Selection of the optimal reperfusion strategy for STEMI: does time matter?

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This editorial refers to 'Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients'† by E. Boersma et al., on page 779

The comprehensive meta-analysis of 25 trials comparing the efficacy of primary percutaneous coronary intervention (PPCI) vs. fibrinolytic (FT) drugs in patients with ST-segment elevation acute myocardial infarction reported by Boersma et al. is a significant contribution to the literature. Strengths of this meta-analysis are the large amount of individual patient data from 22 trials and the rigorous statistical methodologies. The conclusions support and update prior analyses that suggest that 'all things being equal,' PPCI is the superior reperfusion strategy, provided this is carried out in the right institution, by the right operator; in some centres, the day of the week and the time of day may also be relevant. The authors argue (and this is a very controversial point) that irrespective of the delay between symptoms and presentation, PPCI is superior to fibrinolysis, although the absolute reduction in mortality by PPCI widens over time, consistent with the hypothesis that older thrombi become more resistant to FT drugs. With regard to hospital-specific PCI-related delay, when this was <35 min, the relative and absolute mortality reduction was significantly higher than in patients with longer delays, although the point estimate suggesting a benefit from PPCI is noted in each time interval. The title of the article poses the question whether time matters. The authors suggest that a benefit for PPCI is present during all time periods analysed, although the magnitude of the benefit is dependent upon the duration of symptoms prior to presentation and the extent of PCI-related delay, calculated from the time of randomization.

From a clinical standpoint, however, the issues of time to treatment in regard to the selection of a therapeutic modality are viewed from an entirely different perspective. In hospitals with the facilities for on-site PPCI, this is likely to be the preferred strategy over FT, irrespective of the delay between symptom onset and presentation, provided that PPCI can be implemented in a timely fashion. The key clinical issue, however, is the optimal reperfusion strategy for patients presenting to hospitals without the facilities for PPCI. In the large NRMI registry in the USA, among 1432 participating hospitals in 1999, 54% of institutions lacked PCI capability. In this setting, the options are more complex, namely, FT drugs (drip) and continued observation at a local hospital, transfer for PPCI (ship), facilitated PCI (drip and ship for immediate PCI), or a pharmacoinvasive strategy (drip and ship for routine-delayed PCI). There are several critical ingredients that enter into the decision making from this menu of options, including the duration of symptoms, haemodynamic status of the patient, infarct location, the risk of bleeding with FTs, and a realistic expectation of transfer delay for PPCI. Despite the laudable effort of obtaining individual patient data from a large number of trials and performing complex statistical analyses, Boersma et al. could not provide an analytical solution that overcomes the intrinsic biases in the original trials and all the options available to the clinician dealing with the patient at the time of presentation. For example, if the pharmacoinvasive strategy was to be preferred, this information would not be obtainable from the Boersma analysis, as none of the pooled trials tested this approach. Also, it is likely that some patients were not included in a given trial at night (in some centres) when the PCI-related delay time is longer, thus potentially biasing against worse outcomes with longer delays to PCI. Also, it is an established clinical fact that patient characteristics are crucial determinants of the success of any reperfusion strategy. Inspection of Figure 3 of Boersma et al. presents at the same time, a logical but confusing set of analyses. Patients whose presentation delay was ≤1 h had the lowest 30 day mortality with fibrinolysis (6.0%). However, when cared for in hospitals with a PCI-related delay of ≤35 min, those patients treated with fibrinolysis had a mortality of 8.0%, a value that actually falls and then rises again, as the PCI-related delay time increased across the quintiles of PCI-related delay time. The reasons for this are unclear and somewhat puzzling. The authors have placed considerable emphasis on hospital level factors in their modelling of the differences...
in outcome between fibrinolysis and PPCI, but it is difficult to understand how PCI-related delay time influences the absolute mortality with fibrinolysis. This suggests that unmeasured variables may exert an impact upon mortality which cannot be accounted for in the analyses.

Crucial to understanding, whether time matters, is an appreciation of the slope of the curve that describes the relationship between the duration of ischaemia, reduction in mortality, and the extent of myocardial salvage upon the establishment of reperfusion (Figure 1). During the first 2–3 h after symptom onset, a striking benefit of reperfusion upon both mortality and myocardial salvage is present, and in this setting, time to treatment is critical. Subsequently, benefits persist but these are of decreasing magnitude over time. At this stage, the priority is to open the vessel and time to treatment is of less importance. Recent data relating infarct size to the duration of ischaemia provide hard evidence to support the hypothecated construct demonstrated in Figure 1.6

Selection of optimal therapeutic strategies in community hospitals without facilities for PPCI

