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Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE

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Background Enoxaparin treatment is associated with a 20% reduction in clinical events during the acute phase of management of patients with unstable angina/non ST elevation myocardial infarction. Interest in the use of enoxaparin would be enhanced further if evidence of a durable treatment benefit over the long term could be provided.

Methods Event rates at 1 year for the composite end-point of death/non-fatal myocardial infarction/urgent revascularization and its individual components were ascertained from the TIMI 11B and ESSENCE databases.

Results There was no evidence of heterogeneity between TIMI 11B and ESSENCE in tests for interactions between treatment and trial. A significant treatment benefit of enoxaparin on the rate of death/non-fatal myocardial infarction/urgent revascularization was observed at 1 year (hazard ratio 0·88; $P=0·008$). The event rate was 25·8% in the unfractionated heparin group and 23·3% in the enoxaparin group, an absolute difference of 2·5%. A progressively greater treatment benefit of enoxaparin was observed as the level of patient risk at baseline increased. Treatment effects for the individual end-point elements ranged from 9–14%, favouring enoxaparin.

Conclusions The stable absolute difference in event rates of 2·5% seen at 8 days and again at 1 year favouring enoxaparin may be due to more effective control of the thrombotic process surrounding the index event. Once the pharmacological effect of enoxaparin had dissipated there was no rebound increase in events. Thus, those patients who had received enoxaparin acutely were protected from experiencing a deterioration of the original therapeutic benefit. These findings regarding enoxaparin add to the data to be considered by clinicians when selecting an antithrombin for the acute phase of management of unstable angina/non-ST elevation myocardial infarction.
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See page 264, doi:10.1053/euhj.2001.2845 for the Editorial comment on this article

Introduction

The deficiencies of unfractionated heparin have stimulated clinical investigation of novel pharmacological agents as alternative antithrombins to be used in combination with antiplatelet therapy for patients with acute coronary syndromes. Low molecular weight heparins offer the advantages of a stable and predictable anticoagulant response to a given dose, eliminating the need for haematological monitoring, and offering much simpler administration via the subcutaneous route[1–3]. Compared with unfractionated heparin, as demonstrated in a meta-analysis of the TIMI 11B and ESSENCE trials, enoxaparin treatment is associated with a 20% reduction in clinical events during the acute phase of management of patients with unstable angina/non ST elevation myocardial infarction[4].

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Interest in the use of enoxaparin would be enhanced further if evidence of a durable treatment benefit over the long term could be provided. Indeed, the 1-year follow-up of the ESSENCE trial reported a reduced rate of death and cardiac ischaemic events as well as the performance of invasive diagnostic and therapeutic coronary interventional procedures in patients treated with enoxaparin in the acute phase[5].

In an effort to establish more statistically robust estimates of the treatment effects of enoxaparin on death and serious cardiac ischaemic events individually and in various combinations we combined the 1-year follow-up of TIMI 11B with that previously reported for ESSENCE in a prospectively planned meta-analysis[5]. We hypothesized that the treatment effect of enoxaparin would be sustained at 1 year and that there would be a gradient of treatment benefit based on the TIMI Risk Score established at the time of initial presentation with unstable angina/non-ST elevation myocardial infarction[6].

Methods

Data acquisition

The details of TIMI 11B and ESSENCE have been reported previously[7,8]. Both trials compared enoxaparin 1·0 mg . kg^{-1} subcutaneously every 12 h with intravenous unfractionated heparin during the first several days of the index hospitalization for unstable angina/non-ST elevation myocardial infarction. In TIMI 11B, the first subcutaneous dose of enoxaparin was preceded by an intravenous bolus of 30 mg of enoxaparin. Also, in TIMI 11B, a subset of about 60% of the original trial cohort was eligible for the chronic phase and received, in a double-blind fashion, either reduced doses of enoxaparin twice daily as an outpatient or placebo injections for 43 days based on whether the initial treatment assignment during the acute phase was enoxaparin or unfractionated heparin, respectively. As reported previously, the event rate was low during the chronic phase in TIMI 11B and no benefit of the additional period of treatment with enoxaparin was observed[7]. Therefore, as was the case for the previously reported 43-day meta-analysis all patients enrolled in TIMI 11B were eligible for long-term follow-up whether or not they participated in the chronic phase of the trial[4]. One year follow-up was obtained in both ESSENCE and TIMI 11B at each enrolling site, and case report forms along with supporting documentation were submitted to an independent clinical events committee that adjudicated all events in a blinded fashion[4,5].

