Antithrombotic Therapy

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

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Objectives	This study sought to perform an indirect comparison analysis of dabigatran etexilate (2 doses), rivaroxaban, and apixaban for their relative efficacy and safety against each other.
Background	Data for warfarin compared against the new oral anticoagulants (OACs) in large phase III clinical trials of stroke prevention in atrial fibrillation (AF) are now available for the oral direct thrombin inhibitor, dabigatran etexilate, in 2 doses (150 mg twice daily [BID], 110 mg BID), and the oral Factor Xa inhibitors, rivaroxaban and apixaban. A "head-to-head" direct comparison of drugs is the standard method for comparing different treatments, but in the absence of such head-to-head direct comparisons, another alternative to assess the relative effect of different treatment interventions would be to perform indirect comparisons, using a common comparator. Nonetheless, any inter-trial comparison is always fraught with major difficulties, and an indirect comparison analysis has many limitations, especially with the inter-trial population differences and thus, should not be overinterpreted.
Methods	Indirect comparison analysis was performed using data from the published trials.
Results	There was a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg BID) compared with rivaroxaban, as well as hemorrhagic stroke and nondisabling stroke. There were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban; or rivaroxaban versus dabigatran 110 mg BID in preventing stroke and systemic embolism. For ischemic stroke, there were no significant differences between the new OACs. Major bleeding was significantly lower with apixaban compared with dabigatran 150 mg BID (by 26%) and rivaroxaban (by 34%), but not significantly different from dabigatran 110 mg BID. There were no significant differences between apixaban and dabigatran 110 mg BID in safety endpoints. Apixaban also had lower major or clinically relevant bleeding (by 34%) compared with rivaroxaban. When compared with rivaroxaban, dabigatran 110 mg BID was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%). There were no significant differences in myocardial infarction events between the dabigatran (both doses) and apixaban.
Conclusions	Notwithstanding the limitations of an indirect comparison study, we found no profound significant differences in efficacy between apixaban and dabigatran etexilate (both doses) or rivaroxaban. Dabigatran 150 mg BID was superior to rivaroxaban for some efficacy endpoints, whereas major bleeding was significantly lower with dabigatran 110 mg BID or apixaban. Only a head-to-head direct comparison of the different new OACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF. (J Am Coll Cardiol 2012;60:738–46) © 2012 by the American College of Cardiology Foundation

Stroke is a devastating complication associated with atrial fibrillation (AF), which is the most common sustained cardiac rhythm disorder. Effective prevention of stroke requires oral anticoagulation (OAC) therapy, and until recently, this was dependent upon the vitamin K antagonist class of drugs, for example, warfarin (1). The limitations of warfarin, including the

need for regular monitoring, have led to the quest for new OACs that would be safe and effective alternatives to warfarin (2).

Data for warfarin compared against the new OACs in large phase III clinical trials are now available for the oral direct thrombin inhibitor, dabigatran etexilate, in 2 doses (150 mg twice daily [BID], 110 mg BID) and the oral Factor Xa inhibitors, rivaroxaban and apixaban (3–6). Apixaban also has 1 clinical trial against aspirin, among patients deemed unsuitable for or who have refused warfarin (7).

The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial compared 2 doses of dabigatran etexilate against warfarin in AF patients with 1 or more stroke risk factors, and reported that dabigatran 110 mg BID was noninferior to warfarin for the primary endpoint of stroke and systemic embolism, with 20% less major bleeding events (3). Following additional adjudication, some endpoints from the original 2009 publication were updated in a 2010 letter to the *New England Journal of Medicine* (4). The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial studied a high-risk population of patients with AF, and found that rivaroxaban 20 mg once daily (OD) (with a dose adjustment of 15 mg OD for those with moderate renal impairment) was noninferior to warfarin for stroke and systemic embolism, with a similar rate of major bleeding (5). The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial reported that apixaban 5 mg BID (with a dose adjustment to 2.5 mg BID for patients with 2 of 3 criteria: age >80 years, body mass index <60 kg/m^2, and serum creatinine >133 μmol/l) was superior to warfarin (by 21%) for reducing stroke and systemic embolism, with 31% fewer major bleeding events (6). All the drugs demonstrated significantly less hemorrhagic stroke and intracranial hemorrhage, compared with warfarin. The outcome data from these trials are summarized in Online Table 1.

Both dabigatran and rivaroxaban already have regulatory approval and a license for stroke prevention in some countries, and apixaban is anticipated to gain regulatory approval in 2012. Thus, clinicians may have a number of new OACs available, but would need information about how these agents directly compare against each other in terms of efficacy and safety. Head-to-head clinical trials of these new OACs would require huge numbers of patients to achieve statistical power for noninferiority, and may not be viable options in the near future. In the absence of such direct comparisons in large prospective randomized controlled trials, another accepted alternative to assess the relative effect of different treatment interventions would be to perform indirect comparisons on the basis of the published trials so far, using a common comparator (8). In the case of the new OACs, warfarin was the comparator used in common for all the main noninferiority trials.

