Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation

Systematic Review and Meta-Analysis

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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; I^2=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; I^2=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; I^2=26.1%, N=5), but similar to that with warfarin (hazard ratio, 0.99; 95% confidence interval, 0.91–1.07; I^2=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 al[3] 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

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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 effectiveness 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 clinical events; and (3) adjusted hazard ratios (HRs) between rivaroxaban versus dabigatran or rivaroxaban versus warfarin for stroke prevention 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 myocardial 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 original 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 original papers. If available, other collected study characteristics included authors, publication year, study country, period, cohort size, percentage of low-dose rivaroxaban, percentage of low-dose dabigatran, 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% confidence intervals (95% CI) was used to measure the effect sizes in our study. First we used a fixed model and then a random effects model if there was heterogeneity according to I^2 index.[16] Values of ≤25%, 25% to 50%, and ≥50% were defined as low, moderate, and high degrees of heterogeneity, respectively. Begg's correlation test and Egger's regression test were used to assess publication bias.[17–19] Sensitivity analyses were performed in dose-categorized comparisons of NOACs and new user/switcher settings. $P<0.05$ was taken as statistically significant.

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 comparisons were lacking in 16; no separate AF data could be extracted from 1 paper with mixed disease states. Finally, 17 observational studies[7–12,20–31] were included in our analysis, with 3 comparing rivaroxaban versus dabigatran,[9–11] 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 dabigatran[7–11] (HR, 1.02; 95% CI, 0.91–1.13; I^2=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 nonsignificantly different (HR, 0.98; 95% CI, 0.88–1.08; I^2=46.0%; P=0.12; Figure II in the online-only Data Supplement), with

Table 1. Baseline Characteristics in Rivaroxaban Versus Dabigatran Studies

Author, year	Region	Enrolled Period	Cohort Size	LD-R, %	LD-D, %	eFollow-Up
Chan et al[7]	Taiwan	February to December 2013	9837	87	90	1 y
Hernandez and Zhang[10]	US	November 2011 to December 2013	17507	30.7	24.8	1 y
Graham et al[9]	US	November 2011 to June 2014	118891	0	0	0.3 y
Lip et al[12]	US	January 2012 to December 2014	46803	19.6	10.6	0.5 y
Noseworthy et al[11]	US	October 2010 to February 2015	31574	23.1	9.9	NA
Gorst-Rasmussen et al[8]	Denmark	February 2012 to July 2014	11313	32.3	40.3	1.08 y

eFollow-up indicates estimated follow-up; LD-D, low-dose dabigatran; LD-R, low-dose rivaroxaban; NA, not available; and y, years.

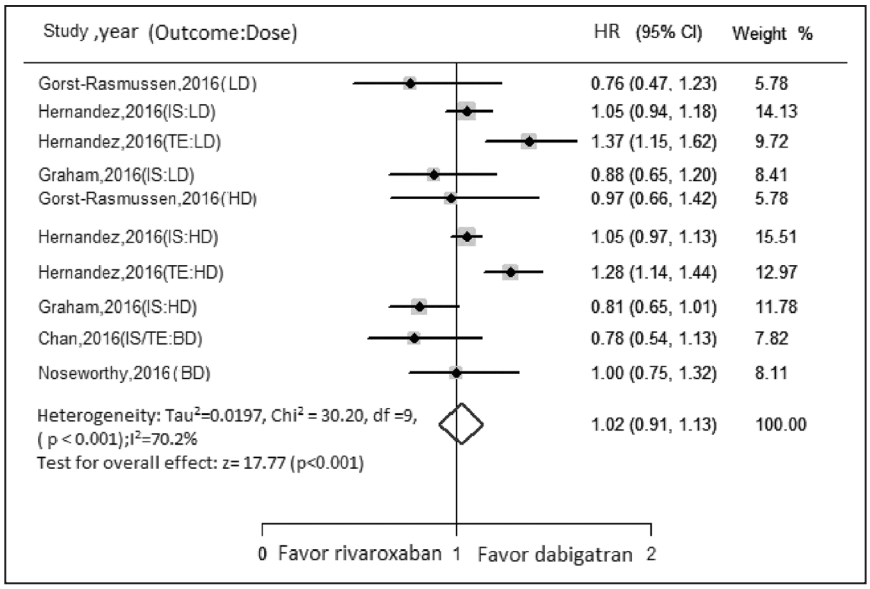

Figure 1. Rivaroxaban compared with dabigatran in risk of stroke/TE in AF patients. AF indicates atrial fibrillation; BD, both dose; CI, confidence interval; HD, high dose; HR, hazard ratio; IS, ischemic stroke; LD, low dose; and TE, thromboembolism.

