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Lessons from the trials

STREAM and FAST-MI – Pharmacoinvasive therapy: A continued role for fibrinolysis in the primary PCI era

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ABSTRACT

Data from the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial[6] and 5-year results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI)[7] are evaluated for further evidence on the effectiveness and safety of a pharmacoinvasive approach for patients presenting with acute ST-segment elevation myocardial infarction (STEMI).

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INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is currently the preferred reperfusion therapy for patients presenting with acute ST-segment elevation myocardial infarction (STEMI) when it can be performed by an experienced team in a timely fashion.[1] Current practice guidelines also recommend the transfer of patients presenting to non-PCI capable hospitals to hospitals offering PPCI services if the first medical contact (FMC)-to-device time is kept to less than 120 minutes. When this is not feasible, as is the case in many areas around the world, a pharmacoinvasive strategy consisting of early fibrinolysis followed by transfer to a PCI-capable hospital for either immediate (rescue) PCI for patients with failed thrombolysis, or for non-urgent coronary angiography to determine the need for additional revascularization within 3–24 is a reasonable alternative.[2,3] This approach should not to be confused with *facilitated PCI* where thrombolysis (full- or half-dose) is followed by immediate pre-planned PCI to mitigate the delay associated with PCI. The latter strategy, while being intuitively appealing, is not recommended owing to increased risk of adverse events including death, intracranial hemorrhage, and paradoxically, ischemic events (likely due to fibrinolysis-induced platelet activation).[4,5]

Data from the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial[6] and 5-year results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI)[7] provide further evidence on the effectiveness and safety of a pharmacoinvasive approach.

STREAM TRIAL

This open-label, multicenter, prospective, randomized trial was designed to test whether fibronlytic therapy – administered before arrival to hospital, or early after admission – coupled with early coronary angiography provides outcomes similar to PPCI in patients presenting with acute STEMI. Patients were eligible for enrollment if they presented within 3 hours from onset of symptoms, had evidence of acute STEMI on their initial electrocardiogram (ECG), and were unable to undergo primary PCI within one hour after the first medical contact (FMC). Over a period of 4 years, 1915 patients were enrolled from 99 sites in 15 countries. 1892 ultimately underwent randomization (81% in the ambulance setting) to either receiving tenecteplase along with antiplatelet and anticoagulant therapy, followed by coronary angiography within 6–24 hours (pharmacoinvasive group) or to primary PCI (PPCI group). According to the investigator's judgment, urgent coronary angiography (and PCI when appropriate) in the pharmacoinvasive group was allowed at any stage in the presence of hemodynamic or electrical instability, worsening ischemia or sustained/progressive ST-segment elevation. The primary end-point was a composite of death from any cause, shock, congestive heart failure or reinfarction at 30 days. Safety end-points included ischemic stroke, intracranial and non-intracranial hemorrhage bleeding. Upon the advice of the data and safety monitoring board, the trial protocol was amended after 21% of the study population had been enrolled: the dose of tenecteplase was reduced by 50% in patients 75 years of age or older because of an excess rate of intracranial hemorrhage observed in that group.

At 30 days, the primary end-point occurred in 116 patients (12.4%) in the pharmacoinvasive group and 135 patients (14.3%) in the PPCI group (relative risk in the pharmacoinvasive group, 0.86; 95% CI, 0.68–1.09; $p = 0.21$). The incidence of the primary end-point in the prespecified subgroups (grouped by age, gender, weight, systolic blood pressure, infarct location, Killip class, TIMI risk score, and diabetes) was generally similar to the overall results. 36% of patients in the pharmacoinvasive group required "rescue" PCI. Significantly more open vessels were found during coronary angiography (before PCI) in the pharmacoinvasive group compared to the PPCI group (TIMI flow grade 0 in 16% vs. 59.3% respectively, $p < 0.001$). Overall, 80% of patients in the pharmacoinvasive group and 90% in the PPCI group eventually underwent PCI ($p < 0.001$). However, significantly more patients in the pharmacoinvasive group underwent coronary artery bypass surgery (4.7% vs. 2.1 %, $p = 0.002$).[6]

An important evaluation of the rates of aborted myocardial infarction (prespecified secondary end-point) was recently published in a separate communication.[8] Aborted myocardial infarction was defined as ST-elevation resolution ≥50% (90 minutes post-initiation of tenecteplase in the pharmacoinvasive group or 30 minutes post-PCI in the PPCI group) with minimal biomarker rise; defined as CK-MB ≤2 times the upper limit of normal (ULN) or cardiac troponin T/I ≤5 times the ULN. Amongst the patients who fulfilled these criteria, those who developed new pathological Q-waves on their discharge ECGs were excluded. Overall, 99 patients (11.1%) in the pharmacoinvasive group had aborted MI compared to 59 patients (6.9%) in the PPCI group ($p < 0.01$), a finding most likely driven by the significantly shorter time delay from onset of symptoms to start of reperfusion therapy in the formed group (100 minutes vs. 178 minutes for the pharmacoinvasive and PPCI groups respectively,

$p < 0.001$). The difference in aborted MI rates observed between both groups did not however have a significant interaction with the primary composite end-point.

