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Antithrombin Therapy in Acute Coronary Syndromes

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Following rupture of a vulnerable plaque, the coagulation cascade is activated and fibrin strands are formed. The classic view of the coagulation cascade postulated that two independent pathways converged on the activation of factor X.[1] The intrinsic pathway (initiated by contact activation) and the extrinsic pathway (activated by tissue factor) are now conceived to be a highly integrated complex system with release of tissue factor playing the integral role. Tissue factor, a protein found on the membrane of many different cell types, is not normally exposed to blood elements but is expressed following injury to activated endothelial cells. It is also found in the subendothelial matrix that is exposed after intimal injury.[2]

Figure 1 shows a simplified diagram of key steps involved in activation of the coagulation cascade via the tissue factor pathway. With rupture or erosion of the surface of a vulnerable plaque, tissue factor is exposed and factor VII is activated. The tissue factor:VIIa complex leads to the activation of factor X. Activated factor Xa is a critical component of the coagulation system because it participates in the assembly of the prothrombinase complex. A single molecule of factor Xa can lead to the production of multiple molecules of thrombin, which can exist in both the fluid phase and the clot-bound phase.

In addition to the coagulation cascade being activated, platelets adhere to the subendothelial matrix in the region of the vulnerable plaque, release ADP (adenosine diphosphate) and thromboxane A2, and amplify the generation of thrombin.[3] Platelet aggregates form as the activated state of the glycoprotein IIb/IIIa receptor is expressed on the surface of activated platelets. Multivalent ligands such as fibrinogen bind to the glycoprotein (GP) IIb/IIIa receptors on multiple platelets, providing cross-linking and propagation of a platelet aggregate.

When coronary blood flow is reduced sufficiently, patients experience ischemic discomfort. Complete occlusion of the culprit coronary vessel results in ST segment elevation on the electrocardiogram, and most of these patients ultimately develop a Q-wave MI (myocardial infarction). A small proportion of patients might sustain only a non-Q-wave MI.[4,5]

If the obstructing thrombus (fibrin mesh and platelet aggregates) is not totally occlusive, the obstruction is only transient or a rich collateral network is present, no ST segment elevation is seen. The majority of such patients are diagnosed as having unstable angina or, if a serum cardiac marker indicative of myocardial necrosis is detected (e.g., CKMB, cardiac-specific troponin I or T), as having a non-Q-wave MI. A minority of patients who initially present without ST segment elevation might ultimately develop a Q-wave MI. The various presentations ranging from unstable angina through non-Q-wave MI and Q-wave MI are collectively referred to as the acute coronary syndromes (figure 2).[4,5]

Antithrombin therapy for the acute coronary syndromes

Thrombin is an important molecule in the acute coronary syndromes because of its extensive procoagulant and prothrombotic actions.[6] In addition to catalyzing the transformation of soluble fibrinogen into fibrin monomers and activating factor XIII to produce cross-linked fibrin, thrombin promotes clot formation by activating factors V and VIII. It is also one of the most potent agents responsible for platelet activation, adhesion, and aggregation. In vessels with a diseased endothelium, thrombin promotes the release of the vasoconstrictor endothelin-1. Thrombin also potentiates the proliferative effects of multiple growth factors and is a key mediator of early smooth-muscle-cell proliferation following arterial injury. Previous investigations have shown that the effects of thrombin can be

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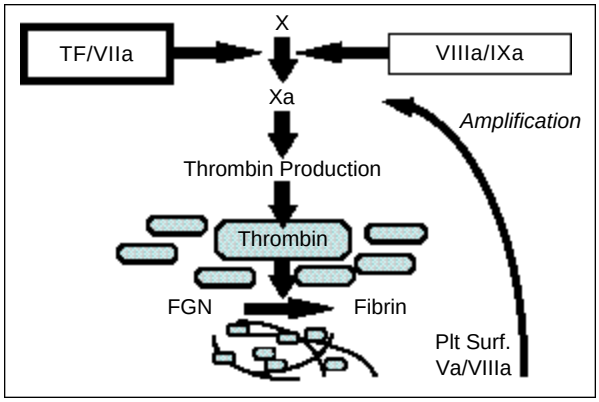
Figure 1: Activation of the coagulation cascade.While the intrinsic and extrinsic pathways can both lead to production of thrombin, current evidence indicates that tissue factor (TF) plays an integral role (heavy boxed area at top left).Production of activated factor X (X_a) is a key step since a single molecule of factor Xa can lead to the production of multiple molecules of thrombin (blue oval structures). Thrombin can exist in both a fluid phase and a clot-bound phase (bottom central portion of diagram;curved elements indicate fibrin strands).



neutralized by either direct or indirect inactivation and by inhibition of thrombin production via the intrinsic or extrinsic limbs of the coagulation pathway.[6]

