Fondaparinux Sodium Compared With Low-Molecular-Weight Heparins for Perioperative Surgical Thromboprophylaxis: A Systematic Review and Meta-analysis

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***Background*—**Fondaparinux sodium has been compared with low-molecular-weight heparins (LMWH) in randomized controlled trials for perioperative surgical thromboprophylaxis. However, the results from these studies are inconsistent in terms of efficacy and safety to reach a clinical decision. The objective of this study was to systematically review the randomized controlled trials comparing the efficacy and safety of fondaparinux and LMWH for perioperative surgical thromboprophylaxis.

***Methods and Results*—**Systematic search in various databases was done to identify randomized controlled trials comparing fondaparinux and LMWH published during the years 2000 to 2017. Outcomes of interest in this study included venous thromboembolism up to day 15, all-cause mortality up to day 90, major bleeding, and minor bleeding during the treatment period. Analyses were performed with the relative odds based on a random-effects model using Mantel-Haenszel statistics. Results were presented as odds ratios with their 95% CIs. The assessment of study quality was performed as per Cochrane collaboration. After screening 10 644 articles, 12 randomized controlled trials including 14 906 patients were included in the final analyses. Pooled analyses showed the odds of venous thromboembolism in the fondaparinux group were 0.49 times the odds in LMWH group (OR=0.49 [0.38–0.64]). However, the odds of major bleeding in the fondaparinux group were 1.48 times the odds in the LMWH group (OR=1.48 [1.15–1.90]).

***Conclusions*—**Fondaparinux was associated with a superior efficacy in terms of reduction of venous thromboembolism in this meta-analysis. However, it was also associated with increased odds of major bleeding. **(*J Am Heart Assoc*. 2019;8:e012184. DOI: 10.1161/JAHA.119.012184.)**

Key Words: effectiveness • fondaparinux • low molecular weight heparin • prevention • safety • systematic review • venous thromboembolism

Venous thromboembolism (VTE) is a leading cause of preventable death among patients undergoing surgical intervention.[1] Major factors contributing to development of VTE among surgical patients may include variations in the flow of blood in the veins (circulatory stasis), changes in the vessel wall because of any injury during the procedure (vascular damage), and any variation in the composition of blood (hypercoagulability). These complex mechanisms interplay in the progression of VTE.[2] A majority of patients undergoing surgeries possess at least 1 risk factor of VTE,[3] making VTE a significant cause of healthcare and financial burden.[4,5]

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Accompanying Data S1 through Data S3, Tables S1 and S2, and Figures S1 through S16 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012184

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Clinical Perspective

What Is New?

- Meta-analyses during the past years have compared fondaparinux sodium with low molecular weight heparins (LMWH) for thromboprophylaxis in orthopedic surgeries; however, the literature lacks a systematic comparison of these drugs in different types of surgeries altogether.
- Among the randomized controlled trials, both drugs have been compared for surgical thromboprophylaxis; nevertheless, the findings are not consistent in terms of efficacy and safety.
- This study systematically reviews the randomized controlled trials comparing safety and efficacy of fondaparinux and LMWHs for perioperative surgical thromboprophylaxis for better clinical judgment.

What Are the Clinical Implications?

- In this study, fondaparinux was associated with lower odds of venous thromboembolism compared with LMWH, but both groups were similar in terms of reduction of symptomatic venous thromboembolism and all-cause mortality.
- Fondaparinux was also associated with increased risk of major bleeding, especially surgical site bleeding, compared with LMWH.
- This analysis suggested a trade-off between safety and efficacy when fondaparinux is used over LMWH; however, net clinical benefit (venous thromboembolism + major bleeding) was in favor of fondaparinux compared with LMWH.

VTE is the most common postoperative complication following surgeries.[2] VTE has been reported to be associated with long-term sequelae such as chronic leg ulcers and venous insufficiency,[6] which could be life threatening. Thus, surgical thromboprophylaxis is strongly recommended by the American College of Chest Physicians.[7] Pharmacological prophylaxis is effective, yet VTE still occurs frequently.[8] Hence, there is a need to improve thromboprophylaxis for surgical patients at risk for VTE.

Among patients undergoing surgical interventions, the management of anticoagulation is challenging, as underlying surgical procedures are associated with bleeding complications, which could be augmented further by anticoagulation for thromboprophylaxis. Thus, a balance between thrombosis prevention and devastating operative site bleeding is crucial in this population.[9] Conventional therapy such as low-molecular-weight heparins (LMWHs) has been used for many years; nevertheless, factor Xa inhibitors are desired because they are more selective in their action.[10] Fondaparinux is the first approved drug among factor Xa inhibitors,[11] which has been compared with LMWH in various clinical trials; however, results are inconsistent in terms of efficacy and safety.[6,11–21] This meta-analysis was performed to examine existing clinical evidence on efficacy and safety of parenteral fondaparinux and LMWH for perioperative surgical thromboprophylaxis in patients at high risk for VTE.

Methods

The authors declare that all supporting data are available within the tables, figures, and online supplemental material of this manuscript. This systematic review and meta-analysis followed the guidelines published by Cochrane Collaboration. We used the Preferred Reporting Items for Systematic Review and Meta-analysis 2009[22] checklist (Table S1) for transparent reporting of this study.

Study Protocol

We developed a protocol for systematic review and meta-analysis to assess overall risk factors as per Virchow's triad (Data S1). However, this paper was developed to specifically address perioperative surgical thromboprophylaxis considering its management very crucial and challenging for this patient population.[9]

Eligibility Criteria

Type of Studies

Only head-to-head randomized controlled trials (RCTs) comparing fondaparinux with LMWHs published in English, and meeting the study inclusion criteria were taken into consideration. LMWHs included enoxaparin sodium, dalteparin sodium, nadroparin calcium, parnaparin sodium, and tinzaparin sodium. Potential studies in other languages were searched for abstracts in English. Studies were included if published between January 2000 and December 2017. This period was selected because the first clinical trial of fondaparinux comparing LMWH was published in 2001.[11]

Participants

RCTs were considered eligible if they included both male and female adults aged ≥18 years old. RCTs enrolling patients undergoing major orthopedic surgeries (eg, total hip replacement, total knee replacement, or hip fracture surgeries), major general surgeries (eg, abdominal surgery, cancer surgery), and related surgical immobility proven to be a risk factor for the development of VTE were included in the analyses.

Interventions

The interventions compared in this review were subcutaneous fondaparinux and subcutaneous LMWHs at titrated dose/manufacturer's recommended dose as per body weight or at the standard dose as per the country of interest. Studies in which the assessment was done up to 15 days after surgery were only taken into consideration for inclusion. Assessment period was chosen as 15 days, as the increased risk of VTE has been cited to be during the first 2 weeks.[23–25]

Information Sources

We conducted a systematic search of the databases (Embase, PubMed, The Cochrane Central Register of Control Trials, ProQuest-Direct, Science Direct, Clinicaltrials.gov), and conference proceedings to find RCTs evaluating fondaparinux and LMWH for the prophylaxis of VTE. Trials presented in conference proceedings but not published were searched for full-text results. When full-text results were not available, the reviewers contacted the authors of the unpublished studies via email to request trial results and full-text manuscripts if available. The reference lists of all identified trials and review articles were hand searched to find any additional trials.

Search

The complete search strategy can be found in Table S2.

Study Selection

Covidence,[26] an online systematic review platform (www.covidence.org) was used to initially screen articles on the basis of the title and abstract. Records were imported from various databases into Covidence, where duplicates were removed. Two review authors (A.K., A.T.) independently screened the titles and abstracts of identified citations for potential eligibility. Full texts of articles retrieved were judged potentially eligible by at least 1 review author.

Data Collection Process

Both review authors then independently screened the full-text article for eligibility using an explicit inclusion and exclusion criteria. The screening process was documented in Preferred Reporting Items for Systematic Review and Meta-analysis flow chart of study selection (Figure 1). A data extraction form was developed in the Covidence web platform to extract the information from relevant clinical trials. Both review authors independently extracted data from each included study. Any disagreements were resolved by discussion or by consulting a third reviewer (WW). After consensus, both reviewers analyzed the resulting papers in full text independently.

Data Items

The primary efficacy outcome of this study was VTE defined as the composite of symptomatic and asymptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE). We also reported symptomatic VTE and PE as an independent outcome, considering it to be an important predictor of death. Considering the differential risk of proximal and distal DVT on PE and death, the events of proximal and distal DVT were also reported separately. Included studies assessed patients for DVT by systematic bilateral ascending venography of the legs, magnetic resonance venography, or D-dimer test. PE was assessed by a lung scan, pulmonary angiography, and helical computed tomography or at autopsy. All-cause mortality at day 90 after surgery was also reported. Mortality assessment at 90 days was chosen, as increased risk of VTE-related mortality has been indicated as 60 to 90 days following surgeries.[12] The safety outcome was the incidence of major bleeding, a composite outcome that included fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; or overt bleeding, with hemoglobin level declined >2 g/dL, or requirement of transfusion of ≥2 units of blood as reported in major clinical trials.[11,12,15,27] Safety measures also included minor bleeding, which included any bleeding event not qualified as major bleeding. To assist clinical decision making, we also reported net clinical benefit in which we combined VTE and major bleeding events for each study.

Risk of Bias in Individual Studies

The assessment of methodological quality of included studies was done using The Cochrane Collaboration's "Risk of Bias" tool. Domains were classified as "low risk," "high risk," or "unclear risk" as per Cochrane Handbook for Systematic Reviews of Interventions.[28]

Summary Measures

All the outcomes in this analysis were binary. Relative treatment effects for each comparison were expressed as odds ratio (OR) with 95% CI. The pooled data for each outcome were used to create a "Forest Plot." The individual participant was the unit of analysis. Finally, we also presented the primary outcomes using L'Abbe plots as a tool to look at the direction of pooled effect graphically and to compare the event rates in fondaparinux compared with LMWH.

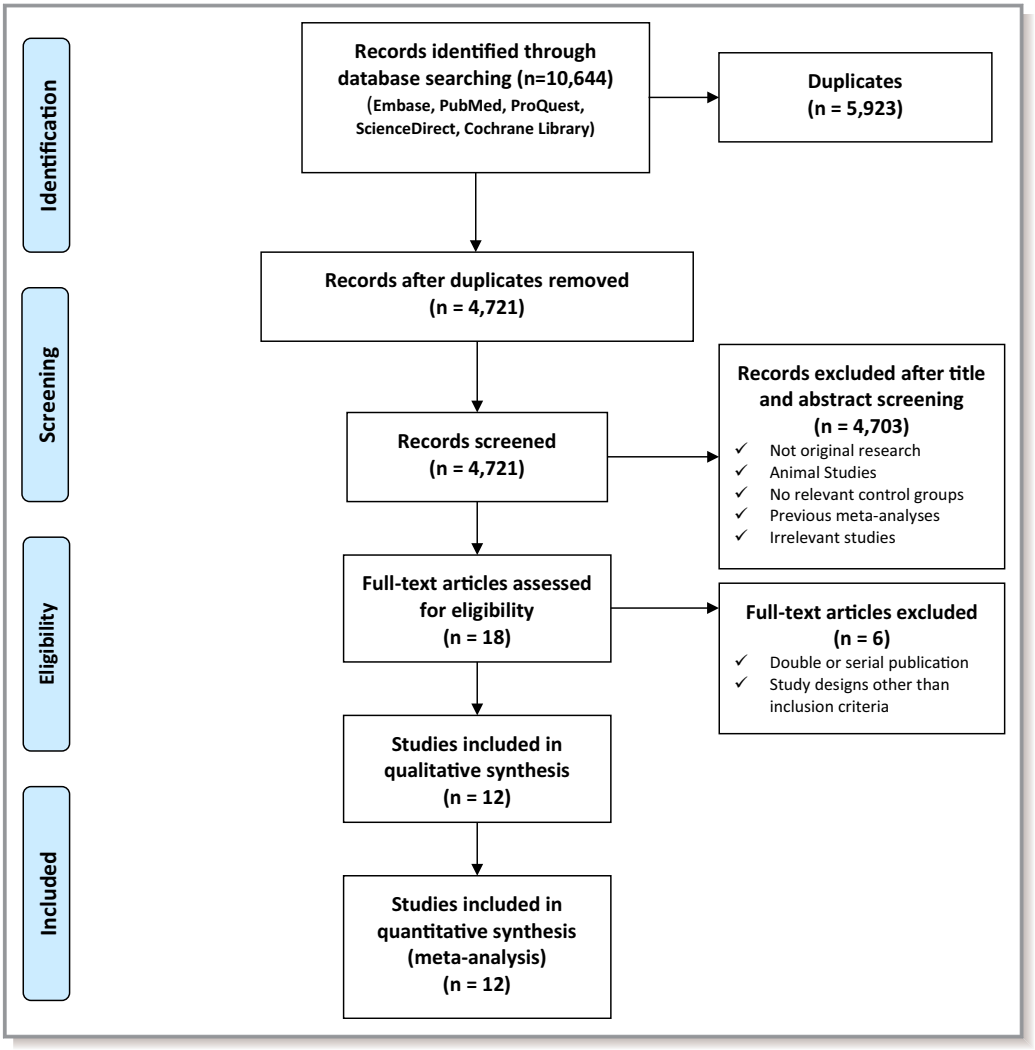

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart for study selection.

Synthesis of Results

Data were analyzed using Mantel-Haenszel statistics. Chi-square tests and I^2 statistics were used to assess heterogeneity. As the studies included in this meta-analysis were from different countries, which might cause unexplained heterogeneity, we used a random-effects model for summary statistics.[29]

Risk of Bias Across Studies

The reporting bias was assessed by use of a "funnel plot" to examine the relationship between treatment effects and their inverted standard errors.[30] Funnel plots were presented only if there were at least 10 studies in any subgroup to maintain power to distinguish chance from real symmetry.[28]

Additional Analyses

Subgroup Analysis

Subgroup analysis was conducted in which studies from different continents were pooled together to see any difference in the results compared with primary analyses. We also reported a subgroup analysis comparing only postoperative thromboprophylaxis to control for possible bias caused by different timings of anticoagulation.

Sensitivity Analysis

The primary analyses included data from all patients in the trials during the period of randomly allocated treatment. A sensitivity analysis was performed to explore the effect that risk of bias had on estimates of treatment effects. The effect

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Table. Description of Included Studies in the Meta-analysis

Characteristics of the Included Studies								Number of Patients		Mean Age in Years		Sex (M/F)		Mean Weight/BMI	
Study	Type of Surgery	N=14 906	Clinical Trial Setting	FPX Dose	LMWH Dose	Assessment Day Post-Surgery	Duration of Prophylaxis	FPX	LMWH	FPX	LMWH	FPX	LMWH	FPX	LMWH
Turpie, 2001[19]	Elective hip replacement surgery	n=437	Multicentered, double blind RCT	3.0 mg OD	Enoxaparin 30 mg BD	10th day	5–10 days	177	260	66	66	80/97	123/137	80/NA	81/NA
Bauer, 2001[18]	Elective major knee surgery	n=1034	Multicentered, double-blind RCT	2.5 mg OD	Enoxaparin 30 mg BD	11th Day	5–9 days	517	517	67.5	67.5	204/313	223/294	89/31.5	88/30.9
Erikss-on, 2001[11]	Hip-fracture surgery	n=1673	Multi-centered, double-blind RCT	2.5 mg OD	Enoxaparin 40 mg OD	11th day	5–9 days	831	842	76.8	77.3	187/644	224/618	64.3/ 23.8	64.223.6
Turpie, 2002[12]	Total hip replacement	n=3841	Multicentered, double-blind RCT	2.5 mg OD	Enoxaparin 30 mg BD	11th day	5–9 days	1915	1926	67	67	942/973	897/1029	80.6/28	79.6/27.6
Lassen, 2002[6]	Elective hip replacement surgery	n=4100	Multicentered, double-blind RCT	2.5 mg OD	Enoxaparin 40 mg OD	11th day	5–9 days	2048	2052	66.4	67	889/1159	875/1177	75/26	75/26.55
Agnelli, 2005[15]	High-risk abdominal surgery	n=2858	Multicentered, double-blind RCT	2.5 mg OD	Dalteparin 5000 IU OD	10th day	5–9 days	1433	1425	66	65	788/645	796/629	74.2/ 26.3	74.3/26.3
Sasaki, 2009[14]	Hip fracture surgery	n=76	Single-centered, open-label RCT	2.5 mg OD	Not disclosed	14th day	14 days	38	38	79.2	80.2	8/30	9/29	NA/21.3	NA/20.35
Yokote, 2011[17]	Total hip replacement	n=167	Single-centered, single-blind RCT	2.5 mg OD	Enoxaparin 20 mg BD	11th day	10 days	84	83	63	64	14/70	16/67	NA/22.5	NA/23.0
Argun, 2013[21]	Elective Hip and Knee Arthroplasty	n=108	Single-centered, open-label RCT	2.5 mg OD	Nadroparin 2850 IU OD	5th day	Not disclosed	55	53	58.7	60	34/21	33/20	NA/NA	NA/NA
Shen, 2014[20]	Esophagectomy	n=116	Single-centered, open-label RCT	2.5 mg OD	Nadroparin 4100 IU OD	Undisclosed-Abstract only	Not disclosed	NA	NA	NA	NA	NA	NA	NA/NA	NA/NA
Steele, 2015[16]	Bariatric surgical patients	n=198	Single-centered, double-blind RCT	5.0 mg OD	Enoxaparin 40 mg BD	14th day	Duration of hospital stay (Average: 2.5 days)	100	98	40.4	41.8	16/84	16/82	NA/NA	NA/NA
Hata, 2016[13]	Uro-oncological surgery	n=298	Single-centered, single-blind RCT	2.5 mg OD	Enoxaparin 2000 IU BD	5th day	5 Days	152	146	63.9	64.7	144/8	138/8	NA/23.9	NA/23.7

BMI indicates body mass index; FPX, fondaparinux sodium; LMWH, low-molecular-weight heparin; RCT, randomized controlled trial.

on the primary outcome was explored using sensitivity analyses by eliminating studies that were at a high risk of bias, had used a dose other than that recommended, did not clearly list the dose, or did not have the full text available. As some included studies in this meta-analysis had a small number of events, we used the recommended Peto method[31] for pooled analyses during sensitivity analyses. All statistical analyses in this meta-analyses were performed using Review Manager[32] (RevMan 5.3) and STATA[33] version 15.1.

Results

Study Selection

A total of 10 644 citations were identified; 5923 duplicate studies were removed, leaving 4721 studies for screening. After screening the full text, 18 studies were retrieved and reviewed. Six of these 18 studies were subsequently excluded because they did not meet the RCT study design criteria or were duplicate publications. The final analysis included 12 studies (Figure 1).

Study Characteristics

The 12 studies[6,11–21] captured data on 14 906 patients for analysis. All 12 studies compared fondaparinux with LMWHs at titrated dose/manufacturer recommendation for surgical thromboprophylaxis. Six of these studies[6,11,12,15,18,19] were multicenter RCTs while the remaining 6[13,14,16,17,20,21] were single-center RCTs (Table). Four studies each were conducted in North American[11,12,16,18] and Asian countries.[13,14,17,20] Three studies[11,12,21] were conducted in European countries, and 1 study was multinational. Average assessment day of VTE was the ninth day in this meta-analysis.

