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Expanding the Horizons in Unstable Coronary Artery Disease

J.H. Chesebro, M.D. and F.W.A. Verheugt, M.D., F.A.C.C, F.E.S.C.
Guest Editors

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Supplement I

Expanding the Horizons in Unstable Coronary Artery Disease

J.H. CHESEBRO, M.D. and F.W.A. VERHEUGT, M.D., F.A.C.C., F.E.S.C., **Guest Editors**

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Contents • Vol. 23, No. 1, January 2000 (Supplement I)

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Introduction: Expanding the Horizons in Unstable Coronary Artery Disease

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Despite recent advances in the understanding of the pathophysiology of unstable coronary artery disease (UCAD) and in improvements in treatments for this condition, patients still face a significantly increased risk of mortality in the weeks and months following the unstable episode. The theme of the papers included in these proceedings is how best to manage patients with UCAD for optimal outcome, particularly with regard to the role of medical and interventional approaches and the new clinical data arising from the FRISC II (Fragmin and Fast Revascularization during InStability in Coronary artery disease) study.[1,2]

The clinical diagnosis of UCAD is made at the time of presentation and covers a spectrum of manifestations including unstable angina (UA) and non-Q-wave myocardial infarction (NQMI). The underlying pathology involves both atherosclerotic inflammatory disease and thrombotic mechanisms. Inflammatory reactions promote the erosion, fissure, or rupture of a preexisting plaque, giving rise to the aggregation and adhesion of platelets and the formation of an intracoronary thrombosis that can partially or totally occlude the vessel. In the unstable coronary syndromes, occlusion of the vessel is only partial, and the subsequent clinical course and electrocardiography (ECG) changes are less predictable than with total occlusion. Detachment of fragments of the thrombus can also cause microemboli downstream of the lesion, which may cause myocardial ischemia and damage.

Unstable coronary artery disease is characterized by transient recurrent symptoms and events, and the mechanical obstruction caused by the plaque, the extent of thrombus formation, and the level of efficacy of collateral circulation all play a part in determining whether the patient suffers myocardial ischemia, necrosis, or a myocardial infarction (MI). Since platelet aggregation is involved in the formation of the culprit thrombus, there is a role for platelet inhibition in the treatment of patients with UCAD. Platelet activation will also cause an increase in coagulation activity, resulting in thrombin activation and fibrin formation. Thus, anticoagulants also play a part in effective antithrombotic therapy.

Management of UCAD aims primarily to stabilize the patient by relieving pain and preventing recurrent ischemia, and to prevent progression to MI or death. Ultimately, the aim is to return the patient to a state of health that will permit resumption of the patient's usual activities.

Antiplatelet agents are an established component of UCAD management; all patients are treated with aspirin or, if aspirin is contraindicated, an alternative antiplatelet agent such as clopidogrel.

The use of unfractionated heparin (UFH) to protect patients from recurrent ischemia or progression to MI or death is also well established in clinical practice. However, UFH requires careful monitoring because of its complex pharmacokinetics, the variability in patient response, and the risk of severe bleeding. At the same time, the relative ease of use of the low-molecular-weight heparins (LMWHs) and accumulating clinical evidence base of their efficacy and safety in UCAD is reflected in their increasing use as agents of choice. These agents have a predictable dose–response curve and therefore can be administered without the need for monitoring blood levels. Among the heparins, only UFH and the LMWH dalteparin sodium (Fragmin®) have been evaluated in placebo-controlled studies. Four small studies compared UFH with placebo (Table I) against a background of aspirin treatment,[3–7] while dalteparin sodium was compared with placebo in aspirin-treated patients in a larger clinical trial.[8] With the exception of the study by Holdright *et al.*,[7] which found no difference in clinical outcomes with aspirin plus UFH versus aspirin alone, all of these trials showed that combined treatment with UFH or

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LMWH and aspirin reduced the rate of death or MI by more than 50% compared with aspirin treatment alone. However, these were all short-term studies and did not address the issue of whether or not the benefits of anticoagulant treatment could be sustained in the long term.

The LMWHs dalteparin sodium and nadroparin calcium have been shown to be as effective as UFH in reducing the rates of the triple endpoint of death, MI, and urgent revascularization.[9,10] Enoxaparin sodium has been shown to reduce the risk of death, MI, and urgent revascularization when compared with UFH in two studies.[11,12] As discussed by Dr. Turpie later in this supplement, the differences between these studies in terms of trial design, assessment methodology and patient populations do not permit between-study comparisons of efficacy to be made.

While the LMWHs have now gained wide acceptance as first-line antithrombotic agents in the treatment of patients with UCAD, the crucial question still remains whether or not the early benefits of anticoagulant treatment can be sustained in the longer term through prolonging the administration of the antithrombotic agent. There are increasing data to suggest that this is so. The long-term effects of UFH were compared with very low placebo doses of inogatran (a thrombin inhibitor) in the ThRombin Inhibition in Myocardial ischemia (TRIM) study.[13] The risk of death or MI was found to be reduced by 60–70% as long as UFH infusion was continued; however, on cessation of the infusion, the risk of death or MI in the active UFH treatment group rose to a level approaching that in the placebo inogatran group (Fig. 1).

Low-molecular-weight heparins can be administered subcutaneously in fixed doses and therefore are not associated with the dose-monitoring problems encountered when treating patients with UFH. This method introduces the possibility of convenient, long-term anticoagulant therapy: the FRagmin during InStability in Coronary artery disease (FRISC) study[8] was designed to investigate whether or not the initial early benefit of treatment with dalteparin sodium could be sustained in the longer term. This study compared dalteparin sodium versus placebo in UCAD patients receiving aspirin. Study participants were randomly assigned either

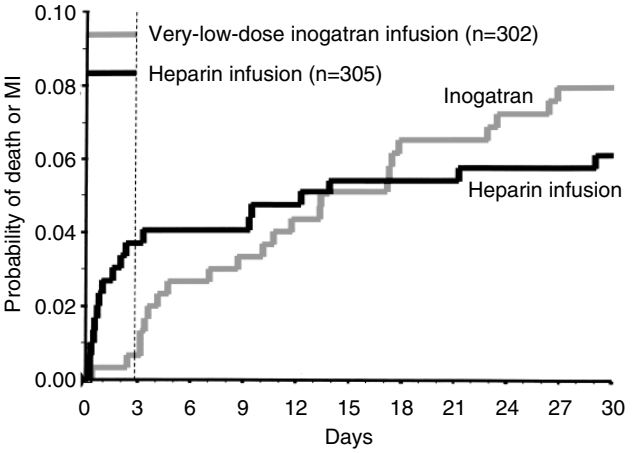

FIG. 1 Long-term effects of unfractionated heparin infusion versus placebo in addition to aspirin in unstable coronary artery disease. MI = myocardial infarction.

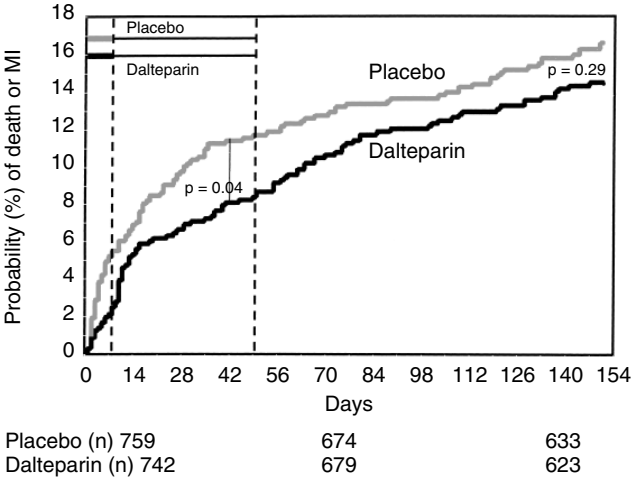

FIG. 2 FRISC — Rates of death or myocardial infarction (MI).[12] Reproduced from Ref. 8 with permission from Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996 Mar 2;347(9001):561–568. ©The Lancet Ltd. 1996

TABLE I Unfractionated heparin or dalteparin sodium versus placebo, in addition to aspirin, in unstable coronary artery disease: Rates of incidence of death or myocardial infarction during randomized treatment[a]

Agent	No. of patients	Days	Incidence of death/MI in placebo group %	Incidence of death/MI in active treatment group %	p	Published report
UFH infusion	484	6	3.7	0.8	0.035	Théroux *et al.,* 1988; 1993 [3,4]
UFH IV/6h	399	5	3.7	1.4	NS	The RISC group, 1990[5]
UFH + warfarin	214	3–4	8.3	3.8	NR	Cohen *et al.*, 1994[6]
UFH infusion	285	2	27.3[b]	30.5[b]	NS	Holdright *et al*., 1994[7]
Dalteparin sodium SC/12 h	1,506	5–6	4.8	1.8	0.001	FRISC study group, 1996[8]

[a]Placebo-controlled, randomized trials with >100 patients in each arm. [b]In-hospital event rate.
Abbreviations: UFH = unfractionated heparin, MI = myocardial infarction, SC = subcutaneous, IV = intravenous, NS = nonsignificant, NR = not reported.

placebo injections or subcutaneous (SC) dalteparin sodium at an initial dosage of 120 IU/kg twice daily for 6 days, followed by 7500 IU once daily for 35 to 45 days. During the first 6 days of the trial, rates of the primary double endpoint of death or MI were significantly lower among patients receiving dalteparin sodium than among those assigned to placebo (1.8 vs. 4.8%, a relative risk reduction of 63%; p=0.001). Prolonged treatment with low-dose dalteparin sodium after the acute phase was associated with a clear benefit in terms of protection from death or MI for more than 6 weeks after the start of treatment (Fig. 2). Although a slight "rebound" effect was observed when the active treatment dosage was reduced at the end of the acute phase, the difference between the two groups remained significant at 45 days (p=0.04). Administration of dalteparin sodium was stopped at this point and, as expected, the effects of treatment then diminished. On follow-up 4–5 months after the end of treatment, no significant difference in the occurrence of death, new MI or revascularization between the groups was found. The FRISC study thus provided some indication that long-term treatment with dalteparin sodium may be beneficial in patients not scheduled for invasive therapy, but this clearly remained an issue that warranted further investigation.

In addition to evaluating the value of prolonged LMWH treatment in patients with UCAD, the authors of the papers included in this special supplement are seeking to answer the following key questions in the management of patients with UCAD:

- Do the apparent differences in patient outcomes seen in the trials of LMWHs in UCAD reflect clinically important differences in the LMWHs themselves, or significant differences in the trial designs?
- Does an early invasive approach afford any real advantages, relative to a conservative, medical therapy-based approach, in which intervention is carried out only when essential?
- Does patient risk stratification identify which patients will benefit from a specific management approach?

