Avoiding Intelligence Failures in the Cardiac Catheterization Laboratory: Strategies for the Safe and Rational Use of Dalteparin or Enoxaparin during Percutaneous Coronary Intervention

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ABSTRACT: Low-molecular-weight heparin (LMWH) has been a mainstay for the management of acute coronary syndromes (ACS) for almost a decade. However, several recent developments have seriously threatened the prominence of this drug class: (i) the adoption of an early invasive strategy, frequently leading to percutaneous coronary intervention (PCI) where the dosing and monitoring of LMWH is unfamiliar to most operators, (ii) the results of the SYNERGY trial, which not only failed to establish the superiority of enoxaparin over unfractionated heparin with respect to efficacy, but also demonstrated more bleeding with LMWH, and (iii) the results of the REPLACE-2 and ACUITY trials, which have demonstrated the advantages of an ACS and PCI treatment strategy based on direct thrombin inhibition with bivalirudin. To confront these challenges, cardiologists committed to the continued use of LMWH must develop safe and user-friendly approaches to transition patients from the noninvasive to invasive settings. This review summarizes an approach that takes advantage of the fact that LMWH can be readily monitored with the point-of-care activated clotting time (ACT) assay. This assay is inexpensive, available in virtually every catheterization laboratory, and familiar to most operators who monitor unfractionated heparin (UFH). A key concept that is presented is that the ACT is a more accurate measure of LMWH-induced anticoagulation than of UFH-induced anticoagulation. Our preliminary work suggests that during PCI operators should target an ACT of 175 seconds in the presence, and 200 seconds in the absence, of adjunctive glycoprotein IIb/IIIa inhibition. Sheath removal is recommended at an ACT < 160. These guidelines may facilitate continued use of LMWH, which has the potential to reduce cost (less expensive than bivalirudin), diminish the need for intravenous medication (can be administered subcutaneously in the noninvasive setting with minimal to no monitoring), and provide an ideal anticoagulant during PCI (easy to monitor with the ACT, at least partially reversible with protamine in the event of coronary perforation, effective antithrombin with no platelet activation, thereby potentially reducing the need for routine adjunctive IIb/IIIa inhibition).

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Low-molecular-weight heparin (LMWH) has been in clinical use for over a decade and has assumed a major role in the management of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). The ESSENCE and TIMI 11B trials support the use of LMWH over unfractionated heparin (UFH) in acute coronary syndromes managed with a predominantly medical approach as opposed to an invasive initial strategy.1,2 Since the publication of the ESSENCE and TIMI 11B trials, the management of acute coronary syndromes (ACS) has evolved to favor an early invasive strategy. This evolution is supported by a number of studies, including the FRISC II and the TACTICS TIMI-18 trials.3,4 The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was therefore designed to extend the observations of ESSENCE and TIMI 11B to an invasively managed population. The SYNERGY trial compared enoxaparin to unfractionated heparin (UFH) in the invasive management of ACS patients and demonstrated similar rates of success post-PCI.5 However, patients randomized to enoxaparin in SYNERGY had a higher rate of bleeding.5 It is noteworthy that in the SYNERGY trial design, monitoring was used for UFH, but not for LMWH. This lack of monitoring of enoxaparin reflects the conventional view that LMWH cannot be readily monitored with bedside assays, such as the activated clotting time (ACT), and may have contributed to the excessive bleeding rate seen in enoxaparin-treated patients. Indeed, one of the principal reasons that LMWH is generally not used during PCI is this notion that LMWH cannot be monitored. The notion that LMWH is not amenable to monitoring was derived from studies using a subcutaneous route of administration, following which relatively low plasma levels are achieved. However, in contrast to the noninvasive setting, LMWH is generally administered as an intravenous (IV) bolus during PCI, thereby achieving higher peak plasma concentrations. We have shown that the level of anticoagulation induced by intravenously administered dalteparin can in fact be measured using the standard ACT test.6 Later, we reported similar observation with enoxaparin.7 More recently we demonstrated that the dose of dalteparin administered intravenously during PCI can be safely adjusted by monitoring the ACT and could constitute a safe and effective strategy during PCI.8 Monitoring of LMWH may be particularly important for those patients undergoing PCI after having already received a dose of subcutaneous (SC) LMWH for the initial management of their ACS. The ACT is the current standard of care for the management of anticoagulation during PCI. The chief
Purpose of this article is to review the LMWH literature as it relates to the issue of monitoring, and to answer key questions that may arise in LMWH-treated patients managed with an invasive strategy.

**Mechanism of action of Low-Molecular-Weight Heparins**

LMWH is an indirect thrombin inhibitor formed by depolymerization of heparin using chemical or enzymatic methods. UMFH preparations have a mean molecular weight of 4,500–5,000 Daltons, with a distribution of 1,000 to 10,000 Daltons. Unfractionated heparin is a more heterogeneous mixture of polysaccharide chains ranging in molecular weight from 3,000–30,000 Daltons, with an average molecular weight of 15,000. Unlike direct thrombin inhibitors, which consist of a single molecular weight entity, LMWH represents a population of molecules with an average molecular weight lower than that of UFH (Figure 1).

