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In this issue of *Circulation*, Dr Gregg Stone offers a thorough review of percutaneous coronary intervention (PCI) strategies to treat ST-segment–elevation myocardial infarction (STEMI). All of the major topics are addressed and comprehensively referenced, and the figures provide a concise summary of much of the evidence base. His ultimate vision is the establishment of STEMI systems of care dedicated to primary PCI. Improving patient outcomes in STEMI is a critical goal, and we agree that continued efforts are needed to expand prehospital and hospital-based emergency medical systems for STEMI patients. However, we also continue to believe that there are currently substantial challenges to delivering primary PCI rapidly and reliably in real-world settings. Given that some of the opinions offered by Stone differ from recommendations made by professional societies, we offer a different perspective on this controversial subject and provide some of the background thinking that led to the development of the 2004 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction and the subsequent 2007 focused update. Our discussion also is informed by the ACC Door-to-Balloon (D2B) Alliance campaign and the AHA Mission: Lifeline initiative. Our goal is not to debate the points made by Stone but to place PCI for STEMI in the broader context of the patient and the healthcare system. We do this by providing additional insights into the development of PCI strategies in STEMI, examining the critical challenges that remain for delivering primary PCI, highlighting the difference between fibrinolytic therapy and a fibrinolytic strategy, and endorsing a new paradigm for reperfusion therapy.

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**PCI Strategies in STEMI**

**Primary PCI**

Primary PCI is clearly preferred to fibrinolytic therapy when time-to-treatment delays are short and the patient presents to a high-volume, well-equipped center with expert interventional cardiologists. Compared with fibrinolytic therapy in randomized clinical trials, primary PCI produces higher rates of infarct artery patency, Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, and access site bleeding and lower rates of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage, and death. Early, successful PCI also greatly decreases the complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, allowing earlier hospital discharge and resumption of daily activities. These advantages were recognized in the 2004 ACC/AHA STEMI guidelines that elevated primary PCI to the preferred strategy for reperfusion therapy when performed in a timely fashion (door-to-ballooned time within 90 minutes) by persons skilled in the procedure (>75 PCI procedures per year) in cardiac catheterization laboratories that performed at least 200 PCI procedures a year (including 36 primary PCI procedures a year). In the 1999 update of the 1996 STEMI guidelines, primary PCI was considered an “alternative to thrombolytic therapy” based on the limited data for superiority that existed at that time.

**Facilitated PCI**

Facilitated PCI refers to a strategy of planned immediate PCI after administration of an initial pharmacological regimen intended to improve infarct artery patency before PCI. The pharmacological regimens have included high-dose heparin, a glycoprotein IIb/IIIa inhibitor, full-dose fibrinolytic therapy, half-dose fibrinolytic therapy, or a combination of half-dose fibrinolytic therapy and a glycoprotein IIb/IIIa inhibitor. Potential advantages include earlier time to reperfusion, smaller infarct size, improved patient stability, lower infarct artery thrombus burden, greater PCI success rates, higher TIMI flow rates, and improved survival rates. Potential risks include increased bleeding complications, especially in older patients. Limitations include drug contraindications and additional cost. Unfortunately, early clinical trials of facilitated PCI did not demonstrate any benefit in reducing infarct size or improving outcomes compared with primary PCI. Nevertheless, selective use of the facilitated strategy with regimens other than full-dose fibrinolytic therapy in subgroups of patients at high risk (large MI or hemodynamic or electric instability) with low risk of bleeding (younger age, absence of poorly controlled hypertension, normal body weight) who...
present early to hospitals without PCI capability might be appropriate when transfer delays for primary PCI are anticipated. Early trials of facilitated PCI were limited by inadequate antplatelet and anticoagulant adjunctive therapy and the rapid performance of PCI. It would be interesting to retest the hypothesis with clopidogrel and enoxaparin because they have been shown to decrease ischemic complications with fibrinolytic therapy and to limit enrollment to patients presenting to hospitals without PCI capability.

Emergency Invasive Strategy After Fibrinolytic Therapy
In unstable patients such as those with cardiogenic shock (especially those <75 years of age), severe congestive heart failure/pulmonary edema, or hemodynamically compromising ventricular arrhythmias (regardless of age), a strategy of emergency coronary angiography with intent to perform PCI is a useful approach regardless of the time since initiation of fibrinolytic therapy, provided further invasive management is not considered futile or unsuitable given the clinical circumstances.

