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SPECIAL SUPPLEMENT

Avoiding Intelligence Failures in the Cardiac Catheterization Laboratory: Low-Molecular-Weight Heparin is a WMD (Weapon Most Desirable) during Percutaneous Coronary Intervention Because it *Can* be Monitored with the Activated Clotting Time

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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: 1) 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; 2) the results of the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, which failed to establish the superiority of enoxaparin over unfractionated heparin (UFH) with respect to efficacy and demonstrated more bleeding with LMWH; and 3) the results of the Randomized Evaluation of Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-2 and Acute Catheterization and Urgent Intervention Triage Strategy (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 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 of adjunctive glycoprotein IIb/IIIa inhibition 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 case of coronary perforation and effective anti-thrombin 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 Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI) 11B trials support the use of LMWH over unfractionated heparin (UFH) in acute coronary syndromes (ACS) managed with a predominantly medical approach as opposed to an invasive initial strategy.[1,2]

Since the publication of the ESSENCE and TIMI 11B trial results, the management of ACS has evolved to favor an early invasive strategy. This evolution is supported by a number of studies, including the Fragmin and fast Revascularisation during InStability in Coronary artery disease (FRISC)-II and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy Thrombolysis in Myocardial Infarction (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 UFH in the invasive management of ACS patients and demonstrated similar rates of success post-percutaneous coronary intervention (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, 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 the notion that LMWH cannot be monitored.

The perception that LMWH is not amenable to monitoring was derived from studies using a subcutaneous route of administration following which relatively low plasma levels were achieved. However, in contrast to the noninvasive setting, LMWH is generally administered as an intravenous 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 activated clotting time test.[6] More recent data suggest that the same is true of enoxaparin.[7] Monitoring of LMWH

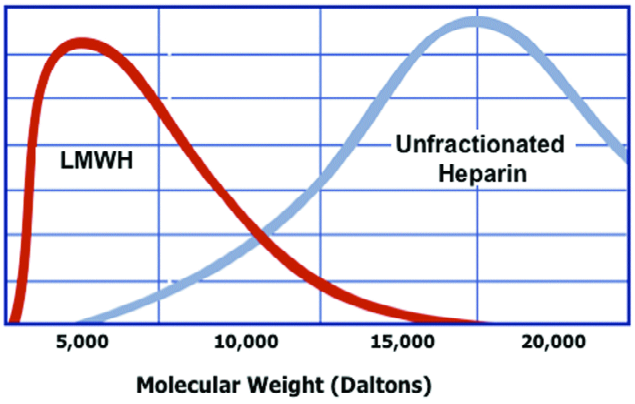

Figure 1. *Size distribution plot for LMWH vs. UFH. Both LMWH and UFH represent heterogeneous populations with molecular weight distribution of 1,000 to 10,000 Daltons and 3,000 to 30,000 Daltons, respectively. Note that LMWH is smaller in molecular size and has a lesser degree of heterogeneity.*

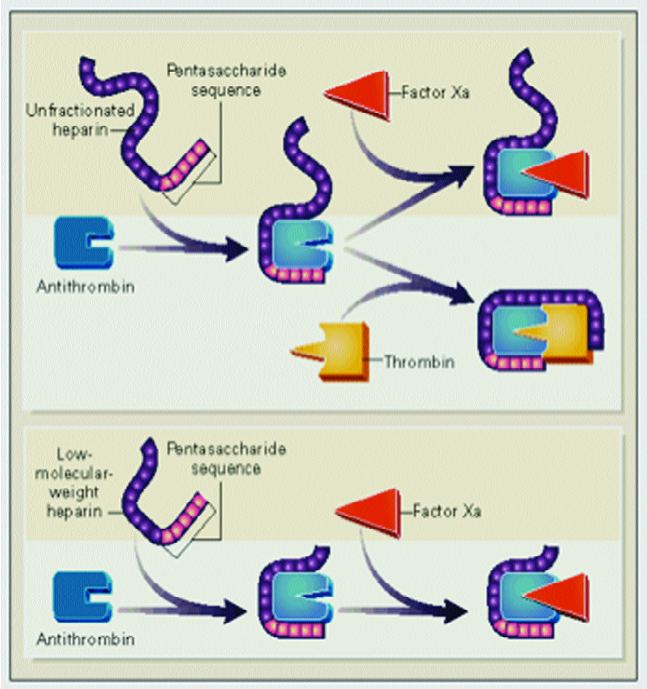

Figure 2. *Catalysis of antithrombin-mediated inactivation of thrombin or factor Xa by UFH or LMWH. The interaction of UFH and LMWH with antithrombin is mediated by the pentasaccharide sequence of the drugs. Binding of either to antithrombin causes a conformational change at its reactive center that accelerates its interaction with factor Xa. Consequently, both UFH and LMWH catalyze the inactivation of factor Xa by antithrombin. In contrast to factor Xa inhibition, catalysis of antithrombin-mediated inactivation of thrombin requires the formation of a ternary heparin–antithrombin–thrombin complex. This complex can be formed only by chains at least 18 saccharide units long. Adapted from* N Engl J Med *1997;337:688–698.*

may be particularly important for those patients undergoing PCI after having already received a dose of subcutaneous LMWH for the initial management of their ACS. The activated clotting time

Table 1. Comparison of LMWH preparations

LMWH Preparation	Mean Molecular Weight (Daltons)	Anti-Xa: Anti-IIa
Ardeparin (Normiflo)	6,000	1.9
Dalteparin (Fragmin)	6,000	2.7
Enoxaparin (Lovenox)	4,200	3.8
Nadroparin (Fraxiparine)	4,500	3.6
Reviparin (Clivarine)	4,000	3.5
Tinzaparin (Innohep)	4,500	1.9

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 LMWH

LMWH is an indirect thrombin inhibitor formed by depolymerization of heparin using chemical or enzymatic methods.[8] LMWH preparations have a mean molecular weight of 4,500–5,000 Daltons with a distribution of 1,000 to 10,000 Daltons.[8] UFH is a more heterogeneous mixture of polysaccharide chains ranging in molecular weight from 3,000 to 30,000 Daltons with an average molecular weight of 15,000 Daltons.[9] 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.[9–11] Antithrombin has 2 active functional sites: the reactive center, Arg 393-Ser 394, and the LMWH binding site located at the amino terminus of the molecule.[12] The binding of LMWH to antithrombin is mediated by a unique pentasaccharide sequence randomly distributed along the LMWH chain.[11,13] Approximately one-third of the chains of UFH, but only 15% to 25% of the chains of LMWHs, contain the pentasaccharide sequence.[9] 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.[14,15]

The binding of LMWH to antithrombin causes less inactivation of coagulation factor IIa (thrombin) when compared with that of UFH.[8] This is because inactivation of factor IIa requires the formation of a ternary complex in which heparin binds to antithrombin and to a binding site on factor IIa (Figure 2).[16] This ternary complex is formed on pentasaccharide containing chains of at least 18 saccharide units. However, unlike UFH, many of the LMWHs do not contain sufficient saccharide units to form the ternary complex.[8] It has been estimated that 25% to 50% of LMWH chains are sufficiently long to bridge

antithrombin to factor IIa.[9,16–19]

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.[9] 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.[9]

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.[20] Platelet factor 4 (PF4) recently was found to induce natural killer (NK) cells' production of inflammatory cytokine IL-8, which may exert a prothrombotic effect in ACS.[20] LMWH is less likely to be bound to PF4 than UFH and thus exerts a less prothrombotic and potentially a less pro-inflammatory effect than UFH.[20]

Pharmacokinetics of LMWH

LMWH exhibits less non-specific binding to plasma proteins, endothelial cells and macrophages and, therefore, has greater bioavailability than UFH.[9] 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.[9]

The pharmacokinetics of LMWH are different from those of UFH after both intravenous and subcutaneous administration. The plasma anti-factor Xa activity is approximately 2 to 4 times longer than that of UFH regardless of the injected dose of the different forms of LMWH.[9] This generally ranges from 2 to 4 hours after intravenous injection and from 4 to 6 hours after subcutaneous injection.[9] 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.[9] The duration of anti-factor IIa activity of LMWH is only slightly longer than that of UFH.[21]

Because its route of elimination is via the renal system, the half-life of LMWH increases in patients with renal failure.[8] LMWH dosing should, therefore, be reduced by 50% in patients with creatinine clearance < 30 mL/min.[22–24]

The pharmacokinetics of LMWH differ substantially from 2 of the newer anticoagulants, bivalirudin and pentasaccharide. 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.[25] Several trials (*i.e.*, the Bivalirudin Angioplasty Trial [BAT], the Randomized Evaluation of Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial, the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial [CACHET] and REPLACE-2) have

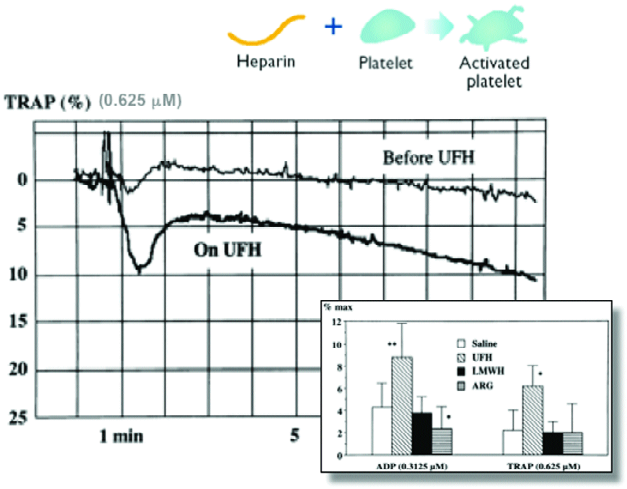

Figure 3. *Enhanced platelet activation on UFH — an example of platelet aggregation to low concentrations of TRAP before and during an infusion of UFH in a patient with unstable angina. Inset shows the results of light transmission aggregometry in platelet-rich plasma from volunteers after adding saline, UFH, enoxaparin or argatroban. Platelet aggregation to low concentrations of ADP and TRAP is signif - icantly increased in the presence of UFH (*p < 0.05, **p < 0.01 vs control). Note the absence of platelet activation in the presence of LMWH or the direct thrombin inhibitor argatroban. Adapted from* Circulation *1998;97:251–256.*

suggested the superiority of bivalirudin over UFH during PCI.[26–29] It has been recently approved by the US Food and Drug Administration (FDA) for use during PCI.[30] Bivalirudin's recommended route of administration is intravenous. Its onset of action is immediate and duration of action is approximately 1 hour.[31] 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 minutes) or severe (57 minutes) renal impairment with creatinine clearance of 30–59 mL/min and < 30 mL/min, respectively.[32] Bivalirudin is eliminated via the renal system and also via proteolytic cleavage.[33]

Fondaparinux, a pentasaccharide derived from the heparin molecule, is an indirect, high-affinity factor Xa reversible inhibitor. By virtue of its short chain length, it does not bind non-specifically to plasma proteins. It also has 100% bioavailability after subcutaneous 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 to 17 hours. The FDA has not approved it for use during PCI.[34] Fondaparinux was recently studied in PCI and showed comparable safety and efficacy outcomes as UFH in the Arixtra Study in Percutaneous Coronary Intervention: A Randomized Evaluation (ASPIRE) Pilot Trial. This data supports the need to further evaluate its use in coronary arterial thrombosis.

