Accelerating Time to Reperfusion in Acute Myocardial Infarction: Prehospital and Emergency Department Strategies, Systems of Care, and Pharmacologic Interventions

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Although primary percutaneous coronary intervention has emerged as the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI), it is available only in a minority of US hospitals. The fundamental problem is that there is presently no organized, uniform, national STEMI triage and treatment system that is comparable to the well-developed, highly successful system in the United States that directs major trauma victims to verified trauma centers. This article reviews prehospital and emergency department triage strategies, systems, and pharmacologic interventions for patients with STEMI that can help shorten the time to reperfusion in these patients.

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The benefits of rapid, expertly performed, primary percutaneous coronary intervention (PCI) over fibrinolysis for patients with ST-segment elevation myocardial infarction (STEMI) are no longer debatable. Keeley and colleagues' meta-analysis[1] of 23 randomized clinical trials showed that primary PCI is superior to fibrinolysis at reducing overall short-term mortality (7% vs

9%; $P = .0002$), nonfatal reinfarction (3% vs 7%; $P < .0001$), stroke (1% vs 2%; $P = .0004$), and the combined endpoint of death, nonfatal reinfarction, and stroke (8% vs 14%; $P < .0001$). The results seen with primary PCI remain superior during long-term follow-up and are independent of both the type of fibrinolytic used as comparator and whether or not the patient is transferred for primary PCI.

Although the relationship between time delay from arrival in the hospital emergency department (ED) to fibrinolytic treatment and increasing mortality is well established,[2] a similar relationship for primary PCI treatment has only recently been proven, after a period of debate and uncertainty prompted by conflicting study results. De Luca and colleagues[3] assessed the association between ischemic time and 1-year mortality in 1791 primary PCI–treated STEMI patients. After adjustment for age, gender, diabetes, and previous revascularization, they showed that each 30 minutes of primary PCI treatment delay is associated with a 7.5% (95% confidence interval [CI] 1.008-1.15, $P = .041$) relative increase in 1-year mortality.

The purpose of this article is to review prehospital and ED triage strategies, systems, and pharmacologic interventions for patients with STEMI that can help shorten the time to reperfusion in these patients.

STEMI Systems of Care for Decreasing the Time to Reperfusion

The fundamental problem in acute care of patients with STEMI is the lack of an organized, uniform, national STEMI triage and treatment system that is comparable to the well-developed, highly successful system that directs major trauma victims to verified trauma centers in the United States. Since the majority of US hospitals do not have primary PCI capability, many communities are currently struggling to determine whether they should direct emergency medical services (EMS)–transported patients with prehospital 12-lead electrocardiogram (ECG)–identified STEMI to only primary PCI facilities, bypassing non–primary PCI hospitals when necessary. Unfortunately, the majority of patients with STEMI do not use the 911 ambulance system for transport to the hospital, the national paramedic training curriculum considers 12-lead ECG training to be an "enhanced" rather than "core" skill, and not all EMS ambulances currently have 12-lead ECG capability.[4] Many US hospitals continue to use fibrinolysis as their primary reperfusion strategy, with transfer of the patient to an interventional facility when needed for rescue. Other hospitals transfer patients more regularly for primary PCI, but even the most recently published National Registry of Myocardial Infarction data on 4278 patients transferred to 419 hospitals for primary PCI show a median initial hospital door-to-balloon time of 180 minutes, with only 4.2% of patients receiving reperfusion in < 90 minutes, the benchmark recommended by national quality guidelines.[5]

need to have systems in place to avoid unnecessary delays. We must continue to educate the public on the signs and symptoms of myocardial infarction (MI), and reinforce the National Heart Attack Alert Program and American Heart Association (AHA) message to "Call 911, Call Fast."[6]

The AHA's Acute MI Advisory Working Group recently released recommendations on how to increase the number of STEMI patients who have timely access to primary PCI in the United States.[7] The group commissioned PricewaterhouseCoopers to conduct national market research, interviewing a wide variety of key stakeholders—including patients, physicians, nurses, EMS representatives, community hospitals and primary PCI facilities, payers, and evaluation/outcomes organizations such as the Agency for Healthcare Research and Quality, the Food and Drug Administration, and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)—to determine the desirability, feasibility, and potential effectiveness of establishing regional systems and/or centers of care for STEMI patients, with a focus on whether and how this might improve patients' access to quality care and outcomes. The researchers found that key stakeholders would support a national primary

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How are we, as a nation, going to bring order out of this chaos? The problem needs to be solved at 2 levels: the community and the hospital. The community needs to be organized into a system of care that directs STEMI patients quickly and efficiently to primary PCI centers whenever possible, and all hospitals, whether primary PCI–capable or not, PCI certification program with the understanding that some non–primary PCI hospitals would experience a modest decline in revenue. Based on these findings, the AHA hosted a national stakeholder meeting in Boston, MA, March 30 to April 1, 2006, to continue development of a more detailed plan for an ideal national system of STEMI patient care.

Model STEMI Community Care Systems

Although many communities are currently developing organized STEMI care plans, 3 sites—a major city, a large region of a state, and an entire state—are well on their way to completing impressive, mature STEMI systems based on the trauma care system model.

