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Safety comparisons among different subcutaneous anticoagulants for venous thromboembolism using FDA adverse event reporting system

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Venous thromboembolism (VTE) remains a significant global health burden, particularly in older adults. While fondaparinux sodium, enoxaparin sodium, and dalteparin sodium are commonly used anticoagulants, their safety profiles require further evaluation. This study analyzes their adverse drug events (ADEs) using data from the FDA Adverse Event Reporting System (FAERS). A retrospective pharmacovigilance study was conducted using FAERS data from Q1 2004 to Q2 2024. Reports identifying fondaparinux sodium, enoxaparin sodium, or dalteparin sodium as the primary suspect drug were extracted. ADEs were classified using MedDRA 23.0 at the System Organ Class (SOC) and Preferred Term (PT) levels. Disproportionality analysis was performed with Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS). FAERS contained 470 reports for fondaparinux sodium, 1,375 for enoxaparin sodium, and 344 for dalteparin sodium. Most cases involved patients aged ≥ 60, with a female predominance. Hospitalization was the most frequent outcome. Fondaparinux showed the strongest signals for intra-abdominal haematoma (ROR = 374.14, PRR = 371.14), muscle haemorrhage (ROR = 354.91, PRR = 347.04), and retroperitoneal haematoma (ROR = 214.97, PRR = 213.25). Enoxaparin demonstrated notable signals for heparin-induced thrombocytopenia (HIT) (ROR = 149.42, PRR = 147.53) and retroperitoneal haemorrhage (ROR = 287.68, PRR = 284.03). Dalteparin showed notable signals for HIT (ROR = 127.88, PRR = 126.49) and retroperitoneal haemorrhage (ROR = 103.23, PRR = 102.75). Distinct ADE profiles were identified among the three anticoagulants, underscoring the need for individualized risk assessment. These findings highlight the importance of close monitoring, particularly in high-risk patients, to optimize anticoagulation safety.

Keywords Venous thromboembolism (VTE), Adverse drug events (ADEs), Fondaparinux sodium, Enoxaparin sodium, Dalteparin sodium

With the aging population and changes in lifestyle and habits, thromboembolic diseases have increasingly become a major global health issue, ranking as the leading cause of mortality worldwide[1]. Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), is the third most common acute cardiovascular syndrome after myocardial infarction and stroke, with an estimated incidence rate of 1–2 cases per 1,000 person-years[2]. DVT is characterized by abnormal coagulation of blood within deep veins due to vascular endothelial injury, hypercoagulable states, and venous stasis, leading to venous outflow obstruction[3]. The lower extremities are the most commonly affected site, although DVT can also involve the upper extremities, cerebral venous sinuses, and intra-abdominal visceral veins. The clinical manifestations of DVT include localized redness, swelling, pain, and fever. In some cases, venous varicosities, pitting edema, and tenderness in the femoral triangle or calf muscles may also be observed[3]. PE is a pathophysiological syndrome primarily characterized by pulmonary circulatory obstruction caused by emboli occluding the pulmonary artery or its

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branches. These emboli can be composed of various substances, including thrombi, fat, air, and amniotic fluid. Among them, pulmonary thromboembolism (PTE) resulting from dislodged thrombi in the lower extremity deep veins is the most common, accounting for more than 90% of all PE cases[4,5]. Consequently, the term "PE" is often used interchangeably with "PTE." When PE occurs, pulmonary infarction may develop due to impaired blood supply to lung tissues. The primary clinical manifestations of PE include dyspnea, shortness of breath, tachypnea, and respiratory distress, with additional symptoms such as chest pain, hemoptysis, and syncope.

VTE is a disease influenced by genetic and environmental factors, as well as their interactions. Risk factors for VTE are broadly categorized into acquired and hereditary factors. Between one-half and two-thirds of VTE cases are triggered by sustained or strong acquired risk factors such as prolonged immobilization, trauma, surgery, cancer, or hospitalization within the past three months[6]. Among these, active cancer is the most common and persistent strong risk factor, accounting for approximately 20% of VTE events. Other acquired risk factors for VTE include advanced age, obesity, a personal or family history of thrombosis, the presence of a central venous catheter or implanted pacemaker, a prior history of VTE, infections, autoimmune diseases, hereditary or acquired thrombophilia, renal disease, neurological disorders causing lower limb immobility, sickle cell disease, and prolonged travel[7,8]. VTE poses risks not only due to its acute complications but also because it can lead to long-term chronic sequelae, such as pulmonary hypertension or recurrent thrombosis[9]. According to statistics, VTE causes millions of deaths worldwide each year[10]. Precise and effective therapeutic strategies are crucial for reducing VTE-related mortality. Anticoagulant therapy remains the primary intervention for VTE, and heparin-based drugs play a significant role in anticoagulation treatment. Low-molecular-weight heparin (LMWH) is the most commonly used anticoagulant, exerting its effect by binding to antithrombin and enhancing antithrombin's inhibition of thrombin activity, thereby achieving anticoagulation[11]. Current guidelines recommend a dosage of 1.0 mg/kg LMWH administered twice daily for the treatment of VTE[12]. However, the use of heparin is associated with certain limitations, including bleeding complications and heparin-induced thrombocytopenia (HIT)[13]. In recent years, factor Xa has been widely targeted in the development of safe and effective anticoagulant agents. Fondaparinux, an indirect factor Xa inhibitor, selectively and efficiently inhibits factor Xa without affecting thrombin activity, demonstrating a favorable safety profile with regard to bleeding risk[14]. Both LMWH and fondaparinux are administered via subcutaneous injection, ensuring effective anticoagulation while maintaining ease of use in clinical settings. Guidelines recommend the following fondaparinux dosages for VTE treatment: 5 mg subcutaneously once daily for patients weighing < 50 kg, 7.5 mg once daily for those weighing 50–100 kg, and 10 mg once daily for those weighing > 100 kg. Notably, fondaparinux currently lacks a specific reversal agent[15]. Compared with LMWH, each has its own advantages and disadvantages. Common LMWHs include enoxaparin, dalteparin, and nadroparin, and differences in therapeutic efficacy, safety profiles, and cost-effectiveness among different LMWHs and between LMWH and fondaparinux warrant further investigation[16].

The FDA Adverse Event Reporting System (FAERS) is a public database managed by the U.S. Food and Drug Administration (FDA) that collects and analyzes adverse event reports related to post-marketing drug use[17]. As nadroparin has not been approved for marketing, it is excluded from this study. Based on real-world data, this study compares the adverse event profiles of two LMWHs (enoxaparin and dalteparin) and fondaparinux in the treatment of VTE, aiming to provide clinical insights into drug safety and optimize individualized treatment strategies.

Materials and methods

Data source

A retrospective pharmacovigilance study was conducted using data extracted from the FAERS database, which is updated quarterly. FAERS is a publicly accessible resource that compiles adverse event reports from healthcare professionals, consumers, and other sources worldwide. This study systematically collected reports related to fondaparinux, enoxaparin, and dalteparin, along with their associated adverse reactions, from the first quarter of 2004 to the second quarter of 2024.All data used in this study were publicly obtained from the FAERS website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) in ASCII dataset format. The extracted data were subsequently processed and analyzed in-depth using FaersR (Version 2024.12).

Data extraction

The FAERS database and the adverse drug reaction (ADR) names involved in this study were coded according to the "Preferred Term" (PT) classification of the Medical Dictionary for Regulatory Activities (MedDRA). ADRs were further categorized based on the System Organ Class (SOC) classification in MedDRA 23.0. This study included reports in which fondaparinux, enoxaparin, or dalteparin were designated as the primary suspect drug (PSD) and utilized Microsoft Excel for data processing.To minimize indication bias (i.e., the misclassification of a drug's indication as an ADR), PTs associated with the indications for fondaparinux, enoxaparin, and dalteparin were excluded from the analysis. The study included parameters such as patient gender, age at ADR onset, body weight, report year, reporting country, reporter type, outcomes, route of administration, indications, and concomitant medications. Additionally, for the indication analysis, all indications relevant to VTE were selected, and the route of administration was restricted to subcutaneous injection and other specified methods.To reduce bias and ensure data reliability, we included only reports submitted by healthcare professionals (e.g., physicians, pharmacists, nurses), excluding those submitted by consumers or lawyers. Additionally, we excluded reports with missing demographic information, such as age, sex, or other critical variables, to ensure the completeness of the dataset.