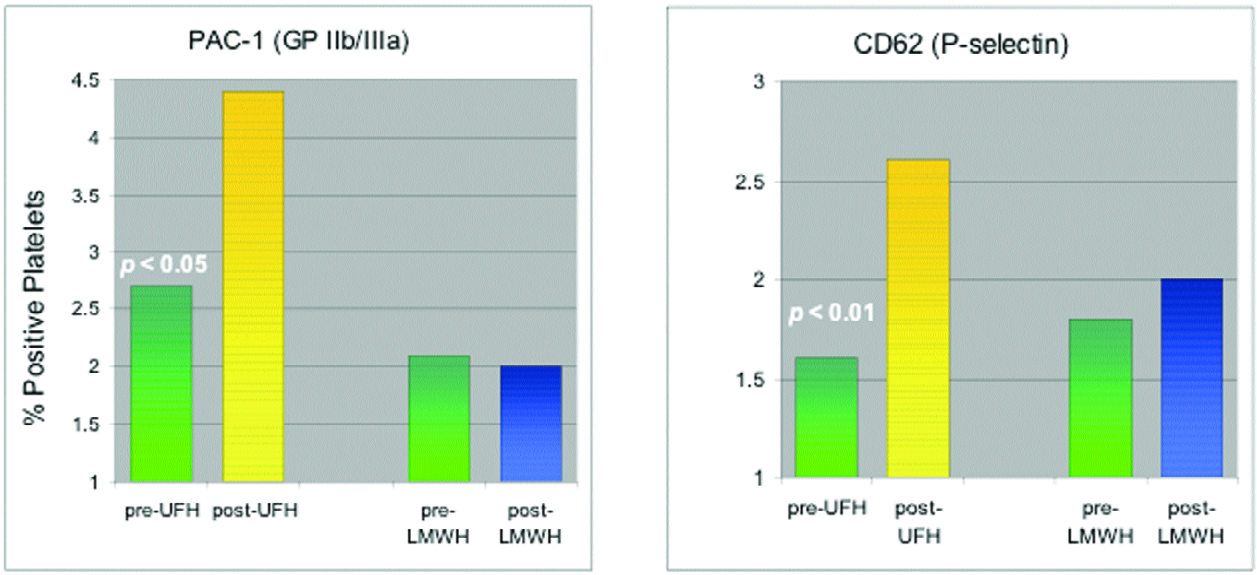

Figure 4. *Flow cytometry and platelet activation by UFH but not by LMWH. PAC-1 is an IgM polyclonal antibody that binds specifically to activated GP IIb/IIIa. Anti-CD62 is a murine monoclonal antibody directed against P-selectin expressed on the platelet surface, an indicator of platelet activation.*

LMWH Versus UFH

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).[35,36] Platelet aggregation requires activation of glycoprotein (GP) IIb/IIIa 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 IIb/IIIa receptors thereby potentiating platelet aggregation (Figure 5).[37–43] The lower pro-aggregatory actions of LMWH have been detected *in vitro* and *in vivo*[40,43–51] and appear to decrease with decreasing molecular weight.[48] In fact, LMWHs with a molecular weight of less than 3,000 Daltons did not result in binding of fibrinogen to the platelet surface.[43] This is of particular relevance to PCI where increased platelet aggregation may contribute to complications.[20]

LMWH is associated with less tissue factor (TF) pathway inhibitor depletion and actually promotes release of TF pathway inhibitor, thereby enhancing LMWH's anti-factor Xa activity.[20,52–54] In contrast, UFH increases the depletion of TF pathway inhibitor.[52–55] As a result, less rebound hypercoagulability may be seen with LMWH compared to UFH.[56]

Increased circulating levels of vWf in patients with ACS post PCI have been implicated as a factor contributing to adverse outcomes.[20] Whereas UFH does not blunt the increased vWf levels seen in patients with ACS, LMWH appears to attenuate this increase.[57]

LMWH is associated with a lower incidence of heparin-induced thrombocytopenia (HIT) when compared to UFH.[8] 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 greater than 50% decrease in platelet count or skin lesions at injection sites.[8] HIT is mediated by the HIT antibody recognizing the epitope on the PF4-heparin complex as an antigen.[58] The HIT antibody binds to one or more PF4 regions conformationally modified by the interaction with heparin.[8] At least 12–14 saccharide units within the heparin molecule are required to form the antigenic complex with PF4.[8] Therefore, the risk of HIT antibody formation is lower during treatment with LMWH than with UFH.[8]

The better bioavailability, dose-independent clearance and decreased affinity for heparin binding proteins make the anticoagulant response to LMWH more predictable than that to UFH.[9]

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

The activated clotting time (ACT). The ACT is a measure of the overall tendency of the blood to thrombose. It was first described by Hattersley in 1966 and came into clinical use in the mid 1970s to guide the administration and reversal of UFH during cardiopulmonary bypass.[59] It is also used in the 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.[60] This activator stimulates clot formation upon contact with whole blood via the intrinsic pathway.[61]

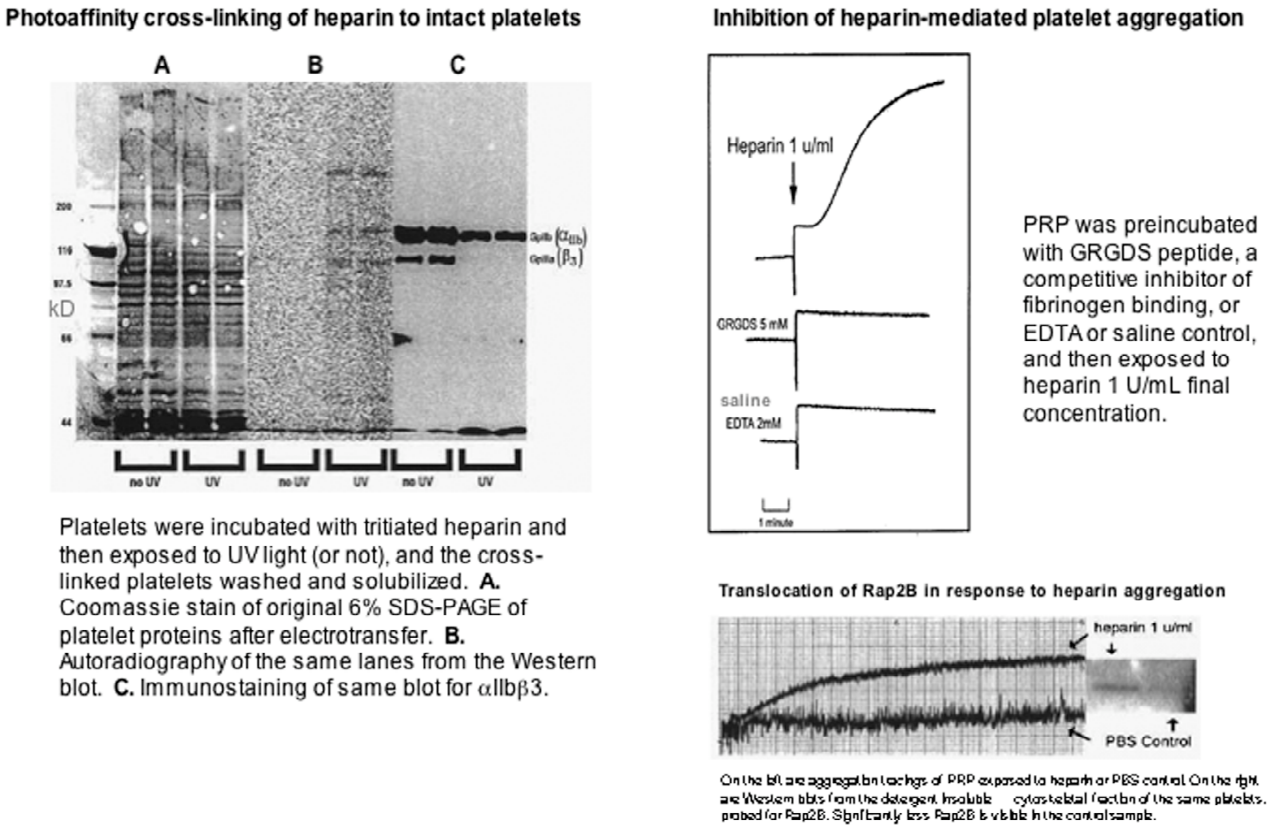

Figure 5. *Heparin binds and activates platelet GP IIb/IIIa. Left panel: Photoaffinity cross-linking of heparin to intact platelets. Platelets were incubated with tritiated heparin and then exposed to UV light (or not), and the cross-linked platelets were washed and solubilized. A, Coomassie stain of 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. Right upper panel: Inhibition of heparin-mediated platelet aggregation. PRP was preincubated with GRGDS peptide, a competitive inhibitor of fibrinogen binding, or EDTA or saline control, and then exposed to heparin 1 U/mL final concentration. Right lower panel: Translocation of Rap2B in response to heparin aggregation. 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, a marker for the early signaling events mediated by the integrin αIIbβ3, is visible in the control sample. Adapted from* J Vasc Surg *2001;33:587–594.*

The tube is placed in a coagulation analyzer (*e.g.*, Hemochron®, International Technidyne Corporation, Edison, NJ).[61] The magnet at the bottom of the tube is displaced once a clot is formed, resulting in the activation of the alarm on the analyzer (Figure 6).[60] An advantage of the ACT in comparison to the activated partial thromboplastin time (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 greater than 1 U/mL. This makes the aPTT unsuitable for monitoring heparin dosage during angioplasty and bypass surgery, as patients may require heparin levels greater than 1 U/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.[62]

