STATE-OF-THE-ART PAPER

Reperfusion Strategies in Acute ST-Segment Elevation Myocardial Infarction

A Comprehensive Review of Contemporary Management Options

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There are an estimated 500,000 ST-segment elevation myocardial infarction (STEMI) events in the U.S. annually. Despite improvements in care, up to one-third of patients presenting with STEMI within 12 h of symptom onset still receive no reperfusion therapy acutely. Clinical studies indicate that speed of reperfusion after infarct onset may be more important than whether pharmacologic or mechanical intervention is used. Primary percutaneous coronary intervention (PCI), when performed rapidly at high-volume centers, generally has superior efficacy to fibrinolysis, although fibrinolysis may be more suitable for many patients as an initial reperfusion strategy. Because up to 70% of STEMI patients present to hospitals without on-site PCI facilities, and prolonged door-to-balloon times due to inevitable transport delays commonly limit the benefit of PCI, the continued role and importance of the prompt, early use of fibrinolytic therapy may be underappreciated. Logistical complexities such as triage or transportation delays must be considered when a reperfusion strategy is selected, because prompt fibrinolysis may achieve greater benefit, especially if the fibrinolytic-to-PCI time delay associated with transfer exceeds ~1 h. Selection of a fibrinolytic requires consideration of several factors, including ease of dosing and combination with adjunctive therapies. Careful attention to these variables is critical to ensuring safe and rapid reperfusion, particularly in the prehospital setting. The emerging modality of pharmacoinvasive therapy, although controversial, seeks to combine the benefits of mechanical and pharmacologic reperfusion. Results from ongoing clinical trials will provide guidance regarding the utility of this strategy. (J Am Coll Cardiol 2007;50: 917–29) © 2007 by the American College of Cardiology Foundation

The estimated annual incidence of new and recurrent myocardial infarction (MI) in the U.S. is 865,000 events (1), with ST-segment elevation myocardial infarction (STEMI) comprising an estimated 500,000 events per year (2). Mortality in patients with STEMI has declined substantially in developed countries over the past 20 years (3). However, up to one-third of eligible patients with STEMI still receive no reperfusion therapy acutely (4,5). Timely reperfusion of the infarct-related coronary artery using fibrinolysis or percutaneous coronary intervention (PCI) is central to optimal STEMI treatment (3,6), reducing infarct size, minimizing myocardial damage, preserving left ventricular function, and decreasing morbidity and mortality (7). However, the principal objective of prompt reperfusion has become overshadowed by debate over which approach (mechanical or pharmacologic) is superior. The more compelling question is how optimal reperfusion can best be achieved in STEMI, mindful of the fact that 60% to 70% of STEMI patients present initially to hospitals without ready access to primary PCI. Data from the National Registry of Myocardial Infarction (NRMI)-3 and -4 registries highlight how few STEMI patients (only 4%) who are transferred for primary PCI achieve door-to-balloon times of <90 min (8), which represents the American College of Cardiology (ACC)/ American Heart Association (AHA) standard of care benchmark (2).

The goal of this paper is to highlight reperfusion options in STEMI, with regard to efficacy and safety, as well as temporal and logistic factors that may affect treatment outcomes and thus clinical decision making.

Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

ECG = electrocardiogram

ED = emergency department

EMS = emergency medical services

MI = myocardial infarction

NRMI = National Registry of Myocardial Infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Utilization of Reperfusion Therapy

As previously noted, reperfusion therapy is underutilized in patients with STEMI. In analyses of data from the NRMI-2 database (4), and the GRACE (Global Registry of Acute Coronary Events) study (5), factors associated with eligible patients not receiving reperfusion therapy included age ≥75 years, female gender, presentation without chest pain, and a history of cardiovascular disease. In addition, the EDQMI (Emergency Department Quality in Myocardial Infarction) study found that failure to identify high-risk electrocardiogram (ECG) findings in patients with acute MI was associated with greater odds of ideal candidates not receiving reperfusion therapy (9). The ECG findings are key in making prompt STEMI treatment decisions, identifying patients with ST-segment elevation who may benefit from reperfusion therapy and patients with increased mortality risk, such as those with left bundle branch block.

The 2004 ACC/AHA guidelines for the management of patients with STEMI recommend that an experienced emergency department (ED) physician should evaluate a 12-lead ECG within 10 min of arrival in the ED for all patients with chest discomfort or other symptoms suggestive of STEMI. If the initial ECG is not diagnostic of STEMI, but the patient continues to experience symptoms and there is a high clinical suspicion of STEMI, the guidelines recommend performing serial ECGs every 5 to 10 min or continuous 12-lead ST-segment monitoring to detect development of ST-segment elevation, which may in turn ensure use of reperfusion therapy in eligible patients. Where available, chest pain centers with established protocols can perform any necessary ongoing monitoring of patients to avoid both inappropriate discharge from the ED due to a missed diagnosis and unnecessary hospitalizations (10).

Percutaneous Coronary Intervention

The ACC/AHA STEMI guidelines recommend PCI as the initial approach to management of STEMI, contingent upon treatment at centers with a skilled PCI laboratory and rapid initiation (within 90 min of first medical contact) (2). This is based on multiple randomized clinical trials demonstrating superiority of rapid primary PCI over fibrinolysis in STEMI (11–16). However, for many patients these criteria for primary PCI to be preferred will not be met, and it is important to note that the ACC/AHA guidelines also state that there is no strong preference between PCI and fibrinolysis as the choice of initial reperfusion therapy in patients who present within 3 h after symptom onset (2). This is based, in part, on the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) and PRAGUE-2 (Primary Angioplasty in Patients Transported From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis-2) trials, which suggested that earlier-presenting patients (within 2 to 3 h) had similar or lower mortality with fibrinolysis than with primary PCI (17,18).

