Systematic Review and Adjusted Indirect Comparison Meta-Analysis of Oral Anticoagulants in Atrial Fibrillation

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Background—Oral anticoagulants such as apixaban, dabigatran, and rivaroxaban are alternatives to warfarin for preventing events in patients with atrial fibrillation. Direct comparative studies between agents are unavailable. Our objective was to conduct an adjusted indirect comparison meta-analysis between new oral agents in atrial fibrillation.

Methods and Results—We searched MEDLINE and Cochrane Central through February 2012 for randomized, controlled trials in patients with atrial fibrillation evaluating apixaban, dabigatran, or rivaroxaban versus warfarin. For dabigatran, only data from the Food and Drug Administration–approved dose were included. Outcomes included the composite of stroke or systemic embolism, any stroke, and major bleeding among, others. Outcomes were initially pooled using standard random-effects methods, producing risk ratio and 95% confidence intervals. Adjusted indirect comparisons using these pooled estimates were then performed. A total of 44 733 patients from 4 studies were analyzed. Most analyses yielded no differences between agents. Dabigatran lowered risk of composite outcome (risk ratio, 0.75; 95% confidence interval, 0.57–1.00), ischemic stroke (0.67; 0.48–0.93), and hemorrhagic stroke (0.45; 0.45–0.99) versus rivaroxaban. No differences in all strokes or mortality were seen. Apixaban lowered the risk of major bleeding (0.74; 0.60–0.91) and gastrointestinal bleeding (0.58; 0.41–0.82) versus dabigatran and major bleeding versus rivaroxaban (0.68; 0.55–0.83), but increased systemic emboli versus rivaroxaban (3.86; 1.17–12.75).

Conclusions—Significant differences in efficacy and safety parameters may exist between oral anticoagulant agents in patients with atrial fibrillation. Apixaban lowers the risk of major and gastrointestinal bleeding versus dabigatran and rivaroxaban. Dabigatran lowers the composite of stroke or systemic emboli, and ischemic stroke versus rivaroxaban. Head-to-head clinical trials are required to confirm these findings. **(*Circ Cardiovasc Qual Outcomes*. 2012;5:711-719.)**

Key Words: atrial fibrillation ■ ischemic stroke ■ warfarin ■ apixaban ■ dabigatran ■ rivaroxaban

Oral anticoagulant agents are the mainstay of therapy for preventing stroke and systemic emboli in patients with nonvalvular atrial fibrillation.[1,2] For years, vitamin K antagonists such as warfarin have been the gold standard, reducing stroke risk by ≈two thirds.[3] Due to significant limitations related to warfarin use, alternative anticoagulants have been evaluated in recent years. Three agents, apixaban, dabigatran, and rivaroxaban, have been studied in patients with nonvalvular atrial fibrillation demonstrating at least noninferiority to warfarin.[4–6] The latter 2 agents, dabigatran and rivaroxaban, now carry approval in the United States for preventing stroke and systemic emboli in this population. In fact, recently published guidelines by the American College of Chest Physicians recommend dabigatran (the only new agent approved in the United States at the time of the guidelines writing) rather than adjusted-dose warfarin for patients with atrial fibrillation at risk for stroke.[2]

The comparative effectiveness of these newer oral anticoagulant agents remains unclear due to a lack of direct comparative studies.[7] Use of indirect comparison meta-analytic techniques allow for adjusted head-to-head comparisons when treatments share a common comparator, in this case warfarin.[8,9] The current systematic review and indirect comparison meta-analysis seeks to characterize the comparative efficacy and safety of the newer oral anticoagulants in the treatment of atrial fibrillation. This information may help inform decision makers until head-to-head comparative studies become available.

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WHAT IS KNOWN

- Direct comparative trials of newer oral anticoagulant agents are not available to help guide treatment choice.
- Adjusted indirect-comparison meta-analysis can be utilized to estimate efficacy and treatment differences when a common comparator is used.

WHAT THE STUDY ADDS

- Most analyses identified no difference between agents.
- Apixaban was associated with a lower risk of major and gastrointestinal bleeding versus dabigatran and rivaroxaban, whereas dabigatran was associated with a lower risk of the composite of stroke or systemic emboli and ischemic stroke versus rivaroxaban.
- Meta-regression analyses identified no confounding of effect when controlled for differences in $CHADS_2$ score or time within the therapeutic international normalized ratio range.

