Vascular Development and Vessel Remodelling

Patterns of use of heparins in ACS

Correlates and hospital outcomes: The Global Registry of Acute Coronary Events (GRACE)

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Summary

A systematic study that compares the patterns of use of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in patients with acute coronary syndromes (ACS) has, to date, not been carried out in the "real-world" setting. The aim of this report is to identify patterns of use of UFH and LMWH and to report their correlates and outcomes in a broad spectrum of ACS patients enrolled in the observational Global Registry of Acute Coronary Events (GRACE).

The use of LMWH and UFH was analysed in 13,231 ACS patients according to patient history, concomitant treatment and invasive procedures in US and non-US sites. Frequency of use in hospitals with and without facilities for percutaneous coronary interventions (PCI) was investigated, and outcomes were analysed.

Results show that younger patients (<60 years), those receiving antiplatelet therapies, thrombolytics, beta-blockers, angiotensin-converting enzyme inhibitors, patients admitted to hospitals with PCI facilities, and patients undergoing invasive procedures were more likely to receive UFH, or both UFH and LMWH than LMWH alone (80.1% enoxaparin, 19.9% other LMWH). LMWH was used less often in US than non-US sites. After adjusting for confounding variables, patients receiving LMWH had significantly lower rates of hospital mortality (*P*=0.009) and major bleeding (*P*<0.0001). Similar results were observed in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction or unstable angina.

We can conclude that UFH tends to be used more frequently than LMWH, but hospital outcomes appeared to be better with LMWH after adjusting for covariables.

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Introduction

Acute coronary syndromes (ACS) constitute a major burden on healthcare resources in industrialized countries and are a frequent cause of emergency admission to hospital (1). Mortality and morbidity remain significant both in patients with unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI) (2) and following ST-segment elevation myocardial infarction (STEMI) (3). Optimizing management approaches to improve patient outcomes remains a key goal. Recent decades have witnessed significant developments in the pharmacological and invasive options for managing ACS; advances in thrombolytic, antithrombotic and antiplatelet therapies offer the prospect of reducing mortality and other adverse outcomes. Large-scale randomized clinical trials have produced evidence supporting the efficacy of these approaches across the spectrum of ACS (4-12), under the controlled conditions and within the selected populations of randomized trials. By contrast, data on how the newer therapies affect outcomes in everyday clinical practice are less readily obtained. In particular, to date no systematic study has been conducted within the "real-world" setting comparing the patterns of use and hospital outcomes of unfractionated heparin (UFH) with those of low-molecular-weight heparin (LMWH) in the full spectrum of patients hospitalized with ACS.

The Global Registry of Acute Coronary Events (GRACE) is a large ongoing prospective multinational observational study of patients hospitalized with ACS. The aim of GRACE is to improve the quality of care for patients with ACS by providing information about differences in, and relationships between, patient characteristics, treatment practices and hospital outcomes. The current report aims to identify patterns of use of UFH and LMWH in the wide spectrum of ACS patients enrolled in GRACE.

Materials and methods

Full details of the GRACE rationale and methodology have been published (13-15). In brief, GRACE is designed to reflect an unbiased population of patients with ACS, irrespective of geographic region. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom, United States) are participating in this observational study. These regions were chosen to represent care received by patients with ACS in populations that varied by demographic, clinical and treatment characteristics.

