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SYSTEMATIC REVIEW

Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world

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Both apixaban and rivaroxaban have been approved for use in acute venous thromboembolism (VTE). Although indirect comparison through network meta-analyses of randomized trials have been performed to compare the efficacy and safety of these agents, further comparison between these agents was lacking until recently. We sought to systematically review and carry out a meta-analysis of studies to further compare apixaban with rivaroxaban from multiple studies done in the real-world settings. Studies comparing rivaroxaban with apixaban in patients with acute VTE were identified through electronic literature searches of MEDLINE, EMBASE, Scopus, and the Cochrane library up to May 2019. Study-specific risk ratios (RRs) were calculated and combined using a random-effects model meta-analysis. In an analysis involving 24,041 patients, recurrent VTE within 6 months occurred in 56 of 4,897 patients (1.14%) in the apixaban group and 258 of 19,144 patients (1.35%) in the rivaroxaban group (RR, 0.89; 95% confidence interval [CI], 0.67-1.19; P = .45). Clinically relevant major bleeding occurred in 85 of 11,559 patients (0.74%) in the apixaban group and 350 of 33,909 patients (1.03%) in the rivaroxaban group (RR, 0.73; 95% CI, 0.58-0.93; P = .01). Clinically relevant nonmajor bleeding occurred in 169 of 3,417 patients (4.95%) in the apixaban group and 1,094 of 12,475 patients (8.77%) in the rivaroxaban group (RR, 0.59; 95% CI, 0.50-0.70; P < .01). Apixaban shows equivalent efficacy in prevention of recurrent VTE but decreased risk of major and minor bleeding events compared with rivaroxaban.

Background

Direct-acting oral anticoagulants (DOACs) such as dabigatran, apixaban, rivaroxaban, and edoxaban are becoming the preferred agents for use in acute venous thromboembolism (VTE; deep vein thrombosis and pulmonary embolism) compared with vitamin K antagonists (VKAs).1 Although dabigatran and edoxaban require the sequence of unfractionated heparin or low-molecular-weight heparin (LMWH) "lead-in" anticoagulation followed by the respective oral agent, dabigatran or edoxaban (also referred to by some as bridging), lead-in anticoagulation is not needed when using apixaban and rivaroxaban. Lead-in anticoagulation with heparin products adds complexity to the treatment regimen and is 1 reason why dabigatran or edoxaban is less often prescribed than apixaban and rivaroxaban.2 Hence, apixaban and rivaroxaban are now increasingly used for acute VTE compared with VKAs and other DOACs.3

Although DOAC use in VTE has been shown to be noninferior to VKAs in noninferiority randomized trials, it is unclear whether any 1 DOAC is superior to the other given lack of head-to-head comparison studies. Network meta-analysis is done to establish indirect treatment comparison, with multiple treatments...
being compared at the same time to the common comparator (LMWH/warfarin in this case). Network meta-analyses in nonvalvular atrial fibrillation have provided some indirect evidence of comparisons, but have yielded mixed results, with some studies favoring apixaban more than rivaroxaban in different circumstances. Apixaban has been reported to be associated with less gastrointestinal bleeding, more favored in patients with chronic kidney disease (CKD) and overall less major bleeding (including those patients with cancer), and a lower rate of total discontinuation.⁴⁻⁶ Results from a randomized controlled trial comparing apixaban and rivaroxaban head to head (COBRRA: NCT03266783) evaluating the relative risk of efficacy between the 2 agents and relative risk of bleeding is pending.⁷ Various retrospective studies (database, registries) have been carried out looking at head-to-head comparisons between apixaban and rivaroxaban on VTE recurrence risk and bleeding risk.⁸⁻¹¹ Although randomized clinical trials are considered to be gold standard for evaluating safety and efficacy of these agents, the population recruited for these trials may not be generalizable. Hence, evidence generated from real-world databases and registry data can help clinicians guide selection between these agents in day-to-day practice.¹²-¹⁵