Methods

The current review conforms to standard guidelines and was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[10,11]

Literature Search

We conducted a systematic literature using MEDLINE (beginning January 1950) and Cochrane Central through February 2012. The search strategy combined the Medical Subject Headings and keywords apixaban, dabigatran, rivaroxaban, oral Xa inhibitor, oral direct thrombin inhibitor combined with atrial fibrillation. The complete search strategy is shown in the in the online-only Data Supplement. No language restrictions were imposed. For the MEDLINE search, we used the Cochrane Collaboration's Highly Sensitive Search Strategy sensitivity maximizing version for randomized, controlled trials (RCTs).[11] A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies. We also conducted a search of http://www.clinicaltrials.gov to identify relevant ongoing clinical studies of the same oral anticoagulants, or future ones.

Study Selection

Both investigators reviewed all potentially relevant articles in a parallel manner by using a priori defined criteria. Studies were eligible for inclusion in the systematic review if they were (1) a RCT in humans; (2) investigated patients with nonvalvular atrial fibrillation; (3) evaluated apixaban, dabigatran, or rivaroxaban compared with warfarin or each other; and (4) reported results of stroke or systemic emboli and major bleeding. These 3 oral anticoagulant agents were chosen as comparisons to warfarin because they are either available for clinical use, or (in the case of apixaban) been submitted for approval with RCT results that have been fully published in a peer-reviewed journal.

Data Abstraction

For each included study, both investigators used a standardized data abstraction tool to independently extract all data, with disagreements resolved by discussion. The following information was sought from each trial: author, year, study design, duration of follow-up, population and setting, time spent within therapeutic international normalized ratio range (TTR), and clinical outcomes. Efficacy outcomes included the composite of stroke or systemic emboli, any stroke, ischemic stroke, systemic emboli, and mortality. Safety outcomes included major bleeding, hemorrhagic stroke, and gastrointestinal bleeding. Only data from the intention-to-treat analysis of each study was included in this analysis. If the United States Food and Drug Administration approved 1 of the drugs for prevention of stroke in atrial fibrillation, only data from the Food and Drug Administration-approved dose for this indication were extracted.

Validity Assessment

Following the Methods Guide for Comparative Effectiveness Reviews, both reviewers assessed the quality of each study by answering yes, no, or unclear to 11 questions regarding similarity of baseline populations, randomization, allocation concealment, blinding of study participants and personnel, outcome adjudication, completeness of follow-up, and conflicts of interest.[12] Studies were given an overall score of good, fair, or poor with disagreements resolved through discussion. We also used methods from the Agency for Healthcare Research and Quality Evidence-Based Practice Centers for grading the strength of evidence (SOE) for each of the main outcomes based on Grading of Recommendations Assessment, Development, and Evaluation.[13] Evidence quality was rated as high (further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect), moderate, low, or insufficient (evidence is unavailable or does not permit a conclusion). Domains evaluated to rate the SOE included (1) risk for bias, (2) consistency, (3) directness, and (4) precision. Grading for each outcome can be found in online-only Data Supplement Tables I to IV.

Statistical Analysis

Traditional pair-wise meta-analysis was first conducted with events analyzed as categorical variables. Analyses were conducted for each pair-wise comparison separately. Weighted averages were reported as risk ratio (RR) with associated confidence intervals (CIs) using a DerSimonian and Laird random-effects model.[14] Statistical significance will be stated using a threshold P value of 0.01 (with corresponding 99% CI provided) given the number of comparisons conducted and small number of studies included. To better evaluate the magnitude of potential differences between agents, absolute risk differences and number needed to treat with associated 95% CI were calculated. Traditional meta-analysis statistics were performed using Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ). Adjusted indirect comparisons of pooled estimates using inverse variance weighting were then performed according to the methods of Bucher and colleagues using the indirect treatment comparison computer program, Version 1.0.[8,15] The likelihood of statistical heterogeneity was assessed using the I^2 statistic (an I^2 >25% is considered representative of important statistical heterogeneity).[16] We evaluated the presence of publication bias and related biases by using funnel plots and Egger tests, but the small number of studies limited the ability of these methods to detect publication bias.[17]

One of the underlying assumptions of adjusted indirect comparison meta-analyses is that the included trials are similar. This includes both methodological as well as patient characteristics. Two patient characteristics that are influential to the rate of both efficacy and safety events in this population is the stroke risk, measured by mean $CHADS_2$ score, and the quality of warfarin management, measured by TTR. To assess whether differences in these 2 variables affected outcomes, random-effects meta-regression analyses were conducted. Meta-regression analyses were performed using Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ).

