Comparative efficacy and safety of anticoagulants for prevention of venous thromboembolism after hip and knee arthroplasty

A network meta-analysis

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Background and purpose — New oral anticoagulants have been developed to prevent venous thromboembolism (VTE) after knee or hip arthroplasty. Although there have been several network meta-analyses (NMA) to compare different regimens, an NMA including 2 different enoxaparin doses and edoxaban has not been performed.

Methods — Standard NMA for fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, and enoxaparin was performed. Outcome variables included a composite of total VTE and major/clinically relevant bleeding. The rank probabilities of each treatment outcome were summarized by the surface under the cumulative ranking curve.

Results — Fondaparinux, rivaroxaban, and apixaban were associated with a reduced risk of VTE compared with enoxaparin, while dabigatran was not. None of these 3 drugs increased bleeding compared with enoxaparin 30 mg twice daily. However, fondaparinux and rivaroxaban increased bleeding compared with enoxaparin 40 mg once daily, while apixaban did not. Apixaban was even associated with decreased major/clinically relevant bleeding compared with enoxaparin 30 mg twice daily or 40 mg once daily. When edoxaban was included in the NMA, edoxaban decreased VTE and did not increase bleeding compared with enoxaparin.

Interpretation — A higher efficacy of fondaparinux and rivaroxaban compared with enoxaparin was associated with increased bleeding tendency, while apixaban was superior to enoxaparin regarding both efficacy and safety. A clustered ranking plot showed that apixaban might be the most preferred regarding efficacy and safety. However, our results were driven by indirect statistical inference and were limited by the heterogeneity of the bleeding outcome definitions, drug initiation and continuation, and different surgery types.

A 10% incidence of venous thromboembolism (VTE) has been reported after knee or hip arthroplasty (White et al. 2003, Miyagi et al. 2007), although recent development of fast-track surgery may have reduced postoperative VTE (Jorgensen and Kehlet 2017). The incidence of symptomatic VTE was estimated to be as high as 4% with no prophylaxis in patients undergoing knee or hip arthroplasty (Falck-Ytter et al. 2012). New anticoagulants have been developed for prophylaxis against VTE, substituting the warfarin and low-molecular-weight heparins (Gomez-Outes et al. 2012, Ageno et al. 2016), including dabigatran, rivaroxaban, apixaban, and edoxaban, which are now available despite varying degrees of approval around the world (Gomez-Outes et al. 2012, Venker et al. 2017). Previous randomized controlled trials (RCTs) have compared the efficacy and safety of these new agents by comparing a single new agent with a previous standard, enoxaparin (Sardar et al. 2015). Most studies reported higher efficacy of the new anticoagulants, but there are conflicting results as to whether the new drugs increase the risk of bleeding.

Previous meta-analyses compared clinically significant bleeding between different anticoagulants. However, neither the definition of bleeding nor the results were consistent. Some studies reported increased bleeding while others did not (Gomez-Outes et al. 2012, Neumann et al. 2012, Sardar et al. 2015). The risk of major bleeding varies according to the indication of use and the type of drugs (Sardar et al. 2015, Venker et al. 2017). Furthermore, previous RCTs used 2 different dose regimens of enoxaparin, 40 mg subcutaneous once daily (q.d. as the European standard and 30 mg subcutaneously twice daily (b.i.d.) as the United States standard. In previous meta-analyses, these 2 different doses were often integrated as an "enoxaparin various dose group"

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and separate comparison of these 2 control groups has not yet been performed. A network meta-analysis (NMA) is a statistical technique for comparing different treatments that have not been directly compared with adequately powered head-to-head in randomized controlled trials (Baker and Kramer 2002, Song et al. 2003). NMA allows head-to-head comparisons of all possible pairs of anticoagulants as well as 2 enoxaparin dose groups.

Several NMAs have shown similar or better efficacy and similar safety of new oral anticoagulants compared with enoxaparin (Maratea et al. 2011, Cohen et al. 2012, Harenberg et al. 2012, Kapoor et al. 2017). However, they did not provide comparison according to the 2 different doses of enoxaparin and did not include edoxaban. Therefore, the primary aim of our NMA was to perform all the possible head-to-head comparisons of 6 currently available and approved new oral anticoagulants to compare efficacy in preventing VTE and safety from the risk of a composite of major/clinically relevant non-major (CRNM) bleeding after hip and knee arthroplasty.

Patients and methods

Data sources

To compare the efficacy and safety of 6 anticoagulants used to prevent VTE after major orthopedic surgery, we performed a systemic review and NMA according to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011) and the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statements (Moher et al. 2009).

Eligibility criteria and search strategy

4 investigators (MH, SK, CK, and PK) independently searched Medline via the PubMed interface, Embase databases, and the Cochrane central register of Controlled Trials (Central, Issue 10 of 2016) from inception to December 2016 (for search strategy, see Supplementary data). They independently reviewed the titles and abstracts of all searched studies to identify eligible trials.

