Optimal Dosing of Prophylactic Enoxaparin after Surgical Procedures: Results of the Double-Blind, Randomized, Controlled FIxed or Variable Enoxaparin (FIVE) Trial

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Background: The accepted "one-size-fits-all" dose strategy for prophylactic enoxaparin may not optimize the medication's risks and benefits after surgical procedures. The authors hypothesized that weight-based administration might improve the pharmacokinetics of prophylactic enoxaparin when compared to fixed-dose administration.

Methods: The FIxed or Variable Enoxaparin (FIVE) trial was a randomized, double-blind trial that compared the pharmacokinetic and clinical outcomes of patients assigned randomly to postoperative venous thromboembolism prophylaxis using enoxaparin 40 mg twice daily or enoxaparin 0.5 mg/kg twice daily. Patients were randomized after surgery and received the first enoxaparin dose at 8 hours after surgery. Primary hypotheses were (1) weight-based administration is noninferior to a fixed dose for avoiding underanticoagulation (anti–factor Xa <0.2 IU/ml) and (2) weight-based administration is superior to fixed-dose administration for avoiding overanticoagulation (anti–factor Xa >0.4 IU/ml). Secondary endpoints were 90-day venous thromboembolism and bleeding.

Results: In total, 295 patients were randomized, with 151 assigned to fixed-dose and 144 to weight-based administration of enoxaparin. For avoidance of underanticoagulation, weight-based administration had a greater effectiveness (79.9 percent versus 76.6 percent); the 3.3 percent (95 percent CI, −7.5 to 12.5 percent) greater effectiveness achieved statistically significant noninferiority relative to the a priori specified −12 percent noninferiority margin ($p = 0.004$). For avoidance of overanticoagulation, weight-based enoxaparin administration was superior to fixed-dose administration (90.6 percent versus 82.2 percent); the 8.4 percent (95 percent CI, 0.1 to 16.6 percent) greater effectiveness showed significant safety superiority ($p = 0.046$). Ninety-day venous thromboembolism and major bleeding were not different between fixed-dose and weight-based cohorts (0.66 percent versus 0.69 percent, $p = 0.98$; 3.3 percent versus 4.2 percent, $p = 0.72$, respectively).

Conclusion: Weight-based administration showed superior pharmacokinetics for avoidance of underanticoagulation and overanticoagulation in postoperative patients receiving prophylactic enoxaparin. (*Plast. Reconstr. Surg.* 147: 947, 2021.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, I.

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Venous thromboembolism is a life- or limb-threatening complication of plastic surgery procedures.[1–7] Over the past decade, plastic surgeons have progressed immensely in their understanding of venous thromboembolism, including the ability to quantify patient-level variation in venous thromboembolism risk using the 2005 Caprini score, demonstrating that chemical prophylaxis is impactful for high-risk plastic surgery inpatients, and generating society-level consensus for approach and management of patients with regard to venous thromboembolism risk.[2,5,8–12] Today, most surgeons recognize that proactive strategies to minimize venous thromboembolism risk should be integrated into their daily practices. However, as we better define which patients are best suited for chemical prophylaxis, one critical question remains: How can surgeons most appropriately dose perioperative anticoagulants to balance the delicate line of venous thromboembolism prevention and risk for postoperative bleeding?

Enoxaparin prevents venous thromboembolism in high-risk plastic surgery patients, but is not uniformly effective. Breakthrough venous thromboembolism events, which are events that occur despite guideline-compliant chemical prophylaxis, can occur in 4 to 10 percent of highest risk patients.[2,13–16] Breakthrough venous thromboembolism may occur because of the pervading "one-size-fits-all" approach to enoxaparin prophylaxis, where all patients receive the same dose and frequency of enoxaparin. This one-size-fits-all approach is conceptually flawed, because patients will metabolize the same dose at different rates, producing variable degrees of anticoagulation, measured by anti–factor Xa level.[16–22]

A series of clinical trials have examined enoxaparin pharmacokinetics in plastic surgery inpatients.[16,17,23] These trials have shown an association between rapidity of enoxaparin metabolism and patient weight, and also confirmed the link between inadequate enoxaparin dosing and symptomatic venous thromboembolism events. One trial[16] enrolled 94 plastic surgery inpatients and demonstrated that 53 percent of patients received inadequate anticoagulation, measured by anti–factor Xa. Importantly, patients with inadequate anti–factor Xa levels were significantly more likely to develop 90-day symptomatic venous thromboembolism (10.2 percent versus 0 percent; $p = 0.041$)—this identified adequacy of prophylactic anticoagulation as an important target for patient safety optimization. A follow-up trial that enrolled 118 plastic surgery inpatients showed that enoxaparin 40 mg twice daily significantly decreased risk for inadequate anti–factor Xa levels, and that twice-daily enoxaparin significantly reduced symptomatic venous thromboembolism when compared to once-daily enoxaparin (0 percent versus 5.3 percent; $p = 0.012$). However, fixed-dose twice-daily prophylaxis increased the risk for high anti–factor Xa levels, and increased clinically relevant bleeding by 3.6 percent.[17,23] Thus, the optimal prophylactic enoxaparin dosing strategy remains elusive.