The mechanism of action of UFH and LMWH starts with the formation of a complex with antithrombin (Figure 2). LMWH’s catalytic activity then converts antithrombin from a slow to a rapid inactivator of coagulation factor Xa, accelerating antithrombin’s interaction with thrombin and Xa by a factor of approximately 1,000. Antithrombin has two active functional sites: the reactive center, Arg 393-Ser 394, and the LMWH binding site located at the amino terminus of the molecule. The binding of LMWH to antithrombin is mediated by a unique pentasaccharide sequence randomly distributed along the LMWH chain. Approximately one-third of the chains of UFH, but only 15–25% of the chains of LMWHs, contain the pentasaccharide sequence. After the LMWH has been bound to the heparin binding site on antithrombin, a conformational change in antithrombin occurs, and this significantly accelerates antithrombin’s inactivation of coagulation factor Xa.

The binding of LMWH to antithrombin causes less inactivation of coagulation factor IIa (thrombin) when compared with that of unfractionated heparin. This is because inactivation of factor IIa requires the formation of a ternary complex in which heparin binds to both antithrombin and to a binding site on factor IIa (Figure 2). This ternary complex is formed on pentasaccharide containing chains of at least 18 saccharide units. However, unlike UFH, many of the LMWH do not contain sufficient saccharide units to form the ternary complex. It has been estimated that 25–50% of LMWH chains are sufficiently long to bridge antithrombin to factor IIa.

Therefore, a major difference between UFH and LMWH is in their relative inhibitory activity against factor Xa and factor IIa (Table 1). Any pentasaccharide-containing heparin chain can inactivate factor Xa, but a minimum number of saccharide units is required to exert an inhibitory effect on factor IIa. Therefore, LMWH has a greater ratio of factor Xa to factor IIa inhibitory activity when compared with UFH, which has equivalent activity against these factors.

Other antithrombogenic effects of LMWH include its promotion of the release of tissue factor pathway inhibitor (TFPI) from vascular endothelium, a reduction in the levels of von
Willebrand factor (vWF), the inhibition of the procoagulant effects of leukocytes, the promotion of fibrinolysis and the inhibition of monocyte adhesion.\textsuperscript{21} Platelet factor 4 recently has been found to induce natural killer (NK) cells’ production of inflammatory cytokine IL-8, which may exert a prothrombotic effect in acute coronary syndromes (ACS).\textsuperscript{21} LMWH is less likely to be bound to platelet factor 4 than UFH, and thus exerts a less prothrombotic and potentially less proinflammatory effect than UFH.\textsuperscript{21}

### Pharmacokinetics of Low-Molecular-Weight Heparins

LMWH exhibits less nonspecific binding to plasma proteins, endothelial cells and macrophages, and therefore has greater bioavailability than UFH.\textsuperscript{10} The diminished binding to macrophages results in reduced clearance by hepatic mechanisms; this is one of the reasons why renal clearance mechanisms are the major determinants of LMWH’s plasma half-life.\textsuperscript{10}

The pharmacokinetics of LMWH are different from those of UFH after both IV and SC administration. The plasma anti-factor Xa activity is approximately two to four times longer than that of UFH, and this is regardless of the injected dose of the different forms of LMWH.\textsuperscript{10} This generally ranges from 2 to 4 hours after IV injection and from 4 to 6 hours after SC injection.\textsuperscript{10} The factor Xa inhibitory activity of LMWH persists longer than its inhibitory activity against factor IIa as a result of the more rapid clearance of longer heparin chains.\textsuperscript{10} The duration of anti-factor IIa activity of LMWH is only slightly longer than that of UFH.\textsuperscript{22}

Because its route of elimination is via the renal system, the half-life of LMWH increases in patients with renal failure.\textsuperscript{9} LMWH dosing should therefore be reduced by 50% in patients with creatinine clearance < 30 ml/min.\textsuperscript{23–25}

The pharmacokinetics of LMWH differ substantially from two of the newer anticoagulants, bivalirudin and fondaparinux. Bivalirudin is a reversible, direct, pure thrombin inhibitor that is administered intravenously. It is a synthetic 20 amino-acid polypeptide modeled after hirudin and comprised of an active site-directed peptide linked via a tetraglycine spacer to a dodecapeptide analogue of the carboxy-terminal of hirudin.\textsuperscript{26} There have been several trials, including BAT, REPLACE-1, CACHET, REPLACE-2, ACUITY and HORIZONS-AMI, which have suggested its superiority over UFH during PCI.\textsuperscript{27–32} It has been recently approved by the U.S. Food and Drug Administration (FDA) for use during PCI.\textsuperscript{31} Bivalirudin’s recommended route of administration is IV, its onset of action is immediate and duration of action is approximately 1 hour.\textsuperscript{34} It does not bind to plasma proteins other than thrombin and its half-life is approximately 25 minutes, assuming normal renal function. However, prolongation may occur in patients with moderate (34 mins) or severe (57 mins) renal impairment, with creatinine clearance of 30–59 ml/min and < 30 ml/min, respectively.\textsuperscript{35} Bivalirudin is eliminated via the renal system and also via proteolytic cleavage.\textsuperscript{36}