Results

Study Selection and Characteristics

The results of our literature search are shown in Figure 1. In brief, after initially screening 237 citations and 26 full-text articles, a total of 4 unique RCTs met our inclusion criteria and were included in the quantitative analysis (Table 1).[4–6,18] A total of 11 citations, primarily representing subgroup analyses of the 4 main RCTs, were included in the qualitative analysis.[19–29]

Of the RCTs, 2 evaluated dabigatran,[4,18] whereas 1 each evaluated rivaroxaban[5]and apixaban.[6] Each of the studies enrolled patients with nonvalvular atrial fibrillation. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared dabigatran versus warfarin in 18 113 patients using a prospective, randomized, open-label, blinded end-point evaluation design, with a median follow-up period of 2 years.[4] Only data from the dabigatran 150 mg arm of RE-LY was included in this analysis, because this was the Food and Drug Administration-approved dose for this indication. Patients in RE-LY had a mean $CHADS_2$ score of 2.1, with around one third of patients having a score ≥3. In the warfarin dosing arm, patients had a mean TTR of 64% with approximately half of the patients being naïve to warfarin prior to study enrollment. The Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation (PETRO) study[18] was unique from RE-LY[4] in that it was a dose-ranging study of 502 patients comparing dabigatran either with or without aspirin versus adjusted-dose warfarin. We only included data from the dabigatran 150 mg (without aspirin) arm in this analysis. The mean $CHADS_2$ score was not reported and the mean TTR was 57.2%. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) was a randomized, double-blind trial of 14 264 patients with nonvalvular atrial fibrillation with a mean duration of follow-up of 1.94 years.[5] Patients had a mean $CHADS_2$ score of 3.5 and patients in the warfarin arm had a mean TTR of 55%. The last included study was the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) study.[6] This randomized, double-blind study included 18 201 patients with nonvalvular atrial fibrillation with a mean duration of follow-up of 1.8 years. Patients had a mean $CHADS_2$ score of 2.1 and patients in the warfarin arm had a mean TTR of 62.2%.

New Agents Versus Warfarin

The comparative effects of newer oral anticoagulants versus warfarin on outcomes of interest are shown in Figure 2. In general, the composite of stroke or systemic emboli (RR, 0.80; 95% CI, 0.70–0.91; SOE moderate) and any stroke (RR, 0.77; 95% CI, 0.64–0.92; SOE high) were significantly reduced with the newer agents compared with warfarin. Similarly, all-cause mortality (RR, 0.87; 95% CI, 0.80–0.97; SOE high) and hemorrhagic stroke (RR, 0.46; 95% CI, 0.27–0.77; SOE low) were also significantly lower with the newer agents. No significant differences were seen for any other outcomes. Significant statistical heterogeneity was seen in a few analyses including any stroke (I^2=28.5%), major bleed (I^2=80.6%),

