Enoxaparin and fibrinolysis: ExTRACTing prognosis from bleeding complications

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This editorial refers to ‘One-year outcomes after a strategy using enoxaparin vs. unfractionated heparin in patients undergoing fibrinolysis for ST-segment elevation myocardial infarction: 1-year results of the ExTRACT-TIMI 25 trial†, by D.A. Morrow et al., on page 2097 and ‘Relations between bleeding and outcomes in patients with ST-elevation myocardial infarction in the ExTRACT-TIMI 25 trial‡, by R.P. Giugliano et al., on page 2103.

Pharmacological reperfusion of an occluded coronary artery using a fibrinolytic agent is still the only treatment option for many patients presenting with acute ST-elevation myocardial infarction (STEMI) in many centres worldwide. To reduce the risk of early reocclusion, anticoagulants need to be given as an adjunct to lytic therapy. In this setting, low molecular weight heparins (LMWHs) offer several advantages over standard unfractionated heparin (UFH): greater bioavailability, better resistance to inhibition by activated platelets, lower incidence of heparin-induced thrombocytopenia, and a higher anti-Xa:IIa ratio and therefore more efficient inhibition of thrombin generation. Furthermore, LMWHs do not need monitoring, have a longer half-life, and can be given subcutaneously, which facilitates daily administration.

LMWHs have been tested extensively as an adjunct to fibrinolysis in STEMI patients. In patency studies, they were found to be associated with higher early patency rates and lower rates of reocclusion. In ASSENT-3, a significant improvement in the primary combined efficacy and safety endpoint was seen with enoxaparin compared with UFH in patients treated with tenecteplase. Unfortunately, a significant increase in intracranial haemorrhages (ICHs) was observed in its companion pre-hospital trial, ASSENT-3 PLUS, using the same treatment combination. The excess of ICHs was observed exclusively in patients above 75 years of age; major non-ICH bleeding complications were also much higher with enoxaparin (7.2%) than with UFH (4.0%) in the elderly. Using an age-adjusted dose (no bolus and 75% of maintenance dose), however, enoxaparin still increased the risk of major bleeding but not of ICH after fibrinolytic therapy in the much larger ExTRACT-TIMI 25 study. The increased risk of non-ICH bleeding complications was offset by a significant reduction of ischaemic events, resulting in an 18% improvement in net clinical benefit compared with UFH. Meta-analyses of STEMI trials comparing LMWHs with UFH indeed confirm that LMWHs reduce the risk of death and reinfarction, but are associated with a higher risk of bleeding complications. As a consequence, the 2008 ESC STEMI guidelines recommend enoxaparin in lytic-treated patients, although not in primary percutaneous coronary intervention (PCI), because no randomized studies have been performed so far. Whether enoxaparin is superior to UFH in primary PCI is currently being examined in the ongoing ATOLL trial.

Two additional analyses from the pivotal ExTRACT trial have now been published. In the first study, the authors offer additional insight into the relationship between in-hospital bleeding complications and 30-day and 1-year outcome, while in the second study the impact of enoxaparin vs. UFH on 1-year outcome was explored. Confirming reports from other lytic trials, mortality rates were considerably higher among patients with TIMI major bleeding (37.6%) during hospitalization, compared with TIMI minor bleeding (9.2%) or no bleeding (6.6%). Elderly, female, and low-body weight patients appeared to be particularly at risk for serious bleeding complications. Mortality was exceptionally high in patients with an ICH, who constituted almost half of the patients with major bleeding. Among patients with non-ICH major bleeding, however, outcome appeared to be affected largely by the occurrence and timing of cardiogenic shock: patients without cardiogenic shock or who developed cardiogenic shock after experiencing non-ICH major bleeding did not have a higher risk of adverse ischaemic events. In contrast, patients developing cardiogenic shock before a non-ICH major bleed had a substantially increased risk of death at 30 days.

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One-year mortality was also found to be extremely high among patients suffering from ICH. In fact, in a multivariate analysis, only ICH but not non-ICH major bleeding or minor bleeding was independently associated with 1-year mortality. The authors also looked into the relationship between in-hospital bleeding and outcome beyond 30 days up to 1 year. Among patients surviving through day 30, mortality was also found to be significantly higher after major compared with minor or no bleeding, but this was to a large extent driven by an excess mortality in patients with an in-hospital ICH who survived beyond 30 days. There appeared to be no excess risk of death associated with non-ICH major bleeding after day 30: mortality between 30 days and 1 year appeared to be mainly affected by patient co-morbidities.