The aim of the present study was to perform an indirect comparison analysis of apixaban against dabigatran etexilate

(2 doses) and rivaroxaban, as well as rivaroxaban against dabigatran etexilate (2 doses), for their relative efficacy and safety against each other. Nonetheless, any intertrial comparison is always fraught with major difficulties, and an indirect comparison analysis has many limitations, especially with the intertrial population differences, and thus should not be over-interpreted. However, this method is a well-accepted analysis in the absence of head-to-head trials.

Methods

The main efficacy and safety endpoints from the RE-LY, ROCKET-AF, and ARISTOTLE clinical trials were reviewed for comparability and consistency of definitions (Online Table 1). RE-LY and ARISTOTLE were broadly similar in patient demography (e.g., age, gender mix, etc.) and baseline stroke risk (average CHADS$_2$ score of 2.1). By contrast, ROCKET-AF patients were slightly older (median age: 73 years), were at higher stroke risk (mean CHADS$_2$ score: 3.5), and 55% were a secondary prevention population. The average time in therapeutic range values in the warfarin-treated patients for RE-LY, ROCKET-AF, and ARISTOTLE were 64%, 55%, and 62%, respectively. RE-LY was conducted as an open trial, (prospective, randomized, open-blinded endpoint evaluation, i.e., PROBE design), whereas the other trials were double-blind trials.

All baseline characteristics, except for age and average CHADS$_2$ score, were described with proportions/risk for reported characteristics. The studies were then compared in terms of risk differences and corresponding 95% confidence intervals, which was considered a relevant measure for the quantification of the difference between trials. Comparison of average CHADS$_2$ score between the trials was a standard 2-sample comparison for normal data. Age differences were not compared statistically due to differences in reporting between the trials.

Our endpoints of interest for this mixed treatment comparisons focused on the primary efficacy and safety endpoints. For all trials, the primary efficacy endpoint was "all stroke and systemic embolism," whereas the primary safety endpoint for all trials, except ROCKET-AF, was major bleeding by International Society on Thrombosis and Haemostasis (ISTH) criteria (3–7). In ROCKET-AF, the primary safety endpoint was the composite of "major and clinically relevant non-major bleeding," results of which were not reported in RE-LY.

"Life-threatening bleeding" was not reported in the ARISTOTLE trial. Also, "major or clinical relevant non-major bleeding" was not reported in RE-LY, but included in ARISTOTLE. The combined endpoint "ischemic or uncertain type of stroke" was not reported for ROCKET-AF, but the

result from ischemic stroke was used because the reported frequencies of uncertain stroke types were very low.

Secondary endpoints of interest were also compared in this study, including individual components of the primary efficacy and safety endpoints. Also, there was reported a numerical increase in myocardial infarction (MI) events in the RE-LY trial (3,4), and some debate has arisen as to whether this is due to dabigatran or reflects a protective effect of warfarin (9). Finally, the endpoint of pulmonary embolism was not reported in ROCKET-AF.

For all endpoints found appropriate for analysis, the reported hazard rate ratio and confidence intervals were extracted from the study publications. In the RE-LY study, the results were reported as risk ratio and confidence intervals. Also, an update was published for the RE-LY study (4), and the data from this update was used for our analysis. Results from intention-to-treat analyses were used throughout.

Statistical methods. We used the so-called Bucher method (10) for indirect comparisons using a common comparator, which is a statistical method for estimating hazard rate ratio and corresponding uncertainty. The method is recommended (8) as a preferred method for indirect comparison, superior to informal methods, as comparison of confidence intervals.

For these comparisons, we let HR_{AB} and HR_{CB} be the reported hazard rate ratio of treatment A versus B and of treatment C versus B. Observing that B is the common reference comparator (warfarin), HR_{AC} may be estimated as $HR_{AC} = HR_{AB}/HR_{CB}$. A confidence interval was estimated using the reported confidence intervals (CI_l, CI_u). The standard error (SE) of log(HR) was estimated by: $\frac{1}{2}(\log(CI_u) - \log(CI_l))/1.96$, where 1.96 is the 97.5% fractile of the standard normal distribution. The variance of

$\log(HR_{AC})$, $(se_{AC})^2$, is under independence given as $(se_{AB})^2 + (se_{CB})^2$, and thus a 95% confidence interval of HR_{AC} is: $\exp(\log(HR_{AC}) \pm 1.96 \times se_{AC})$. Reported p values are for the hypothesis $H0:\log(HR_{AC}) = 0$ versus $HA:\log(HR_{AC}) <> 0$, assuming $\log(HR_{AC})$ as normal with variance $(se_{AC})^2$.

The application of the method relies on a similarity assumption (11) that the hazard rate ratio HR_{AB} was likely also obtained if it was determined on the basis of the population from which HR_{CB} was estimated. Importantly, the most direct way to consider this similarity assumption valid is to require that the clinical studies be absolutely comparable in terms of population characteristics and conduct of experiment (and as highlighted earlier, there are some differences between the trials—see Tables 1 and 2).