We included only the double-blinded RCTs that enrolled adult patients within 48 hours of total hip or knee arthroplasty and compared the incidence of VTE between any of the approved anticoagulants with approved doses including fondaparinux 2.5 mg once daily (q.d.), dabigatran 150 mg or 220 mg q.d., rivaroxaban 10 mg q.d., apixaban 2.5 mg b.i.d., edoxaban 30 mg q.d. and enoxaparin 40 mg q.d. (E40) or 30 mg b.i.d. (E60). The experimental and control arms in included trials were dosed within 30 hours of each other and the incidence of VTE was confirmed. The studies without standard treatment group (enoxaparin) or those that used a dose not approved by the US Food and Drug Administration, the European Medicine Agency, or the Pharmaceutical and Food Safety Bureau of Japan were excluded.

Data extraction and risk of bias assessment

MH, SP, CK and PK reviewed the manuscripts of all studies and extracted data into a uniform data extraction form developed by the authors. The risk of bias of individual studies was assessed (Higgins and Green 2011).

Outcome measures

The pre-specified primary efficacy endpoint was a composite of VTEs that included symptomatic/asymptomatic proximal/distal DVT and/or non-fatal symptomatic pulmonary embolism. The pre-specified primary safety outcome was a composite of major bleeding and clinically relevant non-major bleeding (CRNM bleeding).

Statistics

Data were analyzed using Stata/SE (version 14.0, StataCorp, College Station, Texas, USA) and Review Manager 5.3 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). An arm-based, random-effect NMA was performed by STATA (www.stata.com) using the "mvmeta" and self-programmed STATA routines (White et al. 2012, Chaimani et al. 2013). Estimates from all outcome variables were presented as relative risk (RR) with 95% confidence intervals (CIs).

Our analysis was performed as 2 separate networks with and without edoxaban because edoxaban was compared with enoxaparin 20 mg b.i.d. only, a dose regimen that was never used in other trials. E60 or E40 was used for all trials except the trials for edoxaban. The trials for edoxaban were performed in Japan and used enoxaparin 20 mg b.i.d., a standard dose for the Asian population. Therefore, to include edoxaban in our network, 2 different enoxaparin groups were combined into 1 group called the enoxaparin various dose group.

We performed 2 different network analyses to analyze the effect of different enoxaparin dose regimen groups and also to include the comparison with edoxaban. The first analysis set included 2 separate enoxaparin dose groups and did not include studies of edoxaban, while the second analysis set included the "enoxaparin various dose group" and the studies of edoxaban. The first analysis set included 7 separate treatment network nodes of 5 anticoagulants. The second analysis set included 7 nodes of 6 anticoagulants. In addition, we performed a sensitivity analysis for these 2 safety outcomes separately because the clinical relevance of major bleeding and CRNM bleeding differs significantly.

To rank the treatments for an outcome, the comparative influence of all anticoagulants with the unique dimension was estimated from a multidimensional scaling approach (Chaimani et al. 2013). Clustered ranking plots of the anticoagulants were depicted based on the clustered analysis of surface under the cumulative ranking (SUCRA) probabilities for 2 different outcomes (Li et al. 2015). SUCRA values mean efficacy or safety percentage of each treatment relative to a hypothetical comparator that is the best without uncertainty. SUCRA probabilities can be calculated in the range of 0 to

