Comparative Efficacy and Safety of New Oral Anticoagulants in Patients With Atrial Fibrillation

Sebastian Schneeweiss, MD, ScD; Joshua J. Gagne, PharmD, ScD; Amanda R. Patrick, MS; Niteesh K. Choudhry, MD, PhD; Jerry Avorn, MD

Background—Dabigatran, an oral thrombin inhibitor, and rivaroxaban and apixaban, oral factor Xa inhibitors, have been found to be safe and effective in reducing stroke risk in patients with atrial fibrillation. We sought to compare the efficacy and safety of the 3 new agents based on data from their published warfarin-controlled randomized trials, using the method of adjusted indirect comparisons.

Methods and Results—We included findings from 44,535 patients enrolled in 3 trials of the efficacy of dabigatran (RE-LY), apixaban (ARISTOTLE), and rivaroxaban (ROCKET-AF), each compared with warfarin. The primary efficacy end point was stroke or systemic embolism; the safety end point we studied was major hemorrhage. To address a lack of comparability between trial populations caused by the restriction of ROCKET-AF to high-risk patients, we conducted a subgroup analysis in patients with a CHADS2 score ≥3. We found no statistically significant efficacy differences among the 3 drugs, although apixaban and dabigatran were numerically superior to rivaroxaban. Apixaban produced significantly fewer major hemorrhages than dabigatran and rivaroxaban.

Conclusion—An indirect comparison of new anticoagulants based on existing trial data indicates that in patients with a CHADS2 score ≥3 dabigatran 150 mg, apixaban 5 mg, and rivaroxaban 20 mg resulted in statistically similar rates of stroke and systemic embolism, but apixaban had a lower risk of major hemorrhage compared with dabigatran and rivaroxaban. Until head-to-head trials or large-scale observational studies that reflect routine use of these agents are available, such adjusted indirect comparisons based on trial data are one tool to guide initial therapeutic choices.

Key Words: indirect comparison • anticoagulation • dabigatran • rivaroxaban • apixaban • warfarin • randomized controlled trial

Optimal clinical practice and coverage decision making require assessment of the effectiveness and safety of new medications relative to existing treatments,1 but comparative information is often unavailable at the time of marketing authorization and initial use.2 Recently, phase III trials have been completed comparing each of the 3 new oral anticoagulants to warfarin in the treatment of atrial fibrillation (AF). Dabigatran, an oral direct thrombin inhibitor, was more efficacious than warfarin in reducing the risk of stroke when given at a dose of 150 mg BID to patients with nonvalvular AF (hazard ratio [HR], 0.66; 95% CI, 0.53–0.82).3 Rivaroxaban 20 mg QD and apixaban 5 mg BID, both oral factor Xa inhibitors, were found to be noninferior (rivaroxaban: HR, 0.88; 95% CI, 0.74–1.03) and superior (apixaban: HR, 0.79; 95% CI, 0.66–0.95) to warfarin, respectively, in intention-to-treat analyses.4,5 Warfarin’s narrow therapeutic index and risk of interactions, both of which contribute to the need for frequent monitoring, make alternative agents appealing. These new agents also offer a welcome therapeutic option for patients ineligible for warfarin.

In the absence of data from direct comparisons of the new anticoagulants, clinicians and payors attempting to engage in evidence-based decision making are likely to turn to qualitative comparisons of the results from the treatment arms of the 3 trials. Such comparisons may be helpful or they may be inconclusive or misleading because of the differences in trial design and patient populations.7 The formal method of adjusted indirect comparison, which compares treatment effects versus a common comparator, has been proposed as an alternative to simple, naive indirect comparisons.8 Two recent meta-analyses have compared results of adjusted indirect comparisons, such as ours, with subsequent direct comparisons. These meta-analyses have found the results of adjusted indirect and direct comparisons to be generally consistent, with statistically similar findings in 86%8 to 93%7 of cases.
WHAT IS KNOWN?

- Dabigatran, an oral thrombin inhibitor, and rivaroxaban and apixaban, oral factor Xa inhibitors, have been found to be safe and effective in reducing stroke risk in patients with atrial fibrillation compared with warfarin.
- In the absence of data from direct comparisons of these new anticoagulants, adjusted indirect comparison can be used to compare treatment effects using warfarin as a common comparator group.

WHAT THIS STUDY ADDS

- Patients in 3 major warfarin-controlled randomized trials were comparable when limited to those with a CHADS2 score of ≥3.
- We found no statistically significant differences among the 3 drugs in their efficacy in preventing stroke and systemic embolism, although apixaban and dabigatran were numerically superior to rivaroxaban.
- Apixaban produced statistically significant fewer major hemorrhages than dabigatran and rivaroxaban.

