

# New oral anticoagulants for stroke prevention in atrial fibrillation: impact of study design, double counting and unexpected findings on interpretation of study results and conclusions

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## Summary

Four recently introduced new oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) have been shown to be at least as efficacious and safe as warfarin for stroke prevention in patients with atrial fibrillation in their respective trials. The first three have been approved, while edoxaban is awaiting regulatory approval. Several guidelines have endorsed the approved new oral anticoagulants over warfarin because of their favourable risk-benefit ratio, low propensity for food and drug interactions, and lack of requirement for routine coagulation monitoring. In this invited review, we summarise the results

of the four studies and discuss widely held conclusions. We take a step further and discuss how differences in study design, analysis plan, and unexpected events affect the interpretation of the study results. Finally, we take our re-interpretation of study results and discuss how they might impact clinical practice and anticoagulant choice for patients.

## Keywords

Clinical trials, oral anticoagulants, stroke / prevention, thrombosis

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## Introduction

Since 2005, four new oral anticoagulants (NOACs), dabigatran, rivaroxaban, apixaban and edoxaban have been evaluated in five large phase III trials for the prevention of thromboembolic events in patients with non-valvular atrial fibrillation (AF) (1-5). Each NOAC has been compared to warfarin and in the AVERROES study, which recruited patients who were deemed warfarin-unsuitable, apixaban was compared to aspirin (ASA). The results of their respective studies have led to the approval of the first three NOACs by the Food and Drug Administration (FDA) and regulatory bodies worldwide for the prevention of stroke and systemic embolism in patients with AF. The fourth NOAC, edoxaban, is awaiting regulatory approval for similar indication after the recent publication of the ENGAGE-AF results (4).

Regulatory approval of the NOACs was followed by at least three Consensus Guideline Committees' endorsement of their use in AF. The approved NOACs were broadly recommended as preferable to warfarin in the majority of AF patients by the European Society of Cardiology and the Canadian Cardiovascular Society in 2012 while the American College of Chest Physicians (ACCP) suggested dabigatran 150 mg bid over warfarin; at the time of ACCP guideline publication, other NOACs had not been approved (6-8).

The recommendations by these societies were based on the finding indicating that the approved NOACs were at least as effective as warfarin in preventing stroke in atrial fibrillation, were associated with significantly less intracranial bleeding, and were more convenient. In contrast, in their 2012 guideline update, the American Heart Association/American Stroke Association took a more cautious individualised approach and suggested that the approved NOACs are on par with warfarin rather than preferable to warfarin because of concerns about their use in renal failure, safety in the absence of antidotes, and cost issues that could affect affordability and patient compliance (9).

The results of the studies comparing NOACs with warfarin in AF have been the subject of several reviews; all concluded that the NOACs appear to be at least as effective and safe as warfarin in AF patient (10-16). In this invited review of NOACs in AF, rather than repeat what has been published before, we summarise the data as they were presented in each of the four warfarin-controlled studies as well as the widely held conclusions. Then, we review the sub-components of the efficacy and safety outcomes and discuss how differences in the designs of the studies, controversial issues of analysis, and unexpected side effects affect the interpretation of the results. Finally, we discuss how our interpretation of the results might impact clinical practice.

## Trial characteristics

► Table 1 summarises the key patient characteristics, intervention, comparator, and primary outcomes of the four major clinical trials which compared the NOACs with warfarin: RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF (1-4). The RE-LY study was a prospective, randomised, open, blinded endpoint study that compared blinded doses of dabigatran 110 mg and 150 mg twice daily bid to open-label warfarin, whereas the last three trials were blinded randomised controlled trials comparing rivaroxaban 20 mg daily, apixaban 5 mg bid and two doses of edoxaban (30 mg and 60 mg daily) respectively, to warfarin.

## Summary of main outcomes of the four NOACs studies

► Figure 1A and ► Figure 2A describe the results of primary efficacy and safety outcomes from the four major clinical trials. Estimates are derived from the primary publications when available and when not available, we report estimates from our calculations based on data from the primary publications or from the FDA

medical review documents; we indicated these by marking with “†” such as RR† or ARR†. Results of primary and secondary efficacy outcomes were those of intention to treat (ITT) analyses except for the ROCKET AF in which published estimates for secondary outcomes were only available for the on treatment period.

Investigators of the RE-LY study reported that both doses of dabigatran (110 mg and 150 mg bid) were statistically non-inferior to warfarin in the primary efficacy outcome of stroke and systemic embolism (1). In addition, the results showed that dabigatran 150 mg bid was more effective at preventing stroke and systemic embolism (relative risk [RR]=0.66; 95% CI: 0.53 to 0.82), while dabigatran 110 mg bid was less likely to cause major bleeding (RR=0.80; 95% confidence interval [CI]: 0.69 to 0.93) than warfarin. When directly compared, dabigatran 150 mg bid was more effective at preventing stroke and systemic embolism than dabigatran 110 mg bid (RR=0.73; 95% CI: 0.58 to 0.91), but also showed a strong trend for increased major bleeding (RR=1.16; 95% CI: 1.00 to 1.34; p=0.052). The unfavourable bleeding profile of the higher dose was primarily attributable to an increase in GI bleeding (RR=1.36; 95% CI: 1.09 to 1.07).

