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Original Paper

Effectiveness and Tolerability of Anticoagulants for Thromboprophylaxis after Major Joint Surgery: a Network Meta-Analysis

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Key Words
Anticoagulants • Thromboprophylaxis • Arthroplasty • Replacement • Meta-analysis

Abstract
Background/Aims Venous thromboembolism (VTE) is the most common complication after major joint surgery. VTE can easily develop into pulmonary embolism (PE), leading to cardiopulmonary dysfunction or sudden death. We aimed to comprehensively analyse the thromboprophylactic drugs that are used to prevent thrombosis and reduce bleeding risk. ***Methods:*** We searched the PubMed, EMBASE, and Cochrane databases for randomized controlled trials that evaluated the use of thromboprophylaxis after major joint surgery. The major outcomes were the numbers of all-cause VTE and bleeding events, and the secondary outcomes were major VTE and major bleeding/clinically relevant non-major bleeding events. A random-effects network meta-analysis was used to assess the effectiveness and tolerability of each anticoagulant after major joint surgery. ***Results:*** We included 104 trials that assessed 110,643 patients in our meta-analysis. The cluster ranking of major outcomes indicated that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and avoiding all bleeding events. Nadroparin, recombinant hirudin, and rivaroxaban effectively inhibited VTE but were associated with a high risk of bleeding. For secondary outcomes, we found that betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major bleeding, while rivaroxaban effectively inhibited major VTE but was associated with a high risk of major/clinically relevant non-major bleeding. A sensitivity analysis showed that the effect of apixaban was more robust for major outcomes, while aspirin was more robust for preventing all-cause bleeding events. In secondary outcomes, the effect of warfarin was more robust, while apixaban was still considered an ideal treatment to inhibit major VTE and bleeding events. ***Conclusion:*** Our study indicates that FXI-ASO, ardeparin, aspirin, and apixaban are ideal for preventing all-cause VTE and reducing all bleeding events, among which apixaban is the most reliable. Betrixaban, dalteparin, warfarin, and eribaxaban are ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events, among which warfarin is the most reliable.

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Introduction

Total knee/hip replacement, or arthroplasty, is the preferred method for treating end-stage joint disease [1, 2]. Venous thromboembolism (VTE) is the most common complication after surgical treatment [3, 4]. VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the third leading cause of death by cardiovascular complications after myocardial infarction and stroke [5, 6]. In particular, after a major orthopaedic surgery, thrombosis is the most common cause of death, and it easily develops into PE, which can cause cardiopulmonary dysfunction or sudden death [7, 8].

The incidence of VTE includes three clinical elements: vascular endothelial injury, slow blood flow, and a hypercoagulable state [9, 10]. Patients who undergo major surgery with all of the above risk factors tend to develop DVT as a result of a variety of factors, including surgical injury and limb activity restriction. A previous study showed that in patients who underwent major hip or knee surgery without anticoagulation treatment, the incidence of DVT was 45%-84% [11]. As the population ages, there will be a corresponding increase in joint replacement surgeries, and the incidence of postoperative DVT is also likely to gradually increase [12].

Because DVT is a concealed condition that is difficult to clinically diagnose, high-risk patients need to actively take thromboprophylactics [13]. While the application of anticoagulants is an important routine prevention method, other strategies, such as avoiding prolonged bed rest, mechanical extrusion, and the use of compression stockings, are also recommended. A previous study recommended the use of thromboprophylactic therapy for 35 days after total hip arthroplasty (THA) and for more than 10 days after total knee arthroplasty (TKA) [14, 15].

A variety of anticoagulant drugs are available for clinical applications, including heparin derivatives, vitamin K antagonists, direct thrombin inhibitors, and direct factor Xa inhibitors. When new drugs are initially applied, researchers tend to pay more attention to their effects on the prevention of thrombus formation. However, an increasing number of studies have found that these drugs are associated with a higher incidence of bleeding [16, 17]. Therefore, we aimed to comprehensively analyse the thromboprophylactic drugs that are used to prevent thrombosis and reduce bleeding risk.

There is a long history of research regarding the use of anticoagulant drugs after major joint surgery, and a variety of results have been reported. Many systematic reviews and meta-analyses have been published in this area. Recently, an influential network meta-analysis aiming to compare any two direct factor Xa inhibitors reviewed the efficacy and safety of thromboprophylaxis following total hip or knee replacement [18]. The study included rivaroxaban, apixaban, betrixaban, darexaban, and edoxaban and indicated that the effects of these agents on total VTE risk ranked from low to high as follows: rivaroxaban, apixaban, edoxaban, enoxaparin, darexaban, and betrixaban. Their rankings for effects on major and clinically relevant non-major bleeding were as follows, from low to high: betrixaban, enoxaparin, darexaban, edoxaban, apixaban, and rivaroxaban.

Our analysis further expands on the included anticoagulants by including the results of previous studies. In addition, we increased the surgical category to include major hip or knee replacement, arthroplasty, and major surgery.

Materials and Methods

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines [19].

Data search strategy

We systematic searched the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases using keywords that included “venous thromboembolism”, “deep venous thrombosis”,

"thromboprophylaxis", "knee arthroplasty", "hip arthroplasty", "knee replacement", "hip replacement", "major joint surgery", and "random*" for results published through July 2016. We did not use any language restrictions. The bibliographies of the obtained publications and the references of relevant reviews were also checked to ensure that no relevant studies were inadvertently omitted.

Data selection and extraction

The literature search and selection were independently performed by two authors, and all disagreements were resolved by discussion. A study was eligible for inclusion if it met the following criteria: 1. it included patients after total hip/knee replacement or arthroplasty or major joint surgery; 2. the patients received thromboprophylactic treatment after joint surgery; 3. the study had a randomized controlled design, and one group was treated with an anticoagulant drug, while another group was treated with a blank, placebo or alternate anticoagulant drug; and 4. one of the following outcomes was included in the study: the number of cases of all-cause VTE, major DVT/PE, all-cause bleeding events, and major bleeding/clinically relevant non-major bleeding events.

The exclusion criteria included the following: 1. the study included another type of surgery; 2. no patients were treated with anticoagulation agents (such as anaesthetics); 3. the study did not include the desired results; 4. the study researched the dose-related effects of only one anticoagulant drug; and 5. the study was a mechanical stress treatment-related controlled trial. Additionally, reviews, conference presentations, letters, basic research articles, and editorials without sufficient data were excluded. Studies that failed to present original data were also eliminated.

We extracted the author, publication year, sample size, age, ratio of males to females, type of surgery, experimental intervention, control intervention, intervention time, subsequent treatment regimens, thrombus diagnosis, and follow-up period. We assessed the methodological quality of the included trials using a risk of bias approach according to the methods described by the Cochrane Collaboration [20].

In our analysis, the major effectiveness outcome was all-cause VTE, and the secondary effectiveness outcome was major DVT or PE. The major tolerance outcome was all-cause bleeding events, and the secondary outcomes were major bleeding/clinically relevant non-major bleeding events. For the efficacy outcome analysis, we used data from the intention-to-treat population, which comprised randomized patients who received a study agent. Because all the included studies had a randomized controlled trial design, our analysis did not classify the studies as low-risk and high-risk research. Most of the studies recommended or did not limit the application of compression stockings and mechanical extrusion, and we therefore treated mechanical intervention as a blank treatment. We also used the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to assess the network meta-analysis quality, with four levels graded from high (best) to very low (worst). This method considered the quality of direct and indirect evidence as well as the quality of network evidence according to the inconsistency between direct and indirect evidence and the intransitivity among all related pieces of evidence. We performed "node splitting" to separate the indirect evidence from the direct evidence to inform these evaluations [21].

Statistical analysis

We performed a pairwise meta-analysis using a random-effects model. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the sizes of the effects. We also used a random-effects network meta-analysis for mixed multiple treatment comparisons because this approach fully preserves the within-trial randomized treatment comparisons in each trial [22]. Network plots were produced for each outcome, in which nodes are weighted according to the number of studies evaluating each treatment and edges according to the precision of the direct estimate for each pairwise comparison. When a treatment involved more arms, the node was larger, and when the comparison results were more accurate (small standard error), the edges were more weighted. The network analysis adopted a frequentist framework, and a contrast-based model was used to evaluate multi-arm trials. We used a multivariate random-effects meta-regression to pool data with proportional variance-covariance matrix, and a restricted maximum-likelihood method was used to assess model fit. Consistency within every closed triangle or quadratic loop was investigated using a loop-specific approach to evaluate the coherency between direct and indirect comparisons. During analysis, inconsistency factors (IFs) and their 95% CIs were used to determine their compatibility with zero [23].

To rank the treatments for each outcome, we used surface under the cumulative ranking (SUCRA) probabilities [24, 25]. The effectiveness and tolerance of each treatment are displayed as cluster-ranking plots. We assessed the sensitivity of results for the primary outcome by analysing only studies considered to be at low risk of bias. To address global inconsistency from all possible sources, we used a design-by-treatment interaction model when adjusting results for entire publication bias [26]. Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis [27].

