Strategies to Improve Early Reperfusion in ST-Elevation Myocardial Infarction

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It is well established that rapid and complete reperfusion in ST-elevation myocardial infarction reduces infarct size and improves long-term morbidity and mortality rates. Randomized clinical trials demonstrate that primary angioplasty (percutaneous coronary intervention [PCI]) is superior to fibrinolytic therapy in reducing mortality, reinfarction, and recurrent ischemia if performed in a timely manner by an experienced team. Despite this evidence, a minority of patients are treated with primary PCI in the United States. Efforts to improve access and to develop systems that facilitate the availability of timely primary PCI are being addressed. Suggested solutions include coordination of emergency medical services (EMS) systems, performance of 12-lead electrocardiography in the ambulance, and early notification of the catheterization laboratory team. Improved access would require limited expansion of hospitals capable of primary PCI, particularly in rural areas. Although these strategies may help, there is growing enthusiasm for the development of primary PCI centers, with triage of patients to these centers through either an EMS bypass system or an interhospital transfer system.

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Key words: ST-elevation myocardial infarction • Percutaneous coronary intervention • Fibrinolytic therapy • Emergency medical services • Catheterization laboratory

The treatment of ST-elevation myocardial infarction (STEMI) has undergone enormous change over the past 30 years.[1] Extensive basic and clinical research has definitively shown that early reperfusion reduces infarct size, improves morbidity, and reduces short-term as well as long-term mortality due to an improvement in left ventricular function and a reduction in fatal arrhythmias.[2] Minimizing the ischemic time or the time from the onset of symptoms to successful reperfusion has been shown to correlate with a reduction in mortality and morbidity for both fibrinolytic therapy and primary percutaneous coronary intervention (PCI). In one study of 1729 patients undergoing primary PCI, mortality increased 7.5% for each 30-minute delay in reperfusion.[3] Similar findings have been shown for lytic therapy.[3,4] Efforts to reduce time to reperfusion have the potential to save a significant number of lives.

To develop strategies to achieve a reduction in ischemic time, it is helpful to look at its components.[1] The initial time period from the recognition of the symptoms by the patient until the institution of assessment and initial treatment varies widely. This variation is due to the infrequent activation of emergency medical services (EMS) systems. In some studies, fewer than 50% of patients with STEMI call 9-1-1.[5] To date, efforts to improve the early recognition of symptoms by the public have been only marginally successful. A patient awareness program sponsored by the National Institutes of Health demonstrated only limited improvement in the response time despite considerable public education.[6]

The second component is the transport time, defined as the time between the 9-1-1 call or when the patient recognizes the need for emergency department (ED) evaluation and arrival at the ED. The ambulance transport time to the ED is usually very rapid in most urban settings (usually less than 10 minutes), but when the patient comes alone or is transported by the family, significant delays are frequent.

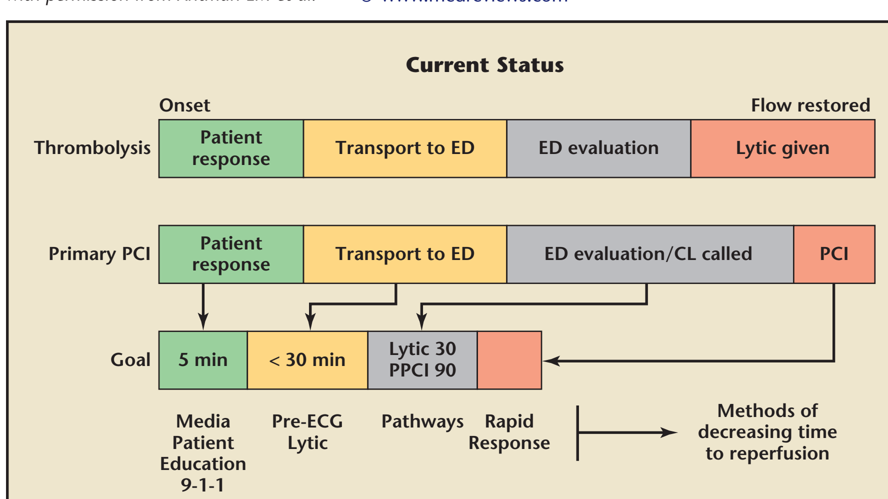
Once the patient reaches the ED, rapid evaluation and initial treatment can be instituted. This phase is critical for rapid identification of those with STEMI and determination of the most appropriate treatment. This final component, the time between ED arrival and reperfusion, consists of the institution of reperfusion therapy and initial medical management in appropriate patients. When a fibrinolytic agent is selected, the time to actual reperfusion is assumed to be 30 minutes after infusion of the drug, based upon the prior clinical trials. For primary PCI, reperfusion is defined as time to the first balloon inflation. Door-to-needle time and door-to-balloon time have been greatly scrutinized because the evidence suggests that in the United States, most patients do not meet the goals established for optimal outcomes, as discussed below.[7]