Fondaparinux, a pentasaccharide derived from the heparin molecule, is an indirect, high-affinity factor Xa reversible inhibitor. By virtue of its very short chain length, it does not bind nonspecifically to plasma proteins. It also has 100% bioavailability after SC administration, reaching its peak serum concentration at 1.7 hours post administration. The half-life of 17 hours is longer than that of LMWH, allowing it to be administered as once-daily dosing. The route of elimination is via the renal system and it is excreted unchanged in the urine, with an elimination half-life of 15–17 hours. It has not been approved by the FDA for use during PCI.\textsuperscript{37} In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, among those who underwent invasive strategy, an increased risk of coronary guide-catheter thrombus formation was reported with fondaparinux compared with enoxaparine (0.9% vs. 0.4%; \textit{p} = 0.001).\textsuperscript{38} It has not been approved by the FDA for use during PCI.\textsuperscript{37}

#### Low-Molecular-Weight Heparins versus Unfractionated Heparin

There are several features of LMWH that support its use during ACS and PCI. The most important advantage of LMWH versus UFH is that there is less platelet activation with LMWH (Figures 3 and 4).\textsuperscript{39,40} Platelet aggregation requires activation of glycoprotein (GP) Ib/IIa receptors located on the surface of platelets, with fibrinogen acting as a cofactor for platelet activation. Standard UFH with its high molecular weight and longer saccharide chain activates platelet GP Ib/IIa receptors, thereby potentiating platelet aggregation (Figure 5).\textsuperscript{41–47} The lower proaggregatory actions of LMWH have been detected \textit{in vitro} and \textit{in vivo}.\textsuperscript{44,47–55} and appear to decrease with decreasing molecular weight.\textsuperscript{52} In fact, LMWHs, with a molecular weight of < 3,000 Daltons did not result in binding of fibrinogen to the platelet surface.\textsuperscript{47} This is of particular relevance to PCI, where increased platelet aggregation may contribute to complications.\textsuperscript{21}

LMWH is associated with less tissue factor (TF) pathway inhibitor depletion, and actually promotes the release of TF pathway inhibitors, thereby enhancing LMWH’s anti-factor Xa activity.\textsuperscript{21,56–58} In contrast, UFH increases the depletion of TF pathway inhibitors.\textsuperscript{56–59} As a result, less rebound hypercoagulability may be seen with LMWH compared to UFH.\textsuperscript{60}

Increased circulating levels of von Willebrand factor (vWF) in patients with ACS post PCI have been implicated as a factor contributing to adverse outcomes.\textsuperscript{21} Whereas UFH does not blunt the increased vWF levels seen in patients with ACS, LMWH does appear to attenuate this increase.\textsuperscript{61}

LMWH is associated with a lower incidence of heparin-induced thrombocytopenia (HIT) when compared to UFH.\textsuperscript{9} HIT is an antibody-mediated adverse reaction to heparin, which unlike other drug-induced thrombocytopenias, causes venous and arterial
Thrombosis rather than bleeding. HIT is a syndrome manifested by HIT antibody formation, a > 50% decrease in platelet count or skin lesions at injection sites. \(^9\) HIT is mediated by the HIT antibody recognizing the epitope on the platelet factor 4 (PF4)-heparin complex as an antigen. \(^62\) The HIT antibody binds to one or more PF4 regions conformationally modified by the interaction with heparin. \(^9\) At least 12–14 saccharide units within the heparin molecule are required to form the antigenic complex with PF4. \(^9\) Therefore, the risk of HIT antibody formation is lower during treatment with LMWH than with UFH. \(^9\)

The better bioavailability, dose independent clearance and decreased affinity for heparin-binding proteins make the anticoagulant response to LMWHs more predictable than that to UFH. \(^10\)

### The Methodology of the Activated Clotting Time (ACT) and the Activated Partial Thromboplastin Time (aPTT)

**Activated Clotting Time (ACT).** The activated clotting time (ACT) is a measure of the overall tendency of the blood to thrombose. It was first described by Hattreley in 1966 and came into clinical use in the mid-1970s to guide the administration and reversal of UFH during cardiopulmonary bypass. \(^63\) It is also used in point-of-care monitoring of the anticoagulation effect of UFH during cardiac catheterization and vascular surgery.

The methodology of the ACT involves the collection of whole blood into a tube containing a magnet and an activator of coagulation, diatomaceous earth. \(^64\) This activator stimulates clot formation upon contact with whole blood via the intrinsic pathways of the coagulation cascade. The ACT measures the time required for the blood to clot, providing an index of the patient's coagulation status.

**Activated Partial Thromboplastin Time (aPTT).** The aPTT is a measure of the activity of the intrinsic pathway of the coagulation cascade. It is performed by adding a reagent containing kaolin and a phospholipid suspension to the patient's plasma. The time required for the clot to form is measured, and a control plasma is used to calibrate the result. A prolonged aPTT indicates a defect in the intrinsic pathway, which can be caused by deficiencies in coagulation factors. The aPTT is commonly used to monitor anticoagulant therapy, such as heparin, and to detect congenital or acquired deficiencies in the intrinsic pathway.