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 studies[7,9–12] (HR, 1.38; 95% CI, 1.27–1.49; I^2=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 mortality[7–10] (HR, 1.23; 95% CI, 1.12–1.33; I^2=31.5%, N=4), any bleeding[8–10] (HR, 1.33; 95% CI, 1.17–1.49; I^2=74.8%, N=3), and GIB[7,9,10] (HR, 1.33; 95% CI, 1.18–1.48; I^2=58.3%, N=3), but similar risk of AMI[7,9] (HR, 0.81; 95% CI, 0.43–1.19; I^2=0.0%, N=2) and ICH[7,9–11] (HR, 1.22; 95% CI, 0.85–1.59; I^2=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; I^2=45.1%, N=9; Figure 3[7,8,21,22,25,26,29–31]). Subgroup analysis was performed through meta-analyzing 6 observational studies evaluating IS risk between rivaroxaban and warfarin,[20,22,25,26,30,31] and rivaroxaban was found to be associated with lower risk of IS (HR, 0.86; 95% CI, 0.75–0.97; I^2=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; I^2=0.0%, N= 6; Figure 4[7,12,24–26,30]) 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; I^2=0.0%, N=5),[8,21,24,26,29] AMI (HR, 0.73; 95% CI, 0.30–1.15; I^2=0.0%, N=2),[7,21] and all-cause mortality (HR, 1.04; 95% CI, 0.64–1.44; I^2=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; I^2=63.6%, N=6),[7,22,24–26,30] but risk of GIB was significantly higher (HR,

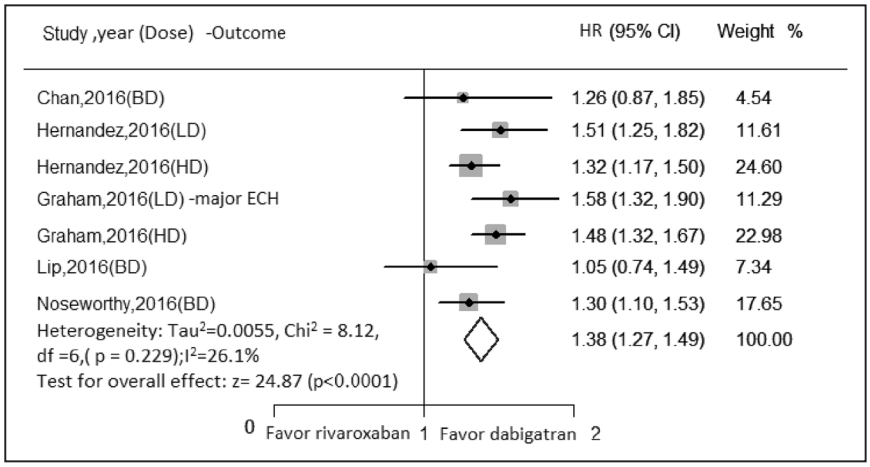

Figure 2. Rivaroxaban compared with dabigatran in risk of major bleeding in AF patients. AF indicates atrial fibrillation; BD, both dose; ECH, extracranial hemorrhage; HD, high dose; HR, hazard ratio; and LD, low dose.

