Letters to the Editor
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A critical amendment to the Meta-analysis of clinical trials comparing Thrombolysis with Primary Angioplasty

I refer to the publication of Zijlstra,¹ who compares two therapeutic concepts in the treatment of acute myocardial infarction. The author concluded that this study demonstrates the advantage of primary angioplasty vs thrombolysis. The analysis mainly focuses on outcome parameters, which of course are of utmost importance, but with a selective pooling of individual results, without addressing limitations or a potential publication bias. Some methodological issues that may affect the conclusions should be addressed:

First, the methodology of meta-analysis always bears a certain risk that important information gets lost. In this meta-analysis the author uses the data of Weaver.² These data, however, also represent a meta-analysis of several studies, and the use of secondary data is critical. Another trial used in Zijlsta’s analysis was the Prague-2 trial, published by Widimsky.³ This trial was not significant in the intention-to-treat analysis. Authors in particular analyze a relatively small subgroup of 299 patients with >3 h of characteristic symptoms. Although, in this subgroup primary PCI was significantly better than thrombolysis, the results should be interpreted with caution due to the limited sample size. An additional critical issue is the long delay between onset of symptoms and randomization (almost 3 hours), which appears unacceptable. However, Prague-2 represents a randomized clinical trial and only the data drawn from Weaver’s analysis⁴ have to be excluded for methodological reasons.

Using the reported database⁵ of 3873 patients enrolled in 10 clinical trials and focusing only on the baseline characteristic ‘previous MI’, from 1947 patients treated with primary PCI, 232 (12.05%) were reported to meet this characteristic, and from 1926 treated with thrombolysis 198 (10.17%) respectively. This 1.9% discrepancy is representing a strong trend (P=0.066, two-sided Fisher test) towards a better prognosis for the angioplasty groups. In an analysis resulting in a difference between strategies ranging between 2.8% and 2.3%, this is definitely relevant. It is even more important, as there are many more characteristics, which may have an impact on trial results (e.g. age, Killip class, location etc) than outcome parameters (mortality or composite end-point).

At the first glance not only mortality but also the adverse events rate (in the publication defined as non-fatal reinfarction and stroke) may be striking. The increased benefit observed in the respective analysis is mainly due to the reduced reinfarction rate in the PCI groups. However, this conclusion neglects the data of recent clinical trials with improved anticoagulation, e.g. the results of ASSENT-3⁶ or AMI-SK,⁷ where also a significant reduction of reinfarction was achieved.

In summary, the presented naı¨ve meta-analysis did not address a possible publication bias, the possible heterogeneity of individual trials and confounding prognostic factors (e.g. previous MI, delay of treatment) with their impact on the outcomes.

Primary PCI offers a highly welcomed alternative for the cardiologist to treat patients with ST-elevation myocardial infarction. Zijlstra’s recommendation, however, appears to be premature and should be substantiated by data from large, prospective, randomized clinical trials or properly conducted meta-analyses.

References


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Reply to letter to the editor

In the January 2003 issue of the European Heart Journal the final results of the randomized national multicentre trial called PRAGUE-2, long distance transport for primary angioplasty versus immediate thrombolysis in acute myocardial infarction were reported by Dr P. Widimsky et al. In the editorial that accompanies this important paper I have attempted to give, within the constraints of an editorial, an overview of the present knowledge with regard to the impact of interhospital transportation on the relative outcome after primary angioplasty compared to lytic therapy for acute myocardial infarction. The pooled data show that outcome after primary angioplasty is better compared to lytic therapy irrespective of the need for additional transportation. With regard to the remarks of Dr Thimme it should be kept in mind that:

1 A pooled analysis is not a meta-analysis, nor thus it pretend to be one
2 There is no reason to exclude the data from Weaver et al.
3 A previous infarction is not associated with better outcome
4 ASSENT-3 and AMI-SK do not compare primary angioplasty and lytic therapy
5 My conclusion is as solid as a rock: The PRAGUE-2 and DANAMI-2 trials are especially important as they show that primary angioplasty therapy for acute myocardial infarction can be applied in large areas of partially urbanized Europe with good results.

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