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Predictors of Initial Nontherapeutic Anticoagulation With Unfractionated Heparin in ST-Segment Elevation Myocardial Infarction

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Background—Although weight-based nomograms have improved the efficacy and safety of dosing unfractionated heparin in ST-segment elevation myocardial infarction, achieving therapeutic anticoagulation in practice remains challenging.

Methods and Results—In the Enoxaparin and Thrombolysis in Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study, 20 506 patients with ST-segment elevation myocardial infarction were randomized to enoxaparin or unfractionated heparin, the latter dosed according to the American College of Cardiology/American Heart Association weight-based nomogram with centrally monitored activated partial thromboplastin times (aPTTs). A total of 6055 patients received study unfractionated heparin and a fibrin-specific lytic and had an initial aPTT drawn within 4 to 8 hours of starting therapy. Despite close adherence to recommended dosing, only 33.8% of initial aPTTs were therapeutic (1.50 to 2.00 times control); 13.2% were markedly low (<1.25 times); and 16.3% were markedly high (≥2.75 times). Markedly high aPTTs were more likely in patients who were older (adjusted risk ratio [RR_{adj}], 1.14 per decade; $P=0.001$), were female (RR_{adj}, 1.46; $P<0.001$), were of lower weight (RR_{adj}, 1.19 per 10-kg decrease; $P<0.001$) or had renal dysfunction (RR_{adj}, 1.08 per 0.2-mg/dL increase in serum creatinine; $P=0.006$). Markedly high aPTTs were associated with increased risk of TIMI major or minor bleeding by 48 hours (odds ratio, 2.11; $P=0.004$); markedly low aPTTs tended to be associated with increased risk of fatal or nonfatal reinfarction by 48 hours (odds ratio, 2.19; $P=0.057$).

Conclusions—Despite the use of a standard weight-based unfractionated heparin nomogram in ST-segment elevation myocardial infarction, nontherapeutic anticoagulation is frequent and more likely among certain vulnerable patient groups, with excess anticoagulation associated with increased bleeding and inadequate anticoagulation associated with reinfarction. These findings should be considered when dosing unfractionated heparin in support of fibrinolytic therapy. **(*Circulation*. 2009;119:1195-1202.)**

Key Words: anticoagulants ■ coronary disease ■ heparin ■ myocardial infarction ■ pharmacology

Unfractionated heparin (UFH) remains the most commonly used anticoagulant in the early treatment of acute coronary syndromes (ACS).[1] Although the development of weight-based nomograms to guide UFH dosing has improved its efficacy and safety,[2–7] achieving therapeutic anticoagulation in treated individuals continues to be challenging.[5,8] Alexander and colleagues[9] have demonstrated that at least part of this problem is due to suboptimal adherence to recommended dosing regimens. We hypothesized that patient characteristics would also be a source of variation in the anticoagulant effect of UFH.[10,11]

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The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial randomized patients presenting with ST-segment elevation myocardial infarction (STEMI) and receiving fibrinolytic therapy to a strategy using enoxaparin versus UFH, the latter to be dosed according to the American College of Cardiology/American Heart Association (ACC/AHA) weight-based nomogram with centrally monitored activated partial thromboplastin times (aPTTs).[12] The ExTRACT-TIMI 25 trial thus offered a unique opportunity to examine the factors associated with both excess and inadequate anticoagulation with UFH in the setting of a large, contemporary clinical study with standardized dosing and centralized monitoring.

Methods

The ExTRACT-TIMI 25 trial was an international, multicenter, randomized, double-blind controlled trial that randomized 20 506

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patients with STEMI (ClinicalTrials.gov number NCT00077792). The design of ExTRACT-TIMI 25 has been described previously.[13] In brief, enrolled patients presented with STEMI and were scheduled to undergo fibrinolysis with streptokinase or a fibrin-specific agent such as tenecteplase, alteplase, or reteplase. Key exclusion criteria included contraindications to fibrinolysis, cardiogenic shock, or severe renal insufficiency (serum creatinine >2.5 mg/dL in men or >2.0 mg/dL in women). All subjects were to receive aspirin and were assigned in a 1:1 fashion to an antithrombotic strategy of enoxaparin or UFH. Of the total sample, 9687 subjects received a fibrinolytic and were randomized to and received UFH.