The ROCKET AF investigators reported that, in the ITT analysis, rivaroxaban 20 mg daily (15 mg daily in patients with a calcu-

Table 1: Study characteristics.

Studies	RE-LY (1)	ROCKET AF (2)	ARISTOTLE (3)	ENGAGE AF-TIMI 48 (4)	
<b>Trial size (n)</b>	18,113	14,264	18,201	21,105	
<b>Patient characteristics</b>	<b>Mean age (years)</b>	71.5	73	70	72
	<b>Male (%)</b>	63.5%	59.3%	64.5%	61.9%
	<b>Mean CHADS<sub>2</sub></b>	2.1	3.5	2.1	2.8
<b>Intervention vs Comparator</b>	<b>Intervention</b>	Two intervention arms: 1. Dabigatran 150 mg bid 2. Dabigatran 110 mg bid	Rivaroxaban 20 mg daily	Apixaban 5 mg bid	Two intervention arms: 1. Edoxaban 30 mg daily 2. Edoxaban 60 mg daily
	<b>Dose modification</b>	No	Yes, at randomisation	Yes, at randomisation	Yes, at randomisation and during study
	<b>Criteria for modified dose</b>	N/A	15 mg daily in patients with CrCl 30–49 ml/min	2.5 mg bid in patients who met 2 of the 3 following criteria: • age >80 years, • weight <60 kg, • creatinine >133 µmol/l	Half dose in patients with any of the following criteria: • CrCl 30–50 ml/min, • weight <60 kg, • concomitant use of potent p-glycoprotein inhibitors such as verapamil, quinidine, dronedarone. Standard dose resumed once these medications ceased.
	<b>Comparators</b>	Open label warfarin	Blinded warfarin	Blinded warfarin	Blinded warfarin
<b>Outcomes</b>	<b>Primary efficacy</b>	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
	<b>Primary safety</b>	Major bleeding	Major bleeding + clinically relevant non major bleeding	Major bleeding	Major bleeding

Bid = twice-daily dose; CrCl = creatinine clearance as per Cockcroft Gault formulas; kg = kilogram; mg = milligram.

lated creatinine clearance of 30–49 ml/minute [min]) was statistically non-inferior to warfarin in preventing stroke and systemic embolism (hazard ratio [HR]=0.88; 95% CI: 0.75 to 1.03) outcome; a result which contrasts with the per protocol analysis (HR=0.79; 95% CI: 0.66 to 0.96) (2). No significant difference between groups was observed in the risk of major bleeding (HR=1.04; 95% CI: 0.90 to 1.20).

The ARISTOTLE investigators reported that apixaban 5 mg bid (2.5 mg bid in patients who met at least two of the following criteria: age >80 years, weight <60 kg, serum creatinine >133 µmol/l) was superior to warfarin in both the primary efficacy (HR=0.79; 95% CI: 0.66 to 0.95) and safety outcomes (HR=0.69; 95% CI: 0.60 to 0.80) in ITT analyses (3).

The ENGAGE AF investigators reported that both edoxaban 30 mg and 60 mg daily regimens (half dose at any time during the study in patients who met any of the following criteria: eGFR 30–50 ml/min, weight <60 kg, concomitant use of potent p-glycoprotein inhibitor) were statistically non-inferior to warfarin in the primary efficacy outcome in the ITT analyses: HR=1.13; 95% CI: 0.96 to 1.34 and HR=0.87; 95% CI: 0.73 to 1.04, respectively (4). The rates of major bleeding were significantly lower for both edoxaban 30 mg (HR=0.47; 95% CI: 0.41 to 0.55) and 60 mg arms (HR=0.80; 95% CI: 0.71 to 0.91) when compared to warfarin.

## Summary of secondary outcomes

### Sub-components of primary efficacy outcome:

► Figure 1B-D examines the individual contribution of the components of the primary efficacy outcome – a composite of (haemorrhagic and ischaemic/unspecified) stroke and systemic embolism. All four NOACs produced a marked and significant reduction in haemorrhagic stroke (median RR†=0.42; range: 0.26 to 0.58) compared to warfarin (► Figure 1B). Upon close examination of the thrombotic components of the primary efficacy outcome, only dabigatran 150 mg bid (► Figure 1C) showed a significant reduction in ischaemic/unspecified (i.e. non-haemorrhagic) stroke (RR=0.76; 95% CI: 0.60 to 0.98 whereas the rate of non-haemorrhagic stroke was higher with edoxaban 30 mg daily than with warfarin (HR=1.41; 95% CI: 1.19 to 1.67). Rivaroxaban produced a significant reduction in systemic embolism (HR=0.23; 95% CI: 0.09 to 0.61), but only in the “as treated” population, not the ITT population (► Figure 1D).

