Pursuing Progress in Acute Coronary Syndromes

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"The difficulty in life is the choice."

George Moore

The sheer scope of the burden of acute ischemic heart disease, initially evident in Western civilization but now increasingly a global problem, places a high priority on understanding its pathophysiology and identifying individuals at increased risk of morbidity and mortality events. So too is there strong impetus for the timely development and introduction of cost-effective therapeutic solutions coupled with concurrent strategies for both primary and secondary prevention.

Patients presenting with ischemic chest pain and transient electrocardiographic abnormalities as part of an acute coronary syndrome have an unfavourable prognosis.1 Their risk is augmented if there are abnormalities in cardiac markers or enzymes and if older age, diabetes, prior myocardial infarction, left ventricular dysfunction, or other unfavourable baseline characteristics are present. Recurrent ischemia, whether clinically evident or silent, further increases the probability of mortality and subsequent myocardial damage.1,2 A bewildering array of therapeutic options has emerged to combat this common and important problem. Accompanying these diverse options over the past 5 years has been an explosion in our knowledge of the pathophysiology of acute coronary syndromes.3 Plaque fissuring promoted by inflammation and possibly infection, as well as a coronary thrombotic process mediated through the coagulation cascade and activated platelets, all of which unfold on a unique genetic template, make it unlikely that a single pharmacological agent will achieve the results we desire for our patients (Figure).

Low Molecular Weight Heparins

The venerability of our traditional therapy with aspirin and intravenous unfractionated heparin, although a tribute to its efficacy, has recently been challenged by the emergence of glycoprotein IIb/IIIa platelet inhibitors and low molecular weight heparins (LMWH). Unfractionated heparin’s new depolymerized progeny offer several advantages over its parent.4,5 Because they bind less strongly to both plasma and tissue proteins and are more bioavailable, they are capable of producing both a longer and more predictable anticoagulant effect without the need for laboratory monitoring. Other advantages of LMWH include enhanced anti-Xa activity, relative resistance to the neutralizing effect of platelet factor IV (it is also able to inhibit factor Xa located on platelet surfaces), inhibition of Von Willebrand factor, and facilitation of tissue factor inhibitor release. LMWH achieve their lighter status (approximately 4500 to 6000 dalton) through enzymatic or chemical depolymerization. The exact mechanisms for their efficacy and hemorrhagic effects are unknown but variation in the ratio of anti-Xa to anti-IIa (between 2 to 4:1) have led to speculation that measuring the anti-Xa activity might provide the potential for meaningful biological monitoring.

Initial studies in patients with venous thromboembolism confirmed stable therapeutic efficacy, avoidance of the need for laboratory monitoring, and acceptance of patient self-administration, thereby improving cost efficacy through reduced length of hospital stay.6 Given the widespread use of heparin, the lower incidence of LMWH-induced thrombocytopenia (presumed secondary to its reduced binding to platelets and platelet factor IV) is a welcome additional advantage.

Because of the initial success with LMWH in venous thromboembolism, application of this therapy to acute coronary syndromes was a logical next step. Unequivocal evidence concerning the dalteparin variety of LMWH as compared to placebo emerged from the FRISC trial, which demonstrated a 3% absolute and 63% relative risk reduction in death or new MI at 6 days. Attenuation of the benefit of q12h dalteparin (120 IU/kg given for 6 days with a once-daily fixed dose regimen of 7500 IU over 35 to 45 days) raised the possibility that a more effective, prolonged treatment regimen might better sustain or even enhance early benefit.7 The FRIC investigators, using a similar dalteparin regimen, found no improvement and possibly less favorable effects compared to unfractionated heparin during the hospital course: no advantage over aspirin was evident after sustained dalteparin therapy for 45 days.8

