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Recent Advances in Antithrombin Therapy for Acute Coronary Syndromes

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CHEN AND LAU: Recent Advances in Antithrombin Therapy for Acute Coronary Syndromes. *Unstable angina and acute myocardial infarction are leading causes of hospital admissions worldwide. Following the initiating event of atherosclerotic plaque rupture, activation of the coagulation cascade plays an important role in mediating local thrombosis. Novel antithrombotic agents have recently been developed and applied in clinical practice. The direct antithrombins have the advantage of inhibiting both fluid-phase and clot-bound thrombin. Despite a sound theoretical basis, the prototypical agent hirudin has been demonstrated to be only equivalent to unfractionated heparin as adjunctive therapy to thrombolysis in ST-elevation myocardial infarction. Although showing a better efficacy than unfractionated heparin in unstable angina/non-Q wave myocardial infarction, hirudin causes more major bleeding complications. Low-molecular-weight heparins have the advantages of a better bioavailability, longer half-life and dose-independent clearance, making subcutaneous administration possible and monitoring unnecessary. Enoxaparin has been proven to be superior to unfractionated heparin in two large randomised trials of unstable angina/non-Q wave myocardial infarction while equivalence is demonstrated for other low-molecular-weight heparins. A higher anti-Xa:anti-IIa ratio may explain the varying efficacy. In the near future low-molecular-weight heparins and newer antithrombin agents may replace unfractionated heparin in the management of acute coronary syndromes as ongoing clinical trials further define their roles. (J HK Coll Cardiol 1999;7:109-118)*

摘要

不穩定型心絞痛和急性心肌梗死是在世界範圍內住院的主要原因。動脈粥樣硬化斑塊破裂起動事件發生後，凝血級聯反應的激活在介導局部血栓形成的過程中起有重要作用。最近，已開發出新的抗血栓藥物並已應用於臨床。直接的抗凝酶藥物具有同時抑制液相和血凝塊結合的凝血酶的優勢。儘管有堅實的理論基礎，已證明在ST段抬高的心肌梗死中，作為溶栓的輔助治療，原始型藥物水蛭素的作用僅和普通肝素的作用相當。儘管在不穩定型心絞痛/非Q波心肌梗死中水蛭素顯示比普通肝素更好的效能，但其引起了更多的嚴重出血併發症。低分子肝素有更好的生物利用度的優勢、更長的半衰期和劑量依賴的清除率，使得皮下注射成為可能且無需進行監測，在兩個不穩定型心絞痛/非Q波心肌梗死的大規模隨機試驗中，已證明Enoxaparin的效能優於普通肝素，而其它低分子肝素與普通肝素療效等同。較高的抗-凝血因子Xa；抗-凝血因子IIa比率有可能解釋不同的效果。在不遠的將來，隨着正在進行的臨床試驗進一步確定其的作用，低分子肝素和新的抗凝血酶藥物可能在治療急性冠狀動脈綜合征中取代普通肝素。

Introduction

Every year more than four million patients are admitted to hospitals worldwide with the diagnosis of unstable angina (UA) or acute myocardial infarction (MI). The initiating event is rupture of an atherosclerotic

plaque followed by local thrombosis. The classic view of the coagulation cascade postulated that two independent pathways converged on the activation of factor X. 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. In vivo, activation of factor VII by tissue factor is the key step in the initiation of coagulation and the intrinsic pathway is not considered important. Tissue factor, a protein found on the membrane of many different cell types, is not normally exposed to blood elements but is expressed following

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injury to activated endothelial cells. It is also found in the subendothelial matrix that is exposed after intimal injury.

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 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 X 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 is the major component of haemostasis in both the fluid phase and the clot-bound phase.

In addition to the coagulation cascade being activated, platelets adhere to the subendothelial matrix at the site of plaque rupture, release thromboxane A₂, serotonin, and adenosine diphosphate, and amplify the generation of thrombin.¹ 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 IIb/IIIa receptors on multiple platelets, providing cross-linking and propagation of a platelet aggregate.