Patients entered in the registry had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (i.e., have symptoms consistent with acute ischemia) and have at least one of the following:

electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease (13). The qualifying ACS must not have been precipitated or accompanied by a significant comorbidity, trauma or surgery. Where required, study investigators received approval from their local hospital ethics or institutional review board. Data were collected at each site by a trained coordinator using a standardized case report form. Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used. All cases were assigned to one of the following categories–STEMI, NSTEMI, unstable angina, and other cardiac/non-cardiac. These definitions take into account clinical presentation, electrocardiographic findings and the results of serum biochemical markers of necrosis:

- STEMI: new or presumed new ST-segment elevation ≥1 mm seen in any location or new left bundle branch block on the index or qualifying electrocardiogram with at least 1 positive cardiac biochemical marker of necrosis (including troponin measurements, whether qualitative or quantitative).
- NSTEMI: presence of at least 1 positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or qualifying electrocardiogram.
- Unstable angina: absence of ST-segment elevation on the electrocardiogram and serum biochemical markers indicative of myocardial necrosis within each hospital laboratory's normal range but with a discharge diagnosis of ACSs. Patients originally admitted for unstable angina but in whom myocardial infarction occurred during the hospital stay were classified as having a myocardial infarction.
- Other cardiac/non-cardiac diagnoses: cases where the presumptive admission diagnosis was acute coronary syndrome or 'chest pain/rule out myocardial infarction'; however, these patients were subsequently shown to have some other cardiac or non-cardiac cause for their presentation.

Standardized definitions were also used for selected hospital complications and outcomes (13).

Statistical analysis

Differences in patient demographics and clinical characteristics and hospital outcomes between patients who received LMWH, UFH or both were assessed using a chi-square test for categorical variables (expressed as frequencies and percentages) and Kruskal-Wallis tests for continuous variables (expressed as medians). Multiple logistic regression was used to examine the association between LMWH, LMWH and UFH or UFH and hospital outcomes of major bleeding, stroke, and mortality, with adjustment for demographics and hospital medications and

procedures that were univariately significant between the two groups (*P*<0.25). The statistical analysis was performed using SAS software, version 8.1.

Results

The use of LMWH and UFH was analysed in 16,116 patients with ACS enrolled in GRACE since April 1999. A total of 2885 patients were excluded from the analysis (2473 patients had taken neither LMWH or UFH and 412 patients had missing data). Data from 13,231 patients were analysed according to patient history, concomitant treatment and invasive procedures in US and non-US sites.
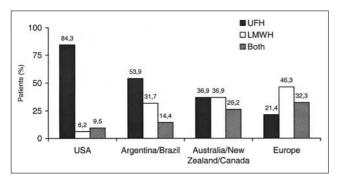
Of the population analysed, 4450 (34%) received a diagnosis of STEMI and 8781 (66%) a diagnosis of UA/NSTEMI. Baseline characteristics of patients and treatments are summarized in Table 1. Overall, 5660 (43%) patients received UFH, 4496 (34%) were treated with LMWH and 3075 (23%)

received both medications during hospitalization. Patterns of LMWH usage varied widely with geographical location and other factors. Patients receiving UFH were more likely to have a diagnosis of NSTEMI or unstable angina than STEMI, be younger (<60 years), be receiving concomitant treatment with antiplatelet agents, thrombolytics, beta-blockers, or angiotensin-converting enzyme (ACE) inhibitors, and to be undergoing invasive procedures (Table 1). Patients receiving both medications were also more likely to undergo invasive procedures. Regional differences were analysed according to the distribution of centers in four geographic regions: Australia, New Zealand and Canada, which were grouped together because they exhibited similar practice patterns with regards to the use of invasive procedures; Argentina and Brazil; Europe; and the United States. LMWH was used less often than UFH in sites located in the United States and Argentina/Brazil, and more frequently than UFH in European locations. Usage was equal in Australia/New Zealand/Canada (Fig. 1). LMWH alone was
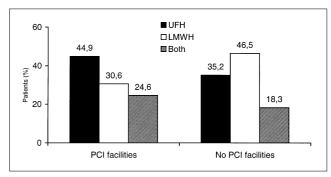
Table 1: Key baseline characteristics and hospital treatments in patients who received unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).