First, the expected effect of "any new anticoagulant" versus warfarin was estimated as a weighted average using the inverse of the variance of the log(HR) as weights. Only results from the dabigatran 150 mg BID arm of the RE-LY study was used in combination with data from ARISTOTLE and ROCKET-AF to ensure independence between the components of the average. No statistical adjustments were made for multiple comparisons within this study. The second focus in this analysis was the indirect comparisons of apixaban versus dabigatran (both doses) and rivaroxaban, as well as rivaroxaban versus dabigatran (both doses). Direct comparisons of dabigatran 110 mg BID versus dabigatran 150 mg BID were already available from the RE-LY trial (3).

Baseline characteristics were tested for homogeneity between trials by reporting risk differences with 95% confidence intervals for categorical data and normal distribution 2-sample comparison with unequal variances for continuous

Table 1	Summary of the Main Clinical Trials Involving Novel Anticoagulants for Stroke Prevention in Nonvalvular AF		
	Dabigatran (RE-LY)	**Rivaroxaban (ROCKET-AF)**	**Apixaban (ARISTOTLE)**
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–9	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% fecal
Dose	150 mg BID	20 mg OD	5 mg BID
Dose in renal impairment	110 mg BID	15 mg OD (if creatinine clearance 30–49 ml/min)	2.5 mg BID
Special considerations	Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors.	Higher levels expected in patients with renal or hepatic failure. Activity lower in fasted patients, so should be taken after food.	
Study characteristics			
Study design	Randomized open label	Multicenter, randomized, double-blind, double-dummy	Randomized control, double-blind, parallel arm
Number of patients	18,113	14,264	18,201
Follow-up period, months	24	40	40
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg BID, 110 mg BID)	Dose-adjusted warfarin vs. rivaroxaban 20 mg OD	Dose-adjusted warfarin vs. apixaban 5 mg BID

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID = twice daily; OD = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Table 2	Risk Differences and Confidence Intervals, in Relation to Differences in the Study Populations at Baseline					
Baseline Characteristics	RE-LY (N = 18,113)	ROCKET-AF (N = 14,264)	ARISTOTLE (N = 18,201)	RE-LY vs. ROCKET-AF	RE-LY vs. ARISTOTLE Percent Point (% Study 1; % Study 2)	ROCKET-AF vs. ARISTOTLE Percent Point (% Study 1; % Study 2)
Age, yrs*	71.5 ± 8.7	73 [65–78]	70 [63–76]	—	—	—
Female, %	36.4	39.7	35.2	−3.3 (−4.3; −2.2)	1.1 (0.2; 2.2)	4.5 (3.3; 5.5)
CHADS$_2$, mean	2.2	3.5	2.1	−1.26 (−1.28; −1.23)	0.1 (0.08; 0.12)	1.36 (1.34; 1.38)
CHADS$_2$ 3–6, %	32.5	87.0	30.2	−54.5 (−55.3; −53.6)	2.2 (1.3; 3.2)	56.7 (55.9; 57.6)
Paroxysmal AF, %	32.8	17.6	15.3	15.2 (14.3; 16.1)	17.5 (16.6; 18.4)	2.3 (1.5; 3.1)
Prior stroke, TIA, or systemic embolism, %	20.0	54.8	19.4	−34.8 (−35.8; −33.8)	0.6 (−0.03; 1.4)	35.3 (43.3; 36.3)
Heart failure, %	32.0	62.5	35.4	−30.5 (−31.5; −29.4)	−3.5 (−4.4; −2.5)	27.0 (26.0; 28.1)
Prior myocardial infarction, %	16.6	17.3	14.2	−0.7 (−1.5; 0.1)	2.4 (1.6; 3.1)	3.1 (2.3; 3.9)
Diabetes, %	23.3	40.0	25.0	−16.6 (−17.6; −15.6)	−1.7 (−2.6; −0.8)	14.9 (13.9;16.0)
Hypertension, %	78.9	90.5	87.5	−11.7 (−12.4; −10.9)	−8.6 (−9.4; −7.8)	3.1 (2.9; 3.7)
Medication						
Aspirin, %	39.8	36.5	30.9	3.3 (2.2; 4.3)	8.8 (7.8; 9.8)	5.5 (4.5; 6.6)
Vitamin K antagonist, %	49.6	62.4	57.2	−12.8 (−13.9; −11.7)	−7.5 (−8.5; −6.5)	5.3 (4.2; 6.3)

*Values for RE-LY: mean ± SD; for ROCKET-AF and ARISTOTLE: median [interquartile range].

AF = atrial fibrillation; TIA = transient ischemic attack; other abbreviations as in Table 1.

data. Stata 11.2 (StataCorp LP, College Station, Texas), R v2.12.1 (R Foundation for Statistical Computing, Vienna, Austria), and Microsoft Excel 2003 (Redmond, Washington) for Windows were used for the statistical analyses and graphical presentation.