Because of thrombin's central role in the pathogenesis of unstable angina and acute MI, antithrombin therapy is applicable across the entire spectrum of acute coronary syndromes. The standard antithrombin agent used in clinical practice is heparin. Unfractionated heparin is a glycosaminoglycan, consisting of chains of alternating residues of D-glucosamine and uronic acid.[7] Clinically available preparations of unfractionated heparin are heterogeneous mixtures of polysaccharide chains ranging in molecular weight from 3,000 to 30,000 daltons. Unfractionated heparin exerts its anticoagulant activity by activating antithrombin III.[8] The mechanism of activation of antithrombin III involves binding to a unique pentasaccharide sequence that is randomly distributed along the heparin chains. Binding of the pentasaccharide sequence on heparin to antithrombin III causes a conformational change in antithrombin III, accelerating its ability to inhibit thrombin and factor Xa by about a thousand-fold.[7,8]

Although familiar to the vast majority of clinicians, unfractionated heparin has the disadvantages of a variable anticoagulant effect (necessitating frequent aPTT [arterial partial thromboblastin time] monitoring), sensitivity to platelet Factor 4, a relative inability to inhibit clot-bound thrombin, and the potential to cause thrombocytopenia and HITS (heparin induced thrombocytopenia syndrome).[7-10] Several novel antithrombin regimens have been proposed (figure 3). One involves using a closed-loop feedback system that automatically measures the patient's aPTT and adjusts an infusion of unfractionated heparin to maintain the level of anticoagulation in the target aPTT range.

Alternative approaches have focused on new pharmacologic agents. To date, the novel pharmacologic regimens most extensively investigated in clinical trials include the antithrombin-III-independent (or direct) antithrombins and the low-molecular-weight heparins.[3,4,7]

Direct antithrombins

Direct antithrombins are novel anticoagulants that inhibit thrombin directly without requiring the cofactor antithrombin III. Although a variety of direct antithrombins has been identified, those that have undergone clinical investigation to date include hirudin, hirulog, argatroban, efegatran, and inogatran.[11-14] All of the direct antithrombins exhibit a concentration-dependent anticoagulant effect. Because of their tight binding to thrombin, hirudin and hirulog are virtually irreversible inhibitors of thrombin while argatroban, efegatran, and inogatran are reversible inhibitors. Although in-vitro observations of the various direct antithrombins have identified some differences among the agents (e.g., binding characteristics to thrombin, ability to inhibit generation of thrombin), it is unclear whether these differences will have any important impact on the clinical use of the direct antithrombins.[15]

To illustrate the mechanism of action of direct antithrombins, the prototypical agent hirudin will be discussed. The carboxy terminus of hirudin binds to the substrate recognition site on thrombin, while the amino terminus inhibits the active catalytic center of thrombin.[11] Since clot-bound thrombin is less effectively inhibited by unfractionated heparin (because the attachment of fibrin to the fibrin-binding domain makes the

Figure 2: Acute coronary syndromes. Patients with ischemic discomfort at rest can present with or without ST-segment elevation on the electrocardiogram. The majority (large arrow) of patients with ST-segment elevation ultimately develop a Q-wave acute myocardial infarction (AMI), whereas a minority (small arrow) develop a non-Q-wave AMI.Of the patients who present without ST-segment elevation, the majority (large arrows) are ultimately diagnosed with either unstable angina or non-Q-wave AMI based on the presence or absence in the serum of a cardiac marker such as CK-MB;a minority of such patients ultimately develop a Q-wave AMI.The spectrum of clinical conditions ranging from unstable angina to non-Q-wave AMI and Q-wave AMI is referred to as the acute coronary syndromes. [Reproduced with permission of W.B. Saunders and Company from Antman EM, Braunwald E.Acute myocardial infarction.In:Braunwald E, ed. Heart Disease:A Textbook of Cardiovascular Medicine.5th ed.Philadelphia, Penna: W.B.Saunders Company;1997: 1184–1288.]

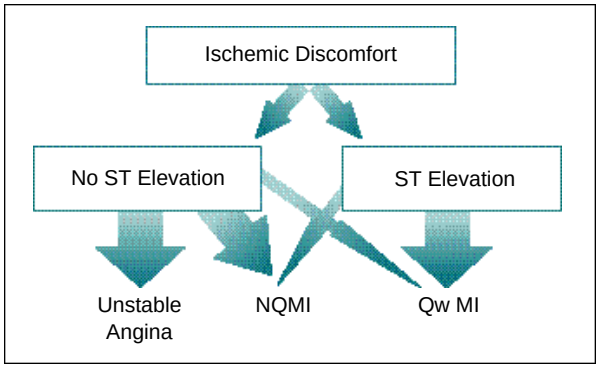
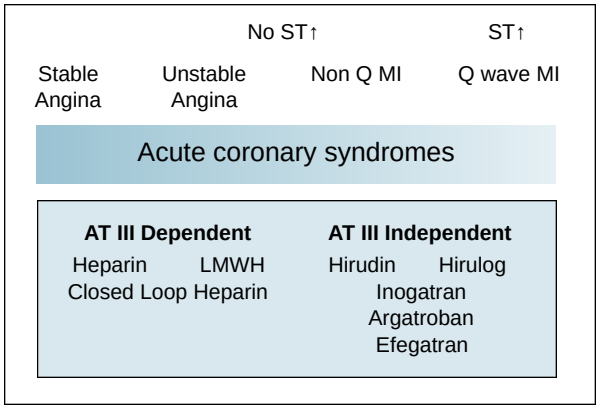


Figure 3: Novel antithrombin regimens for treatment of acute coronary syndromes.(AT III = antithrombin III)



heparin-binding domain inaccessible), it has been proposed that the direct antithrombins have a greater ability to block both fluid-phase and clot-bound thrombin.[16] This concept has been referred to as the "thrombin hypothesis" and was the inspiration for several randomized controlled trials (figure 4).

