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Enoxaparin in Primary and Facilitated Percutaneous Coronary Intervention

A Formal Prospective Nonrandomized Substudy of the FINESSE Trial (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events)

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Objectives The aim of this study was to assess the risk-benefit of enoxaparin (Sanofi-Aventis, Paris, France) in primary percutaneous coronary intervention (PCI).

Background Randomized studies have demonstrated the superiority of enoxaparin over unfractionated heparin (UFH) in acute ST-segment elevation myocardial infarction (STEMI) treated with fibrinolytics.

Methods In the FINESSE (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events) trial—a double-blind, placebo-controlled study—2,452 patients with STEMI were randomized to primary PCI or facilitated PCI with abciximab alone or with half-dose reteplase. In this prospective FINESSE substudy, centers pre-specified use of either enoxaparin (0.5 mg/kg intravenous [IV], 0.3 mg/kg subcutaneous [SC]) or UFH (40 U/kg IV, 3,000 U maximum) with PCI. A logistic-regression model and a propensity multivariate model, both adjusted for baseline variables, were used to evaluate primary safety and secondary efficacy end points for enoxaparin versus UFH.

Results Enoxaparin was administered to 759 patients and UFH to 1,693 patients. Nonintracranial Thrombolysis In Myocardial Infarction (TIMI) major/minor bleeding was not significantly different, but lower nonintracranial TIMI major bleeding was found with enoxaparin (2.6% vs. UFH 4.4%, logistic-regression adjusted odds ratio [OR]: 0.55; 95% confidence interval [CI]: 0.31 to 0.99, $p = 0.045$), whereas intracranial hemorrhage was similar (0.27% vs. 0.24%, adjusted OR: 1.03; 95% CI: 0.11 to 9.68, $p = 0.980$). Lower death, myocardial infarction, urgent revascularization, or refractory ischemia through 30 days was also associated with enoxaparin (5.3%) versus UFH (8.0%, adjusted OR: 0.47, 95% CI: 0.31 to 0.72, $p = 0.0005$) as was all-cause mortality through 90 days (3.8% vs. 5.6%, respectively, adjusted OR: 0.59, 95% CI: 0.35 to 0.99, $p = 0.046$). End points evaluating the net clinical benefit also significantly favored enoxaparin over UFH.

Conclusions Enoxaparin seems to be associated with a lower risk of cardiovascular outcomes compared with UFH in patients with STEMI undergoing primary PCI. Confirmation of these findings in a randomized study is warranted. (A Study of Abciximab and Reteplase When Administered Prior to Catheterization After a Myocardial Infarction [Finesse]; NCT00046228) (J Am Coll Cardiol Intv 2010;3:203–12)

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In primary percutaneous coronary intervention (PCI) of acute ST-segment elevation myocardial infarction (STEMI), unfractionated heparin (UFH) is the only recommended anticoagulant drug, despite having a "C" level of evidence and no standardized dosing aside from rules extended from elective angioplasty (1–3). Compared with UFH, enoxaparin (Sanofi-Aventis, Paris, France) has a more stable and predictable anticoagulant dose-response, eliminating the need for coagulation monitoring; a lower binding affinity for plasma and tissue proteins; and a higher ratio of anti-Xa to anti-IIa, resulting in less thrombin generation and activation. Enoxaparin also reduces platelet activation, von Willebrand factor release, and inflammation (4–6).

See page 213

Abbreviations and Acronyms

ACT = activated clotting time
BMI = body mass index
CI = confidence interval
ECG = electrocardiogram
IV = intravenous
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
SC = subcutaneous
UFH = unfractionated heparin
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Intravenous enoxaparin has been compared with IV UFH in 13 randomized studies of elective PCI. In the largest study of 3,528 patients, enoxaparin (0.5 mg/kg) significantly reduced the primary safety end point of any bleeding, with a 57% reduction in major bleeding, compared with an activated clotting time (ACT)-adjusted UFH regimen (7). Although underpowered for efficacy, 30-day ischemic events were not statistically different in the enoxaparin and UFH groups. A recent meta-analysis of all randomized studies performed in PCI (n = 7,318) confirmed the significant reduction of major bleeding with enoxaparin and showed, with an adequate power, identical ischemic event rates for patients treated with UFH or enoxaparin (8).

Enoxaparin has also been investigated as a heparin substitute in STEMI but almost exclusively in the context of fibrinolysis. In the large ExTRACT (Enoxaparin and Thrombosis Reperfusion for Acute Myocardial Infarction Treatment) trial, treatment with subcutaneous enoxaparin throughout the index hospital stay period was superior to treatment with UFH for at least 48 h in reducing death or recurrent myocardial infarction (MI) but was associated with increased major bleeding episodes (9). A recent meta-analysis of enoxaparin in acute coronary syndromes demonstrated that the increased risk for bleeding was offset by the reduction in death or MI and that the net benefit was significantly greater with enoxaparin than UFH (10).

