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Combination of Low Molecular Weight Heparins with Antiplatelet Agents in Non-ST Elevation Acute Coronary Syndromes

An Update

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Contents

Abstract

This article reviews the use of low molecular weight heparin (LMWH) and antiplatelet agents in the treatment of unstable angina and non-ST segment elevation myocardial infarction (NSTEMI), which together account for 1 million hospitalisations annually in the US alone. Mortality and recurrent myocardial infarction (MI) in these conditions is currently approximately 8 to 16% at 1 month, and there is a need to optimise treatment further.

Since their introduction, LMWHs have been shown to be successful and well tolerated in the treatment of unstable angina and NSTEMI, but differences have

been seen in their efficacy compared with the parent compound, unfractionated heparin (UFH). A meta-analysis of all LMWHs, grouped, versus UFH showed equivalent efficacy and safety. The LMWHs dalteparin sodium and nadroparin calcium have independently been shown to be as effective as UFH. However, enoxaparin sodium has been shown to have greater clinical efficacy than UFH in patients with unstable angina (UA)/NSTEMI.

One area of new research is patients with UA/NSTEMI who later undergo percutaneous coronary interventions (PCI), and early data suggest enoxaparin can be safely used as an anticoagulant instead of UFH in these patients. There is a wealth of data for glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab, eptifibatide, lamifiban, and tirofiban), although some are conflicting. Recent meta-analyses suggest that some benefit is conferred by using these compounds, particularly in patients who undergo PCI.

Recent trials have focussed on combining GP IIb/IIIa antagonists with LMWH, and although data is still scant, the ACUTE (Anti-thrombotic Combination Using Tirofiban and Enoxaparin) and ACUTE II studies indicate the safety and potential clinical benefit of combining enoxaparin with tirofiban in patients with UA/NSTEMI not undergoing PCI, compared with UFH and tirofiban. The NICE (National Investigators Collaborating on Enoxaparin) 4 study collected data on the combination of enoxaparin and abciximab in patients undergoing PCI, and both safety and efficacy data compared well with historical data collected on the use of UFH with abciximab. The more recent NICE 3 study extended this finding to the combination of enoxaparin with abciximab, tirofiban or eptifibatide. The safety of two doses of dalteparin and abciximab had also been investigated, with the higher dose the efficacious, and also with safety, in patients undergoing PCI. In addition, a GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes) IV substudy found that dalteparin had equivalent safety to UFH when co-administered with abciximab in patients not undergoing PCI. The NICE 3 and 4 trials were not randomised comparisons, and as such there results must be interpreted with caution. Recently, the CRUISE (Coronary Revascularisation Utilizing Integrelin [eptifibatide] and Single-bolus Enoxaparin) and INTERACT (Integrelin and Enoxaparin randomised assessment of Acute Coronary Syndromes Treatment) studies have provided evidence for both the safety and efficacy of enoxaparin combined with eptifibatide in non-ST elevation patients with acute coronary syndromes. A further study (SYNERGY [Superior Yield of the New strategy of Enoxaparin, Revascularization and GlYcoprotein IIb/IIIa inhibitors]) will investigate the efficacy of the combination of enoxaparin with abciximab versus that of UFH and abciximab in a large cohort of 8000 patients.

The use of GP IIb/IIIa agents and LMWH in patients with UA/STEMI has led to their use in those with ST-elevation MI, and studies indicate LMWH is efficacious and can be used safely as an adjunct to thrombolysis. New studies will investigate the use of these agents in patients with STEMI not undergoing thrombolysis and we await the results of these studies.

1. Introduction

1.1 Nomenclature of Acute Coronary Syndromes (ACS)

The term acute coronary syndrome (ACS) refers to a group of distinct clinical entities, whose common aetiology is an imbalance between myocardial oxygen supply and requirement (i.e. myocardial ischaemia) distal to the site of a disrupted atheromatous coronary artery plaque. Patients with ischaemic discomfort may present with or without ST-segment elevation on the electrocardiogram (ECG). ST-segment elevation indicates ST-segment elevation myocardial infarction (STEMI), while patients who present without ST-segment elevation are experiencing either unstable angina (UA) or non-STEMI (NSTEMI). The distinction between these two diagnoses is ultimately made on the presence or absence of a cardiac marker (such as creatine kinase myocardial band isoenzymes [CKMB] or troponin) detected in the blood (figure 1). Disruption of a plaque may occur naturally or as a result of mechanical action during percutaneous coronary interventions (PCIs), such as percutaneous transluminal coronary angioplasty (PTCA).

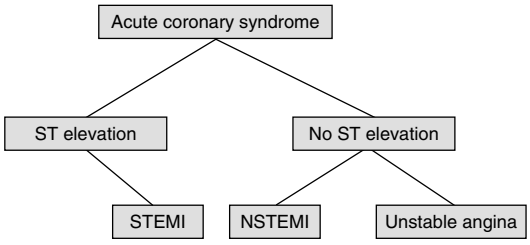

Fig. 1. Nomenclature of UA/NSTEMI. Patients with ischaemic discomfort may present with or without ST-segment elevation on the ECG. Patients with ST-segment elevation are experiencing a STEMI. Patients who present without ST-segment elevation are experiencing either UA or an NSTEMI. The distinction between these two diagnoses is ultimately made on the presence or absence of a cardiac marker detected in the blood. Not shown is Prinzmetal's angina, which manifests itself as transient chest pain and ST-segment elevation, but rarely MI. Adapted from Antman and Braunwald.[1] **ECG** = electrocardiogram; **MI** = myocardial infarction; **NSTEMI** = non-ST–segment elevation myocardial infarction; **STEMI** = ST-segment elevation myocardial infarction; **UA** = unstable angina.

