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Clinical research

Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial

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Aims In high risk patients with non-ST elevation acute coronary syndromes (ACS), enoxaparin is generally preferred to unfractionated heparin (UFH). However, less is known about the relative merits of these two forms of heparin in patients receiving concomitant glycoprotein IIb/IIIa inhibitors.

Methods and results The A phase of the A-to-Z trial was an open label non-inferiority trial in which 3987 patients with non-ST elevation ACS were randomised to receive either enoxaparin or UFH in combination with aspirin and tirofiban. Inclusion required either ST depression or cardiac biomarker elevation. While the selection of an early management strategy (invasive or conservative) was at the discretion of the local investigator, investigators were asked to designate their plans for an invasive or conservative strategy on the case record form. An early conservative strategy was specified for 1778 patients (45%); this subgroup forms the population for the present analyses. Among patients with a planned conservative strategy, baseline characteristics were similar between those randomised to UFH ($n = 872$) and those randomised to enoxaparin ($n = 906$). The primary endpoint of death, new MI, or documented refractory ischaemia within 7 days of randomisation occurred in 10.6% of patients

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randomised to UFH and 7.7% of patients randomised to enoxaparin (HR 0.72; 95% CI 0.53—0.99; $p = 0.04$). The combined rate of TIMI major, minor, or loss no-site bleeding was 1.3% in patients treated with UFH and 1.8% in those treated with enoxaparin ($p = ns$).

Conclusions When a conservative approach to catheterisation and PCI was planned for ACS patients receiving tirofiban and aspirin, enoxaparin was associated with superior efficacy and similar bleeding vs UFH.

Introduction

Antiplatelet and anti-thrombotic strategies for patients with non-ST elevation acute coronary syndromes (ACS) have evolved rapidly in recent years. Early ''upstream'' initiation of the glycoprotein (GP) IIb/IIIa inhibitor tirofiban, together with aspirin and intravenous unfractionated heparin (UFH), has been shown to reduce rates of recurrent ischaemic events in high risk patients with non-ST elevation ACS.[1] Although the relative benefit of GP IIb/IIIa inhibitors appears to be greatest in patients with ACS who subsequently undergo percutaneous coronary intervention (PCI),[2] a recent meta-analysis has demonstrated benefit among patients who are not routinely scheduled for revascularisation.[3] A separate series of studies has demonstrated the superiority of the low molecular weight heparin (LMWH) agent enoxaparin over UFH for patients with non-ST elevation ACS.[4,5] However, GP IIb/IIIa inhibitors were not used routinely in these trials and few data are available to determine whether enoxaparin is safe and effective when used in combination with GP IIb/IIIa inhibitors and aspirin.[6]

The A phase of the Aggrastat to Zocor (A-to-Z) study was an international, open label randomised non-inferiority trial comparing enoxaparin with UFH in 3987 patients with non-ST elevation ACS receiving tirofiban and aspirin. The primary endpoint of death, myocardial infarction (MI), or refractory ischaemia at 7 days occurred in 8.4% of patients randomised to enoxaparin and 9.4% randomised to UFH (hazard ratio 0.88; 95% CI 0.71—1.08); this result fell well within the pre-specified non-inferiority boundary but did not reach criteria for superiority.[7]

An early invasive strategy was planned in over 50% of patients enrolled in the A-to-Z trial, a rate considerably higher than in prior studies comparing enoxaparin with UFH.[4—6] In patients managed invasively in A-to-Z, crossover from enoxaparin to UFH was permitted at the time of PCI. Recently, the *Superior Yield of the New strategy of Enoxaparin, Revascularisation and GlYcoprotein IIb/IIIa inhibitors* (SYNERGY) trial, which employed a routine invasive strategy and high usage of GP IIb/IIIa inhibitors, found that treatment with enoxaparin was associated with a smaller risk reduction vs.UFH than had been observed in previous trials (HR 0.96 vs UFH; 95% CI 0.87—1.06).[8] Because an early invasive approach reduces recurrent ischaemic events in patients receiving GP IIb/IIIa inhibitors,[9] the use of early catheterisation and PCI in a high proportion of patients in A-to-Z and SYNERGY may have mitigated some of the potential beneficial effects of enoxaparin. For these reasons, comparison between enoxaparin and UFH in patients managed with an early conservative strategy may represent a more direct evaluation of the relative efficacy of enoxaparin vs.UFH in patients receiving tirofiban and aspirin. The present report describes results of a prespecified analysis from the A phase of the A-to-Z trial in patients who were selected by the investigator to follow an early conservative management strategy.