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines have suggested the optimal time for each component of the ischemic time (Figure 1).[1] It is recommended that the patient response be no longer than 5 minutes; the transport time be less than 30 minutes; and the initial ED evaluation, including an electrocardiogram (ECG), be within 5 minutes, with initiation of reperfusion therapy within 30 minutes. The overall goal is to have the door-to-needle time for fibrinolytic therapy be within 30 minutes and the door-to-balloon time be within 90 minutes. This review will discuss the factors related to the delay for both reperfusion treatments and the strategies to improve the time to reperfusion.

Choosing a Reperfusion Strategy

More than 23 major randomized trials have compared the outcome of fibrinolytic therapy with primary PCI. In one meta-analysis, Keeley and colleagues[8] showed that in 7739 patients, primary angioplasty was superior to lytic therapy, with a reduction in short-term mortality from 7% to 5% (P = .001; hazard ratio = 0.73), re-infarction from 7% to 3% (P = .01), and recurrent ischemia from 21% to 6% (P = .01). Likewise, this analysis showed favorable results in long-term outcomes in

Figure 1. *The optimal time for each component of the ischemic time, as suggested by the American College of Cardiology/American Heart Association. ED, emergency department; CL, catheterization laboratory; PCI, percutaneous coronary intervention; ECG, electrocardiogram; PPCI, primary percutaneous coronary intervention. Reprinted with permission from Antman EM et al.*[1] www.medreviews.com



DB-DN (min)	Patients (n)	30-Day Mortality (%) Lysis	PPCI
0–35	1417	8.2	2.8
35–50	1292	6.8	5.4
50–62	1425	5.4	4.8
62–79	1280	9.5	6.9
79–120	1349	9.6	6.6
All patients	6763	7.9	5.3

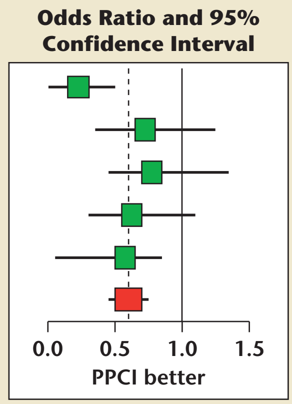


Figure 2. *A meta-analysis of 22 randomized trials showed a benefit of primary PCI at all DB times ranging from 30 minutes to 120 minutes. DB, door-to-balloon; DN, door-to-needle; PPCI, primary percutaneous coronary intervention. Adapted with permission from Boersma E[11] and Oxford University Press.* www.medreviews.com