### Bleeding according to site:

Dabigatran 150 mg bid, rivaroxaban and edoxaban 60 mg daily significantly increased the risk of major gastrointestinal (GI) bleeding. Edoxaban 30 mg produced less GI bleeding (HR=0.67; 95% CI: 0.53 to 0.83) whereas no significant difference in GI bleeding was observed for dabigatran 110 mg bid or for apixaban 5 mg bid (► Figure 2B).

Each NOAC was associated with a significantly lower rate of intra-cranial bleeding than warfarin (► Figure 2C). Apixaban

(HR=0.79; 95% CI: 0.68 to 0.93) and edoxaban 30 mg bid (RR†=0.54; 95% CI: 0.46 to 0.64) also significantly reduced extra-cranial bleeding, whereas, dabigatran, rivaroxaban, and edoxaban 60 mg produced similar rates of extra-cranial bleeding as warfarin.

### Overall mortality, vascular death and fatal bleeding:

There was a strong trend for all four NOACs to reduce overall mortality, which reached statistical significance with apixaban (HR=0.89; 95% CI: 0.80 to 0.998, p=0.047) and edoxaban 30 mg daily (HR=0.87; 95% CI=0.79 to 0.96, p=0.006). The reduction in mortality was derived from both reductions in fatal bleeding and fatal thromboembolism. All four NOACs were associated with lower rates of vascular death which reached statistical significance with dabigatran 150 mg bid (RR=0.85; 95% CI: 0.72 to 0.99), edoxaban 30 mg daily (HR=0.85; 95% CI: 0.76 to 0.96) and edoxaban 60 mg daily (HR=0.86; 95% CI: 0.77 to 0.97). Similarly, all four NOACs were associated with lower rates of fatal bleeding which was statistically significant for all regimens except dabigatran 150 mg bid (RR=0.70; 95% CI: 0.43 to 1.14).

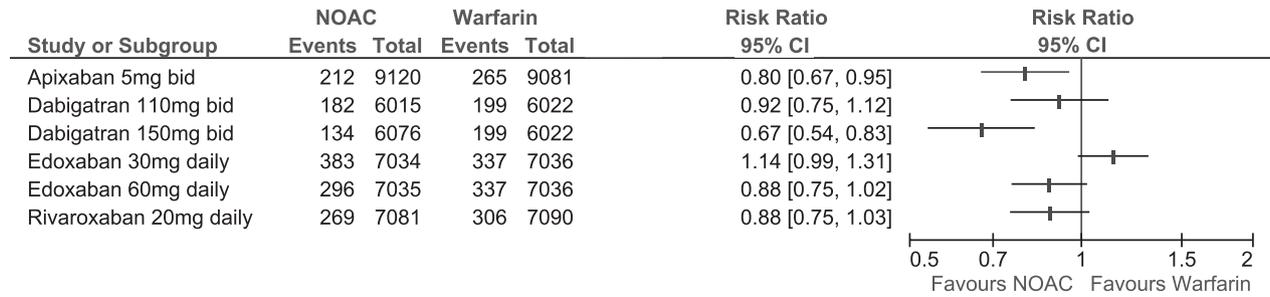
### Net clinical benefit analyses:

Although net clinical benefit was defined differently in the three studies (RE-LY, ARISTOTLE, and ENGAGE-AF) that reported on it, all three analyses suggested improved net clinical benefit. First, in the RE-LY study, both dabigatran 110 mg bid (RR 0.92; 95% CI: 0.82 to 1.02), and 150 mg bid (RR 0.91; 95% CI: 0.82 to 1.00) showed strong trends of improved net clinical benefit (composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction (MI), death and major embolism) when compared to warfarin. Second, the ARISTOTLE study showed consistent superiority of apixaban over warfarin in the two reported net clinical outcome analyses, the first analysis, a composite of stroke, systemic embolism, major bleeding with overall death (HR 0.85; 95% CI=0.78 to 0.92), and the second, without overall death (HR 0.77; 95% CI: 0.69 to 0.86). Third, ENGAGE AF showed superiority of both edoxaban 60 mg and 30 mg daily in net clinical outcome in three analyses. Thus, for edoxaban 30 mg and 60 mg daily, the primary net clinical outcome analyses (stroke, systemic embolism, major bleeding or overall death) were HR=0.83; 95% CI: 0.77 to 0.90 and HR=0.89; 95% CI: 0.83 to 0.96, respectively, the secondary analyses (disabling stroke, life-threatening bleeding or overall mortality) were HR=0.83; 95% CI: 0.76 to 0.91 and HR=0.88; 95% CI: 0.81 to 0.97, respectively, and the tertiary analyses (stroke, systemic embolism, life-threatening bleeding, or overall mortality) were HR=0.89; 95% CI: 0.82 to 0.97 and HR=0.88; 95% CI: 0.81 to 0.96, respectively.

