Primary Percutaneous Coronary Intervention Not Always the Best Reperfusion Strategy?

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For patients with an ST-elevation–myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) is the preferred reperfusion modality. Primary PCI, however, requires a catheterization laboratory and 24/7 availability of an experienced team. Worldwide, only a minority of STEMI patients present directly to a PCI-capable hospital. Most patients are first seen by an ambulance crew or at the emergency room of a non-PCI–capable hospital. Although in some regions almost all STEMI patients can be transferred to a primary PCI center within a guideline-recommended time-frame, in many other regions across the world timely transport remains a major issue because of distance, weather conditions, traffic, and, very often, a poor organization of the emergency medical system (EMS). The organization of regional transfer can indeed be complex and costly. It requires close collaboration among ambulance systems, emergency departments, and catheterization laboratories.

Fibrinolytic therapy given before an already planned PCI to mitigate the delay associated with primary PCI does not improve outcome. In most of these studies, no clopidogrel was given upfront, and anticoagulant therapy was often suboptimal. Several more recent studies, however, suggest that coronary angiography and PCI performed between 3 and 24 hours after administration of the lytic, in case of successful reperfusion, reduces the risk of new ischemic events. As now mentioned in the guidelines, if fibrinolysis is indicated, it needs to be followed by an early coronary angiography. This strategy is often referred to as pharmaco-invasive therapy. Because of the absence of cross-linking of fibrin in the fresh occlusive clot, such a strategy is especially effective in patients presenting early after symptom onset. In a post hoc analysis of the Comparison of Primary Angioplasty and Pre-hospital Fibrinolysis in Acute Myocardial Infarction (CAPTIM) study, prehospital fibrinolysis in the subset of STEMI patients presenting within 2 hours of symptom onset was associated with lower 30-day rates of both cardiogenic shock and death, as compared with transfer for standard primary PCI. A combined analysis of the CAPTIM and Which Early ST-Elevation Myocardial Infarction Therapy (WEST) trials, a comparable trial performed in Canada, also suggests a beneficial effect at 1 year from a pharmaco-invasive therapy in patients presenting early. After 5 years of follow-up in CAPTIM, this strategy was associated with lower mortality compared with transfer for primary PCI among patients treated within 2 hours of symptom onset.

In the recent Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial, a pharmaco-invasive strategy with tenecteplase (half dose in the elderly), clopidogrel, and enoxaparin, and including angiography between 6 and 24 hours or rescue PCI, was compared with standard primary PCI in almost 1900 early presenting patients who could not undergo primary PCI within 1 hour. Patients were randomly assigned in the ambulance or the emergency department of a community hospital. At 30 days, the pharmaco-invasive approach was associated with a 2% lower incidence of death, shock, congestive heart failure, or reinfarction when compared with primary PCI, which was not statistically significant. At 1-year follow-up, total and cardiac mortality rates were very similar.

In this issue of Circulation, Danchin and colleagues report 5-year survival rates in the large French Registry of Acute ST-Elevation and Non-ST–Elevation Myocardial Infarction (FAST-MI) registry, in which a significant proportion of patients were managed similarly to the pharmaco-invasive arm of STREAM. The nationwide FAST-MI registry was set up almost a decade ago to assess contemporary reperfusion practices in STEMI patients across France. Particular to the EMS and network organization in France, two thirds of the patients received fibrinolysis in the prehospital setting, and in most of them (84%) fibrinolysis was followed by a PCI. As already reported, survival rates at 1 year after primary PCI and fibrinolysis with routine early coronary angiography were similar, at 91.8% versus 93.6%, respectively. In the present long-term follow-up analysis, the risk of death at 5-year follow-up tended to be lower in the total population receiving fibrinolysis (given in community hospitals and ambulances) compared with primary PCI, although the difference did not reach statistical significance (hazard ratio, 0.73 [95% CI, 0.50–1.06]). When compared with primary PCI, patients treated with fibrinolysis in the ambulance did have a significantly lower risk of death after adjustment for baseline risk (hazard ratio, 0.57 [95% CI, 0.36–0.88]). However, in a propensity score-adjusted matched analysis, this difference did not remain significant.

Interestingly, the authors also looked at a subgroup of patients treated within time delays similar to those of the STREAM trial. A time window of 90 minutes between initial call and start of reperfusion was used as a proxy for the expected 60-minute delay specifically required by the
STREAM protocol. In this STREAM-like cohort, 5-year survival was significantly better after fibrinolysis compared with primary PCI. As in the overall population, this benefit disappeared in the propensity-matched cohort. Although an expected 60-minute delay was required in STREAM, the actual delay between first medical contact and start of primary PCI was 117 minutes, still within the guideline-recommended maximal delay of 2 hours. The calculated PCI-related time delays were relatively short, 105 minutes in FAST-MI and 78 minutes in STREAM (Figure). These time delays contrast with those of the Danish Multicenter Randomized Study of Invasive Versus Conservative Treatment in Patients with Inducible Ischemia After Thrombolysis in Acute Myocardial Infarction-2 (DANAMI-2) study in which the delay times for both in-hospital lytic therapy and primary PCI were longer on one hand and the PCI-related delays shorter on the other hand, thereby reducing the chance of finding a benefit of earlier reperfusion by giving a lytic agent upfront.14

As the more neutral propensity score-adjusted results suggest, there is likely to be at least some bias in the treatment strategy selected for the patients in FAST-MI. For instance, pharmaco-invasive patients tended to have less baseline comorbidities and were less likely to be women, although the overall Global Registry of Acute Coronary Events (GRACE) risk score was similar in both groups. In addition, there were more patients in the pharmaco-invasive group who sought medical attention within 120 minutes of symptom onset. Patients in the fibrinolysis group were also more likely to be transported by an ambulance with a physician on board. On aggregate, prehospital fibrinolysis was probably more likely given to early presenters with a clear diagnosis and no obvious comorbidity, features that inevitably are associated with better long-term survival.