It is looking increasingly likely that in the future we will be able to tailor treatment to individual patients and the resources of individual centers. While the results of FRISC II indicate that some groups of patients with UCAD benefit from invasive management, not all centers are equipped to be able to perform routine early revascularization in these patients. Professor Wallentin and Dr. Kontny advise us that we may be able to protect patients scheduled for revascularization against ischemic events through administration of dalteparin sodium during the planning period (for up to 60 days), while Dr. Husted discusses the implications of FRISC II for the acute management of patients with UCAD. This study with the LMWH dalteparin sodium is the first to demonstrate clearly the protective effect of prolonged antithrombotic treatment.

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Can We Differentiate the Low-Molecular-Weight Heparins?

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Summary: The low-molecular-weight heparins (LMWHs) have a number of therapeutic advantages, relative to standard unfractionated heparin (UFH). They are readily bioavailable when injected subcutaneously and can be given in fixed doses, allowing for far simpler administration.

Several LMWHs are now commercially available, each demonstrating different physical and chemical properties and different activities in animal models of anticoagulation or hemorrhage. In clinical comparisons with placebo in the treatment of unstable coronary artery disease (UCAD), the LMWHs dalteparin sodium and nadroparin calcium have demonstrated good anticoagulant efficacy. In comparisons with UFH, on the other hand, only enoxaparin has shown superior anticoagulant activity, as reported in the results of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and Thrombolysis In Myocardial Infarction (TIMI) 11B trials. However, close scrutiny of the methodology of the clinical trials in UCAD reveals considerable differences in study designs, dosage regimens, duration of administration of active treatments, and the timing and definition of endpoints. Therefore, it would not be scientifically sound to compare results with the different LMWHs based on the current available studies. It is also not possible to draw any conclusions with regard to the relative efficacy of the different LMWHs, since there are no properly-sized comparative data between dalteparin sodium, enoxaparin sodium, and nadroparin calcium.

Key words: unstable coronary artery disease, low-molecular-weight heparins, anticoagulation, dalteparin sodium, enoxaparin sodium, nadroparin calcium

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Introduction

Unfractionated heparin (UFH) has, for some time, been established in the management of deep vein thrombosis (DVT) and in thromboprophylactic indications. In addition, UFH plays an important role in the primary and secondary prevention of acute coronary syndromes (ACSs), in maintaining coronary artery patency in patients with myocardial ischemia treated with thrombolytic agents, and in preventing the recurrence of embolic stroke.[1]

In spite of its wide acceptance and application, UFH is associated with a number of limitations, including a short duration of action, poor bioavailability after subcutaneous injection, an unpredictable anticoagulant response, a risk of heparin-induced thrombocytopenia (HIT),[2] and the problem of disease reactivation following the withdrawal of treatment.[3,4] Attempts to overcome these problems have been directed principally toward modification of UFH to produce new antithrombotic agents, and this has resulted in the development and introduction of the low-molecular-weight heparins (LMWHs). The following discussions will examine whether it is possible to differentiate between three of the most widely used LMWHs in ACS: dalteparin sodium, enoxaparin sodium, and nadroparin calcium.

Anticoagulant Activity

Unfractionated heparin is a mixture of glycosoaminoglycan polymers with an average molecular weight of 15 kDa (range 5–30 kDa). Chemical or enzymatic depolymerization of UFH yields the LMWHs, which have a mean molecular weight of around 5 kDa. All of these molecules possess a specific pentasaccharide moiety that inhibits activated coagulation factors and thus prevents clotting. In addition, the larger polymers are capable of binding both antithrombin and Factor IIa.

It has been shown that Factor IIa inhibition is determined by the number of monosaccharide units contained within heparin polymers. Compounds with 5 to 18 monosaccharide units inhibit only Factor Xa, whereas those with 18 to 26 monosaccharides will inhibit both Factor Xa and Factor IIa.[5] Since the larger molecules that are necessary for the inhibition of Factor IIa are present in lower numbers in the lower-mass fragments than in UFH, the LMWHs are less potent in-

hibitors of Factor IIa and thus affect the clotting time to a lesser degree than UFH.

Biological and Pharmacokinetic Differences

Although the depolymerization methods used to prepare the LMWHs from UFH result in products with similar properties, structural variations exist among the molecules and influence their respective biological activities (Fig. 1).[6,7] The counter-ions associated with these products also vary: while nadroparin is a calcium salt, the other LMWHs are all sodium salts. Further differences relate to the mean molecular weights, saccharide chain length distributions, ability to inhibit tissue factor pathway inhibitor (TFPI), and susceptibility to inhibition by Platelet Factor 4.[8] All of these factors may impart unique properties to each LMWH and may give rise to variations in response in vivo.

In contrast to UFH, the LMWHs do not bind to plasma proteins. This characteristic is an important contributory factor to the approximately 3- to 4-fold greater bioavailability of the LMWHs following subcutaneous (SC) administration, relative to UFH,[7] and enables the fixed-dose, SC administration that is such an important advantage in clinical use.

The anticoagulant potency of standard UFH is usually measured in terms of USP (US Pharmacopoeia) U/kg. The relative anticoagulant potency of the LMWHs is lower than that of standard UFH (40–75 U/mg for the LMWHs, compared with 150 U/mg for UFH). Using a rabbit stasis thrombosis model, the antithrombotic activity of LMWHs has been measured as anti-Xa activity. The median effective antithrombotic dose of nadroparin and enoxaparin was found to be more than three times higher than that of UFH, while the median effective dose of dalteparin sodium was nearer to twice that of UFH.[7] In animal models of hemorrhage, heparins with higher molecular weights exhibit greater hemorrhagic potential following intravenous (IV) administration than those with lower molecular weights.[7] These data suggest that anti-Xa dose adjustment may not result in therapeutic equivalence of these agents, in terms of antithrombotic efficacy, following IV administration.

Bleeding is the major complication associated with the use of UFH. In cases of serious bleeding, protamine sulphate can be administered to neutralize UFH, but there has been some concern that protamine may not adequately neutralize the LMWHs. When the degree of protamine neutralization was assessed by assaying anti-Xa and anti-IIa activities before and after supplementation of dalteparin sodium, enoxaparin sodium, and nadroparin calcium with protamine, the anti-Xa activity neutralization was found to be only in the region of 30–45%. With UFH, on the other hand, almost 100% neutralization was achieved. Factor IIa activity, by contrast, was completely neutralized in both the LMWHs and in standard UFH.[7]

Heparin-induced thrombocytopenia (HIT) is another well-recognized complication of UFH treatment. Two types of HIT are recognized clinically, namely a mild thrombocytopenia of early onset and a severe, delayed-onset thrombocytopenia, which is caused by an immune mechanism.[9] While there have been reports of LMWHs being used successfully as alternatives to UFH in patients requiring early management for the manifestations of HIT,[10] the level of cross-reactivity of the LMWHs with heparin-induced antibody is still such that it would preclude the administration of LMWHs to patients in whom heparin-induced antibodies have already caused thrombocytopenia, but who still require anticoagulation. For such individuals, the heparinoid, danaparoid sulphate or the direct thrombin inhibitor, hirudin, would be more appropriate therapeutic agents.

Given the demonstrable biological and chemical differences that exist between the LMWHs, it may be expected that these would translate into variations in clinical activity. Plasma clearance characteristics are known to vary among these compounds, giving rise to differences in dosage regimens; however, the question of whether the preclinical differences between the LMWHs also translate into differences in clinical efficacy and associated bleeding complications has yet to be answered.

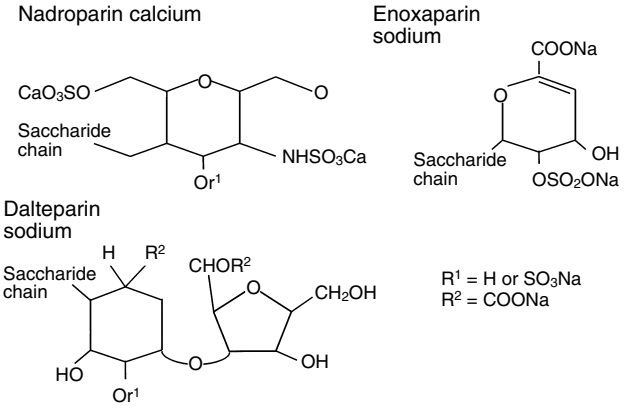

FIG. 1 Chemical structures of low-molecular-weight heparins.

Clinical Trials with Low-Molecular-Weight Heparins

Clinical comparisons have been carried out of the LMWHs versus UFH in the management of patients with unstable angina (UA) or non-Q-wave myocardial infarction (NQMI). Nadroparin calcium was evaluated in the FRAXiparine in Ischaemic Syndromes (FRAX.I.S) study,[11] dalteparin sodium in the FRagmin In unstable Coronary artery disease (FRIC) study,[12] and enoxaparin sodium in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE)[13] and in the Thrombolysis In Myocardial Infarction (TIMI) 11B studies.[14] While both dal-

teparin sodium and nadroparin calcium had previously been found to demonstrate greater efficacy than placebo in the management of UA and NQMI, the FRAX.I.S and FRIC studies showed that clinical outcomes with these products are similar to those obtained with standard UFH. Enoxaparin sodium, however, was found to yield greater clinical outcome benefits than UFH in these indications in both the ESSENCE and the TIMI 11B trials.[15]

So, how can these apparent differences in clinical efficacy be explained? It is possible that the differences in the pharmacokinetic profiles of the agents could be a contributory factor. Of the three molecules, dalteparin sodium has the largest mean molecular weight (5.7 kDa), while nadroparin calcium is somewhat smaller (4.5 kDa), and enoxaparin sodium is the smallest of the three (4.4 kDa).[6] These differences are reflected in the different elimination half-lives of 2.8, 3.7, and 4.4 h for dalteparin sodium, nadroparin calcium, and enoxaparin sodium, respectively.[16]

Besides the intrinsic differences that exist between the molecules themselves, variations in the design and methodology of the clinical trials must also be taken into consideration. A summary of the trial designs is presented in Table I, from which it can be seen that there were significant differences in aspects such as patient selection, relative doses of medication, active treatment duration, and the definition and assessment of endpoints. Of the four trials, FRIC was the only open study, all the others being performed blinded. In the FRIC study, patients were recruited up to 72 h after symptom onset, compared with a cut-off time of 24 h after the last episode of chest pain in the ESSENCE and TIMI 11B trials. Thus, the FRIC trial patient population may have been less acutely ill. It is of importance that, although all these trials compared the LMWHs with UFH, the dosage and duration of UFH treatment varied so widely that not even a direct comparison of the control group data is possible (Table I). Patients randomized to UFH received 5 to 6 days of active treatment in the FRAX.I.S and FRIC trials, but only 2 to 3 days of treatment in ESSENCE and TIMI 11B. Since several days may be required for a good APTT to be established with UFH, it is possible that the trial outcomes may have been significantly influenced by these variations in treatment duration. It has been shown that an average of 5 to 6 days' treatment with UFH plus aspirin reduces the incidence of death or myocardial infarction (MI) relative to aspirin alone,[17,18] whereas no such reduction is seen when the duration of UFH treatment is reduced to 2 days.[19]

The baseline characteristics of the patient populations in the clinical trials are summarized in Table II. The percentages of patients with a previous MI or NQMI were higher in the ESSENCE and TIMI 11B studies than in FRAX.I.S and FRIC. The enoxaparin trials also included patients who were using greater quantities of aspirin at recruitment.

