

# Low-Molecular-Weight Heparins in the Treatment of Acute Coronary Syndromes

Alexander G. G. Turpie, MD; Elliott M. Antman, MD

**P**latelet aggregation and activation of coagulation are key events in the development of acute coronary syndromes. Patients with an acute coronary syndrome are at high risk of death or myocardial infarction, and hence there is a strong rationale for the use of antithrombotic agents. Heparin has been shown to reduce the risk of death or myocardial infarction in aspirin-treated patients with acute coronary syndromes, but it has a number of limitations, including the need for regular monitoring and the risk of hemorrhage and thrombocytopenia. Low-molecular-weight heparins offer a number of practical and clinical advantages over unfractionated heparin, such as higher bioavailability and administration by subcutaneous injection. Several low-molecular-weight heparins are available that differ in their biochemical and pharmacologic properties, and it is not possible to predict their clinical efficacy from their pharmacologic profile. The decision regarding the use of a specific low-molecular-weight heparin should be based on the efficacy and safety data available for each product. In clinical trials comparing low-molecular-weight heparin with heparin, only enoxaparin sodium has been shown to reduce the risk of coronary events in patients with non-ST segment elevation acute coronary ischemia.

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Clinical and pathologic studies have highlighted the importance of plaque rupture and platelet aggregation in the pathogenesis of the acute coronary syndromes (ACS) of Q wave myocardial infarction (MI), non-Q wave MI, and unstable angina.<sup>1,2</sup> Following rupture of an atherosclerotic plaque, tissue factor in the lipid core is exposed to circulating factor VIIa, resulting in the formation of a tissue factor-factor VIIa complex and generation of factor Xa.<sup>3,4</sup> This leads ultimately to the formation of large amounts of thrombin, resulting in fibrin deposition and platelet activation.<sup>5,6</sup> Electrocardiographic evidence of ST segment elevation indicates that the culprit artery is completely occluded and that the patient will most likely subsequently develop ST segment elevation MI. The absence of ST segment elevation in patients with unstable an-

gina and non-Q wave MI indicates that the culprit artery is only partially or intermittently occluded or that a rich collateral circulation exists. Nonocclusive intracoronary thrombi are present in 85% or more of patients with non-ST segment elevation ACS,<sup>1</sup> and autopsy studies in such patients suggest that vascular occlusion that leads to MI or sudden death results from repeated episodes of plaque fissure and mural thrombosis.<sup>2,7</sup> Such lesions are often not stabilized by therapy focused only on symptom relief, but continue to progress and cause ischemic events throughout several months.<sup>8,9</sup> As a result, patients with ACS are at increased risk of death and MI. Death or MI occurs in 9% to 11% of patients with non-ST segment elevation ACS within 4 to 6 weeks after the onset of symptoms,<sup>10,11</sup> and recurrent angina occurs in up to 64% of patients who are hospitalized.<sup>12</sup>

The key roles of thrombin generation and platelet activation in the pathogenesis of ACS create a strong rationale for

*From the Department of Medicine, McMaster University, Hamilton, Ontario (Dr Turpie), and Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, Mass (Dr Antman).*

the use of antithrombotic agents in the management of these conditions. Current management guidelines<sup>13</sup> recommend that patients with unstable angina should receive aspirin, at doses between 75 and 325 mg, unless clear contraindications are present. These guidelines are supported by a 1983 study<sup>14</sup> in which the incidence of death or MI in men with unstable angina who were treated with 325 mg/d of aspirin compared with placebo was reduced by 51% ( $P=.0005$ ). The risk of nonfatal MI was also significantly lower in aspirin-treated patients than in the placebo group and mortality was reduced, although not significantly. Subsequently, several large controlled trials in patients with unstable angina treated with aspirin at daily doses between 75 and 325 mg demonstrated a significant reduction in death, MI, or both.<sup>15-18</sup>