Although it is used to monitor agents that possess both anti-IIa and anti-Xa activities, the ACT (and the aPTT) is 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 seconds to a post-bivalirudin bolus of 300–400 seconds. 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 aPTT. The 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.[61] The aPTT is usually used to monitor therapeutic heparin, hirudin and argatroban anticoagulation. However, as previously noted, at high doses of heparin, use of the 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;[61] this is in contrast to the ACT assay in which the platelets provide phospholipid. The measurement of the aPTT is generally performed in a hospital's core laboratory facility; results are obtained within 30–60 minutes. This delay is an additional reason for which the ACT has been traditionally used in the cardiac catheterization laboratory

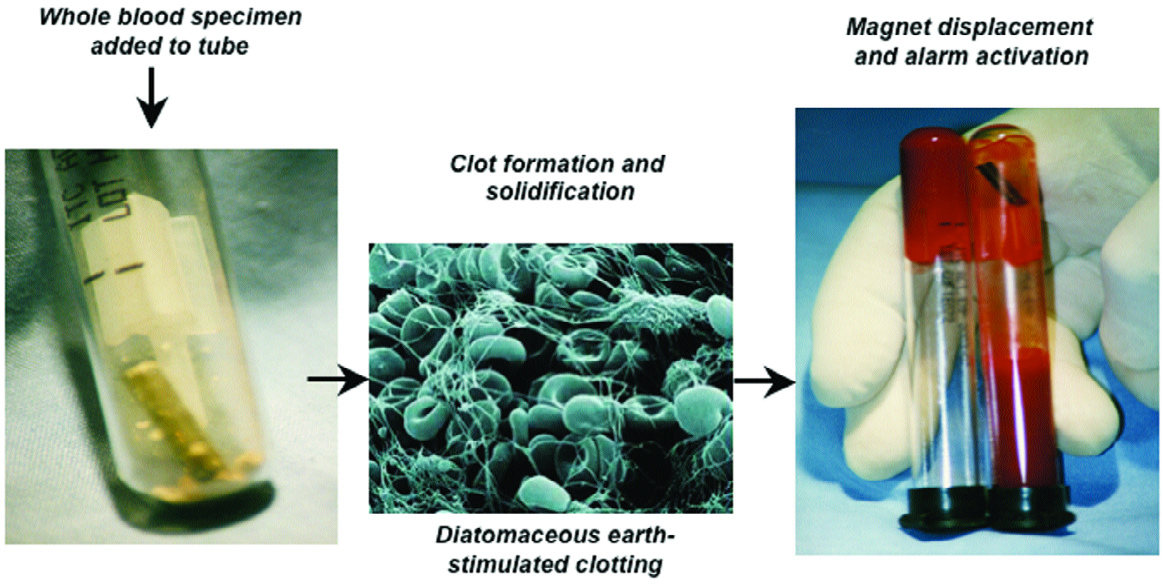

Figure 6. *The ACT methodology: Blood is collected into a tube containing a magnet and diatomaceous earth, which activates clot formation via the intrinsic pathway. This results in displacement of the magnet followed by alarm activation. Results are read in seconds. Clotted blood, in contrast to unclotted blood, remains in the well of the tube after inversion (right panel).*

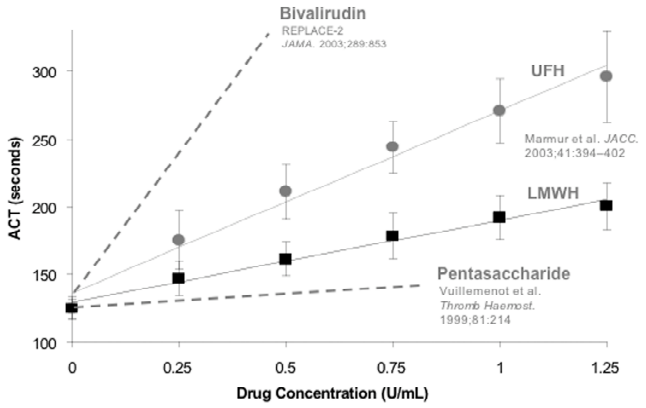

Figure 7. *Composite figure of dose-response of the ACT as a function of increasing concentrations of anticoagulant in whole blood. Solid lines derived from healthy volunteer blood samples spiked with increasing doses of either UFH (circle) or dalteparin (square). Stippled lines represent theoretic correlations derived from the referenced studies. Because the ACT is most sensitive to thrombin inhibition, the slope of the line increases for drugs with greater anti-IIa properties.*

and cardiovascular operating room settings where immediate results are often needed.

Point-of-care monitoring devices. Point-of-care devices have been developed to monitor both the ACT and the aPTT. These include the Hemochron® system from ITC (Edison, New Jersey), which includes the Hemochron Jr., Hemochron 801 and Hemochron 400, and Hemochron Jr. LR.[63–67] Medtronic (Minneapolis, Minnesota) has also developed point-of-care monitoring devices that include the HemoTec and the Medtronic ACT II devices.[68–70] There are other similar devices available, such as Celite i-STAT ACT (Abbott Point-of-Care, East Windsor, New Jersey) and the Hepcon® HMS devices (Medtronic).[71–74]

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 LMWH During PCI

Anticoagulation during percutaneous intervention 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. With the increased use of LMWH in the medical treatment of ACS, particularly in UA and NSTEMI, and with possible future use in STEMI, a significant number of patients who currently present to the cardiac catheterization lab for PCI already have received at least one dose, and occasionally several doses, of LMWH. Such patients pose several challenges and questions to the interventionalist, including the following:

- Is there any value in using LMWH, as opposed to UFH, in PCI?
- Can the LMWH that was administered prior to the patient's arrival to the lab, or any additionally administered LMWH given in the lab, be monitored using a bedside assay?
- 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).[35,36] 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 myocardial infarction patients were randomized to 1 of 3 arms: 1) full-dose fibrinolysis with UFH; 2) half-dose fibrinolysis with UFH plus GP IIb/IIIa inhibition (abciximab); or 3) full-dose fibrinolysis with LMWH (but no abciximab). The composite endpoint to 30 days of death, reinfarction and refractory ischemia was examined. The worst outcome was seen in the group of patients treated with full-dose tenecteplase (TNK) administered with UFH. Combination therapy of half-dose TNK and abciximab, as well as the regimen of TNK with enoxaparin, showed significant reduction in event rates (Figure 8).[75] 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 co-administration 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.[29]

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 2 separate studies, NICE 1 and NICE 4. Patients in NICE 1 were administered intravenous enoxaparin alone at a dose of 1 mg/kg during PCI, while the patients in NICE 4 were administered a reduced dose of 0.75 mg/kg intravenous 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 when administered alone and in combination with abciximab.[75]

Bhatt et al[76] 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 revascularization at 48 hours or 30 days.

Another study by Kereiakes et al[77] was done to assess the anticoagulant effect and clinical safety of dalteparin administered in combination with abciximab during PCI. This study concluded that dalteparin 60 IU/kg intravenously 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.[5] 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 MI at 30 days, and the rate of successful PCI was similar between the 2 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 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 the idea that LMWH cannot be monitored. However, 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 (Figure 9).[6,7]

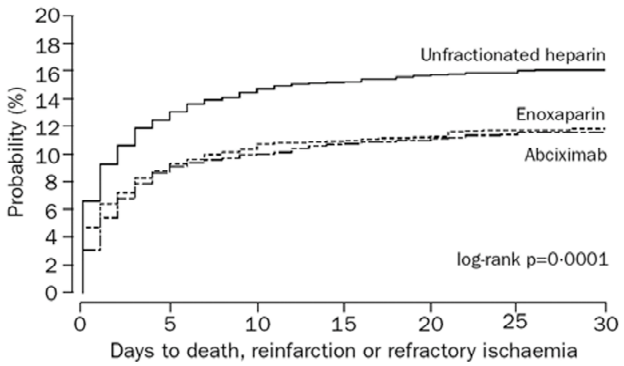

Figure 8. *Results of the ASSENT III trial showing greater probability of death, reinfarction or refractory ischemia in the UFH group. Adapted from* Lancet *2001;358:605–613.*

Table 2. Bleeding rates in the SYNERGY trial

Bleeding definition	Enoxaparin (%)	Unfractionated heparin (%)	*p* value
GUSTO severe bleeding	2.7	2.2	0.08
Decrease in hemoglobin and hematocrit*	15.2	12.5	< 0.001
TIMI major† bleeding (all)	9.1	7.6	0.008
TIMI major† bleeding (CABG-related)	6.8	5.9	0.08
TIMI major† bleeding (not CABG-related)	2.4	1.8	0.03
Any transfusions	17.0	16.0	0.16

CABG = coronary artery bypass grafting; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Arteries; TIMI = Thrombolysis in Myocardial Infarction
* At least a 5 g/dL decrease in hemoglobin or at least a 15% decrease in hematocrit not associated with an overt bleeding event
† Associated with clinical bleed

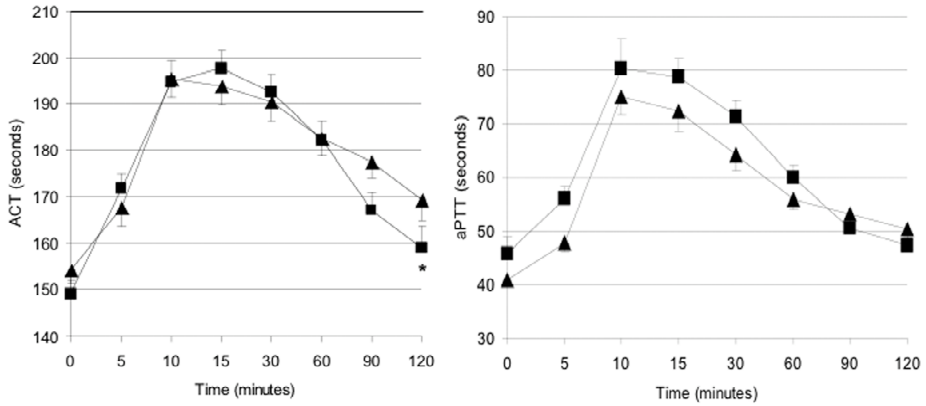

Figure 9. *Time course of the ACT and the aPTT. After obtaining baseline blood samples, enoxaparin (triangle) and dalteparin (square) were administered intravenously as 2 boluses 5 minutes apart to a total dose of 0.5 mg/kg and 50 IU/kg, respectively. The ACT and the aPTT responded similarly to the 2 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. Adapted from* J Invasive Cardiol *2005;17:416–421.*

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

Procedure	Enoxaparin		Unfractionated heparin
Catheterization	Perform catheterization any time after last dose		Continue UFH and perform catheterization
PCI	< 8 hrs from last subcutaneous dose	No additional LMWH	Stop UFH infusion and use IV boluses to achieve an ACT of 250 sec
	> 8 hrs from last dose	0.3 mg/kg IV bolus	
CABG	Elective	Stop > 8 hrs	Stop > 6 hrs
	Urgent	Stop	Stop

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

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. The STEEPLE trial randomized patients to 1 of 2 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 grafting (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 major finding of the study was that the primary endpoint 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 provided 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 the level of anticoagulation during PCI to any measurable degree. 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 subcutaneous enoxaparin and thrombolytic therapy and now arrives at the 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 catheterization laboratories where enoxaparin or dalteparin are administered from small preloaded syringes designed for subcutaneous administration.

