Editorial

Enoxaparin in non-ST segment elevation acute coronary syndromes: duration of therapy is essential to benefit

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This editorial refers to "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" by J.A. de Lemos et al. on page 1688

The topic of anticoagulation in acute coronary syndromes (ACS) is one certain to exact controversy among cardiologists. There are several clinical trials published, and meta-analyses are available, with differing results depending on which trials and which evaluation criteria are considered, allowing us to choose the one suiting our personal belief. Unfractionated heparin (UFH) used to be the standard of care for anticoagulation in ACS. Yet, it is a difficult anticoagulant to manage, largely because of a narrow therapeutic window therefore requiring careful monitoring by the activated partial thromboplastin time (aPTT). In addition, UFH is unable to inhibit clot-bound thrombin, and is associated with platelet activation. Even within the carefully monitored context of randomized clinical trials, almost half of the patients treated with UFH are outside the therapeutic aPTT range 2 days after initiating treatment, with the attendant risks of increased bleeding if overdosed, or conversely reduced antithrombotic efficacy if underdosed.1

Low molecular weight heparins (LMWH) have several pharmacodynamic differences with UFH, but, probably even more importantly, their pharmacokinetics are highly predictable, obviating the need for biological monitoring in most patients and also allowing convenient subcutaneous administration. Finally, LMWH appear to be associated with a lower risk of heparin-induced thrombocytopenia than UFH. In the context of ACS, enoxaparin has been the most widely studied LMWH and the one with the most positive trial results. Several clinical trials have demonstrated the superiority of enoxaparin over UFH in the management of ACS. However, acceptance of these results by the clinical community has been mixed. While generally adopted in Europe as the standard of care for management of ACS, LMWH and specifically enoxaparin have been less used in the US.2 The explanations for this variation in use of therapies appear multiple: first, the trial evidence available so far mostly pertained to patients initially managed in a conservative fashion and there has been a clear trend, especially but not only in the US, towards earlier use of an invasive strategy of early angiography and revascularization. Second, interventionalists, at least in the United States, rely on point of care monitoring of anticoagulation with the ACT and the lack of possibility for monitoring has been perceived as a limitation of LMWH in the context of PCI. Yet, the actual evidence that ACT monitoring is useful during PCI is not rock solid. The optimal target range for ACT is unclear and most of the studies demonstrating improved PCI outcomes with higher ACTs antedate the use of stents and glycoprotein IIb/IIIa blockers and reflect practice in the early 1990s. In fact, more recent analyses from the ESPRIT trial show no improvement in outcomes in patients with higher vs lower ACTs in patients undergoing stenting and receiving GpIIb/IIIa antagonists.3 Finally, the lack of a specific antagonist to effectively reverse the action of LMWH was viewed with concern.

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Data from both sides of the Atlantic have demonstrated that PCI may be performed in ACS patients on subcutaneous enoxaparin, regardless of whether patients receive GpIIb/IIIa antagonists or not, with satisfactory efficacy and safety outcomes. In addition, descriptive uncontrolled cohort studies also reported satisfactory outcomes of patients undergoing elective PCI on intravenous enoxaparin (as opposed to the standard of care UFH in this setting) and the REDUCE trial assessing reviparvin for the prevention of restenosis had already shown that angiographic and early clinical results of patients undergoing PCI on LMWH were at least as good if not superior to those of patients undergoing the procedure under UFH. Yet, because of the lingering uncertainty regarding the applicability of the preceding randomized clinical trials results on the use of enoxaparin to the current aggressive management strategy used for ACS, two large scale additional trials have been performed and just published (alongside an updated meta-analysis incorporating their results to the comparison with UFH): the SYNERGY trial compared enoxaparin with UFH in the context of high-risk ACS managed with an early invasive strategy, the A phase of the A–Z trial compared enoxaparin with UFH in the context of non-ST segment elevation ACS patients treated with tirofiban. SYNERGY showed essentially no difference in outcomes between the two treatment strategies, but interpretation of that trial is made difficult by the high rate of crossover between the two treatment arms and the fact that a majority of patients were treated with antithrombin agents prior to randomization. The main result of the A–Z trial was a 1% absolute reduction (and 12% relative reduction) in the risk of death, recurrent myocardial infarction or refractory ischaemia at 7 days with enoxaparin compared to UFH. This result met the criteria for non-inferiority but not for superiority of enoxaparin. In terms of safety, TIMI major or minor bleeds occurred in 3.0% vs 2.2% in the enoxaparin and UFH groups respectively (p = 0.13) and a “worst-case scenario” analysis of major bleeds based upon both investigator-identified and adjudicated bleeds found an increased risk of major bleeding of 1 in 200 in patients treated with enoxaparin (0.9% vs 0.4%, p = 0.05). The systematic overview of enoxaparin vs UFH in non-ST segment elevation ACS which accompanies these two studies suggests a 0.9% absolute reduction in the risk of death or myocardial infarction at 30 days.

