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The efficacy of various Enoxaparin dosing regimens in general surgery patients: A systematic review

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ABSTRACT

Background: Patients undergoing surgical procedures are at an increased risk of venous thromboembolism events. A fixed Enoxaparin dosing regimen is the standard of care for chemoprophylaxis in most institutions; however, breakthrough venous thromboembolism events are still reported. We aimed to systematically review the literature to determine the ability of various Enoxaparin dosing regimens to achieve adequate prophylactic anti-Xa levels for venous thromboembolism prevention in hospitalized general surgery patients. Additionally, we aimed to assess the correlation between subprophylactic anti-Xa levels and the development of clinically significant venous thromboembolism events.

Methods: A systematic review was conducted using major databases from January 1, 1993, to February 17, 2023. Two independent researchers screened titles and abstracts, followed by a full-text review. Articles were included if Enoxaparin dosing regimens were evaluated by anti-Xa levels. Exclusion criteria included systematic reviews, pediatric population, nongeneral surgery (defined as trauma, orthopedics, plastics, and neurosurgery), and non-Enoxaparin chemoprophylaxis. The primary outcome was peak Anti-Xa level measured at steady state concentration. The risk of bias was assessed using the Risk of Bias in Nonrandomized studies-of Intervention tool.

Results: A total of 6,760 articles were extracted, of which 19 were included in the scoping review. Nine studies included bariatric patients, whereas 5 studies explored abdominal surgical oncology patients. Three studies assessed thoracic surgery patients, and 2 studies included patients undergoing "general surgery" procedures. A total of 1,502 patients were included. The mean age was 47 years, and 38% were males. The percentages of patients reaching adequate prophylactic anti-Xa levels were 39%, 61%, 15%, 50%, and 78% across the 40 mg daily, 40 mg twice daily, 30 mg twice daily, and weight-tiered, and body mass index-based groups, respectively. The overall risk of bias was low to moderate.

Conclusion: Fixed Enoxaparin dosing regimens are not correlated with adequate anti-Xa levels in general surgery patients. Additional research is warranted to assess the efficacy of dosing regimens based on novel physiologic parameters (such as estimated blood volume).

Introduction

Patients undergoing general surgical procedures are at above-average risk for venous thromboembolism (VTE), and these events contribute significantly to preventable morbidity and mortality.[1-3] Guidelines for preventing VTE recommend using mechanical (compression devices or thromboembolic deterrent stockings), pharmacological, or combination in hospitalized surgical patients for VTE prophylaxis.[4,5] A fixed dose of unfractionated heparin or low molecular weight heparin is the standard of care in most hospitals and institutions to prevent VTE.[6] Due to its favorable pharmacokinetics, Enoxaparin has gained popularity and is the preferred pharmacological VTE prevention agent.[7]

Direct monitoring of Enoxaparin efficacy is unavailable in clinical settings. Instead, anti-factor Xa (AFXA) inhibition is used as a surrogate marker to reflect the adequacy of thromboprophylaxis.[8] Recommended target peak AFXA levels range from 0.2 to 0.5 IU/mL and is typically measured at steady state 3 to 5 hours

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after the third consecutive dose.[7] Conflicting results exist regarding the association between AFXA levels and VTE or bleeding events. Prior studies in critically ill and trauma patients have shown a significant correlation between prophylactic AFXA levels and 90-day asymptomatic or symptomatic VTE.[9-12]

Pharmacology data on Enoxaparin demonstrates variable rates of metabolism based on patient-level factors leading to concerns that fixed-dose regimens are insufficient.[9,11,13,14] Breakthrough VTE events are documented in several trials despite appropriate fixed-dose pharmacologic prophylaxis. A recent meta-analysis in the traumatically injured population demonstrated an association between appropriately targeted AFXA levels and reduced VTE events. The present study's goal was to systematically review the literature to determine the ability of various Enoxaparin regimens to achieve adequate prophylactic AFXA blood levels for VTE prevention in hospitalized general surgery patients and to determine if prophylactic AFXA levels impact VTE events.

Methods

Search strategy and study selection

A systematic literature review was conducted using the MEDLINE (OVID), Web of Science, Cochrane Library, and Scopus Database following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines from January 1, 1993, to June 24, 2021, and updated February 17, 2023 (Supplementary Table S1). A medical librarian assisted in the search strategy (E.H.) and performed the search. Supplementary Appendix S1 illustrates the search strategy pertaining to this systematic review. Non-English language articles, gray literature, and conference proceedings were excluded.

All randomized clinical trials, observational trials, and single or multicenter studies were considered for inclusion. Articles assessing bariatric surgery, abdominal surgical oncology, thoracic surgery, and general surgery service were included in this systematic review. Exclusion criteria included systematic reviews, patients <18 years of age, nongeneral surgery patients (eg, orthopedics, plastics, trauma, neurosurgery, urology, gynecology), studies using a low molecular weight heparin other than Enoxaparin, and studies where anti-Xa peak levels were not measured. Although trauma patients undergo many traditional general surgical procedures, a recent meta-analysis has already been performed.[10]

The final search results were compiled into one library. The study selection and extraction tool COVIDENCE (Melbourne, Australia) was used to manage the screening process. Three review authors (E.B., A.H.A.T., C.P.) independently reviewed titles and abstracts for inclusion. This was followed by a full-text review by 3 authors (E.B., A.H.A.T., C.P.) to reach the final selection. Disagreements were resolved by a majority. Articles were eligible if (1) the participants underwent a general surgery procedure, (2) the participants received a prophylactic dose of Enoxaparin, (3) the study compared the current recommended Enoxaparin dose with an intervention, placebo, or no intervention, and (4) Enoxaparin dosing regimens were evaluated with AFXA levels.