Results

The clinical trials being compared for this analysis are summarized in Table 1, with their primary safety and efficacy endpoints summarized in Online Table 2.

Summary patient characteristics and risk differences (with confidence intervals) are presented for the entire study population in Table 2. As expected, there were important differences between the studies, particularly for the CHADS$_2$ score (>50 percentage point difference between ROCKET-AF and the other trials) and the proportion of secondary prevention (approximately 35 percentage point difference between ROCKET-AF and the other trials). Mean/median age was broadly similar, as were the proportions of female patients. There were more patients with paroxysmal AF in RE-LY (36.4%) compared with ROCKET-AF and ARISTOTLE (approximately 15 to 17 percentage point difference). The prevalence of prior heart failure, diabetes, and hypertension was highest in ROCKET-AF (62.5%, 40%, and 90.5%, respectively) compared with the other 2 trials. Prior warfarin use was 62.4% in ROCKET-AF, compared with 50% in RE-LY (by design) and 57% in ARISTOTLE. The proportions with prior MI and prior aspirin use were broadly similar in the 3 trials.

When data with dabigatran 150 mg BID were used for the weighted average effects analysis, the new OACs as a whole were associated with lower stroke or systemic embolism (21%, p < 0.001), lower stroke (23% p < 0.001), and lower hemorrhagic stroke (53%, p < 0.001) than warfarin.

All-cause mortality was lower for any new OAC (by 12%, p < 0.001). Major and intracranial bleeding were lower for any new OAC by 13% (p < 0.001) and 51% (p < 0.001) respectively. Weighted average hazard ratio and confidence intervals are given in Table 3.

Hazard rate ratio point estimates and 95% confidence intervals for the main trial endpoints for all indirect comparisons using warfarin as a common comparator are shown in Table 4 and Figures 1 and 2.

Relative efficacy of dabigatran, apixaban, and rivaroxaban. There was a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg BID) compared with rivaroxaban, as well as less hemorrhagic stroke (by 56%, p = 0.039) and nondisabling stroke (by 40%, p = 0.038). There were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban, or rivaroxaban versus dabigatran 110 mg BID, in preventing stroke and systemic embolism. For the ischemic stroke endpoint, there were no significant differences between the new OACs.

Relative safety of dabigatran, apixaban, and rivaroxaban. Major bleeding was significantly lower with apixaban compared with dabigatran 150 mg BID (by 26%, p = 0.003) and rivaroxaban (by 34%, p < 0.001), but was not significantly different from dabigatran 110 mg BID (Table 4, Fig. 1). Gastrointestinal and extracranial bleeding was also significantly less with apixaban compared with dabigatran 150 mg BID, by 41% (p = 0.003) and 26% (p = 0.007), respectively. There were no significant differences between apixaban and dabigatran 110 mg BID in safety endpoints.

Apixaban also had lower major or clinically relevant bleeding (by 34%, p < 0.001) compared with rivaroxaban. There was an increase (278%, p = 0.027) in systemic embolism for apixaban compared with rivaroxaban with lower bound of 95% confidence interval at 16% increase.

Table 3	Weighted Average Effects of New OAC Versus Warfarin							
	Any NOAC (Dabigatran 110 mg BID, Apixaban, Rivaroxaban) vs. Warfarin				Any NOAC (Dabigatran 150 mg BID, Apixaban, Rivaroxaban) vs. Warfarin			
	Weighted Average Effect HR	95% CI Lower	95% CI Upper	p Value	Weighted Average Effect HR	95% CI Lower	95% CI Upper	p Value
Stroke or systemic embolism	0.856	0.772	0.948	0.003	0.793	0.714	0.881	0.000
Stroke	0.847	0.756	0.949	0.004	0.769	0.684	0.864	0.000
Ischemic or uncertain type of stroke	0.983	0.866	1.116	0.788	0.878	0.771	1.000	0.051
Hemorrhagic stroke	0.485	0.373	0.632	0.000	0.474	0.363	0.619	0.000
Death from any cause	0.890	0.825	0.961	0.003	0.880	0.815	0.950	0.001
Myocardial infarction	0.953	0.810	1.120	0.557	0.949	0.807	1.116	0.525
ISTH major bleeding	0.831	0.765	0.902	0.000	0.875	0.806	0.950	0.001
Intracranial bleeding	0.465	0.378	0.572	0.000	0.490	0.400	0.601	0.000

Only endpoints available in all studies are reported.

BID = twice daily; CI = confidence interval; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; OAC = oral anticoagulation therapy.

Gastrointestinal bleeds were only reported numerically in ROCKET-AF and therefore not used in this analysis.

When compared with rivaroxaban, dabigatran 110 mg BID was associated with less major bleeding (by 23%, p = 0.011) and intracranial bleeding (by 54%, p = 0.006) (Table 4, Fig. 2).

Our indirect comparison analysis did not find any significant differences in MI events between dabigatran (both doses) and apixaban but more MI events were seen with dabigatran (>50%) compared to rivaroxaban (Table 4, Fig. 2).