Statistical analysis

This study employed a set of disproportional analysis techniques to thoroughly detect safety signals associated with heparins, including Reporting Odds Ratio (ROR)[18], Proportional Reporting Ratio (PRR)[19], Bayesian

Confidence Propagation Neural Network (BCPNN)[20], and Multi-item Gamma Poisson Shrinkage (MGPS)[21]. Each method has distinct advantages: ROR corrects for potential bias due to small case numbers, while PRR offers higher specificity compared to ROR. PRR is a measure commonly used in pharmacovigilance to identify potential signals of adverse drug reactions by comparing the frequency of a specific adverse event reported for a drug to the frequency of that event reported for all other drugs. BCPNN facilitates the integration of multi-source data through cross-validation, and MGPS excels at identifying signals for rare events. By combining these complementary methods, this study leveraged their collective strengths, reducing false positives through cross-validation, and identified a broader range of potential rare adverse reactions using threshold and variance adjustments.

A detailed summary of all algorithms, including specific formulas and thresholds, is provided in Supplementary Table S1 and Table S2. A higher metric value indicates a stronger signal, suggesting a stronger association between the drug and the adverse event. By systematically applying these algorithms to mine FAERS data, this study aims to detect clinical safety signals for heparins in a comprehensive and reliable manner. The use of multiple algorithms helps with cross-validation and enhances detection capacity.

Result

Descriptive analysis

From the first quarter of 2004 to the second quarter of 2024, the FAERS database collected a total of 20,862,854 adverse drug event (ADE) reports. Among these, 470 reports were associated with fondaparinux, 1375 with enoxaparin, and 344 with dalteparin (as shown in Fig. 1). Since their inclusion in 2004, the trends in ADE reports for fondaparinux, enoxaparin, and dalteparin have varied. The number of reports related to fondaparinux peaked in 2012 and has since declined annually. Enoxaparin-related reports increased until 2014, after which they showed a slight decline and then stabilized. In contrast, the number of reports for dalteparin exhibited minor fluctuations but remained relatively stable overall (Fig. 2).

Additionally, we compared other baseline characteristics of ADEs associated with the three anticoagulants (Table 1). Across all three drugs, the proportion of female patients was higher than that of male patients for fondaparinux and dalteparin, while enoxaparin had a slightly higher proportion of male patients. The majority of reported cases involved patients aged 60 years or older, particularly for fondaparinux (70.43%). The median age of patients varied across the three groups, with the highest median age observed in the fondaparinux group (71.00 years), followed by enoxaparin (65.00 years) and dalteparin (64.50 years). Regarding body weight, the median weight for fondaparinux was 72.79 kg (IQR: 63.13–90.00 kg), for enoxaparin was 82.00 kg (IQR: 68.00–99.25 kg), and for dalteparin was 73.40 kg (IQR: 62.00–91.65 kg). In terms of report sources, most ADE reports for fondaparinux originated from physicians (68.72%), whereas enoxaparin reports were predominantly submitted by pharmacists (51.56%), and dalteparin reports were more evenly distributed among physicians (34.01%), other health professionals (31.69%), and pharmacists (29.36%).

Table 2 presents the indications and concomitant medications associated with the three anticoagulants. All reports for fondaparinux, enoxaparin, and dalteparin were related to venous thromboembolism (100% in each group). In fondaparinux-related ADE reports, the most commonly reported concomitant medications were acetaminophen (10.85%), furosemide (8.30%), aspirin (7.02%), esomeprazole (5.74%), and omeprazole (5.11%). For enoxaparin, the most frequently reported concomitant medications were warfarin (5.45%), furosemide (5.45%), aspirin (5.31%), pantoprazole (4.72%), and omeprazole (2.91%). In dalteparin-related ADE reports, the most commonly reported concomitant medications were acetaminophen (17.15%), ondansetron (8.43%), omeprazole (7.85%), furosemide (6.4%), and amlodipine (3.78%).

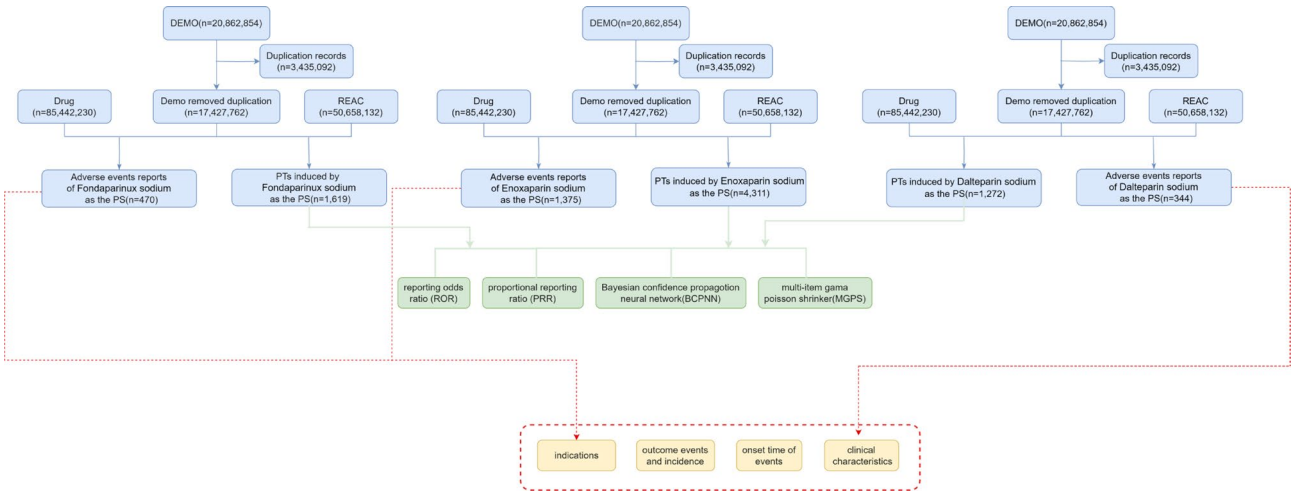

Fig. 1. The process of searching fondaparinux sodium, enoxaparin sodium, and dalteparin sodium-related adverse events from the food and drug administration adverse event reporting database (FAERS) (*DEMO* demographics, *REAC* reactions, *PT* Preferred term).