FAST-MI REGISTRY

The FAST-MI Registry was designed to evaluate the "real world" management of patients with acute MI, and to assess their in-hospital, medium- and long-term outcomes. Patients were recruited consecutively at the end of 2005 from 223 centers across France over a period of one month. Physicians participating in the study cared for their patients according to their usual practice, completely independent from the study.[9] The investigators recently reported the 5-year survival rates of patients with STEMI who sought medical attention within 12 hours from the onset of symptoms.[7] Of the 1492 patients whose data was available, 447 (30%) received fibrinolysis (two thirds of whom had pre-hospital fibrinolysis), 583 (39%) were referred for PPCI, and 462 (31%) received no reperfusion therapy. Patients who did not receive reperfusion therapy were older, more likely to have history of cardiovascular disease and other comorbidities, as well as an overall higher risk profile. On the other hand, patients treated with fibrinolysis and those referred for PPCI had mostly similar risk profiles, including Global Registry of Acute Coronary Events (GRACE) score, but one important difference was significantly shorter time delays before seeking medical attention in the fibrinolysis group. The latter group of patients also received clopidogrel, low molecular weight heparin, or glycoprotein IIb/IIIa inhibitors less frequently than the group referred for PPCI. Among patients treated with fibrinolysis, 96% underwent subsequent coronary angiography (38% within 3 hours of fibrinolysis, 23% between 3 and 24 hours, and 39% beyond 24 hours), with most of them (84%) undergoing PCI. 32% of patients in the fibrinolysis group required urgent referral for "rescue" PCI.

Survival at 5 years was 88% in patients receiving fibrinolysis and 84% for those undergoing PPCI (HR, 0.73; CI, 0.50–1.06; $p = 0.1$). When the timing of administration of fibrinolysis was considered, prehospital fibrinolysis was associated with lower 5-year mortality (HR, 0.57; CI, 0.36–0.88), while in-hospital fibrinolysis was associated with a trend toward increased 5-year mortality (HR, 1.19; CI, 0.72–1.96) compared to PPCI. The investigators also studied the subgroup of patients who sought medical attention within 180 minutes from the onset of symptoms (STREAM-like population). 5-year survival in this population was 88% and 81% in the fibrinolysis and PPCI groups respectively (HR, 0.63; CI, 0.41–0.98; $p = 0.039$). However, in a propensity score-adjusted matched analysis, the benefit seen with prehospital fibrinolysis and with fibrinolysis (pre- or in-hospital) in the STREAM-like population did not remain statistically significant.

DISCUSSION

In agreement with several recent studies[10–13] as well as the current American and European practice guidelines,[2,3] both STREAM and FAST-MI support the current recommendation of performing a coronary angiogram within 3–24 hours after successful fibrinolysis when timely PPCI is unavailable. However, extrapolating these findings to other healthcare systems around the world should be done with caution for the following reasons:

- STREAM randomized a very specific group of STEMI patients, namely those with a symptom onset-to-FMC of less than 3 hours. It is well recognized that the fibrinolytic agents are more effective early in the course of STEMI because of the absence of fibrin cross-linking in the fresh thrombus, and this effect progressively declines after the first 3 hours.[14] Similarly, two-thirds of the FAST-MI patients receiving fibrinolysis did so prior to hospital admission. It remains unclear whether these finding are also applicable to late presenters.
- The fibrinolytic agent used in STREAM and in the majority of FAST-MI patients was tenecteplase (TNK) which has an extended half-life allowing for a single bolus administration. TNK is more fibrin-specific, is associated with less intracranial hemorrhage, and higher rates of infarct artery patency compared to streprokinase – which remains the most frequently administered fibrinolytic agent worldwide.[15] It is unknown whether a pharmacoinvasive approach utilizing streptokinase as the fibrinolytic agent would yield similar results.
- The emergency medical system is France is very well established and often includes physicians. This has undoubtedly contributed not only to the high prehospital fibrinolysis rate (66% of patients), but also to the early initiation of treatment. As a result, PCI-related delay (defined as FMC-to-fibrinolysis time subtracted from FMC-to-PPCI time) was considerable (105 minutes

compared to 78 minutes in STREAM) and might have contributed to the favorable outcomes observed in the fibrinolysis group. This setup and high rate of prehospital fibrinolysis is clearly difficult to reproduce in many countries/regions.

WHAT HAVE WE LEARNED?

Timely PPCI remains the reperfusion strategy of choice in patients with acute STEMI. Findings from STREAM and FAST-MI lend further support to the adoption of a pharmacoinvasive strategy in areas where this cannot be achieved. In this setting, concerted efforts to improve emergency medical services is essential. Prehospital fibrinolysis should probably be considered in remote areas where transport time to a hospital is unacceptably long. Besides proper training of EMS personnel, this can be facilitated by wireless transmission of 12-lead ECGs to an offsite cardiologist, a practice which is currently adopted in many areas around the world.[16] Standardized inter-hospital transfer protocols should be established to allow for routine post-fibrinolysis coronary angiography (and PCI when appropriate) within the recommended time frame, as well as urgent rescue PCI for patients with failed thrombolysis. It is still unclear whether late presenters (>3 hours) and elderly patients derive a similar benefit from such approach.

Finally, while system-related delays have been the focus of numerous studies and scrutiny, which have resulted in remarkable improvements in emergency medical services response, transfer times, door-to-needle and/or door-to-device times;[17] one should not forget that the ultimate objective in patients with acute STEMI is reducing the *total ischemic time* which also includes the time delay to FMC. The latter has received significantly less attention, which in part is related to difficulties in accurate measurement, given its susceptibility to recall bias and the fact that symptoms may be vague or intermittent in a considerable number of STEMI patients. It is worth noting that this patient-related delay – on average – constituted approximately 60% and 30% of the total ischemic time in STREAM's pharmacoinvasive and PPCI populations respectively, while one third of FAST-MI's population had a time-to-FMC of more than 120 minutes (which on its own exceeds the maximum allowed system-related delay). This delay is almost certainly longer in less developed regions/countries where emergency services and public awareness/education programs are not well-established. Further research and efforts aiming at effective reduction of patient-related delays (in addition to system-related delays) are urgently needed, and carry the potential of driving significant improvements in the short- and long-term outcomes of patients with acute STEMI.

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