Although not a primary endpoint, the incidence of recurrent angina was assessed in all the studies comparing LMWHs with UFH. However, once again direct comparisons between studies are not possible, in this case because of differences in the definitions of recurrent angina. In the FRIC study, recurrent angina was defined as chest pain requiring an IV nitroglycerin infusion. In the ESSENCE and TIMI 11B trials, the same condition was defined as (1) rest angina of at least 5-min duration, associated with either a new ST-segment shift or a T-wave inversion on electrocardiography; or (2)

TABLE I Clinical trial designs

Study	FRIC[12]	FRAX.I.S[11]	ESSENCE[13]	TIMI 11B[14,15]
LMWH	Dalteparin sodium	Nadroparin calcium	Enoxaparin sodium	Enoxaparin sodium
Study design	Open	Blind	Blind	Blind
Patients (n)	1,482	3,468	3,171	3,910
UFH regimen	5,000 IU IV bolus IV infusion APTT 1.5 x control (48 h – 6 days) alternatively SC 12,500 IU q 12 h at 48 h – 6 days)	IV infusion APTT optimum range for centre (6 days)	5,000 U IV bolus IV infusion APTT 55–85 s (≥48 h, but ≤8 days; median duration 2.6 days)	70 U/kg IV bolus IV infusion APTT 1.5–2.5 x control (≥3 days, but ≤8 days; median duration 3.0 days)
LMWH regimen during acute phase	120 IU/kg SC q 12 h (6 days)	86 IU/kg SC q 12 h (6 days)	1mg/kg SC q 12 h (≥48 h, but ≤8 days; median duration 2.6 days)	30 mg IV bolus 1 mg/kg SC q 12 h (≤8 days; median duration 4.6 days)
Time from symptom onset to enrollment (h)	≤72	≤48	≤24	≤24
Endpoints	6 and 45 days	6 and 14 days	48 h and14 days	8 and 43 days

Abbreviations: LMWH = low-molecular-weight heparin, IV = intravenous, SC = subcutaneous, UFH = unfractionated heparin, APPT = activated partial thromboplastin time.

TABLE II Baseline patient characteristics in trials of LMWHs

Study	FRIC[12]	FRAX.I.S[11]	ESSENCE[13]	TIMI 11B[15]
Age (years)	65 (median)	64.5	63.5 (mean)	66
Ratio M:F	64:36	59:41	66:34	65:35
NQMI (%)	16	16	21	35
Previous MI (%)	25	24.9	46	32
Aspirin users (%)	56	—	62	84

Abbreviations: M = male, F = female, NQMI = non-Q-wave myocardial infarction, MI = myocardial infarction

angina that prompted revascularization; or (3) postdischarge angina that prompted rehospitalization.

Thus, the number and nature of the differences among the FRIC, FRAX.I.S, ESSENCE, and TIMI 11B study designs (Table I) could explain why differences were observed in the composite outcomes for patients randomized to UFH treatment in these trials. These differences also mean that any conclusions regarding the relative efficacies of the LMWHs in the treatment of UCAD, reached on the basis of these results, should be treated with considerable caution.

Conclusion

It can be concluded that the LMWHs are different products with different antithrombotic activities in model systems. It can also be stated that use of a LMWH rather than UFH simplifies the management of patients with UCAD, offering easier administration and a reduced risk of complications, and obviating the need for plasma monitoring.

However, it is currently not possible to draw any conclusions with regard to relative clinical efficacy of the different LMWHs. This is true not only because there is an absence of comparative studies of dalteparin sodium, enoxaparin sodium and nadroparin calcium, but also because each of the LMWHs has been evaluated in studies in different patient populations with different study designs, endpoints, and endpoint definitions. This follows also for the comparison of the LMWHs with UFH: again, the comparative studies have been designed differently, using for example differing endpoints and differing UFH treatment durations (UFH was administered for only 2 to 3 days in ESSENCE and TIMI-11B, but for 5 to 6 days in FRIC and FRAX.I.S). Therefore, it would not be scientifically sound to compare results with the different LMWHs versus UFH based on the currently available studies.

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Acute Management — How Should We Intervene?

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Summary: A crucial question in the acute management of the patient with unstable coronary artery disease (UCAD) is whether to carry out early intervention, performing angiography soon after presentation and following this with revascularization where appropriate, or whether to follow a noninvasive medical strategy as far as possible unless symptoms necessitate intervention. The body of literature addressing this question is sparse, but the recent Fast Revascularization during InStability in Coronary artery disease (FRISC II) study has provided new insights into the problem.

Using a factorial design to randomize patients to invasive or noninvasive management strategies, and to short- or long-term treatment with the low-molecular-weight heparin (LMWH) dalteparin sodium (Fragmin®), it was shown in FRISC II that early invasive treatment (within 7 days), when combined with optimal medical pretreatment with dalteparin sodium, aspirin, and appropriate antianginal medication, is associated with improved clinical outcomes, relative to a "watchful waiting" approach based on noninvasive therapy. Thus, an early invasive approach following aggressive medical pretreatment should be the preferred strategy for patients with UCAD who present with signs of ischemia on the electrocardiogram or raised biochemical markers of myocardial damage at admission.

Key words: unstable coronary artery disease, invasive intervention, myocardial infarction, low-molecular-weight heparin, dalteparin sodium, noninvasive management

Introduction

There is a continuing debate over whether early intervention or a more conservative strategy is most appropriate for the acute management of patients with unstable coronary artery disease (UCAD); that is, should angiography be performed early after presentation, followed by revascularization where indicated, or should intervention be reserved for those patients in whom medical therapy has failed? A recent study[1] has provided important data concerning this issue by demonstrating that, when combined with optimal medical treatment with the low-molecular-weight heparin (LMWH) dalteparin sodium (Fragmin®), aspirin, and appropriate antianginal medications, an early invasive approach is preferable for patients with UCAD, in whom signs of ischemia are visible on the electrocardiogram (ECG) or biochemical markers of myocardial damage are raised.

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Background

During the past 10 years, there have been only two randomized trials comparing invasive versus noninvasive strategies in the management of patients with UCAD: the Thrombolysis In Myocardial Infarction (TIMI IIIB)[2] and Veterans' Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH)[3] studies. The TIMI IIIB study randomized patients to either angiography within 48 h of admission, followed by revascularization as appropriate (740 patients); or to a more conservative medical strategy, with revascularization being undertaken only when indicated for the treatment of recurrent ischemia (733 patients). Numbers reaching the primary composite endpoint of death, nonfatal myocardial infarction (MI), or signs of ischemia on exercise testing at 6 weeks did not differ significantly between the two groups (18.1% in the conservative group, 16.2% in the early intervention group, p=0.33).[2] Furthermore, similar incidence rates were recorded for the double endpoint of death or MI in the two groups on follow-up at 1 year (12.2% among conservatively managed patients vs. 10.8% in the early intervention group, p=0.42).[4] However, the early invasive strategy was associated with significant reductions in the length of hospitalization, the number of rehospitalizations, and the use of antianginal medication, indicating some advantages for routine early revascularization.

The VANQWISH study[3] included only men with non-Q-wave myocardial infarction (NQMI) and randomized patients to similar invasive or conservative strategies within 72 h of the onset of NQMI. Treatment efficacy was assessed

by means of a primary double endpoint of death or nonfatal MI. This study found a significant increase in the rate of unfavorable — and in particular fatal — outcomes among patients assigned to early intervention, relative to those managed conservatively. Incidence rates of the primary double endpoint were significantly higher among patients managed invasively than among the conservatively managed group at hospital discharge (7.8 vs. 3.3%, p=0.004), at 30 days (10.4 vs. 5.7%, p=0.012) and at 12 months (24.0 vs. 18.6%, p=0.05). Rates of death alone among the invasive versus conservative management groups were 4.5 versus 1.3% (p=0.007) at hospital discharge, 5.0 versus 2.0% (p=0.21) at 30 days, and 12.6 versus 7.9% (p=0.025) at 1 year. Rates of nonfatal MI did not differ significantly between the two treatment groups either at hospital discharge or during follow-up.

In view of the lack of a sizeable evidence base or one that allowed any definitive conclusions to be drawn, the Fast Revascularization during InStability in Coronary artery disease (FRISC II) study was designed to compare a routine early invasive with a conservative, noninvasive management strategy against a background of optimal antithrombotic medication in patients with UCAD.[1]

The FRISC II Study

The FRISC II study was a prospective, randomized, multicenter trial with parallel groups. A factorial design was applied to compare invasive versus noninvasive management and prolonged versus acute-phase dalteparin sodium. The primary objective of the invasive versus noninvasive arm of FRISC II was to compare clinical outcomes obtained with an early invasive strategy versus those associated with a noninvasive, medical therapy-based approach in patients with UCAD. The primary endpoint for this open comparison was a composite of death or MI at 6 months; secondary endpoints assessed effects on symptoms of angina, readmission rates, the need for late revascularization procedures, and incidences of stroke and hemorrhage.

The FRISC II study population comprised 3,489 patients in total: men of at least 40 years of age and postmenopausal women who, within the previous 48 h, had experienced an episode of chest pain associated with ECG changes or elevated biochemical marker levels. Patients were considered eligible for study admission if they exhibited symptoms of ischemia that were either increasing, occurring at rest, or that warranted the suspicion of acute MI. Important exclusion criteria for the FRISC II trial included an increased risk of bleeding, indication for or treatment with thrombolysis during the last 24 h, percutaneous transluminal coronary angioplasty (PTCA) within the last 6 months, and a contraindication to randomized early revascularization (i.e., previous open-heart surgery, advanced age, or other concomitant illnesses). Patients awaiting coronary revascularization, or with any other acute or severe cardiac disease, were also excluded.