These interesting analyses of the relationship between bleeding complications, the type of bleeding, and outcome come timely. In recent trials and registries in acute coronary syndromes, bleeding complications and transfusions have been identified as important markers of outcome. As a consequence, the hypothesis has been put forward that lower rates of ischaemic events observed with newer antithrombotic agents in some trials are likely to be the direct result risk of a reduction in bleeding complications. Nevertheless, other analyses also suggest that baseline risk factors for ischaemic events account for at least a large part of adverse outcome related to bleeding complications. The new insights into bleeding complications after lytic therapy presented here demonstrate that ICH is a major determinant of outcome among patients experiencing major bleeding, while mortality following in-hospital non-ICH bleeding is largely driven by a higher risk profile and the occurrence of cardiogenic shock. These results also underscore the detrimental impact of ICH on mortality rates in lytic-treated STEMI patients. How do these findings then relate to the increased risk of major bleeding complications and lower risk of ischaemic events observed with enoxaparin in the ExTRACT trial? The 1-year analyses reveal that the reduction in ischaemic events associated with enoxaparin was largely confined to the first 30 days. This might indicate that the early benefit in terms of ischaemic events might still, to some extent, be offset beyond 1 month by the higher in-hospital bleeding risk with enoxaparin. Also, as ischaemia-triggered early angiography or PCI was significantly less likely with enoxaparin, a higher rate of revascularization with UFH might also in part have offset the early benefit of enoxaparin. In any case, despite an enoxaparin dose adjusted for age, weight, and renal function, bleeding complications after fibrinolysis are not rare and clearly not benign.

Several questions remain to be answered. First, only one in four patients in ExTRACT received clopidogrel during hospitalization. In the more recent CLARITY-TIMI 28 trial, clopidogrel use was associated with significantly better early patency rates in lytic-treated patients below the age of 75, but only 30% of patients were initially treated with LMWH in this study. While age-adjusted clopidogrel and enoxaparin are recommended by the ESC guidelines for lytic-treated patients, the safety/efficacy balance of enoxaparin in a contemporary setting of systematic use of clopidogrel still needs to be examined across all age categories. Secondly, current ESC STEMI guidelines advocate systematic early (between 3 and 24 h) angiographic control in stable lytic-treated STEMI patients. In ExTRACT, only 23% of patients received an early angiography. Although enoxaparin is recommended as an adjunct to lytic therapy, it remains unclear whether its advantage in reducing ischaemic events is sustained in the setting of systematic early angiography and PCI. In ExTRACT, enoxaparin was given for 8 days or until discharge, while UFH was only administered for up to 48 h, hence at least part of enoxaparin’s advantage might be attributed to longer treatment duration. Systematic intervention within 24 h after lytic therapy might significantly attenuate the benefit of enoxaparin, while perhaps still exposing patients to an increased risk of major bleeding. In a previously published subanalysis from ExTRACT, patients undergoing PCI within the first 30 days had a lower risk of death or myocardial infarction, while experiencing more bleeding complications. In a real-world setting, however, it is unlikely that enoxaparin will be continued beyond the first day in successfully revascularized patients. Part of the answer to this issue will come from ongoing systematic early vs. elective early angiography studies such as the STREAM trial. In this study, patients above 75 years of age receive half-dose tenecteplase and all lytic-treated patients receive age-adjusted doses of clopidogrel and enoxaparin, and, when stable, are required to undergo early angiography between 6 and 24 h; this pharmaco-invasive strategy is compared with standard primary PCI. Finally, the results of ExTRACT obviously do not address the relationship between bleeding complications and outcome in STEMI patients undergoing primary PCI or in NSTEMI-ACS (non-ST-elevation acute coronary syndrome) patients. As the authors suggest, prospectively (and blindly) addressing the relationship between bleeding and ischaemic events for each individual event in ACS trials by a clinical event committee will certainly help to dissect further the deleterious but intriguing interplay between bleeding and outcome. This should result in reliable risk scores for bleeding and ischaemic events, and eventually a more personalized antithrombotic treatment.

Conflict of interest: none declared.

References