Unfractionated heparin (UFH) has also been used, alone or in combination with aspirin, in patients with unstable angina, since it inhibits thrombin-induced platelet aggregation and fibrin formation and thus prevents propagation of an established thrombus. Indeed, combination treatment with aspirin and UFH has previously been recommended for patients with unstable angina or non-ST segment elevation MI because of the accumulating trial evidence showing the benefit of such treatment.<sup>13</sup> In an early clinical trial, treatment with UFH was associated with reduced incidences of MI and refractory angina, compared with placebo, and UFH tended to reduce the incidence of MI to a greater extent than aspirin.<sup>17</sup> In a subsequent extension of this study, the incidence of MI was significantly lower in UFH-treated patients than in patients receiving aspirin (0.8% vs 3.7%;  $P=.035$ ).<sup>19</sup> A meta-analysis of published trials found that the risk of death or MI was reduced by 33% in patients with unstable angina who received both aspirin and UFH, compared with those who received aspirin alone, which suggests that the addition of heparin provides further benefit in aspirin-treated patients.<sup>20</sup> However, the use of UFH is associated with significant disadvantages. The anticoagulant effect produced is unpredictable and doses

need to be continuously adjusted according to the activated partial thromboplastin time, and even with adjustment dosing is often subtherapeutic, making long-term treatment impractical.<sup>21</sup> This is an important issue because long-term treatment may be beneficial in patients with ACS: the risk of ischemic events remains significant for several weeks after the initial episode,<sup>21</sup> and the coagulation system can remain activated for several months.<sup>22,23</sup> Furthermore, UFH treatment is associated with significant complications, including hemorrhage,<sup>19</sup> reactivation of the thrombotic process within hours of discontinuing treatment,<sup>24</sup> heparin-induced thrombocytopenia,<sup>25</sup> and a rebound increase in thrombotic activity and clinical events after discontinuation of treatment.<sup>22,26</sup>

Low-molecular-weight heparins (LMWHs) offer a number of potential advantages over UFH in the management of ACS. They have a higher ratio of anti-Xa-anti-IIa activity than UFH (thereby offering a potentially greater antithrombotic effect), and as a result of the cascading nature of the coagulation system, inhibition of a small quantity of factor Xa prevents the formation of considerably larger amounts of thrombin.<sup>6</sup> Other potential advantages include a high bioavailability after subcutaneous administration; more predictable anticoagulant effect, which avoids the need for therapeutic monitoring; and decreased sensitivity to platelet factor 4.<sup>6</sup> Although these features are common to all LMWHs, it is important to note that LMWHs are a heterogeneous group of compounds that differ markedly in their physical and pharmacologic properties. Thus, each LMWH must be tested in each clinical indication and the results obtained with one LMWH do not apply to another.

#### LMWHs IN ACS: PHARMACOLOGIC CONSIDERATIONS

The potency of LMWH is normally expressed in terms of the anti-Xa activity.<sup>27,28</sup> However, with increasing understanding of the mechanisms of action of LMWHs, it has become clear

that a number of other actions contribute to the antithrombotic effects of these agents. Indeed, it is now recognized that up to 70% to 80% of the material contained in a dose of LMWH acts via mechanisms that are independent of antithrombin.<sup>28,29</sup> Such mechanisms include the following: release of tissue factor pathway inhibitor (TFPI), interaction with heparin cofactor II, inhibition of procoagulant effects of leukocytes, promotion of fibrinolysis, protein binding, and effects on vascular endothelium (receptor mediated and receptor independent). In particular, the effects of LMWHs on TFPI have attracted increasing attention. Tissue factor pathway inhibitor is a glycoprotein that inhibits the factor VIIa-tissue factor complex by forming a quaternary complex with the factor VIIa-tissue factor complex and factor Xa.<sup>30</sup> In addition, it inhibits factor Xa by binding at or near the active site<sup>30</sup> and has a variety of other antithrombotic effects, which include the following: inhibition of tissue factor-mediated activation of platelets and macrophages, inhibition of factor Xa and elastase, multidomain inhibitor of protease generation, interactions with low-density lipoproteins, interactions with vascular endothelium, modulation of endogenous glycosaminoglycans, neutralization of endogenous tissue factor, and possible regulatory functions.<sup>29</sup> Both UFH and LMWHs release TFPI from the vascular endothelium.<sup>30,31</sup>

