

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



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## 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 71 683 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** 42 411 participants received a new oral anticoagulant and 29 272 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.<sup>1,2</sup> 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.<sup>3,4</sup>

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

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predictable anticoagulant effects of the new anticoagulants enable the administration of fixed doses without the need for routine coagulation monitoring, thereby simplifying treatment. Individually, new oral anticoagulants are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation.<sup>5-8</sup> 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,<sup>9-13</sup> 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)<sup>8,14</sup> 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),<sup>5</sup> 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),<sup>6</sup> Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),<sup>7</sup> and the ENGAGE AF-TIMI 48 study (edoxaban).<sup>8</sup>

	RE-LY <sup>5</sup>		ROCKET-AF <sup>6</sup>		ARISTOTLE <sup>7</sup>		ENGAGE AF-TIMI 48 <sup>8</sup>		Combined			
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71.5 (8.8)	71.4 (8.6)	71.6 (8.6)	73 (65-78)	73 (65-78)	70 (63-76)	70 (63-76)	72 (64-68)	72 (64-78)	72 (64-78)	71.6	71.5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS <sub>2</sub> <sup>*</sup>	2.2 (1.2)	2.1 (1.1)	2.1 (1.1)	3.5 (0.94)	3.5 (0.95)	2.1 (1.1)	2.1 (1.1)	2.8 (0.97)	2.8 (0.97)	2.8 (0.98)	2.6 (1.0)	2.6 (1.0)
0-1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3-6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA <sup>*</sup>	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure <sup>†</sup>	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance <sup>‡</sup>												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50-80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use <sup>§</sup>	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years) <sup>¶</sup>	2.0	2.0	2.0	1.9	1.9	1.8	1.8	2.8	2.8	2.8	2.2	2.2
Individual median TTR	NA	NA	67 (54-78)	NA	58 (43-71)	NA	66 (52-77)	NA	NA	68 (57-77)	NA	65 (51-76)

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. CHADS<sub>2</sub>=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. <sup>\*</sup>ROCKET-AF and ARISTOTLE included patients with systemic embolism. <sup>†</sup>ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction <40%. <sup>‡</sup>RE-LY <50 mL/min, 50-79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50-80 mL/min, >80 mL/min. <sup>§</sup>RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. <sup>¶</sup>IQRs not available.

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

## Statistical analysis

We obtained information about the following outcomes from the main trial publications, supplemental appendices, and relevant subsequent analyses:<sup>5–8,15–23</sup> stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage (including haemorrhagic stroke, epidural, subdural, and subarachnoid haemorrhage), and gastrointestinal bleeding. When possible, we did analyses with the intention-to-treat population for efficacy outcomes and with the safety population for bleeding outcomes. In RE-LY<sup>5</sup> and ENGAGE AF–TIMI 48,<sup>8</sup> two doses of dabigatran and edoxaban, respectively, were compared with warfarin. Rather than combining data with both doses into one meta-analysis, which would merge the benefit and risk of different doses, potentially compromising interpretability, we undertook a meta-analysis with both higher doses (dabigatran 150 mg twice daily for RE-LY and edoxaban 60 mg once daily for ENGAGE AF–TIMI 48) combined with the single doses studied in ROCKET AF<sup>6</sup> (rivaroxaban 20 mg once daily) and ARISTOTLE<sup>7</sup> (5 mg twice daily). In a separate analysis we undertook a meta-analysis of the two lower doses (dabigatran 110 mg twice daily for RE-LY and edoxaban 30 mg once daily for ENGAGE AF–TIMI 48). We did two sensitivity analyses including a meta-analysis of only the factor Xa inhibitors, with removal of the thrombin inhibitor dabigatran, and an analysis combining all doses of all drugs (both high and low doses of dabigatran and edoxaban with rivaroxaban and apixaban). We did not use any data from phase 2 dose-ranging studies because of their small sample size and short follow-up, which precluded comparable ascertainment for all the outcomes analysed.

