The Activated Clotting Time (ACT) Can Be Used to Monitor Enoxaparin and Dalteparin after Intravenous Administration

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ABSTRACT: Background. The use of low-molecular weight heparin (LMWH) during percutaneous coronary intervention (PCI) has been limited by the presumed inability to monitor its anticoagulant effect using bedside assays. **Objectives.** This study was designed to compare the dose-response of enoxaparin, dalteparin and unfractionated heparin (UFH) on the activated clotting time (ACT), and to determine whether the ACT or aPTT can be used to monitor intravenous (IV) low molecular weight heparin (LMWH). **Methods.** A total of 130 patients undergoing cardiac catheterization were assigned to intravenous enoxaparin 0.5 mg/kg, dalteparin 50 international units/kg or UFH 50 units/kg. Of the 130 patients, 46 (35%) underwent PCI, all of whom received a glycoprotein (GP) IIb/IIIa inhibitor. We measured ACT, activated partial thromboplastin time (aPTT) and plasma anti-Xa levels after serial sampling. **Results.** Both enoxaparin and dalteparin induced a significant rise in the ACT and aPTT, with an ACT dose-response approximately one-half the magnitude of that obtained using UFH. The time course of changes in the ACT and aPTT after administration of enoxaparin and dalteparin was virtually identical, with a return to baseline at approximately 2 hours. The enoxaparin and dalteparin-treated patients successfully underwent PCI with no major hemorrhagic complications. **Conclusions.** The ACT is equally sensitive to IV enoxaparin and dalteparin. These data support an ACT-guided strategy for intravenously administered LMWH during PCI. Additional studies with larger patient populations may be indicated to determine the ideal target ACT for LMWH in PCI.

A major advance in the use of heparin has been the development of low-molecular weight heparins (LMWH), which inhibit both the action (anti-IIa effect) and the generation (anti-Xa effect) of thrombin.[1,2] Because of their ease of administration and possible clinical superiority, the use of LMWH has increased substantially in recent years, particularly in patients presenting with acute coronary syndromes.[3–5] As such, an increasing number of patients referred for angiography and possible percutaneous coronary intervention (PCI) are presenting to the cardiac catheterization laboratory having received subcutaneous LMWH at various intervals from the time of subcutaneous injection.[6–8]

Because of the pharmacokinetics of LMWH (less binding to plasma proteins and greater anti-Xa inhibition compared with unfractionated heparin), it has been suggested that monitoring the level of anticoagulation with standard and readily available tests based predominantly on anti-factor IIa inhibition (such as the activated clotting time [ACT] or the aPTT) is neither necessary nor possible.[9–14] Despite this contention, however, the interventional community has been reluctant to adopt the use of these agents, largely because of the perception that the ability to monitor anticoagulation during PCI is both desirable and at times critical.[6] In an attempt to overcome such reluctance, an expert consensus panel has recently published guidelines for the use of enoxaparin during PCI which involve an algorithm that guides dosing based upon the interval of time elapsed from the last subcutaneous administration.[15] The proposed algorithm was similar to that used in the recently presented SYNERGY trial, which showed that enoxaparin is non-inferior (but not superior) to unfractionated heparin.[16] However, use of LMWH in this trial was associated with a significant increase in bleeding complications. Although the reasons for excess bleeds have not yet been fully elucidated, the results of SYNERGY highlight the importance of precise titration of anticoagulation in acute coronary syndrome patients committed to an invasive strategy.

We believe that the anticoagulant effects of the LMWH enoxaparin can in fact be monitored during PCI and that the decision regarding the necessity to do so be left to the discretion of the operator based upon a variety of clinical parameters (*e.g.* complexity of intervention, recent administration of thrombolytic agent, renal dysfunction, presence of bleeding diathesis, etc). Thus, the purpose of the present study is: 1) to determine whether the anticoagulant effects of intravenous (IV) enoxaparin can be monitored during PCI by measuring changes in the activated clotting time (ACT), and 2) to compare the dose-response relationships between the ACT and IV enoxaparin, IV dalteparin and unfractionated heparin (UFH).

