

# Diagnosis and Management of ST Elevation Myocardial Infarction: A Review of the Recent Literature and Practice Guidelines

SIGRID A. HAHN, M.D.<sup>1</sup>, AND CHARLES CHANDLER, M.D.<sup>2</sup>

## Abstract

There is a large volume of literature available to guide the peri-infarct management of ST elevation myocardial infarction (STEMI). Most of this literature focuses on improving the availability and efficacy of reperfusion therapy. The purpose of this article is to review contemporary scientific evidence and guideline recommendations regarding the diagnosis and therapy of STEMI.

Studies and epidemiological data were identified using Medline, the Cochrane Database, and an Internet search engine. Medline was searched for landmark and recent publications using the following key words: STEMI, guidelines, epidemiology, reperfusion, fibrinolytics, percutaneous coronary intervention (PCI), facilitated PCI, transfer, delay, clopidogrel, glycoprotein IIb/IIIa, low-molecular-weight heparin (LMWH), beta-blockers, nitrates, and angiotensin-converting enzyme (ACE) inhibitors.

The data accessed indicate that urgent reperfusion with either fibrinolytics or percutaneous intervention should be considered for every patient having symptoms of myocardial infarction with ST segment elevation or a bundle branch block. The utility of combined mechanical and pharmacological reperfusion is currently under investigation. Ancillary treatments may utilize clopidogrel, glycoprotein IIb/IIIa inhibitors, or low molecular weight heparin, depending on the primary reperfusion strategy used. Comprehensive clinical practice guidelines incorporate much of the available contemporary evidence, and are important resources for the evidence-based management of STEMI.

**Key Words:** Diagnosis, fibrinolysis, myocardial infarction, PCI, reperfusion, review, STEMI, therapy, treatment.

## Introduction

WITH THE DEVELOPMENT of reperfusion strategies and ancillary therapies over the past three decades, the prognosis of ST elevation myocardial infarction (STEMI) has improved significantly. There is a large body of literature addressing the optimal management of these patients in the acute setting, much of which has been incorporated into recent clinical practice guidelines (1–4). In fact, data available from the National Registry of Myocardial Infarction (NRMIs) has revealed a steady increase between 1990 and 1999 in the percentage of practitioners who adhere to the published guidelines (5). This evidence-based approach may have helped to reduce the in-hospital mortality among patients with STEMI to the current level of approximately 9.5% (5). The purpose of this article is to review current evidence and recommendations for the evaluation and early treatment of STEMI.

## Epidemiology

Acute myocardial infarction (AMI) remains a public health problem of epidemic proportions. Recent data from the American Heart Association (AHA) reveal a prevalence of myocardial infarction (MI) of 1.9–5.2%, which varies by age, sex, and ethnicity (6). In the United States annually, there are 565,000 first-time, and 300,000 recurrent, myocardial infarctions (6). Interestingly, in the last decade the NRMIs registries have recorded a decrease in the percentage of patients with myocardial infarction who present with ST segment elevation (from 36% to 27%,  $p \leq 0.001$ ), while the percentage presenting without ST segment elevation has increased (from 45% to 63%,  $p \leq 0.001$ ) (5). But rather than representing a true change in the incidence of disease, this may be due to the growing use of troponin assays, which have increased overall diagnostic sensitivity for myocardial infarction.

## Diagnosis

### Symptomatology

Although the formal diagnosis of AMI requires documentation of elevated cardiac biomarkers (7), time delays in biomarker elevation limit their usefulness in early decision making. For this reason,

<sup>1</sup>Clinical Instructor and <sup>2</sup>Resident, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Sigrid A. Hahn, M.D., Department of Emergency Medicine, Box 1149, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; e-mail: Sigrid.Hahn@mssm.edu

This work was not supported by any grants or corporate sponsorship.

Accepted for publication October 2005.

### Glossary

|  |   |
|--|---|
| ACC = American College of Cardiology             | ICH = intracranial hemorrhage                     |
| ACCP = American College of Chest Physicians      | IRA = infarct-related artery                      |
| ACE = angiotensin-converting enzyme              | LBBB = left BBB                                   |
| ACEP = American College of Emergency Physicians  | LMWH = low-molecular-weight heparin               |
| ACS = acute coronary syndrome                    | MI = myocardial infarction                        |
| AHA = American Heart Association                 | MIR = Myocardial Infarction Registry              |
| AMI = acute MI                                   | MITRA = Maximal Individual Therapy in AMI         |
| aPTT = activated partial thromboplastin time     | NRMI = National Registry of Myocardial Infarction |
| ASA = aspirin                                    | PCI = percutaneous coronary intervention          |
| BBB = bundle branch block                        | RBBB = right BBB                                  |
| CABG = coronary artery bypass graft              | RCT = randomized controlled trial                 |
| ECG = electrocardiogram                          | RV = right ventricular                            |
| ED = emergency department                        | STEMI = ST elevation myocardial infarction        |
| ESC = European Society of Cardiology             | TIMI = thrombolysis in myocardial infarction      |
| GP IIb/IIIa = glycoprotein IIb/IIIa              | t-PA = tissue plasminogen activator               |
| GRACE = Global Registry of Acute Coronary Events | UFH = unfractionated heparin                      |

initial diagnostic and treatment decisions rely primarily on clinical features and electrocardiogram (ECG) findings. Time of symptom onset is important, as it affects management options. Symptom onset within 12 hours is the generally accepted window of eligibility for fibrinolytic therapy (1). Despite an absence of data demonstrating a mortality benefit after this 12-hour window (8), guidelines state that fibrinolytics should also be administered to patients presenting between 12 and 24 hours if they have persistent symptoms and ST segment elevation (1). The therapeutic window is similar for primary percutaneous coronary intervention (PCI), with eligibility extending to 12–24 hours after symptom onset if ischemic symptoms are persistent(1).