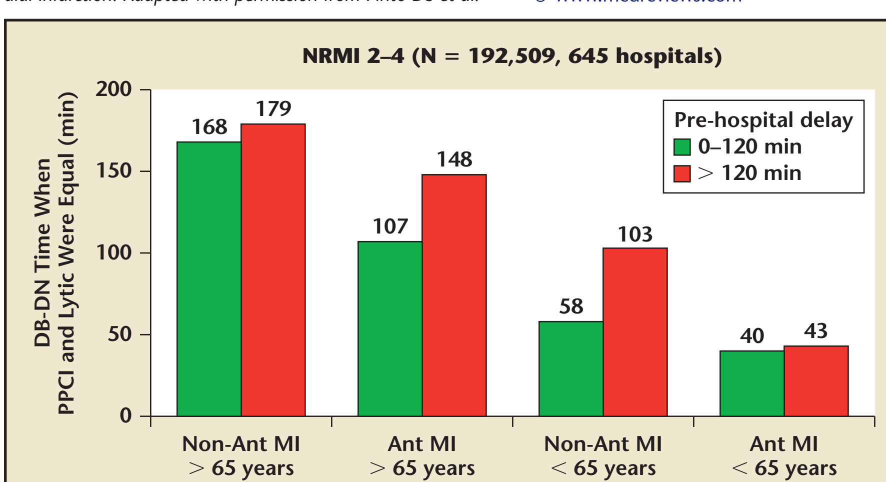
patients treated with primary PCI. In addition, individual studies such as the Primary Coronary Angioplasty vs Thrombolysis (PCAT) trial and the Primary Angioplasty in Acute Myocardial Infarction Patients From General Community Hospitals Transported for Percutaneous Transluminal Coronary Angioplasty Units Versus Emergency Thrombolysis (PRAGUE-2) trial suggested that when the patient presents very early after the onset of symptoms (2 to 3 hours), primary PCI and lytic therapy have similar outcomes.[7,9,10] As a result, the ACC/AHA guidelines recommend either therapy when a patient presents within 3 hours and there is no delay to performing PCI.

When PCI cannot be performed within the 90-minute door-to-balloon time goal, it has been suggested that the mortality advantage of PCI is lost. Therefore, the guidelines recommend lytic therapy when the delay in PCI is significant (eg, door-to-balloon time > 90 minutes or the difference in the door-to-balloon and door-to-needle time > 60 minutes).[7] In contrast, a detailed meta-analysis of 22 randomized trials by Boersma and colleagues[11] showed a benefit of primary PCI at all door-to-balloon times ranging from 30 minutes to 120 minutes (Figure 2). A more recent study using "real world" experience from the National Registry of Myocardial Infarction (NRMI) database suggested that the 2 strategies were equivalent in terms of mortality when the PCI-related delay was 114 minutes.[12]

This study also suggested that the acceptable PCI-related time delay varies depending upon the patient characteristics. Using the data from NRMI 2 to 4 in 192,509 patients, 3 factors were found to impact the PCI time delay: the pre-hospital delay, the patient's age, and the myocardial infarction (MI) location (Figure 3). Thus, when a patient presented within 120 minutes, had an anterior MI, and was younger than 65, the PCI-related delay in which equivalence in mortality occurred was 40 minutes.[12] Conversely, when the patient presented after 120 minutes, was older than 65, and had a non-anterior MI, the tolerable delay was 179 minutes. Other studies have also shown that longer delays are acceptable when the patient is at higher risk, as conferred by factors such as cardiogenic shock or Killip class IV.[13] Recent experience from the Swedish Registry in 26,205 patients suggests that PCI is superior even with significant delays up to 7 hours.[14] These data and others reinforce the concept that the patient characteristics and the duration of symptoms are important factors in deciding on which reperfusion therapy is best in an individual patient.

Also inherent in the strategy of primary PCI is the presence of an

Figure 3. *In an analysis of data from the NRMI 2-4, the DB-DN time when PPCI and lytic therapy were equal varied according to the location of the myocardial infarction. NRMI, National Registry of Myocardial Infarction; DB, door-to-balloon; DN, door-to-needle; PPCI, primary percutaneous coronary intervention; Ant MI, anterior myocardial infarction. Adapted with permission from Pinto DS et al.[12]* www.medreviews.com



experienced team and interventionalist, as observational studies have shown that the advantage of primary PCI is lost in low-volume or inexperienced centers. Primary PCI is also indicated in those patients who have contraindications to fibrinolytic therapy. In the NRMI database 20% of the patients had such contraindications, and only 24% received primary PCI.[15] In those that did, a 43% lower in-hospital mortality rate was observed.