Methods

Patient population. The Institutional Review Board of the Bronx Veterans Administration Medical Center *(Bronx, New York)* and the SUNY Health Science Center at Brooklyn *(Brooklyn, New York)* approved all protocols for this study. The study population consisted of patients older than 18 years of age who were referred for cardiac catheterization and coronary angiography for a variety of indications including stable (*n* = 22) and unstable angina pectoris (*n* = 38), positive exercise stress test (*n* = 19), non-ST-segment elevation myocardial infarction (MI; *n* = 41), or chest pain post-MI (*n* = 10). A total of 130 patients

were enrolled over a 14-month period (12/02 to 2/04). Of the 130 patients, 46 (35%) underwent PCI. The demographics of the study population are shown in Table 1. Informed consent was obtained from each patient before enrollment.

Exclusion criteria for the study included ST-segment elevation MI within 24 hours, active internal bleeding, bleeding diathesis, thrombocytopenia (platelet count < 100,000/ml), the administration of oral anticoagulant within 7 days, and serum creatinine > 2.0. To limit the effects of preprocedural anticoagulation, patients treated with LMWH within 24 hours, or UFH within 12 hours, were excluded.

Study design and medications. Patients undergoing cardiac catheterization and coronary angiography were enrolled and arbitrarily assigned at the discretion of the operator to one of three anticoagulants: unfractionated heparin, dalteparin, or enoxaparin (Figure 1). The total dose of enoxaparin was 0.5 mg/kg IV, dalteparin 50 units/kg IV, and unfractionated heparin 50 units/kg IV. To generate a dose-response curve, the total dose was administered in 2 aliquots 5 minutes apart. Specifically, enoxaparin was administered as a bolus of 0.1 mg/kg IV followed by a second bolus of 0.4 mg/kg IV 5 minutes later, dalteparin as 20 units/kg IV followed by 30 units/kg IV 5 minutes later, and unfractionated heparin as 10 units/kg followed by 40 units/kg 5 minutes later. Patients who underwent PCI immediately following diagnostic catheterization (*n* = 46) all received intravenous GP IIb/IIIa as adjunctive therapy, with the choice of the particular agent (eptifibatide, tirofiban or abciximab) being at the operator's discretion.

Blood samples. Eight blood samples were collected in duplicate from the arterial access sheath in sodium citrate vacutainers at the following time points: baseline, 5, 10, 15, 30, 60, 90 and 120 minutes after anticoagulant administration. Blood samples were centrifuged at 3,000 g for 15 minutes at 22ºC. Platelet-poor plasma was collected and aliquoted into 2 ml eppendorf tubes and stored at -70ºC. Frozen samples were transported on dry ice to the Thrombosis and Hemostasis Research Laboratory at Loyola Medical Center *(Maywood, Illinois)*. Arterial access sheaths were removed when the ACT had fallen below 160 seconds, approximately 2 to 4 hours postprocedure.

Monitoring of the Anticoagulant Effect

Activated Clotting Time (ACT). Fresh whole blood was tested using the ACT-LR Celite®-based activated clotting time cuvette *(Hemochron Jr. Signature Analyzer, International Technidyne, Edison, New Jersey)*. Results were recorded in seconds. The range for ACT-LR in normal donors is 113–149 seconds and the mean value ± one standard deviation is 131 ± 9 seconds.

