Low-Molecular-Weight Heparins
An Intriguing New Twist With Profound Implications
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Modern antithrombotic therapy for acute coronary syndromes rests on a growing body of basic and clinical evidence that rupture or erosion of the surface of a vulnerable plaque sets in motion a sequence of events culminating in thrombus formation in the culprit vessel. When the contents of a vulnerable plaque are exposed to the bloodstream, platelets adhere to the subendothelial matrix, release ADP and thromboxane A₂, and amplify the generation of thrombin. As a result, a platelet aggregate begins to develop. In addition, the coagulation cascade is activated and fibrin strands are formed.

Importance of Thrombin
Thrombin (factor IIa) plays a pivotal role in the processes described above because of its extensive procoagulant and prothrombotic actions. 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 adhesion, activation, and aggregation. In vessels with a diseased endothelium, thrombin promotes the release of the vasoconstrictor endothelin 1. Importantly, thrombin also potentiates the proliferative effects of multiple growth factors and is a key mediator of early smooth muscle cell proliferation after arterial injury.

There is now abundant evidence that thrombus formation can be prevented by direct or indirect inactivation of thrombin or by inhibition of thrombin production via the intrinsic or extrinsic limbs of the coagulation pathway. Unfractionated heparin, the standard antithrombotic agent in clinical practice, is a glycosaminoglycan, consisting of chains of alternating residues of β-glucosamine and uronic acid. Although familiar to the vast majority of clinicians, unfractionated heparin has several disadvantages: (1) a variable anticoagulant effect (necessitating frequent monitoring of activated partial thromboplastin time), (2) neutralization by platelet factor 4, (3) less effective inhibition of clot-bound thrombin versus fluid-phase thrombin, and (4) the potential to cause thrombocytopenia and HITS with paradoxical thrombosis.

Potential Advantages of LMWHs
There is increasing interest in LMWH preparations as an alternative form of antithrombin therapy. They are formed by controlled enzymatic or chemical depolymerization producing saccharide chains of varying lengths but with a mean molecular weight of ≈5000. Much of the discussion regarding potential advantages of the LMWHs centers around their enhanced ratio of anti-Xa:anti-IIa activity. The explanation for this is that a chain length of ≈18 saccharides is required to form a ternary complex between heparin, antithrombin, and thrombin. A critical pentasaccharide sequence is required for attachment of a heparin fragment to antithrombin, and 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. LMWH fragments of <18 saccharides retain the critical pentasaccharide sequence, which is all that is required for formation of a Xa:antithrombin:heparin complex.

It has been argued that the enhanced anti-Xa:IIa ratio offered by the LMWHs provides a therapeutic benefit. Because factor Xa generation occurs several steps earlier in the coagulation cascade than thrombin generation, inhibition of Xa has a profound effect on the later steps in coagulation. Put another way, there is a distinct kinetic advantage to inhibiting early reactions in coagulation: quenching a small amount of Xa may prevent the formation of much larger quantities of thrombin. Other features of LMWHs that are of particular clinical relevance are a decreased sensitivity to platelet factor 4 and a more predictable anticoagulant effect along with lower rates of thrombocytopenia and HITS. In addition, the LMWHs are clinically attractive because of better bioavailability, a more consistent pattern of clearance, and ease of administration via the subcutaneous route. In theory, they allow clinicians to prescribe relatively unsupervised long-term self-administration of antithrombotic therapy by patients at home (ie, “an insulin-like injection for coronary artery disease”).

Additional Antithrombotic Properties of LMWHs
In addition to the anti-Xa activity discussed above, another antithrombotic property of these agents bears discussion. The lipid-rich core of exposed atherosclerotic plaques has abundant supplies of tissue factor, which results in activation of factor VII and stimulation of the extrinsic limb of the coagulation cascade, ultimately leading to formation of factor Xa. TFPI is a 276-amino-acid protease inhibitor that binds to factor Xa and inactivates the tissue factor:VIIa:Xa complex. TFPI circulates...
largely bound to lipoproteins in plasma but can be released after administration of both unfractionated heparin and LMWHs. Each LMWH has a unique TFPI release profile that is also distinct from its anti-Xa activity.\textsuperscript{30} Given the higher bioavailability and more consistent blood concentration of the heparin-like activity of LMWHs, one might speculate that they may also release TFPI more efficiently than unfractionated heparin.