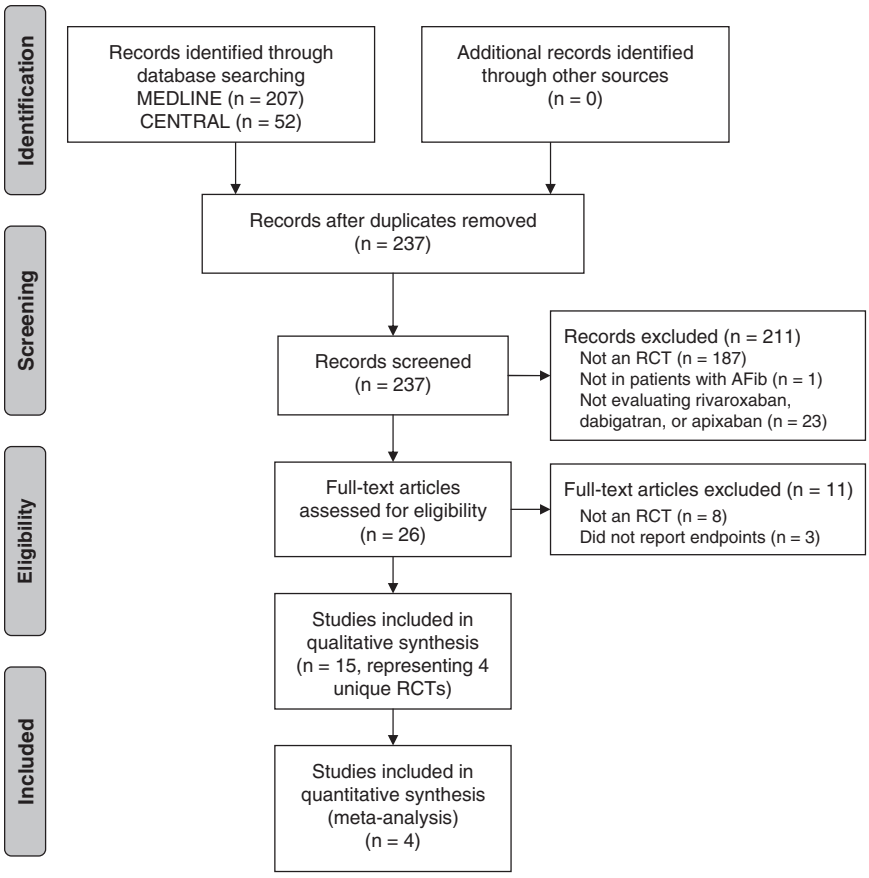


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. RCT indicates randomized, controlled trials.

Table 1. Baseline Characteristics of Trials Evaluating Newer Oral Anticoagulants in Atrial Fibrillation

Study Name	Intervention, n	Age, Mean±SD	Prior VKA Use, %	Mean INR TTR, %	$CHADS_2$ Score, Mean±SD	$CHADS_2$ Components, %	Study Quality
PETRO[18]	Dabigatran 150 mg twice daily (n=166)	70±8.1	NR	57.2%	NR	CHF: 31.3% HTN: 71% Age ≥75: 30.7% DM: 27% Prior TIA or Stroke: 17.5%	Fair
	Warfarin titrated to INR 2–3 (n=70)	69±8.3	NR		NR	CHF: 34.3% HTN: 70% Age ≥75: 27% DM: 21.4% Prior TIA or Stroke: 18.6%	
RE-LY[4]	Dabigatran 150 mg twice daily (n=6076)	71.5±8.8	50.2%	64%	2.2±1.2	CHF: 31.8% HTN: 78.9% Age ≥75: NR DM: 23.1% Prior TIA or Stroke: 20.3%	Good
	Warfarin titrated to INR 2–3 (n=6022)	71.6±8.6	48.6%		2.1±1.1	CHF: 31.9% HTN: 78.9% Age ≥75: NR DM: 23.4% Prior TIA or Stroke: 19.8%	
ROCKET-AF[5]	Rivaroxaban 20 mg daily (n=7131)	Median (IQR) 73 (65–78)	62.3%	55%	3.48±0.94	CHF: 62.6% HTN: 90.3% Age ≥75: NR DM: 40.4% Prior TIA or Stroke: 54.9%	Good
	Warfarin titrated to INR 2–3 (n=7133)	Median (IQR) 73 (65–78)	62.5%		3.46±0.95	CHF: 62.3% HTN: 90.8% Age ≥75: NR DM: 39.5% Prior TIA or Stroke: 54.6%	
ARISTOTLE[6]	Apixaban 5 mg twice daily (n=9120)	Median (IQR) 70 (63–76)	57.1%	62.2%	2.1±1.1	CHF: 35.5% HTN: 87.3% Age ≥75: 31.2% DM: 25.0% Prior TIA or Stroke: 19.2%	Good
	Warfarin titrated to INR 2–3 (n=9081)	Median (IQR) 70 (63–76)	57.2%		2.1±1.1	CHF: 35.4% HTN: 87.6% Age ≥75: 31.1% DM: 24.9% Prior TIA or Stroke: 17.7%	

$CHADS_2$ indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; NR, not reported; TIA, transient ischemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban vs Warfarin in Nonvalvular Atrial Fibrillation; and ARISTOTLE, Apixaban vs Warfarin in Patients with Atrial Fibrillation.

hemorrhagic stroke (I^2=52.1%), and gastrointestinal bleed (I^2=82.5%).

Apixaban Versus Dabigatran

Results of the adjusted indirect comparison between apixaban and dabigatran can be found in Figure 3A. Efficacy outcomes, including the composite of stroke or systemic emboli (RR, 1.19; 95% CI, 0.90–1.58; SOE moderate), ischemic stroke (RR, 1.19; 95% CI, 0.86–1.65; SOE moderate), any stroke (RR, 1.21; 95% CI, 0.91–1.62; SOE moderate), and mortality (RR, 1.01; 95% CI, 0.86–1.19; SOE moderate) did not differ between the agents. Apixaban was associated with a lower risk of major bleeding (RR, 0.75; 95% CI, 0.62–0.92; SOE moderate) and gastrointestinal bleeding (RR, 0.60; 95% CI, 0.43–0.84; SOE moderate), whereas a trend toward a significant increase in hemorrhagic stroke (RR, 1.93; 95% CI, 0.93–4.02; SOE low) was seen compared with dabigatran. Sufficient data were not available to conduct an indirect comparison for systemic emboli.