On admission, all eligible patients received aspirin, beta blockers, calcium antagonists, and nitrates according to current clinical guidelines. As soon as possible after admission (within 72 h), patients were randomly allocated to one of four treatment strategies: long-term dalteparin sodium and a noninvasive strategy; long-term placebo and a noninvasive strategy; long-term dalteparin sodium and an invasive strategy; long-term placebo and an invasive strategy (Fig. 1). Patients with a contraindication to early revascularization (n=666) and late inclusions (n=366) were assigned to a noninvasive strategy and randomized to receive long-term dalteparin sodium or placebo. Prior to randomization (within 72 h of study admission), patients also received open-label dalteparin sodium 120 IU/kg/12 h or standard unfractionated heparin (UFH). Following randomization, all patients received subcutaneous dalteparin sodium 120 IU/kg twice daily for at least 5 days or until early revascularization procedure. (In the invasive management group this was carried out within 7 days of the start of open-label treatment). Revascularization procedures were carried out in patients assigned to noninvasive management only in the event of refractory angina, signs of severe ischemia on exercise testing, or reinfarction.

Randomized patients (n = 2,457) in the invasive and noninvasive management groups were well matched for baseline demography. Some selected patient characteristics are shown in Table I. On the basis of the patient characteristics at study admission, the population of the invasive versus noninvasive management arm of FRISC II could be classified as a medium- to high-risk group.

Results

Overall, percutaneous coronary intervention (PCI) procedures were performed in 42.7% of the invasive group and 17.8% of the noninvasive group. Median times to PCI in the two groups were 4.0 and 16.5 days, respectively. Coronary artery bypass graft (CABG) was performed in 35.2% of patients randomized to invasive management and 18.9% of the noninvasive group, with median times to procedure of 7.0 and 28.0 days, respectively. Surgical mortality rates were low: 2.1% in the invasive group and 1.7% in the noninvasive group. Adverse events related to treatment are summarized in Table II. There was an increase in bleeding in the invasive group, but all other adverse events were rare.

During the initial 6 months of the FRISC II study, the double endpoint of death or MI was reached by 12.1% of the noninvasive group, compared with 9.4% of the invasive group — a significant relative risk reduction of 22% (p=0.031) (Fig. 2). A higher event rate was noted among patients randomized to invasive treatment than among the noninvasively managed group during the first 2 weeks of the trial, reflecting the risk

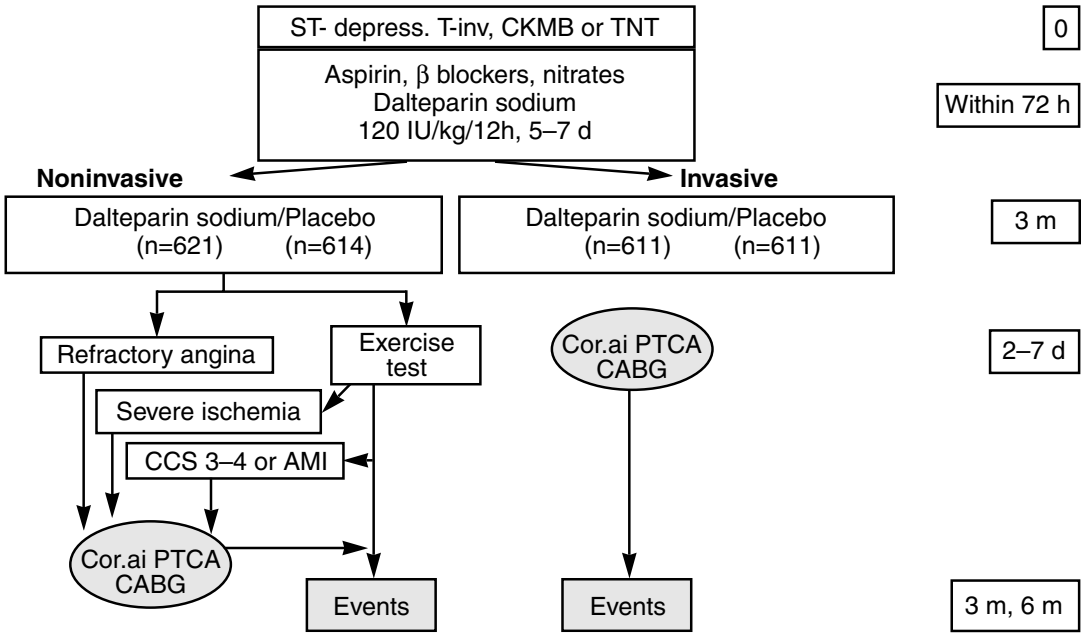

FIG. 1 FRISC II study design. ST-depress. = ST depression, T-inv.=T-wave inversion, CKMB = creatine-kinase MB, TNT = troponin T, PTCA = percutaneous transluminal angioplasty, CABG = coronary artery bypass graft, AMI = acute myocardial infarction, d = days, m = months, CCS = Canadian Society class, Cor. ai = coronary angiography.

TABLE I Selected baseline characteristics of patient groups

	Invasive management group (n=1,222)	Noninvasive management group (n=1,235)
Median age (years)	66	65
Proportion of males in group (%)	71	68
Hypertension (%)	30	31
Diabetes mellitus (%)	13	12
Previous MI (%)	23	22
ST-segment depression at entry (%)	45	46
Troponin-T level ≥ 0.1μg/l (%)	57	58
LVEF <45% (%)	14	12
Current smokers (%)	30	31

Abbreviations: MI = myocardial infarction, LVEF = left ventricular ejection fraction.

associated with invasive procedures. However, after 2 weeks a lower event rate was seen in the invasive than in the noninvasive group. The hazard curves crossed at around 4 weeks and, from this point onward, the separation of the two curves showed an increasing benefit for invasive compared with noninvasive patient management.

Routine early invasive treatment significantly reduced incidences of MI alone: 6-month rates were 10.1% for the noninvasive group and 7.8% for the invasive group (p=0.045). A nonsignificant reduction in mortality rates was observed, from 2.9% in the noninvasive group to 1.9% in the invasive group (p=0.10). Incidences of the secondary endpoints were also reduced by early invasive management, as summarized in Table III.

Thus, the results of the FRISC II study clearly demonstrate that, in most patients with UCAD, an early invasive strategy following medical pretreatment with dalteparin

TABLE II Adverse events with invasive and noninvasive treatment strategies during treatment with dalteparin sodium

Treatment phase	Open-label		Double-blind	
Management strategy group	Invasive (n=1,222)	Noninvasive (n=1,235)	Invasive (n=563)*	Noninvasive (n=582)*
Any serious AE (%)	3.8	1.6	14.8	11.9
Major bleeding (%)	1.6	0.7	2.3	3.6
Minor bleeding (%)	7.6	5.8	22.5	23.1
Stroke (%)	0.2	0.2	1.1	1.0
Allergic reaction (%)	1.0	0.2	2.7	2.3
Thrombocytopenia (%)	0.1	0.1	0.4	0.0

Abbreviation: AE = adverse events.
*Patients randomized to long-term-treatment with dalteparin sodium.

sodium, aspirin, and indicated antianginal medication reduces rates of mortality and nonfatal MI. In this trial, the advantages of early invasive treatment, which were still apparent at the end of the 6-month observation period, were most marked in patients of higher age, in men, and in those with angina of longer duration, chest pain at rest, or ST-segment depression on the ECG.

The findings of FRISC II differ quite profoundly from those of previous trials comparing invasive with noninvasive management strategies in patients with UCAD, which had indicated either no significant difference in patient outcomes with these two strategies[2] or pointed to an excess of adverse outcomes with an approach of routine early intervention.[3] The discrepancies between the findings of these studies and those of FRISC II may be explained by differences in antianginal and antithrombotic medications, timings of procedures, proportions of procedures carried out in each of the patient groups, improvements in technology and equipment during the intervening period, and the low risk of mortality associated with CABG in FRISC II. This low mortality is typical of the rates generally found in Scandinavian institutions.

The FRISC II study further differs from other similar trials in that a comparatively long time period — up to 7 days — elapsed before the early intervention procedures were carried out. While there is no universally accepted definition of "early", the term is often taken to imply that coronary angiography is performed after just 24 to 48 h of medical pretreatment.[5] In the TIMI IIIB study, patients were recruited within 24 h of an episode of chest pain at rest and were randomized to either a conservative strategy or to coronary angiography at 18 to 48 h followed by revascularization as soon as possible, where appropriate. Under the VANQWISH study protocol, patients were randomized within 24 to 72 h, and coronary angiography was performed soon afterward (a median of 2 days from randomization to intervention). It may be that an optimal period exists for stabilization with antithrombotic therapy, and that carrying out the intervention procedure before this period has lapsed results in an increased risk of negative clinical outcomes.

Also worthy of consideration is the fact that no other study comparing invasive versus noninvasive management strategies in UCAD has used such aggressive medication at baseline. In the FRISC II study, the background medical treatment consisted of acute-phase LMWH (dalteparin sodium), long-term aspirin, and beta blockade unless contraindicated, and patients in the early intervention group received open-label dalteparin sodium for a median of 6 days (120 IU/kg subcutaneous twice daily until the procedure, followed by 5,000 or 7,500 IU twice daily or placebo). In addition, nitrates, calcium antagonists and statins were included as required, and angiotensin-converting enzyme (ACE) inhibitors and antidiabetic treatments were administered in line with current guidelines. The placement of stents and administration of abciximab during PCI were also encouraged. This optimization of medical pretreatment and intervention technologies may have contributed significantly to the relatively favorable patient outcomes, as reflected by the low rate of interventions in the noninvasive group (9% at 10 days and 37% at 6 months), compared with other studies (49% at 42 days in the TIMI IIIB trial and 33% after 12 months in the VANQWISH trial).