Overall, the wealth of information demonstrates that primary PCI is a better reperfusion strategy when performed in a timely manner with an experienced team. The question is not whether we should perform primary PCI but rather how to institute a system that will provide PCI to most patients.

Are We Meeting ACC/AHA Guidelines?

Observational registries suggest that in the United States, we are rarely meeting the guideline recommendations.[16] As mentioned previously, fewer than half of patients call 9-1-1 and are transported to the ED by ambulance. Remarkably, 30% of STEMI patients without contraindications do not receive either reperfusion therapy. Of the patients who do receive reperfusion, 60% receive lytic therapy and not primary PCI. Even more disturbing is that 70% of patients with contraindications to fibrinolysis do not receive primary angioplasty.[15] There are wide variations in practice patterns, with the highest-risk patients less likely to receive reperfusion. In the NRMI database administration of a lytic within the recommended 30 minutes occurred in 45% of patients and did not vary between 1999 and 2002.[16] Likewise, primary PCI was performed within 90 minutes in only 36% of patients, and no change was observed over the 4-year observation period. These findings were even more dismal for patients transferred from one hospital to another. In the most recent data from the 2004 NRMI survey, 41% of STEMI patients treated in a hospital with onsite PCI achieved the 90-minute door-to-balloon time goal. However, in patients transferred from another facility, the recommended time was achieved in only 5.4% of patients. Only modest improvement has been seen in both times over the past 10 years.

The strategies to improve these findings have been under intense discussion at many levels. In particular, the AHA has convened all of the constituencies involved in the care of patients with STEMI, including physicians, EMS workers, hospital administrators, payers, and policy experts to examine the problem and propose solutions.[17]

Strategies to Improve System Problems

The factors that influence the delay in door-to-balloon time are multifactorial, and many are specific to the individual hospital. However, some hospitals are highly effective in achieving the 90-minute goal. Bradley and colleagues[18] surveyed 11 hospitals that were high performers in the NRMI registry and had shown improvement in performance over a 4-year period. A number of critical innovations had been instituted that appeared to impact outcome. These included administration of a pre-hospital ECG, allowing the ED staff to activate the catheterization laboratory, and considerable collaboration between the ED and the catheterization laboratory. In the hospitals with a pre-hospital ECG, door-to-balloon times were 60 minutes.

In another survey of 365 acute care hospitals (out of 500 contacted) between April 2005 and November 2006 by Bradley and colleagues,[19] 28 strategies to improve door-to-balloon times were evaluated, and linear models were constructed to determine their value. Six strategies were significantly associated with better door-to-balloon times. They were: having emergency medicine physicians activate the catheterization laboratory (mean reduction in door-to-balloon time, 8.2 minutes), having a single call to a central page operator activate the laboratory (13.8 minutes), having the ED activate the catheterization laboratory while the patient is en route to the hospital (15.4 minutes), expecting staff to arrive in the catheterization laboratory within 20 minutes after being paged (vs $>$ 30 minutes) (19.3 minutes), having an attending cardiologist always on site (14.6 minutes), and having staff in the ED and the catheterization laboratory use real-time data feedback (8.6 minutes). Only 2.2% of hospitals had instituted 4 or more strategies, but these hospitals had the shortest door-to-balloon time of 79 minutes. Even when only 2 strategies were used (15.5% of hospitals), the door-to-balloon time was under 90 minutes, at an average of 88 minutes. Having no strategies resulted in a door-to-balloon time of 110 minutes. On the basis of this study, the D2B: An Alliance for Quality™, was established. This alliance includes a number of organizations, including the ACC, the AHA, Blue Cross/Blue Shield, the Society for Cardiovascular Angiography and Interventions, WellPoint, Aetna, and the Agency for Healthcare Research and Quality. The goal is to enlist hospitals to voluntarily initiate 6 strategies to improve door-to-balloon times. Prehospital ECG was not included because it is not under the control of individual hospitals, despite being recognized as a powerful factor in reducing delays. Detailed information is available on the D2B Web site (www.d2balliance.org).