#### Figures

**Figure 3.** Enhanced platelet activation on unfractionated heparin (UFH). An example of platelet aggregation to low concentrations of TRAP before and during an infusion of UFH in a patient with unstable angina. Inset shows the results of light transmission aggregometry in platelet-rich plasma from volunteers after adding saline, UFH, enoxaparin, or argatroban. Platelet aggregation to low concentrations of ADP and TRAP is significantly increased in the presence of UFH. \(^9\) At least 12–14 saccharide units within the heparin molecule are required to form the antigenic complex with PF4. \(^9\) The methodology of the ACT involves the collection of whole blood into a tube containing a magnet and an activator of coagulation, diatomaceous earth. \(^64\) This activator stimulates clot formation upon contact with whole blood via the intrinsic pathways of the coagulation cascade.

**Figure 4.** Flow cytometry and platelet activation by unfractionated heparin (UFH) but not by low-molecular-weight heparin (LMWH). PAC-1 is an IgM polyclonal antibody that binds specifically to activated GP IIb/IIIa. Anti-CD62 is a murine monoclonal antibody directed against P-selectin expressed on the platelet surface, an indicator of platelet activation. \(^6\) The better bioavailability, dose independent clearance and decreased affinity for heparin-binding proteins make the anticoagulant response to LMWHs more predictable than that to UFH. \(^10\)

**Figure 5.** Heparin binds and activates platelet GP IIb/IIIa. Left panel: Photoaffinity cross-linking of heparin to intact platelets. Platelets were incubated with tritiated heparin, and then exposed to UV light (or not), and the cross-linked platelets washed and solubilized. (A) Coomassie stain of original 6% SDS-PAGE of platelet proteins after electrotransfer. (B) Autoradiography of the same lanes from the Western blot. (C) Immunostaining of same blot for αIIbβ3. On the left are aggregation tracings of PRP exposed to heparin or PBS control. On the right are Western blots from the detergent insoluble cytoskeletal fraction of the same platelets, probed for Rap2B. Significantly less Rap2B is visible in the control sample.
is most sensitive to thrombin inhibition, the slope of the line increases for drugs with greater anti-IIa properties. 

The tube is placed in a coagulation analyzer (e.g., Hemochron®, International Technidyne Corp., Edison, New Jersey). The magnet at the bottom of the tube is displaced once a clot is formed, activating the alarm on the analyzer (Figure 6). An advantage of the ACT in comparison to the aPTT is that at high doses of heparin, the dose-response relationship remains linear for the ACT. The aPTT usually becomes prolonged beyond measurable levels at heparin concentrations > 1 U/ml. This makes the aPTT unsuitable for monitoring heparin dosage during angioplasty and bypass surgery, as patients may require heparin levels > 1U/ml. The ACT has a graded response to heparin concentrations in the range of 1 U–5 U/ml. As a result, monitoring of heparin with the ACT may be more useful.

Although it is used to monitor agents that possess both anti-IIa and anti-Xa activities, the ACT (and aPTT) are influenced predominantly by anti-IIa activity (Figure 7). Thus, if the ACT is used to monitor bivalirudin, one would expect a dramatic increase, e.g., from a baseline of approximately 110–130 sec to a post-bivalirudin bolus of 300–400 sec. In contrast, when using an agent such as LMWH that has a reduced ratio of anti-IIa:anti-Xa activity, the operator must anticipate a reduction in the magnitude of change from baseline values. The target ACT for the LMWH-treated patient is discussed below.

The Activated Partial Thromboplastin Time (aPTT). The activated partial thromboplastin time (aPTT) measures the clotting time from the activation of factor XII to the formation of the fibrin clot, thus measuring the integrity of the intrinsic and common pathways of coagulation. The aPTT is usually used to monitor therapeutic heparin, hirudin and argatroban anticoagulation. However, as noted before, at high doses of heparin, the use of aPTT is not ideal.

To measure the aPTT, blood is collected into a tube containing kaolin, an intrinsic pathway activator. A reagent of phospholipid is also provided in the aPTT assay; this is in contrast to the ACT assay, in which the platelets provide phospholipids. The measurement of the aPTT is generally performed in a hospital’s core laboratory facility, with results obtained within 30–60 minutes. This delay is an additional reason for which the ACT has been traditionally used in the cardiac catheterization laboratory and cardiovascular operating room settings where immediate results are often needed.

Point-of-Care Monitoring Devices. There are point-of-care devices which have been developed to monitor both the ACT and the aPTT. These include The Hemochron® System (International Technidyne Corp.), which include the Hemochron Jr., Hemochron 801 and Hemochron 400 and Hemochron Jr. LR.® Medtronic, Inc. (Minneapolis, Minnesota) has also developed point-of-care monitoring devices, which include the HemoTec and the Medtronic ACT II devices. There are other similar devices available such as Celite i-STAT ACT and the Heparon/HMS devices.

These devices are generally cartridge- or cuvette-based, allowing for less blood drawing and potentially greater reproducibility of results as operator variables such as the shaking of tubes no longer comes into play.