ST-segment-elevation MI: Adjunctive therapy to thrombolysis

Based upon the initial favorable observations in the phase-II trials TIMI 5 and TIMI 6, several phase-III trials of direct antithrombins as adjunctive therapy to thrombolysis were undertaken.[17-18] Table 1 summarizes the main features of the TIMI 9A, GUSTO IIa, and HIT-III trials.[19-21] TIMI 9A and HIT-III focused on patients with ST-segment-elevation MI, and GUSTO IIa enrolled patients with clinical presentations across the acute coronary syndrome spectrum. A feature common to all three trials was that they were stopped prematurely because of unacceptable rates of major hemorrhage, particularly intracranial hemorrhage, underscoring the major anticoagulant activity of antithrombins. Possible reasons for the unacceptable rates of bleeding include high levels of anticoagulation in both the heparin and hirudin groups in TIMI 9A and GUSTO IIa, a low estimate of the hemorrhage risk at the doses of hirudin infused previously in the phase-II trials, and attempts to push the heparin dose to achieve higher aPTT levels in an effort to prevent reocclusion of successfully reperfused vessels.[19] As a result of these findings, the doses of both hirudin and heparin were reduced and the TIMI 9B and GUSTO IIb trials were undertaken (figure 5).

In TIMI 9B, patients were treated with either tPA (tissue plasminogen activator) or streptokinase at the physician's discretion and received a 96-hour infusion of either hirudin or heparin.[22] The rate of development of the primary endpoint (death, recurrent nonfatal myocardial infarction, or severe congestive heart failure or cardiogenic shock by 30 days) was 11.9% in the 1,491 patients in the heparin group and 12.9% in the 1,511 patients in the hirudin group (p = NS).[22] In addition, there was no significant difference in the secondary endpoint of death and nonfatal recurrent myocardial infarction.

Figure 4: Comparative mechanisms of action of heparin and hirudin. Four molecules of thrombin are shown in this diagram with the fibrin (F) and heparin (H) binding domains as well as the catalytic center (C) and substrate recognition domain (S). Unfractionated heparin activates antithrombin III, causing a conformational change in antithrombin III and accelerating its ability to inhibit the catalytic center of thrombin. The direct antithrombin hirudin does not require the antithrombin III cofactor. The thrombin hypothesis proposed that hirudin was a more effective inhibitor of both fluid-phase and clot-bound thrombin and would therefore lead to a reduction in clinical events in patients with an acute coronary syndrome.

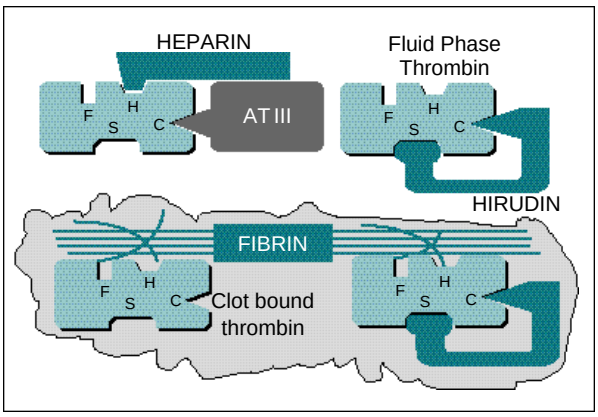


Table 1: Hirudin vs.heparin for acute MI

	TIMI 9A	GUSTO IIa	HIT-III
Age limit	None	None	None
Rx window	12 h	12 h	6 h
Creatinine limit	2.5–2.0	2.5	"renal insufficiency"
Lytic	tPA, SK	tPA, SK	tPA
Heparin	1000 U/h <80 kg 1300 U/h ≥80 kg	1000 U/h <80 kg 1300 U/h ≥80 kg	15 U/kg/h
Hirudin			
bolus (mg/kg)	0.6	0.6	0.4
infusion (mg/kg/h)	0.2	0.2	0.15
aPTT target	60–90 sec	60–90 sec	2.0–3.5 x Control

In the GUSTO IIb trial, patients were stratified into those presenting with ST-segment elevation (N = 4131) or without ST-segment elevation (N = 8011).[23] Hirudin or heparin was infused for a minimum of 3 days and a maximum of 5 days. The primary endpoint of the trial (death or nonfatal myocardial infarction at 30 days) occurred in 9.8% of the heparin group and 8.9% of the hirudin group (odds ratio = 0.89; 95% confidence interval 0.79-1.00; p = 0.06).[23]

