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.[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 anticoagulants are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation.[5–8] Dabigatran, riva-roxaban, 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 Infarc-tion 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 sub-groups 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 pre-vention 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]

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			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%
CHADS2*	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*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	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‡												
<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§	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)¶	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. 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. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction<40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §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. ¶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:[5–8,15–23] 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[5] and ENGAGE AF–TIMI 48,[8] 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[6] (rivaroxaban 20 mg once daily) and ARISTOTLE[7] (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.[24] We assessed the appropriateness of pooling of data across studies with use of the Cochran Q statistic and I^2 test for heterogeneity.[25]

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), $CHADS_2$ 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.[6,16,22] 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 $CHADS_2$ scores of 3–6 (table). Median follow-up ranged from 1·8 years to 2·8 years and the median time in

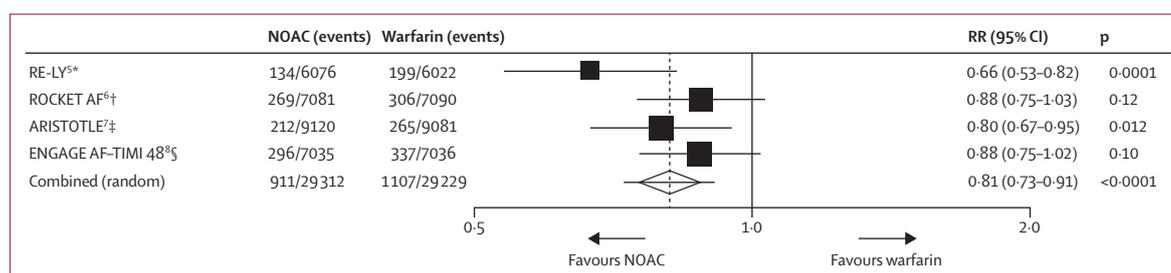|	NOAC (events)	Warfarin (events)		RR (95% CI)	p
RE-LY[5]*	134/6076	199/6022		0·66 (0·53–0·82)	0·0001
ROCKET AF[6]†	269/7081	306/7090		0·88 (0·75–1·03)	0·12
ARISTOTLE[7]‡	212/9120	265/9081		0·80 (0·67–0·95)	0·012
ENGAGE AF–TIMI 48[8]§	296/7035	337/7036		0·88 (0·75–1·02)	0·10
Combined (random)	911/29312	1107/29229		0·81 (0·73–0·91)	<0·0001

Figure 1: **Stroke or systemic embolic events**
Data are n/N, unless otherwise indicated. Heterogeneity: I^2=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
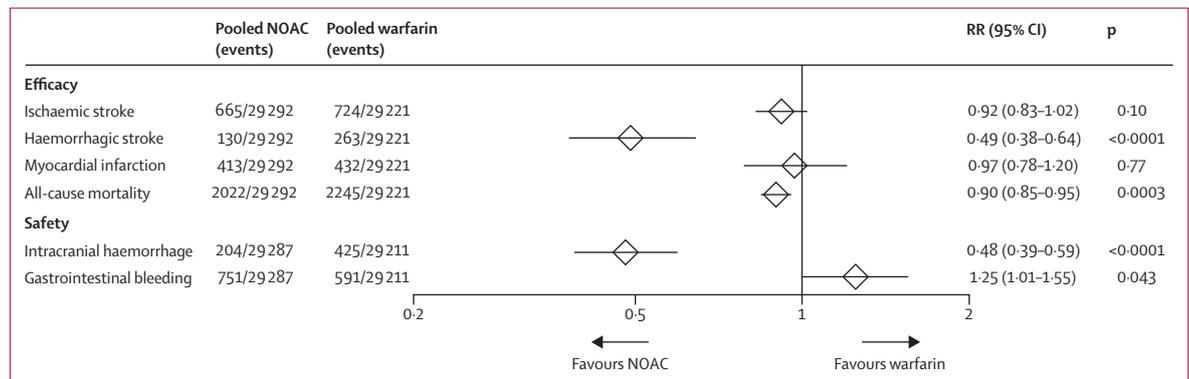

	Pooled NOAC (events)	Pooled warfarin (events)		RR (95% CI)	p
Efficacy					
Ischaemic stroke	665/29292	724/29221		0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29292	263/29221		0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29292	432/29221		0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29292	2245/29221		0·90 (0·85–0·95)	0·0003
Safety					
Intracranial haemorrhage	204/29287	425/29211		0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29287	591/29211		1·25 (1·01–1·55)	0·043

Favours NOAC ← → Favours warfarin

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.