Table 1. Summary of included studies

First author/ year	Trial name	Surgery type	Regimen	No. of patients	Duration (days)	Time of drug initiation	Day of venography	Follow-up (days)
Bauer 2001	PENTAMAKS	Knee	Fondaparinux 2.5 mg q.d.	526	5–9	6–8 h postop.	5–11	35–49
			Enoxaparin 30 mg b.i.d.	523	5–9	12–24 h postop.		
Eriksson 2001	PENTHIFRA	Hip	Fondaparinux 2.5 mg q.d.	849	5–9	6±2 h postop.	5–11	35–49
			Enoxaparin 40 mg q.d.	862	5–9	12±2 h preop.		
Turpie 2002	PENTATHLON	Hip	Fondaparinux 2.5 mg q.d.	1,138	5–9	6–8 h postop.	5–11	35–49
			Enoxaparin 30 mg b.i.d.	1,137	5–9	12–24 h postop.		
Lassen 2002	EPHESUS	Hip	Fondaparinux 2.5 mg q.d.	1,155	5–9	6–8 h postop.	5–11	35–49
			Enoxaparin 40 mg q.d.	1,154	5–9	12h preop.		
Lassen 2007	APROPOS	Knee	Apixaban 2.5 mg b.i.d.	153	12	12–24 h postop.	10–14	42
			Enoxaparin 30 mg b.i.d.	152	12	12–24 h postop.		
Lassen 2009	ADVANCE–1	Knee	Apixaban 2.5 mg b.i.d.	1,599	10–14	12–24 h postop.	10–14	70–84
			Enoxaparin 30 mg b.i.d.	1,596	10–14	12–24 h postop.		
Lassen 2010	ADVANCE–2	Knee	Apixaban 2.5 mg b.i.d.	1,528	10–14	12–24 h postop.	10–14	70–84
			Enoxaparin 40 mg q.d.	1,529	10–14	12 h preop. [a]		
Lassen 2010	ADVANCE–3	Hip	Apixaban 2.5 mg b.i.d.	2,708	35	12–24 h postop.	32–38	90–100
			Enoxaparin 40 mg q.d.	2,699	35	12 h preop.		
Eriksson 2007	RE-MODEL	Knee	Dabigatran 150 mg q.d.	708	6–10	1–4 h postop.	6–10	90
			Dabigatran 220 mg q.d.	694	6–10	1–4 h postop.		
			Enoxaparin 40 mg q.d.	699	6–10	12 h preop.		
Eriksson 2007	RE-NOVATE	Hip	Dabigatran 150 mg q.d.	1,174	28–35	1–4 h postop.	33	94
			Dabigatran 220 mg q.d.	1,157	28–35	1–4 h postop.		
			Enoxaparin 40 mg q.d.	1,162	28–35	12 h preop.		
Ginsberg 2009	RE-MOBILIZE	Knee	Dabigatran 150 mg q.d.	877	12–15	6–12 h postop.	14	90
			Dabigatran 220 mg q.d.	862	12–15	6–12 h postop.		
			Enoxaparin 30 mg b.i.d.	876	12–15	12–24 h postop.		
Eriksson 2011	RE-NOVATE II	Hip	Dabigatran 220 mg q.d.	1,036	28–35	1–4 h postop.	32	90
			Enoxaparin 40 mg q.d.	1,019	28–35	12 h preop.		
Eriksson 2006	ODIXa-HIP	Hip	Rivaroxaban 10 mg q.d.	142	5–9	6–8 h postop.	6–10	35–69
			Enoxaparin 40 mg q.d.	160	5–9	12 h preop.		
Eriksson 2008	RECORD-1	Hip	Rivaroxaban 10 mg q.d.	2,266	31–39	6–8 h postop.	36	66–71
			Enoxaparin 40 mg q.d.	2,275	31–39	12 h preop.		
Kakkar 2008	RECORD-2	Hip	Rivaroxaban 10 mg q.d.	1,252	31–39	6–8 h postop.	32–40	62–75
			Enoxaparin 40 mg q.d.	1,257	10–14	12 h preop.		
Lassen 2008	RECORD-3	Knee	Rivaroxaban 10 mg q.d.	1,154	10–14	6–8 h postop.	11–15	41–50
			Enoxaparin 40 mg q.d.	1,277	10–14	12 h preop.		
Turpie 2009	RECORD-4	Knee	Rivaroxaban 10 mg q.d.	1,584	10–14	6–8 h postop.	11–15	40–49
			Enoxaparin 30 mg b.i.d.	1,564	10–14	12–24 h postop.		
Fuji 2014	STARS E-3	Knee	Edoxaban 30 mg q.d.	360	11–14	6–24 h postop.	12–15	25–35
			Enoxaparin 20 mg b.i.d.	365	11–14	24–36 h postop.		
Fuji 2015	STARS J-V	Hip	Edoxaban 30 mg q.d.	307	11–14	6–24 h postop.	12–15	25–35
			Enoxaparin 20 mg b.i.d.	303	11-14	24-36 h postop.		

q.d. = once daily, b.i.d. = twice daily.
[a] (within 3 h of operation)

100 as a simple transformation of the mean rank in cumulative ranking analysis and a larger SUCRA value means higher rank of the treatment.

Funding and potential conflicts of interest

This study did not receive any external funding. No conflicts of interest were declared.

Results

Eligible studies

Figure 1 (see Supplementary data) shows the search results and reasons for exclusion from the current study. After screening titles and abstracts, 19 studies were finally included (Table 1) (Table 4, see Supplementary data). All studies were sponsored by the manufacturers and the data were collected and analyzed by the study sponsors.

Study characteristics

The 19 double-blind clinical trials were published between 2001 and 2015 and included 43,838 subjects. Among them, 20,609 (47%) had enoxaparin and 3,668 (8%) had fondaparinux. The numbers of patients who received apixaban, dabigatran, rivaroxaban, and edoxaban were 5,988 (14%), 6,508 (15%), 6,398 (15%), and 667 (1.5%), respectively.

