Should intravenous thrombolysis keep a place in the treatment of acute ST-elevation myocardial infarction?

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This editorial refers to ‘Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction’ by E. Björklund et al., on page 1146

Following the recognition of the role of intracoronary thrombus in the pathogenesis of acute myocardial infarction, intracoronary, then intravenous thrombolysis have been documented as the first methods capable of achieving adequate reperfusion of the jeopardized myocardium. The clinical consequence of early reperfusion was a reduction in mortality rates at the acute stage. Subsequently, coronary angioplasty has shown its capacity to reopen recently occluded arteries, and the direct comparison of intravenous thrombolysis with percutaneous coronary angioplasty performed in an ‘ideal’ setting has consistently shown the superiority of the mechanical compared with the pharmacological approach. The most recent randomized trials comparing both modes of reperfusion therapy have shown that better clinical results were achieved using coronary angioplasty, even when the patients had to be transferred from an initial institution to another one, with the capability to perform interventional cardiology. Following these results, one might reasonably wonder whether intravenous thrombolysis should remain a part of the therapeutic armamentarium of acute myocardial infarction.

The answer to this question is obvious in countries where the network of institutions equipped for 24 h a day, 7 days a week interventional cardiology is lacking or insufficient. The recent Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial1 is there to remind us that, in developing countries, intravenous thrombolysis remains the first treatment of acute myocardial infarction. In countries where interventional cardiology is more easily available, however, the question of a 100% shift from thrombolysis to coronary angioplasty is posed, and the paper by Björklund et al.2 is therefore important to clarify this issue.

The authors analysed the data from the permanent Swedish register of acute myocardial infarction from 2001 to 2004. This register represents a major effort to document the outcome of all patients admitted to cardiac intensive care units and includes 75 of the 80 Swedish hospitals. The quality of the data is ensured by extensive audits. In the present analysis, 5375 patients aged <80, treated with intravenous thrombolysis for a first ST-elevation myocardial infarction and transported by ambulance were included. When used, pre-hospital thrombolysis was administered in the ambulance by trained paramedics. In-hospital management and outcomes were compared for patients receiving pre-hospital thrombolysis with those treated in hospital. Overall, patients treated with pre-hospital thrombolysis were younger and had a more favourable risk profile than those receiving in-hospital thrombolysis. Time to administration of the thrombolytics was shortened by 50 min in the pre-hospital group. All in-hospital complications, except intracranial bleeding, were less frequent in the pre-hospital group. More patients in the pre-hospital lysis group had rescue angioplasty or underwent myocardial revascularization within 14 days of admission. More patients in the pre-hospital lysis group received statins and beta-blockers at discharge and fewer received diuretics. One-year mortality was lower in patients treated with pre-hospital thrombolysis and, after adjustment for other predictors, the odds ratio for 1-year mortality in patients receiving pre-hospital vs. in-hospital thrombolysis was 0.71, a highly significant difference.

These results are important as they show that, in the current era of reperfusion therapy, the outcomes of intravenous thrombolysis may differ according to the time of its administration. Although these observational data, even when adjusted for potential confounders, do not have the strength of randomized controlled trials, they reinforce the findings of previous randomized trials comparing pre-hospital and in-hospital thrombolysis. These trials were carried out in the late 1980s and the early 1990s; the largest one included more than 5400 patients, 61 years of age, and pre-hospital thrombolysis was initiated in physician-staffed ambulances; 30-day mortality was 9.7% in the pre-hospital thrombolysis group when compared with 11.1% in the in-hospital thrombolysis group.3 In the meta-analysis of randomized trials of pre-hospital vs. in-hospital thrombolysis,4 the pooled odds ratio for in-hospital death was 0.83. Therefore, this difference between pre-hospital and in-hospital thrombolysis is quite similar to that observed.
10 years later in the Swedish register, in an older population with a different therapeutic background and improved overall outcome, in which the adjusted odds ratio for 30-day mortality was 0.79 (5.4 vs. 8.3%).

An intriguing aspect of the Swedish data is the lack of benefit of pre-hospital thrombolysis, compared with the in-hospital thrombolysis, in women. In the French register, we did not observe such a difference in efficacy, and 1-year mortality was actually nil in the small population of women who had received pre-hospital thrombolysis (data on file). Women, however, pose specific problems at the acute stage of myocardial infarction, and we have found that the mortality of younger women within the first few days following myocardial infarction was much higher than that of younger men. The observation from the Swedish register regarding a potential gender effect will therefore warrant further study.