Two years ago, the ESSENCE investigators first reported on the therapeutic effects of enoxaparin compared with unfractionated heparin in patients with unstable coronary disease.9 The risk of a composite primary end point of death, myocardial infarction, or recurrent angina at 14 days was reduced from 19.8% to 16.6% (odds ratio 0.80; 95% CI 0.67–0.96). Although no benefit was evident at 48 hours, there was persistence of the 14-day benefit, largely driven by recurrent angina, through 30 days. This has recently been found durable at 1-year follow-up.10 An additional mechanism for benefit in these patients may well be the observation of reduced rebound ischemia, previously demonstrated after cessation of unfractionated heparin.10,11
In this issue of *Circulation*, the TIMI 11B investigators add to our knowledge concerning the role LMWH in patients with unstable angina. In a companion article, the TIMI 11B and ESSENCE investigators combine their data in meta-analysis: it is instructive to scrutinize these 2 trials. The TIMI 11B trial evolved from an earlier dose-finding study where a higher dose of enoxaparin, ie, a 30-mg intravenous bolus followed by a subcutaneous q12 hourly administration of 1.25 mg/kg was associated with a major hemorrhage rate of 6.5% within 2 weeks of enrollment. Accordingly, after demonstrating a reduced rate of major hemorrhage of 1.9% using a lower maintenance enoxaparin dose of 1.0 mg/kg, this treatment strategy was used in a randomized and a double-blinded fashion in TIMI 11B. Initially, 1800 patients, required to have at least 5 minutes of ischemic chest pain at rest, within 24 hours of randomization, coupled with some evidence of prior coronary disease defined by history, abnormal coronary angiogram, prior myocardial infarction, ST-segment shift, or elevated cardiac markers, were enrolled over a 10-month period in 10 countries. At this juncture, concern about a lower than expected aggregate event rate prompted modification of the protocol so that all patients were required to have either ST-segment shift or positive cardiac markers at entry. Interestingly, approximately one third of patients in the TIMI 11B trial were receiving intravenous unfractionated heparin for up to 24 hours before enrollment. It would be useful to know whether some of these individuals represented treatment failures of unfractionated heparin before randomization. Unlike the ESSENCE study, the TIMI 11B trial used a weight-adjusted regimen of unfractionated heparin, thereby positioning the control arm in a more advantageous and conventional light. An important distinctive feature of the TIMI 11B protocol was the initiation of LMWH with an intravenous bolus: this may well have contributed to the early evidence of benefit 48 hours after randomization on the triple composite end point of death, myocardial infarction, or urgent revascularization. Whereas death and myocardial infarction provide a reliable end point cluster, this is less clear when considering episodes of recurrent angina leading to coronary revascularization either during or following the index hospitalization: in TIMI 11B these were characterized as urgent. This would be considered by many a somewhat liberal usage of the term urgent in comparison to some other studies. In the ESSENCE study, enoxaparin and unfractionated heparin were given for an equal duration, ie, 2.6 days. By contrast, in TIMI 11B, unfractionated heparin was administered for 3.0 versus 4.6 days for the enoxaparin group. Although this may have disadvantaged the unfractionated heparin patients, especially if rebound ischemic events were operative, the primary end point, ie, a composite of death, myocardial infarction, and urgent revascularization, at 8 days was achieved with a marginally significant 14.4% risk reduction (P=0.048): this would equate to the avoidance of 21 events per 1000 patients treated, 13 of which would be either death or myocardial infarction. Subgroup analysis indicates a clear advantage to those patients with definite ECG changes and no benefit for those without. Interestingly, patients with non–Q-wave myocardial infarctions did not appear to fare as well with enoxaparin as those with unstable angina, although the confidence limits of these subgroups overlap substantially.

Perhaps the most important and novel aspect of the TIMI 11B study is the clear demonstration that continued outpatient therapy through 43 days with 12 hourly weight-adjusted enoxaparin does not produce additional benefit for patients with unstable coronary syndromes. Moreover, the associated promulgation of increased major hemorrhage seems to assure preservation of a biologic effect. In a substantial number of cases, the hemorrhagic events were associated with vascular instrumentation. Because 8 hemorrhagic deaths occurred in the TIMI 11B trial and half of these were in the enoxaparin group, opportunity exists to derive additional therapeutic benefit by reducing unnecessary complications through better monitoring and risk appraisal.