Methods

A-to-Z Study design

Details of the A-to-Z design[10] have been previously reported. The A-to-Z study was performed in two phases; the A phase was an international randomised open-label non-inferiority trial performed in 3987 patients with non-ST elevation ACS between December 1999 and May 2002. The trial compared enoxaparin (1 mg/kg subcutaneously every 12 h) with intravenous weight-adjusted UFH (60 U/kg bolus (maximum 4000 U) followed by 12 U/kg/h infusion (maximum 900 U/h), titrated to aPTT of 50—70 s). All patients were required to receive concomitant therapy with aspirin and tirofiban (10 lg/kg bolus over 3 min, followed by 0.1 lg/kg/min infusion). Tirofiban was given for a suggested minimum of 48 h (or at least 12 h after PCI) and a maximum of 120 h. The primary results of the A phase have been previously reported.[7] The Z phase of the A-to-Z trial is ongoing and is comparing an early aggressive regimen with the HMG-CoA Reductase inhibitor simvastatin to a standard care regimen in patients undergoing guideline-based management of ACS.[10]

Patients were eligible for enrollment into the A phase if they had chest pain at rest within the last 24 h lasting at least 10 min, associated with $\geqslant 0.5$ mm ST segment depression, transient ST elevation $\geqslant 1$ mm, or elevated markers of cardiac necrosis (troponin or CKMB > ULN). Patients were excluded if they were thought to be at increased risk for bleeding, if serum creatinine was >2 mg/dL, or if total cholesterol was >250 mg/dL (to maintain eligibility for the Z phase of the trial). Patients were followed for 30 days to evaluate safety and efficacy outcomes.

Assignment to early invasive or conservative strategy

While the selection of an early management strategy (invasive or conservative) was at the discretion of the local investigator, the investigator was asked to designate their intent for

an invasive or conservative strategy on the case record form. No mechanism was in place to verify that this designation occurred prior to randomisation. Of 3987 patients randomised into the A phase of the A-to-Z trial, an early conservative strategy was specified for 1778 patients (45%); this subgroup forms the population for the present efficacy and safety analyses.

Efficacy and safety endpoints

The primary endpoint was a composite of death, MI, or refractory ischaemia at 7 days. MI was defined as cardiac markers $\geqslant 2$ times upper limit of normal (ULN) and *either* clinical symptoms or ECG changes suggestive of MI. Refractory ischaemia was defined as recurrent chest pain accompanied by either ECG changes or elevation in cardiac markers. The secondary endpoints evaluated at 7 and 30 days included the individual components of the primary endpoint, urgent coronary revascularisation, and documented multiple clinical myocardial ischaemic events (DMCMIE) defined as chest pain requiring intensification therapy without meeting criteria for refractory ischaemia. All endpoints except urgent coronary revascularisation were adjudicated by an independent endpoint committee.

Bleeding events were collected until 24 h after discontinuation of tirofiban. Because investigator-reported bleeding events were low, a second independent and blinded central assessment of bleeding was also conducted prior to study termination, in which haemoglobin values were screened to identify possible missed events by the investigators. The reported bleeding rates include all bleeds identified by either of these methods. The Thrombolysis In Myocardial Infarction (TIMI) criteria were used to classify bleeding.

Statistical methods

In contrast to the overall A phase study, which was a non-inferiority trial, the present subgroup analysis was designed to evaluate the superiority of enoxaparin vs UFH in patients receiving tirofiban, aspirin and an early conservative management strategy. The intention-to-treat population, which included all patients randomised into the study, was used for the efficacy analyses. The cumulative incidence of the primary efficacy endpoints was estimated by the Kaplan–Meier product-limit method. Comparisons between groups were performed using a Cox-proportional hazards model that included a term for treatment group. The assumption of proportional hazards was examined by including a treatment by time covariate in the models (none were statistically significant, $p > 0.05$ for all endpoints). Analyses of the primary endpoint were performed in subgroups defined by age, gender, diabetes, prior aspirin use, troponin elevation, ST segment changes, and TIMI risk score (TRS)[11] by including subgroup and treatment by subgroup interaction terms in the Cox proportional hazard model. Interactions were considered statistically significant if $p \leqslant 0.10$. For the TIMI risk score subgroups, patients were classified as low risk (TRS 0–2) and not-low risk (TRS 3–7). For safety analyses, patients were included if they received at least one dose of study heparin (UFH or enoxaparin) after randomisation, and were classified based on the heparin actually received. If the patient received both UFH and enoxaparin they were assigned to the randomised heparin. Fisher's exact test was used to compare bleeding and transfusion rates between groups. Continuous data are presented as medians and (25th, 75th percentile) and all p values are two sided.