We calculated relative risks (RRs) and corresponding 95% CIs for each outcome and trial separately and checked findings against published data for accuracy. When necessary, we calculated numbers of outcome events on the basis of event rates, sample size, and duration of follow-up. Outcomes were then pooled and compared with a random-effects model.<sup>24</sup> We assessed the appropriateness of pooling of data across studies with use of the Cochran Q statistic and *I*<sup>2</sup> test for heterogeneity.<sup>25</sup>

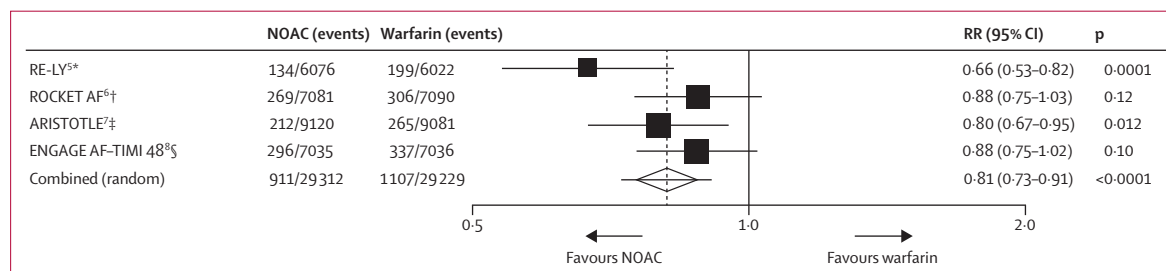
We assessed comparative efficacy and safety for stroke or systemic embolic events and for major bleeding (the primary efficacy and safety outcomes) in important clinical subgroups: age (<75 vs ≥75 years), sex, history of previous stroke or transient ischaemic attack, history of diabetes, renal function (creatinine clearance <50 mL/min, 50–80 mL/min, >80 mL/min), CHADS<sub>2</sub> 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.<sup>6,16,22</sup> 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 CHADS<sub>2</sub> scores of 3–6 (table). Median follow-up ranged from 1·8 years to 2·8 years and the median time in



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

Data are n/N, unless otherwise indicated. Heterogeneity: *I*<sup>2</sup>=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

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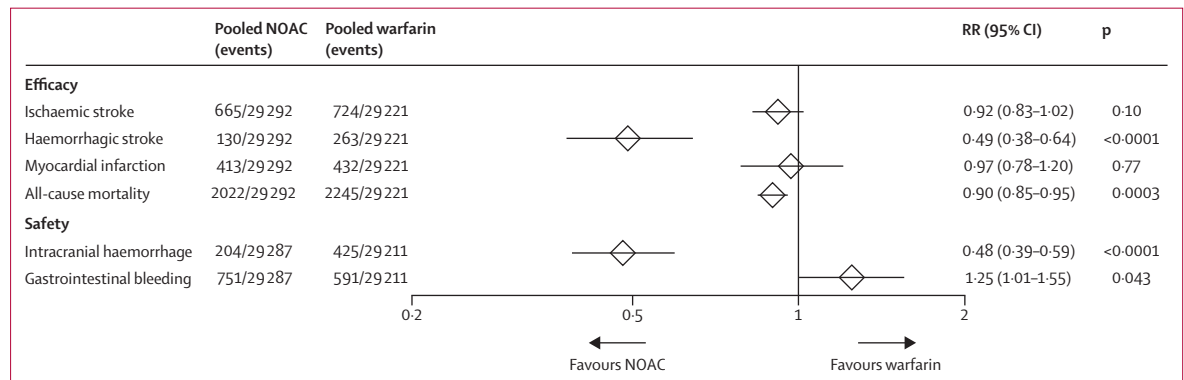


Figure 2: Secondary efficacy and safety outcomes

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke  $I^2=32\%$ ,  $p=0.22$ ; haemorrhagic stroke  $I^2=34\%$ ,  $p=0.21$ ; myocardial infarction  $I^2=48\%$ ,  $p=0.13$ ; all-cause mortality  $I^2=0\%$ ,  $p=0.81$ ; intracranial haemorrhage  $I^2=32\%$ ,  $p=0.22$ ; gastrointestinal bleeding  $I^2=74\%$ ,  $p=0.009$ . NOAC=new oral anticoagulant. RR=risk ratio.