Strategies to Improve Access to Primary PCI

The availability of timely primary PCI is limited in the United States by a number of factors, including an inadequate number and geographic maldistribution of hospitals capable of primary PCI 24 hours a day, 7 days a week. In addition, there is a lack of coordination among EMS transport systems to provide rapid transport to these hospitals. An effective transport system has been available in many parts of Europe because of a more socialized system of medical care and much shorter distances between the patient and the available hospitals. In the United States, there has been an interest in developing systems to improve access, and the AHA will play a leading role in evaluating solutions.

One strategy that has been suggested is to allow hospitals without cardiac surgical back-up onsite to perform primary PCI. The results of one randomized trial and several registries support this approach. The Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) trial was a multicenter trial that evaluated the outcome of 451 patients treated with primary PCI as compared with fibrinolytic therapy in community hospitals without surgical back-up.[20] The study was unable to enroll its predetermined sample size but did show a significant reduction in the primary endpoint of death, MI, or stroke with primary PCI (12.9% vs 19.9%; P = .03). NRMI also showed at least an equal rate of death in 817 hospitals that performed primary PCI without surgical backup.[21] These data, plus the extensive experience in Europe, have led all but 10 states to allow primary PCI to be performed at hospitals without on-site surgical backup.[22]

Several concerns have been raised about this strategy. The widespread adoption of primary PCI without on-site surgery would likely increase the number of low-volume hospitals and operators. This increase is supported by data from the ACC National Cardiovascular Data Registry (NCDR), in which the participating facilities that did not have surgical backup (n = 75, 16.2%) contributed only 3.9% of patients who underwent primary PCI.[22] The C-PORT and many other studies have shown that outcomes are highly linked to both the operator and hospital volume and experience. The ACC/AHA guidelines recommend that operators perform at least 11 primary PCIs per year for STEMI patients and at least 75 PCIs per year for all other patients.[23] Hospital volumes of primary PCI are recommended to be 36 per year. In addition, the majority of community hospitals are located in cities where there are many hospitals that already perform primary PCI. As a result, it has been estimated that this strategy would provide improved access to only 5% to 10% of patients.

Another suggestion has been to develop new primary PCI centers. The American Hospital Association lists 4927 acute care hospitals in the United States, and the Society for Cardiovascular Angiography and Interventions indicates that there are 2200 catheterization laboratories, of which 1200 are PCI-capable. To establish new catheterization/PCI centers in hospitals without catheterization laboratories would be expensive. If a new laboratory costs US$2.5 million to install, it would cost US$3.4 billion to do so in half of those hospitals without laboratories. The ongoing costs would also be prohibitive for centers that would be low-volume and would require coverage 24 hours a day, 7 days a week.

The strategy that has gained the most enthusiasm has been to establish primary PCI centers to which to transfer patients (Figure 4). In more than 6 randomized trials, transfer for primary PCI has been shown to reduce mortality and MI by 30%.[24] Studies have also shown that one of the major reasons for delay in treatment is inter-hospital transfer time, further emphasizing the need for transfer to occur in a timely manner, with door (at the first hospital or contact)-to-balloon times less than 120 minutes or, preferably, less than 90 minutes. As mentioned before, transport systems work well in many European cities due to short distances and a coordinated transport system. In the United States, there are a number of limitations, including the use of EMS in only half of the patients, inability to obtain a 12-lead ECG in the ambulance, poorly coordinated EMS systems, hospital ED diversion, financial disincentives for transport, and prolonged transport in rural areas. In favor of such a system is that 75% of the population live in urban areas and 85% are currently within a 1-hour drive of a PCI-capable hospital.