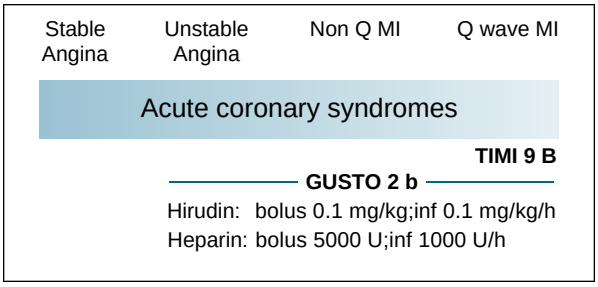
A pooling project between the GUSTO and TIMI investigators showed that hirudin was more effective at achieving and maintaining the target aPTT range.[24] By careful adjustment of the dose of both hirudin and heparin, major bleeding could be reduced. However, there was no difference in mortality in heparin- versus hirudin-treated patients; there was a slight reduction (14%) of reinfarction by 30 days in patients treated with hirudin.[24] The evidence, to date, suggests that, in the clinically acceptable dose range, unfractionated heparin and hirudin are equivalent antithrombin strategies in patients with an acute coronary syndrome.

Potential explanations for the lack of significant benefit of the direct antithrombin hirudin in these large phase-III trials include:

• *Similar net balance of antithrombotic actions between unfractionated heparin and hirudin in the infarct-related artery* Unfractionated heparin is capable of inhibiting the coagulation cascade upstream from thrombin; it thus has an advantage over the direct antithrombins because of its additional ability to decrease thrombin generation along with its ability to inhibit thrombin activity.[9,10] In contrast, hirudin has a greater ability to decrease thrombin activity.[11] However, once the thrombin inhibitory capacity of hirudin is exceeded (e.g., higher concentrations of thrombin relative to the concentration of hirudin), thrombosis by enzymatically active thrombin can proceed.[25,26]

• *Relative potency* Although hirudin is relatively more effective than unfractionated heparin at inhibiting clot-bound thrombin, this relative difference is most evident at the left of the concentration-effect relationship and diminishes at higher concentrations. Thus, in the range of concentrations that could be given safely to patients, hirudin's ability to inhibit clot-bound thrombin is only about 50% as potent as its ability to

Figure 5: Antithrombin dosing regimens in phase-III trials of direct antithrombins



inhibit fluid-phase thrombin.[16] In addition, the concentration of hirudin required to inhibit thrombin-induced platelet activation is ten times that required to inhibit fibrin formation.[27] These observations tend to minimize hirudin's potential advantage over heparin in the clinically relevant, safe-dose range.

• *Catalytic vs. stoichiometric method of inhibition of thrombin* Unfractionated heparin is a catalytic inhibitor of thrombin that is capable of dissociating from the complex of antithrombin III and thrombin, enabling a single molecule of unfractionated heparin to catalyze the action of multiple molecules of antithrombin III. Antithrombin III, acting as a "suicide substrate," liberates unfractionated heparin for further action against other molecules of thrombin (figure 6).[9,10] In contrast, hirudin binds tightly in a 1:1 stoichiometric fashion to thrombin in both the fluid phase and clot-bound phase. It is potentially possible to "exhaust" the supply of hirudin, thus permitting thrombin molecules to remain active for converting fibrinogen to fibrin. As observed in the TIMI 9A and GUSTO IIa trials, increasing the concentration of hirudin to inhibit more thrombin appears to be associated with unacceptable bleeding rates.[19,20]

Hirulog has been evaluated as adjunctive therapy to streptokinase for ST-segment-elevation MI by several investigators. An unusual dose response was observed during analysis of the HERO study and a trial from the Montreal Heart Institute. Lidon et al. found that low-dose hirulog (0.5 mg/kg/hr) produced an 85% rate of TIMI grade-3 flow at 90 minutes, while high-dose hirulog (1 mg/kg/hr) produced a 61% rate of TIMI grade-3 flow.[18] The notion that a low dose of a direct thrombin inhibitor might be more effective than a high dose has been hypothesized as being due to the "thrombin paradox." This states that low doses of antithrombins allow sufficient thrombin activity to persist, leading to stimulation of the inhibitory thrombomodulin and protein C pathway. However, the HERO trial reported a TIMI grade-3 flow rate of 56% after 90–120 minutes in patients receiving high-dose hirulog (0.5 mg/kg/hr) compared with 49% in patients receiving low dose hirulog (0.25 mg/kg/hr).[29] One of the hypotheses put forward by the HERO investigators is that the direct antithrombins must be administered prior to initiation of thrombolytic therapy to maximize the degree of inhibition of thrombin activity. This concept is being tested in the HERO-II trial that will compare hirulog with unfractionated heparin as adjunctive therapy for patients receiving streptokinase 1.5 million units over 30–40 minutes for ST-segment-elevation MI.

