EDITORIAL

Primary percutaneous coronary intervention in acute myocardial infarction: time, time, and time!

P G Steg, J-M Juliard

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Longer door-to-balloon times, total duration of ischaemia, and time of presentation relative to symptom onset all have an impact on outcome following primary percutaneous coronary intervention

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Primary percutaneous coronary intervention (PCI) is now established as the reference treatment for the management of ST segment elevation acute myocardial infarction (STEMI).[1] Randomised controlled trials have demonstrated superiority in reducing mortality and recurrent myocardial infarction compared with thrombolytic treatment. However, because primary PCI requires longer delays than intravenous thrombolysis for implementation, and because its results may vary according to the expertise of the operator and centre, the superiority of primary PCI over intravenous thrombolysis is not universal. In contrast to randomised controlled trials, data from several large scale registries have not found a consistent and clear superiority of primary PCI over thrombolysis and this has usually been interpreted as being at least in part the reflection of variations in the practice of PCI, according to volume and delays.

A TRIPLE IMPACT OF TIME ON OUTCOMES AFTER PRIMARY PCI

The impact of time and delays on the outcome after primary PCI is threefold.

(1) Longer door-to-balloon times are associated with increased mortality after primary PCI

In the GUSTO II study, increasing door-to-balloon (that is, the delay between admission and actual inflation of the PCI balloon in the coronary artery) times were associated with increased 30 day mortality,[2] and this was confirmed in subsequent analyses from larger studies.[3] An obvious explanation is that experienced centres with high volumes would be expected to address STEMI patients more effectively, resulting in shorter door-to-balloon times and reduced mortality. Therefore, door-to-balloon time was a surrogate of volume and expertise rather than having a direct causal effect on mortality. However, subsequent analyses from single centre studies confirmed that increasing door-to-balloon times are associated with sharp increases in mortality,[4] and that there is a "golden hour" of primary PCI, just as there is one for intravenous thrombolysis.

(2) The total duration of ischaemia (symptom-to-balloon time) also impacts on mortality in primary PCI

While there is universal agreement that the benefit of intravenous thrombolysis decreases sharply as time elapses after the onset of symptoms,[5] the relation is less clear for primary PCI, in part because the original studies were small, and the distribution of delays skewed towards long delays. It was originally believed that the outcome of primary PCI might be "time-independent", and, specifically, that after the first two hours following symptom onset, survival was relatively independent of the time to reperfusion.[6] This would have had major implications on the organisation of transfers in acute myocardial infarction. However, recent data have convincingly demonstrated that, although the slope of the correlation is less steep than for intravenous thrombolysis, there is a clear increase in short and long term mortality with increasing delay between symptom onset and primary PCI.[7 8] In fact, for every 30 minutes elapsed, the relative risk for one year mortality is 1.075. This explains why among randomised studies, those which are associated with the longest delays for performing PCI compared to administering thrombolysis were associated with no mortality benefit of primary PCI. It was even possible to compute that when the excess delay of primary PCI over thrombolysis exceeded 60 minutes, then intravenous thrombolysis provided equivalent if not superior results to primary PCI.[9]

(3) The timing of presentation relative to symptom onset may impact on the results of the comparison between reperfusion strategies

Because implementing primary PCI requires time and because intravenous thrombolysis is most effective when given very early after the onset of symptoms, it was expected that very early intravenous thrombolysis might fare best compared to primary PCI when patients are treated very early. In the first 2–3 hours after symptom onset, "losing one hour" for transferring the patient to a catheterisation capable site may be less effective than giving immediate intravenous thrombolysis (which does not preclude immediate transfer to an interventional site). Indeed,

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Abbreviations: ALKK, Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; GUSTO II, global use of strategies to open occluded coronary arteries; STEMI, ST segment elevation acute myocardial infarction

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this was exactly the outcome in two analyses from randomised studies: the PRAGUE-2[10] and the CAPTIM studies,[11] in which very early thrombolysis fared as well or better than primary PCI in the first 2–3 hours after symptom onset, while later in the course of symptoms, primary PCI was associated with a consistent superiority over thrombolysis.

NEW DATA FROM THE ALKK GROUP

In this issue, Zahn and colleagues[12] revisit the impact of in-hospital time to treatment in patients with STEMI treated with primary angioplasty. Registries are well suited to address this question, for which randomised trials have little relevance, and this select group of investigators from the well organised German registry of percutaneous interventions in acute myocardial infarction (ALKK) have already given us a wealth of data on interventions in this setting. In this analysis of nearly 5000 patients treated with primary PCI, they failed to find an impact of "door-to-angiography" time on in-hospital mortality.

What are the hypotheses for the discrepancy with previous observations? The first is that the threshold for increased mortality may be well above the mean door-to-angiography delays observed in Germany (83 minutes). Indeed, when hospital mortality was compared in patients in whom the delay was on either side of the 120 minute threshold, there was a trend towards increased mortality in patients with longer delays (12.2% v 8.8%, adjusted odds ratio (OR) 1.34, 95% confidence interval (CI) 0.97 to 1.85; p = 0.098). This is consistent with the finding from other studies that mortality increases notably for a door-to-balloon time exceeding 120 minutes.[3] Therefore, while our German colleagues need to be congratulated for not "procrastinating" when treating acute myocardial infarction patients, there may very well be a real impact of intra-hospital delay on outcomes.

Another hypothesis is the difficulties of comparisons of non-randomised groups (for example, groups categorised by delay) in which assignment is very likely biased by patient and organisation characteristics, which are very difficult to capture in a comprehensive fashion and for which no multivariate analysis can reliably adjust. The impact of "door-to-needle" time on mortality is also likely to vary according to time elapsed since symptom onset and, particularly, to be lower in patients seen late (for example, in the 6–12 hour interval) compared to patients seen earlier: if STEMI is completed or myocardial salvage is unlikely (as is the case in patients seen late), there is likely little impact of "losing time" en route to the catheterisation laboratory. Conversely, in patients seen very early (that is, in the first 2–3 hours) any delay (including in-hospital delay) is very likely to result in increased mortality.

It remains difficult to ascertain precisely whether the provocative findings of Zahn and colleagues[12] reflect an overall short in-hospital delay in German PCI centres, non-uniform distribution of risk in this categorical analysis of data, lack of power in a "relatively small" (5000 patients)

analysis, or a genuine finding that door-to-angiography delays do not impact on mortality after primary PCI. However, the bulk of experimental and clinical evidence on reperfusion indicates that the longer the ischaemia, the higher the mortality. Suggesting otherwise should never be interpreted as encouraging complacency in primary PCI teams. For the time being, in STEMI patients treated with any reperfusion therapy, time (between symptom onset and start of therapy), time (between symptom onset and recanalisation of the infarct artery), and time (between admission and recanalisation) should always be kept as short as possible.

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