Direct thrombin inhibitors in acute coronary syndrome patients undergoing percutaneous coronary intervention: special effects in selected patients?

Eric Boersma*

Clinical Epidemiology Unit, Thoraxcenter Cardiology, Room Ba563, Erasmus MC, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

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This editorial refers to 'Direct thrombin inhibitors in acute coronary syndromes: effects in patients undergoing early percutaneous coronary intervention' by P.R. Sinnaeve et al., on page 2396

Coronary thrombosis is a pivotal event in the pathogenesis of acute coronary syndromes (ACS) as well as in the incidence of thrombotic complications resulting from percutaneous coronary interventions (PCIs).1 Platelet adhesion and aggregation at the site of spontaneous or provoked plaque rupture is an important contributor of such intracoronary thrombus formation. As activation of the platelet glycoprotein (GP) IIb/IIIa receptor is the final common pathway in the process leading to platelet aggregation, inhibitors of the platelet GP IIb/IIIa are potent agents to prevent progression to myocardial infarction (MI) and death. In a recent meta-analysis of six phase III randomized trials, which enrolled 31 402 ACS patients without ST-elevation who were not scheduled for early PCI, GP IIb/IIIa inhibitors were associated with a modest, but statistically significant 9% reduction in the 30-day incidence of death or MI compared with control therapy (7.4 vs. 8.2% events, odds ratio 0.92, and 95% CI 0.84–0.99).2 Interestingly, in these trials, patients who underwent PCI within 120 h after enrolment had a much larger reduction in the incidence of this composite endpoint (absolute risk difference 2.7%, odds ratio 0.77, and 95% CI 0.64–0.92) than those not undergoing such early intervention (absolute risk difference 0.7%, odds ratio 0.95, and 95% CI 0.87–1.02). Event reductions by GP IIb/IIIa inhibitors were observed before and during the intervention.3

Exposure of blood to tissue factor activates the coagulation cascade and leads to the generation of thrombin. Thrombin is a potent platelet agonist and recruits additional platelets to the site of vascular injury. In addition to converting fibrinogen to fibrin, thrombin activates factor XIII, which stabilises the fibrin clot. Thus, unregulated thrombin generation is an important trigger of (recurrent) ischaemic events. Therefore, besides anti-platelet therapy, effective anti-thrombin therapy, classically by prescribing unfractionated heparin (UFH), is another cornerstone of appropriate ACS management. In a series of six randomized trials, which enrolled 1353 ACS patients, UFH was associated with a 34% reduction in the incidence of death or MI at the completion of study medication, which varied from 48 to 168 h, compared with control therapy (7.9 vs. 10.4% events, odds ratio 0.66, and 95% CI 0.44–0.99).4

When bound to fibrin or fibrin degradation products, thrombin is resistant to inactivation by the heparin/anti-thrombin complex. Bound thrombin, which remains enzymatically active, triggers thrombus growth by factors V, VIII, and XI, thereby amplifying thrombin generation. In contrast to UFH, which catalyse the inactivation of thrombin by anti-thrombin, direct thrombin inhibitors (DTIs) bind to the enzyme and block its interaction with its substrates. Thus, in patients presenting with ACS, DTIs are likely to be more effective to prevent life-threatening thrombotic complications than UFH.

Recently, a meta-analysis was completed of 11 phase III randomized trials that evaluated the efficacy and safety of DTIs compared with UFH.5 Two trials enrolled NSTE-ACS patients who were scheduled for undergoing urgent PCI (n = 5453) and nine trials enrolled ACS patients with (n = 9947) and without (n = 20 570) ST-elevation, who were not scheduled for such early intervention. The DTIs under investigation included argatroban, bivalirudin, efegatran, hirudin, and inogatran and the treatment duration varied from 48 to 168 h. Treatment with a DTI was associated with a statistically significant 8% reduction in the incidence of death or MI at 30 days compared with UFH (7.4 vs. 8.2% events, odds ratio 0.92, and 95% CI 0.84–0.99). Sinnaeve et al.6 present more details of this meta-analytic dataset. They separated the 7049 patients who underwent PCI within 72 h after enrolment, from those not undergoing such early intervention. In the patients undergoing early PCI, treatment with a DTI was associated with a statistically significant 34% reduction in the incidence of death or MI at 30 days compared with UFH (9.5 vs. 13.9%...
The observed difference in treatment effect was statistically significant and remained after adjustment for baseline characteristics.

The similarity between the GP IIb/IIIa and DTI meta-analyses is remarkable, and the obvious question rises why these agents have such amplified effect in patients undergoing early, non-scheduled PCI. First, it should be realized that data with regard to the incidence of cardiac endpoints by allocated treatment in subgroups of patients according to the use and timing of coronary revascularization do not represent strictly randomized comparisons, and the estimates of treatment effect might be biased. In the study of Sinnaeve et al., patients undergoing early PCI were more likely to be men, older, and current smokers, more often had a past history of PCI, whereas they were less likely to have a previous history of ischaemic heart disease, diabetes, or hypertension. In the GP IIb/IIIa meta-analysis, the use of cardiac revascularization was related to gender and baseline cardiac troponin level. Furthermore, patients treated with GP IIb/IIIa inhibitors or DTIs significantly less often underwent early PCI than placebo/control patients. Apparently, the use and timing of revascularization were related to patient’s response to study medication. It is true that the differential DTI effects as observed by Sinnaeve et al. remained significant after multivariable adjustment for a wide range of baseline characteristics and propensity to undergo early PCI, but unmeasured confounders (cardiac troponins?) might still have been present. Therefore, unambiguous conclusions cannot be drawn on the basis of these analyses.

Sinnaeve et al. emphasized that the benefit of DTIs in patients undergoing early PCI was driven by a reduction of MI on the day of the intervention. However, the high pre-procedural event rate was as relevant in this context as the observed DTI effect. Importantly, the relative risk reduction by DTIs before the intervention was of similar magnitude as the effect during the intervention (unadjusted odds ratios 0.55 and 0.46, respectively). Furthermore, the point estimates of treatment effect in patients undergoing PCI between 3 and 7 days (‘late’ PCI) and those undergoing early PCI were close (adjusted hazard ratios 0.76 and 0.62, respectively), whereas 95% confidence intervals were largely overlapping. As most patients undergoing late PCI were off study drug treatment during their procedure, these data suggest also a pre-procedural protection by DTIs in patients undergoing late PCI.

The management of patients with an acute expression of coronary heart disease is a dynamic process. In fact, throughout hospitalization, a continued refinement of the initial treatment strategy is necessary to optimize patient outcome. The recurrence of myocardial ischaemia is one of the main reasons to opt for PCI in ACS patients in whom such intervention was not programmed initially. On the basis of the study by Sinnaeve et al. and meta-analyses of the GP IIb/IIIa inhibitor trials, one might speculate that optimal anti-platelet and anti-thrombin therapies prevent further progression of imminent events in these patients, and thus safely bridge the time to intervention. The ongoing ACUITY trial, in which several strategies incorporating bivalirudin and the GP IIb/IIIa inhibitors abciximab and eptifibatide are being evaluated in ACS patients, addresses this issue and may provide more definite answers.

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References