Although there is evidence for the superiority of enoxaparin in STEMI treated with fibrinolytics, investigation of enoxaparin in primary PCI of acute STEMI is limited to small observational studies or series of patients (11,12). A larger experience with enoxaparin in combination with agents commonly used in acute MI is needed to fully assess the efficacy and safety of enoxaparin in primary PCI of acute STEMI.

The recent multicenter, randomized, double-blind, placebo-controlled FINESSE (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events) trial compared the efficacy of facilitated PCI with abciximab alone or in combination with reteplase versus primary PCI with in-laboratory abciximab in 2,452 patients with acute STEMI. Facilitation with abciximab alone or combined with half-dose reteplase increased major hemorrhage and did not demonstrate significant reduction in the 90-day primary end point of composite all-cause mortality or complications of MI (ventricular fibrillation beyond 48 h, cardiogenic shock, and congestive heart failure requiring repeat hospital stay or emergency room visit) (13). In this prospective, nonrandomized, stratified FINESSE substudy, we obtained clinical data on the safety and efficacy of enoxaparin versus UFH as the sole background antithrombin therapy in conjunction with 3 different randomized strategies assessing the value of pharmacologic facilitation before primary PCI for STEMI. Additionally, we used 2 adjusted analyses to explore the robustness of the differences in clinical outcomes in all patients treated with enoxaparin versus UFH.

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Methods

Patients. Details of the FINESSE trial design and primary outcome have been previously reported (13,14). Briefly, patients presenting within 6 h of symptom onset with ST-segment elevation or new left bundle branch block were enrolled if the estimated time to diagnostic catheterization was 1 to 4 h from randomization and if they were not at low risk (i.e., inferior infarction and age <60 years). Patients who received any UFH within 24 h of randomization or who had a history of allergy to enoxaparin or who had an estimated creatinine clearance <30 ml/min adjusted for sex were excluded from the enoxaparin substudy. However, there was no dose adjustment protocol of enoxaparin for renal function.

Study design. In the FINESSE trial, patients were randomly allocated to combination-facilitated PCI (abciximab [Centocor B.V., Leiden, the Netherlands] 0.25 mg/kg IV bolus + reteplase [Centocor B.V.] 2 5-U boluses separated by 30 min for those <75 years of age or 1 5-U bolus for those ≥75 years of age), abciximab-facilitated PCI (0.25 mg/kg IV bolus), or primary PCI (placebo with blinded crossover therapy to abciximab 0.25 mg/kg IV bolus immediately before PCI). After PCI, all patients were maintained on abciximab 0.125 μg/kg/min IV (maximum 10 μg/min) for 12 h. All patients were to have received aspirin 81 to 325 mg orally (or 250 to 500 mg IV, depending on approval per country) as soon as possible after randomization and daily for at least 90 days after randomization.

In this FINESSE enoxaparin substudy, randomized patients were stratified by study center to receive enoxaparin or UFH. Each study center pre-specified its choice of adjunct anti-thrombin therapy as either UFH (40 U/kg, 3,000 U maximum; 200 to 250 s target ACT) or weight-adjusted enoxaparin (0.5 mg/kg IV and 0.3 mg/kg SC; no target ACT). Additional UFH for PCI was not permitted in the catheterization laboratory for patients stratified to receive enoxaparin. Enoxaparin was not allowed within 24 h of randomization for patients stratified to receive UFH. Additional enoxaparin or UFH was permitted 24 h after randomization for any patient with an indication for longer-term anticoagulation. The primary safety end points were: 1) the incidence of nonintracranial Thrombolysis In Myocardial Infarction (TIMI) bleeding (major or minor); and 2) the incidence of intracranial hemorrhage (including hemorrhagic transformation) through discharge or day 7, whichever was earlier. The secondary efficacy end points were: 1) the FINESSE main study primary end point (all-cause mortality or complications of MI) through 90 days; 2) complications of MI through 90 days; and 3) all-cause mortality through 90 days.

Post-hoc exploratory analyses. Because many primary PCI trials have used 30-day ischemic end points and to fully explore the difference between enoxaparin and UFH therapy on thrombotic events in the setting of primary PCI for STEMI, additional classical ischemic end points (death, re-infarction, stroke, urgent revascularization, refractory ischemia) through 30 days were explored. Net clinical benefit end points combining efficacy outcomes through 90 days and TIMI major bleeding through discharge/day 7 were also evaluated. Because the comparison was not randomized, 2 different approaches correcting for baseline differences were used to explore the enoxaparin and UFH subpopulations.

The protocol was approved by the institutional review board or independent ethics committee for each study center, and all patients provided written informed consent.