Statistical analysis

For TIMI 11B alone and when pooled with ESSENCE using the data reported previously[5], the 1-year follow-up data were analysed according to the intention-to-treat principle via a Cox proportional hazards model. In the pooled dataset, terms for study, treatment and their interaction were included to test for heterogeneity between TIMI 11B and ESSENCE. Prespecified end-points of interest included all-cause mortality, recurrent myocardial infarction, urgent revascularization and the composite outcomes of death/non-fatal myocardial infarction and death/non-fatal myocardial infarction/urgent revascularization as defined previously[7]. Statistical comparisons were made by using the hazard ratio with 95% confidence interval and P value from the Wald chi-square test in the Cox proportional hazards model for time to first event. Comparisons using the Kaplan–Meier survival method were made using the log-rank test. The TIMI Risk Score for unstable angina/non-ST elevation myocardial infarction categorizes patients based on the presence of one or more risk factors present at the time of presentation[6]. In our prior report of the the TIMI Risk Score for unstable angina/non-ST elevation myocardial infarction, the data from TIMI 11B and ESSENCE were analysed separately and outcomes were reported at 14 days of follow-up. In the present analysis of 1-year follow-up, the databases from TIMI 11B and ESSENCE were pooled and patients with 0–2 risk factors were combined into a low risk stratum, those with 3–4 risk factors into an intermediate risk stratum, and 5–7 risk factors into a high risk stratum. The hazard ratios for each stratum were calculated as described above for the entire population. The Cochran–Armitage test for trend was used to evaluate the differences in enoxaparin's treatment effect stratified by the TIMI Risk Score for unstable angina/non-ST elevation myocardial infarction[6].

Results

Of the 7081 patients enrolled collectively in the TIMI 11B and ESSENCE trials, 1-year follow-up was available in 6646 (94%) patients. No differences in the characteristics of the patient populations were noted between the unfractionated heparin and enoxaparin groups for whom 1-year follow-up was available.

Meta-analysis findings

Meta-analyses of each of the end-points of interest showed no evidence of heterogeneity between TIMI 11B and ESSENCE in tests for interactions between treatment and trial. The event rates and and associated hazard ratios for each end-point element and for the double and triple composite end-points were numerically lower in the enoxaparin group for both trials (Table 1).

For the pooled dataset, a significant treatment benefit of enoxaparin on the triple composite end-point of

Table 1 Event rates and treatment effect at 1 year

Event	ESSENCE				TIMI 11B				Combined			
	UFH (n=1564) n (%)	ENOX (n=1607) n (%)	HR (95% CI)	*P*	UFH (n=1957) n (%)	ENOX (n=1953) n (%)	HR (95% CI)	*P*	UFH (n=3521) n (%)	ENOX (n=3560) n (%)	HR (95% CI)	*P*
Lost to follow-up	104	126			100	105			204	231		
D	106 (7·0)	87 (5·7)	0·79 (0·60–1·05)	0·105	147 (7·6)	144 (7·5)	0·98 (0·78–1·23)	0·863	253 (7·4)	231 (6·7)	0·90 (0·75–1·08)	0·25
MI	123 (8·2)	106 (7·0)	0·84 (0·64–1·08)	0·174	174 (9·1)	168 (8·9)	0·96 (0·78–1·19)	0·709	297 (8·7)	274 (8·0)	0·91 (0·77–1·07)	0·249
UR	223 (14·9)	192 (12·5)	0·83 (0·68–1·00)	0·054	296 (15·4)	263 (13·8)	0·88 (0·75–1·04)	0·132	519 (15·2)	455 (13·2)	0·86 (0·76–0·97)	0·016
D/MI	201 (13·2)	173 (11·2)	0·83 (0·68–1·02)	0·071	271 (14·0)	267 (13·8)	0·98 (0·83–1·16)	0·830	472 (13·7)	440 (12·7)	0·92 (0·81–1·04)	0·186
D/MI/UR	390 (25·6)	335 (21·5)	0·81 (0·70–0·94)	0·006	505 (26·0)	478 (24·7)	0·93 (0·82–1·06)	0·263	895 (25·8)	813 (23·3)	0·88 (0·80–0·97)	0·008

Numbers in first row indicate the number of patients originally assigned to the treatment group shown.
The number of patients lost to follow-up by 1 year is shown in the second row.
D=death; ENOX=enoxaparin; HR=hazard ratio; UFH=unfractionated heparin; MI=myocardial infarction; UR=recurrent ischaemia leading to urgent revascularization.