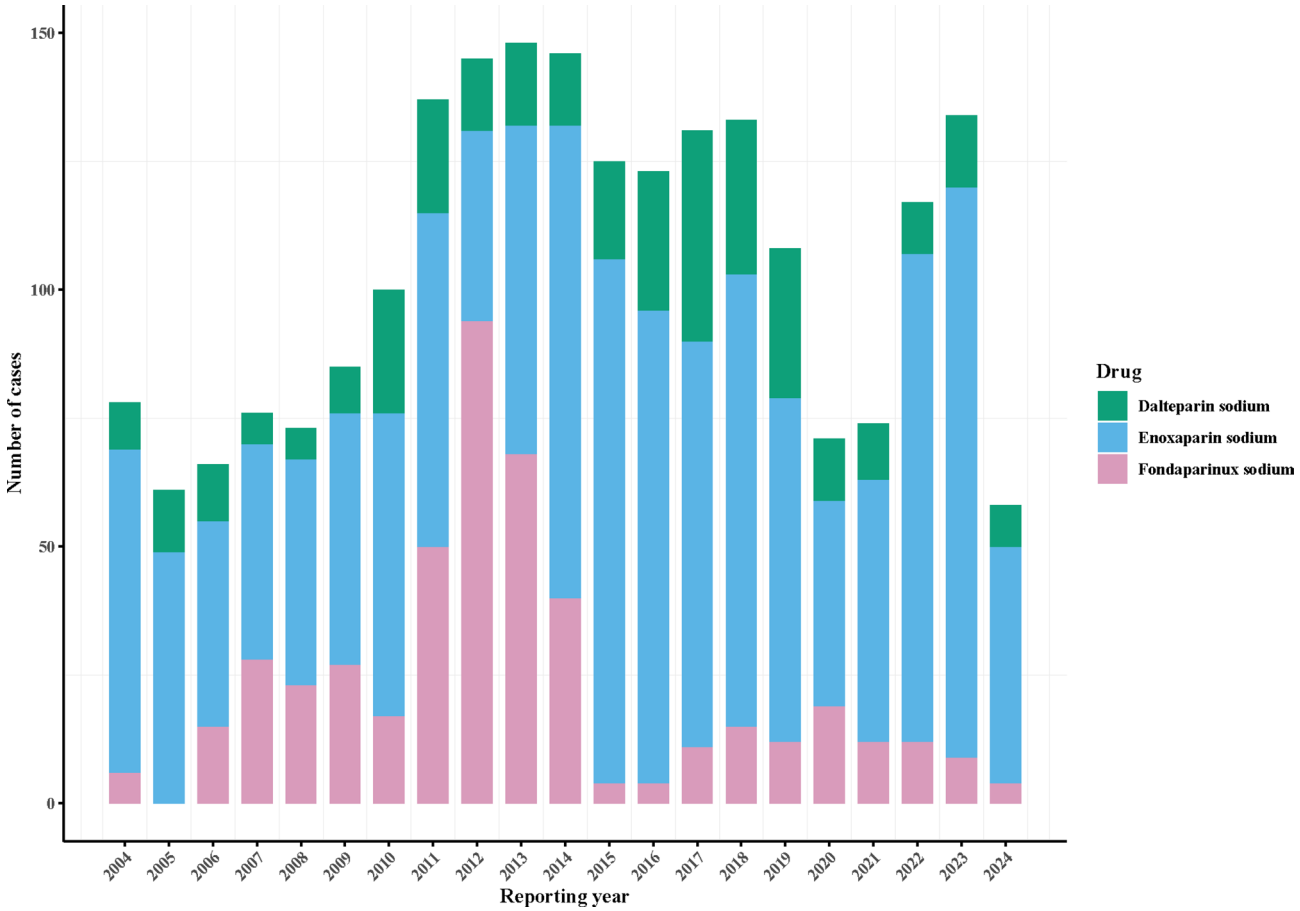

Fig. 2. The number of fondaparinux sodium, enoxaparin sodium, and dalteparin sodium-related ADEs reported yearly after 2004.

Disproportionality analysis

Signal detection at the SOC level

Figure 3 and Supplementary Table 3 present the adverse event (AE) signal detection results for the three anticoagulants in the FAERS database, identifying a total of 21 System Organ Classes (SOCs) associated with these drugs. Among these, vascular disorders and blood and lymphatic system disorders exhibited the strongest signal intensities across all three drugs. Vascular disorders had the highest ROR (Reporting Odds Ratio) values among the three drugs (fondaparinux: 6.83, enoxaparin: 6.02, dalteparin: 3.16), indicating a strong association between these drugs and vascular-related adverse events. This finding was supported by multiple statistical analyses. Similarly, blood and lymphatic system disorders also demonstrated significant signal intensities for all three drugs (fondaparinux: 4.54, enoxaparin: 4.19, dalteparin: 2.84), further highlighting the relevance of these adverse events to anticoagulant therapy.

Signal of preferred terms

At the Preferred Term (PT) level, our study systematically analyzed adverse event reports (AERs) using multiple algorithms and assessed their adherence to different screening criteria (see Supplementary Table S4). The analysis identified the top 20 PTs with the highest signal intensities (Tables 3, 4 and 5).

Bleeding was the most concerning safety signal among these anticoagulants. All three drugs exhibited a high risk of haemorrhage, with Reporting Odds Ratios (RORs) of 8.61 for fondaparinux, 16.06 for enoxaparin, and 5.32 for dalteparin. Additionally, fondaparinux showed significantly higher signals for haematoma (ROR = 106.88, PRR = 101.97) and hemorrhagic shock (ROR = 130.06, PRR = 127.83) compared to enoxaparin and dalteparin. By contrast, enoxaparin demonstrated a stronger signal for hypotension (ROR = 4.24, PRR = 4.2), while fondaparinux had a more pronounced signal for pallor (ROR = 16.60, PRR = 16.48). Enoxaparin and dalteparin exhibited stronger signals for thrombocytopenia and heparin-induced thrombocytopenia (HIT) compared to fondaparinux. However, fondaparinux showed a higher signal intensity for anemia (ROR = 14.64, PRR = 14).

In the gastrointestinal system, the risk patterns varied significantly among the three anticoagulants. Fondaparinux exhibited extremely high signal intensities for retroperitoneal hematoma (ROR = 214.97, PRR = 213.25) and intra-abdominal hematoma (ROR = 374.14, PRR = 371.14), while melena (ROR = 29, PRR = 28.69) and hematemesis (ROR = 16.97, PRR = 16.85) were also significantly more frequent with

Variable	Fondaparinux sodium (n, %) $N=470$	Enoxaparin sodium (n, %) $N=1375$	Dalteparin sodium (n, %) $N=344$
Age (median (Q1, Q3))	71.00(57.00,81.75)	65.00(53.00,74.00)	64.50(54.00,76.00)
Age			
< 18	4(0.85)	34(2.47)	5(1.45)
18 ~ 45	44(9.36)	191(13.89)	41(11.92)
45 ~ 60	91(19.36)	275(20.00)	83(24.13)
>=60	331(70.43)	875(63.64)	215(62.50)
Gender			
Female	269(57.23)	659(47.93)	184(53.49)
Male	201(42.77)	716(52.07)	160(46.51)
Weight (median (Q1, Q3))	72.79(63.13,90.00)	82.00(68.00,99.25)	73.40(62.00,91.65)
Reporter			
Physician	323(68.72)	301(21.89)	117(34.01)
Other health-professional	66(14.04)	261(18.98)	109(31.69)
Pharmacist	68(14.47)	709(51.56)	101(29.36)
Unknown	13(2.76)	104(7.56)	17(4.94)
Outcomes			
Hospitalization	331(51.88)	794(44.58)	194(40.42)
Death	77(12.07)	186(10.44)	89(18.54)
Life threatening	78(12.23)	167(9.38)	39(8.13)
Disability	18(2.82)	33(1.85)	10(2.08)
Required intervention to Prevent permanent impairment/damage	9(1.41)	101(5.67)	14(2.92)
Congenital anomaly	NA	5(0.28)	1(0.21)
Other serious	125(19.59)	495(27.79)	133(27.71)
Reported countries			
United States	41(8.72)	576(41.89)	71(20.64)
France	111(23.62)	140(10.18)	13(3.78)
Other	318(67.66)	659(47.93)	260(75.59)
Time to onset (median(Q1, Q3))	8.00(3.00,25.50)	7.00(3.00,16.00)	17.00(4.00,64.00)

Table 1. Clinical characteristics of reports with drugs from the FAERS database.

	Fondaparinux sodium	(*n*, %)	Enoxaparin sodium	(*n*, %)	Dalteparin sodium	(*n*, %)
Indication	Venous thromboembolism	470(100)	Venous thromboembolism	1375 (100)	Venous thromboembolism	344(100)
Concomitant medication	Acetaminophen	51(10.85)	warfarin	75 (5.45)	Acetaminophen	59(17.15)
	Furosemide	39(8.30)	Furosemide	75 (5.45)	Ondansetron	29(8.43)
	Aspirin	33(7.02)	Aspirin	73 (5.31)	Omeprazole	27(7.85)
	Esomeprazole	27(5.74)	Pantoprazole	65 (4.72)	Furosemide	22(6.4)
	Omeprazole	24(5.11)	Omeprazole	40 (2.91)	Amlodipine	13(3.78)

Table 2. Indications and top five concomitant drugs in ADE reports of drugs.

fondaparinux compared to enoxaparin and dalteparin. In contrast, enoxaparin displayed strong signals for retroperitoneal haemorrhage (ROR = 287.68, PRR = 284.03), with a high ROR value for abdominal wall hematoma (ROR = 268.65, PRR = 266.23). In the nervous system, all three drugs were associated with a certain degree of neurological bleeding risk. Fondaparinux had a higher signal intensity for cerebral haemorrhage (ROR = 25.49, PRR = 25.11) and was associated with coma, whereas dalteparin exhibited the strongest signal for haemorrhage intracranial (ROR = 25.68, PRR = 25.51).