Dabigatran Versus Rivaroxaban

Results of the adjusted indirect comparison between dabigatran and rivaroxaban can be found in Figure 3B. Dabigatran was associated with a significantly lower risk of the composite of stroke or systemic emboli (RR, 0.76; 95% CI, 0.58–0.99; SOE moderate) and ischemic stroke (RR, 0.68; 95% CI, 0.49–0.93;

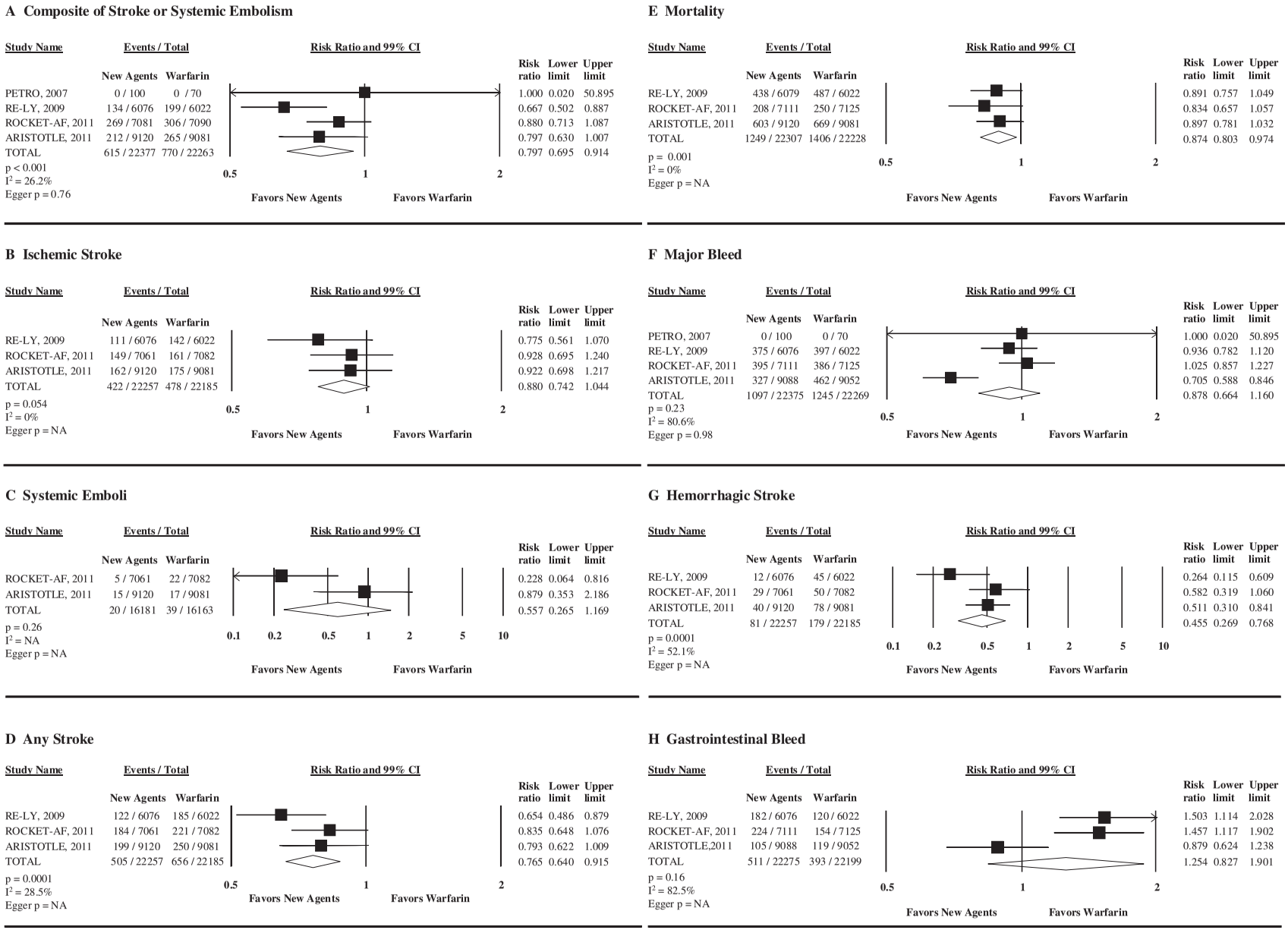
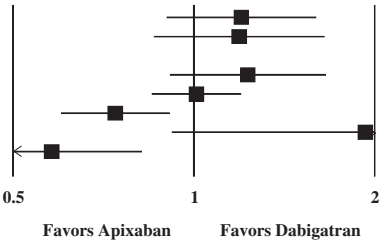


Figure 2. Forest plots comparing newer agents vs warfarin. **A**, Composite of stroke or systemic embolism; **B**, ischemic stroke; **C**, systemic emboli; **D**, any stroke; **E**, mortality; **F**, major bleed; **G**, hemorrhagic stroke; **H**, gastrointestinal bleed.RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban vs Warfarin in Nonvalvular Atrial Fibrillation; ARISTOTLE, Apixaban vs Warfarin in Patients with Atrial Fibrillation; CI, confidence interval; and NA, not available.