Statistical analysis. Descriptive statistics were used where appropriate to evaluate the safety and efficacy of enoxaparin versus UFH. The difference in baseline characteristics between enoxaparin and UFH was tested with the Wilcoxon test for continuous variables and the chi-square test for categorical variables. Safety analyses were performed according to randomized PCI strategy (combination-facilitated, abciximab-facilitated, or primary) and nonrandomized adjunct anti-thrombin therapy (enoxaparin or UFH). Efficacy analyses were performed comparing enoxaparin with UFH irrespective of randomized PCI strategy (intent-to-treat). No formal statistical testing was performed for enoxaparin versus UFH within each PCI strategy, but testing for heterogeneity was performed.

To adjust for multiple risk factors and potential imbalance of other factors between the 2 subpopulations, logistic regression modeling was first used. For verification, a propensity score methodology was then used. Two sets of variables were considered in each of the statistical approaches. The first set was pre-selected before the modeling exercise, and it consisted of age, sex, Killip class (1 vs. >1), anterior MI (Y/N), prior MI (Y/N), hypertension (Y/N), geographic region (Western Europe, Eastern Europe, North America/rest of the world) and hub/spoke (i.e., PCI-capable/not), randomized PCI strategy, time from symptom onset to electrocardiogram (ECG) (taken during the first medical contact [e.g., in the ambulance, spoke hospital]), and time from ECG to balloon. These items were chosen because they are known risk factors, site-related factors (sites selected enoxaparin or UFH strategy), or treatment-related factors. The second set consisted of the variables that had a statistically significant difference ($p < 0.05$) between enoxaparin and UFH in baseline demographic data, medical history, or medication received at baseline (Table 1).

The logistic regression model included all variables in the first set, and then the final model was determined by investigating whether adding demographic variables, medical history-related variables, or medication-related variables in the second set improved the model fitting. The criterion used for model fitting is Akaike's information criterion (15) with respect to predicting 90-day mortality. When demographic, medical history, or medication variables were added to the model including the first set of variables, only the demographic variables body mass index (BMI) and smoking

Table 1. Baseline Characteristics and Concomitant Medications From Randomization Through Day 7

Variable	UFH (n = 1,693)	Enoxaparin (n = 759)	p Value
Pre-selected			
Age (yrs)	63.0	63.0	0.331
Sex (% female)	438 (25.9)	204 (26.9)	0.600
Prior myocardial infarction	194 (11.5)	72 (9.5)	0.146
Anterior myocardial infarction	802 (47.4)	371 (48.9)	0.489
Killip class 1	1,513 (89.4)	655 (86.3)	0.0281
Hypertension or treated for hypertension	875 (51.7)	298 (39.3)	<0.0001
Hub	1,037 (61.3)	431 (56.8)	0.037
Region			<0.0001
Eastern Europe	977 (57.7)	101 (13.3)	
Western Europe	531 (31.4)	625 (82.4)	
North America/rest of the world	185 (10.9)	33 (4.3)	
Symptom onset to electrocardiogram (h)	2.2	1.9	<0.0001
Electrocardiogram to balloon (h)	2.3	2.1	<0.0001
Randomized percutaneous coronary intervention strategy			0.949
Primary	560 (33.1)	246 (32.4)	
Abciximab-facilitated	563 (33.3)	255 (33.6)	
Combination-facilitated	570 (33.7)	258 (34.0)	
Variables significantly different between the UFH and enoxaparin subpopulations			
Body mass index (kg/m^2)	26.9	26.3	0.0007
Smoker	1,081 (63.9)	529 (69.7)	0.0048
Diabetes	286 (16.9)	94 (12.4)	0.0043
Chronic lung disease	103 (6.1)	68 (9.0)	0.0098
Other characteristics			
Medical history			
Prior transient ischemic attack	29 (1.7)	15 (2.0)	0.650
Prior stroke	31 (1.8)	14 (1.8)	0.982
Prior coronary artery bypass graft	29 (1.7)	13 (1.7)	1.000
Prior percutaneous coronary intervention	91 (5.4)	43 (5.7)	0.770
Previous congestive heart failure	28 (1.7)	6 (0.8)	0.091
Peak activated clotting time(s)	230	132	<0.0001
Cardiac medications at baseline*			
Aspirin	1,290 (76.2)	461 (60.7)	<0.0001
Ticlopidine/clopidogrel	141 (8.3)	126 (16.6)	<0.0001
Nitrates	841 (49.7)	319 (42.0)	0.0005
Diuretics	162 (9.6)	93 (12.3)	0.0441
Gastric protective	305 (18.0)	69 (9.1)	<0.0001
Medications after baseline			
Randomization through 24 h after randomization			
Aspirin	1,581 (93.4)	716 (94.3)	0.371
Ticlopidine/clopidogrel	1,494 (88.2)	692 (91.2)	0.031
24 h after randomization through discharge/day 7			
Aspirin	1,600 (94.5)	731 (96.3)	0.057
Ticlopidine/clopidogrel	1,531 (90.4)	692 (91.2)	0.560
Any enoxaparin	308 (18.2)	229 (30.2)	<0.001
Any enoxaparin treatment through discharge/day 7	342 (20.2)	745 (98.2)	
Any UFH treatment through discharge/day 7	1,656 (97.8%)	36 (4.7%)	
Duration of enoxaparin treatment in enoxaparin-treated patients through discharge/day 7, days	3 (2–5)	1 (1–4)	
Any enoxaparin treatment from discharge/day 7 to day 90	69 (4.1)	85 (11.2)	<0.001

Values are median, n (%), or median (interquartile range). Baseline characteristics were analyzed with the chi-square test for the discrete variables and the Wilcoxon test for the continuous variables. *From 7 days before randomization to randomization.