On January 1, 2003, Boston was the first large urban city in the United States to implement a comprehensive system of care in which STEMI patients, identified by paramedics using prehospital 12-lead ECGs, are transported only to designated centers that agree to use primary PCI as a dedicated reperfusion strategy for virtually all patients, except in rare cases where it is clinically not warranted.[8] Participating primary PCI centers must agree to collect and submit performance-measure data to a Central Data Coordinating Center on all EMS- and non-EMS-transported STEMI patients. System oversight is provided by a Steering Committee with representatives from 9 area hospitals and Boston EMS, which developed its performance indicators and minimum standards based on nationally accepted guidelines. A central Data Coordinating Center at Tufts–New England Medical Center receives and tabulates data from EMS and area hospitals, providing aggregated data reports, with receiving hospitals designated A, B, C, D, and so forth, rather than by name. The reports are reviewed by an independent Data and Safety Monitoring Board (DSMB) composed of highly respected cardiologists and a statistician. Any hospital that does not meet preestablished quality-treatment, time-to-treatment, and outcome goals for 2 successive 6-month periods, after discussion between the hospital and DSMB and review by the Steering Committee, is excluded from receiving EMS-transported STEMI patients for the next 6-month period.

From March 2003 through May 2005, 448 STEMI patients were transferred from 31 community hospitals by paramedic-staffed ambulance (n = 149) or paramedic/critical care nurse–staffed helicopter (n = 299) to the Minneapolis Heart Institute in Minneapolis, MN, for primary PCI. A standardized protocol and accompanying checklists were developed based on national guidelines. Community hospitals were required to transfer all patients with STEMI or with new left bundle branch block to the regional interventional center within 12 hours of symptom onset. A "Level 1 MI protocol" was developed and used to specify the sequence of events, diagnostic tests, and treatments. Patients are preregistered by admitting personnel before arrival, using a demographic form faxed from the referring hospital. On arrival at the primary PCI center, patients are admitted directly to the cardiac catheterization laboratory, bypassing the ED except in rare circumstances such as when 2 STEMI patients arrive simultaneously. Prompt verbal and written feedback is provided to the referring hospital physician and nursing staff, and the time intervals, clinical and angiographic data, and clinical outcomes are entered into a database (including 1-month and 1-year follow-up phone calls). Quarterly time and outcome summary reports meeting JCAHO requirements are sent to each community hospital.

Patient treatment times and outcomes have been superb with this regional STEMI care system. No STEMI patients were excluded from transfer, including those with cardiogenic shock (13.7%) and cardiac arrest (9.9%), and elderly patients (17% > 80 years of age). No patient died during transport. The median total door-to-balloon time was reduced from > 3 hours before implementation of the regional system to 97 minutes after implementation for 11 participating hospitals located within 70 miles (Zone 1).[9,10] The median total door-to-balloon time was 117 minutes using a facilitated PCI protocol in 17 participating hospitals located within 210 miles (Zone 2) of the interventional center. The improvements in times to treatment were accompanied by low 30-day mortality rates of 4.3% in Zone 1 and 3.4% in Zone 2.

The common denominator of these 2 models is that they are based on a community system of care rather than centered on a single hospital.

A third model is the Reperfusion of Acute Myocardial Infarction in Carolina Emergency Departments (RACE) project in North Carolina, which is a collaborative effort to increase the rate and speed of coronary reperfusion through systematic changes in emergency care. The project is based on the collaborative efforts of EMS personnel, physicians, nurses, administrators, and payers from 5 regions and 68 hospitals throughout the state. The recommendations of this project are based on established national guidelines, published data, and the knowledge and experience of numerous individuals specializing in STEMI patient care. Detailed information about the program, including transfer criteria, protocols, training materials, and educational posters, is available on the North Carolina Chapter of the American College of Cardiology (ACC) website (www.nccacc.org/race.html).

Prehospital and Emergency Department Strategies

What changes in prehospital and ED practice need to occur to significantly

speed the time to reperfusion for many more STEMI patients? First and foremost, prehospital 12-lead ECG equipment needs to become required for paramedics because the availability and use of this equipment results in earlier identification and treatment of STEMI patients.[11-13] Unfortunately, the majority of EMS ambulances in the United States are staffed at only the basic life-support level and do not have prehospital ECG capability. However, a recent national survey reported that 67% of EMS systems in the 200 largest US cities now have some prehospital ECG equipment and capability, although it is likely that less populous cities and regions are less developed along these lines.[14]

Most prehospital ECG devices currently in use throughout the United States are optional modules that can be incorporated into the paramedic's cardiac monitor/defibrillator rather than stand-alone ECG machines. Such integrated devices now cost $9,000 to $25,000, but the price per unit will most likely decrease as use of this technology becomes more standard. A variety of respected national organizations (including the AHA, ACC, National Association of EMS Physicians, and National Heart Attack Alert Program) and the ACC/AHA STEMI guidelines strongly encourage EMS organizations to implement prehospital 12-lead ECG programs with appropriate medical oversight.[4] Finally, all physicians, especially those caring for patients at high risk or with known coronary artery disease, should educate patients and their families on the signs and symptoms of a heart attack, encouraging them to adopt a "Call 911, Call Fast" plan.

Hospitals should implement protocols and procedures to ensure that both ambulatory and ambulance-transported patients arriving at the ED with symptoms suspicious for STEMI or other acute coronary syndrome receive prompt evaluation, including performance, and physician interpretation, of a 12-lead ECG within 10 minutes of ED arrival. Interventional facilities with primary PCI capability should implement a "cardiac alert" or "STEMI team" activation protocol that empowers emergency physicians to alert and activate the interventional team and laboratory immediately after a 12-lead ECG confirms that a STEMI is present in an ED patient or in a patient being transported to the ED by an EMS unit that has performed and/or transmitted a diagnostic-quality prehospital 12-lead ECG. Jacoby and colleagues[15] showed that a strategy mandating activation of the cardiac catheterization laboratory by the emergency physician without prior cardiology consultation for STEMI reduced door-to-balloon time from 118 to 89 minutes (P = .039) in an active community hospital in Bethlehem, PA.

