SYSTEMATIC REVIEW

blood advances

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

Madan Raj Aryal,[1,*] Rohit Gosain,[1,*] Anthony Donato,[2] Han Yu,[3] Anjan Katel,[4] Yashoda Bhandari,[5] Rashmi Dhital,[2] and Peter A. Kouides[6]

[1]Department of Medicine, Roswell Park Comprehensive Cancer Institute, University at Buffalo, Buffalo, NY; [2]Department of Medicine, Tower Health System, Reading, PA; [3]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Institute, University at Buffalo, Buffalo, NY; [4]Department of Medicine, School of Medical Sciences, Kathmandu University, Dhulikhel, Nepal; [5]School of Nursing, University at Buffalo, Buffalo, NY; and [6]Department of Medicine, Rochester Regional Health, Rochester, NY

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 4897 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 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; $P < .01$). 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

Submitted 10 June 2019; accepted 10 July 2019. DOI 10.1182/bloodadvances.2019000572.

*M.R.A. and R.G. contributed equally to this study and are joint first authors.

The full-text version of this article contains a data supplement.

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]

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 combined using the Boolean operator "AND." 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 al[10] and Lutsey et al[14]) 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

Table 1. Baseline characteristics of included studies

	Sindet-Pedersen et al,[8] 2018	Lutsey et al,[14] 2019	Bott-Kitslaar,[9] 2018	Dawwas et al,[10] 2019	Howe et al,[11] 2018
Source type	Journal article	Journal article	Journal article	Journal article	Journal article
Study design	Retrospective, multicenter registry	Retrospective, market scan data warehouse	Prospective, single-center trial (Mayo Thrombophilia Clinic Registry), observational	Retrospective cohort analysis, market scan and Medicare supplement claims 2014-2016	Retrospective review, single VA center
Mean age, y	70 A*	60.4 A	62.4 A	61.5 A	73 A
	67 R*	56.4 R	58.5 R	56.5 R	68 R
Female sex, %	50.8 A	50.3 A	38.7 A	50.6 A	2 A
	45.3 R	49.2 R	48 R	49.5 R	4.4 R
Mean weight, kg	NS	NS	87.6 A	NS	NS
			91.3 R		
Medications, %	23.6 A	7 A	23.8 A	7.3 A	NS
Antiplatelet agents	18.3 R	5.1 R	21.8 R	4.2 R	
Comorbidities, %	14 A	17 A	47 A	17.7 A	NS
Malignancy	11.4 R	16.1 R	39.9 R	18.9 R	
Chronic kidney	3.9 A	13.2 A	2.3 A†	17.1 A	NS
	2.7 R	7.1 R	0 R†	8.5 R	
Total duration of study, mo	29		58	24	24
Study groups (total no. of patients in each group)	2 groups	2 groups	2 groups	2 groups	2 groups
	A (1504)	A (6786)	A (302)	A (3091)	A (89)
	R (6683)	R (30 982)	R (298)	R (12 163)	R (173)
Primary outcome	All-cause mortality, recurrent VTE, hospitalized bleeding	Hospitalized bleeding	VTE recurrence, major bleeding events	VTE recurrence, major bleeding events	Overall bleeding rates
Secondary outcome	Intracranial and gastrointestinal bleeding		CRNMB, and composite of major bleeding and CRNMB	Minor bleeding events	Time to bleeding and location of bleeding
Recurrent VTE, %	1.71 A	NS	2.32 A	0.81 A	NS
	1.76 R		2.01 R	2.09 R	
Major bleeding, %	1.17 A	0.74 A	3.64 A	0.91 A	0.56 A
	1.28 R	1.15 R	3.20 R	1.55 R	1.99 R
Nonmajor/minor bleeding, %	NS	NS	2.32 A	5.37 A	0.28
			6.71 R	8.90 R	1.77 R
Study outcomes reported at	Average 6 mo	3 mo and 6 mo	3 mo and overall as 100 per year incidence	<3 mo and >3 mo and 100 person-year	At 3 mo and 100 person-year
Major outcomes reported as	Incidence reported as percent events, ARR between 2 groups	Adjusted HR for 100 person-year incidence, number of events at 3 mo		No. of events at <3 mo and >3 mo, HR for the same and also for 100 person-year incidence	No. of events at 3 mo and 100 person-year incidence

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.

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 studies[8-11,14] 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 al[11] because it contributed the