In stable patients, rescue PCI may be reasonable if there is clinical suspicion of failure of fibrinolytic therapy. Historically, rescue PCI was performed 90 minutes after the initiation of fibrinolytic therapy in an infarct artery with TIMI grade 0/1 flow. Presently, the clinical diagnosis of unsuccessful reperfusion is best made when there is <50% ST-segment resolution 90 minutes after initiation of fibrinolytic therapy in the ECG lead showing the greatest degree of ST-segment elevation at presentation. Angiography is required to determine whether this is due to a persistently occluded infarct artery or to unsuccessful microvascular reperfusion.

Given the association between bleeding events and subsequent ischemic events, it also might be reasonable to select moderate- and high-risk patients for rescue PCI and to treat low-risk patients with medical therapy. An ECG estimate of potential infarct size in patients with persistent ST-segment elevation and ongoing ischemic pain can be useful. Anterior MI or inferior MI with right ventricular involvement or precordial ST-segment depression usually predicts increased risk. Conversely, patients with symptom resolution, improving ST-segment elevation, or inferior MI localized to 3 ECG leads probably gain little benefit. Likewise, it is doubtful that PCI of a branch artery (diagonal or obtuse marginal branch) will change the prognosis in the absence of the high-risk criteria noted above. The benefits of rescue PCI are greater the earlier it is initiated after the onset of ischemic discomfort.

Elective Invasive Strategy After Fibrinolytic Therapy
PCI of a hemodynamically significant stenosis in a patent infarct artery >24 hours after STEMI may be considered part of an elective invasive strategy to maintain long-term patency. The presence of clinical ischemia or silent ischemia increases the chance for benefit. In contrast, the Open Artery Trial testing the open artery hypothesis in patients with little myocardial ischemia and an occluded infarct artery, demonstrated no incremental benefit with elective PCI 1 to 28 days after MI in preserving left ventricular function and preventing subsequent cardiovascular events beyond optimal medical therapy with aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins. Importantly, exclusion criteria included New York Heart Association class III or IV heart failure, rest angina, serum creatinine >2.5 mg/dL, left main or 3-vessel disease, clinical instability, or severe inducible ischemia on stress testing if the infarct zone was not akinetic or dyskinetic. Therefore, PCI for an occluded infarct artery in asymptomatic patients with 1- or 2-vessel disease is not recommended.

Primary PCI Strategy Limitations
Access
Primary PCI is available in <25% of acute care hospitals in the United States. Although 80% of the adult population lives within 60 minutes of a hospital with PCI capability and 95% live within 90 minutes, timely access to primary PCI remains a major challenge without regionalized prehospital systems of care to rapidly direct STEMI patients to PCI hospitals. Two emergency medical service model systems have been proposed to address this challenge. The first is the “bypass” model in which patients with a diagnosis of STEMI on a prehospital ECG are transported directly to a PCI center, bypassing a closer hospital without PCI capability. The second is the “transfer” model in which interhospital transfer is accomplished rapidly through carefully established treatment protocols using integrated hospital systems. Another option is to establish primary PCI programs without onsite surgery, but it is unclear whether this option really increases access to primary PCI by skilled operators and experienced teams.

In the US healthcare system, political and economic motivations, in addition to local barriers, influence the development of regionalized STEMI systems. Although the trauma system often is referenced as a model for STEMI care, many gaps remain for regionalizing major trauma care in the United States despite decades of effort. This serves as a powerful reminder of the challenges that will be faced in the implementation of STEMI systems of care within the unstructured US healthcare system. The Mission: Lifeline initiative is a major effort sponsored by the AHA to address these challenges. Its goals are to work within individual communities to address their unique needs, resources, and barriers to implementing STEMI systems of care. The key aspect of this effort is to help stakeholders develop local solutions for their region, an explicit recognition that there is not a one-size-fits-all solution. In fact, substantial barriers that facilities in rural and underserved urban areas face remind us that even if cooperation between hospitals can be improved, fixed resources will still prevent universal access to primary PCI in the near future. There also will be an urgent need for major modifications in reimbursement to ensure that redistribution of patients with suspected acute coronary syndromes will not adversely affect referring hospital revenues or services. For example, a recent proposition for payment reform suggested a single prospective payment that covers care from activation of 9-1-1 to patient transfer, which would allow emergency
medical services, non-PCI hospitals, and PCI hospitals to share gains that would result from coordination of care and would remove inefficiencies inherent in the current reimbursement system.