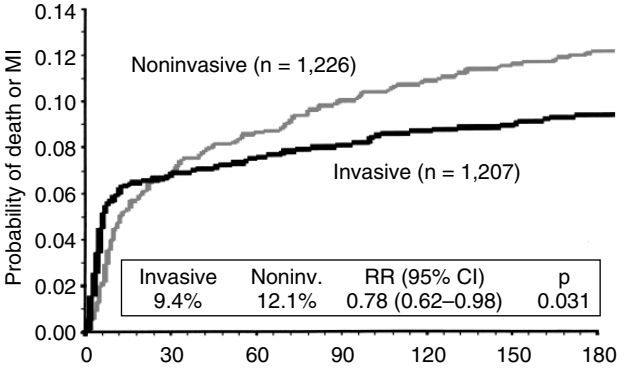

FIG. 2 FRISC II invasive arm — death or myocardial infarction (MI) during 6 months. RR = relative risk, CI = confidence interval. Reproduced from Ref. 1 with permission from Fragmin and Fast Revascularization during InStability in Coronary artery disease Investigators: Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999 Aug 28;354(9180):708–715. ©The Lancet Ltd. 1999

TABLE III Symptoms and readmissions during 6 months' follow-up

	Invasive management group	Noninvasive management group	Risk ratio (95% confidence interval)	p-value
Angina (%)				
6 Weeks	20	52	0.39 (0.34–0.44)	<0.001
3 Months	21	44	0.48 (0.42–0.54)	<0.001
6 Months	22	39	0.56 (0.50–0.64)	<0.001
Canadian Cardiovascular Society angina class III–IV (%)				
6 Weeks	2	12	0.17 (0.11–0.26)	<0.001
3 Months	2	9	0.28 (0.19–0.42)	<0.001
6 Months	3	7	0.38 (0.25–0.56)	<0.001
Readmissions since last visit (%)				
6 Weeks	15	24	0.62 (0.34–0.44)	<0.001
3 Months	10	19	0.51 (0.42–0.63)	<0.001
6 Months	14	24	0.60 (0.50–0.72)	<0.001
Total readmissions during 6 months (%)	31	49	0.62 (0.60–0.69)	<0.001

Conclusions

The main conclusion to be drawn from the FRISC II study is that an early invasive approach (intervention within 7 days), following optimal medical treatment with dalteparin sodium, aspirin, and antianginal medications, should be the preferred strategy for the majority of patients with UCAD who have signs of ischemia on ECG, or raised levels of biochemical markers indicating myocardial damage at admission. This regimen not only reduces the risk of death and MI, but also results in improved symptom control, fewer hospital readmissions, and decreased use of beta blockers, long-acting nitrates, and calcium antagonists.

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Long-Term Management — The Way Forward?

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Summary: The mainstay of treatment for unstable coronary artery disease (UCAD) currently consists of antithrombotic therapy with aspirin plus unfractionated heparin (UFH), together with anti-ischemic treatment with beta blockers and nitrates. Recently, there has been a trend toward replacement of UFH with low-molecular-weight heparins (LMWHs), since these products offer significant advantages over the parent compound. Several lines of evidence suggest that prolongation of treatment with LMWHs beyond the acute phase may be appropriate in patients with UCAD. The Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) study was designed to evaluate this hypothesis using the LMWH dalteparin sodium (Fragmin®).

A factorial design was used to randomize patients enrolled in the FRISC II study to an invasive or noninvasive management strategy, and to treatment with dalteparin sodium or placebo. Treatment with dalteparin sodium significantly reduced incidences of death and/or myocardial infarction (MI) during the first months of treatment (the reduction in the relative risk of double endpoint events was statistically significant at 47.0% at 1 month, and remained so at 2 months, but was no longer statistically significant at the 3-month assessment). However, risk, as defined by the triple endpoint of death, MI, and revascularization, was significantly lower (13.0% relative risk reduction) at 3-month follow-up in the treatment group randomized to dalteparin sodium than among patients receiving placebo. In patients in whom revascularization procedures were carried out, the risk of new, postprocedural events was low in both the placebo and dalteparin sodium arms. Thus, dalteparin sodium appears to protect patients from cardiac events until they undergo invasive procedures, and it can therefore be used as a bridge to revascularization.

Key words: unstable coronary artery disease, low-molecular-weight heparins, dalteparin sodium, revascularization

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Introduction

The majority of episodes of unstable coronary artery disease (UCAD) are due to rupture of an atherosclerotic plaque. This process activates the coagulation cascade, causing platelet activation and leading to thrombus formation at the site of the lesion. Over a period that can last from seconds to days, the thrombus often protrudes into the lumen where it impedes or interrupts — either temporarily or permanently — coronary blood flow. The clinical manifestations of this sequence of events include unstable angina (UA), myocardial infarction (MI), and even death.

Treatment for UCAD has improved considerably over the past few years. The proven ability of a combination of aspirin and unfractionated heparin (UFH) to protect against subsequent ischemic events[1,2] has led to their adoption as the mainstay of therapy in this indication and their recommendation, usually in combination with anti-ischemic beta blockers and nitrates, for all patients in the acute phase following an ischemic episode.[3] More recently, there has been a shift toward the use of low-molecular-weight heparins (LMWHs) in preference to standard UFH, since they possess distinct advantages in terms of pharmacokinetics, hemorrhagic potential, and bioavailability that make them simpler to use in fixed-dose subcutaneous (SC) injection.[4]

In placebo-controlled evaluations, the LMWH dalteparin sodium (Fragmin®) has been found to approximately halve the acute-phase risk of death or MI,[5] while the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) study showed a significant lowering of the acute-phase incidence of death, MI, or recurrent angina by the LMWH enoxaparin sodium.[6] Two other studies have shown that LMWHs afford similar levels of protection to that provided by UFH during 5 to 8 days of treatment.[7,8]

Despite the documented short-term benefits, there is little information concerning advantages of long-term therapy with LMWHs plus aspirin. Nevertheless, there are several reasons to assume that long-term antithrombotic treatment may be beneficial in patients with UCAD. Angiographic examinations have shown that a thrombus remains present for several weeks at the site of a coronary lesion in patients with UCAD, and coagulation activity is known to remain elevated for some 3 to 6 months after an episode of instability, even in the absence of symptoms.[9–11] Consequently, the risk of cardiac

events is increased for several months following an acute ischemic episode.[5–7] Moreover, it has been reported in several trials that there is a reactivation of coagulation activity, or a "rebound phenomenon," resulting in a raised event rate immediately after cessation of UFH treatment, although this may be reduced by the concomitant use of aspirin.[5,12,13] Thus, it would seem reasonable to suggest that prolongation of intense antithrombotic treatment may provide a means of maintaining the initial reduction in cardiac events, especially in high-risk patients.

The present paper examines the value of the LMWH dalteparin sodium in the long-term management of patients with UCAD, in the light of the results of the recent Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial.[14,15] The earlier FRagmin during InStability in Coronary artery disease study (FRISC) indicated a beneficial effect of prolonged administration of dalteparin sodium to a subgroup of high-risk patients with elevated troponin-T levels, who had a low rate of early invasive procedures.[16] Therefore, one of the principal objectives of the FRISC II study was to investigate the effects of long-term treatment with the LMWH dalteparin sodium, compared with placebo, in patients with UCAD who had been assigned to a noninvasive management strategy and in patients with a contraindication to early revascularization.

FRISC II — Noninvasive Arm

FRISC II was a prospective, randomized, multicenter, parallel-group trial, the design of which has already been described in this supplement.[17] Patients were randomized, in a factorial design, to one of four treatment policies (invasive or noninvasive strategy plus dalteparin sodium or placebo). This paper concentrates on those patients assigned to the noninvasive management strategy, that is, the comparison of prolonged treatment with dalteparin sodium versus placebo.[15] Among this patient group, coronary angiography was recommended only for the treatment symptoms that were refractory or recurrent despite maximal medical therapy, or in patients in whom indications of severe ischemia were evident on a predischarge, symptom-limited bicycle exercise test. During long-term follow-up, invasive procedures were considered for patients who experienced incapacitating symptoms, recurrence of instability, or reinfarction.

Results

Patient baseline characteristics did not differ significantly between the two groups (selected parameters are shown in Table I). Both treatment groups comprised mainly men in their late 60s, with a fairly high-risk profile: around 80% of study participants reported chest pain at rest, almost half showed ST-segment depression on electrocardiography (ECG), and levels of troponin-T were elevated in nearly 60% of patients.

The primary endpoint of the FRISC II trial was the composite of death and MI 3 months after randomization to the double-blind phase of the study. A nonsignificant 19.0% relative reduction in the primary endpoint was found in the dalteparin sodium group, compared with patients assigned to placebo (endpoint incidence rates of 6.7 vs. 8.0%; p=0.17). However, the hazard curve (Fig. 1) showed a significant 47% relative risk reduction at 1 month (incidence rates of death and MI of 3.1 and 5.9% among patients randomized to dalteparin sodium and to placebo, respectively; p=0.002), that remained evident up to 60 days. The reasons for the observed erosion of benefit between 60 and 90 days are not apparent.

Data have also been analyzed for the total cohort of patients over the entire treatment period, that is, including both the open-label and double-blind phases (Fig. 2). Again, there was a nonsignificant 11% relative reduction in the risk of death or MI at 3 months (10.0 vs. 11.2% in the dalteparin sodium and placebo groups, respectively; p=0.34), but a significant treatment effect (27% relative risk reduction) at 1 month (incidence rates of 6.2 vs. 8.4%, respectively; p=0.048). Considering the composite triple endpoint of death, MI, and ischemia-driven revascularization that is frequently applied in trials of this nature, there was a significant and sustained reduction in relative risk of 13% at 3 months (Fig. 3). As previously indicated, the greatest difference occurred during the first month of treatment (19.4% in the dalteparin sodium group vs. 25.6% in the placebo group).

Comparing clinical outcomes in all four treatment groups in the FRISC II study, during the first weeks incidence rates of the death/MI double endpoint were higher among patients randomized to routine early invasive treatment, reflecting the risks associated with angioplasty. However, by 90 days the

TABLE I Selected baseline characteristics

	Dalteparin sodium (%) (n=1,049)	Placebo (%) (n=1,056)
Median age (years)	67	67
Male: female ratio in treatment group	68:32	69:31
Previous MI	30	27
Previous PTCA or CABG	18	17
Angina history > 48 h	70	70
Current smokers	25	27
Hypertensive	33	33
Chest pain at rest	82	80
ST-segment depression at study entry	46	50
Troponin-T $\geq$ 0.1 µg/l	57	60
Left ventricular ejection fraction < 45%	14	17

Abbreviations: PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft.

situation had changed, and risk of endpoint events increased more markedly in the noninvasive group than among patients in whom invasive procedures had been carried out. The highest event rate of all was seen in the patient group randomized to noninvasive management plus placebo. Treatment with dalteparin sodium resulted in significant benefits for up to 60 days in all patients assigned to noninvasive management; however, while event rates were still lower among patients treated with dalteparin sodium at 3 months, the difference was no longer significant. The comparison between the invasive and noninvasive strategies in FRISC II is discussed in greater detail elsewhere in this publication.[17]

In summary, treatment with dalteparin sodium was associated with clinical outcome benefits for up to 60 days in all patients in the FRISC II trial; however, further continuation of twice-daily dalteparin sodium did not provide a significant decrease in the incidence of death or MI after 3 months. Nevertheless, a protective effect of long-term treatment with dalteparin sodium was supported by the significant decrease (13% relative risk reduction) in the triple endpoint of death, MI, and revascularization during the total treatment period. The implication of these data is that dalteparin sodium affords protection against adverse coronary events in the period before invasive procedures are carried out, and can therefore be used as a bridge to revascularization. Once the invasive procedure has been carried out, however, the risk of new postprocedural events appears to be low, and continuation of LMWH treatment provides no additional benefits.