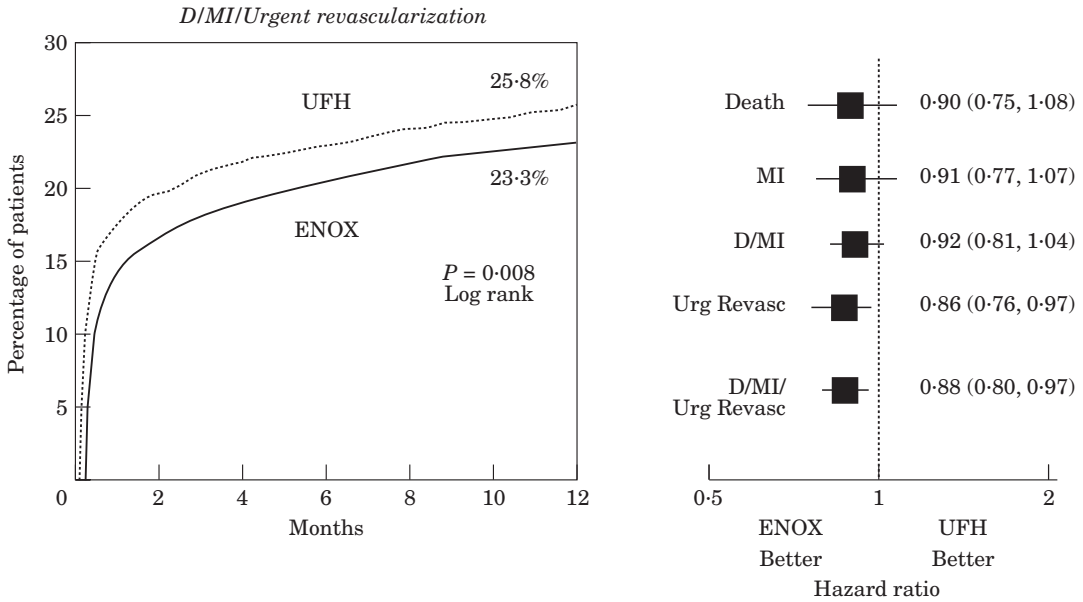

Figure 1 **Meta-analysis of the treatment effect of enoxaparin vs unfractionated heparin at 1 year. The rate of the composite end-point of death/myocardial infarction/urgent revascularization was significantly lower (P=0·008) in the enoxaparin group (left). Point estimates of the hazard ratio for each of the individual elements of the composite end-point as well as the double end-point of death/non-fatal myocardial infarction (D/MI) also favoured enoxaparin. UFH=unfractionated heparin, ENOX=enoxaparin.**

death/non-fatal myocardial infarction/urgent revascularization was observed at 1 year (hazard ratio 0·88; 95% confidence interval 0·80, 0·97). The event rate was 25·8% in the unfractionated heparin group and 23·3% in the enoxaparin group, an absolute difference of 2·5% that was associated with P=0·008 by the log rank test (Fig. 1). The point estimates for the hazard ratio for each individual element of the composite triple end-point favoured the enoxaparin group at 1 year, with treatment effects ranging from 9–14% (Fig. 1). A significant difference was observed for the urgent revascularization end-point, with a hazard ratio of 0·86; 95% confidence interval 0·76, 0·97. The rate of death/non-fatal myocardial infarction was lower in the enoxaparin group (hazard ratio 0·92, 95% confidence interval 0·81, 1·04).