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EMS-transported patients with prehospital 12-lead ECG–confirmed STEMI arriving at primary PCI centers should only stop in the ED, if at all, to receive interventions and pharmacologic therapies that are absolutely necessary and add value to the final outcome. A multidisciplinary team composed of emergency physicians, cardiologists, nurses, pharmacists, and other appropriate personnel should oversee a data-driven process of performance improvement that provides feedback to all participants and further modifies the system based on objective data.

As an example, a retrospective chart review was performed for 95 consecutive STEMI patients who underwent primary PCI at a Charleston, WV, area medical center before and after implementing a STEMI performance improvement program. The program centered on 3 hospital care improvement strategies: (1) a fast-track primary PCI protocol that empowered emergency physicians to activate a multipage "cardiac alert" to the on-call cardiologist, the cardiac catheterization laboratory coordinator, ECG, radiology, and laboratory technicians, and the ED registration clerk; (2) individualized quarterly feedback to cardiologists on treatment times, benchmarked against others in the group; and (3) increased personnel staffing in the cardiac catheterization laboratory to make the service available in-house 24 hours a day, 7 days a week, which cost approximately $120,000 a year.[16] The results of the program were dramatic. Door-to-balloon times were reduced significantly from 134 ± 53 minutes before to 94 ± 37 minutes after implementation of the STEMI hospital care improvement strategies.

Table 1 shows a number of prehospital and hospital interventions that can help to accelerate the time to reperfusion in patients with STEMI.

Prehospital and ED Pharmacologic Interventions

Although the 2004 ACC/AHA STEMI Guidelines provide some guidance on which pharmacologic interventions should be given to STEMI patients during EMS transport and/or

Table 1
Prehospital and Hospital Interventions That Can Shorten the Time to Reperfusion in Patients With STEMI

Prehospital	Hospital
• Prehospital 12-lead ECGs	• Standardized STEMI protocol
• Community STEMI treatment system with primary PCI centers	• ECG < 10 min after arrival at ED
• Destination protocols and written transfer agreements as part of a regional transfer program	• STEMI alert system with a STEMI team
• Performance improvement program	• Preregistration of STEMI patients
	• Transfer protocols
	• Bypass the ED at PCI centers to go straight to the cath lab
	• Multidisciplinary team oversight
	• Performance improvement program

STEMI, ST-segment elevation myocardial infarction; ECG, electrocardiogram; PCI, percutaneous coronary intervention; ED, emergency department.

in the ED before primary PCI,[17] more recent publications, clinical trial results, and ongoing trials are helping to better define more optimal strategies. Virtually all prehospital and ED protocols include standing orders (unless contraindicated) for administration of oxygen, morphine sulfate, and/or nitroglycerin for pain control, aspirin, heparin, and beta-blocker.

Aspirin and Heparin

The ACC/AHA STEMI Guidelines express concern that advising the public to take an aspirin in response to possible STEMI symptoms may be associated with patients' delay in calling EMS, as was seen in the National Institutes of Health–sponsored REACT (Rapid Early Action for Coronary Treatment) study.[18] Instead, the Guidelines suggest that patients should focus on calling 911, which activates the EMS system, from which they may receive instructions from emergency medical dispatchers to chew aspirin (162 to 325 mg) while emergency personnel are en route, or emergency personnel can give an aspirin while transporting the patient to the hospital.[17] Alternatively, patients can be given an aspirin soon after arrival at the hospital.

Does earlier administration of aspirin make a difference? Most paramedic protocols in the United States currently include a dose of chewable aspirin (unless contraindicated) while en route to the hospital, even though published data on the time dependency of aspirin therapy are inconclusive. ISIS-2 (Second International Study of Infarct Survival) was the first large, international, randomized clinical trial to document mortality reduction with aspirin alone or in combination with fibrinolysis (streptokinase), but there was no evidence that the beneficial effects of aspirin were time dependent.[19] More recently, Freimark and colleagues[20] studied 1200 fibrinolytic-treated STEMI patients and found that those who received aspirin early (before fibrinolytic drug administration, n = 364) versus late (after fibrinolytic drug administration, n = 836) had a lower mortality at 7 days (2.5% vs 6.0%; $P = .01$), 30 days (3.3% vs 7.3%; $P = .008$), and 1 year (5.0% vs 10.6%; $P = .002$). Median time from symptom onset to initiation of aspirin treatment was significantly shorter in early versus late users (1.6 vs 3.5 hours; $P < .001$). There were no significant differences between the 2 groups with respect to baseline clinical characteristics.

One possible explanation for the difference between these 2 studies is that ISIS-2 did not include use of heparin,[19] whereas Freimark and colleagues' study randomized patients to either heparin or argatroban, a direct thrombin inhibitor.[20] Theoretically, use of an antithrombin or direct thrombin inhibitor could be more effective early after MI onset because the thrombus is less organized. On this point, Zijlstra and coworkers[21] studied the angiographic data and 30-day clinical outcome of 1702 STEMI patients treated with primary PCI; 860 received aspirin and heparin before transport to the interventional hospital, and 842 received aspirin and heparin after arrival at the interventional hospital. TIMI (Thrombolysis in Myocardial Infarction) grade 2 or 3 flow in the infarct-related artery was higher in

