Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation: Systematic Review and Meta-Analysis

Ying Bai, PhD; Hai Deng, PhD; Alena Shantsila, PhD; Gregory Y.H. Lip, MD

**Background and Purpose**—This study was designed to evaluate the effectiveness and safety of rivaroxaban in real-world practice compared with effectiveness and safety of dabigatran or warfarin for stroke prevention in atrial fibrillation through meta-analyzing observational studies.

**Methods**—Seventeen studies were included after searching in PubMed for studies reporting the comparative effectiveness and safety of rivaroxaban versus dabigatran (n=3), rivaroxaban versus Warfarin (n=11), or both (n=3) for stroke prevention in atrial fibrillation.

**Results**—Overall, the risks of stroke/systematic thromboembolism with rivaroxaban were similar when compared with those with dabigatran (stroke/thromboembolism: hazard ratio, 1.02; 95% confidence interval, 0.91–1.13; R²=70.2%, N=5), but were significantly reduced when compared with those with warfarin (hazard ratio, 0.75; 95% confidence interval, 0.64–0.85; F²=45.1%, N=9). Major bleeding risk was significantly higher with rivaroxaban than with dabigatran (hazard ratio, 1.38; 95% confidence interval, 1.27–1.49; F²=26.1%, N=5), but similar to that with warfarin (hazard ratio, 0.99; 95% confidence interval, 0.91–1.07; F²=0.0%, N=6). Rivaroxaban was associated with increased all-cause mortality and gastrointestinal bleeding, but similar risk of acute myocardial infarction and intracranial hemorrhage when compared with dabigatran. When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality, and acute myocardial infarction, but a higher risk of gastrointestinal bleeding and lower risk of intracranial hemorrhage.

**Conclusions**—In this systematic review and meta-analysis, rivaroxaban was as effective as dabigatran, but was more effective than warfarin for the prevention of stroke/thromboembolism in atrial fibrillation patients. Major bleeding risk was significantly higher with rivaroxaban than with dabigatran, as was all-cause mortality and gastrointestinal bleeding. Rivaroxaban was comparable to warfarin for major bleeding, with an increased risk in gastrointestinal bleeding and decreased risk of intracranial hemorrhage. (Stroke. 2017;48:970-976. DOI: 10.1161/STROKEAHA.116.016275.)

**Key Words:** atrial fibrillation • dabigatran • real-world data • rivaroxaban • warfarin

The use of oral anticoagulants (OACs), such as the vitamin K antagonists (eg, warfarin), in patients with atrial fibrillation (AF) results in a significant reduction in stroke, ischemic stroke (IS), and systematic thromboembolism (TE), as well as all-cause mortality, when compared with placebo or control.1 However, warfarin has many limitations, including the necessity for regular anticoagulation monitoring, dietary and drug interactions, and the potential for serious bleeding if anticoagulation is poorly controlled, as reflected by a poor time in therapeutic range.2

The availability of the non-vitamin K antagonist oral anticoagulants (NOACs) has changed the landscape for stroke prevention in AF, and a meta-analysis of randomized clinical trials (RCTs) by Ruff et al1 has shown that usual-dose NOACs result in a significant reduction in stroke/TE and mortality with NOACs compared with warfarin, with a trend toward less major bleeding and significantly lower intracranial hemorrhage (ICH). However, RCTs have specific inclusion/exclusion criteria, have set protocol-based follow-up, and perhaps represent a highly selected and controlled scenario, but still represent the gold standard of testing the effectiveness and safety of an intervention. Based on RCT data, indirect comparisons have been published showing how the different NOACs may perform relative to each other,4,5 but only a head-to-head RCT can definitively assess the relative efficacy and safety of one NOAC against another.

When a drug is licensed and used in everyday clinical practice, these drugs are then prescribed to a broad spectrum of...
patients, beyond the selected population studied in RCTs.6
Since the publication of the RCT data and regulatory approval
of these drugs (rivaroxaban and dabigatran), numerous real-
world observational cohorts showing the comparative effec-
tiveness and safety of the NOACs have been published.7–12
Our objective was to perform a systematic review and meta-
analysis of data on the effectiveness and safety of rivaroxaban
in real-world practice compared with those of dabigatran or
warfarin for stroke prevention in AF.