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 subcutaneous route of administration following which relatively low plasma levels were achieved. Furthermore, these studies were conducted in an era during which the default management strategy for ACS was non-invasive, 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 subcutaneous dose, such as those used in the SYNERGY trial, are inadequate.[78] First, it is not always possible to determine the timing of the last dose of LMWH; frequently, there is inadequate documentation in the chart, particularly in the case of patients who may have had therapies initiated in one institution and then are transferred to a tertiary care center for interventional services.

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 patient with diabetes with acute MI and hemodynamic compromise may have altered absorption from a subcutaneous 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.

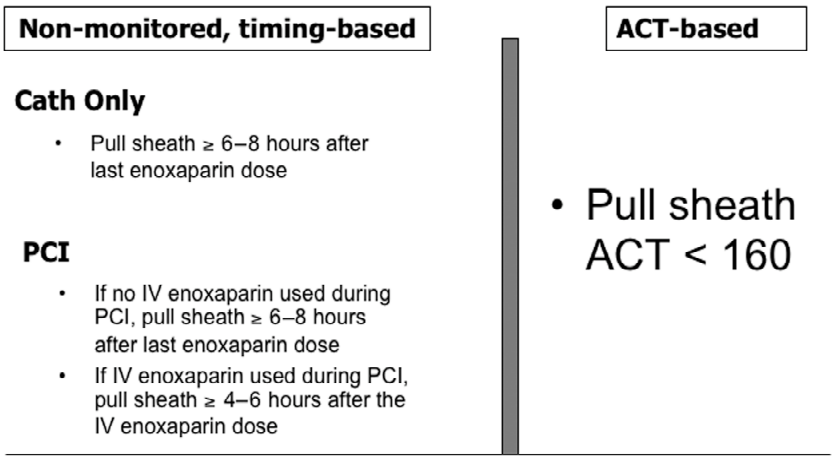

Figure 10. *Strategies for sheath management in LMWH-treated patients. An ACT-based approach eliminates some of the complexities associated with the non-monitored, timing-based sheath management strategy used in the SYNERGY trial.*

The ability to monitor UFH with the ACT or the 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 the ACT (*i.e.*, 300–400 seconds range).[28] In contrast, pentasaccharide, which is almost exclusively anti-Xa, has very little influence on the ACT or the aPTT.[79] UFH, like LMWH, lies somewhere between these extremes, possessing both anti-IIa and anti-Xa activities (Figure 7).

The anti-IIa activity of UFH is determined by the formation of a ternary complex, which requires at least 18 saccharide units.[8] Because most UFH molecules contain at least 18 saccharide units, UFH has an anti-Xa to anti-IIa ratio that approximates unity.[8] 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 ranges between 2 and 4 depending on the molecular weight distribution (Table 1).[8]

We have previously reported that the ACT can be used to monitor dalteparin administered intravenously at the time of PCI.[6] Five minutes after 60 IU/kg of intravenous dalteparin, the ACT increased from levels of 120–130 seconds to levels of 170–180 seconds (and the aPTT increased from 25–30 seconds to 55–70 seconds). 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 10). 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.[29]

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.[4] The tighter distribution of dalteparin-induced (in comparison to UFH-induced) peak ACT values has been confirmed in a recent randomized trial of PCI (Figure 11).[80] These observations suggest that once a target ACT is reached using LMWH, 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 STEEPLE 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 the ACT, the aPTT and anti-Xa levels.[7] Both enoxaparin and dalteparin induced a significant rise in the ACT and the aPTT (Figure 9), with an ACT dose-response approximately one-half the magnitude of that obtained using UFH. The elevation in the ACT was 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 the 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[81] 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 subcutaneous or intravenous enoxaparin. The rate of ischemic events was lowest in the mid-range of ENOX times, and bleeding events increased with increasing ENOX times.

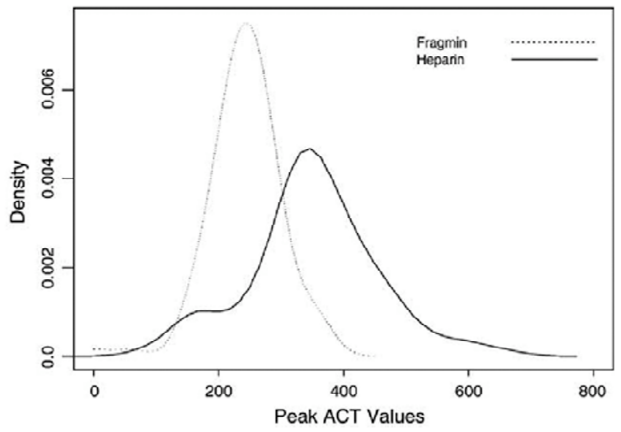

Figure 11. *Distribution of ACT levels during PCI. The distribution of peak ACT levels measured at 30 minutes after a randomized bolus administration of either UFH or dalteparin. Adapted from* Am Heart J *2006;151:175.*

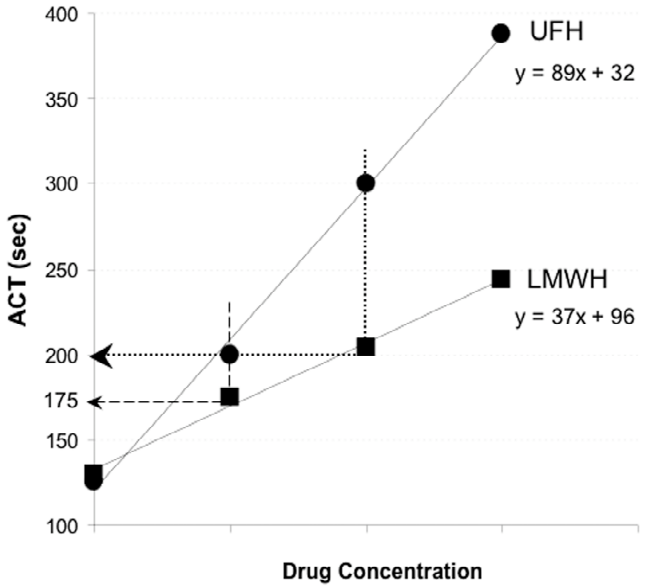

Figure 12. *A composite of the dose-response of the ACT following intravenous administration of LMWH, characterized by a slope that is approximately one-half the magnitude of UFH. Using the UFH ACT targets of 200 and 300 seconds (for patients with and without adjunctive GP IIb/IIIa inhibition, respectively), 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 175 seconds for patients receiving LMWH with GP IIb/IIIa inhibition and a minimum of 200 seconds for patients receiving LMWH alone (without GP IIb/IIIa inhibition) during PCI.*

Lawrence et al[82] studied the effect of intravenous 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 intravenous enoxaparin alone or 0.75 mg/kg of intravenous 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 seconds 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 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. 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 intravenous 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, there is an apparent consensus in current interventional practice that operators should achieve a minimal value of 200 seconds in the presence of adjunctive GP IIb/IIIa inhibition and 300 seconds in its absence.[83–85] In order to convert these UFH targets of 200 and 300 seconds to theoretic values appropriate for enoxaparin or dalteparin, one must take into account the more blunted dose-response of the ACT following LMWH administration. A vertical line perpendicular to the x-axis (drug concentration) is drawn from the 300 (or 200) second intercept for UFH. Assuming similar levels of drug concentration (dalteparin 40 U/kg yields similar anti-IIa levels to that achieved with 40 U/kg of UFH), the intersection of this line with the LMWH dose-response curve will yield a corresponding target ACT on the y-axis (Figure 12).[6] Based on these observations, we propose a minimum target ACT of 175 seconds for patients receiving LMWH with GP IIb/IIIa inhibition and a minimum of 200 seconds for patients receiving LMWH alone (*i.e.*, no adjunctive GP IIb/IIIa inhibition) during PCI (Figure 12). These targets are supported by our unpublished observations that very low doses of LMWH yielding ACT values below 170 seconds were associated with thrombotic complications and those of Kereiakes et al[77] where patients treated with dalteparin 40 IU/kg achieved a maximum mean ACT of less than 175 seconds and experienced a higher rate of thrombotic complications compared with patients treated with 60 IU/kg who had achieved levels of the ACT above 175 seconds. 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 seconds. Using doses from the STEEPLE trial and other published reports,[75] 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 seconds.