Data extraction

Surgical population, demographics, targeted peak AFXA level, Enoxaparin dosing regimen, and complications (VTE or bleeding events) were extracted independently by 2 authors (E.B., A.H.A.T.) from each article. Disagreements were resolved by a consensus-based discussion between both researchers. The review authors were not blinded to the names of journals, authors, institutions, or study outcomes.

Quality assessment

The risk of bias was assessed using the Risk of Bias in Non-randomized studies-of Intervention tool (ROBINS-I). The studies were labeled as either low, moderate, serious, or critical risk, per ROBINS-I criteria.[15] The 2 authors (E.B., A.H.A.T.) independently conducted the quality assessment. Conflicts or disagreements were resolved by a consensus-based discussion.

Outcome measure

The primary outcome was the measure of the peak AFXA level assessed during the patient's initial hospital stay. The secondary outcome measures included bleeding events or the development of VTE. The secondary outcome measures were assessed during the initial hospital stay or follow-up as determined by individual studies.

Statistical analysis

Continuous variables are presented as means with standard deviation (SD), whereas categorical variables are presented as numbers with percentages. In cases where continuous variables are reported as median and interquartile range (IQR), these were converted to mean and SD assuming normal distribution and an IQR of 1.35 SD.[16] Mean AFXA and percentage of patients reaching prophylactic levels are summarized and described as a frequency-weighted mean and percentages, respectively. A meta-analysis was used to evaluate the correlation between prophylactic AFXA levels and clinically significant VTE events. We included studies comparing VTE events between patients who achieved prophylactic AFXA levels and those with subprophylactic AFXA levels. The Peto fixed-effects model was used to conduct the meta-analysis. The included studies were tested for heterogeneity quantified by the I^2 as low (<50%), moderate (50%–75%), or high (>75%). Data were analyzed using StataCorp version 17 (StataCorp LLC, College Station, TX) and RevMan 5.4 software provided by the Cochrane Library (Memphis, TN). Institutional review board approval was exempted from this systematic review.

Results

Study selection and characteristics

A total of 6,760 citations were identified, and 2,548 duplicates were removed (Figure 1). In addition, 344 articles were selected for full-text review based on reviewer agreement. A total of 19 articles published between 2008 and 2022 met the inclusion criteria. Four articles were prospective clinical trials, and 15 articles were prospective cohort/observational studies (Figure 1, Table 1). A total of 1,502 patients were included in the studies; the mean age was 47, and 38% were males.

Nine studies explored patients undergoing bariatric procedures, 5 studies discussed patients undergoing abdominal surgical oncology procedures, 3 studies included thoracic surgery patients, and the rest discussed patients admitted to the general surgery service (Table 1). Nine studies, mainly prospective observational studies, compared the effects of 2 different Enoxaparin prophylaxis regimens. The remaining articles compared the standard fixed Enoxaparin dose to mechanical thromboprophylaxis only. The most used Enoxaparin dose was 40 mg daily ($n = 590$, 39%). For studies that compared different dosing regimens, the additional dosing regimens were 30 mg twice daily, 40 mg twice daily, 60 mg daily, or a body mass index/weight-tiered regimen. Most studies reported the timing of peak AFXA measurement, which ranged from 3 to 5 hours after administering the third dose of Enoxaparin. Most

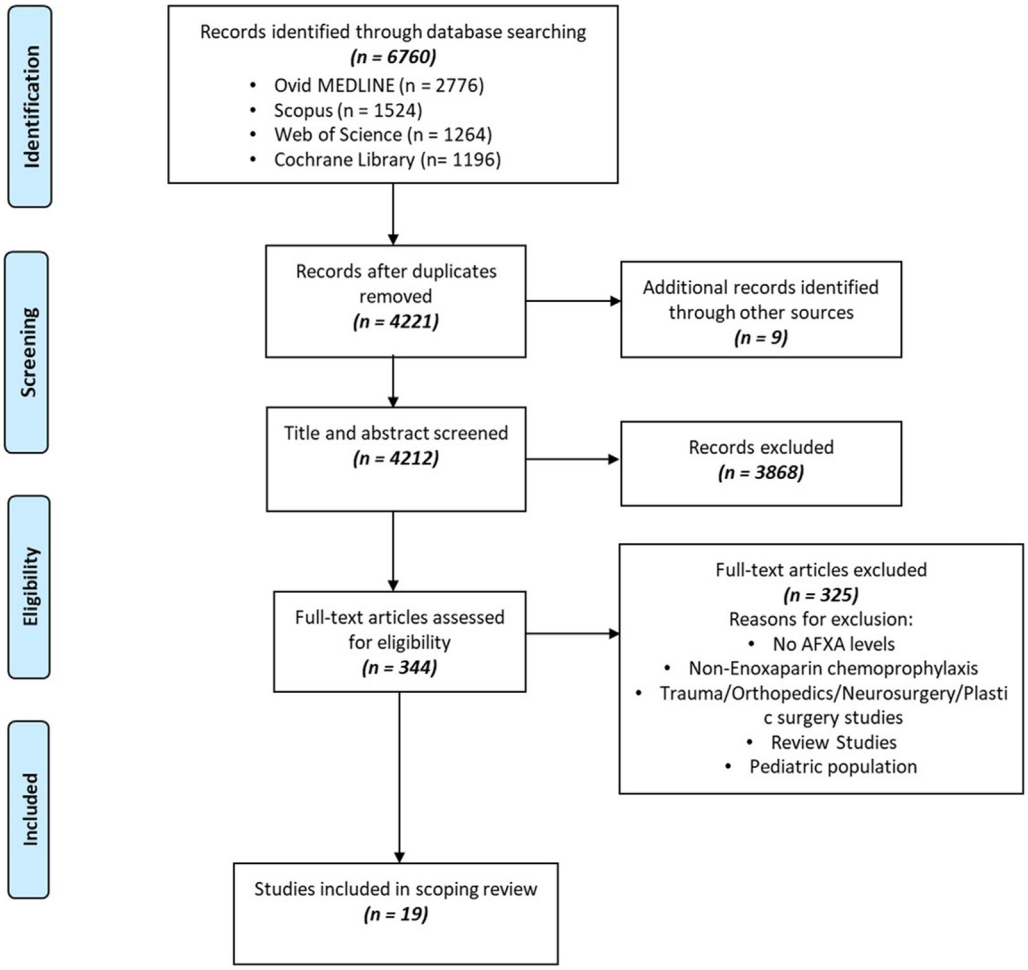

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart.

studies reported the target peak AFXA level as 0.2 to 0.5 IU/mL; however, some studies had a target as low as 0.10 IU/mL or as high as 0.6 IU/mL.

