Who should have a routine early invasive approach after fibrinolytic therapy?

Christopher B. Granger*
Duke Clinical Research Institute and the Division of Cardiology, Duke University Medical Center, Durham, NC 27710, USA

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This editorial refers to ‘Relationship between risk stratification at admission and treatment effects of early invasive management following fibrinolysis: insights from the Trial of Routine ANgioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI)’, by A.T. Yan et al., on page 1994

Reperfusion strategies at non-PCI centres

Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI), especially with primary percutaneous coronary intervention (PCI), can reduce mortality by >25%. Earlier reperfusion provides greater benefit, particularly in the early hours of infarction.1

Of the large number of remaining questions about how best to apply reperfusion therapy for patients with acute STEMI, few are more important than how to manage the patient who presents to the hospital without PCI capability. When it can be done quickly, transfer for primary PCI is generally the best strategy.2 Yet all too often—70% of the time in the USA from 2005 to 20073—the patient is transferred for primary PCI with long delays (of >120 min first door to device) that rob the patient of the benefits of prompt reperfusion therapy with fibrinolysis. Even with fibrinolysis, whether and when to transfer to a PCI-capable centre, to perform angiography, and to perform PCI has been a topic of intense investigation.

There have been at least three published meta-analyses4–6 in the past year of the modest-sized clinical trials that have randomly assigned patients following fibrinolysis to routine early vs. selective (or delayed) coronary angiography and PCI strategies. Of the seven trials that were included, in all three of these meta-analyses (Figure 1), the sample sizes range from 163 to 1059 patients, with average or median times from fibrinolytic therapy to PCI from 1.6 to 17 h. Each trial used a composite primary outcome that included death, reinfarction, and recurrent ischaemia. Three of the larger studies focused on ‘high-risk’ patients that needed to have ECG, or had haemodynamic or clinical features placing them at higher risk.7–9

While none of these trials is definitive in and of itself, the group of trials with ~3000 patients and nearly 500 primary outcome events provides convincing evidence of benefit to the strategy of routine early coronary angiography and PCI following fibrinolysis. Each meta-analysis4–6 provides a consistent message: there was a nearly 50% reduction in recurrent MI and recurrent ischaemia that was highly statistically significant, with no substantial increase in bleeding.

What do the guidelines say?

These data have led to a class I, level of evidence A recommendation for routine urgent PCI (within 24 h) following successful fibrinolysis in the European revascularization guidelines.10 The ACC/AHA 2009 update to the STEMI guidelines11 gave a class IIb recommendation to the strategy of routine early coronary angiography following fibrinolysis, and a class IIa level of evidence B recommendation for this strategy for patients at high risk, mentioning the criteria used in the two largest trials, CARESS-AMI8 and TRANSFER-AMI.9 These criteria included systolic blood pressure $\leq 100$ mmHg, heart rate $\geq 100$ b.p.m., Killip class II to III, $>2$ mm of ST-segment depression in the anterior leads, $>1$ mm of ST elevation in right-sided lead V4 indicative of right ventricular involvement, left ventricular ejection fraction $\leq 0.35$, or new left bundle branch block.

Is there less benefit in the high-risk population in TRANSFER-AMI?

Strong evidence for modest benefit with a routine early invasive approach was the state of the art before the publication of the surprising analysis by Yan et al.12 The TRANSFER-AMI trial7 found a 36% relative risk reduction in the composite of death, reinfarction, recurrent ischaemia, new or worsening congestive heart failure, or cardiogenic shock (and a non-significant 21% relative risk reduction...
in death or reinfarction) within 30 days in high-risk patients with the strategy of early routing angiography and PCI following fibrinolysis. The TRANSFER-AMI investigators now report that the 16% of patients at ‘high risk’ by the GRACE risk score, with an estimated risk of in-hospital mortality of >5%, had harm from the pharmacoinvasive strategy, whereas the low–medium risk patients had benefit, with a highly significant ($P = 0.001$) interaction between baseline risk and treatment effect regarding the outcome of death or reinfarction.\textsuperscript{12}

This type of ‘qualitative’ interaction, with a reversal of treatment effect in subgroups of the same patient population, is so unusual as to be of questionable validity.\textsuperscript{13} It is not unusual for such an interaction,\textsuperscript{14} when followed up by a larger and more definitive trial, to be shown to be due to the play of chance.\textsuperscript{15} This is particularly true when the subgroup was not a major ‘pre-defined’ focus, and it is noteworthy that the subgroups of interest described in the TRANSFER-AMI design study did not include the GRACE risk score.\textsuperscript{16} Moreover, the analysis of Yan et al. focuses on an outcome (death or reinfarction) that was a secondary outcome in the trial without a significant overall treatment effect on that outcome. It is also surprising since there has been a general pattern of higher risk patients deriving more benefit from a more invasive approach—be that the benefit of a routine invasive approach in acute coronary syndrome (ACS) where there may be particular benefit in older patients or patients with elevated troponin, of an earlier invasive approach in ACS where higher GRACE risk had greater benefit, or of an invasive approach in cardiogenic shock. In fact, in one of the meta-analyses of an early routine invasive strategy following fibrinolysis (in which two of the co-authors were also co-authors of the report of Yan et al.), a meta-regression suggested that trials that enrolled higher risk patients had greater treatment effects from the routine invasive approach.\textsuperscript{4} Yan et al. raise the question as to whether there is more of a price of bleeding in the high-risk group, which brings up issues of optimizing antithrombotic therapy and of an interventional approach to reduce bleeding.

**How do we interpret this subgroup finding?**

How can we interpret these ironic results: that the lower risk patients of a population selected to be high risk are those that appear to get greater benefit? For the time being, as the authors have advised, this should be considered hypothesis-generating and should not be used to guide practice. This analysis reminds us that subgroups often provide surprising results, and we too often forget that usually these findings are due to the play of chance. As Sir Richard Peto has said, subgroup analysis is ‘a machine for generating false negatives’. On the other hand, it would be inappropriate to discard these findings completely, and further analyses from other data sets (ideally including a pooling of individual patient data from the meta-analysis) would help to refute or confirm the findings. This would also allow more reliable exploratory analyses of key subgroups such as older age.

There are lots of unanswered questions, including optimal timing of PCI and best selection of antithrombotic therapy, with the evidence from the ASSENT-4 trial\textsuperscript{17} that early (within 2 h) routine PCI following fibrinolytic therapy with low intensity antithrombotic therapy is associated with risk of thrombotic complications. Also, the important question of how an optimized fibrinolytic strategy,
with routine early catheterization, will compare with transfer for primary PCI with inherent delays is the subject of ongoing investigation.18

Until we have further analyses, the totality of the data suggests that a strategy of routine coronary angiography and PCI within 24 h after fibrinolysis will improve the outcome of our patients treated with fibrinolysis.

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