabigatran vs. rivaroxaban) = ln (ORdabigatran vs. warfarin) − ln (ORrivaroxaban vs. warfarin), and var [ln (ORdabigatran vs. rivaroxaban)] = var [ln (ORdabigatran vs. warfarin)] + var [ln (ORrivaroxaban vs. warfarin)]

3. ln (ORapixaban vs. rivaroxaban) = ln (ORapixaban vs. warfarin) − ln (ORrivaroxaban vs. warfarin), and var [ln (ORapixaban vs. rivaroxaban)] = var [ln (ORapixaban vs. warfarin)] + var [ln (ORrivaroxaban vs. warfarin)]