Discussion

In this indirect comparison analysis, the new OACs as a whole resulted in a lower risk of stroke or systemic embolism, stroke, hemorrhagic stroke, and all-cause mortality compared with warfarin, Also, major and intracranial bleeding were lower for any new OAC.
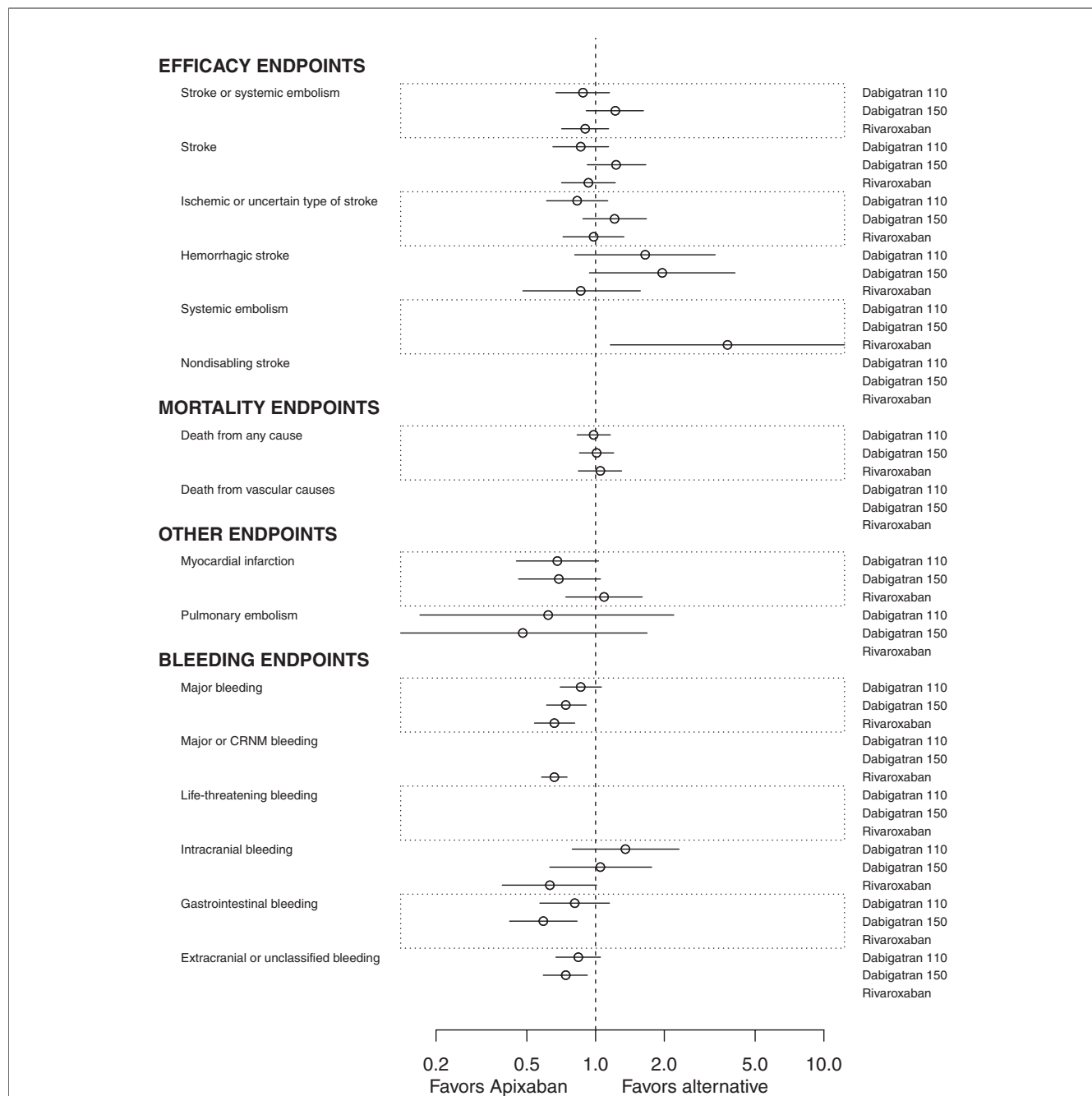
Notwithstanding the limitations of an indirect comparison study, this analysis shows that there were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban; or between rivaroxaban versus dabigatran

