Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials


Summary

Background Four new oral anticoagulants compare favourably with warfarin for stroke prevention in patients with atrial fibrillation; however, the balance between efficacy and safety in subgroups needs better definition. We aimed to assess the relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes.

Methods We searched Medline from Jan 1, 2009, to Nov 19, 2013, limiting searches to phase 3, randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We did a prespecified meta-analysis of all 71683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials. The main outcomes were stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. We calculated relative risks (RRs) and 95% CIs for each outcome. We did subgroup analyses to assess whether differences in patient and trial characteristics affected outcomes. We used a random-effects model to compare pooled outcomes and tested for heterogeneity.

Findings 42411 participants received a new oral anticoagulant and 29272 participants received warfarin. New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; p=0.0001), mainly driven by a reduction in haemorrhagic stroke (0.49, 0.38–0.64; p<0.0001). New oral anticoagulants also significantly reduced all-cause mortality (0.90, 0.85–0.95; p=0.0003) and intracranial haemorrhage (0.48, 0.39–0.59; p<0.0001), but increased gastrointestinal bleeding (1.25, 1.01–1.55; p=0.04). We noted no heterogeneity for stroke or systemic embolic events in important subgroups, but there was a greater relative reduction in major bleeding with new oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was 66% or more (0.69, 0.59–0.81 vs 0.93, 0.76–1.13; p for interaction 0.022). Low-dose new oral anticoagulant regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (1.03, 0.84–1.27; p=0.74), and a more favourable bleeding profile (0.65, 0.43–1.00; p=0.05), but significantly more ischaemic strokes (1.28, 1.02–1.60; p=0.045).

Interpretation This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Funding None.

Introduction Atrial fibrillation, the most common sustained cardiac arrhythmia, predisposes patients to an increased risk of embolic stroke and has a higher mortality than sinus rhythm.1,2 Until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants available. Although these drugs are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. This limitation has translated into poor patient adherence and probably contributes to the systematic underuse of vitamin K antagonists for stroke prevention.3,4

Several new oral anticoagulants have been developed that dose-dependently inhibit thrombin or activated factor X (factor Xa) and offer potential advantages over vitamin K antagonists, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. The
predictable anticoagulant effects of the new anti-coagulants enable the administration of fixed doses without the need for routine coagulation monitoring, thereby simplifying treatment. Individually, new oral anti-coagulants are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation.\(^1\)\(^-\)\(^4\) Dabigatran, rivaroxaban, and apixaban have been approved by regulatory authorities, whereas edoxaban has completed late-stage clinical assessment.

Although previously published meta-analyses have been done of trials comparing new oral anticoagulants with warfarin in patients with atrial fibrillation,\(^9\)\(^-\)\(^13\) this analysis is the first to include data from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48)\(^8\)\(^,\)\(^14\) with edoxaban, the largest of the four trials. All four trials were powered to address their primary endpoints; however, the balance between efficacy and safety in important clinical subgroups needs better definition. We aimed to enhance precision in assessment of the relative benefit of new oral anticoagulants in key subgroups, and the effects of these drugs on important secondary outcomes, to offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in patients with atrial fibrillation.

**Methods**

**Study selection**

We undertook a prespecified analysis of the four phase 3, randomised trials comparing the efficacy and safety of new oral anticoagulants with warfarin for stroke prevention in patients with atrial fibrillation: Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY; dabigatran),\(^5\) Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF),\(^6\) Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),\(^7\) and the ENGAGE AF–TIMI 48 study (edoxaban).\(^8\)