### Why Did Outpatient LMWH Antithrombin Therapy Fail to Provide Additional Benefit?

Although it could be argued that events before hospital discharge would screen out a lower risk population ultimately proceeding to the outpatient phase of the TIMI 11B trial, the baseline characteristics and subsequent events within the
control group argue that this was not the case. Perhaps what is required to achieve the desired therapeutic effect is a more pluri-potential approach directed not only towards the coagulation system but also coupled with strategies to reduce inflammation and promote plaque healing. The combined analysis of TIMI 11B and ESSENCE, also published in this issue of Circulation, was prospectively planned because neither trial demonstrated a reduction, nor was adequately powered to test the effects, on death and myocardial infarction alone.\textsuperscript{13} It should be noted that the least robust component of the triple composite end point differed between the 2 studies, ie, it was recurrent angina in ESSENCE and urgent revascularization in TIMI 11B. Using this combined approach, the authors found an \textasciitilde{}20\% reduction in death and myocardial infarction with enoxaparin, which achieved statistical significance at day 8 and persisted through days 14 and 43. The meta-analysis of hemorrhage underestimates its actual incidence, given that the results are truncated to the acute phase of treatment unlike the data for efficacy. On balance, it appears that the risks of major hemorrhage are approximately the same as with unfractionated heparin, but minor hemorrhage is clearly increased with enoxaparin. Given the anticipated frequency of vascular instrumentation and interventional procedures in this patient population, this is a nontrivial issue, especially because the duration of effect of enoxaparin is protracted and specific antidotes to its anticoagulant effect do not exist.

**Should This Meta-Analysis Have Incorporated the Results of Other LMWH?**

The authors argue that it is inappropriate to do so because of some differences in trial design and agent(s) properties; however, this is debatable because similar issues have not precluded insightful overviews embracing both fibrinolytic and glycoprotein IIb/IIIa inhibitor agents of differing properties among patient populations with acute coronary syndromes. In this regard, nadroparin, the LMWH used in the FRAXIS trial, has a similar molecular weight and anti-Xa:anti-IIa ratio as enoxaparin, yet in a study of 3468 patients randomized to BID nadroparin (Fraxiparin) and compared to unfractionated heparin, no difference in the primary end point of death, myocardial infarction or refractory angina was evident at 6 days.\textsuperscript{14} Patients treated for 14 days actually fared worse in the Fraxiparin group when reevaluated at 3 months. These data and that emerging from the FRISC trial that compared dalteparin with unfractionated heparin emphasize that we still have much to learn from future research on these compounds. Head-to-head comparisons of differing LMWH, the use of LMWH in association with fibrinolytic therapy, and glycoprotein IIb/IIIa inhibitors all provide fertile soil for much needed future research. A better understanding of which patients derive maximum benefit and which are at increased risk to hemorrhage (possibly coupled with sensitive and appropriate laboratory monitoring) would be welcome and has been further developed in TIMI 11B.\textsuperscript{15}

**How Do We Interpret This Data as It Relates to Clinical Implications and Practice?**

It would seem that the lessons of TIMI 11B and the meta-analysis—incorporating ESSENCE provide evidence that LMWH used early, commencing with an intravenous bolus followed by a 12 hourly subcutaneous injection of weight-adjusted enoxaparin, will not only reduce death and myocardial infarction but also reduce repeat hospitalization and the need for revascularization in suitable selected patients. These benefits are maintained at 1 year and cannot be augmented by out-of-hospital sustained therapy. The shorter course of enoxaparin therapy (2.6 days) used in ESSENCE seems likely to minimize the risk of hemorrhagic complications without compromising long-term benefits. The simplicity of administration, avoidance of the need for laboratory monitoring, and favorable cost-benefit profile now demonstrated in both the United States and Canada are all positive aspects supporting the introduction of LMWH in acute coronary syndromes.\textsuperscript{16,17} Care, however, should be taken when using LMWH in circumstances where coronary interventions are either planned or anticipated, given its long half-life and absence of specific antidote. In such circumstances, unfractionated heparin used before and during such procedures may retain its traditional desirability.

George Moore, the Irish playwright, opined that life provided difficult choices. This is surely true for physicians managing patients with acute coronary syndromes. The continuing morbidity and mortality of such patients should provide substantial incentive to patients, physicians, granting agencies, and sponsors to support the necessary research required to integrate and derive a coherent therapeutic strategy (Figure) so that intelligent choices can be made amidst an exciting array of options.

**References**


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