The LMWHs are prepared by a variety of chemical and enzymatic depolymerization techniques, resulting in marked differences in their physical and biochemical properties.<sup>27,28,32</sup> Such variations in biological activity among LMWHs include the following: variations in affinity for coagulation proteins (eg, antithrombin, platelet factor 4, fibrinogen, protamine, factor VIII), differences in binding to endothelial cells and blood cells, differences in protease inhibition, and differences in bioavailability and pharmacokinetics. Typically, LMWHs have molecular weights between 4000 and 8000 kd, but the available preparations differ in their molecular weight distribution: some show a wide distribution of low- and high-molecu-

lar-weight components, whereas with others the distribution is much narrower.<sup>32</sup> Because the antithrombotic effects of LMWHs depend on the relative distribution of medium- (>9500 kd) and low- (<3500 kd) molecular-weight components,<sup>32</sup> this variation has important implications for the biological activity of LMWHs. Furthermore, chemical depolymerization processes tend to reduce antithrombin binding activity, contributing to the variation in anti-Xa activity among products.<sup>27,28</sup>

Differences in biological activity among LMWHs have been documented in a series of studies.<sup>27-29</sup> In anticoagulant assays, the specific activity ranges from 35 to 45 anti-IIa U/mg or 80 to 120 anti-Xa U/mg,<sup>28</sup> and the ratios of anti-Xa to anti-IIa activities also differ; enoxaparin sodium and nadroparin calcium, for example, have anti-Xa-anti-IIa ratios of approximately 3:1, whereas dalteparin sodium has a ratio of approximately 2:1.<sup>29</sup> Similarly, the antithrombotic effect of different products varies markedly. In a rabbit model of venous thrombosis, for example, enoxaparin and nadroparin were found to be more effective than dalteparin and logiparin.<sup>27</sup> Moreover, LMWHs also differ in their ability to release endogenous TFPI; following intravenous administration of 100-U/kg doses in primates, circulating TFPI concentrations ranged from 110 (dalteparin) to 150 ng/mL (logiparin).<sup>27</sup>

Such findings raise the question of whether differences in pharmacologic properties among LMWHs are clinically relevant. In laboratory studies, the antithrombotic and bleeding effects of a given LMWH depend on a number of factors, including the animal model used and the route of administration<sup>32</sup>; thus, the clinical significance of such differences is difficult to assess. Differences in efficacy and safety between LMWHs have been considered to be small in clinical practice.<sup>28,33</sup> However, most comparisons between different agents have been made on the basis of the clinical experience obtained with the low doses required for the prophylaxis of deep vein thrombosis.<sup>28</sup> Higher doses, where any pharmacologic differences may

be magnified, are required for the prevention of ischemic events in patients with ACS, and thus differences in efficacy and safety may become clinically evident in these situations. The efficacy of a given LMWH in ACS depends on interactions between numerous biological activities that are complex and not yet completely understood, including anti-Xa and anti-IIa activities, release of TFPI, and effects on the vascular endothelium. As a result, it is currently not possible to predict the clinical effect of LMWHs from their pharmacologic profiles in laboratory studies. Hence, the use of a given LMWH in ACS must be based on firm evidence from well-designed clinical trials.

#### LMWHs IN ACS: A REVIEW OF THE CLINICAL EVIDENCE

A number of controlled clinical trials have investigated the use of LMWHs in patients with ACS.<sup>11,34-39</sup> Details of these trials are summarized in the **Table**.

##### Placebo-Controlled Trials

The Fragmin during Instability in Coronary Artery Disease (FRISC) study,<sup>11</sup> which was the only large placebo-controlled trial we found, compared the effects of subcutaneous dalteparin and placebo in 1506 aspirin-treated patients with unstable angina or non-Q wave MI. During the first 6 days, the incidence of death or MI was significantly lower in dalteparin-treated patients than in the placebo group (1.8% vs 4.8%;  $P=.001$ ). However, during long-term treatment for 35 to 45 days with a lower dosage of dalteparin (7500 IU/d), there was an apparent reactivation of disease, and therefore the incidence of death or MI at 40 days did not differ significantly between the groups. In the subsequent FRISC II study,<sup>34</sup> patients received open-label dalteparin for at least 5 days, they were then randomly assigned either invasive or noninvasive treatment, and they were randomly allocated treatment with dalteparin or placebo for 3 months. The risk of death or MI was reduced by 47% ( $P=.002$ ) in dalteparin-treated patients at 30 days, but

the observed reduction was not statistically significant between the groups after 3 months. The incidence of death or MI at 6 months was 13.3% in the dalteparin group and 13.1% in the placebo group, and long-term dalteparin treatment was associated with an increased risk of major bleeding complications, compared with that in the placebo group (3.3% vs 1.5%, respectively).