**Time to Treatment**

It is a biological fact that ischemic time is related to MI size and mortality rates. Although some continue to argue that time delays are unimportant with primary PCI, there is overwhelming evidence to the contrary, and this is acknowledged in the review by Stone. However, the review then embraces 2 reports that suggest that time delays are largely unimportant in primary PCI. The Primary Coronary Angioplasty Versus Thrombolysis (PCAT) analysis is limited by a statistical curiosity in which a U-shaped relationship was found between PCI-related delays and death with fibrinolytic therapy after multivariable adjustments. It is difficult to understand how institutional performance with time to treatment in PCI directly affected outcomes in patients receiving fibrinolytic therapy. The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA) may suffer from the same selection bias that led another Swedish registry to first conclude that drug-eluting stents were dangerous and then 6 months later conclude that they were safe. The RIKS-HIA registry also is limited by the inclusion of only those patients who underwent primary PCI. As many as 10% of patients with STEMI may not undergo primary PCI despite emergency coronary angiography because of unsuitable anatomy or multivessel disease. These high-risk patients may be particularly susceptible to death and other early complications.

We elicited a firestorm of protest from the interventional cardiology community that continues to resonate by publishing a meta-regression analysis of 20 randomized clinical trials that showed an inverse relationship between PCI-related treatment delays (door-to-balloon time minus door-to-needle time) and mortality and establishes PCI as a separate step of PCI versus fibrinolytic therapy. The point of equipoise between reperfusion strategies was 60 minutes, which, when added to a 30-minute door-to-needle time, conveniently adds up to 90 minutes for door-to-balloon time. The data we abstracted were from the same meta-analysis that has been used to show the superiority of primary PCI and included a PCI-related treatment delay of only 40 minutes. Many have suggested that our analysis was used to formulate the ACC/AHA guideline recommendation for the 90-minute door-to-balloon goal or that it established a 90-minute threshold beyond which fibrinolytic therapy would be preferable to primary PCI. Neither concept is correct. In fact, the European Society of Cardiology (ESC) guidelines had been published 9 months earlier with a first-medical-contact-to-balloon goal of 90 minutes, a more rigorous standard, and the ACC/AHA guidelines committee had already agreed to reduce the door-to-balloon goal from 120 minutes in the 1999 update to 90 minutes. We were simply challenging the PCI-centric view that time to treatment did not matter with primary PCI and that transfer delays of up to 3 hours were acceptable as an alternative to immediate fibrinolytic therapy.

The argument about where the point of equipoise between therapies falls is important but misses the larger concept that infarct size and complications from STEMI are greater with time delays. The point of equipoise is shorter in randomized clinical trials than in registries, in trials with alteplase than in trials with streptokinase, and in high-risk patients than in low-risk patients. In addition, any analysis is confounded by whether the patient is treated early after symptom onset when greater myocardial salvage is possible or treated later when infarct artery patency becomes the goal of reperfusion therapy. Most important, the 90-minute door-to-balloon time is a systems goal to drive quality improvement programs, not a “line in the sand” to choose a reperfusion strategy for an individual patient. Although we interventional cardiologists like to think that we are the reason for better outcomes compared with fibrinolytic therapy, much of the advantage for the patient also may be due to receiving specialist care instead of generalist care and being treated in centers with better nursing staffs, more ancillary services, and greater compliance with delivery of evidence-based therapies, including cardiac rehabilitation programs.

**Logistics of Care**

The ACC/AHA guidelines state that STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact as a systems goal, not an individual patient goal. The best outcomes are achieved by offering this strategy 24 hours per day, 7 days per week. The systems goal of the D2B Alliance campaign exceeded these recommendations in nontransfer patients by requiring at least 75% of patients to be treated within 90 minutes of hospital presentation. The D2B Alliance campaign promotes the use of recent evidence-based strategies to reduce needless delays that are inherent in many PCI hospitals in the United States. The 75% goal recognized that some patients have clinically relevant non–system-based delays that do not represent quality-of-care issues. These include patient variables (uncertainty about diagnosis, evaluation and treatment of other life-threatening conditions, obtaining informed consent, etc) that delay the patient’s arrival in the cardiac catheterization laboratory or anatomic challenges (issues of arterial, coronary, or lesion access) that prolong the PCI procedure. In the absence of such circumstances, however, primary PCI should be achievable within this time frame. Indeed, many PCI hospitals with refined systems are now approaching median door-to-balloon times of 60 to 70 minutes and showing concomitant improvement in mortality rates. The new focus for primary PCI is to move toward reducing time from first medical contact because extra time may be taken to transport patients to a PCI center in regionalization strategies.

