Lessons learned from the TIMI trials in rescue interventions for elderly patients after failed fibrinolytic therapy: look beyond the TIMI flow

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In ST-segment elevation myocardial infarction (STEMI), acute reperfusion of the infarct-related artery (IRA) is the main goal in the early minutes after the patient seeks medical attention. Fibrinolytic therapy (FT) and/or primary coronary intervention (PCI) were proven to be effective in opening the IRA.

The benefits of FT were limited because of complications (e.g. intracranial bleeding), failure to establish TIMI-3 flow in > 50% of patients, and high rates of recurrent ischemia and reocclusion. By contrast, nearly all STEMI patients were eligible for primary PCI, which established TIMI-3 flow to > 90% of patients and resulted in lower rates of mortality.\(^1,2\) Accordingly, primary PCI has emerged as the preferred reperfusion strategy, especially for high risk and elderly patients.

Although the advantages of PCI have been demonstrated, the majority of patients presenting with STEMI on a worldwide basis still received FT, due to availability and affordability. This situation inevitably led to many STEMI patients requiring rescue PCI for failed FT. As these patients undergo rescue PCI, we don’t know how safe and effective this strategy is in further lowering high mortality of elderly patients in comparison with younger ones.

In this issue of the Journal of Geriatric Cardiology, Kirtane et al.\(^4\) examined the association between age (≥70 years) and outcomes of the 1,472 STEMI patients who underwent rescue PCI following FT in seven TIMI trials. No one was surprised by the fact that, at baseline, the 218 elderly patients had more comorbidities. However, even though they had significant angiographic improvement in TIMI Frame Counts and rates of TIMI Grade 3 flow following rescue PCI, these elderly patients had higher (slower) post-PCI TIMI Frame Counts compared to the younger cohort (25 vs 22 frames, \(P = 0.039\)), and achieved post-PCI TIMI Grade 3 flow less often (80.1 vs 86.4%, \(P = 0.017\)). This study is the first to show the association between older age and slower post-PCI flow, independent of gender, time to treatment, LAD lesion location, heart rate and blood pressure on admission. Unexpectedly, the delay of 3 more frame counts and the 6% less of TIMI-3 flow after rescue PCI was translated into a 400% increase in 30-days mortality (12.0 vs 2.7%, \(P = 0.001\)). Why did this happen? Can it be corrected?

The causes of this higher mortality are speculated in many ways. Generally, there is a continued deterioration of cardiac structures and function with aging, such as increased intimal thickening, arterial stiffening, increased arterial pressure and pulse pressure, impaired endothelial function, reduced acute response to stress, reduced chronic adaptive capacity of the older heart, deficits in sympathetic modulation of heart rate, and left ventricular contractility.\(^5,7\) There is also evidence that neointimal growth in response to injury is markedly enhanced in older versus younger laboratory animals;\(^8\) on the other hand, angiogenesis is impaired with advancing age in animal models.\(^9\) Meanwhile, the left ventricular systolic and diastolic function decreases with aging even in the asymptomatic elderly cohort.\(^10,11\) All these findings suggest an important link between age-associated changes in cardiac structures and functions and worse clinical outcomes, even after successful coronary reperfusion. Solving coronary blood dynamics is only one factor in a complex equation.

During primary PCI, after perfect stenting, can we further improve the TIMI flow with pharmacological means? As soon as slow flow appears in the IRA, anything or everything (calcium channel blockers, nitroglycerine, adenosine, epinephrine, etc.) is given to improve the distal flow. If we lower 3 frames of the post-PCI TIMI Frame Counts and increase flow of the post-PCI TIMI-3
flow in 6% of patients, will the mortality of the elderly patients become equal to the ones of younger patients? Absolutely not. There are situations where no drug can fasten further the coronary blood flow because of irreversible damage in the distal endothelium or microvascular from prolonged occlusion of the IRA, or prior repeated myocardial infarctions.

What else can we do to lower mortality? We can prescribe betablockers, ACE inhibitors, etc. in order to preserve the ventricular systolic function, prevent inadvertent worsening of diastolic function and reverse endothelial dysfunction. All preventive measures are to be put in place so no pulmonary, cerebral, hepatic or renal complications can happen to destabilize the precarious condition of an elderly patient after primary PCI.

Conclusion: In the care of elderly patients with STEMI, the main goal is to recanalize the IRA. In patients with failed FT, rescue PCI improved the 30-day mortality, however at a lower level than the ones of younger patients. Can we further improve the TIMI flow and lower the number of TIMI frame count by pharmacological or mechanical means? The answer is likely to be negative. What else can be done to lower mortality? Betablockade, ACE inhibition, effective prevention of possible mechanical and electrical complications would help avoiding further fatality. The lesson is that the key opening the door to heaven for 9% of elderly patients lies within the 3 slower frames of the post-PCI TIMI Frame Counts and within the 6% decrease of post-PCI TIMI Grade 3 flow. Then on earth, in the fight for survival after rescue PCI of failed FT, physicians (including interventional cardiologists) should navigate away, from the mythical TIMI-3 flow and concentrate on the clinical management of patients. The source of salvation is nowhere far away, it is right there, at the bedside of the patient, where you are standing.

References