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Choosing Between Enoxaparin and Fondaparinux for the Prevention of Thromboembolism: A Meta-Analysis of Randomized Trials

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Abstract

Background: Venous thromboembolism (VTE), are few of the most serious complications in ICU. There are Pharmacological and mechanical prophylaxis methods are used to reduce the risk of thromboembolism and the most efficient is the pharmacological methods which is based on a fine balance between their efficacy and the adverse effects associated with them.

Objectives: To evaluate, effectiveness, and clinical impact of VTE prophylaxis with fondaparinux and enoxaparin on patient outcomes in different clinical practices.

Study design: Meta-analysis was used to address this concern.

Sittings: Meta-analysis-based study following the PRISMA (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) guidelines.

Methods: Online databases (PubMed/Medline, EMBASE, and Cochrane library) were used for randomized studies which compared differences in clinical outcomes observed with the use of Fondaparinux and enoxaparin in patients who were treated for thromboembolism.

Results: Thirteen studies were identified for inclusion in this study, involving a total of 64,350 patients. The risk of bias was low. Meta-analysis found that Fondaparinux result in significant reduction in incidence of bleeding than Enoxaparin (R.R. = 0.85 [0.81, 0.88]; 95% CI; $I^2 = 100\%$; $P < .00001$) also showed that that Fondaparinux result in significant decrease in venous thromboembolism than enoxaparin (R.R. = 0.52 [0.47, 0.58]; 95% CI; $I^2 = 62 + \%$; $P < .00001$). There was no significant difference in the incidence of mortality, pulmonary embolism, stroke, and incidence of transfusion between two groups among the studies included in the meta-analysis.

Conclusion: Fondaparinux was associated with superior efficacy in reduction of incidence of bleeding and incidence of occurrence of venous thromboembolism.

Keywords: enoxaparin, fondaparinux, meta-analysis, randomized trials, thromboembolism

1. Introduction

Critically ill patients appear to be at high risk of developing deep vein thrombosis (DVT) and pulmonary embolism during their stay in the intensive care unit (ICU) because of many factors such as premorbid medical and surgical conditions, invasive tests and treatments, prolonged immobility, vascular injury, and acute and chronic renal insufficiency.[1] In addition, critical illness activates the coagulation cascade which may mediate the increased developing of venous thromboembolism (VTE)[2] Prevention of arterial and venous thrombosis forms a major part of clinical practice in all medical and surgical specialties. Thrombosis prophylaxis decreases the incidence of VTE, and guidelines have suggested pharmacologic prophylaxis for all critically ill patients if there is no contraindication.[3,4] Fondaparinux belongs to a new group of anticoagulant compounds, the synthetic oligosaccharides. It is a single chemical entity composed of five saccharides, designed specifically to bind strongly and exclusively to anti thrombin. Its structure prevents the nonspecific binding to plasma proteins and therefore, Fondaparinux is more than 95% bound to ant thrombin in plasma.[5] Although Fondaparinux does not mediate the inhibition of coagulation factors other than Factor Xa, it inhibits thrombin generation in a dose-dependent manner whether triggered via the extrinsic or intrinsic pathway, independently of the presence of platelets.[6]

Heparin, the most used anticoagulant, especially in an ICU setting, is isolated from porcine intestine where it is stored in the mast cell granules. Unfractionated heparin (UFH) is a combination of 3000- to 30,000-Dalton (da) fragments. Heparin binds to ant thrombin III (also called ant thrombin/AT), increasing the rate of thrombin-AT complex formation, but also inhibits other

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steps in coagulation.[7] Heparin anticoagulation has major advantages in an ICU setting.

LMWHs are anticoagulants acting by inhibition of the final common pathway of the coagulation cascade.[8] The coagulation cascade's goal is to fluid blood into a clot, thus preventing bleeding. The final common pathway is the conversion of fibrinogen into fibrin by the activity of thrombin. LMWH inhibits coagulation by activating antithrombin III. Antithrombin III binds to and inhibits factor Xa. In doing so, it prevents activation of the final common pathway. LMWH administration is via subcutaneous injection; this has long-term implications on the choice of anticoagulant for prophylaxis.[9]

LMWHs have many advantages over UFH. These agents have a greater bioavailability, can be administered by subcutaneous injections, and have a longer duration of anticoagulant effect. A fixed dose of LMWH can be used, and laboratory monitoring of aPTT is not necessary, also it decrees incidence pf heparin induced thrombocytopenia which giving more advantage to heparin analogues.[10]

This study purposed to detect the effect of fondaparinux relative to enoxaparin on patient outcomes in different clinical practices.

2. Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

2.1. Search strategy and selection criteria

This analysis was performed using MEDLINE, EMBASE, PubMed, and Cochrane to identify all published randomized and prospective clinical trials comparing the Fondaparinux with Enoxaparin in management of thromboembolism. Relevant articles were distinguished using the following search terms: "Fondaparinux" and "Enoxaparin" sufficient information regarding the efficacy and safety outcome was available. Studies without any reference to the comparative assessment of the efficacy and safety of fondaparinux and enoxaparin. And for the studies with the same results published in different journals we selected the most complete report. Retrospective studies, reviews, animal studies, and studies lacking sufficient data were excluded. Studies were limited to human and English language. Reference lists of related articles were also reviewed. No approval from the Institutional Review Board was required.

2.2. Inclusion criteria

1. They were randomized and prospective clinical trials studies comparing enoxaparin with fondaparinux in patients in different studies.
2. They reported adverse outcomes (bleeding, transfusions, and incidence of stroke and mortality rate) as their clinical endpoints.
3. They involved relevant data which could be used in this analysis.

2.3. Exclusion criteria

Studies were excluded if they satisfied the following criteria:

1. They were systematic reviews, meta-analyses, observational studies letter to editors, or case studies.
2. Their data were absent or deficient.
3. The study authors were inaccessible or did not reply if extra data from their trials were required.
4. Its outcomes not of interest.

2.4. Data extraction

Data extraction was undertaken from included randomized trial on the first author, year of publication, study design, sample size, setting, as well as all outcomes of interest. The primary outcome of this analysis was venous thromboembolism and pulmonary embolism or both.

Secondary outcomes were the incidence of the complication of anticoagulant drugs as their clinical endpoints Included incidence of bleeding, stroke, transfusion, and mortality rate.

2.5. Quality assessment and risk of bias

The quality of trials was evaluated using the risk of bias tool recommended by the Cochrane Collaboration.[12] We appointed an estimation of high, unclear, or low to the following items: Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Any disparities were identified and resolved through discussion.

2.6. Statistical analysis

We conducted this analysis to pool the results of trials comparing Enoxaparin and Fondaparinux for the management of thromboembolism using Review Manager (Remikm vMan), Version 5.3. Copenhagen (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) with risk ratio (RR) and 95% confidence intervals (CI) as the analytical parameters.

Heterogeneity was assessed using the I^2 statistic. A fixed effects model or a random effects model was used during the analysis depending on the value of I^2.A fixed effects model was recommended if an I^2 value $< 50\%$ was obtained, whereas if the I^2 value was $> 50\%$, a random effects model was recommended.

A P value $\leq .05$ was considered as statistically significant whereas a P value $\geq .05$ was considered as statistically insignificant.

3. Results

3.1. Search results

Our search identified 266 studies through database searching and other sources. Of these articles, 90 were excluded after the removal of duplicates. Righty-seven articles were screened. Of these articles, 60 were excluded after screening, and 27 were assessed for eligibility. Ultimately, 13 randomized trials were included for analysis, with the remainder excluded as outlined in the PRISMA flow diagram (Fig. 1).

3.2. Characteristics and quality of clinical studies included in the meta-analysis

The studies included in the analysis are detailed in Table 1. Thirteen randomized studies were identified for inclusion in this study,[11–23] involving a total of 64,350 patients. Of which 6 were orthopedic surgery,[11–14,17,22] 5 were acute coronary syndrome,[16,18–21] 1 was symptomatic deep venous thrombosis,[15]