In a recent indirect comparison of new oral anticoagulants in patients with AF, the authors failed to assure comparability of trials, as ROCKET-AF required a CHADS2 score ≥2, whereas the other trials also included patients with scores of 0 and 1. Because CHADS2, is a strong predictor of the primary end point in all trials, the findings of such an indirect comparison are likely confounded. They further violated the comparability of trials by contrasting the major bleed rates from an ITT analysis of RE-LY to the results from the on-treatment analyses of ARISTOTLE and ROCKET-AF. We conducted an adjusted indirect comparison using the clinical trial data available on the 3 new anticoagulants, with warfarin as a common reference treatment. To overcome limitations of the previous study, we abstracted additional data so as to compare more similar analyses and patient populations.

Methods

Search Strategy
We searched PubMed and clinicaltrials.gov in October 2011 for all phase III randomized controlled trials (RCTs) of patients receiving apixaban, rivaroxaban, or dabigatran versus warfarin (the only studied common comparison treatment) for the prevention of thrombotic events in AF. We restricted our analysis to studies reporting event rates among warfarin-treated control patients across the different trials, except that ROCKET-AF participants were required to have a CHADS2 score ≥2; this was reflected in the higher proportions of patients with stroke risk factors in both the rivaroxaban and the warfarin control groups of ROCKET-AF (Table 1). The trial populations were similar in age, sex distribution, systolic blood pressure, and prevalence of a history of myocardial infarction at baseline. A higher proportion of warfarin-treated patients in RE-LY were classified as having paroxysmal AF (33.8%) than those in ARISTOTLE (15.5%) or ROCKET-AF (17.8%). Prior vitamin K antagonist use was more common in warfarin users in ROCKET-AF (62.5%) than in those in ARISTOTLE (57.2%) or RE-LY (48.6%).

Stroke or systemic embolism was the primary efficacy end point in all 3 trials. Major bleeding was defined consistently across trials as clinically overt bleeding that occurred at a critical site or bleeding that was accompanied by a drop in hemoglobin of at least 2 g/dL or transfusion of at least 2 units of packed red cells, or death. Major bleeding was the primary safety outcome in ARISTOTLE and RE-LY and was a component of the primary safety outcome of major or nonmajor clinically relevant bleeding in ROCKET-AF. Primary efficacy data were analyzed according to an intention-to-treat principle in all trials, although the ITT analysis was reported as a secondary analysis in ROCKET-AF. Only RE-LY reported results from an ITT analysis as the primary safety analysis; as-treated results were available from all trials. Two-year treatment discontinuation rates in RE-LY were 20.7% for 110 mg dabigatran,
21.2% for 150mg dabigatran, and 16.6% for warfarin; 2-year discontinuation rates in ROCKET-AF were 34.7% for rivaroxaban and 33.5% for warfarin; and total discontinuation rates in ARISTOTLE were 25.3% for apixaban and 27.5% for warfarin.

The trials differed in blinding and warfarin dosing. ROCKET-AF investigators were blinded to anticoagulation group assignment and were provided with real (warfarin arm) or sham (rivaroxaban arm) INR values; ARISTOTLE investigators were similarly blinded to group assignment and were provided with a blinded dose adjustment algorithm and feedback. In contrast, RE-LY investigators were unblinded to warfarin-group status, regulating its dose with advice on INR control. During the trials, INR control was better in the warfarin arms of ARISTOTLE (62% mean time in therapeutic range) and RE-LY (64% mean time in therapeutic range) than in ROCKET-AF (55% mean time in therapeutic range). The stroke and embolism event rate was substantially higher in the warfarin arm of ROCKET-AF (2.42 per 100 patient-years; estimated 95% CI, 2.16–2.71) compared with the arm in RE-LY (1.71 per 100 patient-years; estimated 95% CI, 1.49–1.96) or ARISTOTLE (1.60 per 100 patient-years; estimated 95% CI, 1.42–1.80) (Table 2). These differences were not present when patients with CHADS2 scores ≥3 were compared (Table 3).
Table 2. Users of Dabigatran (RE-LY*), Apixaban (ARISTOTLE), and Rivaroxaban (ROCKET-AF) and Rates of Stroke and Systemic Embolism, Ischemic Stroke, Death of Any Cause, and Major Hemorrhage Compared With Warfarin