In the respiratory, thoracic, and mediastinal system, dalteparin demonstrated a certain degree of specificity in respiratory system-related adverse events, with epistaxis showing the significant signal (ROR = 4.80, PRR = 4.77). In terms of laboratory abnormalities, all three anticoagulants exhibited a strong signal for decreased hemoglobin, suggesting a potential increased risk of anemia. The ROR values were 7.3 for fondaparinux, 11.27 for enoxaparin, and 8.72 for dalteparin. Regarding general disorders and administration site reactions, fondaparinux showed a notably high risk of subdural hematoma (ROR = 31.91, PRR = 31.66). Additionally, fondaparinux exhibited a signal for skin necrosis (ROR = 74.01, PRR = 73.51). Enoxaparin showed a higher risk of contusion (ROR = 4.66,

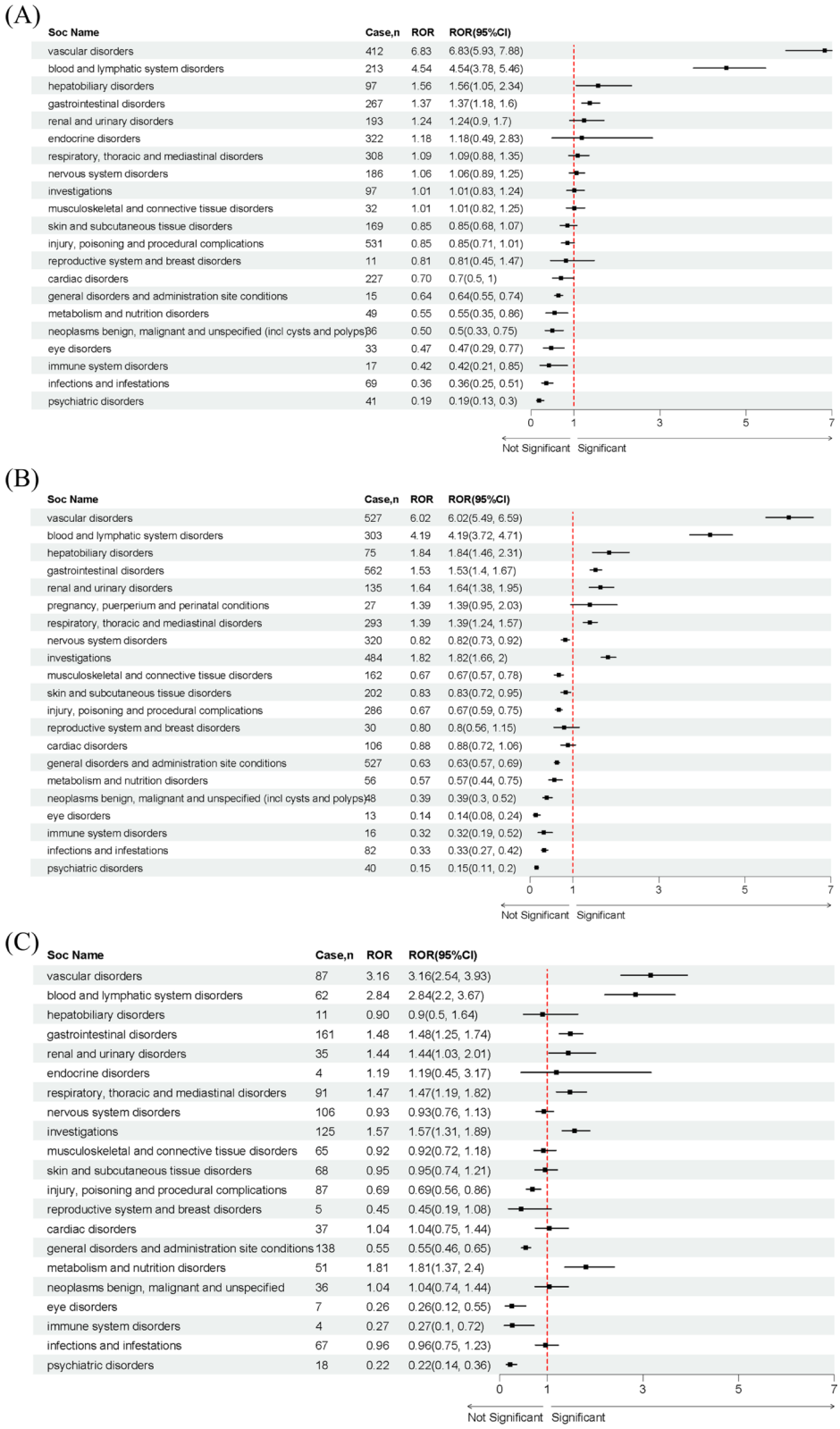

Fig. 3. SOC Signals for Drugs (**A**) Fondaparinux sodium (**B**) Enoxaparin sodium (**C**) Dalteparin sodium.

System organ class	PTs	Case reports	ROR(95% CI)	PRR(95% CI)	χ^2	IC(IC025)	EBGM(EBGM05)
Vascular disorders	Anaemia	76	14.64(11.62, 18.43)	14(11.28, 17.37)	919.76	3.81(3.48)	13.99(11.54)
Blood and lymphatic system disorders	Haematoma	75	106.88(84.73, 134.81)	101.97(82.19, 126.5)	7474.36	6.67(6.33)	101.6(83.66)
Musculoskeletal and connective tissue disorders	Muscle haemorrhage	36	354.91(254.54, 494.85)	347.04(248.7, 484.27)	12267.42	8.42(7.95)	342.72(259.51)
Vascular disorders	shock haemorrhagic	28	130.06(89.44, 189.15)	127.83(88.08, 185.51)	3507.7	6.99(6.46)	127.25(93.01)
Nervous system disorders	Cerebral haemorrhage	25	25.49(17.17, 37.85)	25.11(16.97, 37.16)	578.68	4.65(4.09)	25.09(18.03)
Gastrointestinal disorders	Abdominal pain	24	3.76(2.52, 5.63)	3.72(2.51, 5.51)	48.01	1.9(1.33)	3.72(2.66)
Vascular disorders	Haemorrhage	24	8.61(5.76, 12.89)	8.5(5.74, 12.58)	159.1	3.09(2.52)	8.5(6.07)
Investigations	Haemoglobin decreased	21	7.3(4.74, 11.22)	7.22(4.69, 11.11)	112.61	2.85(2.24)	7.21(5.03)
Gastrointestinal disorders	Melaena	18	29(18.22, 46.16)	28.69(18.28, 45.03)	480.67	4.84(4.19)	28.66(19.42)
General disorders and administration site conditions	Oedema peripheral	15	4.22(2.54, 7.01)	4.19(2.52, 6.97)	36.48	2.07(1.36)	4.19(2.74)
Gastrointestinal disorders	Gastrointestinal haemorrhage	13	5.52(3.2, 9.54)	5.49(3.17, 9.5)	47.77	2.46(1.7)	5.49(3.48)
Gastrointestinal disorders	Intra-abdominal haematoma	13	374.14(215.98, 648.12)	371.14(214.39, 642.51)	4735.07	8.52(7.75)	366.21(231.24)
Gastrointestinal disorders	Retroperitoneal haematoma	13	214.97(124.29, 371.82)	213.25(123.18, 369.17)	2725.3	7.73(6.96)	211.62(133.8)
Vascular disorders	Pallor	13	16.6(9.62, 28.66)	16.48(9.52, 28.53)	188.96	4.04(3.28)	16.47(10.43)
Injury, poisoning and procedural complications	Subdural haematoma	13	31.91(18.48, 55.09)	31.66(18.29, 54.81)	385.65	4.98(4.22)	31.62(20.03)
Blood and lymphatic system disorders	Thrombocytopenia	13	4.24(2.45, 7.31)	4.21(2.43, 7.29)	31.87	2.07(1.31)	4.21(2.67)
Gastrointestinal disorders	Haematemesis	12	16.97(9.61, 29.95)	16.85(9.54, 29.75)	178.87	4.07(3.29)	16.84(10.47)
Nervous system disorders	Coma	12	9.19(5.21, 16.22)	9.13(5.17, 16.12)	86.93	3.19(2.4)	9.13(5.68)
Gastrointestinal disorders	Abdominal wall haematoma	11	197.08(108.69, 357.33)	195.74(108.72, 352.41)	2116.25	7.6(6.78)	194.37(118.14)
Skin and subcutaneous tissue disorders	Skin necrosis	11	74.01(40.87, 134.01)	73.51(40.83, 132.35)	784.74	6.2(5.38)	73.32(44.61)