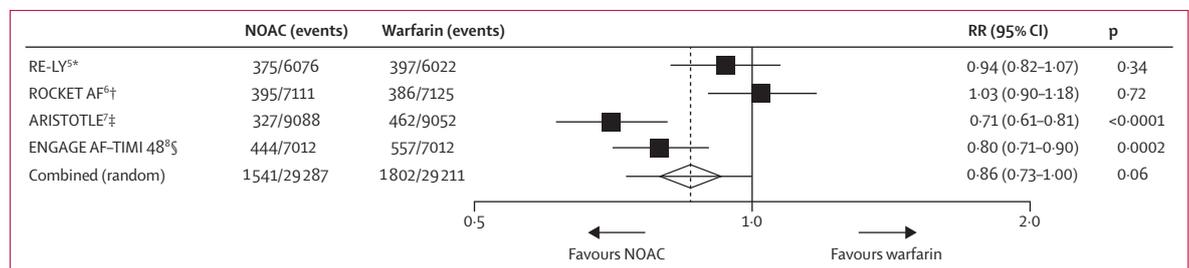|	NOAC (events)	Warfarin (events)		RR (95% CI)	p
RE-LY[5]*	375/6076	397/6022		0·94 (0·82–1·07)	0·34
ROCKET AF[6]†	395/7111	386/7125		1·03 (0·90–1·18)	0·72
ARISTOTLE[7]‡	327/9088	462/9052		0·71 (0·61–0·81)	<0·0001
ENGAGE AF–TIMI 48[8]§	444/7012	557/7012		0·80 (0·71–0·90)	0·0002
Combined (random)	1541/29287	1802/29211		0·86 (0·73–1·00)	0·06

Favours NOAC ← → Favours warfarin

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.
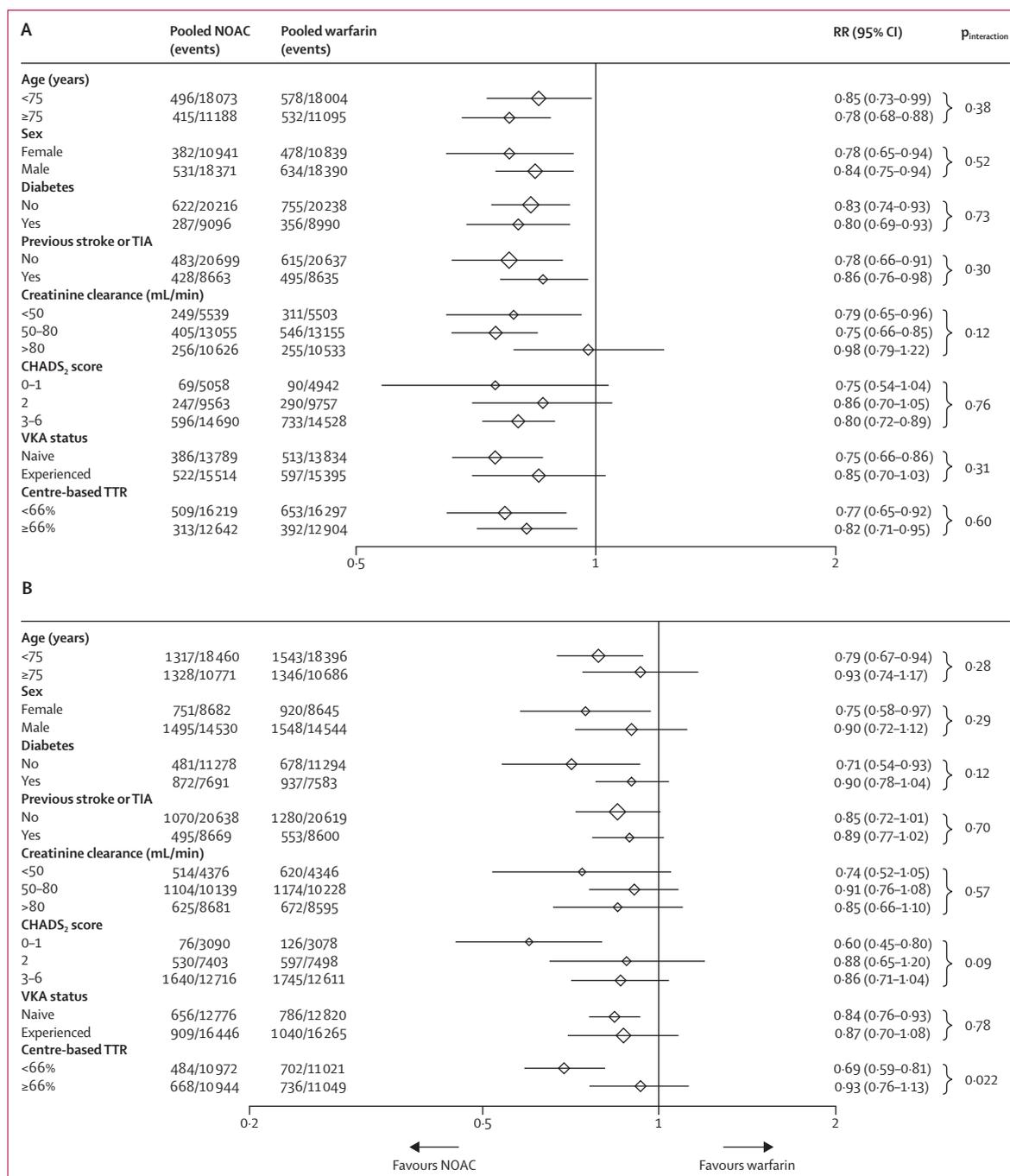
A