In the setting within which the ACC/AHA guidelines recommend primary PCI, it offers several important potential advantages over pharmacologic reperfusion: It is suitable for ≥90% of patients (2), establishes initial Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in 70% to 90% of patients (2), nearly eliminates the risk of intracranial hemorrhage, and is preferable to alternative treatments in high-risk patients, such as those with cardiogenic shock, severe congestive heart failure, or hemodynamic or electrical instability (2,19).

Appropriately selected patients undergoing primary PCI were shown to have lower rates of nonfatal reinfarction, stroke, and short-term mortality than fibrinolytic recipients in a meta-analysis of data from 23 randomized trials enrolling fibrinolytic-eligible patients with STEMI (20). It should be noted, however, that 24% of patients in the fibrinolytic group received the nonfibrin-specific agent streptokinase, which is rarely used in the U.S. and has been shown to be less effective than alteplase in reducing mortality in STEMI (21). Based on 5 studies that compared emergent hospital transfer for primary PCI (with additional transfer-related delay averaging 39 min) with on-site fibrinolysis, PCI was still associated with significantly better outcomes; however, the difference was mainly driven by less reinfarction in the setting of low rates of rescue and early angiography (20). Moreover, the transfer-related delays from first-door-to-balloon were much shorter (100 to 120 min) compared with U.S. registry data (180 to 240 min) (8,22). Thus, while these trials show that transfer can be done rapidly in selected centers with good outcomes in Europe, they have limited direct relevance to current U.S. practice.

Benefits of Early Reperfusion: The Early-Open-Artery Theory

The early-open-artery theory suggests that benefits of reperfusion in patients with STEMI are directly related to the speed and completeness with which patency of the infarct-related coronary artery is re-established. Mortality has been shown to be lower among patients in whom TIMI flow grade 2 to 3, compared with TIMI flow grade 0 to 1, was achieved within 90 min after acute MI (23).

This is strongly supported by clinical studies confirming the important relationship between achieving prompt ante-

grade coronary flow of the infarct artery and improved clinical outcomes, for both primary PCI (22,24–27) and fibrinolysis (21,28,29). An analysis by Boersma et al. indicated that the 35-day mortality benefit associated with early treatment equated to 1.6 lives per 1,000 patients per hour of delay from symptom onset to treatment, with even more of an impact of time in the early hours (Fig. 1) (28). However, the recent Occluded Artery Trial showed that PCI provided no delayed benefit over optimal medical therapy alone in stable patients with persistent total occlusion of the infarct-related coronary artery 3 to 28 days after acute MI who met criteria for high risk (30), indicating that there is no indication to open an occluded vessel outside the therapeutic window in an asymptomatic patient following STEMI.

ACC/AHA Guidelines for Selecting a Reperfusion Strategy

The 2004 ACC/AHA guidelines provide recommendations on selecting a reperfusion strategy for patients with STEMI (Fig. 2). The first step is to determine time from onset of symptoms, the presence of high-risk attributes, the relative risks associated with fibrinolysis, and estimated total time required for achieving PCI balloon inflation; these factors logically determine treatment selection. An invasive strategy is generally preferred if first door-to-balloon time can be realistically achieved within 90 min if there is high risk from STEMI or fibrinolysis is contraindicated (2). The first of these criteria sets an important benchmark, and it should be noted that the goal of performing primary PCI within 90 min of first medical contact represents the longest time that should be considered acceptable rather than the ideal time frame (31). Yet registry data have shown that a door-to-

balloon time of <90 min is not achieved in the majority of patients undergoing primary PCI, particularly if transfer is required (8,32). These data suggest that many STEMI patients are being denied the optimal treatment for prompt reperfusion.

Fibrinolysis is preferred if <3 h have elapsed from symptom onset, there is an anticipated delay that decreases the potential advantage of PCI, or an invasive strategy is not an option (e.g., owing to vascular access difficulties or lack of access to a skilled PCI laboratory with skilled operators) (2). Thus, within 3 h of symptom onset, in the absence of delays to initiating an invasive strategy, the ACC/AHA guidelines indicate that there is no preference for either PCI or fibrinolysis (2), although if primary PCI can be performed rapidly, it is generally preferred in the U.S. owing to safety and cost-effectiveness (i.e., shorter length of stay) (33,34). A recent pooled analysis suggested a consistent advantage of primary PCI over fibrinolysis regardless of time from symptom onset to presentation (35). However, Gersh and Antman (36) have commented that this conclusion is controversial, and cautioned that analyses such as this should not be used as justification for exclusively choosing a strategy of primary PCI without taking into account a realistic estimate of the time needed to implement this strategy in all clinical settings.

Regardless of the reperfusion strategy, the guidelines recommend treatment with unfractionated or low-molecular-weight heparin (2). The EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)–TIMI-25 (37) and CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)–TIMI-28 (38) studies indicated that low-molecular-weight heparins provided improved clinical outcomes over unfractionated heparin. Treatment with enoxaparin in the first of these studies (37) was associated with modestly increased bleeding compared with unfractionated heparin, although the rate of the composite end point of death, nonfatal reinfarction, and nonfatal major bleeding was lower with enoxaparin (37). In the OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes-6) study, the factor Xa inhibitor fondaparinux also improved outcomes versus usual care (unfractionated heparin or placebo if heparin was not indicated), although this was seen in patients who received fibrinolysis or no reperfusion therapy but not with primary PCI (39).
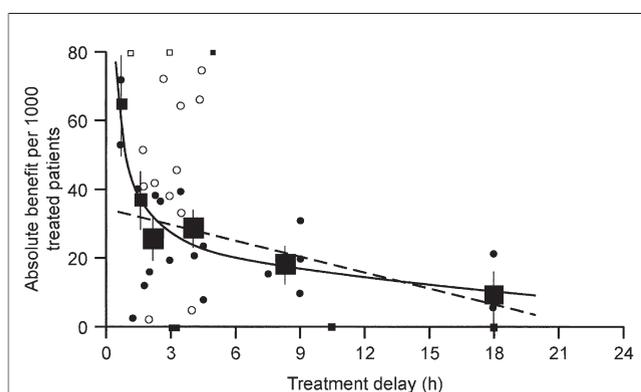
Figure 1   **Absolute 35-Day Mortality Versus Fibrinolytic Treatment Delay***