Risk of bias among included studies

All trials were judged to be at unclear or high risk of bias (Figure 2, see Supplementary data). 13 studies did not describe

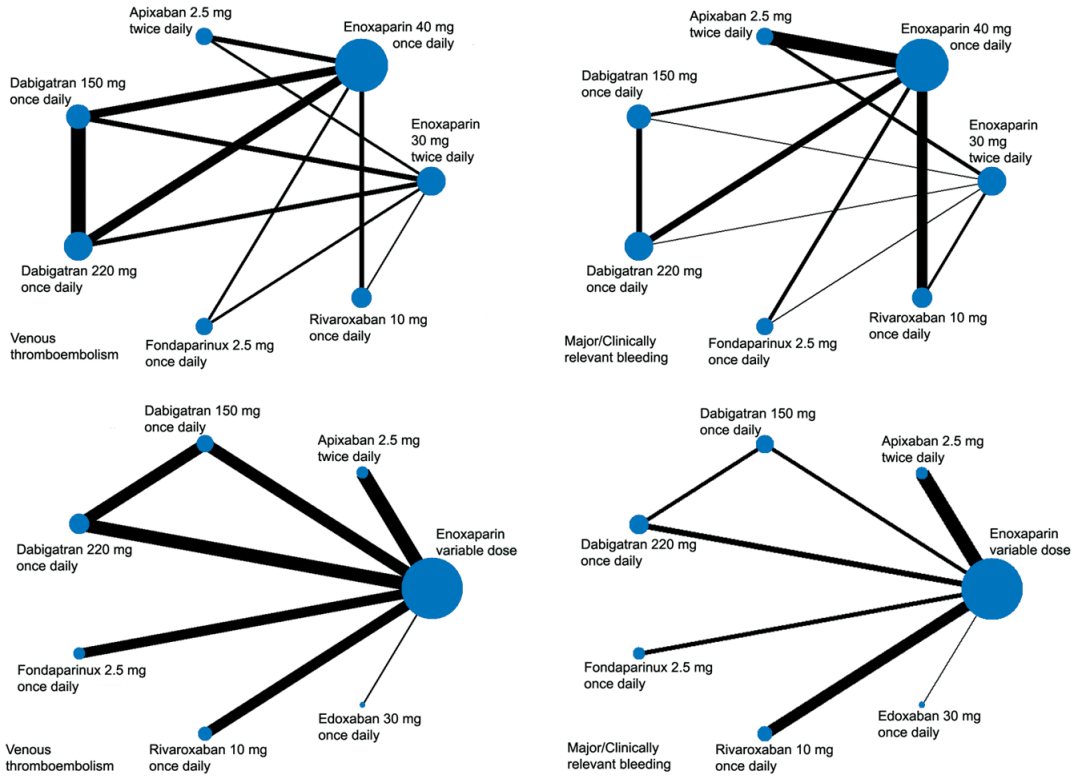

Figure 3. Network plots of anticoagulants depicted according to the 2 outcomes of venous thromboembolism and major/clinically relevant non-major bleeding. The upper row shows the first analysis set including 2 enoxaparin dose groups and excluding edoxaban. The lower row shows the second analysis set including 1 enoxaparin dose group and including edoxaban. Nodes are weighted according to the number of patients with the respective interventions. Edges are weighted according to the number of studies between the 2 connected modalities.

in detail how participants and personnel were blinded. 8 trials were considered to report incomplete outcome data. All trials were considered to have industrial sponsorship bias.

Data synthesis and analysis

42,503 patients from 17 studies except for 2 studies of edoxaban (Fuji et al. 2014, 2015) were available for the first analysis set for the 3 outcomes. 43,838 patients from 19 studies were available for the second analysis set for all 3 outcomes. Eligible direct comparisons for 3 outcomes between drugs of the first and second analysis set in the NMA showed predominantly pairwise comparisons of enoxaparin with other drugs (Figure 3). The means and CIs of network comparison of VTE and major/CRNM bleeding in both analysis sets are given in Tables 2 and 3.

Network comparison in the first analysis set: 2 enoxaparin groups without edoxaban

Patients treated with fondaparinux 2.5 mg q.d. and rivaroxaban 10 mg q.d. were associated with a reduced risk of VTE compared with those treated with either E60 or E40. Apixaban 2.5 mg b.i.d. statistically significantly decreased the incidence of VTE compared with E40 but not compared with E60. With respect to safety outcomes, none of the 3 drugs increased the risk of major/CRNM bleeding compared with E60. The risk of major/CRNM bleeding of apixaban was even lower than that of E60 (RR 0.75, CI 0.57–0.98). However, fondaparinux and rivaroxaban increased the risk of major/CRNM bleeding compared with E40, while apixaban did not. The comparison between 2 different enoxaparin regimen groups, albeit indirect, exhibited that E60 was associated with less VTE, but was not associated with increased bleeding tendency. Meanwhile, the comparison between 2 different doses of dabigatran showed no difference regarding efficacy and safety in either analysis set. Sensitivity analysis of major bleeding and CRNM bleeding showed that most of the results were similar to the analysis using the combined safety outcome of major/CRNM bleeding (Tables 5 and 6, see Supplementary data).