In this article, we report the results of the FIxed or Variable Enoxaparin (FIVE) trial, a randomized, double-blind, clinical trial that compared the pharmacokinetic and clinical outcomes of enoxaparin 40 mg twice daily versus enoxaparin 0.5 mg/kg twice daily. The trial's primary aims were to (1) examine whether enoxaparin 0.5 mg/kg twice daily is superior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of overanticoagulation (anti–factor Xa >0.4 IU/ml) and (2) examine whether enoxaparin 0.5 mg/kg twice daily is not inferior to enoxaparin 40 mg twice daily for the pharmacokinetic endpoint of underanticoagulation (anti–factor Xa <0.2 IU/ml).

PATIENTS AND METHODS

The complete trial methodology, including a detailed analysis plan, sample size calculation, and sample size justification, was published in April of 2019.[24] A more succinct trial overview is presented here.

Study Design and Oversight

The Fixed or Variable Enoxaparin trial was a randomized, double-blind, clinical trial conducted at the University of Utah. Before enrollment, the study received institutional review board approval (no. 00100416) and was registered at clinicaltrials.gov (NCT03212365). The study was monitored biannually by a data safety and monitoring board. The university's investigational pharmacy was responsible for randomization and blinded drug provision.

Patients

Eligible patients were aged 18 years or older, had a planned definitive plastic and reconstructive surgery operation under a general anesthetic,

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and had planned postoperative admission of at least 2 overnights. All patients had sequential compression devices placed in the operating room and continued during inpatient admission. Patients were ineligible if they had any one of the following: contraindication to use of enoxaparin, intracranial bleeding or stroke, hematologic or bleeding disorder, known heparin-induced thrombocytopenia, creatinine clearance less than or equal to 30 ml/minute, serum creatinine greater than 1.6 mg/dl, epidural anesthesia, or patient/surgeon desire to be provided with non-enoxaparin chemical prophylaxis after surgery. Patients who received perioperative aspirin were eligible for the study. Patients whose gross weight was more than 150 kg were excluded. There was no minimum study weight. All patients provided written informed consent before their planned definitive operation (Fig. 1).

Study Procedures

Patients were randomized immediately after their planned definitive operation, following a direct conversation between the principal investigator (C.J.P.), primary plastic surgeon, and consultant surgeons or physicians. Primary surgeons had the discretion to decline study participation based on intraoperative events, such as procedure less invasive than planned or concern for intraoperative bleeding. Eligible patients were randomized to enoxaparin 40 mg twice daily or enoxaparin 0.5 mg/kg twice daily.

The investigational pharmacy randomized patients and then provided study drug in identical syringes containing clear liquid; all doses were diluted to 1.0-cc volume. Patients received the first dose of study drug as a subcutaneous injection between 7 and 8 hours after the procedure ended and every 12 hours thereafter until discharge from the hospital.

Patients had peak and steady state anti–factor Xa levels drawn after the third enoxaparin dose, at steady state. Goal peak steady state anti–factor Xa was 0.2 to 0.4 IU/ml.[17,18,25–27] The investigational pharmacy identified patients with out-of-range peak anti–factor Xa levels and performed real-time enoxaparin dose adjustment (Fig. 2). Dose adjustment was performed because initial low anti–factor Xa levels are associated with a significantly increased risk of venous thromboembolism and high anti–factor Xa levels have been associated with bleeding.[16,19,20,25,28,29] Therefore, not providing real-time dose adjustment in response to documented anti–factor Xa levels would have been ethically marginal. Patients whose level was in-range continued on their initial enoxaparin dose until discharge. Patients who received real-time dose adjustment underwent dose optimization until in-range peak anti–factor Xa level was achieved, and then received that dose until discharge.

Patients did not routinely receive postdischarge enoxaparin prophylaxis; this was provided only at attending physician discretion. When applicable, the resident physician received unblinded dose information, allowing the attending physician to remain blinded and objectively identify secondary outcome events while providing patients with a pharmacokinetically optimized dose.

The primary outcome (anti–factor Xa level in response to initial enoxaparin dose) occurred 36 hours after surgery and could not be confounded by dose adjustment or receipt of postdischarge enoxaparin. Patients received standard postoperative care from the primary surgeon. The study team contacted all randomized patients at 90 days to identify secondary outcomes.

Study Outcomes

Study outcomes were defined before enrollment of patient 1, and definitions were published previously.[24] Both primary outcomes were pharmacokinetic outcomes derived from the initial peak steady state anti–factor Xa level, drawn at 36 hours after conclusion of the operation (Fig. 2). The initial peak steady state level was in response to the initial enoxaparin dose; when dose adjustment was required, this level was not considered in the primary outcome. The primary effectiveness outcome was avoidance of underanticoagulation (peak anti–factor Xa <0.20 IU/ml). The primary safety outcome was avoidance of overanticoagulation (peak anti–factor Xa >0.40 IU/ml). Post–dose-adjustment anti–factor Xa levels, if drawn, were not considered in the primary outcomes. Both secondary outcomes were obtained at 90 days after surgery. The secondary effectiveness outcome was 90-day symptomatic venous thromboembolism, and the secondary safety outcome was 90-day clinically relevant bleeding.

