Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients

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A B S T R A C T

Background: Warfarin, despite its known limitations, is the reference standard treatment for patients with AF and risk factors for stroke. We performed a meta-analysis of phase III trials that compare novel oral anticoagulants (NOACs) with warfarin to determine whether they improve clinical outcomes of patients with non-valvular atrial fibrillation (AF).

Methods: Three randomized trials that compared NOACs with warfarin in AF were selected. The primary efficacy endpoint was the incidence of stroke or systemic embolism. The primary safety endpoint was the incidence of major bleeding.

Results: A total of 50578 patients were included. NOACs significantly decreased stroke or systemic embolism (2.8% vs 3.5%, odds ratio [OR] 0.82, 95% confidence interval [CI] 0.74–0.91, P<0.001), death (6.0% vs 6.3%, OR 0.88, 95% CI 0.82–0.95, P=0.001) and stroke (2.4% vs 3.0%, OR 0.79, 95% CI 0.71–0.88, P<0.001). The reduction in stroke was mainly driven by fewer hemorrhagic strokes (0.3% vs 0.8%, OR 0.79, 95% CI 0.71–0.88, P=0.001). Major bleeding occurred in 5.0% and 5.6% of patients in the NOACs and warfarin groups (OR 0.85, 95% CI 0.69–1.05, P=0.14 in the random-effects model). NOACs were associated with lower rates of intracranial bleeding (0.6% vs 1.3%, P<0.001) and higher rates of gastrointestinal bleeding (2.3% vs 1.3%, P=0.036).

Conclusions: In patients with non-valvular AF, NOACs decrease stroke or systemic embolism, hemorrhagic stroke and mortality, with similar risk of major bleeding compared to warfarin.

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minimization of bias. No formal scoring system was used. Reviewers were not blinded to journal, authors, or institution of publication.

1.2. Data extraction

All data were extracted independently by 2 evaluators (D.C. and C.T.); discrepancies were resolved by consensus. The following efficacy outcomes were extracted: the composite of stroke or systemic embolism (primary efficacy endpoint); stroke (hemorrhagic and/or ischemic); all-cause death; myocardial infarction. The following safety outcomes were extracted: major bleeding (primary safety endpoint); intracranial hemorrhage; gastrointestinal bleeding. The clinical endpoint definitions were similar among the trials. Each trial had independent adjudication of clinical events.

1.3. Statistical analysis

Data were analyzed according to intention-to-treat. The results of all studies were combined using a fixed-effects model, and confirmed by a random-effects model to minimize heterogeneity between groups. A 2-tailed alpha of 5% was used for hypothesis testing. Statistical heterogeneity was assessed with Cochran Q via a chi-square test and quantified with the I^2 test. The influence of single trials was examined by excluding individual studies, and testing for systematic bias was performed using funnel plots and Begg's test. Statistical analysis was performed using Comprehensive Meta-Analysis v2.0 (Biostat, Englewood NJ).

2. Results

2.1. Search Results

As shown in Fig. 1, 338 potentially eligible studies were identified, 3 of which met the pre-specified inclusion criteria. Main features of these studies are listed in Tables 1 and 2. All trials compared NOACs and warfarin in non-valvular AF [8–10]. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) tested two doses of the direct thrombin inhibitor dabigatran etexilate (110 and 150 mg twice daily), while the factor Xa inhibitors rivaroxaban (20 mg once daily or 15 mg in patients with moderate renal impairment) and apixaban (5 mg twice daily) were studied in the ROCKET-AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for the Prevention of Stroke Subjects With Atrial Fibrillation), respectively. In the RE-LY, the assignments to dabigatran or warfarin were not concealed. In contrast, the ROCKET AF and ARISTOTLE trials shared a double-blind design.

Of 50,578 randomized patients, 28,342 were assigned to NOACs and 22,236 were assigned to warfarin (Table 1). Patients were on aspirin and vitamin K antagonists prior to enrollment in 31–40% and 50–62% of cases, respectively. The mean CHADS2 score ranged from 2.1 to 3.5, with patients enrolled in the ROCKET-AF presenting with the higher baseline risk for stroke, a feature also reflected by the higher prevalence of prior stroke or transient ischemic attack (TIA) (55%) compared to the RE-LY and the ARISTOTLE (20% and 19%, respectively) (Table 2).