Activated partial thromboplastin time (aPTT). The activated partial thromboplastin time cuvette was used to measure
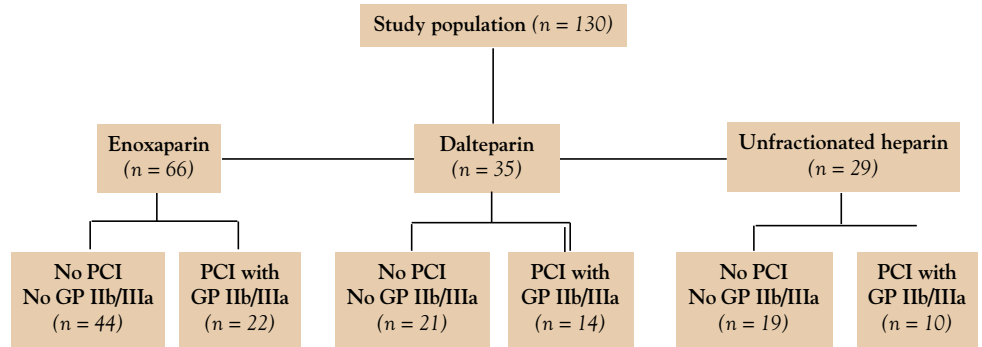
Figure 1. *Patient flow. All patients underwent angiography for which they received one of three anticoagulants. Only patients who subsequently underwent PCI received glycoprotein IIb/IIIa inhibitor therapy. PCI = percutaneous coronary intervention.*
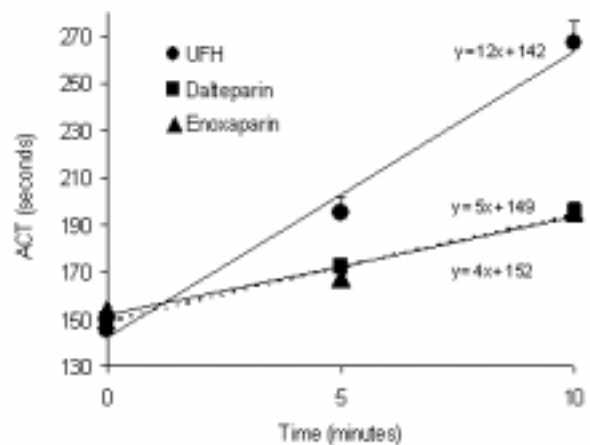

Figure 2. *Dose-response of the ACT as a function of cumulative dose of anticoagulant. Following measurement of baseline ACT (0 min), patients received either 10 U/kg of unfractionated heparin (UFH), 20 IU/kg dalteparin, or 0.1 mg/kg enoxaparin and the ACT was measured 5 minutes later. Patients then received an additional dose, resulting in the cumulative doses of 50 U/kg, 50 IU/kg, and 0.5 mg/kg, respectively. The ACT was then re-measured 5 minutes after the second dose. ACT = activated clotting time.*

Table 1. Patient demographics.

Total number of patients *(n)*	130
Age *(mean ± SD)*	63 ± 11
Male *(%)*	74 (57%)
Diabetes *(%)*	55 (42 %)
Hypertension *(%)*	99 (76%)
Hyperlipidemia *(%)*	81 (62%)
Smoking *(%)*	35 (27%)
History of CAD	47 (36%)
Previous PCI	29 (22%)
CABG	13 (10%)
Previous MI	20 (15%)