*****Solid circles** = information from trials included in Fibrinolytic Therapy Trialists' Collaborative Group analysis; **open circles** = information from additional trials; **small squares** = data beyond scale of x/y cross. The linear and nonlinear regression lines are fitted within these data, weighted by inverse of the variance of the absolute benefit in each datapoint. **Solid squares** = average effects in 6 time-to-treatment groups (areas of squares inversely proportional to variance of absolute benefit described). Reproduced with permission from Boersma et al. (28).

Practical Limitations of Primary PCI as a Universal Reperfusion Strategy

Primary PCI would likely become the universal "dominant default strategy" for prompt early reperfusion if resource and logistical constraints did not limit its more broad-based adoption. As discussed previously, time to reperfusion is the most critical variable in STEMI management and is particularly important for PCI. Availability of invasive facilities is another important determinant of the feasibility of PCI. It

STEP 1: Assess time and risk
- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time required for transport to a skilled PCI lab

STEP 2: Determine if fibrinolysis or invasive srtategy is preferred

If presentation is less than 3 hours and there is no delay to an invasive strategy, there is no preference for either strategy

Fibrinolysis is generally preferred if:
- *Early presentation (3 hours from symptom onset and delay to invasive strategy) (see below)*
- *Invasive strategy is not an option*
  Catheterization lab occupied/not available
  Vascular access difficulties
  Lack of access to a skilled PCI lab[†‡]
- *Delay to invasive strategy*
  Prolonged transport
  (Door-to- balloon) – (door-to-needle) is >1 hour[*§]
  Medical contact-to-balloon or door-to-balloon is >90 minutes

An invasive strategy is generally preferred if:
- *Skilled PCI lab available with surgical backup[†‡]*
  Medical contact-to-balloon or-door-to-balloon is <90 minutes
  (Door-to-balloon) – (door-to-needle) is <1 hour[*]
- *High risk from STEMI*
  Cardiogenic shock
  Killip class is ≥3
- *Contraindications to fibrinolysis including increased risk of bleeding and ICH*
- *Late presentation*
  Symptom onset was >3 hours ago
- *Diagnosis of STEMI is in doubt*

Figure 2   **American College of Cardiology/American Heart Association Guidelines for Selecting a Reperfusion Strategy**

*Operator experience >75 primary PCI cases per year. †Team experience >36 primary PCI cases per year. ‡Applies to fibrin-specific agents. §This calculation implies that the estimated delay to the implementation of the invasive strategy is >1 h versus initiation of fibrinolytic therapy immediately with a fibrin-specific agent. Reprinted with permission from Antman et al. (2). ICH = intracerebral hemorrhage; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

has been estimated that <25% of acute-care hospitals in the U.S. have PCI programs (8); unless rapid transfer to an appropriately staffed facility is available and systems are in place to make it possible, PCI generally involves unacceptable delays. Door-to-balloon times of <90 min are achieved in only approximately one-third of patients who do not require transfer (32) and in a much smaller proportion of patients presenting to hospitals without ready access to primary PCI. Real-world data from the NRMI-3 and -4 databases (n = 4,278) showed that total door-to-balloon times of <90 and <120 min were achieved in only 4.2% and 16.2%, respectively, of STEMI patients transferred for PCI (median 180 min) (Fig. 3) (8).

Because an estimated 80% of the U.S. population lives within 60 min of a PCI hospital (40), programs are being developed and evaluated nationwide which involve direct emergency medical services (EMS) delivery to the nearest primary PCI center and rapid transfer systems (41). However, at present few such programs are operational. The emergency medical transportation systems that are currently in place are likely to remain in place for the foreseeable future and are not conducive to making primary PCI a realistic alternative for most of the U.S. population. Additional barriers to the rapid transport of patients with STEMI to primary PCI facilities include a minority of

EMS systems having 12-lead ECG capabilities; a minority of patients with chest pain transported by EMS having STEMI; mandates to transport patients to the nearest facility, even when the facility is not primary PCI capable and fibrinolysis is contraindicated; and long transport
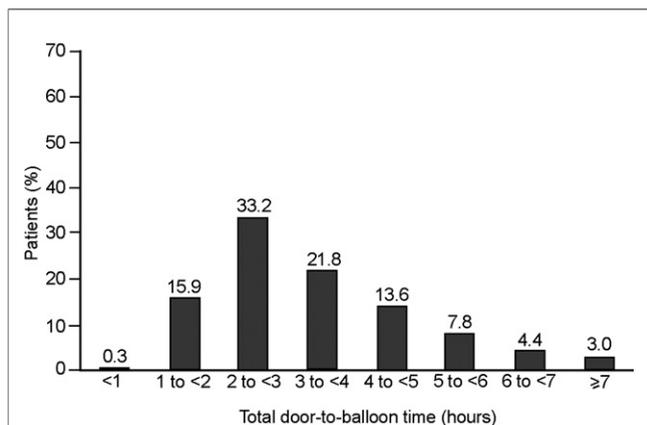
Figure 3   **Door-to-Balloon Time for Patients Transferred for Primary Percutaneous Coronary Intervention**

Reprinted with permission from Nallamothu et al. (8).

times in both metropolitan and rural areas (31). In addition, when a patient is initially brought to a non–PCI-capable facility and is considered appropriate for primary PCI, they may have to wait for the next available ambulance for transport (31).