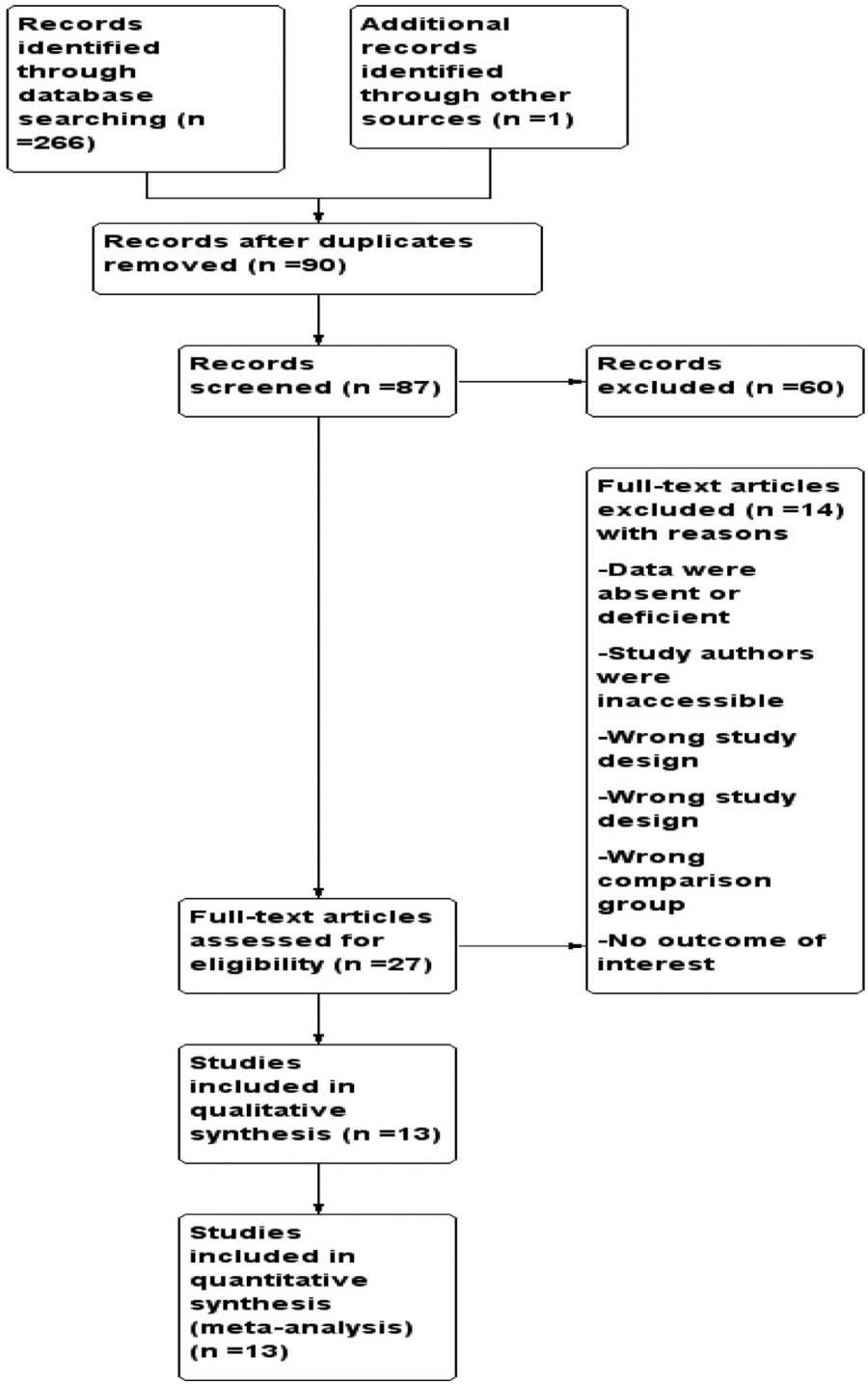

Figure 1. The PRISMA flow diagram.

and 1 was bariatric surgery. Bias risk in the thirteen trials was assessed to be generally low (Figs. 2, 3)[23]

3.3. Venous Thromboembolism

The forest plot diagrams (Fig. 4) showed that that fondaparinux result in significant decrease in venous thromboembolism than enoxaparin (R.R.=0.52 [0.47, 0.58]; 95% CI; $I^2=62+\%$; $P<.00001$).

3.4. Pulmonary embolism

The forest plot showed that fondaparinux result in insignificant decrease in the incidence of pulmonary embolism than enoxaparin ((R.R.=1.38 [0.86, 2.21]; 95% CI; $I^2=1\%$; $P=.18$) (Fig. 5).