Data presented as mean ± SD or number (percentage) of patients. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention.
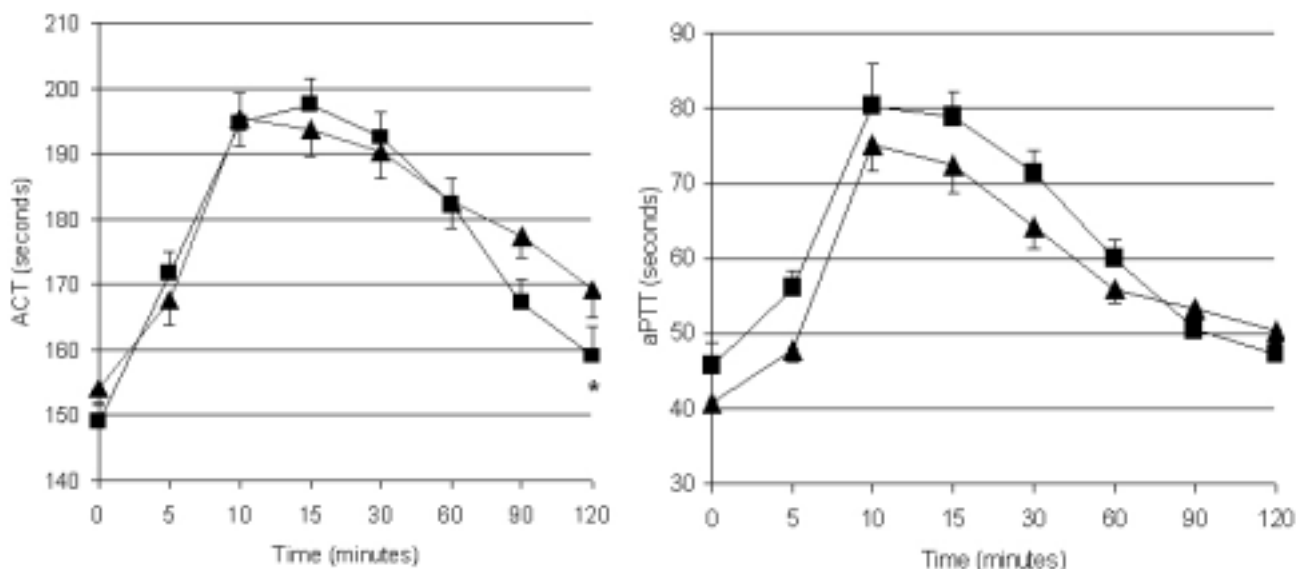
Figure 3. *Time course of the ACT and aPTT. After obtaining baseline blood samples, enoxaparin (triangles) and dalteparin (squares) were administered intravenously as 2 boluses 5 minutes apart. The ACT and aPTT responded similarly to the two forms of LMWH and approached baseline values at 2 hours. Following the administration of each of the boluses, there was a statistically significant change in the ACT at all time points compared to baseline, with the exception of dalteparin at 2 hours.* Data presented as mean ± SEM (standard error of the mean). ACT = activated clotting time aPTT = activated partial thromboplastin time; LMWH = low molecular weight heparin.*

aPTT (Hemochron Jr. Signature Analyzer). Results were recorded in seconds.

Antiprotease assays. The anti-Xa assay was performed as previously described.[6,27]

Assessment of safety. A new myocardial infarction was defined as an elevation in CK-MB (or total creatine kinase in absence of CK-MB) more than three times the upper limit of normal. Blood for CK-MB analysis was drawn before PCI and every 8 hours for 24 hours. Severe thrombocytopenia was defined by a platelet count below 50,000/ml. Mild thrombocytopenia was defined as a platelet count below 100,000/ml or a count 50% of the baseline value. Minor and major bleeding was defined according to the criteria used by the Thrombolysis in Myocardial Infarction (TIMI) Trial.[17] Major hemorrhage was defined as a decrease in hemoglobin > 5 g/dL (hematocrit decrease > 15% when hemoglobin was not available) or intracranial bleeding. Minor hemorrhage was defined as spontaneous and observed gross hematuria, hematemesis or observed blood loss associated with a decrease in hemoglobin ≥ 3 g/dL or hematocrit decrease ≥ 10% when hemoglobin was not available.