	Overall ACS			STEMI			UA/NSTEMI		
	UFH	LMWH	Both	UFH	LMWH	Both	UFH	LMWH	Both
	n=5660	n=4496	N=3075	n=2209	n=995	n=1246	n=3451	n=3501	n=1829
Patient history									
Median age (years)	65.0	67.6	65.4	63.1	67.5	63.9	66.2	67.7	66.4
Age <60 years (%)	37.4	30.7	35.2	42.5	31.0	40.3	34.2	30.6	31.7
Male (%)	67.0	65.5	70.3	71.5	70.9	71.7	64.1	63.9	69.3
Current smoker (%)	27.5	23.9	26.7	37.2	32.7	33.9	21.3	21.4	21.9
Concomitant treatments									
ACE inhibitors (%)	59.0	52.5	67.1	65.2	64.0	77.1	55.0	49.2	60.2
GP IIb/IIIa inhibitors (%)	24.4	10.5	24.8	29.5	21.7	30.4	21.1	7.3	20.9
Antiplatelets (excluding aspirin) (%)	2.6	1.1	2.2	2.2	0.9	2.4	2.8	1.1	2.1
Beta-blockers (%)	82.5	75.4	83.3	83.9	76.7	85.2	81.6	75.0	82.0
Thrombolytics (%)	24.3	7.5	20.2	53.5	26.9	42.2	5.6	2.0	5.3
Invasive procedures									
CABG (%)	7.7	4.4	9.1	5.2	3.7	5.8	9.4	4.7	11.3
PCI (%)	32.8	21.0	42.7	44.8	34.0	48.6	25.0	17.3	38.6

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

Figure 1: Geographic variations in the use of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH).

Figure 2: Use of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) in hospitals with or without access to percutaneous coronary intervention (PCI) facilities.

more often used in sites without PCI facilities (Fig. 2). Of patients treated with LMWH, 80.1% received enoxaparin.

For all ACS patients, rates of stroke, major bleeding, and mortality are shown in Table 2. After adjusting for covariables, compared with UFH, use of LMWH was associated with a 37% lower risk of mortality (*P*=0.009) and 55% lower bleeding rates (*P*<0.0001) across all ACS categories. Similar results were observed in the STEMI and UA/NSTEMI subgroups (Figs. 3a and 4a). This result was paralleled in the lower risk of mortality and bleeding also observed in patients receiving both LMWH and UFH, versus UFH alone (Figs. 3b and 4b). The risk of major bleeding in patients aged 75 years and over was similar to that in patients aged less than 75 years, both overall and across all ACS categories (Table 3).

Discussion

Outcomes from major randomized controlled trials support the use of LMWH as an alternative to UFH in the acute management of non-ST-segment elevation ACS (4-8). While two trials – FRIC (Fragmin in Unstable Coronary Artery Disease,

dalteparin) and FRAXIS (Fraxiparin Versus Unfractionated Heparin in Acute Coronary Syndromes, nadroparin) (5, 6) – suggested equivalence of LMWH and UFH, a further two trials have shown improved outcomes with LMWH compared with UFH. The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) study and the TIMI 11B (Thrombolysis in Myocardial Infarction) study demonstrated a significant reduction in the incidence of the composite endpoint of death, myocardial infraction and recurrent angina leading to revascularization in patients with unstable angina or non-Q-wave myocardial infarction with enoxaparin versus UFH, without increasing the risk of major bleeding (7, 8). Efficacy benefits were maintained at 1 year (16). It should be noted that in the TIMI 11B study the durations of the two treatments were different (median duration 4.6 days with enoxaparin versus 3 for UFH). However, differences in the clinical endpoints between groups emerged in the first 48 hours of treatment, during the treatment period for both drugs, suggesting that the difference in clinically endpoints can be attributed at least in part, to the different drugs. Several clinical studies have also investigated the role of LMWH in STEMI,

Table 2: Hospital outcomes: rates of mortality, major bleeding and stroke.