Rapid mobilization of the multidisciplinary catheterization team is a critical time-dependent variable specific to primary PCI, especially during routine "off-shift" night and weekend hours. In an analysis of NRMI-3 and -4 data, the factors associated with delayed treatment included hospital presentation during off-hours (Table 1) (8). Another analysis of NRMI-3 and -4 data found that presentation during off-hours prolonged door-to-balloon times by 21.3 min (p < 0.001) and reduced the proportion of patients undergoing primary PCI within the ACC/AHA guideline-recommended time frame (Fig. 4A) (42). The increase in door-to-needle time during off-hours, although statistically significant, was only 1 minute (p < 0.001). Almost all of the observed delay for PCI during off-hours was attributed to additional time between ECG completion and arrival in the catheterization laboratory (20.8 min; p < 0.001) (Fig. 4B). Adjusted in-hospital mortality for patients presenting during off-hours was significantly higher than for patients admitted during regular hours (p = 0.02); this difference was no longer significant after adjustment for reperfusion treatment time. Thus, time of day and day of week, as well as the institutional ability to activate the

cardiac catheterization laboratory in an expedient manner, must be considered when a reperfusion strategy is selected.

Another study using NRMI-3 and -4 data highlighted the importance of door-to-balloon times in STEMI. In patients with STEMI (n = 29,222) who underwent PCI within 6 h of presentation, longer door-to-balloon times were associated with higher in-hospital mortality (3.0%, 4.2%, 5.7%, and 7.4% for door-to-balloon times of ≤90, 91 to 120, 121 to 150, and >150 min, respectively; p < 0.01); this was seen within each of the subgroups of patients with symptom onset-to-door times of ≤1 h, 1 to 2 h, or >2 h (43). Although this type of analysis may be confounded because delays are also more common in sicker patients, it supports the overwhelming data showing the relationship of time to reperfusion and outcome. Other studies suggest that delay to primary PCI is especially important in earlier presenting patients (24).

The findings of these studies underscore the importance of realistically assessing transfer and catheterization laboratory activation times before selecting a reperfusion strategy, and implementing organizational strategies to reduce door-to-balloon time for patients transferred for primary PCI. Henry et al. reported that implementation of a standardized protocol and integrated transfer system significantly reduced door-to-balloon times (44). Several studies have shown a relationship between obtaining prehospital ECGs and more rapid treatment with both fibrinolytic therapy and primary

Table 1	Characteristics Associated With Total Door-to-Balloon Time After Multivariate Adjustment	
Characteristic	**Door-to-Balloon Time, min (95% CI)**	**p Value**
Diabetes mellitus	+8.2 (2.5 to 14.0)	0.004
Prior coronary artery bypass graft	+17.4 (7.0 to 28.0)	<0.001
No chest pain at presentation	+17.9 (7.0 to 29.1)	0.001
Primary ECG findings		
Left bundle branch block	—	<0.001
2 leads with ST-segment elevation	−8.3 (−21.5 to 5.7)	
3 or 4 leads with ST-segment elevation	−31.7 (−42.5 to −20.5)	
≥5 leads with ST-segment elevation	−43.8 (−54.6 to −32.5)	
Symptoms before arrival		
≤2 h	—	<0.001
>2–6 h	+13.5 (7.5 to 19.7)	
>6–12 h	+30.4 (20.7 to 40.4)	
Time and day of arrival		
Weekday between 12 AM and 7:59 AM*	+12.9 (5.4 to 20.8)	<0.001
Weekend between 12 AM and 7:59 AM*	+16.2 (5.3 to 27.4)	0.003
Facility type		
Urban and nonteaching	—	<0.001
Urban and teaching	+23.9 (12.6 to 35.6)	
Rural and nonteaching	+28.0 (4.4 to 53.2)	
Rural and teaching	+73.0 (30.6 to 121.2)	
Percentage of reperfusion therapy patients receiving PCI		
<20	+21.2 (−5.9 to 50.5)	
20–90	—	0.16
>90	−7.3 (−19.8 to 5.9)	