We sought to systematically assess the available evidence on the effectiveness and safety of apixaban compared with rivaroxaban in terms of recurrent VTE and bleeding risks in the real world settings.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews as recommended by the Cochrane Collaboration was used for this systematic review.¹³ This qualitative systematic review included studies published from database inception up to May 2019. Searches of MEDLINE, Cochrane Library, and EMBASE were carried out to identify eligible studies. Comprehensive searches for conference abstracts were also carried out. These databases were searched using the search terms under 2 broad search themes and synonyms for apixaban, rivaroxaban, and factor Xa inhibitor. For the theme “rivaroxaban,” we used a combination of medical subject headings (MeSH), entry terms, and text words “rivaroxaban” and “factor Xa inhibitor.” For the theme “apixaban,” we used a combination of MeSH, entry terms, and text words “apixaban” and “factor Xa inhibitor.” For the theme “acute venous thromboembolism,” synonyms for “venous thromboembolism,” “deep vein thrombosis,” and “pulmonary embolism” were used. Study designs including case controls, observational studies, randomized controlled trials, and meta-analyses of clinical trials were reviewed. No language restriction was used. Bibliographies belonging to included articles, known reviews, and relevant articles were hand-searched to identify additional trials. To minimize data duplication as a result of multiple reporting, we compared articles from the same investigator. Two investigators (R.G. and A.K) screened and retrieved reports and excluded irrelevant studies. Relevant data were extracted by 2 investigators (R.G. and Y.B) and checked by another (A.K.). An additional investigator (M.R.A.) participated in the review process when uncertainty about eligibility criteria arose.

From each study, we extracted and tabulated details on study source type, design, patients with acute VTE, mean age in years, percentage of female patients, estimated recurrent VTE risk, estimated bleeding risk (major and nonmajor), VTE events, and duration of anticoagulation; different outcomes at different time points were also recorded (Table 1). End points across the studies were also listed. After reviewing all of the literature, selected studies included all observational studies that compared the use of apixaban with rivaroxaban. The steps of the literature search process are summarized in Figure 1. Published full-text articles were included for this study. The eligibility criteria for this systematic review were: (1) human subjects with a diagnosis of acute VTE; (2) reported outcomes comparing rivaroxaban with apixaban; (3) minimum reported data of VTE or acute bleeding up to 3 months of time. Studies comparing apixaban vs rivaroxaban but indicated for the use of atrial fibrillation (AF) were not included in our review as these looked at stroke outcomes and outcomes were heterogeneous. In addition, studies that compared use of rivaroxaban or apixaban to warfarin or LMWH were excluded as these studies did not have direct comparison of apixaban with rivaroxaban. Finally, studies not reporting VTE and bleeding outcomes were also excluded from our analysis. In studies that had inclusion of both AF and VTE patients, data were extracted for patients with VTE only.¹¹ The study by Lutsey et al was included only for major bleeding outcome because the VTE events and minor bleeding events were not recorded.¹⁴ A total of 5 studies were included for analysis: 1 study included a review of data from a thrombophilia clinic registry, 1 study included a review of retrospective data of veterans, and 3 were database studies from the United States and Denmark.⁸⁻¹¹,¹⁴ Study quality was formally evaluated by 2 investigators using a modified Newcastle-Ottawa Quality Assessment Scale for retrospective studies (supplemental Table 2).

One efficacy outcome (VTE recurrence up to 6 months) and 2 safety outcomes (major and minor bleeding) were assessed. Efficacy was defined as recurrence of VTE (composite of any recurrent deep vein thrombosis or pulmonary embolism) reported as positive imaging findings on ultrasound Doppler or computed tomography. For our safety outcomes, clinically relevant major bleeding was reported (composite of bleeding requiring intervention or transfusion, cardiac tamponade, or pericardial effusion requiring drainage, retroperitoneal bleeding, intracranial bleed, massive hemoptysis, hemithorax, bleeding requiring extra hospital stay) and patients requiring hospitalization. Minor bleeding was defined by gastrointestinal bleeding, puncture site bleeding, thigh ecchymosis, hematoma, epistaxis, or bleeding with no intervention or without transfusion. Minor bleeding was considered to be secondary end point for analysis. For our analysis, we chose studies reporting outcomes up to 6 months. For studies reporting outcomes both at 3 months and 6 months, for uniformity, 3-month outcomes were chosen for analysis, as most studies reported outcomes at the 3-month interval. For the calculation of hazard ratio (HR), given the heterogeneous data reporting, 2 studies (Dawwas et al¹⁰ and Lutsey et al¹¹) reported 3-month outcomes, and these studies were used. Thus, all of the studies could not be combined for overall major bleeding events based on HR. Outcomes from the individual studies were calculated with RevMan version 5.3 (Cochrane Collaboration, Oxford, United Kingdom). A formal systematic review was performed applying the Mantel-Haenszel test using the software. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using a random-effects method to control the heterogeneity, as their assumption accounts for the presence of variability among the studies. HR was calculated using the same software. When provided, we used the CI and HRs from the included studies.
at the 3-month interval. The $I^2$ statistic was used to assess heterogeneity among the studies. $P$ value was computed and was considered significant if $<.05$, and CIs were calculated.

**Results**

Although the 5 selected studies8-11,14 assessed similar efficacy end points and outcomes, they were slightly different in terms of overall design and outcome definitions (Table 1).