In order to exclude any impact of prolonged treatment with enoxaparin during the chronic phase of TIMI 11B, we compared the composite event curves for the enoxaparin and unfractionated heparin groups at 1 year in the combined TIMI 11B and ESSENCE dataset, excluding those patients who participated in the chronic phase of TIMI 11B. The event rate was 29·0% in the unfractionated heparin group and 24·3% in the enoxaparin group, an absolute difference of 4·7% and hazard ratio of 0·81 that was associated with P=0·0002 by the log rank test (data not shown).

Stratification by risk score

Among the patients in the combined dataset, 2101 (32%) were classified as low risk, 3696 (56%) as intermediate risk, and 849 (12%) as high risk based on the TIMI Risk Score for unstable angina/non-ST elevation myocardial infarction. The point estimates for the hazard ratio for the triple end-point of death/non-fatal myocardial infarction/urgent revascularization were numerically lower in the enoxaparin groups for each stratum. There was a progressively greater treatment effect of enoxaparin as the level of patient risk increased (Fig. 2; P=0·02 by Cochran–Armitage test for trend). A statistically significant treatment benefit of enoxaparin was observed in the intermediate (hazard ratio 0·87; 95% CI 0·77, 0·99; P=0·04) and high risk (hazard ratio 0·80; 95% CI 0·65, 0·98; P=0·03) groups.

Discussion

The majority of the evidence of enoxaparin's treatment effect in unstable angina/non-ST elevation myocardial infarction centres around the acute phase of management of unstable angina/non-ST elevation myocardial infarction. The treatment benefit of enoxaparin appeared early (within 48 h) when a direct head-to-head comparison with unfractionated heparin was occurring[7], was present even in patients who had optimal levels of anticoagulation with unfractionated heparin[9], was of a similar magnitude in patients who were treated exclusively medically and in those who underwent a percutaneous revascularization procedure after a period of initial medical stabilization[10], and was evident in troponin positive patients even if creatine kinase MB levels were not elevated[11]. Following discontinuation of

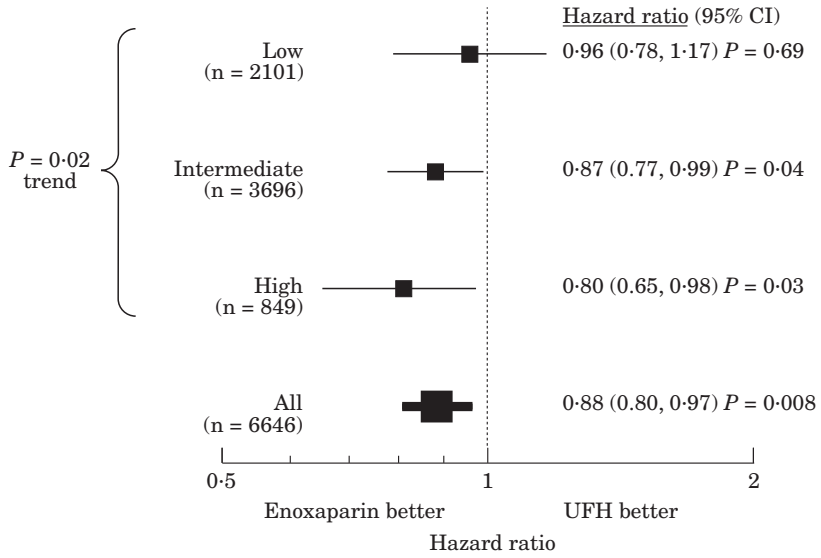

Figure 2 **Treatment effect of enoxaparin stratified by risk score. The progressively smaller hazard ratios favouring enoxaparin moving from the low to high risk groups indicates an increasing treatment benefit of enoxaparin as the level of patient risk at the initial presentation increases (P=0·02 by Cochran–Armitage test for trend). The number of risk factors based on the TIMI Risk Score for unstable angina/non-ST elevation myocardial infarction was 0–2 in the low risk stratum, 3–4 in the intermediate risk stratum, and 5–7 in the high risk stratum.**

treatment, a rebound increase in ischaemic episodes on ST monitoring is seen more frequently with unfractionated heparin than enoxaparin[12]. Although the unit cost of treatment with enoxaparin is greater than that of unfractionated heparin, by reducing the rate of events and the need for revascularization procedures, enoxaparin therapy was found to be an economically dominant strategy[13,14]. Using a simple bedside risk score, it is clear that the treatment effect of enoxaparin during the acute phase increases progressively as a patient's level of risk increases[6,10].

