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

William L. Baker, PharmD, BCPS; Olivia J. Phung, PharmD

**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. For years, vitamin K antagonists such as warfarin have been the gold standard, reducing stroke risk by two thirds. 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. 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.

The comparative effectiveness of these newer oral anticoagulant agents remains unclear due to a lack of direct comparative studies. Use of indirect comparison meta-analytic techniques allow for adjusted head-to-head comparisons when treatments share a common comparator, in this case warfarin. 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.
WHAT IS KNOWN

• Direct comparative trials of newer oral anticoagu-
lant 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 associ-
  ated 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,
  score or time within the therapeutic international nor-
  malized 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).12 A manual search of references from 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) evalu-
ated apixaban, dabigatran, rivaroxaban, oral Xa inhibitor, oral direct
thrombin inhibitor combined with atrial fibrillation; (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 an-
swering yes, no, or unclear to 11 questions regarding similarity of baseline populations, randomization, allocation concealment, blind-
ing 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 re-
solved 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.16 Evidence quality was rated as high (further research is very unlikely to change the confidence in the esti-
mate 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) preci-
sion. 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 re-
ported as risk ratio (RR) with associated confidence intervals (CIs)
using a DerSimonian and Laird random-effects model.18 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 evalu-
ate 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 per-
formed 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 treat-
ment comparison computer program, Version 1.0.6,5,13 The likelihood
of statistical heterogeneity was assessed using the I^2 statistic (an
I^2 >25% is considered representative of important statistical hetero-
geney).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 compari-
son 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, 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).

A total of 11 citations, primarily representing subgroup analyses of the 4 main RCTs, were included in the qualitative analysis.

Of the RCTs, 2 evaluated dabigatran, whereas 1 each evaluated rivaroxaban and apixaban. 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. 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 CHADS2 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 was unique from RE-LY 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 CHADS2 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. Patients had a mean CHADS2 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. 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 CHADS2 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 (I²=28.5%), major bleed (I²=80.6%),...
hemorrhagic stroke (I²=52.1%), and gastrointestinal bleed (I²=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; SOE moderate).
### A Composite of Stroke or Systemic Embolism

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Events / Total</th>
<th>Risk Ratio and 99% CI</th>
<th>Risk Lower Limit</th>
<th>Risk Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Agents</td>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETRO, 2007</td>
<td>0 / 100</td>
<td>0.891</td>
<td>0.757</td>
<td>1.049</td>
</tr>
<tr>
<td>RE-LY, 2009</td>
<td>122 / 6076</td>
<td>1.254</td>
<td>0.826</td>
<td>1.901</td>
</tr>
<tr>
<td>ROCKET-AF, 2011</td>
<td>0 / 153</td>
<td>0.864</td>
<td>0.678</td>
<td>1.119</td>
</tr>
<tr>
<td>ARISTOTLE, 2011</td>
<td>0.228</td>
<td>0.654</td>
<td>0.463</td>
<td>0.915</td>
</tr>
<tr>
<td>TOTAL</td>
<td>249 / 22307</td>
<td>1.254</td>
<td>0.826</td>
<td>1.901</td>
</tr>
</tbody>
</table>

**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.
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 Risk Difference**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Lower Limit</th>
<th>Risk Upper Limit</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Emboli</td>
<td>-</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Systemic Emboli</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figure 3.** Indirect comparisons between newer agents. GI indicates gastrointestinal; CI, 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 CHADS2 score and TTR. Sufficient data were not available to conduct meta-regression on systemic emboli. No significant association was found between either CHADS2 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). 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 CHADS2 score and TTR on warfarin. These 2 factors related to the baseline stroke risk in the trial populations (CHADS2) and the adequacy of the warfarin control (TTR). The ROCKET-AF study included patients at a higher stroke risk (mean CHADS2=3.5) compared with RE-LY (mean CHADS2=2.1) and ARISTOTLE (mean CHADS2=2.1). 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 CHADS2 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, which showed that although risk of clinical events was higher with increasing CHADS2 scores, the benefits of dabigatran compared with warfarin were seen across all CHADS2 score strata.

Two prior indirect comparison meta-analyses have been published evaluating pharmacological strategies to prevent stroke in atrial fibrillation. Roskell et al performed an indirect comparison 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. 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 and rivaroxaban 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 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. Some have argued that adjusted indirect comparisons produce less bias than direct comparative studies, although this hypothesis requires further research. 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. A task force on indirect treatment comparisons good research practices, formed by the International Society of Pharmacoeconomics 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. Specific to stroke prevention in atrial fibrillation, the baseline stroke risk of the population (CHADS2 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.

References


research and quality and the effective health-care program. *J Clin Epide-

als*. 1986;7:177–188.