The recruitment of patients in FAST-MI started before the results of the facilitated PCI trials were known. In these trials PCI was performed immediately after fibrinolysis (irrespective of its success) and was associated with a high rate of early thrombotic complications. This negative outcome is likely attributed to the procoagulant effect of the lytic agent in the absence of adequate antithrombotic cotherapy. In FAST-MI, only 23% of patients had an angiography within the 3- to 24-hour time window, the time window recommended by the current guidelines, whereas the remainder of the patients had a catheterization beyond 24 hours. This probably reflects sustained reperfusion because of the routine coadministration of clopidogrel and enoxaparin.15,16 Almost 4 of 10 patients in FAST-MI underwent an angiography within the first 3 hours, similar to the 36% of urgent catheterizations performed in STREAM. At present, it remains unclear whether a routine invasive procedure immediately after fibrinolysis should still be avoided if optimal antithrombotic cotherapy is given upfront.

Are the long-term results from FAST-MI also representative of other EMS services across the world? The prehospital medical system in France is well established and often includes physicians. Remarkably, 66% of patients receiving fibrinolysis were treated in the prehospital setting, and 60% to 75% of patients in the FAST-MI registry were transferred by ambulance or helicopter with a physician on board. Compared with primary PCI patients, more fibrinolysis-treated patients were transported by a medical EMS as well. The presence of a physician during transport very likely affects the early management of STEMI patients by expediting the start of treatment and also diagnosis in the case of atypical presentation. It remains uncertain whether the high 5-year survival rates can be obtained with other healthcare systems, especially those with exclusively paramedical ambulance personnel. Physician-equipped EMSs are a rarity rather than the norm. In the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) Plus trial, the outcome of prehospital fibrinolysis was not affected by the presence or absence of a physician in the ambulance.17 Outside the setting of a clinical trial, however, it remains unclear whether patients benefit from the presence of a physician. Wireless ECG transfer to offsite cardiologists has become standard procedure in many EMSs and has certainly shortened treatment delays. However, the decision to give lytic therapy or to transfer the patient for primary PCI is complex and does not exclusively depend on the presence of ST-elevation in a 12-lead ECG.

In conclusion, after 5-year follow-up, STEMI patients treated with a prehospital-initiated pharmaco-invasive strategy fare as good as those transported for primary PCI in the real-world FAST-MI registry. In early presenters, a pharmaco-invasive therapy was also associated with a survival benefit compared with a primary PCI that was delayed for 60 minutes or more.

Figure. Important time delays with a pharmaco-invasive strategy vs primary percutaneous coronary intervention (PCI) are shown. PCI-related time delays in patients unable to undergo timely PCI in Strategic Reperfusion Early After Myocardial Infarction (STREAM) and French Registry of Acute ST-Elevation and Non-ST–Elevation Myocardial Infarction (FAST-MI) were 78 and 105 minutes, respectively. In both studies patients received either prehospital fibrinolysis followed by early rescue or planned coronary angiography (in the case of successful fibrinolysis) or were transported for primary PCI. A PCI-related delay in essence indicates the time possibly gained by administering a lytic agent in the ambulance versus routine transport for (delayed) primary PCI. Because fibrinolytic therapy requires time to achieve clot dissolution, the actual time difference in obtaining reperfusion between the 2 strategies is shorter than the PCI-related delay if time to first balloon inflation is used. With a contemporary pharmaco-invasive management rescue PCI is needed in approximately one third of the patients, whereas a planned coronary angiography (with PCI in most cases) can be performed in the remaining patients.
for >90 minutes after the initial call. The results are in line with the 30-day and 1-year results from STEMI patients presenting early who were unable to undergo primary PCI within 60 minutes in the STREAM trial. Taken together and awaiting long-term follow-up from STREAM, a contemporary pharmaco-invasive management appears to be at least as good as primary PCI in STEMI patients presenting early after symptom onset when a timely PCI is not an option.

Disclosures
Dr Sinnaeve received speaker’s and consultancy fees from Boehringer Ingelheim. Dr Van de Werf received a research grant for performing the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial and speaker’s and consultancy fees from Boehringer Ingelheim.

References
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In the article by Sinnaeve and Van de Werf, “Primary Percutaneous Coronary Intervention Not Always the Best Reperfusion Strategy?,” which published in the April 22, 2014 issue of the journal (*Circulation*. 2014;129:1623–1625), an error was made.

In the fifth paragraph, the following sentence appears: “In this STREAM-like cohort, 5-year survival was significantly lower after fibrinolysis compared with primary PCI.”

This sentence should read: “In this STREAM-like cohort, 5-year survival was significantly better after fibrinolysis compared with primary PCI.”

The online version of the article has been corrected. The authors regret the error.