Network comparison in the second analysis set: 1 enoxaparin group with edoxaban

Fondaparinux, apixaban, rivaroxaban, and edoxaban statistically significantly decreased the incidence of VTE compared with the various doses of enoxaparin. However, fondaparinux and rivaroxaban statistically significantly increased the incidence of major/CRNM bleeding compared with various doses

Table 2. Comparison of 7 interventions regarding 2 outcomes by using network odds ratios in the first analysis set

Outcome	Enoxaparin 30 mg b.i.d.	Enoxaparin 40 mg q.d.	Apixaban 2.5 mg b.i.d.	Dabigatran 150 mg q.d.	Dabigatran 220 mg q.d.	Fondaparinux 2.5 mg q.d.	Rivaroxaban 10 mg q.d.
Venous thromboembolism							
Enoxaparin 30 mg b.i.d.		0.65 [a] (0.50–0.83)	1.26 (0.94–1.71)	0.60 [a] (0.45–0.81)	0.76 (0.57–1.01)	1.73 (1.30–2.29)	1.70 [a] (1.24–2.33)
Enoxaparin 40 mg q.d.	1.54 [a] (1.20–1.98)		1.95 [a] (1.46–2.60)	0.93 (0.72–1.20)	1.17 (0.92–1.48)	2.66 [a] (2.01–3.53)	2.61 [a] (1.99–3.44)
Apixaban 2.5 mg b.i.d.	0.79 (0.59–1.07)	0.51 [a] (0.39–0.68)		0.48 [a] (0.33–0.69)	0.60 [a] (0.42–0.85)	1.37 (0.95–1.97)	1.34 (0.93–1.93)
Dabigatran 150 mg q.d.	1.66 [a] (1.23–2.23)	1.07 (0.83–1.39)	2.09 [a] (1.46–3.01)		1.25 (0.98–1.60)	2.86 [a] (2.01–4.07)	2.81 [a] (1.96–4.03)
Dabigatran 220 mg q.d.	1.32 (0.99–1.76)	0.86 (0.67–1.09)	1.67 [a] (1.18–2.37)	0.80 (0.62–1.02)		2.28 [a] (1.62–3.21)	2.24 [a] (1.58–3.17)
Fondaparinux 2.5 mg q.d.	0.58 [a] (0.44–0.77)	0.38 [a] (0.28–0.50)	0.73 (0.51–1.06)	0.35 [a] (0.25–0.50)	0.44 [a] (0.31–0.62)		0.98 (0.68–1.42)
Rivaroxaban 10 mg q.d.	0.59 [a] (0.43–0.81)	0.38 [a] (0.29–0.50)	0.75 (0.52–1.07)	0.36 [a] (0.25–0.51)	0.45 [a] (0.32–0.51)	1.02 (0.70–1.47)	
Major/ clinically relevant non-major bleeding							
Enoxaparin 30 mg b.i.d.		1.13 (0.88–1.47)	1.34 [a] (1.03–1.75)	0.97 (0.72–1.33)	0.98 (0.73–1.33)	0.75 (0.51–1.11)	0.88 (0.66–1.17)
Enoxaparin 40 mg q.d.	0.88 (0.68–1.14)		1.18 (0.98–1.43)	0.86 (0.68–1.09)	0.87 (0.70–1.08)	0.67 [a] (0.48–0.93)	0.77 [a] (0.62–0.96)
Apixaban 2.5 mg b.i.d.	0.75 [a] (0.57–0.98)	0.85 (0.70–1.02)		0.73 [a] (0.54–0.97)	0.73 [a] (0.55–0.97)	0.56 [a] (0.39–0.82)	0.65 [a] (0.50–0.86)
Dabigatran 150 mg q.d.	1.03 (0.75–1.40)	1.16 (0.92–1.47)	1.38 [a] (1.03–1.84)		1.01 (0.80–1.26)	0.77 (0.52–1.16)	0.90 (0.66–1.21)
Dabigatran 220 mg q.d.	1.02 (0.75–1.38)	1.15 (0.93–1.44)	1.37 [a] (1.03–1.81)	0.99 (0.79–1.25)		0.77 (0.52–1.14)	0.89 (0.66–1.21)
Fondaparinux 2.5 mg q.d.	1.32 (0.90–1.95)	1.50 [a] (1.07–2.10)	1.78 [a] (1.22–2.59)	1.29 (0.86–1.93)	1.30 (0.88–1.93)		1.16 (0.79–1.72)
Rivaroxaban 10 mg q.d.	1.14 (0.85–1.52)	1.29 [a] (1.04–1.60)	1.53 [a] (1.16–2.01)	1.11 (0.81–1.52)	1.12 (0.83–1.51)	0.86 (0.58–1.27)	

95% confidence intervals are displayed in parenthesis. Odds ratios in the upper diagonal are reciprocals of those in the corresponding lower diagonal and they provide the same information in a slightly different way. Row interventions (numerator) were compared to column intervention (denominator). q.d.= once daily, b.i.d. = twice daily. Odds ratio <1 favors row-defining treatment.
[a] Statistically significant.

of enoxaparin, while apixaban and edoxaban did not. The risk of major/CRNM bleeding for apixaban was even lower than the risk for enoxaparin.

