Routine Angioplasty after Fibrinolysis — How Early Should “Early” Be?

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Reperfusion therapy has represented a great leap forward in the management of myocardial infarction with ST-segment elevation. Its goal is early and complete recanalization of the infarct-related artery to salvage myocardium and improve both early and late clinical outcomes. Complete reperfusion can be achieved with either fibrinolysis or primary percutaneous coronary intervention (PCI), but with primary PCI the success rate is higher than 90%, whereas current fibrinolytic therapy leads to full reperfusion in only 50 to 55% of recipients. Primary PCI, therefore, looks like the most appropriate reperfusion tool, but there are substantial logistic restrictions associated with it. The door-to-balloon time with primary PCI is typically longer than the time within which in-hospital fibrinolytic therapy can be initiated, and primary PCI requires a network of dedicated ambulances and emergency departments to shorten the door-to-balloon time as much as possible.1,2 Primary PCI is an especially attractive strategy in the United States, where nearly 80% of the adult population lives within 1 hour’s drive of a PCI center.3

Investigators have tried to combine the best of both therapies by performing PCI immediately after fibrinolysis. The concept of fibrinolysis followed immediately by PCI (termed facilitated PCI) seems attractive: early reperfusion with the use of a widely available strategy to salvage as much myocardium as possible, followed by PCI to ensure both reperfusion in the case of fibrinolytic failure and prevention of recurrent thrombosis that may result in reocclusion and reinfarction. Studies of PCI performed immediately after fibrinolysis were initiated in the late 1980s, but a meta-analysis in 2005 showed that this approach was not usually beneficial,4 probably in part because of the use of outdated fibrinolytic and antiplatelet regimens and PCI equipment in those studies but also because of the increased risk of bleeding. The latter concern, especially, made many interventional cardiologists reluctant to intervene after fibrinolysis, although the results of a trial of rescue PCI after failed fibrinolysis suggest that this procedure is effective and relatively safe.5 Since the major problem with the combination of fibrinolytic therapy with immediate PCI is thought to be the short interval between fibrinolysis and PCI, some later studies have investigated the outcome when a longer interval is used. Besides reducing the risk of bleeding, this approach enables the transfer of patients from centers that do not have the capability of performing PCI (where initial fibrinolysis is performed) to a PCI center. These studies showed that the approach was successful; however, the sample sizes in the studies were relatively small.6-9

In this issue of the Journal, Cantor et al. report the results of the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI; ClinicalTrials.gov number, NCT00164190), a large study on this topic.10 More than 1000 Canadian patients with myocardial infarction with ST-segment elevation who were treated with fibrinolysis were randomly assigned to interhospital transfer for intended routine early PCI (within 6 hours after fibrinolysis) or an ischemia-guided strategy, in which patients were transferred for angiography only in the case of failed fibrinolysis or of recurrent ischemia. As in the four smaller trials, the rate of recurrent ischemia was significantly reduced with early routine PCI as compared with a selective invasive approach. Given the sample size and the study design, and with little evidence to
Five major randomized clinical trials have evaluated routine early percutaneous coronary intervention (PCI) after fibrinolysis, as compared with fibrinolysis alone followed by a selective invasive approach, in patients with myocardial infarction with ST-segment elevation. The five trials are the brinolysis alone followed by a selective invasive approach, in patients with neous coronary intervention (PCI) after fibrinolysis, as compared with fibrinolysis alone in Acute Myocardial Infarction (CAPITAL AMI), Five major randomized clinical trials have evaluated routine early percutaneous coronary intervention (PCI) after fibrinolysis, as compared with fibrinolysis alone in Acute Myocardial Infarction (CAPITAL AMI, NCT00004562), the Combined Abciximab Retepase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI, NCT00220571), the Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III), the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI, NCT00164190), and Grupo de Análisis de la Cardiopatía Isquémica Aguda-1 (GRACIA-1) trial.

Figure 1. Rate of Ischemic Events at the Available Follow-up.

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The interval from fibrinolysis to PCI and the rate of ischemic events in the five available studies are shown in Figure 1. The time to PCI was well within 24 hours after fibrinolysis in each study, and there was no difference among the trials in efficacy relative to the time to PCI. The intervals ranged from 2 to 17 hours. The former interval should be considered to be the lowest acceptable one, since PCI immediately after fibrinoly has proved to be ineffective. On the other hand, an interval of 17 hours seemed to be as good as PCI at 2 hours. Waiting longer than 24 hours can be disadvantageous given the increas-


Cancer Genomes on a Shoestring Budget
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In a remarkably short time, the use of massively parallel technologies has greatly reduced the cost of DNA sequencing. Already, these technologies have permitted the whole-genome sequencing of several persons and one tumor for a small fraction of the cost of the sequencing of the first human genome. However, the cost of whole-genome sequencing is still many tens of thousands of dollars — too expensive for routine application to even modest numbers of samples in either a research or a clinical setting.

In this issue of the Journal, Shah et al. describe the identification of a likely “driver” mutation of the FOXL2 gene in adult-type granulosa-cell tumors (GCTs), relatively uncommon neoplasms that account for 3 to 5% of all ovarian cancers. The discovery was made by sequencing the transcriptome of tumor specimens, rather than by sequencing genomic DNA (gDNA). The transcriptome is defined as the full set of messenger RNA (mRNA) present in a population of cells. The usual goal of characterizing a transcriptome is to quantify the relative abundance with which individual genes are expressed in a given tissue (e.g., with microarrays). In contrast, the objective of this study was to mine transcribed sequences to indirectly identify nonsynonymous mutations in the tumor genome — that is, those altering protein-coding sequences.

To put this in context, more than 98% of the human genome comprises sequences with regulatory or unknown function, interspersed with nearly 200,000 exons that collectively encode mRNA (the “exome” contributing 1 to 2% of the genome in aggregate); mRNA, in turn, encodes proteins. The vast majority of somatic mutations that have been identified to date and that clearly drive the development of cancer in humans are either large-scale structural changes (e.g., rearrangements and copy-number changes) or small mutations that alter protein-coding sequences. Whole-genome sequencing of a tumor (and...