This meta-analysis of the ESSENCE and TIMI 11B trials builds on the acute phase data noted above and shows a sustained benefit of enoxaparin at 1-year follow-up. The treatment effects observed at 1 year are of a similar magnitude for each of the individual end-point elements, suggesting that the benefit is not driven exclusively by one type of event (Fig. 1). Consistent with the findings reported in TIMI 11B, there does not appear to be any benefit from prolonged treatment with enoxaparin beyond the acute hospitalization.

Particularly instructive observations are made when comparing the absolute event rates at day 8 and at 1 year in the two treatment groups for the composite end-point of death/myocardial infarction/urgent revascularization. At day 8, the rates were 13·5% in the unfractionated heparin group and 11·0% in the enoxaparin group, an absolute difference of 2·5% and a relative risk difference of 0·81[4]. Following the brisk rate of development of events during the first week of observation in the trials, the rate slowed, so that 51 weeks later at the end of 1 year the rates had doubled in the two treament groups but the absolute difference remained 2·5% and remained significantly lower in the enoxaparin group (Fig. 1). As observed for the acute phase, the treatment effect of enoxaparin observed at 1 year increased progressively as the level of patient risk increased (Fig. 2)[6]. About two-thirds of the population analysed in the combined dataset (intermediate plus high risk strata) achieved significant reductions in the triple end-point at 1 year favouring enoxaparin.

Potential mechanisms of sustained benefit of enoxaparin

Reactivation of the coagulation cascade and an attendant rebound in clinical events within 24 h after discontinuation of unfractionated heparin may be related to incomplete suppression of thrombin activity and relatively rapid clearance of the antifactor IIa (thrombin) activity of unfractionated heparin by the reticuloendothelial system[3,15,16]. Features of enoxaparin that may permit a greater degree of suppression of thrombin generation than with unfractionated heparin include a higher antifactor Xa: antifactor IIa ratio (3·8:1), a prolonged duration of antifactor Xa activity, a higher level of antifactor IIa activity due to better bioavailability, less sensitivity to the inhibitory effects of platelet factor 4, a greater capacity to release tissue factor pathway inhibitor, a lower propensity to promote

activation and aggregation of platelets, and potential antiplatelet effects via higher degrees of suppression of von Willebrand factor[17–26].

We hypothesize that for the reasons outlined above, enoxaparin compared with unfractionated heparin achieved more effective control of the thrombotic process surrounding the index event leading to enrollment in TIMI 11B and ESSENCE. Once the pharmacological effect of enoxaparin dissipated there was no rebound increase in events. Thus those patients who had received enoxaparin acutely were protected from experiencing a deterioration of the original therapeutic benefit. Of note, however, in both treatment groups a disturbing number of events continued to occur over the long term, indicating the need for more effective therapy over the long term. Potential candidates for long-term antithrombotic therapy include warfarin and the oral forms of direct antithrombins[27].

Clinical implications

The 20% reduction in clinical events with enoxaparin during the acute phase of management of unstable angina/non-ST elevation myocardial infarction is of a magnitude that most clinicians would consider sufficient to change their practice pattern. Enoxaparin's durable treatment effect at 1 year, noted in the entire population but most marked in the two-thirds of the patients at highest baseline risk, also compares quite favourably with the more transitory benefits of intravenously administered direct antithrombins and the reported experience to date with dalteparin[28,29]. These findings, coupled with the encouraging open label experience combining enoxaparin with intravenous glycoprotein IIb/IIIa inhibitors[30] add to the data to be considered by clinicians when selecting an antithrombin for the acute phase of management of unstable angina/non-ST elevation myocardial infarction.

References

[1] Barrowcliffe T, Johnson E, Thomas D. Low molecular weight heparin. Chicester: John Wiley & Sons, 1992: 209.

[2] Bounameaux H. Low-molecular-weight heparins in prophylaxis and therapy of thromboembolic disease. New York: Marcel Dekker, Inc, 1994: 323.

[3] Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337: 688–98.

[4] Antman EM, Cohen M, Radley D *et al*. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. Circulation 1999; 100: 1602–8.