Results

Baseline characteristics were similar between subjects randomised to UFH ($n = 872$) and those randomised to enoxaparin ($n = 906$). These characteristics were also similar to the overall A phase trial population, with the exception that patients in the planned conservative subgroup were more likely to receive pre-study enoxaparin than was the overall A phase trial population (Table 1). Use of guideline-based therapies, including aspirin, β-blockers, and ACE-inhibitors was high and not different between the two treatment groups. The median duration of study drug therapy was 49 (47, 71) h in the UFH arm and 60 (45, 84) h in the enoxaparin arm. Crossover to the alternative form of heparin was rare (<5% in each group) and adherence to the planned early conservative strategy was high, with only 7.3% patients undergoing catheterisation or PCI by 48 h in the UFH arm and 6.3% in the enoxaparin arm. (Table 2)

Among patients specified for an early conservative strategy, the primary composite endpoint of death, MI, or refractory ischaemia at 7 days occurred in 10.6% of patients randomised to UFH and 7.7% of patients randomised to enoxaparin (HR 0.72, 95% CI 0.53–0.99; $p = 0.04$) (Fig. 1). The secondary composite outcome of death, MI, refractory ischaemia, urgent revascularisation or MCMIE at 7 days was similarly reduced from 13.4% in the UFH arm to 10.0% in the enoxaparin arm (HR 0.73, 95% CI 0.56–0.96; $p = 0.03$). At 30 days, a trend toward reduction in the composite of death, MI and refractory ischaemia was seen in the enoxaparin arm, but this was no longer statistically significant (HR 0.80, 95% CI 0.61–1.05; $p = 0.10$). However, rates of the secondary composite endpoint of death, MI, refractory ischaemia, urgent revascularisation or MCMIE remained significantly lower in the enoxaparin arm at 30 days (HR 0.78, 95% CI 0.62–0.99; $p = 0.04$). Similar trends favouring enoxaparin over UFH were observed for each of the individual components of the composite endpoints at 7 and 30 days except for mortality, which occurred by 7 days in 1.3% of patients randomised to UFH and 1.7% of patients randomised to enoxaparin ($p = 0.49$). At 30 days, mortality occurred in 1.8% of patients randomised to UFH and 2.8% of patients randomised to enoxaparin ($p = 0.20$) (Table 3).

Trends favouring enoxaparin over UFH for the primary endpoint were consistent across subgroups defined by age, diabetes, prior aspirin therapy, and risk status (TIMI risk score (low vs not-low risk), troponin elevation, and ST segment changes) (Fig. 2). While the magnitude of risk reduction was proportionally greater in men than women, the number of events in women was small and no statistical interaction between gender and treatment assignment was observed (p interaction 0.19).

Bleeding events were infrequent in the early conservative management subgroup: only 7 patients suffered a TIMI major bleed and only 8 patients required transfusions of packed red blood cells. A small but statistically significant difference in TIMI major bleeding was observed: no patient receiving UFH experienced a TIMI major bleeding event while 0.8% of those receiving

