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Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: a meta-analysis

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Abstract

Background—Venous thromboembolism (VTE) is a common and potentially fatal complication of arthroplasty.

Methods—We reviewed randomized trials to determine which anticoagulant has the best safety and efficacy in hip/knee arthroplasty patients. We searched PubMed, MEDLINE, and EMBASE through January 2016.

Results—Compared to enoxaparin (most commonly dosed 40 mg once daily), the relative risk (RR) of VTE was lowest for edoxaban 30 mg once daily (0.49, 95% CI 0.32–0.75), fondaparinux 2.5 mg once daily (0.53, 95% CI 0.45–0.63), and rivaroxaban 10 mg once daily (0.55, 95% CI 0.46–0.66), and highest for dabigatran 150 mg once daily (1.19, 95% CI 0.98–1.44). The RR of major/clinically relevant bleeding was lowest for apixaban 2.5 mg twice daily (0.84, 95% CI 0.70–0.99), and highest for rivaroxaban (1.27, 95% CI 1.01–1.59) and fondaparinux (1.64, 95% CI 0.24–11.35). Fondaparinux was the only agent that was more effective than enoxaparin 30 mg twice daily (VTE RR = 0.58, 95% CI 0.43–0.76).

Conclusion—With the possible exception of apixaban, newer anticoagulants that lower the risk of post-operative VTE increase bleeding.

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Keywords

arthroplasty; anticoagulant; bleed; deep vein thrombosis; meta-analysis; thromboembolism

Introduction

In the United States alone, venous thromboemboli (VTEs) cause 600,000 hospitalizations and 60,000 deaths each year.[1] Even with thromboprophylaxis, VTE rates exceed 10% in studies that have screened patients for VTE after hip or knee arthroplasty.[2] As the baby boomers age and the prevalence of obesity rises, VTE rates may also rise.[3]

These high rates of post-operative VTE have inspired the development of convenient alternatives to warfarin and low-molecular-weight heparins (LMWHs), the traditional thromboprophylaxis in arthroplasty patients. Like LMWHs, fondaparinux, apixaban, rivaroxaban, and edoxaban prevent clotting by inhibiting clotting factor Xa. Fondaparinux is administered subcutaneously, while apixaban, rivaroxaban, and edoxaban are administered orally. Dabigatran is another new oral anticoagulant with a different mechanism of action: it directly inhibits thrombin (factor IIa). None of these new agents require therapeutic monitoring, creating convenient alternatives for VTE prophylaxis.

These novel oral anticoagulants have varying degrees of approval. Apixaban, fondaparinux, and rivaroxaban are approved by the United States Food and Drug Administration (FDA) for VTE prophylaxis in patients undergoing hip or knee arthroplasty. Dabigatran is approved for both hip and knee arthroplasty in Europe, Australia, and Canada, but only for hip arthroplasty in the US. Edoxaban is approved for arthroplasty in Japan, but in Europe and the US, edoxaban is approved for indications other than arthroplasty.

The varied acceptance and usage of these newer agents for VTE prophylaxis brings up a salient clinical issue: which of these anticoagulants has the highest level of efficacy and safety in the hip and knee arthroplasty population? To answer this question, we conducted meta-analyses of the new anticoagulants. The first meta-analysis focused on efficacy, with the endpoint being the incidence of VTE. The second focused on safety, with two endpoints: the composite of major and/or clinically relevant bleeding and major bleeding alone. Based on the original trial designs, we were able to compare each of the novel anticoagulants to enoxaparin.

Methods

Data sources and searches

We searched PubMed, MEDLINE (through PubMed), and EMBASE through January 2016 using the following keywords: (*apixaban OR dabigatran OR rivaroxaban OR fondaparinux OR edoxaban) AND (hip OR knee)* AND *arthroplasty*. Additionally, references of included studies were reviewed as potential candidate trials. No betrixaban or darexaban trials met our inclusion criteria.

Study selection

Inclusion criteria were: double-blinded, randomized controlled trials that enrolled adult patients within 48 hours of surgery, prescribed anticoagulants for VTE prophylaxis after hip or knee surgery, dosed the experimental and control arms within 30 hours of each other, and confirmed VTE. VTE was defined in all trials as the presence of an objectively confirmed deep vein thrombosis (DVT) or an objectively confirmed pulmonary embolism. Exclusion criteria were the lack of a standard treatment arm (enoxaparin) or use of a dose not approved by the US Food and Drug Administration (FDA), the European Medicines Agency, or the Pharmaceutical and Food Safety Bureau of Japan.

Data extraction and quality assessment

Two researchers collected and assessed the eligibility of over 400 trials by viewing the title, abstract, and entire paper, in that order. Most trials were eliminated after viewing either the title or abstract based on the inclusion/exclusion criteria. Once trials that met the inclusion criteria were identified, two researchers assessed quality using the Jadad Criteria.[4] All trials scored either a 4 or 5 on the Jadad scale, indicating high-quality trials. Once quality was established, independent data extraction was performed by at least two researchers using a standardized extraction form and comparing their findings to ensure data accuracy.

Outcome measures

Our efficacy outcome was the incidence of VTE. Our primary safety outcome was the composite of major/clinically relevant bleeding, and our secondary safety outcome was major bleeding alone. Outcomes were obtained from each study's treatment period, which varied from 5 to 39 days. Major bleeding was defined similarly in all trials with one exception.[5] The apixaban, dabigatran, and rivaroxaban trials defined *major bleeding* as the transfusion of 2 or more units of packed red blood cells or bleeding into a critical organ (including bleeding into the operated joint, if surgical intervention was needed), whereas the edoxaban trials defined *major bleeding* as the transfusion of four or more units. The definition of *clinically relevant bleeding* was not consistent throughout all trials but was similar. Clinically relevant bleeding was not available from the fondaparinux trials.

