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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Low-Molecular-Weight Heparin, Lytics, and Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes

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Reported and discussed by:
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Acute coronary syndromes (ACS) encompass a range of clinical presentations, outcomes, and risk. The choice of antiplatelet, antithrombotic, and fibrinolytic agents is based on the initial clinical, electrocardiographic (ECG), and biochemical observations. Whereas an immediate reperfusion strategy with either fibrinolysis or primary angioplasty is confined to patients with electrocardiographic evidence of ST segment elevation or left bundle branch block (STE-ACS), both antiplatelet and antithrombotic agents are pivotal to prevent rethrombosis in the management of both STE-ACS and non-ST segment elevation ACS (NSTE-ACS). Early cardiac catheterization and revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery is appropriate in a subset of high-risk patients with NSTE-ACS. Although randomized clinical trials have demonstrated the benefit and safety of these strategies in patients with ACS, the implementation of this evidence into clinical practice has been far from ideal. Observations suggest that patients with ACS have better outcomes when receiving appropriate therapy as designated by evidence-based medicine. The current use of fibrinolytic, antithrombotic, antiplatelet agents and early coronary angiography has been recorded in a number of ACS registries. Evidence for treatment gaps have been identified in both the STE-ACS and NSTE-ACS.

Current recommendations for managing ACS

The AHA/ACC guidelines for NSTE-ACS[1] indicate that low-molecular-weight heparins (LMWHs) are equivalent to unfractionated heparin (UFH) (class l indication, level A evidence). However, since both the ESSENCE[2] and TIMI 11b[3,4] studies demonstrated that enoxaparin was superior to UFH, the guidelines have recommended enoxaparin as the optimal LMWH for managing ACS (class 2a, level A). The early use of the small molecule platelet glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide and tirofiban) is recommended for high-risk patients who are destined for early cardiac catheterization and revascularization (class 1, level A). Clopidogrel is recommended, provided early CABG is not contemplated (class 1, level A). An algorithm that incorporates a Canadian perspective was recently published (Figure 1).[5]

For the patient with STE-ACS presenting within 12 hours of symptom onset, the early restoration of coronary patency by either fibrinolysis or primary coronary intervention is the recognized standard of care. Adjuvant therapy with heparin and aspirin is essential treatment to prevent coronary reocclusion and reinfarction. Recent studies have evaluated the efficacy and safety of LMWH and the GP IIb/IIIa inhibitor, abciximab, with the goals of both improving initial patency and maintaining reperfusion.

Are there treatment gaps in the management of ACS in the "real world?"

The Canadian Acute Coronary Syndrome Registry[6,7] was a prospective observational study of patients hospitalized between September 1999 and June 2001 with ACS. ASA and a heparin were widely utilized in the vast majority, while LMWH was administered in approximately half of the patients. Yet, despite the recommendations, GP IIb/IIIa inhibitors were used in only 8%-9% of patients. When the population was risk-stratified according to the presenting ECG and the presence of markers of myocardial necrosis (CK-MB or troponin) (Figure 2), heparin was used at the same rate in high- and low-risk patients. GP IIb/IIIa inhibitors were used, albeit at very low rates in the higher risk patients. The GRACE registry[8,9] indicates that this treatment gap is an international problem with only 58% of eligible patients with NSTE-ACS and ST segment depression or positive cardiac markers receiving either LMWH or a GP IIb/IIIa inhibitor.

Canadian[6,7] and worldwide registries[10] show a failure to optimally deploy reperfusion therapy to the patient with STE-ACS. In both the Canadian ACS and the FASTRAK II registries,[11] approximately

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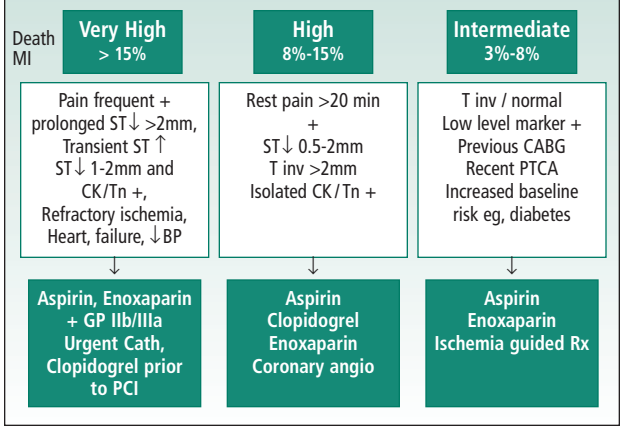
Figure 1: Management of NSTE-ACS by risk stratification: A Canadian perspective



one-third of eligible patients receive neither fibrinolysis nor primary PCI. The more global GRACE registry[10] also indicates that 30% of apparently eligible patients receive no reperfusion therapy.