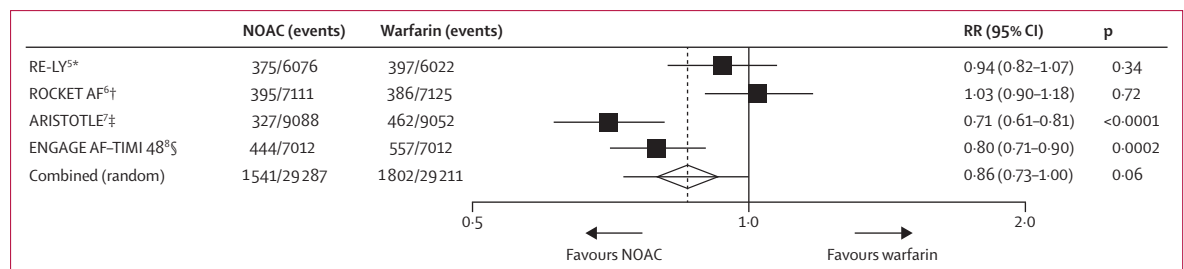
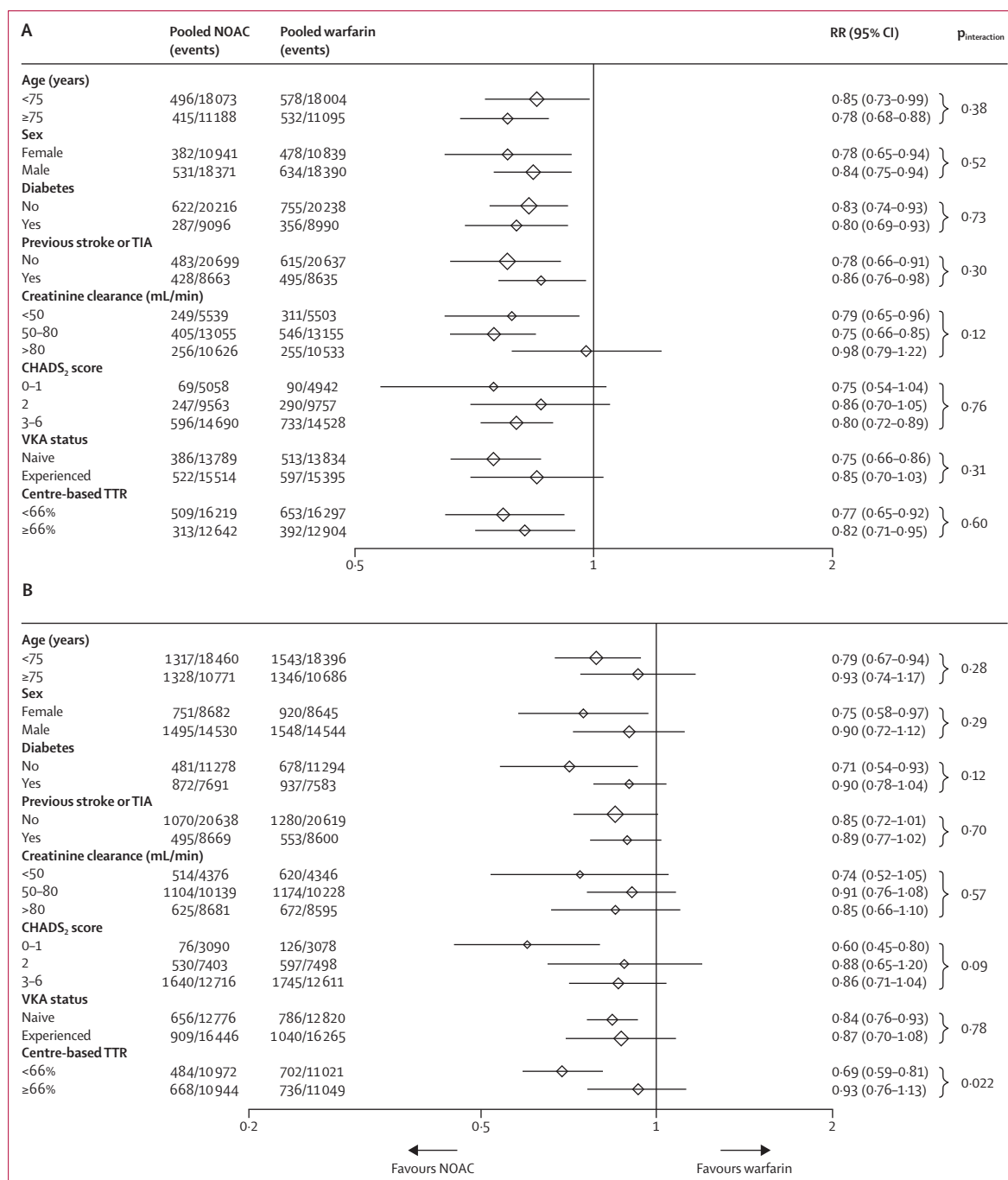


Figure 3: Major bleeding

Data are n/N, unless otherwise indicated. Heterogeneity:  $I^2=83\%$ ;  $p=0.001$ . 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.



**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 CHADS<sub>2</sub> 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, CHADS<sub>2</sub> score, and creatinine clearance. NOAC=new oral anticoagulant. RR=risk ratio. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range

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).

## 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.<sup>26</sup> 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.<sup>27</sup> 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.