Risk of Bias Within Studies

Eight of the studies[6,11–13,15,16,18,19] were funded by pharmaceutical industries, which could have been a source of bias. These studies were indicated to be at high risk of bias. Review authors' judgment about each risk is presented by a "risk of bias graph" and a "risk of bias summary" for each study in Figures 2 and 3, respectively. A detailed description of the risk of bias can be found in Data S2 and Data S3.

Results of Individual Studies

Summary data for each study are indicated in Table and Data S3.

Synthesis of Results

Efficacy Outcome

Venous thromboembolism up to postoperative day 15

All 12 trials reported on the outcome measure of VTE; 243 of 4309 patients had VTE in the fondaparinux group versus 471 of 4357 patients in the LMWH group. The odds of VTE in the fondaparinux group were 0.49 times the odds of VTE in the LMWH group (OR, 0.49; 95% CI, 0.38–0.64; $P<0.001$; Figure 4). Sensitivity analysis (Figure S1) did not impact the effect size (OR, 0.50; 95% CI, 0.42–0.58; $P<0.001$). The L'Abbe plot (Figure 5) shows that most of the studies lie in the bottom right (under the null effect line) of the plot. This indicates that the VTE event rates were higher in the LMWH group compared with fondaparinux. The overall trendline (OR line) shows that fondaparinux has a protective effect against VTE compared with LMWH. Reporting bias was not evident, as the funnel plot was symmetric (Figure S2).

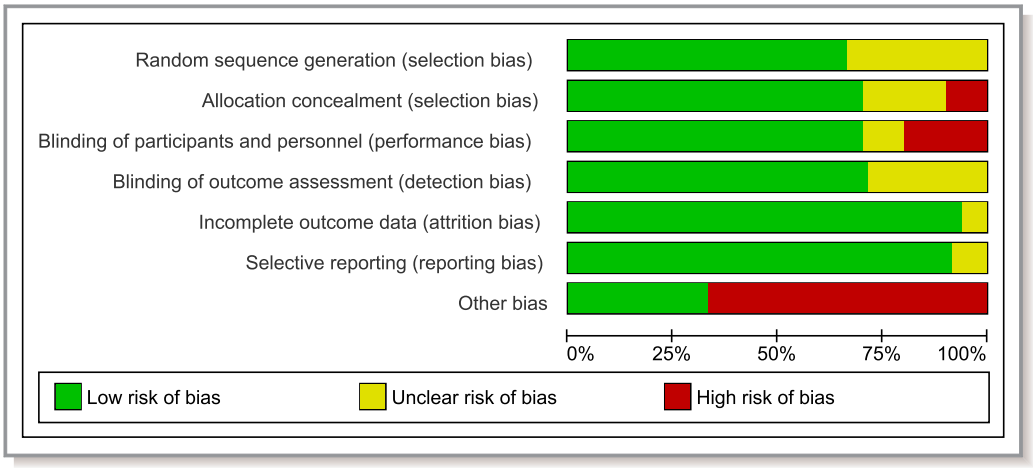

Figure 2. Risk-of-bias graph: review authors' judgments about each risk-of-bias item presented as percentages across all included studies.

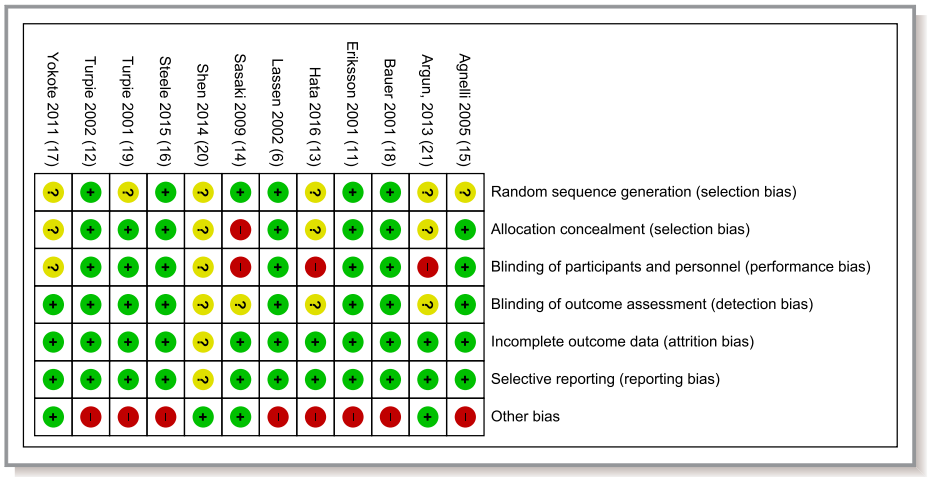

Figure 3. Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each included study.

Deep vein thrombosis up to postoperative day 15

The odds of total DVT in the fondaparinux group was 0.48 times the odds in the LWMH group (OR, 0.48; 95% CI, 0.38–0.61; $P<0.001$; Figure S3). The odds for proximal DVT in the fondaparinux group were 0.49 times the odds in the LMWH group (OR, 0.49; 95% CI, 0.29–0.84; $P=0.009$; Figure S4). As far as distal DVT was concerned, the odds in the fondaparinux group were 0.50 times the odds in the LMWH group (OR, 0.50; 95% CI, 0.39–0.64; $P<0.001$; Figure S5). Not much impact on effect size was observed during sensitivity analysis (Figures S6, S7, and S8). Reporting bias was not evident as presented by funnel plot (Figure S9).

Symptomatic VTE up to postoperative day 15

We observed 29 events among 5152 patients in the fondaparinux arm and 20 events among 5153 patients on LMWH. We did not observe any statistically significant difference between the 2 groups (OR, 1.33; 95% CI, 0.62–2.86; $P=0.47$; Figure S10).

Pulmonary embolism up to postoperative day 15

Sixteen events each among 5373 and 5425 patients on fondaparinux and LMWH, respectively, were observed. There was no difference between the PE events of the two arms (OR, 1.01; 95% CI, 0.49–2.11; $P=0.97$; Figure S11).

All-cause mortality up to postoperative day 90

Six studies reported on number of deaths. Odds in the fondaparinux group were 0.87 times the odds in the LMWH group (OR, 0.87; 95% CI, 0.62–1.23; $P=0.44$), but results were statistically insignificant (Figure S12). Sensitivity analysis (Figure S13) did not impact the effect size.

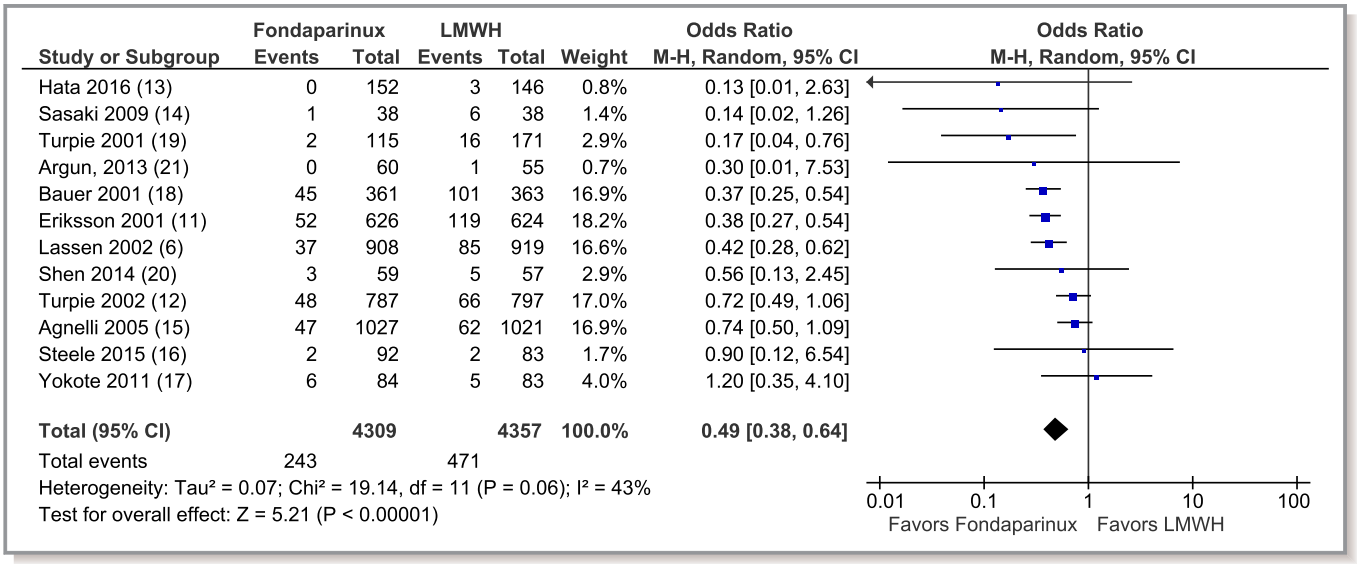

Figure 4. Fondaparinux compared with low-molecular-weight heparins (LMWH) for venous thromboembolism up to postoperative day 15.

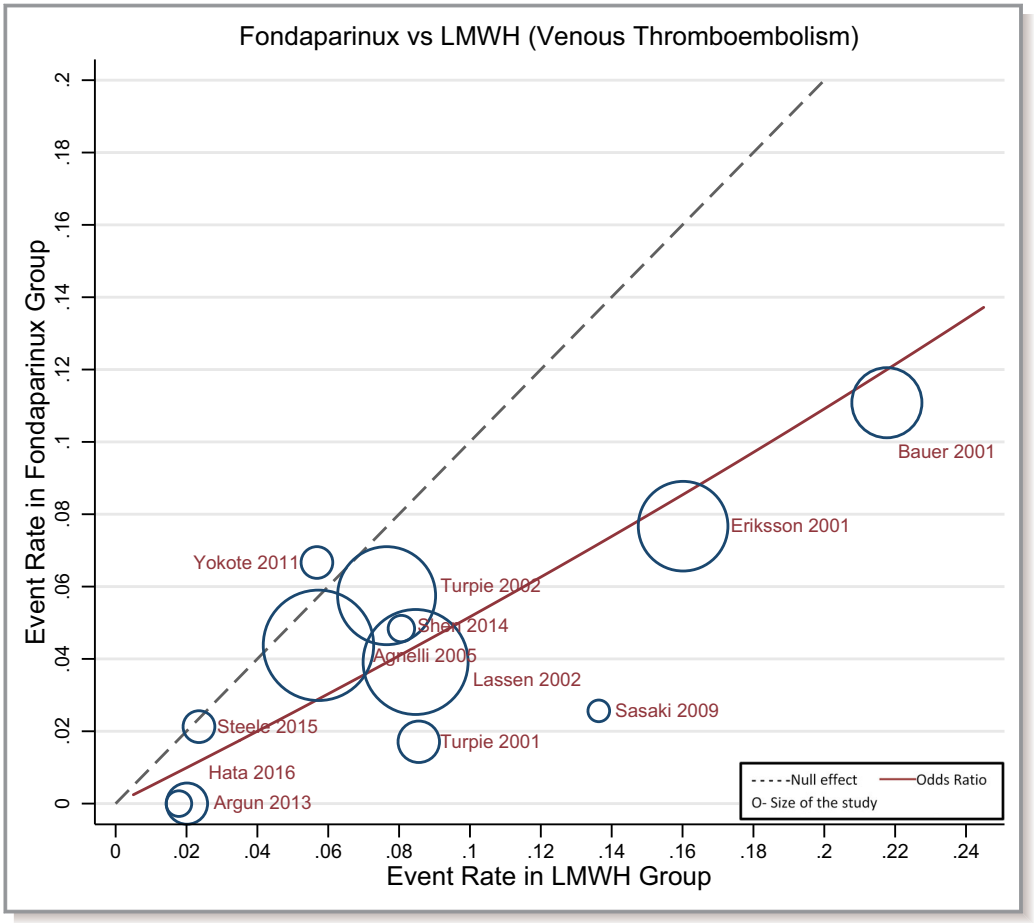

Figure 5. Comparison of events rates of venous thromboembolism in fondaparinux and low-molecular-weight heparins (LMWH) group.

Safety Outcome

Major bleeding during the treatment period

Nine studies reported on the incidences of major bleeding. The odds in the fondaparinux group for major bleeding were 1.48 times the odds in the LMWH group (OR, 1.48; 95% CI, 1.15–1.90; *P*=0.002; Figure 6). Sensitivity analysis did not have much impact on the effect size (OR, 1.49; 95% CI, 1.17–1.91; *P*=0.001; Figure S14). The L'Abbe plot (Figure 7) showed that most of the studies lie above the null effect line of the plot, which indicates that major bleeding event rates were higher in the fondaparinux group compared with the LMWH group. The overall trendline shows that LMWH has a protective effect against major bleeding compared with fondaparinux.

We also specifically looked at events of fatal bleeding and bleeding at surgical site between the 2 groups. For fatal bleeding, Agnelli et al[15] reported 2 events each in both arms. Eriksson et al[11] reported 1 event of fatal bleeding in LMWH, but no event of fatal bleeding was observed with fondaparinux in this study. As very few studies reported on fatal bleeding, pooled analysis could not be performed. However, for bleeding at the surgical site, we observed 82 events and 54 events in the fondaparinux arm and LMWH arm, respectively. In the pooled analysis, the odds of surgical site bleeding in fondaparinux were 1.43 times the odds in the LMWH arm (OR, 1.43; 95% CI, 1.01–2.04; *P*=0.05). The association was found to be statistically significant (Figure 8). The L'Abbe plot (Figure 9) shows that of 7 studies included in this analysis, 3 studies lie on the null effect line. However, the overall trendline shows that LMWH administration has a protective effect against surgical site bleeding compared with fondaparinux.

Minor bleeding during the treatment period

Nine studies reported minor bleeding (any bleeding event that did not meet the criteria for major bleeding previously defined). In the summary statistics, it was indicated that fondaparinux odds for minor bleeding were 1.13 times the odds in LMWH (OR, 1.13; 95% CI, 0.89–1.43; *P*=0.31); however, the results were not significant (Figure S15). Results were consistent following sensitivity analysis (Figure S16).

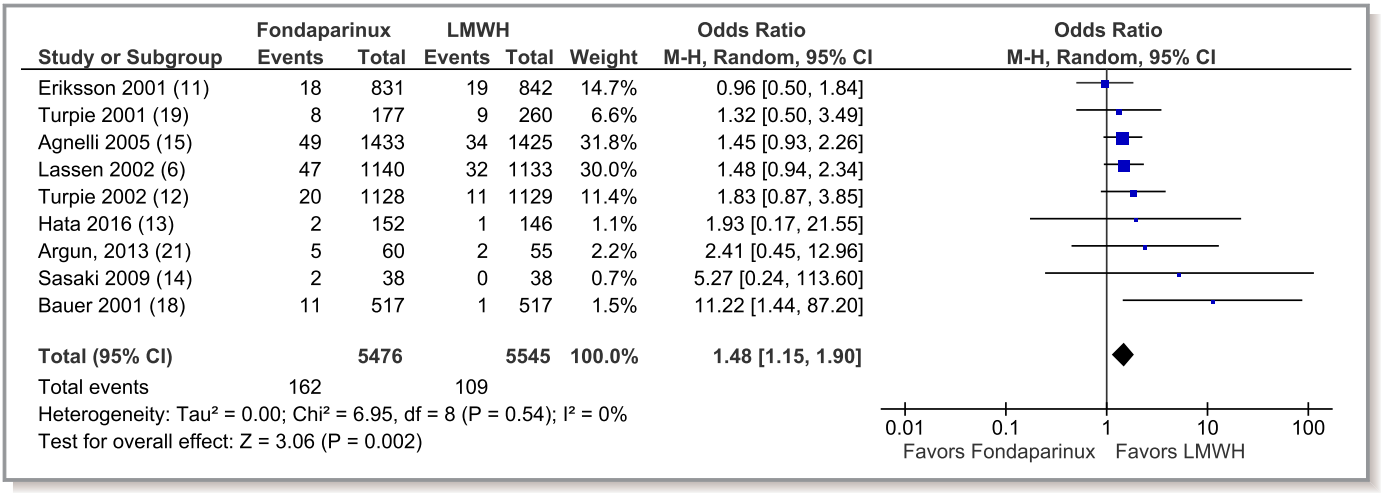

Figure 6. Fondaparinux compared with low-molecular-weight heparins (LMWH) for major bleeding during the treatment period.

Net clinical benefit

Eight studies were included in this analysis. Pooled analysis showed significant difference in net clinical benefit in favor of the fondaparinux arm (OR, 0.66; 95% CI, 0.51–0.84; *P*=0.001; Figure 10). The L'Abbe plot (Figure 11) shows that most of the studies lie under the null effect line. This indicates that the net

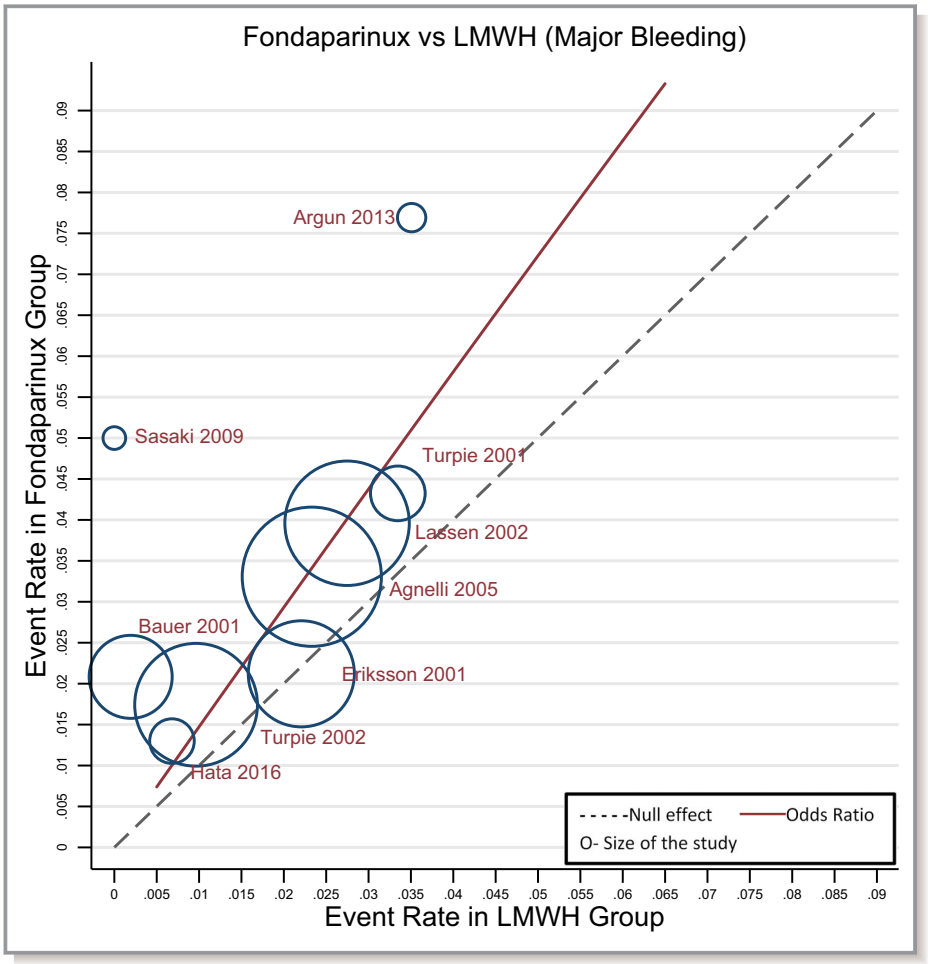

Figure 7. Comparison of events rates of major bleeding in fondaparinux and low-molecular-weight heparin (LMWH) group.