Table 3. The top 20 AEs signal strength of Fondaparinux sodium at the PTs level in FAERS database detected by four algorithms.

System organ class	PTs	Case reports	ROR(95% CI)	PRR(95% CI)	χ^2	IC(IC025)	EBGM(EBGM05)
Vascular disorders	Haematoma	133	68.92(57.97, 81.95)	66.83(56.02, 79.72)	8579.12	6.05(5.81)	66.45(57.49)
Vascular disorders	Haemorrhage	120	16.06(13.39, 19.25)	15.64(13.11, 18.66)	1644.79	3.97(3.7)	15.62(13.42)
Blood and lymphatic system disorders	Anaemia	98	6.9(5.65, 8.44)	6.77(5.57, 8.24)	483.23	2.76(2.47)	6.77(5.72)
Investigations	Haemoglobin decreased	87	11.27(9.12, 13.94)	11.07(8.92, 13.73)	797.32	3.47(3.16)	11.06(9.26)
Vascular disorders	Hypotension	63	4.24(3.31, 5.44)	4.2(3.26, 5.42)	153.79	2.07(1.71)	4.19(3.41)
Gastrointestinal disorders	Retroperitoneal haemorrhage	55	287.68(219.8, 376.53)	284.03(215.87, 373.71)	15146.23	8.12(7.73)	277.35(221.42)
Blood and lymphatic system disorders	Heparin-induced thrombocytopenia	55	149.42(114.33, 195.27)	147.53(114.35, 190.34)	7905.7	7.19(6.8)	145.71(116.47)
Blood and lymphatic system disorders	Thrombocytopenia	53	6.49(4.95, 8.51)	6.42(4.88, 8.45)	243.01	2.68(2.3)	6.42(5.12)
Gastrointestinal disorders	Abdominal pain	45	2.63(1.96, 3.52)	2.61(1.95, 3.5)	44.84	1.38(0.96)	2.61(2.04)
Vascular disorders	Shock haemorrhagic	41	71.4(52.45, 97.2)	70.73(51.69, 96.78)	2802.1	6.14(5.7)	70.31(54.32)
Gastrointestinal disorders	Abdominal wall haematoma	39	268.65(195.32, 369.53)	266.23(194.56, 364.29)	10077.24	8.02(7.57)	260.36(199.4)
Investigations	International normalised ratio increased	38	16.35(11.88, 22.51)	16.22(11.85, 22.19)	542.16	4.02(3.56)	16.2(12.4)
Gastrointestinal disorders	Gastrointestinal haemorrhage	37	5.64(4.08, 7.79)	5.6(4.09, 7.66)	139.8	2.48(2.02)	5.59(4.27)
Gastrointestinal disorders	Retroperitoneal haematoma	37	227.05(163.78, 314.77)	225.11(161.32, 314.12)	8100.4	7.79(7.32)	220.9(168.07)
Renal and urinary disorders	Haematuria	36	13.71(9.88, 19.04)	13.61(9.75, 18.99)	420.33	3.76(3.3)	13.59(10.33)
Musculoskeletal and connective tissue disorders	Muscle haemorrhage	35	122.14(87.43, 170.63)	121.15(86.82, 169.06)	4128.36	6.91(6.43)	119.93(90.66)
Investigations	Haematocrit decreased	34	21.69(15.47, 30.41)	21.53(15.43, 30.04)	664.55	4.43(3.95)	21.49(16.2)
Injury, poisoning and procedural complications	Contusion	33	4.66(3.31, 6.57)	4.64(3.33, 6.47)	94.21	2.21(1.73)	4.63(3.48)
Gastrointestinal disorders	Gastric haemorrhage	31	34.26(24.05, 48.8)	34.02(23.91, 48.41)	990.82	5.08(4.58)	33.92(25.23)
Cardiac disorders	Tachycardia	29	4.39(3.05, 6.33)	4.37(3.01, 6.34)	75.51	2.13(1.61)	4.37(3.22)

Table 4. The top 20 AEs signal strength of Enoxaparin sodium at the PTs level in FAERS database detected by four algorithms.

System organ class	PTs	Case reports	ROR(95% CI)	PRR(95% CI)	χ^2	IC(IC025)	EBGM(EBGM05)
Investigations	Haemoglobin decreased	20	8.72(5.61, 13.56)	8.6(5.59, 13.24)	134.49	3.1(2.48)	8.6(5.94)
Blood and lymphatic system disorders	Anaemia	16	3.76(2.3, 6.16)	3.73(2.29, 6.09)	32.05	1.9(1.21)	3.73(2.47)
Nervous system disorders	Cerebral haemorrhage	16	20.2(12.34, 33.08)	19.96(12.23, 32.58)	288.18	4.32(3.63)	19.95(13.2)
Blood and lymphatic system disorders	Heparin-induced thrombocytopenia	14	127.88(75.45, 216.74)	126.49(74.51, 214.73)	1737.39	6.98(6.24)	126.08(81.08)
Vascular disorders	Haematoma	14	23.9(14.11, 40.47)	23.64(13.93, 40.13)	303.57	4.56(3.83)	23.63(15.21)
Blood and lymphatic system disorders	Thrombocytopenia	12	4.97(2.82, 8.78)	4.93(2.79, 8.7)	37.7	2.3(1.51)	4.93(3.07)
Vascular disorders	Haemorrhage	12	5.32(3.01, 9.39)	5.28(2.99, 9.32)	41.67	2.4(1.61)	5.28(3.28)
Investigations	International normalised ratio increased	11	15.9(8.78, 28.79)	15.77(8.76, 28.39)	152.2	3.98(3.16)	15.76(9.59)
Gastrointestinal disorders	Gastrointestinal haemorrhage	11	5.6(3.1, 10.15)	5.56(3.09, 10.01)	41.24	2.48(1.66)	5.56(3.39)
Metabolism and nutrition disorders	Dehydration	11	3.7(2.05, 6.71)	3.68(2.04, 6.63)	21.52	1.88(1.06)	3.68(2.24)
Injury, poisoning and procedural complications	Contusion	10	4.78(2.56, 8.9)	4.75(2.54, 8.89)	29.62	2.25(1.39)	4.75(2.82)
Nervous system disorders	Haemorrhage intracranial	9	25.68(13.33, 49.48)	25.51(13.36, 48.71)	211.84	4.67(3.77)	25.49(14.72)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	9	6.6(3.43, 12.72)	6.56(3.44, 12.53)	42.46	2.71(1.82)	6.56(3.79)
Respiratory, thoracic and mediastinal disorders	Epistaxis	8	4.8(2.39, 9.61)	4.77(2.4, 9.47)	23.89	2.25(1.31)	4.77(2.67)
Musculoskeletal and connective tissue disorders	Muscle haemorrhage	7	81.86(38.91, 172.19)	81.41(38.66, 171.45)	554.84	6.34(5.34)	81.24(43.61)
Metabolism and nutrition disorders	Hyponatraemia	7	5.59(2.66, 11.75)	5.57(2.64, 11.73)	26.24	2.48(1.47)	5.56(2.99)
General disorders and administration site conditions	Injection site haemorrhage	7	4.13(1.97, 8.69)	4.12(1.96, 8.68)	16.53	2.04(1.04)	4.12(2.21)
Gastrointestinal disorders	Retroperitoneal haemorrhage	6	103.23(46.24, 230.46)	102.75(46, 229.5)	602.98	6.68(5.61)	102.48(52.34)
Infections and infestations	Cellulitis	6	5.26(2.36, 11.72)	5.24(2.35, 11.7)	20.58	2.39(1.32)	5.24(2.68)

Table 5. The top 20 AEs signal strength of Dalteparin sodium at the PTs level in FAERS database detected by four algorithms.