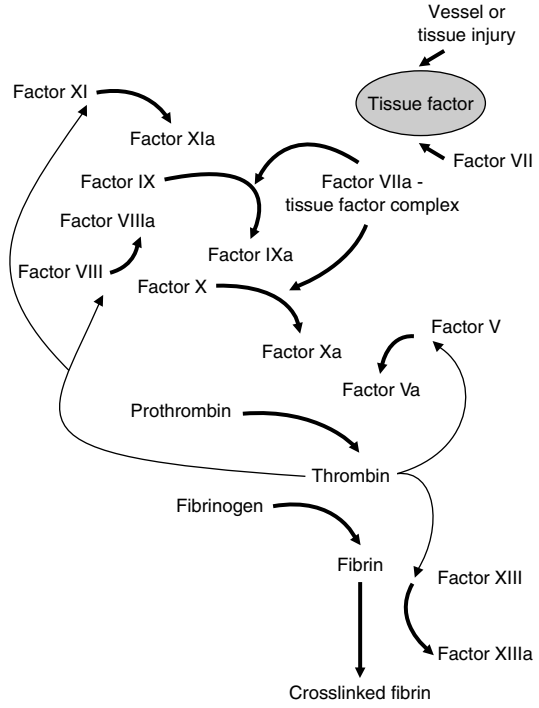

Fig. 2. Coagulation cascade.

Where the plaque is disrupted, collagen and tissue factor are exposed to the circulation, triggering both platelet aggregation and blood coagulation (figure 2).

1.2 Morbidity and Mortality Burden

Unstable angina and NSTEMI account for 1 million hospitalisations annually in the US, and between 2 and 2.5 million hospitalisations worldwide.[2,3] Studies from the 1960s and 1970s found that the incidence of major adverse clinical events (e.g. death, myocardial infarction [MI]) ranged from 10% at 3 months to 17% at 24 months. Recent clinical trials of antithrombotic and antiplatelet drugs still show that the risk of death or non-fatal MI complicating UA ranges from 8 to 16% at 1 month.[4-10] In addition, data from the European Heart Survey show the mortality rate for ACS at 6 months is 13%.[11]

1.3 Current Treatment

The pharmacological approach currently recommended by both American and European guidelines is a combination of antiplatelet and antithrombotic therapy.[12,13] This is designed to prevent the progression of UA/NSTEMI to MI or death. The American College of Cardiology/American Heart Association guidelines recommend prompt initiation of aspirin (or a thienopyridine if aspirin is not tolerated) and LMWH in patients not scheduled for PCI.[12] A platelet glycoprotein (GP) IIb/IIIa receptor antagonist should be added in patients at higher risk. The European Society of Cardiology (ESC) guidelines recommend UFH or LMWH.[13] The ESC guidelines also stress the relative reduction in the gastrointestinal adverse-effect profile of aspirin at the recommended dose of 75 to 325 mg/day.

2. Overview of Pharmacology

2.1 Role of Antithrombotic Therapy

Following endothelial damage or rupture of a coronary plaque, inactive circulating coagulation factors become activated in a series of amplified steps, culminating in the conversion of prothrombin (factor II) to thrombin (figure 2). Thrombin promotes the conversion of soluble fibrinogen (factor I) to insoluble fibrin, which forms a cross-linked mesh in which circulating cells are trapped to form a thrombus. Haemostatic balance is achieved through the presence of circulating factors such as antithrombin, which inhibits a range of prothrombotic factors, including factor Xa (active early in the cascade) and thrombin itself. The activity of antithrombin is potentiated some 1000-fold when it forms a complex with UFH or LMWH. This is despite the fact that differences exist between UFH and LMWH, and between the LMWHs themselves, in their relative activities against factor Xa and factor IIa, and in their effects on markers of cellular activation.[14] These may translate into differences in clinical efficacy and this is discussed in section 3.

2.2 Role of Antiplatelet Therapy

Rupture of an atheromatous plaque also exposes collagen to the circulation. Platelets adhere to collagen, where they become activated (figure 3). This brings about conformational changes to GP IIb/IIIa receptors on the platelet surface, which allow circulating fibrinogen to bind to platelets and promote cross-linking, aggregation and ultimately thrombus formation. The antiplatelet effect of aspirin arises indirectly through its inhibition of thromboxane A2, which is involved in the processes of both platelet aggregation and vasoconstriction. However, the existence of non-thromboxane-dependent aggregation pathways offers pharmacological alternatives. GP IIb/IIIa inhibitors exert a direct anti-aggregatory effect by denying circulat-

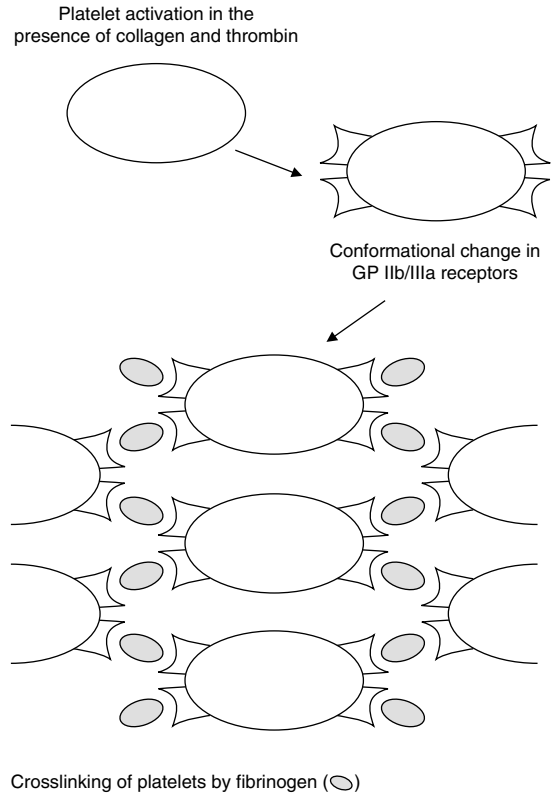

Fig. 3. Platelet aggregation.