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**Table:** Baseline characteristics of the intention-to-treat populations of the included trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY(^5)</th>
<th>ROCKET-AF(^6)</th>
<th>ARISTOTLE(^7)</th>
<th>ENGAGE AF–TIMI 48(^8)</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>71·5 (8·8)</td>
<td>71·4 (8·6)</td>
<td>71·6 (8·6)</td>
<td>71·5 (8·6)</td>
<td>71·6 (7·4)</td>
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<tr>
<td>≥75 years</td>
<td>40%</td>
<td>38%</td>
<td>39%</td>
<td>43%</td>
<td>36%</td>
</tr>
<tr>
<td>Women</td>
<td>37%</td>
<td>36%</td>
<td>37%</td>
<td>40%</td>
<td>36%</td>
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<tr>
<td>Atrial fibrillation type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent or permanent</td>
<td>67%</td>
<td>68%</td>
<td>66%</td>
<td>81%</td>
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<td>Paroxysmal</td>
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<td>34%</td>
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<td>25%</td>
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<td><strong>CHADS2</strong></td>
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<tr>
<td>2</td>
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<td>35%</td>
<td>37%</td>
<td>13%</td>
<td>46%</td>
</tr>
<tr>
<td>3-6</td>
<td>33%</td>
<td>33%</td>
<td>32%</td>
<td>87%</td>
<td>54%</td>
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<td></td>
<td></td>
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</tr>
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<tr>
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<td>79%</td>
<td>79%</td>
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<td>Prior myocardial infarction</td>
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<tr>
<td>&lt;50 mL/min</td>
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<td>19%</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>50–80 mL/min</td>
<td>48%</td>
<td>49%</td>
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<td>47%</td>
<td>43%</td>
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<tr>
<td>&gt;80 mL/min</td>
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<td>32%</td>
<td>32%</td>
<td>32%</td>
<td>38%</td>
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<tr>
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<td>Aspirin at baseline</td>
<td>39%</td>
<td>40%</td>
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<tr>
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<tr>
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<td>NA</td>
<td>67 (54–78)</td>
<td>58 (43–71)</td>
<td>66 (52–77)</td>
</tr>
</tbody>
</table>

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. CHADS2=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. \(\dagger\)ROCKET-AF included patients with left ventricular ejection fraction <55%. ARISTOTLE included those with left ventricular ejection fraction ≤40%. RE-LY <50 mL/min, 50–79 mL/min, >80 mL/min, <50 mL/min, >50–79 mL/min, >80 mL/min, <50–79 mL/min, >80 mL/min, <50–79 mL/min, >80 mL/min, <50–79 mL/min, >80 mL/min. **Aspirin use not available. 

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1. Dabigatran, rivaroxaban, and apixaban have been approved by regulatory authorities, whereas edoxaban has completed late-stage clinical assessment. 
2. Although previously published meta-analyses have been done of trials comparing new oral anticoagulants with warfarin in patients with atrial fibrillation, this analysis is the first to include data from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) with edoxaban, the largest of the four trials. 
3. All four trials were powered to address their primary endpoints; however, the balance between efficacy and safety in important clinical subgroups needs better definition. 
4. We aimed to enhance precision in assessment of the relative benefit of new oral anticoagulants in key subgroups, and the effects of these drugs on important secondary outcomes, to offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in patients with atrial fibrillation.

**Methods**

**Study selection**

We undertook a prespecified analysis of the four phase 3, randomised trials comparing the efficacy and safety of new oral anticoagulants with warfarin for stroke prevention in patients with atrial fibrillation: Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY; dabigatran), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and the ENGAGE AF–TIMI 48 study (edoxaban).
We assessed comparative efficacy and safety for stroke or systemic embolic events and for major bleeding (the primary efficacy and safety outcomes) in important clinical subgroups: age (<75 vs ≥75 years), sex, history of previous stroke or transient ischaemic attack, history of diabetes, renal function (creatinine clearance <50 mL/min, 50–80 mL/min, >80 mL/min), CHADS₂ risk score (0–1, 2, 3–6), vitamin K antagonist status at study entry (naive or experienced), and centre-based time in therapeutic range (threshold of <66% vs ≥66%). The centre-based time in therapeutic range is the mean time in therapeutic range at each enrolling centre achieved in its patients randomised to warfarin. The range is used as a surrogate of the quality of control of international normalised ratio for all the patients receiving warfarin at that site. All four of the trials reported the centre-based time in therapeutic range achieved in their respective warfarin groups by quartiles. We selected our threshold of centre-based time in therapeutic range because RE-LY, ROCKET AF, and ARISTOTLE all had a quartile boundary near 66% and because the threshold differentiates the efficacy and safety of oral anticoagulants from dual antiplatelet therapy.²⁵ Because we had access to the clinical database in ENGAGE AF–TIMI 48, we could run this analysis at a threshold of 66%. We did all analyses with Comprehensive Meta-Analysis software (version 2).

### Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin. The table shows baseline characteristics for each study. The average age of patients was similar between trials as was the proportion of women recruited (table). However, the underlying risk for stroke differed significantly across the trials as shown by the proportion of patients with CHADS₂ scores of 3–6 (table). Median follow-up ranged from 1-8 years to 2-8 years and the median time in

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**Figure 1**: Stroke or systemic embolic events

Data are n/N, unless otherwise indicated. Heterogeneity: I²=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. §Apixaban 5 mg twice daily. ¶Edoxaban 60 mg once daily.
therapeutic range in patients in the warfarin groups ranged from 58% to 68% (table).

Figure 1 shows the comparative efficacy of high-dose of new oral anticoagulants and warfarin. Allocation to a new oral anticoagulant significantly reduced the composite of stroke or systemic embolic events by 19% compared with warfarin (figure 1). The benefit was mainly driven by a large reduction in haemorrhagic stroke (figure 2). New oral anticoagulants were also associated with a significant reduction in all-cause mortality (figure 2). The drugs were similar to warfarin in the prevention of ischaemic stroke and myocardial infarction (figure 2).

Randomisation to a high-dose new oral anticoagulant was associated with a 14% non-significant reduction in major bleeding (figure 3). In line with the reduction in haemorrhagic stroke, a substantial reduction in intracranial haemorrhage was observed, which included haemorrhagic stroke, and subdural, epidural, and subarachnoid bleeding (figure 2). New oral anticoagulants were, however, associated with increased gastrointestinal bleeding (figure 2).

The benefit of new oral anticoagulants compared with warfarin in reducing stroke or systemic embolic events was consistent across all subgroups examined (figure 4). The safety of new oral anticoagulants compared with warfarin was generally consistent for the reduction of major bleeding across subgroups, with the exception of a significant interaction for centre-based time in therapeutic range (figure 4). We noted a greater relative reduction in bleeding with new oral anticoagulants at centres that achieved a centre-based time in therapeutic range of less than 66% than at those achieving a time in therapeutic range of 66% or more (figure 4).

The low-dose new oral anticoagulant regimens had similar efficacy to warfarin for the composite of stroke or systemic embolic events (appendix). When differentiated by stroke type, the low-dose regimens were associated with an increase in ischaemic stroke compared with warfarin, which was balanced by a large decrease in haemorrhagic stroke (appendix). Similar to the higher-dose regimens, the low doses showed a significant reduction in all-cause mortality (appendix). Significantly more myocardial infarctions were reported with the low-dose regimens than with warfarin (appendix). The low-dose regimens were associated with a non-significant reduction in major bleeding, but with a significant reduction in intracranial haemorrhage. Gastrointestinal bleeding was similar between low-dose new oral anticoagulants and warfarin (appendix).

A meta-analysis of only the factor Xa inhibitors, with removal of dabigatran, showed similar results to the...
main meta-analysis for both stroke or systemic embolic events and major bleeding (appendix). An additional analysis was done combining all doses of all drugs in one meta-analysis (including both high and low doses of dabigatran and edoxaban with rivaroxaban and apixaban; appendix). Inclusion of low doses of dabigatran and edoxaban decreased the magnitude of the reduction in risk of stroke or systemic embolic events with new oral anticoagulants and resulted in less bleeding than warfarin (appendix).