PRR = 4.64), while dalteparin demonstrated a stronger signal for injection site hemorrhage (ROR = 4.13, PRR = 4.12).

Comparison of safety signals across nine SOCs

We compared the adverse event (ADE) signals across nine different System Organ Classes (SOCs) and found that the three anticoagulants (fondaparinux, enoxaparin, and dalteparin) exhibited distinct signal characteristics in different SOC categories (Fig. 4).

In the vascular disorders category, fondaparinux showed the strongest signals for hematoma and hemorrhagic shock, with ROR values significantly higher than those of the other anticoagulants. Additionally, these signals were associated with extremely high chi-square values, suggesting a potential risk of bleeding-related adverse events. In the blood and lymphatic system disorders category, heparin-induced thrombocytopenia (HIT) was the strongest signal for both enoxaparin and dalteparin, demonstrating high statistical significance and indicating a strong association between these drugs and HIT occurrence. In the gastrointestinal disorders category, enoxaparin and fondaparinux exhibited strong ADE signals, particularly for retroperitoneal hemorrhage and abdominal wall hematoma, with high ROR values, suggesting a potential risk of gastrointestinal bleeding-related events. In the musculoskeletal and connective tissue disorders category, fondaparinux demonstrated a significantly stronger signal for muscular hemorrhage than enoxaparin and dalteparin, suggesting a higher likelihood of muscle-related bleeding events with this drug. In the investigations category, enoxaparin showed the strongest signal for decreased hemoglobin, with a higher ROR than the other two anticoagulants, indicating a possible increased risk of anemia. In the nervous system disorders category, all three drugs exhibited strong signals for intracranial hemorrhage, with fondaparinux showing the highest ROR, followed closely by dalteparin and enoxaparin, suggesting a higher impact on central nervous system bleeding with these drugs. In the injury, poisoning, and procedural complications and general disorders and administration site conditions categories, all three anticoagulants exhibited strong signals for injection site injuries, highlighting the need for careful monitoring of local administration-related adverse reactions. In the renal and urinary disorders category, enoxaparin demonstrated the strongest signal for hematuria.

Overall, the three anticoagulants displayed distinct ADE signal characteristics across multiple SOC categories. Fondaparinux was notably associated with hematoma, muscular hemorrhage, and intracranial hemorrhage, enoxaparin exhibited higher risks for HIT, decreased hemoglobin, and hematuria, while dalteparin showed strong signals for HIT. These findings highlight the importance of individualized drug selection based on patient-specific risk factors and underscore the need for enhanced monitoring of specific ADE signals in clinical practice.

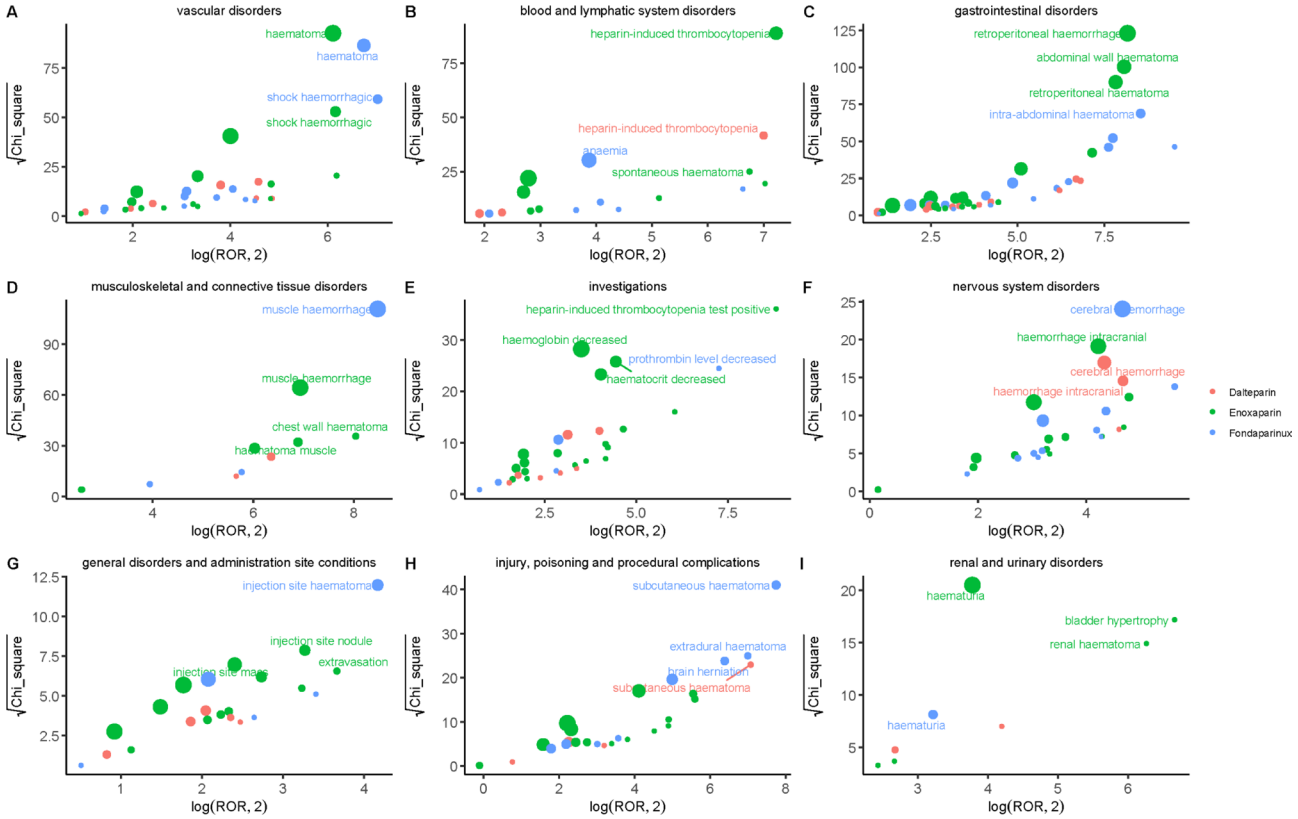

Fig. 4. Comparison of safety signals across nine SOCs for fondaparinux sodium, enoxaparin sodium, and dalteparin sodium (The x-axis represents log2ROR, and the y-axis represents the square root of the χ2 value. In this graph, each point indicates a mined AE signal, with the size of the point corresponding to the quantity of reported AEs. The location of each AE in the graph is determined by the ROR (Reporting Odds Ratio) and PRR (Proportional Reporting Ratio) methods. If a point is located higher and further to the right in the graph, both algorithms suggest that the signal for that AE is strong).