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the prehospital- than in the hospital-treated group (31% vs 20%; relative risk [RR] 0.65, 95% CI 0.55-0.78, $P <$ .001). Patients with TIMI-2 or -3 flow on the initial angiogram had a higher PCI success rate (94% vs 89%; $P <$ .001), a smaller enzymatic infarct size, a higher left ventricular ejection fraction, and a lower 30-day mortality (1.6% vs 3.4%; $P =$ .04). The primary limitation of the study was that it was not randomized, although the results are probably valid since the authors were able to demonstrate no interaction between treatment effect and age, gender, MI location, ischemic time, or the presence of multivessel disease. Thus, although it is not possible to determine whether the apparent benefit from earlier combination aspirin/heparin treatment is due to the aspirin, heparin, or both, these findings raise the question of whether heparin, which is relatively inexpensive and easy to administer (particularly in its low molecular weight form), should be added to prehospital EMS protocols for use in 12-lead ECG–confirmed STEMI patients. If so, one minor practical issue is that paramedics are typically not trained to perform rectal examinations to check for occult blood, and it is not always possible to obtain adequate privacy until the patient is loaded into the ambulance.

Facilitated PCI Using Half- or Full-Dose Fibrinolytic

A combined strategy of immediate fibrinolysis in the ambulance or ED followed by primary PCI could theoretically provide some early reperfusion, with subsequent mechanical intervention to ensure complete, sustained reperfusion. Of the 8 clinical trials that compared fibrinolysis with facilitated PCI, only the 2 most recent studies (GRACIA-1 and CAPITAL AMI) deserve mention, since the others did not involve "modern" PCI with its expanded arsenal of stents and glycoprotein (GP) IIb/IIIa inhibitors.[22] GRACIA-1 (Grupo de Analisis de la Cardiopatia Isquimica Aguda), which randomized 500 STEMI patients who had received tPA (tenecteplase) to PCI within 24 hours or to a conservative ischemia-guided approach, showed a 1-year reduction in death/reinfarction/revascularization from 21% to 9% in the facilitated PCI group.[23] CAPITAL AMI (Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction) enrolled 170 patients and showed a reduction in recurrent unstable ischemia at 6 months, from 20.7% in a tenecteplase-only group to 8.1% in the facilitated PCI group ($P =$ .03).[24] Thus, there seems to be some modest benefit of facilitated PCI over fibrinolysis alone in the era of modern angioplasty.

Results of trials comparing facilitated PCI preceded by full- or half-dose fibrinolysis with primary PCI have been far less favorable. The largest and most recent ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment for Acute Myocardial Infarction) trial randomized patients to PCI with or without full-dose tenecteplase, with a primary endpoint of 90-day death, cardiogenic shock, or congestive heart failure. The trial was stopped by the DSMB because of the worse outcomes observed in the facilitated PCI arm after investigators had randomized only 1667 patients. Patients receiving facilitated PCI had significantly higher rates of recurrent MI (6% vs 4%; $P =$ .0279), repeat target vessel revascularization (TVR) (7% vs 3%; $P =$ .0041), stroke (1.8% vs 0%; $P <$ .0001), and the combined endpoint of death, congestive heart failure, or shock (18% vs 13%; RR 1.3, 95% CI 1.11-1.74, $P =$ .0045). Pending results of the ongoing FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial (see below),[25] which is randomizing 3000 primary PCI STEMI patients to abciximab plus reduced-dose reteplase, abciximab alone, or placebo, Borden and Faxon[22] concluded in a recent review on facilitated PCI that "the ASSENT-4 trial raises serious concerns about continued use of facilitated PCI."

Keeley and colleagues[26] recently completed a quantitative review of randomized clinical trials comparing primary and facilitated PCI in STEMI patients (Figure 1). The facilitated approach more than doubled the number of patients with initial TIMI-3 flow compared with the primary approach (37% vs 15%; OR 3.18, 95% CI 2.22-4.55). Final rates did not differ (89% vs 88%; OR 1.19, 95% CI 0.86-1.64). Significantly more patients assigned to the facilitated approach than to the primary approach died (5% vs 3%; OR 1.38, 95% CI 1.01-1.87), had higher nonfatal reinfarction rates (3% vs 2%; OR 1.71, 95% CI 1.16-2.51), and had higher urgent TVR rates (4% vs 1%; OR 2.39, 95% CI 1.23-4.66). The increased rates of adverse events seen with the facilitated approach were mainly in fibrinolytic-therapy regimens rather than those involving platelet GP IIb/IIIa inhibitors. Facilitated intervention (all studies combined) was associated with higher rates of major bleeding than primary intervention (7% vs 5%; OR 1.51, 95% CI 1.10-2.08), hemorrhagic stroke (0.7% vs 0.1%; $P =$ .0014), and total stroke (1.1% vs 0.3%; $P =$ .0008). The authors concluded that facilitated PCI offers no benefit over primary PCI in STEMI patients and should not be used outside randomized controlled trials. They also believe that fibrinolytic-based facilitated regimens should be avoided.