There were a total of 45,468 patients analyzed for the primary efficacy of recurrent VTE and the safety outcomes of major bleeding and minor bleeding events. One study had combined patients with both AF and VTE, however, we included only those evaluated for VTE.11

In 3 studies involving 24,041 patients, recurrent VTE up to 6 months occurred in 56 of 4897 patients (1.14%) in the apixaban group and 258 of 19,144 patients (1.35%) in the rivaroxaban group (RR, 0.89; 95% CI, 0.67-1.19; $P = .45$; $I^2 = 0\%$) (Figure 2). Clinically relevant major bleeding occurred in 85 of 11,559 patients (0.74%) in the apixaban group and 350 of 33,909 patients (1.03%) in the rivaroxaban group (RR, 0.73; 95% CI, 0.58-0.93; $P = .01$; $I^2 = 0\%$) (Figure 3). Sensitivity analysis for major bleeding was carried out, excluding the study by Howe et al11 because it contributed the

<table>
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<th>Table 1. Baseline characteristics of included studies</th>
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<td><strong>Source type</strong></td>
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<td><strong>Mean age, y</strong></td>
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<td><strong>Female sex, %</strong></td>
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<td><strong>Malignancy</strong></td>
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<td><strong>Chronic kidney</strong></td>
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<td><strong>Total duration of study, mo</strong></td>
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<td><strong>Study groups (total no. of patients in each group)</strong></td>
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<td><strong>Primary outcome</strong></td>
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<td><strong>Major outcomes reported as</strong></td>
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A, apixaban; ARR, absolute risk reduction; CRNMB, clinically relevant nonmajor bleeding; NS, not specified; R, rivaroxaban; VA, Veterans Affairs; W, warfarin.

*Median.

†Creatinine clearance <30 mL/min.
least number of patients to the analysis (supplemental Figure 1). Further sensitivity analysis was also carried out excluding Sindet-Pedersen et al, as the major bleeding outcomes were reported at mean of 6 months, compared with others, which reported outcomes at 3 months (supplemental Figure 2). Both of these sensitivity analyses did not change the reported outcome of major bleeding favoring apixaban. Clinically relevant nonmajor bleeding occurred in 169 of 3417 patients (4.95%) in the apixaban group and 1094 of 12,475 patients (8.77%) in the rivaroxaban group (RR, 0.59; 95% CI, 0.50-0.70; P < .01; I² = 0%) (supplemental Figure 3). The composite outcomes of VTE and major bleeding occurred in 102 of 4897 patients (2.08%) in the apixaban group and 483 of 19,144 (2.52%) in the rivaroxaban group (RR, 0.79; 95% CI, 0.58-1.06; P = .12; I² = 38%) (supplemental Figure 4). Major bleeding was also calculated utilizing HR at 3 months. The risk of major bleeding at 3 months used HR, including the Dawwas et al and Lutsey et al studies (HR, 0.56; 95% CI, 0.43-0.72; P < .01; I² = 0%) (supplemental Figure 5).

Furthermore, analysis was carried out for clinically relevant composite outcomes of major and minor bleeding, and composite outcomes of VTE and major bleeding. The composite outcomes of major and minor bleeding occurred in 190 of 3417 patients (5.56%) in the apixaban group and 1186 of 12,475 patients (9.51%) in the rivaroxaban group (RR, 0.60; 95% CI, 0.52-0.70; P < .01; I² = 0%) (supplemental Figure 3). The composite outcomes of VTE and major bleeding occurred in 102 of 4897 patients (2.08%) in the apixaban group and 483 of 19,144 (2.52%) in the rivaroxaban group (RR, 0.79; 95% CI, 0.58-1.06; P = .12; I² = 38%) (supplemental Figure 4). Major bleeding was also calculated utilizing HR at 3 months. The risk of major bleeding at 3 months used HR, including the Dawwas et al and Lutsey et al studies (HR, 0.56; 95% CI, 0.43-0.72; P < .01; I² = 0%) (supplemental Figure 5).

An outcome table summarizing the results is also provided (supplemental Table 1). Outcomes of intracranial hemorrhage, gastrointestinal bleeding or cardiac bleeding, and mortality could not be looked at separately as they were inconsistently reported. Also, the comparison between apixaban and rivaroxaban, for treatment in cancer and CKD patients, could not be made, as
these are not available in all studies. On further analysis, of the number needed to harm using relative risk, we found that on average, 345 patients would have to receive apixaban (instead of rivaroxaban) for 1 additional patient to not have the study outcome of major bleeding (number needed to harm).