Finally, our earlier study with dalteparin demonstrated that

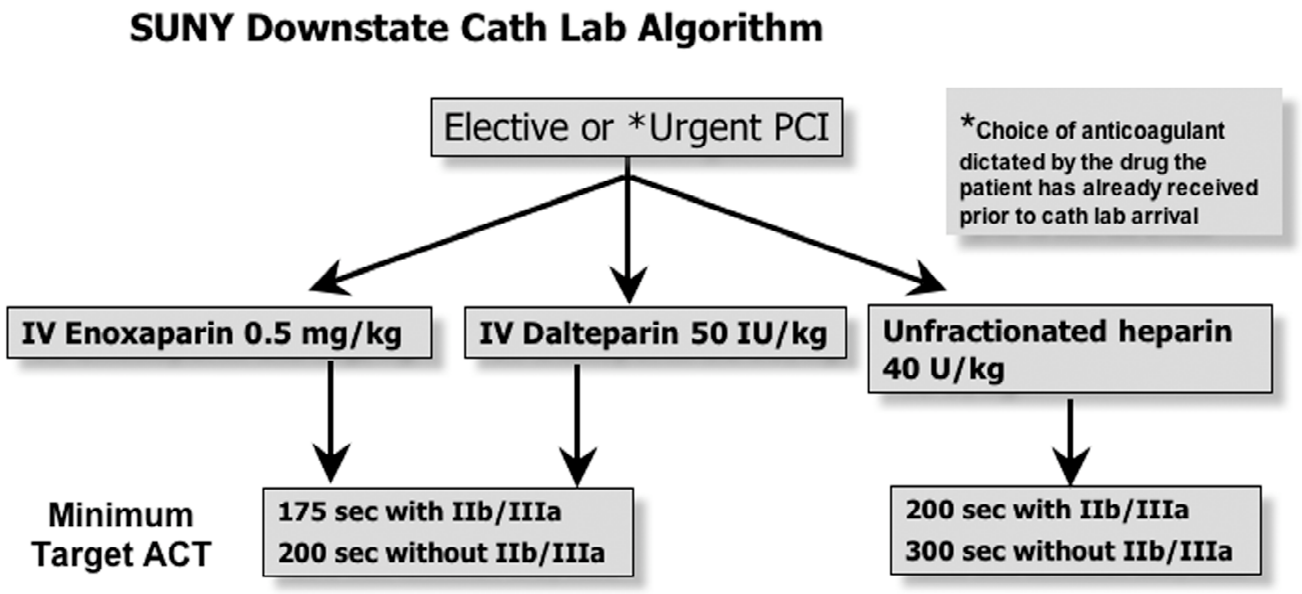

Figure 13. *Algorithm for the use of LMWH during PCI in use at SUNY Downstate Medical Center, Brooklyn, New York.*

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 minutes with a decline in values at approximately 90 minutes.[6] This raises the possibility that a decline in the ACT to a target level (*e.g.*, < 160 seconds) could be used to determine the timing of sheath removal, a potentially simpler approach compared to one based on calculating the time from the last dose administered (Figure 10).

Conclusion

LMWH has been in use for over a decade and appears to be superior to UFH in the noninvasive treatment of patients with ACS. The SYNERGY trial was designed to extend the indication of LMWH to include ACS patients managed with an early invasive approach and, when appropriate, 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 2 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 study 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 seconds for LMWH in PCI performed with GP IIb/IIIa inhibition and a minimum target ACT of 200 seconds for LMWH in PCI without GP IIb/IIIa inhibition (Figure 13). We have also a proposed a target ACT value of < 160 seconds for sheath removal.

References

1. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447–452.
2. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593–1601.
3. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999;354:708–715.
4. Cannon CP, Weintraub WS, Demopoulos LA, et al for the TACTICS—Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–1887.
5. Ferguson JJ, Califf RM, Antman EM, et al for the SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45–54.
6. Marmur JD, Anand SX, Bagga RS, et al. The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration. *J Am Coll Cardiol* 2003;41:394–402.

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.
8. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001;119:64S–94S.
9. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688–698.
10. Hirsh J, Anand SS, Halperin JL, Fuster V; American Heart Association. Guide to anticoagulant therapy: Heparin: A statement for healthcare professionals from the American Heart Association. *Circulation* 2001;103:2994–3018.
11. Hirsh J, Warkentin TE, Raschke E, et al. Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1998;114:489S–510S.
12. Perry DJ. Antithrombin and its inherited deficiencies. *Blood Rev* 1994;8:37–55.
13. Choay J, Petitou M, Lormeau JC, et al. Structure-activity relationship in heparin: A synthetic pentasaccharide with high affinity for antithrombin III and eliciting high anti-factor Xa activity. *Biochem Biophys Res Commun* 1983;116:492–499.
14. Marcum JA, McKenney JB, Rosenberg RD. Acceleration of thrombin-antithrombin complex formation in rat hindquarters via heparinlike molecules bound to the endothelium. *J Clin Invest* 1984;74:341–350.
15. Klein B, Faridi A, von Tempelhoff GF, et al. A whole blood flow cytometric determination of platelet activation by unfractionated and low molecular weight heparin *in vitro*. *Thromb Res* 2002;108:291–296.
16. Danielsson A, Raub E, Lindahl U, Bjork I. Role of ternary complexes, in which heparin binds both antithrombin and proteinase, in the acceleration of the reactions between antithrombin and thrombin or factor Xa. *J Biol Chem* 1986;261:15467–15473.
17. Anderson W, Harthill JE. Molecular weight dependence of heparin anti-factor Xa activity: Influence of method. *Thromb Res* 1981;21:557–564.
18. Rosenberg RD, Jordan RE, Favreau LV, Lam LH. Highly active heparin species with multiple binding sites for antithrombin. *Biochem Biophys Res Commun* 1979;86:1319–1324.
19. Jordan RE, Favreau LV, Braswell EH, Rosenberg RD. Heparin with two binding sites for antithrombin or platelet factor 4. *J Biol Chem* 1982;257:400–406.
20. Selwyn AP. Prothrombotic and antithrombotic pathways in acute coronary syndromes. *Am J Cardiol* 2003;91:3H–11H.
21. Bara L, Samama M. Pharmacokinetics of low molecular weight heparins. *Acta Chir Scand Suppl* 1990;556:57–61.
22. Caranobe C, Barret A, Gabaig AM, et al. Disappearance of circulating anti-Xa activity after intravenous injection of standard heparin and of a low molecular weight heparin (CY 216) in normal and nephrectomized rabbits. *Thromb Res* 1985;40:129–133.
23. Palm M, Mattsson C. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. *Thromb Haemost* 1987;58:932–935.
24. Collet JP, Montalescot G, Choussat R, et al. Enoxaparin in unstable angina patients with renal failure. *Int J Cardiol* 2001;80:81–82.
25. Maraganore JM, Bourdon P, Jablonski J, et al. Design and characterization of hirulogs: A novel class of bivalent peptide inhibitors of thrombin. *Biochemistry* 1990;29:7095–7101.
26. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001;142:952–959.
27. Lincoff AM, Bittl JA, Kleiman NS. The REPLACE 1 trial: A pilot study of bivalirudin versus heparin during percutaneous coronary intervention with stenting and GP IIb/IIIa blockade. *J Am Coll Cardiol* 2002;39:16A–17A.
28. Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: Results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am Heart J* 2002;143:847–853.
29. Lincoff AM, Bittl JA, Harrington RA, et al for the REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853–863.
30. Leung LL. New anticoagulants. Available at: http://www.utdol.com/utd/content/topic.do?topicKey=coagulat/8976&type=A&selectedTitle=5~199. Accessed June 29, 2006.
31. Lexi-Comp, Inc. Bivalirudin: drug information. Available at: http://www.utdol.com/utd/content/topic.do?topicKey=drug_a_k/18639&type=A&selectedTitle=2~10. Accessed June 29, 2006.
32. Maraganore JM, Adelman BA. Hirulog: A direct thrombin inhibitor for management of acute coronary syndromes. *Coron Artery Dis* 1996;7:438–448.
33. Robson R, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: Effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002;71:433–439.
34. Bauer KA. Clinical use of fondaparinux. Available at: http://www.utdol.com/utd/content/topic.do?topicKey=coagulat/14857&type=A&selectedTitle=1~13. Accessed June 29, 2006.
35. Cella G, Girolami A, Sasahara AA. Platelet activation with unfractionated heparin at therapeutic concentrations and comparison with low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1999;99:3323.
36. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1998;97:251–256.
37. Sobel M, Fish WR, Toma N, et al. Heparin modulates integrin function in human platelets. *J Vasc Surg* 2001;33:587–594.
38. Komarnicki M, Kazmierczak M, Haertle D. Standard heparin and low molecular weight heparin effect on spontaneous platelet aggregation measured in whole blood and in platelet-rich plasma. *Acta Haematol Pol* 1993;24:263–265.
39. Eika C. Platelet refractory state induced by heparin. *Scand J Haematol* 1972;9:665–672.
40. Salzman EW, Rosenberg RD, Smith MH, et al. Effect of heparin and heparin fractions on platelet aggregation. *J Clin Invest* 1980;65:64–73.
41. Chong BH, Ismail F. The mechanism of heparin-induced platelet aggregation. *Eur J Haematol* 1989;43:245–251.
42. Chen JH, Karlberg KE, Sylven C. Heparin and low molecular weight heparin but not hirudin stimulate platelet aggregation in whole blood from acetylsalicylic acid treated healthy volunteers. *Thromb Res* 1991;63:319–329.
43. Heinrich D, Gorg T, Schulz M. Effects of unfractionated and fractionated heparin on platelet function. *Haemostasis* 1988;18 Suppl 3:48–54.
44. Dunn FW, Soria C, Thomaidis A, et al. Interactions of platelets with standard heparin and low molecular weight fractions. *Nouv Rev Fr Hematol* 1984;26:249–253.
45. Mikhailidis DP, Barradas MA, Mikhailidis AM, et al. Comparison of the effect of a conventional heparin and a low molecular weight heparinoid on platelet function. *Br J Clin Pharmacol* 1984;17:43–48.
46. Kawano K, Ikeda Y, Handa M, et al. Enhancing effect by heparin on shear-induced platelet aggregation. *Semin Thromb Hemost* 1990;16 Suppl:60–65.
47. Mastacchi R, Stanzani L, Barbanti M, et al. Interaction of heparin and heparin fractions with human platelets. *Thromb Res* 1982;28:275–280.
48. Brace LD, Fareed J. Heparin-induced platelet aggregation: Dose/response relationships for a low molecular weight heparin derivative (PK 10169) and its subfractions. *Thromb Res* 1986;42:769–782.
49. Westwick J, Scully MF, Poll C, Kakkar VV. Comparison of the effects of low molecu-

lar weight heparin and unfractionated heparin on activation of human platelets *in vitro*. *Thromb Res* 1986;42:435–447.