Outcomes (%)	Overall ACS				STEMI				UA/NSTEMI			
	UFH	LMWH	Both	P	UFH	LMWH	Both	P	UFH	LMWH		P
Mortality	6.0	3.9	3.6	<0.0001	7.7	6.7	5.3	0.025	5.0	3.1	2.4	<0.0001
Major bleeding	4.9	2.1	3.7	<0.0001	5.8	3.0	4.6	0.0021	4.4	1.9	3.2	<0.0001
Stroke	1.2	0.7	1.0	0.0167	1.9	1.2	1.5	0.3869	0.8	0.5	0.7	0.286
Re-MI	3.0	1.6	2.8	0.0012	3.7	2.3	3.5	0.136	2.1	1.0	2.0	0.0521

ACS, acute coronary syndrome; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina
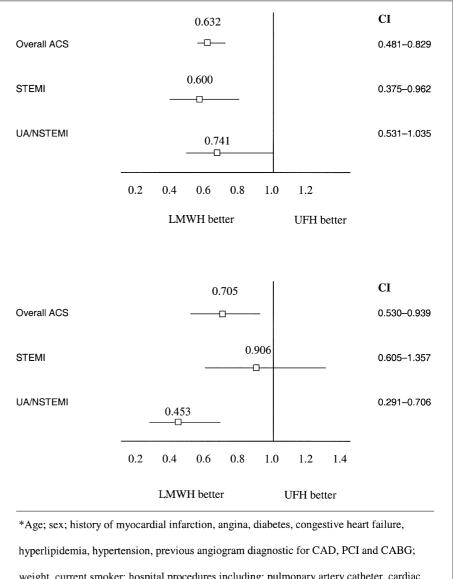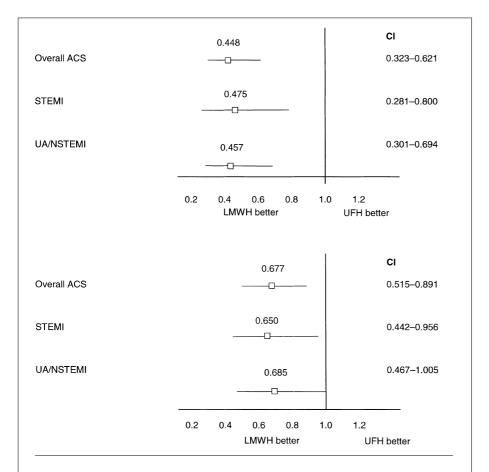
Figure 3: Hospital outcomes – death: adjusted* odds ratios and 95% confidence intervals for mortality in patients treated with (a) low-molecular-weight heparin (unfractionated heparin is the referent group) and (b) low-molecular-weight heparin and unfractionated heparin.

*Age; sex; history of myocardial infarction, angina, diabetes, congestive heart failure, hyperlipidemia, hypertension, previous angiogram diagnostic for CAD, PCI and CABG; weight, current smoker; hospital procedures including: pulmonary artery catheter, cardiac catheterization, PCI, CABG; hospital medications including: aspirin, warfarin, thienopyridines and other antiplatelet or antithrombin agents, glycoprotein IIb/IIIa inhibitc ACE inhibitors, beta-blockers and thrombolytics

both as an adjunct to thrombolytic therapy (9-12) and in patients ineligible for pharmacological reperfusion (17). Available data suggest that LMWH provides effective anticoagulation in these instances, with clear evidence of improved reperfusion with LMWH enoxaparin as an adjunct to thrombolysis in STEMI (12). Some results with enoxaparin also indicate an efficacy advantage over UFH in this indication (9).

Uncertainties remain as to whether outcomes observed under trial conditions, with carefully selected populations, have direct relevance to the »real world« of emergency cardiac care. Previous studies (18) have demonstrated the wide variation in management practices between different centers and different countries, which may influence outcomes and potentially negate differences between therapies. Further, the spectrum of patients admitted with ACS inevitably includes many with characteristics and comorbidities that would be excluded from most randomized controlled trials, casting further doubt on the real-world applicability of trial findings.

