Fibrinolysis may widen the time window for primary angioplasty

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This editorial refers to 'Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial'† by F. Fernández-Avíles et al., on page 949

Recently published clinical trials have demonstrated superiority of primary percutaneous coronary intervention (PPCI) over lysis in ST-elevation myocardial infarction (STEMI) treatment. Current practice guidelines¹ have established PPCI as a preferred method of reperfusion in STEMI, as long as it can be performed within 90 min from patient’s first medical contact. However, in the majority of cases achieving this 90 min time goal proves impossible, mainly because the STEMI care is not streamlined enough between different levels and components of health care system. Accordingly, the optimization of treatment strategy in STEMI patients, who for one reason or another exceed the 90 min delay, is one of the hottest topics in cardiology today. The GRACIA-2 study is certainly an important contribution to that issue.

Clinical trials with lytics have shown a significant correlation between the time of their administration after the symptoms onset and the mortality. First studies with primary PCI demonstrated no such correlation, which was attributed to higher efficacy of angioplasty to re-open the infarct related artery (IRA) than what lytic therapy could provide² (irrespective of ischaemia duration). Only 'door-to-balloon time' and not 'symptoms onset-to-balloon time' have appeared to correlate with patient mortality.³ An additional factor contributing to that effect might have been a low patient risk profile. It was later confirmed by Antoniucci et al.,⁴ who concluded that a relationship between pain onset to PCI and mortality is evident only in 'non-low risk' patients. Brodie et al.⁵ demonstrated a relationship of the delay of PPCI in STEMI and the presence or absence of left ventricular contractile function recovery in long-term follow-up. More recently, a convincing relationship between the ischaemia duration and mortality assessed at 1 year was found by De Luca et al.,⁶ who correlated every additional 30 min delay with an increase in 1 year mortality by 7.5%.

In patients with full reperfusion after lysis, there is no optimal time set for coronary intervention. A message from the prematurely terminated ASSENT-4 study seems to be that one should avoid combination of full dose lytic followed by immediate angioplasty⁷ because it might be associated with transient prothrombotic effect of lytics and lack of optimal antiplatelet (clopidogrel) treatment regimen.

However, the main limitations of ASSENT-4 study were that it was an open-label study and it was stopped before the pre-specified number of patients was enrolled. The time from randomization to balloon inflation was rather short (<120 min in both groups, median time between bolus tenecteplase and PCI was only 104 min). Due to this reason, the time gain for reperfusion with this lytic treatment was probably short in many patients. Also due to the absence of an infusion after bolus administration of unfractioned heparin and no loading dose of clopidogrel might have led to lower than expected IRA patency in baseline angiography, and decreased potential benefit of early reperfusion in tenecteplase treated patients.

On the other hand, the WEST study investigators concluded that combination of lytic (preferably pre-hospital) with interventional treatment is safer when a slightly prolonged time interval was observed between lytic administration and PCI than in ASSENT-4 trial.⁸ However, it is known that the excessive prolongation of this timeframe increases risk of refractory ischaemia. Recurrent myocardial infarction (reMI) has a significant impact on 30-day and 1 year survival. According to the European Society of Cardiology guidelines, every patient after successful lysis should be transferred for coronary angiography within 24 h. The GRACIA-2 authors report angioplasty performed at 3–12 h after initial lysis, with the mean time to PCI 6 h (median –4.6 h).⁹ It certainly is a significant difference in comparison to ASSENT-4 trial, where time to PCI was much shorter, and likely reflects the problems of daily practice more adequately.

Furthermore, transfer of patients for primary PCI in DANAMI-2 and PRAGUE-2 trials was associated with the reduction in composite end-point in 30-day follow-up (death/reMI/stroke) in comparison to lysis without routine angiography/PCI. The composite end-point occurrence was...
15.2% in lytic group and 8.4% in primary PCI group in PRAGUE-2 study ($P < 0.003$). It was similar in DANAMI-2: 14.2% vs. 8.5% in lytic and PPCI groups, respectively ($P = 0.002$). The reduction in reMI was a chief contributor to overall benefit (1.6% vs. 6.3%, $P < 0.001$ in favour of primary PCI), while a non-significant trend in mortality (6.6% vs. 7.8%, respectively, in favour of PPCI, $P = 0.35$) and the occurrence of stroke (1.1% vs. 2.0%, respectively, $P = 0.15$) were noted between groups at 30-day follow-up. Nevertheless, lack of clear definition of reMI in PRAGUE-2 as well as different criteria for reMI diagnosis in DANAMI-2 trial in lytic, primary PCI, and coronary artery bypass grafting groups (that according to the current definitions might be considered justified) may account for varied interpretation of published results.

Taken altogether, if the estimated time from the first medical contact to PCI is to be longer than 90–120 min, lysis administration seems reasonable, however, immediate transfer to PCI centre is to be followed, especially for STEMI patients with early presentation (< 3 h). Rescue PCI should be advised in patients without reperfusion and deferred angioplasty in patients with successful reperfusion. The REACT trial has shown that rescue PCI is associated with better clinical outcome in comparison to patients treated conservatively or with re-admission of lytic.