Results

Literature search

In our study, 890 articles were identified after duplicates were removed. A total of 757 of these articles were excluded after the titles and abstracts were screened. The full text of the remaining 133 articles was assessed, and the following studies were removed: secondary research studies (8), mechanical treatment-related studies (8), studies that included other types of surgery (4), studies of anaesthetics and other drugs (3), studies that evaluated the duration of treatment (2), studies with undesired results (1), duplicate publications (1), studies without a randomized, controlled design (1), and studies that compared preoperative and postoperative drug treatments (1). Finally, 108 treatment comparisons that assessed 110,643 patients from 104 trials were collected in our systematic review (Fig. 1, Table 1) [28-135].

Study characteristics

The age range of the included patients was 30-80 years. Eight of these studies failed to clearly define the ages of the included patients, and three of the studies included patients who were more than 40 years old. In this type of surgery, most of the included studies included patients with knee or hip replacement or arthroplasty, and thirteen trials included patients with major joint surgery, such as hip or knee fracture (Table 1).

Thirty drugs were included in our analysis. They included vitamin K antagonists (acenocoumarol and warfarin), direct factor Xa inhibitors (apixaban, betrixaban, darexaban, edoxa-

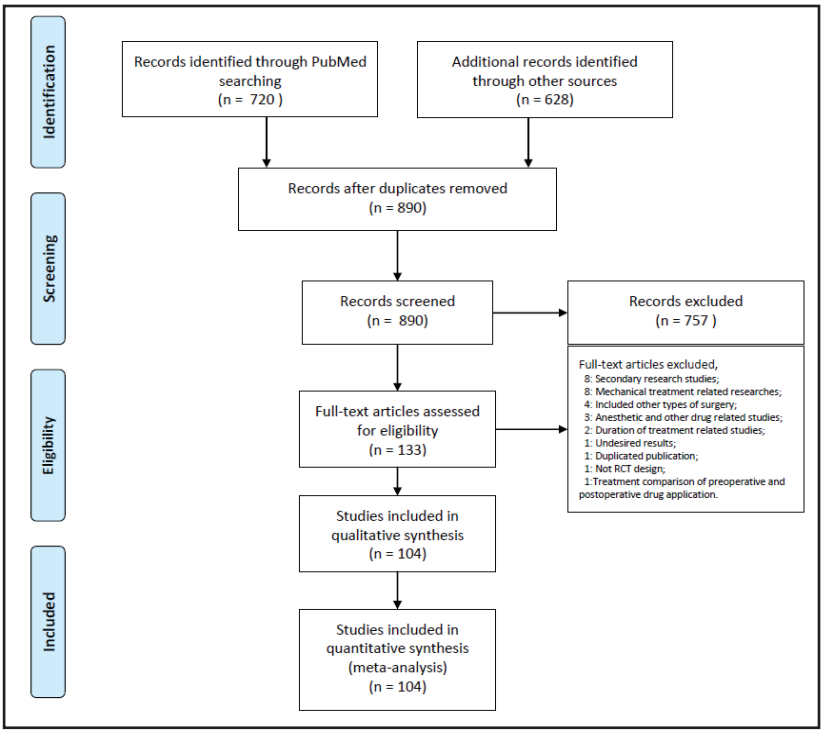

Fig. 1. PRISMA flowchart illustrating the selection of studies included in our analysis.

Table 1. Characteristics of subjects in eligible studies. Abbreviations: THA: total hip arthroplasty; TKA: total knee arthroplasty; THR: total hip replacement; TKR: total knee replacement; EHR: elective hip replacement; SNAC: a novel drug delivery agent; CECT: continuous enhanced circulation therapy; PEPTCG: Pulmonary Embolism Prevention Trial Collaborative Group; DESG: Danish Enoxaparin Study Group; NA: not available. #: Means±standard deviation; median (minimum-maximum). ##: D: days; W: weeks; M: months

Author	Year	Sample size	Age#	M/F	Type of surgery	Experimental	Control	Intervention time##	Follow-up treatment	Thrombus diagnosis	Follow-up##
Malhotra et al. [28]	2016	179	49.3±14.4	112/67	THA	Dabigatran 220 mg	Enoxaparin 40 mg	28-35 D	NA	Venography, ultrasonography	91±7 D
Bauer et al. [29]	2015	300	63#9	55/238	TKA	FXI-ASO: 200; 300 mg	Enoxaparin 40 mg	8 D	NA	Venography	47-136 D
Bern et al. [30]	2015	355	61.4±8.7	NA	THR/TKR	Fondaparinux: 2.5 mg	Warfarin 1.0 mg	28±2 D	Compression stockings	Ultrasonography	30-45 D
Fuji et al. [31]	2015	610	62.8±9.72	71/432	THA	Edoxaban: 30 mg	Enoxaparin 40 mg	11-14 D	Compression stockings	Venography	35-49 D
Fuji et al. [32]	2014	716	72.4±7.8	120/474	TKA	Edoxaban: 30 mg	Enoxaparin 40 mg	11-14 D	Mechanical compression +compression stockings	Venography	49 D
Fuji et al. [33]	2014	264	60.6±10.7	33/191	THA	Edoxaban: 15; 30 mg	Enoxaparin 40 mg	11-14 D	Mechanical compression +compression stockings	Venography	17 D
Gomhar et al. [34]	2014	122	69±9.7	33/89	THA	Enoxaparin: 40 mg	Dabigatran: 150;220 mg	28-35 D	Physiotherapy	Venography	3 M
Fuji et al. [35]	2014	771	67.1±11	134/637	THA/TKA	Darexaban: 30; 60 mg; Enoxaparin: 40 mg	Placebo	10-14 D	Compression stockings	Venography	3-5 W
Fuji et al. [36]	2014	92	76±12	18/70	Hip fracture	Enoxaparin: 40 mg	Enoxaparin: 50 mg	11-14 D	Compression stockings	Venography	36-49 D
Jiang et al. [37]	2014	120	64.45±7.5	9/111	TKA	Aspirin: 100 mg	Edoxaban: 30; 60; 10 mg	14 D	Compression stockings	Ultrasonography	6 W
Zou et al. [38]	2014	324	64(47-82)	80/244	TKA	Rivaroxaban: 10 mg; Enoxaparin: 40 mg	Aspirin: 100 mg	14 D	Compression therapy	Ultrasonography	4 W
Mirdamadi et al. [39]	2014	90	70.2±10.1	32/58	TKA	Enoxaparin: 40 mg	Dabigatran: 225 mg	14-15 D	NA	Sonography	3 M
Anderson et al. [40]	2013	778	57.9±12.2	444/341	THA	Dalteparin: 5000 U	Aspirin: 81 mg	8-28 D	NA	Objective	90 D
Eriksson et al. [41]	2013	1992	60±12.13	931/991	THA	Darexaban: 30; 60 mg	Enoxaparin: 40 mg	35 D	Compression stockings	Venography	65 D
Cohen et al. [42]	2013	1411	66.8±9.7	495/894	TKR	Eribaxaban: 0.1-10 mg	Enoxaparin: 60 mg	6-14 D	Compression stockings	Ultrasonography; venography	32±4 D
Chahal et al. [43]	2013	387	NA	NA	THR/TKR	Enoxaparin: 40 mg	Rivaroxaban: 10 mg	NA	Compression therapy	NA	12 M
Lassen et al. [44]	2012	2308	59.5(19-90)	1070/1238	THR	Enoxaparin: 40 mg	Semuloparin: 20 mg	8.2±1.5 D	NA	Venography	35-42 D
Lassen et al. [44]	2012	987	75(18-102)	350/637	Hip fracture	Enoxaparin: 40 mg	Semuloparin: 20 mg	8.3±1.6 D	NA	Venography	35-43 D
Lassen et al. [44]	2012	1141	65(22-88)	331/810	TKR	Enoxaparin: 60 mg	Semuloparin: 20 mg	8.4±1.6 D	NA	Venography	35-44 D
Verhammme et al. [45]	2011	352	65(39-81)	69/246	TKR	TB-402: 0.3, 0.6, 1.2 mg/kg	Enoxaparin: 40 mg	10 D	NA	Venography	90 D
Eriksson et al. [46]	2011	2055	62±11.5	971/1042	THA	Dabigatran: 220 mg	Enoxaparin: 40 mg	28-35 D	NA	Venography	28-35 D
Schulte et al. [47]	2010	255	63±12	46/204	THR	Fondaparinux: 2.5 mg; Enoxaparin: 40 mg	Placebo	10 D	Compression therapy	Ultrasonography	12 W
Raskob et al. [48]	2010	903	57.8±12.2	360/543	THA	Edoxaban: 15; 30; 60; 90 mg	Dalteparin: 5000 U	7-10 D	NA	Venography	60 D
Lassen et al. [49]	2010	5407	60.5(19-93)	4363/4910	THR	Apixaban: 5 mg	Enoxaparin: 40 mg	32-38 D	NA	Venography	95 D
Lassen et al. [50]	2010	3057	67(59-79)	841/2216	TKR	Apixaban: 5 mg	Enoxaparin: 40 mg	10-14 D	NA	Venography	60 D
Eriksson et al. [51]	2010	1017	60(22-85)	449/511	THA	Darexaban: 5; 10; 30; 60; 120 mg	Enoxaparin: 40 mg	5 W	NA	Venography	10 W
Lassen et al. [52]	2009	3195	65.8(26-93)	1212/1983	TKR	Apixaban: 5 mg	Enoxaparin: 60 mg	10-14 D	NA	Venography	60 D
Turpie et al. [53]	2009	3148	64.5±9.7	1060/1974	TKA	Rivaroxaban: 10 mg	Enoxaparin: 60 mg	10-14 D	Compression forbidden	Venography	17 D
Raskob et al. [48]	2010	903	57.8±12.2	360/543	THA	Edoxaban: 15; 30; 60; 90 mg	Dalteparin: 5000 U	7-10 D	NA	Venography	60 D
Lassen et al. [49]	2010	5407	60.5(19-93)	4363/4910	THR	Apixaban: 5 mg	Enoxaparin: 40 mg	32-38 D	NA	Venography	95 D
Lassen et al. [50]	2010	3057	67(59-79)	841/2216	TKR	Apixaban: 5 mg	Enoxaparin: 40 mg	10-14 D	NA	Venography	60 D
Eriksson et al. [51]	2010	1017	60(22-85)	449/511	THA	Darexaban: 5; 10; 30; 60; 120 mg	Enoxaparin: 40 mg	5 W	NA	Venography	10 W
Lassen et al. [52]	2009	3195	65.8(26-93)	1212/1983	TKR	Apixaban: 5 mg	Enoxaparin: 60 mg	10-14 D	NA	Venography	60 D
Turpie et al. [53]	2009	3148	64.5±9.7	1060/1974	TKA	Rivaroxaban: 10 mg	Enoxaparin: 60 mg	10-14 D	Compression forbidden	Venography	17 D
Geel et al. [54]	2009	238	40.9(19-74)	147/98	Knee fracture	Dalteparin: 5000 U	Placebo	14 D	NA	Venography	6 W
Ginsberg et al. [55]	2009	1896	66.1±9.3	1099/1497	TKA	Dabigatran: 150; 220 mg	Enoxaparin: 60 mg	12-15 D	Compression stockings	Venography; scintigraphy; angiography; iconography; autopsy	3 M
Turpie et al. [56]	2009	215	63(43-75)	85/129	TKR	Betrixaban: 30; 80 mg	Enoxaparin: 60 mg	10-14 D	NA	Venography	6±2 W
Agnelli et al. [57]	2009	1158	69.4(21-94)	480/628	THR/Hip fracture	Melagatran: 6 mg +ximelagatran: 48 mg	Enoxaparin: 40 mg	32-38 D	Compression stockings	Ultrasonography	90 D
Eriksson et al. [58]	2008	2531	67.6(28-91)	781/1678	TKA	Rivaroxaban: 10 mg	Enoxaparin: 40 mg	10-14 D	NA	Venography; ultrasonography	30-35 D
Camporese et al. [59]	2008	1761	42.2±15.3	1091/670	Knee arthroscopy	Nadroparin: 3800 U	Stockings	7/14 D	NA	Ultrasonography	3 M
Sukkar et al. [60]	2008	2509	61.5±13.5	1139/1318	THA	Rivaroxaban: 10 mg	Enoxaparin: 40 mg	10-39 D	Compression forbidden	Venography	30-42 D
Eriksson et al. [61]	2008	4541	63.2(18-93)	1971/2462	THA	Rivaroxaban: 10 mg	Enoxaparin: 40 mg	35 D	Compression forbidden	Venography	30-42 D
Fuji et al. [62]	2008	832	65.6±10.4	268/564	THA/TKA	Enoxaparin: 20; 40 mg	Placebo	14 D	Compression stockings	Venography	90 D
Eriksson et al. [63]	2007	2076	68±9	706/1370	TKR	Dabigatran: 150; 220 mg	Enoxaparin: 40 mg	6-10d	Low-dose aspirin+ cyclooxygenase-2 inhibitors+ compression stockings	Venography	3 M
Lapidus et al. [64]	2007	272	48.5±14	124/148	Ankle fracture	Dalteparin: 5000 U	Placebo	7 D	Dextran 60: 1000 ml	Phlebography; sonography	6 W
Markovits et al. [65]	2007	175	30.1±7.2	108/67	Knee arthroscopy	Enoxaparin: 40 mg	Placebo	12-17 D	NA	Venography	23-28 D
Lapidus et al. [66]	2007	105	39.5±9	83/22	Achilles tendon rupture	Dalteparin: 5000 U	Placebo	6 W	NA	Phlebography	6 W