When coronary blood flow is reduced significantly, patients experience ischaemic discomfort. Complete occlusion of the culprit vessel results in ST segment elevation on the electrocardiogram, and most

of these patients ultimately develop a Q-wave MI (QWMI). A small proportion of patients may sustain only a non-Q-wave MI (NQWMI). 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 UA or, if a serum cardiac marker indicative of myocardial necrosis is detected (e.g. creatine kinase MB, troponin I or T), as having a NQWMI. A minority of patients who initially present without ST segment elevation might ultimately develop a Q-wave MI. The various presentations from UA through NQWMI and QWMI are collectively referred to as the acute coronary syndromes (ACS; figure 2).²

While avoidance of smoking, improved diet and exercise, treatment of hypertension, use of aspirin and management of dyslipidaemia will reduce the incidence of ACS, medical treatment to interrupt the cascade towards thrombin formation constitutes a major advance in cardiology. The role of novel antiplatelet agents has recently been highlighted.³ The purpose of the present article is to review the role of drugs on the coagulation cascade.

Antithrombin therapy for acute coronary syndromes

Thrombin is an important molecule in the ACS

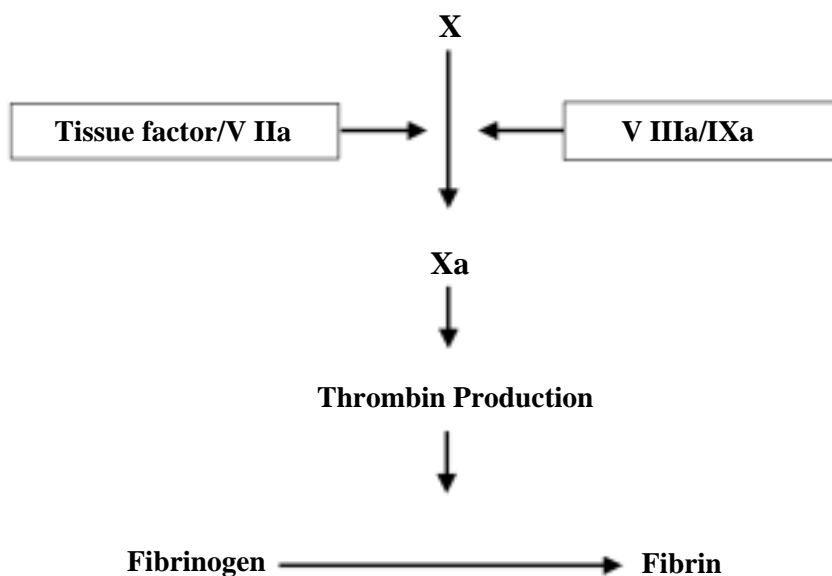


Figure 1. Activation of the coagulation cascade

because of its extensive procoagulant and prothrombotic actions.⁴ In addition to catalyzing the transformation of soluble fibrinogen to 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 for platelet adhesion, activation, 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 neutralised by either direct or indirect inactivation and by inhibition of thrombin production via the intrinsic or extrinsic limbs of the coagulation cascade.⁴

Because of thrombin's central role in the pathogenesis of UA and acute MI, antithrombin therapy is applicable across the entire spectrum of ACS. The standard agent used in clinical practice is heparin. Unfractionated heparin (UFH) is a glycosaminoglycan, consisting of chains of alternating residues of D-glucosamine and uronic acid.⁵ Clinically available preparations of UFH are heterogeneous mixtures of polysaccharide chains ranging in molecular weight from 3,000 to 30,000 daltons. UFH exerts its anticoagulant effect by activating antithrombin III (AT III). The mechanism involves binding to a unique pentasaccharide sequence that is randomly distributed

along the heparin chains. The binding results in a conformational change in AT III, accelerating its ability to inhibit thrombin and factor Xa by about a thousand-fold.⁵