Figure 4: Stroke or systemic embolic events subgroups (A) and major bleeding subgroups (B)

Data are n/N, unless otherwise indicated. No data available from RE-LY for the following major bleeding subgroups: sex, creatinine clearance, diabetes, and CHADS2 score. For ROCKET AF no major bleeding data available in the TTR and diabetes subgroup and major and non-major clinically relevant bleeding was used for subgroups of age, sex, CHADS2 score, and creatinine clearance. NOAC=new oral anticoagulant. RR=risk ratio. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range.
Discussion
Our results show that stroke and systemic embolic events were significantly reduced in patients receiving new oral anticoagulants. This benefit was mainly driven by substantial protection against haemorrhagic stroke, which was reduced by half. Conceptually, haemorrhagic stroke is a complication of anticoagulant treatment even though it is part of the overall efficacy assessment of these drugs. Importantly, overall intracranial haemorrhage (which includes haemorrhagic stroke) was reduced by roughly half, which represents a substantial benefit of treatment with new oral anticoagulants. Intracranial haemorrhage is a feared and often fatal complication of anticoagulant treatment and about one in six first hospital admissions for this disorder are related to such treatment. For the prevention of ischaemic stroke, the new oral anticoagulants had similar efficacy to warfarin, which itself is very effective in this regard and reduces ischaemic stroke by two-thirds compared with placebo. In general, the new oral anticoagulants had a favourable safety profile compared with warfarin; however, they were associated with an increase in gastrointestinal bleeding. They were also associated with a significant reduction in all cause-mortality compared with warfarin.

A separate analysis of the two low-dose new oral anticoagulant regimens showed that although they have a similar efficacy to warfarin for protection against all stroke or systemic embolic events, they are not as effective for protection against ischaemic stroke in particular. However, they do have a safer profile than warfarin and preserve the mortality benefit noted with the high-dose regimens. Consequently, low-dose regimens might be an appealing option for frail patients or for those who have a high risk for bleeding with full-dose anticoagulation.

Panel: Research in context
Systematic review
We searched Medline from Jan 1, 2009 to Nov 19, 2013. Keywords were “atrial fibrillation”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, “oral factor Xa inhibitor”, “oral thrombin inhibitor”, and “warfarin”. We also did a search of ClinicalTrials.gov to identify relevant ongoing clinical studies. We restricted our analysis to phase 3, randomised trials that included patients with atrial fibrillation who were randomly assigned to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We assessed the quality of identified studies to ensure minimisation of bias. No formal scoring system was used to assess the quality of the evidence.

Interpretation
This meta-analysis is the first to include results from all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention in patients with atrial fibrillation. New oral anticoagulants showed a favourable risk-benefit profile with significant reductions in stroke, intracranial haemorrhage, and mortality with similar major bleeding as warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of the anticoagulants was consistent across a wide range of patients with atrial fibrillation. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

A criticism of meta-analyses in this specialty is that the large phase 3 trials for stroke prevention in patients with atrial fibrillation were well powered to evaluate the main treatment effect of their individual drug to reduce the risk of stroke or systemic embolic events compared with warfarin. However, most trials are underpowered to detect differences in secondary outcomes and subgroups. An example is the analysis of all-cause mortality; only apixaban and low-dose edoxaban were associated with significant reductions in all cause-mortality, yet the point estimates for the hazard ratios for all drugs (and doses) are very similar. The results of the meta-analysis support the premise that compared with warfarin, the new oral anticoagulants, as a class, reduce all-cause mortality by about 10% in the populations enrolled in the clinical trials.

Perhaps, more important than the provision of robust estimates of secondary outcomes is the ability of meta-analyses to enhance precision in assessment of the relative benefits of new oral anticoagulants in important, clinically relevant subgroups. Both risk of stroke and bleeding vary significantly across the range of patients with atrial fibrillation. For example, vulnerable populations, such as elderly people (aged ≥75 years), patients with a previous history of stroke, and those with renal dysfunction, have an increased risk of both ischaemic and bleeding events. Inclusion of these individuals in trials is variable and they are often underrepresented. Consequently, each trial alone can only offer partial reassurance that the overall balance of efficacy and safety is preserved in these high-risk groups. For example, variations in the proportion of participants with a CHADS2 score of 3–6 were mainly attributable to differential enrolment of patients with previous stroke or transient ischaemic attack. This robust meta-analysis is the first to show that the relative efficacy and safety of new oral anticoagulants is consistent across a broad range of vulnerable patients (panel).