Outcomes

Due to the different methods adopted by each study, patients were grouped based on the dosing regimen explored in individual studies. Some studies compared multiple dosing regimens; therefore, they were included in multiple dosing sections. The AFXA levels, adequate prophylactic range percentage, VTE events, and bleeding events were compared across individual studies.

40 mg Enoxaparin daily

A total of 11 studies, including 590 patients, assessed AFXA levels with 40 mg of Enoxaparin daily. Four studies included abdominal surgical oncology patients, 3 studies included bariatric patients, 3 studies included thoracic surgery patients, and 1 study included "general surgery" patients. The mean AFXA level was 0.22 IU/mL, and 38.7% of patients reached adequate prophylactic levels (ranging from 0.2–0.5 IU/mL). A total of 15 patients (2.8%) had a bleeding event, and 5 patients (0.9%) had a VTE event (Table 2).

40 mg Enoxaparin twice daily

A total of 4 studies, including 134 patients, assessed AFXA with 40 mg Enoxaparin twice daily (BID). All 4 studies included bariatric patients. The mean AFXA was 0.29 IU/mL, and 61% of patients reached adequate prophylactic levels. Three out of the 4 studies reported bleeding events; of these studies, 10.9% of patients experienced a bleeding event. Three studies reported VTE events, and no patients suffered a VTE event (Table 3).

30 mg Enoxaparin BID

A total of 3 studies, including 65 patients, assessed AFXA with 30 mg Enoxaparin BID. One study included abdominal surgical oncology patients, one included "general surgery" patients and one included bariatric patients. The mean AFXA was 0.11 IU/mL, and 15.5% of patients reached adequate prophylactic levels. No patients had a bleeding event, and 2.5% of patients experienced a VTE event (Table 4).

Weight-tiered Enoxaparin. A total of 2 studies, including 118 patients, assessed AFXA levels based on weight-tiered Enoxaparin dosing regimens. One study included thoracic surgery patients, and one study included abdominal surgical oncology patients. In addition, 50% of patients reached adequate prophylactic levels. A total of 3 patients (5%) had a bleeding event, and no patients had a VTE event (Table 5).

Body mass index-based Enoxaparin

A total of 3 studies, including 425 patients, assessed AFXA levels based on body mass index (BMI)-based Enoxaparin dosing regimens. All 3 studies assessed bariatric patients. The mean AFXA was

Table I
Characteristics of included studies

Study	Year	Population	Groups	N	Total size	Age, y, mean ± SD	Male (%)	BMI, kg/m^2, mean ± SD	Caprini score, mean ± SD
Baumgartner etl[17]	2018	Surgical oncology	30 mg BID	18	73	59 ± 3*	56	26 ± 1	NR
			40 mg daily	55		57 ± 2*	40	26 ± 1	
Borkgren-Okonek et al[18]	2008	Bariatrics	BMI-based	223	223	45 ± 10	25	51 ± 5	NR
Celik et al[13]	2015	Bariatrics	40 mg BID	51	51	44 ± 10	26	42 ± 7	NR
Gelikas et al[19]	2017	Bariatrics	40 mg daily	31	54	37 ± 12	32	42 ± 1	NR
			60 mg daily	23		39 ± 11	35	44 ± 1	
Goslan et al[20]	2018	Bariatrics	40 mg daily	34	60	33 ± 8	9	39 ± 3	NR
			40 mg bid	25		34 ± 10	15	42 ± 5	
Hakeam et al[21]	2020	General surgery	30 mg daily	131	131	45 ± 19	62	17 ± 3	6 ± 3
Karas et al[22]	2021	Bariatrics	BMI-based	105	105	47 ± 14	15	46 ± 9	NR
Kramme et al[23]	2023	Surgical oncology	40 mg daily	46	46	62 ± 12	61	29 ± 7	8 ± 2
Kramme et al[24]	2020	Surgical oncology	40 mg daily	64	64	60 ± 13	53	28 ± 7	8 ± 3
Khoursheed et al[25]	2013	Bariatrics	40 mg daily	39	39	32 ± 11	21	45 ± 6	NR
Pannucci et al[6]	2019	Surgical oncology	40 mg daily	113	113	52 ± 51	44	26 ± 20	6 ± 3
Pannucci et al[26]	2018	Thoracic	40 mg daily	89	89	55 ± 47	54	29 ± 23	7 ± 3
Pannucci et al[27]	2020	Thoracic	40 mg daily	65	131	61 ± 16	43	29 ± 6	7 ± 3
			Weight-tiered	66		59 ± 17	52	29 ± NR	7 ± 3
Parviainen et al[28]	2022	Thoracic	40 mg daily	19	19	69 ± 4	95	28 ± 2	NR
Riha et al[29]	2012	General surgery	30 mg BID	28	63	54 ± NR	68	36 ± NR	NR
			40 mg daily	35		59 ± NR	57	34 ± NR	
Rowan et al[30]	2008	Bariatrics	30 mg BID	19	52	42 ± 11	26	48 ± 7	NR
			40 mg BID	33		41 ± 9	18	49 ± 9	
Simone et al[31]	2008	Bariatrics	40 mg BID	24	40	40 ±10	13	49 ± 7	NR
			60 mg BID	16		41 ±10	6	47 ± 7	
Wagner et al[32]	2022	Bariatrics	BMI-based	97	97	42 ± 11	34	51 ± 9	NR
Verhoeff et al[33]	2022	Surgical oncology	Weight-tiered	52	52	61 ± 15	60	28 ± 6	8 ± 2

BID, twice daily; *NR*, not reported; *SD*, standard deviation.
* SEM.