Use of Low-Molecular-Weight Heparins during Percutaneous Coronary Intervention

Anticoagulation during PCI is used to prevent thrombotic complications, including abrupt or subacute closure of the coronary vasculature and myocardial necrosis. LMWH offers theoretic advantages over UFH as an anticoagulant to prevent thrombotic arterial complications. However, UFH remains the most commonly used anticoagulant in PCI, in part because it is familiar and can be monitored easily. LMWH has seen increased use in the medical treatment of ACS, including patients with STEMI. A significant number of patients currently present to the cardiac catheterization laboratory for PCI already having received at least one, and occasionally several, doses of LMWH. Such patients pose several challenges and questions to the interventionist, such as: 1) Is there any value in using LMWH, as opposed to UFH, in PCI? 2) Can the LMWH that was administered prior to the patient’s arrival to the cath lab, or any
additionally administered LMWH given in the cath lab be monitored using a bedside assay? 3) If so, what ACT value should be targeted? These questions and concerns have become all the more relevant and urgent given the emerging consensus, based on the SYNERGY trial, that switching antithrombotic agents appears to be associated with an increase in adverse events.

**Question 1. Is there any value in using LMWH, as opposed to UFH, in PCI?**

*Theoretic advantages of LMWH versus UFH in PCI:* LMWH demonstrates less platelet activation and less platelet endothelial interactions when compared with UFH (Figures 3–5). Although not proven, the propensity of UFH to activate platelets may have important clinical implications. For example, in the ASSENT III trial, over 6,000 acute MI patients were randomized to one of three arms: (i) full-dose fibrinolysis with UFH; (ii) half-dose fibrinolysis with UFH plus GP IIb/IIIa inhibition (abciximab); or (iii) full-dose fibrinolysis with LMWH (but no abciximab), and the composite endpoint to 30 days of death, reinfarction and refractory ischemia was examined. The worst outcomes were seen in the group of patients treated with full-dose tenecteplase (TNK) administered with UFH. Both combination therapy of half-dose TNK and abciximab, as well as the regimen of TNK with enoxaparin, showed a significant reduction in event rates (Figure 8). Thus, the beneficial effects of GP IIb/IIIa inhibition appear to be replicated by the use of LMWH, or seen from another perspective, the platelet activating effects of UFH require coadministration of GP IIb/IIIa inhibition to achieve results that could be achieved by using an antithrombin agent that does not activate platelets in the first place. This raises the question as to whether better antithrombins might reduce, or even eliminate, the need for adjunctive anti-GP IIb/IIIa therapy, as suggested by the results of the REPLACE-2 trial.

**Use of LMWH in elective and/or urgent PCI:** Several studies have been conducted to evaluate the safety and efficacy of LMWH alone or in combination with GP IIb/IIIa inhibitors in PCI. The National Investigators Collaborating on Enoxaparin (NICE) group conducted two separate studies: NICE 1 and NICE 4. Patients in NICE 1 were administered IV enoxaparin alone at a dose of 1 mg/kg during PCI, while the NICE 4 group of patients were administered a reduced dose 0.75 mg/kg of IV enoxaparin, along with a standard dose of abciximab during PCI. In both groups of patients, bleeding complications and ischemic outcomes in hospital and at 30 days post PCI were infrequent. Thus, enoxaparin appears to be a safe and effective anticoagulant during PCI, both when administered alone and in combination with abciximab.

Bhatt et al assessed the use of enoxaparin in combination with eptifibatide during PCI. The study was conducted on 261 PCI patients randomized to either LMWH plus eptifibatide, or UFH plus eptifibatide. There were no significant differences in the rates of bleeding nor in the rates of death, myocardial infarction or urgent target revascralization at 48 hours or 30 days.

Another study by Kerelakes et al was conducted to assess the anticoagulant effect and clinical safety of dalteparin administered in combination with abciximab during PCI. This study concluded that IV dalteparin 60 IU/kg appeared to be safe and effective when administered in conjunction with a standard dose of abciximab.

The SYNERGY trial. The SYNERGY trial was designed to be the definitive investigation for establishing the superiority of LMWH over UFH in the context of ACS managed invasively. Approximately 10,000 ACS patients were randomized to anticoagulation with either enoxaparin or UFH prior to undergoing PCI. There were no significant differences in the primary composite endpoint of death and myocardial infarction (MI) at 30 days, and the rate of successful PCI was similar between the two groups. However, bleeding complications were significantly greater in the LMWH group compared with UFH (Table 2). With respect to the increased bleeding in the enoxaparin arm, it is noteworthy that the UFH group was monitored using the ACT, while the LMWH group was not (Table 3). The failure to include monitoring of enoxaparin in the SYNERGY study design reflects the unsubstantiated conventional view that LMWH cannot be readily monitored with bedside assays, such as the activated clotting time (ACT), and may have contributed to the excessive bleeding rate seen in enoxaparin-treated patients. Indeed, one of the principal reasons that LMWH is generally not used during PCI is this notion that LMWH cannot be monitored. However, as discussed below, we have shown that the level of anticoagulation induced by intravenously administered dalteparin and enoxaparin can in fact be measured using the standard ACT test.

The Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) Trial. The STEEPLE trial is the most important trial to address the potential role of LMWH in PCI. It is the first large (n = 3,528 patients), multicenter (n = 124 sites), prospective, randomized trial of LMWH versus UFH in PCI. STEEPLE randomized patients to one of two doses of IV enoxaparin (0.5 mg/kg or 0.75 mg/kg) or IV UFH, with GP IIb/IIIa inhibition use at the discretion of the operator. The primary endpoint of the study was non-coronary artery bypass graft surgery (CABG) major and minor bleeding at 48 hours. Secondary endpoints included various combinations of non-CABG major bleeds at 48 hours, death, nonfatal MI, or urgent target vessel revascularization at 30 days. The
The ability to monitor UFH with the ACT or aPTT is determined predominately by its anti-IIa activity, rather than by its anti-Xa activity (Figure 7). Thus, agents that are mainly anti-IIa, such as bivalirudin result in very high levels of ACT (i.e., 300–400

Table 2. Bleeding rates in the SYNERGY trial.