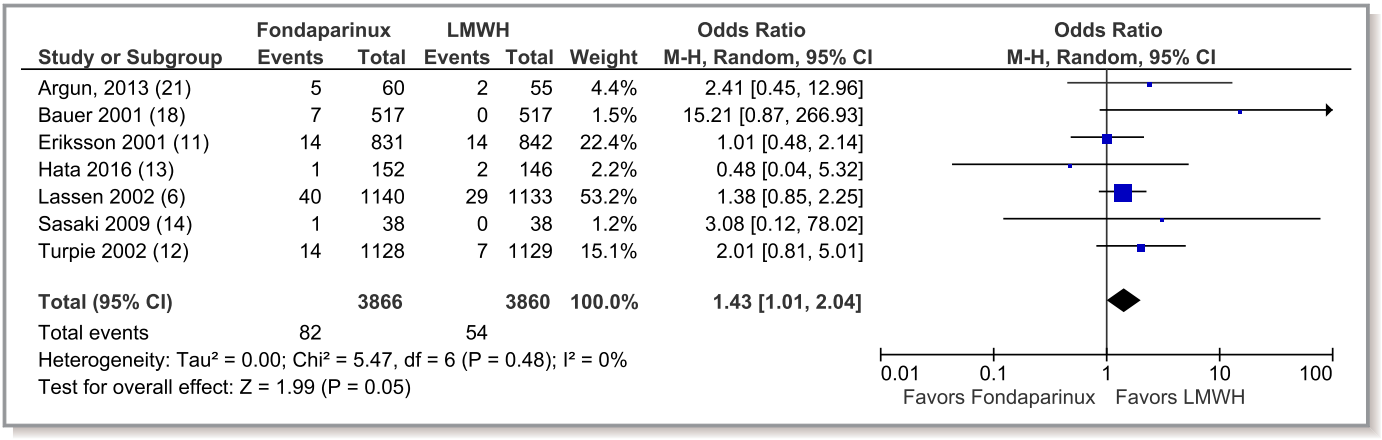

Figure 8. Fondaparinux compared with low-molecular-weight heparins (LMWH) for surgical site bleeding.

clinical benefit is higher in the fondaparinux group compared with LMWH. The overall trendline shows that fondaparinux is better than LMWH in terms of net clinical benefit.

Risk of bias across studies

Reporting bias was presented with funnel plots in the outcome variables above.

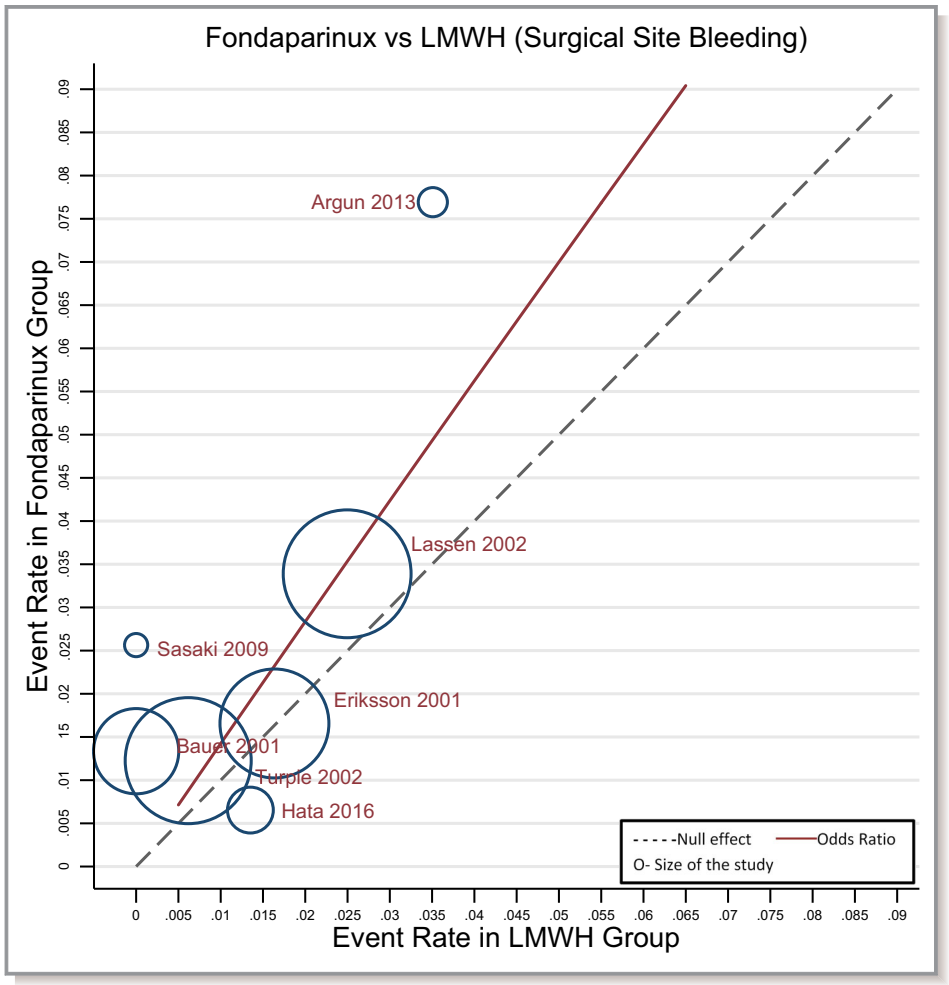

Figure 9. Comparison-of-events rates of surgical site bleeding in fondaparinux and low-molecular-weight heparins (LMWH) group.

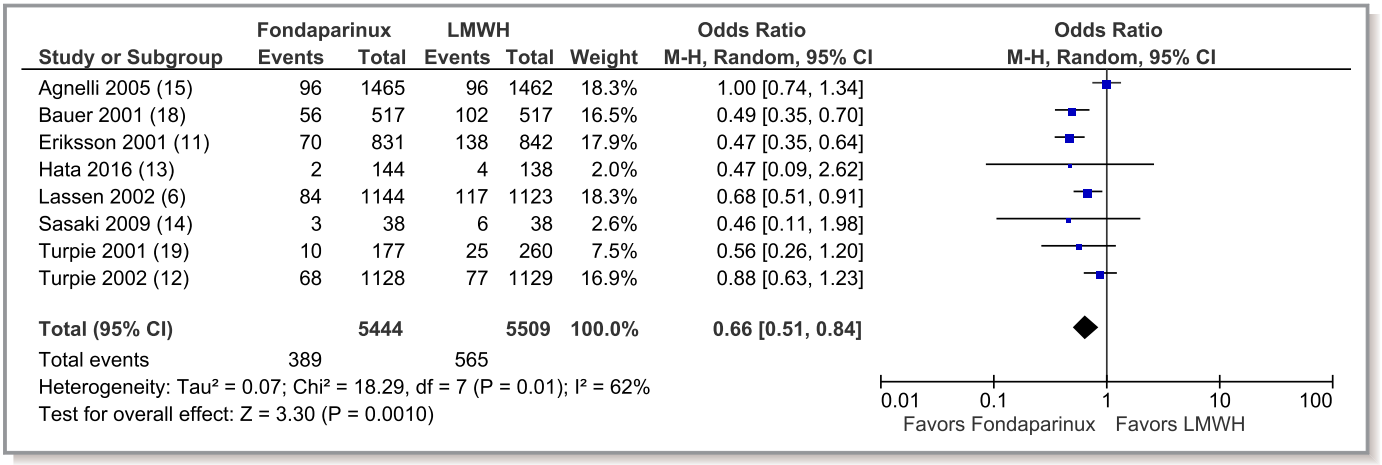

Figure 10. Fondaparinux compared with low-molecular-weight heparins (LMWH) for net clinical benefit.

Subgroup Analysis

A subgroup analysis was performed stratifying studies within each of the different continents to examine any difference in the effect sizes.

North American and Australian Population

Four studies were conducted on the North American and Australian continents. For VTE, the odds in the fondaparinux group were 0.47 times the odds in the LMWH group (OR, 0.47; 95% CI, 0.27–0.84; *P*=0.01; Figure 12). For major bleeding, the odds in the fondaparinux group were 2.09 times the odds in the LMWH group, but the association was not statistically significant (OR, 2.09; 95% CI, 0.89–4.89; *P*=0.09; Figure 13).

European Population

Three studies were conducted on the European continent. Odds in the fondaparinux group were 0.40 times the odds in LMWH group for VTE (OR, 0.40; 95% CI, 0.31–0.52; *P*<0.001; Figure 14). For major bleeding, the odds in the fondaparinux group were 1.27 times the odds in the LMWH group but were not statistically significant (OR, 1.27; 95% CI, 0.85–1.91; *P*=0.25; Figure 15).

Asian Population

Four of the trials were conducted on the Asian continent. The summary statistics indicated that the odds for VTE in the fondaparinux group were 0.52 times the odds in the LMWH group (OR, 0.52; 95% CI, 0.19–1.41; *P*=0.20; Figure 16). As only 2 studies with very few events of major bleeding were estimable for the meta-analysis, summary statistics for major bleeding were not performed for Asian studies.

Fondaparinux Versus LMWH in Postoperative Thromboprophylaxis

To estimate the effect of "timing of dose" on the results, we included only the studies in which thromboprophylaxis was given postoperatively in this subgroup analysis. We continue to find results similar to the main analyses. The odds in the fondaparinux group for VTE were 0.49 times the odds in the LMWH group (OR, 0.49; 95% CI, 0.28–0.87; *P*=0.02; Figure 17). At the same time, fondaparinux was associated with an increased risk of major bleeding compared with LMWH (OR, 1.95; 95% CI, 1.02–3.76; *P*=0.04; Figure 18).

Discussion

Our study suggests a significant reduction of the risk of VTE associated with fondaparinux compared with LMWH for perioperative surgical thromboprophylaxis. This is consistent with the findings of a previous meta-analysis conducted on 4 RCTs by Turpie et al[27] in which better efficacy of fondaparinux over LMWH was indicated with a 45.3% reduction of risk of total VTE. In their meta-analysis, Turpie et al focused only on the patients undergoing major orthopedic surgeries, whereas our meta-analysis extends the current existing knowledge to overall surgical interventions. Among the RCTs and large cohort studies, PE has been cited as a major cause of death in patients with VTE.[34,35] To the reviewers' knowledge, previous studies have not reported PE as an independent outcome. PE events were reported independently in our study, which could be useful in clinical decision making. Our results suggest no significant difference in the incidence of PE between fondaparinux and LMWH combining data across available published studies. Because the patients after randomization in each trial were given prophylaxis

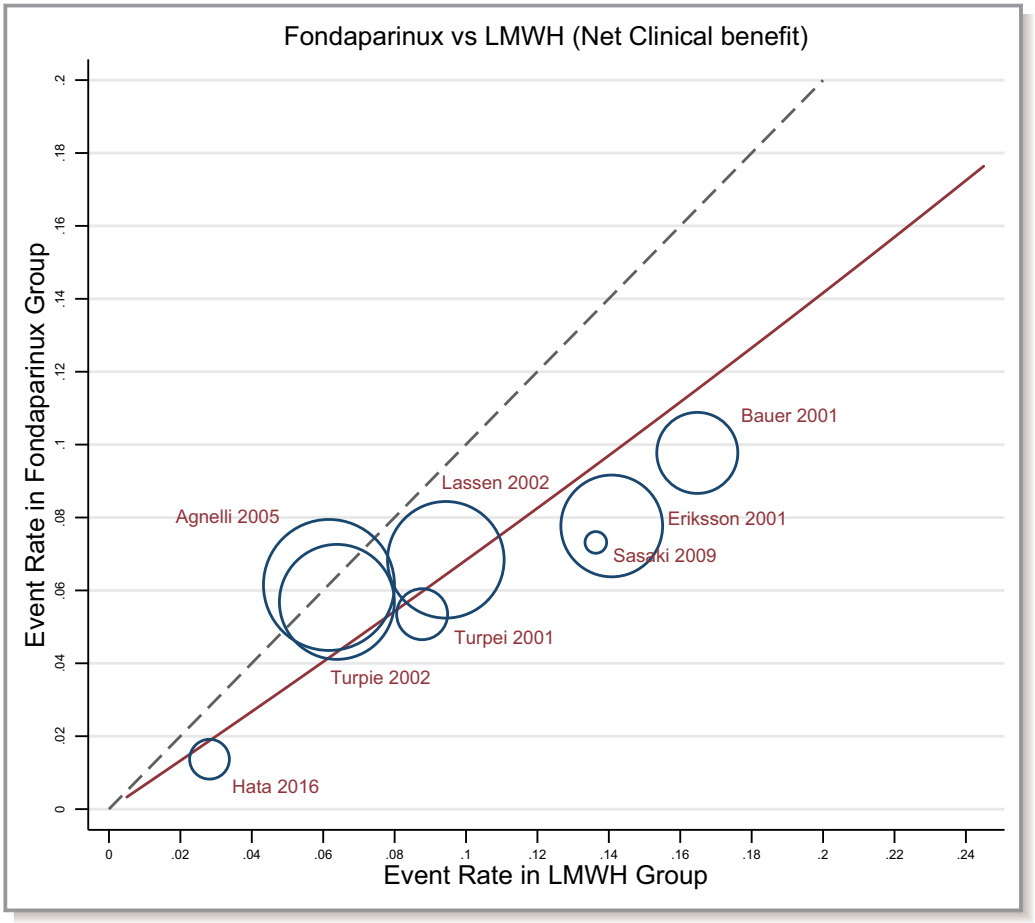

Figure 11. Comparison-of-events rates of net clinical benefit in fondaparinux and low-molecular-weight heparins (LMWH) group.

treatment, events of PE in these trials might have been small compared with real clinical practice.

This meta-analysis reported a significant reduction in the risk of total DVT associated with fondaparinux compared with LMWH, which is consistent with the results of previous meta-analyses.[27,36,37] Studies have indicated proximal DVT as a substantial risk factor for PE and mortality.[38] As almost half of the patients with proximal DVT suffer fatal PE if untreated,[39,40] detection and treatment of proximal DVT is important.[40] Fondaparinux significantly reduced the risk of proximal DVT compared with LMWH in our study. To the best of our knowledge, the recent meta-analyses did not report the

Study or Subgroup	Fondaparinux Events	Total	LMWH Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bauer 2001 (18)	45	361	101	363	40.6%	0.37 [0.25, 0.54]
Steele 2015 (16)	2	92	2	83	7.2%	0.90 [0.12, 6.54]
Turpie 2001 (19)	2	115	16	171	11.5%	0.17 [0.04, 0.76]
Turpie 2002 (12)	48	787	66	797	40.7%	0.72 [0.49, 1.06]
Total (95% CI)		**1355**		**1414**	**100.0%**	**0.47 [0.27, 0.84]**
Total events	97		185			

Heterogeneity: Tau² = 0.17; Chi² = 8.11, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 2.55 (P = 0.01)

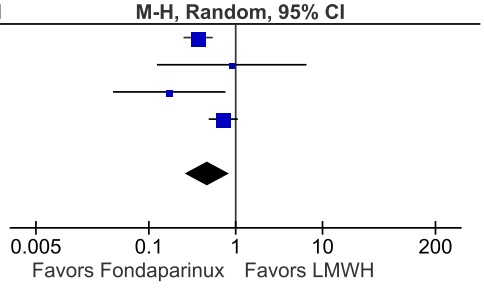

Figure 12. Fondaparinux compared with low-molecular-weight heparins (LMWH) for venous thromboembolism in the North American and Australian population.

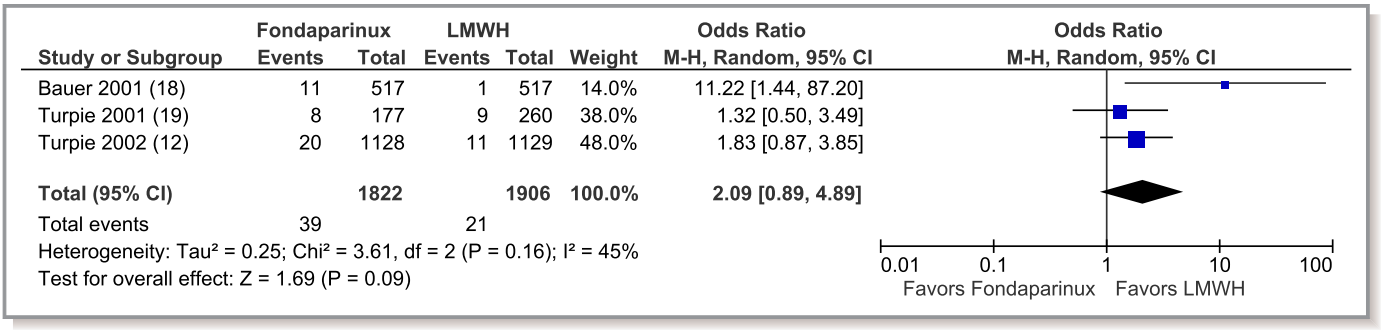

Figure 13. Fondaparinux compared with low-molecular-weight heparins (LMWH) for major bleeding in the North American and Australian population.

results pertinent to the proximal DVT;[36,37] thus, our study improves the current knowledge in this discipline. Also, although proximal DVT has a 3-fold higher risk of recurrent VTE than distal DVT,[41] there is a high probability that distal DVT may extend to proximal DVT and increase the risk of PE and death.[40] Our study indicated a significant reduction of distal DVT by fondaparinux. The observed differences in the efficacy in both drugs might be related to the selective inhibition of factor Xa by fondaparinux compared with LMWH (by which both factor Xa and IIa are inhibited). It could also be attributable to longer half-life and the linear pharmacokinetic profile of fondaparinux.[42]

Major bleeding in institutionalized surgical patients in VTE prevention trials is a strong predictor of mortality.[43] Our pooled analysis indicated a greater risk of major bleeding with fondaparinux compared with LMWH consistent with previous studies.[36,37] More importantly, we observed a significantly increased risk of bleeding at the surgical site with fondaparinux, which is of high clinical relevance.[27] Turpie et al pointed out a significant risk of major bleeding by fondaparinux;[27] however, they reported no difference in clinically relevant bleeding between the 2 groups. Major bleeding in our study was reported as per the standard definition reported in the first major clinical trials assessing the efficacy and safety of these comparators[11] to produce the most current and comprehensive evidence. The association of fondaparinux with major bleeding might be linked to differences in timing of the administration of fondaparinux and LMWH as reported in the previous study.[27] We conducted a subgroup analysis in which we included only postsurgical thromboprophylaxis to control for bias, which may be caused by different timings of fondaparinux and LMWH. However, we found the results similar to the main analysis.