Methods
We followed the PRISMA (preferred reporting items for
systematic reviews and meta-analyses) and the reporting MOOSE (Meta-
analyses of Observational Studies in Epidemiology) when performing
this meta-analysis.13,14
Two independent reviewers (Y. Bai and H. Deng) conducted a
search of Medline and the Cochrane Library using the following
items: atrial fibrillation, AF, rivaroxaban, dabigatran, warfarin, real-
world, observational studies until October 4, 2016, respectively. We
also reviewed the lists of references in eligible studies and reviews.
Disagreement was resolved by consensus.
To be included in the meta-analysis, the observational studies
needed to fulfill the following criteria: (1) with OACs used for stroke
prevention in patients with AF; (2) available quantitative data on clini-
cal events; and (3) adjusted hazard ratios (HRs) between rivaroxaban
versus dabigatran or rivaroxaban versus warfarin for stroke preven-
tion in AF. The following studies were excluded:
1. Animal-based studies
2. Non-English-based papers
3. Abstracts, editorials, case reports, reviews, and case series
4. Specific studies on AF patients undergoing ablation or
   cardioversion
We recorded clinical events related to effectiveness outcomes as IS,
TE, the combination of stroke and TE (stroke/TE), and acute myocard-
ial infarction (AMI) of rivaroxaban in comparison with dabigatran
or warfarin. Separate IS, hemorrhagic stroke, stroke, or TE outcomes
were used instead if no data on stroke/TE were available in the origi-
nal papers. Safety outcomes were major bleeding, any bleeding, ICH,
gastrointestinal bleeding (GIB), or all-cause mortality. Definitions of
these effectiveness and safety outcomes were extracted from the origi-
nal papers. If available, other collected study characteristics included
authors, publication year, study country, period, cohort size, percent-
age of new users or switchers of NOACs, and estimated follow-up duration.
Quality score for each study was assessed by the Newcastle–Ottawa
scale.15

Statistical Analysis
The analysis was conducted using STATA, version 12.0 (Stata
Corp). Event rates of various outcomes were evaluated using count
of events/person-years of observation. Adjusted HRs with 95% con-
fidence intervals (95% CI) was used to measure the effect sizes in

Table 1. Baseline Characteristics in Rivaroxaban Versus Dabigatran Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Region</th>
<th>Enrolled Period</th>
<th>Cohort Size</th>
<th>LD-R, %</th>
<th>LD-D, %</th>
<th>eFollow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al12</td>
<td>Taiwan</td>
<td>February to December 2013</td>
<td>9837</td>
<td>87</td>
<td>90</td>
<td>1 y</td>
</tr>
<tr>
<td>Hernandez and Zhang13</td>
<td>US</td>
<td>November 2011 to December 2013</td>
<td>17507</td>
<td>30.7</td>
<td>24.8</td>
<td>1 y</td>
</tr>
<tr>
<td>Graham et al9</td>
<td>US</td>
<td>November 2011 to June 2014</td>
<td>118891</td>
<td>0</td>
<td>0</td>
<td>0.3 y</td>
</tr>
<tr>
<td>Lip et al12</td>
<td>US</td>
<td>January 2012 to December 2014</td>
<td>46803</td>
<td>19.6</td>
<td>10.6</td>
<td>0.5 y</td>
</tr>
<tr>
<td>Noseworthy et al11</td>
<td>US</td>
<td>October 2010 to February 2015</td>
<td>31574</td>
<td>23.1</td>
<td>9.9</td>
<td>NA</td>
</tr>
<tr>
<td>Gorst-Rasmussen et al6</td>
<td>Denmark</td>
<td>February 2012 to July 2014</td>
<td>11313</td>
<td>32.3</td>
<td>40.3</td>
<td>1.08 y</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics in Rivaroxaban Versus Dabigatran Studies

We recorded clinical events related to effectiveness outcomes as IS,
TE, the combination of stroke and TE (stroke/TE), and acute myocard-
ial infarction (AMI) of rivaroxaban in comparison with dabigatran
or warfarin. Separate IS, hemorrhagic stroke, stroke, or TE outcomes
were used instead if no data on stroke/TE were available in the origi-
nal papers. Safety outcomes were major bleeding, any bleeding, ICH,
gastrointestinal bleeding (GIB), or all-cause mortality. Definitions of
these effectiveness and safety outcomes were extracted from the origi-
nal papers. If available, other collected study characteristics included
authors, publication year, study country, period, cohort size, percent-
age of new users or switchers of NOACs, and estimated follow-up duration.
Quality score for each study was assessed by the Newcastle–Ottawa
scale.15