## Published conclusions

The authors of the studies comparing each of the NOACs with warfarin concluded that:

A. Primary Efficacy Outcome



B. Haemorrhagic stroke



C. Non-haemorrhagic stroke



D. Systemic Embolism

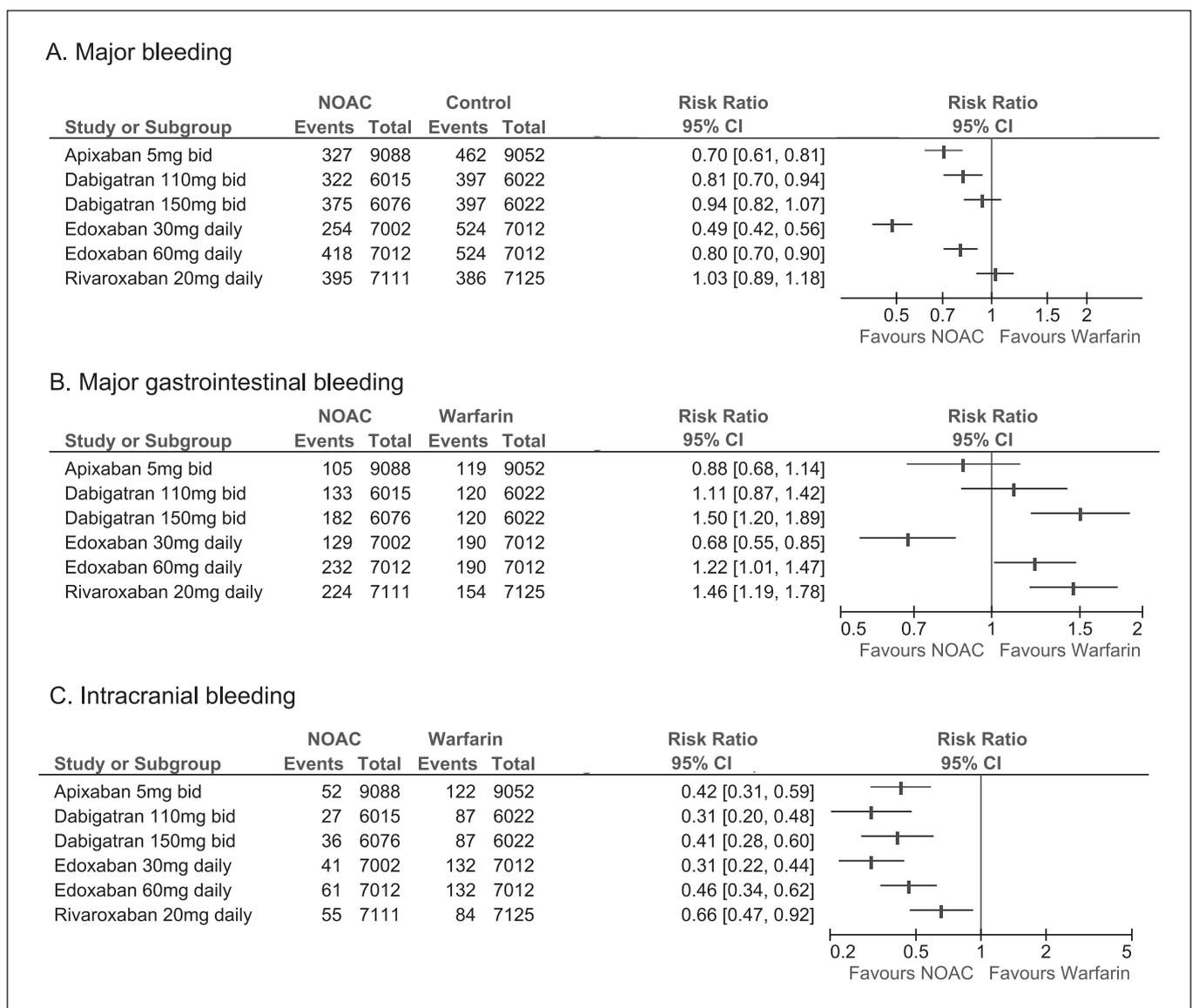


Figure 1: Primary efficacy outcome and its sub-components. A) Primary efficacy outcome: All four new oral anticoagulants (NOACs) were at least as effective as warfarin in patients with atrial fibrillation. Apixaban and dabigatran 150 mg were superior to warfarin in preventing the primary efficacy outcome (stroke + systemic embolism) while dabigatran 110 mg, both doses of edoxaban, and rivaroxaban were non-inferior to warfarin in ITT analyses. B) Haemorrhagic stroke: All three NOACs reduced the risk of haemorrhagic stroke. C) Non-haemorrhagic stroke consisting of ischaemic stroke and

uncertain stroke: Dabigatran 150 mg was the only NOAC showing a statistically significant reduction in the risk of non-haemorrhagic stroke in comparison to warfarin. The rate of ischaemic stroke with edoxaban 30 mg was higher than warfarin. D) Systemic embolism: This sub-component had the lowest event rates. Point estimate for rivaroxaban was based on the on treatment population (data from the ITT population was not available for rivaroxaban). Note: Plots constructed with different RR scales on the x-axis.