Subjects in the UFH treatment arm were required by protocol to receive intravenous UFH dosed according to the standard ACC/AHA weight-based nomogram[14,15]: 60-U/kg bolus (maximum, 4000 U) followed by a 12-U · kg^{-1} · h^{-1} infusion (maximum, 1000 U/h), with actual[3] or estimated weights used. The protocol mandated that the UFH infusion be continued for at least 48 hours (median actual duration, 48 hours; interquartile range, 48 to 53 hours), with serial aPTT monitoring performed approximately every 6 hours. From the results of serial aPTT monitoring, UFH dose adjustments were also mandated per protocol (Table I of the online-only Data Supplement).

Of subjects in the UFH treatment arm, we restricted our study to the 7553 subjects who did not receive open-label UFH before randomization, had an initial aPTT drawn within 4 to 8 hours after initiating UFH therapy, and did not have study UFH stopped or undergo cardiac catheterization before their initial aPTT. We further restricted analyses to the 6055 of these subjects who received a fibrin-specific fibrinolytic agent as opposed to streptokinase, which is known to markedly deplete fibrinogen[14] and increase fibrin degradation products, causing an anticoagulant effect and aPTT elevation.

All aPTTs were measured locally with trial-supplied encrypted Hemochron Jr Signature Microcoagulation Systems (ITC, Edison, NJ). Hemochron Jr aPTT values are highly correlated with plasma aPTT values determined with standard hospital laboratory reagents (r=0.92).[16] All aPTTs were centrally monitored with an interactive voice response system (COVANCE, Princeton, NJ) and categorized according to the standardized nomogram as follows: markedly low (<1.25 times control), requiring UFH rebolus; low (1.25 to 1.49 times control), requiring adjusting the infusion rate higher; therapeutic (1.50 to 2.00 times control); high (2.01 to 2.74 times control), requiring adjusting the infusion rate lower; or markedly high (≥2.75 times control), requiring temporary UFH cessation (online-only Data Supplement Table I). Ischemic events, including fatal and nonfatal recurrent myocardial infarction, and TIMI major or minor bleeding were adjudicated by a clinical events committee that was blinded to treatment assignment.[13,17]

Statistical Analysis

We assessed the median and interquartile range of initial aPTT values by baseline characteristics. Variation of aPTT values across age groups (decade increments of ≤50, 51 to 60, 61 to 70, >70 years, which approximate quartiles), weight categories (<67, 67 to 83, ≥84 kg, based on the cut points at which UFH bolus and infusion dosing switch from being weight-based to capped), and creatinine levels (0.2-mg/dL increments of <0.8, 0.8 to <1.0, 1.0 to <1.2, ≥1.2 mg/dL, which approximate quartiles) was assessed with Kruskal-Wallis tests. Mean aPTT values between sexes were compared by use of Wilcoxon rank-sum tests. We used χ^2 tests to compare the frequency of achieving initial aPTT-to-control ratios within the above-defined categories (markedly low, low, therapeutic, high, or markedly high) across baseline characteristics. We then used univariate and multivariable multinomial logistic regression to determine the independent association between clinical factors, modeled as continuous variables when possible and by categories using multiple indicator variables, and the probability of achieving markedly nontherapeutic anticoagulation. Multivariable models included age, sex, weight, and creatinine. We deliberately used serum creatinine rather than creatinine clearance to avoid colinearity in multivariable models that contained terms for age, sex, and weight. However, we also performed sensitivity analyses in which we used estimated glomerular filtration rate (as calculated with the modification of Diet in Renal Disease equation[18]) instead of serum creatinine. Tests for the association between aPTT-to-control ratio categories and outcomes were performed with univariate and multivariable logistic regression models. All analyses were performed with STATA version 9 (STATA Corp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

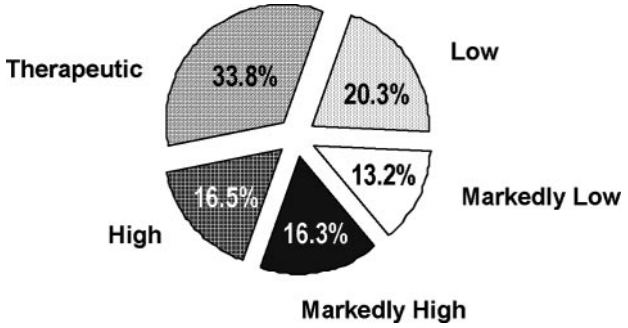

Figure 1. Distribution of initial anticoagulation levels within the total study sample. Frequencies are shown for markedly low, low, therapeutic, high, and, markedly high anticoagulation achieved with UFH based on initial aPTT-to-control ratios achieved (<1.25, 1.25 to 1.49, 1.50 to 2.00, 2.01 to 2.74, and ≥2.75, respectively).