Table 4	Indirect Comparison Using Warfarin as Single Common Comparator, on the Basis of the RE-LY, ROCKET-AF, and ARISTOTLE Trials									
	Apixaban ←→ Dabigatran 110		Apixaban ←→ Dabigatran 150		Apixaban ←→ Rivaroxaban		Dabigatran 110 ←→ Rivaroxaban		Dabigatran 150 ←→ Rivaroxaban	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67–1.15)	1.22	(0.91–1.62)	0.90	(0.71–1.13)	1.02	(0.79–1.32)	**0.74**	**(0.56–0.97)**
Stroke	0.86	(0.65–1.14)	1.23	(0.92–1.66)	0.93	(0.71–1.22)	1.08	(0.81–1.44)	0.75	(0.56–1.02)
Ischemic or uncertain type of stroke	0.83	(0.61–1.13)	1.21	(0.88–1.67)	0.98	(0.72–1.33)	1.18	(0.86–1.62)	0.81	(0.58–1.13)
Hemorrhagic stroke	1.65	(0.81–3.34)	1.96	(0.94–4.08)	0.86	(0.48–1.57)	0.53	(0.25–1.12)	**0.44**	**(0.20–0.96)**
Systemic embolism	NA		NA		3.78	(1.16–12.31)	NA		NA	
Nondisabling stroke	NA		NA		NA		0.83	(0.53–1.32)	**0.60**	**(0.37–0.97)**
Mortality endpoints										
Death from any cause	0.98	(0.83–1.16)	1.01	(0.85–1.20)	1.05	(0.84–1.30)	1.07	(0.85–1.34)	1.04	(0.82–1.30)
Death from vascular causes	NA		NA		NA		1.01	(0.78–1.31)	0.96	(0.74–1.24)
Other endpoints										
Myocardial infarction	0.68	(0.45–1.03)	0.69	(0.46–1.05)	1.09	(0.74–1.60)	**1.59**	**(1.07–2.37)**	**1.57**	**(1.05–2.33)**
Pulmonary embolism	0.62	(0.17–2.20)	0.48	(0.14–1.68)	NA		NA		NA	
Bleeding endpoints										
Major bleeding	0.86	(0.7–1.06)	**0.74**	**(0.61–0.91)**	**0.66**	**(0.54–0.81)**	**0.77**	**(0.63–0.94)**	0.89	(0.73–1.09)
Major or clinically relevant nonmajor bleeding	NA		NA		**0.66**	**(0.58–0.75)**	NA		NA	
Life-threatening bleeding	NA		NA		NA		1.36	(0.82–2.27)	1.62	(0.97–2.70)
Intracranial bleeding	1.35	(0.79–2.32)	1.05	(0.63–1.76)	0.63	(0.39–1.01)	**0.46**	**(0.27–0.80)**	0.60	(0.35–1.01)
Gastrointestinal bleeding	0.81	(0.57–1.15)	**0.59**	**(0.42–0.83)**	NA		NA		NA	
Extracranial or unclassified bleeding	0.84	(0.67–1.05)	**0.74**	**(0.59–0.92)**	NA		NA		NA	

See Online Table 1 for availability and endpoint definition in original study. How to read: Drug A ←→ Drug B, HR <1.00 means hazard risk of Drug A is smaller than hazard risk of Drug B, indirectly compared via 1 common comparator, warfarin (A ←→ warfarin ←→ B). Comparisons with HR = 1.00 outside 95% confidence interval are in boldface. The **bold** values indicate significant values.

NA = not available; other abbreviations as in Table 2.