Because of access issues and the critical importance of time to treatment, fibrinolytic therapy may be generally preferred in hospital systems that do not have the capability of meeting the time goal for primary PCI. Transfer protocols should be in place for arranging rescue PCI when clinically indicated or transferring lytic-ineligible patients. Several examples of regional systems now in use in Europe and the...
United States have incorporated these strategies into a comprehensive system for managing STEMI. In the Vienna STEMI Registry, a citywide program was instituted that was based largely on the implementation of the ACC/AHA and ESC STEMI guidelines and was led by 5 high-volume interventional cardiology departments. The system improved not only access to primary PCI but also the appropriate use of fibrinolytic therapy in eligible patients in whom mortality rates equivalent to those with primary PCI were achieved. As a consequence, overall in-hospital mortality rates in STEMI decreased by 40% over a 2-year period. The Mayo Clinic STEMI Protocol instituted a similar strategy across 28 referring hospitals in the region and found marked improvements in time to treatment. Again, a strategy that targeted the judicious use of fibrinolytic therapy appeared to be safe and effective.

**Risk Stratification and Patient Subgroups**

A strong argument can be made against the emergency transfer of all patients with STEMI to a PCI regional center. Studies evaluating patient risk clearly demonstrate that the mortality advantage of primary PCI over fibrinolytic therapy is limited to high-risk patients. There is no difference in death between treatments in patients with nonanterior MI, age <70 years, or hemodynamic stability. In contrast, patients with cardiogenic shock, congestive heart failure, tachycardia, hypotension, or anterior STEMI fare better with primary PCI. In the Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2), the advantage for primary PCI was limited to the 25% of patients with TIMI risk scores ≥5. In the still-unpublished SENIOR-PAMI trial, there was no significant difference between primary PCI and fibrinolytic therapy in death and disabling stroke in patients ≥70 years of age, but there was a trend toward lower reinfarction with primary PCI. These studies suggest that STEMI systems of care that target use of primary PCI to a minority of the ∼400 000 patients with STEMI each year in the United States may improve patient outcomes to the same extent without requiring a fundamental restructuring of the healthcare system.

**Myocardial Salvage**

Claims that primary PCI produces smaller infarct size and greater myocardial salvage than fibrinolytic therapy fail to recognize that infarct size reduction from early, successful reperfusion therapy is different from myocardial salvage as measured by single-photon emission computed tomography (SPECT) 1 to 2 weeks after STEMI. Infarct size reduction from acute therapy would best be measured by the difference in cumulative cardiac enzyme release, as was done earlier with fibrinolytic therapy. In the Munich studies on myocardial salvage, it appears that few patients were crossed over to early revascularization, so the late SPECT measurement was influenced by infarct artery reocclusion and reinfarction. Importantly, no data on biomarker levels or left ventricular ejection fraction are included in the Munich reports. We know of no evidence that suggests that primary PCI is associated with smaller initial infarct size or better preservation of left ventricular ejection fraction than fibrinolytic therapy, presumably because of delays in reperfusion time with primary PCI. It would be interesting to reassess this question in the current era in which symptom-onset-to-balloon times are at least an hour shorter than in previous studies because of the increased emphasis focused on time to treatment.