The current study was designed to address these uncertainties by analyzing LMWH and UFH usage and outcomes in the unselected population enrolled in the GRACE registry, encompassing a wide range of patients admitted to a variety of hospi-

Figure 4: Hospital outcomes – major bleeding: adjusted* odds ratios and 95% confidence intervals for major bleeding patients treated with (a) low-molecular-weight heparin (unfractionated heparin is the referent group) and (b) low-molecular-weight heparin and unfractionated heparin.

*Age; sex; history of myocardial infarction, angina, diabetes, congestive heart failure, hyperlipidemia, hypertension, previous angiogram diagnostic for CAD, PCI and CABG; weight, current smoker; hospital procedures including: pulmonary artery catheter, cardiac catheterization, PCI, CABG; hospital medications including: aspirin, warfarin, thienopyridines and other antiplatelet or antithrombin agents, glycoprotein IIb/IIIa inhibitors, ACE inhibitors, beta-blockers and thrombolytics

tal types with varying facilities and management practices. In patients treated in the "real world" setting of emergency ACS management, included in this registry, compared with UFH, use of LMWH appeared to be associated with significantly lower rates of hospital mortality, major bleeding, stroke and re-myocardial infarction across all patients with ACS. Many patients treated with LMWH may also receive UFH (for example, if they are later to undergo PCI or CABG), and this would lead to a "selection bias" in the LMWH alone patients, as the higher risk patients were most likely to follow this treatment course. We therefore included in our analysis the group of patients receiving both treatments. When the LMWH plus UFH patients are compared to those on UFH alone, it was also found that patients receiving both therapies had significantly lower rates of mortality and major bleeding. In contrast to the recently presented results from the ASSENT III Plus study (19), patients aged 75 years and over who were treated with LMWH

alone or with UFH had similar rates of major bleeding to those aged less than 75 years. For stroke and re-myocardial infarction the picture was not as clear: although the rates were lower with LMWH and UFH than with UFH alone, statistical significance was not achieved. Variations in mortality reduction were apparent in the unadjusted outcomes for UA/NSTEMI compared with STEMI, with greater apparent benefit with LMWH versus UFH in the UA/NSTEMI group (Table 2). After adjusting for a wide range of clinically relevant covariables, however, similar benefits were observed in both subgroups, suggestive of a genuine treatment difference across all types of ACS. Further study is required to determine if other covariates not collected in this registry play a role, or if the benefits persist beyond the period of hospitalization, and if late treatment differences emerge.

It has been claimed that benefits of LMWH are largely confined to high-risk ACS patients (20); the current study investigates the use of LMWH in an unselected study population that

Table 3: Hospital outcomes – major bleeding in patients aged ≥75 years and those aged <75 years.

Overall ACS	Treatment	Adjusted* odds ratio (95% confidence interval)
Age ≥75 years		
Major bleeding	LMWH only	0.441 (0.271, 0.717)
	LMWH and UFH	0.522 (0.323, 0.845)
Age <75 years		
Major bleeding	LMWH only	0.441 (0.286, 0.679)
	LMWH and UFH	0.758 (0.544, 1.05)
ST-segment elevation myocardial infarction		
Age ≥75 years		
Major bleeding	LMWH only	0.415 (0.175, 0.981)
	LMWH and UFH	0.451 (0.217, 0.939)
Age <75 years		
Major bleeding	LMWH only	0.508 (0.266, 0.970)
	LMWH and UFH	0.753 (0.479, 1.18)
Non-ST-segment elevation myocardial infarction		
Age ≥75 years		
Major bleeding	LMWH only	0.503 (0.276, 0.916)
	LMWH and UFH	0.612 (0.323, 1.16)
Age <75 years		
Major bleeding	LMWH only	0.416 (0.260, 0.666)
	LMWH and UFH	0.727 (0.455, 1.16)

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.
*Age; sex; history of myocardial infarction, angina, diabetes, congestive heart failure, hyperlipidemia, hypertension, previous angiogram diagnostic for CAD, PCI and CABG; weight, current smoker; hospital procedures including: pulmonary artery catheter, cardiac catheterization, PCI, CABG; hospital medications including: aspirin, warfarin, thienopyridines and other antiplatelet or antithrombin agents, glycoprotein IIb/IIIa inhibitors, ACE inhibitors, beta-blockers and thrombolytics.

is sufficiently large to assume inclusion of the full spectrum of both low- and high-risk ACS patients.