Table I. Acronyms of trials of low molecular weight heparins and/or antiplatelet agents in patients with acute coronary syndromes

Acronym	Trial
ACUTE	Anti-thrombotic Combination Using Tirofiban and Enoxaparin
ADMIRAL	Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up
ARMADA	Attribution Randomisée énoxaparine/héparine/daltéparine pour évaluer les Margueurs d'Activation cellulaire Dans l'Angor instable
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPTURE	C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina
CRUISE	Combined use of Eptifibatide and enoxaparin in patients undergoing Percutaneous Coronary Interventions
ENTIRE	Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction
EPIC	Evaluation of 7E3 for the Prevention of Ishemic Complications
EPILOG	Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade
ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events
FRISC	Fragmin during Instability in Coronary Artery Disease
FRAXIS	FRAXiparine in Ischaemic Syndrome
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes
IMPACT	Integrelin to Minimize Platelet Aggregation and Coronary Thrombosis
INTERACT	Integrelin and Enoxaparin randomised assessment of Acute Coronary Syndromes Treatment
NICE	National Investigators Collaborating on Enoxaparin
PARAGON	Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network
PEPCI	Pharmacokinetics of Enoxaparin in Percutaneous Coronary Intervention
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy
RAPPORT	ReoPro and Primary PTCA Organization and Randomised Trial
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
SYNERGY	Superior Yield of the New strategy of Enoxaparin, Revascularization and GIYcoprotein IIb/IIIa inhibitors
TACTICS	The Treat Angina with Aggrastat (tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy Trial
TETAMI	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
TIMI	Thrombolysis in Myocardial Infarction
VANQWISH	Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital

ing fibrinogen the site of action on platelet surfaces where it brings about cross-linkage of platelets and consequent aggregation.[15-17]

3. Clinical Efficacy

3.1 Low-Molecular-Weight Heparin (LMWH)

The beneficial effect of aspirin in UA was established almost 30 years ago and that of UFH has been known for almost as long.[18,19] A rebound increase in ischaemia has been reported on cessation of UFH treatment.[20] This phenomenon has also been observed with dalteparin sodium (dalteparin) and argatroban, but not with enoxaparin sodium (enoxaparin).[21,22] In addition, UFH requires laboratory monitoring, in order to adjust for correct dose, and even then the activated partial thromboplastin time (aPTT) values achieved are unpredictable. LMWHs are manufactured from UFH by a variety of different processes that yield different products.[23] Therefore, they are not an homogeneous group of products and their therapeutic profiles differ.

An analysis of the French cohort of patients in the ESSENCE study (see table I for definition of trial acronyms) demonstrated that a change in von Willebrand factor (ΔvWF: defined as a rise greater than the median rise in vWF) during the first 48

hours of hospitalisation was predictive of clinical events at 30 days, and that vWF levels tended to remain raised in patients with adverse outcomes at 1 year. Furthermore, while raised troponin I levels (>2 μg/L) were not in themselves predictive of adverse outcome, the presence of either a large ΔvWF and/or a high troponin level identified patients at high risk of subsequent ischaemic events during the following year.[24]

3.2 Effects of Heparins on von Willebrand Factor Release

A study of data from 154 patients enrolled in other clinical trials tested the hypothesis that the choice of anticoagulant may affect the release of vWF in patients with UA by examining the effects dalteparin and enoxaparin, together with that of UFH and the direct thrombin inhibitor long-acting PEG-hirudin, on vWF release.[25] The ΔvWF over the first 48 hours was predictive of poor outcome: at 30 days, ΔvWF was seven-fold higher in patients with an endpoint than in those free of events (53 *vs* 7, p = 0.004).[25] The study also found that UFH-treated patients experienced a rise in vWF, but that this rise was significantly reduced in both enoxaparin- and PEG-hirudin–treated patients, although not in those receiving dalteparin. The ARMADA study found clear differences between UFH and two LMWHs (dalteparin and enoxaparin) on markers of cellular activation in 141 patients with UA. After multivariate analysis, a large change in the plasma level of vWF was found to predict adverse outcome at 30 days, as was a small increase in the expression of platelet GP Ib/IX receptors.[14] Enoxaparin, dalteparin and UFH had differing effects on both of these factors. The conclusion is that not all antithrombotic therapies offer equal protection against the release of vWF or GP Ib/IX during UA, and that this finding may partly explain the different levels of benefit seen in clinical trials discussed in this article.[4-10]

3.3 Efficacy of LMWHs in Patients with Unstable Angina/Non-ST Elevation Myocardial Infarction

The FRISC study[4] established that dalteparin, when added to aspirin, was protective against new cardiac events in patients with UA/NSTEMI, compared with aspirin alone. The FRAX.I.S. study, (figure 4) designed to investigate whether short-term therapy (6 days) with nadroparin calcium (nadroparin) offered benefit over UFH and whether a longer duration of nadroparin therapy (14 days) conferred any further benefit, failed to show any advantage for either regimen.[5] Enoxaparin was found to offer superior protection when compared with UFH in the ESSENCE trial,[6] a finding that was confirmed in the TIMI 11B trial,[7] while a meta-analysis of these two studies showed the composite endpoint of death, MI or urgent revascularisation to be an absolute 2.5% lower among patients receiving enoxaparin, an effect which was maintained until 1 year.[9,26] In addition,