**Fibrinolytic Therapy Versus a Fibrinolytic Strategy**

The benefit of primary PCI over fibrinolytic therapy is likely to be smaller in real-world settings than in randomized trials. Patients in the trials summarized by Keeley et al were selected for randomization, delays to PCI were short, and performance of PCI was presumably excellent. Comparative results with less experienced centers or operators are less impressive and suggest similar in-hospital mortality rates between treatments at low-volume PCI hospitals. Differences between treatments also were magnified by the inclusion of studies with streptokinase compared with alteplase or duteplase as the fibrinolytic agent. Moreover, bleeding and intracerebral hemorrhage rates may have been increased by higher anticoagulation targets than we now use, and reinfarction rates may have been higher than in the current era in which clopidogrel and enoxaparin have shown utility with fibrinolytic therapy. Most important, fibrinolytic therapy was tested as monotherapy, with crossover to rescue PCI or the early invasive strategy discouraged by most protocols. In clinical practice, as measured by observational reports, the emergency invasive strategy is used in 33% to 44% of patients, and the elective invasive strategy is used in 74% to 90%. In large national registries including a broader spectrum of patients, time delays, interventional cardiologists, and hospitals, there has been no difference in the rates of death between primary PCI and a fibrinolytic strategy that includes fibrinolytic therapy and rescue or elective PCI. In fact, the best treatment strategy has been prehospital fibrinolytic therapy, presumably because half of the patients contact theprehospital system within 2 hours of symptom onset.

**Time for a New Reperfusion Paradigm**

The concept that primary PCI is needed for all patients is not evidence based and is currently impractical given geographical limitations and the variability of hospital system resources. Because a reduction in hospital death rates between strategies has yet to be reliably demonstrated in real-world settings and absent early differences in infarct size and left ventricular function, it is more likely that the 30-day benefit seen with primary PCI in the randomized clinical trials is due to failure to provide rescue PCI to fibrinolytic failures and early PCI to those after successful fibrinolysis to prevent infarct artery reocclusion (Figure). However, primary PCI has several important advantages that extend beyond its impact on death. These include the ability to extend reperfusion therapy to the 30% of patients with STEMI who are frequently denied it and the facilitation of early hospital discharge. Whether these advantages are worth the possible restructuring that will be required to establish STEMI systems of care is an important question that individual communities will need to assess.
mize the benefit of sustained infarct artery patency.\textsuperscript{3,37} Next-day transfer for coronary angiography and same-day return of the patient to the referring hospital could decrease some of the logistical problems of transferring all patients emergently to PCI centers.

The 25-year debate about primary PCI or fibrinolytic superiority is no longer useful. The argument that longer reperfusion delays for PCI are acceptable, usually made by interventional cardiologists or hospitals that stand to gain by increased procedure volumes, will not maximize the potential patient benefit from earlier reperfusion therapy. Rather, it is time to focus on a new reperfusion paradigm that is based on shortening the overall time period from symptom onset to initiation of reperfusion therapy. This will require increasing awareness of symptoms among vulnerable populations, improving access to the healthcare system, and restructuring of the emergency medical system to improve the coordination of care between hospitals.\textsuperscript{67} Hospitals with PCI capability, to reproduce the results from randomized clinical trials, will need to perform primary PCI as rapidly as possible and strive to offer 24-hour service. Substantial gains have already been made in this area as a result of efforts such as the ACC D2B Alliance. Hospitals without primary PCI capability will need to develop reperfusion therapy algorithms that may include fibrinolytic therapy and will provide early access to coronary angiography, perhaps for all patients. The AHA Mission: Lifeline initiative is an excellent step in that direction.

Thus, the conclusion by Stone\textsuperscript{1} that “mortality could be reduced and event-free survival enhanced by withholding fibrinolytic therapy for the performance of primary PCI in most patients” is off target. Instead of supporting primary PCI for patients who present >3 hours after symptom onset, the emphasis should be on treating a greater percentage of patients with reperfusion therapy within 3 hours of symptom onset, preferably within 2 hours.\textsuperscript{28,29,64} This requires increased educational efforts directed at early symptom recognition, early activation of the emergency medical system, and performance of prehospital ECGs. This may increase the number of patients treated with fibrinolytic therapy, with the small attendant risk for intracerebral hemorrhage, but the net clinical benefit would favor treatment because of the reduction in infarct size and the rates of cardiogenic shock and death associated with early reperfusion therapy.\textsuperscript{28,29,64} To amplify the potential benefit of early fibrinolytic therapy, coronary angiography should be strongly considered as soon as necessary and clinically feasible so that PCI could be performed both to decrease the complications of persistent infarct artery occlusion\textsuperscript{12,13} or reocclusion,\textsuperscript{65,66} and to maximize the benefit of sustained infarct artery patency.\textsuperscript{3,37}

References


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