##### Comparisons With UFH

**Dalteparin.** In the Fragmin in Unstable Coronary Artery Disease (FRIC) study, 1482 patients received either dalteparin, 120 IU/kg twice daily, or adjusted doses of UFH for 6 days, after which they were randomly assigned dalteparin, 7500 IU once daily, or placebo for a further 39 days.<sup>37</sup> The incidence of death, MI, or recurrent angina during the first 6 days was 7.6% in patients receiving UFH and 9.3% in dalteparin-treated patients; during the double-blind treatment period, the incidence of this composite end point was 12.3% in both the placebo and dalteparin groups. Thus, treatment of ACS with dalteparin did not show long-term benefits.

**Nadroparin.** In clinical trials of the LMWH nadroparin, inconsistent results have been reported. For example, in the recent Fraxiparine in Ischemic Syndrome (FRAXIS) study (N=3468), the incidence of coronary events (death, MI, refractory angina, or recurrence of unstable angina) in patients receiving nadroparin, 86 anti-Xa U/kg twice daily, for 5 to 7 days or for 14 days was comparable with that in patients treated with UFH at doses adjusted according to the activated partial thromboplastin time.<sup>35</sup> By contrast, in a previous smaller study of just 219 patients,<sup>36</sup> the incidence of coronary events in patients receiving aspirin plus a high dosage of nadroparin (214 Institut Choay units per kilogram twice daily) was significantly lower than in patients treated with aspirin plus UFH or aspirin alone.

**Enoxaparin.** Two recent studies with enoxaparin<sup>38,39</sup> have independently shown that this agent is more effec-

### Clinical Trials With Low-Molecular-Weight Heparins in Patients With Acute Coronary Syndromes\*

Trial	Patients	Treatment	Outcome
<b>Placebo-Controlled Trials</b>			
FRISC <sup>11</sup>	1506 Patients with unstable angina or non-Q wave MI	Placebo or dalteparin, 120 IU/kg twice daily, for 6 d, then 7500 IU once daily for 35-45 d	63% Reduction in risk of death or MI during first 6 d ( $P = .001$ ); 25% reduction (not significant) at day 40
FRISC II <sup>34</sup>	2267 Patients with ischemic symptoms at rest or increasing in frequency	Open-label phase: dalteparin, 120 IU/kg twice daily for at least 5 d Double-blind phase: placebo or dalteparin, 7500 IU twice daily (5000 IU in men weighing <70 kg or women weighing <80 kg), for 3 mo	47% Reduction ( $P = .002$ ) in risk of death or MI at 30 d; no significant difference at 3 mo
<b>Comparisons With UFH</b>			
Gurfinkel et al <sup>36</sup>	219 Patients with unstable angina	Aspirin, 200 mg/d, alone or with UFH, 400 IU/kg titrated according to aPTT, or nadroparin, 214 UIC/kg every 12 h, for 5-7 d	Nadroparin treatment was associated with lower incidences of recurrent angina, MI, or urgent revascularization compared with aspirin plus UFH
FRAXIS <sup>35</sup>	3468 Patients with unstable angina or non-Q wave MI	Nadroparin, 86-anti-Xa U/kg bolus followed by 86-anti-Xa U/kg twice daily for 6 ± 2 or 14 d, or UFH, 5000-IU bolus followed by infusion at doses adjusted according to aPTT	No significant difference between the groups in incidence of death, MI, refractory angina, or recurrence of unstable angina
FRIC <sup>37</sup>	1482 Patients with unstable angina or non-Q wave MI	Open phase: dalteparin, 120 IU/kg twice daily, or UFH for 6 d Double-blind phase: dalteparin, 7500 IU once daily or placebo	No significant difference between dalteparin and UFH in risk of death, MI, or recurrent angina at day 6 (7.6% vs 9.3%, respectively); no difference between dalteparin and placebo groups at day 45 (incidence, 12.3% in both groups)
ESSENCE <sup>38</sup>	3171 Patients with unstable angina or non-Q wave MI	Enoxaparin, 1 mg/kg twice daily, or UFH, adjusted according to aPTT, for 2-8 d	20% Reduction ( $P = .02$ ) in risk of death, MI, or recurrent angina at 14 d; 19% reduction ( $P = .02$ ) at 30 d; 10% risk reduction at 1 y ( $P = .022$ )
TIMI 11B <sup>39</sup>	3910 Patients with unstable angina or non-Q wave MI	Acute phase: enoxaparin, 30-mg bolus followed by 1 mg/kg twice daily, or UFH, adjusted according to aPTT, for 28 d Outpatient phase: enoxaparin, 60 mg twice daily (40 mg twice daily for patients weighing <65 kg) or placebo (in patients originally assigned to UFH) until day 43	17% Reduction ( $P = .048$ ) in death, MI, or urgent revascularization at day 8; 15% reduction ( $P = .048$ ) at day 43