<table>
<thead>
<tr>
<th>New Anticoagulant</th>
<th>Warfarin</th>
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<tbody>
<tr>
<td></td>
<td>Event Rate per 100 Person-Years</td>
</tr>
<tr>
<td></td>
<td>Subjects</td>
</tr>
<tr>
<td><strong>Primary efficacy end point: stroke or systemic embolism (intention-to-treat analysis)</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>9120</td>
</tr>
<tr>
<td>Dabigatran 110 mg (RE-LY)</td>
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<tr>
<td>Dabigatran 150 mg (RE-LY)</td>
<td>6076</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)†‡</td>
<td>7081</td>
</tr>
<tr>
<td><strong>Death of any cause (intention-to-treat analysis)</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>9120</td>
</tr>
<tr>
<td>Dabigatran 110 mg (RE-LY)</td>
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<tr>
<td>Dabigatran 150 mg (RE-LY)</td>
<td>6076</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)¶</td>
<td>7081</td>
</tr>
<tr>
<td><strong>Major hemorrhage (on-treatment analysis)</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>9088</td>
</tr>
<tr>
<td>Dabigatran 110 mg (RE-LY)¶</td>
<td>NR</td>
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<tr>
<td>Dabigatran 150 mg (RE-LY)¶</td>
<td>NR</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)#</td>
<td>7111</td>
</tr>
</tbody>
</table>

†95% CIs were estimated using the method for person-time data described in Ref. 15. We estimated person-time by dividing the number of events by the event rate.
‡The primary analysis in ROCKET-AF was per-protocol, restricted to subjects who received at least 1 study dose followed through 2 days after the last dose.
¶The published RE-LY safety analysis was intention-to-treat (hazard ratio, 0.93; 95% CI, 0.81–1.07 for dabigatran 150 mg and hazard ratio, 0.80; 95% CI, 0.69–0.93 for dabigatran 110 mg). Hazard ratios and 95% CIs for the on-treatment analysis were presented in the FDA Advisory Committee briefing documents.
#The primary analysis in ARISTOTLE was per-protocol, restricted to subjects who received at least 1 study dose followed through 2 days after the last dose.
§Mortality rates in ROCKET-AF were published to only 1 decimal point.
||The published RE-LY safety analysis was intention-to-treat (hazard ratio, 0.93; 95% CI, 0.81–1.07 for dabigatran 150 mg and hazard ratio, 0.80; 95% CI, 0.69–0.93 for dabigatran 110 mg). Hazard ratios and 95% CIs for the on-treatment analysis were presented in the FDA Advisory Committee briefing documents.
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**Discussion**

Formal adjusted indirect comparisons of randomized trials can be a useful tool to estimate the comparative efficacy of newly marketed medications before any head-to-head trials or pharmacoepidemiological studies become available, if certain study characteristics are met. We compared all subjects in ARISTOTLE and RE-LY anticoagulant trials, as well as patients with an elevated risk for stroke (CHADS2 ≥3). Among all participants, apixaban had a lower risk of major bleeding than dabigatran, with no significant differences in efficacy. Among patients with CHADS2 ≥3, dabigatran and apixaban trended toward greater efficacy than rivaroxaban, but the differences were not significant. Major bleeding risk on apixaban was significantly less than that on rivaroxaban or dabigatran.

We used intention-to-treat results for efficacy end points and on-treatment analyses for safety end points. Intention-to-treat is arguably the preferred approach for analyzing data from an RCT because it preserves random treatment assignment. The lack of complete intention-to-treat safety data from ARISTOTLE and RE-LY is a limitation. The use of an on-treatment approach with a short risk window of only 2 days after the last dose anticoagulant for the safety analysis raises the possibility that bleeding events attributable to anticoagulant use that manifest after 2 days would have been missed. In RE-LY, where an ITT analysis was reported as the primary safety analysis, the ITT HR for major bleeding for 110 mg dabigatran compared with warfarin was 0.80 (95% CI, 0.69–0.93) versus 0.83 (95% CI, 0.71–0.96) for an...
Table 3. Primary Efficacy and Safety in Subgroups of Trial Patients With CHADS2 Score ≥3