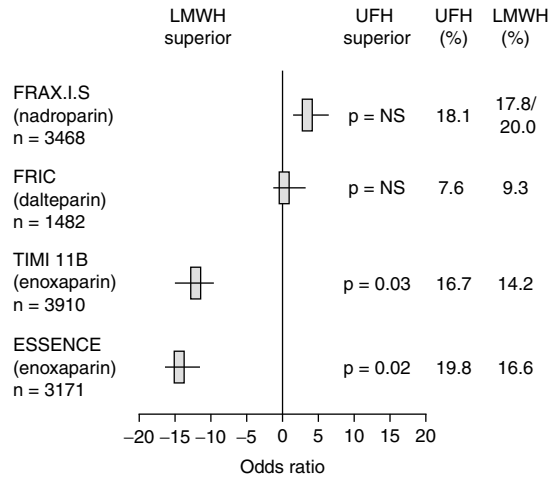

Fig. 4. Meta-analyses of LMWH trials in patients with unstable angina and non-ST-segment elevation myocardial infarction (FRAX.I.S., FRIC, TIMI 11B and ESSENCE). Odds ratios for combined endpoint of death, MI and recurrent angina (except TIMI 11B where combined endpoint was death, MI and urgent revascularisation). For trial acronyms see table I. Reproduced with permission from Cohen.[27] **LMWH** = low-molecular-weight heparins; **UFH** = unfractionated heparin.

in the ESSENCE study the 'hard' composite endpoint of death and MI was statistically significantly lower with enoxaparin at 43 days (6.2% enoxaparin, UFH 8.2%, odds ratio [OR] 0.73; 95% confidence interval [CI] 0.56-0.96).[9] The FRISC II study permitted an evaluation of the long-term benefits of dalteparin among noninvasively-managed patients with UA/NSTEMI.[10] The composite endpoint of death or MI was 47% lower among dalteparin-treated patients at 30 days, but this benefit was not sustained at 3 months.

Heparins do not appear to confer equal benefit in the treatment of patients with UA/NSTEMI (figure 4). For example, superior efficacy to UFH has been shown for enoxaparin, but this has not been demonstrated for the other LMWHs. It is of course possible that differences in study design and endpoint definition have led to the differing trial results. In a recent meta-analysis by Eikelboom et al.,[28] the results of all major trials with LMWH versus UFH were pooled, irrespective of LMWH type, and it appeared that LMWH and UFH were equivalent with respect to efficacy and safety. One of the key criticisms levied at the TIMI 11B-ESSENCE meta-analysis claim of superiority of enoxaparin over UFH is the selective combination of two positive trials; however, it does seem logical to combine trials using the same therapeutic agent, given that data exist on the differing biochemical effects of the differing LMWHs and UFH.[25] Furthermore, it would seem that performing a meta-analysis of different agents may well blur the beneficial effects of one of the agents by diluting the results with other less favourable compounds. On the other hand, if trial design and endpoint selection resulted in the positive results obtained with enoxaparin, then it would seem prudent to suggest a large head-to-head trial be performed with the other LMWHs to ascertain if a real difference in efficacy does exist.

There is much less data regarding safety and efficacy for therapy with LMWH followed by PCI. What data there are suggest that enoxaparin can safely be used in place of UFH in this situation (table II).[29-31] When pre-treated for 48 hours with

Table II to go here

Table II. Overview of studies of the use of enoxaparin in patients undergoing percutaneous coronary interventions (PCI)

Study	Patient population (n)	Study treatments	Outcomes assessed	Primary outcomes
NICE-1[31]	PCI in patients without planned GPIIb/IIIa use (n = 828)	Enoxaparin 1 mg/kg IV	Major bleeding	1.1
			Death	0.8
			MI	3.0 (4.8 if CKMB used)
			Revascularisation	2.5
			Combined endpoint (death/MI/revasc.)	5.4
ESSENCE/TIMI 11B meta- analysis[29]	Patients with UA or NQWMI later undergoing PCI within initial hospitalisation (n = 906)	ESSENCE: 1 mg/kg SC bid or UFH, adjusted according to aPTT, for 2-8d TIMI 11B: enoxaparin 30mg IV bolus followed by 1 mg/kg SC bid or UFH, adjusted according to aPTT, for 2-8d	Death, MI at 43d	Enoxaparin: 10.1 UFH: 11.6 Risk ratio 0.87 (95% CI 0.60-1.27)
Collet et al.[30]	Consecutively presenting patients with UA/NQWMI (n = 451). 132 subsequently underwent PCI within 8h of enoxaparin.	Enoxaparin 1 mg/kg SC every 12h	Major bleeding, death, MI, or urgent revascularisation at. 30 days	PCI group: 3 Non-catheter group: 10.8

aPTT = activated partial thromboplastin time; **bid** = twice daily; **CI** = confidence interval; **CKMB** = creatine kinase myocardial band isoenzymes; **ESSENCE** = Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events; **GP** = glycoprotein; **IV** = intravenous; **MI** = myocardial infarction; **NICE** = National Investigators Collaborating on Enoxaparin; **NQWMI** = non-Q-wave MI; **SC** = subcutaneous; **TIMI** = Thrombolysis in MI; **UA** = unstable angina; **UFH** = unfractionated heparin.

enoxaparin, patients with UA/NSTEMI undergoing PCI do not require additional anticoagulation or monitoring,[30] while the NICE 1 study found that enoxaparin safely gave adequate and effective anticoagulation during PCI.[31] A subsequent PCI study, PEPCI, investigated the pharmacokinetics of enoxaparin in 55 patients scheduled to undergo PCI. The study found that a dose administration regimen of subcutaneous enoxaparin 1 mg/kg twice daily supplemented by an additional intravenous bolus of 0.3 mg/kg immediately before PCI 8 to 12 hours after the last dose of subcutaneous enoxaparin provided adequate anti-Xa levels for PCI in 95% of patients.[32] Trials where LMWH are combined with GPIIb/IIIa inhibitors are discussed in section 3.4. Ongoing studies are addressing these issues, including the large-scale SYNERGY study, which will examine the efficacy and safety of enoxaparin compared with UFH in 8000 patients with UA/NSTEMI undergoing PCI.[33]

3.4 Glycoprotein (GP) IIb/IIIa Antagonists

The established value of aspirin[18] in UA/NSTEMI is now being augmented by the newer, more specific antiplatelet drugs, the GP IIb/IIIa antagonists.

