Systems of Care: Need for Hub-and-Spoke Systems for Both Primary and Systematic Percutaneous Coronary Intervention After Fibrinolysis

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Editorial

Systems of Care

Need for Hub-and-Spoke Systems for Both Primary and Systematic Percutaneous Coronary Intervention After Fibrinolysis

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Primary percutaneous coronary intervention (PCI) is currently considered the best reperfusion therapy if performed in a timely manner. However, in many developed countries, it is difficult to offer primary angioplasty to more than 20% to 30% of eligible patients because of logistical issues. Fibrinolytic therapy has recently improved, with the addition of clopidogrel resulting in both improved infarct artery patency[1] and mortality[2] and enoxaparin reducing reinfarction.[3] In addition, rescue PCI has been shown to reduce reinfarction after fibrinolytic therapy by 42% ($P<0.05$),[4] and in a meta-analysis of 8 trials that included 1117 patients, rescue PCI resulted in a reduction in death, reinfarction, and heart failure at 6 months from 41.0% to 29.2% ($P<0.001$) compared with fibrinolysis and PCI only for recurrent ischemia.[5] There also was a trend for a reduction in mortality (odds ratio [OR], 0.69; 95% CI, 0.46 to 1.05; $P=0.09$).

Article p 268

For many years, it has been controversial as to whether coupling PCI with fibrinolysis to ensure durable patency of the infarct-related artery is beneficial or harmful. Earlier trials, often without aspirin and without stenting, showed harm,[6] and recent facilitated angioplasty trials (fibrinolysis followed by rapid PCI) also have shown harm or no benefit.[7–9] This is probably due to the prothrombotic milieu induced by fibrinolytic therapy in the first few hours after administration. At a later time point, when the prothrombotic situation has lessened and glycoprotein IIb/IIIa antagonists have been administered, systematic PCI may be beneficial.

A number of recent trials help clarify the optimal timing of systematic PCI after fibrinolysis (the Figure). Less than 3 hours is harmful, and there seems to be a window between 3 and 6 hours when there is likely to be a benefit, as indicated by the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS)[10] and Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER AMI),[11] with glycoprotein IIb/IIIa antagonists used in a large proportion of patients.

In the CARESS in Acute Myocardial Infarction trial of 600 patients, a composite of death, reinfarction, or refractory ischemia at 30 days occurred in 4.4% of patients having immediate PCI (angiography 3 hours after fibrinolysis) after transfer and receiving aspirin, half-dose reteplase, heparin, and abciximab compared with 10.7% in patients receiving the same therapies and having standard care (with rescue PCI in 30.3%; $P=0.004$). There was no difference in major bleeding.

In the TRANSFER AMI trial, 1030 patients were randomized to immediate PCI with urgent transfer to a PCI center and PCI performed 4 hours after the administration of tenecteplase or to standard treatment with rescue PCI performed for failed reperfusion. Patients in the standard treatment arm received aspirin, tenecteplase, enoxaparin (55%), and clopidogrel (69%). The composite of 30-day death, reinfarction, congestive heart failure, severe recurrent ischemia, or shock occurred in 10.6% of the immediate PCI arm and 16.6% of the standard arm (OR, 0.537; 95% CI, 0.368 to 0.783; $P=0.0013$). There was no difference in bleeding.

Deferral of systematic PCI for >6 hours also is supported by a number of trials.[12,13] However, the data relating to timing are not robust, and further research is needed.[13]

Several small trials with fibrinolysis and systematic PCI have shown outcomes similar to primary PCI, as has another recent registry from Vienna.[14] In the Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA 2) trial,[15] fibrinolysis with tenecteplase and enoxaparin and systematic PCI between 3 and 12 hours (median, 4.6 hours) resulted in outcomes similar to primary PCI. Similarly, in the Which Early ST-Elevation Myocardial Infarction Therapy (WEST) study,[13] systematic PCI within 24 hours (median, 8.9 hours) after administration of tenecteplase resulted in outcomes similar to primary PCI.

In this issue of *Circulation*, Danchin and colleagues[16] report on a registry of 1714 patients with acute ST-elevation myocardial infarction from 223 centers throughout France in October 2005. The registry compared outcomes from primary PCI with those from fibrinolytic therapy with a high rate of

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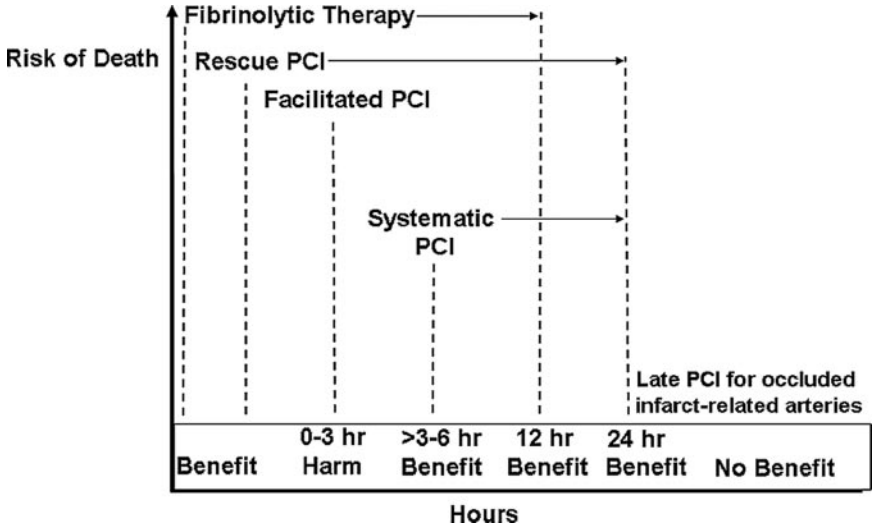