continued

ban, rivaroxaban, eribaxaban, and rivaroxaban), a factor XI antisense oligonucleotide (FXI-ASO), a factor VIII inhibitor (TB402), direct thrombin inhibitors (dabigatran, melagatran (withdrawn from market), ximelagatran (withdrawn from market), desirudin, and recombinant hirudin), non-steroidal anti-inflammatory agents (aspirin and sudoxicam), heparin and its derivatives (ardeparin (withdrawn from market), certoparin, dalteparin enoxaparin, fondaparinux, unfractionated heparin, logiparin, nadroparin, reviparin, and semuloparin), a platelet aggregation inhibitor (triflusal), and others (dextran and dihydroergotamine).

Author	Year	Sample size	Age#	M/F	Type of surgery	Experimental	Control	Intervention time##	Follow-up treatment	Thrombus diagnosis	Follow-up##
Lassen et al. [67]	2007	1238	66.7(28-90)	454/784	TKR	Enoxaparin: 60 mg; Apixaban: 5, 10; 20 mg	Warfarin	12±2 D	NA	Venography	42 D
Eriksson et al. [68]	2007	3494	64(11)	1509/1954	THR	Dalteparin: 150 mg; 220 mg	Enoxaparin: 40 mg	28-35 D	Compression stockings	Venography	3 M
Eriksson et al. [69]	2007	625	65(30-92)	260/365	THR	Rivaroxaban: 5; 10; 20; 30; 40; 60 mg	Enoxaparin: 40 mg	5-9 D	Compression stockings	Venography	30-60 D
Eriksson et al. [70]	2007	174	63.3(35-87)	80/98	THR	Darexaban: 3; 10; 30; 60 mg	Enoxaparin: 40 mg	7-10 D	NA	Venography	4 W
Agnelli et al. [71]	2007	511	62.8(31-75)	230/277	THR/TKR	Betrixaban: 25, 50; 75; 100; 125; 150 mg	Enoxaparin: 40 mg	5-9 D	Compression forbidden	Venography	30±7 D
Eriksson et al. [72]	2006	873	64.9(27-93)	347/498	THR	Rivaroxaban: 5; 10; 20; 30; 40 mg	Enoxaparin: 40 mg	5-9 D	Compression forbidden	Venography	6-10 D
Senaran et al. [73]	2006	100	53.8±11.2	29/71	THR	Enoxaparin: 40 mg	Unfractionated heparin: 15000 U	7-10 D	Compression stockings	Ultrasonography	45 D
Eriksson et al. [74]	2006	704	65(26-93)	284/420	THR	Rivaroxaban: 2.5; 5; 10; 20; 30 mg	Enoxaparin: 40 mg	5-9 D	Compression stockings	Venography	30-60 D
Geller et al. [75]	2006	121	68±10.4	44/77	THA/TKA	CECT system +aspirin: 100 mg	Enoxaparin: 40 mg	5-9 D	NA	Venography	3 M
Westrich et al. [76]	2006	275	69±12.1	99/176	TKA	Enoxaparin: 40 mg	Aspirin: 650 mg	4 W	Compression device	Ultrasonography; venography	4-6 W
Turpie et al. [77]	2005	621	66(39-92)	236/377	TKR	Rivaroxaban: 5; 10; 20; 40; 60 mg	Enoxaparin: 60 mg	5-9 D	Compression stockings	Venography	30-60 D
Kolbel et al. [78]	2003	360	77±0.4	54/256	Endoprosthetic joint replacement or Osteosynthesis	Certoparin: 3000 U	Placebo	28 D	NA	Venography	42 D
Berkowitz et al. [79]	2003	123	63.2±14.5	61/62	THA	SNAC/heparin; heparin: 15000 U	Placebo	5 D	NA	Venography; ultrasonography	30 D
Eriksson et al. [80]	2003	656	79(23-96)	190/466	Hip fracture	Fondaparinux: 2.5 mg	Placebo	19-23 D	Compression forbidden	Venography	25-32 D
Eriksson et al. [81]	2003	2788	66.1(25-93)	1064/1724	THR/TKR	Melagatran: 3 mg +ximelagatran 48 mg	Enoxaparin: 40 mg	8-11 D	Aspirin+compression stockings	Venography	4-6 W
Colwell et al. [82]	2003	1557	64.3±12.9	479/808	THR	Ximelagatran: 48 mg	Enoxaparin: 60 mg	7-12 D	NA	Venography	6±2 W
Eriksson et al. [83]	2003	2835	67(20-89)	1051/1713	THR/TKR	Ximelagatran: 48 mg	Enoxaparin: 40 mg	8-11 D	NA	Venography	4-6 W
Eriksson et al. [84]	2002	1876	66.4(29-85)	736/1140	THR/TKR	Melagatran: 2; 3; 4.5; 6 mg +ximelagatran: 16; 24; 36; 48 mg	Dalteparin: 5000 U	7-10 D	Compression stockings	Venography	4-6 W
Prandoni et al. [85]	2002	360	68(44-87)	162/198	THA	Warfarin: 5 mg	Blank	4 W	NA	Ultrasonography; phlebography	3 M
Turpie et al. [86]	2002	2275	67(18-92)	1078/1179	EHR	Fondaparinux: 2.5 mg	Enoxaparin: 60 mg	11 D	Physiotherapy+compression stockings	Venography	6 W
Lassen et al. [87]	2002	2309	67(24-97)	966/1307	EHR	Fondaparinux: 2.5 mg	Enoxaparin: 40 mg	11 D	Physiotherapy+compression stockings	Venography	6 W
Samama et al. [88]	2002	1279	65.5±12	638/651	THR	Reviparin: 4200 U	Acenocoumarol	6 W	NA	Ultrasonography; venography	52.7±19.2 D
Eriksson et al. [89]	2002	360	68(44-87)	162/198	THA	Melagatran: 2; 4; 8 mg +ximelagatran: 1; 2; 4 mg	Dalteparin: 5000 U	8-11 D	NA	Venography	4-6 W
Bauer et al. [90]	2001	724	67.5±10.7	427/607	Major knee surgery	Fondaparinux: 2.5 mg	Enoxaparin: 60 mg	5-9 D	Compression forbidden	Venography	35-49 D
Comp et al. [91]	2001	873	65.1(26-90)	404/469	THR/TKR	Enoxaparin 40 mg	Placebo	18-21 D	Compression stockings	Venography	27-29 D
Heit et al. [92]	2001	600	67±10	291/309	TKR	Ximelagatran: 16; 24; 36; 48 mg	Enoxaparin: 60 mg	6-12 D	NA	Venography	4 W
Eriksson et al. [93]	2001	1711	77.1±12.5	411/1262	Hip fracture	Fondaparinux: 2.5 mg	Enoxaparin: 40 mg	5-9 D	Compression stockings	Venography	49 D
Turpie et al. [94]	2001	933	67(18-92)	433/500	THR	Fondaparinux: 0.75; 1.5; 3; 6; 8 mg	Enoxaparin: 60 mg	5-10 D	NA	Venography	42 D
Hull et al. [95]	2000	569	63±12	287/282	TKA	Dalteparin: 5000 U	Warfarin	35±2 D	Compression forbidden	Venography	35±2 D
PEPTCG [96]	2000	13356	79	2805/10551	Hip fracture	Aspirin: 160 mg	Placebo	35 D	Other thromboprophylaxis	Venography; ultrasonography	35 D
PEPTCG [96]	2000	4088	67	1921/2167	THA/TKA	Aspirin: 160 mg	Placebo	35 D	Other thromboprophylaxis	Venography; ultrasonography	35 D
Heit et al. [97]	2000	1195	65.5±11	540/655	THR/TKR	Ardeparin: 100 U/kg	Placebo	46-52 D	Compression stockings	Duplex ultrasonography or venography	12 W
Hull et al. [98]	2000	569	63±12	287/282	THA	Dalteparin: 5000 U	Warfarin	35±2 D	Compression stockings	Bilateral ascending venography	35±2 D
Blanchard et al. [99]	1999	130	73(43-88)	31/99	TKA	Nadroparin: 2850-5700 U	Mechanical compression	10-12 D	Physiotherapy	Venography	6-8 W