Prior studies have pointed out heterogeneity in definitions of major bleeding across different clinical trials,[44] which might lead to confusion among clinicians about bleeding risk associated with VTE prophylaxis.[45] To assist with clinical decision making, the incidences of minor bleeding were also compared in our study, which has not been reported in any previous meta-analyses[36,37] to the best of our knowledge. We observed a nonsignificant increased risk of minor bleeding with fondaparinux in comparison with LMWH. In case the patients undergoing surgeries are at increased risk of bleeding, these results may help the clinicians in decision making.

In our analysis, the incidence of all-cause mortality up to day 90 was also compared between treatment arms, which was not reported in the recent meta-analyses.[36,37] Although not statistically significant, reduction in the odds of mortality was associated with fondaparinux compared with LMWH.

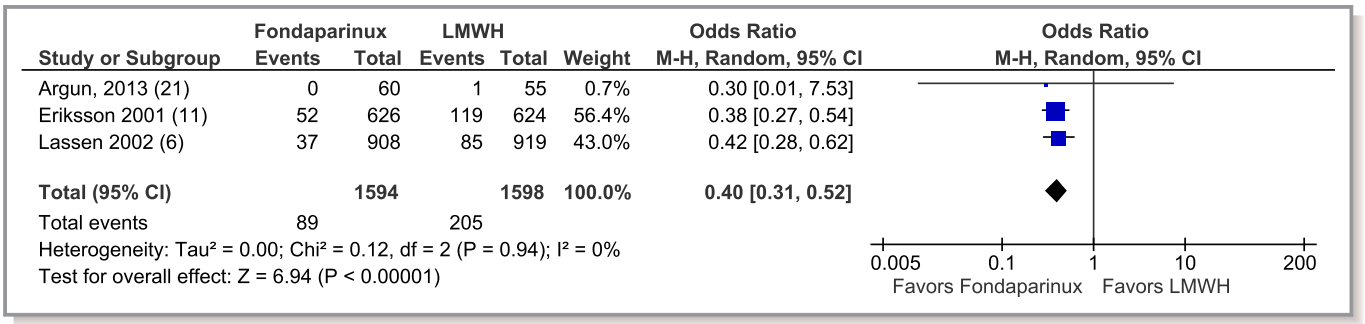

Figure 14. Fondaparinux compared with low-molecular-weight heparins (LMWH) for venous thromboembolism prophylaxis in the European population.

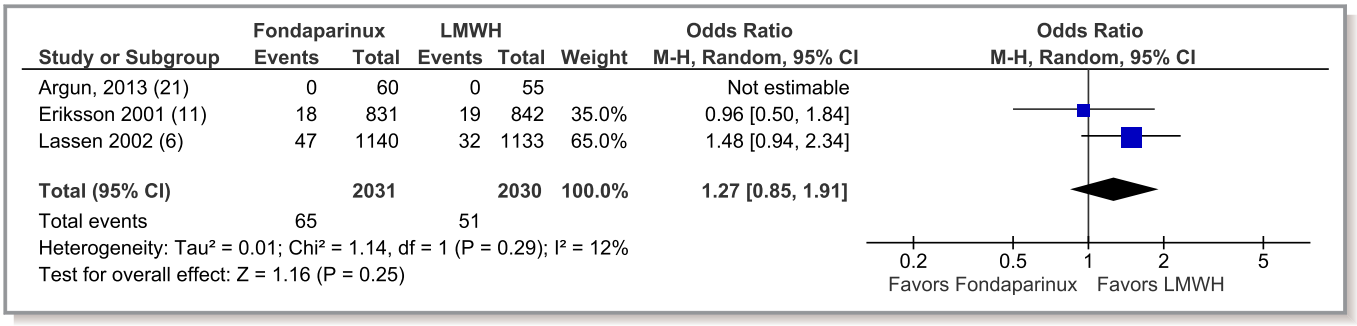

Figure 15. Fondaparinux compared with low-molecular-weight heparins (LMWH) for major bleeding in the European population.

Another meta-analysis that was conducted to report the effect on mortality considered LMWH and placebo in the same group compared with fondaparinux[46] and reported a statistically nonsignificant 21% reduction in the odds associated with fondaparinux. This difference in the results might be attributable to the fact that of the 8 studies included in the meta-analysis by Eikelboom et al,[46] 2 studies compared fondaparinux with placebo. These 2 studies accounted for 2158 patients among the 13 085 patients, which might have caused the difference in mortality between our meta-analysis and meta-analysis by Eikelboom et al.

A meta-analysis of 173 case-control studies reported a significant association of genetic factors with VTE.[47] As our analysis included trials from different continents, we also tested if there were any differences in the outcomes by the population. In our subgroup analysis, a significant 60% and 53% reduction in the odds of VTE was associated with fondaparinux among the European and North American and Australian populations, respectively. We also reported a 48% reduction in VTE in the Asian population, which was nonsignificant. The North American and Australian population was found to be at a greater risk of major bleeding compared with other races. These findings might be related to the differences in genetic factors related to venous thrombosis such as factor V, prothrombin G20210A, prothrombin G11991A, PAI-1 4G/5G, or alpha-fibrinogen Thr312Ala in different populations.[47] As gene mutations may lead to variable risk of VTE in different populations, we hypothesize that exposure to anticoagulants in different populations may also differentiate the risk of major bleeding. This particular finding of our study could act as a hypotheses for future researchers to explore more on the effectiveness and safety of these drugs in different patient populations using real-world data, which could be a significant addition to the existing literature. It may also be hypothesized that the low dose of LMWH in Japanese studies might have contributed, at least to some extent, to difference in the odds ratios across countries.

Limitations

This study had several limitations. Reviewers had access to the full text of all of the studies included in this meta-analysis except 1 study from China.[20] Efforts to contact the principal investigators of this study were made but were unsuccessful; consequently, reviewers labeled this study as having "unclear bias" during study bias assessment. This study was excluded during the sensitivity analysis as well. The clinical trial by Sasaki et al[14] compared the fondaparinux with the non-fondaparinux group. This non-fondaparinux group was

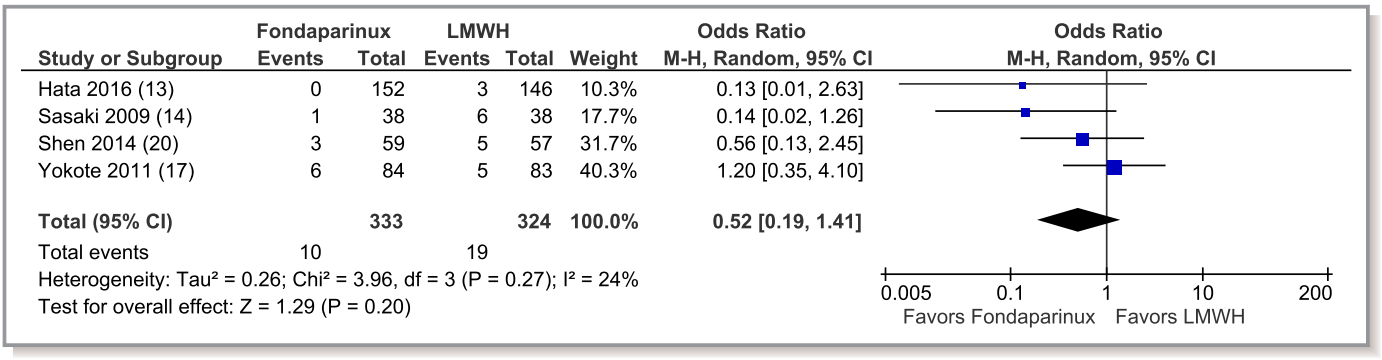

Figure 16. Fondaparinux compared with low-molecular-weight heparins (LMWH) for venous thromboembolism in the Asian population.

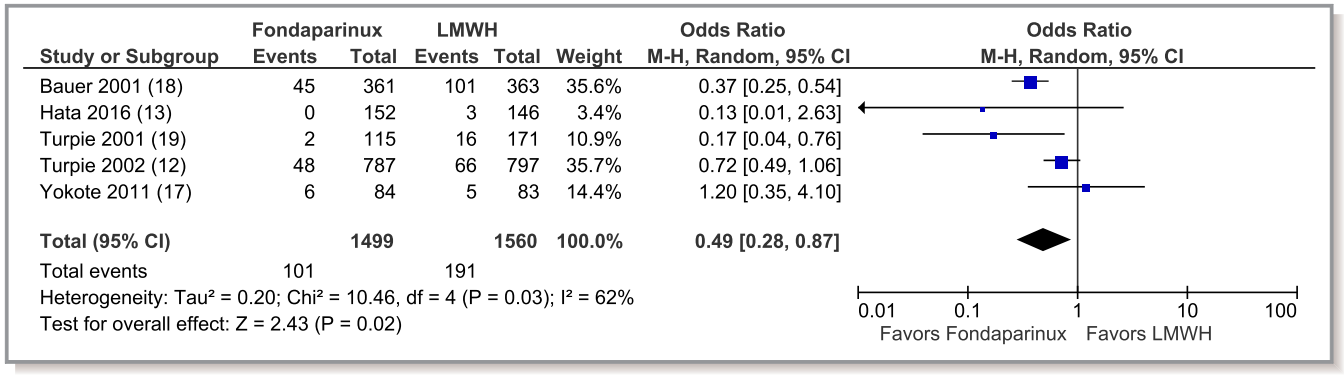

Figure 17. Postoperative fondaparinux compared with low-molecular-weight heparins (LMWH) for venous thromboembolism.

considered to be the LMWH group, as all the major clinical trials[11,12,18] considered LMWH as the comparator to fondaparinux. However, in the sensitivity analysis, this study was excluded and the results were consistent. The clinical trial by Steele et al[16] used a double dose of both fondaparinux and LMWH as a titration to the weight (body mass index, 35–59 kg/m^2) of the participants randomized in the clinical trial. This study was included in the analysis because the dose was doubled in both arms. Nevertheless, this study was excluded as well during the sensitivity analysis, with no meaningful change to the results. In the clinical trial by Hata et al,[13] randomized patients received low-dose (5000 IU) unfractionated heparin for thromboprophylaxis during the first 24 hours after surgery. Low-dose unfractionated heparin was administered initially because in Japan neither fondaparinux nor LMWH are approved to be prescribed immediately after surgery.[13] After 24 hours, patients received either fondaparinux or LMWH for 5 days postoperatively. As patients in both arms received low-dose unfractionated heparin, outcomes might have been affected similarly in each group.

Included studies in our meta-analysis were from different countries. Thus, we reported pooled analysis of these studies, which were from different clinical settings, that might have impacted the results. Studies were also subgrouped by population (eg, North American and Australian, European, and Asian population) as well to address this issue. Two RCTs[12,19] conducted in North America had some of their centers in Australia. We could not separate the American population from the Australian population because of the limitation to data access. Thus, we presented pooled analyses of these 2 populations. Our study considered all LMWHs in 1 group whether it was enoxaparin, nadroparin, or dalteparin. Nevertheless, it has been indicated by a meta-analysis of 20 RCTs that all LMWHs produce similar relative safety and efficacy when compared for VTE prophylaxis.[48] There was a difference in the dose of the LMWH in studies from different countries, which might have impacted the outcomes as well. Also, there was a difference in the duration of the prophylaxis. This limitation is justified because of the fact that with the time there is a variation in the guidelines for the prophylaxis of VTE.[7,49–51]

Strengths

To our knowledge, this is the most current comprehensive meta-analysis comparing subcutaneous fondaparinux with

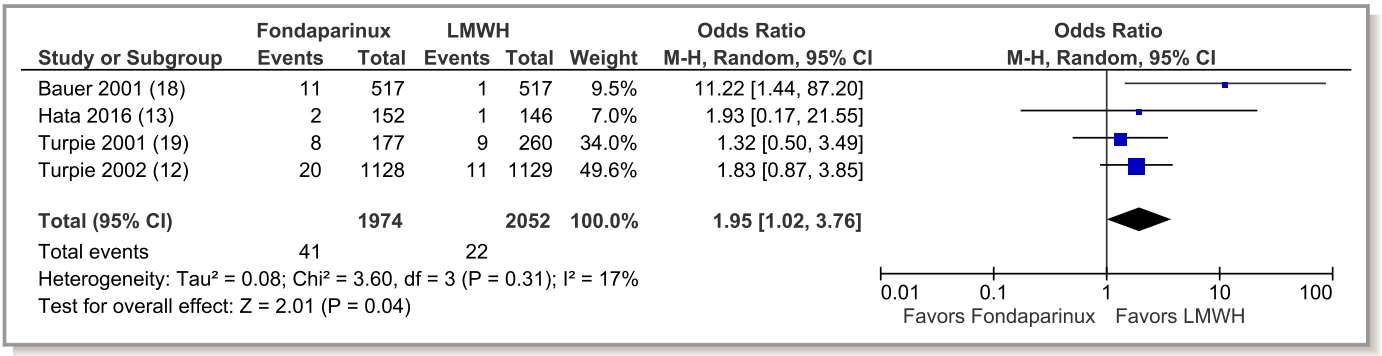

Figure 18. Postoperative fondaparinux compared with low-molecular-weight heparins (LMWH) for major bleeding.

LMWH for perioperative surgical thromboprophylaxis. To maintain the high quality of systematic review, this study considered only randomized clinical trials in the analyses as per the Cochrane Handbook for Systematic Reviews of Interventions.[28] We kept the definition of our outcomes consistent while analyzing the results. The cutoff point for the assessment of our study was set to 15 days. If any study among the included studies assessed the outcomes after 15 days, we excluded the event from our analysis. For example, Argun et al[21] reported an event of proximal DVT at day 19 with LMWH, which was not considered in our summary statistics. Thus, we maintained consistency throughout our study. To present the most comprehensive and robust results, we conducted several sensitivity and subgroup analyses as well to assist with the best clinical decision.

Conclusion

The results of this systematic review and meta-analysis suggest that fondaparinux is significantly better in terms of reduction of VTE (composite of DVT and PE) for perioperative surgical thromboprophylaxis. However, for the symptomatic VTE and all-cause mortality, fondaparinux was not found to be superior to LMWH in this study. Clinicians should be aware of the higher risk of major bleeding, especially surgical site bleeding with fondaparinux compared with LMWH. Nevertheless, net clinical benefit as per this study was in favor of fondaparinux compared with LMWH.

Acknowledgments

This study represents original work. It was completed recently and has not been published elsewhere. All of the authors of this paper contributed to the work, contributed in preparation of the manuscript, and have provided their final approval for the manuscript submission. The authors thank Dr. Wendy St. Peter, Professor, University of Minnesota (College of Pharmacy) for her contribution in preparation of the manuscript.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

DATA S1. STUDY PROTOCOL

TITLE: Fondaparinux Sodium Compared with Low Molecular Weight Heparins for Thromboprophylaxis among Patients at Risk as per Virchow's Triad: A Systematic Review and Meta-Analysis

CONTENT:

1. Background
   - 1.1. Venous Thromboembolism
   - 1.2. Epidemiology And Disease Burden
     - 1.2.1. Incidence And Prevalence
     - 1.2.2.Case Fatality Rate
   - 1.3. Virchow's Triad And Pathophysiology Of Venous Thromboembolism (Vte)
   - 1.4. Pharmacotherapy For Prophylaxis Of Vte
2. Rationale For The Study
3. Research Objective
4. Research Hypothesis
5. Methods
   - 5.1. Criteria For Considering Studies For This Review
     - 5.1.1.Types Of The Study
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1. BACKGROUND

1.1. VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), manifested as deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality in the hospitalized patients causing a significant cardio-vascular death and disability.[1,2] VTE usually progresses in the deep veins of the leg such as femoral, iliac, tibial, and popliteal veins or sometimes in the superficial veins of the extremities. Venous thrombosis of superficial veins is relatively not a serious disorder unless it is extended to the deep venous system.

Thrombosis related to deep veins of the legs is divided into two categories:

a. Distal vein thrombosis (Distal DVT), in which thrombi remains attached to the deep calf veins. This is also known as calf vein thrombosis and,
b. Proximal vein thrombosis (Proximal DVT), in this type thrombosis is confined to the femoral, popliteal, or iliac veins.[3]

The concern in patients with DVT is that they are at substantial risk of PE, which is a life-threatening condition.[4] Additionally, DVT in the proximal region (above the knee) presents a greater risk of PE than thrombosis in the distal region (below the knee). If progressed to the proximal region, patients are more likely to suffer soft tissue swelling, distention of the veins, erythema, warmth, and pain on dorsiflexion of foot. DVT in the legs is often asymptomatic if it is small. The thrombi developed in the deep veins of the leg detaches from its origin, moves to the right heart and lodges in the pulmonary vasculature and cause thrombosis.[5]

Thrombosis is a complication in the hospitalized patients admitted for surgery, or with acute medical illness. PE accounts for a significant preventable hospital death in institutionalized patients.[6] From a clinical standpoint, DVT and PE are considered as the progression of the same disease and both of them are collectively known as VTE.[7]

1.2 EPIDEMIOLOGY AND DISEASE BURDEN

VTE is known to be a leading cause of preventable mortality in the hospitalized patients. It is estimated that majority of the hospitalized patients are at least one or more risk factors[8] and about 40% of the hospitalized patients are at more than three risk factors. In addition, almost half of all the VTE episodes are linked with recent hospitalization and surgeries.[9]

1.2.1 Incidence and Prevalence

VTE is recognized to be associated with a major global disease burden. DVT occurs more often in women, and the incident rate of first VTE is estimated to be 1.32 per 1,000 patient-years. Asian race seems to have lowest incidence compared to whites and black race i.e. 1.22, 1.91 and 2.03 person-years respectively when incident rate is standardized by age.[10] There are annually more than 150,000 deaths from PE in the United states, which is the most common preventable cause of in-hospital deaths.[11]

Thrombosis progression in deep veins affects at least 1 in 500 patients per year in North America, and as a result almost 1 in every 300 adult patients in emergency room are diagnosed with VTE. Additionally, VTE has been found to increase with the age with at least 1 in 100 patients at age 80.[12] It is assumed that approximately half of the patients diagnosed with proximal DVT will suffer PE if untreated; also about 10 in 100 patients with symptomatic PE are fatal in an hour of onset. Moreover, about 5% of the patients

with PE die even if on optimal treatment, also 25% of the patients with proximal DVT suffer post-thrombotic symptoms, which debilitates the patients.[13]

1.2.2 Case Fatality Rate

Approximately 35% of the patients with VTE suffer with PE, and more than 60% present with DVT in the clinical setting. PE compared to DVT is more likely to be fatal and is associated with severe long term thromboembolic complications. Almost 40% of the patients suffering proximal DVT suffer PE, whereas, more than 50% of the patients presented with PE also have DVT.[12] Case fatality rate is proportional to the degree of homodynamic severity of the PE, comorbid conditions, and age; embolism with circulatory shock accounts for more than 40% case fatality rate. Furthermore, autopsy data indicates PE as the second largest cause of unexpected sudden death. Case fatality rate is estimated to be 1% among the patients under age 50 years who suffer with hemodynamically stable PE without any other comorbid conditions.[12]