Relative ranking of anticoagulants

The clustered ranking plot depicted according to SUCRA values showed that apixaban is located in the most favorable position in terms of both VTE and major/CRNM bleeding in both analysis sets (Figure 4). Relative ranking plots of sensitivity analyses are shown in Figure 5 (see Supplementary data).

Discussion

We undertook an NMA comparing 6 anticoagulants used in the approved dose to prevent VTE after total hip or knee arthroplasty. Our network-pooled estimates of outcomes revealed that fondaparinux, rivaroxaban, and apixaban may have a higher efficacy of reducing VTE than enoxaparin, but fondaparinux and rivaroxaban were associated with a higher risk of major/CRNM bleeding than enoxaparin, while apixaban showed a lesser incidence. The relative ranking plot showed that apixaban may be the most favorable anticoagulant in terms of both efficacy and safety. Edoxaban also exhibited a higher efficacy without increasing bleeding risk, but wide confidence interval precludes a firm conclusion. Our results also suggest that the bleeding risk of new oral anticoagulants may differ depending on the dose regimen of enoxaparin. However, our results were limited by the significant heterogeneity of definition of bleeding outcome, initiation and continuation of drug, and surgery type.

Previous systemic reviews evaluated individual oral factor Xa inhibitors in major orthopedic surgery (Cao et al. 2010, Huang et al. 2011, Turun et al. 2011). Rivaroxaban was superior to enoxaparin in reducing the incidence of VTE (Cao et al. 2010, Turun et al. 2011). The risk of proximal DVT decreased with apixaban compared with enoxaparin (Huang et al. 2011). Oral anticoagulants can achieve a small absolute risk reduction in symptomatic DVT without increasing bleeding (Neumann et al. 2012). However, a higher efficacy of new anticoagulants including rivaroxaban, dabigatran, or apixaban was generally

Table 3. Comparison of 7 interventions regarding 2 outcomes by using network odds ratios in the second analysis set

Outcome	Enoxaparin various dose	Apixaban 2.5 mg b.i.d.	Dabigatran 150 mg q.d.	Dabigatran 220 mg q.d.	Fondaparinux 2.5 mg q.d.	Rivaroxaban 10 mg q.d.	Edoxaban 30 mg q.d
Venous thromboembolism							
Enoxaparin various dose		1.68 [a] (1.18–2.39)	0.81 (0.57–1.15)	1.04 (0.75–1.43)	2.15 [a] (1.53–3.01)	2.42 [a] (1.74–3.38)	2.24 [a] (1.19–4.24)
Apixaban 2.5 mg b.i.d.	0.59 [a] (0.42–0.84)		0.48 [a] (0.29–0.79)	0.62 [a] (0.38–0.99)	1.28 (0.78–2.08)	1.44 (0.89–2.33)	1.33 (0.64–2.75)
Dabigatran 150 mg q.d.	1.24 (0.87–1.75)	2.08 [a] (1.27–3.42)		1.28 (0.90–1.82)	2.66 [a] (1.63–4.32)	3.00 [a] (1.85–4.86)	2.77 [a] (1.34–5.73)
Dabigatran 220 mg q.d.	0.96 (0.70–1.33)	1.62 [a] (1.01–2.61)	0.78 (0.55–1.11)		2.07 [a] (1.30–3.29)	2.34 [a] (1.47–3.70)	2.16 [a] (1.06–4.40)
Fondaparinux 2.5 mg q.d.	0.47 [a] (0.33–0.65)	0.78 (0.48–1.28)	0.38 [a] (0.23–0.61)	0.48 [a] (0.30–0.77)		1.13 (0.70–1.81)	1.04 (0.51–2.15)
Rivaroxaban 10 mg q.d.	0.41 [a] (0.30–0.58)	0.69 (0.43–1.12)	0.33 [a] (0.21–0.54)	0.43 [a] (0.27–0.68)	0.89 (0.55–1.42)		0.93 (0.45–1.89)
Edoxaban 30 mg q.d.	0.45 [a] (0.24–0.84)	0.75 (0.36–1.55)	0.36 [a] (0.17–0.75)	0.46 [a] (0.23–0.94)	0.96 (0.47–1.97)	1.08 (0.53–2.21)	
Major/ clinically relevant non-major bleeding							
Enoxaparin various dose		1.22 [a] (1.02–1.46)	0.88 (0.70–1.11)	0.89 (0.71–1.10)	0.68 [a] (0.49–0.95)	0.78 [a] (0.64–0.97)	0.79 (0.45–1.38)
Apixaban 2.5 mg b.i.d.	0.82 [a] (0.69–0.98)		0.72 [a] (0.54–0.97)	0.73 [a] (0.55–0.96)	0.56 [a] (0.39–0.82)	0.64 [a] (0.49–0.85)	0.65 (0.36–1.17)
Dabigatran 150 mg q.d.	1.13 (0.90–1.43)	1.38 [a] (1.03–1.85)		1.01 (0.80–1.26)	0.78 (0.52–1.16)	0.89 (0.65–1.21)	0.90 (0.49–1.64)
Dabigatran 220 mg q.d.	1.13 (0.91–1.40)	1.37 [a] (1.04–1.82)	0.99 (0.79–1.25)		0.77 (0.52–1.15)	0.88 (0.66–1.19)	0.89 (0.49–1.62)
Fondaparinux 2.5 mg q.d.	1.46 [a] (1.05–2.03)	1.78 [a] (1.22–2.59)	1.29 (0.86–1.93)	1.29 (0.87–1.92)		1.14 (0.78–1.69)	1.15 (0.60–2.21)
Rivaroxaban 10 mg q.d.	1.28 [a] (1.04–1.57)	1.55 [a] (1.18–2.04)	1.12 (0.82–1.54)	1.13 (0.84–1.53)	0.87 (0.59–1.29)		1.01 (0.56–1.83)
Edoxaban 30 mg q.d.	1.26 (0.72–2.21)	1.54 (0.86–2.77)	1.11 (0.61–2.04)	1.12 (0.62–2.04)	0.87 (0.45–1.66)	0.99 (0.55–1.80)	