*Compared with weekday arrival between 4 PM and 12 AM. Reprinted with permission from Nallamothu et al. (8).
CI = confidence interval; ECG = electrocardiogram; PCI = percutaneous coronary intervention.
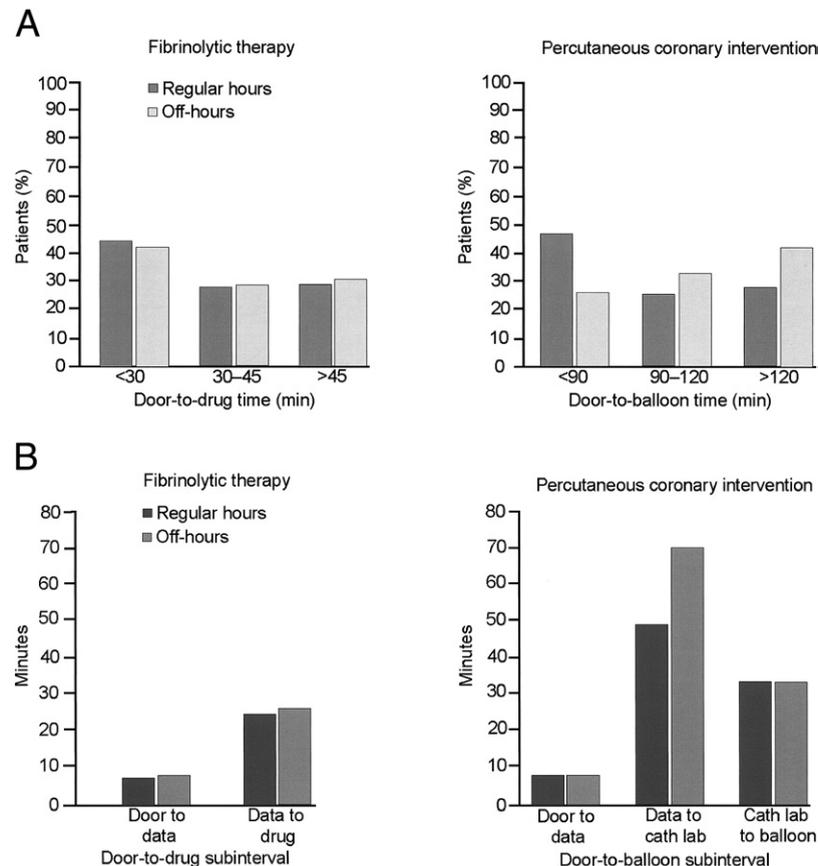
Figure 4   **Influence of Patient Arrival Period on Time to Treatment**

Regular hours include weekdays, 7 AM to 5 PM. Off hours include weekdays, 5 PM to 7 AM, and all weekend times. **(A)** Guideline adherence for fibrinolytic therapy and percutaneous coronary intervention (PCI) by patient arrival period. The American College of Cardiology/American Heart Association guidelines recommend that door-to-drug times be ≤30 min and door-to-balloon time ≤90 min. **(B)** Door-to-drug and door-to-balloon subintervals by patient arrival. Door to data is time from hospital arrival to electrocardiogram (ECG) completion. Data to drug is time from ECG completion to administration of fibrinolytic therapy. Data to catheter lab is time from ECG completion to arrival at catheterization laboratory. Catheter lab to balloon is time from arrival at cardiac catheterization laboratory to balloon inflation. Reprinted with permission from Magid et al. (42).

PCI (45–47). As a consequence, the coordinating committee of the National Heart, Lung, and Blood Institute's National Heart Attack Alert Program called for implementation of prehospital 12-lead ECG programs by EMS systems providing advanced life support, to identify patients with STEMI before arrival at the ED and thus facilitate more rapid treatment (48). It has also been suggested that a national policy for the treatment of patients with STEMI should be adopted in the U.S., to develop a coordinated system of care, modeled after the Level I Trauma System, within which patients with STEMI are transported directly to designated centers (49). However, this issue remains controversial; in a recent paper, Rathore et al. (50) cautioned that the expected benefits of "regionalization" of STEMI care may not be fully realized, and suggested that more compelling evidence of potential benefits and greater understanding of potential consequences are needed before such a policy could be feasibly implemented nationally.

Clinical outcomes following PCI have been shown to be influenced by the institutional volume of primary PCI performed, with significantly better outcomes achieved in higher-volume centers (25,51). The ACC/AHA STEMI guidelines specify that one of the criteria for an invasive reperfusion strategy to be preferred is availability of a skilled PCI laboratory (operator and team experience of >75 and >36 primary PCI cases per year, respectively) (2). The guidelines include availability of surgical backup as another criterion for preferring an invasive strategy (2). However, a report from the ACC National Cardiovascular Data Registry indicates that PCI is increasingly being performed at facilities without on-site surgical backup (52), and it has been suggested that such a recommendation may be unwarranted, based on recent data from the Swedish Coronary Angiography and Angioplasty Registry (53).

Overall, in the appropriate clinical, temporal, and logistical setting, PCI has greatly advanced the care of

STEMI patients. However, when the criteria required for optimal benefit of PCI cannot realistically be achieved, as is the case for many patients, pharmacologic reperfusion should not be delayed. When necessary, rescue PCI remains an important option after fibrinolytic therapy, with studies showing that appropriate use of rescue PCI improves outcomes compared with conservative therapy (54,55), with a similar risk of major bleeding complications to that seen with primary PCI (56).
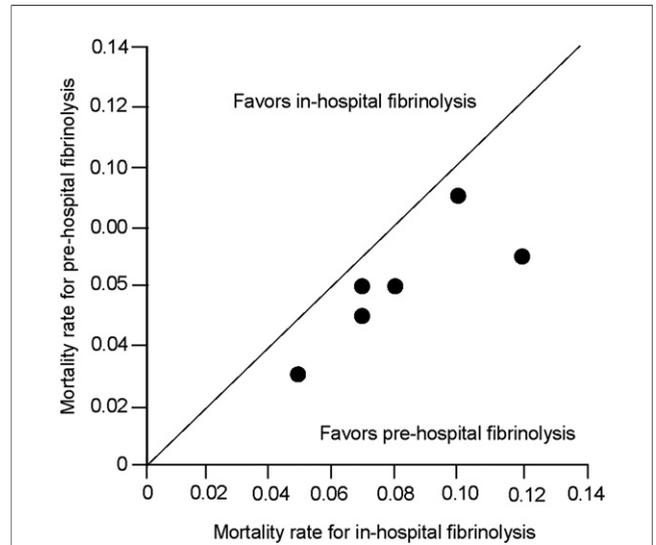
Role of Fibrinolysis