1.3 VIRCHOW'S TRIAD AND PATHOPHYSIOLOGY OF VENOUS THROMBOEMBOLISM (VTE)

In the mid nineteenth century, Rudolf Virchow introduced the phenomena of thrombosis and embolism. Virchow proposed three main factors responsible for the development of VTE which is known as Virchow's triad (Figure A): venous stasis, hypercoagulability, and endothelial injury.[14] Till date this basic classification is helpful to assess the risk involved in the development of VTE among the patients. There is interplay between genetic and acquired factors of an individual that leads to the progression and development of VTE.[15,16] Hypercoagulability, inflammation, and endothelial injury recruits activated platelets which in turn release microparticles. Consequently, proinflammatory mediators inside these microparticles bind the neutrophils which in turn help them form neutrophil extracellular traps which act as web-like extracellular network. These networks contain histones which aggravate platelet aggregation and thrombin generation. Stasis, proinflammatory genes, and low oxygen tension makes an ideal environment for the development of a thrombi.[11,17]

Risk Factors: As per the Virchow's triad, there are several risk factors (Figure: A) which are documented to cause VTE.[18] Major orthopedic surgeries such as total hip replacement, total knee replacement, and hip fracture surgeries carry particularly higher risk for the development of VTE.[19] If not prescribed with prophylaxis, almost half of the patients suffer DVT and the disease progresses to cause PE simultaneously.[20] Among the patients recovering from major orthopedic surgeries, most of the proximal DVT occurs at operated bed side.[21]

Risks associated with thrombosis and major surgeries are extensively documented in the literature.[22] Major general surgery refers to the patients who undergo abdominal, or thoracic surgeries and the surgeries requiring anesthesia for at least 30 minutes.[21] The risk of DVT in various general surgeries depends on the type of surgery e.g. neurosurgery, abdominal surgery, and the clinical condition of the patients. If not on prophylaxis treatment, there is a 25% risk that the patients will suffer VTE.[23] Malignancy has also been associated with VTE. The role of malignancy in the activation of coagulation is well established and the probability of VTE further increases with the chemotherapy, and cancer related surgery.[24,25] Advanced staged cancer, and malignancy related to pancreas, gastrointestinal tract, lungs, and brain are the major risk factors for the development of VTE.[21]

Since many years immobility has been recognized to be a significant risk factor in the progression of thrombosis as per Virchow's triad.[26] VTE due to prolonged immobility among bed ridden patients is serious and has been found to be associated with death at autopsy.[27]

1.4 PHARMACOTHERAPY FOR THE PROPHYLAXIS OF VTE

ACCP recommends guidelines for the prevention of VTE for the patients at risk.[28] Evidence-based consensus guidelines for VTE prophylaxis have been available for more than 15 years. In spite of the existence of these guidelines, VTE prophylaxis remains underused.[29]. Despite the use of currently available thromboprophylaxis, VTE is still frequently seen as a life-threatening complication among patients who are at risk of VTE as per Virchow's triad.

In the past, Unfractionated heparin (UFH) was the mainstay of anticoagulation for the prevention of thrombosis. Newer agents with more predictable pharmacokinetic profiles such as LMWH, Fondaparinux sodium, and Novel Oral Anticoagulants (NOACs) have been proven to be effective for VTE prophylaxis. Although these agents share similarities, differences in their mechanism of action, pharmacokinetic profiles, and contraindications warrant their utilization for thromboprophylaxis.

2. RATIONALE FOR THE STUDY

Different clinical trials have been conducted in the past in process of better anticoagulation for thromboprophylaxis. Although the complex abnormalities of the coagulation system are linked with UFH (substantial risk of bleeding), it is used for thromboprophylaxis for many years.[30] In different clinical trials, LMWHs have been compared with UFH wherein, LMWHs proved their safety and efficacy over UFH and now has been used as a reference therapy in the clinical trials.[31-33] Better selective inhibition by LMWHs is cited to be linked with improved safety and efficacy over UFH.[34]

Nevertheless, in the era wherein potent selective inhibitors of factor Xa are available as oral and subcutaneous therapy, clinical trials have been conducted to study their efficacy and safety compared to reference therapy (LMWHs). Novel Oral Anticoagulants as Factor Xa inhibitors are also available and have shown promising results; however, NOACs being an oral therapy might not suitable for hospitalized critically ill patients. Thus, subcutaneous Fondaparinux Sodium seems to be a better option for thromboprophylaxis among such patients. Since the approval of Fondaparinux Sodium, various clinical trials have been conducted to assess the efficacy and safety of Fondaparinux Sodium. Thromboprophylaxis by Fondaparinux Sodium have been compared with standard LMWH therapy for VTE to find the relative efficacy and safety of these drugs. Results from different clinical trials showed better safety and efficacy of one over the other. But consensus couldn't be reached for which anticoagulant should be used. Hence, controversies remain about the ideal anticoagulant.

In a major clinical trial for the prevention of VTE in patients undergoing elective major knee surgery, Fondaparinux Sodium once daily was found to be significantly more effective than LMWH. However, major bleeding (including overt bleeding with a bleeding index of 2 or more) occurred more frequently in the Fondaparinux group at a significant level of 0.05. Nevertheless, the two groups did not differ significantly with respect to fatal bleeding, bleeding in critical organs, or bleeding leading to reoperation.[35] In another RCT among the patients undergoing hip fracture surgery, the incidence of VTE in the Fondaparinux Sodium group was significantly less than the LMWH group with p value less than 0.05. There were no reported significant differences between the two groups in the incidence of clinically relevant bleeding. Fondaparinux Sodium was reported to be more effective than LMWH in preventing VTE and was equally safe in this clinical trial.[36]

Among the patients undergoing high risk abdominal surgery in a clinical trial, Fondaparinux Sodium was found to impart no significant better efficacy (p=0.144) over LMWH, thus was reported as non-inferior to LMWH. The major bleeding in this trial was more (3.4%) in the case of Fondaparinux Sodium as compared to LMWH (2.3%), but was not statistically significant (p=0.122). However, in the same study Fondaparinux Sodium was indicated to be better in terms of efficacy among abdominal cancer surgery patients than LMWH with relative risk reduction of 38.6% (6.7, 59.7).[37] Another randomized clinical trial showed that in elective hip-replacement surgery, VTE were recorded in 5% fewer patients on Fondaparinux Sodium than those on LMWH with a significance level of less than 0.05, without an increase in risk of clinically relevant bleeding and death.[38]

In Japanese population, Fondaparinux was found to be effective in a prospective randomized trial as on administration, it demonstrated positive effects on the prevention of VTE after hip fracture surgery. However, careful postoperative observation was warranted to prevent serious side effects after Fondaparinux Sodium administration.[39] In another Japanese study, Fondaparinux Sodium was proved to be a potent anticoagulant with a favorable benefit to-risk ratio in the prevention of VTE in these study patients.[40] Contrarily, in patients undergoing orthopedic surgery, Fondaparinux Sodium once daily, showed a major benefit over LMWH in terms of efficacy without increasing the risk of clinically relevant bleeding.[41]

A clinical trial conducted by Hata et al., which was performed to demonstrate the safety of Fondaparinux Sodium among Japanese patients reported that there was no difference among the two groups as far as major bleeding was concerned when compared with LMWH.[42] A Chinese clinical trial for thromboprophylaxis against esophagectomy as a risk factor reported Fondaparinux Sodium to be equally effective compared to LWMH; however, it mentioned the risk of bleeding with Fondaparinux Sodium.[43] However, the sample size of this study was low to confirm any significant findings. In Japan, another RCT reported LMWH to be better than Fondaparinux Sodium in terms of efficacy. As far as bleeding was concerned, there was no difference between the two groups.[42] A North-American RCT which was conducted on the patients undergoing bariatric surgeries reported that there was no difference in the efficacy of Fondaparinux Sodium and LMWH among the patients receiving them for thromboprophylaxis. Also, no major bleeding was reported in both arms.[44] We thus, see a lot of disparities in the outcomes of efficacy and safety among the Fondaparinux Sodium and LMWH in the clinical trials for thromboprophylaxis.

Fondaparinux Sodium and LMWHs are widely accepted in various countries; however, among the existing studies there are no consistent findings which comprehensively states which thromboprophylaxis can be best utilized in the hospital settings for the risk factors for VTE in which anticoagulation is considered necessary. Overall, it appears that the ideal anticoagulant has not yet been identified which could be best utilized.

Hence, there is a need of a comprehensive meta-analysis to provide an additional evidence to settle the controversy about efficacy and safety of Fondaparinux Sodium and LMWH, and to provide clinicians with the most current evidence which they may use for the prophylactic treatment of VTE for the patients at risk as per Virchow's triad. We thus, proposed a meta-analysis of clinical trials to compare Fondaparinux Sodium once daily with LMWH at the titrated dose/manufacturers' recommendation for the prophylactic treatment of VTE for the patients at risk as per Virchow's triad.

3. RESEARCH OBJECTIVE

The primary objective of this systematic review and meta-analysis is to assess the efficacy and safety of Fondaparinux Sodium as compared to LMWH to prevent the venous thromboembolism among the patients who are at risk as per Virchow's triad.

4. RESEARCH HYPOTHESES

To reach the objective, the following research hypotheses will be tested,

1. Fondaparinux Sodium is more effective in terms of reduction of incidence of VTE which is a composite of DVT and PE up to day 15.

2. Fondaparinux Sodium is more effective in terms of reduction of incidence of total DVT, any proximal and distal DVT up to day 15.

3. Fondaparinux Sodium is more effective in terms of reduction of PE (composite of fatal and non-fatal) up to day 15.

4. Fondaparinux Sodium increases the incidence of major bleeding which includes the following four categories i.e. fatal bleeding, retroperitoneal bleeding, intracranial, intra-spinal, or any other critical organ bleeding or overt bleeding with bleeding index of 2 or more as compared to LMWH during the treatment period.

5. Fondaparinux Sodium increases the incidence of minor bleeding (not qualified to be regarded as major bleeding) as compared to LMWH during the treatment period.

6. Fondaparinux Sodium reduces the all-cause mortality rate up to day 90 post-operatively.

METHODS

5.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

5.1.1 TYPE OF STUDIES

Only head to head randomized clinical trials comparing Fondaparinux Sodium with LMWH, published in English language as full-text, and meeting our study inclusion criteria will be taken into consideration. Potential studies in other languages will also be searched for with their abstracts in English language, to be included into our study.

Trials presented in the conference proceedings and unpublished will be searched for full text studies. Also, authors of the unpublished studies will be contacted to have access to the relevant information in case the full texts of the studies aren't available. The unpublished studies will be excluded in the sensitivity analysis.

5.1.2 TYPE OF THE PARTICIPANTS

RCTs will be considered eligible for our study if they had recruited adults (aged ≥ 18 years old) and both sex with at least one risk factor to develop VTE as per Virchow's Triad. RCTs which enrolled patients undergoing major orthopedic surgeries (e.g. total hip replacement, total knee replacement, or hip fracture surgeries), major general surgeries (abdominal surgery, cancer surgery), or any immobility which is a risk factor for the development of VTE will be included in this study. Trials which included the patients with (1) coagulation disorders, (2) any major surgeries in the past 3 months, (3) any trauma affecting multiple organs, (4) any contraindication to anticoagulation therapy (5) congenital or acquired bleeding disorder, will be excluded.

5.1.3 TYPE OF INTERVENTIONS

The interventions in this review will be subcutaneous Fondaparinux Sodium and subcutaneous LMWHs at titrated dose/manufacturer's recommended dose as per body weight and at the standard dose as per the country of interest. Enoxaparin Sodium, Dalteparin Sodium, Nadroparin Calcium, Parnaparin Sodium, and Tinzaparin Sodium at titrated dose will be considered in the LMWHs arm. The RCTs will be included only if these compared Fondaparinux Sodium with LMWHs head to head. Inclusion will be based on the time-period of the assessment of the study. Studies in which the assessment was done up to 15 days will be taken in to consideration for inclusion.

5.1.4 TYPES OF OUTCOME MEASURES

The main outcomes of interest will be as follows:

1. The efficacy outcome of this study will be VTE defined as the composite of DVT, PE. We assessed for total DVT, proximal DVT, distal DVT, and PE individually as well up to day 15. Included studies had assessed the patients for DVT by systematic bilateral ascending venography of the legs or D-Dimer test, and PE by a lung scan, pulmonary angiography, or helical computed tomography or at autopsy. Assessment for all-cause mortality at day 90 of the start of the treatment will also be done.
2. The safety outcome will be the incidence of major bleeding, which includes fatal bleeding; bleeding that is retroperitoneal, intracranial, or intra-spinal or if involved any other critical organ; bleeding leading to re-operation; and overt bleeding with a bleeding index of 2 or more during the treatment. Major bleeding will be reported as a composite outcome of all these events. The bleeding index is calculated as the number of units of packed red cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin values after the episode (in grams per deciliter as reported in major clinical trials comparing Fondaparinux and LMWH.[36,38,52,53] Safety also included other bleeding which will not be qualified to be categorized as major bleeding.

5.2 SEARCH METHODS FOR IDENTIFICATION OF THE STUDIES

The search will include a comprehensive search for trials of anticoagulation comparing Fondaparinux Sodium with LMWHs for the prevention of VTE. Systematic search in the databases e.g. EMBASE, PubMed, MEDLINE, The Cochrane Central Register of Control Trials (CENTRAL), ProQuest-Direct, ProQuest ABI/INFORM Complete, Science Direct will be done to find the RCTs evaluating Fondaparinux and LMWH for the prophylaxis of VTE among the patients with at least one risk as per Virchow's triad published in English language. The search will be restricted from 2000 to 2017 as the first trial of Fondaparinux was reported in November 2001. "Fondaparinux" [MeSH], "Enoxaparin" [MeSH], "Venous thrombosis" [MeSH], "Nadroparin" [MeSH], "Dalteparin" [MeSH], "Heparin, Low-Molecular-Weight" [MeSH] and Clinical trial will be used as key-words to systematically search for the potential studies to be included in this analysis. "Clinical trials" will be set as filter criteria. The reference lists of all identified trials and review articles will be hand searched to find out any relevant trials. Search for the unpublished studies by exploring conference proceedings will also be done. The authors of the studies of which full text studies aren't available, will be contacted.

5.3 DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

We will use Covidence (www.covidence.org) to initially screen the articles based on the title and abstract. Covidence[45] is an online systematic review platform which will be used for screening and selecting citations. A training session will be conducted to familiarize the authors with the process, and a subset of studies from the screening process will be jointly coded. To ensure accurate coding and clear directions, an abstraction will be piloted before training the primary and secondary authors. Records will be imported from EMBASE, PubMed, MEDLINE, The Cochrane Central Register of Control Trials (CENTRAL), ProQuest-Direct, ProQuest ABI/INFORM Complete, Science Direct into the Covidence, where duplicates will be removed**.** Two review authors Arun Kumar and Ashna Talwar will independently screen the title and abstract of identified citations for potential eligibility.

The full text of articles judged potentially eligible by at least one review author will be retrieved. Two review authors will then independently screen the full text article for eligibility using a standardized form with explicit inclusion and exclusion criteria. The two review authors will resolve any disagreements about which articles are eligible by discussion or by consulting a third reviewer Dr. Wenchen Wu. The screening process will be documented in preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of study selection.

5.4 DATA EXTRACTION AND MANAGEMENT

A data extraction form will be developed in the Covidence web platform to extract the information from relevant clinical trials. Two review authors will independently extract the data from each included study and resolve their disagreements by discussion. A third author will be consulted in case of disagreement. After consensus, both reviewers will analyze the resulting papers in full text using the online Covidence review manager independently.

We aim to collect the following data as per data collection form:

STUDY IDENTIFICATION which includes sponsorship source, country, setting, comment (if any), author's name, institution, email IDs and addresses of authors and institutions where the trials was conducted.

METHODS including study design of the clinical trial.

POPULATION: Inclusion criteria, exclusion criteria, and group differences (if any). In this section, the baseline characteristics of patients under Fondaparinux Sodium and LMWH groups will include number of patients, age (in years), sex, weight in kg, body-mass index.

INTERVENTION AND COMPARISONS will include the drugs in comparison.

OUTCOMES section includes venous thromboembolism, total deep vein thrombosis, any proximal deep vein thrombosis, distal deep vein thrombosis only, pulmonary-embolism, major bleeding, other bleeding (Not qualified as major bleeding), and Mortality.

5.5 ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Two reviewers will independently assess the methodological quality of included studies using The Cochrane Collaboration's "Risk of Bias" tool.
The following domains will be assessed:

a) Random sequence generation (Selection Bias),
b) Allocation concealment (Selection Bias),
c) Blinding of participants and personnel (Performance Bias),
d) Blinding of outcome assessment (detection bias),
e) Incomplete outcome data (attrition bias),
f) Selective reporting (reporting bias), and
g) other bias.

We will classify the domains as *'low risk', 'high risk',* or *'unclear risk'* as per Cochrane Handbook for Systematic Reviews of Interventions.[46] Disagreements will be resolved by discussion or by consulting a third reviewer.

5.6 MEASURES OF TREATMENT EFFECT

All the outcomes in this analysis will be binary. The incidence of VTE, major bleeding, minor bleeding, and mortality for the Fondaparinux Sodium and LMWH arms will be used to calculate an odds ratio (OR) separately for each trial to summarize the safety and efficacy of the both arms. Total DVT, any proximal DVT, distal DVT only, and PE (fatal or non-fatal), minor bleeding (Not qualified as major bleeding) will also be reported.

Relative treatment effect for each comparison will be expressed as odds ratio (OR) with 95% confidence Interval (CI). The OR in this study describes the relative odds of reduction in the events in the efficacy and safety outcomes. The pooled data for each outcome will be used to create a meta-analysis graphs (Forest Plots) by calculating ORs with 95% confidence intervals (CIs), as all outcomes. Where there will be sufficient data, a summary statistic for each outcome will be calculated using a fixed-effect model unless there is an evidence of a large amount of heterogeneity (discussed in the assessment of heterogeneity section 3.7), in which case a random-effects model will be implemented.

5.7 UNIT OF ANALYSIS

The individual participant will be the unit of analysis in all included studies.

5.8 ASSESSMENT OF HETEROGENEITY

Assessment of the consistency of effects across studies is an essential part of meta-analysis.[47] A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect. The statistical appropriateness of combining the trials will be based on tests of heterogeneity, which considers whether differences in treatment effect for individual trials are consistent with natural variation around a constant effect.[48] We will utilize Chi^2 test, and I^2 statistics to assess heterogeneity, which describes the variability (in percentage) in effect estimates due to heterogeneity rather than sampling error (chance). In this analysis I^2 value of 30% to 60% will be categorized as "Moderate heterogeneity". And I^2 value between 50% to 90%, and 75% to 100% will be "Substantial heterogeneity" and "Considerable heterogeneity" respectively.[47] We will use fixed-effect model if no apparent heterogeneity is evident. In case the heterogeneity is more than 40% (moderate), we will utilize random-effect model for the summary statistics as a rule of thumb. Wherever a significant heterogeneity is observed, the results from the outcomes will be reported by random effect model.