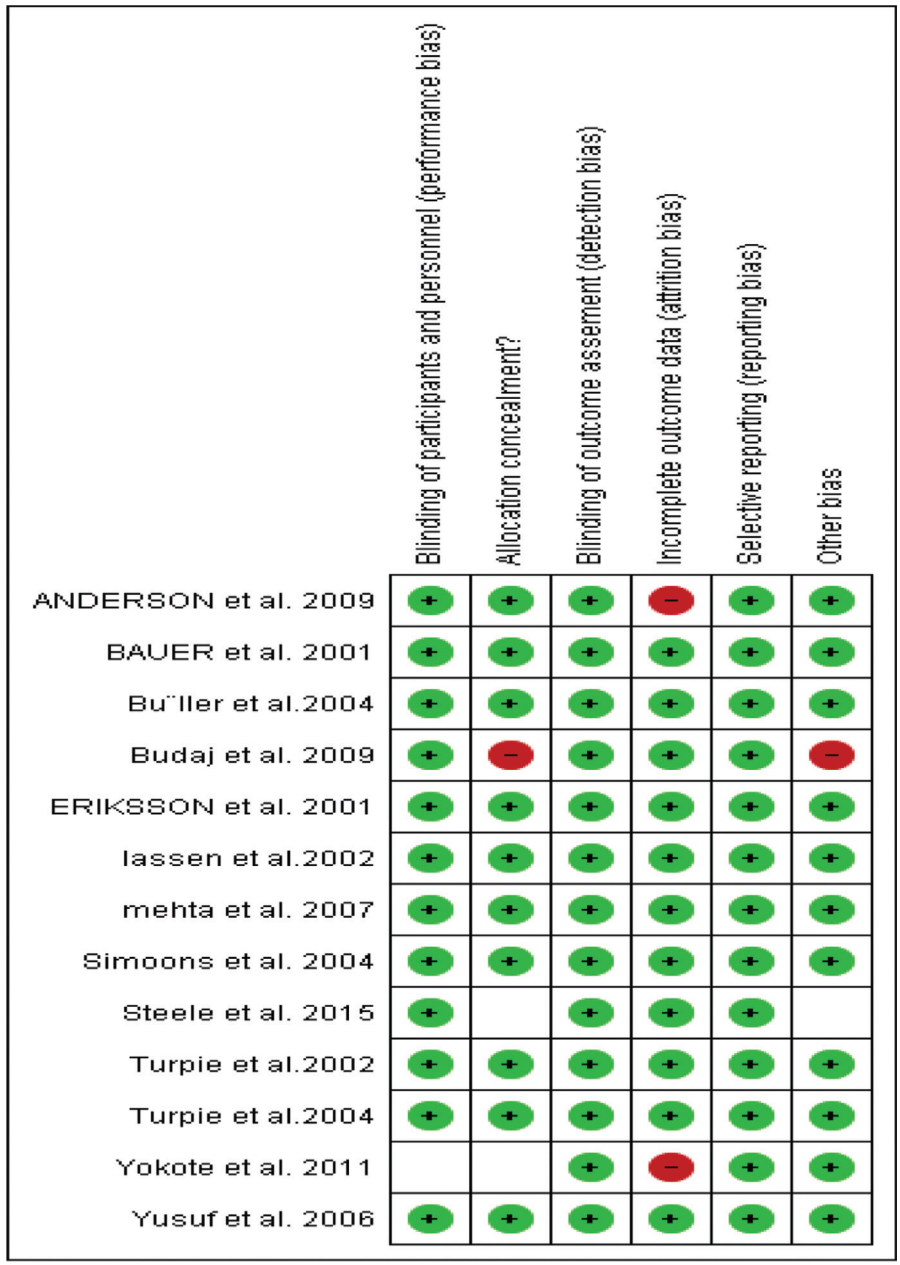

Figure 2. Risk of bias summary.

3.5. Venous Thromboembolism and pulmonary embolism

The forest plot diagrams (Fig. 6) showed that fondaparinux result in insignificant decrease in the incidence of Venous Thromboembolism pulmonary embolism than enoxaparin. (R.R. = 0.55 [0.49, 0.62]; 95% CI; $I^2 = 100\%$; $P < .00001$).

3.6. Bleeding

The forest plot diagrams (Fig. 7) showed that fondaparinux result in significant decrease in bleeding than enoxaparin (R.R. = 0.85 [0.81, 0.88]; 95% CI; $I^2 = 100\%$; $P < .00001$).

3.7. Mortality

The forest plot diagrams (Fig. 8) showed that fondaparinux result in insignificant decrease in the rate of mortality than enoxaparin (R.R. = 0.91 [0.72, 1.16]; 95% CI; $I^2 = 0\%$; $P = .45$).

3.8. Stroke

The forest plot diagrams (Fig. 9) showed that fondaparinux result in insignificant decrease in the incidence of stroke than enoxaparin (R.R. = 0.79 [0.47, 1.36]; 95% CI; $I^2 = 0\%$; $P = .40$).

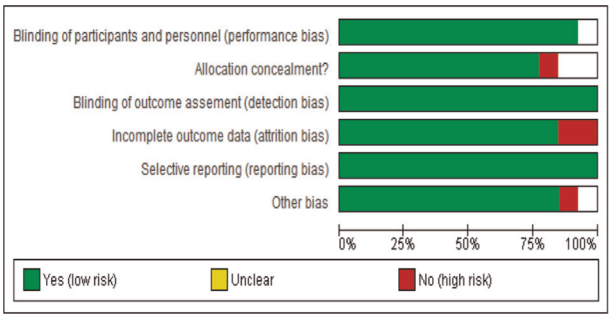

Figure 3. Risk of bias graph.

3.9. Transfusions

The forest plot diagrams (Fig. 10) showed that the two drugs result in insignificant decrease in transfusions (R.R. = 1.00 [0.96, 1.04]; 95% CI; $I^2 = 78\%$; $P = .89$).

4. Discussion

Venous thromboembolism (VTE) is a common complication of serious illness and is associated with considerable morbidity and mortality in hospitalized patients.[24–25] It represents the third most common cause of vascular death, after myocardial infarction and stroke, and is the leading preventable cause of death in hospitalized patients.[26] Within the United States, there are approximately 600,000 to 900,000 cases annually with an overall mortality rate ranging between 15% and 53%.[27] Within the ICU, patients with VTE are more likely to have a longer duration of mechanical ventilation (9 vs. 6 days; $P = .02$), ICU stay (17.5 vs. 9days; $P = 0.005$), and hospitalization (51 vs. 21 days; $P < 0.001$). These patients also have significantly higher inhospital mortality (56% vs. 38%).[28]