UFH = unfractionated heparin.

status improved the model fitting for 90-day mortality. Therefore, the adjusted safety and efficacy analysis results shown in the following text were based on the final model, which included covariates of the first set of variables and BMI and smoking status.

The second approach developed to verify the results of the first model was an analysis based on propensity scores (16). The propensity score of receiving enoxaparin, the probability of receiving enoxaparin, was estimated for each patient by the logistic regression model with covariates of both sets of the aforementioned variables. Then patients were stratified by the quintiles of the estimated propensity scores and were analyzed with the Cochran-Mantel-Haenszel method, stratified by the quintiles of the propensity score and geographic region. Because the geographic region was not adequately balanced by the quintiles of the estimated propensity score, the region was excluded for the propensity model and was adjusted independently from the propensity score.

Adjusted odds ratios (ORs), confidence intervals (CIs), and p values reported in the article are from the logistic regression model unless noted otherwise. No adjustments were made for multiple comparisons. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Population characteristics. Of the 2,452 patients in the FINESSE trial, 759 (U.S. n = 33, Europe n = 726) were enrolled in the enoxaparin substudy and 1,693 received UFH. Study centers in 8 countries pre-specified the use of enoxaparin (Table 1). In the enoxaparin subpopulation, significantly greater proportions of patients were enrolled in Western Europe (vs. Eastern Europe or North America/rest of the world), were smokers, had Killip class >1, or had chronic lung disease (Table 1). In the UFH subpopulation, median BMI was higher, the median times from symptom onset to ECG or from ECG to balloon were longer, and a significantly greater proportions of patients were enrolled at hub sites or had hypertension or diabetes. The distribution of TIMI risk score was similar across UFH and enoxaparin groups (TIMI risk score >5: 9.8% enoxaparin vs. 10.6% UFH, p = 0.51). Concomitant medication use at baseline and after randomization had some differences between UFH and enoxaparin groups (Table 1).

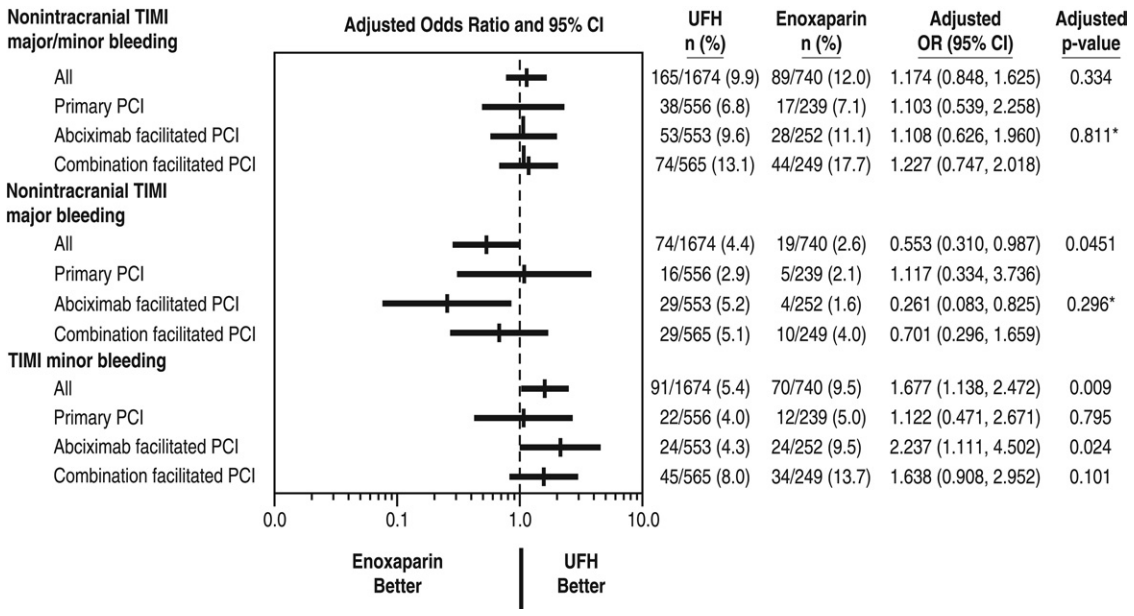
The recommended maximum bolus dose of 3,000 U of UFH was lower than that of many prior studies, although additional heparin was recommended before PCI to maintain the ACT at 200 to 250 s, which was achieved in approximately 40% and which was >250 s in approximately 37% in those in whom it was measured. Relatively few patients received additional heparin during the PCI in the UFH group (n = 86) with a median dose of 2,545 U. The median cumulative dose (IV and SC) of enoxaparin during the hospital stay was 70 mg.