Lassen et al. [100]	1998	281	69(28-94)	128/153	THA	Dalteparin: 5000 U	Placebo	28 D	Compression stockings	Venography	35 D
Bader et al. [101]	1998	246	69±12	74/172	THA/TKA	Enoxaparin: 40 mg	Unfractionated heparin: 15000;22500 U	13-21 D	Compression stockings	Ultrasonography	7.8±2.3 D
Kim et al. [102]	1998	150	53.6	119/31	THR	Aspirin: 1.2 g	Dextran: 500 ml	14 D	NA	Venography	7-10 D
Yoo et al. [103]	1997	100	53	83/17	THR	Nadroparin: 41-62 U/kg	Blank	10 D	Compression forbidden	Venography	10 D
Dahl et al. [104]	1997	227	71.2	66/161	THR	Dalteparin: 5000 U	Placebo	4 W	Dalteparin+dextran+ compression stockings (7 D)	Venography; scintigraphy; chest X-ray	7-35 D
Samama et al. [105]	1997	170	67.2(31.6-89.2)	99/71	THR	Enoxaparin: 40 mg	Placebo	10±2 D	Compression stockings	Venography	3 M
Andersen [106]	1997	41	67(34-84)	23/18	THA	Dalteparin: 5000 U	Placebo	5 W	Dalteparin: 5000 U	Phlebography	35 D
Eriksson et al. [107]	1997	2079	66.5(18-90)	867/1212	THR	Desirudin: 30 mg	Enoxaparin: 40 mg	8-12 D	NA	Venography	6 W
Bergqvist et al. [108]	1996	262	70(44-87)	113/149	THR	Enoxaparin: 40 mg	Placebo	10-11 D	NA	Phlebography	19-23 D

continued

One study was not included in the meta-analysis because two of the drugs researched in the study clearly did not overlap with other drugs. The drugs included in this study were acenocoumarol and reviparin [88]. Enoxaparin was the most frequently investigated intervention. All trials were found to have a low risk of bias for randomness, 90% for concealment of allocation, 58% for blinding of patients, and 73% for blinding of therapists. The included studies were all randomized controlled trials, and their overall quality was therefore ideal. All the tri-

Author	Year	Sample size	Age##	M/F	Type of surgery	Experimental	Control	Intervention time##	Follow-up treatment	Thrombus diagnosis	Follow-up##
Stone et al. [109]	1996	50	64(37-83)	18/32	THR	Enoxaparin: 40 mg	Compression	10 D	NA	Ultrasonography	1-6 W
Kalodiki et al. [110]	1996	77	NA	NA	THR	Enoxaparin: 40 mg; Compression stockings	Blank	8-12 D	NA	Venography	8-12 D
Stannard et al. [111]	1996	75	NA	NA	THR	Heparin+aspirin; compression	Heparin+aspirin+ compression	1/2 W	NA	Ultrasonography	2 W
Levine et al. [112]	1996	246	68±10.4	99/147	Major knee surgery	Ardeparin: 50 U/kg	Compression stockings	14 D	NA	Venography	14 D
Perhoniemi et al. [113]	1996	165	NA	NA	THR/TKR	Heparin: 1 mg +dihydroergotamine: 10000 U	Enoxaparin: 40 mg	3-5 D	NA	Ultrasonography; phlebography	7 D
Planes et al. [114]	1996	179	69(9.1)	102/77	THR	Enoxaparin: 40 mg	Placebo	19-23 D	Compression stockings	Venography	3 M
Eriksson et al. [115]	1996	1119	66.4±9.8	422/697	THR	Recombinant hirudin: 20; 30; 40 mg	Unfractionated heparin: 15000 U	8-11 D	NA	Venography	6 W
Warwick et al. [116]	1995	156	NA	NA	THR	Enoxaparin: 40 mg	Blank	1.5 D	Compression stockings	Venography	8-10 D
Monreal et al. [117]	1995	459	72±14	179/280	EHR/hip fracture	Aspirin: 600 mg; Trifusal: 900 mg	Placebo	9 D	Unfractionated heparin: 15000 U	Venography	8 D
Colwell et al. [118]	1995	453	68±9.2	198/255	TKA	Enoxaparin: 60 mg	Unfractionated heparin: 15000 U	14 D	NA	Ultrasonography; venography; ventilation perfusion lung scan; angiography	3 W
Avikainen et al. [119]	1995	167	NA	NA	THR	Enoxaparin: 40 mg	Unfractionated heparin: 10000 U	10 D	NA	Ultrasonography; venography	10 D
Colwell et al. [120]	1994	610	65.4±11	298/309	EHR	Enoxaparin: 60 mg; Enoxaparin: 40 mg	Unfractionated heparin: 15000 U	7 D	NA	Venography; ultrasonography	4-7 D
Faunq et al. [121]	1994	185	70±10	73/112	TKA	Enoxaparin: 40 mg	Unfractionated heparin 15000 U	6-9 D	Compression stockings	Venography	2 M
Leclerc et al. [122]	1992	131	NA	NA	TKA	Enoxaparin: 60 mg	Placebo	14 D	NA	I^{125} Fibrinogen; impedance plethysmography; Venography	14 D
Lassen et al. [123]	1991	210	67(40-86)	92/98	THR	Heparin: 50 U/kg	Placebo	7 D	Compression stockings	Phlebography	8-10 D
Borris et al. [124]	1991	206	69(33-87)	NA	EHR	Enoxaparin: 40 mg	Dextran: 500 ml	8 D	NA	Phlebography	7-11 D
Torholm et al. [125]	1991	120	66(43-85)	50/62	THR	Dalteparin: 2500/5000 U	Placebo	7 D	NA	I^{125} Fibrinogen; phlebography	9 D
DESG [126]	1991	219	71(33-87)	91/128	THR	Enoxaparin: 40 mg	Dextran 70: 500 ml	7 D	NA	Phlebography	7-11 D
Woolson et al. [127]	1991	196	65.4	95/122	THR	Aspirin: 1300 mg; warfarin: 7.5-10 mg	Blank	4-13 D	Compression stockings	Venography; ultrasonography	4-13 D
Levine et al. [128]	1991	665	66.5±9.74	305/360	THR	Enoxaparin: 60 mg	Unfractionated heparin: 15000 U	14 D	NA	I^{125} Fibrinogen; venography	10-14 D
Sorensen et al. [129]	1990	40	72(40-86)	16/24	THR	Logiparin: 50 U/kg	Placebo	7 D	Compression stockings	Phlebography	8-10 D
Fredin et al. [130]	1989	150	66±11	57/87	THA	Dextran	Compression stockings (14 D)	14 D	NA	Phlebography	30 D
Planes et al. [131]	1988	237	NA	NA	THR	Enoxaparin: 40 mg	Unfractionated heparin: 15000 U	15 D	NA	Venography	15 D
Turpie et al. [132]	1986	100	67.0±9.2	48/52	Elective hip surgery	Enoxaparin: 60 mg	Placebo	14 D	NA	I^{125} Fibrinogen; venography	14 D
Alfaro et al. [133]	1986	120	62.13±10.99	65/55	THR	Aspirin: 0.25 g; 1 g; Heparin-dihydroergotamine	Blank	7 D	NA	Phlebography; I^{125} fibrinogen	3-7 D
Harris et al. [134]	1977	95	>40	48/47	THR	Aspirin: 1.2 g	Placebo	2 W	NA	Phlebography	7-10 D
Hume et al. [135]	1973	103	>40	-	THR	Sudoxicam: 20-50 mg	Warfarin: 10 mg	NA	Compression stockings	Phlebography	NA
Hume et al. [135]	1973	54	>40	-	THR	Heparin: 5000 U; Warfarin	Blank	NA	Compression stockings	Phlebography	NA