Symptomatic venous thromboembolism was defined as (1) any imaging-confirmed deep venous thrombosis event, including upper limb, lower limb, or central; (2) any imaging-confirmed pulmonary embolus event; (3) any autopsy-proven venous thromboembolism; and/or (4) 90-day mortality in which venous thromboembolism could not be excluded (e.g., pulseless electrical activity arrest without autopsy). Patients were

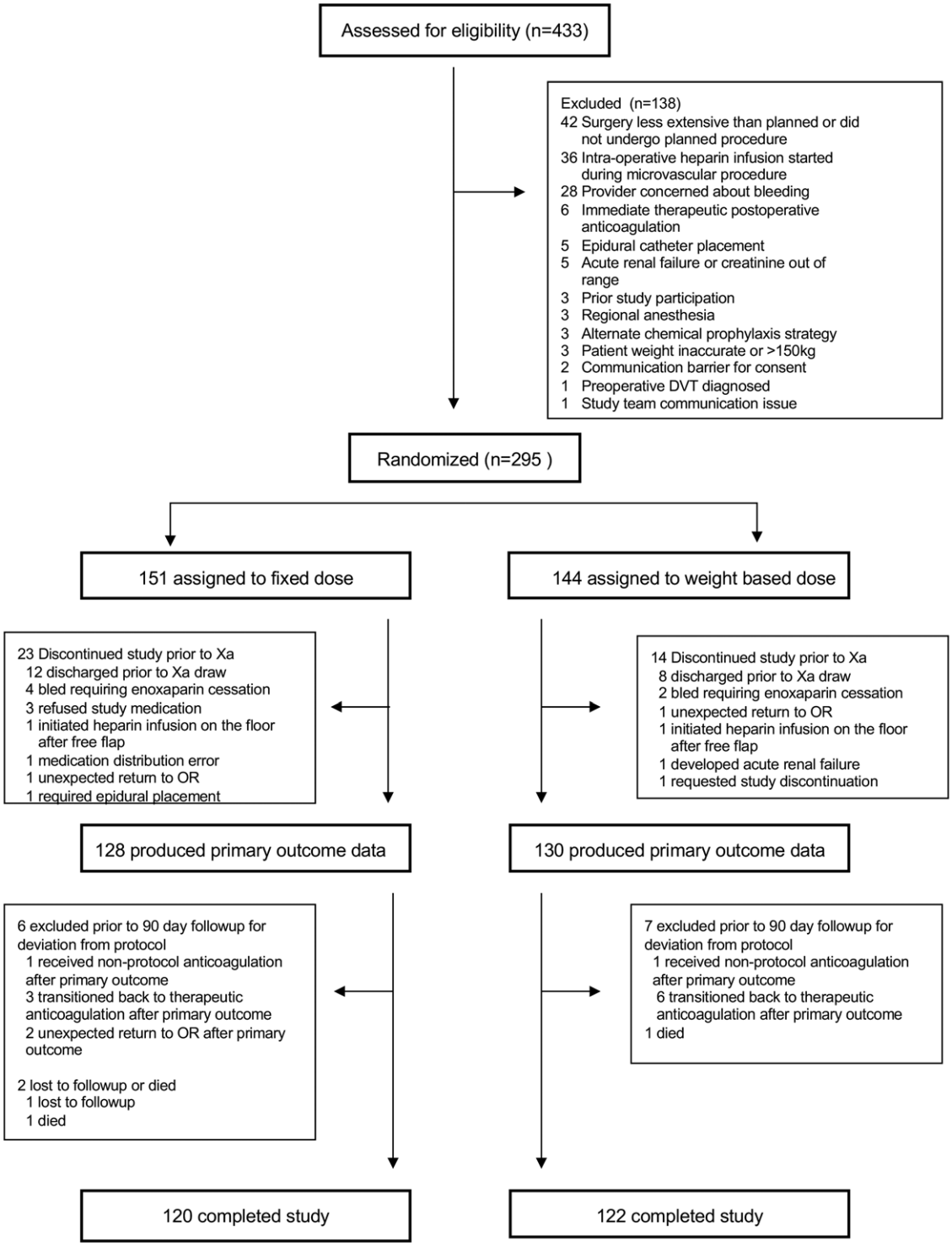

Fig. 1. Consolidated Standards of Reporting Trials diagram of screening, randomization, and 90-day follow-up. *DVT*, deep venous thrombosis; *Xa*, anti–factor Xa; *OR*, operating room.

not screened for venous thromboembolism events unless symptoms were present.[10]

Major bleeding was defined using the published consensus definition of major bleeding for randomized controlled trials that examine antihemostatic drugs from the International Society of Thrombosis and Hemostasis.[30] Major bleeding included any of the following events: bleeding requiring 2 or more units of blood transfusion, bleeding requiring bedside hematoma