Studies of patients who received DVT prophylaxis in medical ICUs suggest that the existence of PE is detected in less than 2.5% of these populations.[29–31] Of note, a small proportion of patients will enter the ICU with undiagnosed proximal DVT. Studies of ICU patients who received DVT prophylaxis and underwent lower extremity venous compression ultrasound screening once to twice a week, and additional testing when clinically indicated, have a DVT incidence rate of 5.4% to 23.6%[29,32,33] In autopsy studies of critically ill patients, PE was found in 7% to 27%, and clinicians did not suspect PE in about one-third of these patients.[34–38]

According to the study outcomes, the rate of bleeding was substantially lower in the fondaparinux group than in the enoxaparin group (R.R. = 0.85 [0.81, 0.88]; 95% CI; $I^2 = 100\%$; $P < .00001$), which is based on 11 studies. In line with our results trial which was a double blinded randomized trial which comparing fondaparinux with enoxaparin in 6238 patients who

Table 1

Characteristics of included studies

Study ID	Intervention	Dose	No. of patients	Age (yr)	Timing of injection	Type of surgery
Bauer et al. 2001[11]	Fondaparinux group	2.5 mg SC once daily	517	67.5	Postoperative	Knee surgery
	Enoxaparin group	30 mg SC twice daily	517	67.5		
Eriksson et al. 2001[12]	Fondaparinux group	2.5 mg SC once daily	626	76.8	Postoperative	Surgery for fracture of the upper third of the femur
	Enoxaparin group	40 mg SC once daily	624	77.3	Preoperatively for at least five days.	
lassen et al. 2002[13]	Fondaparinux group	2.5 mg SC once daily	1140	66	Postoperatively	Total hip replacement Surgery
Turpie et al. 2002[14]	Enoxaparin group	40 mg SC once daily	1133	67	Preoperatively	
	Fondaparinux group	2.5 mg SC once daily	1128	67	Postoperative	Hip-replacement surgery
	Enoxaparin group	30 mg SC twice daily	1129	67		
Buller et al. 2004[15]	Fondaparinux group	7.5 mg SC once daily	1098	61		Symptomatic deep venous thrombosis
	Enoxaparin group	1 mg/kg SC twice daily	1107	61		
Simoons et al. 2004[16]	Fondaparinux group	Four doses(2.5, 4, 8, or 12 mg) SC once daily	908	62		ACS without persistent ST-segment elevation
	Enoxaparin group	1 mg/kg SC twice daily	230	60		
Turpie et al.2004[17]	Fondaparinux group	2.5 mg SC once daily	3,668	>18	Postoperative	Major orthopedic surgery
Yusuf et al. 2006[18]	Enoxaparin group	30 mg SC twice daily	3,676	>18		
	Fondaparinux group	2.5 mg SC daily	10,021	66		Acute coronary syndromes
Mehta et al. 2007[19]	Enoxaparin group	1 mg/kg SC twice daily	10,057	66		
	Fondaparinux group	2.5 mg SC once daily	3,134	64		Acute Coronary Syndromes Undergoing PCI.
	Enoxaparin group	mg/kg SC twice daily	3,104	64		
Anderson et al. 2009[20]	Fondaparinux group	2.5 mg SC daily	48	69		Acute Coronary Syndromes
	Enoxaparin group	1 mg kg SC twice daily	42	71		
Budaj et al. 2009[21]	Fondaparinux group	2.5 mg SC once daily	10,057	60		Non-ST-elevation ACS
	Enoxaparin group	1 mg/kg SC b.i.d	10,021	60		
Yokote et al. 2011[22]	Fondaparinux group	2.5 mg SC once daily	84	63	Postoperative	Total hip replacement
	Enoxaparin group	40 mg, 20 mg SC twice daily	83	64		
Steele et al. 2015[23]	Fondaparinux group	5 mg SC once daily	100	19–68	Postoperative	Bariatric surgery
	Enoxaparin group	40 mg SC twice daily	98	18–65	Preoperative	