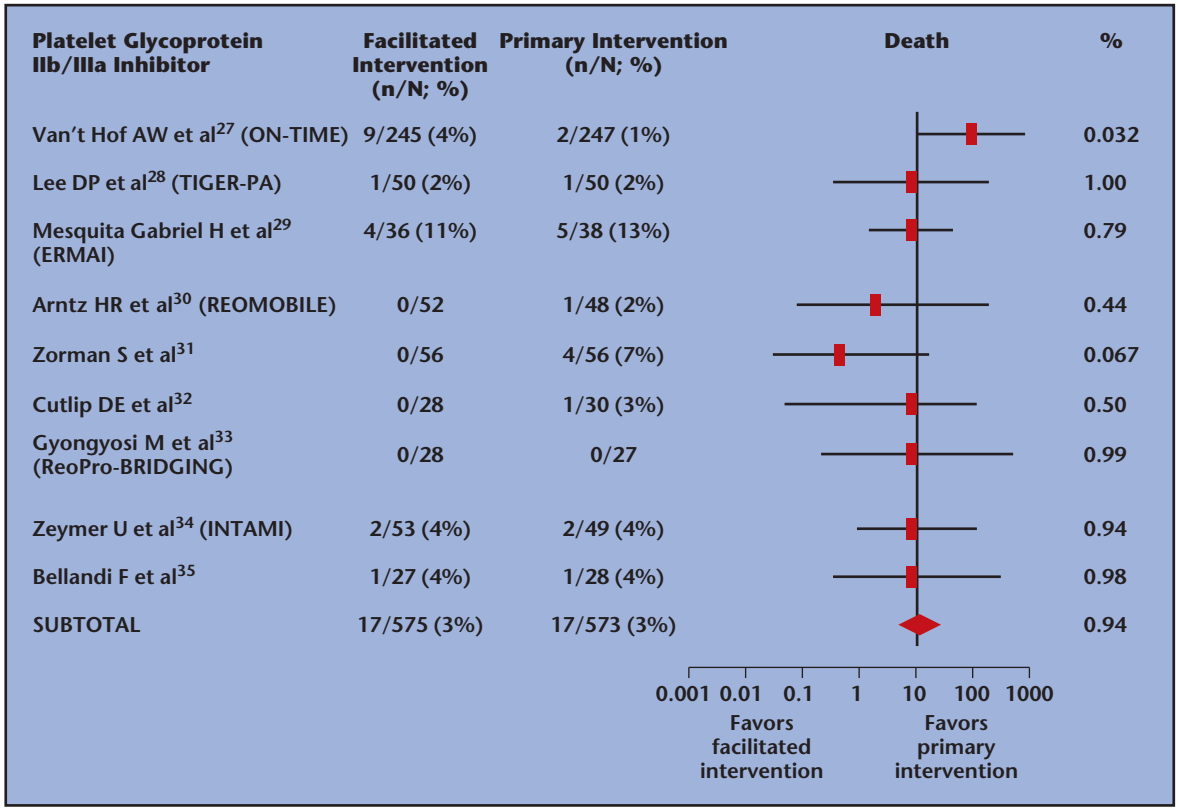


Figure 1. *Facilitated versus primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). Adapted with permission from Keeley EC et al.*[26]

Platelet GP IIb/IIIa Inhibitor Therapy

The benefit of platelet GP IIb/IIIa inhibitor therapy in STEMI patients has recently been clarified, particularly for abciximab, which has been studied more than any other agent in its class. De Luca and colleagues[36] performed a meta-analysis of 11 randomized clinical trials involving 27,115 STEMI patients randomized to abciximab or control. Eight of the trials used PCI as the primary reperfusion strategy. When compared with control therapy, abciximab was associated with a significant reduction in 30-day mortality (2.4% vs 3.4%; $P = .047$) and 6- to 12-month mortality (4.4% vs 6.2%; $P = .01$) in patients undergoing primary PCI (Figures 2 and 3), but not in those treated with fibrinolysis or in all trials combined. Abciximab was associated with a significant reduction in 30-day reinfarction in all trials combined (2.1% vs 3.3%; $P < .001$), in primary PCI (1.0% vs 1.9%; $P = .03$), and in fibrinolysis trials (2.3% vs 3.6%; $P < .001$). Abciximab did not result in an increased risk of intracranial bleeding (0.61% vs 0.62%; $P = .62$), but it was associated with an increased risk of major bleeding complications when combined with fibrinolysis (5.2% vs 3.1%; $P < .001$)

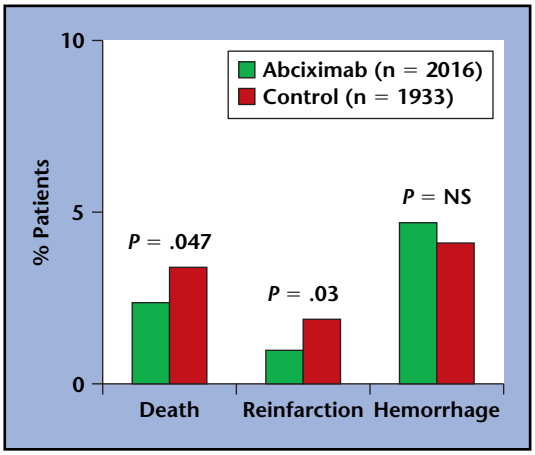


Figure 2. *Short-term (30-day) results from a meta-analysis of trials comparing abciximab with control therapy in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Adapted with permission from De Luca G et al.*[36] *JAMA, April 13, 2005, 293;1762,*