<table>
<thead>
<tr>
<th>Bleeding Definition</th>
<th>Enoxaparin (%)</th>
<th>Unfractionated Heparin (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO severe bleeding</td>
<td>2.7</td>
<td>2.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Decrease in hemoglobin and hemocrit†</td>
<td>15.2</td>
<td>12.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TIMI major† bleeding (all)</td>
<td>9.1</td>
<td>7.6</td>
<td>0.008</td>
</tr>
<tr>
<td>TIMI major† bleeding (CABG-related)</td>
<td>6.8</td>
<td>5.9</td>
<td>0.08</td>
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<tr>
<td>TIMI major† bleeding (not CABG-related)</td>
<td>2.4</td>
<td>1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Any Transfusions</td>
<td>17.0</td>
<td>16.0</td>
<td>0.16</td>
</tr>
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</table>

CABG = coronary artery bypass grafting; GUSTO = global utilization of streptokinase and t-PA for occluded arteries; TIMI = thrombolysis in myocardial infarction
† Associated with clinical bleed
‡ At least a 5 g/dL decrease in hemoglobin or at least a 15% decrease in hematocrit not associated with an overt bleeding event.

Table 3. The study drug in the SYNERGY trial and cardiac procedures.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Enoxaparin</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization</td>
<td>Perform catheterization any time after last dose</td>
<td>Continue UFH and perform catheterization</td>
</tr>
<tr>
<td>PCI</td>
<td>&lt; 8 hrs from last subcutaneous dose</td>
<td>No additional LMWH</td>
</tr>
<tr>
<td></td>
<td>&gt; 8 hrs from last dose</td>
<td>0.3 mg/kg IV bolus to achieve ACT of 250 sec</td>
</tr>
<tr>
<td>CABG</td>
<td>Elective</td>
<td>Stop &gt; 8 hrs</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>Stop</td>
</tr>
</tbody>
</table>

PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

major finding of the study was that the primary end point of major bleeding was 57% lower in the enoxaparin arms than in the UFH arm. There were no significant differences in rates of death, death or MI, or death, MI and urgent target vessel revascularization, suggesting that the reduction in bleeding was not achieved at the expense of increased vulnerability to cardiac events.

The STEEPLE trial provides important data to support the use of LMWH in elective PCI. However, one limitation of the trial was the failure to monitor the effects of enoxaparin with the ACT. Although some have emphasized the advantage of “no need to monitor,” many operators remain skeptical about the safety of using a strategy that precludes the ability to determine to any measurable degree the level of anticoagulation during PCI. While the advantage of not monitoring may be appealing in elective, low risk situations, there are a number of circumstances in which the ability to rapidly assess the anticoagulant status of the patient may be useful, including patients presenting with complex histories (e.g., a chronic renal failure patient who had recently received SC enoxaparin, thrombolytic therapy and now arrives at the cath lab with skin hypoperfusion due to cardiogenic shock), patients in whom the implications of thrombosis could be life-threatening (e.g., unprotected left main stenting), patients who initially were deemed low-risk who become high-risk in the course of their PCI (e.g., the unexpected appearance of intraluminal thrombus), and finally, in circumstances that are not entirely in the control of operators (e.g., medication dosing errors and drug administration errors; this latter point may be particularly relevant in cath labs where enoxaparin or dalteparin are administered from small preloaded syringes designed for SC administration).

Meta-analysis. Dumaine et al reported a meta-analysis of randomized trials comparing the efficacy and safety of LMWH versus UFH as anticoagulants in the setting of PCI. The authors concluded that LMWH use during PCI is associated with similar efficacy and significantly reduced major bleeding complications when compared to UFH. Again, all the studies included in the analysis used a fixed dose of LMWH without monitoring the anticoagulant effect of LMWH.

Question 2. Can LMWH be monitored readily and accurately with the ACT? The notion that LMWH is not amenable to monitoring was derived from studies using a SC route of administration, following which relatively low plasma levels are achieved. Furthermore, these studies were conducted in an era during which the default management strategy for ACS was noninvasive, where accurate knowledge of the specific level of anticoagulation in an individual patient may not have been as critical as in today’s era of invasive management.

It is our contention that the anticoagulant effect of LMWH administered during PCI can and should be monitored, and that algorithms based on the timing from the last administered SC dose, such as those used in the SYNERGY trial, are inadequate. First, it is not always possible to determine the timing of the last dose of LMWH; not infrequently, there is inadequate documentation in the chart, particularly in the case of patients who may have had therapies initiated at one institution, and then are transferred to a tertiary care center for intervention. Second, the timing approach is based on a presumption that the pharmacokinetics of LMWH are always predictable. While this may be true in healthy volunteers, such is not the case for patients presenting with a variety of conditions such as obesity and renal dysfunction, conditions associated with an ever-increasing proportion of patients undergoing PCI. For example, an elderly diabetic patient with acute MI and hemodynamic compromise may have altered absorption from a SC dose because of poor skin perfusion, and altered elimination because of changes in an already compromised glomerular filtration rate. Thus, LMWH-treated patients most in need of accurate levels of anticoagulation are likely to be the most at risk for inaccurate dosing and excessive bleeding. These issues are likely to have contributed to the disappointing results of the SYNERGY trial.