[5] Goodman SG, Cohen M, Bigonzi F *et al*. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: 1-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. J Am Coll Cardiol 2000; 36: 693–8.

[6] Antman EM, Cohen M, Bernink PJLM *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. J Am Med Assoc 2000; 284: 835–42.

[7] Antman EM, McCabe CH, Gurfinkel EP *et al*. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999; 100: 1593–601.

[8] Cohen M, Demers C, Gurfinkel EP *et al*. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. N Engl J Med 1997; 337: 447–52.

[9] Bozovich GE, Gurfinkel EP, Antman EM *et al*. Superiority of enoxaparin versus unfractionated heparin for unstable angina/non-Q-wave myocardial infarction regardless of activated partial thromboplastin time. Am Heart J 2000; 140: 637–42.

[10] Antman EM. Enoxaparin: a new standard of care. Eur Heart J 2000; 2 (Suppl F): F7–F11.

[11] Morrow DA, Antman EM, Tanasijevic M *et al*. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. J Am Coll Cardiol 2000; 36: 1812–7.

[12] Goodman SG, Barr A, Sobtchouk A *et al*. Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST segment monitoring substudy. J Am Coll Cardiol 2000; 36: 1507–13.

[13] Mark DB, Cowper PA, Berkowitz SD *et al*. Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial. Circulation 1998; 97: 1702–7.

[14] O'Brien BJ, Willan A, Blackhouse G *et al*. Will the use of low-molecular-weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada? Am Heart J 2000; 139: 423–9.

[15] Theroux P, Waters D, Lam J *et al*. Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 1992; 327: 141–5.

[16] Mombelli G, Marchetti O, Haeberli A *et al*. Effect of intravenous heparin infusion on thrombin-antithrombin complex and fibrinopeptide A in unstable angina. Am Heart J 1998; 136: 1106–13.

[17] Lane DA, Denton J, Flynn AM *et al*. Anticoagulant activities of heparin oligosaccharides and their neutralization by platelet factor 4. Biochem J 1984; 218: 725–32.

[18] Abildgaard U, Lindahl AK, Sandset PM. Heparin requires both antithrombin and extrinsic pathway inhibitor for its anticoagulant effect in human blood. Haemostasis 1991; 21: 254–7.

[19] Hoppensteadt DA, Jeske W, Fareed J *et al*. The role of tissue factor pathway inhibitor in the mediation of the antithrombotic actions of heparin and low-molecular-weight heparin. Blood Coagul Fibrinolysis 1995; 6 (Suppl 1): S57–64.

[20] Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation 1998; 97: 251–6.

[21] Montalescot G, Philippe F, Ankri A *et al*. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. French Investigators of the ESSENCE Trial. Circulation 1998; 98: 294–9.

[22] Antman EM, Handin R. Low-molecular-weight heparins: an intriguing new twist with profound implications. Circulation 1998; 98: 287–9.

[23] Brieger D, Dawes J. Long-term persistence of biological activity following administration of Enoxaparin sodium (clexane) is due to sequestration of antithrombin-binding low molecular weight fragments — comparison with unfractionated heparin. Thromb Haemost 1996; 75: 740–6.

[24] Lindhout T, Hemker H. Anticoagulant mechanism of action of low molecular weight heparins. In: Doutremepuich C. ed. Low Molecular Weight Heparins in Clinical Practice. New York: Marcel Dekker, Inc, 1992: 23–50.

[25] Agnelli G. Pharmacological activities of heparin chains: should our past knowledge be revised? Haemostasis 1996; 26: 2–9.
[26] Montalescot G, Collet JP, Lison L *et al*. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. J Am Coll Cardiol 2000; 36: 110–4.
[27] Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. J Am Med Assoc 1999; 282: 2058–67.
[28] FRISC II Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999; 354: 701–7.
[29] Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularization procedures in patients with acute myocardial ischemia without ST elevation: a randomised trial. Lancet 1999; 353: 429–38.
[30] Kereiakes DJ, Grines C, Fry E *et al*. Combination enoxaparin and abciximab during percutaneous coronary intervention: a new standard of care? Curr Intervent Cardiol Rep 2000; 2: 157–64.