Despite familiarity to many clinicians, UFH has the following disadvantages: (1) a variable anticoagulant effect (requiring frequent activated partial thromboplastin time [aPTT] monitoring), (2) neutralization by platelet factor 4, (3) less effective inhibition of clot-bound versus fluid-phase thrombin, and (4) the potential to cause thrombocytopenia and heparin-induced thrombocytopenia syndrome (HITS).⁵⁻⁷

Several novel antithrombin regimens have been proposed. One involves using a closed-loop feedback system that automatically measures the patient's aPTT and adjusts an infusion of UFH to maintain the level of anticoagulation in the target aPTT range. Alternative approaches have focused on new pharmacologic agents. The agents most extensively investigated in clinical trials include the AT III-independent (or direct) antithrombins and the low-molecular-weight heparins (LMWHs).

Direct antithrombins

Direct antithrombins are novel anticoagulants that inhibit thrombin directly without requiring the cofactor

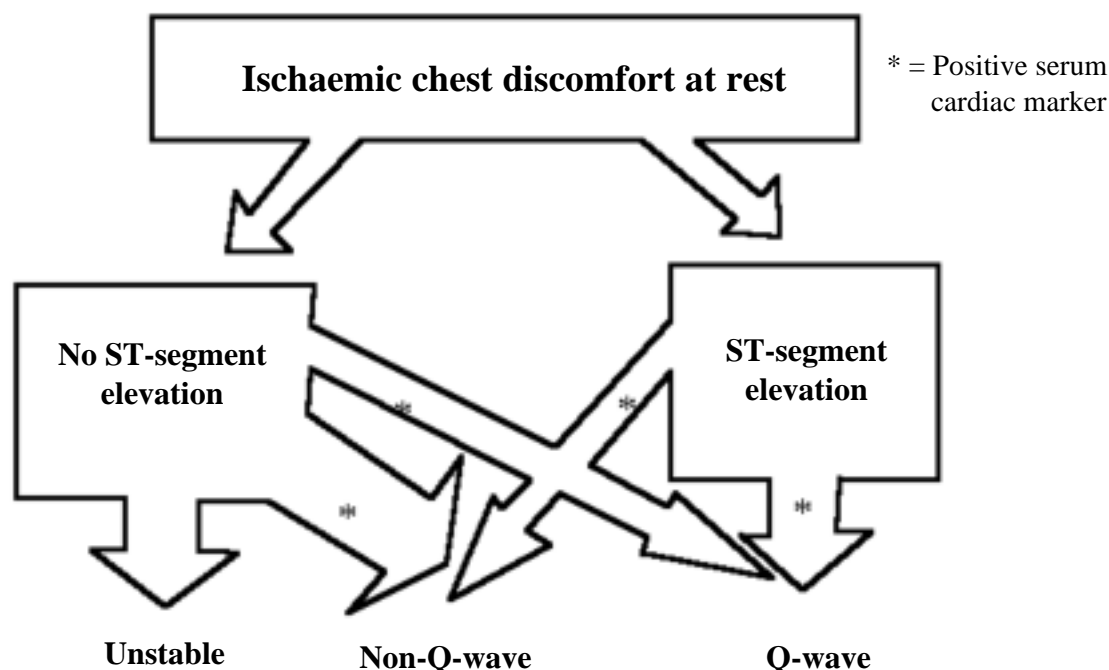


Figure 2. Acute coronary syndromes

AT III. Although a variety of direct antithrombins have been identified, those that have undergone clinical investigation to date include hirudin, hirulog, argatroban, efegatran, and inogatran.⁸⁻¹⁰ All of the direct antithrombins exhibit a concentration-dependent anticoagulant effect. Because of their tight binding to thrombin, hirudin and hirulog are virtually irreversible thrombin inhibitors while argatroban, efegatran, and inogatran are reversible inhibitors. Although in-vitro differences among the various direct antithrombins have been identified (e.g., binding characteristics to thrombin, ability to inhibit thrombin generation), it is unclear whether these differences will have any important impact on the clinical use of the direct antithrombins.¹¹

Hirudin is a prototype of the direct antithrombins and has been extensively studied. The carboxy terminus of hirudin binds to the substrate recognition site on thrombin, while the amino terminus inhibits the catalytic center of thrombin.⁸ Since clot-bound thrombin is less effectively inhibited by UFH (because the attachment of fibrin to the fibrin-binding domain makes the heparin-binding domain inaccessible, figure 3), it has been suggested that the direct antithrombins have a greater ability than UFH to inhibit both fluid-phase and clot-bound thrombin.¹² This concept has been referred to as the "thrombin hypothesis" and was the inspiration for several randomised controlled trials.