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

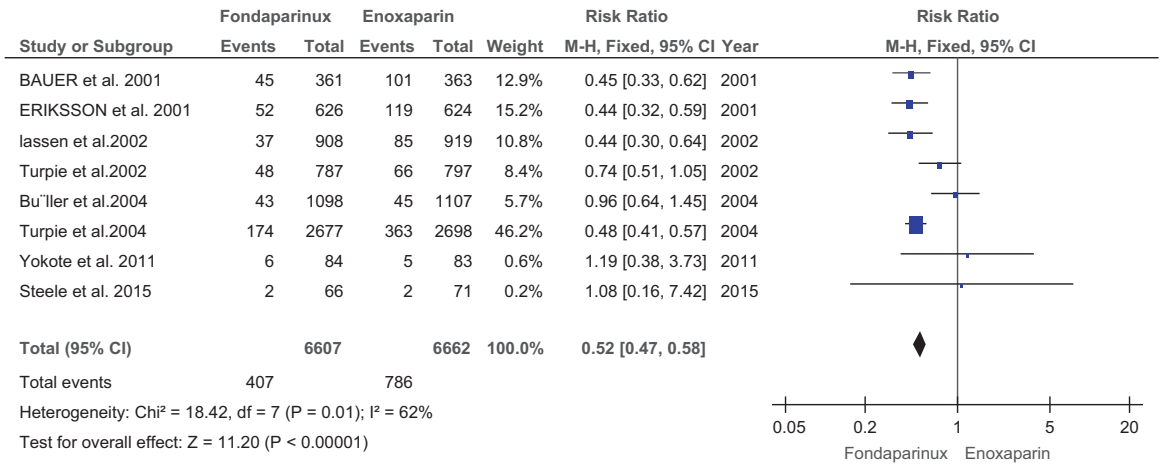

Figure 4. Incidence of venous thromboembolism.

underwent PCI showed decreased bleeding events in fondaparinux group without any increase in mortality.[39] On the other hand, 6 trial (12,092 patients obtained from 447 hospitals in 41 countries around the globe) which compared fondaparinux with placebo or unfractionated heparin in patients with STEMI showed that in patients who were not undergoing PCI, were associated with a lower mortality and re-infarction without increasing stroke or bleeding events.[40] Another meta-analysis showed that In patients who were treated for ACS, fondaparinux might be a better than enoxaparin in terms of short to midterm bleeding events. This result was limited to patients with NSTEMI.[41]

However, results from the French Registry of ST segment elevation and non-ST segment elevation MI (FAST-MI) 2010 showed a same incidence of bleeding and mortality between fondaparinux and enoxaparin.[42] Also Almendro-Delia et al. also found in current clinical practice, the use of fondaparinux instead of enoxaparin among NSTE-ACS patients seems to provide a favourable net clinical benefit.[43]

In our study, reported data on the in-hospital mortality. There was no statistically significant difference in the overall mortality between two groups (R.R. = 0.91 [0.72, 1.16]; 95% CI; $I^2 = 0\%$; P = .45). Another meta-analysis that was conducted to report the effect on mortality considered LMWH and placebo in the same group compared with fondaparinux[44] andreportedastatistical-lynon-significant 21% reduction in the odds associated with fondaparinux.

But on the line of this study, a total of 8 studies, including, showed that that fondaparinux result in significant decrease in venous thromboembolism than Correlation with our study meta-analysis done by Min Hur et al.,[45] comparing 6 anti-coagulants used in the approved dose to prevent VTE after total hip or knee arthroplasty. Our network-pooled estimates of outcomes revealed that fondaparinux, may has a higher efficacy of reducing VTE than enoxaparin, but fondaparinux and was associated with a higher risk of major/CRNM bleeding than enoxaparin after hip and knee arthroplasty. Another, meta-analysis by Wen-Jun Dong et al.,[46] revealed that fondaparinux had a superior efficacy compared to enoxaparin in the prevention of VTE after total hip replacement in terms of total VTE and DVT, also systematic review and meta-analysis done by Arum Kumar et al. Fondapar-inux 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.[47]

On the other hand, study which done by Büller et al. showed that subcutaneous fondaparinux was less effective (not inferior) and safe when compared by twice-daily, body weight-adjusted

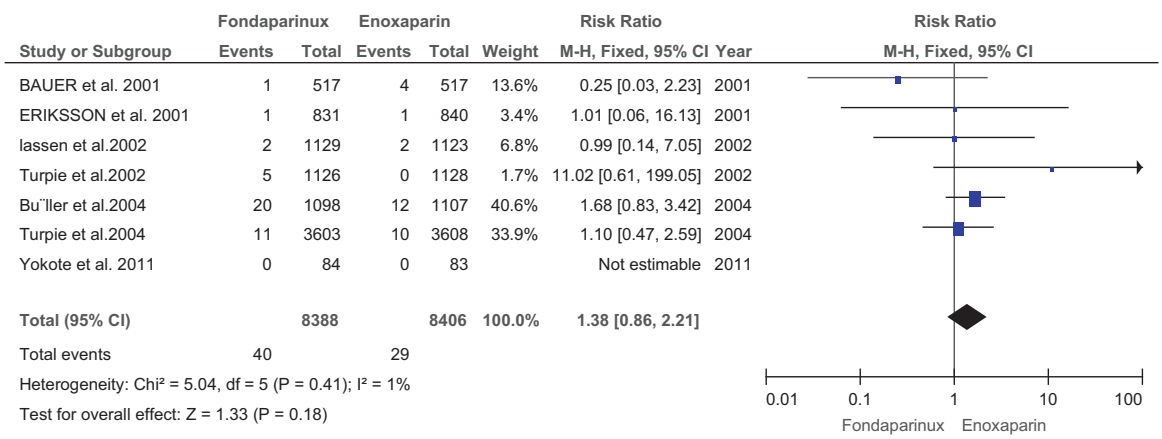

Figure 5. Incidence of pulmonary embolism.