1. Dabigatran 150 mg bid is more effective in preventing stroke or systemic embolism than warfarin without significantly increasing major bleeding (1).
2. Dabigatran 110 mg bid is non-inferior to warfarin for the prevention of stroke or systemic embolism and causes less major bleeding (1).
3. Rivaroxaban is non-inferior to warfarin for the prevention of stroke or systemic embolism without significantly increasing major bleeding (2).
4. Apixaban is superior to warfarin in preventing stroke or systemic embolism, reducing bleeding and mortality (3).
5. Edoxaban 60 mg is non-inferior to warfarin for the prevention of stroke or systemic embolism, reduces the risk of major bleeding and cardiovascular death (4).
6. Edoxaban 30 mg is non-inferior to warfarin for the prevention of stroke or systemic embolism, reduces the risk of major bleeding and cardiovascular death (4).

The authors of meta-analyses concluded that all four new oral anticoagulants are at least as safe and effective as warfarin in patients with AF and all reduce the risk of haemorrhagic stroke (10-16). These conclusions are supported by post marketing analyses of effectiveness, safety and net benefit of NOACs in large registries and modelling studies (17-21).



**Figure 2: Bleeding outcomes.** A) Major bleeding: All four new oral anticoagulants (NOACs) were at least as safe as warfarin in patients with atrial fibrillation. Apixaban, dabigatran 110 mg and both doses of caused less major bleeding than warfarin. B) Major gastrointestinal bleeding: Dabigatran

150 mg, edoxaban 60 mg and rivaroxaban caused more major gastrointestinal bleeding than warfarin. C) Intracranial haemorrhage: All four NOACs caused less intracranial haemorrhage than warfarin. Note: Plots constructed with different RR scales on the x-axis.

## Re-evaluation of these conclusions after critical examination of the data

We have identified several issues that influence our interpretation of the results and the resultant recommendations. These are:

1. "Double counting" of intracerebral haemorrhage (haemorrhagic stroke) by including these events as strokes (efficacy outcome) and major bleeds (safety outcome) in all four trials.
2. The higher early discontinuation rates of study drug in ROCKET AF and ENGAGE AF, which disadvantage rivaroxaban and edoxaban in the ITT analyses.
3. Unanticipated side effects in the RE-LY, ROCKET AF and ENGAGE AF trials.
4. Unanticipated mortality benefit of low-dose edoxaban.

## Double counting of intracerebral haemorrhage:

Traditionally, for studies of stroke prevention in AF patients, the primary efficacy outcome is a composite of stroke (including haemorrhagic and ischaemic) and systemic embolism. In each of the four trials, the evaluated NOAC reduced the risk of intracerebral bleeding – a complication of anticoagulation therapy. Therefore, inclusion of haemorrhagic stroke in both the primary efficacy and safety outcomes leads to an overestimate of the net benefit of the NOACs relative to warfarin. Removal of intracerebral haemorrhage from the efficacy outcome changes the interpretation of the relative benefits of the NOACs compared to warfarin in three important ways: first it exposes the exaggerated estimates of net clinical benefit of all four NOACs, second it reveals that only dabi-

**Table 2: Impact of early discontinuation and off treatment events on the comparisons of on treatment and ITT analyses.**