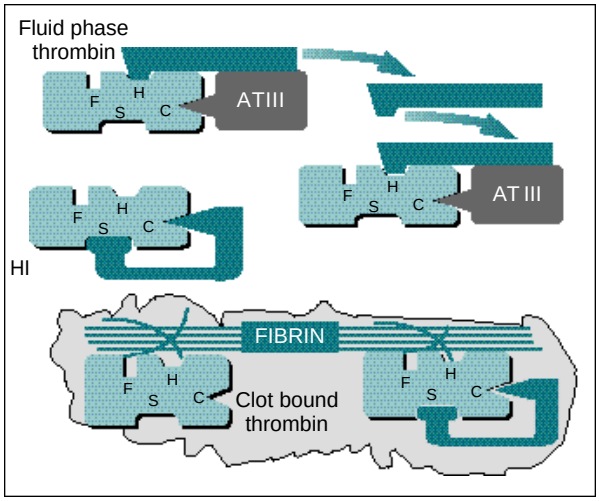
Dose-ranging phase-II angiographic trials have also been performed with efegatran (PRIME[30] and ESCALAT[31] studies) and argatroban (ARGAMI[32] and MINT trials). Despite a sound theoretical basis for anticipating improvements in the rate of TIMI grade-3 flow when these direct antithrombins were compared with unfractionated heparin, either no improvement was seen or only slightly higher rates of TIMI grade-3 flow were observed. Based upon the phase-II experience with efegatran, the sponsor has terminated further development of that direct antithrombin.

Despite initial promise, no additional benefits of direct antithrombins are seen in acute ST-elevation MI.

Trials of direct antithrombins in unstable angina

The OASIS (Organization to Assess Strategies for Ischemia Syndromes) pilot study compared heparin with low-dose hirudin (bolus 0.2 mg/kg; infusion 0.1 mg/kg/hr) or medium-dose hirudin (bolus 0.4 mg/kg; infusion 0.15 mg/kg/hr) for 72 hours in patients with unstable angina or suspected non-Q-wave MI.[33]

Figure 6: Schematic diagram comparing the actions of heparin with hirudin on fluid-phase and clot-bound thrombin.[Reproduced with permission of Kluwer Academic Publishers from Giugliano RP, Antman EM, Braunwald E.Reexamination of the thrombin hypothesis:What we have learned from TIMI 9B and GUSTO IIb. *J Thrombosis Thrombolysis* 1997;4:321–323]



There were no significant differences among the treatment groups for the endpoint of cardiovascular death or myocardial infarction. It is of note that this was an open-label trial, but randomization to the two different doses of hirudin was blinded. Only when composite endpoints, including various definitions of angina, were used did a suggestion of a reduction of events emerge in the medium-dose hirudin group. This served as the foundation for the current OASIS trial that is comparing hirudin and heparin as the acute-phase treatment for unstable angina/non-Q-wave MI followed by long-term anticoagulant therapy with warfarin versus placebo.

The direct antithrombin inogatran has been evaluated in the TRIM study (Thrombin Inhibition in Myocardial Ischemia).[14] A total of 1,209 patients with unstable angina received a 72-hour treatment with a low, medium, or high dose of inogatran or standard heparin. Although a dose-dependent prolongation of the aPTT was observed in inogatran-treated patients – with greater stability of the anticoagulant effect compared with heparin – the primary endpoint of death, recurrent infarction, and refractory or recurrent ischemia was not reduced by inogatran compared with heparin treatment.

Low-molecular-weight heparins

Low-molecular-weight heparin (LMWH) preparations are formed by controlled enzymatic or chemical depolymerization producing saccharide chains of varying length but with a mean molecular weight of about 5,000.[7] As illustrated in figure 7, a critical chain length of 18 saccharides is required to form the ternary complex consisting of a heparin fragment, antithrombin III, and thrombin. In addition to the pentasaccharide sequence discussed above that is critical for attachment of a heparin fragment to antithrombin III, an additional 13 saccharide residues are necessary to allow the heparin fragment to simultaneously attach itself to the heparin-binding domain of thrombin, thus creating the ternary complex.[34]

Short-chain or low-molecular-weight heparin fragments of less than 18 saccharides retain the critical pentasaccharide sequence but are of insufficient length to permit attachment to the heparin-binding domain of thrombin, and therefore thrombin is not inhibited by such short-chain fragments.

However, only the critical pentasaccharide sequence is required for binding to antithrombin III and inhibiting factor Xa. Thus, by creating a mixture of short-chain and long-chain heparin fragments, preparations of varying anti-Xa:anti-IIa activity can be developed (table 2). Additional features of LMWHs of particular clinical relevance are a decreased sensitivity to platelet factor IV and a more stable, reliable anticoagulant effect, and lower rates of thrombocytopenia and HITS. Thus, the low-molecular-weight heparins are clinically attractive because of better bioavailability, ease of administration via the subcutaneous (SC) route, and enriched anti-Xa activity.[35] Higher anti-Xa activity is important because of the multiplier effect such that a single molecule of Factor Xa leads to the production of many molecules of thrombin (figure 1).