The PRISM study showed that tirofiban could reduce ischaemic events at 48 hours, a difference that was not sustained at day 30 (figure 5a).[34] However, the drug did have a beneficial effect on the 30-day mortality rate. In a further study (PRISM-PLUS) involving tirofiban in higher-risk patients with UA/NSTEMI, there was a significant excess in the 7-day mortality of patients receiving tirofiban and aspirin without UFH compared with those receiving UFH and aspirin.[35] This interim finding brought about the premature termination of that arm of the study. Nonetheless, composite endpoint data of death/MI or refractory ischaemia at 7 days, 30 days and 6 months demonstrated a significant superiority among patients treated with the triple combination of tirofiban, UFH and aspirin, over those receiving UFH and aspirin alone.

A beneficial effect of eptifibatide was shown in the PURSUIT study.[37] The primary endpoint was

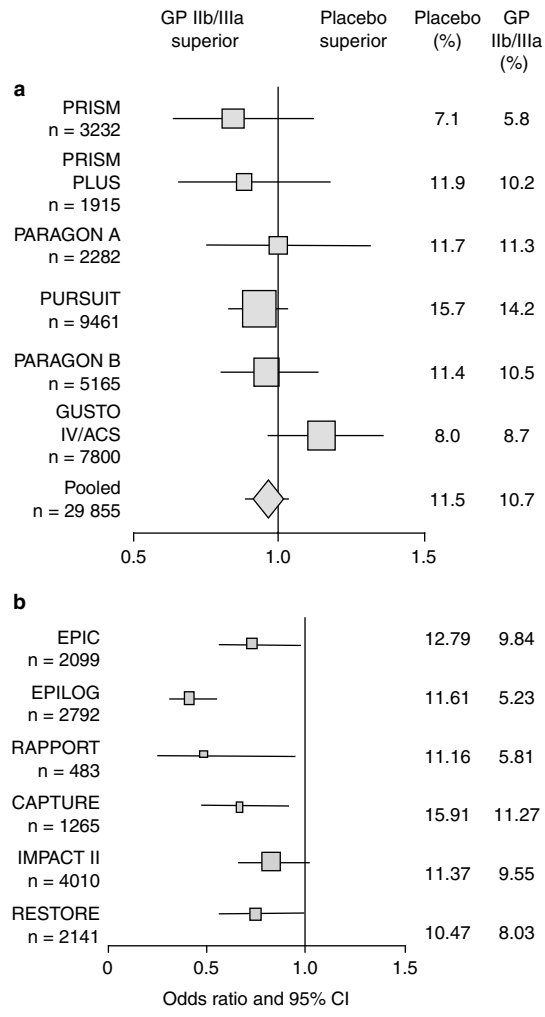

Fig. 5. (a) Meta-analysis of unstable angina and non-ST–segment elevation myocardial infarction noninvasive trials using glycoprotein (GP) IIb/IIIa antagonists. Composite endpoint of death/MI/UR at 30 days. Reproduced with permission from the American College of Cardiology Foundation[36] **(b)** Meta-analysis of percutaneous coronary intervention trials using GP IIb/IIIa antagonists. Composite endpoint of death/MI/UR at 30 days. For trial acronyms, see table I. **CI** = confidence interval; **MI** = myocardial infarction; **UR** = urgent revascularisation.

the composite of death or non-fatal MI at 30 days, and the benefit began to emerge at 96 hours, persisting up to 30 days.

The PARAGON-B troponin T substudy compared the effects of two different doses of lamifiban

in a factorial design; control patients received placebo plus UFH, and all patients received aspirin.[38] At 30 days, neither dose of lamifiban appeared to have an effect, irrespective of UFH administration. At 6 months, death or MI was reduced by the lower dose of lamifiban (1 μg/min). In contrast to these results, the GUSTO IV-ACS trial suggested no benefit from abciximab treatment in patients with UA/NSTEMI who were not undergoing early revascularisation.[39]

Meta-analysis of the above studies indicates modest benefit for patients from the use of GP IIb/IIIa antagonists. Among patients with unstable ischaemic syndromes who are treated medically, the use of GP IIb/IIIa antagonists reduced the pooled incidence of death or MI at 30 days by 8% ($p = 0.037$).[36]

The potential benefits of GP IIb/IIIa antagonists in patients undergoing PCI have also been investigated in a series of studies (figure 5b).

The EPIC trial in patients scheduled for PCI found that abciximab reduced the incidence of death, non-fatal MI or unplanned procedure by 35% compared with placebo,[40] while the EPILOG trial shed further light on potential risks and benefits of abciximab by comparing the combined effects of abciximab and either of two dose schedules of UFH in patients undergoing PCI.[41] The composite event rate was significantly lower in both UFH groups than in groups receiving abciximab. The EPILOG trial found that abciximab reduced ischaemic complications of percutaneous coronary revascularisation procedures by 56%, while the CAPTURE trial found a similar reduction in death, MI or urgent revascularisation among patients with refractory UA scheduled for PTCA.[42] Both trials were halted early after positive interim findings.