Comparison Between Rivaroxaban and Dabigatran

Rivaroxaban was associated with a similar risk of stroke/TE
compared with dabigatran11–13 (HR, 1.02; 95% CI, 0.91–1.13;
I²=70.2%, N=5; Figure 1), with pooled rates for rivaroxaban
being 0.3%/year versus dabigatran 0.3%/year. No significant
publication bias was seen among the included studies using
Begg’s test (P=0.21) and Egger’s test (P=0.25). Subanalysis
was performed through pooling 3 studies evaluating the IS risk
between rivaroxaban and dabigatran.9–11 which was nonsig-
ificantly different (HR, 0.98; 95% CI, 0.88–1.08; I²=46.0%;
P=0.12; Figure II in the online-only Data Supplement), with

Results
A total of 1086 studies were initially identified (including 829
online and 257 from references). After screening titles and
abstracts, we excluded 1007 papers and 79 remained for a
detailed evaluation. Of these studies, 62 were excluded as they
did not meet the inclusion criteria (6 were reviews and meta-
analysis); 25 studies on OACs in specific AF populations, such
as ablation or cardioversion, were excluded because of their
modest size and short period of follow-up (<30 days). Also,
12 papers lacked outcome data in AF patients. Comparison
of separate data for rivaroxaban with warfarin could not be
extracted from 2 papers; adjusted HRs between OAC compari-
sions were lacking in 16; no separate AF data could be extracted
from 1 paper with mixed disease states. Finally, 17 observa-
tional studies7–12,20–31 were included in our analysis, with 3
comparing rivaroxaban versus dabigatran9–11 11 comparing
rivaroxaban versus Warfarin.20–27,29–31 and 3 evaluating both
comparisons.7,8,12 Studies with new users and switchers are
shown in Table I in the online-only Data Supplement. Quality
scoring revealed moderate-to-high scores of the included
studies. The selection process and baseline characteristics of
included studies are summarized in Figure I in the online-only
Data Supplement and Tables 1 and 2. Anticipated outcomes
evaluated are summarized in Table II in the online-only Data
Supplement. The end points in various comparison settings are
shown in Table III in the online-only Data Supplement.

Comparisons Between Rivaroxaban and Dabigatran

Rivaroxaban was associated with a similar risk of stroke/TE
compared with dabigatran11–13 (HR, 1.02; 95% CI, 0.91–1.13;
I²=70.2%, N=5; Figure 1), with pooled rates for rivaroxaban
being 0.3%/year versus dabigatran 0.3%/year. No significant
publication bias was seen among the included studies using
Begg’s test (P=0.21) and Egger’s test (P=0.25). Subanalysis
was performed through pooling 3 studies evaluating the IS risk
between rivaroxaban and dabigatran.9–11 which was nonsig-
ificantly different (HR, 0.98; 95% CI, 0.88–1.08; I²=46.0%;
P=0.12; Figure II in the online-only Data Supplement), with
pooled rates for rivaroxaban being 0.57%/year versus dabigatran 0.54%/year. No significant publication bias was seen among the included studies using Begg’s test (P=0.46) and Egger’s test (P=0.08).

The pooled rate of major bleeding was 1.45%/year for rivaroxaban and 0.55%/year for dabigatran. Major bleeding risk was significantly higher with rivaroxaban than with dabigatran after pooling the 5 studies7,9–12 (HR, 1.38; 95% CI, 1.27–1.49; I²=26.1%, N=5; Figure 2). No significant publication bias was seen among the included studies using Begg’s test (P=0.76) and Egger’s test (P=0.39).

Rivaroxaban was associated with increased risk in all-cause mortality7–10 (HR, 1.23; 95% CI, 1.12–1.33; I²=31.5%, N=4), any bleeding8–10 (HR, 1.33; 95% CI, 1.17–1.49; I²=74.8%, N=3), and GIB7,9,10 (HR, 1.33; 95% CI, 1.18–1.48; I²=58.3%, N=3), but similar risk of AMI7–10 (HR, 0.81; 95% CI, 0.43–1.19; I²=0.0%, N=2) and ICH7–9,10 (HR, 1.22; 95% CI, 0.85–1.59; I²=64.5%, N=4) when compared with dabigatran.

