ST-segment elevation acute myocardial infarction: reperfusion at any cost?

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This editorial refers to ‘Long-term clinical outcomes after rescue angioplasty are not different from those of successful thrombolysis for acute myocardial infarction’\(^1\) by P.G. Steg et al., on page 1831

Acute myocardial infarction (AMI) is defined as an acute ischaemic insult to the myocardium resulting in myocardial necrosis. ST-segment elevation AMI (STEMI) identifies a condition in which the ischaemic insult is the result of an abrupt cessation of coronary flow due to thrombotic occlusion of a relatively large and proximal branch of the coronary circulation. Early, effective, and persistent recanalization of the coronary bed and reperfusion of the myocardium are the goals of the treatment in STEMI.\(^1\) Indeed, the earlier the reperfusion the greater the benefits.\(^2\) Experimental studies and the results of the early fibrinolytic trials provided useful information on this topic and led to increased awareness among health care providers and general population regarding the concepts of ‘golden hour’ and ‘time is muscle’.\(^2\) Thereafter, fibrin-specific agents became available and were shown to be superior to non-specific agents, timely treatment became available in emergency departments throughout the world, and survival benefits were achieved.\(^1,2\)

Nonetheless, a relatively high failure rate in achieving optimal recanalization and reperfusion together with a relatively high complication rate became apparent shortly after the widespread implementation of such treatment strategy. In the meanwhile, the progressive diffusion of percutaneous coronary intervention (PCI) and the development of newer and more powerful antiplatelet agents led to the performance of trials comparing fibrinolysis vs. angioplasty.

More recently, the superiority of primary angioplasty over fibrinolysis in the treatment of STEMI has been established as an undisputable fact.\(^1,3\) Specifically, acute recanalization by means of balloon angioplasty with or without stent implantation provides better immediate results and less recurrence than fibrinolysis, and is associated with significantly lower stroke rates ultimately leading to a survival advantage, as proved in a recent meta-analysis.\(^3\)

Therefore, according to the ESC guidelines (and AHA/ACC guidelines too), when primary angioplasty is available in a ‘timely’ fashion and the procedure can be performed by an ‘experienced’ operator in a ‘large volume’ centre, primary angioplasty should be considered the preferred reperfusion strategy.\(^1\)

Debate over lysis vs. PCI in STEMI has however continued as several issues still remain unclear. Indeed, it is unknown what a ‘timely’ fashion is and how long of a delay would be acceptable in order to prefer PCI over lysis. The ESC guidelines identified a door-to-balloon time of ≤90 min as optimal strategy, but unfortunately many centres in Europe and USA still fail to comply with such requirements. Most importantly, on many occasions, the patient would be seen initially in a non-tertiary centre where cardiac catheterization is unavailable and therefore delay in treatment unavoidable. As a consequence, many centres continue to perform fibrinolysis as a first line strategy and PCI for particularly high risk subjects (such as cardiogenic shock), and progresses in the fibrinolytic arm of treatment have been made and are still actively pursued, especially in further reducing time to treatment.

In the CAPTIM trial, French investigators compared pre-hospital fibrinolysis with primary angioplasty showing non-significant differences in primary and secondary outcomes.\(^4\) The study however was underpowered to detect such differences (as it was terminated early for withdrawing of economical support), and, although not statistically significant, an absolute 2% difference in primary endpoint at 30 days (death, non-fatal AMI, and disabling stroke) was found.\(^5\) The CAPTIM trial however highlighted a 60 min difference in time from symptoms onset to treatment between the two arms, favouring the fibrinolysis.\(^5\) Whether the benefits of angioplasty outweighed the potential harm of 60 min delay remained unclear.

The DANAMI-2 study performed in Denmark showed that when primary angioplasty is available even at a different site, as long as transport is expected to be <3 h, primary angioplasty should be preferred to fibrinolysis.\(^5\) In the DANAMI-2 study, there were no significant differences in...
outcomes in patients originally admitted to a facility with interventional capabilities vs. those who needed transfer. Ambulance transfer was safe, with no deaths occurring during transport. Mean transport time was 67 min (50 Km). Therefore, according to the DANAMI-2 trial, when transport may be arranged within 2 h, transfer of a patient to another facility is safe and should be preferred to onsite fibrinolysis. Although this is true in Denmark, what happens in the rest of the world? Whether the results of the DANAMI-2 study may be applied to the rest of the world is unfortunately unknown. Presumably, the Danish health system should not be significantly different than the health care settings of the remaining countries of western Europe or USA. Geographical and local organization issues however may interfere with such strategy, in a complex and hitherto incompletely characterized fashion.