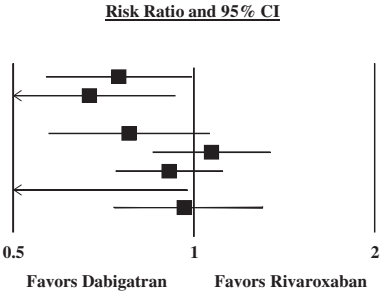
A Forest Plots Comparing Apixaban vs Dabigatran

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	1.193	0.902	1.579
Ischemic Stroke	1.190	0.860	1.645
Systemic Emboli	Not Available		
Any Stroke	1.213	0.907	1.622
Mortality	1.007	0.855	1.185
Major Bleed	0.753	0.619	0.916
Hemorrhagic Stroke	1.933	0.929	4.017
GI Bleed	0.603	0.434	0.838



B Forest Plots Comparing Dabigatran vs Rivaroxaban

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.758	0.580	0.992
Ischemic Stroke	0.676	0.490	0.933
Systemic Emboli	Not Available		
Any Stroke	0.783	0.582	1.053
Mortality	1.069	0.859	1.331
Major Bleed	0.913	0.753	1.107
Hemorrhagic Stroke	0.454	0.210	0.983
GI Bleed	0.970	0.715	1.314



C Forest Plots Comparing Apixaban vs Rivaroxaban

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.905	0.712	1.150
Ischemic Stroke	0.804	0.598	1.082
Systemic Emboli	3.854	1.202	12.356
Any Stroke	0.949	0.727	1.238
Mortality	1.077	0.873	1.328
Major Bleed	0.688	0.566	0.835
Hemorrhagic Stroke	0.878	0.487	1.583
GI Bleed	0.585	0.414	0.826

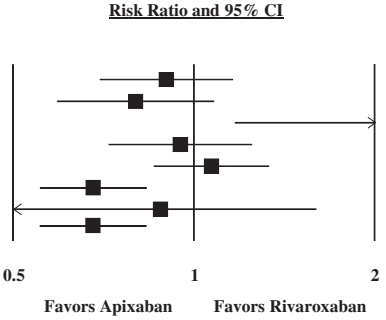


Figure 3. Indirect comparisons between newer agents. GI indicates gastrointestinal; CI, confidence interval.

SOE moderate) versus rivaroxaban, whereas no difference in any stroke (RR, 0.78; 95% CI, 0.58–1.05; SOE moderate) or mortality (RR, 1.07; 95% CI, 0.86–1.33; SOE moderate) was seen. No significant difference in either major bleeding (RR, 0.91; 95% CI, 0.75–1.11; SOE moderate) or gastrointestinal bleeding (RR, 0.97; 95% CI, 0.72–1.31; SOE moderate) was seen between the agents, whereas dabigatran significantly reduced the risk of hemorrhagic stroke (RR, 0.45; 95% CI, 0.21–0.98; SOE moderate) compared with rivaroxaban. Sufficient data were not available to conduct indirect comparisons for either systemic emboli or gastrointestinal bleeding.

Apixaban Versus Rivaroxaban

Results of the adjusted indirect comparison between apixaban and rivaroxaban can be found in Figure 3C. No significant differences in the composite of stroke of systemic emboli (RR, 0.91; 95% CI, 0.71–1.15; SOE moderate), ischemic stroke (RR, 0.80; 95% CI, 0.60–1.08; SOE moderate), any stroke (RR, 0.95; 95% CI, 0.73–1.24; SOE moderate), or mortality (RR, 1.08; 95% CI, 0.87–1.33; SOE moderate) was seen between the agents, although apixaban was associated with an increased risk of systemic emboli (RR, 3.85; 95% CI, 1.20–12.36; SOE low) versus rivaroxaban. Apixaban decreased the risk of major bleeding (RR, 0.69; 95% CI, 0.57–0.84; SOE moderate) versus rivaroxaban, although no difference in hemorrhagic stroke (RR, 0.88; 95% CI, 0.49–1.58; SOE low) was seen. Sufficient data were not available to conduct an indirect comparison for gastrointestinal bleeding.