Comparisons Between Rivaroxaban and Warfarin

The pooled annual rate of stroke/TE was 2.57%/year for rivaroxaban and 2.86%/year for warfarin in AF patients (HR, 0.75; 95% CI, 0.64–0.85; I²=45.1%, N=9; Figure 37,8,21,22,25,26,29–31). Subgroup analysis was performed through meta-analyzing 6 observational studies evaluating IS risk between rivaroxaban and warfarin20,22,25,26,30,31 and rivaroxaban was found to be associated with lower risk of IS (HR, 0.86; 95% CI, 0.75–0.97; I²=0.0%, N=6; Figure III in the online-only Data Supplement). No publication bias was seen according to Begg’s test (IS, P=1.0; stroke/SE, P=0.37) and Egger’s test (IS, P=0.87; stroke/SE, P=0.1).

The pooled rate of major bleeding was 3.70%/year for rivaroxaban and 3.73%/year for warfarin, based on meta-analysis of 6 studies (HR, 0.99; 95% CI, 0.91–1.07; I²=0.0%, N=6; Figure 47,12,24–26,30) No publication bias was seen in this study according to Begg’s test (P=0.26) and Egger’s test (P=0.22).

Rivaroxaban was associated with similar risk of any bleeding (HR, 1.01; 95% CI, 0.94–1.08; I²=0.0%, N=5),7,8,21,22,25,26,29 AMI (HR, 0.73; 95% CI, 0.30–1.15; I²=0.0%, N=2),7,21 and all-cause mortality (HR, 1.04; 95% CI, 0.64–1.44; I²=92.7%, N=3),7,8,26 compared with warfarin. The risk of ICH was significantly lower (HR, 0.54; 95% CI, 0.43–0.64; I²=63.6%, N=6),7,22,24,26,30 but risk of GIB was significantly higher (HR, 9.35).

### Table: Comparison of Rivaroxaban and Warfarin

<table>
<thead>
<tr>
<th>Study Year (Dose)</th>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan,2016(BD)</td>
<td></td>
<td>1.20 (0.87, 1.58)</td>
<td>4.54</td>
</tr>
<tr>
<td>Hernandez,2016(LD)</td>
<td></td>
<td>1.51 (1.25, 1.82)</td>
<td>11.61</td>
</tr>
<tr>
<td>Hernandez,2016(HD)</td>
<td></td>
<td>1.32 (1.17, 1.50)</td>
<td>24.60</td>
</tr>
<tr>
<td>Graham,2016(LD)-major ECH</td>
<td></td>
<td>1.58 (1.32, 1.90)</td>
<td>11.29</td>
</tr>
<tr>
<td>Graham,2016(HD)</td>
<td></td>
<td>1.46 (1.32, 1.67)</td>
<td>22.98</td>
</tr>
<tr>
<td>Lip,2016(BD)</td>
<td></td>
<td>1.05 (0.74, 1.49)</td>
<td>7.34</td>
</tr>
<tr>
<td>Noseworthy,2016(BD)</td>
<td></td>
<td>1.30 (1.10, 1.53)</td>
<td>17.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.36 (1.27, 1.49)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 1.** Rivaroxaban compared with dabigatran in risk of stroke/TE in AF patients. AF indicates atrial fibrillation; BD, both dose; CI, confidence interval; HD, high dose; HR, hazard ratio; IS, ischemic stroke; LD, low dose; and TE, thromboembolism.

**Figure 2.** Rivaroxaban compared with dabigatran in risk of major bleeding in AF patients. AF indicates atrial fibrillation; BD, both dose; ECH, extracranial hemorrhage; HD, high dose; HR, hazard ratio; and LD, low dose.
1.2; 95% CI, 1.07–1.33; I^2=27.5%, N=5)\(^7,20,24,25,30\) with rivaroxaban compared with warfarin.

### Sensitivity Analysis

The results were consistent among studies for both low-dose and high-dose rivaroxaban versus dabigatran comparisons on the clinical outcomes, except for the end point of AMI, where studies did not report on low-dose rivaroxaban versus dabigatran comparisons (Figure IV in the online-only Data Supplement).