For footnotes, see Table 2.
[a] Statistically significant.

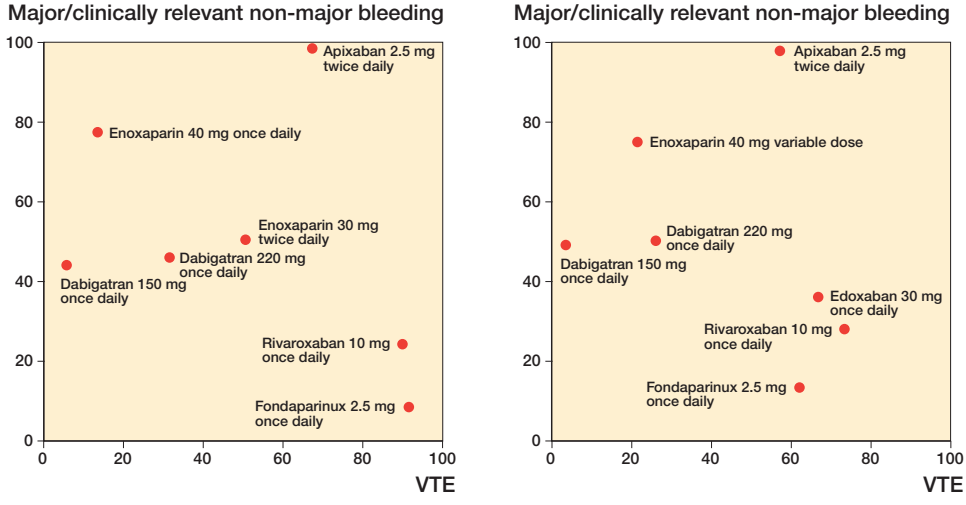

Figure 4. Clustered ranking plots of the anticoagulant network based on the analysis of the surface under the cumulative ranking curve (SUCRA) values for venous thromboembolism (X-axis) and a composite of major/clinically relevant non-major bleeding (Y-axis). Each dot was located according to the 2 SUCRA values of each drug for the 2 outcomes. The larger SUCRA values mean the better the rank of the drug. The drug located in the right upper corner has higher SUCRA values for both variables of the X and Y axes and is regarded as the most preferred of the drugs compared. Left and right panels correspond to first and second analysis set, respectively.

associated with a higher bleeding tendency (Gomez-Outes et al. 2012). A recent meta-analysis attempted to indirectly compare new anticoagulants using the effect sizes obtained by comparison with enoxaparin (Yoshida Rde et al. 2013). A composite of efficacies favored fondaparinux and rivaroxaban, and the incidence of proximal DVT favored apixaban. Regarding safety outcomes, fondaparinux exhibited a higher bleeding risk compared with enoxaparin, while apixaban showed a reduced bleeding risk.