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  $\geq 75$  years),<sup>28</sup> patients with a previous history of stroke,<sup>29,30</sup> and those with renal dysfunction,<sup>31,32</sup> 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 CHADS<sub>2</sub> score of 3–6 were mainly attributable to differential enrolment of patients with previous stroke or transient ischaemic attack.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35,36</sup> In the ACTIVE W trial,<sup>37</sup> 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

### 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.

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,<sup>6,16,22</sup> 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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40</sup>

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, GlaxoSmith Kline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, and Pfizer; uncompensated personal fees for consultancy from Merck & Co; personal fees for consultancies from Genzyme, Amocyte, Medicines Co, CardioRentis, 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, and Daiichi Sankyo. BSL 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. TY has received honoraria from 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

- 1 Camm AJ, Kirchhof P, Lip GY, et al, and the European Heart Rhythm Association, and the European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31**: 2369–429.
- 2 Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; **349**: 1019–26.
- 3 Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* 2006; **37**: 1070–74.
- 4 Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007; **115**: 2689–96.
- 5 Connolly SJ, Ezekowitz MD, Yusuf S, et al, and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–51.
- 6 Patel MR, Mahaffey KW, Garg J, et al, and the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883–91.
- 7 Granger CB, Alexander JH, McMurray JJ, et al, and the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981–92.
- 8 Giugliano RP, Ruff CT, Braunwald E, et al. Once-daily edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093–104.

- 9 Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation* 2012; **126**: 2381–91.
- 10 Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 711–19.
- 11 Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2012; **60**: 738–46.
- 12 Dogliotti A, Paolasso E, Giugliano RP. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. *Clin Cardiol* 2013; **36**: 61–67.
- 13 Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012; **110**: 453–60.
- 14 Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010; **160**: 635–41.
- 15 Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L, and the Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med* 2010; **363**: 1875–76.
- 16 Wallentin L, Yusuf S, Ezekowitz MD, et al, and the RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010; **376**: 975–83.
- 17 Ezekowitz MD, Wallentin L, Connolly SJ, et al, and the RE-LY Steering Committee and Investigators. Dabigatran and warfarin in vitamin K antagonist-naïve and -experienced cohorts with atrial fibrillation. *Circulation* 2010; **122**: 2246–53.
- 18 Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011; **123**: 2363–72.
- 19 Diener HC, Connolly SJ, Ezekowitz MD, et al, and the RE-LY study group. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010; **9**: 1157–63.
- 20 Mahaffey KW, Wojdyla D, Hankey GJ, et al. Clinical outcomes with rivaroxaban in patients transitioned from vitamin K antagonist therapy: a subgroup analysis of a randomized trial. *Ann Intern Med* 2013; **158**: 861–68.
- 21 Hankey GJ, Patel MR, Stevens SR, et al, and the ROCKET AF Steering Committee Investigators. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012; **11**: 315–22.
- 22 Wallentin L, Lopes RD, Hanna M, et al, and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation* 2013; **127**: 2166–76.
- 23 Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012; **33**: 2821–30.
- 24 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
- 25 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
- 26 Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* 2007; **68**: 116–21.
- 27 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146**: 857–67.
- 28 Hughes M, Lip GY, and the Guideline Development Group, National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care, National Institute for Health and Clinical Excellence. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008; **99**: 295–304.
- 29 Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007; **69**: 546–54.
- 30 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138**: 1093–100.
- 31 Go AS, Fang MC, Udaltsova N, et al, and the ATRIA Study Investigators. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009; **119**: 1363–69.
- 32 Piccini JP, Stevens SR, Chang Y, et al, and the ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index 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 ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013; **127**: 224–32.
- 33 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–70.
- 34 Garcia DA, Lopes RD, Hylek EM. New-onset atrial fibrillation and warfarin initiation: high risk periods and implications for new antithrombotic drugs. *Thromb Haemost* 2010; **104**: 1099–105.
- 35 Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. *Thromb Res* 2009; **124**: 37–41.
- 36 Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011; **106**: 968–77.
- 37 Connolly SJ, Pogue J, Eikelboom J, et al, and the ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008; **118**: 2029–37.
- 38 Cleophas TJ, Zwinderman AH. Meta-analysis. *Circulation* 2007; **115**: 2870–75.
- 39 Cabral KP, Ansell J, Hylek EM. Future directions of stroke prevention in atrial fibrillation: the potential impact of novel anticoagulants and stroke risk stratification. *J Thromb Haemost* 2011; **9**: 441–49.
- 40 Larsen TB, Rasmussen LH, Skjøth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in “real-world” patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 2013; **61**: 2264–73.