The risk of stroke/TE was similar (HR, 1.08; 95% CI, 0.95–1.21; I^2=70.7%, N=4)\(^7–10\) when we conducted sensitivity analysis, including studies with NOAC (rivaroxaban versus dabigatran) new users. When sensitivity analysis was performed for new users of rivaroxaban versus warfarin, there was general consistency with the summary comparisons. Although new users of rivaroxaban showed significant reductions in IS (HR, 0.85; 95% CI, 0.72–0.97), stroke/TE (HR, 0.78; 95% CI, 0.69–0.87), and ICH (HR, −0.64; 95% CI, 0.51–0.77). No significant difference in major bleeding, any bleeding, mortality, and GIB was evident among new users (Figure V and Tables I and III in the online-only Data Supplement).

For other end points, the results were broadly similar with the summary analysis except for an increased risk of mortality in low-dose rivaroxaban and similar risk of IS in high-dose rivaroxaban, when compared with warfarin (Figure VI in the online-only Data Supplement).

To minimize any confusion, we also show that numbers needed to treat and numbers needed to harm were calculated for the absolute effectiveness and safety comparison.

### Discussion

This systematic review and meta-analysis using real-world observational studies has the following principal findings: (1) when compared with dabigatran, rivaroxaban had similar risks of IS, stroke/TE, AMI, and ICH, but increased risks of major bleeding, any bleeding, and GIB; (2) when compared with warfarin, rivaroxaban was associated with lower risks of IS, stroke/TE, and ICH, with an increased risk of GIB, and similar risks of major bleeding, any bleeding, and mortality; and (3) new users of rivaroxaban had superiority to warfarin for the prevention of IS and stroke/TE and a lower risk of ICH, but similar risk of GIB.

Our results are partially discordant from previous indirect comparisons of R versus D for the risk of stroke/TE and major bleeding in AF patients.\(^4,5\) The large randomized trials\(^22,33\) differed in inclusion criteria based on stroke risk profile. Bias could easily be produced with unadjusted confounding, which was considered but unresolved in previous indirect
Table 2. Baseline Characteristics in Rivaroxaban Versus Warfarin Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>Region</th>
<th>Enrolled Period</th>
<th>Cohort Size</th>
<th>LD-R, %</th>
<th>eFollow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouillon et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>RC</td>
<td>France</td>
<td>January 2011 to November 2012</td>
<td>17 410</td>
<td>NA</td>
<td>0.8 y</td>
</tr>
<tr>
<td>Coleman et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>January 2012 to October 2014</td>
<td>38 831</td>
<td>17.3</td>
<td>NA</td>
</tr>
<tr>
<td>Lip et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>January to December 2013</td>
<td>29 338</td>
<td>NA</td>
<td>0.3 y</td>
</tr>
<tr>
<td>Abraham et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>November 2010 to September 2013</td>
<td>219 027</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maura et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>RC</td>
<td>France</td>
<td>July to November 2012</td>
<td>32 807</td>
<td>38.5</td>
<td>0.2 y</td>
</tr>
<tr>
<td>Coleman et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>RC</td>
<td>Germany</td>
<td>January 2012 to October 2013</td>
<td>5108</td>
<td>NA</td>
<td>0.5 y</td>
</tr>
<tr>
<td>Halvorsen et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Registry</td>
<td>Norway</td>
<td>November 13 to June 2015</td>
<td>32 675</td>
<td>27</td>
<td>0.5 y</td>
</tr>
<tr>
<td>Chan et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RC</td>
<td>Taiwan</td>
<td>November 13 to December 2013</td>
<td>304 252</td>
<td>87</td>
<td>1 y</td>
</tr>
<tr>
<td>Larsen et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>RC</td>
<td>Denmark</td>
<td>August 2011 to October 2015</td>
<td>61 678</td>
<td>0</td>
<td>1.9 y</td>
</tr>
<tr>
<td>Yao et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>October 2010 to June 2015</td>
<td>125 243</td>
<td>21.5</td>
<td>0.6 y</td>
</tr>
<tr>
<td>Laliberte et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>May 2011 to July 2012</td>
<td>30 479</td>
<td>NA</td>
<td>0.3 y</td>
</tr>
<tr>
<td>Lip et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>RC</td>
<td>US</td>
<td>January 2012 to December 2014</td>
<td>33 262</td>
<td>NA</td>
<td>0.5 y</td>
</tr>
<tr>
<td>Gorst-Rasmussen et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Registry</td>
<td>Denmark</td>
<td>November 2012 to February 2014</td>
<td>22 358</td>
<td>32.3</td>
<td>1.08 y</td>
</tr>
<tr>
<td>Staerk et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Registry</td>
<td>Denmark</td>
<td>November 2011–2015</td>
<td>43 299</td>
<td>NA</td>
<td>0.6 y</td>
</tr>
</tbody>
</table>