We investigated whether the benefit of new oral anticoagulants was dependent on whether patients had experience with use of vitamin K antagonists before enrolment in the trial. Previous findings suggested that patients with little to no prior exposure to vitamin K antagonists (ie, naive) had a higher risk of both ischaemic and bleeding events than experienced patients. A concern has remained that new oral anticoagulants might have reduced benefit in experienced patients who have shown an ability to tolerate treatment with vitamin K antagonists. The results of our meta-analysis show that the benefit of new oral anticoagulants is consistent irrespective of a patient’s history with vitamin K antagonists.

We also investigated whether the benefit of new oral anticoagulants was dependent on how well warfarin was managed during the trial, as assessed by the centre-based time in therapeutic range. In the ACTIVE W trial, anticoagulant treatment had no significant benefit compared with clopidogrel plus aspirin in centres with a centre-based time in therapeutic range that was less than
the median of 65%, whereas a reduction of more than two times was reported for vascular events in centres with a time in therapeutic range of more than 65%. The trials included in this meta-analysis had varying success in management of warfarin (median time in therapeutic range 58–68%), and although they reported no heterogeneity in the results across their trial-specific quartiles, 5,6,22 each trial was underpowered to detect a difference. In this meta-analysis, we examined a threshold of 66% for centre-based time in therapeutic range, which is similar to that used in the ACTIVE W analysis. We showed that the reduction in stroke or systemic embolism compared with warfarin is not dependent on how well warfarin is managed, within the limitations of analyses based on centre-based time in therapeutic range. However, an even more pronounced relative reduction in bleeding with new oral anticoagulants seems to take place in patients who have difficulty maintaining a therapeutic international normalised ratio.

Because we did not have individual participant data for all the trials, our statistical approach was done at a study level. We pooled the data for the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the thrombin inhibitor (dabigatran). Although these drugs inhibit different coagulation factors, we believe that pooling of the results is justified for several reasons: the drugs are all specific inhibitors of important factors in the coagulation cascade, the phase 3 warfarin-controlled trials of all four drugs are qualitatively similar in design, published guidelines refer to these drugs together as new oral anticoagulants, and previous meta-analyses have taken a similar approach. Additionally, sensitivity analyses removing dabigatran and including only factor Xa inhibitors showed similar results. Important differences also exist in drugs, patient demographics, and trial characteristics that might affect outcomes not accounted for in this analysis. We noted statistical heterogeneity across the trials with respect to major bleeding and gastrointestinal bleeding, which could show true differences across trials or between drugs. However, some heterogeneity is expected to be reported in large meta-analyses, and complete uniformity can show consistency in bias rather than consistency in real effects. 39 Use of a random-effects model and the robustness of the data across important clinical subgroups can help mitigate the potential effect of heterogeneity on the validity of the results. We included data from only clinical trials, which could affect the generalisability of the results because patients in clinical trials are often thought to be at lower risk for adverse events than are those in routine clinical practice. 39 However, post-approval experience with the new oral anticoagulants has approximated what was noted in the clinical trial population. For example, in a nationwide cohort study in Denmark with dabigatran, the first approved new oral anticoagulant, no excess of events in a clinical practice was reported compared with what was shown in the RE-LY trial. 40

In summary, the new oral anticoagulants show a favourable balance between efficacy and safety compared with warfarin, which is consistent across a wide range of patients with atrial fibrillation known to be at high risk for both ischaemic and bleeding events.

Contributors
CTR wrote the first draft of the manuscript; all authors contributed to subsequent drafts. CTR, ND, and EBH undertook the statistical analyses.