Statistical analysis

We calculated the relative risk (RR) for each trial compared to enoxaparin, weighed them using the inverse variance method, and calculated pooled RRs for each anticoagulant using the classic random-effect approach.[6] In the analysis of major bleeds, we excluded one trial because it had no major bleeds.[7] We tested for heterogeneity between trials using Cochran's Q statistic. If heterogeneity was found, we performed subgroup analyses that focused on different doses of the anticoagulants.

Results

Initial searches located 435 trials. After applying inclusion/exclusion criteria (Figure 1), 4 apixaban trials, 4 dabigatran trials, 4 fondaparinux trials, 4 rivaroxaban trials, and 2 edoxaban trials were included. All 18 trials were sponsored by the manufacturers. The control in every trial was enoxaparin (given subcutaneously). Although the enoxaparin

regimen varied across trials, its consistent use enabled us to compare the safety and efficacy of each new anticoagulant against enoxaparin. With the exception of fondaparinux, there were no more than 5 VTE-related deaths per treatment arm for each trial and no differences between treatment groups. Because of this very low event rate and lack of difference, we did not include these numbers in the results below.

Apixaban (Eliquis)

Four trials comparing apixaban and enoxaparin were identified: APROPOS, ADVANCE-1, ADVANCE-2, and ADVANCE-3.[7,8,9,10] Apixaban 2.5 mg twice per day was compared to enoxaparin 40 mg once per day in the first two trials and compared to enoxaparin 30 mg twice per day in the last two trials (Table 1), respectively. On average, apixaban reduced VTE by 29% (RR=0.71, 95% CI 0.52–0.96; p = 0.026). It failed the homogeneity test (Cochran's Q = 9.7; I^2 = 9.3%), reflecting differences in efficacy among trials: compared to enoxaparin 40 mg once daily, apixaban had greater efficacy in preventing VTE (RR = 0.57, 95% CI 0.46–0.72; p < 0.001).[9,10] Alternatively, compared to enoxaparin 30 mg twice daily, apixaban did not prevent VTE (RR = 0.98, 95% CI 0.68–1.42).[7,8] Apixaban significantly reduced major/clinically relevant bleeding by 16% (RR=0.84, 95% CI 0.70–0.99; p = 0.043), but had no effect on major bleeding (RR=0.85, 95% CI 0.53–1.34; p = 0.48). Bleeding analyses passed the homogeneity test.

Dabigatran (Pradaxa)

Four trials comparing dabigatran and enoxaparin were identified: RE-MODEL, RE-MOBILIZE, RE-NOVATE, and RE-NOVATE II.[11,12,13,14] RE-MOBILIZE compared subcutaneous enoxaparin 30 mg twice daily to dabigatran 150 and 220 mg orally once daily. The other three trials compared subcutaneous enoxaparin 40 mg once daily to dabigatran 150 mg or 220 mg once daily (Table 2).

Efficacy and safety of dabigatran were not significantly different from enoxaparin. Dabigatran 150 mg once per day tended to increase VTE compared to enoxaparin (RR=1.19, 95% CI 0.98–1.44; p = 0.072) yet had no significant effect on major/clinically relevant bleeding (RR=1.22, 95% CI 0.89–1.67; p = 0.22) or major bleeds (RR=0.78, 95% CI 0.48–1.27; p = 0.32). Dabigatran 150 mg passed homogeneity tests for all outcomes.

Dabigatran 220 mg per day also had no effect on VTE (RR=1.04, 95% CI 0.87–1.24; p = 0.68) when compared to enoxaparin. Similarly, rates of major/clinically relevant bleeding (RR=1.14, 95% CI 0.93–1.4; p = 0.20) and major bleeding (RR=1.19, 95% CI 0.80–1.77; p = 0.40) were equivalent between enoxaparin and dabigatran 220 mg, which passed homogeneity tests for all outcomes as well.

Fondaparinux (Arixtra)

Four trials comparing fondaparinux and enoxaparin were identified: PENTAMAKS, PENTHIFRA, PENTATHLON 2000, and EPHESUS.[15,16,17,18] Subcutaneous fondaparinux 2.5 mg once daily was compared to subcutaneous enoxaparin 30 mg twice daily in PENTAMAKS and PENTATHLON 2000; the other two trials compared the same fondaparinux dose to enoxaparin 40 mg once daily (Table 3).

Compared to enoxaparin, fondaparinux decreased VTE by 47% (RR=0.53, 95% CI 0.45–0.63; p < 0.001). Compared to enoxaparin 30 mg twice daily, fondaparinux decreased VTE (RR = 0.58, 95% CI 0.43–0.76; p < 0.001). However, fondaparinux tended to increase major bleeds (RR=1.64, 95% CI 0.24–11.3; p = 0.62). Fondaparinux passed homogeneity testing for VTE while failing homogeneity testing for major bleeds, due to the 11-fold RR of bleeding in one trial.15 No fondaparinux data were available for clinically relevant bleeding.

Rivaroxaban (Xarelto)

Four trials comparing rivaroxaban and enoxaparin were identified: ODIXa-HIP, RECORD-1, RECORD-3, and RECORD-4; we excluded RECORD-2 because 31–39 days of rivaroxaban were compared to 10–14 days of enoxaparin.[19,20,21,22,23] Rivaroxaban 10 mg once daily was compared to subcutaneous enoxaparin 40 mg once daily in all trials except RECORD-4, which compared rivaroxaban to enoxaparin 30 mg twice daily (Table 4).