Data were presented as mean or median. eFollow-up indicates estimated follow-up; LD-R, low-dose rivaroxaban; NA, not available; RC, retrospective cohort; and y, years.

comparison analyses. In contrast, our included real-world studies have used adjusted HRs and compared subjects with broadly similar stroke risks taking rivaroxaban or dabigatran during the same time period within each study.

Different percentages of patients received low-dose NOACs in the published real-world studies (eg, for low-dose rivaroxaban and dabigatran: nearly 90% in Hernandez et al<sup>10</sup> and ≈30% in Chan et al<sup>7</sup>). However, there were generally consistent results between low-dose and high-dose rivaroxaban versus dabigatran in most clinical outcomes.

Our findings provide an estimate of the various anticipated outcomes of rivaroxaban when used in everyday clinical practice compared with warfarin. Rivaroxaban was a noninferior alternative to warfarin in IS and stroke/TE prevention. Although the results were similar to the summary data, low-dose and high-dose rivaroxaban versus warfarin data were limited when the sensitivity analysis was done. Our results also provide some insights regarding whether to switch patients from warfarin to NOACs. Rivaroxaban new users showed superior effectiveness to warfarin for IS and stroke/TE prevention, but switchers showed similar risks. The exact reason(s) are unknown, but could be partly explained by the assumption of poor compliance for OACs in those switched from warfarin because usually AF patients would be transferred to take rivaroxaban for poor compliance to warfarin for IS and stroke/TE prevention, but switchers showed similar risks.

In safety evaluations, both ROCKET-AF<sup>10</sup> and our analysis have shown that patients treated with rivaroxaban have increased GIB risk and decreased ICH risk compared with those treated with warfarin. An ancillary analysis of ROCKET-AF has ascribed the higher GIB to a history of GIB or older age.<sup>34</sup> Our results could partially provide supportive evidence for this hypothesis because new rivaroxaban users had a similar risk of GIB compared with warfarin users, with GIB risk evaluated using HRs adjusted for age and bleeding history, within the included studies.<sup>20,24</sup> ICH is the most feared complication for OACs, and consistent with trial data, we show that rivaroxaban users had significantly less ICH compared with warfarin users.

Limitations and Strengths

To our knowledge, this is the first meta-analysis of the head-to-head comparison among NOACs. There are several limitations inherent to the interpretation of these results. First, only studies in English were included for the analysis, which increased the potential language bias. However, a tendency toward publication in English journals minimized this effect.<sup>35</sup> Second, high heterogeneity across studies in stroke/TE should not be neglected, though a random effects model was used for adjustment. Nonetheless, results were broadly similar even if sensitivity analysis (eg, new users or different dose prescription) and subgroup analysis in IS, which decreased the heterogeneity, were performed. Third, different inclusion/exclusion criteria and follow-up periods in the included studies led to high heterogeneity, so it is necessary to cautiously interpret the noticeable differences in some event rates between the rivaroxaban versus dabigatran cohort and rivaroxaban versus warfarin comparisons (eg, stroke/TE rate 0.3%/year in the former versus 2.8%/year in the latter; major bleeding was 1.45%/year in the former versus 3.89%/year in the latter). To provide some perspective, we also show numbers needed to treat and numbers needed to harm for the absolute effectiveness and safety comparisons in Table IV in the online-only Data Supplement. Fourth, inherent limitations in the majority of meta-analysis, such as lack of access to raw data and the variety in definitions of outcomes in the included studies are unavoidable. However, we have enhanced the robustness of
the analysis through extracting the effect sizes with adjusted HRs from the original studies. Indeed, low heterogeneity in the safety evaluations enhances the clinical applicability of our observations. No publication bias and the moderate-to-high quality scores according to Newcastle–Ottawa scale both increase the reliability of the pooled estimate. Finally, the analysis covers the whole population of AF patients and no separate outcome information could be extracted for some subgroups, for example, patients with TIA or prior stroke.