5.9 ASSESSMENT OF REPORTING BIASES

"Funnel Plot" will be used to assess the reporting bias which is a scatterplot examining the relationship between the treatment effects and their inverted standard errors. This is the commonly used tool for the assessment of the presence of small-study effects in the pooled analysis. We will use asymmetry with respect to the line of summary effect in funnel plots to assess reporting bias.[49] We will report the funnel plots only if there are at least 10 studies in any subgroup to maintain power to distinguish chance from real symmetry.[50]

5.10 DATA SYNTHESIS

After systematic review in the "Covidence", the data will be imported to "RevMan 5.3". The data file will be extracted from "Covidence" and used to enter the data in each outcome in RevMan. Arun Kumar independently will enter the data in each outcome. Calculated odds ratios from the individual trials will be combined across trials, giving weight to the number of events in each of the two treatment groups in each separate trial, using the Mantel Haenszel procedure.[51] We will use 95% CI for these estimates of treatment effects. If heterogeneity exists above moderate i.e. 40%, we will use the random effect model for summary statistics.

5.11 SENSITIVITY ANALYSIS

Sensitivity analyses will be conducted to explore the effect that risk of bias have on estimates of treatment effects. We will explore the effect on the principle outcome by eliminating the studies (if any) which are at the "High Risk" of bias during the sensitivity analysis.

Data S2. Description of "Risk of Bias" among the included studies.

For the random sequence generation, 6 studies were considered at low risk as these studies clearly defined how the participants were randomized in the respective studies. There were 7 studies which had adequately concealed the allocation of the patients and had low-risk of selection bias. Seven studies were at Low-risk of performance bias as these were double blinded studies. In eight of the trials, the evaluation of the outcomes in the trials was undertaken by blinded assessors and therefore had lower risk for detection bias. Attrition bias was low in the 11 trials. These studies considered all the randomized patients into the final analysis. if the patients were not included, these studies clearly mentioned how many patients were excluded with the reasons of exclusion with the treatment groups retained. Eleven studies had lower risk of reporting bias as there was no evidence of selective outcome reporting. Eight of the studies were privately funded, which could have been a source of bias. These studies were indicated at high risk of bias. Reviewers didn't have an access to the full text of one of the study of which the risk of bias couldn't be assessed. Review authors' judgment about each risk has been presented by "risk of bias graph", and "risk of bias summary" for each study in the Figure 3A and 3B respectively.

Data S3. Detailed description of each included study (DATA EXTRACTION FORM)

1. TURPIE, 2001:

Title: A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement[52]

Characteristics:

METHODOLOGY	**Study Design**	Multicenter, double blind and randomized controlled trial	
	Country	70 centers in the United states, Canada, and Australia.	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	177	260
	Age in years (Mean)	66	66
	Sex (M/F)	80/97	123/137
	Weight in kg (Mean)	80	81
	Body-mass index (Mean)	N/A	N/A
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 3.0 mg BD	
	Control	Enoxaparin Sodium (LMWH) 30 mg BD	
	Duration	10 days	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence	Unclear	Randomized controlled trial but the method of	

generation (selection bias)		randomization wasn't disclosed
Allocation concealment (Selection bias)	Low	• Randomization done in a central office. • All committees were independent
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind RCT
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis.
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results.
Other bias	High	Supported by Sanofi–Synthelabo Research

2. BAUER, 2001:

Title: Fondaparinux compared with Enoxaparin for the prevention of venous thromboembolism after elective major knee surgery[53]

Characteristics:

METHODOLOGY	**Study Design:**	Muticenter, double blind, RCT	
	Country	North America, 64 centers	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	517	517
	Age in years (Mean)	67.5	67.5
	Sex (M/F)	204/313	223/294
	Weight in Kg (Mean)	89	88
	Body-mass index(Mean)	31.5	30.9
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg BD	
	Control	Enoxaparin Sodium 30 mg BD	
	Duration	5 to 9 days.	
OUTCOMES	Venous thromboembolism, Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence generation (selection	Low	• Randomized controlled trial. • Randomization was done with patients assigned in 1:1	

bias)		ratio in four blocks and also stratified by center.
Allocation concealment (Selection bias)	Low	Medications were concealed in identical boxes.
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis.
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes in the method section were reported in results.
Other bias	High	Sponsors (NV Organon and Sanofi–Synthelabo)

3. TURPIE, 2002:

Title: Postoperative Fondaparinux versus postoperative Enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomized double-blind trial[41]

Characteristics:

METHODOLOGY	**Study Design**	Multicenter, double blind and randomized controlled trial	
	Country	139 centers in the United States, Canada, and Australia.	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	1915	1926
	Age in years (Mean)	67	67
	Sex (M/F)	942/973	897/1029
	Weight in kg (Mean)	80.6	79.6
	Body-mass index (Mean)	28	27.6
INTERVENTIONS	**Treatment**	Fondaparinux sodium 2.5 mg BD	
	Control	Enoxaparin Sodium (LMWH) 30 mg BD	
	Duration	Day 5 to day 9th.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence	Low	• Randomized controlled trial	

generation (selection bias)		• central computer-derived randomization • Randomization done in four blocks (done independently)
Allocation concealment (Selection bias)	Low	Medications were concealed in identical boxes.
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis.
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes in the methods section were reported in the results section
Other bias	High	Study supported by a grant from Sanofi-Synthelabo and NV Organon

4. ERIKSSON, 2001:

Title: Fondaparinux compared with Enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery[36]

Characteristics:

METHODOLOGY	**Study Design**	Double blind, Randomized	
	Country	Sweden	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	831	842
	Age in years (Mean)	76.8	77.3
	Sex (M/F)	187/644	224/618
	Weight in kg (Mean)	64.3	64.2
	Body-mass index (Mean)	23.8	23.6
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg BD	
	Control	Enoxaparin Sodium (LMWH) 40 mg OD	
	Duration	Day 5 to day 9th.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence	Low	• Randomized controlled trial	

generation (selection bias)		• Randomization done using computer-generated randomization list
Allocation concealment (Selection bias)	Low	Medications were concealed in identical boxes.
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis.
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes in the method section were reported in the results section.
Other bias	High	Study supported by a grant from Sanofi-Synthelabo and NV Organon".

5. LASSEN, 2002:

Title: Postoperative Fondaparinux versus preoperative Enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomized double-blind comparison[38]

Characteristics:

METHODOLOGY	**Study Design**	Multicenter, double blind and randomized controlled trial	
	Country	73 centers in 16 European countries	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	2048	2052
	Age in years (Mean)	66.4	67
	Sex (M/F)	889/1159	875/1177
	Weight in kg (Mean)	75	75
	Body-mass index (Mean)	26	26.55
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg BD	
	Control	Enoxaparin (LMWH) 40 mg OD	
	Duration	Day 5 to day 9th.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence	Low	• Randomized controlled trial	

generation (selection bias)		• Randomization done in four blocks by a computer-generated randomization list
Allocation concealment (Selection bias)	Low	Medications were concealed in identical boxes.
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results.
Other bias	High	Supported by Sanofi–Synthelabo Research

6. AGNELLI, 2005:

Title: Randomized clinical trial of postoperative Fondaparinux versus perioperative Dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery[54]

Characteristics:

METHODOLOGY	**Study Design**	Double blind, double dummy, Multi-centered randomized clinical trial.	
	Country	22 countries.	
	Drugs	**Fondaparinux Sodium**	**LMWH**
	Number of patients	1433	1425
	Age in years (Mean)	66	65
	Sex (M/F)	788/645	796/629
	Weight in kg (Mean)	74.2	74.3
	Body-mass index (Mean)	26.3	26.3
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg OD	
	Control	Dalteparin Sodium (LMWH) 5000 IU OD	
	Duration	5-9 days	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	

Random sequence generation (selection bias)	Unclear	Randomization was done. However, the way of randomization was not disclosed.
Allocation concealment (Selection bias)	Low	Medications were concealed in identical boxes.
Blinding of participants and personnel (performance bias), All outcomes	Low	This was a double-blind double-dummy randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results
Other bias	High	This study was supported Sanofi Synthelabo and NV Organon

7. SASAKI, 2009:

Title: Prospective randomized controlled trial on the effect of fondaparinux sodium for prevention of venous thromboembolism after hip fracture surgery[39]

Characteristics:

METHODOLOGY	**Study Design**	Prospective, open label, randomized controlled trial	
	Country	Japan	
	Drugs	**Fondaparinux Sodium**	**Non-Fondaparinux group**
	Number of patients	38	38
	Age in years (Mean)	79.2±8.2	80.2±10.4
	Sex (M/F)	8/30	9/29
	Body-mass index (Mean)	21.34±4.10	20.35±3.07
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg OD	
	Control	Dalteparin Sodium (LMWH) 5000 IU OD	
	Duration	Up to 14 days.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence	Low	• Randomized controlled trial	

generation (selection bias)		• Simple randomization
Allocation concealment (Selection bias)	High	Eligible patients undergoing hip fracture surgery were assigned to fondaparinux group first and then to non-fondaparinux group. And then patients were assigned in the same order afterwards. Thus, the drugs under study were not concealed
Blinding of participants and personnel (performance bias), All outcomes	High	Open label
Blinding of outcome assessment (detection bias), All outcomes	Unclear	Study didn't disclose who did the assessment of study outcomes.
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results.
Other bias	Low	The study appears to be free of other sources of bias. No external funding

8. YOKOTE, 2011:

Title: Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population?[55]

Characteristics:

METHODOLOGY	**Study Design**	Randomized controlled trial	
	Country	Japan	
	Drugs	**Fondaparinux Sodium**	**Non-Fondaparinux group**
	Number of patients	84	83
	Age in years (Mean)	63±10.0	64±11.0
	Sex (M/F)	14/70	16/67
	Body-mass index (Mean)	22.5 ± 4.8	23.0 ± 3.3
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 2.5 mg OD	
	Control	Enoxaparin Sodium (LMWH) 40 mg OD	
	Duration	10 days	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence generation (selection bias)	Unclear	Patients were randomized but method wasn't disclosed	

Allocation concealment (Selection bias)	Unclear	Method of allocation of the patients to drugs was not revealed in the study
Blinding of participants and personnel (performance bias), All outcomes	Unclear	This study didn't disclose whether the study was a blinded study or open-label.
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by independent committee
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results
Other bias	Low	No external funding. Thus, the study appears to be free of other sources of bias.

9. ARGUN, 2013:

Title: Fondaparınux versus Nadroparın for Preventıon of VenousThromboembolısm After Electıve Hıp and Knee Arthroplasty[56]

Characteristics:

METHODOLOGY	**Study Design**	Open-label, prospective, comparative randomized study.	
	Country	Turkey	
	Drugs	**Fondaparinux Sodium**	**Non-Fondaparinux group**
	Number of patients	55	53
	Age in years (Mean)	58.7±13.6	60±8.4
	Sex (M/F)	34/21	33/20
INTERVENTIONS	**Treatment**	Fondaparinux 2.5 mg OD	
	Control	Nadroparin calcium at manufacturer's recommendation.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence generation (selection bias)	Unclear	Patients were randomized but method wasn't disclosed	
Allocation concealment (Selection bias)	Unclear	Method of allocation of the patients to drugs was not revealed in the study	

Blinding of participants and personnel (performance bias), All outcomes	High	Open label randomized clinical trial
Blinding of outcome assessment (detection bias), All outcomes	Unclear	This study didn't disclose who did the assessment of outcome.
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis.
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results.
Other bias	Low	No external funding. Thus, the study appears to be free of other sources of bias.

10. STEELE, 2015:

Topic: The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: A randomized double-blind pilot trial[44]

Characteristics:

METHODOLOGY	**Study Design**	Single centered, randomized double-blind pilot trial.	
	Country	United States	
	Drugs	**Fondaparinux Sodium**	**Non-Fondaparinux group**
	Number of patients	100	98
	Age in years (Mean)	40.4±10.2	41.8±9.0
	Sex (M/F)	16/84	16/82
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 5 mg OD	
	Control	Enoxaparin Sodium (LMWH) 40 mg BD	
	Duration	Until discharge from the hospital. Average hospital stay was 2.5 days.	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence generation (selection	Low	• Randomized controlled trial. • Randomization was done with patients assigned in 1:1	

bias)		ratio in four blocks
Allocation concealment (Selection bias)	Low	Allocation was performed by the pharmacy and was concealed from patients and study personnel"
Blinding of participants and personnel (performance bias), All outcomes	Low	Double blind randomized clinical trial
Blinding of outcome assessment (detection bias), All outcomes	Low	Safety and efficacy measures were assessed by radiologists independently.
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results
Other bias	High	This study was supported by GlaxoSmithKline.

11. HATA, 2016:

Topic: Safety of Fondaparinux for prevention of postoperative venous thromboembolism in urological malignancy: A prospective randomized clinical trial[42]

Characteristics:

METHODOLOGY	**Study Design**	Prospective, single-blind, non-inferiority randomized study.	
	Country	Japan	
	Drugs	**Fondaparinux Sodium**	**Non-Fondaparinux group**
	Number of patients	152	146
	Age in years (Mean)	63.9±7.5	64.7±7.5
	Sex (M/F)	144/8	138/8
	Body-mass index	23.9±2.6	23.7±2.6
INTERVENTIONS	**Treatment**	Fondaparinux Sodium 5 mg OD	
	Control	Low molecular weight heparin 2000 units	
	Duration	Up to day 5	
OUTCOMES	Venous thromboembolism (Primary Outcome), Any deep vein thrombosis, Any proximal deep vein thrombosis, Distal deep vein thrombosis only, Symptomatic venous thromboembolism, Symptomatic deep vein thrombosis, Nonfatal pulmonary embolism, Fatal pulmonary embolism, Major bleeding (Primary Outcome), Other bleeding (Not qualified as major bleeding), Post-operative transfusions, Mortality.		
RISK OF BIAS ASSESSMENT			
BIAS	**Author's judgement**	**Support for judgement**	
Random sequence generation (selection	Unclear	Randomization was done but the method of randomization was not disclosed in the study.	

bias)		
Allocation concealment (Selection bias)	Unclear	Researchers didn't reveal whether the concealment of allocation of treatment was done.
Blinding of participants and personnel (performance bias), All outcomes	High	Prospective, single-blind, non-inferiority randomized trial.
Blinding of outcome assessment (detection bias), All outcomes	Unclear	• Two radiologists evaluated images for VTE assessment. • Researcher didn't mention whether these radiologists were blinded to the treatment assigned.
Incomplete outcome data (attrition bias), All outcomes	Low	• No missing outcome data. • Clearly mentioned the reason of dropouts and patients in the final analysis
Selective reporting (reporting bias)	Low	Pre-specified primary and secondary outcomes mentioned in the method sections were reported in the results
Other bias	High	This study was supported by Glaxo Smith KlineK. K. and Kaken Pharmaceutical Co. LTD.

Table S1. PRISMA 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page line # 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.	Page # 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page # 3 at line # 14-21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page # 3 at line # 21-23
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Supplemental material Page #4 (line 7-10)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page # 4 at line # 11-23, continued on page # 5 at line # 1-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page # 5 at line 7-13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental material (Table S2) Page #5 at line #14
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page # 5 at line # 15-19

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page # 5 at line # 20-23 and page # 6 at line # 1-3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page # 6 at line # 4-19
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page # 6 at line# 20-22
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page # 7 at line # 1-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page # 7 at line # 6-9

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page # 7 at line # 10-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page # 7 at line # 14-23 and page #8 at line1-4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page # 9 at line # 2-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page # 9 at line # 6-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page # 9 at line # 12-16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	For all outcomes, forest plots were presented with simple summary data, effect estimates, and CIs for each outcome. All forest plots were presented at appropriate place in the manuscript.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page # 9(line # 19-

			-23; Page # 10 (line # 1-24); Page # 11 (Line # 1-25); Page # 12 (Line # 1-8);
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page # 12 at line # 9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page # 12 (at line # 11-22); page # 13 (at line #1-11)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page # 14 (line # 1-24); Page # 15 (1-23); Page # 16 (1-23).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page # 17 (Line # 1-24) Page # 18 (1-16)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page # 18 (line # 17-22)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page # 19 (Line # 10)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6: e1000097. doi:10.1371/journal.pmed1000097

Table S2. Search strategy for study inclusion.