0.24IU/mL, and 78% of patients reached adequate prophylactic levels. A total of 14 patients (3.3%) had a bleeding event, and 3 (0.7%) patients had a VTE event (Table 6).

Meta analysis

A total of 5 studies comparing VTE events in patients who reached prophylactic AFXA levels to those with subprophylactic AFXA levels were included in the meta-analysis (Table 7). A total of 8 VTE events were reported, of which 2 occurred in the prophylactic range. In 2 studies, zero VTE events were reported. On meta-analysis, subprophylactic AFXA levels were not associated with an increased risk of clinically significant VTE events, and a moderate level of heterogeneity existed between the 5 studies (odds ratio, 0.24; 95% CI, 0.05, 1.10; $P = .07$; I^2: 59%; Figure 2).

Quality assessment

Most studies had either a low or moderate overall risk of bias. The most common source of bias was due to missing data. A summary of the quality assessment ROBINS-I tool is depicted in Table 8.

Discussion

This systematic review and meta-analysis summarize studies assessing the impact of a standard fixed and weight-tiered doses of Enoxaparin in general surgical patients on achieving appropriate AFXA levels and the impact on VTE events. A body mass index (BMI)-based Enoxaparin regimen achieved the highest percentage (74%) of prophylactic range patients. Despite this, there was no clear association between achieving prophylactic AFXA levels and VTE events (adjusted odds ratio, 0.24; 95% CI, 0.05–1.10).

Low molecular weight heparins have become the pharmacologic thromboprophylaxis agent of choice since 1996.[34] Enoxaparin has a fast mode of action, long half-life, and high bioavailability and therefore has become the preferred chemical VTE prophylactic choice.[7,35] Although superior to heparin in preventing VTE events, Enoxaparin may be metabolized at a different rate between patients,[11,13,14] and, therefore, individualization of chemoprophylaxis based on VTE event risk or risks of sub-therapeutic dosing (such as BMI) has been attempted.[36,37]

The use of AFXA is particularly relevant in the obese population, consistent with most of our included articles studying the bariatric population. Obese patients are traditionally given special consideration when prescribing chemical VTE prophylaxis,[38,39] and it is debated whether these patients should be given a weight-based dose or a fixed dose of Enoxaparin.[3,19,40] A higher fixed dose is usually preferred, and the administered dosing regimen (dose and frequency) varies based on a patient's weight, BMI, or the surgeon's preference.[41,42] In our review, multiple different dosing regimens were evaluated in bariatric patients. The mean AFXA levels were 0.26, 0.29, 0.29, and 0.43 IU/mL in bariatric patients receiving a fixed Enoxaparin regimen of 40 mg daily, 40 mg twice daily, 60 mg daily, and 60 mg twice daily, respectively. Although mean AFXA levels were in the prophylactic range, many patients receiving fixed Enoxaparin dosing regimens did not reach adequate prophylactic levels. It is important to note that many patients in the 60 mg BID group had supraprophylactic AFXA levels, which theoretically could place them at a higher risk of bleeding.

Conversely, most bariatric patients who received only 30 mg twice daily dose were subprophylactic, with only 9.1% reaching adequate AFXA levels. Additionally, Riha et al reported a high VTE incidence rate of 2.5% in obese patients who received a 30 mg twice daily dose. This is consistent with prior literature showing the association between subprophylactic AFXA levels and the incidence of VTE.[43] Conflicting results were reported in bariatric patients who received a 40 mg twice daily dose. The percentages of patients who achieved adequate AFXA levels were 42%, 56%, and 74.5% in the 3 studies that assessed this dose in bariatric patients. This might

Table II
Anti-Xa levels and complication rates in patients receiving 40 mg Enoxaparin daily

	Baumgartner et al (2018)	Gelikas et al (2017)	Goslan et al (2018)	Kramme et al (2021)	Pannucci et al (2019)	Pannucci et al (2018)	Riha et al (2012)	Kramme et al (2020)	Khoursheed et al (2013)	Pannucci et al (2020)	Parviainen et al (2022)	Total
Population	Surgical oncology	Bariatrics	Bariatrics	Surgical oncology	Surgical oncology	Thoracic	General surgery	Surgical oncology	Bariatrics	Thoracic	Thoracic	
Sample size	55	31	34	46	113	89	35	64	39	65	19	590
Mean AFXA (IU/mL)	0.22	0.25	0.4	0.16	NR	NR	0.21	NR	0.13	NR	0.23	0.22*
Prophylactic levels (%)	54	81	NR	26	29	30	56	22	41	48	NR	39*
VTE events *n* (%)	0	0	0	0	3 (3)	0	1 (3)	0	NR	1 (2)	NR	5 (0.9)
Bleeding events *n* (%)	0	1 (3)	2 (7)	2 (4)	4 (3)	1 (1)	NR	2 (3)	NR	1 (2)	NR	15 (2.8)

AFXA, anti-factor Xa; *VTE*, venous thromboembolism; *NR*, not reported.
* Weighted average.

indicate that an Enoxaparin regimen of 40 mg BID might be adequate in certain bariatric patients but not others.