Several NMAs have been published on the same topic. Maratea et al. (2011) reported that rivaroxaban and apixaban were more effective than dabigatran and E40, and rivaroxaban was superior to apixaban regarding VTE. They included E40 only and did not include edoxaban. Cohen et al. (2012) published another NMA also comparing rivaroxaban, apixaban, dabigatran, and E40. Notably, they performed direct analysis, indirect analysis, and NMA, and compared them in both hip and knee replacement subgroups. The efficacy of apixaban and rivaroxaban was superior to dabigatran and all three had comparable safety profiles. Harenberg et al. (2012) performed cluster analysis before performing NMA to identify homogeneous studies for the trial programs. Among the characteristics of interventions of the included studies, duration of treatment including 10 ± 5 days and 34 ± 5 days was the only homogeneous parameter. They compared different anticoagulants according to these two durations of treatment. Kapoor et al. (2017) performed a comprehensive NMA that included a vitamin K antagonist, aspirin, a mechanical device, and heparin, as well as an oral Xa inhibitor. The oral anticoagulant was analyzed as a single integrated group and it showed a 4-fold decrease in symptomatic VTEs compared with E40, while all other interventions did not show a more favorable profile than E40.

The definitions of major bleeding as a primary safety outcome vary considerably among the trials (Hull et al. 2009, Dahl et al. 2010). This is an important limitation of previous and our NMA and should be considered when interpreting our results. Trials of rivaroxaban did not include surgical site bleeding in the definition of major bleeding. Studies of rivaroxaban and fondaparinux did not include bleeding that required treatment discontinuation in major bleeding. Also, most rivaroxaban and apixaban trials used first postoperative day hemoglobin level as a baseline to determine whether a major drop in hemoglobin occurred. Major bleeding rates were about 10 times lower in studies that did not include surgical site bleeding in their definition of major bleeding compared with the studies that did. Non-major bleeding was also reported using a variety of terms (Dahl et al. 2010).

Different regimens in dosing and in the timing of drug initiation–continuation were chosen for each drug compared, therefore our NMA is not merely a comparison of drugs but a comparison of the regimens. For example, apixaban was initiated much later than other oral anticoagulants or fondaparinux. Therefore, the incidence of bleeding may be influenced not only by the different drug but also by the different regimens. Comparison between 2 different enoxaparin dose groups was also limited by the different duration and time of drug initiation.

The rate of VTE with enoxaparin at the same dose also varied considerably among trials. For example, the incidence of VTE ranged from 6% to 19% with E60 for knee arthroplasty and VTE rates ranged from 3% to 17% with E40 for hip arthroplasty in the results of enrolled studies. This may be because the patients had considerably different patient-related risk factors of VTE, possibly due to varying baseline medical conditions and perioperative care. This potential source of heterogeneity should be considered.

Our meta-analysis has some limitations. First, all trials were vulnerable to unclear or high risk of bias. All trials were performed by drug sponsors that contributed to data collection and statistical analysis. Many studies did not provide the method of random sequence generation and details of blinding of participants and personnel. Second, as discussed earlier, potential sources of heterogeneity in study design preclude a firm conclusion on our NMA. Different type of surgery, the timing of enoxaparin administration, definitions of primary efficacy outcomes, follow-up period, and use of compression stockings can be a source of heterogeneity. The initiation of enoxaparin as well as other study drugs varies among the trials, which ranged from 12 hours preoperatively to 6 to 24 hours postoperatively. This may play a role in the rate of VTE and bleeding. Third, various durations of drug administration from 5 days to 39 days were integrated into a single drug group and the impact of the drug administration period was neglected. A recent Cochrane review of 16 studies comparing extended-duration anticoagulants (5 to 7 weeks) to prevent VTE concluded that extended-duration oral anticoagulants showed reduced symptomatic VTE, although the extended duration compared in this review was longer than any of the drug administration durations used in the trials included in our NMA. Fourth, whether the indirectly estimated statistical superiority of one drug over another by NMA can be translated into a clinically relevant significance should be determined.

In summary, our network analysis systemically evaluated the 6 anticoagulants by efficacy and safety outcomes. However, this was limited by substantial heterogeneity regarding the definition of major bleeding, the initiation, and duration of treatment and type of surgery. Fondaparinux, rivaroxaban, and apixaban were associated with reduced VTE, but fondaparinux and rivaroxaban were associated with increased bleeding, while apixaban showed decreased bleeding. Apixaban 2.5 mg twice daily might have advantages over enoxaparin in terms of both efficacy and safety and is a preferable anticoagulant in clustered ranking plots. In addition, by comparing 2 enoxaparin doses, we found that new oral anticoagulants may have higher efficacy without higher bleeding tendency compared with E60, whereas they may have higher efficacy as well as higher bleeding tendency compared with E40. However, our conclusions were driven by moderate-quality evidence and indirect statisti-

cal inference of NMA of heterogeneous studies. Further direct head-to-head comparisons of new anticoagulants are needed to draw a more reliable conclusion.

Supplementary data

Tables 4–6 and Figures 1, 2, and 5 are available in the online version of this article, http://dx.doi.org/ 10.1080/17453674.2017.1361131

WK designed the protocol and search strategy; M H, S P, C K, and P K screened citations and extracted data from primary publications; M H, and W K performed the statistical analysis; W K wrote the initial draft manuscript; S P, C K, D J, P K, J K, C J, and J B added significant intellectual contributions through revisions.

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