als were randomly grouped, and only 2% of trials did not mention the means of random sequence generation. Additionally, 11% of trials did not explicitly mention allocation concealment. Therefore, randomization was completely reliable. In addition, 4% of trials did not explicitly define the reasons for the loss of participants. However, for application of blinding method, 44% of trials did not set blinding of participants and personnel, and 28% of trials did not set blinding for outcome assessments. Therefore, the most important bias was the influence of blinding methods on the results and the influence of subjective assessment bias factors. In the results of these trials, the diagnosis of thrombus was generally based on venography, colour duplex Doppler, or other relatively objective methods if the assessor could be completely concealed; thus, the impact of low assessment blinding quality on the results was small. However, it still was not possible to exclude the influence of psychological suggestion of the participants and the investigator on the assessor. The judgement of bleeding results is often subjective, particularly if blinding methods are not well designed; therefore, this subjectivity would have a certain impact on the results.

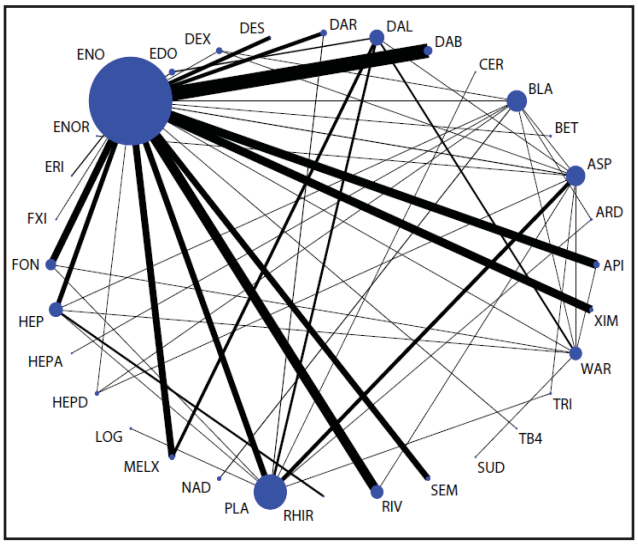

Fig. 2. Network of comparisons for all-cause VTE included in the analyses. The nodes are weighted according to the number of studies and edges according to the precision of the direct estimate for each pairwise comparison. API=apixaban; ARD=ardeparin; ASP=aspirin; BET=betrixaban; BLA=blank; CER=certoparin; DAB=dabigatran; DAL=dalteparin; DAR=darexaban; DES=desirudin; DEX=dextran; EDO=edoxaban; ENO=enoxaparin; ENOR=enoxaparin+rivaroxaban; ERI=eribaxaban; FXI=FXI-ASO; ON=fondaparinux; HEP=heparin; HEPA=heparin+aspirin; HEPD=heparin-dihydroergotamine; LOG=logiparin;MELX=melagatran+ximelagatran; NAD=nadroparin; PLA=placebo; RHIR=recombinant hirudin; RIV=rivaroxaban; SEM=semuloparin; SUD=sudoxicam; TB4=TB402; TRI=triflusal; WAR=warfarin; and XIM=ximelagatran.

Results of network meta-analysis

In the network meta-analysis, eligible comparisons of all-cause VTE outcomes are presented (Fig. 2), which show the predominantly pairwise comparisons of different anticoagulants used for thromboprophylaxis after major joint surgery. Treatments in the network that are not well connected should be interpreted with caution. Moreover, probabilities of which treatment is the best can be fragile when the network is sparse. We removed one study because no other interventions were associated with its interventions. Thus, 103 studies and 107 comparisons were included for the VTE results (Table 2). An inconsistency plot was produced to assume the loop-specific heterogeneity estimate; it found 23 triangular loops and 17 quadratic loops. Although there was no significant difference between direct and indirect comparisons, we found that there was a relatively large difference between direct and indirection comparisons related to placebo and blank interventions. These inconsistencies may have resulted from differences in the methods used to define thrombosis. We therefore used an inconsistency model to research pairwise comparisons, and the forest plot showed that enoxaparin was more advantageous than dextran (logOR, 1.39; 95% CI, 0.74-2.04; p<0.001), and nadroparin was superior to blank treatment (logOR, 1.09; 95% CI, 0.66-1.52; p<0.001). Other results showed no significant differences between anticoagulants, and only one study was included in that analysis [Data not shown]. It is notable that it may be improper to include data contained in multi-arm studies in a pairwise comparison analysis. Furthermore, we ranked the comparative effects of all anticoagulants in all VTE with SUCRA probabilities (%). The results indicated that rivaroxaban (88.4%), recombinant hirudin (85.6%), and ardeparin (82.7%) were most likely to reduce thrombosis after major joint surgery. These agents were followed by nadroparin (81.0%) and TB402 (76.9%). The comparison-adjusted funnel plot used to assess publication bias and to determine the presence of small-study effects did not suggest that there was any publication bias. However, the global inconsistency analysis showed that there was significant inconsistency among the studies (p = 0.0068).

Eligible comparisons of major VTE outcomes are presented in Fig. 3. The exp(IF) of the inconsistency plot that included 10 triangular loops and 3 quadratic loops showed that there was no significant difference among the studies. Therefore, we used a consistency model to research pairwise comparisons, and there were no observable low-heterogeneity differences among the comparisons. The comparative effects of all treatments and their SUCRA probabilities revealed that eribaxaban (85.9%), rivaroxaban (80.5%), and warfarin (71.9%) were most likely to reduce the risk of major thrombosis after major joint surgery, followed

by apixaban (71.5%). The comparison-adjusted funnel plot did not reveal any publication bias, and the global inconsistency plot also showed that there was no significant difference (p=0.7907).

The network plot for all-cause bleeding outcomes is shown in Fig. 4. The inconsistency plot included 15 triangular loops and 16 quadratic loops shows an exp(IF) with 4 loops larger than zero. Significant inconsistencies were found in the loops of ardeparin-blank-heparin-placebo (p = 0.003), aspirin-blank-heparin-placebo (p = 0.01), fondaparinux-heparin-placebo-warfarin (p = 0.016), and enoxaparin-heparin-placebo (p = 0.038) [Data not shown]. The consistency model was used to research pairwise comparisons, and no observable differences were found among the comparisons. The SUCRA probabilities showed that sudoxicam (92.2%), FXI-ASO (89.4%), and betrixaban (88.3%) were likely to be associated with the lowest risk of all-cause bleeding after major joint surgery. Additionally, there was no publication bias in the comparison-adjusted funnel plot. The global inconsistency showed no significant difference (p = 0.2292).

The network plot for major bleeding outcomes is shown in Fig. 5. ENO included the three most frequently researched treatments. The inconsistency plot including four triangular loops and six quadratic loops showed that there were no significant differences among the loops. The consistency model was used to research pairwise comparisons, and there were no observable differences in low heterogeneity among the comparisons. The SUCRA probability scores showed that betrixaban (86.9%), dalteparin (74.6%), and warfarin (66.1%) were associated with the lowest risk of major bleeding/non-major clinically relevant bleeding events. Additionally, there was no clear publication bias in the comparison-adjusted funnel plot, and there was no significant difference in global inconsistency (p = 0.184).