2.2. Efficacy Outcomes

NOACs were associated with a significant 18% reduction in the composite of stroke or systemic embolism compared to warfarin (2.8% vs 3.5%, odds ratio [OR] 0.82, 95% confidence interval [CI] 0.74–0.91, P<0.001, Fig. 2), with no heterogeneity (I^2=0%, P=0.62) or systematic bias apparent across the studies (P=0.60). None of the studies was found to unduly influence this primary efficacy endpoint estimate.

Compared with warfarin, NOACs significantly reduced the risk of all-cause death (6.0% vs 6.3%, OR 0.88, 95% CI 0.82–0.95, P=0.001) and stroke (2.4% vs 3.0%, OR 0.79, 95% CI 0.71–0.88, P<0.001) in both the fixed- and random-effects models, with no heterogeneity or evidence of systematic bias (Table 3). The stroke reduction seen with NOACs was mainly driven by a decreased risk of hemorrhagic strokes (0.3% vs 0.8%, OR 0.79, 95% CI 0.71–0.88, P<0.001), although

Table 1

Studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>NOACs, n</th>
<th>Warfarin, n</th>
<th>Period in the therapeutic INR range (median)</th>
<th>Primary Efficacy Outcome</th>
<th>Primary Safety Outcome</th>
<th>Duration of follow up (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY [8]</td>
<td>2009</td>
<td>Double-blind</td>
<td>18113</td>
<td>12091</td>
<td>6022</td>
<td>64%</td>
<td>Stroke, systemic embolism</td>
<td>Major bleeding</td>
<td>2 years</td>
</tr>
<tr>
<td>ROCKET-AF [9]</td>
<td>2011</td>
<td>Double-blind</td>
<td>14264</td>
<td>7131</td>
<td>7133</td>
<td>58%</td>
<td>Stroke, systemic embolism</td>
<td>Major bleeding clinically relevant bleeding</td>
<td>1.9 years</td>
</tr>
<tr>
<td>ARISTOTLE [10]</td>
<td>2011</td>
<td>Double-blind</td>
<td>18201</td>
<td>9120</td>
<td>9081</td>
<td>66%</td>
<td>Stroke, systemic embolism</td>
<td>Major bleeding ‡</td>
<td>1.8 years</td>
</tr>
</tbody>
</table>

INR = International Normalized Ratio; NOACs = Novel Oral Anticoagulants.

* Defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.

† Major bleeding defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability.

‡ Major bleeding defined as acute or subacute clinically overt bleeding accompanied by ≥1 of the following: a decrease in hemoglobin level of ≥2 g/dL, a transfusion of ≥2 U of packed red blood cells, bleeding that was fatal or occurred in the following critical sites: intracranial, intra-spinal, intra-ocular, pericardial, intra-articular, intra-muscular with compartment syndrome, retroperitoneal.

Please cite this article as: Capodanno D, et al, Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients, Int J Cardiol (2012), doi:10.1016/j.ijcard.2012.03.148
this outcome was associated with a non-significant 59% level of heterogeneity (p = 0.09). No differences in the rates of myocardial infarction were noted between the two groups (1.3% vs 1.3%, OR 0.99, 95% CI 0.71–1.38 in the random-effects model, P = 0.94) (Table 3).

2.3. Safety Outcomes

A total of 22.5% in the NOACs group and 22.4% in the warfarin group discontinued the allocated drug during the study period (OR 1.10, 95% CI 0.86–1.42, P = 0.44 in the random-effects model). Major bleeding occurred in 5.0% of patients in the NOACs group and in 5.6% of patients in the warfarin group (OR 0.85, 95% CI 0.79–0.92, P < 0.001 in the fixed-effects model and OR 0.85, 95% CI 0.69–1.05, P = 0.14 in the random-effects model) (Fig. 3). There was a high level of heterogeneity regarding this endpoint (I² = 86%; P < 0.001) but no systematic bias was apparent across the trials (P = 0.60). After excluding the ARISTOTLE, the ORs for the primary safety endpoint were 0.93 (95% CI 0.85–1.03, P = 0.16) and 0.94 (95% CI 0.80–1.05, P = 0.14) in the fixed- and random-effects model, respectively. NOACs were associated with lower rates of intracranial bleeding (0.6% vs 1.3%, P < 0.001) and higher rates of gastrointestinal bleeding (2.3% vs 1.3%, P = 0.036), but both endpoints were associated with high heterogeneity among the trials. Of note, NOACs were not associated with a significant increased risk of liver enzymes and bilirubin elevation compared with warfarin (p = 0.28) (Table 3).