Table 1 Selected baseline characteristics by treatment group

	Planned conservative therapy subgroup		Overall A phase population	
	Unfractionated heparin (n = 872)	Enoxaparin (n = 906)	Unfractionated heparin (n = 1961)	Enoxaparin (n = 2026)
Age (years)	63 (54, 70)	62.5 (53, 70)	61 (53, 69)	61 (52, 69)
Male gender	70.3	69.9	71.2	71.4
US site of enrollment	3.6	3.3	19.5	20.9
Race				
White	86.8	88.3	85.2	85.6
Black	1.7	1.4	3.3	3.2
Asian	6.0	5.8	4.4	4.2
Prior cardiovascular history				
Angina (past 6 weeks)	54.1	59.5	55.2	58.2
Myocardial infarction	20.8	19.4	18.3	17.8
Coronary revascularisation	8.7	6.6	9.8	9.1
Bypass surgery	5.3	4.1	5.4	4.7
Percutaneous intervention	3.8	2.2	4.4	4.2
Risk factors				
Cerebrovascular disease	6.1	6.1	5.8	5.7
Peripheral vascular disease	7.2	7.9	6.9	6.5
Diabetes	17.2	18.5	18.2	19.5
Hypertension	51.1	50.1	52.3	50.0
Current smoking	39.1	34.9	39.4	36.0
Congestive heart failure (CHF) (in past 6 weeks)	7.5	7.9	5.8	6.7
Left ventricular dysfunction	9.9	9.3	11.2	10.9
Prior medications				
Angiotensin-converting enzyme inhibitor	25.8	25.2	25.5	24.6
β-blocker	48.1	48.7	51.2	50
Nitrate	66.3	66.3	67.6	68.3
Diuretic	15.9	16.2	15.5	15.8
Long-term aspirin	40.4	37.7	41.0	40.9
Unfractionated heparin before randomisation	25.2	22.4	38.5	37.2
Low molecular weight (LMW) heparin before randomisation	43.2	40.6	34.2	34.3
Neither UH or LMW heparin	35.2	38.4	30.2	31.1
Qualifying event				
Investigator-determined myocardial infarction	71.0	71.2	72.8	74.5
ST change >1 mm	76.0	75.7	71.9	70.3

Note: Data are medians (25th, 75th percentiles) or percentages.

enoxaparin did (p = 0.02). No significant differences were noted in rates of TIMI minor bleeding or total bleeding events. Transfusion rates were identical between the two groups (Table 4).

Discussion

When a conservative approach to catheterisation and PCI was planned for patients with non-ST elevation ACS receiving tirofiban and aspirin in the A-to-Z trial, enoxaparin significantly reduced the rate of the composite endpoint of death, MI, or refractory ischaemia by at 7 days compared with UFH. Consistent benefit was observed for most secondary endpoints and across multiple subgroups defined by demographic factors and risk strata. The effect of enoxaparin on the primary endpoint was slightly attenuated and no longer statistically significant at 30 days (20% relative risk reduction vs 28% at 7 days), but significant benefit was maintained with a broader composite ischaemic endpoint that included urgent revascularisation and recurrent ischaemic events. In a recent meta-analysis of all 6 trials comparing enoxaparin with UFH in non-ST elevation ACS, which includes results of the A-to-Z trial, no attenuation of the effect of enoxaparin was observed between 48 h and 30 days in 21,946 patients.[12] Although mortality rates were higher in the enoxaparin arm, the study was not statistically powered to evaluate mortality; in the meta-analysis described above, mortality rates were identical between enoxaparin and UHF.[12]

Table 2 Hospital course

	Unfractionated Heparin (n = 872)	Enoxaparin (n = 906)
Received LMW heparin post-randomisation	4.4	98.7
Received unfractionated heparin post-randomisation	98.5	4.5
Study drug administration (h)	49 (47, 71)	60 (45, 84)
Tirofiban duration (h)	49 (48, 70)	49 (48, 71)
Catheterisation or PCI by 48 h	7.3	6.3
Catheterisation or PCI by 108 h	18.8	16.9
Concomitant medications		
Angiotensin converting enzyme inhibitor	41.2	41.0
Angiotensin receptor blocker	2.6	2.8
β-blocker	83.1	84.8
Nitrate	82.9	79.0
Calcium-channel blocker	25.3	23.1
Potassium-sparing diuretic	3.0	3.5
Other diuretic	16.4	15.5
Aspirin	99.1	98.7

Note: Data are medians (25th, 75th percentiles) or percentages.

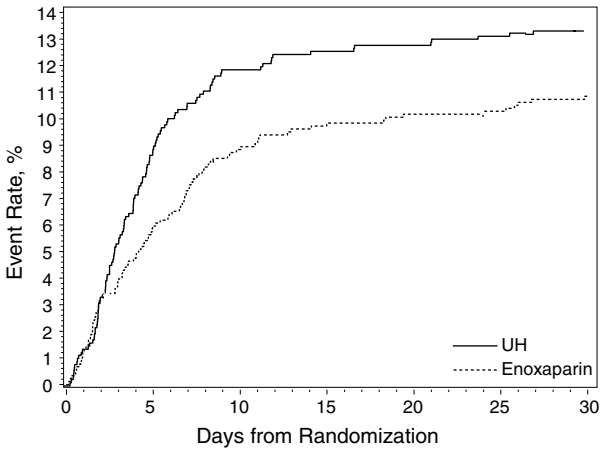

Fig. 1 Kaplan–Meier curve showing rates of the primary composite outcome of death, MI, or refractory ischaemia in patients with a planned early conservative management strategy.

