Editorial comment

ST-elevation acute myocardial infarction: can we improve the results of primary percutaneous coronary intervention?

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(Ital Heart J 2004; 5 (9): 684-687)

The opinions expressed in this editorial comment are not necessarily those of the Editors of the Italian Heart Journal.

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The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology recommends primary percutaneous coronary intervention (pPCI), together with abciximab and low-dose heparin, as the treatment of choice for ST-elevation acute myocardial infarction (STEMI) lasting < 12 hours, if performed by an experienced team in < 90 min after first medical contact (class 1, level of evidence A)[1]. Even when transfer to an interventional center is necessary, pPCI confers a 42% reduction in the rate of combined events (death, reinfarction, stroke) if compared to fibrinolysis performed in non-interventional hospitals[2].

The next step should be to organize workable cardiology care networks and fast pathways within the involved centers, along with trials addressed to establish whether the combination of a pharmacological and mechanical approach may further improve the results of reperfusion treatment in STEMI.

The report by La Scala et al.[3] published in this issue of the *Italian Heart Journal* is focused on the latter issue. The main conclusion by the authors is that administering half dose of reteplase prior to PCI is safe. Although the key-point of clinical outcomes could not be adequately investigated in this observational study with a relatively low number of patients, their report is of interest because it addresses some questions which are relevant in everyday clinical practice, such as the time factor, infarct-related artery (IRA) patency and type of pharmacological treatment to be associated with PCI.

Time factor

After fibrinolysis, both the functional recovery of the left ventricle and survival are directly influenced by the time interval between symptom onset and treatment[4].

In patients treated with pPCI, this relationship seems to be more complex: older data from large registries and randomized studies indicated that survival was less dependent on the symptom onset-to-balloon time and more influenced by the door-to-balloon time, mainly because the latter represents a marker of the overall hospital performance[5-7]. Those conclusions were in contrast with the knowledge that the total ischemic time is of utmost importance for left ventricular recovery, an independent predictor of survival. Not surprisingly, more recent studies showed that in non-low-risk patients who underwent successful pPCI, the mortality was indeed related to the delay from symptom onset to treatment[8], that the 1-year mortality increased from 2.5 to 4.5% (p = 0.04) if pPCI was performed > 3 hours after symptom onset[9], that a symptom onset-to-balloon time > 4 hours was an independent predictor of the 30-day mortality[10] and that a door-TIMI 3 time > 60 min was an independent predictor of death in a single high-volume center[11]. So, just as for fibrinolysis, a more prompt recanalization of the IRA is associated with a better outcome in patients treated with pPCI. The survival of patients receiving fibrinolysis < 2 hours from symptom onset and of those treated with pPCI within the same interval was also shown to be similar[12].

La Scala et al.[3] report that in their patients in whom pPCI was expected to be feasible within 30 min, the actual emergency room-to-balloon time was 98 ± 92 min. This datum highlights the difficulties in performing pPCI within a short time interval, even in centers with dedicated programs, when the center is a busy one, as well as the need for constant monitoring of this important factor. This delay was prolonged in their patients when the patient was first admitted to a non-interventional hospital (despite a striking reduction in the actual door-to-balloon time within the referral center), while it was actually 80 ± 50 min in non-transfer patients; in the United States, pPCI was reported to be performed > 120 min from the diagnosis in 87% of the transferred patients[13].

It is fair to conclude that, in candidates for pPCI, the target should be earlier vessel recanalization with pharmacological tools, with particular regard to early comers for whom pPCI is not immediately available.

Importance of the infarct-related-artery patency prior to primary percutaneous coronary intervention

The presence of a spontaneously normalized flow (TIMI 3) in the IRA prior to pPCI is associated with a strong benefit in terms of both survival and left ventricular recovery[14]. The same holds true in case of pharmacological recanalization before pPCI. In the PACT trial[15], the convalescent left ventricular ejection fraction was significantly higher (62.4 vs 57.3%, p = 0.004) in those patients presenting with a TIMI 2-3 flow before PCI, regardless of whether it had been achieved spontaneously or after half dose of tissue-type plasminogen activator. In the SIAM III trial[16], all patients received full-dose reteplase and were then randomized to immediate or delayed stenting: in the former group, the left ventricular ejection fraction at 6 months was 63.5% in those with a TIMI 2-3 flow prior to stenting vs 54.8% (p = 0.013) in those with a TIMI 0-1 flow. Similar benefits were obtained when abciximab was administered prior to pPCI[17].