Adherence to evidence-based treatment guidelines appears to result in better patient outcomes. The early use of GP IIb/IIIa inhibitors was associated with lower mortality in the CRUSADE database (presented by Drs. D. Peterson and M. Roes at a Satellite Symposium at the American Heart Association Meeting in Chicago in November, 2002). The same database showed a gap in treatment adherence between leading and lagging institutions, with improved outcomes related to the degree of adherence to recommendations. Real world practice consistent with evidence-based guidelines appears to result in the optimal outcome for patients with ACS.

LMWH as an adjuvant to fibrinolysis

The use of adjunctive LMWH compared to UFH with fibrinolysis in phase 2 trials resulted in improved late coronary patency rates and more rapid ST segment resolution, indicating improved tissue perfusion. The ASSENT 3,[12] HART 2,[13] and ENTIRE[14] studies randomized 4,717 patients treated with fibrinolysis (either tPA or TNK) to either enoxaparin or UFH. The meta-analysis (Figure 3) shows that enoxaparin reduced the combined endpoint of death, reinfarction, or recurrent myocardial ischemia by 20%.[15] However, there was a strong trend (albeit with wide confidence intervals) for increased major bleeding in the enoxaparin group. Much of the increased

Figure 2: Canadian ACS Registry: The use of antiplatelet and anticoagulation based on an estimate of risk.

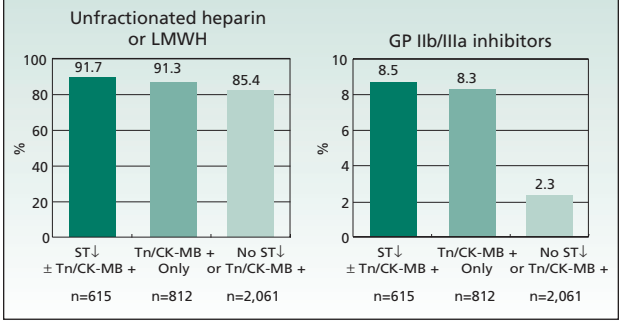
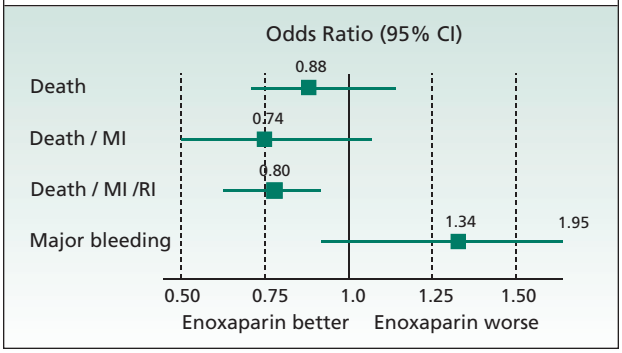


Figure 3: Meta-analysis of studies of enoxaparin vs. UFH with fibrinolysis (ASSENT 3, HART II and ENTIRE, n=4,717)[15]



bleeding, especially intracranial hemorrhage, was in patients >75 years of age. In the ASSENT 3 Plus study, prehospital administration of enoxaparin also resulted in high bleeding rates that were largely confined to the elderly.

Can we safely use enoxaparin as an adjunct to fibrinolysis based on available evidence in younger patients? Similar major bleeding rates were found for LMWH and UFH in the majority of studies. Yet, a combined analysis of ASSENT 3 and ASSENT 3 Plus indicates a 3-fold increase in major bleeding in females <75-years-old compared to males in the same age range (5.8% vs. 1.9%, Figure 4). The ExTRACT TIMI 25 study will address the role of enoxaparin in 21,000 patients eligible for fibrinolysis and should give us more confidence to safely use this combination. A reduced dosage regimen of enoxaparin will be used in patients >75-years-old (0.75 mg/kg twice daily subcutaneous injections and no intravenous bolus). Until the results of this study are available, it is necessary to be cautious about initiating adjunctive enoxaparin with fibrinolysis.