There were 170 centers that were pre-specified to administer UFH and 42 centers pre-specified to administer enoxaparin as the primary antithrombin. Of the 759 patients enrolled at hospitals that chose to administer enoxaparin, 93.4% actually received at least 1 dose within the first 24 h after randomization, whereas 18 (2.4%) also received UFH in this period. Of the 1,698 patients enrolled at hospitals that chose to administer UFH, 91.4% received at least 1 dose of UFH within 24 h after randomization, whereas 67 (3.9%) also received enoxaparin in this period.

Safety. Nonintracranial TIMI major bleeding was significantly lower in patients who received enoxaparin (2.6%) versus UFH (4.4%; adjusted OR: 0.55; 95% CI: 0.31 to 0.99, p = 0.045) (Fig. 1, Table 2). However, nonintracranial TIMI minor bleeding was significantly more frequent with enoxaparin, resulting in similar rates of nonintracranial major or minor bleeding in the 2 groups (adjusted OR: 1.17; 95% CI: 0.85 to 1.63, p = 0.334) (Fig. 1). No interaction was observed between PCI strategy and either nonintracranial TIMI major bleeding (p = 0.296) or major or minor bleeding (p = 0.811). Intracranial hemorrhage occurred in 6 patients overall (all in patients <75 years of age), 5 of whom were randomized to combination-facilitated PCI. The frequency of intracranial hemorrhage was similar across the enoxaparin and UFH groups (0.27% vs. 0.24%, adjusted OR: 1.03, 95% CI: 0.11 to 9.68, p = 0.980). Results from the propensity-adjusted model were generally consistent with those from the logistic regression-adjusted model.

Several sensitivity analyses were performed to evaluate populations previously identified to be at increased risk of bleeding. Patients who received both enoxaparin and UFH within 24 h after randomization tended, although infrequently, to have higher rates of bleeding than those receiving only 1 antithrombin (data not shown). For patients 75 years of age or older, although overall bleeding rates were higher than those in younger patients for all categories evaluated, bleeding rates tended to be lower with enoxaparin than with UFH (e.g., nonintracranial TIMI major or minor bleeding 11.7% vs. 20.1%, p = 0.067).

Efficacy. The FINESSE 90-day primary end point of composite all-cause mortality or complications of MI (ventricular fibrillation beyond 48 h, cardiogenic shock, and congestive heart failure requiring repeat hospital stay or emergency room visit) occurred in 9.6% of patients who received enoxaparin and 10.6% of patients who received UFH (p = 0.45) (Table 3). After adjustment for baseline variables, a trend for lower risk of reaching the primary end point was associated with enoxaparin use (adjusted OR: 0.73; 95% CI: 0.52 to 1.03, p = 0.075). Complications of MI through 90 days tended to be lower with enoxaparin versus UFH (7.1% vs. 8.3%; adjusted OR: 0.70; 95% CI: 0.47 to 1.02, p = 0.066). A lower risk of all-cause



	UFH n (%)	Enoxaparin n (%)	Adjusted OR (95% CI)	Adjusted p-value
Nonintracranial TIMI major/minor bleeding				
All	165/1674 (9.9)	89/740 (12.0)	1.174 (0.848, 1.625)	0.334
Primary PCI	38/556 (6.8)	17/239 (7.1)	1.103 (0.539, 2.258)	
Abciximab facilitated PCI	53/553 (9.6)	28/252 (11.1)	1.108 (0.626, 1.960)	0.811*
Combination facilitated PCI	74/565 (13.1)	44/249 (17.7)	1.227 (0.747, 2.018)	
Nonintracranial TIMI major bleeding				
All	74/1674 (4.4)	19/740 (2.6)	0.553 (0.310, 0.987)	0.0451
Primary PCI	16/556 (2.9)	5/239 (2.1)	1.117 (0.334, 3.736)	
Abciximab facilitated PCI	29/553 (5.2)	4/252 (1.6)	0.261 (0.083, 0.825)	0.296*
Combination facilitated PCI	29/565 (5.1)	10/249 (4.0)	0.701 (0.296, 1.659)	
TIMI minor bleeding				
All	91/1674 (5.4)	70/740 (9.5)	1.677 (1.138, 2.472)	0.009
Primary PCI	22/556 (4.0)	12/239 (5.0)	1.122 (0.471, 2.671)	0.795
Abciximab facilitated PCI	24/553 (4.3)	24/252 (9.5)	2.237 (1.111, 4.502)	0.024
Combination facilitated PCI	45/565 (8.0)	34/249 (13.7)	1.638 (0.908, 2.952)	0.101

Figure 1. Primary Safety End Points Through Discharge or Day 7

*Interaction p value among the 3 percutaneous coronary intervention (PCI) strategies. CI = confidence interval; OR = odds ratio; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

mortality at 90 days was associated with enoxaparin compared with UFH (3.8% vs. 5.6%; adjusted OR: 0.59; 95% CI: 0.35 to 0.99, p = 0.046) that was more pronounced in the primary PCI group (Fig. 2); however, a test for interaction across the 3 PCI strategies was not significant (p = 0.285). Results from the propensity-adjusted model were generally consistent with those from the logistic regression-adjusted model.