Results

A total of 6055 patients did not receive open-label UFH before randomization, received study UFH and a fibrin-specific fibrinolytic, had an initial aPTT drawn within 4 to 8 hours of starting UFH therapy, and did not have study UFH stopped or undergo cardiac catheterization before having their initial aPTT drawn. Their average age was 59.6±11.9 years, weight was 77.0±13.9 kg, and serum creatinine was 1.04±0.30 mg/dL; 23.2% were women.

The median bolus of UFH was 60.0 U/kg (interquartile range, 60.0 to 60.3 U/kg) for subjects weighing <67 kg, and the initial infusion rate was 12.0 U · kg^{-1} · h^{-1} (interquartile range, 12.0 to 12.0 U · kg^{-1} · h^{-1}) for subjects weighing <84 kg. Of subjects weighing ≥67 kg, 99.5% received an appropriately capped 4000-U bolus; similarly, 99.0% of subjects weighing ≥84 kg received a 1000-U · kg^{-1} · h^{-1} initial infusion rate as per the protocol. Adherence was similarly high regardless of age, sex, or creatinine. Despite such a high degree of adherence to the recommended dosing regimen, only 33.8% of initial aPTTs were therapeutic, 13.2% were markedly low (requiring rebolusing UFH), and 16.3% were markedly high (requiring temporary UFH cessation) (Figure 1).

Variation in Anticoagulation

Marked variation was found in aPTT values, with significantly higher initial aPTT values in patients who were older, were female, were lighter in weight, or had higher creatinine (Table 1). Accordingly, initial aPTTs categorized as high or markedly high were more frequent among these same patient groups (Table 2, Figure 2A). Conversely, initial aPTTs categorized as low or markedly low were more frequent in patients who were younger, were heavier in weight, or had lower creatinine (Table 2, Figure 2B).

Table 1. Baseline Characteristics and Initial aPTT Values

	n (%)	Initial aPTT, Median (IQR)	*P*
Age, y			
≤50	1503 (24.8)	48 (40–60)	<0.001
51–60	1700 (28.1)	51 (43–64)	
61–70	1541 (25.5)	56 (46–75)	
>70	1311 (21.7)	60 (49–83)	
Sex			
Female	1402 (23.2)	57 (45–80)	<0.001
Male	4653 (76.8)	52 (43–67)	
Weight, kg			
<67	1296 (22.3)	57 (46–81)	<0.001
67–83	2843 (49.0)	55 (45–71)	
≥84	1662 (23.7)	48 (40–60)	
Creatinine, mg/dL			
<0.8	895 (14.9)	53 (42–67)	<0.001
0.8–<1.0	2309 (38.5)	52 (43–68)	
1.0–<1.2	1438 (24.0)	53 (44–69)	
≥1.2	1354 (22.6)	56 (45–75)	

IQR indicates interquartile range. n=6055, barring missing data.

Independent Predictors of Nontherapeutic Anticoagulation

In multivariable analyses, markedly high anticoagulation, represented by an aPTT ≥2.75 times control, was significantly more likely to occur in patients who were older, were female, were lower in body weight, or had higher serum creatinine (Table 3). Specifically, a decade increase in age was associated with a 14% increase ($P=0.001$) in the adjusted risk of markedly high anticoagulation. Women had a 46% increase ($P<0.001$) in the adjusted risk of markedly high anticoagulation. A 10-kg lower weight was associated with a 19% increase ($P<0.001$) and a 0.2-mg/dL higher serum creatinine (used instead of creatinine clearance to avoid colinearity with age, sex, and weight in the multivariable models) was associated with an 8% increase ($P=0.006$) in the adjusted risk of markedly high anticoagulation. In multivariable models in which estimated glomerular filtration rate was substituted for serum creatinine, a 15–mL · min^{-1} · 1.73 m^{-2} decrease in estimated glomerular filtration rate was associated with an 8% increase in the adjusted risk of markedly high anticoagulation ($P=0.003$), and the adjusted risk ratios for age, sex, and weight were largely unchanged and remained highly statistically significant.

Conversely, markedly low anticoagulation, defined by an aPTT <1.25 times control, was independently associated with decreasing age and increasing weight (Table 4). Renal function was not an independent predictor of markedly low anticoagulation. Interestingly, after adjustment for age, weight, and creatinine, women were 55% more likely than men to have markedly low anticoagulation ($P<0.001$).