It remains unclear when one should intervene after full dose lysis or half dose lysis administered together with full dose GP IIb/IIIa receptor blocker. In the registry of STEMI patients with transfer delay more than 120 min, administration of half dose alteplase and abciximab with immediate transport to PCI centre for angiography helped to obtain 83% IRA patency prior to PCI and to perform it safely. In their study, Aviles et al. had 87.2% IRA patency after lysis (TIMI 2 + 3). This may be due to the relatively long time of drug action and optimal antiplatelet therapy along with low molecular weight heparin usage. PCI procedure was safe to perform in this group of patients and was not related with excess bleeding risk.

It should be emphasized, however, that the success STEMI treatment is not warranted with just re-establishing the IRA patency. Full reperfusion at the level of myocardium is equally or more important as impaired tissue perfusion is a key factor that influences both mortality in long-term observation and progression of heart failure. In the GRACIA 2, there was a high rate of full reperfusion at myocardium level in patients treated with lysis (TMPG-3 55.3%), which made coronary angioplasty having no effect on final myocardial perfusion. In primary PCI group, only 25.3% of cases had full myocardial reperfusion in comparison to 50% after lysis and PCI. There are, though, studies indicating that immediate PCI in patients with full reperfusion after lytic therapy (fast PCI after lytic) may even worsen myocardial perfusion and has a negative impact on left ventricle remodelling.

Considering recently published clinical trials, including GRACIA-2, it seems that after lysis administration, STEMI patients should be transferred for rescue angioplasty if no clinical signs of reperfusion are observed, whereas in all other cases a routine angiography should be performed within 24 h. There is no data so far demonstrating that immediate angioplasty after full dose lytic is reasonable. The question if half dose lytic and abciximab with immediate transfer for PCI takes advantage over primary PCI or conservative strategy in patients with estimated long time transfer is likely to be answered when results of FINESSE and CARESS in AMI trials will be presented at the ESC Congress 2007. These trials assume that with state-of-the-art anti-platelet therapy, performing immediate PCI after lysis will be safe and efficient.

Current knowledge suggests that proper planning, education, and communication to create local hospital network systems for the treatment of acute coronary syndromes (networking for AMI treatment) have at least solid theoretical grounds and may help diminish unnecessary time delays and facilitate the decision-making process. The opening of PCI centres with 24/7 duty, with experienced staff for populations of approximately 0.5 million inhabitants could provide primary angioplasty within 90 min from first medical contact for almost every patient. However, the implementation of it may be extremely difficult to accomplish.

In GRACIA-2 trial, there was a mean 60 min delay in performing PCI, and abciximab was administered relatively late. Upstream abciximab along with shortening time to PPCI could potentially lead to improvement in myocardial perfusion of STEMI patients transferred for angioplasty. Data answering the above questions will be presented at ESC Congress 2007 when FINESSE trial and EUROTRANSFER Registry are presented.

One should also keep in mind another important limitation of initial lytic therapy before angioplasty. This therapy is only reserved for patients with no contraindications to lytics, commonly 75 years of age and younger. Patients randomized to lytic therapy in GRACIA-2 received enoxaparin, which was shown to contribute to less deaths and reMI in comparison to standard unfractionated heparin in ExTRACT-TIMI 25 study. Moreover, recommended reduction of enoxaparin bolus for patients over 75 years of age can lead to lower rates of bleeding complications in patients treated with lysis. Luckily enough, primary angioplasty has no such limitations and is feasible also in older patients (>75 years) and with contraindications to lysis. In other words, pursuit of building local hospital networks for STEMI treatment will follow. The GRACIA-2 trial is of great importance as it demonstrates that in case of expected substantial delay to PCI:

- PCI may be safely performed 3–12 h later after lytic administration
- The administration of lysis leads to opening of IRA before PCI in a significant number of patients, thus making PCI easier to perform (e.g. more frequent direct stenting)
- The above-mentioned strategy has helped to achieve better myocardial reperfusion in comparison to primary angioplasty (primary PCI was performed without upstream abciximab administration)

In summary, PPCI remains to be the first choice method of treatment in STEMI patients. One should ensure the shortest possible time from first medical contact to PPCI. For regions without easy access to PPCI, the suggested strategy that remains for patients with early presentation is the full dose lytic administration followed by elective angiography. The PCI procedure should not be performed immediately after full dose of lytic, if there are clear signs of reperfusion (lytic facilitated PCI). It seems that PCI delayed for a few
hours after lysis is safer (pharmacoinvasive therapy). If there are no signs of reperfusion, one should perform rescue PCI without hesitation. Will combo therapy (half dose lytic with GPIIb/IIIa) allow for earlier intervention (combo facilitated PCI)? Hopefully, the answers will be given by FINESSE and CARESS in AMI investigators in 2007.

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References