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Age (years)				
<75	496/18073	578/18004	0·85 (0·73–0·99)	0·38
≥75	415/11188	532/11095	0·78 (0·68–0·88)	
Sex				
Female	382/10941	478/10839	0·78 (0·65–0·94)	0·52
Male	531/18371	634/18390	0·84 (0·75–0·94)	
Diabetes				
No	622/20216	755/20238	0·83 (0·74–0·93)	0·73
Yes	287/9096	356/8990	0·80 (0·69–0·93)	
Previous stroke or TIA				
No	483/20699	615/20637	0·78 (0·66–0·91)	0·30
Yes	428/8663	495/8635	0·86 (0·76–0·98)	
Creatinine clearance (mL/min)				
<50	249/5539	311/5503	0·79 (0·65–0·96)	
50–80	405/13055	546/13155	0·75 (0·66–0·85)	0·12
>80	256/10626	255/10533	0·98 (0·79–1·22)	
CHADS₂ score				
0–1	69/5058	90/4942	0·75 (0·54–1·04)	
2	247/9563	290/9757	0·86 (0·70–1·05)	0·76
3–6	596/14690	733/14528	0·80 (0·72–0·89)	
VKA status				
Naive	386/13789	513/13834	0·75 (0·66–0·86)	0·31
Experienced	522/15514	597/15395	0·85 (0·70–1·03)	
Centre-based TTR				
<66%	509/16219	653/16297	0·77 (0·65–0·92)	0·60
≥66%	313/12642	392/12904	0·82 (0·71–0·95)	

(scale axis: 0·5 1 2)

B

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Age (years)				
<75	1317/18460	1543/18396	0·79 (0·67–0·94)	0·28
≥75	1328/10771	1346/10686	0·93 (0·74–1·17)	
Sex				
Female	751/8682	920/8645	0·75 (0·58–0·97)	0·29
Male	1495/14530	1548/14544	0·90 (0·72–1·12)	
Diabetes				
No	481/11278	678/11294	0·71 (0·54–0·93)	0·12
Yes	872/7691	937/7583	0·90 (0·78–1·04)	
Previous stroke or TIA				
No	1070/20638	1280/20619	0·85 (0·72–1·01)	0·70
Yes	495/8669	553/8600	0·89 (0·77–1·02)	
Creatinine clearance (mL/min)				
<50	514/4376	620/4346	0·74 (0·52–1·05)	
50–80	1104/10139	1174/10228	0·91 (0·76–1·08)	0·57
>80	625/8681	672/8595	0·85 (0·66–1·10)	
CHADS₂ score				
0–1	76/3090	126/3078	0·60 (0·45–0·80)	
2	530/7403	597/7498	0·88 (0·65–1·20)	0·09
3–6	1640/12716	1745/12611	0·86 (0·71–1·04)	
VKA status				
Naive	656/12776	786/12820	0·84 (0·76–0·93)	0·78
Experienced	909/16446	1040/16265	0·87 (0·70–1·08)	
Centre-based TTR				
<66%	484/10972	702/11021	0·69 (0·59–0·81)	0·022
≥66%	668/10944	736/11049	0·93 (0·76–1·13)	

(scale axis: 0·2 0·5 1 2)
← Favours NOAC   Favours warfarin →

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

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.[26] 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.[27] 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),[28] patients with a previous history of stroke,[29,30] and those with renal dysfunction,[31,32] 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$_2$ score of 3–6 were mainly attributable to differential enrolment of patients with previous stroke or transient ischaemic attack.[33] 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.[34] 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.[35,36] In the ACTIVE W trial,[37] 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,[6,16,22] 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.[38] 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 anticogulants 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.

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