Death or reinfarction through 30 days was less frequent with enoxaparin compared with UFH (4.0% vs. 5.6%, adjusted OR: 0.58; 95% CI: 0.35 to 0.96, p = 0.036), as was the composite of death, reinfarction, urgent revascularization, or refractory ischemia through 30 days (5.3% vs. 8.0%, adjusted OR: 0.47; 95% CI: 0.31 to 0.72, p = 0.0005) (Fig. 2).

Net adverse clinical outcome. The composite of death, MI, urgent revascularization, or stroke through 90 days or major bleeding through discharge/day 7 occurred in 8.2% of patients treated with enoxaparin versus 11.7% of patients treated with UFH (crude p = 0.009) (Table 3). This 3.5% absolute reduction with enoxaparin was consistent across all 3 PCI strategies (adjusted OR: 0.64; 95% CI: 0.45 to 0.91, p = 0.013). Similarly, the composite of death, MI, or stroke through 90 days or major bleeding through discharge/day 7 was lower in patients treated

Table 2. Safety

	Crude				Adjusted (Logistic Regression)		Propensity-Adjusted	
Outcome	Enoxaparin (n = 740)	UFH (n = 1,674)	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Nonintracranial TIMI major or minor bleeding through discharge/day 7	89 (12.0%)	165 (9.9%)	1.25 (0.95–1.64)	0.1096	1.17 (0.85–1.63)	0.3338	1.05 (0.79–1.54)	0.5676
Nonintracranial TIMI major bleeding through discharge/day 7	19 (2.6%)	74 (4.4%)	0.57 (0.34–0.95)	0.0312	0.55 (0.31–0.99)	0.0451	0.52 (0.28–0.95)	0.0417
TIMI minor bleeding through discharge/day 7	70 (9.5%)	91 (5.4%)	1.82 (1.31–2.51)	0.0003	1.68 (1.14–2.47)	0.0089	1.57 (1.06–2.34)	0.0292
Intracranial hemorrhage through discharge/day 7	2 (0.27%)	4 (0.24%)	1.13 (0.21–6.19)	0.887	1.03 (0.11–9.68)	0.9804	1.17 (0.15–9.36)	0.8941

CI = confidence interval; OR = odds ratio; TIMI = thrombolysis in myocardial infarction; UFH = unfractionated heparin.

Table 3. Efficacy

Outcome	Crude				Adjusted (Logistic Regression)		Propensity-Adjusted	
	Enoxaparin (n = 759)	UFH (n = 1,693)	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
FINESSE primary composite end point (all-cause mortality or complications of myocardial infarction) through 90 days	73 (9.6%)	180 (10.6%)	0.89 (0.67–1.19)	0.4456	0.73 (0.52–1.03)	0.0749	0.75 (0.53–1.05)	0.1062
All-cause mortality through 90 days	29 (3.8%)	95 (5.6%)	0.67 (0.44–1.02)	0.0630	0.59 (0.35–0.99)	0.0462	0.64 (0.39–1.04)	0.0660
Complications of myocardial infarction through 90 days	54 (7.1%)	140 (8.3%)	0.85 (0.61–1.18)	0.3279	0.70 (0.47–1.02)	0.0660	0.70 (0.47–1.04)	0.0883
Death or myocardial infarction through 30 days	30 (4.0%)	94 (5.6%)	0.70 (0.46–1.07)	0.0965	0.58 (0.35–0.96)	0.0356	0.58 (0.35–0.95)	0.0332
Death, myocardial infarction, or urgent revascularization through 30 days	33 (4.4%)	101 (6.0%)	0.72 (0.48–1.07)	0.1049	0.63 (0.39–1.03)	0.0630	0.62 (0.39–1.00)	0.0561
Death, myocardial infarction, urgent revascularization or refractory ischemia through 30 days	40 (5.3%)	135 (8.0%)	0.64 (0.45–0.92)	0.0170	0.47 (0.31–0.72)	0.0005	0.52 (0.34–0.78)	0.0012
Death, myocardial infarction, or stroke through 30 days	35 (4.6%)	103 (6.1%)	0.75 (0.50–1.11)	0.1450	0.62 (0.39–1.00)	0.0478	0.63 (0.40–1.01)	0.0604
Death, myocardial infarction, urgent revascularization, or stroke through 90 days or major bleeding through discharge/day 7	62 (8.2%)	198 (11.7%)	0.67 (0.50–0.91)	0.0091	0.64 (0.45–0.91)	0.0134	0.64 (0.45–0.90)	0.0129
Death, myocardial infarction, or stroke through 90 days or major bleeding through discharge/day 7	59 (7.8%)	190 (11.2%)	0.67 (0.49–0.91)	0.0093	0.61 (0.43–0.88)	0.0085	0.57 (0.39–0.84)	0.0060
Death, myocardial infarction, stroke, TIMI major bleed (including ICH) through discharge/day 7	42 (5.5%)	140 (8.3%)	0.65 (0.46–0.93)	0.0176	0.57 (0.38–0.88)	0.0129	0.56 (0.37–0.85)	0.0064
Death, myocardial infarction, urgent revascularization, TIMI major bleed (including ICH) through discharge/day 7	40 (5.3%)	137 (8.1%)	0.63 (0.44–0.91)	0.0132	0.57 (0.37–0.87)	0.0122	0.56 (0.37–0.86)	0.0081