50. Mastacchi R, Barbanti M, Bianchini P, Osima B. Interaction of a new low molecular weight heparin (OP/LMWH) with human platelets. *Agents Actions* 1986;17:512–514.
51. Cella G, Scattolo N, Luzzatto G, Girolami A. Effects of low-molecular-weight heparin on platelets as compared with commercial heparin. *Res Exp Med (Berl)* 1984;184:227–229.
52. Hansen JB, Sandset PM. Differential effects of low molecular weight heparin and unfractionated heparin on circulating levels of antithrombin and tissue factor pathway inhibitor (TFPI): A possible mechanism for difference in therapeutic efficacy. *Thromb Res* 1998;91:177–181.
53. Hansen JB, Sandset PM, Huseby KR, et al. Differential effect of unfractionated heparin and low molecular weight heparin on intravascular tissue factor pathway inhibitor: Evidence for a difference in antithrombotic action. *Br J Haematol* 1998;101:638–646.
54. Hansen JB, Naalsund T, Sandset PM, Svensson B. Rebound activation of coagulation after treatment with unfractionated heparin and not with low molecular weight heparin is associated with partial depletion of tissue factor pathway inhibitor and antithrombin. *Thromb Res* 2000;100:413–417.
55. Sandset PM, Bendz B, Hansen JB. Physiological function of tissue factor pathway inhibitor and interaction with heparins. *Haemostasis* 2000;30 Suppl 2:48–56.
56. Wong GC, Giugliano RP, Antman EM. Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention. *JAMA* 2003;289:331–342.
57. Montalescot G, Philippe E, Ankri A, et al. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: Beneficial effects of enoxaparin. French Investigators of the ESSENCE Trial. *Circulation* 1998;98:294–299.
58. Chong BH. Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003;1:1471–1478.
59. Bowers J, Ferguson JJ. Use of the activated clotting time in anticoagulation monitoring of intravascular procedures. *Tex Heart Inst J* 1993;20:258–263.
60. Marmur JD. Low Molecular Weight Heparin in the Cardiac Catheterization Laboratory: CD-ROM. 2002.
61. Van Cott EM, Laposta M. Coagulation. In: Jacobs DS, De Mott WR, Oxley DK (eds). *The Laboratory Test Handbook, 5th Edition*. Cleveland, OH: Lexi-Comp, Inc.; 2001:327–358.
62. Hirsh J, Raschke R, Warkentin TE, et al. Heparin: Mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995;108:258S–275S.
63. Fitch JC, Mirto GP, Geary KL, et al. Point-of-care and standard laboratory coagulation testing during cardiovascular surgery: Balancing reliability and timeliness. *J Clin Monit Comput* 1999;15:197–204.
64. Searles B, Nasrallah F, Graham S, Tozer M. Electronic data management for the Hemochron Jr. Signature coagulation analyzer. *J Extra Corpor Technol* 2002;34:182–184.
65. Jaryno S, Bennett K, Loder C, et al. Validation of a new whole blood coagulation monitoring system. *J Extra Corpor Technol* 2002;34:271–275.
66. Uden DL, Seay RE, Kriesmer PJ, et al. The effect of heparin on three whole blood activated clotting tests and thrombin time. *ASAIO Trans* 1991;37:88–91.
67. Colby CE, Sheehan A, Benitz W, et al. Maintaining adequate anticoagulation on extracorporeal membrane oxygenation therapy: Hemochron Junior Low Range versus Hemochron 400. *J Extra Corpor Technol* 2003;35:35–38.
68. Avendano A, Ferguson JJ. Comparison of Hemochron and HemoTec activated coagulation time target values during percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1994;23:907–910.
69. Cohen M. Monitoring anticoagulation during percutaneous coronary interventions. *J Thromb Thrombolysis* 1995;1:285–288.
70. Koster A, Despotis G, Gruendel M, et al. The plasma supplemented modified activated clotting time for monitoring of heparinization during cardiopulmonary bypass: A pilot investigation. *Anesth Analg* 2002;95:26–30.
71. Paniccia R, Fredi S, Carbonetto F, et al. Evaluation of a new point-of-care celite-activated clotting time analyzer in different clinical settings. The i-STAT celite-activated clotting time test. *Anesthesiology* 2003;99:54–59.
72. Raymond PD, Ray MJ, Callen SN, Marsh NA. Heparin monitoring during cardiac surgery. Part 1: Validation of whole-blood heparin concentration and activated clotting time. *Perfusion* 2003;18:269–276.
73. Murray DJ, Brosnahan WJ, Pennell B, et al. Heparin detection by the activated coagulation time: A comparison of the sensitivity of coagulation tests and heparin assays. *J Cardiothorac Vasc Anesth* 1997;11:24–28.
74. Iqbal O, Ahmad S, Lewis BE, et al. Monitoring of argatroban in ARG310 study: Potential recommendations for its use in interventional cardiology. *Clin Appl Thromb Hemost* 2002;8:217–224.
75. Kereiakes DJ, Grines C, Fry E, et al for the NICE 1 and NICE 4 Investigators. National Investigators Collaborating on Enoxaparin. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J Invasive Cardiol* 2001;13:272–278.
76. Bhatt DL, Lee BI, Casterella PJ, et al. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: Results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol* 2003;41:20–25.
77. Kereiakes DJ, Kleiman NS, Fry E, et al. Dalteparin in combination with abciximab during percutaneous coronary intervention. *Am Heart J* 2001;141:348–352.
78. Kereiakes DJ, Montalescot G, Antman EM, et al. Low-molecular-weight heparin therapy for non-ST-elevation acute coronary syndromes and during percutaneous coronary intervention: An expert consensus. *Am Heart J* 2002;144:615–624.
79. Vuillemenot A, Schiele F, Meneveau N, et al. Efficacy of a synthetic pentasaccharide, a pure factor Xa inhibitor, as an antithrombotic agent—a pilot study in the setting of coronary angioplasty. *Thromb Haemost* 1999;81:214–220.
80. Natarajan MK, Velianou JL, Turpie AG, et al. A randomized pilot study of dalteparin versus unfractionated heparin during percutaneous coronary interventions. *Am Heart J* 2006;151:175.
81. Moliterno DJ, Hermiller JB, Kereiakes DJ, et al for the ELECT Investigators. A novel point-of-care enoxaparin monitor for use during percutaneous coronary intervention. Results of the Evaluating Enoxaparin Clotting Times (ELECT) Study. *J Am Coll Cardiol* 2003;42:1132–1139.
82. Lawrence M, Mixon TA, Cross D, et al. Assessment of anticoagulation using activated clotting times in patients receiving intravenous enoxaparin during percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2004;61:52–55.
83. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: Aggregate results from 6 randomized, controlled trials. *Circulation* 2001;103:961–966.
84. Brener SJ, Moliterno DJ, Lincoff AM, et al. Relationship between activated clotting time and ischemic or hemorrhagic complications: Analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 2004;110:994–998.
85. Valgimigli M, Percoco G, Barbieri D, et al. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: The ADVANCE Trial. *J Am Coll Cardiol* 2004;44:14–19.

Lessons Learned from the Use of Low-Molecular-Weight Heparin in the Cardiac Catheterization Laboratory — A Series of Case Reports

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Abstract: The potential value of activated clotting time (ACT) monitoring prior to and during percutaneous coronary intervention (PCI) in patients treated with low-molecular-weight heparin (LMWH) is demonstrated in a series of case reports. In particular, these cases highlight the potential of the ACT to assist operators in 1) avoiding an overdose of LMWH in patients with impaired renal function, 2) determining whether additional LMWH is needed in patients already receiving subcutaneous therapy and 3) guiding the titration of protamine to reverse at least a portion of the anticoagulant effect of LMWH in patients suffering coronary perforation as a complication of PCI. Finally, measurement of the ACT may be helpful in guiding the timing of sheath removal.

Low-molecular-weight heparin (LMWH) has assumed a major role in the management of acute coronary syndromes (ACS), in part because of the results from the Efficacy and Safety Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and the Thrombolysis in Myocardial Infarction (TIMI) 11B studies.[1,2] However, over the past several years, the management of ACS has evolved from a noninvasive, conservative approach to an invasive one. This new era of invasive management has been substantiated by several trials, such as the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI)-18 trial and the Fragmin and fast Revascularisation during InStability in Coronary artery disease (FRISC)-II trial.[3,4] On the basis of this evolution in the management of ACS, the use of LMWH during percutaneous coronary intervention (PCI) has become increasingly relevant. Unfortunately, there has been resistance to the use of LMWH during PCI, in part due to the perceived notion that LMWH cannot be monitored using a bedside assay, such as the activated clotting time (ACT). It has also been suggested that monitoring of LMWH during PCI is not necessary. The idea 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. In contrast to the noninvasive setting, LMWH is generally administered intravenously during PCI.

There are also several theoretic advantages of LMWH over unfractionated heparin (UFH); the most important of which is decreased platelet activation and platelet endothelial interactions with LMWH when compared with UFH.[5–7] Although not proven, the propensity of UFH to activate platelets may have important clinical implications as may have been made evident in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial.[8]

The National Investigators Collaborating on Enoxaparin (NICE) 1 and 4 trials as well as a study by Kereiakes et al have supported the efficacy of LMWH during PCI.[9,10] The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was designed to definitively support the use of LMWH in invasively managed patients, often leading to PCI.[11] This large trial involved > 10,000 ACS patients who were treated with an invasive strategy and were randomized to anticoagulation with either enoxaparin or UFH. Although similar PCI and efficacy results were evident in both

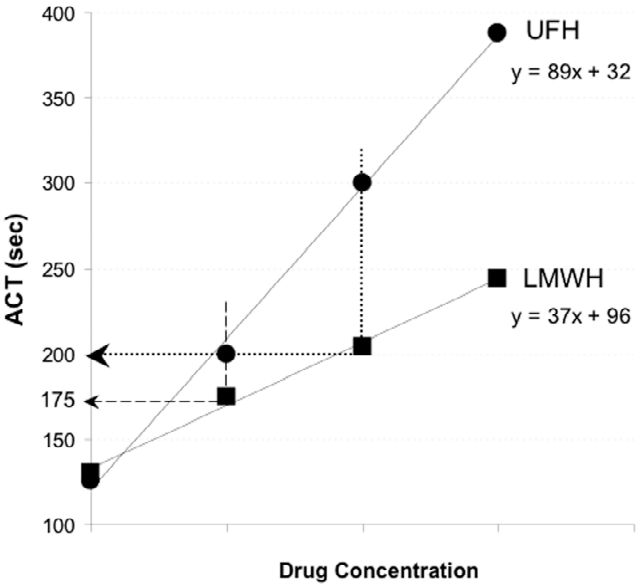

Figure 1. *A composite of the dose-response of ACT following intravenous LMWH, characterized by a slope that is approximately one half the magnitude of UFH. Using the UFH ACT targets of 200 and 300 seconds, a vertical line started at the drug concentration that is associated with the target ACT for UFH 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.*

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Table 1. Case studies and lessons learned using LMWH during PCI