The practical limitations of primary PCI that limit its becoming the universal "dominant default strategy" for prompt reperfusion inevitably lead to a strategy of early fibrinolysis as having a more prominent role. Results from many studies have demonstrated time dependence of the benefit of PCI versus fibrinolysis (17,18,57). An analysis of 21 trials showed that as PCI-related time delay increased, absolute mortality reduction at 4 to 6 weeks favoring primary PCI versus fibrinolysis decreased (0.94% decrease per additional 10-min delay; $p = 0.006$) (Fig. 5), with apparent equivalence after a PCI-related time delay of 62 min (57). This is reflected by the ACC/AHA STEMI guidelines, which indicate that fibrinolysis is generally preferred when there is a delay to implementing an invasive strategy such that door-to-balloon time minus door-to-needle time exceeds 1 h. Thus, where PCI cannot be performed within the optimal time frame, fibrinolysis can provide rapid reperfusion. Prehospital fibrinolysis offers the best potential to improve outcomes for patients with STEMI in the U.S. by providing even more rapid reperfusion.

Figure 6 — **Mortality Benefit With Prehospital Fibrinolysis Versus Inhospital Fibrinolysis**

Diagonal line represents equal rates; **above line** favors inhospital fibrinolysis and **below line** favors prehospital fibrinolysis. Reprinted with permission from Morrison et al. (61).

Prehospital Fibrinolysis

A number of studies have demonstrated that prehospital fibrinolytic administration can significantly decrease time from symptom onset to treatment (58–61). Patients receiving prehospital fibrinolysis achieved resolution of ST-segment elevation earlier than historical controls, indicating a decrease in time to reperfusion (60). This is reflected by several studies showing improved outcomes, such as mortality (Fig. 6), with prehospital fibrinolysis (59,61,62).

In a large meta-analysis, mortality was significantly lower among patients receiving prehospital versus inhospital fibrinolysis (odds ratio 0.83; 95% confidence interval 0.70 to 0.98) (61). Early administration of prehospital fibrinolysis is particularly beneficial (58,62). Comparison of prehospital fibrinolysis with transfer to a hospital for immediate PCI in the CAPTIM trial revealed no statistically significant between-treatment difference regarding the composite primary end point (death, nonfatal reinfarction, and nonfatal disabling stroke within 30 days) or mortality, suggesting that PCI did not confer an event-free survival advantage (63). Among patients randomized <2 h after symptom onset, there was a strong trend toward lower 30-day mortality with prehospital fibrinolysis (2.2% vs. 5.7%; $p = 0.058$) (17).

Clinical trials data support the safety and efficacy of prehospital fibrinolysis in the treatment of STEMI. Based on the many studies showing the benefit of early initiation of fibrinolytic therapy, the ACC/AHA STEMI guidelines state that "it seems reasonable to expect that if fibrinolytic therapy could be started at the time of prehospital evaluation, a greater number of lives could be saved" (2). This

Figure 5 — **Absolute RR in 4- to 6-Week Mortality Rates With Primary PCI as a Function of PCI-Related Time Delay**

Circle size reflects the sample size of the individual study. The **solid line** represents the weighted meta-regression. Values >0 favor PCI and values <0 favor fibrinolysis. PCI = percutaneous coronary intervention; RR = risk reduction. Reprinted with permission from Nallamothu et al. (57).

treatment is feasible in locations where the fibrinolytic is administered by paramedics (under the supervision of a physician), general practitioners, or medical intensivists. Prehospital fibrinolysis may also decrease time to treatment in other settings, including rural or congested urban areas where transportation times are long, as well as areas in which primary PCI facilities are not immediately available or where time to mobilize the appropriate team may be excessive. Unfortunately, while there have been a few successful programs in rural U.S. settings, the U.S. health care system has not fostered the availability of prehospital fibrinolysis. This may relate to generally poor funding of EMS, especially in rural environments, and to concerns over legal liability, particularly when critical decisions are made outside of traditional hospital settings. Implementation of prehospital fibrinolysis will require interest, support, and participation from civic and community leaders, hospital administrators, cardiologists, and ED physicians; appropriate structuring, resourcing and medical direction for EMS services; and resolution of cost issues relating to provision of prehospital treatment, e.g., through fee-for-service reimbursement of EMS agencies for drugs administered by EMS personnel (64).

The choice of a fibrinolytic agent. There are several fibrinolytic agents currently approved for the management of STEMI; key characteristics of these agents are summarized in Table 2 (2,65–76). The fibrinolytics approved for STEMI appear to differ in a number of ways, such as fibrin specificity.

DOSING CONSIDERATIONS. The development of bolus and of nonweight-based dosing as alternatives to intravenous infusion regimens with dosing based on body weight has the potential to simplify fibrinolytic administration (60,63,77), which may be especially important in the prehospital setting. The use of bolus fibrinolytic therapy, such as reteplase or tenecteplase, is appealing to EMS personnel and may enable treatment to be initiated more quickly than with an agent administered by infusion (78). Nonweight-based dos-

ing may have the potential to decrease treatment errors, because visual approximation of a patient's weight is subject to substantial errors (79–83). In the ASSENT-3 PLUS (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Plus) study, approximately 20% of patients received >105% of the correct dosage of weight-based single-bolus tenecteplase administered prehospital; this was associated with an approximately 2-fold rate of intracerebral hemorrhage versus lower doses among patients receiving unfractionated heparin as the concomitant antithrombin agent (84). Mortality was also shown to be increased in patients receiving an incorrect dosage of streptokinase or alteplase, which are dosed by intravenous infusion based on body weight (85).