FINESSE = Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events trial; ICH = intracranial hemorrhage; other abbreviations as in Table 2.

with enoxaparin versus UFH (7.8% vs. 11.2%, crude p = 0.009; adjusted OR: 0.61; 95% CI: 0.43 to 0.88, p = 0.009). The composite of death, MI, urgent revascularization, or recurrent ischemia through day 30 or any TIMI major or TIMI minor bleeding through discharge/day 7 was similar in the enoxaparin and the UFH groups (16.5% vs. 16.4%, crude p = 0.9761).

Discussion

Our findings suggest a lower risk of TIMI major bleeding and ischemic end points as well as all-cause mortality with the use of enoxaparin compared with standard UFH in primary PCI of STEMI. The main limitation of this substudy was the nonrandomized nature of the comparisons. However, the use of 2 different statistical models (logistic regression and propensity analysis) to adjust for baseline imbalances in the groups helps to support the robustness of these findings.

Presently, UFH has not been officially approved for use in PCI, and no placebo-controlled trials of UFH have been conducted in this indication. The optimal UFH dosing and/or ACT targets remain uncertain. Guidelines from the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the American College of Chest Physicians recommend 3 alternative ACT target levels depending on the type of measurement device and the concomitant use of glycoprotein IIb/IIIa inhibitors (1–3). Several studies and meta-analyses have reported conflicting results for the utility of these recommendations (17,18).

Lower molecular weight heparin has a more predictable anticoagulant activity compared with UFH. The intravenous use of enoxaparin affects immediate anticoagulation, with anti-Xa levels >0.5 IU/ml for 2 h; rapid clearance; and a pharmacokinetic profile well-suited for PCI (19). In the large, randomized STEEPLE (SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation) trial, IV enoxaparin 0.5 mg/kg demonstrated a better safety profile than IV UFH in elective PCI, with a significant reduction of major bleeding and similar efficacy.

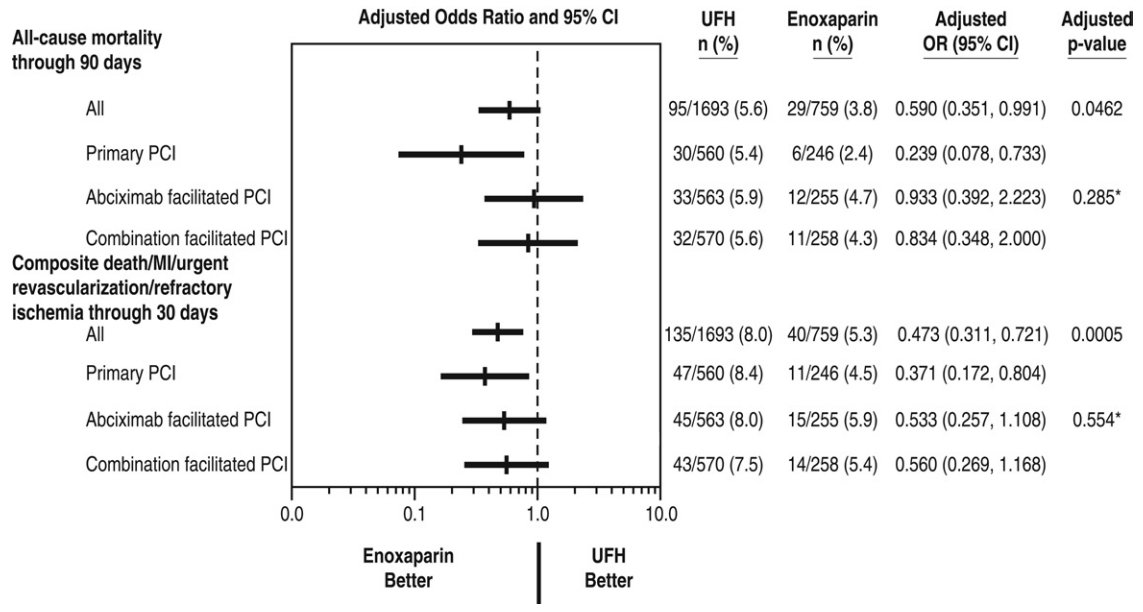


Figure 2. Secondary Efficacy End Points Through 30 and 90 Days

*Interaction p value among the 3 PCI strategies. Abbreviations as in Figure 1.