Case	Time	ACT (sec)	Medication Administered at PCI	Case Summary	Lessons Learned
1	Baseline	161	Dalteparin 50 units/kg IV	Chronic hemodialysis patient had rotational atherectomy and stenting of LAD; the patient received dalteparin 50 units/kg IV bolus	In patients with severe chronic renal failure, the half-life of LMWH appears acceptable after IV administration
	5 min	219		No GP IIb/IIIa inhibitor was given	Without GP IIb/IIIa antagonists, the target ACT for LMWH is ≥ 200 sec
	120 min	164		Sheath pulled	The ACT can be used to guide sheath removal
2	Baseline	219	No additional LMWH (or UFH) given during PCI; although the ACT on LMWH was > 200 sec, we elected to administer eptifibatide due to the high-risk nature of the intervention	This patient had unstable angina and had urgent PCI of RCA; 3 doses of subcutaneous 1 mg/kg enoxaparin were given prior to the PCI with the last dose given 8 hours prior to the procedure; the ACT just before PCI was > 200, so patient was not given any additional heparin for the PCI	The ACT may be useful to determine the need for anticoagulation in patients where the timing of the last LMWH subcutaneous dose is documented
3	Baseline	121	Dalteparin 80 units/kg IV plus abciximab	This patient underwent cutting balloon angioplasty of the LAD	
	5 min	202			
	40 min	172		PCI was complicated by perforation	
	45 min	119	Protamine 10 mg IV	Dramatic and rapid decrease in the ACT after protamine	
	70 min	133		The ACT increased to 133 sec	The rise in the ACT after protamine was unexpected and raises the question of whether the effects of protamine on LMWH are transient
	80 min	119	Protamine 5 mg IV	The ACT decreased to 119 sec and bleeding stopped	LMWH is partially reversible with protamine, and the ACT monitoring may help guide protamine dosing

groups, it is noteworthy that the UFH group, which was monitored with the ACT, had fewer bleeding complications when compared to the LMWH group, which was not monitored.[11] These observations suggest a potential benefit in favor of monitoring LMWH during PCI.

Our previous work has demonstrated the ability to monitor the LMWH dalteparin using the ACT.[12] Other study groups have demonstrated similar monitorability with enoxaparin using bedside assays, such as the ACT and the Rapidpoint ENOX test.[13,14]

Based on our clinical experience, review of the literature and theoretic extrapolations from *in-vitro* observations, we developed minimum target ACT values for the use of LMWH during PCI (Figure 1), specifically 200 seconds if no glycoprotein (GP) IIb/IIIa inhibitor is used and 175 seconds if adjunctive GP IIb/IIIa inhibition is used.[10,12,15–17]

The purpose of this article is to review the lessons learned from a series of PCI cases in which we utilized the ACT to guide our management of LMWH-based anticoagulation.

The following cases demonstrate the principles we have adopted for the use of LMWH in the cardiac catheterization laboratory at the State University of New York (SUNY) Health Science Center at Brooklyn (Downstate Medical Center).

Case report 1. *A 65-year-old man on hemodialysis with end-stage renal failure was admitted to the hospital for unstable angina and was found to have a 95% stenotic lesion of his left anterior descending (LAD) artery (Figure 2). He was referred to the cardiac catheterization laboratory for PCI (rotational atherectomy) of the LAD lesion. He had received several doses of a LMWH agent prior to his arrival to the cath lab; however, no documentation of the precise*

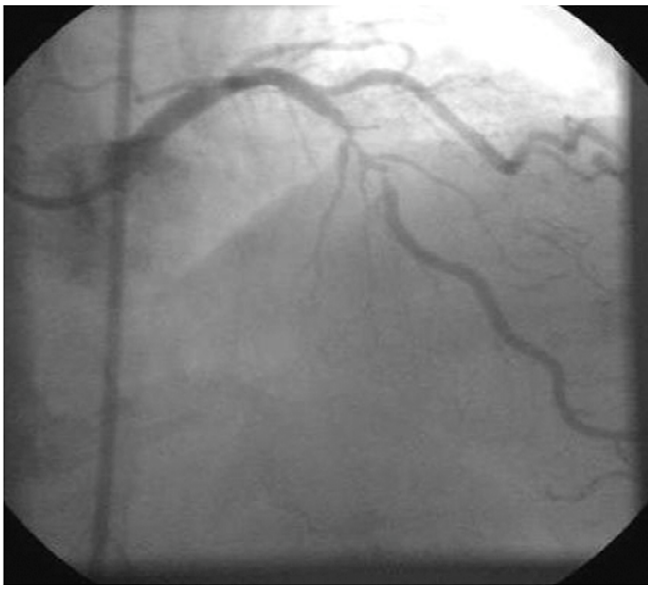

Figure 2. *Case report 1: 95% stenosis of LAD artery.*

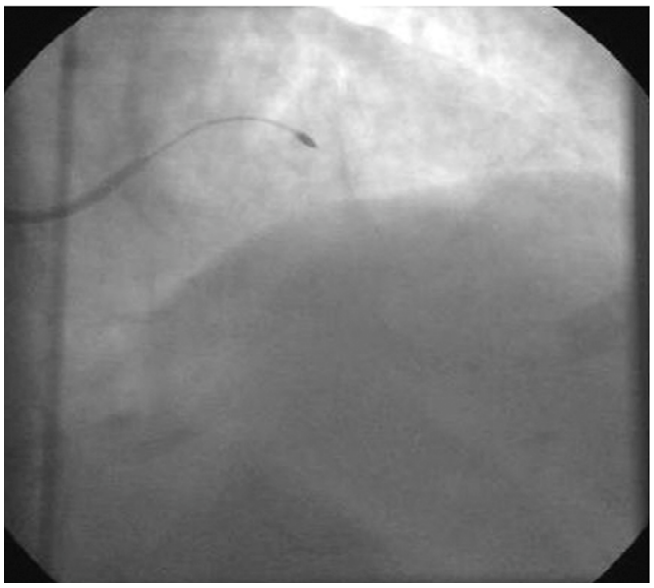

Figure 3. *Case report 1: Rotational atherectomy of LAD stenotic lesion.*

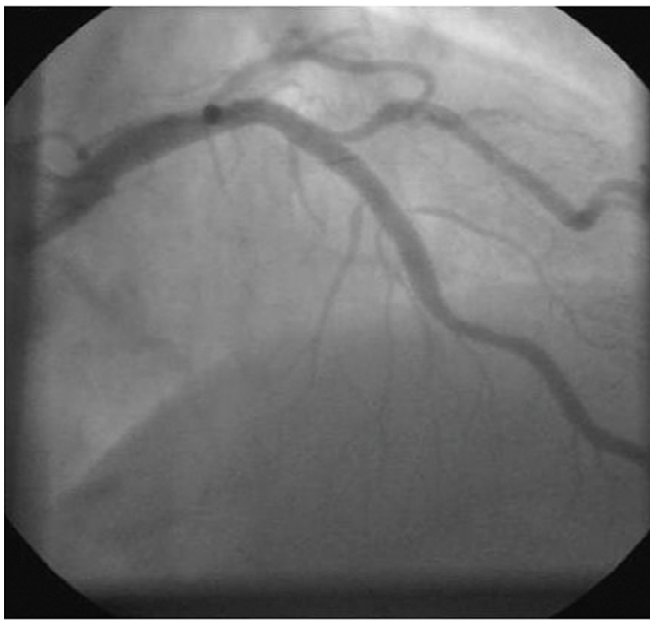

Figure 4. *Case report 1: LAD artery post rotational atherectomy and post PCI.*

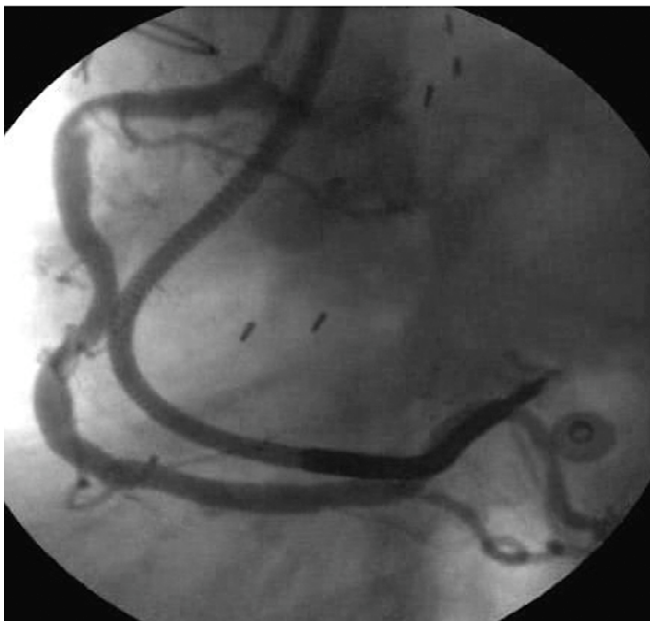

Figure 5. *Case report 2: Significant 70% stenotic RCA lesion.*

timing of the last dose of LMWH was found in his chart upon presentation to the cath lab. After documenting an ACT of 161 seconds on presentation, he was given dalteparin 50 units/kg intravenously; 5 minutes later, his ACT was 219 seconds. Based on our proposed minimum target ACT, no GP IIb/IIIa inhibitor was given. Two hours after administration of the dalteparin bolus, his ACT returned to 164 seconds, and the femoral sheath was pulled. The procedure was completed successfully with no bleeding or thrombotic complications (Table 1, Figures 2–4).