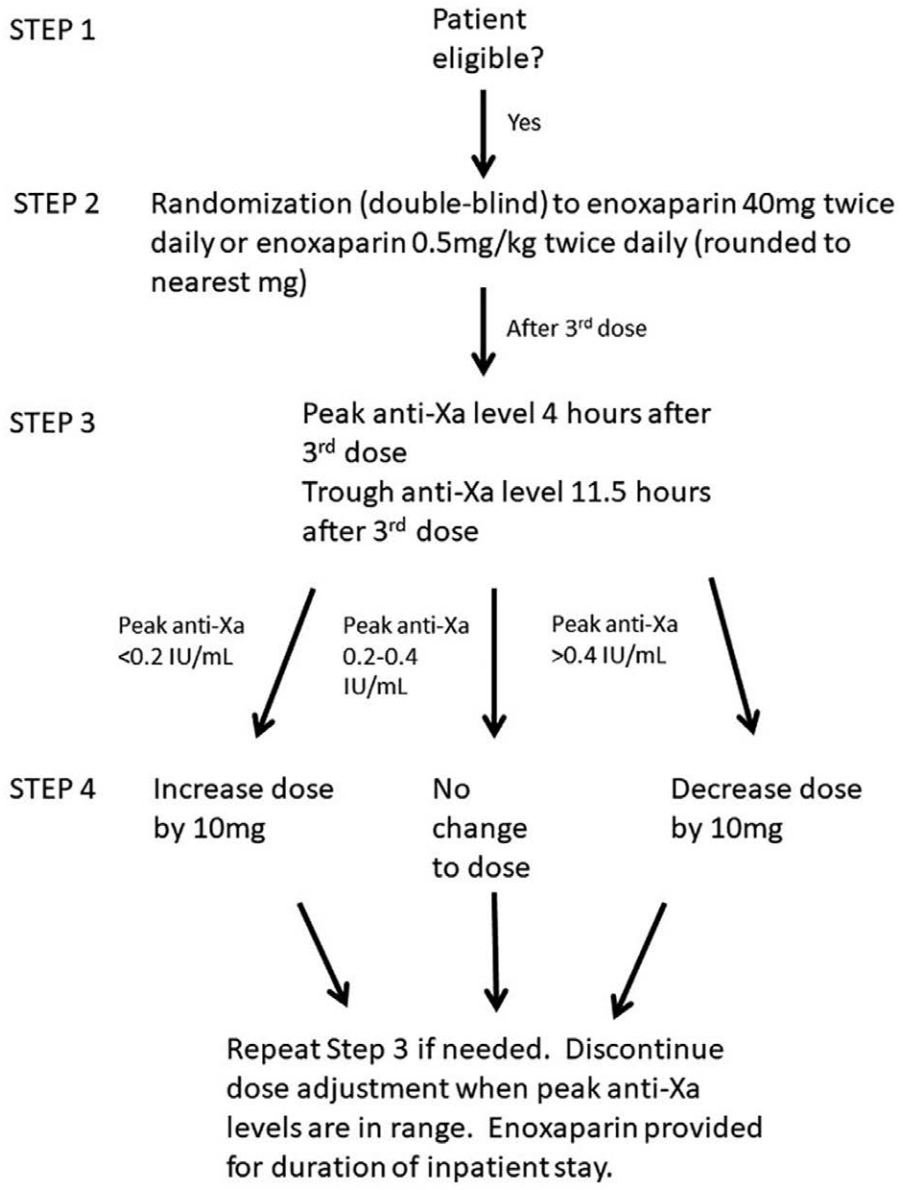

Fig. 2. FIVE study protocol for inpatient stay. (Reprinted from Pannucci CJ, Fleming KI, Bertolaccini C, Prazak AM, Stoddard GJ, Momeni A. Double-blind randomized clinical trial to examine the pharmacokinetic and clinical impacts of fixed dose versus weight-based enoxaparin prophylaxis: A methodologic description of the FIxed or Variable Enoxaparin (FIVE) trial. *Plast Reconstr Surg Glob Open* 2019;7:e2185; copyright owned by C.J.P.).

evacuation or interventional radiology procedure, bleeding requiring unplanned return to the operating room, bleeding into a critical anatomical space, or fatal bleeding. In addition, we tracked clinically relevant bleeding, which was defined more broadly to include bleeding that required enoxaparin cessation in addition to all major bleeding factors. Ninety-day bleeding and venous thromboembolism were compared between groups using a survival analysis log-rank test. Outcome events were blindly adjudicated.

Statistical Analysis

The FIVE trial's sample size calculations and justifications were previously published.[24] Statistical analyses were performed using Stata15 (StataCorp, College Station, Texas). We compared patient-level variables (Tables 1 and 2) between groups using the *t* test for continuous variables, chi-square or Fisher's exact test for dichotomous variables, and Wilcoxon rank sum test for ordinal variables.