Gurfinkel and colleagues[36] compared placebo treatment, unfractionated heparin (UFH), and the LMWH nadroparin in 219 patients with unstable angina who were also treated with aspirin. In this single-blind study, patients were randomized to receive aspirin (200 mg/day orally), aspirin plus IV heparin (5,000 IU bolus IV, followed by IV infusion of 400 IU/kg/day, with a target aPTT of 2 times control), or aspirin plus nadroparin (214 IU Institute Choay [UIC]/kg SC twice per day). Treatment was continued for 5–7 days (until hospital discharge) or until the occurrence of a primary endpoint (recurrent angina, acute MI, need for urgent intervention, major bleeding, or death). The study was stopped prematurely on a recommendation from the Data Safety Monitoring Committee. Combination therapy with aspirin plus nadroparin significantly reduced the number of patients with an adverse endpoint event during the study period, from 59% in the aspirin group and 63% in the aspirin plus heparin group to 22% in the aspirin plus nadroparin group ($p < 0.0001$ for the comparisons of the nadroparin group with each of the other 2 groups). Bleeding complications were rare in this study and were largely related to cardiac catheterization access sites.

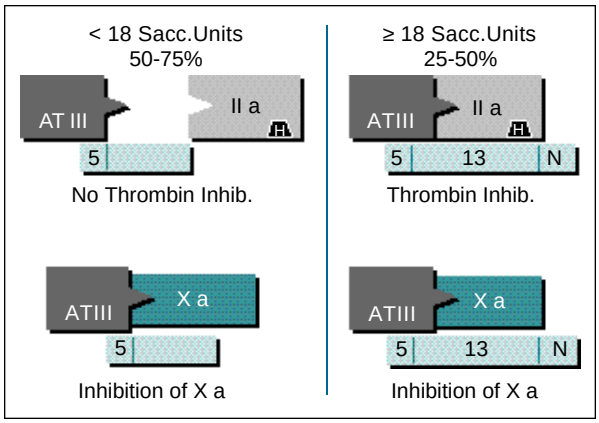
Following the publication of the Gurfinkel study, two larger trials examining the LMWH dalteparin (Fragmin) were reported. The FRISC trial (Fragmin During Instability in Coronary Artery Disease)[37] was designed to determine whether SC administration of dalteparin would reduce ischemic events during the acute in-hospital period following an episode of UA/NQMI (unstable angina/non-Q-wave MI). A secondary goal was to determine whether long-term anticoagulation therapy would provide additional benefit compared with anticoagulation restricted only to the acute phase (the first few days following hospitalization) of an acute coronary syndrome. Patients presenting within 72 hours of the onset of UA/NQMI were randomly assigned to receive either dalteparin (120 IU/kg SC twice daily for 6 days followed by daily SC injections of 7,500 IU for an additional 35–45 days; n = 746) or placebo (n = 760). All patients received aspirin. Compared with the placebo arm, dalteparin-treated patients experienced a 63% reduction in death and nonfatal MI at the 6-day evaluation (4.8% in the placebo group compared with 1.8% in the dalteparin group, $p = 0.001$). However, with longer-term follow-up, event rates for the two groups began to converge, and a nonsignificant trend toward improved outcome was observed in the dalteparin group (10.7% event rate for the placebo group, compared with 8.0% with dalteparin; relative risk 0.75, $p = 0.07$) by 40 days. By 150 days, there was no significant difference between the two groups.

Table 2: Comparison of low-molecular-weight heparin preparations

Preparation	Method of Preparation	Mean Molecular Weight	Anti-Xa: Anti-IIa Ratio*
ardeparin	peroxidative depolymerization	6000	1.9
dalteparin	nitrous acid depolymerization	6000	2.7
enoxaparin	benzylation and alkaline depolymerization	4200	3.8
nadroparin	nitrous acid depolymerization	4500	3.6
reviparin	nitrous acid depolymerization, chromatographic purification	4000	3.5
tinzaparin	heparinase digestion	4500	1.9

*The ratios were calculated by dividing the anti-factor Xa (A=anti-Xa) activity by the antithrombin (anti-IIa) activity. The ratios are based on information provided by the manufacturers. (Reproduced with permission by Massachusetts Medical Society from Weitz JI. Low-molecular-weight heparins. *NEJM* 1997;337:688–698.)

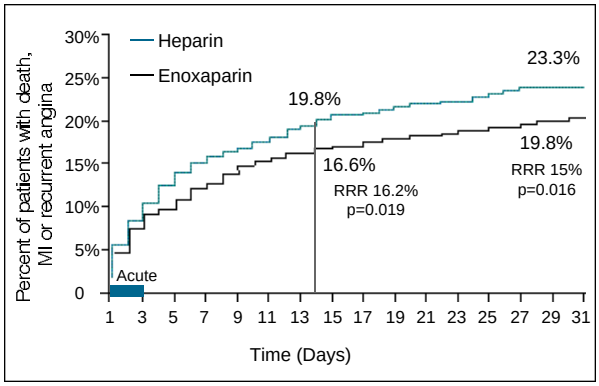
Figure 7: Mechanism of action of low-molecular-weight heparin. Heparin fragments containing the critical pentasaccharide sequence for binding to antithrombin III and an additional 13 sugar residues (to reach the heparin binding domain of thrombin factor IIa) are capable of inhibiting both thrombin and factor Xa. In contrast, short heparin fragments with a lower molecular weight can bind to antithrombin III – provided the critical pentasaccharide sequence is present. If less than 18 saccharide units are contained within the heparin fragment, no thrombin inhibition can occur although inhibition of factor Xa can occur. The relative balance of long- and short-chain heparin fragments in LMWH preparations determines the anti-Xa:anti-IIa activity.