The true question at present in most European countries, however, is to determine whether intravenous thrombolysis should be abandoned altogether, in favour of primary coronary angioplasty. Only one randomized controlled trial, the Comparison of Angioplasty and Prehospital Thrombolysis in acute Myocardial Infarction (CAPTIM) trial, compared primary angioplasty with pre-hospital thrombolysis; although the trial, because of difficulties in recruiting patients, did not achieve the expected population size and was therefore slightly underpowered, it failed to show a significant difference in the rate of severe vascular events between the two reperfusion techniques. Mortality at 1 month and 12 months was even lower in patients with pre-hospital thrombolysis compared with those with primary angioplasty (3.8% vs. 4.8% and 5.4% vs. 7.3%, respectively). In a register of patients admitted for acute myocardial infarction in France at the end of 2000, pre-hospital thrombolysis yielded results that were at least comparable to those of primary angioplasty in terms of early and 1-year mortality: in patients with reperfusion therapy, pre-hospital thrombolysis was associated with an odds ratio of 0.52 for 1-year mortality (95% confidence interval: 0.25–1.08; \( P = 0.08 \)), compared with either in-hospital thrombolysis or primary coronary angioplasty (1-year survival: 94% vs. 89%, respectively). Both in the CAPTIM trial and in the French register, pre-hospital thrombolysis was found to be superior to primary angioplasty when the treatment could be initiated very early. In CAPTIM, 1-month mortality was 2.2% in patients randomized to pre-hospital thrombolysis, compared with 5.7% in those randomized to primary coronary angioplasty, when the patients were randomized \(<2\) h after symptom onset; however, the reverse trend was observed when the patients were randomized at a later time (5.9% mortality in thrombolysis patients vs. 3.7% in patients undergoing primary angioplasty). In the French register, 1-year survival was 99% when the patients were admitted \(<3.5\) h after symptom onset after receiving pre-hospital thrombolysis. Unfortunately, the data from the Swedish register presented here do not compare the results of pre-hospital thrombolysis with those of primary coronary angioplasty. But although the register provides no direct comparison with primary coronary angioplasty, the results observed in Sweden give indirect evidence that pre-hospital thrombolysis is a valid therapeutic option and they support the findings of both the CAPTIM trial and the French register. Indeed, in this real-world setting, the magnitude of the survival benefit associated with pre-hospital thrombolysis compared with in-hospital thrombolysis is similar to that found with primary coronary angioplasty in the meta-analyses of randomized trials comparing this interventional technique with thrombolytic treatment, thereby suggesting that pre-hospital thrombolysis may offer results quite comparable to those of primary angioplasty (Table 1).

On the whole, the data presented by Björklund et al. give additional support to the current recommendations from the European Society of Cardiology. Although primary coronary angioplasty should remain the reference in terms of reperfusion therapy for ST-elevation myocardial infarction, intravenous thrombolysis remains a valuable therapeutic option and may give results that are as good as those obtained with primary angioplasty, provided it is administered sufficiently early and particularly in the pre-hospital setting. Therefore, in patients seen early after the onset of symptoms, pre-hospital thrombolysis remains a worthwhile strategy, particularly when the expected time delay before angioplasty is long.

**Conflict of interest:** N.D. has been a speaker in symposia organised by Boehringer-Ingelheim, which manufactures TNK tPA.

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PCI, percutaneous coronary intervention; PHT, pre-hospital thrombolysis; RCT, randomized controlled trial.

**Clinical vignette**

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Late coronary thrombosis in a sirolimus-eluting stent due to the lack of neointimal coverage

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A 44-year-old man was admitted to our hospital because of a diagnosis of acute myocardial infarction (AMI). Thirty-one months before the onset, he underwent elective percutaneous coronary intervention of the first diagonal branch, with one sirolimus-eluting stent (SES; Cypher, 2.5 mm diameter, 18 mm long) due to a diagnosis of prior AMI. Clopidogrel was discontinued at the 3-month clinical follow-up after stenting. The regular intake of aspirin 150 mg/day had been continued. Immediately, coronary angiography was performed. The struts of the SES that had previously been deployed were recognized through fluoroscopy (white arrow-heads in Panel A). A coronary angiogram showed a total occlusion in the SES (white arrow in Panel B). Coronary angiography showed some of the struts were visible under a thin neointima at the proximal portion of the SES (black arrow in Panel C, asterisk indicates the guidewire). At the mid-portions, the struts covered with a very thin neointima were seen more clearly (black arrows in Panel D). Massive and protruding red thrombi adjacent to the exposed struts were found. Parts of the thrombi were located outside the struts, and the exposed struts had become detached from the vessel wall (white arrows in Panels E and F).

Our angioscopic findings verified the lack of neointimal coverage following the stent malapposition was related to the occurrence of late stent thrombosis. Although it has been believed that the stent malapposition after drug-eluting stent deployment does not result in any adverse events, further careful long-term follow-up studies, especially for cases of stent malapposition, are required.