Time	Dalt.sodium	Placebo	RR (95% CI)	p
1 month	3.1%	5.9%	0.53 (0.35–0.80)	0.002
3 months	6.7%	8.0%	0.81 (0.60-1.10)	0.170

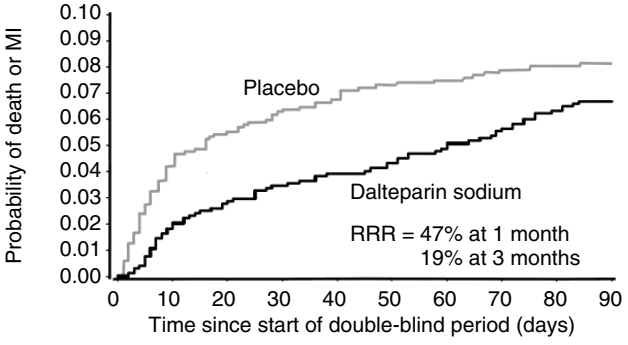

FIG. 1 Probability of death or myocardial infarction (MI) during the double-blind phase of FRISC II. RR = relative risk, RRR = relative risk reduction, CI = confidence interval. Reproduced from Ref. 15 with permission from Fragmin and Fast Revascularization during InStability in Coronary artery disease Investigators: Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999 Aug 28;354(9180):701–707. © The Lancet Ltd. 1999

FRISC II and TIMI 11B — How Do the Studies Compare?

A comparison of long-term treatment with LMWH versus acute-phase UFH had been carried out previously in the Thrombolysis In Myocardial Infarction (TIMI) 11B trial,[18] the final report of which has recently been published.[19] Under the protocol adopted in the TIMI 11B study, the acute-

Time	Dalt.sodium	Placebo	RR (95% CI)	p
1 month	6.2%	8.4%	0.73 (0.54–0.99)	0.048
3 months	10.0%	11.2%	0.89 (0.70-1.13)	0.340

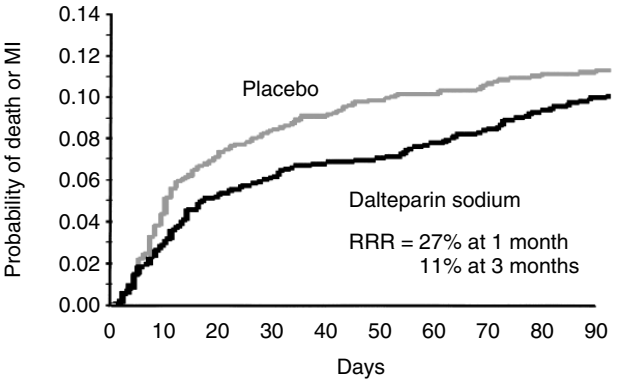

FIG. 2 Probability of death or myocardial infarction (MI) during the total treatment period. Abbreviations as in Figure 1. Reproduced from Ref. 15 with permission from Fragmin and Fast Revascularization during InStability in Coronary artery disease Investigators: Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999 Aug 28;354(9180):701–707. © The Lancet Ltd. 1999

Time	Dalt.sodium	Placebo	RR (95% CI)	p
1 month	19.5%	25.7%	0.76 (0.65–0.89)	0.001
3 months	29.1%	33.4%	0.87 (0.77-0.99)	0.031

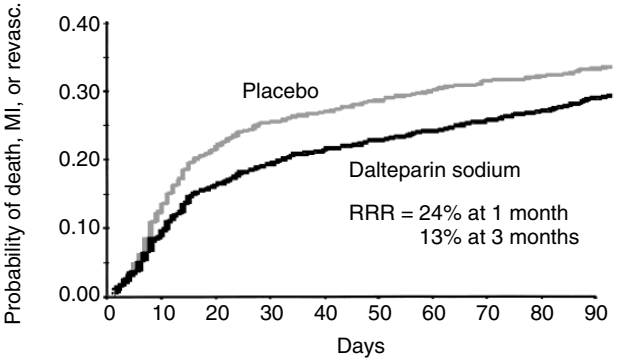

FIG. 3 Probability of death, myocardial infarction (MI), or revascularization during the total treatment period. Abbreviations as in Figure 1. Reproduced from Ref. 15 with permission from Fragmin and Fast Revascularization during InStability in Coronary artery disease Investigators: Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999 Aug 28;354(9180):701–707. © The Lancet Ltd. 1999

phase LMWH regimen comprised enoxaparin sodium, administered initially as a 30 mg intravenous (IV) bolus and subsequently as 12-hourly 1.0 mg/kg SC injections until either hospital discharge or Day 8 of the study, whichever arrived first. Acute-phase UFH was administered as an initial 70 U/kg IV bolus followed by an infusion of 15 U/kg/h, titrated to an activated partial thromboplastin time or 1.5–2.5 times the control value and continued for at least 72 h. During the long-term phase of the TIMI 11B study (counted from hospital discharge or from Day 8, depending on which arrived first, until Day 43), patients randomized to enoxaparin sodium received the SC LMWH 12-hourly at a dosage of either 60 or 40 mg, depending on body weight. Long-term treatment for patients in the UFH arm comprised 12-hourly SC injections of placebo.[18,19]

Results obtained from the TIMI 11B study showed an initial statistically significant treatment response at 14 days (14.9% relative risk reduction for the triple endpoint of death/MI/revascularization with enoxaparin sodium vs. UFH/placebo). This difference was maintained up until 40 days, but continuation of treatment with enoxaparin sodium for a further 35 days conferred no additional benefits. At Day 43, treatment with enoxaparin sodium resulted in a relative risk reduction of 12.3% for the primary triple endpoint (17.3% incidence rate among patients randomized to LMWH, compared with 19.7% in the placebo group; p=0.048), which has been interpreted as indicating that prolonged treatment with enoxaparin sodium for an additional 35 days affords no greater benefits than short-term treatment alone — a result that differs markedly from the findings of the FRISC II study using the LMWH dalteparin sodium.

The discrepancy between the FRISC II and TIMI 11B studies in the prolonged treatment phase may be explained by differences in active treatment dosage regimens. Dalteparin sodium has already been investigated in prolonged use in two earlier studies, the FRagmin In unstable Coronary artery disease (FRIC) and FRISC trials. These trials highlighted the need to identify the optimal dosage and duration of prolonged therapy. Using the dosage of 5,000 IU or 7,500 IU every 12 h, the FRISC II study has proven the efficacy and safety of dalteparin sodium for 30 days of treatment.

Tolerability of Prolonged Treatment with Dalteparin Sodium

It is inevitable that the prolonged administration of an anticoagulant in addition to aspirin will be associated with an increased risk of bleeding. Indeed, this has been found in all the trials of long-term LMWH plus aspirin treatment. Table II shows the incidence of bleeding events in the two arms of the FRISC II trial. Both major and minor bleeding occurred to a greater extent in patients randomized to dalteparin sodium, although the increase in the risk of major bleeding was considered to be acceptable given the reduction in risk of MI and death. Although the rate of hemorrhagic stroke was very low, this was also higher among patients treated with the LMWH than among those assigned to placebo (0.8 vs. 0.0%). On the other hand, more nonhemorrhagic strokes were recorded in patients randomized to placebo than in those treated with dalteparin sodium (0.8% among the placebo group vs. 0.2% among patients assigned to dalteparin sodium), and the long-term, high-dose dalteparin sodium treatment regimen used in the FRISC II study was not associated with an increased risk of heparin-induced thrombocytopenia, allergic reactions, or fractures indicative of osteoporosis.

Conclusion

Studies have now shown that there are three LMWHs — dalteparin sodium, enoxaparin sodium, and nadroparin calcium — that, when administered to patients with UCAD for 3 to 7 days following an ischemic event, provide early benefits above those obtained with aspirin alone.[5–7] In the FRISC II study, 3 months' treatment with dalteparin sodium, in addition to antianginal medication, significantly reduced the risk of death and MI during the first 60 days of treatment, although this benefit was reduced and became nonsignificant by 3 months in patients managed according to a noninvasive treatment strategy. However, incidences of the composite endpoint of death, MI, and ischemia-driven revascularization were reduced over the 3 months of treatment with dalteparin sodium. Prolonged administration of dalteparin sodium was seen to be beneficial in patients waiting to undergo invasive procedures.

TABLE II Adverse events in the FRISC II trial[15]

	Dalteparin sodium (%) (n = 1,049)	Placebo (%) (n = 1,056)
Bleeding		
Major bleeding[a]	3.3	1.5
Minor bleeding[b]	23.0	8.4
Stroke		
Total stroke	1.0	0.8
Hemorrhagic stroke	0.8	0.0
Nonhemorrhagic stroke	0.2	0.8
Other safety endpoints		
Thrombocytopenia (platelet count < 100×10^9/l)	0	0.5
Allergic reaction	2.3	1.8

[a]Defined at fulfilling ≥ 1 of the following criteria: leading to death; intracranial; requiring blood transfusion; decrease in hemoglobin of ≥ 40 g/l; decrease in hemoglobin of ≥ 20 g/l associated with symptoms of bleeding.

[b]All bleeding episodes not classified as major.

As in other trials that have studied the long-term use of a LMWH,[8,19] there was a higher incidence of bleeding with prolonged treatment in FRISC II. However, while patients may run a 1.8% greater risk of bleeding if they receive dalteparin sodium for 3 months, they benefit from a 19% reduction in risk of death and MI. Thus, the early benefit in reduced MI and death achieved through prolonging treatment with dalteparin sodium will outweigh the raised risk of bleeding, at least during the first months when the relative risk reduction is greatest (47% reduction in risk of death or MI at 1 month), a benefit that was still evident up to 60 days.[10]

In conclusion, treatment with dalteparin sodium can be used as a bridge to revascularization, providing the patient with the time to become stabilized while the physician considers the most appropriate plan for an invasive procedure. Following revascularization, continuation of LMWH treatment appears to provide no additional benefits.