In studies involving coronary stent implantation, eptifibatide brought about a reduction in ischaemic complications at 48 hours and 30 days, a benefit that was sustained at 6 months (rate of death and MI 7.5% in the eptifibatide arm versus 11.5% in the placebo arm),[43] while abciximab was shown to reduce death following stent implantation (rate of death, MI and urgent revascularisation 5.3% in the stent plus abciximab group, and 10.8% in the stent plus placebo group).[44] In contrast, in the subsequent CADILLAC study, the addition of abciximab had no beneficial effect on the rate of major cardiac outcomes (event rate 11% in stent alone and stent plus abciximab group).[45] However, in the ADMIRAL study, where patients received abciximab prior to stenting, showed a reduction in the composite of death, reinfarction, or urgent revascularisation of the target vessel (6.0% abciximab group *vs* 14.6% in the placebo group; $p = 0.01$).[46]

Platelet inhibition with abciximab was also found to be beneficial in patients with acute MI treated by PTCA, and substantial reductions in the 30-day death/reinfarction/urgent revascularisation rate were observed at a cost of excessive bleeding rates, figure 5b (16.6% abciximab versus 9.5% with placebo, $p = 0.02$).[47]

As a result, these studies suggest that the GP IIb/IIIa antagonists do not necessarily all offer the same level of benefit; moreover, benefit with any one of them may vary with the clinical setting. Some of these differences may in part be explained by differing responses in patients at higher or lower risk, for example troponin status can be a marker of higher risk[38,42] and the definition of MI varies between studies.[39] For example, the combined rate of death and MI appeared to be relatively low in the GUSTO IV-ACS trial, reflecting the recruitment of a lower risk population. Elsewhere, the PARAGON-B troponin T substudy found that troponin T-positive patients (troponin T ≥0.1 μg/L) were at significantly higher risk of death, MI or severe recurrent ischaemia within 30 days.[38] Moreover, the beneficial effect of lamifiban in the study viewed as a whole was confined to the troponin T-positive patients, and there was a similar finding in the CAPTURE study, which used abciximab.[42] In addition, an analysis of actual platelet inhibition levels by Steinhubl et al.[48] has shown substantial between patient variability in the level of platelet inhibition achieved by GPIIb/IIIa inhibitors, but also showed a correla-

tion between a high inhibition and a lowered risk of major adverse cardiac events. This study suggests that point-of-care measurement of the level of platelet inhibition achieved may increase the overall success rate of this class of drugs.

The TARGET study established that the GP IIb/IIIa antagonists might not all confer equal protection against ischaemic events following PCI.[49] The 30-day endpoint of death/MI/revascularisation among tirofiban-treated patients (n = 2398) occurred 26% more often than among those receiving abciximab (n = 2411) [7.6 *vs* 6.0%, hazard ratio 1.26, p = 0.038]. The benefit appeared to arise primarily from the effects of the two drugs on the incidence of MI, and was not at the expense of an increase in major bleeding rates. This effect should be reviewed in the light of 6-month data (recently released on http://www.theheart.org), which suggest that the effects of the two drugs may converge over a longer period.

One debate that has been reopened by the advent of GP IIb/IIIa antagonists is that of early invasive versus conservative strategies for the management of patients with UA/NSTEMI. Prior to this development, FRISC II found that early invasive management saved lives and prevented MI for at least a year, whereas the VANQWISH study[50] found higher mortality with an invasive strategy. This apparent contradiction may have arisen because the studies employed different criteria for the establishment of ischaemia and reported different rates of cardiac catheterisation. Both of these studies were conducted before the impact of GP IIb/IIIa antagonists had been implemented in the management of UA/NSTEMI, or before GP IIb/IIIa antagonists had an impact on the widespread use of intracoronary stenting. The TACTICS-TIMI 18 study was designed to re-examine the benefit of early invasive versus conservative management strategies in the light of new therapeutic developments.[51] An early invasive approach (which included routine catheterisation and revascularisation as appropriate) was found to reduce the composite endpoint of death, MI, and rehospitalisation by 22%, compared with more conservative management, which included catheterisation only when there was objective evidence of recurrent ischaemia or an abnormal stress test (15.9 *vs* 19.4%, odds ratio 0.78, p = 0.025).

4. Combinations of LMWH and GP IIb/IIIa Antagonists

The argument for combining LMWHs and GP IIb/IIIa antagonists in the treatment of patients with UA/NSTEMI is essentially a development of the argument supporting the current pharmacological approach.[11,12] When compared with UFH, enoxaparin has been shown to reduce cardiac ischaemic events, and GP IIb/IIIa antagonists have been shown to be beneficial in certain circumstances (e.g. high risk patients, patients undergoing PCI), making the combination attractive.[6,7,36,40-42,44,52,53] Any pharmacological manipulation of the pathological processes in UA/NSTEMI must nonetheless tread the safest path between preventing a recurrent cardiac event on the one hand, and provoking a major haemorrhage or intracranial haemorrhage on the other. Preliminary data is encouraging for combining the two strategies.

4.1 For Noninvasive Treatment

Transfusion requirements, as well as both major and minor bleeding rates, in the subset of patients from GUSTO-IV receiving dalteparin (instead of UFH) did not appear to be significantly different from those of the population as a whole; neither was there any difference in the efficacy data between these two populations.[54]

The ACUTE pilot study conducted on 55 patients with ACS compared the effects of UFH with enoxaparin on a variety of pharmacological, pharmacokinetic and pharmacodynamic properties of tirofiban, as well as the overall safety of the combinations.[55] The degree to which platelet aggregation was inhibited tended to be greater and more predictable among patients treated with enoxaparin and tirofiban than among those receiving UFH and tirofiban (figure 6). With this factor taken into account, the adjusted bleeding time was 21% lower among patients receiving enoxaparin and

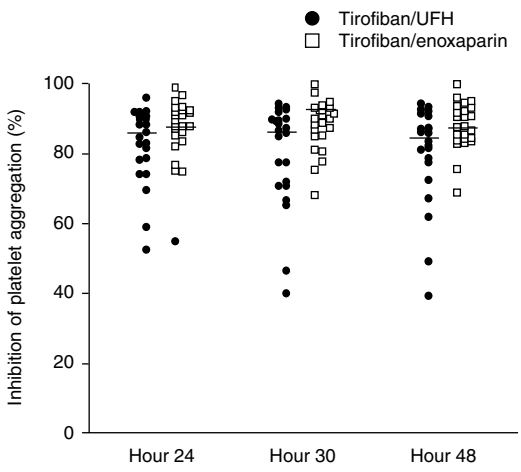

Fig. 6. Platelet inhibition for each patient from the Anti-thrombotic Combination Using Tirofiban and Enoxaparin (ACUTE) pilot study in 55 patients with acute coronary syndromes. Reprinted with permission from Elsevier Science.[55] **UFH** = unfractionated heparin.

tirofiban (19.6 *vs* 24.9 min, p = 0.02). Taken with the observation that there were no bleeding events (major or minor, by TIMI criteria) in either group, these results support the use of enoxaparin and tirofiban in the treatment of patients with ACS.