La Scala et al.[3] report that 42% of their patients who received half dose of reteplase had a TIMI 2-3 flow at the time of pPCI: this proportion is significantly higher than that observed for patients not receiving lytic treatment, but is still low as an overall percentage; furthermore, the IRA flow before PCI was TIMI grade 3 in only 16% of cases, despite an emergency room-to-balloon time of 89 ± 50 min. Such a limited influence on the IRA patency prior to PCI can hardly translate into clinical benefits in the global population and, as pointed out by the authors, this occurrence of IRA patency is not much different from that observed when anti-glycoprotein (GP) IIb/IIIa antagonists are administered prior to PCI.

This raises the question: was the treatment administered adequate to the target?

Which pharmacological agents should be administered prior to percutaneous coronary intervention?

So far, the pharmacological options are fibrinolytics and GP IIb/IIIa antagonists (alone or in combination) with unfractionated or low-molecular-weight heparin. TIMI 3 flow is achieved at 90 min after full-dose lytics in a variable proportion of patients (54 to 74%), depending on the type and combination of agents[18-21]; this is significantly higher than in patients receiving half-dose lytics, as reported by La Scala et al.[3]. The colleagues from Cuneo[3] adopted half dose of reteplase in the year 2000; this choice was probably driven by safety concerns, because early studies showed disappointing results and unacceptable bleeding when PCI was performed immediately after full-dose fibrinolysis[22-24]. On one hand, the PACT trial[15] had demonstrated the safety of half dose of tissue-type plasminogen activator and on the other, a significant clinical benefit from the use of abciximab during pPCI had not been convincingly documented at that time.

In recent studies, however, major bleeding was not increased in patients randomized to PCI + stenting shortly after full-dose reteplase[16] or tenecteplase (unpublished data of GRACIA-2 and CAPITAL AMI trials), if compared to those with delayed or no intervention. So far, there are no published comparisons between pPCI and PCI after full-dose lytics and this issue will be investigated in the ongoing ASSENT-4 trial. In the BRAVE trial[25], a non-significant trend toward an increase in major bleeding (5.6 vs 1.6%) was observed in patients treated with combo therapy (half-dose fibrinolytic + abciximab) prior to PCI, as compared to those randomized to abciximab only. Dudek et al.[26] reported that only 3% of patients < 75 years had major hemorrhage (but 2 deaths out of 5 were directly due to bleeding) if PCI was performed shortly after combo therapy. In the ASSENT-3 trial[27], if urgent PCI was performed, those randomized to combo therapy or enoxaparin had a higher incidence of major bleeding (hazard ratio 2.87, p = 0.0124) than those randomized to full-dose tenecteplase and unfractionated heparin. Finally, the combination of GP IIb/IIIa antagonists with PCI and a reduced heparin dose does not significantly increase major bleeding[28].

In conclusion, an adequate IRA patency prior to PCI (especially a TIMI 3 flow) may be obtained in a minority of patients with half-dose lytics or GP IIb/IIIa antagonists, and only their combination or full-dose lytics seem adequate to the target. In the contemporary era, with improved PCI technology and weight-adjusted thrombolytics and heparin, PCI after full-dose lytic treatment seems reasonably safe, with some caution to be reserved for combo therapy.

Elderly patients

With regard to patients > 75 years, no randomized study ever demonstrated significant advantages of fib-

rinolysis vs placebo, and only a re-analysis of the FTT database showed a significant reduction in mortality after fibrinolysis (from 29.4 to 26%, p = 0.03)[29]. As the relative reduction in mortality is only 11.5%, with a high risk of bleeding and stroke, the best reperfusion treatment to be employed in the elderly is still a matter of debate. The combination of half-dose lytics plus abciximab is contraindicated in such patients because of an unacceptable high risk of intracranial hemorrhage[1].

So, in patients > 75 years scheduled for pPCI, adjunctive fibrinolytic treatment should be administered with caution.

Conclusions

In patients with STEMI who are scheduled for PCI, a faster IRA recanalization by pharmacological tools may be of relevant clinical interest, especially in early comers for whom pPCI is not immediately available.

In patients < 75 years, this target may be reached with full-dose lytics or using the combination of half-dose lytics with GP IIb/IIIa antagonists prior to PCI; it is possible, however, that the latter combination may increase the incidence of bleeding complications (this strategy is under investigation in the ongoing FINESSE and CARESS trials).

The administration of half-dose lytics alone prior to PCI does not seem much superior to GP IIb/IIIa antagonists in achieving an adequate IRA patency before PCI and, therefore, seems to have little room in clinical practice.

Appropriate investigations are awaited to find out which is the best combination of pharmacological and mechanical interventions to achieve a rapid IRA recanalization and minimize myocardial reperfusion injury.

In the meantime, any deviation from the recommended standard of care in STEMI, fibrinolysis or pPCI with abciximab plus a reduced dose of heparin, should be done only in the context of adequate randomized or observational clinical trials.

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