Discussion

Treating VTE presents multiple challenges, particularly when it comes to balancing drug efficacy against adverse reactions in clinical management. Subcutaneous anticoagulants have proven both highly effective and stable in treating VTE[22]. Despite their proven efficacy in VTE treatment, the potential adverse reactions associated with their use remain a significant concern in clinical practice. Therefore, a thorough investigation of the adverse reactions and safety of subcutaneous anticoagulant drugs is essential to ensure their maximum benefit in clinical use. This is especially important given that their safety in real-world settings may differ from the results of clinical trials, underscoring the urgent need for further systematic evaluation.In this study, an in-depth analysis of clinical adverse events associated with fondaparinux sodium, enoxaparin sodium, and dalteparin sodium was conducted using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database. The results indicate that continued pharmacovigilance is crucial. This importance is underscored by the widespread use of these three drugs and the potential underreporting of adverse events in clinical trials[23].

Basic information

In this study, we conducted a comprehensive comparative analysis of adverse event (AE) reports for fondaparinux, enoxaparin, and dalteparin in the FAERS database. In terms of age distribution, the average age of patients receiving fondaparinux was 71 years, whereas the average ages of patients using enoxaparin and dalteparin were 65 years and 64.5 years, respectively. This suggests that fondaparinux may be more commonly used in older patients. Furthermore, the efficacy of fondaparinux in preventing VTE in elderly patients with acute illness has been validated in the ARTEMIS trial, in which more than 50% of participants were aged ≥ 75 years. These findings further support the extensive clinical use of fondaparinux in elderly patients[24]. Regarding gender distribution, the proportion of female patients was higher than that of male patients across all three drugs. This may be related to the higher safety profile of these drugs in preventing thrombosis during pregnancy[23,25]. For clinical outcomes, fondaparinux had the highest hospitalization rate (51.88%), compared to 44.58% for enoxaparin and 40.42% for dalteparin. However, the proportion of other serious adverse events was higher for enoxaparin (27.79%) and dalteparin (27.71%). In terms of route of administration, all three drugs were primarily administered via subcutaneous injection. Regarding geographical distribution, most AE reports related to enoxaparin originated

from the United States, whereas reports for fondaparinux and dalteparin were predominantly from other countries, indicating potential geographical bias.

SOC analysis

SOC analysis revealed safety signals for fondaparinux, enoxaparin, and dalteparin across multiple physiological systems. Our findings indicated significant signals in vascular disorders and blood and lymphatic system disorders. Fondaparinux had the highest reporting proportion for vascular disorders, with an ROR of 6.83 (95% CI: 5.93, 7.88), while the RORs for enoxaparin and dalteparin were 6.02 and 3.16, respectively, indicating a potential impact of these drugs on the vascular system, consistent with previous findings[26,27].

Additionally, strong signals were also observed in blood and lymphatic system disorders across all three drugs. The ROR for fondaparinux was 4.54 (95% CI: 3.78, 5.46), while enoxaparin and dalteparin had RORs of 4.19 (95% CI: 3.72, 4.71) and 2.84 (95% CI: 2.2, 3.67), respectively, highlighting the need for careful monitoring of hematological and lymphatic changes when using these anticoagulants[28].

PT analysis

In this study, we analyzed the adverse reactions associated with fondaparinux, enoxaparin, and dalteparin.In the vascular disorders category, fondaparinux was primarily associated with a high incidence of hematoma and hemorrhagic shock. The number of fondaparinux-related hematoma cases was 75, with an ROR of 106.88, significantly higher than that of low-molecular-weight heparins (LMWHs). This difference may be attributed to fondaparinux's longer half-life and the absence of a reversal agent, making it more difficult to control bleeding complications, which further increases the risk of severe hemorrhagic events, such as hemorrhagic shock. Therefore, fondaparinux is not recommended for patients at high risk of bleeding[29]. The risk of hematoma associated with LMWHs was significantly lower than that of fondaparinux, possibly due to the fact that protamine sulfate can partially reverse the anticoagulant effect of unfractionated heparin (UFH). However, some studies have shown that the use of protamine sulfate may lead to life-threatening adverse effects, such as systemic hypotension[30], which aligns with our findings. LMWHs were associated with a higher incidence of bleeding and hemorrhagic shock in the vascular system. Although LMWHs can partially inhibit coagulation factors Xa and IIa, resulting in a mild and sustained anticoagulant effect, they are typically used as bridge therapy in long-term anticoagulation regimens and have a shorter duration of use, making them relatively safer[29,31].

Regarding bleeding events, our study found that all three anticoagulants were strongly associated with severe bleeding complications. In the gastrointestinal system, enoxaparin exhibited the strongest signal, particularly for retroperitoneal hematoma and abdominal wall hematoma. Notably, fondaparinux had a significantly stronger signal for muscular hemorrhage than enoxaparin and dalteparin, with higher frequency and severity. For nervous system adverse events, fondaparinux exhibited a strong signal, possibly associated with intracranial hemorrhage, suggesting that patients at high risk for intracranial bleeding should be closely monitored. In the renal and urinary disorders category, enoxaparin demonstrated the strongest signal for hematuria. In the injury, poisoning, and procedural complications and general disorders and administration site conditions categories, all three anticoagulants exhibited strong signals for injection site injuries, suggesting the need for careful monitoring of local adverse reactions during administration.

Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated adverse reaction associated with heparin-based drugs. It is characterized by the formation of platelet factor 4 (PF4)-heparin complexes, which stimulate an immune response, leading to the release of anti-PF4-H antibodies (HIT antibodies). These antibodies can persist in circulation for 50–90 days, causing platelet destruction and endothelial damage, with clinical manifestations including thrombocytopenia and thromboembolism[32]. HIT is classified into Type I and Type II. Type I is a mild, early-onset thrombocytopenia that does not cause thromboembolism, whereas Type II is an immune-mediated severe condition that can lead to both thrombocytopenia and thrombosis[33]. Our study found significant differences in HIT risk among the three anticoagulants. Fondaparinux did not show a significant HIT signal, which may be due to its low binding affinity to PF4, resulting in a lower potential for immune system activation and a relatively favorable safety profile. In contrast, LMWHs demonstrated a higher HIT risk, as their stronger binding affinity to PF4 increases immune activation, thereby raising the likelihood of HIT[34]. As a result, fondaparinux may be a preferred option for patients with HIT, particularly those requiring long-term anticoagulation therapy. Notably, all three anticoagulants exhibited strong signals for decreased hemoglobin, emphasizing the need for regular hematological monitoring during clinical use.

Limitations

This study has several limitations. The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a database used for collecting and analyzing reports on adverse events related to drugs and medical devices. However, FAERS has inherent limitations, including reporting biases and structural biases within the database. Issues such as population bias, underreporting, incomplete information, and the lack of adverse event severity grading may affect the reliability of the findings. Additionally, the disproportionality analysis (DPA) method was primarily used in this study. DPA is a statistical approach for detecting drug-adverse event associations within pharmacovigilance databases, but its results can only reflect statistical associations rather than establish causal relationships. For instance, while an adverse event occurring after drug administration may suggest a potential association, DPA does not provide information on causality. Furthermore, the study faced challenges in obtaining and categorizing consistent drug usage data, as the information regarding frequency of use (prescriptions, etc.) was partially missing and varied in description. This limitation makes it difficult to draw definitive conclusions about the relationship between drug use frequency and the occurrence of adverse events. Future studies will aim to incorporate more detailed drug usage data.

Our findings should also be interpreted within the context of pharmacovigilance data rather than as absolute incidence rates of ADEs. While the total number of ADE reports may not fully reflect real-world event rates, this study provides a unique comparative perspective on the safety profiles of three commonly used subcutaneous anticoagulants (fondaparinux, enoxaparin, and dalteparin), which has been less explored in previous research. Therefore, given these limitations and potential biases, results should be interpreted with caution, and further clinical studies are needed to validate these associations.