Clinical Outcomes

A markedly high aPTT was associated with a significant 2-fold increased risk of TIMI major or minor bleed by 48 hours (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.27 to 3.53; $P=0.004$; Figure 3A). After adjustment for age, sex, weight, and creatinine, the OR was 1.72 (95% CI, 0.98 to 3.00; $P=0.057$). Conversely, a markedly low aPTT was associated with a 2-fold increased risk for fatal or nonfatal recurrent myocardial infarction by 48 hours (OR, 2.19; 95% CI, 0.98 to 4.91; $P=0.057$; Figure 3B). After adjustment for age, sex, weight, and creatinine, the OR was 3.00 (95% CI,

Table 2. Initial aPTT-to-Control Ratios by Baseline Characteristics

	Initial aPTT-to-Control Ratio, %						
	<1.25 (n=797)	1.25–1.49 (n=1231)	1.50–2.00 (n=2046)	2.01–2.74 (n=997)	≥2.75 (n=984)	χ^2	*P*
Age, y							
≤50	19.8	27.0	31.1	11.0	11.2	350.1	<0.001
51–60	14.1	24.4	34.5	14.8	12.3		
61–70	10.1	16.7	34.7	19.2	19.3		
>70	8.1	11.6	35.0	21.7	23.6		
Sex							
Female	12.3	15.9	31.0	18.2	22.5	70.3	<0.001
Male	13.4	21.7	34.6	16.0	14.4		
Weight, kg							
<67	10.8	15.6	32.6	18.1	22.8	207.8	<0.001
67–83	11.2	18.8	35.0	18.3	16.7		
≥84	18.5	26.9	32.4	12.2	10.0		
Creatinine, mg/dL							
<0.8	15.9	19.4	34.5	14.5	15.6	32.1	0.001
0.8–<1.0	13.5	21.7	33.2	16.3	15.3		
1.0–<1.2	14.1	19.8	33.5	17.1	15.7		
≥1.2	10.0	19.0	34.5	17.5	19.0		

