Hotline Editorial

ASSENT-3: implications for future trial design and clinical practice

New fibrinolytic agents have failed to further reduce 30-day mortality after ST-segment elevation acute myocardial infarction. Although the reduced plasma clearance of TNK-tPA and n-PA and the increased fibrin-specificity of TNK-tPA are clinically relevant, mortality rates with these agents were not lower than with accelerated infusion of t-PA. Yet another way to improve pharmacological reperfusion is the co-administration of better antithrombotic agents. In phase II trials, both low-molecular-weight heparins and glycoprotein IIb/IIIa antagonists have shown the potential to improve reperfusion. With low-molecular-weight heparins, higher late patency rates, less reocclusion and/or fewer reinfarctions have consistently been observed[1–4]. With glycoprotein IIb/IIIa antagonists, higher patency rates of the epicardial coronary artery and signs of improved tissue reperfusion have been found[5–7]. Against this background, the ASsessment of the Safety and Efficacy of a New Thrombolytic regimen (ASSENT)-3 was designed. The ASSENT-3 trial[8] was a randomized open-label trial of an intermediate size (6095 patients) designed to compare the efficacy and safety of three reperfusion regimens: (1) full-dose TNK-tPA plus prolonged subcutaneous administration of enoxaparin, a low-molecular-weight heparin, for a maximum of 7 days; (2) half-dose TNK-tPA with intravenous abciximab, a glycoprotein IIb/IIIa antagonist for 12 h plus reduced dose unfractionated heparin for 48 h; (3) full-dose TNK-tPA plus weight-adjusted unfractionated heparin for 48 h with early monitoring (at 3 h) of the aPTT.

The dose of unfractionated heparin used in this reference arm is the dose recommended in the 1999 guidelines of the ACC/AHA[9]: 60 U.kg\(^{-1}\) bolus (maximum 4000 U) and initial infusion of 12 U.kg\(^{-1}\).h\(^{-1}\) (maximum 1000 U.h\(^{-1}\)). Remarkably, this dose has not been tested in large-scale trials so far. The results of ASSENT-3 indicate that both enoxaparin and abciximab significantly reduce the risk of ischaemic complications of an acute myocardial infarction treated with TNK-tPA. Thirty per cent to 50% reductions in the risk of in-hospital reinfarction or in-hospital refractory ischaemia were observed with the experimental treatments. The results obtained with half-dose TNK-tPA and abciximab essentially confirm those with half-dose reteplase and abciximab in the larger GUSTO-V trial[10] and support the hypothesis that a more potent antiplatelet agent increases and preserves flow in the infarct-related coronary artery. This beneficial effect, however, was counterbalanced by a significantly higher rate of thrombocytopenia and major bleeding complications. The risk of bleeding complications was particularly high in patients above the age of 75 in whom the rates were three times higher than with unfractionated heparin.

The reductions in ischaemic complications in the enoxaparin arm were similar to those in the abciximab arm. With enoxaparin more bleeding complications were observed but this increase was smaller than with abciximab. Importantly, no significant differences in intracranial haemorrhage rates were observed among the three groups. Taking into account efficacy and safety, the ease of administration and the lack of need for monitoring anticoagulation, the combination of single-bolus TNK-tPA and enoxaparin emerged as the best treatment in the trial. This simple treatment appears to be a very attractive reperfusion strategy for the pre-hospital and emergency department setting. Whether it also has a role in conjunction with early coronary interventions or as a co-therapy with glycoprotein IIb/IIIa antagonists needs to be determined in future trials. Such trials are underway. The pre-hospital use of single-bolus TNK-tPA and enoxaparin is currently being tested in the ASSENT-3 Plus trial (±1600 patients) of which the results are expected in 2002. Although it is very likely that enoxaparin is also beneficial in combination with other fibrinolytic agents such as tPA, no large-scale data are currently available to support its use with other agents.

The reduction in ischaemic complications with abciximab and half-dose TNK-tPA was larger than with enoxaparin during the first 24 h. This observation suggests that this combination treatment may...
benefit patients at high risk who, most likely, will undergo an early coronary intervention. Thus, the combination of a half-dose fibrinolytic with a glycoprotein IIb/IIIa antagonist may be particularly useful in a subset of younger patients with a low bleeding risk but with large amounts of myocardial tissue at stake who will undergo an early coronary intervention. This concept of ‘facilitated’ coronary interventions will be tested in the near future.

The results observed in the reference arm of ASSENT-3 are also of interest. In this treatment arm weight-adjusted unfractionated heparin was given with early (at 3 h) aPTT monitoring. The clinical outcomes observed were very similar to those of ASSENT-2\[11\] in which a higher and not fully weight-adjusted dose of unfractionated heparin was given with the first aPTT drawn after 6 h. Total mortality, reinfarction, total stroke and intracranial haemorrhage rates were almost identical in the two trials. However, fewer major bleeding complications (2.2% vs 4.7%) and less need for blood transfusion (2.3% vs 4.3%) were observed in ASSENT-3 than in ASSENT-2. These results very much support the use of a more fully weight-adjusted dose of unfractionated heparin when given in conjunction with fibrinolytic agents as is recommended by the current guidelines.

Finally, the design of this study, more particularly the absence of a primary hypothesis, and the use of composite efficacy and safety end-points deserve some further comments. Given the large number of promising agents that are or will be available for the treatment of acute coronary syndromes and the need to combine them in appropriate doses, intermediate size trials like ASSENT-3 appear to be very useful for testing promising regimens before embarking on a definitive, large-scale (mortality) trial.

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References