Trials of direct antithrombins as adjunctive therapy to thrombolysis in ST-segment-elevation ACS

Based on the initial favorable observations in the phase-II Thrombolysis in Myocardial Infarction (TIMI) 5 and 6 trials,¹³⁻¹⁴ several phase-III trials of direct antithrombins as adjunctive therapy to thrombolysis were undertaken.¹⁵⁻¹⁷ Table 1 summarises the main features of the TIMI 9A, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa, and r-hirudin for Improvement of Thrombolysis (HIT-III) trials. TIMI 9A and HIT-III focused on patients with ST-segment-elevation MI, and GUSTO IIa enrolled patients with clinical presentations across the ACS spectrum. A feature common to all three trials was that they were stopped prematurely because of unacceptable rates of major haemorrhages, particularly intracranial hemorrhage. Possible reasons include high levels of anticoagulation in both the heparin and hirudin groups in TIMI 9A and GUSTO IIa, a low estimate of the haemorrhagic risk at the doses of hirudin used in the previous phase-II trials, and attempts to push the heparin dose to achieve higher aPTT levels to prevent reocclusion of successfully reperfused vessels.¹⁴ As a result of these findings, the doses of both heparin and hirudin were reduced and the TIMI 9B and GUSTO IIb

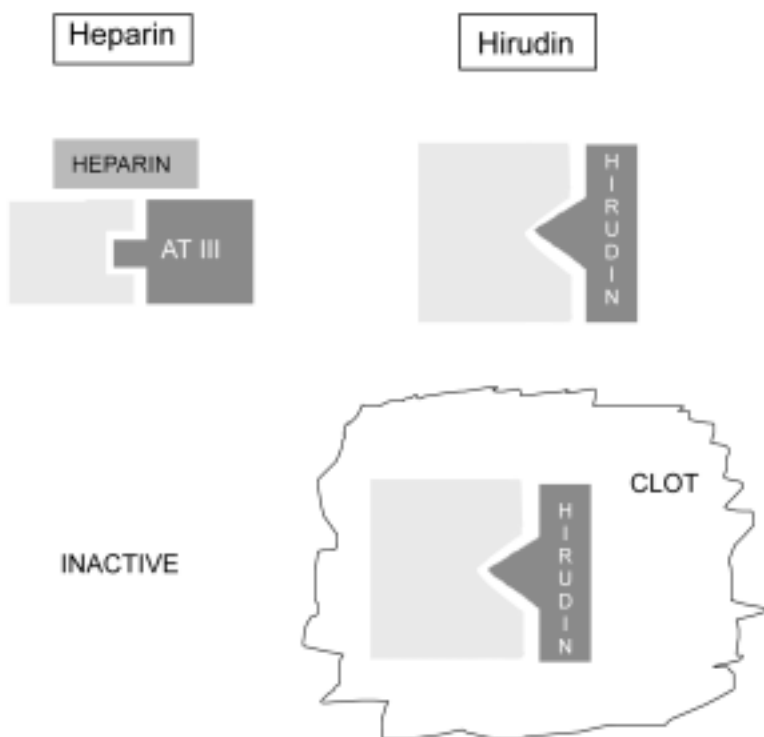


Figure 3. Comparative mechanisms of action of heparin and hirudin. Heparin inactivates fluid-phase thrombin via the action of AT III, but is ineffective for clot-bound thrombin as the heparin-binding domain is inaccessible. Hirudin binds to the substrate recognition site of thrombin, and is active for both fluid-phase and clot-bound thrombin.

trials were undertaken.