The FRIC (Fragmin in Unstable Coronary Artery Disease) study[38] compared dalteparin with IV heparin in patients with UA/NQMI presenting within 72 hours of an episode of ischemic chest pain. During the acute phase (the first 6 days following hospitalization), patients received either twice-daily SC dalteparin or UFH infused IV during the first 48 hours; during the chronic phase, SC dalteparin or placebo was continued until day 45. All patients received aspirin throughout the course of the study. The occurrence of the composite outcome of death, MI, or recurrent angina was similar for the UFH and dalteparin groups during the 6-day acute period (7.6% vs. 9.3% for the UFH and dalteparin groups, respectively). Similarly, after 45 days, the incidence of death, MI, and recurrent angina was 12.3% for both groups.

The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) study[39] examined the effectiveness of enoxaparin in UA/NQMI. In this large, multicenter, double-blind trial, 3,171 patients were randomized to receive either twice-daily SC injections of enoxaparin (1 mg/kg), or continuous IV infusion of UFH, during the acute period (2–8 days) following hospitalization for UA/NQMI. The primary endpoint was a composite of death, MI, or recurrent angina within 14 days following hospitalization (figure 8). The median duration of treatment with the study drug was 2.6 days. The rate of endpoint events was significantly reduced in the enoxaparin group compared with the UFH group (16.6% vs. 19.8% for the enoxaparin and UFH groups, respectively; $p = 0.019$). The enoxaparin group

Figure 8: ESSENCE Study – main findings.Kaplan-Meier plots of the time to a first event over a period of 30 days for the composite endpoint of death, myocardial infarction, or recurrent angina.RRR = relative risk reduction [Adapted with permission of the Massachusetts Medical Society from Cohen M, Demers C, Gurfinkel EP, et al.A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447–452.]



continued to have fewer events compared with the UFH group through 30 days, at which time a primary endpoint event had occurred in 19.8% of the enoxaparin group and 23.3% of the UFH group (p = 0.016). Patients treated with enoxaparin were also significantly less likely to require revascularization procedures within 30 days (27% vs. 32.2%; p = 0.001).

Although LMWHs share many pharmacological similarities, they also vary in significant respects, and it is important to consider each drug individually rather than as a member of a class of interchangeable compounds. The varying effectiveness of these drugs in clinical trials might reflect differing anti-Xa:anti-IIa ratios.[7] For example, nadroparin and enoxaparin, both of which have been shown to reduce ischemic events following UA or UA/NQMI, have in-vitro anti-Xa:anti-IIa ratios between 3 and 4; dalteparin, which appeared to be less effective, has an anti-Xa:anti-IIa ratio of approximately 2.2. It is currently not clear to what extent these pharmacologic parameters influence the clinical usefulness of the various LMWHs. However, it is also possible that the lack of sustained effect of LMWH in the FRISC and FRIC trials was due to the long patient enrollment period after the last episode of qualifying chest pain (72 hours in both studies), in contrast to a 24-hour enrollment period employed in most other studies.

TIMI 11 studies

TIMI 11A was a dose-finding study to assess the safety and tolerability of 2 enoxaparin doses in patients with UA/NQMI.[40] During the initial in-hospital phase, patients assigned to the first-dose group (n = 321) received an IV bolus of 30 mg enoxaparin followed by SC administration of weight-adjusted enoxaparin (1.25 mg/kg) every 12 hours for 2–8 days. Following the acute in-hospital phase, prolonged SC administration of fixed-dose enoxaparin (60 mg for patients ≥ 65 kg, 40 mg for patients <65 kg, every 12 hours) was continued for a total study period of 14 days. Although the study initially had an escalating-dose design, an analysis of the first group of patients indicated an unacceptably high incidence of major bleeding complications. The enoxaparin dose was therefore reduced in the second-dose group (n = 309), which received the same IV bolus dose and long-term fixed-dose enoxaparin as the first group but a weight-adjusted enoxaparin dose of 1 mg/kg SC every 12 hours.

The incidence of major hemorrhage was 6.5% (95% CI 4.2% to 10%) in dose tier 1, which was significantly higher than an estimated hemorrhage rate associated with UFH treatment in UA/NQMI (approximately 4%) determined from previous clinical trials. The incidence of major bleeding was highest in patients in dose tier 1 who were also undergoing cardiac catheterization (7.9%, compared with 2.7% of patients in dose tier 2 who underwent cardiac catheterization; p = 0.011). The incidence of major hemorrhage was reduced to 1.9% (95% CI 0.8% to 4.4%) in dose tier 2, suggesting that the lower enoxaparin dose provided *similar* therapeutic benefit but with a *reduced* risk of bleeding complications.