An important point to note is that 80% of patients treated with LMWH in the current study received the same agent: enoxaparin. It may not be possible to generalize the results obtained to all LMWHs.

The substantial geographic variation in LMWH usage observed in the current study reinforces previous reports highlighting major variations in treatment approaches for ACS. Caution must be exercised in interpreting registry data, and the treatment groups in this study were not randomized and may thus be biased. However, the significant improvements in outcomes with LMWH observed here suggest that LMWH may offer benefit across a highly heterogeneous patient population, irrespective of local management practices. Recent studies investigating the use of LMWH within the context of percutaneous coronary interventions and concomitant administration of

glycoprotein IIb/IIIa receptor antagonists demonstrate that LMWH offers safe anticoagulation as an adjunct to these different approaches (10, 21, 22). Together the data suggest that LMWH may be used in initial emergency therapy across a broad spectrum of patients without compromising later treatment choices.

Xiao and Theroux (14) demonstrated, in the experimental setting, that enoxaparin in contrast to UFH is able to inhibit platelet activation. This finding might explain the superiority of LMWH over UFH in ACS treatment, and is supported by the observation in ASSENT-3 (Assessment of the safety and Efficacy of a New Thrombolytic Regimen III) (9) that enoxaparin was more effective than UFH alone. Previous studies have shown LMWH offers practical advantages over UFH. In contrast to UFH, the greater bioavailability, more predictable dose response and longer half-life of LMWH allow subcutaneous 12-hourly dosing of a fixed dose, based on body weight,

without the need for monitoring or dose adjustment (20). These logistic benefits provide additional support for LMWH use in emergency ACS management.

Study limitations

It should be noted that this analysis was observational, post-hoc and non-randomized. Analysis of registry data is useful for developing hypotheses, but does not replace randomized controlled trials. In this registry, the adjustment of covariables may not be complete, but the major predictors of risk such as age, history of myocardial infarction, diabetes, and congestive heart failure are taken into account. In this analysis, very few patients (<25%) received glycoprotein IIb/IIIa blockers, which may not reflect practice patterns in some regions of the world, especially at invasive centers. Four-fifths of patients treated with LMWH in the current study received enoxaparin, but it may not be possible to generalize the results to all LMWHs.

Conclusions

For patients within the GRACE registry, UFH and LMWH are used with approximately equal frequency in patients diagnosed with unstable angina or NSTEMI. UFH is used more frequently than LMWH in patients diagnosed with STEMI. Both UFH and LMWH are used in 23% of patients, often in patients undergoing PCI or CABG. Patterns of usage of LMWH versus UFH vary widely with geographical location and other factors. Compared with LMWH, UFH usage is far greater in the United States and somewhat greater in Argentina and Brazil. LMWH tends to be used more often than UFH in Europe; usage is equal in Australia, Canada and New Zealand.

Overall rates of hospital mortality for all patients with ACS and the UA/NSTEMI subgroup were significantly lower with LMWH alone or in combination with UFH than with UFH alone. This difference is significant for both STEMI and UA/NSTEMI subgroups after adjusting for the covariables

recorded in GRACE. Overall rates of major bleeding and stroke were significantly lower with LMWH than with UFH; bleeding rates were significantly lower in both subgroups and after adjusting for covariables.