\*FRISC indicates Fragmin during Instability in Coronary Artery Disease; MI, myocardial infarction; UFH, unfractionated heparin; aPTT, activated partial thromboplastin time; FRAXIS, Fraxiparine in Ischemic Syndrome; FRIC, Fragmin in Unstable Coronary Artery Disease; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; TIMI 11B, Thrombolysis in Myocardial Infarction 11B; and UIC, Institut Choay units. Dalteparin was given as dalteparin sodium, nadroparin as nadroparin calcium, and enoxaparin as enoxaparin sodium.

tive than UFH in preventing coronary events in patients with ACS. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) study,<sup>38</sup> 3171 patients with angina at rest or non-Q wave MI were randomly assigned either enoxaparin, 1 mg/kg (100 anti-Xa U/mg) every 12 hours, or adjusted doses of UFH for up to 8 days; in addition, all patients received oral aspirin at daily doses between 100 and 325 mg. After 14 days, death, MI, or recurrent angina had occurred in 19.8% of patients receiving UFH, compared with 16.6% of patients in the enoxaparin group; this corresponds to a risk

reduction of 20% ( $P = .019$ ). The reduction in the incidence of the composite end point was maintained and was significantly lower in the enoxaparin group at 30 days (19.8% vs 23.3%, respectively;  $P = .016$ ). The proportion of patients requiring coronary revascularization was also significantly lower in the enoxaparin group at this time (27% vs 32.2%;  $P = .001$ ). Long-term follow-up showed that the beneficial effect of enoxaparin was still evident after 1 year.<sup>40</sup> There was no significant difference in the incidence of serious hemorrhagic complications between the 2 groups, but there was an increase in minor hemorrhage,

largely ecchymosis at the injection sites.

The Thrombolysis in Myocardial Infarction (TIMI) 11B study<sup>39</sup> (N=3910) was similar in design to the ESSENCE study, except that enoxaparin was given as an initial 30-mg intravenous bolus, followed by injections of 1 mg/kg every 12 hours, and the short-term treatment phase was followed by a 5-week outpatient placebo comparison using a lower dose of enoxaparin. After 8 days, the composite end point of death, MI, or urgent revascularization had occurred in 14.5% of patients receiving UFH and 12.4% of enoxaparin-treated patients, which

corresponds to a risk reduction of 17% ( $P=.048$ ). The corresponding figures at 14 days for the same composite end point were 16.7% and 14.2%, respectively ( $P=.029$ ). At the end of the outpatient phase on day 43, the beneficial effects of enoxaparin seen during the short-term phase were maintained during 7 weeks of long-term treatment (although continued treatment provided no additional benefit); the composite end point had occurred in 19.7% of UFH-treated patients and 17.3% of enoxaparin-treated patients ( $P=.048$ ). As in the ESSENCE study, there was no significant difference in the rates of major bleeding complications during the initial hospitalization between treatment groups. However, during the outpatient phase, major hemorrhages occurred in 2.9% of enoxaparin-treated patients and 1.5% of placebo-treated patients ( $P=.021$ ).