<table>
<thead>
<tr>
<th>New Anticoagulant</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td><strong>Events</strong></td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>2758 94</td>
</tr>
<tr>
<td>Dabigatran 110 mg (RE-LY)‡</td>
<td>1968 82‡</td>
</tr>
<tr>
<td>Dabigatran 150 mg (RE-LY)‡</td>
<td>1981 74‡</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)¶</td>
<td>6156 239</td>
</tr>
<tr>
<td><strong>Major Hemorrhage (on-treatment analysis)</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>NR#</td>
</tr>
<tr>
<td>Dabigatran 110 mg (RE-LY) approximated**</td>
<td>1966 147</td>
</tr>
<tr>
<td>Dabigatran 150 mg (RE-LY) approximated**</td>
<td>1979 188</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)††</td>
<td>6187 337</td>
</tr>
</tbody>
</table>

*95% CIs were estimated using the method for person-time data described in Ref. 15. We estimated person-time by dividing the number of events by the event rate.
†Event rates in ARISTOTLE were published to only 1 decimal point.
‡This analysis does not include the updated data published by Connolly et al in *N Engl J Med*, 2010, as subgroup-specific data were not reported.
§The number of events in this subgroup was not reported in RE-LY; we estimated these by multiplying the number of subjects by the median follow-up time (2.0 years) and then multiplying this by the event rate.
||CIs around the hazard ratio for RE-LY were estimated using the mid-P-value function described in Ref. 15. We estimated person-time by dividing the number of events by the event rate.
¶The primary analysis in ROCKET-AF was per-protocol, restricted to subjects who received at least 1 study dose followed through 2 days after the last dose.
The intention-to-treat analysis of the primary efficacy end point presented here was published as a secondary analysis.
The number of subjects included in the on-treatment analysis was not presented in the publication.
**An on-treatment analysis was not reported for subgroups within RE-LY. The numbers presented here are from the intention-to-treatment analysis presented in the FDA Advisory Committee briefing documents.
††For the ROCKET-AF trial, the number of subjects is greater in the on-treatment safety analysis than in the intention-to-treatment efficacy analysis because the latter excluded data on 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) due to violations in Good Clinical Practice guidelines at 1 participating site. NR indicates not reported.

on-treatment analysis, for 150 mg dabigatran, the ITT HR was 0.93 (0.81–1.07) versus 0.98 (0.85–1.13) for an on-treatment analysis. ARISTOTLE reported a 27% reduction in major bleeding from a secondary ITT analysis compared with a 31% reduction in an on-treatment analysis.

Bucher’s method of adjusted indirect comparisons assumes that the trials are sufficiently similar to one another in terms of potential modifiers of treatment effects, such that the relative efficacy of a given treatment compared with a common comparator would be homogeneous across each of the study populations. This assumption was likely violated for ROCKET-AF, which was restricted to patients with a CHADS2 score ≥2, and therefore restricted our comparisons of rivaroxaban to subgroups with CHADS2 scores ≥3. Reassuringly, event rates in the warfarin comparison groups of all 3 trials among this subgroup were similar. However, it is still possible that other factors, such as the poorer INR control in the warfarin arm of ROCKET-AF, could threaten the validity of our analysis.

Although primary outcome event rates were similar among warfarin-treated patients across trials, the major hemorrhage rate was slightly lower among warfarin-treated patients in the ROCKET-AF trial compared with other trials, raising the possibility that another unobserved factor could influence our results. Data on the baseline characteristics of the subgroups with CHADS2 scores ≥3 were not available, precluding further evaluation of differences in baseline risk.

In addition to clinical similarity, Bucher’s method requires methodological similarity. Biases inherent to each of the trials may cause indirect comparisons to be biased, unless trials are all biased in the same direction and to the same extent. It is not possible to predict the direction and magnitude of bias in specific instances. Although complete blindness reduces bias, the lack of complete blindness in RE-LY may have resulted in its greater mean time in therapeutic range on warfarin, thus increasing the apparent relative effectiveness of warfarin compared with dabigatran. Lack of complete blindness can have a smaller effect on end point ascertainment if objectively measured end points are of interest, as in our study.

Our analysis was limited by the available RCT data. Apixaban has not yet been reviewed by FDA for the indication of thromboembolic event prophylaxis in AF, and thus advisory committee briefing materials are not yet available. Rivaroxaban has not been evaluated in lower-risk patients, and although it was possible to compare rivaroxaban with apixaban and dabigatran in patients with CHADS2 ≥3, this restriction resulted in reduced statistical power.

Adjusted indirect treatment comparisons such as ours generally produce reliable estimates. A recent study found that results of indirect and head-to-head comparisons were statistically similar in 86% of 112 analyses, which covered a wide range of clinical indications, and in only 1 case (<1%) the indirect comparison results were statistically significant and in the opposite direction of the corresponding head-to-head comparison results. Statistical inconsistency was more common when fewer trials were available, outcomes were subjective, and a statistically significant treatment effect was found by either the direct or indirect comparison. Indirect comparisons were less likely to find statistically significant
Power was further limited in our analysis because we focused on a high-risk patient subgroup to enhance comparability across trials. These findings underscore the importance of evaluating clinical and methodological similarity when conducting indirect comparisons, as we have done, and following up initial preapproval trials with rigorously conducted observational studies, which can provide direct comparisons in large populations.