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Targeting Treatment for Optimal Outcome

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Summary: Rapid assessment of patients presenting with acute chest pain is essential, in order to distinguish between those who have a life-threatening condition, such as myocardial infarction or unstable angina, and the substantial proportion who do not have an acute coronary syndrome. It is thus of vital importance that reliable techniques are available to facilitate rapid risk stratification, as an aid to both clinical diagnosis and management strategy decisions. Assessments based on clinical findings, electrocardiographic monitoring, symptom-limited exercise testing, and biochemical marker measurements, used either singly or in various combinations, can fulfill this role. The present paper reviews some of the recent data that demonstrate the value of these techniques.

Very few studies allow conclusions to be drawn about optimal treatment strategies in relation to groups stratified according to prognostic markers, and the question of whether intense medical treatment or early invasive intervention is most beneficial is one that clinical trials have yet to address adequately. In the recently completed Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) study, comparisons were made of clinical outcomes achieved with early invasive versus noninvasive (i.e., medical) management strategies, and with short-term versus prolonged anticoagulation with dalteparin sodium (Fragmin®), in patients with unstable coronary artery disease. All study participants underwent symptom-limited exercise testing and provided blood samples for measurements of biochemical markers; continuous electrocardiography monitoring and echocardiography were also performed in a high proportion of patients. Data from the FRISC II trial thus shed further light on the issue of risk stratification and its use to determine optimal treatment strategies.

Key words: unstable coronary artery disease, electrocardiogram, troponin, risk stratification

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Introduction

The short- and long-term prognoses of patients with unstable angina (UA) and non-Q-wave myocardial infarction (NQMI) can differ markedly. This prognostic variability is dependent not only on case mixture, but also on differences in local hospital admission policies, intensity of medical therapy, and the availability and use of invasive treatment. The practical clinical classification system proposed by Braunwald[1] provides a reasonable prediction of outcomes in patients with UA. However, while it appears to be useful for detecting a subpopulation of patients at low risk of future events, the Braunwald system is less accurate in identifying patients in high-risk groups. Thus, other prognostic markers must be taken into account when stratifying patients with unstable coronary syndromes (UCSs) with respect to risk.

Patient risk stratification, using a variety of prognostic markers, is a crucial part of the management of unstable coronary artery disease (UCAD, encompassing the syndromes of both UA and NQMI). The general practitioner will most likely be responsible for early recognition of acute coronary syndromes (ACSs), hence some degree of risk assessment will be involved in reaching a decision on whether to send a patient to hospital. Risk assessment and stratification will certainly be a consideration for the emergency room or casualty doctor and could be imperative to identify a life-threatening myocardial infarction (MI) or episode of UA. At this point, the question will be whether to send the patient to a coronary care unit (CCU), or whether treatment in the emergency room and an early discharge home would be more appropriate. The patient will also need to be risk stratified to facilitate decisions regarding whether intensive antithrombotic treatment is appropriate or whether immediate early or elective revascularization by percutaneous techniques is required.

There is no universally accepted system for risk stratification, and a variety of methods has been employed. Among the approaches most commonly encountered are clinical evaluation based on history and symptoms at presentation, electrocardiography (ECG) on admission, continuous ECG monitoring, biochemical marker measurements, exercise or stress-induced ischemia testing; and angiography. The overall goal of risk stratification is to assess the likelihood of a patient suffering a fatal MI or sudden arrhythmia, progression of the condition to MI, or a recurrence of symptoms after the initial episode has subsided.[2] Symptom recurrence, which is fre-

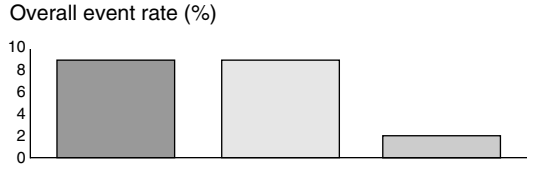
quently the main risk, is related to ongoing and continued inflammatory activity and limitation of coronary arterial flow at the lesion site. Approaches to the prevention of this phenomenon usually comprise either prolonged intense antithrombotic treatment or the undertaking of invasive procedures.

Prognostic Factors in Unstable Coronary Artery Disease

Attempts have been made to correlate clinical presentation with risk in patients with UCAD. Rizik *et al.*[3] related clinical presentation, in terms of the grade of UA, to risk over a 30-day observation period (Fig. 1). Angina was graded from class IA to class IV, where IA referred to an acceleration of previously existent chronic stable angina without ECG changes, while patients in class IV had protracted chest pain (>20 min duration per episode) at rest with persistent abnormalities of subendocardial ischemia. In this study, class IV patients were found to be at the greatest risk of MI and death, while those with a lower class score had a very low risk of events during the 30 days.

Several possible biochemical markers have been evaluated in high-risk UA patients (Braunwald class IIIB).[4] Biasucci *et al.*[4] evaluated levels of C-reactive protein (CRP), a nonspecific but sensitive marker of inflammation, serum amyloid-A (SAA) protein, fibrinogen, total cholesterol, and *Helicobacter pylori* and *Chlamydia pneumoniae* antibody titers. Analysis showed that the incidence of readmission to hospital for the treatment of instability or acute MI in the following 12 months was related to CRP levels. Patients could be divided into low-, middle- and high-risk groups on the basis of CRP levels of ≤2.5mg/l, 2.5–8.6mg/l and ≥8.7mg/l, with associated rates of readmission of 13, 42 and 67%, respectively ($p<0.001$). The prognostic value of SAA was close to that of CRP, and a similar but nonsignificant trend was seen for fibrinogen. A significant correlation was observed between *C. pneumoniae*, but not *H. pylori*, antibody titers and CRP plasma levels.

IA Acceleration of previous exertional angina without ECG changes
IV Protracted rest angina with ECG changes



Class	Myocardial infarction	Intractable angina	Death
IA (%)	2.7	0	0
IB (%)	5.6	3.5	0
II (%)	5.7	3.9	0
III (%)	8.8	11.0	1.5
IV (%)	17.7	19.1	6.4

FIG. 1 Prognostic classification of unstable angina pectoris.[3] ECG = electrocardiogram.

Electrocardiographic monitoring is commonly used to facilitate risk stratification in patients with chest pain suggestive of an ACS. Experience over many years has shown that standard 12-lead ECG provides valuable prognostic information with respect to patient outcomes. In the Global Use of Strategies To open Occluded coronary arteries (GUSTO) IIB trial,[5] it was shown that ST-segment changes are predictive of a high risk of coronary events over the following 30 days. In comparison with patients with T-wave inversion, those with ST-segment elevation were older, more often female, more likely to have prior congestive heart failure, and also more likely to have experienced MI. ST-segment elevation was associated with twice the risk of MI or death (10.8%), compared with T-wave inversion, the latter being associated with a relatively low risk (5.4%) of further events at 30 days.

In spite of its proven value, ECG monitoring can only provide information for risk assessment retrospectively. Computer-assisted continuous multi-lead ECG ischemia monitoring [24-h vectorcardiography (VCG)] is a new technique that allows on-line, noninvasive monitoring of perfusion status, enables measurement of very small ST-segment changes, and is even capable of detecting silent ischemic episodes. In the first FRagmin during InStability in Coronary artery disease (FRISC) trial,[6] it was shown that ST-segment changes are directly related to patient outcome: as the number of episodes of ischemia recorded by VCG increased, so did the risk of acute MI or death within 30 days. Thus, this technology provides a very sensitive predictor of prognosis in patients with UCAD.

Symptom-limited exercise tests have greater diagnostic and prognostic value than submaximal tests in patients with UCAD.[7] The first FRISC study demonstrated the value of a predischarge, symptom-limited exercise test in both men and women following an episode of UCAD.[8,9] It was found that, by combining the number of leads with ST-depression >1 mm with measurements of maximal workload, it was possible to stratify patients into groups at high, intermediate, and low risk of death or MI during 6 months of follow-up.[8,9]

Troponin-T is a troponin isoform that is expressed exclusively in cardiac myocytes. Elevated troponin-T levels are, therefore, a sensitive and specific indicator of myocyte damage and have been investigated as potential prognostic markers of clinical outcome in patients with UCAD in several studies. Möckel *et al.*[10] assessed the significance of troponin levels in patients with low-grade, Braunwald class IB angina. Patients with plasma troponin-T levels ≥0.2 μg/l (troponin-positive) at presentation or 4 h later were shown to be at significantly greater risk of cardiovascular events ($p<0.05$) and MI ($p<0.001$), both while in hospital and after discharge, than those with troponin-T levels below this threshold value. Thus,

troponin-T levels provide a means of identifying patients with low-grade or atypical angina who are at risk of severe cardiovascular events both in the short and the long term. This adds further weight to the suggestion that clinical presentation alone is insufficient to predict patient outcomes.

A subanalysis of the FRISC trial was reported by Lindahl *et al*.[11, 12] This demonstrated that troponin-T is a very powerful predictor of coronary risk (Fig. 2). Rates of MI or death were very low in patients in whom troponin-T levels were not elevated at admission, and increased directly with increasing admission troponin-T levels. Measurement of admission troponin levels provided a more accurate separation of low- and high-risk patients than the more conventional division on the basis of UA or MI. Furthermore, troponin-T was found to be an independent predictor of risk. Prognostic data provided by troponin-T measurements proved to be additive to those obtained by both inclusion ECG and the results of predischarge exercise tests and were of greater value than the prognostic information obtained from measurements of creatine kinase-MB (CKMB).

Since both VCG and measurements of troponin-T levels are independently valuable prognostic techniques, the possibility that combinations of these two approaches could provide additional prognostic information has been investigated as part of the ThRombin In Myocardial ischemia (TRIM) study.[13] These investigations have shown that the combination of elevated troponin-T levels with episodes of ischemia detectable by VCG monitoring (ST-VM episodes) is the strongest predictor of risk (Table I). A 25.8% risk of death or MI was reported in patients with elevated troponin-T plus more than one ST-VM episode, compared with a 1.7% risk in patients without rises in troponin-T or ischemic events. Thus, the combination of biochemical and VCG methods provides a powerful risk stratification tool in UCAD.