LMWH with GP IIb/IIIa inhibition in the early management of NSTE-ACS

The small molecule GP IIb/IIIa inhibitors, eptifibatide and tirofiban, achieve their maximum efficacy when used with heparin. UFH was used in the major clinical trials of GP IIb/IIIa inhibitors such as PRISM, PRISM PLUS, and PURSUIT. However, when enoxaparin was shown to have greater efficacy than UFH in NSTE-ACS,[16] the role of enoxaparin in combination with GP IIb/IIIa

Figure 4: Major bleeding in ASSENT 3 and ASSENT 3 Plus combined, for enoxaparin and UFH by age and sex

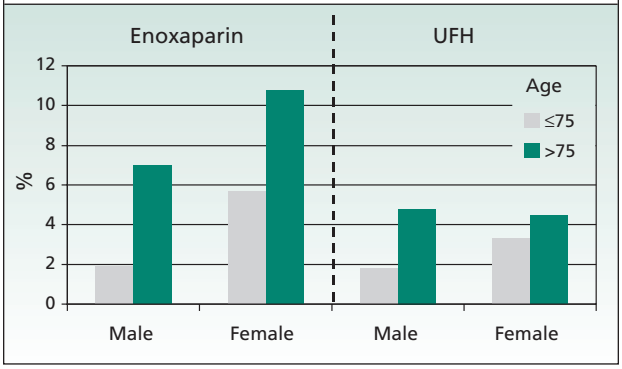
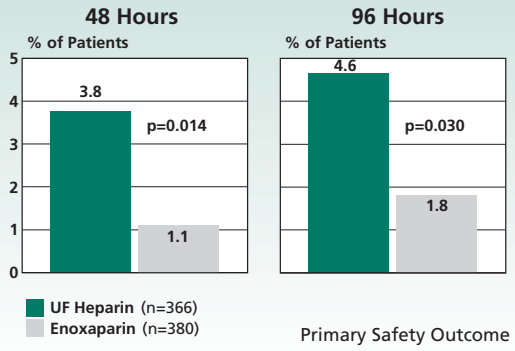


Figure 5: The INTERACT Trial[18] – Comparison of major non-CABG TIMI bleeding in patients receiving eptifibatide and randomized to either enoxaparin or UFH



inhibitors was investigated. The ACUTE II study[17] demonstrated similar rates of 30-day death or MI, but significantly lower rates of refractory ischemia requiring urgent revascularization or rehospitalization in NSTE-ACS patients given tirofiban and enoxaparin as compared to tirofiban and UFH. Yet, major non-CABG bleeding with enoxaparin was one-third that observed with UFH.

The INTERACT trial[18] randomized 746 patients with high risk NSTE-ACS to receive either enoxaparin or UFH for 48 hours. Although the trial was primarily a safety study, efficacy was assessed by the occurrence of myocardial ischemia, detected by continuous ECG during the initial 96 hours and by clinical outcomes at 30 days. Major bleeding (excluding cardiac surgical bleeding) as assessed by standard criteria was significantly lower in the enoxaparin-treated group (Figure 5). Myocardial ischemia was less at both 48 and 96 hours (48 hours after discontinuation of heparin) in the enoxaparin group (Figure 6). Thirty days after randomization, death and nonfatal myocardial infarction was significantly reduced by enoxaparin (10.1 vs. 11.8%, p=0.03, Figure 7). Other studies that did not randomly allocate LMWH or UFH, such as NICE 3[19] and PARAGON B,[20] support the safety of the combination LMWH and GP IIb/IIIa inhibitors. Large trials in progress (eg, A to Z and SYNERGY) will confirm the efficacy and safety of the combination of enoxaparin and

Figure 6: The INTERACT Trial[18] – Proportion of patients with myocardial ischemia identified by ECG monitoring a) during the first 48 hours while receiving either UFH or enoxaparin b) during the subsequent 48 hours after stopping UFH or enoxaparin.

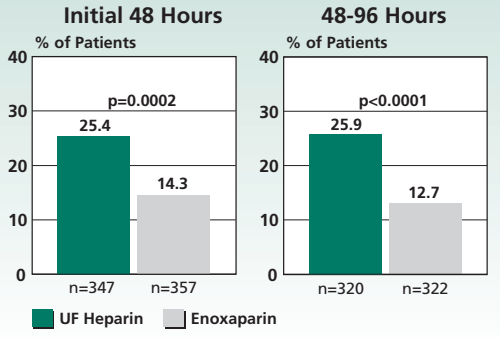
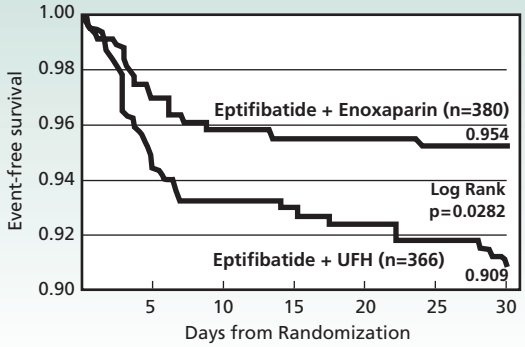


Figure 7: The INTERACT Trial[18] – 30-day death and (re-) MI after eptifibatide with either enoxaparin or UFH



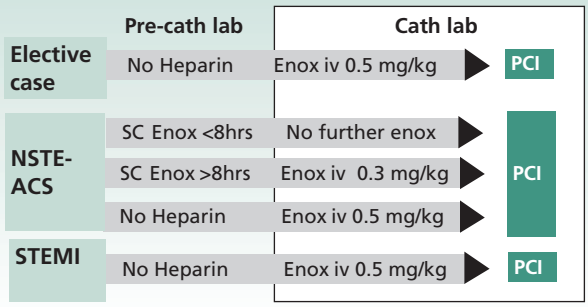
GP IIb/IIIa inhibitors for the up-front management of NSTE-ACS. Meanwhile, sufficient data have accumulated strongly supporting the safety of using enoxaparin with a small molecule GP IIb/IIIa inhibitor in the early management of NSTE-ACS.