Duration of symptoms

In patients presenting within 60–90 min of symptoms, albeit a minority and a markedly under-represented group in the Boersma analysis, the impact of FT therapy upon mortality is striking. In one study, 25% of patients treated within 1 h of symptoms had an ‘aborted’ myocardial infarction based upon ECG and biomarker abnormalities.7 In such patients who present within the golden but narrow window of maximal opportunity, delays incurred by transport for PPCI could be harmful.3 This is suggested by the CAPTIM trial in which the pre-hospital administration of FT therapy (followed by rescue PCI in 26%) in patients presenting within 2 h of symptoms, demonstrated a reduction in mortality (P = 0.06) and in the development of cardiogenic shock in comparison to PPCI.3 In patients presenting after 2 h (regrettably the majority), time dependence is less of an issue, and PPCI is clearly superior to lytics not only in restoring patency but also doing so without the risk of intracranial haemorrhage. The latter is an inherent risk of FT therapy, but one that is generally accepted when the presentation delay is short and the time to implementation to PPCI is long.3

Haemodynamic instability

In patients with cardiogenic shock, which is typically an evolving process, there is little to lose by the administration of an FT drug followed by urgent transfer angiography and reperfusion as appropriate. Moreover, there is some trial evidence to suggest that mortality may be lowered by the use of FT drugs prior to transfer for immediate angiography.3

Risk of bleeding

Several factors increase the risk of bleeding and intracranial haemorrhage. In the ASSENT 3 trial, the independent predictors were older age, lower weight, female sex, and a history of hypertension. Rates of intracranial haemorrhage were 2.22% in patients aged 78 or older and 4.4% in patients weighing <52 kg.8 The presence of these risk factors for bleeding needs to be taken into account when making a determination of the risks and benefits of lytics vs. transfer for PCI.

Transport delays

In an analysis from the NRMI registry, only 19.3% of patients who underwent transport for PPCI were treated within 2 h of symptoms.3 This is very different from the transport times reported in the DANAMI and other European trials.3 The time from randomization to PPCI in DANAMI 2 and PRAGUE 2 trials was ~90 min, an important point that figured heavily in the door-to-balloon recommendation of <90 min in the STEMI Guidelines on both sides of the Atlantic.9,10 Factors such as long distances in rural communities, the availability of rapid helicopter transport, and the vagaries of inclement weather are crucial factors in determining the choice of therapy in a community hospital without facilities for on-site PCI. In some regions and depending upon logistical constraints, a compelling argument can be made for the strategy of pre-hospital FT therapy.3

Randomized, controlled trials provide answers to specific questions and remain the standard for minimizing selection bias. Nonetheless and as has been the case in trials of revascularization therapies for patients with stable coronary artery disease, the randomized trial populations may not be representative of the majority of patients seen in clinical practice. In the case of trials of reperfusion therapy, stratifying patients on the basis of PCI-related delays is appropriate for analytical purposes, but it should be emphasized that in this situation, the clock begins to tick at the time of randomization. In routine clinical practice, of paramount concern is the total ischaemic time prior to reperfusion, i.e. the delay from symptom onset to the start of therapy. In many situations, PCI-related delay may exceed the 90 min window recommended by guidelines. Two meta-analyses have suggested that the benefits of PCI are lost when the door-to-balloon time exceeds the

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Figure 1 Hypothetical relationship between time to treatment and the reduction in mortality and extent of salvage. During the first 2–3 h after symptom onset, time to treatment is a critical determinant of the extent of salvage and reduction in mortality. Subsequently, a benefit persists but the ‘flattening of the curve’ emphasizes that time to treatment is less of a factor and the major priority is opening of the infarct-related artery. [Source: Modified from figure in Gersh BJ et al. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? JAMA 2005;293:979–986.] with permission. Copyright © 2005, American Medical Association. All rights reserved.
door-to-needle time by 60–110 min. This meta-analysis by Boersma et al. does not address this question and in the context of the process of randomization, cannot do so.

In summary, time to treatment remains a fundamental tenet of reperfusion therapy but should not supersede considerations of the total ischaemic time in a given patient. From a clinical perspective, the decision in hospitals with on-site PCI faculties is simple—PPCI is the preferred form of therapy, but the systems need to be in place to perform this expeditiously, 7 days a week and 24 h a day. In hospitals without this option, the selection of the optimal reperfusion modality is dependent, at least in part, upon an assessment of the duration of ischaemia prior to therapy. To what extent the concept of facilitated angioplasty or a pharmacoinvasive strategy may modify current approaches remains to be determined by randomized trials, but to date, the strategy, while theoretically attractive, has not withstood the rigorous scrutiny of trials.

After almost three decades of trials of reperfusion therapy, we know what to do—it is primarily an issue of logistics and the coordination of services. As these vary by region and country, the watchword is to meticulously audit outcomes in one’s own hands and not to extrapolate excessively from trials and registries that may not be relevant to local circumstances. These may play a major role in the development of policies, but the efficacy of their execution is dependent upon the performance of individual institutions. Analyses such as these reported by Boersma et al. should not be used to justify a decision to implement a strategy of PPCI exclusively without taking into account realistic considerations of the time it takes to implement such a strategy in a specific clinical setting.

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References