Recent studies have been conducted to assess the efficacy of weight-tiered chemoprophylactic dosing regimens in obese patients. Al-Otaib et al, Freeman et al, and Ludwig et al, studied medically or surgically ill obese patients, and these patients were given a weight-based thromboprophylaxis regimen (0.5 mg/kg). All 3 cohorts concluded that the weight-based Enoxaparin regimen led to adequate AFXA levels in most patients and was superior to the fixed regimen.[38,39,41] He et al conducted a systematic review in 2017 to compare the clinical and laboratory outcomes between obese patients who received a fixed dose (40 mg daily) and a weight-based dose (0.5 mg/kg) of Enoxaparin. Results suggested that a higher percentage of patients who received a weight-based dose achieved adequate AFXA levels (52.2%) compared to a fixed dose (16%).[43] In our review, 3 studies used a BMI-based dosing regimen in bariatric patients. Patients with a BMI >60 kg/m^2 and patients with a BMI $\leq$50 kg/m^2 received chemoprophylaxis of 60 mg and 40 mg Enoxaparin BID, respectively. A high percentage of patients who received BMI-tiered chemoprophylaxis reached adequate prophylactic levels. The BMI and total body weight (TBW)-based dosing regimens have led to improved AFXA levels and prophylactic ranges in obese patients; however, these parameters do not address the variations in blood volume and pharmacological volume of distribution across individuals.[44] Additional research is warranted to assess the efficacy of estimated blood volume (EBV)-based dosing in bariatric patients.

Historically, most research on VTE prophylaxis was conducted in trauma and orthopedic surgical populations due to the increased risk of VTE in both groups (up to 40% and 60%, respectively).[45,46] Prior studies have shown the inadequacy of fixed Enoxaparin doses in achieving adequate AFXA levels in trauma and orthopedic patients.[12,47–49] In a similar systematic review and meta-analysis, Verhoeff et al showed that 63% of trauma patients had sub-prophylactic AFXA levels, and weight-based dose adjustment protocols regimens were superior to fixed-dosing regimens in achieving adequate AFXA levels.[10] Furthermore, patients out of the prophylactic range had a higher incidence of VTE; this was significant, unlike in our review. A recent retrospective study on trauma patients shows that EBV-based enoxaparin dosing was more closely correlated with adequate AFXA than TBW and BMI-based dosing.[44] Trauma, immobility, and obesity are known risk factors for VTE. Additionally, malignancy increases the risk of VTE events. In our review, multiple studies have been conducted in abdominal surgical oncology populations, particularly colorectal surgery.[50,51] Similar to trauma and orthopedic patients, most patients undergoing abdominal surgical oncologic procedures received a standard fixed 40 mg daily dose and did not achieve adequate peak AFXA levels. This was also true for abdominal surgical oncology patients that received a 30 mg twice daily dose.

Based on previous studies assessing trauma and plastic surgery patients, AFXA levels are inversely correlated with the development of VTE events. However, a paucity of data exists in general surgery patients. In our study no significant correlation between sub-prophylactic ranges and VTE events in general surgery patients, although the odd's ratio was below 1. Additionally, the one-size-fits-all approach of fixed Enoxaparin dosing appears to provide inadequate chemoprophylaxis in general surgery patients based on the results of this review with respect to AFXA. In addition to bariatric surgeons, general surgeons face the challenge of achieving adequate chemoprophylaxis in obese patients undergoing non-bariatric general surgeries. Using novel dosing regimens based on certain individualized parameters (such as EBV, BMI, and TBW) should be explored in patients undergoing general surgery procedures.

Table III
Anti-Xa levels and complication rates in patients receiving 40 mg Enoxaparin BID

	Celik et al (2015)	Goslan et al (2018)	Rowan et al (2008)	Simone et al (2008)	Total
Population	Bariatrics	Bariatrics	Bariatrics	Bariatrics	
Sample size	51	26	33	24	134
Mean AFXA (IU/mL)	0.37	0.40	0.15	0.21	0.29*
Prophylactic levels (%)	75	NR	42	56	61*
VTE events *n* (%)	0	0	NR	0	0
Bleeding events *n* (%)	8 (16)	2 (8)	NR	1 (4)	11 (11)

AFXA, anti-factor Xa; *BID*, twice daily; *VTE*, venous thromboembolism; *NR*, not reported.
* Weighted average.

Table IV
Anti-Xa levels and complication rates in patients receiving 30 mg Enoxaparin BID

	Baumgartner et al (2018)	Riha et al (2012)	Rowan et al (2008)	Total
Population	Surgical oncology	General surgery	Bariatrics	
Sample size	18	28	19	65
Mean AFXA (IU/mL)	0.14	0.15	0.08	0.11*
Prophylactic levels (%)	22	NR	9	16*
VTE events *n* (%)	0	7 (3)	NR	3
Bleeding events *n* (%)	0	0	NR	0

AFXA, anti-factor Xa; *BID*, twice daily; *VTE*, venous thromboembolism; *NR*, not reported.
* Weighted average.

Table V
Anti-Xa levels and complication rates in patients receiving weight-tiered Enoxaparin

	Pannucci et al (2020)	Verhoeff et al (2022)	Total
Population	Thoracic	Surgical oncology	
Sample size	66	52	118
Mean AFXA (IU/mL)	NR	NR	NR
Prophylactic levels (%)	44	58	50*
VTE events *n* (%)	0	NR	0
Bleeding events *n* (%)	3 (5)	NR	3 (5)

AFXA, anti-factor Xa; *VTE*, venous thromboembolism; *NR*, not reported.
* Weighted average.

Table VI
Anti-Xa levels and complication rates in patients receiving BMI-based Enoxaparin

	Borkgren-Okonek et al (2018)	Karas et al (2021)	Wagner et al (2022)	Total
Population	Bariatrics	Bariatrics	Bariatrics	
Sample size	223	105	97	425
Mean AFXA (IU/mL)	0.29	0.30	0.18	0.24*
Prophylactic levels (%)	69	85	93	78*
VTE events *n* (%)	1 (0.5)	1 (1)	1(1)	3 (0.7)
Bleeding events *n* (%)	5 (2)	9 (9)	0	14 (3.3)

AFXA, anti-factor Xa; *BMI*, body mass index; *VTE*, venous thromboembolism.
* Weight-average.