Data base (N= 10,644)	Search Strategies
PubMed	**January 1st 2000 to 18th December 2016:** 1. "fondaparinux"[Supplementary Concept] AND "Enoxaparin"[Mesh] AND (Clinical Trial[ptyp] AND "loattrfull text"[sb] AND "humans"[MeSH Terms]) 2. ("Venous Thrombosis"[Mesh] AND "Enoxaparin"[Mesh]) AND "fondaparinux"[Supplementary Concept] 3. ("Enoxaparin"[Mesh] AND "fondaparinux"[Supplementary Concept]) AND "Pulmonary Embolism"[Mesh] 4. "Dalteparin"[Mesh] AND "fondaparinux"[Supplementary Concept] AND "humans"[MeSH Terms]) 5. "Nadroparin"[Mesh] AND "fondaparinux"[Supplementary Concept] 6. "tinzaparin"[Supplementary Concept] AND "fondaparinux"[Supplementary Concept] 7. ("heparin, low-molecular-weight"[MeSH Terms] OR ("heparin"[All Fields] AND "low-molecular-weight"[All Fields]) OR "low-molecular-weight heparin"[All Fields] OR ("low"[All Fields] AND "molecular"[All Fields] AND "weight"[All Fields] AND "heparin"[All Fields]) OR "low molecular weight heparin"[All Fields]) AND ("fondaparinux"[Supplementary Concept] OR "fondaparinux"[All Fields] OR "fondaparinux sodium"[All Fields]) AND ("loattrfull text"[sb] **December 18th 2016 to December 31st 2017:** 1. ("fondaparinux"[Supplementary Concept] AND "Heparin, Low-Molecular-Weight"[Mesh]) AND "Venous Thromboembolism"[Mesh] AND ("2016/12/18"[PDAT] : "2017/12/31"[PDAT])
Embase	**January 2000 to December 18th 2016:** 1. ('fondaparinux'/exp OR fondaparinux) AND ('low molecular weight heparin'/exp OR 'low molecular weight heparin') AND ('venous thromboembolism'/exp OR 'venous thromboembolism') 2. ('fondaparinux'/exp OR fondaparinux) AND ('enoxaparin'/exp OR enoxaparin) AND ('venous thromboembolism'/exp OR 'venous thromboembolism') AND 'fondaparinux'/de 3. ('fondaparinux'/exp OR fondaparinux) AND ('low molecular weight heparin'/exp

	OR 'low molecular weight heparin') AND ('lung embolism'/exp OR 'lung embolism') AND [1-1-2000]/sd NOT [2-9-2016]/sd AND 'deep vein thrombosis'/de **4.** ('fondaparinux'/exp OR fondaparinux) AND ('dalteparin'/exp OR dalteparin) AND [1-1-2000]/sd NOT [7-9-2016]/sd AND 'heparin'/de **December 18, 2016 to December 31, 2017:** **1.** ('fondaparinux'/exp OR fondaparinux) AND ('low molecular weight heparin'/exp OR 'low molecular weight heparin') AND ('venous thromboembolism'/exp OR 'venous thromboembolism') AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [18-12-2016]/sd NOT [31-12-2017]/sd **2.** ('fondaparinux'/exp OR fondaparinux) AND ('enoxaparin'/exp OR enoxaparin) AND ('venous thromboembolism'/exp OR 'venous thromboembolism') AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [18-12-2016]/sd NOT [31-12-2017]/sd **3.** ('fondaparinux'/exp OR fondaparinux) AND ('nadroparin'/exp OR nadroparin) AND ('venous thromboembolism'/exp OR 'venous thromboembolism') AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [18-12-2016]/sd NOT [31-12-2017]/sd
ProQuest	**January 2000 to December 18th 2016:** **1.** fondaparinux AND enoxaparin AND (venous thromboembolism) Filters: 2000 -2016-09-06 **2.** fondaparinux AND (heparin of low molecular weight) AND (venous thromboembolism) Filters: 2000 - 2016-09-10 **December 18th 2016 to December 31st 2017** 1. (Fondaparinux sodium) AND (low molecular weight heparin) AND (venous thromboembolism) **Filter:** Date: From December 18 2016 to December 31 2017
ScienceDirect	"Fondaparinux Sodium" AND "Enoxaparin" AND “Venous thromboembolism”
Cochrane Library	"Fondaparinux" AND "Enoxaparin" AND "Clinical Trials"

Figure S1. Fondaparinux vs LMWH for venous thromboembolism up to day 15 (Sensitivity Analysis)

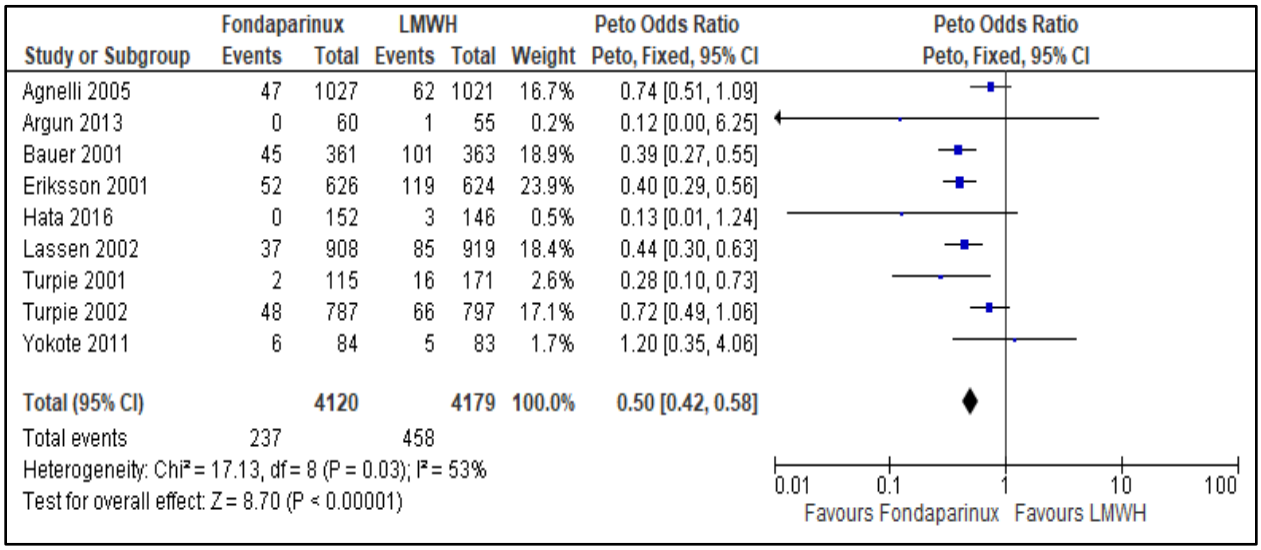


Figure S2. Funnel plot for "Reporting Bias" of venous thromboembolism up to day 15

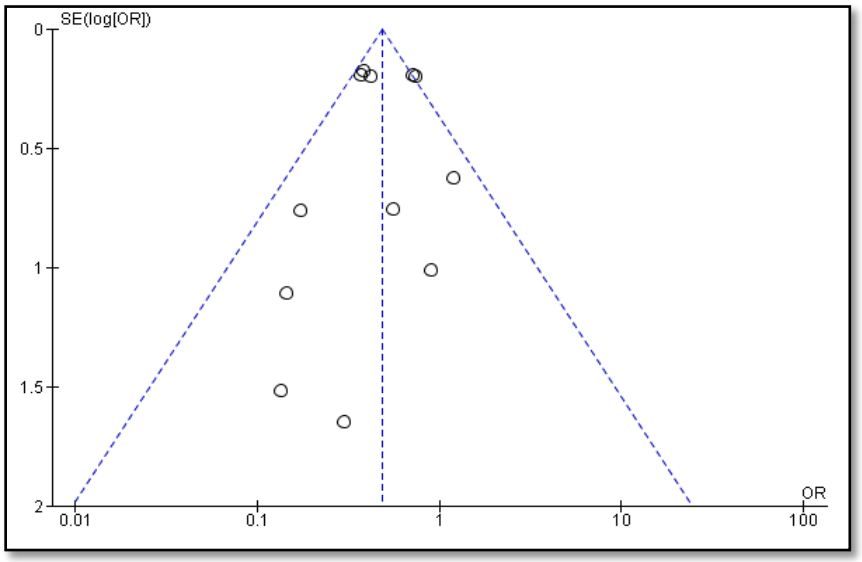


Figure S3. Fondaparinux vs LMWH for total deep vein thrombosis up to day 15

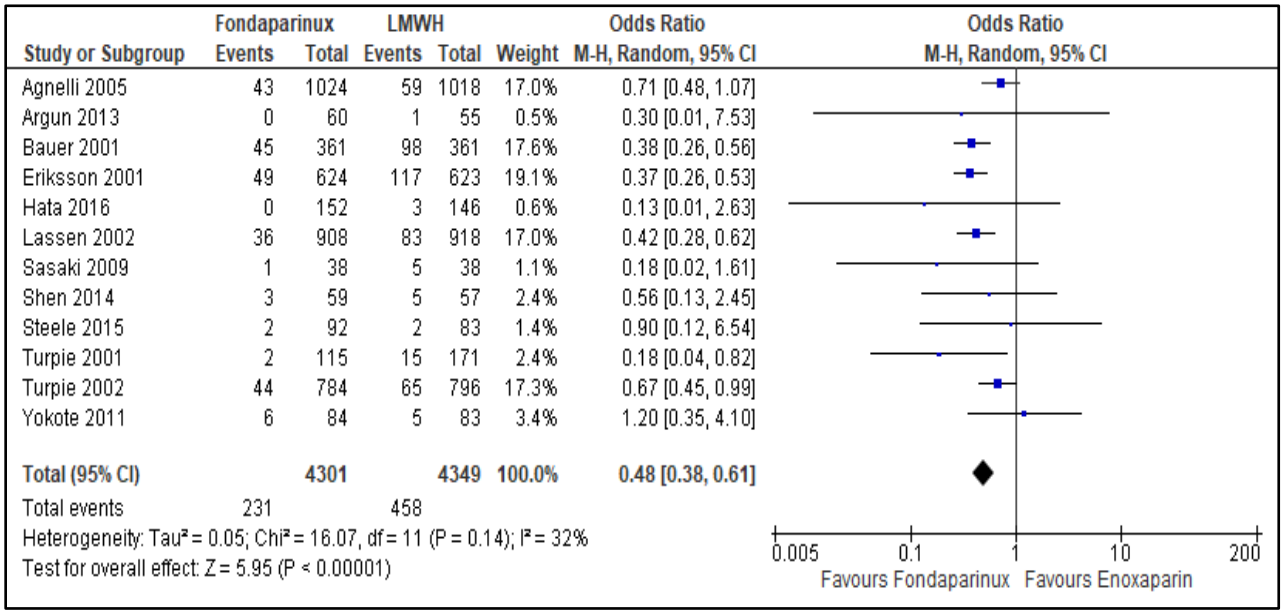


Figure S4. Fondaparinux vs LMWH for proximal deep vein thrombosis up to day 15

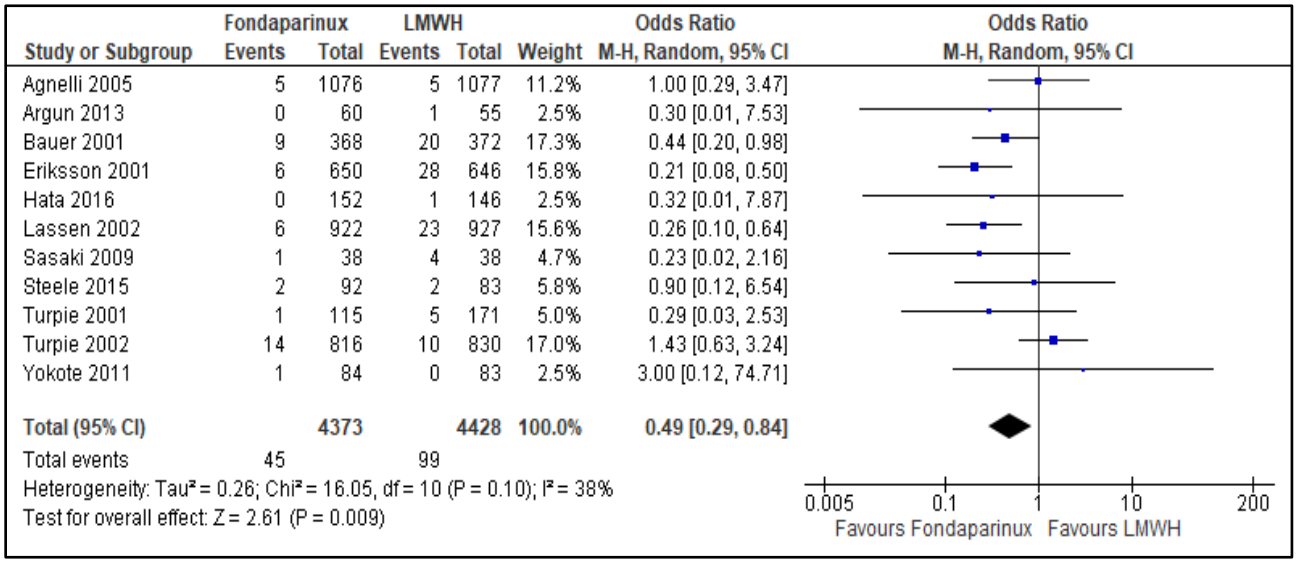


Figure S5. Fondaparinux vs LMWH for distal deep vein thrombosis up to day 15

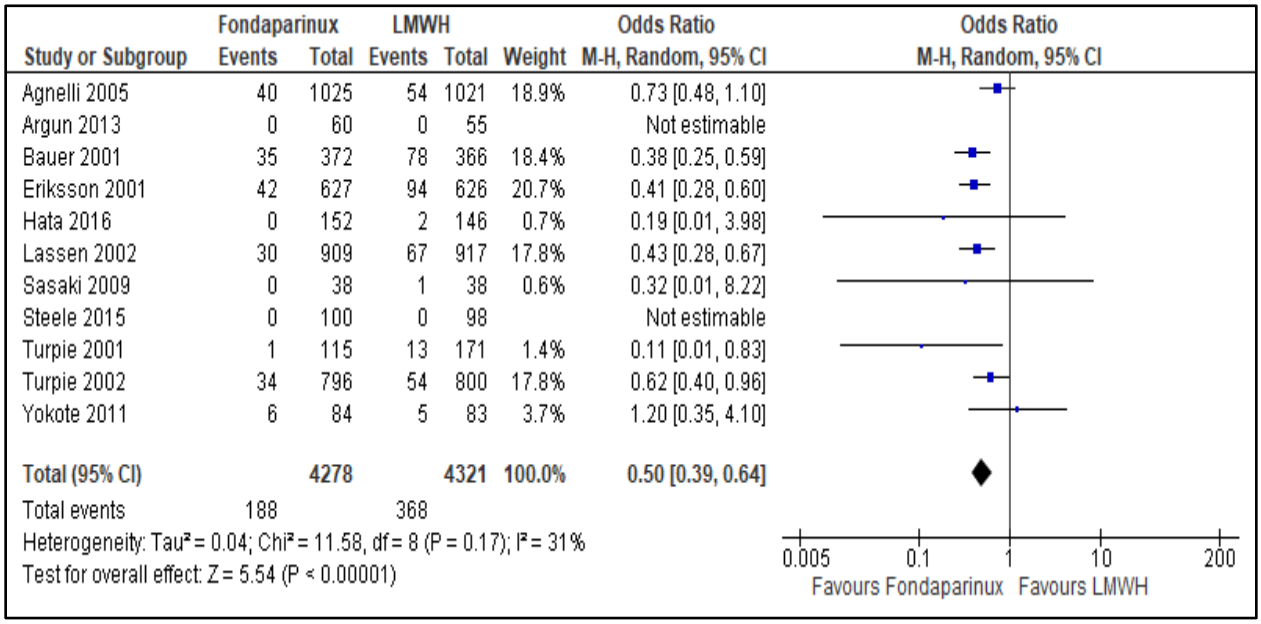


Figure S6. Fondaparinux vs LMWH for total deep vein thrombosis up to day 15 (Sensitivity Analysis)

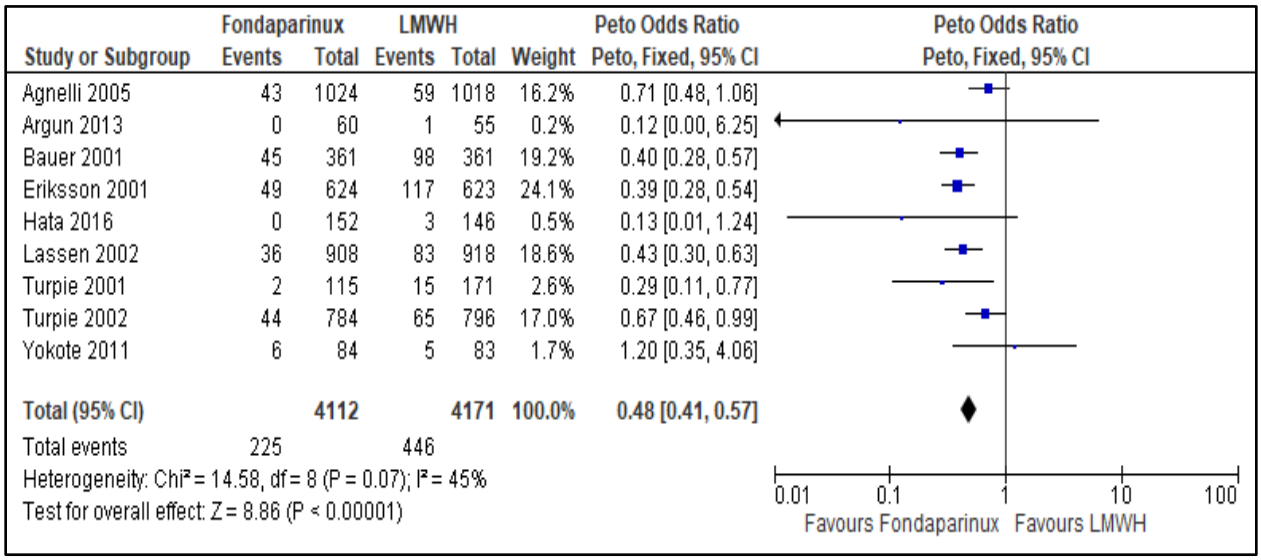


Figure S7. Fondaparinux vs LMWH for proximal deep vein thrombosis up to day 15 (Sensitivity Analysis)

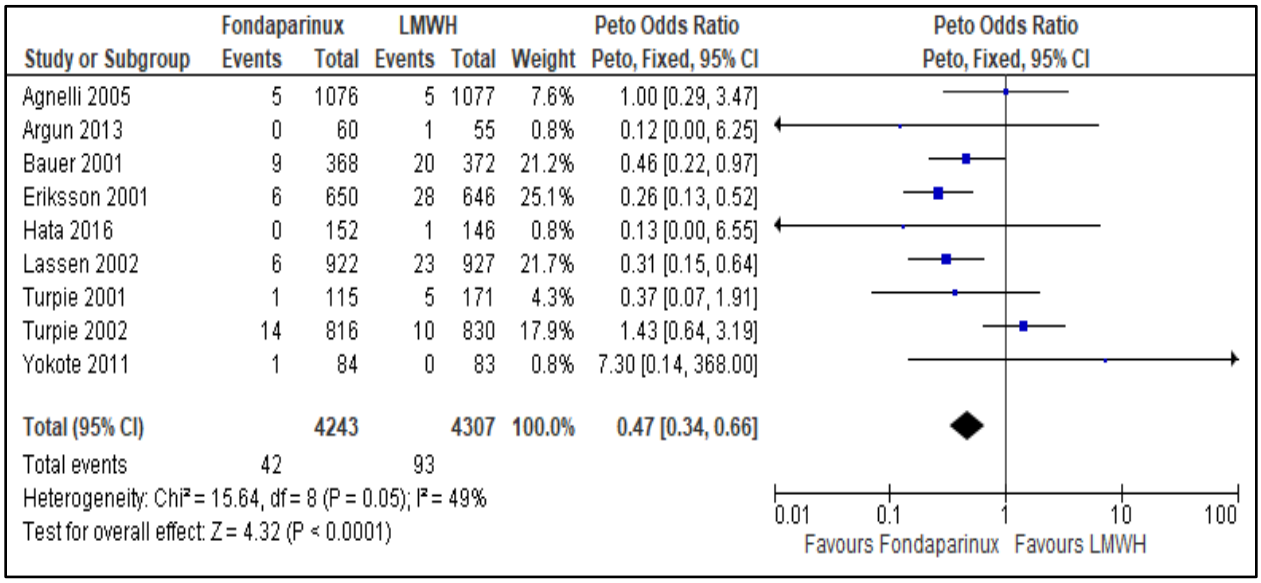


Figure S8. Fondaparinux vs LMWH for distal deep vein thrombosis up to day 15 (Sensitivity Analysis)