Statistical analysis. Patient demographic and coagulation parameter data were described using mean ± SD and mean ± SEM, respectively. Analysis of variance was used to compare the effect of drug on coagulation parameters across the 8 sampling time points for each dose of enoxaparin, dalteparin and UFH. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Comparative effects of dalteparin, enoxaparin and UFH on the ACT. Dalteparin, enoxaparin and unfractionated heparin
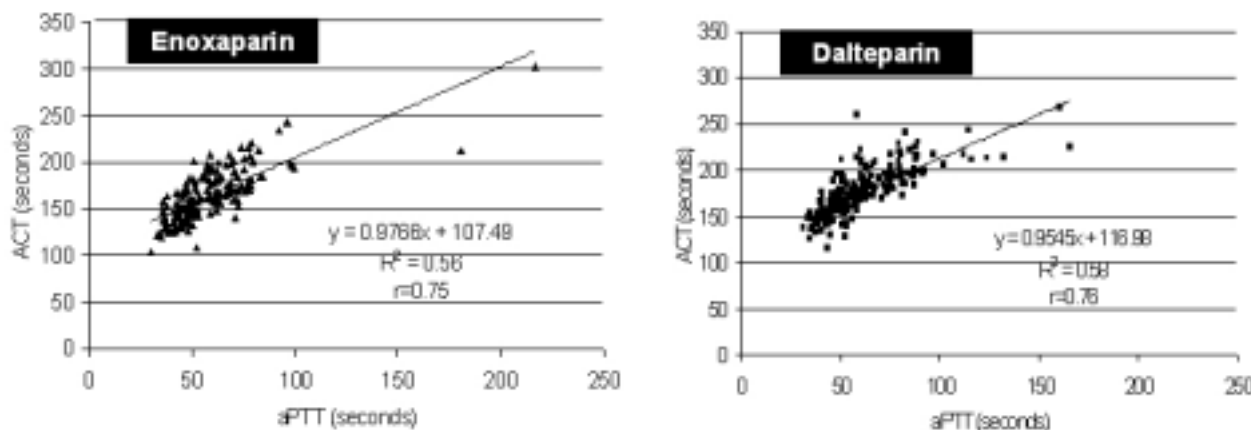
Figure 4. *Correlations between the ACT and aPTT for enoxaparin (left) and dalteparin (right). ACT = activated clotting time; aPTT = activated partial thromboplastin time.*

all demonstrated a significant dose response with respect to the ACT (Figures 2 and 3). Although a two- to three-fold greater slope was seen with UFH, a moderate slope was present in the dalteparin- and enoxaparin-induced responses (Figure 2). Notably, the slopes of the two low-molecular heparins were almost super-imposable. Following the administration of the initial smaller boluses of dalteparin and enoxaparin there was a significant rise in the ACT which was detectable within 5 minutes. Compared to baseline, the changes in the ACT remained significant at all time points, with the exception of dalteparin at 2 hours (Figure 3).

Comparative effects of dalteparin, enoxaparin and UFH on other coagulation parameters. The rise in the ACT induced with these agents was paralleled by a concordant rise in the aPTT (Figure 3). A correlation between the ACT and aPTT suggests that the changes observed in the ACT represent a non-spurious anticoagulant effect. The correlation between the ACT and the aPTT was similar for both LMWHs ($r = 0.76$ for dalteparin; $r = 0.75$ for enoxaparin) (Figure 4). The administration of dalteparin and enoxaparin was associated with changes in anti-Xa activity that paralleled the time course of the ACT (Figure 5). A weak, but statistically significant correlation was observed between anti-Xa activity and the ACT after the administration of either LMWH ($r = 0.45$; $p = 0.01$).

Safety outcomes. PCI was successful in all patients undergoing intervention. There were no deaths, abrupt closures, or urgent revascularization in the study population during the hospital course. One of the 46 PCI patients (2%) had a periprocedural non-Q-wave MI.

None of the patients suffered major bleeding, and no patient received a transfusion. There were no groin complications, nor were there any episodes of thrombocytopenia.