3. Discussion

In this meta-analysis of randomized clinical trials involving patients with non-valvular AF, NOACs were found to be significantly superior to warfarin with respect to a composite of stroke or systemic embolism, with no increased risk of major bleeding at a median follow-up ranging between 1.8 and 2 years. In addition, NOACs significantly reduced the risk of death and hemorrhagic stroke, while no benefit signal was seen in reducing the risk of ischemic stroke and myocardial infarction.

The trials included in this meta-analysis had a number of similar conclusions that strengthen our results particularly regarding the efficacy outcomes. Dabigatran and apixaban significantly reduced stroke or systemic embolism in the RE-LY and ARISTOTLE [8,10], respectively, while the superiority of rivaroxaban over warfarin was not demonstrated in the intention-to-treat analysis of the ROCKET-AF, despite a strong directional trend was present in the intention-to-treat analysis and superiority in the as-treated analysis [9]. The reductions in the primary efficacy endpoints were driven by lower rates of hemorrhagic stroke, while only the 150 mg dose of dabigatran was found to significantly reduce the risk of ischemic stroke as compared with warfarin in the RE-LY [8]. Even with the higher dose of dabigatran, however, the main benefit was a reduction in hemorrhagic stroke than on ischemic cerebrovascular events [8], consistent with our results. Importantly, we found small significant 0.3% absolute and 12% relative risk reductions in mortality. Apixaban was the first of the NOACs to show a significant reduction in the risk of death from any cause as compared with warfarin but both dabigatran and rivaroxaban showed a similar tendency, thus contributing to the consistency of our findings, although obtained in a very large pooled population, a scenario which increases the likelihood to achieve statistical significance for clinically unimportant effect sizes.

As far as safety is concerned, the risk of major bleeding was reduced with dabigatran in the RE-LY and dramatically with apixaban in the ARISTOTLE, while rivaroxaban did not result in lower rates of protocol-defined major bleeding compared to warfarin in the ROCKET-AF. It is of note that, for the purposes of the present study, the available data on each dabigatran dose were combined, while in the RE-LY the safety benefit was most attributable to the lower 110 mg dose [8]. The above findings resulted in a pooled 15% relative reduction in major bleeding with NOACs, which lost its statistical significance when moving from a fixed-effects to a random-effects model. In the presence of a significant heterogeneity that cannot readily be explained, as in this case, the more conservative interpretation coming from a random-effects model may be preferable. Of importance, the safety results have been largely influenced by the performance of apixaban in the ARISTOTLE trial, therefore caution is

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>CHADS2 score (mean)</th>
<th>AF type (persistent or permanent / paroxysmal, %)</th>
<th>Prior stroke / SE / TIA (%)</th>
<th>Prior MI (%)</th>
<th>Hypertension (%)</th>
<th>Previous medications use (ASA/VKA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY [8]</td>
<td>71</td>
<td>63</td>
<td>2.1</td>
<td>67/33</td>
<td>20</td>
<td>17</td>
<td>79</td>
<td>40/50</td>
</tr>
<tr>
<td>ROCKET-AF [9]</td>
<td>73</td>
<td>60</td>
<td>3.5</td>
<td>81/18</td>
<td>55</td>
<td>17</td>
<td>90</td>
<td>36/62</td>
</tr>
<tr>
<td>ARISTOTLE [10]</td>
<td>70</td>
<td>65</td>
<td>2.1</td>
<td>85/15</td>
<td>19</td>
<td>14</td>
<td>87</td>
<td>31/57</td>
</tr>
</tbody>
</table>

AF = Atrial Fibrillation, ASA = aspirin; MI = Myocardial Infarction; SE = Systemic Embolism; TIE = Transient Ischemic Attack; VKA = Vitamin K Antagonists.
required and no “class-effect” can be claimed from the present data. However, even if one were to consider the degree of heterogeneity to be so significant so as to preclude quantitative assessment of a summary estimate, from this systematic review, it appears that the preponderance of the evidence does not suggest a severe adverse safety signal with NOACs, with the possible exception of more gastrointestinal bleedings compared with warfarin. Even so, the favorable net clinical benefit of NOACs over warfarin suggested by this study (lower stroke and – at least – similar major bleedings), with the additional practical advantage of no requirement for INR monitoring or dose adjustment, is quite evident. On the other side, shortcomings of NOACs compared to warfarin include the short half-life, thus potential increasing the risk of stroke or systemic embolism due to poor drug adherence, lack of coagulation assays to precisely measure the anticoagulation effect, lack of antidote for reversing anticoagulation, and costs [11]. Importantly, NOACs are not currently recommended in AF patients with other reasons for warfarin therapy, such as those with prosthetic heart valves.