Conflicts of interest
CTR has served as a consultant and has received honoraria from Daiichi Sankyo, Boehringer Ingelheim, and Bristol-Myers Squibb. RPG has served as a consultant and has received honoraria from Bristol-Myers Squibb, Janssen, Daiichi Sankyo, Merck, Sanofi, and is a member of the TIMI Study Group, which has received research grant support from Daiichi Sankyo, Johnson & Johnson, and Merck. EB has received grants and personal fees for lectures from Daiichi Sankyo; grants from Duke University, AstraZeneca, Johnson & Johnson, Merck & Co, Sanofi-Aventis, GlassSmithKline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, and Pfizer; uncompensated personal fees for consultancy from Merck & Co; personal fees for consultancies from Genzyme, Amoacyte, Medicines Co, CardiosRents, and Sanofi-Aventis; uncompensated personal fees for lectures from Merck and CVRx; and personal fees for lectures from Eli Lilly, Menarini International, Medscape, and Bayer outside the submitted work. MDE has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Johnson & Johnson, Janssen, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Sanofi, Portola, Medtronic, Aegerion, Merck, Gilead, and Pozen. AJC has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. JIW has served as a consultant and has received honoraria from Boehringer Ingelheim, Bayer, Janssen, Bristol-Myers Squibb, Pfizer, Pfizer, and Daiichi Sankyo. ESL has served as a consultant to Bayer, Bristol-Myers Squibb, and Pfizer and received research grants in these trials from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. AP has received a research grant from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo. EMA has received a research grant from Daiichi Sankyo. All other authors declare that they have no conflicts of interest.

References


Warfarin or novel oral anticoagulants for atrial fibrillation?

Stroke prevention is central to the management of atrial fibrillation and, until recently, the focus was to identify high-risk patients who would be given a so-called inconvenient drug, warfarin. Nowadays, the landscape for stroke prevention has changed with the availability of novel oral anticoagulants, and an increased appreciation that vitamin K antagonists (eg, warfarin) work best with high-quality anticoagulation control (shown by the average individual time in therapeutic range at an international normalised ratio of 2.0–3.0). Thus, contemporary guidelines have focused on the initial identification of low-risk patients (ie, those aged <65 years with lone atrial fibrillation, or those with a CHA2DS2-VASc score of 0 [if male] or 1 [if female]). Subsequent to this step, stroke prevention can then be offered to patients with atrial fibrillation and one or more stroke risk factors, and the bottom line is that effective stroke prevention means oral anticoagulation, whether given as a vitamin K antagonist or a novel oral anticoagulant.

Several novel oral anticoagulants now exist, offering similar (or better) effectiveness, safety, and convenience to the vitamin K antagonists; those with evidence from large randomised trials of stroke prevention in patients with atrial fibrillation fall into two drug classes: the direct thrombin inhibitors (eg, dabigatran), and the oral factor Xa inhibitors (eg, rivaroxaban, apixaban, and, most recently, edoxaban).

In The Lancet, Christian Ruff and colleagues present findings from their meta-analysis of all 71 683 patients included in the four phase 3 randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin. The investigators conclude that, compared with warfarin, high-dose regimens of new oral anticoagulants significantly reduced stroke or systemic embolism events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91), mainly driven by a reduction in haemorrhagic stroke (0.49, 0.38–0.64). High-dose regimens also significantly reduced all-cause mortality (0.90, 0.85–0.95) and intracranial haemorrhage (0.48, 0.39–0.59), but increased gastrointestinal bleeding (1.25, 1.01–1.55; p=0.04), with no difference in myocardial infarction (0.97, 0.78–1.20). Low-dose regimens had similar efficacy to that of warfarin for the composite of stroke or systemic embolism events (1.03, 0.84–1.27), but were associated with an increase in ischaemic stroke (1.28, 1.02–1.60; p=0.04). The low-dose regimens reduced all-cause mortality (0.89, 0.83–0.96), but resulted in more myocardial infarctions (1.25, 1.04–1.50) than warfarin. Furthermore, these regimens were associated with a non-significant reduction in major bleeding (0.65, 0.43–1.00; p=0.05) and gastrointestinal bleeding (0.89, 0.57–1.37), but a significant reduction in intracranial haemorrhage (0.31, 0.24–0.41).

Such a meta-analysis assumes that all the novel oral anticoagulant drugs are the same (which they are not) and work on the basis of a class effect or are broadly equivalent; and that the randomised trials are homogeneous, which again they are not. Indeed, Ruff and colleagues’ meta-analysis does not really answer the question of which novel oral anticoagulant is best, whether from an efficacy or safety perspective. Although indirect comparisons between novel oral anticoagulants have been both criticised and justified, these comparisons suggest that, ultimately, the drug could be fitted to the patient, or the patient to the drug, dependent on a focus on safety or efficacy, and on other patient factors, such as renal function and drug compliance. Indeed, post-marketing safety reports provide some reassurance that these drugs work well, if used correctly.