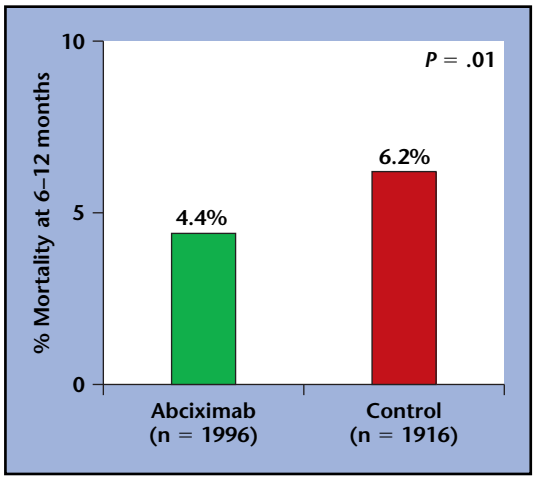


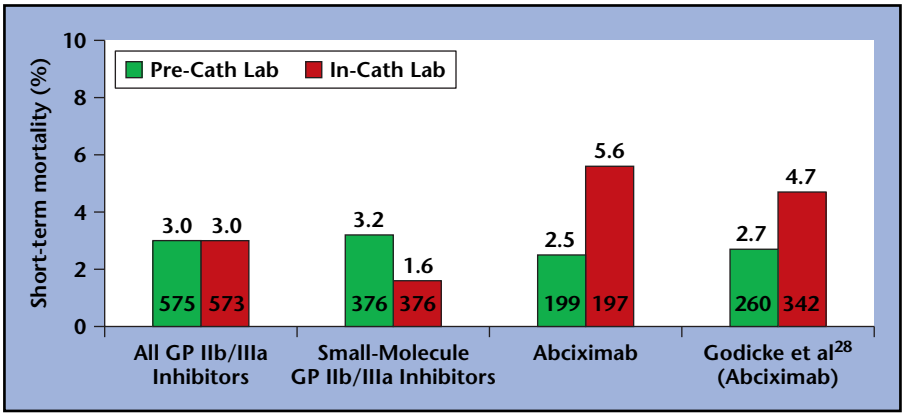
Figure 3. *Long-term (6- to 12-month) mortality results from meta-analysis of trials comparing abciximab with control therapy in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Adapted with permission from De Luca G et al.[36] JAMA, April 13, 2005, 293;1762,* Copyright © 2005 American Medical Association. *All Rights Reserved.*

but not with primary PCI (4.7% vs 4.1%; *P* = .36).

In their pooled analysis of all published trials, Keeley and colleagues[26] stratified their analysis of facilitated PCI into platelet GP IIb/IIIa inhibitors only, fibrinolytics only, and reduced-dose fibrinolytics in combination with platelet GP IIb/IIIa inhibitors. Unfortunately, the authors "lumped" all GP IIb/IIIa inhibitors together and did not separate small-molecule GP IIb/IIIa inhibitors and abciximab. If one does so (Figure 4), a directionally divergent difference in mortality is evident for patients receiving abciximab "upstream" en route to primary PCI (vs administration in the cardiac catheterization laboratory) and patients receiving small-molecule inhibitors "upstream" or in the cardiac catheterization laboratory. Small-molecule inhibitor–treated patients have an ~50% increase in mortality if treated upstream, whereas abciximab-treated patients have an ~50% decrease in mortality.

The results of Keeley and coauthors' meta-analysis[26] are strongly supported by the pooled analysis of Godicke and colleagues[37] (also shown in Figure 4), which analyzed 602 patients from 6 trials in which patients were given either early abciximab in the ambulance or ED before undergoing planned primary PCI, or "late" abciximab in the cardiac catheterization laboratory at the time of primary PCI. This analysis showed an ~50% reduction in mortality with "upstream" abciximab administration. Bellandi and coworkers[38-40] conducted a prospective randomized trial to evaluate the impact of early abciximab administration on angiographic findings, myocardial salvage, and left ventricular function (Figures 5 and 6). Fifty-five consecutive STEMI patients with no prior history of MI who underwent primary PCI were randomized to abciximab administration either in the ED (early group, n = 27) or in the catheterization laboratory after coronary angiography (late group, n = 28). The primary outcome measures were initial TIMI grade flow, corrected TIMI frame count, myocardial blush grade, salvage index, and left ventricular function recovery as assessed by serial scintigraphic scans performed at admission and at 7 days and 1 month after PCI. Angiographic analysis showed a significant difference in initial TIMI-3 flow, corrected TIMI frame count, and myocardial blush grade favoring the early abciximab group. Myocardial salvage index and left ventricular function recovery were significantly greater in the early group (*P* = .007 and .043, respectively). The authors concluded that early abciximab administration improves myocardial salvage and left ventricular function recovery, probably by starting early recanalization of the infarct-related artery in primary PCI–treated STEMI patients. These findings support the current ACC/AHA Guideline II-A indication for abciximab[41], and for

Figure 4. *Facilitated percutaneous coronary intervention (PCI) with glycoprotein (GP) IIb/IIIa inhibitors. Data from Keeley et al.[26] and (where indicated) adapted with permission from Godicke J et al.[37]*