The primary effectiveness outcome was avoidance of underanticoagulation (peak anti–factor

Table 1. Patient Demographics and Surgical Details, by Group

Characteristic	Fixed Dose (%)	Weight Tiered (%)	*p*
No. of patients	151	144	
Mean age ± SD, yr	49.0 ± 15.6	52.7 ± 14.8	0.04
Ethnicity			0.50
White	137 (90.7)	135 (93.8)	
African American	1 (0.7)	0 (0)	
Native American/Alaskan Native	1 (0.7)	0 (0)	
Hispanic or Latino	11 (7.3)	8 (5.6)	
Pacific Islander	1 (0.7)	0 (0)	
Other	0 (0)	1 (0.7)	
Mean BMI ± SD, kg/m^2	28.9 ± 6.9	28.8 ± 6.6	0.87
Mean gross weight ± SD, kg	82.8 ± 21.4	83.3 ± 20.2	0.85
Mean height ± SD, in	66.8 ± 5.0	67.1 ± 4.8	0.65
Female sex	81 (53.6)	70 (48.6)	0.39
Diabetes receiving treatment	30 (19.9)	33 (22.9)	0.52
Hypertension	42 (27.8)	48 (33.3)	0.30
Coronary artery disease	10 (6.6)	7 (4.9)	0.52
Mean creatinine ± SD, mg/dl	0.77 ± 0.21	0.78 ± 0.23	0.89
Smoking history			
Current smoker	13 (8.6)	18 (12.5)	0.28
Past smoker	68 (45.3)	63 (43.4)	0.79
2005 Caprini score			
Median	6	7	
Range	2–15	2–16	0.10
General anesthesia	151 (100)	144 (100)	—
Surgery combined with second surgeon	57 (37.8)	65 (45.1)	0.20
Surgery location			0.23
Head/neck	6.0 (9)	9 (6.3)	
Nonbreast chest	0 (0)	2 (1.4)	
Breast	46 (30.5)	35 (24.3)	
Abdomen/genitals	10 (6.6)	6 (4.2)	
Back including pressure ulcers	28 (18.5)	36 (25.0)	
Upper extremity	23 (15.2)	14 (9.7)	
Lower extremity	35 (23.2)	42 (29.2)	
Mean total body surface area surgically injured ± SD, %	4.9 ± 3.5	5.2 ± 3.4	0.41
Length of operation, min			
Median	223	235	
IQR	125–453	154–436	0.93
Postoperative aspirin	65 (43.0)	58 (40.3)	0.63
Length of hospital stay, days			
Median	6	6	
IQR	5–8	5–8	0.91
Received postdischarge enoxaparin	28 (18.5)	35 (24.3)	0.23
Mean length of enoxaparin ± SD, days	8.6 ± 8.7	10.1 ± 9.8	0.16

Xa <0.20 IU/ml). Initial sample size estimates for underanticoagulation avoidance were obtained from a prior clinical trial, which established that 90.4 percent of patients who received enoxaparin 40 mg twice daily were not underanticoagulated.[17] We assumed that the rate of not being underanticoagulated was 90.4 percent in the weight-based group. The primary effectiveness analysis was a noninferiority analysis with a two-sided test at the 0.05 level. The noninferiority margin was set at −12 percent. To achieve 90 percent power using a two-sided comparison with alpha of 0.05, using a two-sided 95 percent confidence interval around the difference in proportions, 127 patients per group were needed. The noninferiority hypothesis was tested by a Poisson regression model for binary outcomes with robust standard errors. After the Poisson model was fit, marginal estimation was used to calculate the 95 percent confidence interval around the difference in proportions.[31,32] This method took the two estimated proportions used in the risk ratio, subtracted then, and computed the confidence interval for noninferiority testing. To obtain a two-sided noninferiority test *p* value, we used a Wald posttest to compare the difference in proportions to the noninferiority margin constant −0.12.

The primary safety outcome was avoidance of overanticoagulation (peak anti–factor Xa >0.40 IU/ml). Initial sample size estimates for overanticoagulation were obtained from a prior clinical trial, which showed that 72.2 percent of patients who received enoxaparin 40 mg twice daily were not overanticoagulated.[17] We assumed that weight-based dosing would increase the proportion of patients not overanticoagulated to 90 percent. To detect this difference with 90 percent power using a two-sided comparison with alpha of 0.05, 100 patients per group were needed. For this

Table 2. Patient-Specific Venous Thromboembolism Risk Factors, by Group

Characteristic	Fixed Dose (%)	Weight Based (%)	*p*
No. of patients	151	144	
One-point factors			
Age 41–59 yr	64 (42.4)	55 (38.2)	0.46
Minor surgery planned	2 (1.3)	0 (0)	0.50
Major surgery within 30 days	18 (11.9)	12 (8.3)	0.34
Varicose veins	6 (3.4)	10 (6.9)	0.31
History of IBD	9 (6.0)	10 (6.9)	0.73
Swollen legs (current)	1 (0.66)	6 (4.2)	0.062
BMI >25 kg/m^2	96 (63.6)	98 (68.1)	0.42
Acute myocardial infarction <3 mo	0 (0)	0 (0)	—
Congestive heart failure <1 mo	0 (0)	0 (0)	—
Sepsis <1 mo	3 (2.0)	5 (3.5)	0.49
Serious lung disease (including pneumonia) <1 mo	2 (1.3)	0 (0)	0.50
Chronic obstructive pulmonary disease	5 (3.3)	7 (4.9)	0.57
Medical patient currently at bedrest	0 (0)	0 (0)	—
Two-point factors			
Age 60–74 yr	31 (20.5)	46 (31.9)	0.026
Arthroscopic surgery	0 (0)	0 (0)	—
Malignancy (present or previous)	59 (39.1)	61 (42.4)	0.57
Major surgery >45 min	149 (98.7)	144 (100)	0.17
Laparoscopic surgery >45 min	0 (0)	0 (0)	—
Immobilizing plaster cast	0 (0)	0 (0)	—
Central venous access	48 (31.8)	64 (44.4)	0.025
Three-point factors			
Age ≥75 yr	9 (6.0)	9 (6.3)	1.00
History of DVT/PE	19 (12.6)	28 (19.4)	0.11
Family history of DVT/PE	24 (15.9)	14 (9.7)	0.11
Any genetic hypercoagulable state	1 (0.66)	0 (0)	1.00
Five-point factors			
Elective lower extremity arthroplasty	1 (0.66)	0 (0)	1.00
Hip, pelvis, or leg fracture <1 mo	2 (1.3)	3 (2.1)	0.68
Stroke <1 mo	0 (0)	0 (0)	—
Multiple trauma <1 mo	2 (1.3)	2 (1.4)	1.00
Acute spinal cord injury/paralysis <1 mo	0 (0)	0 (0)	—
No. of female patients	81	70	
One-point factors (female patients only)			
Oral contraceptives	12 (14.8)	8 (11.4)	0.63
Pregnancy or postpartum (<1 mo)	0 (0)	0 (0)	—
History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant	4 (4.9)	1 (1.4)	0.37

