Editorial

Combining glycoprotein blockers with fibrinolysis: a bold stroke?

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For the future treatment of ST-elevation myocardial infarction, fibrinolytic therapy will be the most widely used therapy, because of its simplicity, worldwide availability and relatively low cost. In comparison to primary angioplasty, which will continuously be hampered by its limited availability and inherent time delay, fibrinolytic therapy has two major drawbacks: partial efficacy and a small, but significant risk of major life-threatening bleeding. Several modifications in fibrinolytic drug design have optimized simplicity and efficacy in that 90 min patency of about 60% can be achieved with

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Fig. 1 Meta-analysis of the incidence of severe extracranial bleeding in the published acute ST elevation infarction trials comparing full dose fibrinolysis to reduced dose fibrinolysis combined with glycoprotein IIb/IIIa receptor antagonists (test for heterogeneity=ns). Shown are odds ratios and 95% confidence intervals.

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the bolus agents tenecteplase and reteplase. But life-threatening bleeding, especially intracranial bleeding, remains a serious problem.

To increase efficacy and decrease bleeding much effort has been put in modification of adjunctive therapy to fibrinolysis. By replacing unfractionated heparin with low molecular weight heparin efficacy of modern lysis seems to be increased, but cerebral bleeding remains the major problem. Lowering the dose of the lytic has only a limited effect on efficacy, but may decrease bleeding. By combining dose-lowering with enhancing antiplatelet therapy using stronger agents than aspirin alone the idea came up to study the combination of reduced dose lytic with full dose glycoprotein IIb/IIIa antagonists in comparison to full dose lytic alone. The first angiographic dosing trials were promising, but cerebral bleeding remains the major problem. Lowering the dose of the lytic has only a limited effect on efficacy, but may decrease bleeding. By combining dose-lowering with enhancing antiplatelet therapy using stronger agents than aspirin alone the idea came up to study the combination of reduced dose lytic with full dose glycoprotein IIb/IIIa antagonists in comparison to full dose lytic alone. The first angiographic dosing trials were promising, but the results of the clinical megatrials GUSTO-V and ASSENT-3 were disappointing with regard to efficacy in that 30 day and 1-year mortality were not reduced in comparison to lytic alone. Even more disappointing, when all the published trials on combo-therapy are analysed, were both the significant increase in major bleeding (Fig. 1) and the absence of a decrease in cerebral haemorrhage (Fig. 2). The most disturbing point in the lack of safety in the trials on combo therapy is that reducing the dose of the lytic does not reduce bleeding, whereas the use of glycoprotein IIb/IIIa blockers in the absence of lytic therapy seems to be rather safe.

In the current issue the interesting paper by Savonitto et al. provides some insight into this paradox. In the large GUSTO-V trial, in which overall cerebral haemorrhage was not decreased by the half dose of a lytic plus abciximab, it was shown that younger patients had significant less cerebral bleeding with half dose lytic plus abciximab than full dose lytic, and that it was the other way around in the elderly. That the risk of lytic induced cerebral bleeding is significantly increased with age, is not new. But that this risk follows the exact line of age is an important new finding, that, of course, can only be derived from the large number of patients in the GUSTO-V megatrial. In fact, experience with the IIb/IIIa blocker abciximab in patients over the age of 75 was rather scarce before the megatrials GUSTO-IV, GUSTO-V and ASSENT-3. Abciximab had almost exclusively been used in trials with percutaneous intervention and high age was a common exclusion criterion in these studies. It was a courageous step to include the elderly in the abciximab megatrials, but, quite frankly, it ended at the same time the role of the agent for routine use in acute coronary syndrome with or without ST elevation.

Should we now administer half dose lytic plus abciximab to all patients younger than 55? The study published today is well performed, but is a post-hoc analysis. Although well controlled for confounding factors, it is not more than an observation, which learns us more about the relationship of age with drug-induced...
cerebral bleeding than about new therapeutic strategies in subsets of patients. For that purpose a prospective randomized study exclusively in younger patients is required. It is unlikely that such a trial will ever be initiated.

References