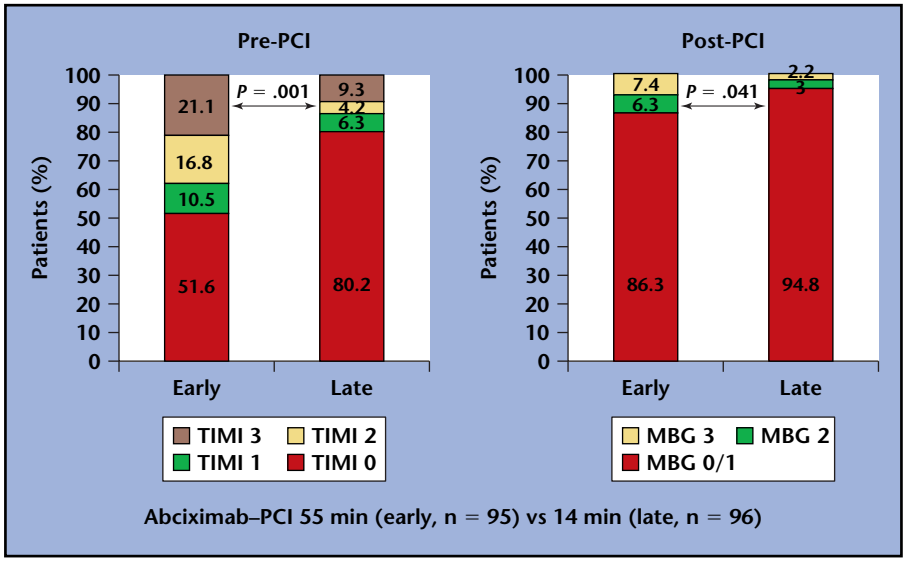


Figure 5. *TIMI (Thrombolysis in Myocardial Infarction) flow and perfusion grade by timing of abciximab administration: results from the RELAX-AMI study. PCI, percutaneous coronary intervention; MBG, myocardial blush grade. Data adapted with permission from Bellandi F et al.*[38]

abciximab to be started "as soon as possible prior to planned PCI."

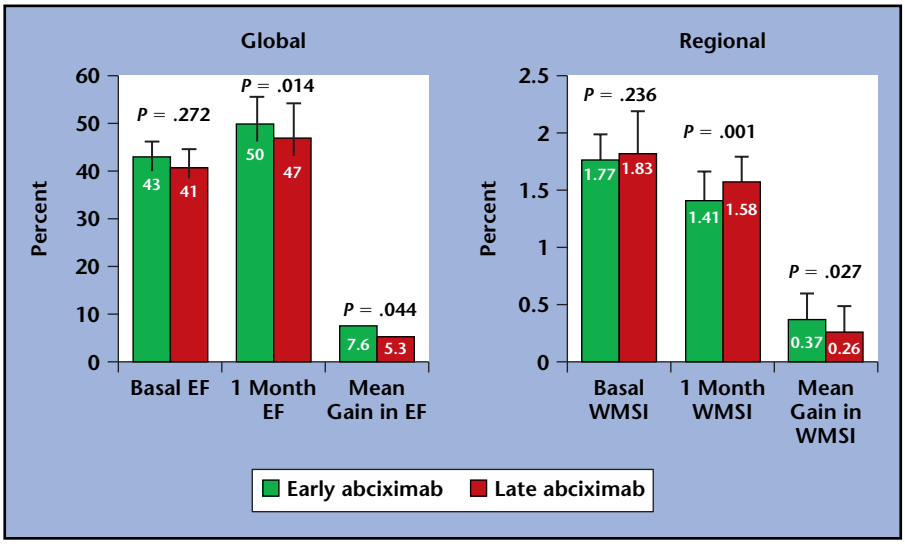
Finally, the FINESSE study will test whether PCI facilitated by early ED administration of abciximab alone or combined with reduced-dose reteplase is superior to primary PCI with abciximab just prior to the procedure.[25] The primary endpoint is a 90-day composite of all-cause mortality or MI complications (resuscitated ventricular fibrillation > 48 hours after randomization, rehospitalization or ED visit for congestive heart failure, or cardiogenic shock). Results of this study will help to clarify whether abciximab should be started early "upstream" in the ED or prehospital setting for STEMI patients before primary PCI.

Clopidogrel

An increasing number of clinical trials indicate that clopidogrel can reduce mortality and morbidity in STEMI patients treated with fibrinolysis. The CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)–TIMI 28 investigators randomized 3491 STEMI patients to receive clopidogrel (300 mg loading dose, followed by 75 mg once daily) or placebo. Patients received a fibrinolytic agent, aspirin, and, when appropriate, heparin (dispensed according to body weight) and were scheduled to undergo angiography 48 to 192 hours after the start of study medication. The primary efficacy endpoint was a composite of an occluded infarct-related artery (TIMI-0 or -1) on angiography or death or recurrent MI before angiography. The rates of the primary efficacy endpoint were 21.7% in the placebo group and 15.0% in the clopidogrel group (95% CI 24-47, $P < .001$). By 30 days, clopidogrel therapy reduced the odds of the composite endpoint—death from cardiovascular causes, recurrent MI, or recurrent ischemia leading to the need for urgent TVR—from 14.1% to 11.6% ($P = .03$). The rates of major bleeding and intracranial hemorrhage were similar in the 2 groups. An ECG substudy (ECG CLARITY-TIMI 28) showed that clopidogrel seems to improve late coronary patency and clinical outcomes by preventing reocclusion of open arteries rather than by facilitating early reperfusion.[33]

The COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) randomized 45,852 STEMI

Figure 6. *Left ventricular function by timing of abciximab administration: results from the RELAX-AMI study. EF, ejection fraction; WMSI, wall motion score index. Data adapted with permission from Bellandi F et al.*[38]



patients admitted to 1250 hospitals within 24 hours of symptom onset to clopidogrel 75 mg/day (n = 22,961) or matching placebo (n = 22,891) in addition to aspirin 162 mg/day. Treatment was to continue until discharge or up to 4 weeks in hospital (mean of 15 days in survivors), and 93% of patients completed treatment. Clopidogrel-treated patients experienced a highly significant 9% (95% CI 3-14) proportional reduction in death, reinfarction, or stroke (9.2% clopidogrel vs 10.1% placebo; $P = .002$), corresponding to 9 fewer events per 1000 patients treated. No significant excess bleeding risk was noted with clopidogrel, even in patients over 70 years of age or patients receiving fibrinolysis.