IBD, inflammatory bowel disease; BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism.

outcome, a Poisson regression model for binary outcomes with robust standard errors was fitted.[31]

The Data Safety and Monitoring Board reviewed unblinded 90-day venous thromboembolism and bleeding data every 6 months. To avoid an increased risk for type I error, no interim analyses were performed on primary outcomes.

After 254 patients were randomized, the study statistician reviewed unblinded data to determine the number of patients who did not produce primary outcome data. No interim statistical analysis was performed at this phase, to avoid an increased risk for type I error. The planned sample size was adjusted upward to 295, to include at least 127 patients in each group who produced primary outcomes data.

RESULTS

Through the practices of 11 surgeons, 433 patients were screened and provided informed consent between July 1, 2017, and May 31, 2019 (Fig. 1). Two hundred ninety-five patients were randomized, including 151 in the fixed-dose group and 144 in the weight-based group. Table 1 shows the characteristics of the patients at baseline, and Table 2 describes their baseline risk for venous thromboembolism, quantified using the 2005 Caprini score.[8]

Primary Outcomes

Among 295 randomized patients, 87 percent (n = 258) produced primary outcome data. Our first hypothesis was that weight-based enoxaparin is not inferior to fixed-dose enoxaparin for avoidance of underanticoagulation (peak anti–factor Xa <0.2 IU/ml).

Randomization did not achieve complete balance of the groups on patient age, with the weight-based group having a higher mean age of

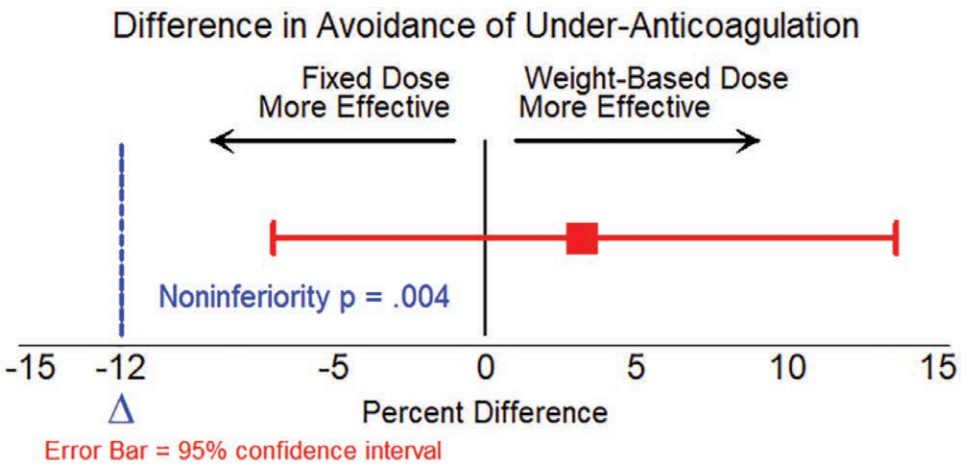

Fig. 3. Avoidance of underanticoagulation between groups. A value of −12 percent indicates the prespecified noninferiority margin.

3.7 years ($p = 0.04$). The weight-based group also had a significantly higher proportion of patients with central venous catheters (44 percent versus 32 percent; $p = 0.03$). Consistent with our prespecified statistical analysis plan,[24] we controlled for both factors when testing for noninferiority. In the multivariable model, the weight-based group had a 3.3 percent greater effectiveness at avoidance of underanticoagulation (95 percent CI, −7.5 to 12.5 percent), which achieved statistically significant noninferiority relative to the a priori specified −12 percent noninferiority margin ($p = 0.004$) (Fig. 3).