Conclusions

In this systematic review and meta-analysis, rivaroxaban was as effective as dabigatran for the prevention of IS and stroke/TI in AF patients, but was more effective than warfarin for stroke prevention in AF patients. Major bleeding risk was significantly higher with rivaroxaban than with dabigatran, as was all-cause mortality and GIB. Rivaroxaban was comparable to warfarin for major bleeding, with an increased risk in GIB and decreased risk of ICH.

Hence, the risks and benefits of rivaroxaban use should be carefully accounted for, especially the individual's risk of GIB. Based on the real-world evidence to date, rivaroxaban was not superior to dabigatran for stroke prevention in AF patients, but had more bleeding risks.

Acknowledgments

This work was conducted independent of any industry collaboration or sponsorship.

Disclosures

Dr Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daichii-Sankyo. The other authors report no conflicts.

References


Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation: Systematic Review and Meta-Analysis
Ying Bai, Hai Deng, Alena Shantsila and Gregory Y.H. Lip

*Stroke*. 2017;48:970-976; originally published online February 17, 2017;
doi: 10.1161/STROKEAHA.116.016275

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/4/970

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2017/02/15/STROKEAHA.116.016275.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* 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 *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/
ONLINE SUPPLEMENT
Rivaroxaban vs. Dabigatran or warfarin in ‘real-world’ studies of stroke prevention in atrial fibrillation: Systematic review and meta-analysis

Ying Bai, PhD, Hai Deng, Alena Shantsila, PhD, Gregory Y H Lip, MD, FRCP

Supplemental Tables Page 2
Supplemental Figures Page 6
SUPPLEMENTAL TABLES

Table I

New starters and Switchers in Rivaroxaban versus Warfarin studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>New</th>
<th>Switch</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouillon, 2015(^1)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Coleman, 2016(^2)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lip, 2016(^3)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Abraham, 2016(^4)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Maura, 2015(^5)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Coleman, 2015(^6)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Halvorsen, 2016(^7)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Chan, 2016(^8)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Larsen, 2016(^9)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Yao, 2016(^10)</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Laliberte, 2014(^11)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lip, 2016(^12)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Gorst-Rasmussen, 2016(^13)</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Staerk, 2016(^14)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
## Table II Various outcomes included in studies of Rivaroxaban versus Warfarin

<table>
<thead>
<tr>
<th>Author, year</th>
<th>IS</th>
<th>Stroke/TE</th>
<th>major bleeding</th>
<th>any bleeding</th>
<th>AMI</th>
<th>ICB</th>
<th>GIB</th>
<th>All-cause mortality</th>
<th>Other clinical events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouillon, 2015&lt;sup&gt;1&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Composite events, composite events</td>
</tr>
<tr>
<td>Coleman, 2016&lt;sup&gt;2&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>Combined IS and ICH</td>
</tr>
<tr>
<td>Lip, 2016&lt;sup&gt;3&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>IS/TE/death</td>
</tr>
<tr>
<td>Abrham, 2016&lt;sup&gt;4&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalized for bleeding/death</td>
</tr>
<tr>
<td>Maura, 2015&lt;sup&gt;5&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Composite end</td>
</tr>
<tr>
<td>Coleman, 2015&lt;sup&gt;6&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>CRNM</td>
</tr>
<tr>
<td>Halvorsen, 2016&lt;sup&gt;7&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>IS/TE/death</td>
</tr>
<tr>
<td>Chan, 2016&lt;sup&gt;8&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>hemorrhagic stroke</td>
</tr>
<tr>
<td>Larsen, 2016&lt;sup&gt;9&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hemorrhagic stroke</td>
</tr>
<tr>
<td>Yao X, 2016&lt;sup&gt;10&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>TE</td>
</tr>
<tr>
<td>Laliberte, 2014&lt;sup&gt;11&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>VTE</td>
</tr>
<tr>
<td>Lip, 2016&lt;sup&gt;12&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DVT</td>
</tr>
<tr>
<td>Gorst-Rasmussen, 2016&lt;sup&gt;13&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PE with or without DVT</td>
</tr>
<tr>
<td>Staerk, 2016&lt;sup&gt;14&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>net clinical benefit</td>
</tr>
</tbody>
</table>