Absolute Risk Difference

To put the potential differences in outcomes between agents into clinical context, we calculated the absolute difference in events per 1000 patients treated (Table 2). As compared with warfarin, the newer agents resulted in 7 fewer composite

Table 2. Absolute Differences in Events per 1000 Patients Treated

Outcome	Agents vs Warfarin	Apixaban vs Dabigatran	Dabigatran vs Rivaroxaban	Apixaban vs Rivaroxaban
Stroke or systemic emboli	−7 (−11 to −3)	−5 (−12 to 3)	−6 (−14 to 3)	−1 (−9 to 7)
Ischemic stroke	−3 (−6 to 1)	4 (−3 to 10)	−9 (−16 to −1)	−5 (−11 to 2)
Systemic emboli	0 (−2 to 1)	NA	NA	2 (0 to 4)
Any stroke	−7 (−11 to −3)	5 (−2 to 12)	−5 (−13 to 2)	−1 (−8 to 7)
Mortality	−7 (−12 to −2)	1 (−11 to 13)	−3 (−14 to 8)	−2 (−11 to 8)
Major bleed	−6 (−18 to 6)	−11 (−21 to 0)	−6 (−14 to 3)	−16 (−26 to −7)
Hemorrhagic stroke	−4 (−6 to −2)	1 (−2 to 5)	−3 (−6 to 1)	−1 (−5 to 2)
Gastrointestinal bleed	6 (−5 to 17)	−12 (−18 to −5)	0 (−8 to 8)	−11 (−18 to −5)

NA indicates not available.
Data are presented as risk difference (95% confidence interval).

(stroke or systemic emboli) events, 7 fewer strokes, 7 fewer deaths, and 4 fewer hemorrhagic strokes per 1000 patients treated. Apixaban resulted in 12 fewer gastrointestinal bleeds than dabigatran and 11 fewer than rivaroxaban, as well as 16 fewer major bleeds than rivaroxaban. Dabigatran resulted in 9 fewer ischemic strokes than rivaroxaban.

Meta-Regression

Random-effects meta-regression was run for each of the efficacy and safety outcomes controlling for differences in mean $CHADS_2$ score and TTR. Sufficient data were not available to conduct meta-regression on systemic emboli. No significant association was found between either $CHADS_2$ score or TTR and any of the efficacy or safety outcomes (online-only Data Supplement Figure 1A through 1E).

Ongoing Research

We identified phase III clinical trials for other new oral anticoagulants for preventing stroke in patients with atrial fibrillation. Edoxaban, an oral factor Xa inhibitor, is being compared with dose-adjusted warfarin in the Effective Anticoagulation With Factor xA Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48) trial, which is still ongoing (NCT00781391).[30] Although a number of other agents have been evaluated in phase I and II trials, no other agents have active phase III trials ongoing in this area.

Comment

This meta-analysis of >44 000 patients from 4 clinical trials found that, compared with dose-adjusted warfarin, newer oral anticoagulants resulted in significant reductions in stroke or systemic embolism, all strokes, mortality, and hemorrhagic stroke with similar rates of ischemic stroke, hemorrhagic stroke, major bleed, and gastrointestinal bleed. When the newer oral agents were indirectly compared, a few potential differences were seen. As compared with rivaroxaban, dabigatran was associated with lower risk of stroke or systemic embolism, ischemic stroke, and hemorrhagic stroke, whereas apixaban was associated with lower risk of major and gastrointestinal bleeds and higher risk of systemic emboli. As compared with dabigatran, apixaban was associated with lower risk of major and gastrointestinal bleeds. With the lack of available head-to-head studies, these data provide the first indirect comparisons between these newer oral anticoagulant agents in patients with nonvalvular atrial fibrillation.

One of the main criticisms with undertaking such adjusted indirect comparison relates to differences in pertinent factors between the clinical trials, most specifically the $CHADS_2$ score and TTR on warfarin.[31] These 2 factors related to the baseline stroke risk in the trial populations ($CHADS_2$) and the adequacy of the warfarin control (TTR). The ROCKET-AF study[5] included patients at a higher stroke risk (mean $CHADS_2$=3.5) compared with RE-LY[4] (mean $CHADS_2$=2.1) and ARISTOTLE (mean $CHADS_2$=2.1).[6] Patients in the adjusted-dose warfarin arm also had poorer international normalized ratio control, as reflected by a mean TTR of 55% compared with 64% in RE-LY and 62.2% in ARISTOTLE. In an attempt to quantify the association between $CHADS_2$ score and TTR in these studies, we conducted meta-regression analyses. These results showed no association between these factors and any of the efficacy or safety outcomes of interest. This suggests that, although nominal differences in these factors exist between the studies, they may not significantly modify the treatment effect seen when comparing the newer oral anticoagulants to warfarin. Our findings are supported by the results of a subgroup analysis of the RE-LY trial,[27] which showed that although risk of clinical events was higher with increasing $CHADS_2$ scores, the benefits of dabigatran compared with warfarin were seen across all $CHADS_2$ score strata.