The ability to monitor UFH with the ACT or aPTT is determined predominantly by its anti-IIa activity, rather than by its anti-Xa activity (Figure 7). Thus, agents that are mainly anti-IIa, such as bivalirudin result in very high levels of ACT (i.e., 300–400
seconds range). In contrast, an agent such as pentasaccharide, which is almost exclusively anti-Xa, has very little influence on the ACT or aPTT. UFH, like LMWH, lies somewhere between these extremes, possessing both anti-IIa and anti-Xa activities (Figure 7).

Among the LMWH agents, each agent has a relatively predictable and measurable anti-IIa activity. Because the ACT correlates with the anti-IIa activity, ACT is a reasonable measure of each drug concentration and is dependent on the anti-IIa inhibitory activity of that particular agent. Thus ACT should be a good guide to monitor the degree of anticoagulation and minimize bleeding risk provided that the operator recognizes that each agent impacts ACT to a variable but predictable level.

The anti-IIa activity of UFH is determined by the formation of a ternary complex which requires at least 18 saccharide units. Because most UFH molecules contain at least 18 saccharide units, UFH has an anti-Xa to anti-IIa ratio that approximates unity. LMWHs, by virtue of their lower molecular weight and fewer saccharide units, have less anti-IIa activity and therefore a decreased ability to form the required ternary complex. The anti-Xa:anti-IIa ratio of several forms of commercially available LMWH range between 2 and 4, depending on the molecular weight distribution (Table 1).

We have previously reported that the ACT can be used to monitor dalteparin administered intravenously at the time of PCI. Five minutes after 60 IU/kg of IV dalteparin, the ACT increased from levels of 120–130 sec to levels of 170–180 sec (and aPTT increased from 25–30 sec to 55–70 sec). Approximately 1 hour after the bolus dose, a decrease in the ACT and anti-IIa and anti-Xa levels was observed. This time course is favorable in the current era of stenting, where procedures are often completed within a half-hour, and raises the question as to whether the ACT could be used not only to determine the dosing of LMWH, but also to determine the timing of sheath removal (Figure 9). In addition, the rapid decline in LMWH concentration after IV bolus administration provides an anticoagulant profile that is more similar to bivalirudin, where hemostatic competence is rapidly restored after cessation of drug infusion, thereby reducing bleeding complications.

An additional previously reported observation is that although UFH induced a greater increase in the ACT compared with dalteparin, there was a corresponding greater degree of variability in the response of the ACT to UFH compared with dalteparin. The tighter distribution of dalteparin-induced (in comparison to UFH-induced) peak ACT values has been confirmed in a recent randomized trial of PCI. This suggests that once a target ACT is reached, the corresponding blood levels of anticoagulant may be more reliably predicted than had UFH been administered.

To extend our observations to enoxaparin, we performed additional monitoring studies using doses that more closely reflect those used in the STEEPEL trial. Specifically, in a population of 130 patients undergoing cardiac catheterization, the effects of intravenously administered enoxaparin 0.5 mg/kg, dalteparin 50 IU/kg, and UFH 50 units/kg were assessed with respect to changes in ACT, aPTT and anti-Xa levels. Both enoxaparin and dalteparin induced a significant rise in the ACT and aPTT (Figure 11), with an ACT dose-response approximately one-half the magnitude of that obtained using UFH. The elevation in the ACT was both significant and rapidly detectable; for example, within minutes of receiving IV enoxaparin 0.5 mg/kg, the ACT increased on average 41 seconds. 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, suggesting a return to hemostatic competence that is as rapid as that seen using bivalirudin.

An additional strategy for monitoring LMWH, specifically enoxaparin, is based on a bedside anti-Xa assay (ENOX test). Moliterno et al studied the ENOX test in the ELECT study to determine a target range of anticoagulation for enoxaparin during PCI. This study was a prospective multicenter trial involving 445 patients receiving SC or IV enoxaparin. The rate of ischemic events was lowest in the mid-range of ENOX times, and bleeding events increased with increasing ENOX times.

Lawrence et al studied the effect of IV enoxaparin on both the ACT and the ENOX test in the setting of PCI. Sixty-seven consecutive patients undergoing PCI were given either 1 mg/kg of IV enoxaparin alone, or 0.75 mg/kg of IV enoxaparin plus eptifibatide. The ACT was measured before and 5 minutes following enoxaparin administration. The mean increase in the ACT was 77 ± 26 seconds in the 1 mg/kg group, and 69 ± 23 sec in the 0.75 mg/kg group (p < 0.0001). There was a significant correlation between the ACT and the ENOX test (r = 0.86). The study had concluded that enoxaparin at clinically relevant doses increases the ACT, further supporting the idea that point-of-care monitoring of enoxaparin during PCI may be achieved by measuring the ACT. Finally, it is noteworthy that because the ACT correlates with the more costly ENOX test, it may not be necessary to use the ENOX, or other anti-Xa assays altogether. Most operators, in fact, have not embraced this assay, which has led to its withdrawal from the market.