Table 2. The number of arms, events, and patients for each treatment group of each outcome. Abbreviations: VTE: Venous thromboembolism

Treatment	All-cause VTE(103 studies)			Major VTE(63 studies)			All bleeding events(85 studies)			Major Blooding(63 studies)		
	No. of arms	No. of events	No. of patients	No. of arms	No. of events	No. of patients	No. of arms	No. of events	No. of patients	No. of arms	No. of events	No. of patients
Apixaban	4	307	4695	4	47	5631	4	564	6687	4	139	6687
Ardeparin	2	37	704	2	4	704	2	31	729	1	2	607
Aspirin	12	188	9843	6	63	9070	7	680	9428	3	13	6773
Betrixaban	2	95	429	1	9	135	1	2	417	2	3	588
Blank	14	235	1414	7	11	534	7	36	1004	4	2	949
Certoparin	1	8	161				1	1	161			
Dabigatran	7	994	5545	5	140	4964	7	718	6626	5	177	6474
Dalteparin	12	314	2059	1	0	20	5	125	1463	6	9	1580
Darexaban	4	335	2251	3	34	2211	4	279	2985	4	118	2985
Desirudin	1	144	773	1	41	802				1	20	1028
Dextran	4	92	357	1	0	111	2	28	161	1	0	50
Edoxaban	5	156	1380	2	0	301	5	156	1614	3	24	1086
Enoxaparin	73	3801	26558	47	592	25754	60	2334	30799	48	599	31715
Enoxaparin/Rivaroxaban	1	11	60	1	0	60						
Eribaxaban	1	119	561	1	2	561	1	86	992	1	5	992
FXI-ASO	1	39	205				1	6	221			
Fondaparinux	8	217	3508	6	23	4041	8	294	4819	6	134	4616
Heparin	11	311	1544	5	6	676	9	194	1399	4	35	879
Heparin+Aspirin	1	5	25	1	1	25						
Heparin dihydroergotamine	2	8	111	1	2	81						
Logiparin	2	40	113	1	1	93	2	13	113			
Melagatran+ximelagatran	4	669	2779	1	65	1144	1	34	556	3	70	3450
Nadroparin	3	40	1218	1	1	50	2	64	1151	2	9	1168
Placebo	26	861	11879	10	125	10706	21	690	11704	12	30	8967
Recombinant hirudin	1	126	643	1	2	643	1	143	842			
Rivaroxaban	10	455	6118	8	95	6792	8	731	8415	7	211	7727
Semuloparin	3	225	1722	3	1	1722	3	37	2214	3	12	2214
Sudoxicam	1	12	51				1	0	51			
TB-402	1	47	218				1	14	236			
Trifusal	1	21	154	1	3	154	1	0	154			
Warfarin	8	148	982	4	1	592	7	91	886	4	1	695
Ximelagatran	3	370	2269	3	93	2266	3	288	2753	3	55	2753

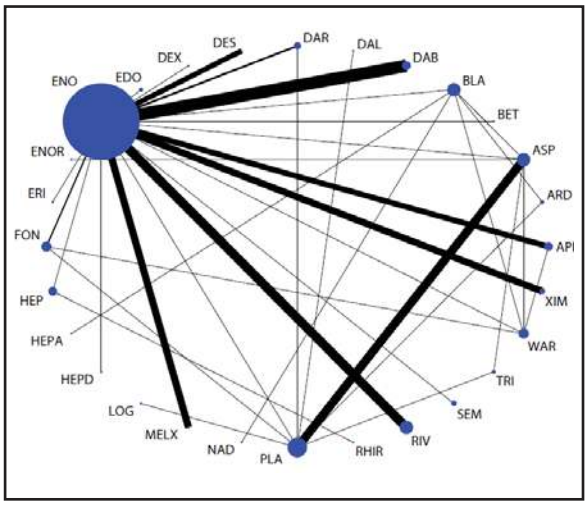

Fig. 3. Network of comparisons for major VTE included in the analyses. API=apixaban; ARD=ardeparin; ASP=aspirin; BET=betrixaban; BLA=blank; DAB=dabigatran; DAL=dalteparin; DAR=darexaban; DES=desirudin; DEX=dextran; EDO=edoxaban; ENO=enoxaparin; ENOR=enoxaparin+rivaroxaban; ERI=eribaxaban; FON=fondaparinux; HEP=heparin; HEPA=heparin+aspirin; HEPD=heparin-dihydroergotamine; LOG=logiparin; MELX=melagatran+ximelagatran; NAD=nadroparin; PLA=placebo; RHIR=recombinant hirudin; RIV=rivaroxaban; SEM=semuloparin; TRI=triflusal; WAR=warfarin; and XIM=ximelagatran.

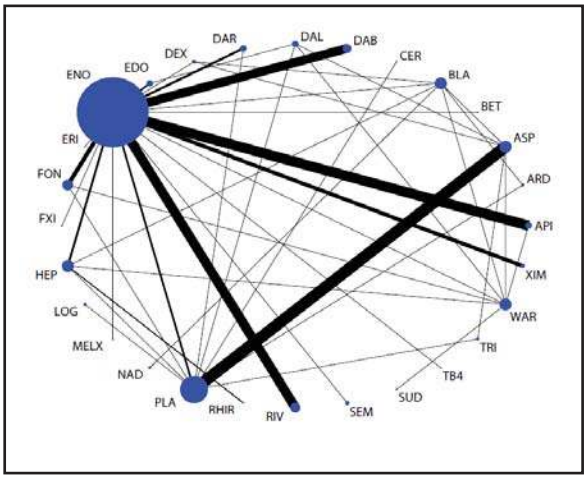

Fig. 4. Network of comparisons for all-cause bleeding included in the analyses. API=apixaban; ARD=ardeparin; ASP=aspirin; BET=betrixaban; BLA=blank; CER=certoparin; DAB=dabigatran; DAL=dalteparin; DAR=darexaban; DEX=dextran; EDO=edoxaban; ENO=enoxaparin; ERI=eribaxaban; FON=fondaparinux; FXI=FXI-ASO; HEP=heparin; LOG=logiparin; MELX=melagatran+ximelagatran; NAD=nadroparin; PLA=placebo; RHIR=recombinant hirudin; RIV=rivaroxaban; SEM=semuloparin; SUD=sudoxicam; TB4=TB-402; TRI=triflusal; WAR=warfarin; and XIM=ximelagatran.

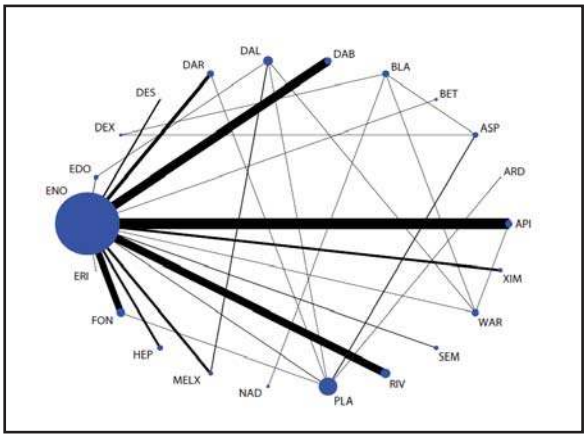

Fig. 5. Network of comparisons for major bleeding/clinically relevant non-major bleeding included in the analyses. API=apixaban; ARD=ardeparin; ASP=aspirin; BET=betrixaban; BLA=blank; DAB=dabigatran; DAL=dalteparin; DAR=darexaban; DES=desirudin; DEX=dextran; EDO=edoxaban; ENO=enoxaparin; ERI=eribaxaban; FON=fondaparinux; HEP=heparin; MELX=melagatran+ximelagatran; NAD=nadroparin; PLA=placebo; RIV=rivaroxaban; SEM=semuloparin; WAR=warfarin; and XIM=ximelagatran.

After we performed a comprehensive analysis of all-cause VTE and all bleeding events, the cluster ranking showed that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and avoiding all bleeding events. Nadroparin, recombinant hirudin, and rivaroxaban all effectively inhibited VTE but were associated with a high risk of bleeding events (Fig. 6). The cluster-ranking analysis of major VTE and major/clinically relevant non-major bleeding events showed that betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major bleeding events. Rivaroxaban effectively

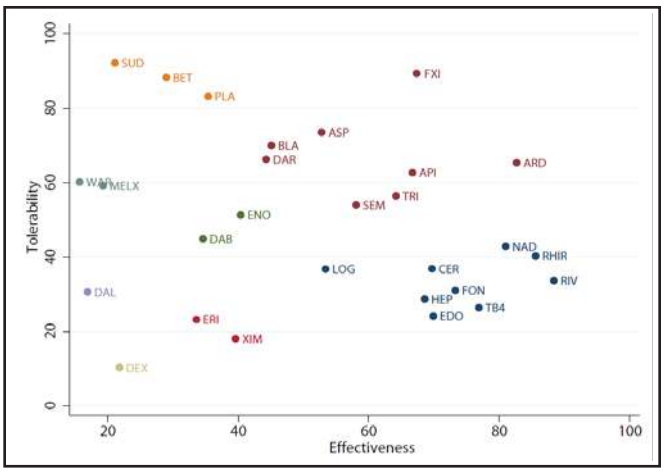

Fig. 6. Clustered ranking plot for all-cause VTE and bleeding events.