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A number of programs have been initiated to evaluate the feasibility of rapid transfer to a primary PCI center. Two models are currently being studied: EMS bypass or direct hospital transport. A number of cities, such as Boston, MA, and Durham, NC, are evaluating the EMS bypass system.[25] In Boston, the Department of Public

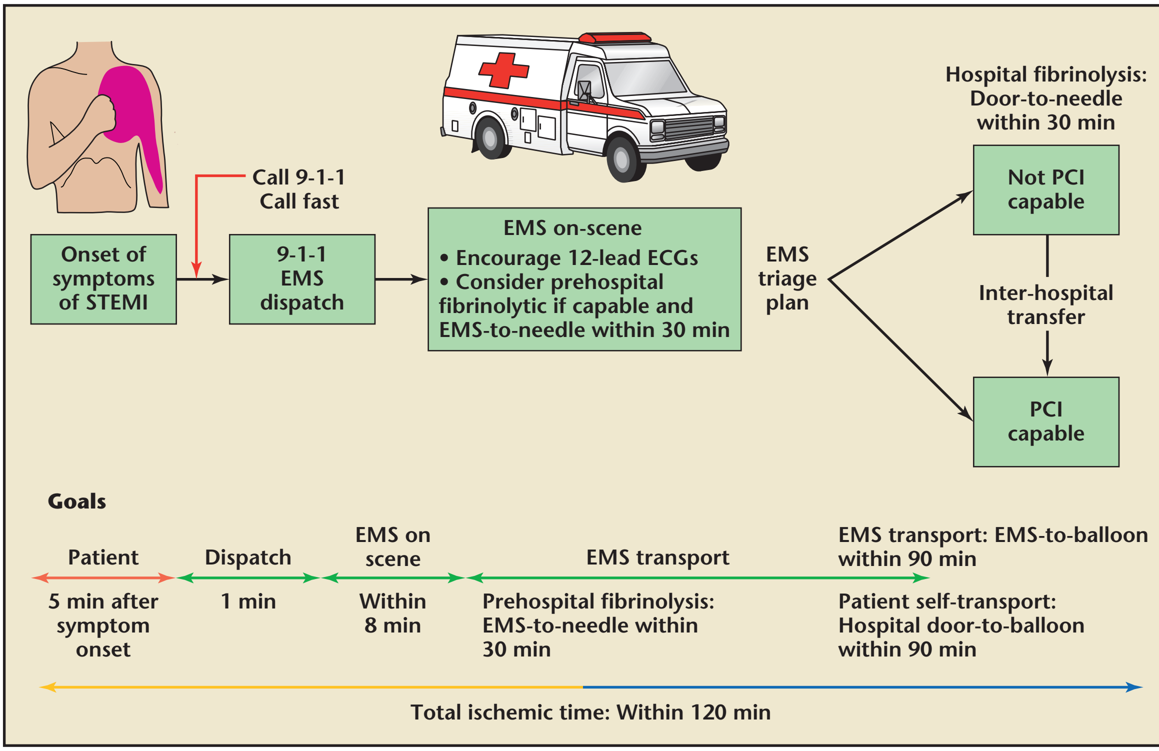

Figure 4. *The options for transport and goals for each component of ischemic time. STEMI, ST-elevation myocardial infarction; EMS, emergency medical services; ECG, electrocardiogram; PCI, percutaneous coronary intervention. Reprinted with permission from Antman EM et al.*[1]
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Health has sponsored a trial to evaluate the effectiveness of EMS bypass of hospitals that do not provide primary PCI on a 24-hours-a-day, 7-days-a-week basis and meet strict volume and outcome criteria.[26] The Minneapolis Heart Institute program is an example of an inter-hospital transfer program that has worked closely with rural community hospitals to develop a rapid triage and transport system to the Minneapolis Heart Institute facility for primary PCI.[27] Over 30 hospitals have been trained, and during a 39-month period over 1121 patients were transferred from as far away as 200 miles. The average door-to-balloon time was 120 minutes for those hospitals beyond 80 miles and 95 minutes for those within 80 miles. The mortality for both groups is not different from those who presented to the Minneapolis Heart Institute directly.