The STEEPLE results were recently confirmed in a global meta-analysis of 13 randomized studies reporting a 43% reduction of major bleeding and similar ischemic event rates with lower molecular weight heparin (7,8). Similarly, in the present enoxaparin substudy of the FINESSE study, the same IV regimen of 0.5 mg/kg enoxaparin provided a 35% relative risk reduction of major bleeding in all patients who received abciximab. This benefit of enoxaparin was observed in comparison with a dose of 40 IU/kg of UFH, a dose much lower than in any of the previous randomized studies.

In our enoxaparin substudy, enoxaparin use was associated with a lower risk of all ischemic end points compared with UFH. The observed 30% lower relative risk in death or MI through 30 days is comparable to the 23% risk reduction in the same end point observed in the randomized ExTRACT-PCI study and the 31% reduction recorded in the ACOS (Acute Coronary Syndromes) registry, both performed in STEMI patients (20,21); other studies evaluating enoxaparin in mechanical reperfusion of STEMI were too small to evaluate clinical outcomes (22,23). The ExTRACT-PCI patients, who underwent PCI approximately 5 days after thrombolysis of STEMI, were possibly at lower risk for periprocedural complications than FINESSE patients, who underwent primary PCI approximately 2 h after presentation. Our adjusted multivariable analyses demonstrate a lower risk in the double end point of death or MI and an approximately one-third reduction in the incidence of the composite ischemic end point including urgent revascularization and refractory ischemia ($p = 0.0005$). Regional differences in revascularization strategies, some of which were not adjusted for, could have confounded some of these results. All-cause mortality also seemed to be lower with enoxaparin than with UFH. This is an interesting finding, given that only bivalirudin (vs. UFH + glycoprotein IIb/IIIa inhibitors) and abciximab (vs. placebo) have been associated with a survival benefit in primary PCI (24–26) and that all patients in this study were to have received abciximab. A similar trend was observed for mortality in the recent meta-analysis of the enoxaparin trials of STEMI reperfused with thrombolysis (OR: 0.92, 95% CI: 0.84 to 1.01) as well as significant reductions in mortality in the large ACOS, FAST-MI (French Registry on Acute ST-Elevation Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) registries (10,24,27,28). The possible determinants for the decreased mortality with enoxaparin are several: more stable and predictable anticoagulation, pleiotropic effects of enoxaparin on markers such as von Willebrand factor that have been associated with mortality, and finally, reduction of early major bleeding and ischemic events that have been shown to predict mortality (4–6,29,30).

Our findings should be interpreted in light of the nonrandomized comparison, despite the large number of patients enrolled, the formal and prospective nature of the study, and the multivariable analyses performed to adjust for potential confounders. Additionally, there was a significant imbalance in the proportion of patients treated with enoxapa-

rin versus UFH in Western and Eastern Europe. In a sensitivity analysis restricted to patients within Western Europe, mortality rates through 90 days tended to be lower with enoxaparin (25 of 625 [4.0%] vs. 30 of 531 [5.7%], p = 0.191). Similarly, in Western Europe, 35 of 625 (5.6%) enoxaparin patients versus 57 of 531 (10.7%) UFH patients experienced death, MI, urgent revascularization or refractory ischemia through 30 days (p = 0.0016). Other end points were more similar between groups.

The open-label use of the anticoagulant might be seen as another limitation, although each site selected the anticoagulant strategy they were comfortable with and used it in all their patients enrolled in the study. Also, patients in the enoxaparin group more frequently received at least 1 additional dose of enoxaparin compared with the FINESSE main study group from 24 h after randomization through discharge/day 7 (30.2% vs. 18.2%, p < 0.001) and from discharge/day 7 through day 90 (11.2% vs. 4.1%, p < 0.001). It is very difficult to adjust for this, as a post-randomization event, in modeling; and it might need to be viewed as part of the treatment strategy difference that could have contributed to the better outcomes observed. Finally, our results might have been influenced by the variations of the selected model and by any confounders we might have overlooked.

Conclusions

Findings from the enoxaparin substudy of the FINESSE trial suggest that a strategy of intravenous enoxaparin over UFH was associated with a lower risk of both major TIMI bleeding and ischemic events in primary PCI of STEMI. Confirmation from a randomized study, such as the currently recruiting ATOLL (Angioplasty and Intravenous Lovenox or Unfractionated Heparin) trial comparing intravenous enoxaparin (0.5 mg/kg) with intravenous UFH in primary PCI, is warranted.

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Key Words: heparin ■ inhibitors ■ reperfusion.

APPENDIX

For a list of investigators who participated in the FINESSE LMWH substudy, please see the online version of this article.