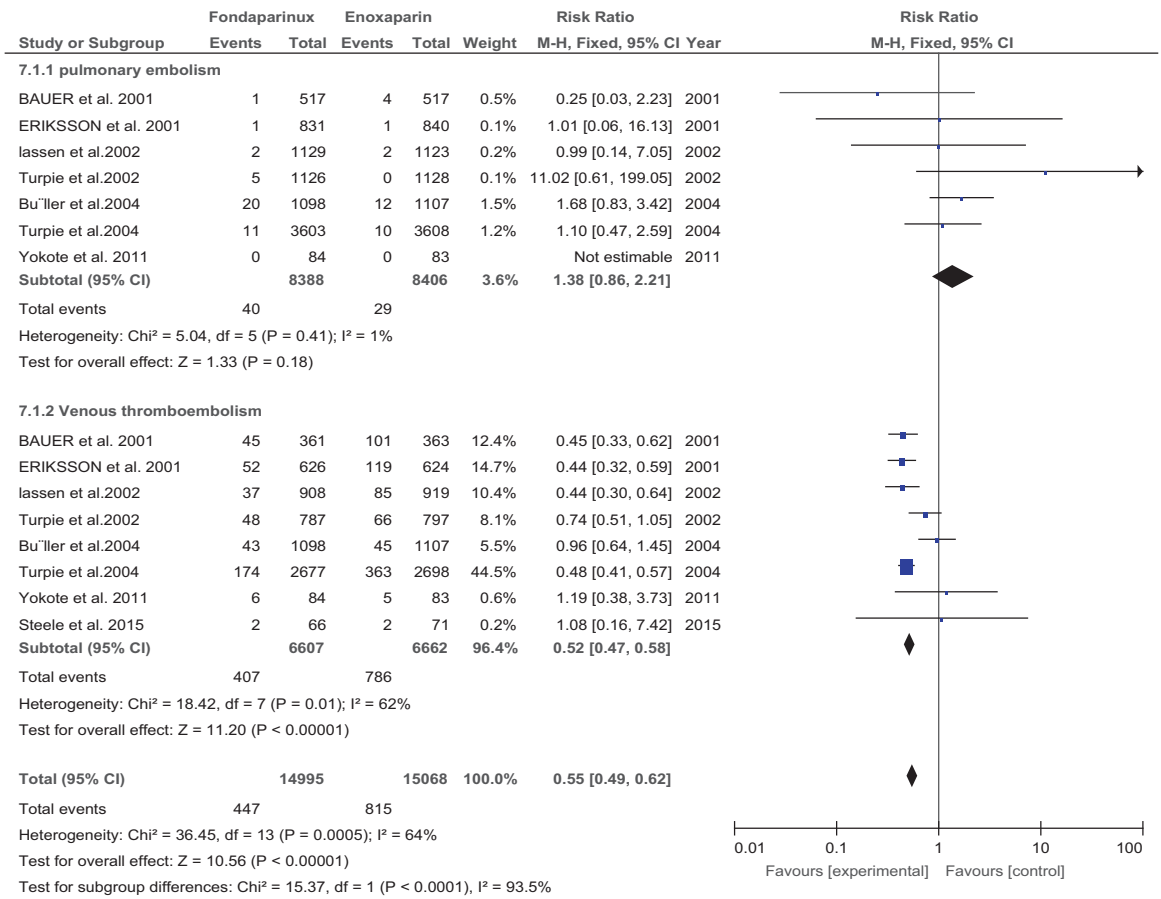

Figure 6. Incidence of venous thromboembolism and pulmonary embolism.

enoxaparin in the initial treatment of patients with symptomatic deep venous thrombosis.[48]

Our meta-analysis has some limitations. First, all trials were performed by drug sponsors that contributed to data collection and statistical analysis. Many studies did not provide the method of random sequence generation and details of blinding of participants and personnel. Second, potential sources of heterogeneity in study design preclude a firm conclusion on