In TIMI 9B, patients were treated with either tissue plasminogen activator (tPA) or streptokinase (SK) at the physician's discretion and received a 96-hour infusion of either hirudin or heparin.¹⁸ The rate of development of the primary endpoint (death, recurrent nonfatal MI, 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 ($p = \text{NS}$). In addition, there was no significant difference in the secondary endpoint of death and recurrent nonfatal MI.

In the GUSTO IIb trial, patients were stratified into those presenting with ST-segment elevation ($N = 4,131$) or without ST-segment elevation ($n = 8,011$). Hirudin or heparin was infused for a minimum of 3 days and a maximum of 5 days. The primary endpoint (death or nonfatal MI at 30 days) occurred in 9.8% of the heparin group and 8.9% of the hirudin group ($p = 0.06$).¹⁹

A meta-analysis of the GUSTO IIb and TIMI 9B trials showed that hirudin was more effective than heparin at achieving and maintaining the target aPTT range. Major bleeding could be reduced by careful adjustment of both hirudin and heparin. 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.²⁰ The evidence suggests that, in the clinically acceptable dose range, UFH and hirudin are equivalent antithrombin strategies in patients with an ACS.

Hirulog has been evaluated as adjunctive therapy to SK for ST-segment-elevation MI by several investigators. An unusual dose response was observed during analysis of the Hirulog Early Reperfusion/Occlusion (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-3 flow²¹

at 90 minutes, while high-dose (1 mg/kg/hr) produced a 61% rate of TIMI-3 flow.²² 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-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).²³ 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 maximise the degree of inhibition of thrombin activity.

Dose-ranging phase-II angiographic trials have also been performed with efegatran (Promotion of Reperfusion in Myocardial Infarction [PRIME]²³ and [ESCALAT] studies)²⁴ and agatrobato (Argatroban in Myocardial Infarction [ARGAMI]).²⁵ Despite a sound theoretical basis for anticipating improvements in the rate of TIMI-3 flow when these direct antithrombins were compared with UFH, either no improvement was seen or only slightly higher rates of TIMI-3 flow were observed. Although initially promising, no additional benefits of direct antithrombin are seen in ST-segment-elevation MI.

Trials of direct antithrombins in UA/NQWMI

The direct antithrombin inogatran has been evaluated in the Thrombin Inhibition in Myocardial Infarction (TRIM) study.¹⁰ A total of 1,209 patients with UA received a 72-hour treatment with a low, medium or high dose of inogatran or UFH. Although a dose-

Table 1. Hirudin vs. heparin for acute myocardial infarction

	TIMI 9A	GUSTO IIa	HIT-III
Rx window	12 h	12 h	6 h
Lytic	tPA, SK	tPA, SK	tPA
Heparin	1000 U/h <80 kg 1300 U/h >80 kg	1000 U/h <80kg 1300 U/h >80kg	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

dependent prolongation of the aPTT with a greater stability of the anticoagulant effect compared with UFH was observed in inogatran-treated patients, the primary endpoint of death, recurrent MI, and refractory or recurrent ischaemia was not reduced by inogatran.

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study compared UFH 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 909 patients with UA or suspected acute MI without ST-elevation.²⁶ The aPTT was monitored every 6-8 hours and was maintained between 60-100 seconds. The medium-dose hirudin group had a significant reduction in the risk of cardiovascular death, MI, or refractory ischaemia at 7 days. As this trial was only moderate in size, a larger OASIS-2 trial was conducted to extend the pilot study results and investigated whether hirudin is superior to UFH in reducing the risk of cardiovascular death or MI at 7 days (primary outcome) and the composite of cardiovascular death, MI, or refractory angina at 7 days (secondary outcome). Patients were randomised to receive UFH (5000 units bolus then 15 units/kg/hr; n = 5058) or hirudin (0.4 mg/kg bolus then 0.15 mg/kg/hr; n = 5083) for 72 hours. There were no significant differences among the treatment groups for the primary outcome (3.6% in the hirudin group and 4.2% in the UFH group; p = 0.077). The secondary outcome was significantly reduced in the hirudin group compared with the UFH group (5.6% vs 6.7% respectively; p = 0.0125). There was an excess of major bleeding