**Discussion**

This meta-analysis directly compared apixaban to rivaroxaban in patients with acute VTE, and identified no difference in VTE recurrence and composite outcome of recurrent VTE and major bleeding between apixaban and rivaroxaban. However, both major bleeding and minor bleeding events were significantly higher in the rivaroxaban group. Our results are consistent with a prior network meta-analysis that indirectly compared these agents. Previous studies have shown apixaban to be safer in patients with advanced age, baseline active cancer, CKD, and provoked VTE. It is interesting to note that the overall incidence of VTE was very low in both groups, which had been reported in prior randomized controlled trials (RCTs) but had not been confirmed in real-world patients with less adherence compared with randomized trial participants.

Bleeding complications are an important consideration when choosing any systemic anticoagulation. Major bleeding, such as central nervous system bleeding and cardiac tamponade, can be a dreaded complication with any factor Xa inhibitors. Although a reversal agent, andexanet, has been recently approved for apixaban and rivaroxaban, it has several limitations in terms of short half-life, potential increased risk of thrombosis, absence of RCTs on its efficacy, and cost. Hence, complications are often managed conservatively. Our study provides further evidence that apixaban might be a better choice for anticoagulation than rivaroxaban in terms of bleeding risk pending the ongoing RCT previously mentioned. The very least, our results would appear to favor the use of apixaban in patients with a preexisting increased risk to bleed, for example, those with CKD, heavy menses, or history of gastrointestinal bleed. In these circumstances, our findings suggest that patients who are taking long-term rivaroxaban will likely benefit if switched to apixaban if they are able to adhere to twice-daily treatment. However, it should be noted that our findings are applicable to VTE patients (not AF) only, and whether this study’s findings would continue to hold true beyond 6 months follow-up is unclear. Although decreased bleeding with apixaban exists, it may be small as evidenced by number needed to harm, which can be useful information while discussing the options of anticoagulation between these agents with our patients.

Although confounders are possible in retrospective studies (eg, weight not being consistently addressed), they appear to have been well matched and propensity scoring was carried out in these

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**Figure 3. Major bleeding events.**

**Figure 4. Clinically relevant nonmajor bleeding.**
studies. Furthermore, the coding for bleeding was not identical in all studies, varying from International Classification of Diseases (ICD) codes to International Society on Thrombosis and Haemostasis (ISTH) bleeding definition. A previous meta-analysis had shown that in various settings, including in CKD patients, apixaban was safer than other agents like rivaroxaban and dabigatran. Safety of apixaban compared with rivaroxaban has been explained in relation to pharmacokinetic properties. Persistence of anticoagulation effects beyond the half-life of rivaroxaban allows for once-daily dosing whereas apixaban is dosed twice daily. For this to happen, rivaroxaban concentrations must remain higher than the minimum concentration necessary to prevent thrombosis with the short half-life, hence the maximum serum concentration is needed to facilitate once-daily dosing. Peak-to-trough ratio of rivaroxaban is ~10 (at a dose of 10-20 mg once daily) whereas for apixaban is ~3 (at a dose of 5 mg twice daily). Hence, the more favorable bleeding profile is proposed to be a result of the decreased peak-to-trough ratios afforded by twice-daily DOAC dosing.

**Strengths and limitations**

This meta-analysis compared apixaban “directly” short of head-to-head RCT to rivaroxaban and included a large patient sample that was representative of real-world data rather than clinical trial events. Heterogeneity (heterogeneity) of the studies is low in most of the outcomes, pointing toward consistent results of our analyzed outcomes. At the same time, the presence of unaccountable confounders must be considered when interpreting our results, especially in light of the nonrandomized designs, despite various analyses performed in the included studies to reduce the confounders. Underdosing has been reported with DOACs, with some studies suggesting that it might be more prevalent with apixaban (24%) than rivaroxaban (13%), which could be associated with increased VTE events and fewer bleeding complications. Given that this was based on database and registry data, it is impossible to know the doses and compliance of each agent used. Relatively uniform reporting of the events within 6 months allowed us to combine these studies. It should also be noted that major outcomes such as intracranial bleeding, gastrointestinal bleeding, and mortality were inconsistently reported with the studies included. This was also true for other minor outcomes.

**Conclusion**

In conclusion, this real-world meta-analysis comparing apixaban to rivaroxaban suggests similar efficacy but better safety for patients on apixaban.

**Authorship**

Contribution: R.G. and A.K. screened and retrieved reports and excluded irrelevant studies; relevant data were extracted by investigators R.G. and Y.B. and checked by another, A.K.; M.R.A and R.D. were involved in synthesis as well as analyzing and reviewing the accuracy of the data; M.R.A and R.G. interpreted the data and wrote and revised the first and subsequent manuscript; P.A.K. and A.D. interpreted the overall manuscript and gave an expert opinion; and H.Y. was involved in providing expert statistical analysis and opinions.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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