EFFICACY ENDPOINTS

Stroke or systemic embolism

Stroke

Ischemic or uncertain type of stroke

Hemorrhagic stroke

Systemic embolism

Nondisabling stroke

MORTALITY ENDPOINTS

Death from any cause

Death from vascular causes

OTHER ENDPOINTS

Myocardial infarction

Pulmonary embolism

BLEEDING ENDPOINTS

Major bleeding

Major or CRNM bleeding

Life-threatening bleeding

Intracranial bleeding

Gastrointestinal bleeding

Extracranial or unclassified bleeding

0.2   0.5   1.0   2.0   5.0   10.0
Favors Apixaban   Favors alternative

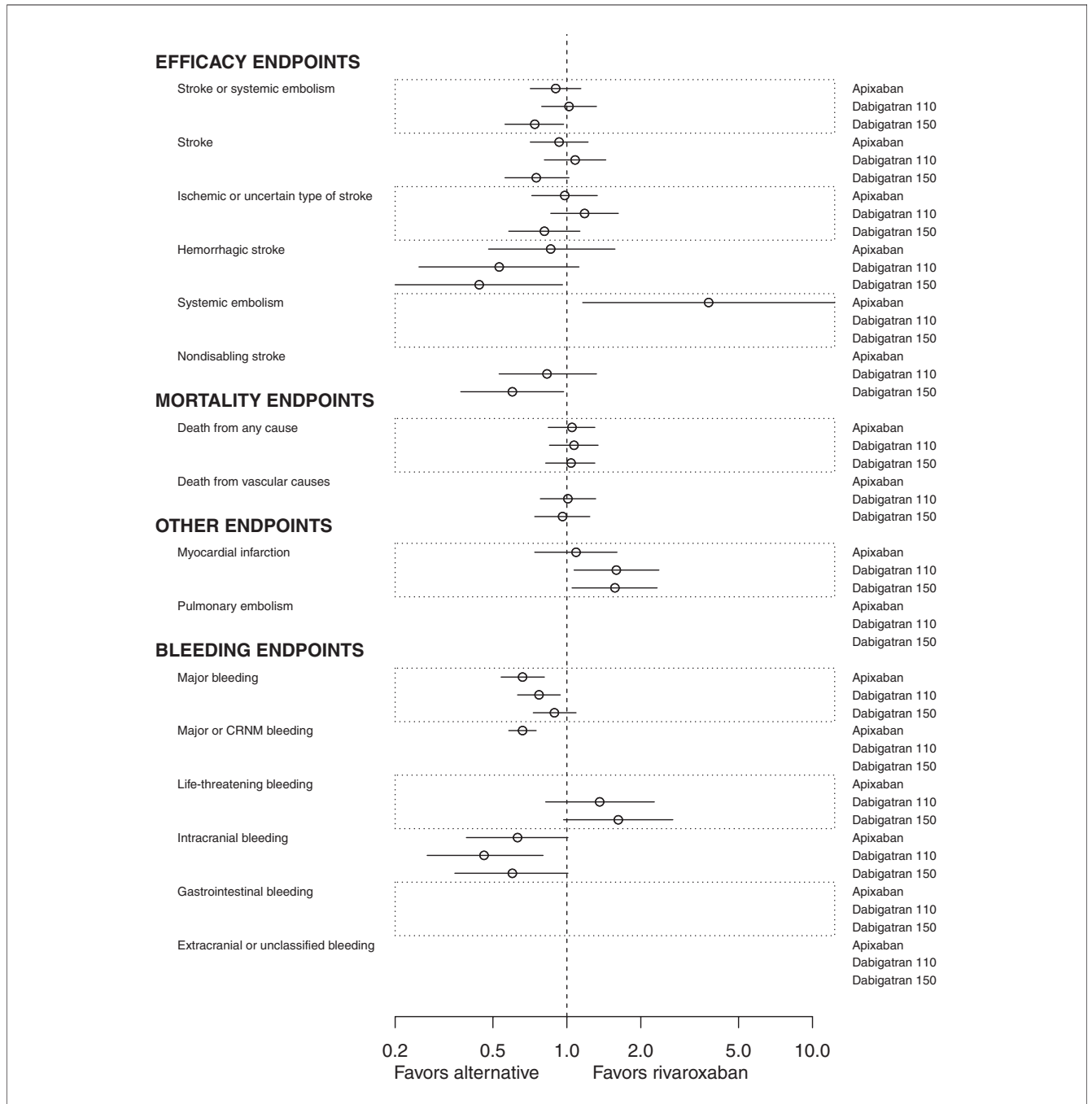| Figure 1 | Apixaban Versus Dabigatran 110 mg BID, Dabigatran 150 mg BID, and Rivaroxaban |

The plot shows the relative risk and 95% confidence interval of each outcome with apixaban versus comparators estimated from the indirect comparisons. BID = twice daily; CRNM = clinically relevant non-major bleeding.

110 mg BID in preventing stroke and systemic embolism, although dabigatran 150 mg BID was superior to rivaroxaban for preventing stroke and systemic embolism, hemorrhagic stroke, and nondisabling stroke. There were no differences between the new OACs in the ischemic stroke endpoint.

We found no significant differences between dabigatran 110 mg BID and apixaban in the main safety endpoints. When compared with dabigatran 150 mg BID, apixaban had significantly less major bleeding and gastrointestinal bleeding, but there were no significant differences between apixaban and dabigatran 110 mg BID in the safety endpoints. When compared with rivaroxaban, apixaban had lower major bleeding, whereas dabigatran 110 mg BID was associated with less major bleeding and lower intracranial bleeding.

The indirect comparison using a common comparator could be considered the gold standard approach of perform-

Figure 2   **Rivaroxaban Versus Apixaban, Dabigatran 110 mg BID, and Dabigatran 150 mg BID**

The plot shows the relative risk and 95% confidence interval of each outcome with rivaroxaban versus comparators estimated from the indirect comparisons. Abbreviations as in Figure 1.

ing indirect comparisons in the absence of head-to-head clinical trials with these new agents (8). Such a trial would require huge numbers of study subjects to demonstrate noninferiority, especially in a broad group of AF patients with ≥1 stroke risk factors and given that overall stroke rates may be declining (12,13).

In the RE-LY trial, which did directly compare dabigatran 110 mg BID against dabigatran 150 mg BID (and both against warfarin), there was a significant reduction in the primary endpoint of stroke and systemic embolism with dabigatran 150 mg BID over dabigatran 110 mg BID (relative risk: 0.73, 95% confidence interval: 0.58 to 0.91, p < 0.001) (3). Even for ischemic stroke, where this endpoint was significantly reduced compared with warfarin in the RE-LY trial per se, the present analysis does not support any statistically significant differences in this end-

point between apixaban versus dabigatran (both doses) or rivaroxaban, or even rivaroxaban versus dabigatran (both doses). Nonetheless, dabigatran 150 mg BID did appear to have significantly less hemorrhagic stroke and nondisabling stroke compared with rivaroxaban.