Our second hypothesis was that weight-based enoxaparin is superior to fixed-dose enoxaparin for avoidance of overanticoagulation (peak anti–factor Xa >0.4 IU/ml). Consistent with our prespecified statistical analysis plan,[24] we controlled for age and central venous catheter when testing for superiority. In the multivariable model, the weight-based group achieved absence of overanticoagulation in 90.6 percent of patients, whereas the fixed-dose group achieved this in 82.2 percent of patients. The absolute 8.4 percent (95 percent CI, 0.1 to 16.6 percent) greater absence of overanticoagulation showed statistically significant safety superiority for weight-based dosing ($p = 0.046$). (Fig. 4)

Secondary Outcomes

Two hundred thirty-five patients had initial steady state trough anti–factor Xa levels drawn. When compared to a fixed dose, weight-based dosing did not significantly increase the proportion of patients who achieved a trough anti–factor Xa level greater than or equal to 0.1 IU/ml (43.0 percent versus 33.5 percent; $p = 0.14$), and did not significantly decrease the proportion of patients who had a trough anti–factor Xa level greater than 0.2 IU/ml (8.3 percent versus 7.9 percent; $p = 0.33$).

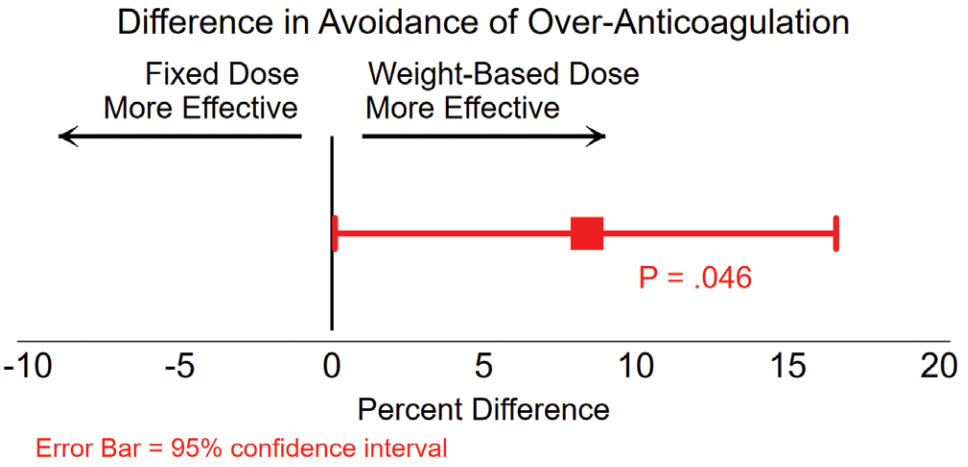

Fig. 4. Avoidance of overanticoagulation between groups.

Major bleeding events included patients who required unexpected blood transfusion, return to the operating room, or an interventional radiology procedure. Major bleeding was not significantly different between fixed-dose and weight-based enoxaparin (3.3 percent versus 4.2 percent; log rank $p = 0.72$). (**See Figure, Supplemental Digital Content 1**, which shows 90-day major bleeding by group, *http://links.lww.com/PRS/E385*.)

Clinically significant bleeding events included those with major bleeding, plus one patient who bled before study drug administration, two who bled after five half-lives of final drug administration, and seven whose only bleeding sequela was study drug discontinuation. Clinically significant 90-day bleeding was not significantly different between fixed-dose and weight-based enoxaparin (6.0 percent versus 8.3 percent; log rank $p = 0.33$). (**See Figure, Supplemental Digital Content 2**, which shows 90-day all-cause bleeding by group, *http://links.lww.com/PRS/E386*.)

Ninety-day symptomatic venous thromboembolism was not significantly different between fixed-dose and weight-based enoxaparin (0.66 percent versus 0.69 percent; log rank $p = 0.98$). (**See Figure, Supplemental Digital Content 3**, which shows 90-day symptomatic venous thromboembolism by group, *http://links.lww.com/PRS/E387*.)

DISCUSSION

The FIVE trial examined the pharmacokinetics of weight-based or fixed-dose enoxaparin in plastic surgery inpatients. The trial's goal was identification of the optimal enoxaparin dosing strategy to minimize risk of both venous thromboembolism and enoxaparin-associated bleeding. We found that weight-based enoxaparin (0.5 mg/kg twice daily) was not inferior to fixed-dose enoxaparin (40 mg twice daily) for avoidance of underanticoagulation, and that weight-based enoxaparin was superior to fixed-dose enoxaparin for avoidance of overanticoagulation. FIVE trial data have relevance beyond pharmacokinetic optimization, because studies in plastic surgery,[16] orthopedic surgery,[25,33] trauma surgery,[19,20,29] and surgical patients in general[34] have shown that inadequate anticoagulation significantly increases postoperative venous thromboembolism risk, and studies in orthopedic surgery have correlated high anti–factor Xa levels with increased risk for bleeding.[25]

Our data are consistent with prior nonrandomized studies suggesting that weight-based enoxaparin dosing is pharmacokinetically superior to fixed-dose enoxaparin in surgical patients. Berndtson et al. showed that weight-tiered enoxaparin allowed a significantly increased proportion of trauma surgery patients to achieve in-range peak anti–factor Xa levels when compared to fixed-dose enoxaparin (79.5 percent versus 29.5 percent; $p < 0.001$).[18] Similar findings have been published in the medically ill population with morbid obesity.[35] Overcash et al., in a study of morbidly obese women after cesarean delivery, showed that enoxaparin 0.5 mg/kg significantly increased rates of in-range peak anti–factor Xa levels when compared to a body mass index–tiered dose strategy (86 percent versus 26 percent; $p < 0.001$).[36]