ACUTE II, a larger study, assessed the safety of the combination of tirofiban and enoxaparin in 525 patients with UA/NSTEMI compared with a control group that received tirofiban and UFH.[56] The primary objective of the study was to evaluate the bleeding risk of either combination, and no difference was found between the two groups in the rates of major and minor TIMI bleeding, transfusion requirements, death or MI, and non-haemorrhagic cerebrovascular accident (figure 7). However, the rate of recurrent angina was significantly reduced in the enoxaparin group. This provides further evidence to support the use of enoxaparin and GP IIb/IIIa antagonists in combination. It is important to note, however, that neither study possessed the statistical power necessary to evaluate relative efficacy outcomes.

4.2 With Percutaneous Coronary Interventions

The NICE 4 study offers insight into the suitability of enoxaparin and GP IIb/IIIa antagonists during PCI.[31] Interpretation of the study must be cautious because it was not randomised, but the study shows that integration of the two treatments is realistic and that it compares well with an historical control study (figure 8). Patient demographics of the two studies were similar, and the primary endpoint of both was the incidence of major haemorrhage in and out of hospital up to day 30 after PCI. Secondary endpoints included the incidence of minor haemorrhage, transfusion requirements, death, MI, and requirement for urgent coronary revascularisation. NICE 4 used enoxaparin 0.75 mg/kg as well as abciximab (bolus + infusion of 0.125 μg/kg). This reduced dose of enoxaparin was designed to simulate weight-adjusted dose administration of UFH used in other studies.[41,44]

In the NICE 3 observational study, 616 patients with UA/NSTEMI were evaluated for major bleeding excluding those due to coronary artery bypass graft surgery (CABG) following treatment with

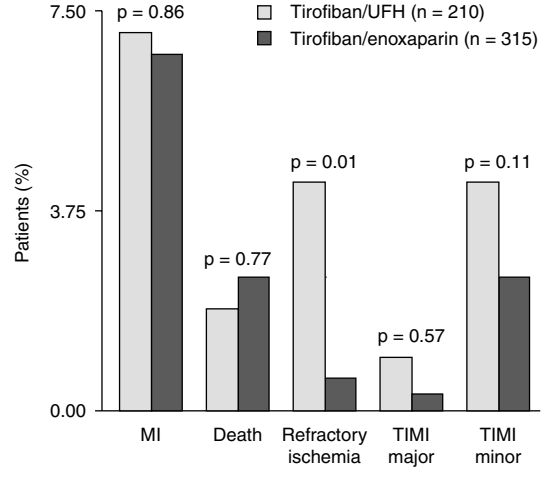

Fig. 7. Clinical event rates in the second Anti-thrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) trial.[56] **MI** = myocardial infarction; **TIMI** = thrombolysis in myocardial infarction; **UFH** = unfractionated heparin.

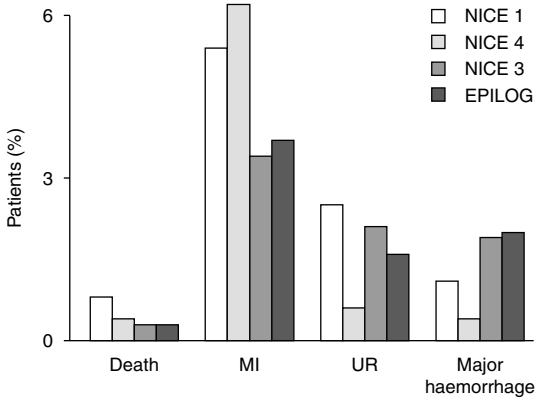

Fig. 8. Clinical and bleeding event rates in EPILOG, and NICE 1, 3 and 4. For trial acronyms, see table I.[31,41,57] **MI** = myocardial infarction; **UR** = urgent revascularisation.

enoxaparin and a GP IIb/IIIa antagonist (abciximab, n = 147; eptifibatide, n = 252; or tirofiban, n = 217) and PCI if required.[57] The overall incidence of the endpoints of death, MI and urgent revascularisation, and major bleeding, compared well with historical control studies using UFH and abciximab (figure 8). In total, 292 patients underwent PCI and in these patients the overall rate of non-CABG bleeding was 1.0%. Among its conclusions, the study proposes that treatment with enoxaparin and GP IIb/IIIa antagonists does not result in an excess of non-CABG major bleeding and that patients receiving such combinations can safely undergo PCI. It also suggests that patients who do undergo PCI do not require UFH if they are treated with a combination of enoxaparin and a GP IIb/IIIa antagonist.

The potential for combining dalteparin with abciximab during PCI has also been investigated.[58] 107 patients undergoing PCI with abciximab were randomised to either 40 or 60 IU/kg of dalteparin. The higher dose of dalteparin provided greater efficacy (i.e. a lower incidence of procedural thrombosis and a more consistent antithrombotic effect) with no apparent adverse-event penalty (i.e. similar rate of major bleeding as the lower dose of dalteparin).