Two prior indirect comparison meta-analyses have been published evaluating pharmacological strategies to prevent stroke in atrial fibrillation.[32,33] Roskell et al[33] conducted indirect comparisons and network meta-analyses of all pharmacological agents as compared with dabigatran. They suggested that dabigatran reduced stroke, systemic embolism, and mortality versus warfarin as well as antiplatelet agents and placebo. Their results are supported by a recently published study that showed apixaban to be superior to aspirin in reducing the risk of stroke or systemic embolism without affecting risk of major bleeding or intracranial hemorrhage in patients unsuitable for warfarin.[34] Our study differed from theirs in that we limited the analyses to only the newer oral anticoagulants as compared with warfarin and included 2 newer agents, rivaroxaban and apixaban, data for which were not available for the prior meta-analyses. In addition, given the small number of studies included in our analysis, we did not feel that a network meta-analysis performed using a Bayesian framework

would yield reliable results. Thus, we chose a more conservative approach using adjusted indirect comparison methods.

One of the biggest questions facing clinical practitioners caring for patients with atrial fibrillation at risk for stroke is which oral anticoagulant should be initiated? A number of factors have to be taken into consideration, including the effectiveness, convenience of administration, cost, ease of reversal, and adverse events. Dabigatran and apixaban are each taken twice daily, whereas rivaroxaban can be taken once daily. A number of studies have demonstrated dabigatran[35–37] and rivaroxaban[38] to be cost-effective strategies for preventing stroke in atrial fibrillation. A common concern with these new oral agents is the ability to reverse their anticoagulant properties in emergency situations. A study by Eerenberg et al[39] showed that use of prothrombin complex concentrate reversed the activity of rivaroxaban, but not dabigatran in a small study of healthy volunteers. These factors, in addition to the potential differences in efficacy and safety seen in our study, have to be taken into account when deciding on the most appropriate agent for a specific patient. Additional studies are required to better elucidate the situations under which each specific agent is appropriate for use in place of warfarin.

Adjusted indirect comparison meta-analysis is an established statistical technique that can provide useful information in the absence of sufficient head-to-head evidence.[8,40–42] Some have argued that adjusted indirect comparisons produce less bias than direct comparative studies, although this hypothesis requires further research.[37] A concern with using this method to indirectly compare the efficacy and safety of oral anticoagulant agents in atrial fibrillation is variation in the patient populations of the included studies.[31] A task force on indirect treatment comparisons good research practices, formed by the International Society of Pharmacoeconomic and Outcomes Research, stated that a degree of relative variation in the patient populations is welcome for comparative evaluations, as they may more adequately reflect real-world clinical situations.[42] Specific to stroke prevention in atrial fibrillation, the baseline stroke risk of the population ($CHADS_2$ score) and the adequacy of warfarin control (TTR) are of importance. When we conducted meta-regression analyses to control for these variables, no significant association was found with any of the efficacy or safety variables. This further strengthens the assumptions that underlie our adjusted indirect comparison analyses. However, given the small number of studies included in the meta-regression, the results are likely underpowered and should be interpreted accordingly. Moreover, results from our study should be viewed as hypothesis generating, and should be confirmed with head-to-head comparisons. Another limitation to this analysis is the potential for statistical, as well as clinical and methodological, heterogeneity between studies. Our analysis showed significant statistical heterogeneity in a few analyses, which may be the result of differences in the individual agents on outcome risk.

Conclusions

Significant differences in pertinent efficacy and safety parameters may exist between oral anticoagulant agents in patients with nonvalvular atrial fibrillation. Apixaban lowers the risk of major and gastrointestinal bleeding versus dabigatran and rivaroxaban. Dabigatran lowers the composite of stroke or systemic emboli, and ischemic stroke versus rivaroxaban. Although direct head-to-head clinical trials are required to confirm the findings of this adjusted indirect comparison analysis, they are unlikely to be conducted. Data from real-world patient registries may shed light on differences between these agents.

Disclosures

None.

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