3.1. Limitations

Variation in study design, inclusion criteria, endpoint definitions, lengths of follow up and possible publication bias are limitations of all meta-analyses. The major limitation may be due to the disparity of the agent characteristics. Because different drugs cannot be compared across trials despite the use of a common comparator (i.e. patients were at low-to-moderate risk for stroke in the RE-LY and ARISTOTLE, and at moderate-to-high risk in the ROCKET-AF; the achievement of therapeutic INRs, a metric that assesses the quality of warfarin dosing, sensibly varied in the warfarin arms of each trial), the only way to determine which drug is more effective would be a head-to-head study, which is hardly to be performed because such comparison is beyond the interest of the companies. With more >50000 patients in the present study, our analysis may have overemphasized the statistical significance of small, non-clinically relevant differences between the compared drugs. Finally, heterogeneity was present especially regarding bleeding endpoints. To account for this issue, random-effects models were privileged. Despite these limitations, a notable improvement in survival and other hard clinical outcomes was observed, with no heterogeneity issues, which is particularly interesting for patients with AF.

4. Conclusions

In patients with non-valvular AF, NOACs decrease the composite of stroke or systemic embolism, hemorrhagic stroke and mortality compared to warfarin, with no significant increase of major bleeding. Based on these results, NOACs approved from regulatory agencies should be used as first-line agents for antithrombotic management of patients with non-valvular AF.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [12].

### Table 3

<table>
<thead>
<tr>
<th>Endpoint, % (n/N)</th>
<th>NOACs (n = 28342)</th>
<th>Warfarin (n = 22236)</th>
<th>Fixed Effects (OR, 95% CI)</th>
<th>Random Effects (OR, 95% CI)</th>
<th>P value</th>
<th>I², %</th>
<th>Heterogeneity, p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>2.8 (797/28292)</td>
<td>3.5 (770/22193)</td>
<td>0.82 (0.74–0.91)</td>
<td>0.82 (0.74–0.91)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.62</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.4 (688/28292)</td>
<td>3.0 (670/22193)</td>
<td>0.79 (0.71–0.88)</td>
<td>0.79 (0.71–0.88)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.80</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.3 (95/28292)</td>
<td>0.8 (173/22193)</td>
<td>0.44 (0.30–0.66)</td>
<td>0.45 (0.35–0.58)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.09</td>
</tr>
<tr>
<td>Ischemic or unspecified</td>
<td>2.0 (588/28292)</td>
<td>2.2 (489/22193)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.1</td>
<td>0</td>
<td>0.96</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6.0 (1695/28292)</td>
<td>6.3 (1406/22193)</td>
<td>0.88 (0.82–0.95)</td>
<td>0.88 (0.82–0.95)</td>
<td>0.001</td>
<td>0</td>
<td>0.76</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.3 (366/28292)</td>
<td>1.3 (291/22193)</td>
<td>0.99 (0.71–1.38)</td>
<td>0.98 (0.83–1.15)</td>
<td>0.94</td>
<td>76</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.0 (1419/28290)</td>
<td>5.6 (1245/22199)</td>
<td>0.85 (0.69–1.05)</td>
<td>0.85 (0.79–0.92)</td>
<td>0.14</td>
<td>86</td>
<td>0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.6 (170/28290)</td>
<td>1.3 (295/22199)</td>
<td>0.46 (0.38–0.55)</td>
<td>0.46 (0.33–0.65)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.036</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2.3 (644/28290)</td>
<td>1.3 (291/22199)</td>
<td>1.68 (1.03–2.72)</td>
<td>1.70 (1.47–1.96)</td>
<td>0.036</td>
<td>91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT or AST &gt;3× ULN with concurrent bilirubin &gt;2× ULN</td>
<td>0.3 (89/27990)</td>
<td>0.4 (87/21903)</td>
<td>0.85 (0.63–1.14)</td>
<td>0.85 (0.63–1.14)</td>
<td>0.28</td>
<td>0</td>
<td>0.44</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = Confidence Interval; NOACs = Novel Oral Anticoagulants; OR = odds ratio; ULN = Upper Limit of Normality.

**Fig. 3.** Effect of novel anticoagulants (NOAC) vs. warfarin on the safety endpoint of major bleeding.

Please cite this article as: Capodanno D, et al, Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients, Int J Cardiol (2012), doi:10.1016/j.ijcard.2012.03.148
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