Case report 2. *A 65-year-old woman was admitted to the hospital for unstable angina and was placed on enoxaparin 1 mg/kg subcutaneously. A 70% stenotic lesion of her right coronary artery (RCA) was identified (Figure 5). The patient underwent urgent PCI of the RCA lesion. Three doses of enoxaparin were given from admission to the hospital to her presentation to the cardiac cath lab. Her last dose was given 8 hours prior to the procedure (PCI). On presentation to the cath lab, her ACT was 219 seconds, and based on our proposed minimum target ACT for LMWH, no additional LMWH (nor UFH) was given. She was given a bolus of eptifibatide intravenously and had a successful, uncomplicated PCI of the RCA (Table 1, Figures 5 and 6).*

Case report 3. *A 50-year-old man with no significant past medical history was admitted to the hospital for unstable angina. Cardiac catheterization revealed a 90% LAD lesion, and PCI was planned*

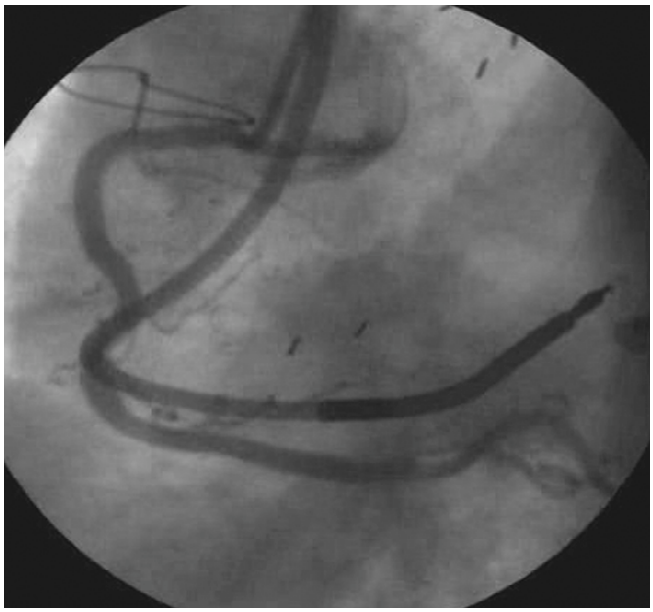

Figure 6. *Case report 2: RCA lesion post PCI.*

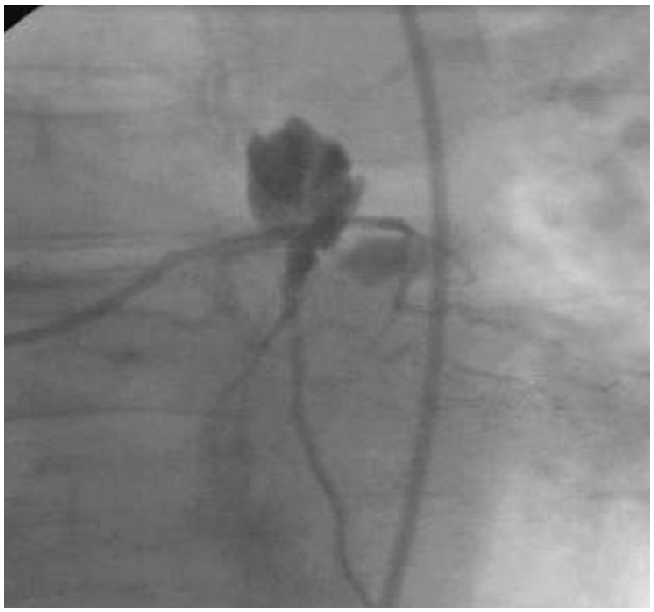

Figure 7. *Case report 3: PCI complicated by perforation of the coronary vasculature.*

subsequently. After documenting a baseline ACT of 121 seconds, he was given intravenous dalteparin 80 units/kg and abciximab. Five minutes later, his ACT increased to 202 seconds. Dilatation of the lesion with a 3.0 mm diameter cutting balloon was complicated by perforation and, shortly thereafter, manifestations of cardiac tamponade. An ACT measured at the approximate time of the perforation (40 minutes after the bolus dose) was 172 seconds. A 10 mg dose of protamine was given with a resultant decrease in the ACT to 119 seconds 5 minutes later. However, at 70 minutes from baseline, the ACT increased to 133 seconds, and an additional 5 mg of protamine was given followed by a decrease of the ACT to baseline 119 after 10 minutes (Table 1, Figure 7).

Discussion. One of the important points noted from these case reports, particularly the first case, was the value of the ACT to determine the need for additional LMWH anticoagulation in high-risk patients, such as those with renal failure in whom the half-life of LMWH is longer and difficult to estimate. Unlike patients with normal creatinine clearance, patients with renal failure may display unpredictable pharmacokinetics of LMWH, even after being dose-adjusted for their decreased creatinine clearance. As such, the algorithm based on timing of last administered subcutaneous LMWH dose would be inadequate.[18] The ACT is also valuable in determining the need for additional anticoagulation in patients in whom the timing of the last LMWH subcutaneous dose cannot be determined from the patients' charts on arrival to the cath lab. In these patients, the time-based algorithm would be impractical, as was also demonstrated in the first case.

The ACT may still be useful to determine the need for further anticoagulation in patients where the timing of the last LMWH subcutaneous dose is documented. This was noted in the second case; although the patient's last LMWH dose was 8 hours prior to arrival to the cath lab, her ACT was greater than 200 seconds on presentation, and therefore, additional LMWH was not required. This is in contrast to the time-based algorithm, which states that patients in whom catheterization is begun between 8 and 12 hours of last subcutaneous dose will require an additional LMWH intravenous bolus prior to PCI.[18]

The ACT may be used to guide the timing of sheath removal, based on a proposed ACT value of ≤ 160 seconds

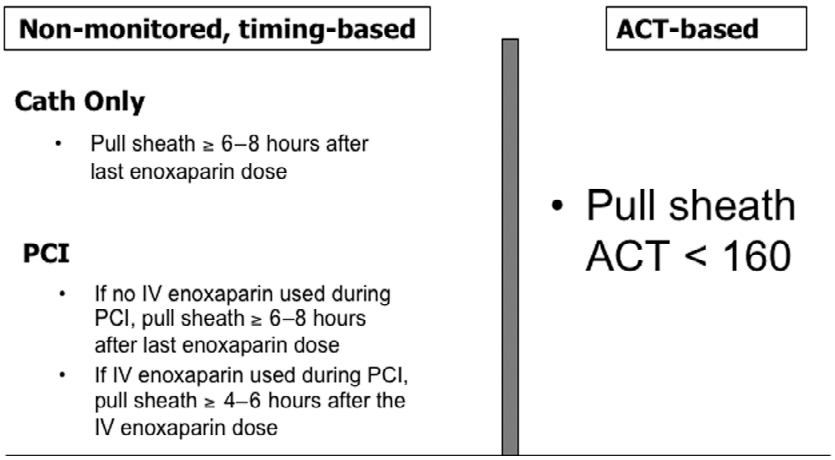

Figure 8. *Strategies for sheath management in LMWH-treated patients. An ACT-based approach eliminates some of the complexities associated with the non-monitored, timed-based sheath management strategy used in the SYNERGY trial.*

Table 2. Protamine neutralization of LMWH correlates with the degree of sulfation

Heparin	% Anti-factor Xa Neutralized	% Sulfate
Fraxiparin	58	35
Tinzaparin	86	39
Dalteparin	74	37
Clivarin	51	35
Enoxaparin	54	32
SSLMWH	100	42
SSLMWH: Super sulfonated low-molecular-weight heparin		

(Figure 8). This was demonstrated in the first case in which the patient's femoral sheath was pulled successfully 2 hours after his intravenous dalteparin bolus when the ACT returned to baseline of 164 seconds. This is in comparison to the non-monitored time-based approach in which the timing of sheath removal is determined to be 4–6 hours after the last intravenous LMWH bolus in patients undergoing PCI.

LMWH activity may be partially reversed by protamine during hemorrhagic complications in PCI. This was demonstrated in the third case in which the patient's PCI was complicated by perforation 5 minutes after receiving intravenous LMWH, which increased his ACT from 121 seconds to 202 seconds. The patient was given 10 mg of intravenous protamine, which decreased his ACT to 119 seconds. This suggests that in the case of an acute hemorrhage, the ACT may be used to guide the appropriate dose of protamine administration. However, protamine does not completely neutralize the effect of LMWH on the coagulation system. A study by Crowther et al suggested that the degree of protamine neutralization of anti-Xa effect of LMWH appears to correlate with the sulfate charges on LMWH.[19] The degree of neutralization varies from 50% to 86% following protamine administration (Table 2).

Conclusion. These case reports suggest that the ACT is valuable in determining the need for additional LMWH anticoagulation in complex patients, such as renal failure patients, and also in patients in which the timing of the last subcutaneous LMWH dose prior to presentation to the cath lab is not documented. These case reports also suggest that the time-based algorithm may not be a precise means of determining the need for additional LMWH anticoagulation in PCI. Additionally, the ACT may be used to guide the timing of sheath removal post-PCI. Lastly, the effect of LMWH may be partially reversed with protamine, and the ACT may be valuable to guide protamine administration during hemorrhagic complications.

References

1. Cohen M, Blaber R, Demers C, et al. The Essence trial: Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI: A Double-Blind, Randomized, Parallel-Group, Multicenter Study Comparing Enoxaparin and Intravenous Unfractionated Heparin: Methods and Design. *J Thromb Thrombolysis* 1997;4:271–274.
2. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593–1601.
3. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999;354:708–715.
4. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–1887.
5. Cella G, Girolami A, Sasahara AA. Platelet activation with unfractionated heparin at therapeutic concentrations and comparison with low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1999;99:3323.
6. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 1998;97:251–256.
7. Sobel M, Fish WR, Toma N, et al. Heparin modulates integrin function in human platelets. *J Vasc Surg* 2001;33:587–594.
8. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;108:135–142.
9. Kereiakes DJ, Grines C, Fry E, et al. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J Invasive Cardiol* 2001;13:272–278.
10. Kereiakes DJ, Kleiman NS, Fry E, et al. Dalteparin in combination with abciximab during percutaneous coronary intervention. *Am Heart J* 2001;141:348–352.
11. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45–54.
12. Marmur JD, Anand SX, Bagga RS, et al. The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration. *J Am Coll Cardiol* 2003;41:394–402.
13. Lawrence M, Mixon TA, Cross D, et al. Assessment of anticoagulation using activated clotting times in patients receiving intravenous enoxaparin during percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2004;61:52–55.
14. Moliterno DJ, Hermiller JB, Kereiakes DJ, et al. A novel point-of-care enoxaparin monitor for use during percutaneous coronary intervention. Results of the Evaluating Enoxaparin Clotting Times (ELECT) Study. *J Am Coll Cardiol* 2003;42:1132–1139.
15. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: Aggregate results from 6 randomized, controlled trials. *Circulation* 2001;103:961–966.
16. Brener SJ, Moliterno DJ, Lincoff AM, et al. Relationship between activated clotting time and ischemic or hemorrhagic complications: Analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 2004;110:994–998.
17. Valgimigli M, Percoco G, Barbieri D, et al. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: The ADVANCE Trial. *J Am Coll Cardiol* 2004;44:14–19.
18. Kereiakes DJ, Montalescot G, Antman EM, et al. Low-molecular-weight heparin therapy for non-ST-elevation acute coronary syndromes and during percutaneous coronary intervention: An expert consensus. *Am Heart J* 2002;144:615–624.
19. Crowther MA, Berry LR, Monagle PT, Chan AK. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol* 2002;116:178–186.

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