Bleeding events and blood transfusions were infrequent among patients with a planned conservative strategy. While TIMI major bleeding occurred more often in patients receiving enoxaparin than those receiving UFH, the rate was still <1% in the enoxaparin arm; more reassuring is that no differences were seen in total bleeding events or transfusions between the two groups.

In the A-to-Z trial, if catheterisation or PCI was planned, use of UFH was permitted at the time of the procedure in patients randomised to enoxaparin. While this practice of crossover from enoxaparin to UFH is consistent with contemporary catheterisation laboratory practice in many institutions, it limits direct comparison of enoxaparin with UFH in patients managed invasively. The SYNERGY trial allowed a more direct comparison of enoxaparin with UFH in patients managed invasively. In both the invasive subgroup of A-to-Z and in the SYNERGY trial, no significant benefit was observed for enoxaparin compared to UFH.[7,8]

Crossover between enoxaparin and UFH was rare among patients specified for an early conservative management strategy in A-to-Z, allowing a more direct comparison of the relative efficacy of the two antithrombotic agents when combined with tirofiban. Baseline characteristics in the early conservative subgroup were similar to those in the overall A phase population; moreover, there was no difference in the proportion of patients specified for an early conservative strategy in the two treatment arms. These factors suggest that post-randomisation factors (such as actions of the study drugs) had minimal influence on the composition of the early conservative subgroup. Randomisation remained effective in the early conservative subgroup, as evidenced by the balance in baseline characteristics between the two treatment groups shown in Table 1.

Previous studies have demonstrated the superiority of enoxaparin over UFH in patients with non-ST elevation ACS who are not receiving concomitant GP IIb/IIIa inhibitor therapy.[4,5] Until recently, data comparing LMWHs with UFH in patients receiving GP IIb/IIIa inhibitors have been limited to registries,[13,14] non-randomised comparisons within clinical trials designed to evaluate other agents,[15,16] and pilot clinical trials.[17] The largest randomised trial other than A to Z to address the safety and efficacy of combined therapy with a LMWH and a GP IIb/IIIa inhibitor is the INTegrilin and Enoxaparin Randomised Assessment of acute Coronary syndrome Treatment (INTERACT) trial, which compared enoxaparin with UFH in 746 patients receiving concomitant therapy with eptifibatide and aspirin for non-ST elevation ACS.[6] The patient characteristics, rates of early catheterisation and PCI, and the clinical outcomes observed in the INTERACT trial are similar to those reported here. For example, fewer than 15% of patients enrolled in the INTERACT trial underwent coronary angiography within 48 h of randomisation, a rate comparable to the early conservative subgroup from the A-to-Z trial. The 30-day rate of death, MI, or refractory ischaemia at 30 days

Table 3 Day 7 and day 30 efficacy endpoints in patients with planned early conservative approach

	UFH (%)	Enoxaparin (%)	HR (95% CI)	*P* value
Day 7 endpoints				
Death	1.3	1.7	1.32 (0.61, 2.87)	0.49
MI	2.9	1.5	0.50 (0.26, 0.98)	0.04
Refractory ischaemia	7.4	5.1	0.69 (0.47, 1.00)	0.05
Composite-3 (primary endpoint)	10.6	7.7	0.72 (0.53, 0.99)	0.04
Urgent revascularisation	3.7	2.5	0.66 (0.39, 1.14)	0.14
Documented MCMIE	2.4	1.2	0.50 (0.24, 1.04)	0.06
Composite-5	13.4	10.0	0.73 (0.56, 0.96)	0.03
Day 30 endpoints				
Death	1.8	2.8	1.51 (0.81, 2.83)	0.20
MI	4.6	3.1	0.67 (0.41, 1.08)	0.10
Refractory ischemia	8.3	6.5	0.77 (0.54, 1.08)	0.13
Composite-3	13.3	10.8	0.80 (0.61, 1.05)	0.10
Urgent revascularisation	5.1	4.6	0.90 (0.59, 1.37)	0.61
Documented MCMIE	4.3	1.9	0.44 (0.25, 0.78)	0.005
Composite-5	17.8	14.2	0.78 (0.62, 0.99)	0.04

Endpoint percentages are Kaplan–Meier estimates.
Composite-3 is composite of death, MI, and refractory ischaemia.
Composite-5 is composite of death, MI, refractory ischaemia, urgent revascularisation, and documented MCMIE.