Table VII
VTE and bleeding events stratified by AFXA ranges

	Borkgren-Okonek et al (2018)	Hakeam et al (2020)	Kramme et al (2020)	Pannucci et al	Kramme (2023)
Prophylactic range, *n*	153	80	12	31	14
Subprophylactic range, *n*	37	41	34	72	50
Supraprophylactic range, *n*	16	0	0	3	0
Bleeding events, *n*					
Prophylactic	4	5	0	0	1
Subprophylactic	0	2	2	0	1
Supraprophylactic	1	0	0	0	0
VTE events, *n*					
Prophylactic	1	0	0	1	0
Subprophylactic	0	4	0	2	0
Supraprophylactic	0	0	0	0	0

AFXA, anti-factor Xa; *VTE*, venous thromboembolism.

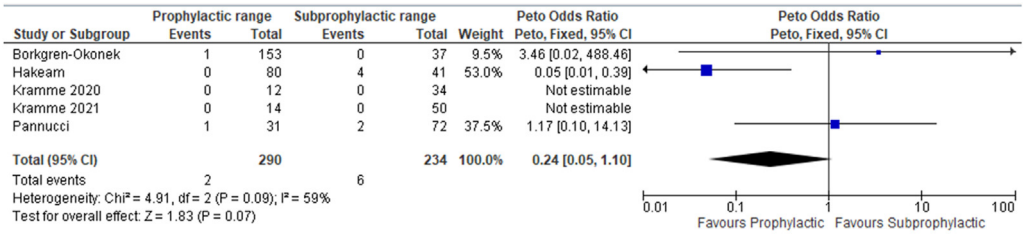

Figure 2. Comparison of venous thromboembolism events between patients with prophylactic anti-factor Xa levels and those with subprophylactic anti-factor Xa levels. *AFXA*, anti-factor Xa.

Table VIII
ROBINS-I tool for quality assessment

Study	Confounding bias	Selection bias	Classification bias	Deviation bias	Missing data bias	Outcome measurement bias	Selection reported result bias	Overall bias
Baumgartner et al (2018)	Low	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Borkgren-Okonek et al (2018)	Low	Low	Low	Low	Low	Low	Low	Low
Celik et al (2015)	Low	Low	Low	Low	Low	Low	Low	Low
Gelikas et al (2017)	Low	Low	Moderate	Low	Low	Moderate-high	Low	Moderate
Goslan et al (2018)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Hakeam et al (2020)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Karas et al (2021)	Low	Low	Low	Low	Low	Low	Low	Low
Kramme (2023)	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Kramme (2020)	Low-moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Khoursheed et al (2013)	N/A	Low	Low	Low	Low	Low	Low	Low
Pannucci	N/A	Low	Low	Low	Moderate	Low	Low	Moderate
Pannucci	N/A	Low	Low	Low	Moderate	Low	Low	Moderate
Pannucci	Low	Low	Low	Low	Low-moderate	Low	Low	Moderate
Parviainen et al (2022)	Low	Low	Low	Low	Low-moderate	Low	Low	Moderate
Riha et al (2012)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Rowan et al (2008)	Low	Low	Low	Low	Low	Low	Low	Low
Simone et al (2008)	Low	Low	Moderate-high	Low	Moderate	Low	Low	Serious
Wagner et al (2022)	Low	Low	Low	Low	Low	Low	Low	Low
Verhoeff et al (2022)	Low	Low	Low	Low	Low	Low	Low	Low

N/A, not available.

Study limitations

Our study has several limitations. This systematic review analyzes nonrandomized trials, which is a source of confounding biases. Heterogeneity in the patient population and the reporting of outcomes existed between individual studies, limiting our ability to group and collectively analyze patients. Furthermore, distinct differences in VTE risks, such as obesity and malignancy, may introduce bias in VTE event rates. Similarly, regarding complications, the reporting of bleeding and VTE events were ambiguous or not reported in some studies, which limited our ability to better determine the incidence of these important outcomes. Current research is divided on whether AFXA is the best parameter for VTE chemoprophylaxis monitoring.

However, AFXA is one of the only and most broadly used parameters to monitor the efficacy of Enoxaparin. Additionally, AFXA is readily available and easy to obtain. Venous thromboembolism is rare; therefore, large population studies are necessary to detect any significant correlation with low AFXA levels. Our meta-analysis only included studies that compared VTE events based on AFXA levels. A total of 5 articles ($n = 290$) were included in the meta-analysis. The negative findings of our analysis might be due to the modest number of patients and low VTE rate. Our results are therefore limited by the low number of patients, low number of events, and the retrospective nature of most studies. Our results provide a framework for appropriately sized future studies and insight into AFXA timing and levels. Based on prior work, Caprini risk has been validated to stratify patients into high or low risk for VTE groups. Prior research has shown that higher Caprini scores are associated with higher VTE events. In this systematic review, 7 studies reported Caprini scores, all of which were low risk (<10). None of the included studies compared VTE events based on Caprini scores. To control for potential confounders, incorporating Caprini scores and risk stratification should be considered in future work pertaining to VTE prophylaxis. Finally, unpublished or nonindexed studies were not searched for, and this could be a source of missing data.

In conclusion, this study highlights the variation in thromboprophylaxis protocols and regimens throughout the general surgical literature. Based on the results of this systemic review and previous studies, a fixed dosing regimen of 40 mg daily is inadequate in the general surgery population, and a twice-daily, weight-based dose should be considered. Overall, our study reiterates the need for improvement in Enoxaparin dosing regimens to improve rates of adequate prophylactic AFXA levels. Additional research is

warranted to determine the relationship between prophylactic AFXA levels and VTE events.