Trial	Method	Analysis population*/ observation period#	Early discontinuation of treatment (%)	Stroke/SE rates (NOAC vs warfarin) On treatment (+2 days following last dose) HR (95% CI)	Stroke/SE rates (NOAC vs warfarin) ITT overall study period HR (95% CI)	Off treatment events (% of all ITT events)
RE-LY (23)	RCT, open, PROBE design	Non-inferiority 1 <sup>o</sup> ITT –overall study period	Dabigatran 110 mg arm: 22.9% 150 mg arm: 23.6% Warfarin arm: 19.2%	110 mg vs warfarin: NA  150 mg vs warfarin: 250 events in total 0.64 (0.50–0.81)	110 mg vs warfarin: 182/6015 vs 199/6022 381 events in total 0.91 (0.74–1.11)  150 mg vs warfarin: 134/6076 vs 199/6022 333 events in total 0.66 (0.53–0.82)	NA  83 events (24.9%) NA
ROCKET AF (2, 22)	RCT, blinded	Non-inferiority 1 <sup>o</sup> PP- On treatment 2 <sup>o</sup> ITT- overall study period	Rivaroxaban: 35.4% Warfarin: 34.6%	188/6958 vs 241/7004 429 events in total 0.79 (0.66–0.96)	269/7081 vs 306/7090 575 events in total 0.88 (0.75–1.03)	146 events (25.4%) (81 in rivaroxaban vs 66 in warfarin)
ARISTOTLE (24)	RCT, blinded	Non-inferiority 1 <sup>o</sup> ITT – overall study period	Apixaban arm: 25.3% Warfarin arm: 27.5%	176/9088 vs 225/9052 401 events in total 0.77 (0.63–0.93)	212/9120 vs 265/9081 477 events in total 0.79 (0.66–0.95)	76 events (15.6%) (36 in apixaban vs 40 in warfarin)
ENGAGE AF (4)	RCT, blinded	Non-inferiority 1 <sup>o</sup> mITT – On treatment 2 <sup>o</sup> ITT- overall study period	Edoxaban 30 mg arm: 32.8% 60 mg arm: 34.3% Warfarin arm: 34.4%	30 mg vs warfarin 485 events in total 1.07(0.87–1.31)  60 mg vs warfarin 414 events in total 0.79 (0.63–0.99)	30 mg vs warfarin 720 events in total 1.13 (0.96–1.34)  60 mg vs warfarin 633 0.87 (0.73–1.04)	235 events (32%) (130 in edoxaban 30 mg vs 105 in warfarin)  219 (34.5%) 114 in edoxaban 60 mg vs 105 in warfarin)

\*Definitions of analysis population: ITT population=all randomised patients whether or not they receive a single dose of study drug; mITT=all randomised patients who receive at least one dose of study drug; PP=all randomised patients who receive at least one dose of study drug and who do not have any major protocol violation. #Definitions of observation period: On treatment period= cumulative time period that a patient is taking study drug up to 2 or 3 days of the last dose i.e. off treatment periods, when patients either temporarily or permanently discontinue study drug, are not included; Overall study period=time from randomization to end of study. HR=hazard ratio; ITT=Intention to treat; mITT=modified intention to treat; NA=not available; NOAC=new oral anticoagulant; PP=per protocol; PROBE=prospective, randomised, open label, blinded endpoint; RCT=randomised controlled trial; SE=systemic embolism. Data obtained from original publications and FDA medical review documents (references 2, 4, 22, 23, 24).

gatan 150 mg bid is more effective than warfarin in reducing the risk of ischaemic stroke; and third it shows that the perceived superiority of apixaban over warfarin in both stroke reduction and intracranial bleeding is explained by including haemorrhagic stroke in both outcomes.

### The impact of premature termination on ITT analyses in the four trials:

Each publication reported the ITT analysis, although the primary analysis for ROCKET AF and ENGAGE AF were on-treatment analyses. When the results are reported as per ITT, rivaroxaban and high-dose edoxaban were non-inferior to warfarin, whereas apixaban and the higher dose of dabigatran were superior to warfarin. The lack of superiority of rivaroxaban and high-dose edoxaban in the ITT analyses should not be interpreted to indicate that these anticoagulants are less effective than the other two NOACs. Apart from the fact that the comparisons are indirect, there were important differences among the four trials in the number of premature discontinuations and off-treatment events included in the ITT analyses that occurred during the study period (see ► Table 2).

Of the four trials, ROCKET AF and ENGAGE AF had higher rates of premature discontinuation of study drug, possibly as a result of sicker populations with higher mean CHADS2 scores (4, 22-24). Thus, in ROCKET AF, 35.4% of patients assigned rivaroxaban and 34.6% assigned warfarin stopped prematurely, while in ENGAGE AF, 34.3% and 34.4% assigned high-dose edoxaban and warfarin, respectively, stopped study drug prematurely. Because more patients stopped the NOAC prematurely in the ROCKET AF and ENGAGE AF than in the other two AF trials, the treatment effect in the ITT analyses in these two studies were most diluted by off-treatment events. Premature discontinuation was also associated with an unfavourable imbalance of off-treatment events in the two arms in ROCKET AF (81 additional events in rivaroxaban arm compared to 66 in the warfarin arm) and in the ENGAGE AF (114 additional events in high dose edoxaban compared to 105 in the warfarin arm).

As a result of higher premature discontinuations, for ROCKET AF, the HR which was 0.79 in the on-treatment analysis (significant for superiority,  $p=0.02$ ) rose to 0.88 which was no longer significant for superiority in the ITT analysis, whereas, for ENGAGE AF, the HR for edoxaban 60 mg which was 0.79 in the on-treatment analysis (significant for superiority,  $p=0.02$ ) rose to 0.87 and was no longer significant.