BLEEDING COMPLICATIONS. Bleeding complications are the main risks associated with fibrinolysis, although these are usually only minor (e.g., puncture site bleeding after PCI). Major bleeding occurs in approximately 5% to 6% of patients treated with fibrinolytics (75,76), and may be reduced by using more fibrin-specific agents and/or using heparin more carefully. Although severe bleeding complications such as intracranial hemorrhage can be associated with high mortality, such serious complications occur in approximately 1% to 2% of patients treated with fibrinolytics (75,76), although more commonly in the elderly, who comprise a larger proportion of patients in general practice than in clinical trials.

Importance of Heparin Dosing

The ACC/AHA STEMI guidelines call for careful weight-based dosing of unfractionated heparin with fibrinolytic therapy: The bolus should be 60 U/kg up to a maximum of 4,000 U and initial infusion 12 U/kg/h up to a maximum initial dose of 1,000 U/h (2). A comparison of the ASSENT-2 and -3 trials showed that this careful dosing, when combined with down-titration of heparin as early as 3 h based on high activated partial thromboplastin times,

Table 2	Characteristics of Fibrinolytics Commonly Used in the Treatment of STEMI			
	Streptokinase	**Alteplase**	**Reteplase**	**Tenecteplase**
Dose	1.5 MU over 30–60 min	Up to 100 mg in 90 min (based on weight)*	10 U × 2 (30 min apart), each over 2 min	30–50 mg based on weight†
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
TIMI flow grade 3, %	~30	~50	~60	~60
TIMI flow grade 2/3, %	~55	~75	~83	~83
Rate of intracerebral hemorrhage, %	~0.4	~0.4–0.7 (100 mg dose)	~0.8	~0.9
Fibrin specificity	−	++	+	+++
Fibrin affinity	−	+++	+	++++
Cost per recommended MI dose (U. S.$)‡	562.50	3,404.78	2,872.50	2,917.48 for 50 mg

*Bolus 15 mg, infusion 0.75 mg/kg times 30 min (maximum 50 mg), then 0.5 mg/kg not to exceed 35 mg over the next 60 min to an overall maximum of 100 mg. †30 mg for weight <60 kg, 35 mg for 60 to 69 kg, 40 mg for 70 to 79 kg, 45 mg for 80 to 89 kg, and 50 mg for 90 kg or more. ‡Red Book, 2005.
MI = myocardial infarction; MU = megaunits; STEMI = ST-elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

was associated with half the bleeding rate compared with nonfully weight-adjusted dosing (86).

Facilitated PCI and Pharmacoinvasive Therapy

Pharmacoinvasive therapy is a strategy of planned PCI after initial pharmacologic reperfusion. In addition to potentially reducing time to initiation of treatment, an important rationale for this strategy is that patients with TIMI flow grade 2 to 3 before PCI achieve better clinical outcomes (87–90).

A number of recent studies have evaluated so-called "facilitated PCI," where pharmacologic therapy is followed immediately by PCI, but at present the data suggest that it is not beneficial and may be harmful. Worse outcomes were seen with facilitated PCI versus primary PCI in a recent meta-analysis (91). However, that meta-analysis was largely driven by the largest trial to date, the ASSENT-4 PCI trial, which showed that routine immediate PCI following full-dose tenecteplase therapy was associated with higher rates of abrupt vessel closure, reinfarction, and death versus primary PCI alone in patients with only modest treatment delays and treated with low-dose heparin (92). One implication of this trial is that patients receiving full-dose fibrinolytic therapy who have signs of reperfusion should not undergo routine immediate PCI, because there may be an early prothrombotic state following fibrinolytic therapy that may increase PCI risk.

Abciximab has been shown to modestly reduce mortality, given either prehospital, as seen in the ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up) study (93), or in general in the setting of primary PCI (but not with fibrinolysis), as shown in a meta-analysis (94).

The WEST (Which Early ST-Elevation Myocardial Infarction Therapy) trial randomized 304 patients to fibrinolytic therapy at the earliest contact (prehospital or in referral hospital, with clopidogrel and enoxaparin), with or without routine rescue or early invasive therapy, or to primary PCI (95). Tenecteplase and enoxaparin followed by routine early invasive therapy had similar death and MI rates to primary PCI. This supports the need for further trials to assess the role of optimal early fibrinolytic therapy (including prehospital) and antithrombotic therapy versus primary PCI in settings where very rapid PCI is not available.

Recently, the Leipzig Prehospital Fibrinolysis Group compared prehospital combination fibrinolysis with half-dose reteplase (two 5-U boluses) plus intravenous abciximab in conjunction with standard care and an alternative strategy of prehospital combination fibrinolysis followed by facilitated PCI and found that the facilitated PCI strategy was associated with significantly smaller infarct size and a significantly higher rate of complete ST-segment resolution (96), supporting the need for further trials. Thus, the use of adjunctive glycoprotein IIb/IIIa inhibition may be impor-

tant to the success of this approach. Additionally, a recent cost-effectiveness study suggests that a facilitated PCI strategy may have the potential for cost benefits in addition to clinical benefits for patients with STEMI being transferred from community hospitals to undergo PCI (97).

Although a facilitated PCI approach remains controversial, and is presently regarded as a class IIb recommendation in the ACC/AHA STEMI management guidelines (2), these data nonetheless suggest that there may be benefit in selected instances where tertiary hospitals and community hospitals can develop an integrated care delivery model. It is hoped that the FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) study, examining primary PCI with intravenous abciximab or facilitated PCI with abciximab alone or with reteplase, will further answer questions regarding the interaction between medical and interventional care in STEMI (98). In addition, future studies may determine the optimal time frame for PCI after fibrinolysis; data suggest that delayed PCI may have benefits over immediate PCI after fibrinolysis (99).