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Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Supplementary materials

Supplementary materials associated with this article can be found in the online version 10.1016/j.surg.2023.04.032.

References

1. Amin AN, Lin J, Ryan A. Need to improve thromboprophylaxis across the continuum of care for surgical patients. *Adv Ther*. 2010;27:81–93.
2. Murphy PB, Vogt KN, Lau BD, et al. Venous thromboembolism prevention in emergency general surgery: a review. *JAMA Surg*. 2018;153:479–486.
3. Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on bodyweight and current doses may be inadequate in obese patients. *Br J Surg*. 2003;90:547–548.
4. Ohta H, Miyake T, Shimizu T, et al. The impact of pharmacological thromboprophylaxis and disease-stage on postoperative bleeding following colorectal cancer surgery. *World J Surg Oncol*. 2019;17:110.
5. Hussain Z, Peterson GM, Mirkazemi C, Curtain C, Zaidi STR. Risk of venous thromboembolism, use of enoxaparin and clinical outcomes in obese patients undergoing laparoscopic adjustable gastric band surgery: a retrospective study. *Medicine (Baltimore)*. 2020;99, e20174.
6. Pannucci CJ, Fleming KI, Bertolaccini CB, Prazak AM, Huang LC, Pickron TB. Assessment of anti-factor Xa levels of patients undergoing colorectal surgery given once-daily enoxaparin prophylaxis: a clinical study examining enoxaparin pharmacokinetics. *JAMA Surg*. 2019;154:697–704.
7. Pannucci CJ, Prazak AM, Scheefer M. Utility of anti-factor Xa monitoring in surgical patients receiving prophylactic doses of enoxaparin for venous thromboembolism prophylaxis. *Am J Surg*. 2017;213:1143–1152.
8. Pannucci CJ, Varghese TK, Graves KK, Prazak AM. Supratherapeutic anti-factor Xa levels in patients receiving prophylactic doses of enoxaparin: a case series. *Int J Surg Case Rep*. 2016;28:114–116.
9. Pannucci CJ, Fleming KI, Momeni A, Prazak AM, Agarwal J, Rockwell WB. Twice-daily enoxaparin among plastic surgery inpatients: an examination of pharmacodynamics, 90-day venous thromboembolism, and 90-day bleeding. *Plast Reconstr Surg*. 2018;141:1580–1590.
10. Verhoeff K, Raffael K, Connell M, et al. Relationship between anti-Xa level achieved with prophylactic low-molecular weight heparin and venous thromboembolism in trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2022;93:e61–e70.
11. Malinoski D, Jafari F, Ewing T, et al. Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. *J Trauma*. 2010;68:874–880.
12. Costantini TW, Min E, Box K, et al. Dose adjusting enoxaparin is necessary to achieve adequate venous thromboembolism prophylaxis in trauma patients. *J Trauma Acute Care Surg*. 2013;74:128–133:discussion 134–135.
13. Celik F, Huitema AD, Hooijberg JH, van de Laar AW, Brandjes DP, Gerdes VE. Fixed-dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels. *Obes Surg*. 2015;25:628–634.
14. Kopelman RT, O'Neill PJ, Pieri PG, et al. Alternative dosing of prophylactic Enoxaparin in the trauma patient: is more the answer? *Am J Surg*. 2013;206:911–915:discussion 915–916.
15. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
16. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Intervention*. Chichester (UK): The Cochrane Collaboration; 2011.
17. Baumgartner JM, McKenzie S, Block S, Costantini TW, Lowy AM. Prophylactic Enoxaparin doses may be inadequate in patients undergoing abdominal cancer surgery. *J Surg Res*. 2018;221:183–189.
18. Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. *Surg Obes Relat Dis*. 2008;4:625–631.
19. Gelikas S, Eldar SM, Lahat G. Anti-factor Xa levels in patients undergoing laparoscopic sleeve gastrectomy: 2 different dosing regimens of Enoxaparin. *Surg Obes Relat Dis*. 2017;13:1753–1759.
20. Goslan CJ, Baretta GAP, de Souza HGP, et al. Profilaxia da trombose venosa profunda em cirurgia bariatrica: estudo comparativo com doses diferentes de heparina de baixo peso molecular. *J Vasc Bras*. 2018;17:26–33.
21. Hakeam HA, Al Duhailib Z, Alsemari M, Alwaibah RM, Al Shannan MF, Shalhoub M. Anti-factor Xa levels in low-weight surgical patients receiving Enoxaparin for venous thromboembolism prophylaxis: a prospective cohort study. *Clin Appl Thromb Hemost*. 2020;26, 1076029620931194.
22. Karas LA, Nor Hanipah Z, Cetin D, et al. Assessment of empiric body mass index-based thromboprophylactic dosing of Enoxaparin after bariatric surgery: evidence for dosage adjustment using anti-factor Xa in high-risk patients. *Surg Obes Relat Dis*. 2021;17:153–160.
23. Kramme K, Sarraf P, Shebrain S, Munene G. Safety and efficacy of prophylactic Enoxaparin adjusted by anti-factor Xa peak levels in pancreatic surgery. *Am Surg*. 2023;89:300–308.
24. Kramme K, Paya S, Gitonga M. Prophylactic Enoxaparin adjusted by anti-factor Xa peak levels compared with recommended thromborpophylaxis and rates of clinically evident venous thromboembolism in surgical oncology patients. *J Am Coll Surg*. 2020;230:314–321.
25. Khoursheed M, Al-Bader I, Al-Asfar F, et al. Therapeutic effect of low-molecular weight heparin and incidence of lower limb deep venous thrombosis and pulmonary embolism after laparoscopic bariatric surgery. *Surg Laparosc Endosc Percutan Tech*. 2013;23:491–494.
26. Pannucci CJ, Fleming KI, Holoyda K, Moulton L, Prazak AM, Varghese Jr TK. Enoxaparin 40 mg per day is inadequate for venous thromboembolism prophylaxis after thoracic surgical procedure. *Ann Thorac Surg*. 2018;106:404–411.
27. Pannucci CJ, Fleming KI, Bertolaccini C, et al. Fixed or weight-tiered Enoxaparin after thoracic surgery for venous thromboembolism prevention. *Ann Thorac Surg*. 2020;109:1713–1721.
28. Parviainen MK, Vahtera A, Anas N, et al. Anti-factor X activity levels with continuous intravenous infusion and subcutaneous administration of Enoxaparin after coronary artery bypass grafting: a randomized clinical trial. *Acta Anaesthesiol Scand*. 2022;66:1083–1090.
29. Riha GM, Van PY, Differding JA, Schreiber MA, Oregon H. Science University Trauma Research G. Incidence of deep vein thrombosis is increased with 30 mg twice daily dosing of Enoxaparin compared with 40 mg daily. *Am J Surg*. 2012;203:598–602.
30. Rowan BO, Kuhl DA, Lee MD, Tichansky DS, Madan AK. Anti-Xa levels in bariatric surgery patients receiving prophylactic Enoxaparin. *Obes Surg*. 2008;18:162–166.
31. Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. *Surg Endosc*. 2008;22:2392–2395.
32. Wagner J, Wruck H, Lautenbach A, et al. Comparison of anti-factor Xa levels in female and male patients with obesity after Enoxaparin application for thromboprophylaxis. *Obes Surg*. 2022;32:861–867.
33. Verhoeff K, Connell M, Shapiro AJ, Strickland M, Bigam DL, Anantha RV. Rate of prophylactic anti-Xa achievement and impact on venous thromboembolism following oncologic hepato-pancreatico-biliary surgery: a prospective cohort study [e-pub ahead of print]. *Am J Surg*. https://doi.org/10.1016/j.amjsurg.2022.12.001. Accessed August 22, 2022.
34. Jay RM, Code CI, Chen E, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboemvolism after major trauma. *N Engl J Med*. 1996;335:701–707.
35. Dhillon NK, Hashim YM, Berezin N, et al. Characterizing the delays in adequate thromboprophylaxis after TBI. *Trauma Surg Acute Care Open*. 2021;6: e000686.
36. Bickford A, Majercik S, Bledsoe J, et al. Weight-based Enoxaparin dosing for venous thromboembolism prophylaxis in the obese trauma patient. *Am J Surg*. 2013;206:847–851;discussion 851–852.
37. Ebeid A, Cole E, Stallwood-Hall C. The efficacy of weight-based Enoxaparin dosing for venous thromboembolism prophylaxis in trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2022;93:e71–e79.
38. Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three Enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. *Am J Hematol*. 2012;87:740–743.
39. Kay AB, Majercik S, Sorensen J, et al. Weight-based Enoxaparin dosing and deep vein thrombosis in hospitalized trauma patients: a double-blind, randomized, pilot study [e-pub ahead of print]. *Surgery*. https://doi.org/10.1016/j.surg.2018.03.001. Accessed 23 April 2018.
40. Al Otaib N, Bootah Z, Al Ammari MA, et al. Assessment of anti-factor Xa activity of Enoxaparin for venous thromboembolism prophylaxis in morbidly obese surgical patients. *Ann Thorac Med*. 2017;12:199–203.
41. Ludwig KP, Simons HJ, Mone M, Barton RG, Kimball EJ. Implementation of an Enoxaparin protocol for venous thromboembolism prophylaxis in obese surgical intensive care unit patients. *Ann Pharmacother*. 2011;45:1356–1362.
42. Berndtson AE, Costantini TW, Lane J, Box K, Coimbra R. If some is good, more is better: an Enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis. *J Trauma Acute Care Surg*. 2016;81:1095–1100.
43. He Z, Morrissey H, Ball P. Review of current evidence available for guiding optimal Enoxaparin prophylactic dosing strategies in obese patients-actual weight-based vs fixed. *Crit Rev Oncol Hematol*. 2017;113:191–194.