The last strategy to gain additional time in transport has been the idea of early or preadmission administration of fibrinolytic therapy followed by transport to a primary PCI center for PCI (the so-called "drip and ship" or facilitated PCI approach). Unfortunately, this strategy has not been shown to improve outcomes compared with primary PCI alone.[28] In a meta-analysis of 17 trials of facilitated PCI, Keeley and colleagues[29] showed a worse outcome with facilitated PCI as compared with primary PCI in terms of death, MI, urgent revascularization, and major bleeding (Figure 5).

Figure 5. *A meta-analysis of 17 trials of facilitated PCI showed a worse outcome with facilitated PCI as compared with PPCI in terms of death, myocardial infarction, urgent revascularization, and major bleeding. PPCI, primary percutaneous coronary intervention; reMI, re-infarction; TVR, target vessel revascularization. Data from Keeley EC et al.*[29]
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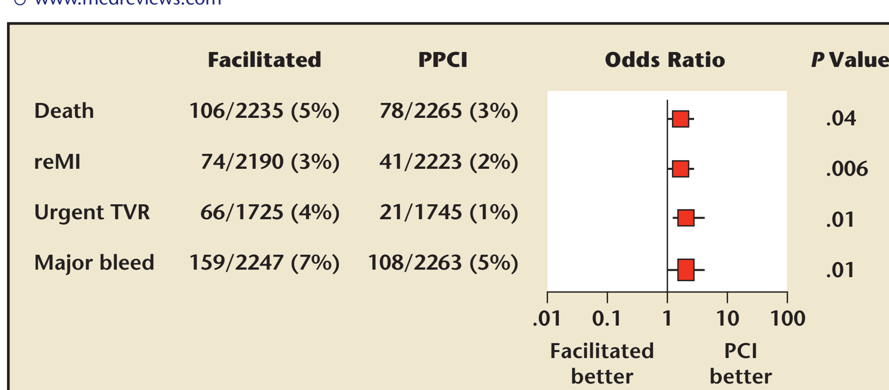

The large Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT-4) trial was particularly disappointing,[30] and unless future trials demonstrate benefit, this strategy does not appear to hold promise.[31]

Conclusion

There is an urgent need to address the problem of timely access to primary PCI systematically in the United States. The solutions must include regional coordination of the EMS system, performance of 12-lead ECGs in all ambulances in the field, and development of standardized bypass and hospital triage protocols. The identification of hospitals that are willing to be and are capable of being primary PCI centers is also critical. These centers would perform primary PCI on a 24-hours-a-day, 7-days-a-week basis, and the hospital would never be on diversion for patients with STEMI. These primary PCI centers would have to maintain adequate numbers of patients and be able to achieve door-to-balloon times within 90 minutes for most patients. It is also likely that a limited number of catheterization laboratories will need to be established to provide primary PCI in rural areas where transport times preclude rapid transfer to a regional center. The establishment of these centers should not be a financial hardship on the non–PCI-capable hospitals. Participating hospitals should develop systems to ensure rapid triage and mobilization of the catheterization laboratory staff using the techniques developed in the D2B program. Only when these goals have been accomplished can we provide the best care for the majority of patients with acute STEMI in this country. ■

References

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:E1-E211.
2. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet*. 1994; 343:311-322.
3. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation*. 2004;109:1223-1225.
4. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348:771-775.
5. McGinn AP, Rosamond WD, Goff DC, et al. Trends in prehospital delay time and use of emergency medical services for acute myocardial infarction: experience in 4 US communities from 1987-2000. *Am Heart J*. 2005;150:392-400.
6. Educational strategies to prevent prehospital delay in patients at high risk for acute myocardial infarction: a report by the National Heart Attack Alert Program. *J Thromb Thrombolysis*. 1998;6:47-61.
7. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. 2003;92:824-826.
8. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003; 361:13-20.
9. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J*. 2003;24:94-104.
10. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (< 2 h), intermediate (2-4 h) and late (> 4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J*. 2002;23:550-557.
11. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. 2006;27:779-788.
12. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation*. 2006; 114:2019-2025.
13. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341:625-634.
14. Stenestrand U, Lindback J, Wallentin L. Long-term outcome of primary percutaneous coronary