Based on these 2 studies, it is reasonable to consider adding clopidogrel to the therapeutic treatment regimen for STEMI patients receiving fibrinolysis. But does the same hold true for STEMI patients treated with primary PCI? The PCI-CLARITY substudy sheds light on this issue. PCI-CLARITY was a prospectively planned analysis of the 1863 patients undergoing PCI after mandated angiography in the CLARITY-TIMI 28 study. As noted above, patients received aspirin and were randomized to receive either clopidogrel (300 mg loading dose, then 75 mg once daily) or placebo initiated with fibrinolysis and given until coronary angiography, performed 2 to 8 days after initiation of the study drug. For patients undergoing coronary artery stenting, open-label clopidogrel (including a loading dose) was recommended for administration after the diagnostic angiogram. Pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI, or stroke following PCI (3.6% vs 6.2%; adjusted OR 0.54, 95% CI 0.35-0.85, $P = .008$). Pretreatment with clopidogrel also reduced the incidence of MI or stroke before PCI (4.0% vs 6.2%; OR 0.62, 95% CI 0.40-0.95, $P = .03$) and resulted in a highly significant reduction in cardiovascular death, MI, or stroke, from randomization through 30 days (7.5% vs 12.0%; adjusted OR 0.59, 95% CI 0.43-0.81, $P = .001$; number needed to treat = 23). There was no significant excess in rates of TIMI major or minor bleeding (2.0% vs 1.9%; $P > .99$).

Beta-blockers

The ACC/AHA STEMI Guidelines[17] recommend that "beta blockers should be initiated early in the course of STEMI and continued unless adverse effects have been observed." Since publication of the Guidelines, the CCS-2 study randomly allocated 45,852 patients to receive metoprolol (up to 15 mg intravenously then 200 mg/day orally) or matching placebo.[43] The 2 prespecified co-primary outcomes were a composite of death, reinfarction, or cardiac arrest, and death from any cause during the scheduled treatment period. Neither of the co-primary outcomes was significantly reduced by allocation to metoprolol. For death, reinfarction, or cardiac arrest, 9.4% of the metoprolol-treated patients had at least 1 such event, compared with 9.9% of controls (OR 0.96, 95% CI 0.90-1.01, $P = .1$). For death alone, the rate was 7.7% in the metoprolol group versus 7.8% in controls (OR 0.99, 95% CI 0.92-1.05, $P = .69$). Allocation to metoprolol was associated with 5 fewer people having reinfarction (2.0% metoprolol vs 2.5% placebo; OR 0.82, 95% CI 0.72-0.92; $P = .001$) and 5 fewer having ventricular fibrillation (2.5% vs 3.0%; OR 0.83, 95% CI 0.75-0.93, $P = .001$) per 1000 treated. These reductions were counterbalanced by 11 more per 1000 developing cardiogenic shock (5.0% vs 3.9%; OR 1.30, 95% CI 1.19-1.41, $P < .00001$). The excess of cardiogenic shock occurred mainly during days 0 to 1 after admission, whereas the reductions in reinfarction and ventricular fibrillation emerged more gradually. The authors concluded that early beta-blocker therapy reduces the risks of reinfarction and ventricular fibrillation but increases the risk of cardiogenic shock, especially during the first day or so after admission for STEMI. The results of this trial may have been different if administration of intravenous beta-blockers had been avoided during the acute phase of treatment of MI in patients who were hemodynamically unstable or had developed advanced heart block.

Based on these 2 studies, it is reasonable to consider adding clopidogrel to the therapeutic treatment regimen for STEMI patients receiving fibrinolysis.

Conclusion

Cardiologists (especially interventional cardiologists), emergency physicians, nurses, and emergency medical services providers must work together to establish effective regional community systems of care for patients with STEMI, similar to the well-developed, highly successful systems that direct major trauma victims to verified trauma centers in the United States. All hospitals, whether primary PCI–capable or not, should develop a STEMI protocol that includes procedures for expediting time to reperfusion treatment. A multidisciplinary committee should oversee the

process and provide performance improvement. The protocol should include use of evidence-based, early pharmacologic adjunctive therapies. ■

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Main Points

- Each 30 minutes of primary percutaneous coronary intervention (PCI) treatment delay is associated with a 7.5% (95% confidence interval [CI] 1.008-1.15, $P = .041$) relative increase in 1-year mortality.
- A fundamental problem in acute care of patients with ST-segment elevation myocardial infarction (STEMI) is the lack of an organized, uniform, national STEMI triage and treatment system in the United States.
- Hospitals should have protocols to ensure that all patients with symptoms suspicious for an acute coronary syndrome receive evaluation within 10 minutes of arrival in the emergency department (ED).
- Recent studies find some modest benefit of facilitated PCI over fibrinolysis alone, but studies comparing primary and facilitated PCI in STEMI patients concluded that facilitated PCI offers no benefit over primary PCI.
- The benefit of platelet glycoprotein (GP) IIb/IIIa inhibitor therapy in STEMI patients is well established.
- When compared with control therapy, abciximab was associated with a significant reduction in 30-day mortality (2.4% vs 3.4%; $P = .047$) and 6- to 12-month mortality (4.4% vs 6.2%; $P = .01$) in patients undergoing primary PCI.
- The ongoing FINESSE study will test whether PCI facilitated by early ED administration of abciximab alone or combined with reduced-dose reteplase is superior to primary PCI with abciximab just prior to PCI.
- Clinical trials indicate that clopidogrel can reduce mortality and morbidity in STEMI patients treated with fibrinolysis, and STEMI patients undergoing primary PCI who were pretreated with clopidogrel had significantly fewer adverse cardiovascular events.

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