Rivaroxaban decreased VTE by 45% (RR=0.55, 95% CI 0.46–0.66; p < 0.001). It increased major/clinically relevant bleeds by 27% (RR=1.27, 95% CI 1.01–1.59; p =0.039) but did not significantly increase major bleeds (RR=1.88, 95% CI 0.67–5.29; p = 0.23). Rivaroxaban passed homogeneity testing for all outcomes.

Edoxaban (Savaysa)

Two trials comparing edoxaban and enoxaparin were identified: STARS E-3 and STARS J-V, which were conducted in Japan and Taiwan.[24,25] Both trials compared oral edoxaban 30 mg once daily to subcutaneous enoxaparin 20 mg twice daily (Table 5), the standard dose in Asian populations. Likewise, the average weight of participants in these trials was only 60 kg. Compared to enoxaparin 20 mg twice daily, edoxaban nearly halved VTE risk (RR=0.49, 95% CI 0.32–0.75; p = 0.001), yet did not significantly increase major/clinically relevant bleeds (RR=1.33, 95% CI 0.64–2.76; p = 0.44) or major bleeds (RR=1.58, 95% CI 0.05–54.38; p =0.65). Edoxaban passed homogeneity tests for VTE and major/clinically relevant bleeds, but not for major bleeds (Q = 6.9; I^2 = 6.7%).

Pooled Result

Overall, fondaparinux, rivaroxaban, and edoxaban had the highest efficacy in preventing VTE (Figure 2), but they also had the greatest risk of bleeding (Figure 3). Apixaban and dabigatran 150 mg had the lowest risk of bleeding yet apixaban was more effective. Dabigatran 220 mg was not inferior to enoxaparin, however it was neither safer nor more effective (Figure 4).

Discussion

As compared to subcutaneous enoxaparin, four newer anticoagulants reduced the rate of VTE after arthroplasty (Figure 2). Their RR (95% CI) were: apixaban 0.71 (0.52–0.96), rivaroxaban 0.55 (0.46–0.66), fondaparinux 0.53 (0.45–0.63), and edoxaban 0.49 (0.32–0.75). Apixaban also protected against major/clinically relevant bleeding: RR (95% CI) of 0.84 (0.70–0.99). In contrast, rivaroxaban increased major/clinically relevant bleeds (RR=1.27, 95% CI 1.01–1.59). The effect of fondaparinux and edoxaban on major/clinically

relevant bleeding was not precise because the fondaparinux trials did not report non-major bleeds and only two edoxaban trials met inclusion criteria.

On average, oral apixaban 2.5 mg twice daily reduced the risks of both major/clinically relevant bleeding and of VTE. However, compared specifically with enoxaparin 30 mg twice daily, apixaban did not affect VTE rate (RR = 0.98); compared to enoxaparin 40 mg once daily, apixaban had greater efficacy.[9, 10] In a prior analysis of the ADVANCE-2 and 3 trials, Raskob et al. reached a similar conclusion: arthroplasty patients randomized to apixaban had half as many VTEs as patients randomized to enoxaparin 40 mg daily.[26] The FDA and EU have approved apixaban 2.5 mg twice daily beginning 12–24 hours post-operatively for approximately 32–38 days after hip arthroplasty and for 10–14 days after knee arthroplasty.[27] Based primarily on its lower risk of bleeding, apixaban is an excellent alternative to enoxaparin for arthroplasty patients.

Like apixaban, rivaroxaban was significantly more effective than enoxaparin at preventing VTE. Unlike apixaban, oral rivaroxaban 10 mg once daily *increased* the RR (95% CI) of major/clinically relevant bleeding by 1.27 (1.01–1.59) (Figure 3). The decreased safety of rivaroxaban may reflect the timing of administration: in the RECORD trials, rivaroxaban was started 6–8 hours after arthroplasty, whereas in the ADVANCE trials apixaban was initiated 12–24 hours after arthroplasty. Rivaroxaban administered 6–8 hours after arthroplasty may be appropriate for patients at high risk of VTE, but suboptimal for patients at high risk of bleeding.

Compared to twice daily apixaban, the once daily dosing of rivaroxaban results in higher peak anti-Xa activity, which may also contribute to rivaroxaban's increased bleeding.[28] Our conclusion contrasts to that of Lassen et al. who concluded that bleeding events "occurred at similar rates in the rivaroxaban and enoxaparin groups."[29] Specifically, they reported that rivaroxaban had a RR (95% CI) for major/clinically relevant bleeding of 1.21 (0.99 to 1.48). However, we note that Lassen et al. included RECORD-2, while we excluded that study because of the different duration of thromboprophylaxis in the two study arms.

Edoxaban 30 mg once daily halved the rate of VTE (RR = 0.49; 95% CI 0.32–0.75). It did not increase the RR (95% CI) of bleeding significantly: for major bleeding the RR was 1.58 (0.05–54.38); for major/clinically relevant bleeding the RR was 1.33 (0.64–2.76). However, with only 2 eligible trials, the effect of edoxaban on bleeding was not precise. In both trials, edoxaban was compared to enoxaparin 20 mg twice daily, the standard dose in Japan and Taiwan where the STARS E-3 and STARS J-V trials were conducted. Thus, how edoxaban compares to enoxaparin 30 mg twice daily is unknown.