The safety and efficacy of enoxaparin co-administered with eptifibatide has been the focus of two recent studies. The recent CRUISE study, showed no significant differences in bleeding events or clinical outcomes between enoxaparin and UFH enoxaparin in patients undergoing elective PCI also receiving eptifibatide.[59]

A recently presented study also investigated the safety of enoxaparin in combination with eptifibatide. [60] The INTERACT study reported significantly lower rates of major bleeding at 96 hours, and a 44% lower rate of death or MI at 30 days, with enoxaparin compared to UFH in 746 high risk patients with ACS.

5. Tolerability

Pharmacological manipulation of the balance between thrombosis and haemorrhage might be expected to influence bleeding rates or even transfusion requirements. Some of the clinical trials previously discussed have employed factorial designs in order to stratify the potential bleeding risk attached to different dose schedules. The PARAGON study found no difference between groups of patients assigned low-dose compared with high-dose lamifiban in their effect on the primary composite outcome of death or non-fatal MI at 30 days. However, the bleeding rates in the groups were different. Compared with the control group (placebo plus UFH), high-dose lamifiban and UFH resulted in more intermediate or major bleeding events with no corresponding efficacy benefit, whereas those assigned low-dose lamifiban plus UFH experienced similar bleeding rates to the control patients but fewer ischaemic events at 6 months. Elsewhere, the EPILOG study found no difference in major bleeding rates but minor bleeding was more frequent among patients receiving abciximab and standard-dose UFH. The EPIC study produced a similar picture: bleeding and transfusions were more frequent among the more effective therapeutic regimen. Any excess of bleeding rates must therefore be balanced against the anticipated effect upon the rate of ischaemic events.

Major haemorrhage data collected in the TIMI 11B and ESSENCE studies showed comparable frequencies for both enoxaparin and UFH. The rate at end of hospitalisation was 1.5% in the enoxaparin group, and 1.0% in the UFH group in TIMI 11B, p = 0.143, whereas the rate of major haemorrhage at 30 days in the ESSENCE study was 6.5% with enoxaparin and 7.0% with UFH.[6,7] Data collected in the ESSENCE study showed that major bleeding was no higher in enoxaparin treated patients who subsequently underwent CABG (major bleeding rate of 4.8% for enoxaparin *vs* 5.5% for UFH, p = NS).[61]

Both the ACUTE studies give promising data on the safety of combining enoxaparin and tirofiban in UA/NSTEMI patients not undergoing PCI. There were no major bleeds in either treatment group in the ACUTE study, and in the ACUTE 2 study, TIMI major haemorrhage was 4.3% in patients on UFH and tirofiban versus 2.5% with enoxaparin and tirofiban.[55,56] In patients undergoing PCI, the NICE 4 study, which combined enoxaparin and abciximab, and the NICE 3 study, designed to assess the safety profile of enoxaparin in combination with tirofiban or eptifibatide or abciximab in patients undergoing PCI, found no excess of non-CABG major bleeding (figure 8), allowing the authors to conclude that it is not necessary to use UFH in patients with UA/NSTEMI who have been treated with enoxaparin and who undergo PCI, and established a promising basis for future large studies.[31,58] In addition, data from recent studies of enoxaparin and eptifibatide (CRUISE and INTERACT) indicate this combination is can be used safely.[59,60]

6. Conclusion

6.1 Clinical Potential

Antiplatelet therapy with aspirin and antithrombotic therapy with UFH have in their turn improved the treatment of patients with UA/NSTEMI. Percutaneous procedures have become more popular, and more potent antiplatelet drugs and enoxaparin have been shown to improve patient survival still further. Caution has been exercised in combining the newer agents but promising data are emerging to suggest that a rational combination will offer yet further improvements to treatment with an acceptable safety profile. We still need further data but await the results of new trials such as the SYNERGY study with interest and optimism.

6.2 Future Perspectives in ST Elevation ACS

Recent trial results have generated interest in the potential use of enoxaparin and GP IIb/IIIa antagonists in patients with STEMI. The recent large-scale ASSENT-3 trial examined the efficacy (a composite of mortality, reinfarction and refractory ischaemia at 30 days) and efficacy plus safety (efficacy endpoint plus in-hospital major haemorrhage or intracranial haemorrhage at 30 days) of three pharmacological strategies.[62] The thrombolytic employed throughout the study was tenecteplase, and antithrombotic therapy was with either enoxaparin or UFH, while a third arm evaluated thrombolysis with half-dose tenecteplase together with low-dose UFH supplemented by antiplatelet therapy with abciximab. The enoxaparin regimen was superior to the UFH regimen for both the efficacy and the efficacy plus safety endpoints (11.4 *vs* 15.4%, relative risk [RR] 0.74, p = 0.0002 for efficacy, and 13.7 *vs* 17.0%, RR 0.81, p = 0.0037 for efficacy plus safety). Moreover, the regimen that included abciximab provided similar superiority over the UFH regimen (11.1 *vs* 15.4%, RR 0.72, p = 0.0001 for efficacy, and 14.2 *vs* 17.0%, RR 0.84, p = 0.01416 for efficacy plus safety). This finding suggests that platelet inhibition may have role in the acute treatment of STEMI, although the added benefit was the same as that found with enoxaparin alone, and the authors suggest that the practical simplicity of tenecteplase plus enoxaparin warrants further study. The smaller angiographic ENTIRE study, designed to assess TIMI flow in patients randomised to one of a series of combinations of tenecteplase, abciximab, UFH and enoxaparin, confirmed the safety and efficacy of enoxaparin in combination with tenecteplase.[63] The TETAMI study[64] will

employ a factorial design to evaluate the efficacy and safety of enoxaparin, with and without tirofiban, and UFH with and without tirofiban, in 900 patients with STEMI ineligible for early reperfusion therapy. In addition, the A-Z study is investigating the efficacy and safety of enoxaparin versus UFH in NSTEMI patients treated with aspirin and tirofiban, and also the subsequent effect of a high dose statin therapy with the currently recommended regimen of lower-dose statin.

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