How would the novel oral anticoagulants have compared against excellent-quality anticoagulation control? In the trials, median time in therapeutic range ranged between 58% and 68%. In the meta-analysis by Ruff and colleagues, the only significant interaction noted for various subgroups was a greater relative reduction in cause mortality (0.89, 0.83–0.96), but resulted in more myocardial infarctions (1.25, 1.04–1.50) than warfarin. Furthermore, these regimens were associated with a non-significant reduction in major bleeding (0.65, 0.43–1.00; p=0.05) and gastrointestinal bleeding (0.89, 0.57–1.37), but a significant reduction in intracranial haemorrhage (0.31, 0.24–0.41).

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### Table: Definition of the SAMe-TT2R2 score

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Sex (female)</td>
<td>1</td>
</tr>
<tr>
<td>A Age (&gt;60 years)</td>
<td>1</td>
</tr>
<tr>
<td>M Medical history*</td>
<td>1</td>
</tr>
<tr>
<td>e</td>
<td></td>
</tr>
<tr>
<td>T Treatment (interacting Rx†)</td>
<td>1</td>
</tr>
<tr>
<td>T Tobacco use (within 2 years)</td>
<td>2</td>
</tr>
<tr>
<td>R Race (non-white)</td>
<td>2</td>
</tr>
<tr>
<td>Maximum points</td>
<td>8</td>
</tr>
</tbody>
</table>

SAMe-TT2R2 = Sex female, Age less than 60, Medical history, Treatment strategy (rhythm control), Tobacco use (doubled), Race (doubled). *Two of the following: hypertension, diabetes, coronary artery disease, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease. †Eg, amiodarone for rhythm control.
in major bleeding with novel oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was more than 66%. High times in therapeutic range (>70%) are associated with the best efficacy and safety of vitamin K antagonists, with low rates of stroke and bleeding.\(^8\) By contrast, low values are associated with an increased risk of stroke, serious bleeding, and mortality,\(^7,9\) and the patient might do worse if given warfarin than if they were untreated.

A major dilemma of clinical management is how to predict newly diagnosed non-anticoagulated patients with atrial fibrillation who would do well on vitamin K antagonists with high time in therapeutic range, because the main benefits of novel oral anticoagulants compared with warfarin might be only marginal in those with high times in therapeutic range, although the reduction in intracranial haemorrhage is still evident. The SAMe-TT\(_2\)R\(_2\) score (table) offers a user-friendly validated score based on simple clinical variables, which aids decision making for physicians by identifying patients with atrial fibrillation who are likely to do well on warfarin (SAMe-TT\(_2\)R\(_2\) score 0–1) or those who are more likely to have poor anticoagulation control (score >2).\(^10\) The latter patient population could benefit from being started on novel oral anticoagulants as initial therapy, or could be identified for use of more aggressive interventions to help achieve an acceptable level of anticoagulation control.\(^11\)

Effective stroke prevention in patients with atrial fibrillation with more than one stroke risk factor means oral anticoagulation, whether delivered by use of a novel oral anticoagulant, or as well-controlled vitamin K antagonists with high time in therapeutic range (SAMe-TT\(_2\)R\(_2\) score might identify these patients). Previously the only available anticoagulant was a vitamin K antagonist, but clinicians now have a choice and can fit the drug to the patient, and vice versa. With the availability of four novel oral anticoagulants, perhaps we are now spoilt for choice.

*Torben Bjerregaard Larsen, Gregory Y H Lip*
Department of Cardiology, Aalborg AF Study Group, Aalborg University Hospital, Aalborg DK-9000, Denmark (TBL); Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark (TBL, GYHL); and Centre for Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, UK (GYHL)
tobl@rm.dk

TBL has been an investigator for Janssen Scientific Affairs and Boehringer Ingelheim, and served on speaker bureaux for Bayer, Bristol-Myers Squibb/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim, and as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daichi Sankyo, and Sanofi-Aventis.