Dabigatran (at either 150 or 220 mg/d) had efficacy and safety that was not significantly different than enoxaparin. Dabigatran 150 mg/d trended toward a higher VTE rate (RR =1.19; 95% CI 0.98–1.44) than enoxaparin and had a similar bleed risk, thus we found no advantage to dabigatran in the arthroplasty population.

Fondaparinux significantly reduced the rate of VTE (by 47%). It was the only agent that was more effective than enoxaparin 30 mg twice daily (VTE RR = 0.58, 95% CI 0.43–0.76). However, because of its subcutaneous administration and trend (RR 1.64) for more major

bleeding, we would recommend it only for arthroplasty patients at high risk for VTE and low risk for bleeding.

A clinical prediction rule for post-operative VTE would allow orthopedists to select thromboprophylaxis based on VTE. A classic clinical prediction rule can predict post-operative VTE overall, but classifies all arthroplasty patients as high risk.[30] However, Kulshrestha et al. found that nearly half of TKA patients could be identified prospectively as having a low enough VTE risk that they could be treated with post-operative aspirin, rather than an anticoagulant.[31] Although this approach could reduce the risk of post-operative hemorrhage, aspirin is only modestly effective at preventing VTE after arthroplasty.[32, 33] Thus, the future treatment for low VTE risk arthroplasty patients may be the combination of aspirin plus a mobile compression device continuing after hospital discharge.[34, 35]

Variations in endpoints and methods explain the differences between our analysis and prior meta-analyses. The primary endpoint in the meta-analysis by Gómez-Outes et al. was symptomatic VTE.[36] They concluded that rivaroxaban halved the risk of symptomatic VTEs (RR = 0.48). Although the RR we calculated for rivaroxaban was similar (0.55), because we included *all* VTEs, our 95% CI was more precise (0.46–0.66). In another meta-analysis, Neumann et al. reported that per 1000 patients, factor Xa inhibitors (as a class) prevented 4 symptomatic DVT and 0 pulmonary emboli and caused 2 major bleeds as compared with enoxaparin.[37] We too found reductions in VTEs with Factor Xa inhibitors when compared to enoxaparin. Loke and colleagues' findings are consistent with ours: They found rivaroxaban to be superior to enoxaparin for VTE prevention (RR 0.56), but with an increased risk of hemorrhage (RR 1.26).[38] They also found dabigatran to be equivalent in safety (RR 1.10) and efficacy (RR 1.12) to enoxaparin. Indirectly, they suggested that rivaroxaban was more efficacious than dabigatran, but with more bleeding. An important difference between our study and prior meta-analyses is that we included fondaparinux and edoxaban.

There were limitations to our meta-analyses. Although the risk of VTE after arthroplasty persists for months, the trials had incongruent treatment periods, sometimes for less than 30 days.[39] Second, in clinical practice, objective DVT screening is not done routinely, and screening in the trials might have prevented some DVTs from becoming symptomatic. Third, all trials were sponsored by the manufacturer of the newer drug. Furthermore, none of the studies were powered to detect reductions in symptomatic VTEs or death. Finally, the individual studies excluded patients at a higher risk of bleeding, suggesting that rates of bleeding may be greater in clinical practice than in the trials.

Our meta-analyses also had several important strengths. All of the included trials objectively confirmed DVTs with venography and were randomized controlled and double-blind, thereby minimizing bias. Finally, we included both efficacy and safety, thereby quantifying relevant tradeoffs. The tradeoffs could be used in future guidelines to favor more potent anticoagulants in the arthroplasty subpopulation at highest risk of VTE and lowest risk of bleeding.

There would be additional advantages to substituting the new anticoagulants for enoxaparin or fondaparinux: cost and route of administration. Enoxaparin and fondaparinux require

subcutaneous administration while the newer anticoagulants are taken orally. Patients prefer oral administration, and subcutaneous administration can decrease compliance.[40] At a cost of $14.32 for 30 mg twice daily or $9.58 for 40 mg once daily (plus nursing time to administer the injection), enoxaparin is also more expensive than the newer anticoagulants. In the US, the wholesale prices are $13.30 for rivaroxaban (10 mg once daily), $13.34 for dabigatran (150 mg once daily), $13.34 for apixaban (2.5 mg twice daily), and $11.65 for edoxaban (30mg once daily). These anticoagulants are cheaper in other countries.[41] Additionally, an antidote for dabigatran (idarucizumab) is currently available and an antidote for Xa inhibitors (andexanet alfa) will likely be available soon.[42]