IS, ischemic stroke; TE, thromboembolism; AMI, acute myocardial infarction; GIB, gastrointestinal bleeding; ICB, intracranial bleeding; CRNM, clinically relevant non-major bleeding; VTE, venous thromboembolism; DVT, deep venous thromboembolism; PE, pulmonary embolism.
<table>
<thead>
<tr>
<th></th>
<th>IS</th>
<th>Stroke/TE</th>
<th>Major bleeding</th>
<th>Any bleeding</th>
<th>Mortality</th>
<th>AMI</th>
<th>GIB</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>R vs. D</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
<td>→</td>
</tr>
<tr>
<td>R vs. W</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>R vs. D(LD)</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>R vs. D(HD)</td>
<td>→</td>
<td>→</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>R vs. W(LD)</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>R vs. W(HD)</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>R vs. W(New)</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>R vs. W(Switch)</td>
<td>→</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IS, ischemic stroke; TE, thromboembolism; AMI, acute myocardial infarction; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; R vs. D, rivaroxaban versus dabigatran; R vs. W, rivaroxaban versus warfarin; R vs. D(LD), low-dose rivaroxaban versus low-dose dabigatran; R vs. D (HD), high-dose rivaroxaban versus high-dose dabigatran; R vs. W(LD), low-dose rivaroxaban versus warfarin; R vs. W(HD), high-dose rivaroxaban versus warfarin; R vs. W(New), rivaroxaban new-users versus warfarin; R vs. W(Switcher), rivaroxaban switcher versus warfarin; →, similar risk; ↑, increased risk; ↓, decreased risk; blanket indicates not available; Other abbreviations see footnotes in Table II.
Table IV Number needed to treat or number needed to harm of rivaroxaban compared with dabigatran or warfarin on the risk of stroke/systematic thromboembolism and major bleeding

<table>
<thead>
<tr>
<th>I-agent</th>
<th>C-agent</th>
<th>outcomes</th>
<th>No.of patients in I-agent arm</th>
<th>No.of patients in C-agent arm</th>
<th>IR of I-agent</th>
<th>IR of C-agent</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
<td>Stroke/TE</td>
<td>122,497</td>
<td>104,724</td>
<td>0.296(0.238-0.355)</td>
<td>0.296(0.242-0.350)</td>
<td>+∞</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>137,893</td>
<td>100,477</td>
<td>1.452(1.304-1.600)</td>
<td>0.550(0.469-0.632)</td>
<td></td>
<td>111</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>Stroke/TE</td>
<td>58,769</td>
<td>157,118</td>
<td>2.569(1.817-3.321)</td>
<td>2.856(1.968-3.744)</td>
<td>348</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>55,555</td>
<td>98,366</td>
<td>3.705(2.770-4.640)</td>
<td>3.733(2.970-4.495)</td>
<td></td>
<td>3571</td>
</tr>
</tbody>
</table>

Stroke/TE, stroke and systematic thromboembolism; NNT, number needed to treat; NNH, number needed to harm; I-agent, interest-agent; C-agent, control-agent; IR, incidence rate; +∞, without upper limit.
Figure I Study selection process.
OACs, oral anticoagulants; R vs. D, rivaroxaban versus dabigatran; R vs. W, rivaroxaban versus warfarin; AF, atrial fibrillation.
Figure II Rivaroxaban compared with Dabigatran for risk of IS in AF patients.
IS, ischemic stroke; LD, low-dose; HD, high-dose; BD, both-dose; AF, atrial fibrillation.
Figure III Rivaroxaban compared with Wafarin in risk of IS in AF patients.
IS, ischemic stroke; AF, atrial fibrillation.
Figure IV Comparisons between HD- Rivaroxaban vs. HD- Dabigatran and LD-Rivaroxaban vs. LD-Dabigatran in various outcomes in AF patients.

IS, ischemic stroke; TE, thromboembolism; AMI, acute myocardial infarction; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; LD, low-dose; HD, high-dose; HR, hazard ratio.
**Figure V Rivaroxaban new users/switchers compared with warfarin in various outcomes in AF patients.**

IS, ischemic stroke; TE, thromboembolism; AMI, acute myocardial infarction; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; HR, hazard ratio.
Figure VI Rivaroxaban at different doses compared with warfarin for various outcomes in AF patients.

IS, ischemic stroke; TE, thromboembolism; AMI, acute myocardial infarction; ICH, intracranial hemorrhage; HR, hazard ratio.
References