Conclusion

This study, based on the FAERS database, analyzed adverse event (ADE) reports associated with fondaparinux, enoxaparin, and dalteparin from the first quarter of 2004 to the second quarter of 2024. The analysis indicated that ADE reports for all three drugs were predominantly concentrated in patients aged 60 years and older, with a higher proportion of female patients. The median body weight of patients varied across the three drugs. Reports related to fondaparinux were mostly submitted by healthcare professionals, similar to those for enoxaparin and dalteparin. Hospitalization was among the most frequently reported ADE outcomes, and death was also reported in a portion of severe cases. Signal detection analyses suggested that all three anticoagulants exhibited potential safety signals across several System Organ Classes (SOCs), particularly within the vascular, blood and lymphatic, gastrointestinal, nervous, and renal and urinary systems. At the Preferred Term (PT) level, fondaparinux appeared to be associated with higher reporting frequencies for events such as hematoma, hemorrhagic shock, muscular hemorrhage, and certain gastrointestinal bleeding events. Enoxaparin showed stronger signals for heparin-induced thrombocytopenia (HIT), decreased hemoglobin, and hematuria, while dalteparin exhibited relatively higher signals for HIT. In terms of nervous system-related ADEs, all three drugs demonstrated signals suggestive of bleeding-related risks. Fondaparinux was more frequently associated with reports of cerebral hemorrhage and coma, whereas enoxaparin and dalteparin were more commonly linked to reports of intracranial hemorrhage.

Overall, these findings provide insights into the differential safety signal profiles of these anticoagulants. However, given the limitations of spontaneous reporting data, such as underreporting and potential confounding, these results should be interpreted with caution. Further clinical studies are needed to confirm these associations. Clinicians should consider patient-specific risk factors and remain vigilant regarding the ADE profiles of each drug during treatment.

Data availability

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

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References

1. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396** (10258), 1204–1222 (2020).
2. Wolberg, A. S. et al. Venous thrombosis. *Nat Rev Dis Primers*. **1**, 15006 (2015).
3. Stone, J. et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. *Cardiovasc. Diagn. Ther.* **7** (Suppl 3), S276–s284 (2017).
4. Nagamalesh, U. M. et al. Acute pulmonary thromboembolism: epidemiology, predictors, and long-term outcome - A single center experience. *Indian Heart J.* **69** (2), 160–164 (2017).
5. Zhang, Z. et al. Diabetes mellitus is associated with increased bleeding in pulmonary embolism receiving conventional anticoagulant therapy: findings from a real-world study. *J. Thromb. Thrombolysis*. **43** (4), 540–549 (2017).
6. Ay, C., Pabinger, I. & Cohen, A. T. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb. Haemost*. **117** (2), 219–230 (2017).
7. Lutsey, P. L. et al. Atrial fibrillation and venous thromboembolism: evidence of bidirectionality in the atherosclerosis risk in communities study. *J. Thromb. Haemost*. **16** (4), 670–679 (2018).
8. Goldhaber, S. Z. et al. Profile of patients diagnosed with acute venous thromboembolism in routine clinical practice: the RE-COVERY DVT/PE™ study. *Am. J. Med.* **133** (8), 936–945 (2020).
9. Robert-Ebadi, H. & Righini, M. The 2019 ESC guidelines on pulmonary embolism: some further insights. *Eur. J. Intern. Med.* **77**, 6–8 (2020).
10. Raskob, G. E. et al. Thrombosis: a major contributor to global disease burden. *Arterioscler. Thromb. Vasc Biol.* **34** (11), 2363–2371 (2014).
11. Hirsh, J. et al. Heparin and low-molecular-weight Heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* **119** (1 Suppl), 64s–94s (2001).
12. Kakkos, S. K. et al. Choice - European society for vascular surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. *Eur. J. Vasc. Endovasc. Surg.* **61** (1), 9–82. (2021).
13. Hogan, M. & Berger, J. S. Heparin-induced thrombocytopenia (HIT): review of incidence, diagnosis, and management. *Vasc Med.* **25** (2), 160–173 (2020).
14. Bauersachs, R. M. Fondaparinux sodium: recent advances in the management of thrombosis. *J. Cardiovasc. Pharmacol. Ther.* **28**, 10742484221145010 (2023).
15. Yin, Q. et al. Unlocking the potential of Fondaparinux: guideline for optimal usage and clinical suggestions (2023). *Front. Pharmacol.* **15**, 1352982 (2024).
16. Lassen, M. R., Bauer, K. A., Eriksson, B. I. & Turpie, A. G. Postoperative Fondaparinux versus preoperative Enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* **359** (9319), 1715–1720 (2002).
17. Hoffman, K. B., Dimbil, M., Tatonetti, N. P. & Kyle, R. F. A pharmacovigilance signaling system based on FDA regulatory action and Post-Marketing adverse event reports. *Drug Saf.* **39** (6), 561–575 (2016).
18. Rothman, K. J., Lanes, S. & Sacks, S. T. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf.* **13** (8), 519–523 (2004).

19. Evans, S. J., Waller, P. C. & Davis, S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* **10** (6), 483–486 (2001).
20. Bate, A. et al. A bayesian neural network method for adverse drug reaction signal generation. *Eur. J. Clin. Pharmacol.* **54** (4), 315–321 (1998).
21. Chen, M., Huang, Y., Ke, C. & Chen, M. Safety assessment of Tafamidis: a real-world adverse event analysis from the FAERS database. *Expert Opin. Drug Saf.* 1–9. (2024).
22. Kearon, C. et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians Evidence-Based clinical practice guidelines. *Chest* **141** (2 Suppl), e419S–e496S (2012).
23. Deruelle, P. & Coulon, C. The use of low-molecular-weight heparins in pregnancy–how safe are they? *Curr. Opin. Obstet. Gynecol.* **19** (6), 573–577 (2007).
24. Bauersachs, R. M. Use of anticoagulants in elderly patients. *Thromb. Res.* **129** (2), 107–115 (2012).
25. Muhamad, N. et al. Safety and effectiveness of Fondaparinux as a postpartum thromboprophylaxis during puerperium among Muslim women: A single centre prospective study. *Front. Pharmacol.* **13**, 887020 (2022).
26. Van Matre, E. T. et al. Evaluation of unfractionated heparin versus low-molecular-weight heparin and Fondaparinux for Pharmacologic venous thromboembolic prophylaxis in critically ill patients with cancer. *J. Thromb. Haemost.* **16** (12), 2492–2500 (2018).
27. Dinwoodey, D. L. & Ansell, J. E. Heparins, low-molecular-weight heparins, and pentasaccharides. *Clin. Geriatr. Med.* **22** (1), 1–15 (2006). vii.
28. Prince, M. & Wenham, T. Heparin-induced thrombocytopaenia. *Postgrad. Med. J.* **94** (1114), 453–457 (2018).
29. Frontera, J. A. et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: A statement for healthcare professionals from the neurocritical care society and society of critical care medicine. *Neurocrit Care.* **24** (1), 6–46 (2016).
30. Sokolowska, E., Kalaska, B., Miklosz, J. & Mogielnicki, A. The toxicology of heparin reversal with Protamine: past, present and future. *Expert Opin. Drug Metab. Toxicol.* **12** (8), 897–909 (2016).
31. Frydman, A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. *Haemostasis* **26** (Suppl 2), 24–38 (1996).
32. Marchetti, M., Zermatten, M. G., Bertaggia Calderara, D., Aliotta, A. & Alberio, L. Heparin-Induced thrombocytopenia: A review of new concepts in pathogenesis, diagnosis, and management. *J. Clin. Med.* **10** (4). (2021).
33. Arepally, G. M. & Padmanabhan, A. Heparin-Induced thrombocytopenia: A focus on thrombosis. *Arterioscler. Thromb. Vasc Biol.* **41** (1), 141–152 (2021).
34. Malik, J., Javed, N. & Kamin, M. Fondaparinux-associated thrombocytopenia. *Pak J. Med. Sci.* **37** (2), 598–599 (2021).

Author contributions

All authors made a significant contribution to the work reported and agreed to be accountable for all aspects of the work. B.-w.L. and J.-c.L. designed the work. G.L., D.L., Y.-q.G. and M.-t.W. performed the study. B.-w.L., and J.-c.L. prepared the initial draft of the manuscript. D.L., and G.L. reviewed the manuscript critically for important intellectual content during the submission of the manuscript. G.L. agreed final approval of the version to be published and to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had given final approval of the version to be submitted and agreed on the journal to be published.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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