"Hub and Spoke" Network Model

Another potentially attractive approach to enhancing clinical outcomes in STEMI is the establishment of integrated systems of care between participating hospitals without cardiac catheterization capability (spoke hospitals) and a high-volume tertiary center (hub hospital) whereby the early management of STEMI can be systematically coordinated by emergency medicine and cardiology personnel at all participating hospitals. The appeal of this approach is that it seeks to make optimal use of existing personnel and resources at hub and spoke hospitals without incurring additional institutional costs and recurring expenditures at those spoke hospitals that would require considerable additional capital to mount and maintain a primary PCI program. In such a model, it is essential that both cardiologists and emergency physicians at the hub and spoke hospitals communicate closely and achieve, through consensus, a coordinated management approach to expedite prompt early pharmacologic reperfusion at the spoke hospitals followed by prompt triage and transport to the hub facility for primary PCI.

One such model has been developed in the Hartford, Connecticut, area, comprising 5 spoke hospitals without on-site catheterization or PCI capability in surrounding communities and a single high-volume tertiary center with full 24/7 primary PCI capability. Over the past 6 years, 1,560 consecutive STEMI patients have been followed prospectively, of which 60% had their initial medical contact at community hospitals. Among the first cohort of STEMI patients in 2000 to 2003, 808 patients with acute STEMI within 6 h of symptom onset were eligible for a pharmacoinvasive approach. The 30-day mortality was 1.6% among patients who initially presented to community hospitals and received bolus fibrinolytic and glycoprotein IIb/IIIa inhibi-

tor therapy and 1.7% for patients who presented initially to the hub hospital and proceeded directly to primary PCI. By contrast, patients who presented initially to community hospitals, did not receive antecedent fibrinolytic therapy and/or glycoprotein IIb/IIIa inhibitors, and were transferred directly to the hub hospital for primary PCI had a 30-day mortality of 5.5% (100). In patients presenting initially to community hospitals, total ischemic time (time from first medical contact at spoke hospital to first intracoronary balloon inflation at hub hospital) was 241 min. These data underscore some of the logistical complexities and inevitable time delays encountered in patient transport from outlying community hospitals and highlight some of the benefits that might be achievable by combining early pharmacologic reperfusion with expedited PCI using an integrated "hub and spoke" network approach.

Time to treatment for regional management of STEMI patients who require transfer has been shown to be improved by implementation at the Mayo Clinic in Rochester, Minnesota, of a Fast Track protocol to minimize delays (101). Similarly, a standardized protocol and integrated system of transfer for patients with STEMI requiring PCI has been successfully implemented at 29 community hospitals in Minnesota, resulting in significant reductions in door-to-balloon times (44).

These examples demonstrate that it is feasible to implement procedures to minimize transfer-related time delays in initiating STEMI treatment. There is continuing interest in pharmacoinvasive strategies, which developed out of the unacceptably long delays associated with transfer for PCI. Trials assessing different adjunctive pharmacologic regimens are ongoing; in particular, there is interest in using a reduced dose of fibrinolytics to attempt to minimize the risk of intracerebral and other bleeding complications, in combination with glycoprotein IIb/IIIa inhibitors to enhance clot lysis and prevent additional platelet aggregation on the clot (102).

Conclusions

Re-establishing prompt coronary blood flow and myocardial tissue perfusion as quickly as possible remains the most important principle underlying early STEMI management. Primary PCI and fibrinolysis are the 2 principal methods proven to accomplish this and thus decrease mortality. Primary PCI is a superior strategy when performed within 90 min of medical contact; however, this ACC/AHA quality of care benchmark is very often not achieved. Patients who initially present to hospitals without PCI capabilities remain one of the largest challenges to achieving a more widespread survival benefit with early reperfusion. Although primary PCI remains the "gold standard" of early treatment for STEMI, the degree to which this can be feasibly expanded in the U.S. remains uncertain. Logistical, financial, and political issues abound, and it is unclear to what degree expanding PCI capability and access will lead

to improved clinical outcomes, especially given that low-volume (or stand-alone) primary PCI centers may struggle to achieve true 24/7 capability for prompt mechanical reperfusion. In addition, expansion of PCI capability and access alone may be offset by the costs of the transportation system and keeping low-volume catheterization laboratories open during off-hours and the potential dangers of performing primary PCI by unskilled low-volume operators.

Beyond the window of opportunity of achieving door-to-balloon times of <90 min, the advantage of PCI over fibrinolysis is diminished. For STEMI patients who present within 3 h of symptom onset, data showing superiority of mechanical versus pharmacologic reperfusion are less compelling, and more rapid treatment is even more important. Equally importantly, studies based on U.S. registries of STEMI often show a substantial delay to treatment in patients who undergo primary PCI, particularly in those who may not have access to qualified PCI facilities, require transfer for primary PCI, or who present for medical care during off-hours. These delays must be considered when a reperfusion strategy is selected, because such patients may achieve greater benefit with prompt fibrinolysis versus delayed primary PCI.

Many groups are working on developing highly organized networks of EMS, ED, hospital administrations, and cardiology to enhance the availability of rapid primary PCI, as well as the use of rapid fibrinolytic therapy when rapid PCI is not available. To date, trials of fibrinolytic therapy followed by immediate routine PCI show no benefit and perhaps harm, although ongoing trials of facilitated PCI will provide additional information. The role for primary PCI for patients with modest delays beyond 90 min, compared with earliest fibrinolytic therapy with routine rescue PCI, is also being studied. In the meantime, the most compelling need is to work toward providing rapid reperfusion therapy to all eligible patients with STEMI. For the many patients who will not undergo primary PCI within optimal time frames, this may be most effectively achieved by administration of fibrinolytics either prehospital or at a spoke hospital, followed by transfer to a hospital with PCI facilities available at all times.

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