The data from the TIMI 11B and ESSENCE studies were combined in a prospectively planned meta-analysis to provide statistically robust estimates of the effects of enoxaparin on specific end points.<sup>41,42</sup> This analysis showed that the incidence of death or MI was significantly reduced in enoxaparin-treated patients from day 8 to day 43; similarly, the incidence of death, MI, or urgent revascularization was consistently about 20% lower in enoxaparin-treated patients than in patients treated with UFH from day 2 to day 43. The pooled incidence of major hemorrhagic complications during short-term treatment was 1.3% in the enoxaparin group and 1.1% in the UFH group ( $P=.35$ ). The incidence of minor hemorrhages during the short-term phase was 10.0% and 4.3%, respectively ( $P<.001$ ). A recently published meta-analysis by Eikelboom et al<sup>43</sup> commented that the pooled LMWH trial data did not show a benefit of LMWH over UFH in unstable angina and non-ST segment elevation MI. The article highlighted that in the TIMI 11B and ESSENCE studies, at 72 hours (when the treatment durations of both UFH and enoxaparin were equal in most patients) there was no real benefit of enoxaparin over UFH in the "hard end point" of death and MI. Neither of these trials were powered to

examine differences in efficacy at just 72 hours; to do so would have necessitated a much larger trial because of the low number of events at this early time point. It is notable, however, that when the data from TIMI 11B and ESSENCE are combined, there is a strong trend toward a benefit of enoxaparin for the composite end point of death and MI (enoxaparin, 1.9%, vs UFH, 2.5%; odds ratio, 0.77; 95% confidence interval, 0.56-1.01) and a significant benefit in the composite end point of death, MI, and recurrent angina requiring urgent revascularization (enoxaparin, 6.4%, vs UFH, 8.1%; odds ratio, 0.78; 95% confidence interval, 0.65-0.94).

Economic analysis of the data from the ESSENCE trial has shown that the added treatment benefits of enoxaparin and the reduction in hospital costs due to the ease of use and lack of need for coagulation monitoring result in cost benefits of using enoxaparin in place of UFH.<sup>44</sup>

#### VARIATION IN EFFICACY OF LMWHs IN ACS: FACT OR ARTIFACT?

Although the differing results obtained in clinical trials with different LMWHs in ACS would be consistent with the heterogeneous nature of this group of agents, it is necessary to consider the possibility that these discrepancies are attributable to differences in study designs or study populations rather than true differences in efficacy among the LMWHs.

#### Differences in Study Designs

The doses of LMWH and UFH used in these studies differed, as did the duration of treatment and the timing of the first dose after the onset of symptoms. In the study by Gurfinkel et al,<sup>36</sup> the ESSENCE study,<sup>38</sup> and the TIMI 11B study,<sup>39</sup> for example, patients were allocated treatment within 24 hours of the onset of chest pain, whereas in the FRISC,<sup>11</sup> FRISC II,<sup>34</sup> and FRAXIS<sup>35</sup> studies, patients were randomly assigned treatment up to 48 or 72 hours after the onset of symptoms. Differences in the definitions of clinical

end points may also have contributed to the differences between individual trial results.<sup>45</sup>

#### Differences in Study Populations

Differences in the patient populations studied may have contributed to the variation in outcome, since there is some evidence that patients at the highest risk of coronary events derive even greater benefit from treatment with LMWH compared with UFH therapy. In the FRISC II study, treatment with dalteparin was associated with a reduced incidence of death or MI at 3 months in patients with elevated troponin T concentrations at baseline, but not in patients with normal troponin T concentrations.<sup>34</sup> In the ESSENCE and TIMI 11B studies, for example, although there was a relative reduction in coronary events achieved with enoxaparin in all patients compared with UFH, the benefit was greater in patients with risk factors such as ST-segment depression or electrocardiographic changes at baseline or a previous history of aspirin use.<sup>38,41</sup> Similarly, in trials with glycoprotein IIb/IIIa inhibitors, patients at highest risk have derived the greatest treatment benefit.<sup>46</sup> Differences in study designs, however, do not preclude genuine differences in efficacy among LMWHs.

#### POTENTIAL BIOCHEMICAL BASIS FOR PRODUCT DIFFERENCES

The LMWHs show considerable variation in their biochemical properties, and it is this variation that may underlie the differing results seen in clinical trials focusing on ACS.