To date, in many countries, an organized web for transfer of STEMI patients to the nearest interventional facility is lacking, and fibrinolysis is still largely employed. As fibrinolysis represents a suboptimal treatment strategy, these issues are extremely relevant, although what is the optimal treatment for STEMI in cases where interventional facilities are not on-site and transfer to a tertiary centre is not pre-arranged remains controversial.

Dr Steg et al. present the results of the experience they had in Paris. Dr Steg provides the results of an early fibrinolysis with scheduled angiography in all patients. The major issues with fibrinolysis is the failure to achieve optimal reperfusion, the use of an early fibrinolysis combined with an early scheduled angiography to assess efficacy and perform culprit lesion angioplasty in case of suboptimal results of fibrinolysis as proposed by Steg et al. may represent a way to address fibrinolysis’ failures. In this non-randomized study, the authors show that the 8 year actuarial survival rates for patients who had successful 90 min angioplasty for fibrinolysis failure were identical to that of those patients who had effective fibrinolysis, thus showing that one of the limitations of fibrinolysis was surpassed by the early scheduled angiography strategy in all patients.

Far from being conclusive, the data presented by this largely experienced French group provide information that may prove extremely useful at present and in future for the clinical cardiologist. How should a patient who has received fibrinolysis in the emergency department or perhaps in the ambulance be treated once arrived at a tertiary centre? The answer is that angiography should be scheduled as soon as possible and angioplasty performed for suboptimal results of fibrinolysis (TIMI flow 0–1), as supported also by recent randomized trials (i.e. the Spanish GRACIA-1 trial). The study by Steg et al. also provides the opportunity to reconsider the reperfusion paradigm. The fact that the 8 year survival was identical in patients with effective lysis and those with effective angioplasty for lysis failure strongly supports Braunwald’s ‘expanded paradigm’ and ‘open-artery hypothesis’, which propose that the benefits of a patent infarct-related artery (IRA) extend beyond acute myocardial salvage.

Clear benefits of ‘late’ IRA revascularization, however, are not supported by randomized trials. Several observational studies argue in favour of late revascularization, and our own meta-analysis showed that, although there were no significant survival benefits (perhaps due to the small number of cases), there were benefits in terms of cardiac remodelling (i.e. a significant increase in ejection fraction in patients undergoing late PCI vs. those on best medical therapy). The ‘open-artery hypothesis’ is therefore alive and doing well, and while awaiting for larger randomized trials (i.e. the OAT), observational studies and small randomized trials suggest a possibly favourable effect of late revascularization that meet our expectations in terms of pathophysiological mechanisms of post-infarction remodelling. We have indeed recently learned that the post-infarction period is characterized by highly dynamic processes including myocardiocyte death (due to apoptosis) and regeneration, for several weeks after the initial event. One of the potential benefits of late revascularization may be due to a shift towards cell survival in this period (Figure 1).

In conclusion, effective and permanent myocardial reperfusion is the goal of STEMI treatment. Primary angioplasty is the preferred method given its superior performance in achieving better results with lower complication rates. Delay in treatment up to 2 h for transfer of a patient with STEMI to a facility with interventional capabilities is appropriate, and all non-tertiary medical centres should pre-arrange transfer modalities (as it happens for trauma patients). Patients who do not receive primary angioplasty should be evaluated as soon as possible for IRA patency and angioplasty should be performed to restore anterograde flow in order to prevent early and late complications of IRA occlusion, especially if residual/recurrent ischaemia or high risk features are present. Facilitated PCI with the use of a reduced dose of fibrinolytic prior to intervention may become an option in the future as currently being assessed.
in larger trials (i.e. FINESSE trial), although smaller trials have so far failed to show any additional benefit from facilitated PCI.

References