Optimal clinical practice and policy making require assessing the comparative effectiveness of newly approved medications as soon as possible after their market authorization. The 3 new oral anticoagulants that we compared have all been found to be superior or at least noninferior to warfarin in large randomized trials of stroke prevention in patients with AF, and they may be particularly good options for patients ineligible for warfarin or for whom INR monitoring cannot be performed adequately. The differences we found among the new anticoagulants, and between each of them and warfarin, are modest in scale compared with the substantial differences in outcome between no anticoagulant and any anticoagulant in AF patients.

In the absence of head-to-head comparisons from randomized trials or effectiveness studies using routine care data, adjusted indirect comparisons using data from RCTs can provide useful approximations for clinical decision makers, information that can be generated even before a drug is authorized for marketing for a given indication, as with apixaban. By supplementing data published in the medical literature with data from FDA advisory committee briefing documents for dabigatran and rivaroxaban, examining results from secondary and subgroup analyses to increase comparability across trials in study designs and populations, performing a
quantitative evaluation, and highlighting differences between the trials, our analysis provides an improvement over the qualitative comparisons that decision makers may undertake, which may be inconclusive or misleading because of the differences in trial design. Failure to insure comparable populations may bias results. However, the fact that apixaban has not yet been reviewed by FDA for the indication of stroke prophylaxis in AF limits the availability of supplemental data for this particular agent. In the case of the new anticoagulants, our understanding of the relative effectiveness and safety of these drugs may well change in the context of routine care depending on actual adherence patterns, baseline risks of patients who are prescribed these drugs outside of trial criteria, and other real-world differences that may not be predicted by trial results. Follow-up active observational studies that monitor the comparative safety and effectiveness of newly marketed drugs using health care claims data can then provide such follow-up information in a timely manner. Because such studies can themselves take some time to organize and conduct, rigorous comparisons of existing trial data—if feasible and responsibly conducted—may offer the best basis for evidence-based decision making when new drugs are first brought to market.

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References
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SUPPLEMENTAL MATERIAL

Appendix Figure 1: The relative efficacy and safety of dabigatran (150mg), apixaban, and rivaroxaban from adjusted indirect comparisons of three randomized trials. Hazard ratios with 95% confidence intervals. The agent at the head of the arrow is the referent agent (i.e. the denominator term).
A. Primary efficacy (any stroke or systemic embolism, ITT)

Dabigatran$^{110}$

$\text{HR}_{D \text{ vs } A} = 1.14$

(0.87 to 1.49)

Apixaban

$\text{HR}_{A \text{ vs } \text{War}} = 0.79$

B. Safety (major hemorrhage, as treated)

Dabigatran$^{110}$

$\text{HR}_{D \text{ vs } A} = 1.20$

(0.98 to 1.48)

Apixaban

$\text{HR}_{A \text{ vs } \text{War}} = 0.69$
C. Primary efficacy in patients with CHADS$_2 \geq 3$, ITT

- **Dabigatran$_{110}$**
  - $HR_{D \ vs \ War} = 0.79$
  - $HR_{D \ vs \ R} = 0.90$
    - (0.64 to 1.26)
  - $HR_{D \ vs \ A} = 1.16$
    - (0.79 to 1.72)

- **Apixaban**
  - $HR_{A \ vs \ War} = 0.68$

- **Rivaroxaban**
  - $HR_{R \ vs \ War} = 0.88$
  - $HR_{R \ vs \ R} = 0.77$
    - (0.56 to 1.06)

D. Safety (major hemorrhage, as treated) in patients with CHADS$_2 \geq 3$

- **Dabigatran$_{110}$**
  - $HR_{D \ vs \ War} = 0.82$
  - $HR_{D \ vs \ R} = 0.81$
    - (0.62 to 1.06)
  - $HR_{D \ vs \ A} = 1.19$
    - (0.86 to 1.64)

- **Apixaban**
  - $HR_{A \ vs \ War} = 0.69$

- **Rivaroxaban**
  - $HR_{R \ vs \ War} = 1.01$
  - $HR_{R \ vs \ R} = 0.68$
    - (0.52 to 0.90)