requiring transfusion with hirudin (1.2% vs 0.7% with UFH; p = 0.01), although there was no difference in life-threatening episodes (20 in each group) or strokes (14 in each group).²⁷ The data suggest that hirudin is superior to UFH in reducing cardiovascular death, MI, or refractory angina in patients with non-ST-elevation ACS but at a cost of increased bleeding complications.

Low-molecular-weight heparins

LMWH preparations are produced by controlled enzymatic or chemical depolymerization of UFH to yield chains with a mean molecular weight of 5000.⁵ Both UFH and LMWHs exert their anticoagulant effect by activating AT-III, mediated through binding of a pentasaccharide sequence. Figure 4 illustrates that a critical length of 18 saccharides is required to form the ternary complex consisting of a heparin fragment, AT-III, and thrombin. In addition to the pentasaccharide sequence discussed above that is critical for attachment of a heparin fragment to AT-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.

Short-chain or LMWH 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.

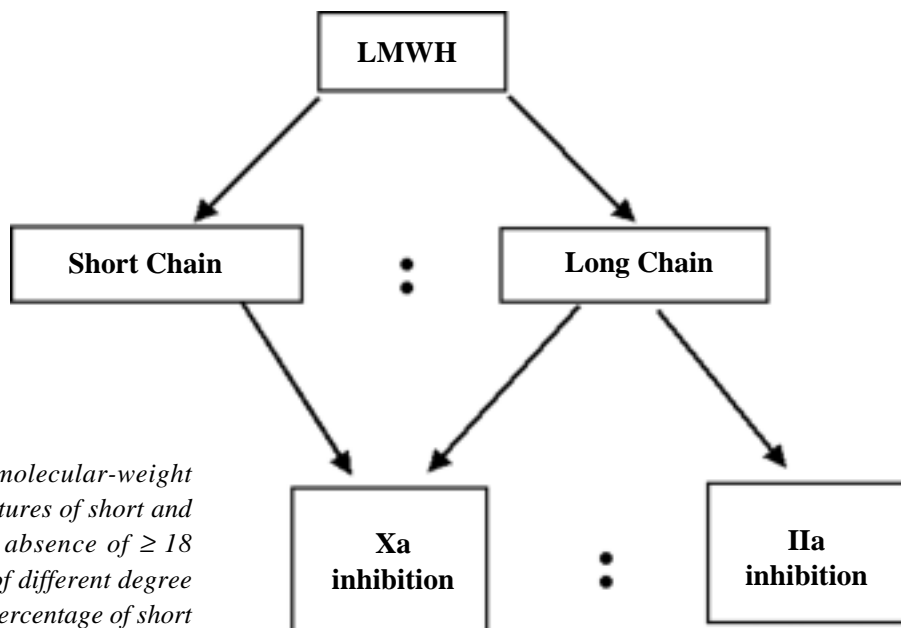


Figure 4. Mechanism of action of low-molecular-weight heparins. LMWHs consist of varying mixtures of short and long chain components (presence and absence of ≥ 18 saccharide units, respectively), capable of different degree of factor IIa and Xa inhibition. A higher percentage of short chain components enables a more potent anti-Xa activity.

However, only the critical pentasaccharide sequence is required for binding to AT-III and inhibiting factor Xa. 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). 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.

Decreased binding to plasma proteins, endothelial cells and macrophages explains the pharmacokinetic differences between UFH and LMWHs. LMWHs have a better bioavailability, longer half-life, and dose-independent clearance. Thus, a more reliable, stable anticoagulant effect is produced. Laboratory monitoring is unnecessary except in patients with renal insufficiency and possibly those with a body weight of less than 50 kg or more than 80 kg.⁵ Together with the ease of administration by the subcutaneous route, a decreased sensitivity to inactivation by platelet factor IV and lower rates of thrombocytopenia and HITS, LMWHs are clinically attractive alternatives to UFH.