Figure. Impact of PCI with fibrinolytic therapy. Fibrinolytic therapy reduces mortality up to 12 hours after symptom onset. Rescue PCI also is beneficial for ongoing symptoms or failure of resolution of ST elevation by 50%.[5] Facilitated PCI within 3 hours of administration of fibrinolytic therapy is harmful.[7–9] Systematic PCI between 3 and 6 hours after fibrinolysis appears beneficial.[10,11,21] After 6 hours, there may be benefit.[12,13,22] Opening an occluded infarct artery after 24 hours from symptom onset provides no patient benefit.[23]

rescue and systematic PCI. The registry included 60% of the centers treating myocardial infarction in France. In France, mobile intensive care units (Service d'aide médicale urgente) are staffed by physicians able to give fibrinolytic therapy, clopidogrel, antithrombotic agents, and glycoprotein IIb/IIIa antagonists. Fibrinolysis was administered to 29% of patients, with two thirds receiving fibrinolysis in the ambulance before hospital admission. The time delay between a call to the mobile care unit and administration of fibrinolysis was 40 minutes, whereas the time to primary PCI, which was performed in 33% of patients, was 130 minutes. Strikingly, 40% of eligible patients received no reperfusion therapy.

Almost all the patients (96%) who received fibrinolysis underwent coronary angiography while in hospital, with 84% having PCI; the median time from fibrinolysis was 220 minutes. Rescue PCI, which was recommended if there were persisting symptoms or persisting ST-segment elevation 60 minutes after administration of fibrinolysis, was performed in 37% of fibrinolysis patients, with a median time to PCI of 168 minutes. There was a high rate of clopidogrel (91%), low-molecular-weight heparin (56%), and glycoprotein IIb/IIIa antagonist (16%) use in fibrinolysis-treated patients. Perhaps surprisingly, there was no increase in bleeding with fibrinolysis following the high rate of PCI compared with primary PCI (major bleeding, 1.7% versus 2.3%; $P=0.353$).

There has been a marked increase in both primary PCI from 13% in 1995 to 33% in this registry in 2005, along with a marked increase in prehospital fibrinolysis rates from 9.4% in 2000 to 18%.[17] These changes have been paralleled by a reduction in hospital mortality from 9.3% to 6.6%. Survival at 12 months was 94.7% for prehospital fibrinolysis, 91.5% for in-hospital fibrinolysis, and 91.8% for primary PCI ($P=0.31$, fibrinolysis versus primary PCI). In addition, outcomes in patients who were transferred after fibrinolysis were similar to those in patients treated in hospital with primary PCI facilities. After propensity matching and score adjustment using the GRACE score and baseline comorbidities, including chronic renal failure, 12-month survival was similar in the fibrinolytic (prehospital and in-hospital administration) and primary PCI groups (93.8% and 93.3%).

Of interest in this nonrandomized registry, PCI after fibrinolysis at ≤128 minutes was associated with a higher mortality, consistent with a meta-analysis of facilitated PCI trials[7] and the recent Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention (ASSENT-4 PCI)[8] and Facilitated Intervention for Enhanced Reperfusion Speed to Stop Events (FINESSE) trials.[9]

It is also interesting that mortality increased with rescue PCI with quartile time cuts of ≤128, 129 to 220, and >220 minutes (third and fourth quartiles) after fibrinolysis and rescue PCI (2.6%; 5.4%, 10.2%), whereas mortality decreased with systematic PCI (5.2%, 2.6%, 1.5%), implying that if systematic PCI had been done before 220 minutes, the very high mortality with rescue PCI (10.5%) may have been avoided. However, the rescue patients are highly selected and would be expected to do poorly because they failed lysis and have either ongoing symptoms or hemodynamic compromise. In addition, the longer the delay to systematic PCI is, the more likely it is that nonfatal ischemic events will occur. Unfortunately, this registry provides no information on the occurrence of reinfarction.

Given that registries cannot assess the benefits of treatments and that findings need to be confirmed by clinical trials, what are the lessons from the French registry? First, the registry shows the benefit of applying evidence-based guidelines in clinical practice with high rates of clopidogrel and enoxaparin use and short "from first seen to needle" and "from first seen to balloon" times. Second, as in other registries,[18] a large group of patients received no reperfusion therapy, and these patients had the highest hospital mortality (9.5%).

Primary angioplasty also has improved recently, with the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS) trial[19] showing that bivalirudin reduced 30-day mortality from 3.1% to 2.1% ($P=0.048$) and reduced major bleeding by 41%. This

is the first time that an improvement in mortality has been shown with primary angioplasty, and again, the balance of evidence has tilted toward primary angioplasty as the preferred reperfusion strategy if performed in a timely manner.

The largest gains in terms of lowering mortality from ST-elevation myocardial infarction are likely to come from the development of systems to apply the evidence that we already have.[20] For example, treating the ≈40% of patients who currently do not receive reperfusion[18] with primary angioplasty within 2 hours of symptom onset would save 270 lives per 10 000 patients compared with introducing all reperfusion eligible patients to a novel therapy and reducing mortality by 20%, which would save 180 lives.[20] Adding a novel therapy to optimal reperfusion (primary PCI within 2 hours) to all eligible patients would save 1 life per 10 000 patients treated.

A pharmacoinvasive strategy of rapid administration of fibrinolysis (prehospital or in hospital) followed by systematic PCI within 24 hours would be practical in many communities and most countries. Systems of care may involve "hub-and-spoke" systems in which catheterization laboratories perform primary PCI and patients are directly transported from the surrounding communities or peripheral hospitals or systems in which prehospital or in-hospital fibrinolysis is followed by rescue and systematic PCI. In some communities, both approaches, as shown in this registry from France, may work well together and deliver excellent care to patients.

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