44. O'Keefe MM, Carver TW, Herrmann DJ, et al. Evaluation of anti-factor Xa concentrations using a body mass index-based Enoxaparin dosing protocol for venous thromboembolism prophylaxis in trauma patients. *Pharmacotherapy*. 2022;42:216–223.
45. Villarreal JV, Shibuya N, Jupiter DC. Thromboprophylaxis and bleeding complications in orthopedic and trauma patients: a systematic review. *J Foot Ankle Surg*. 2021;60:1014–1022.
46. Whiting PS, Jahangir AA. Thromboembolic disease after orthopedic trauma. *Orthop Clin North Am*. 2016;47:335–344.
47. Haas CE, Nelsen JL, Raghavendran K, et al. Pharmacokinetics and pharmacodynamics of Enoxaparin in multiple trauma patients. *J Trauma*. 2005;59:1336–1343:discussion 1343–1344.
48. Rutherford EJ, Schooler WG, Sredzienski E, Abrams JE, Skeete DA. Optimal dose of Enoxaparin in critically ill trauma and surgical patients. *J Trauma*. 2005;58:1167–1170.
49. Jones DL, Jones WA, Fleming KI, et al. Underdosing of prophylactic Enoxaparin is common in orthopaedic trauma and predicts 90-day venous thromboembolism. *J Orthop Trauma*. 2019;33:570–576.
50. Rottenstreich A, Elazary R, Kalish Y. Abdominal thrombotic complications following bariatric surgery. *Surg Obes Relat Dis*. 2017;13:78–84.
51. Rottenstreich A, Kalish Y, Kleinstern G, Yaacov AB, Dux J, Nissan A. Factors associated with thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol*. 2017;116:914–920.