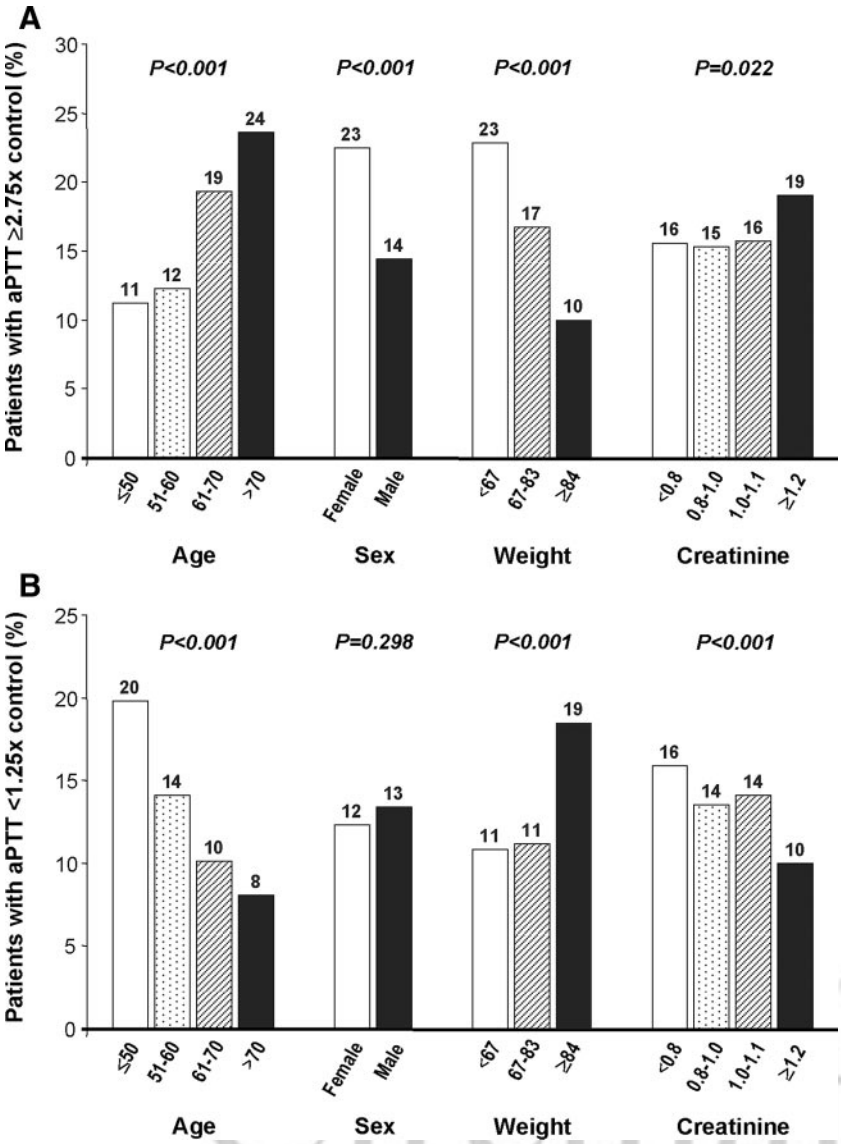

Figure 2. Probability of markedly high aPTT (A; ≥2.75 times control) and markedly low aPTT (B; <1.25 times control) values across baseline characteristic and lytic treatment groups, with *P* values for trend and frequencies (in percent) shown for each subgroup.

1.28 to 7.04; $P=0.011$). Of note, even a low aPTT (1.25 to 1.49 times control) was associated with an increased risk of myocardial infarction by 48 hours in univariate (OR, 2.06; 95% CI, 0.99 to 4.30; $P=0.054$) and multivariable (OR, 2.24; 95% CI, 0.99 to 5.07; $P=0.052$) analyses.

Discussion

Although some of the first major ACS trials that included UFH treatment described difficulties in achieving therapeutic aPTTs in a majority of patients,[5,19] frequent out-of-range aPTTs at that time were attributed largely to variable UFH distribution between patients of different plasma volume.[19] Subsequently, weight-based nomograms were developed and incorporated into practice guidelines for treating ACS and venous thromboembolic disease.[3,11,14,15]

Indeed, the use of weight-based nomograms substantially improved the ability to appropriately administer UFH in ACS and is now considered standard of care.[4,6,7,20] However, our data demonstrate that significant limitations to safe and effective dosing of UFH remain. We observed that even with nearly perfect adherence to a standard weight-based nomogram, the majority of patients treated with UFH fail to achieve initial therapeutic anticoagulation. The patient groups who are especially at risk for marked over-anticoagulation and its associated bleeding complications were women, the elderly, patients with lower body weight, and those with reduced renal function. Compounding the problem is the observation that in the absence of protocol-mandated adherence to dosing guidelines, these same patient groups are at risk for inappropriate excess dosing of antithrombotic and antiplatelet agents and for adverse events overall.[9,21]

Interestingly, we found that despite the use of weight-based UFH dosing, the ability to achieve the targeted aPTT was independently correlated with body weight. Whereas every 10-kg decrease in body weight was associated with a 19% increased risk of achieving markedly high anticoagulation, every 10-kg increase in weight was associated with a 23% increased risk of markedly low anticoagulation. The likelihood of achieving a markedly low aPTT was most prominent for patients ≥84 kg, likely resulting in part from the dosing

Table 3. Predictors of Markedly High Initial Anticoagulation (Initial aPTT ≥2.75 Times Control)

	Univariate		Multivariable	
Risk Factor	RR (95% CI)	*P*	RR_{adj} (95% CI)	*P*
Age				
Per decade increase	1.26 (1.17–1.34)	<0.001	1.14 (1.06–1.23)	0.001
>70 vs 51–60 y	1.89 (1.52–2.34)	<0.001	1.52 (1.21–1.91)	<0.001
Female vs male sex	1.75 (1.48–2.08)	<0.001	1.46 (1.21–1.78)	<0.001
Weight				
Per 10-kg decrease	1.25 (1.18–1.33)	<0.001	1.19 (1.11–1.27)	<0.001
<67 vs 67–83 kg	1.47 (1.22–1.76)	<0.001	1.31 (1.08–1.59)	0.006
Creatinine				
Per 0.2-mg/dL increase	1.06 (1.01–1.12)	0.014	1.08 (1.02–1.13)	0.006
≥1.2 vs 0.8–<1.0 mg/dL	1.19 (0.98–1.46)	0.078	1.24 (1.00–1.52)	0.045

RR indicates risk ratio.