A one-size-fits-all strategy for enoxaparin prophylaxis was supported by clinical trials from the early 1990s showing that fixed dosing was effective for venous thromboembolism prevention among high-risk surgical patients.[13,37–40] At the group level, postoperative anticoagulation clearly decreases the risk for venous thromboembolism. However, the one-size-fits-all strategy fails when considered at the individual patient level. Specifically, between 4 and 10 percent of patients have "breakthrough" venous thromboembolism—that which occurs despite administration of enoxaparin prophylaxis.[2,13,14] This was clearly demonstrated in plastic surgery inpatients by the Venous Thromboembolism Prevention Study, where 4.1 percent of the highest risk patients developed symptomatic 60-day venous thromboembolism *despite* enoxaparin prophylaxis.[2] The burn literature has correlated patient weight with rapidity of enoxaparin metabolism,[22,41] and burn and trauma literature suggest that a patient-centric enoxaparin dose regimen improves venous thromboembolism risk reduction.[29,42] Subsequent trials in plastic surgery inpatients confirmed that patients metabolized a one-size-fits-all enoxaparin dose at different rates, that patients experienced different degrees of anticoagulation as a result, and that patients with inadequate anticoagulation were at significantly elevated risk for breakthrough venous thromboembolism events.[16]

Thus, prior work has identified inadequate enoxaparin dosing as a risk factor for venous thromboembolism, and as a novel target for venous thromboembolism prevention. The FIVE trial provides Level I data to support enoxaparin 0.5 mg/kg twice daily as an effective and safe way to achieve adequate enoxaparin dosing that improves on the current one-size-fits-all standard.

Limitations

The FIVE trial was designed to identify the enoxaparin regimen that optimized pharmacokinetics,

and its sample size calculations were based on pharmacokinetic endpoints. Statistical significance was demonstrated for both primary study endpoints, meaning that the authors are confident in the truth of their findings—but statistical significance does not walk hand-in-hand with clinical relevance. The FIVE trial was never designed to be adequately powered to evaluate differences in 90-day venous thromboembolism or bleeding (both rare events); unsurprisingly, 90-day venous thromboembolism or bleeding were not significantly different between groups. What is clear from this study is that observed rates of symptomatic venous thromboembolism are low (<1 percent) with a twice-daily enoxaparin regimen, and that weight-based dosing was associated with a small (0.9 percent) increase in 90-day clinically relevant bleeding. Readers may interpret these findings as they choose. Worth noting is that pharmacokinetic optimization directly impacts patient-level outcomes. A retrospective study in trauma surgery patients receiving twice-daily enoxaparin demonstrated a significant increase in asymptomatic deep venous thrombosis among patients with low versus adequate peak anti–factor Xa levels (22 percent versus 7 percent; $p = 0.02$).[19] Our group's aggregate data from 577 surgical patients receiving twice-daily enoxaparin clearly show a significant increased risk for 90-day symptomatic venous thromboembolism in patients with low versus adequate peak anti–factor Xa levels (6.2 percent versus 1.5 percent; $p = 0.003$).[17,33,34,43]

Whether these data are generalizable to all surgical patients is unknown. Arguably, the plastic and reconstructive surgery population is the ideal population on which to test concepts for surgical patients in general, as plastic surgery inpatients represent a cross-section of surgical patients. Many are referred for immediate postoperative complications from other providers, or are operated on in combined procedures with other surgeons. Among patients randomized in this trial, 40 percent of patients had a combined definitive operation with another surgical specialty, and 10 percent had a prior surgical procedure within 30 days. The trial was conducted among the inpatient population only and its generalizability to the ambulatory or 23-hour stay population is unclear.

Enoxaparin is provided in prefilled 10-mg/0.1-cc syringes, and cannot reliably be used to administer doses that are not in 10-mg increments. The weight-based arm received enoxaparin 0.5 mg/kg, rounded to a 1-mg standard, and all study drug was provided by the investigational pharmacy. Provision of weight-based enoxaparin to a 1-mg standard may not be possible in day-to-day practice, as it requires custom compounding by the inpatient pharmacy. Inpatient pharmacies will commonly round enoxaparin to a 10-mg standard to allow use of the prefilled syringes—a fact we discovered during a before-and-after trial of fixed or weight-based enoxaparin in thoracic surgery patients at our own institution (NCT03251963). This represents an institution-specific barrier to implementation of our study results.

CONCLUSIONS

The FIVE trial showed that for plastic surgery inpatients, enoxaparin 0.5 mg/kg twice daily showed pharmacokinetic superiority to enoxaparin 40 mg twice daily for avoidance of overanticoagulation (anti–factor Xa >0.4 IU/ml), and was not inferior for avoidance of underanticoagulation (anti–factor Xa <0.2 IU/ml). This trial provides Level I evidence to guide the plastic surgeon's postoperative enoxaparin dose strategy for inpatients.

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