15. Wells GA, Salutran SA, Chen L, Khan M, Coyle D. Indirect treatment com-
parison [computer program]. Version 1.0. Ottawa: Canadian Agency for
Drugs and Technologies in Health; 2009.

16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsis-

17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis

18. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R,
Dabigatran with or without concomitant aspirin compared with warfarin
alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J

19. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S,
Xavier D, Di Pasquale G, Yusuf S; RE-LY study group. Dabigatran
compared with warfarin in patients with atrial fibrillation and previous
transient ischaemic attack or stroke: a subgroup analysis of the RE-LY

20. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Old-
gren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi
of dabigatran compared with warfarin in older and younger patients with
atrial fibrillation: an analysis of the randomized evaluation of long-term

J, Aikens TH, Yang S, Reilly PA, Lip GY, Yusuf S; RE-LY Steering Com-
mittee and Investigators. Dabigatran and warfarin in vitamin K antago-
nist-naive and -experienced cohorts with atrial fibrillation. *Circulation*
2010;122:2246–2253.

22. Fox KA, Piccini JP, Woidyla D, Becker RC, Halperin JL, Nessel CC,
Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM.
Prevention of stroke and systemic embolism with rivaroxaban compared
with warfarin in patients with non-valvular atrial fibrillation and moderate

RE-LY Investigators. Efficacy and safety of dabigatran vs. warfarin in
patients with atrial fibrillation–sub-analysis in Japanese population in RE-

SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analy-

25. Ogawa S, Shinohara Y, Kannmuri K. Safety and efficacy of the oral direct
factor xa inhibitor apixaban in Japanese patients with nonrheumatic atrial fibrillation.

Kamensky G, Reilly PA, Yang S, Yusuf S, Wallentin L, Connolly
SJ; RE-LY Investigators. Risks for stroke, bleeding, and death in patients
with atrial fibrillation receiving dabigatran or warfarin in relation to the
CHADS2 score: a subgroup analysis of the RE-LY trial. *Am Intern Med*

27. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG,
Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Conno-
elly SJ; RE-LY investigators. Efficacy and safety of dabigatran compared
with warfarin at different levels of international normalised ratio control
for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial.

Eikelboom J, Brueckmann M, Yusuf S, Connolly SJ. Myocardial ischemic
events in patients with atrial fibrillation treated with dabigatran or warfa-
rin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation

Diener HC, Donnan GA, Halperin JL, Mahaffey KW, Mas JL, Massaro A,
Norring B, Nessel CC, Paolini JF, Roine RO, Singer DE, Wong L, Califf
RM, Fox KA, Hacke W; ROCKET AF Steering Committee Investigators.
Rivaroxaban compared with warfarin in patients with atrial fibrillation
and previous stroke or transient ischaemic attack: a subgroup analysis of

30. Ruff CT, Giugliano RP, Antman EM, Cugnatale SE, Bocanegra T, Mercuri
M, Han yok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E.
Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin
in patients with atrial fibrillation: design and rationale for the Effective
aNticoaGulation with factor xa next GEneration in Atrial Fibrillation-
Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48).

31. Katnelson M, Socco RL, Moscussi M. Progress for stroke prevention with
atrial fibrillation. Emergence of alternative oral anticoagulants. *Circula-

32. Cooper NJ, Sutton AJ, Liu G, Khunti K. Mixed comparison of stroke pre-
vention treatments in individuals with nonrheumatic atrial fibrillation.
*Arch Intern Med*. 2006;166:1269–1275.

33. Roskell NS, Lip GY, Noack H, Clemens A, Plumb JM. Treatments for
stroke prevention in atrial fibrillation: a network meta-analysis and in-
104:1106–1115.

34. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S,
KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lancas-Zanetti F,
Gonzalez-Hernosillo A, Dans AL, Munawar M, O’Donnell M, Law-
rence J, Lewis G, Afzal R, Yusuf S; AVEROES Steering Committee and

35. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS,
Wang PJ, Turakhia MP. Cost-effectiveness of dabigatran compared with
warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*
2011;154:1–11.

36. Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-
Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etoxetate for
the prevention of stroke and systemic embolism in atrial fibrillation: a Cana-

37. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis

of rivaroxaban compared to warfarin for stroke prophylaxis in atrial fibril-

39. Eerenberg ES, Kamphuisen PW, Sippkens MK, Meijers JC, Buller HR,
Levi M. Reversal of rivaroxaban and dabigatran by protamine complex
concentrate: a randomized, placebo-controlled, crossover study in healthy

40. Song F, Harvey I, Lif ford R. Adjusted indirect comparison may be less
biased than direct comparison for evaluating new pharmaceutical inter-

41. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary

Boersma C, Annemans L, Cappelleri JC. Interpreting indirect treatment
comparisons and network meta-analysis for health-care decision making:
report of the ISPOR Task Force on Indirect Treatment Comparisons Good
Systematic Review and Adjusted Indirect Comparison Meta-Analysis of Oral Anticoagulants in Atrial Fibrillation
William L. Baker and Olivia J. Phung

Circ Cardiovasc Qual Outcomes. 2012;5:711-719; originally published online August 21, 2012; doi: 10.1161/CIRCOUTCOMES.112.966572

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/5/5/711

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2012/08/21/CIRCOUTCOMES.112.966572.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Appendix 1. Search Strategy

1. apixaban.mp.
2. BMS-562247.mp.
3. dabigatran.mp.
4. bay 59-7939.mp.
5. rivaroxaban.mp.
6. BIBR 1048.mp.
7. oral xa inhibitor.mp.
8. oral direct thrombin inhibitor.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Atrial Fibrillation/
11. afib.mp.
12. 10 or 11
13. 9 and 12
### eTable 1. Quality of Evidence for Newer Anticoagulants versus Warfarin

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Summary of findings</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect</td>
<td>Absolute (95% CI)</td>
<td>Relative (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or Systemic Emboli</td>
<td>4 RCTs</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>615/22377 (2.7%)</td>
<td>770/22,263 (3.5%)</td>
<td>0.78 (0.70-0.91)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>3 RCTs</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>422/22257 (1.9%)</td>
<td>478/22185 (2.2%)</td>
<td>0.88 (0.74-1.04)</td>
</tr>
<tr>
<td>Systemic Emboli</td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious imprecision</td>
<td>None</td>
<td>20/16181 (0.1%)</td>
<td>39/16163 (0.2%)</td>
<td>0.56 (0.27-1.17)</td>
</tr>
<tr>
<td>Any Stroke</td>
<td>3 RCTs</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>505/22257 (2.3%)</td>
<td>656/22185 (3.0%)</td>
<td>0.77 (0.64-0.92)</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 RCTs</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>1249/22307 (5.6%)</td>
<td>1406/22228 (6.3%)</td>
<td>0.87 (0.80-0.97)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>4 RCTs</td>
<td>No serious limitations</td>
<td>Serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>1097/22375 (4.9%)</td>
<td>1245/22269 (5.6%)</td>
<td>0.88 (0.66-1.16)</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>3 RCTs</td>
<td>No serious limitations</td>
<td>Serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious imprecision</td>
<td>None</td>
<td>81/22257 (0.4%)</td>
<td>179/22185 (0.8%)</td>
<td>0.45 (0.27-0.77)</td>
</tr>
<tr>
<td>Gastrointestinal Bleed</td>
<td>3 RCTs</td>
<td>No serious limitations</td>
<td>Serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious imprecision</td>
<td>None</td>
<td>511/22275 (2.3%)</td>
<td>393/22199 (1.8%)</td>
<td>1.25 (0.83-1.90)</td>
</tr>
</tbody>
</table>

Footnotes: ¹ Lack of or inadequate information about blinding
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Summary of findings</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>Stroke or Systemic Emboli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Any Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Major Bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
<tr>
<td>Gastrointestinal Bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
<td>Serious indirectness</td>
</tr>
</tbody>
</table>

Footnotes: 
1 Number of studies included in the indirect comparison. None were available for direct comparisons.
**eTable 3. Quality of Evidence for Dabigatran versus Rivaroxaban**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td>No of studies¹</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
</tr>
<tr>
<td><strong>Stroke or Systemic Emboli</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>615/22377 (2.7%)</td>
<td>770/22,263 (3.5%)</td>
<td>0.76 (0.58-0.99)</td>
</tr>
<tr>
<td><strong>Ischemic Stroke</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>422/22257 (9%)</td>
<td>478/22185 (9%)</td>
<td>0.68 (0.49-0.93)</td>
</tr>
<tr>
<td><strong>Any Stroke</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>20/16181 (8.1%)</td>
<td>39/16163 (9%)</td>
<td>0.78 (0.58-1.05)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>505/22257 (8.1%)</td>
<td>656/22185 (9%)</td>
<td>1.07 (0.86-1.33)</td>
</tr>
<tr>
<td><strong>Major Bleed</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1552/19077 (8.1%)</td>
<td>1714/19059 (9%)</td>
<td>0.91 (0.75-1.11)</td>
</tr>
<tr>
<td><strong>Hemorrhagic Stroke</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1552/19077 (8.1%)</td>
<td>1714/19059 (9%)</td>
<td>0.45 (0.21-0.98)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleed</strong></td>
<td>2 RCTs</td>
<td>No serious limitations</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1552/19077 (8.1%)</td>
<td>1714/19059 (9%)</td>
<td>0.97 (0.72-1.31)</td>
</tr>
</tbody>
</table>