Table 4. Predictors of Markedly Low Initial Anticoagulation (Initial aPTT <1.25 Times Control)

	Univariate		Multivariable	
Risk Factor	RR (95% CI)	*P*	RR_{adj} (95% CI)	*P*
Age				
Per decade decrease	1.40 (1.31–1.51)	<0.001	1.42 (1.31–1.54)	<0.001
≤50 vs 51–60 y	1.56 (1.26–1.92)	<0.001	1.57 (1.26–1.94)	<0.001
Female vs male sex	1.03 (0.84–1.25)	0.80	1.55 (1.24–1.95)	<0.001
Weight				
Per 10-kg increase	1.26 (1.18–1.33)	<0.001	1.23 (1.15–1.31)	<0.001
≥84 vs 67–83 kg	1.78 (1.48–2.15)	<0.001	1.66 (1.37–2.02)	<0.001
Creatinine				
Per 0.2-mg/dL decrease	1.05 (0.99–1.12)	0.091	1.03 (0.97–1.10)	0.32
<0.8 vs 0.8–<1.0 mg/dL	1.13 (0.89–1.43)	0.32	1.08 (0.84–1.39)	0.53

RR indicates risk ratio.

cap mandated by the nomogram at this weight cutoff. Nevertheless, these data overall suggest that simple linear dose adjustments for weight may be inadequate.[22,23]

In this study, the ability to achieve therapeutic anticoagulation also was influenced by sex, independent of weight and other baseline characteristics. Although differences in UFH treatment response between women and men have been observed in earlier ACS studies,[19,24,25] ours is the first large study to confirm persistent sex-based differences despite the strict use of a weight-based nomogram. We found that after adjustment for age, weight, and renal function, women were still 46% more likely than men to achieve markedly high anticoagulation but also 55% more likely to achieve markedly low anticoagulation. The reason for such marked variability of UFH response in women is unclear, although it may be related to differences between women and men in lean mass and blood volume even after adjustments for weight.[26,27]

Variation in anticoagulation by age also has been reported in earlier ACS trials of UFH without weight-based dosing.[5,19,24,25] Our data demonstrate persistent age-based variation despite the strict use of a weight-based nomogram, suggesting a significant age effect on the pharmacokinetics of UFH beyond that represented by weight alone. In fact, we found that patients ≤50 of age were 57% more likely to be markedly under-anticoagulated, whereas patients >70 years of age were 52% more likely to be markedly over-anticoagulated. Sources of age-based variation may be related to any number of possible age-related phenomena: modified body composition and pharmacokinetics,[28] altered concentrations of coagulation factors,[29] and depletion of heparin-binding proteins.[28,30]

The role of renal function in UFH metabolism is not straightforward. Low and therapeutic doses of UFH are cleared predominantly and rapidly through a saturable mechanism involving endothelial cell uptake and desulfation by mononuclear phagocytes.[8,30] On the other hand, higher doses of UFH are cleared primarily by the kidney through a slower, nonsaturable mechanism, essentially resulting in a prolonged UFH half-life in the setting of renal impairment.[8,30,31] Our data showed that elevated creatinine was associated with higher risk for overanticoagulation, which suggests that patients with impaired renal function may be receiving higher effective doses.[26]

Nontherapeutic Anticoagulation and Outcomes

The inability to achieve a therapeutic initial aPTT with UFH, despite weight-based dosing, was associated with adverse outcomes. Specifically, we observed that markedly high anticoagulation was associated with a higher rate of TIMI major or minor bleed within 48 hours. These findings are of particular interest given recent studies demonstrating an association between bleeding and long-term poor outcomes.[32,33] Moreover, recent work has demonstrated that only 30% of ACS patients are correctly dosed UFH according to the ACC/AHA weight-based nomogram in practice, with 33% of patients receiving UFH bolus and/or infusion in excess of recommended doses.[9] Taken together, these data suggest that patients being treated with UFH for ACS are at a high risk for bleeding complications, even with strict adherence to a standard weight-based nomogram in controlled settings, and potentially even more so when actual dosing deviates from such a nomogram in clinical practice.

Conversely, markedly low aPTTs were associated with an increased risk of fatal or nonfatal myocardial reinfarction by 48 hours. The relation of subtherapeutic aPTTs with ischemic events has been observed previously,[25,34,35] and these data, along with the frequency of inadequate anticoagulation observed in the present study, may well contribute to the poorer