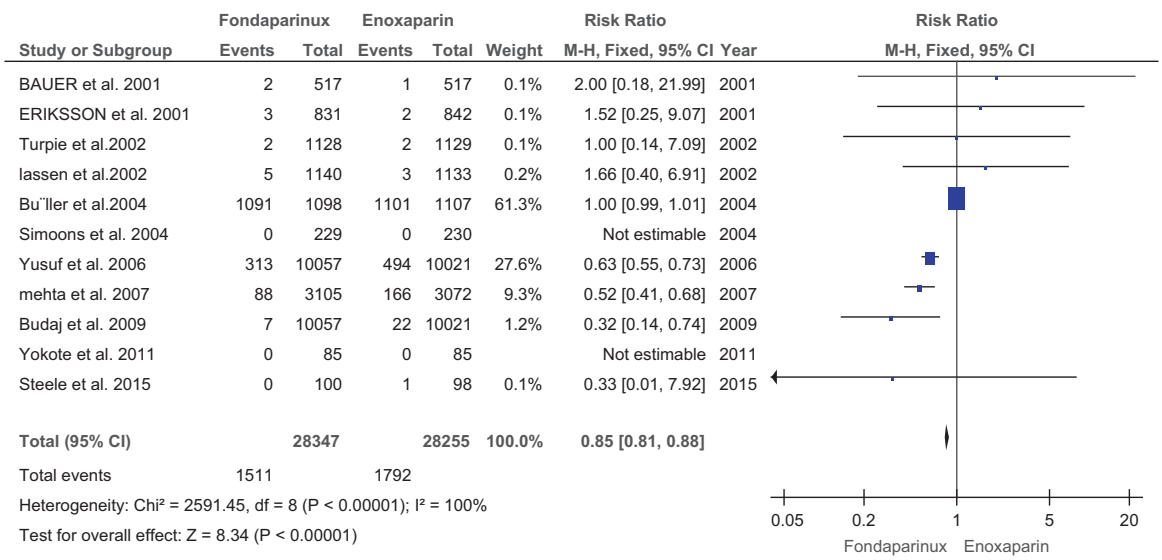

Figure 7. Incidence of bleeding.

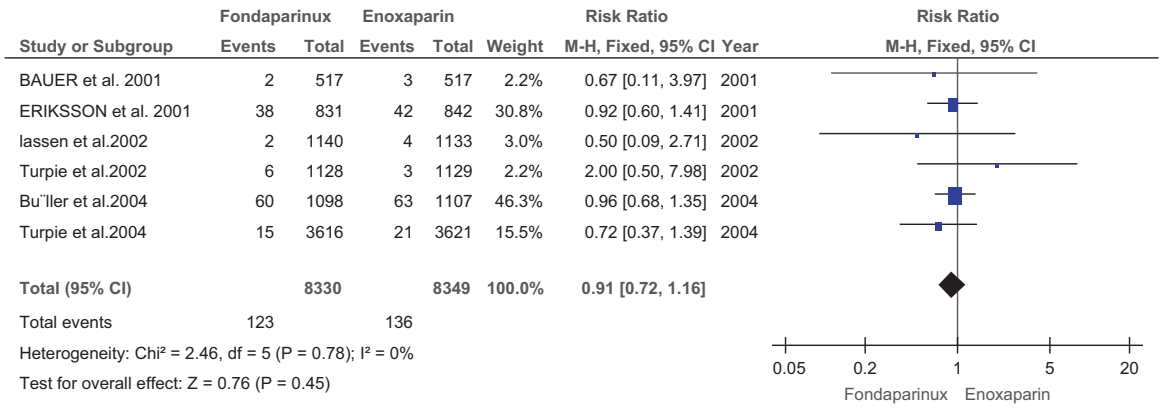

Figure 8. Incidence of Mortality.

Figure 9. Incidence of stroke.

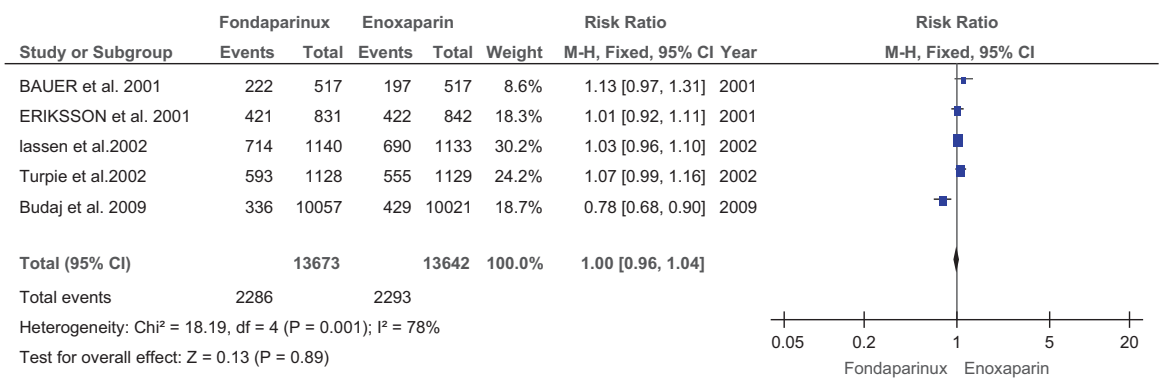

Figure 10. Incidence of transfusions.

our study. The timing of anticoagulant administration, definitions of primary efficacy outcomes, follow-up period, and use of compression stockings included and 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 can be a source of heterogeneity.

5. Conclusion

Fondaparinux was associated with noteworthy reduction in the incidence of bleeding time and the incidence of venous thromboembolism, however results showed that both anti-coagulants to have similar mortality and stroke rates and the same transfusion and pulmonary embolism rate.

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