Given that the above techniques are available and are of value in the identification of risk, an important question is "When is the most appropriate time for risk stratification: on admission to the emergency room or while the patient is in the CCU?" Recently, Klootwijk and Hamm[14] proposed an emergency department protocol to facilitate rapid exclusion of myocardial ischemia in patients admitted with chest pain (Fig. 3). This protocol utilizes ECG monitoring, measurements of plasma troponin levels, and also stress testing.

The possibility that risk stratification could guide selection of the most appropriate management strategy once the patient is in the CCU is one that is worthy of consideration. If the release of troponin is interpreted as resulting from thromboembolic myocardial injury, it could be postulated that more effective antithrombotic treatment or more potent platelet blockade may be necessary. In the FRISC study,[15] it was shown that administration of the low-molecular-weight heparin (LMWH) dalteparin sodium (Fragmin®) did not have a significant effect on the clinical outcome of patients with admission troponin-T levels < 0.1µg/l, whereas treatment with the LMWH resulted in a significant (p=0.01) risk reduction in patients with admission troponin-T ≥ 0.1 µg/l. Similarly, data from the C7E3 fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) study,[16] which enrolled

TABLE I Troponin-T and ischemia monitoring combined: Death and myocardial infarction at 30 days[13]

	Number of ST-VM episodes on ischemia monitoring	
	< 1 ST-VM episode	≥ ST-VM episode
Troponin-T ≥ 0.2 µg/l	0% (n=27)	25.8% (n=31)
Troponin-T < 0.2 µg/l	1.7% (n=117)	5.3% (n=38)

Abbreviation: VM = vectorcardiography monitoring.

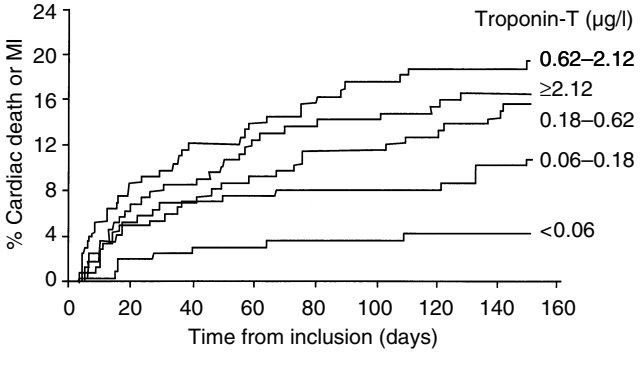


FIG. 2 Troponin-T in unstable coronary artery disease.[11]
MI = myocardial infarction. Reproduced with permission from Lindahl B, Venge P, Wallentin L: Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996 May 1;93(9):1651–1657.

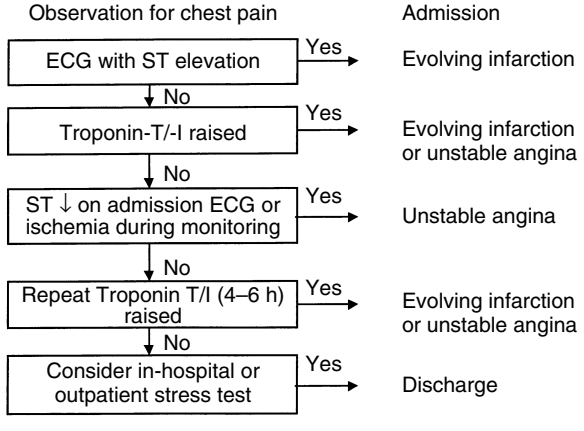


FIG. 3 Emergency room protocol for chest pain.[14]
ECG = electrocardiogram.

high-risk patients with refractory UA, showed that the effects of 18 to 24 h treatment with the glycoprotein (GP) IIb/IIIa inhibitor abciximab differed strikingly in patients with low admission troponin-T levels, compared with those with elevated plasma levels of this biochemical marker. In patients with troponin-T levels < 0.2 µg/l, no significant benefits were derived from abciximab treatment, whereas a 13.8% reduction in events at 30 days was seen in patients with troponin-T ≥0.2 µg/l, and was still evident at 6 months (cumulative event rates 9.5% with abciximab compared with 23.9% with placebo; p=0.002).

In the light of the above study findings, it is clearly of importance to assess the sub-groups in the recent Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial[17,18] in order to investigate whether baseline patient characteristics can be used to identify individuals who are likely to benefit from long-term anticoagulation with dalteparin sodium. More detailed reviews of this trial are given elsewhere in the present supplement.[19, 20] Analysis of patients in the medical part of the trial (i.e., patients randomized to a noninvasive strategy, and in whom invasive procedures were performed only for the treatment of recurrent or re-

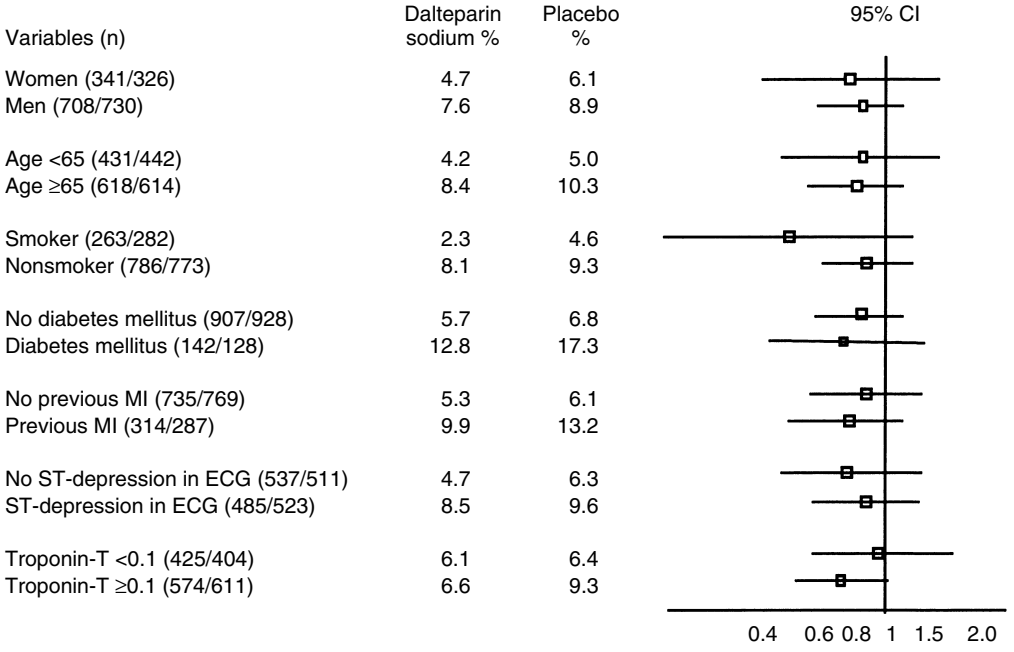


FIG. 4 FRISC II medical arm — sub-group results (death or MI at 3 months).[17] ECG = electrocardiogram, MI = myocardial infarction.

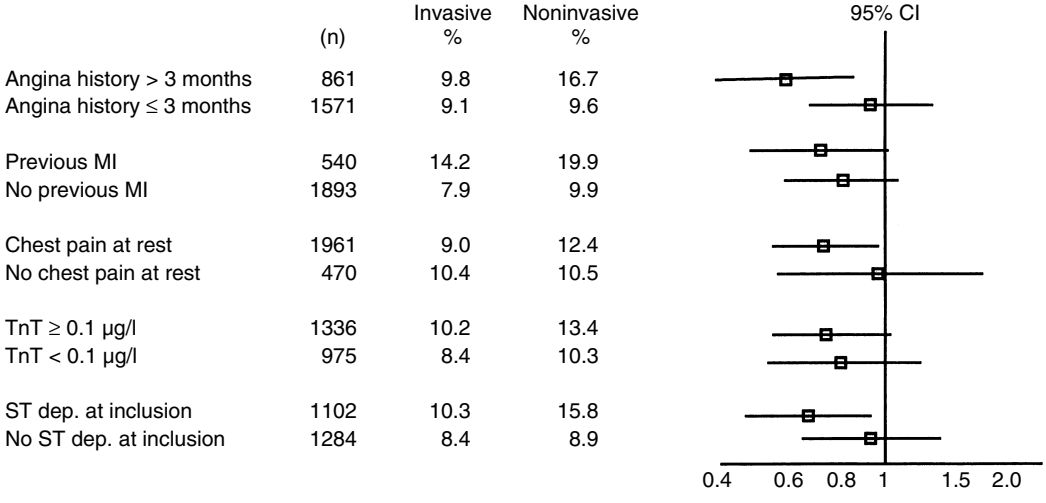


FIG. 5 FRISC II invasive versus noninvasive arm — sub-group results (death or MI at 6 months).[18] MI = myocardial infarction, TnT = Troponin-T, dep. = depression.

fractory ischemia) showed that long-term treatment with dalteparin sodium was beneficial to most patients, regardless of factors such as age and various coronary risk factors, but that these benefits were mainly confined to those patients with elevated troponin-T levels on admission (Fig. 4).[17]

Considering the results obtained at 6-month follow-up in the FRISC II study, and focusing on the comparison of an early invasive with a noninvasive management strategy,[18] it appears that routine early revascularization is more beneficial to men than to women, to the elderly (>65 years of age) than to younger patients, and, although the differences between the two treatment groups in this study were not significant, to nonsmokers than to smokers. In addition, patients with a longer history of angina, those with chest pain at rest, and those with ST-segment depression at admission derive greater benefits from invasive treatment (Fig. 5).

Conclusion

The findings discussed in this paper, and particularly those of the FRISC II trial, enable the proposition of an acute management strategy for patients with UCAD. It would seem to be appropriate for all patients presenting with non-ST elevation UCAD to receive aspirin and treatment with dalteparin sodium. There is increasing evidence to suggest that those with refractory ischemia, and possibly those with a positive troponin-T test, would benefit from treatment with a GP IIb/IIIa inhibitor, particularly if undergoing an invasive procedure. Early angioplasty, with revascularization where appropriate, should ideally be offered to patients with UCAD who have signs of ischemia on ECG monitoring and raised levels of biochemical markers of myocardial damage. Where further stratification is necessary, it appears that patients over 65 years of age, males, and those with angina of more than 3 months' duration benefit most from an invasive management approach following medical pretreatment with dalteparin sodium plus antianginal medications. For patients with raised troponin-T levels, in whom revascularization is contraindicated, prolonged treatment with dalteparin sodium for up to 90 days has been shown to reduce the risk of death or MI significantly.

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