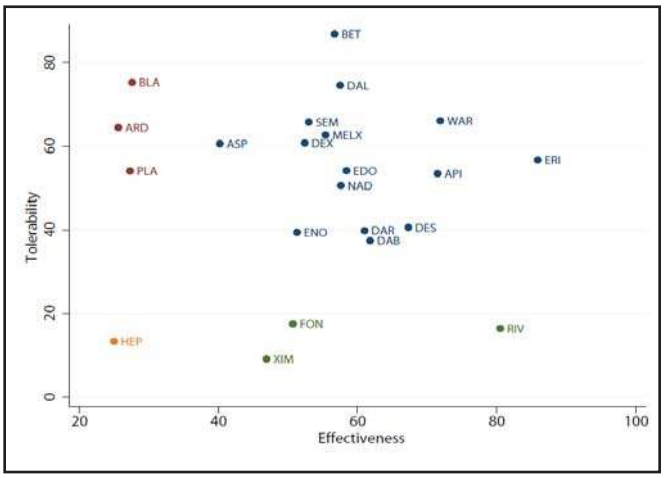

Fig. 7. Clustered ranking plot for major VTE and major/non-major clinically relevant bleeding.

inhibited major VTE but was associated with a high risk of major/clinically relevant non-major bleeding events (Fig. 7).

Quality of evidence and sensitivity analysis

We simplified the results of all the comparisons in the GRADE assessment and only listed treatments related to the final conclusion and its direct comparisons (Table 3). For all-VTE outcomes, apixaban had five direct comparisons with moderate and high quality. Although the quality level of aspirin in the network comparisons was generally low, the seventeen related direct comparisons increased the robustness of the results. Ardeparin had only two comparisons with moderate and low levels, and FXI-ASO had only one low-quality comparison. Thus, the results of these two treatments lacked robustness. In addition, there was incoherence between the direct and indirect comparisons of apixaban versus enoxaparin, ardeparin versus blank, ardeparin versus placebo, and aspirin versus placebo. For the all-cause bleeding outcome, apixaban had five direct comparisons with a high level of quality, and aspirin had ten direct comparisons with a generally moderate level. The results of ardeparin and FXI-ASO still lacked robustness.

For the major VTE outcome, warfarin had six direct comparisons with moderate and low quality; betrixaban, dalteparin, and eribaxaban all included only one direct comparison without robustness. For the major bleeding outcome, dalteparin had seven comparisons with a moderate-high level of quality; warfarin had four comparisons of a low-moderate level of quality. The results of betrixaban and eribaxaban were still not robust because of fewer comparisons. Additionally, for major VTE and bleeding outcomes, most included trials contained small sample sizes and zero-event results, which reduced the quality of evidence because of imprecision.

Table 3. Summary comparisons of the effect size and quality of major outcomes. Abbreviations: CIs: confidence intervals; LogOR: logarithm odds ratios; NA: not available. *: Study limitation; †: Indirectness; ‡: Imprecision; #: Incoherence

Outcomes/Interventions		Direct comparisons		Indirect comparisons		Network comparisons	
	No. of studies	LogOR(95%CIs)	Quality	LogOR(95%CIs)	Quality	LogOR(95%CIs)	Quality
All-cause VTE							
Apixaban vs.							
Enoxaparin	4	-0.60 (-0.96,-0.23)	High	0.63 (-1.18,2.45)	Moderate‡	-0.54 (-0.89,-0.18)	Moderate#
Warfarin	1	-1.39 (-2.20,-0.59)	High	-1.89 (-2.57, -1.22)	High	-1.69 (-2.20,-1.17)	High
Ardeparin vs.							
Blank	1	-1.21(-2.06,-0.36)	High	-0.49(-1.68,0.70)	Low*‡	-0.97 (-1.66,-0.27)	Moderate#
Placebo	1	-0.33(-1.39,0.74)	Moderate‡	-1.05(-2.04,-0.05)	Low*‡	-0.71 (-1.44,0.02)	Low#
Aspirin vs.							
Blank	3	-1.38(-2.23,-0.53)	Low*†	-0.64(-1.28,-0.00)	Low*†	-0.91 (-1.43,-0.39)	Low
Dalteparin	1	-1.57(-3.81,0.66)	Moderate‡	0.00(-0.43,0.45)	High	-0.05 (-0.49,0.38)	High
Dextran	1	0.19 (-1.74,2.11)	Low*‡	-1.24(-1.96,-0.52)	Low*‡	-1.07 (-1.74,-0.40)	Low
Enoxaparin	3	-0.11(-0.70,0.48)	Low*†	0.55 (0.12,0.97)	Moderate*	0.32 (-0.03,0.67)	Low
Enoxaparin/Rivaroxaban	1	-0.12(-1.24,1.01)	Moderate*	NA	NA	-0.12 (-1.24,1.01)	Moderate
Heparin-dihydroergotamine	1	-1.47(-3.04,0.11)	Low*‡	0.73(-1.10,2.56)	Very Low*†‡	-0.52 (-1.66,0.62)	Low
Placebo	4	-0.32(-0.73,0.10)	High	-1.17(-1.69,-0.65)	High	-0.66 (-0.99,-0.32)	Moderate#
Rivaroxaban	1	1.65(0.35,2.96)	Low*‡	0.97(0.50,1.44)	Low*†	1.05 (0.62,1.49)	Low
Triflusal	1	0.32(-0.55,1.19)	High	-1.28(-2.93,0.37)	Moderate‡	-0.02 (-0.80,0.76)	High
Warfarin	1	-1.22(-2.57,0.12)	Moderate*	-0.76(-1.32,0.19)	Low*†	-0.83 (-1.35,-0.31)	Low
FXI-ASO vs.							
Enoxaparin	1	-0.62(-1.50,0.25)	Moderate*	NA	NA	-0.74 (-1.05,-0.42)	Low
Major VTE							
Betrixaban vs.							
Enoxaparin	1	-0.13(-1.88,1.63)	Moderate‡	NA	NA	-0.13 (-1.88,1.63)	Moderate
Dalteparin vs.							
Placebo	1	-1.10(-4.54,2.35)	Moderate‡	NA	NA	-1.10 (-4.54,2.35)	Moderate
Eribaxaban vs.							
Enoxaparin	1	-1.51(-3.63,0.60)	Low*‡	NA	NA	-1.51 (-3.63,0.60)	Low
Warfarin vs.							
Apixaban	1	0.36(-1.96,2.69)	Moderate‡	-0.59(-2.77,1.60)	Moderate‡	-0.15 (-1.85,1.56)	Moderate
Aspirin	1	0.04(-4.05,4.13)	Low*‡	-1.40(-3.57,0.77)	Low*‡	-1.09 (-3.00,0.83)	Low
Blank	2	-1.76(-4.05,0.52)	Low*‡	-1.33(-4.14,1.48)	Low*‡	-1.59 (-3.37,0.18)	Low
Enoxaparin	1	-1.28(-3.76,1.19)	Moderate‡	-0.34(-2.31,1.63)	Moderate‡	-0.69 (-2.33,0.95)	Moderate
Fondaparinux	1	-0.72(-4.80,3.37)	Moderate‡	-0.73(-2.70,1.25)	Moderate‡	-0.72 (-2.50,1.05)	Moderate
All blooding events							
Apixaban vs.							
Enoxaparin	4	0.13(-0.01,0.28)	High	-0.47(-2.22,1.29)	Moderate‡	-0.13 (-0.27,0.01)	High
Warfarin	1	-0.33(-1.04,0.39)	High	0.13(-0.33,0.58)	High	-0.01 (-0.40,0.39)	High
Ardeparin vs.							
Blank	1	0.51(-0.95,1.97)	Moderate‡	-0.71(-2.08,0.65)	Low*‡	0.14 (-0.86,1.14)	Moderate
Placebo	1	-0.37(-0.97,0.23)	High	0.85(-1.05,2.76)	Low*‡	0.26 (-0.31,0.83)	High
Aspirin vs.							
Blank	2	-0.50(-2.56,1.55)	Low*‡	0.25(-0.90,1.41)	Low*‡	0.06 (-0.92,1.04)	Low
Dalteparin	1	-0.85(-1.70,-0.01)	High	-0.42(-0.95,0.11)	High	-0.54 (-1.00,-0.09)	Moderate#
Dextran	1	-1.13(-3.94,1.68)	Low*‡	-0.99(-1.76,-0.21)	Moderate*	-1.00 (-1.74,-0.26)	Very Low#
Placebo	4	0.19(0.02,0.36)	High	-0.24(-1.13,0.66)	High	0.18 (-0.00,0.36)	Moderate#
Triflusal	1	0.02(-3.91,3.95)	Moderate‡	0.34(-6.47,7.15)	Moderate‡	0.10 (-3.30,3.50)	Moderate
Warfarin	1	-0.04(-2.84,2.75)	Low*‡	-0.19(-0.65,0.26)	High	-0.19 (-0.64,0.25)	High
FXI-ASO vs.							
Enoxaparin	1	-1.18(-2.35,-0.01)	Low*‡	NA	NA	-1.18 (-2.35,-0.01)	Low
Major blooding							
Betrixaban vs.							
Enoxaparin	2	-1.49(-3.10,0.10)	Moderate‡	NA	NA	-1.50 (-3.10,0.10)	Moderate
Dalteparin vs.							
Edoxaban	1	-1.95(-4.79,0.88)	Moderate‡	-0.19(-1.40,1.02)	Moderate‡	-0.46 (-1.60,0.67)	Moderate
Melagatran+ximelagatran	1	-0.15(-0.93,0.62)	High	-1.20(-2.90,0.50)	Moderate‡	-0.34 (-1.05,0.38)	High
Placebo	3	-0.51(-2.62,1.60)	Moderate‡	-0.45(-1.62,0.71)	Moderate‡	-0.46 (-1.48,0.55)	Moderate
Warfarin	2	-0.77(-3.55,2.01)	High	0.73(-1.91,3.36)	Moderate‡	0.02 (-1.90,1.94)	High
Eribaxaban vs.							
Enoxaparin	1	-0.41 (-1.87,1.06)	Low*‡	NA	NA	-0.41 (-1.87,1.06)	Low
Warfarin vs.							
Apixaban	1	-2.13(-4.72,0.46)	Moderate‡	0.78(-1.60,3.16)	Moderate‡	-0.53 (-2.43,1.37)	Moderate
Blank	1	1.06(-2.16,4.28)	Low*‡	-0.59(-5.15,3.97)	Low*‡	0.51 (-2.12,3.14)	Low
Dalteparin	2	0.77(-2.01,3.55)	Moderate‡	-0.73(-3.36,1.91)	Moderate‡	-0.02 (-1.94,1.90)	Moderate
Enoxaparin	1	-0.13(-3.95,3.92)	Moderate‡	-0.97(-3.13,1.19)	Moderate‡	-0.75 (-2.64,1.14)	Moderate