**Question 3.** If LMWH can be monitored in the cath lab, what ACT value should be targeted? The *in vitro* and *in vivo* dose response of the ACT following IV LMWH is characterized...
by a slope that is approximately one-half the magnitude of UFH (Figure 12). This relationship provides an opportunity to derive a theoretic LMWH ACT target value based on the generally accepted UFH ACT target values. Although the ideal target ACT for UFH has not been defined, in current interventional practice there is an apparent consensus that operators should achieve a minimal value of 200 sec in the presence of adjunctive GP IIb/IIIa inhibition, and 300 sec in its absence. Based on our clinical experience, a convenient rule of thumb for achieving a target ACT level is that for every 0.1 mg/kg of enoxaparin IV or for every 10 IU/kg of dalteparin IV, the ACT will increase by approximately 10 sec. The mean baseline ACT was 138 ± 41 sec; after the initial bolus of dalteparin, the mean ACT was 261 ± 76 sec. In the 68 patients who achieved the target ACT after the initial bolus of dalteparin, the mean ACT was 261 ± 76 sec. In the 36 patients who required a supplemental bolus to achieve the target ACT, the mean initial post-dalteparin bolus ACT value was 188 ± 59 sec. The mean supplemental dose administered was 14 ± 6 IU/kg of dalteparin. The mean ACT after the supplemental dose was 239 ± 78 sec. The incidence of ischemic endpoints in our study was comparable to the ischemic endpoints reported in the SYNERGY5 and STEEPLE trials.63 However, bleeding complications in our study appeared to be lower than those reported in the LMWH arms of these trials possibly due to the close monitoring of the anticoagulant activity of dalteparin, nevertheless this finding could be entirely due to small sample size in our study. Based on our clinical experience, a convenient rule of thumb for achieving a target ACT level is that for every 0.1 mg/kg of enoxaparin IV or for every 10 IU/kg of dalteparin IV, the operator can anticipate a rise in the ACT of approximately 10 sec.6 Using doses from the STEEPLE trial63 and other published reports,80 a starting dose of enoxaparin 0.5 mg/kg IV or dalteparin 50 IU/kg appears reasonable, and will yield an elevation in the ACT of approximately 50 sec.

Finally, our earlier study with dalteparin demonstrated that the increase in the ACT was sustained for a period of time relevant to current interventional practice. Using IV LMWH, the ACT is elevated for 40–60 min, with a decline in values at approximately 90 min.6 This raises the possibility that a decline in the ACT to a target level, for example < 160 sec, could be used to determine the timing of sheath removal, a potentially
and, when appropriate, percutaneous coronary intervention (PCI). The results of SYNERGY demonstrate that enoxaparin-treated patients may undergo PCI with a similar rate of success compared to UFH-treated patients. However, patients who were randomized to enoxaparin suffered a significantly greater rate of hemorrhagic complication. It is noteworthy that a major distinction between the two groups was that monitoring was used in the UFH-treated patients, but not in the LMWH-treated group. This failure to include monitoring in the trial design reflects an unsubstantiated bias that LMWH-treated patients are not amenable to monitoring with a readily available bedside assay such as the ACT. Arguably, the reluctance of PCI operators to embrace LMWH, despite a number of theoretic and practical advantages (e.g., less thrombocytopenia, diminished platelet activation, low cost, partial reversibility with protamine), is related in a large part to the perceived inability to monitor LMWH.

Our earlier studies and more recent observations have demonstrated that, in fact, both dalteparin and enoxaparin can be monitored with the ACT. Based on these preliminary observations, we have proposed a minimum target ACT of 175 sec for LMWH in PCI performed with GP IIb/IIIa inhibition and a minimum target ACT of 200 sec for LMWH in PCI without GP IIb/IIIa inhibition, which are supported by our previous observation and others (Figure 13). We have also proposed a target ACT value of < 160 sec for sheath removal.

References
7. Cavusoglu E, Lakhani M, Marmur JD. The activated clotting time (ACT) can be used to monitor enoxaparin and dalteparin after intravenous administration. J Invasive Cardiol 2005;17:416–421.

Figure 12. A composite of the dose-response of the activated clotting time (ACT) following intravenous administration of low-molecular-weight heparin, characterized by a slope that is approximately one-half the magnitude of unfractionated heparin (UFH). Using the UFH ACT targets of 200 and 300 seconds (for patients with and without adjunctive GP IIb/IIIa inhibition, respectively), a vertical line started at the drug concentration that is associated with the target ACT for UFH can be extrapolated to intersect with the dose response slope for LMWH. The point of intersection with the LMWH dose response slope would then represent the target LMWH ACT. Based on study observations and these calculations, we have proposed a minimum target ACT of 200 sec for patients receiving LMWH alone (without GP IIb/IIIa inhibition), a minimum of 175 sec for patients receiving LMWH with GP IIb/IIIa inhibition, and a minimum of 200 sec for patients receiving LMWH alone (without GP IIb/IIIa inhibition) during percutaneous coronary intervention.

Figure 13. Algorithm for the use of low-molecular-weight heparin during percutaneous coronary intervention in use at SUNY Downstate Medical Center, Brooklyn, New York.