Enoxaparin and percutaneous coronary intervention (PCI)

Enoxaparin is not only a better anticoagulant than UFH, it also results in better outcomes in patients with NSTE-ACS. Consequently, the early use of enoxaparin is replacing UFH, which has resulted in a number of management issues, especially in patients going to the catheterization laboratory. Concerns are expressed about the prolonged action and difficulty of measuring anticoagulant activity. The use of enoxaparin with PCI is of increasing relevance now that there are several studies demonstrating the superiority of an invasive over a conservative strategy in the management of NSTE-ACS. There are data to suggest that enoxaparin monotherapy for PCI is safe in the setting of PCI for both elective intervention and in the setting of NSTE-ACS. When evaluating these data, it must be remembered that the current standards for UFH use were decided empirically and based on the levels of heparinization used for CABG. Hence, the accepted standard usage of UFH titrated to an ACT 200-250 seconds is based on clinical experience and not on objective trial data. A similar empirical approach from the deep venous thrombosis literature has been used to decide the appropriate level of factor anti-Xa activity (>0.5-1.8 IU/ml) required for PCI. Using enoxaparin 1 mg/kg twice daily and an intravenous "top-up" bolus of 0.3 mg/kg if the procedure is performed >8 hours after the last dose of enoxaparin, anti-Xa levels can be achieved within the therapeutic range in 98% of patients.[21]

The ESSENCE-TIMI 11B PCI substudy[22] evaluated 924 patients undergoing PCI during the index admission who had been randomized to either enoxaparin or UFH as part of the NSTE-ACS trial. In this post-hoc analysis, enoxaparin reduced death/MI compared to UFH (enoxaparin 3.3%, UFH 5.9%, p=0.06) without any difference in major bleeding. Several uncontrolled trials have supported the claim of a similar efficacy of LMWH and UFH for PCI at the empirical doses chosen for the evaluations. Choussat et al using low doses of enoxaparin achieved target anti-Xa levels (0.5-1.5 IU/ml) in 94.6% and showed PCI could be performed with both a low rate of major adverse cardiac events (MACE) of 2.5% and major bleeding of 0.4%.[23]

Figure 8: Algorithm for enoxaparin application in PCI for both elective and ACS cases[26]



When LMWH and a GP IIb/IIIa inhibitor are used together for both urgent and elective PCI, observational studies suggest similar outcomes when compared to historical control observations using UFH. The CRUISE study[24] compared the combination of eptifibatide with either enoxaparin or UFH in 261 patients undergoing either elective or urgent PCI. The rates of death, myocardial infarction, the need for urgent revascularization, and major bleeding did not differ between the enoxaparin and the UFH groups. Further information about the safety and efficacy of enoxaparin and a GP IIb/IIIa inhibitor in the PCI setting will be forthcoming from the ongoing A to Z and SYNERGY trials. Meanwhile, an expert consensus group has published recommendations for the use of LMWH for PCI.[25] A practical algorithm devised by Montalescot mirrors the guidelines of the consensus group (Figure 8).[26]

Conclusions

The LMWH enoxaparin is rapidly becoming standard patient care for the early antithrombotic management of high- and intermediate-risk patients with NSTE-ACS based on clinical trial evidence and its ease of use. The GP IIb/IIIa inhibitors are recommended for very high-risk NSTE ACS patients who need very early revascularization. A recent study reveals that the combination of enoxaparin with the GP IIb/IIIa inhibitor eptifibatide is not only associated with less severe bleeding, it also reduces early ischemic episodes and clinical events when compared to the combination of eptifibatide and UFH.

For patients needing early cardiac catheterization and PCI, there is an accumulating body of evidence to support the safety and efficacy of enoxaparin in this setting. The safety and efficacy of the combination of fibrinolysis and enoxaparin has not yet been established with sufficient confidence to advocate its widespread use. In studies thus far, TNK-tPA combined with enoxaparin reduced recurrent coronary events, but there was an important increase in severe bleeding, especially in the elderly female population. Ongoing clinical trials will clarify the safety of this combination.

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