### Unanticipated findings

There were several unanticipated findings:

1. Each NOAC caused fewer intracranial haemorrhages (ICH) than warfarin (1-4, 25).
2. There was an excess of GI bleeding associated with the higher dose of dabigatran, rivaroxaban and higher dose of edoxaban (1, 3, 4, 26, 27).

3. There was an excess of MIs in dabigatran-treated patients (1, 28, 29).
4. Despite higher rate of ischaemic stroke, low dose edoxaban significantly reduced vascular and total mortality (4).

### Intracranial bleeding:

A striking and consistent feature of the three NOACs was a significantly reduced risk of ICH compared to warfarin (median  $RR\ddagger=0.40$ ; range: 0.26 to 0.67). Data from RE-LY and ROCKET AF demonstrate that the majority of these intracranial bleeds were intracerebral haemorrhages (46% and 72%, respectively), followed by subdural haemorrhages (45% and 24%, respectively) (30, 31). The reason for this reduction in ICH is uncertain. Unlike warfarin, the NOACs are stoichiometric inhibitors and therefore, have the potential to be overwhelmed by intense local tissue factor-mediated generation of factor Xa and thrombin at sites of spontaneous intra-cranial micro-bleeding, thereby preventing the conversion of a cerebral micro-bleed into an overt ICH. In contrast, warfarin modulates factor Xa and thrombin generation, and therefore, reduces the concentrations of tissue factor-mediated, activated coagulation factors at sites of spontaneous micro-bleeding. This hypothesis is supported by the results of laboratory experiments which showed that plasma containing dabigatran at therapeutic concentrations is less effective than warfarinised plasma (international normalized ratio [INR] 2.0 to 3.0) at attenuating tissue-factor mediated thrombin generation (32).

### Gastrointestinal (GI) bleeding:

In contrast to their effects on intracranial bleeding, dabigatran 150 mg bid, rivaroxaban and higher dose edoxaban were associated with higher rates of major GI bleeding compared to warfarin (1, 2, 4). On the other hand, apixaban showed a trend to lower rate of GI bleeding while low dose edoxaban was associated with a significantly lower rate of GI bleeding compared to warfarin, although these reductions in the risk of GI bleeding were the least favourable reductions among the bleeding outcomes (3, 4). It is plausible to posit that the increase in GI bleeding with dabigatran, rivaroxaban and high dose edoxaban is contributed to by high concentrations of active drugs in the GI tract. Active metabolites of all four NOACs are present in faeces (33-36). Based on their respective doses and recovery of active drug in the faeces, we estimated that dabigatran has the highest concentration of active drug in faeces. Interestingly, among the NOACs (dabigatran, apixaban, and edoxaban) for which data are available, dabigatran showed a similar proportion of upper and lower GI bleeding whereas for the other two, upper GI bleeding predominated, occurring in two thirds (4, 37, 38). It is possible that the difference in distribution of GI bleeding with dabigatran is caused by the high concentrations of active drug in distal GI tract resulting from the bioactivation by gut esterases of the poorly absorbed dabigatran etexilate.

**Table 3: Absolute event rates and risk reduction of low-dose edoxaban in comparison to warfarin.**

Outcome % per year	Edoxaban 30 mg Event rate	Warfarin Event rate	ARR
Stroke	1.91%	1.69%	-0.22%
Ischaemic stroke	1.77%	1.25%	-0.52%
Major bleeding	1.61%	3.43%	1.82%
GI bleeding	0.82%	1.23%	0.41%
Intracranial bleeding	0.26%	0.85%	0.59%
Haemorrhagic stroke	0.16%	0.47%	0.31%
Total mortality	3.80%	4.35%	0.55%
Vascular mortality	2.71%	3.17%	0.46%
Fatal bleeding	0.13%	0.38%	0.25%
Fatal intracranial bleeding	0.08%	0.27%	0.19%
Fatal stroke	0.38%	0.45%	0.07%

Data derived from published absolute incidence per year (4). ARR=Absolute risk reduction for the comparison of edoxaban 30 mg vs warfarin. A negative sign represents an absolute risk increase. Vascular death is a composite outcome of death due to cardiovascular cause and bleeding.

### Myocardial infarction (MI):

Compared to warfarin, dabigatran was associated with an increased risk of MI in the phase III studies in both AF and VTE treatment (28, 29). A similar increase in MI was observed in several phase III studies with ximelagatran, another stoichiometric thrombin inhibitor. In contrast, no such effect was observed with the factor Xa inhibitors. The mechanism of the increase in MI with dabigatran (compared to warfarin) is unknown. The magnitude of the effect was small, but was statistically significant when the results are pooled with the data from the venous thromboembolism treatment trials. The increase in MI could reflect the play of chance or the effect could be real and, in a similar fashion to the hypothesis proposed for the reduced risk of ICH, could reflect differences in the ability of dabigatran and warfarin to attenuate the effect of high local concentrations of thrombin at the site of a ruptured atherosclerotic plaque.