Discussion

This is the first study to prospectively analyze the comparative effects of intravenously administered enoxaparin, dalteparin, and unfractionated heparin on the ACT. We have previously reported the utility of the ACT for dalteparin monitoring.[6] Our current findings suggest that the ACT may also constitute a reliable assay for monitoring enoxaparin during PCI for the following reasons. First, the elevation is significant and rapidly detectable; within 10 minutes of receiving IV enoxaparin 0.5 mg/kg, the ACT increased on average 41 seconds. Second, there is an apparent dose-response relationship. Third, the increase in ACT is sustained for approximately 60 minutes, a period generally sufficient for current interventional practice, and is followed by a relatively steep decline. In fact, the rate of return to baseline ACT after bolus administration of IV enoxaparin or dalteparin is similar to that traditionally associated with bivalirudin (within 120 minutes). This suggests that IV LMWH may share with bivalirudin the profile of an ideal anticoagulant for use during PCI (*i.e.* potent anticoagulant effect with short duration of action), with the advantage of at least partial reversibility with protamine.[17–19] The rapid decline in the ACT also raises the possibility that a targeted level (*e.g.* < 150 seconds) could be used to determine the timing of sheath
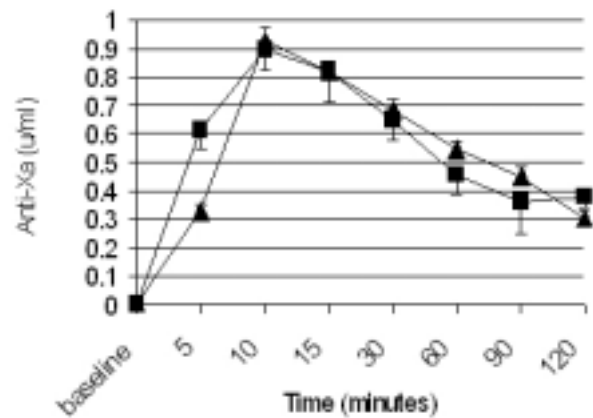

Figure 5. *Time course of anti-Xa activity following the administration of enoxaparin (triangles) and dalteparin (squares) as 2 boluses 5 minutes apart. Data presented as mean ± SEM (standard error of the mean).*

removal. Finally, these observations are consistent with previous reports. In a study using IV enoxaparin (1 mg/kg) during PCI, the mean ACT increased from 130 to 188 seconds.[20] A more recent study reported a mean increase from 122–199 seconds using the same dose of enoxaparin.[21] In addition to confirming these observations, our current study provides a comparative dose-response and detailed time course of both commercially available LMWHs and unfractionated heparin. Furthermore, this study demonstrates the ability to monitor enoxaparin even after very low intravenous doses (0.1 mg/kg) of enoxaparin.

To determine whether the elevation seen in the ACT following IV enoxaparin occurred in isolation or in conjunction with changes in other indices of anticoagulation, the aPTT and plasma anti-Xa activity were also measured. The aPTT rose significantly after IV enoxaparin administration and to a level traditionally regarded as therapeutic in the context of medical management for unstable angina (1.5- to 2-fold above baseline). The aPTT values correlated with the ACT, supporting the notion that the elevated ACT post-enoxaparin reflected an anticoagulated state. A similar correlation was noted between the aPTT and the ACT, consistent with our previously published data.[6]

We were unable to demonstrate a correlation between the ACT and anti-Xa activity in patients treated with enoxaparin. These findings are in accord with our earlier published data with dalteparin,[6] and they are consistent with the conflicting nature of the data in the literature regarding the correlation between the ACT and anti-Xa activity in patients treated with UFH.[22,23]

We believe that our data support the use of an ACT-guided strategy for monitoring the effects of enoxaparin during PCI. However, others have proposed a strategy based upon measuring anti-Xa activity.[11,24,25] Measurement of anti-Xa levels alone does not take into account the multiple levels of the coagulation cascade at which a LMWH acts.[6] Indeed, previous clinical studies have demonstrated only weak correlations between anti-Xa levels and thrombus formation.[26,27] In addition, the optimal therapeutic range for LMWH's anti-Xa level has not been clearly defined since most clinical studies have either not measured anti-Xa levels or convincingly correlated them to

clinical outcomes. In contradistinction to anti-Xa and anti-IIa levels, however, the ACT has been correlated to clinical outcomes in UFH-treated patients.[28,29] Chew et al. have demonstrated a significant relationship between the ACT and ischemic/bleeding events after PCI in patients receiving UFH.[28] A pooled analysis of more recent PCI trials has also demonstrated a significant correlation between the ACT and hemorrhagic complications.[30] Furthermore, anti-Xa assays used for monitoring are cumbersome and have not been standardized.[31,32] While a new point-of-care device based upon anti-Xa activity was recently developed to measure clotting times with enoxaparin *(ENOX, PharmaNetics, Morrisville, North Carolina)*, it is noteworthy that this device was not embraced by the interventional community and has since been withdrawn from the market. Thus, there is little evidence to support the notion that anti-Xa activity monitoring would be superior to ACT monitoring in patients receiving intravenous LMWH.