These results support the findings from prior randomized controlled trials demonstrating efficacy benefits of enoxaparin over UFH in the acute management of non-ST-segment elevation coronary syndromes. Further studies are required to determine whether the relative reduction in mortality rate with LMWH is sustained beyond the in-hospital period, and whether other treatment differences manifest later.

Acknowledgements

Appendix

GRACE Scientific Advisory Committee
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References

1. Fox KAA, Cokkinos DV, Deckers J, et al. on behalf of the ENACT (European Network for Acute Coronary Treatment) investigators. The ENACT study: a pan-European survey of acute coronary syndromes. Eur Heart J 2001; 21: 1440-9.
2. Turpie AGG, Antman EM. Low-molecular-weight heparins in the treatment of acute coronary syndromes. Arch Intern Med 2001; 161: 1484-90.
3. Almeda FQ, Snell RJ, Paririllo JE. The contemporary management of acute myocardial infarction. Crit Care Clin 2001; 17: 411-34.
4. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996; 347: 561-8.
5. Klein W, Buchwald A, Hillis SE, et al. for the FRIC Investigators. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for six weeks in the management of unstable coronary artery disease: Fragmin in Unstable Coronary Artery Disease Study (FRIC). Circulation 1997; 96: 61-8.
6. The FRAX.I.S. Study Group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAX.I.S. FRAXiparine in Ischaemic Syndrome. Eur Heart J 1999; 20: 1553-62.
7. 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.
8. 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.
9. The Assessment of the safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenec-

teplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001; 358: 605-13.

10. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction. Results of the ENTIRE-Thrombolysis In Myocardial Infarction (TIMI) 23 Trial. Circulation 2002; 105: r27-r34.

11. Ross AM, Molhoek P, Lundergan C, et al. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin. Second trial of Heparin and Aspirin Reperfusion Therapy (HART II). Circulation 2001; 104: 648-52.

12. Simoons M, Krzeminska-Pakula M, Alonso A, et al.. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. Eur Heart J. 2002; 23: 1282.

13. The GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: A multinational registry of patients hospitalized with acute coronary syndromes. Am Heart J 2001; 141; 190-9.

14. Steg PhG, Goldberg RJ, Gore JM, et al., for the GRACE Investigators. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). Am J Cardiol 2002; 90: 358-63.

15. Eagle KA, Goodman SG, Avezum Á, Budaj A, Sullivan CM, López-Sendón J, for the GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment elevation myocardial infarction – findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 2002; 359: 373-7.

16. Goodman SG, Cohen M, Bigonzi F, et al. for the ESSENCE study group. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease. One-year results of the ESSENCE study. J Am Coll Cardiol 2000; 36: 693-8.

17. The TETAMI trial: the safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and of tirofiban versus placebo in the treatment of acute myocardial infarction for patients not thrombolyzed: methods and design. J Throm Thrombolysis 2000; 10: 241-6.

18. Fox KAA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variations in practice and outcome. Findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2002; 23: 1177-89.

19. Wallentin L, Armstrong P, Granger C, et al., for the ASSENT-III PLUS investigators. Assessment of the safety and efficacy of a new thrombolytic regimen in the pre-hospital setting (ASSENT III Plus). Circulation 2002; 106: 2986.

20. Kaul S, Shah PK. Low molecular weight heparin in acute coronary syndrome: evidence for superior or equivalent efficacy compared with unfractionated heparin? J Am Coll Cardiol 2000; 35: 1699-712.

21. Young JJ, Kereiakes DJ, Grines CL, for the National Investigators Collaborating on Enoxaparin (NICE) Investigators. Low-molecular-weight heparin therapy in percutaneous coronary intervention: the NICE 1 and NICE 4 trials. J Invas Cardiol 2000; 12 (Suppl E): E14-E18.

22. Ferguson JJ. Combining low-molecular-weight heparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: The NICE 3 story. J Invas Cardiol 2000; 12 (Suppl E): E10-E13.