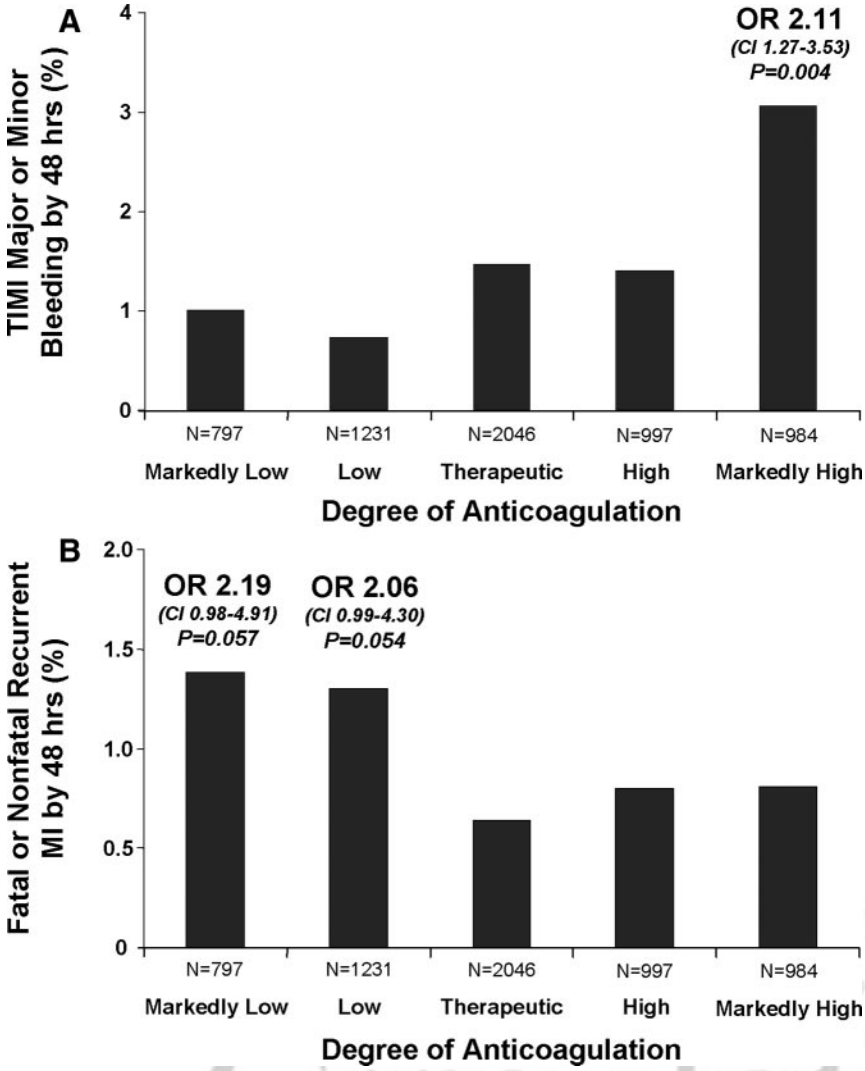

Figure 3. A, Rate of TIMI major or minor bleed by 48 hours across initial anticoagulation categories (markedly low, low, therapeutic, high, and markedly high), which correspond to initial aPTT-to-control ratios (<1.25, 1.25 to 1.49, 1.50 to 2.00, 2.01 to 2.74, and ≥2.75, respectively). B, Rate of fatal or nonfatal myocardial reinfarction by 48 hours across these same initial anticoagulation categories. Odds ratios (OR) and 95% CI are relative to risk in patients with therapeutic anticoagulation (ie, those patients with an initial aPTT of 1.50 to 2.00 times control).

outcomes associated with UFH compared with low-molecular-weight heparin in multiple ACS trials.[12,36] In total, our findings highlight the strong association between nontherapeutic initial anticoagulation and the magnitude of risk for a variety of adverse outcomes.

Study Limitations

Several potential limitations of this study merit consideration. In addition to the clinical variables identified in the present investigation, it should be noted that other biological factors discussed above, including intravascular volume, concentration of coagulation proteins, and concentration of heparin-binding proteins, can influence the response to UFH. However, in the setting of a large, multinational trial, we elected to focus on factors easily and immediately assessable by clinicians. Compared with measurement of factor Xa levels, aPTT is subject to greater variability in representing circulating concentrations of plasma heparin; however, aPTT is the most widely used and accepted method for monitoring UFH.[8,37] In addition, small experimental studies that used factor Xa levels have suggested that UFH efficacy is variable by patient characteristics in a pattern similar to what we found in this study.[26] Nonetheless, anti-Xa assays, if they could be reported in a timely manner, might offer advantages over aPTT. Because aPTT was nonnormally distributed, with some values above and below the device detection thresholds, we had to use aPTT categories as the outcomes of interest; however, we selected markedly low or high levels of anticoagulation that are guideline based, clinically meaningful, and prespecified to trigger rebolusing or temporary cessation of therapy. Therefore, aPTT was analyzed in a semiquantitative fashion rather than as a continuous variable. We studied only patients with STEMI as opposed to those with non–ST-segment elevation ACS. Because of the possible influence of acute phase reactants, variability of UFH binding may be higher in patients with STEMI compared with those with non–ST-segment elevation ACS. Although we speculate that the same qualitative relationships would exist between the baseline characteristics we identified and nontherapeutic anticoagulation in ACS patients without ST-segment elevation, these associations need to be formally studied and quantified in such a population. We excluded patients treated with streptokinase because streptokinase is known to influence aPTT. Our study sample was limited to a predominantly white population (>85%), so race/ethnicity-based variation in UFH efficacy could not be analyzed. Although creatinine