Recognizing the difficulties of measuring anti-Xa during PCI, still others have proposed algorithms that guide dosing based upon the interval of time elapsed from the last subcutaneous dose of LMWH.[12,13,15] However, such an approach is in fact based upon an anti-Xa strategy because the algorithms are designed to reflect the time course of anti-Xa activity following the administration of subcutaneous enoxaparin. As such, they still suffer from many of the limitations of using anti-Xa activity as the basis for monitoring. Furthermore, such algorithms assume that the pharmacokinetics of these agents are predictable, which may not be true in many patients with unique pharmacokinetics. For example, rigorous dosing studies have not been performed in patients who are pregnant, morbidly obese, or who have renal dysfunction, or other conditions that may affect subcutaneous absorption, such as cardiogenic shock.[1,33] In addition, such algorithms are limited by the difficulties in determining the timing of medication administration performed outside the catheterization laboratory, for example, in cases of transfer between facilities. Arguably, the most compelling data that points to the limitations of a timing-based approach derives from the SYNERGY trial comparing enoxaparin to UFH in the invasive management of acute coronary syndrome patients.[16] In this trial, the use of such an algorithm for enoxaparin was associated with a higher rate of bleeding despite similar rates of success.[16] It is noteworthy that in the SYNERGY trial design, ACT-guided monitoring was used for UFH but not for enoxaparin. While the reasons for excess bleeds have not yet been fully elucidated, it is conceivable that the lack of precise titration of anticoagulation in ACS patients randomized to enoxaparin contributed significantly to the excess bleeding.

Finally, others have argued that LMWH is not amenable to any form of monitoring. This notion was derived from studies using a subcutaneous route of administration, following which relatively low plasma levels are achieved. However, in contrast to the non-invasive setting, LMWH is generally administered intravenously during PCI. In a single center study of approximately 100 patients, we have previously demonstrated that IV dalteparin significantly elevates the ACT, and that the strategy of ACT-guided dalteparin appears to be associated with a low

periprocedural complication rate.[6] In the present study, we have extended these observations to include the LMWH enoxaparin.

In summary, we hypothesize that an ACT-guided dosing strategy for LMWH in PCI can lead to superior outcomes as seen in a number of earlier LMWH trials, but without the increased rate of bleeding noted in SYNERGY.[16] Specifically, the observation that even very low doses of IV LMWH elevate the ACT may allow for accurate titration into a target range. Given that the ACT has not been directly correlated to outcomes in patients treated with LMWH, the optimal target ACT using such a strategy will need to be validated in a larger randomized study.

Study limitations. There are several limitations associated with this study. First, ACTs were measured using the Hemochron system, and thus our data may not be readily extrapolated to the Hemotech system *(Medtronic, Parker, Colorado)*. Second, the study design was nonrandomized and open label, and patients were assigned to one of the three anticoagulation regimens arbitrarily. Third, in those patients undergoing PCI, eptifibatide was the GP IIb/IIIa inhibitor used most often, and therefore the results may not apply to patients receiving abciximab or tirofiban. Fourth, because patients with an elevated serum creatinine level were excluded, our findings may not apply to patients with renal insufficiency. Finally, Figure 5 demonstrates a 20–30 minute period of time of what is believed to be therapeutic anti-Xa levels; this may not be sufficient in those cases of more complex and prolonged PCI.

In conclusion, the ACT and aPTT are sensitive to IV enoxaparin and dalteparin at clinically relevant doses. These data suggest that the ACT may have the potential to be integrated into an IV LMWH monitoring strategy. The ability to monitor enoxaparin may facilitate the use of LMWH in PCI and in other invasive procedures such as coronary artery bypass surgery.

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