**Clinical Trials of LMWHs in UA/NQMI**

Beginning with the initial encouraging open-label trial with nadroparin (anti-Xa:anti-IIa ratio of 3:1) conducted by Gurfinkel and colleagues,\textsuperscript{11} a series of trials of LMWHs in the management of UA and NQMI have been undertaken in the past several years.\textsuperscript{15} The FRISC trial demonstrated that dalteparin (anti-Xa:anti-IIa ratio of 2:1) was superior to placebo for the acute-phase management of UA/NQMI.\textsuperscript{12} However, with longer-term follow-up and continued treatment with a once-daily injection of dalteparin, event rates for the dalteparin and placebo groups began to converge, and there was no significant difference in event rates in the 2 groups by 150 days. The FRIC trial demonstrated equivalence between dalteparin and intravenous unfractionated heparin during the acute-phase management of patients with UA/NQMI.\textsuperscript{13} The ESSENCE study showed, after a median duration of treatment of 2.6 days, a 16.2% reduction in the relative risk of death, MI, or recurrent ischemia in the group treated with enoxaparin (anti-Xa:anti-IIa ratio of 3:1) compared with unfractionated heparin.\textsuperscript{14} It has been argued that the superiority of nadroparin and enoxaparin compared with unfractionated heparin is derived in part from their anti-Xa:anti-IIa ratios of 3:1. LMWHs with a lower anti-Xa:anti-IIa ratio, such as dalteparin (2:1), appear to be equivalent to unfractionated heparin in the acute phase of UA/NQMI management.

**Intriguing New Data on LMWH Preparations**

In this issue, Montalescot and colleagues report the results of a French substudy from the ESSENCE trial.\textsuperscript{15} This substudy sheds new light on another potential difference between unfractionated heparin and enoxaparin that may translate into a clinical advantage. The purpose of the substudy was to evaluate the prognostic value of a variety of markers of inflammation, hemostasis, myocardial necrosis, and the vasoconstrictor peptide endothelin 1. The essential observations of Montalescot and coworkers are that the baseline levels of such acute-phase markers as C-reactive protein, fibrinogen, and von Willebrand factor were all elevated when patients were admitted and that these markers increased further over the next 48 hours, consistent with the concept of an ongoing inflammatory process. However, only the increment in von Willebrand factor during this 48-hour period was an independent predictor of adverse clinical outcome at both 14 and 30 days of follow-up. Although elevations of von Willebrand factor have been reported previously in patients with acute coronary syndromes,\textsuperscript{16,17} the unique contribution of the French substudy is the finding that enoxaparin blunted the increase in von Willebrand factor compared with unfractionated heparin. Why is this observation potentially so important, and what are its implications?

*von Willebrand factor* is a heterogeneous, multimeric plasma glycoprotein with 2 major functions: (1) It promotes platelet interaction with the damaged vessel wall under conditions of high shear stress by binding to the platelet glycoprotein Ib and IIb/IIIa receptors, and (2) it is the carrier of factor VIII, an essential cofactor in the generation of factor Xa. Binding of factor VIII to von Willebrand factor protects factor VIII from inactivation by activated protein C.

von Willebrand factor can also promote platelet aggregation by cross-linking multiple activated platelets. Although fibrinogen is the predominant plasma molecule that binds to the activated glycoprotein Ib/IIa receptor, this is related in part to the higher concentration of fibrinogen compared with von Willebrand factor. Given its combined effects on platelet adhesion/aggregation and its procoagulant effect, von Willebrand factor plays an important role in thrombus formation and propagation. The multiplier effects and feedback loops involved in the dynamic interplay between the coagulation cascade and platelet aggregation promote the release of additional stores of von Willebrand factor from the \( \alpha \)-granules of platelets and the Weibel-Palade bodies of endothelial cells.\textsuperscript{18}