In the sensitivity analysis, we removed the relatively low-design-quality trials. For the all-cause VTE outcome, fondaparinux (SUCRA: 67% to 93.9%), rivaroxaban (SUCRA: 88.4% to 93%), edoxaban (SUCRA: 69.9% to 92.8%) were generally best. In conclusion-relative treatment, apixaban (SUCRA: 66.7%-82.8%) was still ideal, while aspirin (SUCRA: 52.8% to 26.1%), ardeparin (SUCRA: 82.7% to 23.2%), and FXI-ASO (miss) were less dominant. For the all-cause bleeding outcome, betrixaban (SUCRA: 88.3% to 90.5%), aspirin (SUCRA: 73.6% to 82.7%), and warfarin (SUCRA: 60.2% to 78.9%) were best. In key treatment, apixaban (SUCRA: 62.7% to 62.2%), aspirin (SUCRA: 73.6% to 82.7%), and ardeparin (SUCRA: 65.4% to 56.6%) were best. Combined with the GRADE results, apixaban and aspirin were relatively robust. Further, when only considering well-designed trials, the result of apixaban was more robust.

For the major VTE outcome, rivaroxaban (SUCRA: 80.5% to 85.8%), apixaban (SUCRA: 71.5% to 73.5%), and warfarin (SUCRA: 71.9% to 70.8%) were generally best after removing low-quality studies. In key treatment, only warfarin had ideal results; other treatments were missing. For the major bleeding outcome, dalteparin (SUCRA: 74.6% to 81.6%), warfarin (SUCRA: 66.1% to 76.7%), and semuloparin (SUCRA: 65.8% to 72.7%) were the best treatments. In conclusion-related treatment, dalteparin, warfarin, and betrixaban (SUCRA: 86.9% to 56.8%) were still ideal; the result of eribaxaban was missing. Thus, in terms of secondary outcomes, warfarin had a robust effect, and apixaban still showed advantages in inhibiting major VTE and bleeding.

Discussion

In this study, we performed a network meta-analysis to analyse VTE and bleeding events in patients who underwent major joint surgery and were subsequently treated with thromboprophylactics. We included several types of anticoagulant in the analysis, including vitamin K antagonists, direct factor Xa inhibitors, factor XI antisense oligonucleotides, factor VIII inhibitors, direct thrombin inhibitors, non-steroidal anti-inflammatory agents, heparin and its derivatives, and platelet aggregation inhibitors. The results showed that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and reducing all bleeding events, while betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events.

All-cause VTE events that have been described in clinical records typically include asymptomatic DVT, objective symptomatic VTE, and fatal PE, and the diagnostic methods used to evaluate these conditions have included venography (phlebography), ultrasonography, and an objective review of records [136]. The bleeding events that occur after anticoagulant treatment typically include clinically relevant bleeding (major or clinically non-major bleeding) and minor bleeding. Major bleeding was defined as a decrease in haemoglobin of 2 g per decilitre or necessitating transfusion of 2 or more units of blood [137], and clinically relevant non-major bleeding included non-major bleeding that required intervention or consultation with a physician and had clinical consequences [29]. Minor bleeding included haemorrhagic wound complications or other bleeding-related adverse events [138]. However, there may be slight differences among the assessors for VTE and bleeding judgement, especially in non-major events.

The loop-specific inconsistency analysis and GRADE assessment revealed some differences between direct and indirect comparisons. The cause of these inconsistencies may include differences in adjuvant therapy or physiotherapy, especially in blank and placebo intervention arms. In these empty intervention arms, other adjuvant therapy would be used to prevent thrombosis. The decision whether to undergo physiotherapy was due to the daily activity of patients. In addition, the zero-event trials may have made the direct and indirect comparisons less robust. In the comprehensive analysis, the effectiveness of apixaban was ideal and robust. Apixaban is a direct inhibitor of factor Xa that can directly combine with factor Xa to prevent coagulation cascades and is therefore widely applied in the clinical setting [139]. This mechanism of this anticoagulant may play a significant role in thromboprophylaxis after major joint surgery.

The sensitivity analysis revealed that aspirin was not ideal in preventing thrombosis, but it still had high tolerability to inhibit bleeding. We also found that five of twenty-five patients developed VTE in an arm that combined the use of heparin and aspirin and even applied compression treatment at the same time [111]. This finding sugests the combination of heparin and aspirin has negative synergistic effects for thromboprophylaxis.

In the global inconsistency assessment, we found the all-VTE outcome had complete inconsistency. It was notable that improvements in surgical technology and perioperative nursing could reduce thrombosis and bleeding events. Therefore, in theory, if more of these

trials are conducted, a smaller number of patients should experience thrombosis and bleeding.

Major VTE was usually considered as a secondary outcome in the included studies. These cases included proximal DVT, non-fatal PE or deaths associated with VTE during follow-up. However, major bleeding events were usually treated as a major safety outcome in these studies. Our results indicated that betrixaban, dalteparin, apixaban, warfarin, and eribaxaban were ideal for preventing major VTE and reducing the risk of major bleeding. Rivaroxaban was effective at preventing thrombosis but was more likely to cause major bleeding events. It is interesting that betrixaban and eribaxaban, which are direct factor Xa inhibitors, were not ideal for preventing all-cause thrombosis or bleeding but provided advantages when treating major thrombosis and bleeding events. These drugs were potent, orally active and highly selective for factor Xa, and they were selected from a group of similar compounds because of their low affinity for the human ether-à-go-go-related gene (hERG) and showed favourable effectiveness for preventing PE in particular [140]. The U.S. Food and Drug Administration has granted a Fast Track designation to betrixaban for the extended-duration prevention of VTE in acutely ill patients. In this study, dalteparin and warfarin, a heparin derivative and vitamin K antagonist, respectively, were ideal for inhibiting major thrombosis and bleeding events. The effect of rivaroxaban was similar to the above all-cause results, which showed that this drug was effective at preventing major thrombosis but was associated with a high risk of major bleeding events.

Research aimed at preventing thrombosis after joint surgery is generally focused on the use of various types of anticoagulants. Therefore, a network meta-analysis could help us to obtain a more comprehensive understanding of the effectiveness of these drugs and patient tolerability in addition to allowing us to perform indirect comparisons. A previous network meta-analysis of direct factor X inhibitors described results that were similar to ours with regard for the ranking of drugs according to total VTE risk. These rankings were as follows, from high to low: rivaroxaban, apixaban, edoxaban, enoxaparin, darexaban, and betrixaban. The rankings for the ability to reduce major and clinically relevant non-major bleeding were as follows, from low to high: betrixaban, enoxaparin, darexaban, edoxaban, apixaban, and rivaroxaban. Our research also included other types of anticoagulants in addition to direct factor X inhibitors, such as factor XI antisense oligonucleotides, factor VIII inhibitors, direct thrombin inhibitors, non-steroidal anti-inflammatory agents and vitamin K antagonists. We comprehensively analysed all-cause thrombosis/bleeding events and major thrombosis/bleeding events to provide a valuable reference for clinical applications. However, as some anticoagulants included in our work are under development, those findings are of limited value for clinicians. Most importantly, surgical techniques and perioperative nursing have greatly evolved from the time of the first studies included in our work until now, such that the impact of such improvements on bleeding events and possibly on VTE events is potentially important.

There are several limitations to our study. First, our analysis was performed at the study level but not at the individual level. Second, there is unexplained heterogeneity in our analysis. This may result from differences in daily drug doses, application times, mechanical treatment effects, follow-up times, or thrombosis/bleeding event-related criteria because this field has gradually matured in recent years. Third, our study did not evaluate the use of haemoglobin, blood transfusion amounts, or blood drainage as assessment indexes in the analysis of results.

Conclusion

In conclusion, our study indicates that FXI-ASO, ardeparin, aspirin, and apixaban are ideal for preventing all-cause VTE and reducing all bleeding events, among which apixaban is the most reliable. Betrixaban, dalteparin, warfarin, and eribaxaban are ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events, among which

warfarin is the most reliable. Overall, the results of apixaban for thromboprophylaxis after major joint surgery are particularly encouraging.

Disclosure Statement

The authors declare no conflict of interest.

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