Main Points

- Efforts to reduce time to reperfusion have the potential to save a significant number of lives.
- It is recommended that the patient response to a myocardial infarction (MI) event be no longer than 5 minutes; the transport time be less than 30 minutes; and the initial emergency department evaluation, including an electrocardiogram, be within 5 minutes, with initiation of reperfusion therapy within 30 minutes.
- The wealth of information demonstrates that primary percutaneous coronary intervention (PCI) is a better reperfusion strategy when performed in a timely manner with an experienced team.
- Strategies to improve access to primary PCI that appear to positively impact outcome include administration of a pre-hospital electrocardiogram, activation of the catheterization laboratory by the emergency department staff, and considerable collaboration between the emergency department and the catheterization laboratory.
- In more than 6 randomized trials, transfer to a primary PCI center has been shown to reduce mortality and MI by 30%.

intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *JAMA*. 2006;296:1749-1756.

15. Grzybowski M, Clements EA, Parsons L, et al. Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: a propensity analysis. *JAMA*. 2003;290:1891-1898.
16. McNamara RL, Herrin J, Bradley EH, et al. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. *J Am Coll Cardiol*. 2006;47:45-51.
17. Jacobs AK, Antman EM, Ellrodt G, et al. Recommendation to develop strategies to increase the number of ST-segment-elevation myocardial infarction patients with timely access to primary percutaneous coronary intervention. *Circulation*. 2006;113:2152-2163.
18. Bradley EH, Curry LA, Webster TR, et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. *Circulation*. 2006;113:1079-1085.
19. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. 2006;355:2308-2320.
20. Aversano T, Aversano LT, Passamani E, et al. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA*. 2002;287:1943-1951.
21. Sanborn TA, Jacobs AK, Frederick PD, et al. Comparability of quality-of-care indicators for emergency coronary angioplasty in patients with acute myocardial infarction regardless of on-site cardiac surgery (report from the National Registry of Myocardial Infarction). *Am J Cardiol*. 2004;93:1335-1339.
22. Dehmer GJ, Blankenship J, Wharton TP, et al. The current status and future direction of percutaneous coronary intervention without on-site surgical backup: an expert consensus document from the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2007;69:471-478.
23. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. Available at: http://www.americanheart.org/presenter.jhtml?identifier=3035436. Accessed June 28, 2007.
24. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation*. 2003;108:1809-1814.
25. Jollis JG, Mehta RH, Roettig ML, et al. Reperfusion of acute myocardial infarction in North Carolina emergency departments (RACE): study design. *Am Heart J*. 2006;152:851.e1-11.
26. Moyer P, Levine FJ, Beshansky J, et al. Implications of the mechanical (PCI) vs thrombolytic controversy for ST segment elevation myocardial infarction on the organization of emergency medical services: the Boston EMS experience. *Crit Path Cardiol*. 2004;3:53-61.
27. Henry T. Transfer for direct percutaneous coronary intervention for ST-elevation myocardial infarction: the Minneapolis Heart Institute Level 1 Myocardial Infarction Program. Paper presented at: Annual Scientific Sessions of the American Heart Association; November 13-16, 2005; Dallas, TX.
28. Borden WB, Faxon DP. Facilitated percutaneous coronary intervention. *J Am Coll Cardiol*. 2006;48:1120-1128.
29. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet*. 2006;367:579-588.
30. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367:569-578.
31. ADVANCE MI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. *Am Heart J*. 2005;150:116-122.