In summary, compared to enoxaparin 40 mg daily, apixaban, rivaroxaban, fondaparinux, and edoxaban reduced the rate of VTE after arthroplasty. Only fondaparinux proved superior to enoxaparin 30 mg twice daily. With the exception of apixaban, which reduced major/clinically relevant bleeding, the newer anticoagulants that lowered the risk of post-operative VTE increased bleeding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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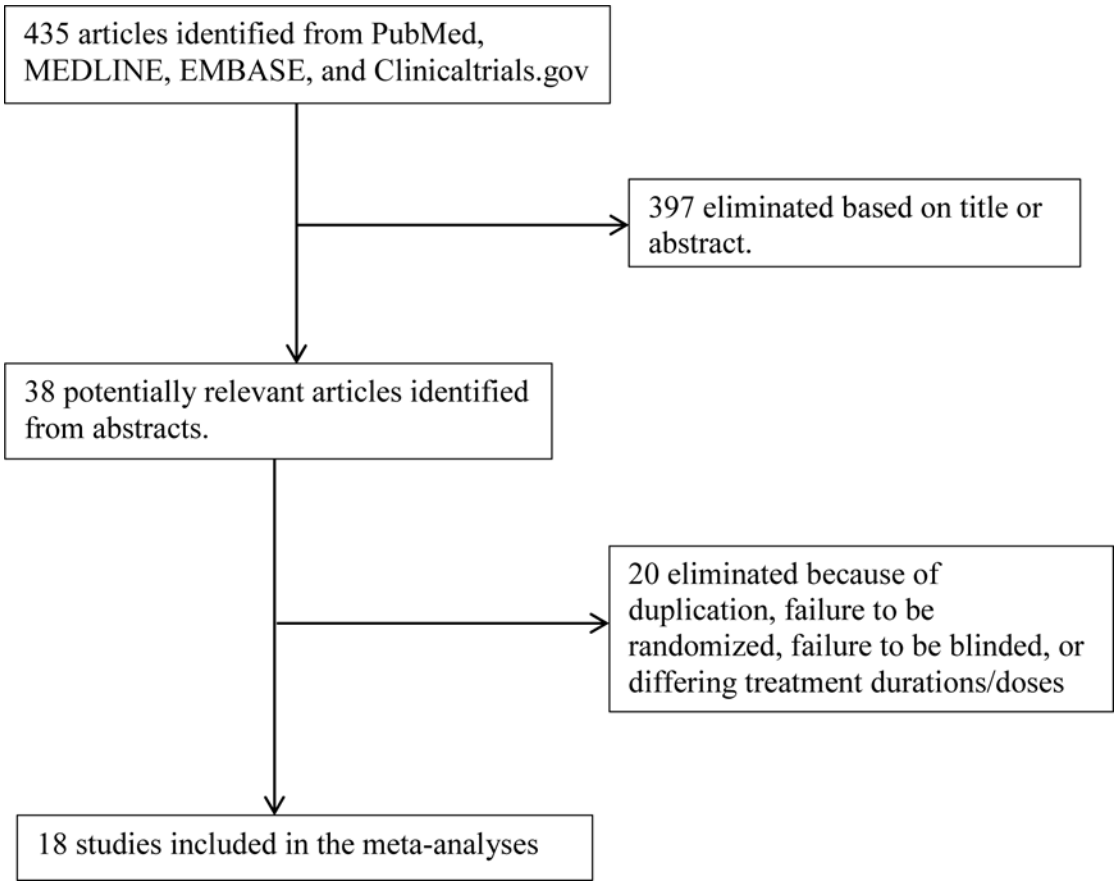

Figure 1.
Selection process for trials included in meta-analyses

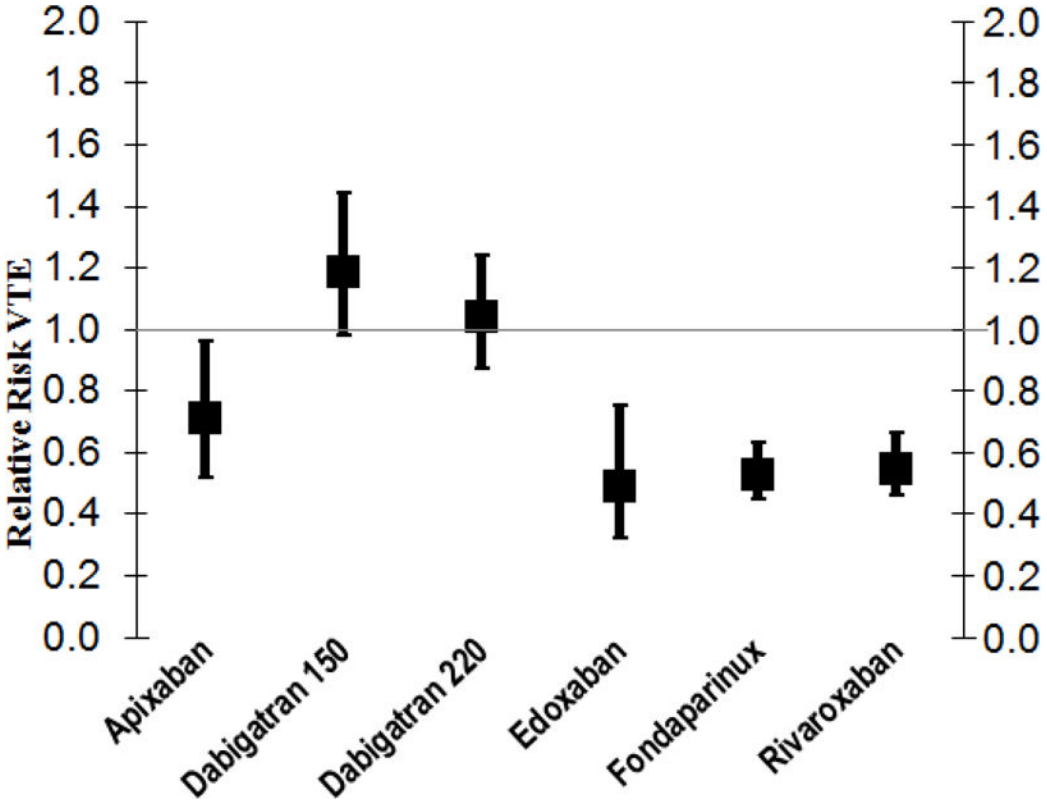

Figure 2.