clearance or estimated glomerular filtration rate is preferred over serum creatinine to quantify renal function, we deliberately used serum creatinine to avoid colinearity in multivariable models that contained terms for age, sex, and weight. Inclusion of these terms allows serum creatinine to represent renal function adjusted for the key determinants of muscle mass. Nevertheless, in multivariable analyses in which we used estimated glomerular filtration rate instead of serum creatinine, the results were quite similar. Because ExTRACT-TIMI 25 excluded patients with severe renal dysfunction, we cannot comment on their risk for nontherapeutic anticoagulation.

Conclusions

Despite major advances in the treatment of ACS, current strategies remain susceptible to a variety of efficacy and safety limitations. In this large, contemporary clinical trial of STEMI patients treated with UFH in support of fibrin-specific fibrinolytic therapy, only a minority achieved initial therapeutic anticoagulation. Of the patients who achieved nontherapeutic anticoagulation, a large proportion was subject to marked initial overanticoagulation and, in turn, increased risk for bleeding. The patients at highest risk were older, were female, were of lower body weight, or had impaired renal function. Of patients with nontherapeutic initial anticoagulation, a smaller but substantial subset was subject to markedly inadequate anticoagulation and, in turn, a significantly increased risk for myocardial reinfarction. These data suggest that dosing of UFH to support fibrinolysis may need to be tailored on the basis of factors beyond weight alone.

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Disclosures

Dr Morrow has served as a consultant for and received honoraria for educational presentations from Sanofi-Aventis. Dr Antman has received research grant support and honoraria for educational presentations from Sanofi-Aventis. Dr Sabatine has received research grant support and honoraria for educational presentations and consulting from Sanofi-Aventis. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although weight-based nomograms have improved the efficacy and safety of dosing unfractionated heparin in ST-segment elevation myocardial infarction, achieving therapeutic anticoagulation in practice remains challenging. The Enoxaparin and Thrombolysis in Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study provided the opportunity to investigate the contemporary efficacy and safety of unfractionated heparin, dosed according to the American College of Cardiology/American Heart Association weight-based nomogram. Despite close adherence to recommended dosing, only 33.8% of initial activated partial thromboplastin times (at 4 to 8 hours after the start of unfractionated heparin) were therapeutic (1.50 to 2.00 times control); 13.2% were markedly low ($<$1.25 times control); and 16.3% were markedly high ($\geq$2.75 times control). Markedly high activated partial thromboplastin times were more likely in patients who were older (14% increased risk per decade), were female (46% increased risk), were of lower weight (19% increased risk per 10-kg decrease), or had renal dysfunction (8% increased risk per 0.2-mg/dL increase in creatinine). Markedly high activated partial thromboplastin times also were associated with a 2-fold increased risk of TIMI major or minor bleeding by 48 hours; conversely, markedly low activated partial thromboplastin times were associated with a 2-fold increased risk of fatal or nonfatal reinfarction by 48 hours. Thus, despite the use of a standard weight-based unfractionated heparin nomogram in ST-segment elevation myocardial infarction, nontherapeutic anticoagulation is frequent and more likely among certain vulnerable patient groups, with excess anticoagulation associated with increased bleeding and inadequate anticoagulation associated with reinfarction. These findings should be considered when dosing unfractionated heparin in support of fibrinolytic therapy.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Unfractionated heparin dose adjustment protocol.

aPTT/control Ratio	aPTT (sec)	Bolus Dose	Stop Infusion	Change Infusion Rate (U/hr)	Change Infusion Rate (mL/hr)
<1.25	<39	3000 U	0	+100	+2
1.25-1.49	39-46	0	0	+50	+1
1.50-2.00	47-62	0	0	no change	no change
2.01-2.74	63-85	0	0	-50	-1
2.75-3.30	86-102	0	30 min	-100	-2
3.31-5.00	103-155	0	60 min	-150	-3
>5.00	>155	0	60 min	-300	-6