Bleeding is clearly an endpoint of concern in anticoagulated AF patients (14). The present analysis clearly shows significantly lower major bleeding rates with apixaban compared with dabigatran 150 mg BID and rivaroxaban, and a nonsignificant difference between apixaban and dabigatran 110 mg BID. In the ARISTOTLE trial, major bleeding was 31% lower with apixaban compared with warfarin, and our observations in the present analysis would be consistent with this. For the endpoint of major and clinically relevant nonmajor bleeding, apixaban also did better than rivaroxaban. Of note, major bleeding with dabigatran 110 mg BID was not significantly different from apixaban, but significantly less (as was intracranial bleeding) when compared with rivaroxaban.

Bleeding risk in AF is multifactorial (14), and indeed, the addition of apixaban to antiplatelet therapy in the setting of acute coronary syndromes resulted in a significant increase in major bleeding with no evidence of efficacy (15). In the setting of acute coronary syndromes, a low-dose (2.5 mg and 5.0 mg), twice-daily regime of rivaroxaban resulted in a significant reduction in the primary endpoint (a composite of death from cardiovascular causes, MI, or stroke) compared with placebo among patients taking dual antiplatelet therapy, at the cost of more major bleeding events and intracranial hemorrhage (16).

Another safety endpoint of concern in the AF trials was a numerical increase in MI events in the RE-LY trial (0.8%/year with dabigatran compared with warfarin, 0.6%/year), and this indirect comparison analysis did not show any statistically significant differences in MI events between dabigatran (both doses) and apixaban. However, our indirect comparison analysis found both doses of dabigatran were associated with >50% more MI events compared to rivaroxaban but this needs to be put in context of the low absolute rates and the positive net clinical benefit overall of using these new drugs. A recent detailed analysis from RE-LY found that whereas MI events were numerically increased, other myocardial ischemic events were not (17). Also, the relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI (17). Of note, vascular mortality was significantly reduced with dabigatran 150 mg BID compared with warfarin in the RE-LY trial (3). One meta-analysis was suggestive of a significant increase in MI events with dabigatran use in various different clinical trials for AF, acute coronary syndromes, and venous thromboembolism, although total mortality was significantly less with dabigatran versus comparator (18).

Study limitations. This indirect comparison addresses the main efficacy and safety endpoints reported in the trials, and the fundamental challenges for such an approach are as

follows: 1) the differences in patient population; 2) differences in definition of major bleeding; and 3) unblinded versus nonblinded/double-blinded comparisons. Indeed, deviations from similarity are potentially more confounding in this approach than in a traditional meta-analysis. However, major bleeding and major plus clinically relevant nonmajor bleeding were all defined by ISTH criteria. Also, "stroke and systemic embolism" is a standardized primary endpoint for clinical trials of stroke prevention in AF (19). Other adverse effects, such as dyspepsia, were not compared, although this was increased with dabigatran compared with warfarin in the RE-LY trial (3).

Clearly, there are a number of constraints and limitations related to the method used for an indirect comparison analysis, but this is still considered a reasonable statistical tool to qualify a comparison of effects that have not yet been investigated head to head. The method and its usage, pros, and cons have been the subject of many papers in recent years, and is an accepted technique and method (8,10,20).

Another limitation is that this analysis cannot adjust for patient demography and stroke risk of the different trial populations, and some differences are evident (Tables 1 and 2, Online Table 2), with, e.g., ROCKET-AF studying a higher-risk population. Furthermore, we cannot account for differences in warfarin control between the trials, with mean time in therapeutic range in the RE-LY and ARISTOTLE trials being much better than that seen in the ROCKET-AF trial. An alternative technique to the Bucher method used in this paper would be a network-based indirect comparison, which is a Bayesian Markov chain Monte Carlo method. The latter has its strengths in situations where there are many trials and with trials that have several treatment arms. We feel that in this particular setting with only 3 trials, each with its own treatment, that the Bucher method was preferred because it is much more simple and transparent method. Differences in inclusion and exclusion criteria, patient population, data collection methods, and outcome definitions or adjudication may result in residual confounding and persisting heterogeneity. Indeed, the statistical technique used somewhat assumes that the patients entered in the various trials and the level of anticoagulation were comparable.

Also, although all patients had AF, the risk of stroke and perhaps other endpoints differed between trials, and no statistical adjustments were made for multiple comparisons within this study. Finally, we have only used data from the published phase III trials for this analysis, and there is still 1 large ongoing trial with the oral Factor Xa inhibitor edoxaban in AF, which has yet to report (21).

Conclusions

Notwithstanding the limitations of an indirect comparison study, we found no profound significant differences in efficacy between apixaban and dabigatran etexilate (both doses) or rivaroxaban. Dabigatran 150 mg BID was superior

to rivaroxaban for efficacy (with less stroke and systemic embolism and hemorrhagic stroke). Major bleeding was significantly lower with dabigatran 110 mg BID or apixaban. Only a head-to-head direct comparison of the different new OACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF.

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▶ **APPENDIX**

For supplemental tables, please see the online version of this article.