Previous epidemiological observations suggest that an elevated level of von Willebrand factor is a risk factor for the development of coronary heart disease. In addition, elevated levels of von Willebrand factor have been reported in patients with acute MI, with UA, and after coronary angioplasty.\textsuperscript{16–19} An elevated von Willebrand factor level may arise from a combination of increased biosynthesis, perhaps mediated by inflammatory cytokines, or enhanced release of preformed von Willebrand factor stored in endothelial cell Weibel-Palade bodies. Successful coronary reperfusion with thrombolysis blunts the rise in von Willebrand factor levels after acute MI.\textsuperscript{16}

What does all this information about von Willebrand factor have to do with heparin fragments, and where does enoxaparin fit in? Structure-function studies of von Willebrand factor have begun to identify key domains of the molecule.\textsuperscript{15} In addition to domains responsible for binding to factor VIII and the glycoprotein Ib and IIb/IIIa receptors, there are also heparin-binding domains on the von Willebrand factor molecule. Sobel et al\textsuperscript{20,21} showed that unfractionated heparin as well as specific novel fractions of standard heparin are capable of binding to von Willebrand factor via its heparin-binding domain and inhibiting platelet interactions with von Willebrand factor.

The data from Montalescot et al\textsuperscript{15} raise several hypotheses. It is possible that enoxaparin is more efficient than unfractionated heparin in binding to the heparin-binding domain of von Willebrand factor, ultimately leading to less von Willebrand factor–dependent platelet adhesion and aggregation and the release of less von Willebrand factor from platelet \( \alpha \)-granules. Alternatively, or in addition, the greater anti-Xa activity of enoxaparin compared with unfractionated heparin may result in less thrombin generation, which could also lead to less platelet activation and smaller amounts of von Willebrand factor released from...
storage depots. It is also possible that LMWHs may decrease the rate of von Willebrand factor synthesis by endothelial cells.

Given the small sample size of the Montalescot study (n=68), it is appropriate to interpret the data cautiously and consider them to be hypothesis-generating rather than conclusive and definitive. If additional data emerge supporting the notion that enoxaparin more efficiently inhibits the interaction of von Willebrand factor with platelets and the ultimate release of additional von Willebrand factor in acute coronary syndromes, one may then add an antiplaquette action to enoxaparin’s portfolio as an antithrombotic agent.

Test of a New Antithrombotic Strategy for UA/NQMI

As emphasized by Merlini and colleagues, increased activity of the coagulation cascade is seen in patients with UA and MI not only during the acute phase of their illness but also persisting for several months. It seems logical, therefore, to provide effective antithrombotic therapy during both the acute phase and the chronic phase of management of patients with UA/NQMI. The constellation of properties discussed so far for LMWHs (enriched anti-Xa activity, more effective release of TFPI, potential suppression of and inhibition of von Willebrand factor, and high bioavailability by the subcutaneous route) makes them attractive candidates for testing new strategies of antithrombotic therapy.

The TIMI 11B trial, which recently concluded enrollment, randomized patients with UA/NQMI to the standard strategy of unfractionated heparin in the acute phase (for 3 days) followed by no additional antithrombotic therapy other than aspirin in the chronic phase versus the novel strategy of subcutaneous enoxaparin twice daily during the acute phase and continued twice daily in a slightly reduced dose for an additional month after hospital discharge.

Investigators have sought to improve on unfractionated heparin since purified extracts of it were introduced into clinical trials 50 years ago in Canada and Sweden. Previous interest in direct antithrombins has been tempered by a combination of lackluster results in clinical trials to date, failure to achieve a durable treatment effect, and a narrow therapeutic:toxic ratio. In contrast, the available data suggest that LMWHs are clearly superior, depending on the agent studied. Additional data on the role of enoxaparin in the acute and chronic phases of management of UA/NQMI will be forthcoming from TIMI 11B; valuable information on its role in angioplasty will come from the ENTICES and ATLAST trials, and its use as adjunctive therapy to tissue plasminogen activator for ST-segment elevation MI will come from HART-II. Exciting times are ahead—clinicians may have a replacement for unfractionated heparin as the new millennium arrives.

References


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