Pooled Relative Risks of VTE (Venous Thromboembolism) with Newer Anticoagulants Compared to Enoxaparin

Abbreviations: RR, relative risk; VTE, venous thromboembolism

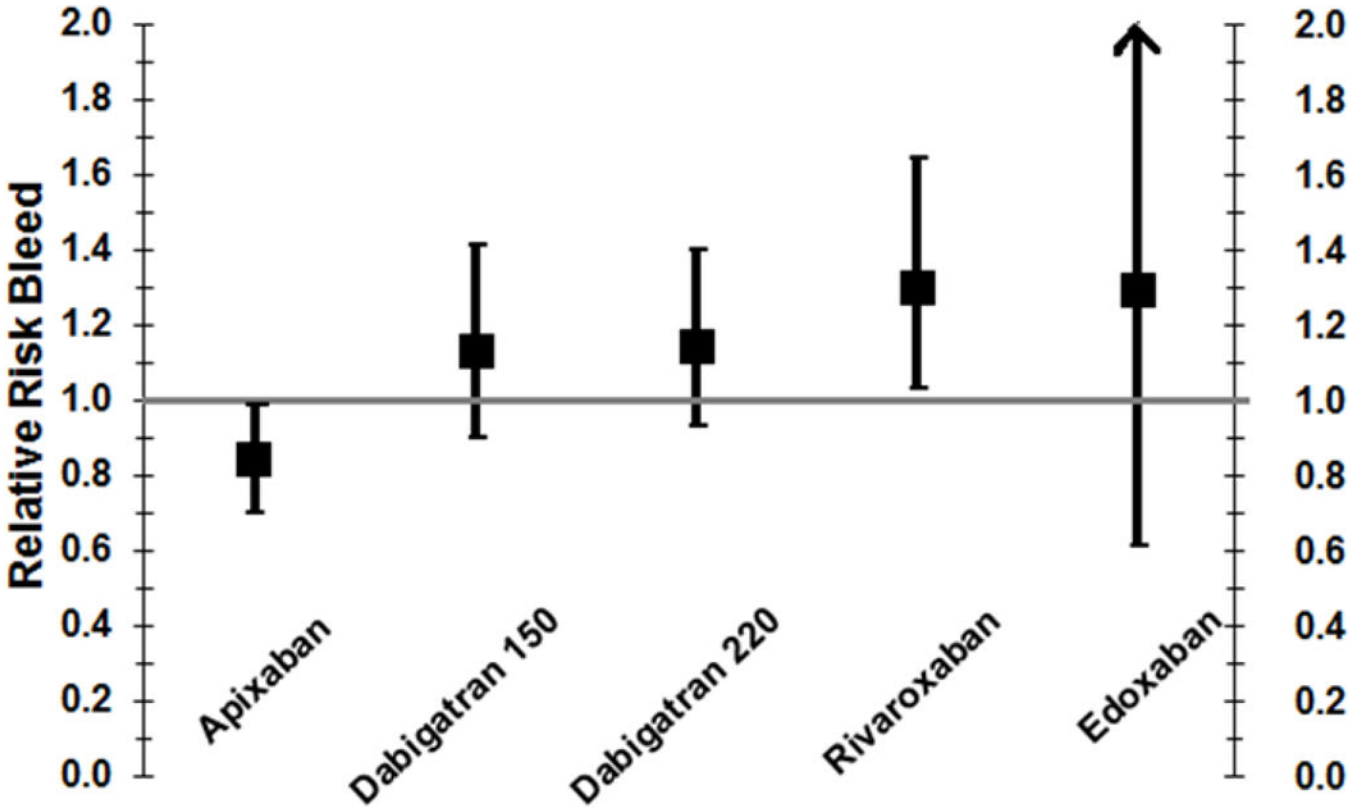

Figure 3.
Pooled RR of Major/Clinically Relevant Bleeding for Newer Anticoagulants Compared to Enoxaparin