#### Anti-Xa Activity

Although the anti-Xa activity of a LMWH does not directly predict antithrombotic activity,<sup>29</sup> it is noteworthy that there were marked variations in the anti-Xa activities and the anti-Xa-anti-IIa ratios of the LMWHs used in different trials. Enoxaparin has a higher anti-Xa-anti-IIa ratio than LMWHs, such as dalteparin, which have not shown consistently favorable results in clinical

cal trials, although the anti-Xa-anti-IIa ratio of nadroparin is similar to enoxaparin and the clinical study results to date with nadroparin have not shown a consistent treatment benefit.<sup>6,35,36</sup> Moreover, the trough anti-Xa activities reported with dalteparin in the FRIC study<sup>37</sup> (0.35-0.37 anti-Xa IU/mL) were lower than those obtained with the enoxaparin dose used in the ESSENCE and TIMI 11B studies (0.5-0.6 anti-Xa IU/mL).<sup>47</sup> The finding in the FRIC study that long-term treatment with dalteparin did not reduce the incidence of coronary events suggests that the dose of dalteparin may have been too low or the interval between doses too long to provide effective anticoagulant cover.<sup>37</sup> Importantly, the higher anti-Xa activities obtained with enoxaparin in ESSENCE and TIMI 11B were not associated with an increased risk of major bleeding.

#### TFPI Release

A number of the effects of LMWHs are mediated via mechanisms that are independent of antithrombin binding and anti-Xa activity. Release of TFPI may contribute to the prolonged antithrombotic effect seen after subcutaneous administration of LMWH, which is maintained after the disappearance of circulating anti-Xa activity.<sup>29</sup> Recently, Bendz et al<sup>48</sup> have shown a differential effect of UFH and LMWHs (enoxaparin and dalteparin) on TFPI release in a small group of patients (N=12). Repeated administration of UFH resulted in partial depletion of free TFPI plasma levels, a phenomenon that was not observed in patients treated with either enoxaparin or dalteparin. The differing action of UFH and LMWH on TFPI release could be a potential biochemical basis for the different clinical benefits of these compounds.

#### von Willebrand Factor

A recent substudy<sup>49</sup> of the ESSENCE trial has highlighted another potential mechanism by which enoxaparin may exert its beneficial effect in ACS. This study showed that circulating concentrations of von Willebrand factor (vWF) increased 48

hours after admission with ACS and that the magnitude of this increase was predictive of a poor outcome. In addition, vWF mediates platelet adhesion to the vascular endothelium and thus plays a key role in thrombus formation. In enoxaparin-treated patients, the increase in vWF concentrations was significantly attenuated (mean increase of 8.7% compared with 93.9% in patients receiving UFH,  $P < .001$ ).<sup>49</sup> The reduction in vWF concentrations seen in the ESSENCE substudy may therefore contribute to the antithrombotic effect of enoxaparin. This reduction may be a result of the binding of enoxaparin to the heparin-binding domain of vWF, resulting in impaired binding of vWF to platelets, or to a decrease in thrombin-induced release of vWF.<sup>6</sup> Recently, a small study<sup>50</sup> of vWF in 154 patients with ACS revealed that patients treated with enoxaparin or polyethylene glycol-hirudin had a significantly smaller increase in vWF after 48 hours than those treated with UFH or dalteparin. At present, the effects of other LMWHs on vWF concentrations are unknown.

#### CONCLUSIONS

Although its usefulness has been limited by an unpredictable anticoagulant effect and a risk of complications, UFH has played an important role in the short-term management of ACS. Currently, LMWHs offer a number of practical and clinical advantages over UFH. The various LMWHs differ markedly in their biochemical and pharmacologic properties and have been studied under many different trial designs, which make direct comparisons of published studies difficult. As a result, clinical decisions regarding the use of a given LMWH should be based on the efficacy and safety data available for each specific product. The LMWHs have been shown to be effective in reducing ischemic outcomes in ACS.

The LMWH enoxaparin has been shown to reduce the risk of acute coronary events and the need for revascularization in patients with ACS when compared with UFH treatment. There are potential bio-

chemical bases for differences in efficacy among LMWHs, but direct comparisons among the LMWHs are required to determine the superiority of one over another.

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Corresponding author and reprints: Alexander G. G. Turpie, MD, HHSC-General Division, 237 Barton St E, Hamilton, Ontario, Canada L8L 2X2 (e-mail: turpie@mcmaster.ca).

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