Trials of LMWHs in UA/NQWMI

Gurfinkel and colleagues²⁸ compared placebo treatment, UFH, and the LMWH nadroparin in 219 patients with UA who were also treated with aspirin. In this single-blind study, patients were randomised to receive aspirin (200 mg/day), aspirin plus UFH (5,000 units bolus IV, followed by IV infusion of 400 units/kg/day, with a target APTT of 2 times control), or aspirin plus nadroparin (214 IU/kg SC twice daily). 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 terminated prematurely on a recommendation from the Data Safety Monitoring Committee. Combination therapy with

aspirin plus nadroparin significantly reduced the incidence of a primary endpoint event from 59% in the aspirin group and 63% in the aspirin plus UFH 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 and were largely related to cardiac catheterisation access sites.

Following the Gurfinkel study, two larger trials examining the LMWH dalteparin (Fragmin) were reported. The Fragmin During Instability in Coronary Artery Disease (FRISC)²⁹ trial tested whether SC administration of dalteparin would reduce ischemic events during the acute in-hospital period following an episode of UA/NQWMI. A secondary goal was to determine whether long-term anticoagulation therapy would provide additional benefit compared with anticoagulation restricted to the acute phase (the first few days following hospitalisation). Patients presenting within 72 hours of the onset of UA/NQWMI 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. Dalteparin-treated patients had a 63% reduction in death and nonfatal MI at the 6-day analysis (4.8% in the placebo group compared with 1.8% in the dalteparin group, $p = 0.001$). With longer-term follow-up, event rates for the two groups began to converge, and a non-significant trend toward improved outcome was observed in the dalteparin group by 40 days (10.7% for the placebo group compared with 8.0% in the dalteparin group, $p = 0.07$). By 150 days, there was no significant difference between the two groups.

The Fragmin in Unstable Coronary Artery Disease (FRIC)³⁰ study compared dalteparin with UFH in patients with UA/NQWMI presenting within 72 hours of an episode of ischaemic chest pain. During the acute phase (the first 6 days following hospitalisation),

Table 2. Low-molecular-weight heparin preparations

Preparation	Method of Preparation	Mean Molecular Weight (Dalton)	Anti-Xa: Anti-IIa Activity*
dalteparin (Fragmin)	nitrous acid depolymerization	6000	2.7
enoxaparin (Clexane)	benzylation and alkaline depolymerization	4200	3.8
nadroparin (Fraxiparine)	nitrous acid depolymerization	4500	3.6
reviparin (Clivarine)	nitrous acid depolymerization, chromatographic purification	4000	3.5
tinzaparin (Innohep)	heparinase digestion	4500	1.9

patients received either twice-daily SC dalteparin or IV UFH for 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 the composite endpoint was 12.3% for both groups.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE)³¹ trial examined the use of enoxaparin in UA/NQWMI. This large, multicentre, double-blind trial randomised 3,171 patients within 24 hours of onset of ischaemic chest pain to receive either twice-daily SC enoxaparin (1 mg/kg), or IV UFH during the acute period (2-8 days) following hospitalisation. The primary endpoint was a composite of death, MI, or recurrent angina within 14 days of hospitalisation. 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%, $p = 0.019$). The enoxaparin group 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 ($p = 0.016$). The incidence of major bleeding complications was similar between the two groups.

