Acute coronary syndrome: the struggle for the best in risk stratification and therapy

See doi:10.1053/euhj.2001.3043 for the article to which this Editorial refers

It is a common dilemma in clinical trials dealing with acute coronary syndromes without persistent ST elevation that there are no hard criteria identifying the patient with coronary artery disease at risk. Up to 15% of patients with typical symptoms will have normal vessels or insignificant disease in the coronary angiograms. This dilutes any patient cohort at risk and thereby reduces the likelihood of showing significant treatment benefits. Accordingly, study designs have to balance between limiting the inclusion criteria to patients not representative of the ‘real world’ or to enormously increasing the trial size. Alternatively, it is a common practice to analyse pre-defined high-risk subgroups after study completion. In acute coronary syndrome trials these are commonly the cohorts with ST segment deviations or elevated cardiac biomarkers, particularly troponins. Both may be understood as markers of an ongoing thrombotic process. Elevated troponins indicate minor but irreversible cell injury caused by repetitive thrombus embolization downstream of the culprit lesion. Similarly, depression of the ST segment in the ECG of more than 1 mm reflects ischaemia resulting from active thrombus formation at the site of a ruptured atherosclerotic plaque.

There is ample evidence that unfractionated heparin as well as low molecular weight heparins compared with placebo improve the short-term outcome in patients with acute coronary syndromes[1]. Enoxaparin was shown in two trials to be more effective than unfractionated heparin[2,3]. A similar benefit was shown for glycoprotein IIb/IIIa inhibitors when added to unfractionated heparin and aspirin[4]. Post-hoc analyses revealed consistently that the benefit was mainly accomplished in patients with elevated troponin[5–9]. Furthermore, patients with elevated troponins seem to have the best outcome with early invasive management (<48 h) after upstream treatment with the glycoprotein IIb/IIIa inhibitor tirofiban[10]. Accordingly, the concept for hospitals with direct access to invasive facilities seems to be well delineated. For other places, however, two questions remain open: which patient must be sent on to coronary angiography, and what is the best treatment for the time in between.

The FRISC II study is a landmark trial, because it established the important role of coronary interventions for the outcome of patients with unstable angina as opposed to a very conservative strategy[11]. In fact, it is the first study to establish that percutaneous coronary interventions reduce the risk for death and myocardial infarction. The effect of extended anticoagulant treatment with dalteparin on the outcome in the other arm of this study was less convincing. Only marginal benefit was shown in patients with elevated troponin T[12]. In this issue, the results of continuous 12-lead ECG or vectorcardiography over 24 hours as prognostic marker are presented[13]. Patients with ischaemic episodes at study entry had a significant 34% reduction of the triple end-point death, myocardial infarction, or revascularization when treatment with dalteparin was continued for 3 months after 5 days of open label treatment. Although the study population of 629

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A considerable number of patients escape our risk assessment protocols despite all achievements during the last decade. In FRISC II, Patients treated with low molecular weight heparin still had a 3 months risk for the hard end-points death or myocardial infarction of 4-7% when there was no ST depression on study entry, of 6-1% when troponin T was not elevated, and 8-9% when no ischaemic episodes could be documented on continuous recordings[12,13]. Accordingly, there is still some room for better identifying more patients at risk who consequently should benefit from improved treatment. However, only specific markers or simple algorithms will have a chance to find acceptance in the emergency room setting. A risk score combining different markers is too complex to handle and may be no major advantage[16,20]. Therefore, the search for the ideal marker continues.

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References
Reperfusion damage or no-reflow damage in primary coronary interventions in acute myocardial infarction?

See doi:10.1053/euhj.2001.3035 for the article to which this Editorial refers

Primary percutaneous coronary intervention has become the preferred (first choice) therapy for acute myocardial infarction with ST elevations in most developed countries. Percutaneous coronary intervention is more effective than thrombolysis in restoring TIMI-3 flow and thus decreasing mortality [1–3]. By dilating of the culprit lesion percutaneous coronary intervention markedly decreases the incidence of re-infarction.

Patients presenting later in the course of myocardial infarction (i.e. between 4–12 h, and maybe even up to 24 h) also benefit from percutaneous coronary intervention, while thrombolysis in these patients is usually less effective [4]. The proportion of patients with ST elevation myocardial infarction treated by primary percutaneous coronary intervention and by thrombolysis is continuously shifting in favour of primary percutaneous coronary intervention in many developed countries [5,6]. For example, in the Czech Republic in 2001 it was expected that 60–70% of reperfusion therapy for acute myocardial infarction would be primary percutaneous coronary intervention and 30–40% thrombolysis. However, despite the high technical success rate, the in-hospital mortality of non-selected consecutive patients with acute myocardial infarction undergoing primary percutaneous coronary intervention remains between 4–7% [7,8]. How can this be improved?

The question to solve today in everyday cardiology practice is not whether to use thrombolysis or primary percutaneous coronary intervention: thrombolysis should be used only when primary percutaneous coronary intervention is not available within a comparable time. However, with primary percutaneous coronary intervention emerging as the new gold standard of therapy new questions are arising:

- What is the best pharmacological treatment before primary percutaneous coronary intervention?
- Could reperfusion damage be prevented?
- What is the mysterious ‘no-reflow’ phenomenon?
- How can distal coronary embolizations be prevented?

The solutions for these answers, along with improved public knowledge of the crucial importance of time in the acute phase of myocardial infarction and with improved health care system organization, can further decrease mortality.

In this issue, Henriques, Zijlstra and the Zwolle group [9] describe the analysis of the incidence and clinical significance of distal embolization during primary percutaneous coronary intervention. The observed incidence of 15% and the related marked increase in the long term (5 years) mortality when distal embolization occurred (44% vs 9% in patients without distal embolization) clearly show the clinical importance of this phenomenon. Until recently, more attention was focused on ‘reperfusion damage’ than on ‘no-reflow damage’.

Despite the extensive literature on reperfusion injury, there is no direct clinical evidence for increased mortality from this phenomenon [10,11]. Furthermore, all available evidence suggests that the benefits of reperfusion markedly ‘outweigh’ the theoretical risks of reperfusion injury. Despite the fact that reperfusion injury is a real and well known process, its clinical relevance is still questionable. This uncertainty is currently enhanced by the accumulating