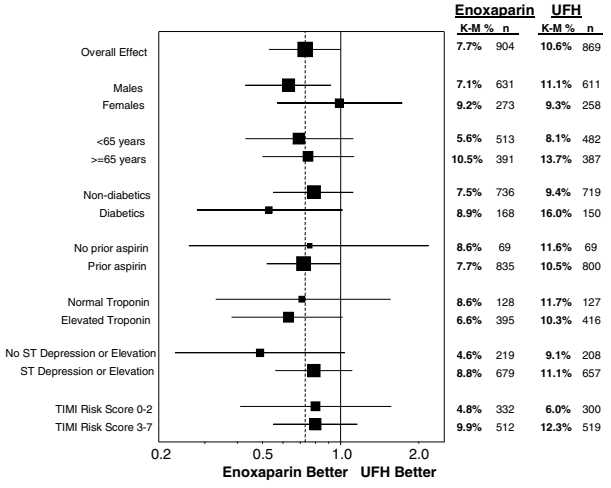

Fig. 2 Hazard Ratios (95% CIs) for the primary composite endpoint of death, MI, or refractory ischaemia at 7 days in selected subgroups among patients with a planned early conservative management strategy.

Table 4 Bleeding events and transfusions from start of tirofiban to 24 h post-tirofiban infusion

Bleed category	Unfractionated heparin (*n* = 868)	Enoxaparin (*n* = 905)
TIMI major bleed	0 (0.0%)	7 (0.8%)[a]
TIMI minor/loss no site	11 (1.3%)	9 (1.0%)
TIMI major or minor	7 (0.8%)	14 (1.5%)
TIMI major/minor/loss no site	11 (1.3%)	16 (1.8%)
Transfusions of PRBC	4 (0.5%)	4 (0.4%)

PRBC, packed red blood cells.
[a] $p < 0.05$ for difference between treatment groups.

was 12.6% in the UFH arm and 9.0% in the enoxaparin group in INTERACT, results consistent with those observed here. Bleeding and transfusion rates tended to be lower in patients receiving enoxaparin than those receiving UFH in INTERACT, supporting our observation that enoxaparin is not associated with excess bleeding compared to UFH when a conservative management strategy is employed.

Limitations

The A phase of the A-to-Z trial was not blinded, so we cannot exclude the possibility that knowledge of treatment assignment resulted in changes in therapy that may have impacted the findings of the study. However, therapy initiated post-randomisation, including cardiac catheterisation and PCI, as well as guideline-based medical therapies, was similar between the two groups. Assignment to an early invasive or early conservative strategy was not randomised and was left to the discretion of the investigator. Because the case record form was not submitted to the Data Co-ordinating Centre prior to randomisation, it is possible that the decision to pursue an early invasive or early conservative strategy was made after randomisation in some patients, a feature that could introduce selection bias. However, the early conservative group did not appear to differ from the overall A-to-Z population in terms of baseline characteristics or medical therapy received. Duration of anti-thrombin therapy was slightly longer in patients treated with enoxaparin than UFH, a finding that could have contributed to the benefit observed in the enoxaparin arm. Because safety events were captured through 24 h after discontinuation of tirofiban, we cannot exclude the possibility that bleeding differences emerged after this time. Finally, while clopidogrel use was not captured on the case record form, use of this agent was likely to have been low in the conservative subgroup, since during the peak period of enrollment in the A phase, clopidogrel was largely restricted to patients receiving intracoronary stents. The impact concomitant therapy with clopidogrel would have on the

safety and efficacy of combined therapy with enoxaparin, tirofiban, and aspirin remains to be determined.

Conclusions

When a conservative approach to catheterisation and PCI was planned for patients with non-ST elevation ACS receiving tirofiban and aspirin, enoxaparin significantly reduced rates of non-fatal recurrent ischaemic events without increasing the need for blood transfusions when compared to UFH. When considered together with prior trials in which GP IIb/IIIa inhibitors were not given, as well as the INTERACT trial which evaluated enoxaparin with eptifibatide, these results suggest that enoxaparin is the preferred anticoagulant agent for medical management of non-ST elevation ACS, whether or not an ''upstream'' GP IIb/IIIa inhibitor is used.

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