In this issue of the Journal, de Lemos et al. present the results of an important subgroup analysis of the A–Z trial focusing on patients assigned by investigators to early conservative initial management. This subgroup represented approximately half of the overall trial population and baseline characteristics were evenly distributed between the two treatment groups. Using the same primary endpoint as the main trial (death, new myocardial infarction and documented refractory ischaemia within 7 days), enoxaparin was superior to UFH (7.7% vs 10.6%, HR: 0.72; 95% CI 0.3–0.99, p = 0.04). At 30 days, a non-significant trend persisted (HR: 0.80, 95% CI 0.61–1.05, p = 0.10). In this conservatively managed group, bleeding events were remarkably unfrequent, and all combined bleedings occurred in 1.3% vs 1.8% of the UFH and enoxaparin groups respectively (NS). Importantly, in patients assigned to the early invasive management, event rates were similar in the UFH and enoxaparin groups (8.5% vs 8.8% respectively, NS).

Subgroup analyses are always viewed with caution, and generally considered as merely hypothesis-generating because of the major methodological issues with their interpretation and this is no exception. There are also other issues with this analysis:

- Duration of therapy was uneven between the two groups (median of 49 vs 60 h in the UFH vs enoxaparin groups), favouring enoxaparin in this open-label trial.
- Randomization was not stratified according to allocation to the early conservative or early invasive groups.
- In this open-label study, patients could receive UFH at the time of intervention if PCI was indeed decided despite the initial assignment to an early conservative strategy and patients having received both study anticoagulants after antithrombin were counted in the UFH arm for the sake of safety analyses, which may have led to underestimation of the bleedings related to enoxaparin. However, actual rates of early catheterization or PCI were low in both treatment arms (roughly 6% in both arms at 48 h) and it is reassuring that bleedings were actually quite infrequent in both arms of the analysis.

Despite these theoretical concerns, this subgroup analysis is actually important: in this open-label trial, due to the possibility of giving open-label UFH to all patients at the time of PCI, this conservatively managed large subgroup represents a “clean subset” in which the vast majority of patients did not experience crossover of therapies. In addition, the magnitude of the benefit seen with enoxaparin is large enough to achieve clear statistical significance despite an analysis of roughly half of the total patient cohort from the overall trial. Most importantly, this subgroup analysis is not merely hypothesis-generating but rather “hypothesis-confirming”. As outlined by Das and Moliterno, most studies of intervention in non-ST segment elevation ACS, the occurrence of adverse events abates soon after completing interventional procedures, and the benefits of potent antithrombotic therapy are most marked prior to and during percutaneous coronary revascularization. These authors further point out that there was little difference in outcomes in the early hours of the previous major trials of enoxaparin in ACS (ESSENCE and TIMI 11B) and that, likewise, SYNERGY, using enoxaparin, yielded small absolute reductions in adverse outcomes in a population in whom interventions were performed aggressively within the first hours after randomization. Therefore, for the benefits of enoxaparin to be apparent, it is necessary that some time elapses on therapy, even if revascularization is ultimately performed. In this respect, the results of the subset analysis presented by De Lemos provide confirmation that enoxaparin is probably most useful as an “upstream” therapy in patients who are not directly going to the catheterization laboratory following admission. In patients who do go to the catheterization
laboratory immediately or within a few hours, the SYN-
ERGY and A–Z trial suggest non-inferiority but fail to
provide a strong incentive to "switch" routine practice
from UFH to enoxaparin. They certainly strongly suggest
the need to avoid combining both anticoagulants in the
same patient. Conversely, on both sides of the Atlantic
Ocean, a very substantial fraction of ACS patients still
undergoes initial conservative management, because
PCI is either not immediately available, not required
or not feasible. For these patients, enoxaparin appears
to be both convenient and most effective.

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