### Mortality benefit with low dose edoxaban:

In the earlier placebo controlled trials, warfarin significantly reduced mortality because it prevented fatal thromboembolism; an effect which outweighed the harm it produced by causing fatal bleeding (39). Although bleeding was considered an important side effect of warfarin, the main objective of using anticoagulant in AF was to reduce ischaemic stroke. However when one anticoagulant is compared with another, as in the four trials with NOACs, the harm from excessive bleeding assumes greater importance in the assessment of net clinical benefit. This shift in dynamics between trials comparing anticoagulants with placebo and those comparing one effective anticoagulant regimen with another is vividly demonstrated in the comparison between low dose edoxaban and warfarin in ENGAGE-AF (► Table 3).

In the ENGAGE AF study, the edoxaban dose spans a four-fold range from 15 mg (in patient who met criteria for 50% reduction in dose) to 60 mg. Compared to warfarin, low dose edoxaban was associated with a significant increase in ischaemic stroke (Absolute risk increase [ARI]†=0.52% per year), but was also associated with a significant reduction in total mortality (absolute risk reduction [ARR]†=0.55% per year) and in vascular mortality (ARR†=0.46% per year). It is likely that the significant reduction in mortality with low-dose edoxaban is attributable to a reduction in bleeding. Thus, there was a significant and large reduction in major bleeding (ARR†=1.82% per year), and a significant reduction in fatal bleeding (ARR† = 0.25 % per year), most of which resulted from fatal intracranial bleeding (ARR†= 0.19% per year).

The mortality difference between low-dose edoxaban and warfarin cannot be explained, entirely on the rates of fatal intracranial bleeding, since the ARR in fatal stroke (ischaemic and haemorrhagic combined) was 0.07% and the ARR in total mortality was 0.55%. Other causes of fatal bleeding only account for about one tenth (0.06%) of ARR, and the majority of the remaining causes of ARR in mortality were listed as “vascular”. It is plausible that major bleeding could contribute to non-hemorrhagic vascular deaths by a variety of mechanisms, including discontinuation of anticoagulant therapy, sustained hypotension, and reactive hypercoagulability.

### Discussion

Our re-evaluation of the trials has modified our initial interpretation of the results in several ways. First, it shows that, by removing intracerebral haemorrhage from the efficacy outcome, only high dose dabigatran is more effective than warfarin in reducing cerebral ischaemic events. Second, it indicates that the lack of su-

periority of rivaroxaban and edoxaban 60 mg in the ITT analysis (while apixaban and higher dose dabigatran were superior to warfarin) is likely due to the higher rate of premature discontinuation of study drug in ROCKET AF and ENGAGE AF, and highlights the problems with indirect across-study comparisons. Third, consistent with other reports, it showed that dabigatran, rivaroxaban and high dose edoxaban are associated with an increase in GI bleeding. Fourth, it highlights the important contribution of reduction in bleeding to the mortality benefit in warfarin-controlled trials, especially when a lower dose NOAC is used.

Each NOAC has unique features, which might influence their selection for a particular patient. Thus, the use of either apixaban or low-dose edoxaban is appealing in patients at high risk of bleeding as they show the best bleeding profile and are not associated with a higher rate of GI bleeding compared to warfarin. Low-dose edoxaban showed higher rates of ischaemic stroke than warfarin, whereas apixaban showed a trend to lower rates of ischaemic stroke. Rivaroxaban and higher dose edoxaban have the advantage of once daily dosing but appear to be associated with a higher rate of GI bleeding than warfarin. Dabigatran 150 mg bid was the only regimen that showed significant superiority over warfarin in preventing non-haemorrhagic stroke, thereby supporting the 2012 European Society of Cardiology guidelines, which suggested the use of dabigatran 150 mg bid in patients who suffer a non-haemorrhagic stroke while taking usual doses of apixaban or rivaroxaban (6). This high-dose dabigatran regimen, however, has the disadvantage of being associated with an increased risk of MI and GI bleeding and therefore should be used with caution and perhaps avoided in patients at high risk for GI bleeding and/or acute coronary syndrome.

In the absence of head-to-head comparisons, the choice among NOACs for AF is likely to be influenced by considerations of efficacy for ischaemic stroke prevention, major bleeding risk (especially ICH and GI bleeding), MI risk, mortality benefit and the convenience of once-daily dosing.

## Conclusions

All four NOACs offer consistent advantages over warfarin in AF because each is more convenient to use, each reduces the risk of ICH, each is at least as effective for the prevention of stroke or systemic embolism and each is associated with reduced mortality. Definitive conclusions about the relative efficacy and safety among the NOACs must be tempered by the lack of head to head comparisons.

## Conflicts of interest

JWE has received consulting fees and/or honoraria from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis. He has received grants and/or in-kind support from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis. JSP has received

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