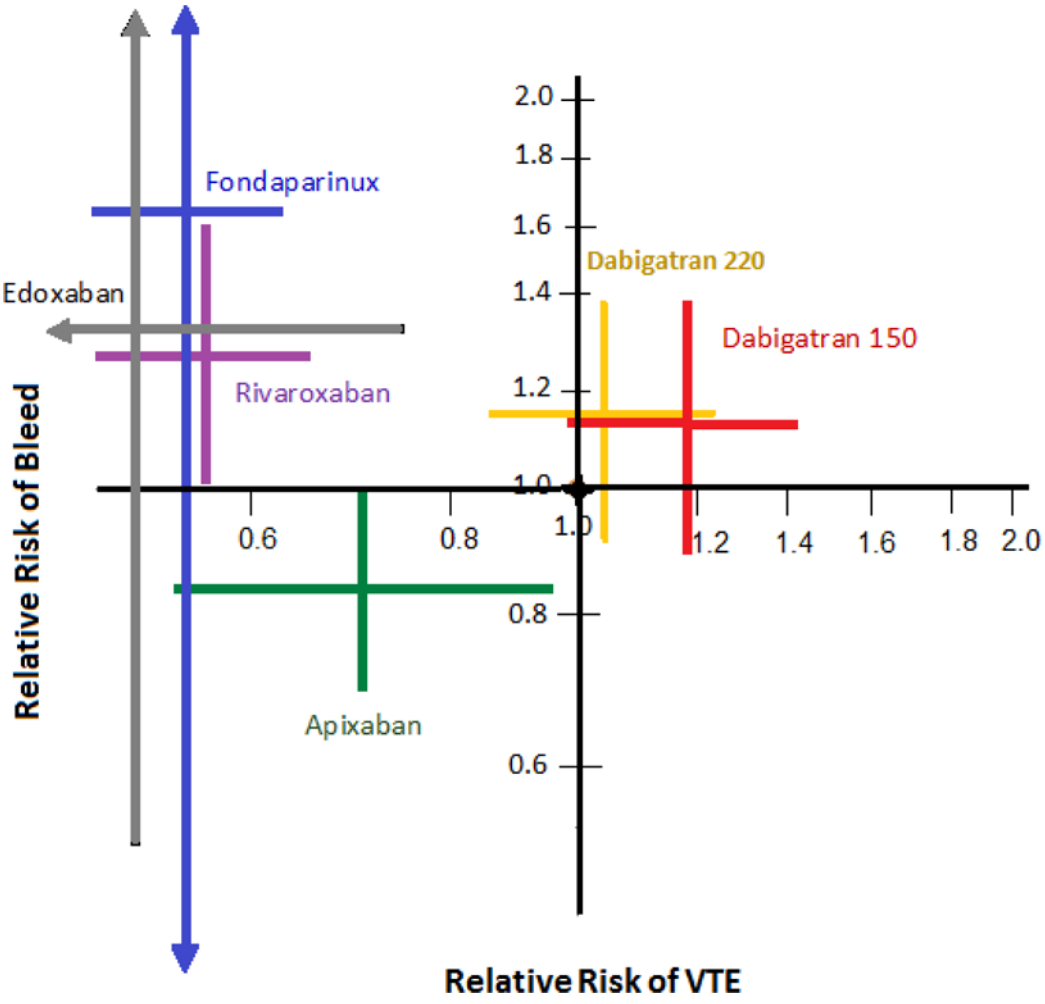

Figure 4.

Relative risk of bleeding vs. relative risk of VTE

*The black circle at the origin (1.0, 1.0) shows enoxaparin, the referent therapy.

The relative risk of bleeding—either major or non-major clinical relevant bleeding (vertical axis) and the relative risk of venous thromboembolism (VTE) (horizontal axis). Each cross shows the 95% confidence intervals of the relative risk from a meta-analysis.

Table 1

Meta-analysis of Apixaban Trials

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR Major Bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
APROPOS	2007	Apixaban 2.5 mg BID	153	12 days	10	0.58 (0.28–1.20)	0	NA	0	0.20 (.01–4.07)
		Enoxaparin 30 mg BID	152		17	–	0		0	
ADVANCE-1	2009	Apixaban 2.5 mg BID	1599	10–14 days	103	1.04 (0.80–1.35)	11	0.50 (0.24–1.02)	46	0.66 (0.46–0.96)
		Enoxaparin 30 mg BID	1596		97	–	22	–	69	–
ADVANCE-2	2010	Apixaban 2.5 mg BID	1528	10–14 days	146	0.61 (0.51–0.74)	9	0.65 (0.28–1.49)	53	0.74 (0.52–1.05)
		Enoxaparin 40 mg QD	1529		243	–	14	–	72	–
ADVANCE-3	2010	Apixaban 2.5 mg BID	2708	35 days	25	0.34 (0.21–.53)	22	1.22 (0.65–2.26)	129	0.96 (0.76–1.21)
		Enoxaparin 40 mg QD	2699		73	–	18	–	134	–
Meta-analysis	**2007–2010**	**Apixaban 2.5 mg BID**	**5988**	**10–35 days**	**284**	**0.71 (0.52–0.96)**	**42**	**0.85 (0.53–1.34)**	**228**	**0.84 (0.70–0.99)**
		Enoxaparin variable dose	**5976**		**430**	–	**54**	–	**275**	–

*RR compared to enoxaparin. Values in parentheses denote a 95% confidence interval.

Abbreviations: RR, relative risk; VTE, venous thromboembolism; NA: Not available

Table 2

Meta-analysis of Dabigatran Trials

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR major bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
RE-MODEL	2007	Dabigatran 150 mg QD	708	6–10 days	212	1.07 (0.92–1.25)	9	0.99 (0.39–2.47)	57	1.22 (0.84–1.78)
		Dabigatran 220 mg QD	694		182	0.96 (0.82–1.13)	10	1.14 (0.46–2.78)	50	1.11 (0.76–1.63)
		Enoxaparin 40 mg QD	699		193	–	9	–	46	–
RE-MOBILIZE	2009	Dabigatran 150 mg QD	877	12–15 days	218	1.33 (1.11–1.60)	5	0.42 (0.15–1.17)	27	0.82 (0.49–1.34)
		Dabigatran 220 mg QD	862		187	1.22 (1.02–1.46)	5	0.42 (0.15–1.19)	28	0.86 (0.52–1.41)
		Enoxaparin 30 mg BID	876		163	–	12	–	33	–
RE-NOVATE	2007	Dabigatran 150 mg QD	1174	28–35 days	74	1.27 (0.91–1.76)	15	0.83 (0.42–1.63)	70	1.20 (0.85–1.68)
		Dabigatran 220 mg QD	1157		51	0.87 (0.60–1.24)	23	1.29 (0.70–2.37)	71	1.23 (0.88–1.73)
		Enoxaparin 40 mg QD	1162		60	–	18	–	58	–
RE-NOVATE II	2011	Dabigatran 220 mg QD	1036	28–35 days	61	0.88 (0.63–1.22)	14	1.54 (0.67–3.55)	37	1.27 (0.79–2.04)
		Enoxaparin 40 mg QD	1019		69	–	9	–	29	–
Meta-analysis	**2007–2011**	**Dabigatran 150 mg QD**	2759	**6–35 days**	**504**	**1.19 (0.98–1.44)**	**29**	**0.78 (0.48–1.27)**	**154**	**1.13 (0.90–1.41)**
		Enoxaparin variable dose (compared to dabigatran 150 mg)	2737		**416**	–	**39**	–	**137**	–
		Dabigatran 220 mg QD	3749		**481**	**1.04 (0.87–1.24)**	**52**	**1.19 (0.80–1.77)**	**186**	**1.14 (0.93–1.40)**