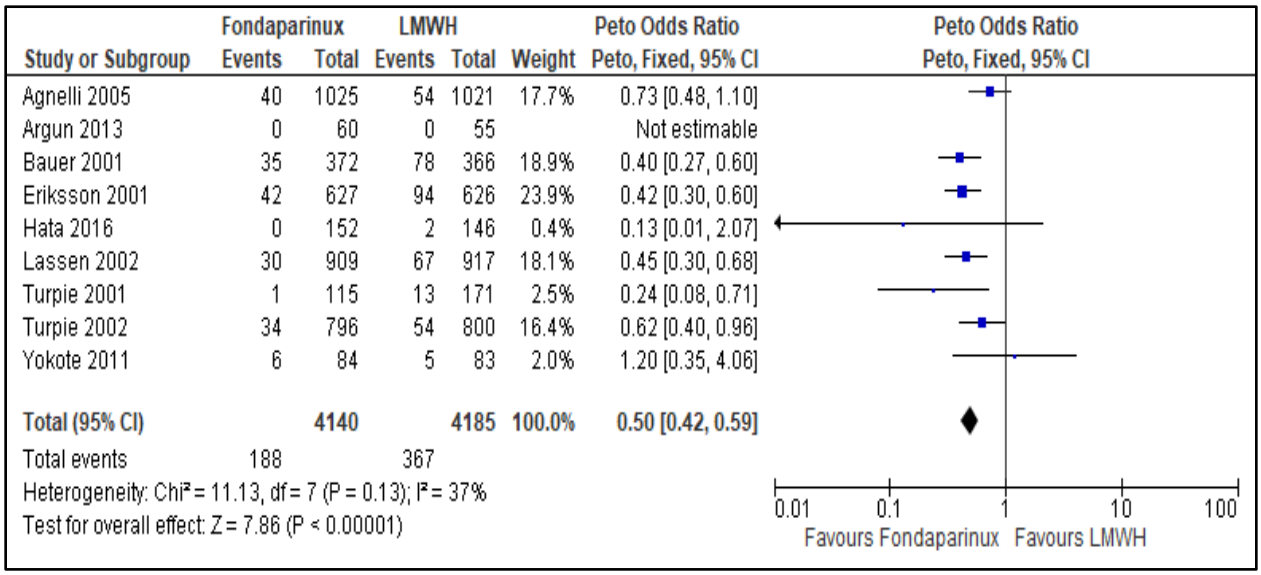


Figure S9. Funnel plot for "Reporting Bias" of total deep vein thrombosis up to day 15

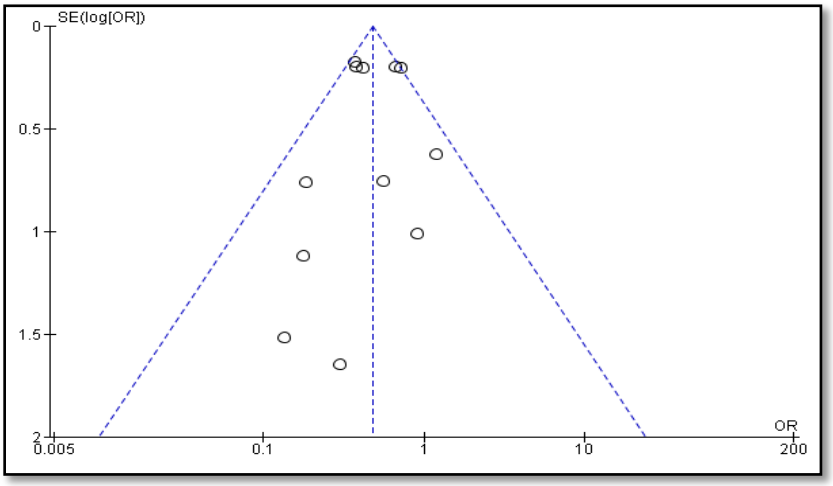


Figure S10. Symptomatic VTE up to post-operative day 15

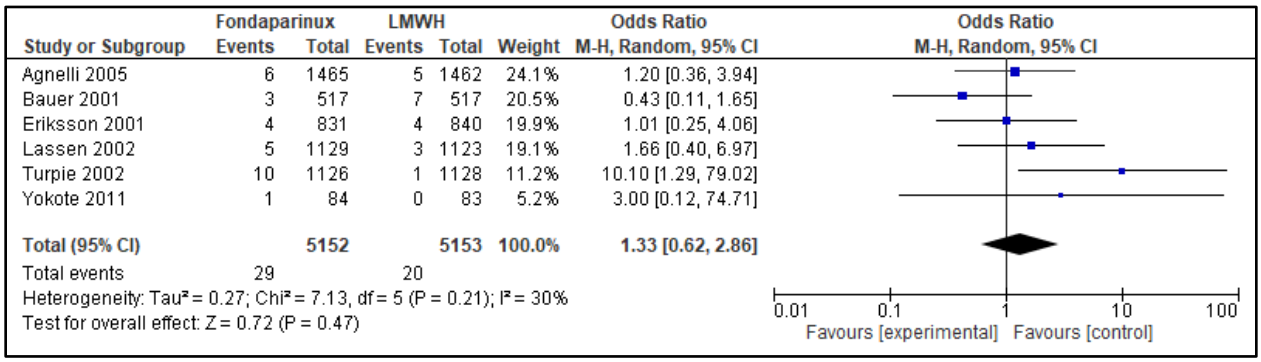


Figure S11. Pulmonary embolism up to post-operative day 15

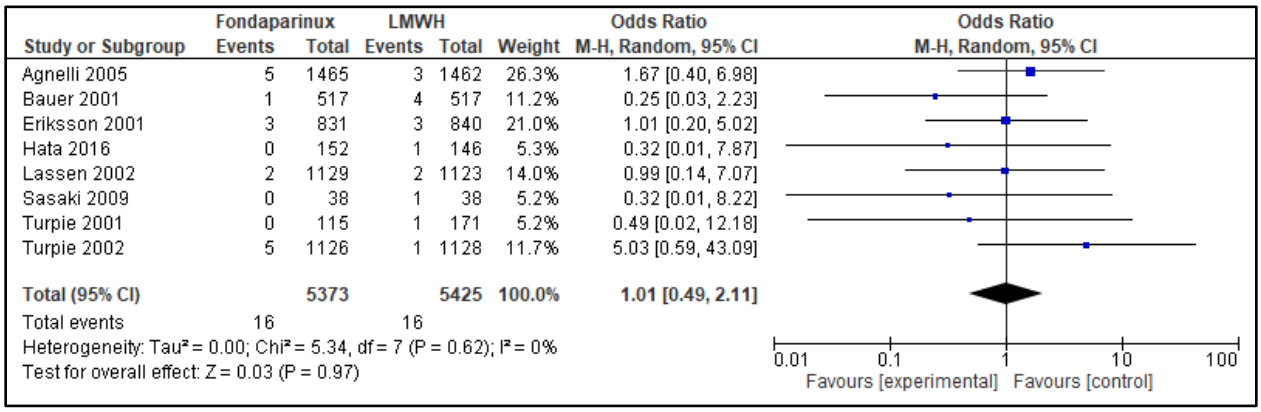


Figure S12. Fondaparinux vs LMWH for all-cause mortality at day 90

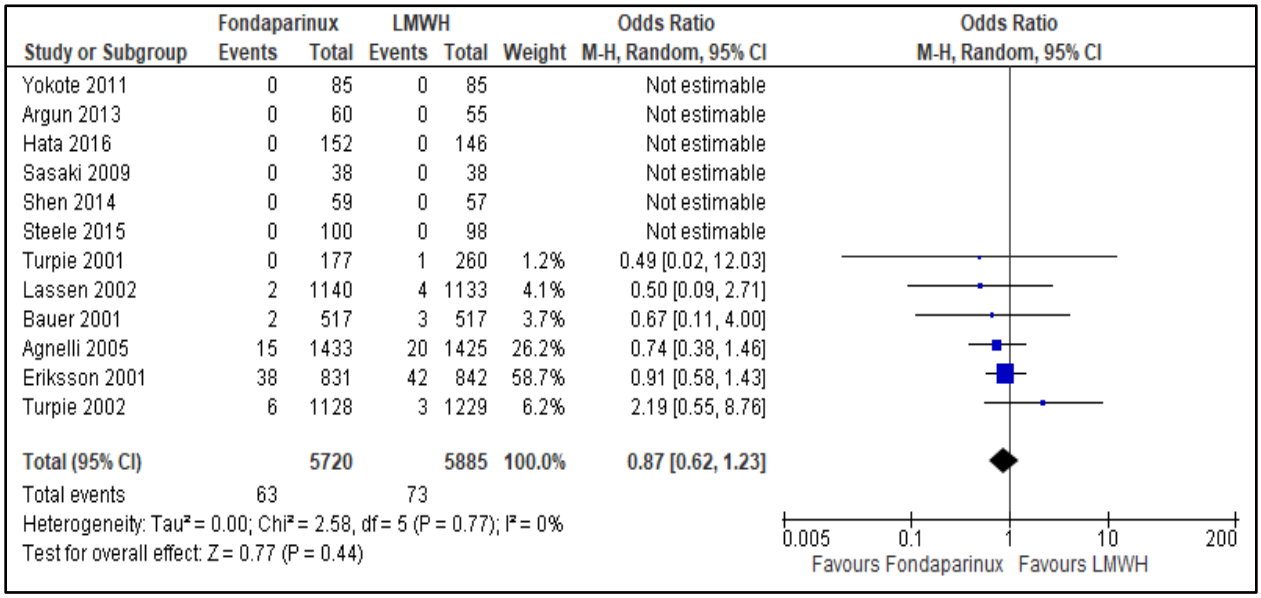


Figure S13. Fondaparinux vs LMWH for all-cause mortality at day 90 (Sensitivity Analysis)

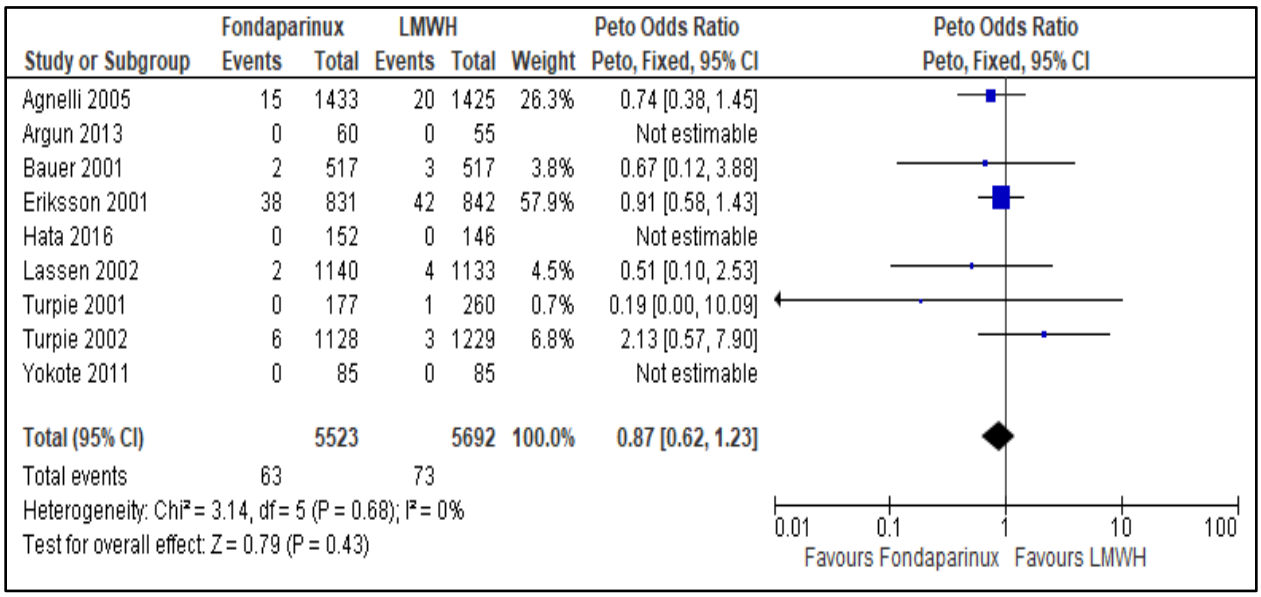


Figure S14. Fondaparinux vs LMWH for major bleeding during the treatment period (Sensitivity Analysis)

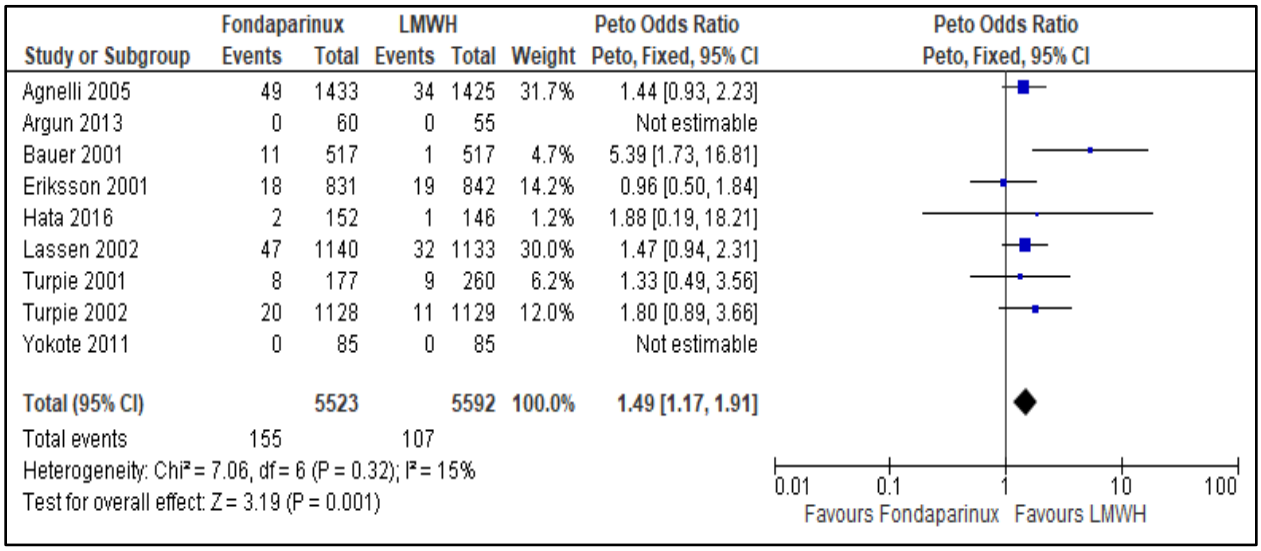


Figure S15. Fondaparinux vs LMWH for minor bleeding during the treatment period

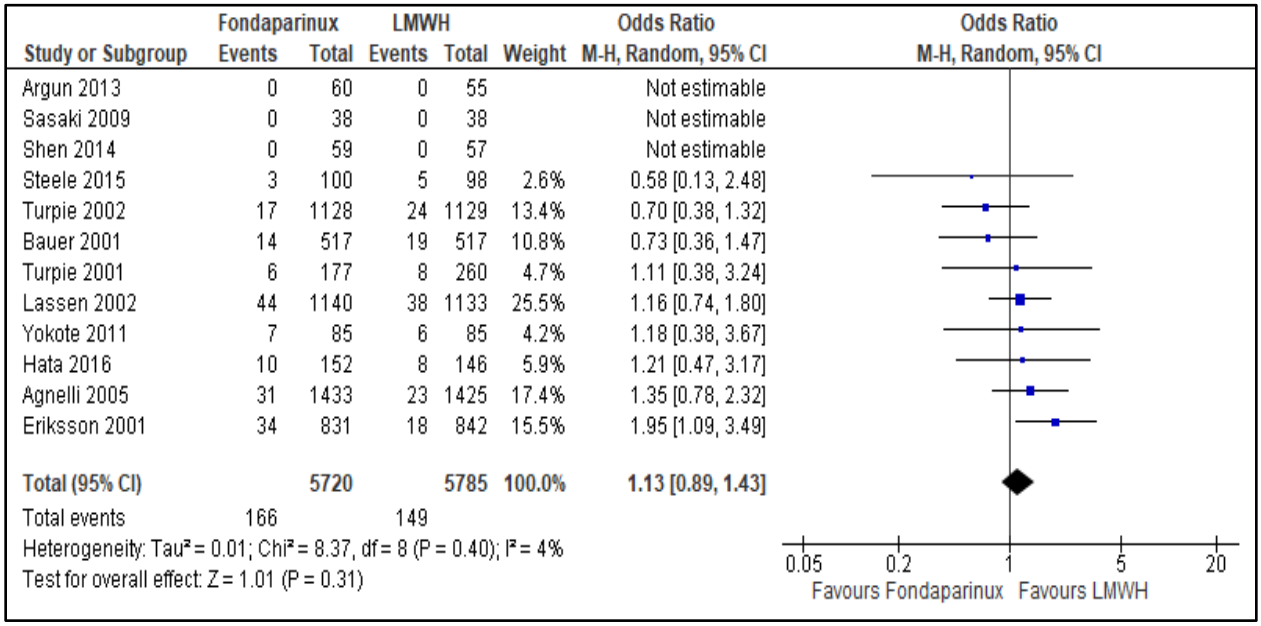
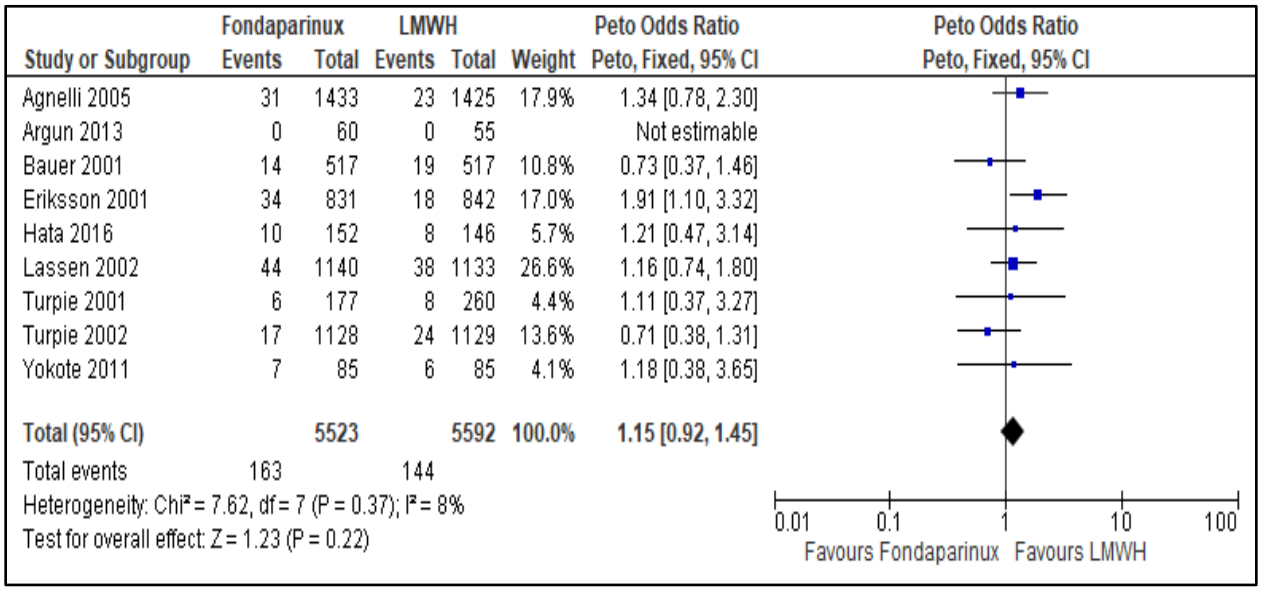


Figure S16. Fondaparinux vs LMWH for minor bleeding during the treatment period (Sensitivity Analysis)



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