TIMI 11B is an ongoing trial that will eventually enroll 4,000 UA/NQMI patients from sites in North America, South America, and Europe. Two strategies of antithrombotic therapy for UA/NQMI are being compared: unfractionated heparin during the acute phase followed by placebo subcutaneous injections during the chronic phase versus uninterrupted therapy with subcutaneous enoxaparin during both the acute and chronic phases. Dosing for the acute-treatment phase commences with enrollment into the trial and ends with hospital discharge or day 8 (whichever comes first). Dosing for the chronic treatment phase commences at the time of hospital discharge or day 8, and continues for an additional 35 days. The primary efficacy endpoint is the occurrence through day 43 of the sum of death, nonfatal MI not present at enrollment, or severe recurrent ischemia requiring urgent revascularization. The primary safety endpoint is the development of major hemorrhage or serious adverse event(s) related to study drug.

LMWH as an adjunct to thrombolysis

Another phase-II trial in progress, the HART-II study, is comparing the low-molecular-weight heparin enoxaparin with unfractionated heparin as adjunctive antithrombin therapy for patients receiving a front-loaded tPA regimen for ST-segment elevation MI. The primary endpoint is TIMI grade-3 flow at 90 minutes following initiation of thrombolytic therapy.

Conclusion

Despite current widespread use of UFH across the spectrum of acute coronary syndromes, it seems likely that it will be used less frequently in the future as the role of newer antithrombin agents and LMWHs is clarified by additional research. Based on the findings of clinical trials to date, the direct antithrombins preparations provide a more consistent anticoagulant effect. The therapeutic range for the direct antithrombins appears to be much narrower than originally appreciated; within the range of clinically acceptable doses, unfractionated heparin appears to be therapeutically similar to the direct antithrombins. When LMWHs with a relatively low anti-Xa:anti-IIa ratio are used, efficacy findings are similar to those for unfractionated heparin. However, when LMWHs with higher anti-Xa:anti-IIa ratios are used, superiority over unfractionated heparin is observed. Because of the risk of rebound clinical events following acute-phase treatment, the benefit of continuing antithrombotic therapy in the chronic phase requires testing.

Based on all the available evidence to date, I anticipate that LMWH preparations will be used more frequently across the entire spectrum of acute coronary syndromes. The results of ongoing trials, as well as the cost and ease of use of the new agents, will influence the transition away from unfractionated heparin.

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Appendix

Initialism	Name	Focus of investigation
ARGAMI	Argatroban in Myocardial Infarction	argatroban vs.heparin in tPA-treated patients with ST-elevation MI
ESCALAT	Efegatran and Streptokinase to Canalize Arteries Like Accelerated tPA	efegatran + streptokinase vs.heparin + tPA in patients with ST elevation MI
ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in non-Q-wave Coronary Events	enoxaparin vs.unfractionated heparin in unstable angina/non-Q MI
FRIC	Fragmin in Unstable Coronary Artery Disease	dalteparin vs.heparin in unstable angina/non-Q MI
FRISC	Fragmin During Instability in Coronary Artery Disease	dalteparin vs.placebo in unstable angina/non-Q MI
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries	IIa and IIb = hirudin vs.heparin in acute coronary syndromes
HART	Heparins and Reperfusion Therapy	enoxaparin vs.heparin in tPA-treated patients with ST-elevation MI
HERO	Hirulog Early Reperfusion/Occlusion	hirulog vs.heparin in streptokinase-treated patients with ST-elevation MI
MINT	Myocardial Infarction using Novastan and tPA	argatroban vs.heparin in tPA-treated patients with ST elevation MI
OASIS	Organization to Assess Strategies for Ischemia Syndromes	hirudin vs.heparin in patients with unstable angina/non-Q MI
PRIME	Promotion of Reperfusion in Myocardial Infarction	efegatran vs.heparin in tPA-treated patient with ST-elevation MI
TIMI	Thrombolysis in Myocardial Infarction	9A and 9B = hirudin vs.heparin in ST-elevation MI patients treated with either tPA or streptokinase 11A = dose-ranging trial of enoxaparin in unstable angina/non-Q MI 11B = double-blind trial of enoxaparin vs.heparin in unstable angina/non-Q MI

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Dr. Antman's research interests involve the clinical pharmacology of cardiovascular agents and their evaluation in randomized clinical trials. He is a senior investigator in the TIMI research program and is the principal investigator of the TIMI 11, TIMI 14, and TIMI 17 trials dealing with new treatments for acute coronary syndromes. These ongoing projects are evaluating the following novel anti-ischemic therapies: LMWH for unstable angina, ReoPro and thrombolytics for MI, and lanoteplase for MI. Additional research interests of Dr. Antman include the use of new serum markers such as the cardiac-specific troponins for prognostication in acute coronary syndromes, and biostatistical techniques such as meta-analysis for synthesis of the results of randomized trials.

Editor's note: This issue marks the first *Cardiology Rounds* publication since the official announcement by Dr. Victor Dzau that, after an extensive national search, Dr. Peter Libby has been chosen as the next Chief of the Cardiovascular Division of the Brigham and Women's Hospital. Dr. Libby was chosen for his demonstrated abilities, vision,creativity, and impeccable standards as a clinician-investigator. The Cardiovascular Division members are confident that Dr. Libby will continue the tradition and legacy of leadership in clinical medicine and research established by the late Dr. Thomas W. Smith. We welcome Dr. Libby as our new chief and look forward to working with him to address the issues that will confront academic cardiology in the 21st century.

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