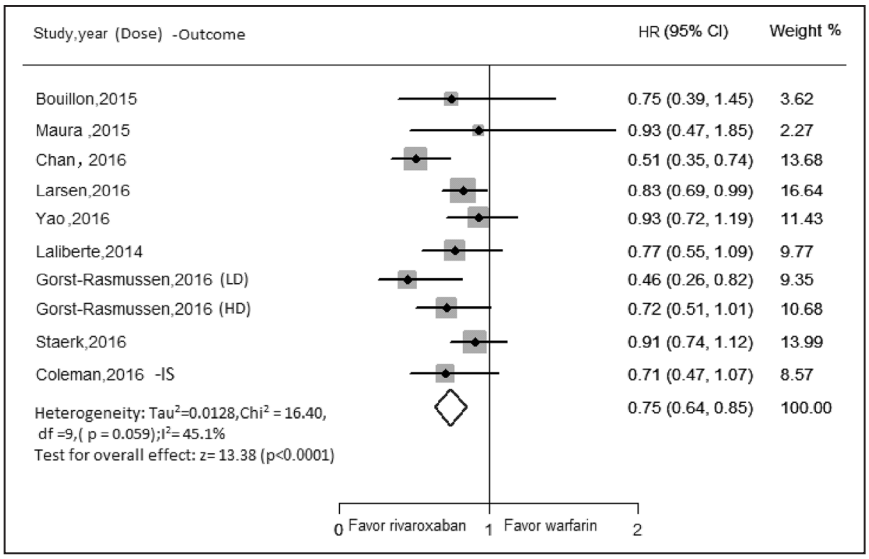

Figure 3. Rivaroxaban compared with warfarin in risk of stroke/TE in AF patients. AF indicates atrial fibrillation; CI, confidence interval; HD, high dose; HR, hazard ratio; IS, ischemic stroke; LD, low dose; and TE, thromboembolism.

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[32,33] 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

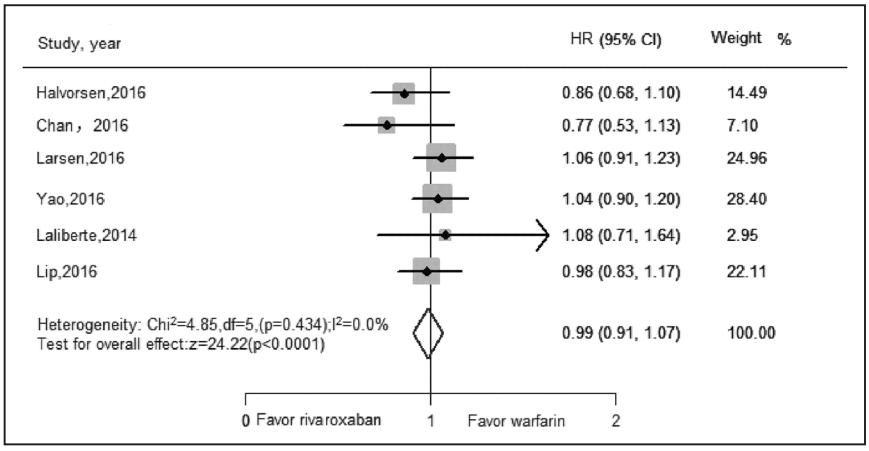

Figure 4. Rivaroxaban compared with warfarin in risk of major bleeding in AF patients. AF indicates atrial fibrillation; CI, confidence interval; and HR, hazard ratio.

Table 2. Baseline Characteristics in Rivaroxaban Versus Warfarin Studies

Author, year	Study Design	Region	Enrolled Period	Cohort Size	LD-R, %	eFollow-Up
Bouillon et al[21]	RC	France	January 2011 to November 2012	17 410	NA	0.8 y
Coleman et al[22]	RC	US	January 2012 to October 2014	38 831	17.3	NA
Lip et al[27]	RC	US	January to December 2013	29 338	NA	0.3 y
Abraham et al[20]	RC	US	November 2010 to September 2013	219 027	NA	NA
Maura et al[29]	RC	France	July to November 2012	32 807	38.5	0.2 y
Coleman et al[23]	RC	Germany	January 2012 to October 2013	5108	NA	0.5 y
Halvorsen et al[24]	Registry	Norway	January 2013 to June 2015	32 675	27	0.5 y
Chan et al[7]	RC	Taiwan	February 2013 to December 2013	304 252	87	1 y
Larsen et al[26]	RC	Denmark	August 2011 to October 2015	61 678	0	1.9 y
Yao et al[30]	RC	US	October 2010 to June 2015	125 243	21.5	0.6 y
Laliberte et al[25]	RC	US	May 2011 to July 2012	30 479	NA	0. 3 y
Lip et al[12]	RC	US	January 2012 to December 2014	33 262	NA	0.5 y
Gorst-Rasmussen et al[8]	Registry	Denmark	February 2012 to July 2014	22 358	32.3	1.08 y
Staerk et al[31]	Registry	Denmark	2011–2015	43 299	NA	0.6 y

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[10] and ≈30% in Chan et al[7]). 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 when 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 rivaroxban 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 time in therapeutic range of warfarin. Importantly, our study reflects real-world clinical practice, given that patients included in ROCKET-AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) had a higher stroke risk profile.[33]

In safety evaluations, both ROCKET-AF[33] 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.[34] 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.[20,24] 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.[35] 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/TE, 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.

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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 Daiichi-Sankyo. The other authors report no conflicts.

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