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR major bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
		Enoxaparin variable dose (compared to dabigatran 220 mg)	3756		**485**	–	**48**	–	**166**	–

*RR compared to enoxaparin. Values in parentheses denote a 95% confidence interval. Abbreviations: RR, relative risk; VTE, venous thromboembolism

Table 3

Meta-analysis of Fondaparinux Trials

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR major bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
PENTAMAKS	2001	Fondaparinux 2.5 mg QD	526	5–9 days	45	0.45 (0.33–0.62)	11	11.00 (1.43–84.90)	11	NA
		Enoxaparin 30 mg BID	523		101	–	1		1	–
PENTHIFRA	2001	Fondaparinux 2.5 mg QD	849	5–9 days	52	0.52 (0.38–0.70)	18	0.96 (0.51–1.82)	18	NA
		Enoxaparin 40 mg QD	862		119	–	19	–	19	–
PENTATHLON 2000	2002	Fondaparinux 2.5 mg QD	1138	5–9 days	48	0.74 (0.51–1.05)	20	1.82 (0.88–3.78)	20	NA
		Enoxaparin 30 mg BID	1137		66	–	11	–	11	–
EPHESUS	2002	Fondaparinux 2.5 mg QD	1155	5–9 days	37	0.44 (0.30–0.64)	47	1.46 (0.94–2.27)	47	NA
		Enoxaparin 40 mg QD	1154		85	–	32	–	32	–
Meta-analysis	**2001–2002**	**Fondaparinux 2.5 mg QD**	3668	**5–9 days**	**182**	**0.53 (0.45–0.63)**	**96**	**1.64 (0.24–11.35)**	**96**	**NA**
		Enoxaparin variable dose	3676		**371**	–	**63**	–	**63**	–

*RR compared to enoxaparin. Values in parentheses denote a 95% confidence interval.

Abbreviations: RR, relative risk; VTE, venous thromboembolism

Table 4

Meta-analysis of Rivaroxaban Trials

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR major bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
ODIXa-HIP	2006	Rivaroxaban 10 mg QD	147	5–9 days	12	0.42 (0.22–0.79)	1	0.37 (0.04–3.50)	4	0.55 (0.17–1.80)
		Enoxaparin 40 mg QD	160		27	–	3	–	8	–
RECORD-1	2008	Rivaroxaban 10 mg QD	2266	31–39 days	16	0.28 (0.16–0.49)	6	3.02 (0.61–14.95)	71	1.28 (0.90–1.80)
		Enoxaparin 40 mg QD	2275		55	–	2	–	56	–
RECORD-3	2008	Rivaroxaban 10 mg QD	1254	10–14 days	79	0.51 (0.40–0.66)	7	1.18 (0.40–3.52)	40	1.19 (0.76–1.87)
		Enoxaparin 40 mg QD	1277		164	–	6	–	34	–
RECORD-4	2009	Rivaroxaban 10 mg QD	1584	10–14 days	57	0.73 (0.53–1.02)	10	2.47 (0.78–7.86)	49	1.42 (0.92–2.19)
		Enoxaparin 30 mg BID	1564		79	–	4	–	34	–
Meta-analysis	**2007–2010**	**Rivaroxaban 10 mg QD**	5251	**5–39 days**	**164**	**0.55 (0.46–0.66)**	**24**	**1.88 (0.67–5.29)**	**164**	**1.27 (1.01–1.59)**
		Enoxaparin variable dose	5276		**325**	–	**15**	–	**132**	–

*RR compared to enoxaparin. Values in parentheses denote a 95% confidence interval.

Abbreviations: RR, relative risk; VTE, venous thromboembolism

Table 5

Meta-analysis of Edoxaban Trials

Trial	Year	Regimen	No. of Patients Randomized	Treatment Duration	No. of VTEs	RR VTE*	No. of Major Bleeds	RR major bleeding*	No. of Major/ Clinically Relevant Bleeds	RR Major/ Clinically Relevant Bleeding*
STARS E-3	2014	Edoxaban 30 mg QD	360	11–14 days	22	0.53 (0.32–0.87)	4	3.94 (0.44–35.11)	22	1.67 (0.85–3.26)
		Enoxaparin 20 mg BID	365		41	–	1	–	13	–
STARS J-V	2015	Edoxaban 30 mg QD	307	11–14 days	6	0.34 (0.14–0.86)	2	0.33 (0.07–1.63)	8	0.72 (0.29–1.77)
		Enoxaparin 20 mg BID	303		17	–	6	–	11	–
Meta-analysis	**2014–2015**	**Edoxaban 30 mg QD**	667	**11–14 days**	**28**	**0.49 (0.32–0.75)**	**6**	**1.58 (0.05–54.38)**	**30**	**1.33 (0.53–3.34)**
		Enoxaparin 20 mg BID	668		**58**	–	**7**	–	**24**	–

*RR compared to enoxaparin. Values in parentheses denote a 95% confidence interval.

Abbreviations: RR, relative risk; VTE, venous thromboembolism