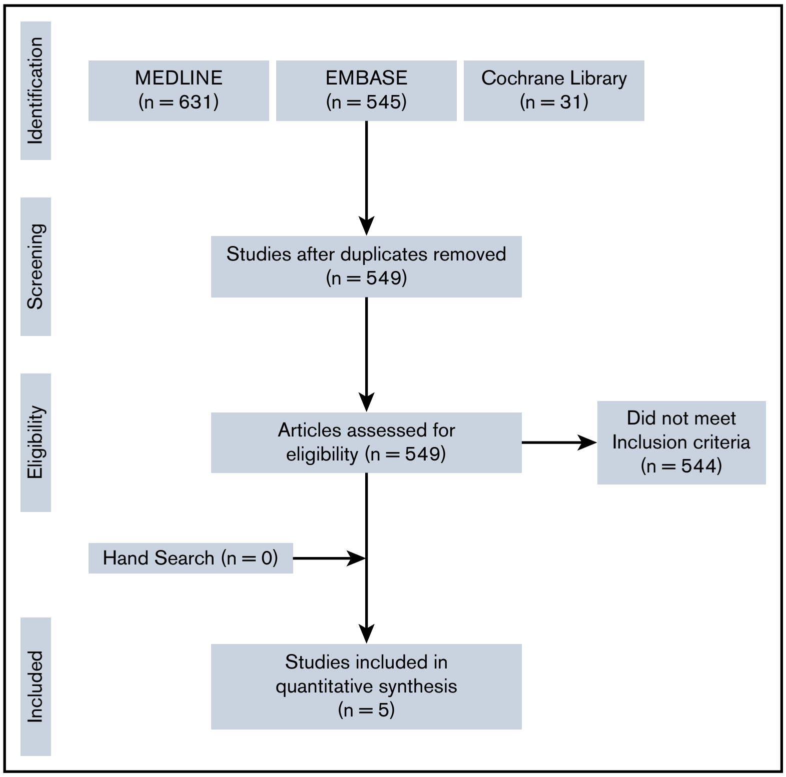

Figure 1. Flow chart describing systematic research search and study selection process.

least number of patients to the analysis (supplemental Figure 1). Further sensitivity analysis was also carried out excluding Sindet-Pedersen et al,[8] 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; $P < .01$; $I^2 = 0\%$) (Figure 4).

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; $P < .01$; $I^2 = 0\%$) (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; $P = .12$; $I^2 = 38\%$) (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[10] and Lutsey et al[14] studies (HR, 0.56; 95% CI, 0.43-0.72; $P < .01$; $I^2 = 0\%$) (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

	Apixaban		Rivaroxaban			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Bott-Kitslaar 2018	3	302	2	298	2.6%	1.48 [0.25, 8.79]
Dawwas 2019	20	3091	108	12163	37.1%	0.73 [0.45, 1.17]
Sindet-Pedersen 2018	33	1504	148	6683	60.3%	0.99 [0.68, 1.44]
Total (95% CI)		**4897**		**19144**	**100.0%**	**0.89 [0.67, 1.19]**
Total events	56		258			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.31$, df = 2 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 0.76 (P = 0.45)

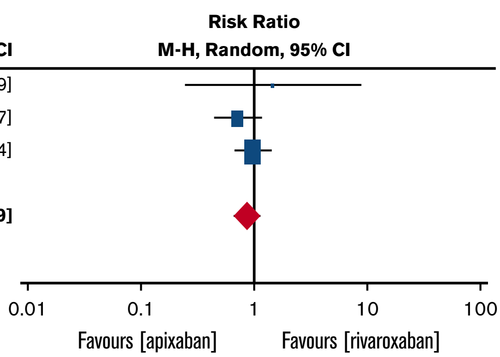

Figure 2. VTE events.

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Bott-Kitslaar 2018	6	302	6	298	4.5%	0.99 [0.32, 3.02]
Dawwas 2019	14	3091	84	12163	17.9%	0.66 [0.37, 1.15]
Howe 2018	1	24	2	14	1.1%	0.29 [0.03, 2.93]
Lutsey 2019	38	6638	132	14751	44.0%	0.64 [0.45, 0.92]
Sindet-Pedersen 2018	26	1504	126	6683	32.5%	0.92 [0.60, 1.39]
Total (95% CI)		**11559**		**33909**	**100.0%**	**0.73 [0.58, 0.93]**
Total events	85		350			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.68$, df = 4 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 2.58 (P = 0.010)

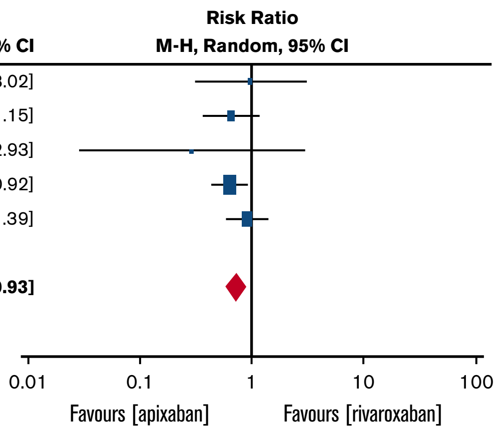

Figure 3. **Major bleeding events.**

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.[4] 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.[15,16]

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.[17] 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.[7] At 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

Study or Subgroup	Apixaban Events	Apixaban Total	Rivaroxaban Events	Rivaroxaban Total	Weight	Risk Ratio M-H, Random, 95% CI
Bott-Kitslaar 2018	3	302	11	298	1.7%	0.27 [0.08, 0.95]
Dawwas 2019	166	3091	1082	12163	98.0%	0.60 [0.52, 0.71]
Howe 2018	0	24	1	14	0.3%	0.20 [0.01, 4.60]
Total (95% CI)		**3417**		**12475**	**100.0%**	**0.59 [0.50, 0.70]**
Total events	169		1094			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.00$, df = 2 (P = 0.37); $I^2 = 0\%$
Test for overall effect: Z = 6.16 (P < 0.00001)