The FRAX.I.S study compared the efficacy and safety of the treatment with UFH versus a 6-day or a 14-day treatment with nadroparin in patients with UA or NQWMI.³² Altogether 3,468 patients presenting within 2 days of the qualifying episode of ischaemic pain were randomized to one of the 3 groups: UFH 5,000 IU bolus IV followed by infusion for 6 days, nadroparin bolus followed by SC 87 IU/kg twice daily for 6 days in the short term group, and twice daily for 14 days in the longer term group. The primary endpoint was a composite of cardiovascular death, MI, or refractory or recurrent angina at 2 weeks. There was no significant difference in the primary endpoint between the three groups: 18.1% for the UFH group, 17.8% for the 6-day and 20% for the 2-week nadroparin groups. Major haemorrhages occurred more often in the long term nadroparin group (3.5%) than the UFH group (1.5%) and the short term nadroparin group (1.6%).

The TIMI 11B trial assessed the effect of enoxaparin compared to UFH on death and cardiac ischaemic events in the management of UA/NQWMI.³³ Eligible patients (presenting within 24 hours of onset of ischaemic chest pain; $n = 3,910$) were treated

with aspirin and randomised to double-blind treatment with either UFH (70 units IV bolus followed by 15 units/kg/hr to maintain the aPTT 1.5-2.5 times control) for at least 3 days or enoxaparin (30 mg IV bolus followed by 1 mg/kg SC twice daily) for an average of 4.6 days. Following treatment in the acute phase, eligible patients proceeded to the chronic phase and received enoxaparin or placebo up to day 43 (enoxaparin 40 mg SC daily for those < 65 kg; 60 mg SC daily for those ≥ 65 kg). The primary endpoint of all-cause mortality/recurrent MI/recurrent ischaemia prompting urgent revascularisation at day 14 was reduced from 16.6% in the UFH group to 14.2% in the enoxaparin group ($p = 0.03$). All individual elements of the composite endpoint were reduced in the enoxaparin group. There was no increase in the rate of either spontaneous or instrumented major haemorrhage. The initial benefit of enoxaparin therapy was maintained in the chronic phase (primary endpoint event rate of 19.7% for the placebo group vs. 17.3% for the enoxaparin group, $p < 0.05$) but there was no additional relative decrease in events. There was an increase in the rate of major haemorrhage (both spontaneous and instrumented; placebo group 1.5% vs. enoxaparin group 2.9%, $p < 0.05$). In a meta-analysis of TIMI 11B and ESSENCE, enoxaparin was associated with a significant 20% reduction in the incidence of death and MI compared with UFH.

Conclusions

It seems likely that UFH will be used less frequently in the future when the role of newer antithrombin agents and LMWHs is clarified by additional research. Based on the evidence from clinical trials to date, the direct antithrombins provide a more consistent anticoagulant effect compared with UFH. However, the therapeutic window appears to be much narrower than originally appreciated. Within the range of clinically acceptable doses to minimise bleeding complications, the direct antithrombins have similar efficacy to UFH in ST-elevation acute MI. Although demonstrated to be superior to UFH in reducing ischaemic cardiac events in non-ST-elevation ACS, hirudin produces more major bleeding complications than UFH. Considering the efficacy, safety, and ease of administration, hirudin is a less attractive alternative compared with LMWHs to be used in UA/NQWMI.

Despite sharing many pharmacologic similarities, LMWHs vary in significant aspects. It is important to consider each drug individually rather than as a member of a class of interchangeable compounds. The varying efficacy of LMWHs in clinical trials might reflect

differing anti-Xa:anti-IIa ratios. Having an in-vitro anti-Xa:anti-IIa ratio of 3.8, enoxaparin has been shown in two large randomised trials to reduce ischaemic events following UA/NQWMI. Although the evidence is less strong, nadroparin, which has an anti-Xa:anti-IIa ratio of 3.6, also appears to be superior to UFH in this setting. On the other hand, dalteparin appears to be less effective, possibly related to an anti-Xa:anti-IIa ratio of 2.2 only. However, it is also possible that the lack of sustained effect of dalteparin in the FRISC and FRIC trials was due to the long patient enrollment period after the episode of qualifying chest pain (72 hours in both studies), in contrast to a 24-hour enrollment period in most other studies.

It is anticipated that LMWHs will be used more frequently in patients with ACS and UFH may be replaced as the role of LMWHs is further defined by ongoing clinical trials.

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