**Footnotes:** ¹ Number of studies included in the indirect comparison. None were available for direct comparisons.
# eTable 4. Quality of Evidence for Apixaban versus Rivaroxaban

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
</tr>
</tbody>
</table>

| Stroke or Systemic Emboli | 2 RCTs | No serious limitations | NA | Serious indirectness | No serious imprecision | None | 615/22377 (2.7%) | 770/22,263 (3.5%) | 0.91 (0.71-1.15) | -1 (-9 to 7) | MODERATE | CRITICAL |

| Ischemic Stroke | 2 RCTs | No serious limitations | NA | No serious indirectness | No serious imprecision | None | 422/22257 (9%) | 478/22185 (9%) | 0.81 (0.60-1.08) | -5 (-11 to 2) | MODERATE | CRITICAL |

| Systemic Emboli | 2 RCTs | No serious limitations | NA | Serious indirectness | Serious imprecision | None | 20/16181 (8.1%) | 39/16163 (9%) | 3.85 (1.20-12.36) | 2 (0 to 4) | LOW | IMPORTANT |

| Any Stroke | 2 RCTs | No serious limitations | NA | Serious indirectness | No serious imprecision | None | 20/16181 (8.1%) | 39/16163 (9%) | 0.95 (0.73-1.24) | -1 (-8 to 7) | MODERATE | CRITICAL |

| Mortality | 2 RCTs | No serious limitations | NA | Serious indirectness | No serious imprecision | None | 505/22257 (8.1%) | 656/22185 (9%) | 1.08 (0.87 to 1.33) | -2 (-11 to 8) | MODERATE | CRITICAL |

| Major Bleed | 2 RCTs | No serious limitations | NA | Serious indirectness | No serious imprecision | None | 1552/19077 (8.1%) | 1714/19059 (9%) | 0.29 (0.57 to 0.84) | -16 (-26 to -7) | MODERATE | CRITICAL |

| Hemorrhagic Stroke | 2 RCTs | No serious limitations | NA | Serious indirectness | Serious imprecision | None | 1552/19077 (8.1%) | 1714/19059 (9%) | 0.88 (0.49 to 1.58) | -1 (-5 to 2) | LOW | CRITICAL |

| Gastrointestinal Bleed | 2 RCTs | No serious limitations | NA | Serious indirectness | No serious imprecision | None | 1552/19077 (8.1%) | 1714/19059 (9%) | 0.59 (0.41 to 0.83) | -11 (-18 to -5) | MODERATE | IMPORTANT |

**Footnotes:**

'1 Number of studies included in the indirect comparison. None were available for direct comparisons.
eFigure 1. Results of Meta-Regression Analyses

A. Composite of Stroke or Systemic Embolism

Regression of TTR on Log risk ratio

Regression of CHADS2 Score on Log risk ratio

p = 0.13

p = 0.27
B. Ischemic Stroke

Regression of TTR on Log risk ratio

Regression of CHADS2 Score on Log risk ratio

p = 0.49

p = 0.52
C. Any Stroke

Regression of TTR on Log risk ratio

![Graph showing the regression of TTR on Log risk ratio with p = 0.30.](image)

Regression of CHADS2 Score on Log risk ratio

![Graph showing the regression of CHADS2 Score on Log risk ratio with p = 0.42.](image)
D. Mortality

Regression of TTR on Log risk ratio

Regression of CHADS2 Score on Log risk ratio
E. Major Bleeding

Regression of TTR on Log risk ratio

Regression of CHADS2 Score on Log risk ratio

p = 0.67

p = 0.39
E. Hemorrhagic Stroke

**Regression of TTR on Log risk ratio**

```
Log risk ratio
  0.00
  -0.20
  -0.40
  -0.60
  -0.80
  -1.00
  -1.20
  -1.40
  -1.60
  -1.80
  -2.00
TTR:
  0.54
  0.55
  0.56
  0.57
  0.58
  0.59
  0.60
  0.61
  0.62
  0.63
  0.64
  0.65
```

\[ p = 0.35 \]

**Regression of CHADS2 Score on Log risk ratio**

```
Log risk ratio
  0.00
  -0.20
  -0.40
  -0.60
  -0.80
  -1.00
  -1.20
  -1.40
  -1.60
  -1.80
  -2.00
CHADS2 Score:
  1.96
  2.13
  2.30
  2.46
  2.63
  2.80
  2.97
  3.14
  3.30
  3.47
  3.64
```

\[ p = 0.46 \]
E. Gastrointestinal Bleed

Regression of TTR on Log risk ratio

\[ p = 0.58 \]

Regression of CHADS2 Score on Log risk ratio

\[ p = 0.53 \]