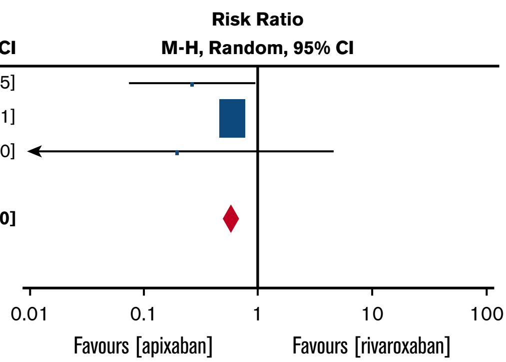

Figure 4. **Clinically relevant nonmajor bleeding.**

studies. Furthermore, the coding for bleeding was not identical in all studies, varying from International Classification of Diseases (ICD) codes[10] to International Society on Thrombosis and Haemostasis (ISTH) bleeding definition.[9] A previous meta-analysis had shown that in various settings, including in CKD patients, apixaban was safer than other agents like rivaroxaban and dabigatran.[18] 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.[19]

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. I^2 (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.[20] 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.[21] 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.

ORCID profiles: M.R.A., 0000-0002-5560-451X; R.G., 0000-0003-0803-8698; R.D., 0000-0003-1974-7844; P.A.K., 0000-0002-3857-8313.

Correspondence: Madan Raj Aryal, Roswell Park Comprehensive Cancer Institute, University at Buffalo, 665 Elm St, Buffalo, NY 14203; e-mail: madan.aryal@roswellpark.org.

References

1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in *Chest.* 2016;150(4):988]. *Chest.* 2016;149(2):315-352.

2. Lippi G, Mattiuzzi C, Cervellin G, Favaloro EJ. Direct oral anticoagulants: analysis of worldwide use and popularity using Google trends. *Ann Transl Med.* 2017;5(16):322.

3. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med.* 2015;128(12):1300-1305.e2.

4. Cohen AT, Hill NR, Luo X, Masseria C, Abariga SA, Ashaye AO. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: a comparison of efficacy and safety following treatment with direct oral anticoagulants. *Int J Cardiol.* 2018;269:174-181.

5. Mitchell SA, Simon TA, Raza S, et al. The efficacy and safety of oral anticoagulants in warfarin-suitable patients with nonvalvular atrial fibrillation: systematic review and meta-analysis. *Clin Appl Thromb Hemost.* 2013;19(6):619-631.

6. Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. *Blood Adv.* 2018;2(3):200-209.

7. Clinicaltrials.gov. Comparison of bleeding risk between rivaroxaban and apixaban for the treatment of acute venous thromboembolism (COBRRA). https://clinicaltrials.gov/ct2/show/NCT03266783. Accessed 6 May 2019.

8. Sindet-Pedersen C, Staerk L, Pallisgaard JL, et al. Safety and effectiveness of rivaroxaban and apixaban in patients with venous thromboembolism: a nationwide study. *Eur Heart J Cardiovasc Pharmacother.* 2018;4(4):220-227.

9. Bott-Kitslaar DM, McBane RD, Casanegra AI, et al. Apixaban and rivaroxaban in patients with acute venous thromboembolism. *Mayo Clin Proc.* 2019;94(7):1242-1252.

10. Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. *Lancet Haematol.* 2019;6(1):e20-e28.

11. Howe Z, Naville-Cook C, Cole D. Bleeding rates of veterans taking apixaban or rivaroxaban for atrial fibrillation or venous thromboembolism. *J Thromb Thrombolysis*. 2019;47(2):280-286.

12. Clinicaltrials.gov. Register for new oral anticoagulants (NOAC). https://clinicaltrials.gov/ct2/show/NCT01588119. Accessed 15 May 2019.

13. Beller EM, Glasziou PP, Altman DG, et al; PRISMA for Abstracts Group. PRISMA for Abstracts: reporting systematic reviews in journal and conference abstracts. *PLoS Med*. 2013;10(4):e1001419.

14. Lutsey PL, Zakai NA, MacLehose RF, et al. Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism. *Br J Haematol*. 2019;185(5):903-911.

15. Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA*. 2018;320(21):2221-2230.

16. Manzoor BS, Lee TA, Sharp LK, Walton SM, Galanter WL, Nutescu EA. Real-world adherence and persistence with direct oral anticoagulants in adults with atrial fibrillation. *Pharmacotherapy*. 2017;37(10):1221-1230.

17. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12):1131-1141.

18. Pathak R, Pandit A, Karmacharya P, et al. Meta-analysis on risk of bleeding with apixaban in patients with renal impairment. *Am J Cardiol*. 2015;115(3):323-327.

19. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol*. 2013;76(5):776-786.

20. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2018;49(1):98-106.

21. Moudallel S, Steurbaut S, Cornu P, Dupont A. Appropriateness of DOAC prescribing before and during hospital admission and analysis of determinants for inappropriate prescribing. *Front Pharmacol*. 2018;9:1220.