Ischemic symptoms are often described as “typical” (with chest pain) or “atypical” (without chest pain) (Table 1, [9]). Recently, the multinational Global Registry of Acute Coronary Events (GRACE) found that of 20,881 patients with acute coronary syndrome (ACS), 1,763 (8.4%) presented without chest pain; of those patients without chest pain, the most common atypical chief complaint was dyspnea (9). Although it is frequently assumed that a typical presentation is more commonly associated with ECG changes, in fact, patients with

both typical and atypical symptoms are equally likely to have ischemic changes on the index ECG (9). Of concern, delayed diagnosis for patients with atypical symptoms appears common. In the GRACE registry, this group received an admitting diagnosis other than ACS 24% of the time (vs. 2.4% of the typical presenters). Presumably as a result, patients with atypical presentations were significantly less likely to receive fibrinolysis (25.6% vs. 45.6%,  $p < 0.001$ ), primary PCI (11.0% vs. 21.0%,  $p < 0.001$ ), or ancillary therapy such as aspirin (ASA) or beta-blockers. Not surprisingly, many of the risk factors associated with an atypical presentation (Table 2, [10]) have also been identified as risk factors for delayed reperfusion (11, 12).

### Electrocardiographic Diagnosis

The ECG is the primary diagnostic tool used to identify an STEMI, and is of central importance because it identifies those patients who are candi-

**TABLE 1**

*Most Common “Atypical” Chief Complaints with Myocardial Infarction (9)*

|                        |       |
|------------------------|-------|
| Dyspnea                | (49%) |
| Diaphoresis            | (26%) |
| Nausea or vomiting     | (24%) |
| Pre-syncope or syncope | (19%) |

**TABLE 2**

*Risk Factors for Presentation with and without Chest Pain (10)*

| With Chest Pain      | Without Chest Pain  |
|----------------------|---------------------|
| Tobacco use          | Older age           |
| Hypercholesterolemia | Diabetes            |
| Prior PCI or CABG    | Prior heart failure |
|                      | Nonwhite race       |
|                      | Female sex          |

PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

dates for emergent reperfusion therapy. The definition of ST elevation “indicative of myocardial ischemia,” as proposed by the Joint Committee of the European Society of Cardiology (ESC) and American College of Cardiology (ACC) for the redefinition of MI, is a new, or presumed new, ST segment elevation in 2 or more contiguous leads of at least 2 mm at the J point in leads V1–V3, or 1 mm in other leads (7). It should be noted that, historically, inclusion criteria for reperfusion trials have varied in the amount of ST elevation required to diagnose a myocardial infarct. In the 2004 guidelines for management of STEMI, the ACC and AHA recommend that patients with symptoms of AMI and ST segment elevation of 1 mm in any 2 contiguous leads be considered for reperfusion therapy (1). In their discussion, the ACC and AHA acknowledge that using a 2 mm cut-off would increase the specificity of diagnosis of anteroseptal MI in the setting of early repolarization. Recognizing this diagnostic ambiguity, the American College of Emergency Physicians (ACEP) provided more detailed ECG criteria for emergent fibrinolytic therapy: ST segment elevation greater than 1 mm in 2 or more contiguous leads that are not characteristic of early repolarization or pericarditis, nor of a repolarization abnormality from left ventricular hypertrophy or bundle branch block (BBB) (4).

Decision-making is more complicated when a BBB confounds ECG interpretation. The ACC and AHA recommend reperfusion therapy for patients with “new or presumably new” left bundle branch block (LBBB) (1), and the American College of Chest Physicians (ACCP) recommends treatment for “LBBB of unknown duration” (3). However, several trials and the large meta-analysis of fibrinolytic therapy by the FTT Collaborative Group found a significant mortality benefit for patients presenting with any BBB, not just new LBBB (8, 13, 14). ACEP therefore recommends considering emergent reperfusion therapy for patients with clinical presentation suggestive of AMI and with a right, left, paced, atypical, new, or old BBB (4).

Reperfusion of any patient with suggestive symptoms and a BBB, while an option, is a strategy favoring diagnostic sensitivity over specificity. For this reason, attempts have been made to improve diagnostic accuracy in the setting of a conduction delay. A right bundle branch block (RBBB) generally confounds the ECG interpretation of an acute infarct less than does an LBBB; findings of myocardial infarction are usually evident with RBBB because electrocardiographic signs of early activation of the left ventricle are not altered (15). In contrast, identification of myocardial ischemia in

the presence of LBBB is quite difficult. Numerous criteria exist for the diagnosis of AMI in this setting, of which the most widely accepted are those developed by Sgarbossa (Table 3, [16]). When used in combination, these criteria were initially reported to have a sensitivity of 36% and specificity of 96%. Performance characteristics in follow-up studies have been somewhat variable, and inter-observer agreement on the ECG interpretation has ranged from excellent to fair (17, 18).

Two additional points should be kept in mind when evaluating an ECG for evidence of possible AMI. First, ST segment depression in the anteroseptal precordial leads may actually represent posterior ST segment “elevation.” In fact, the occurrence of maximal ST segment depression in leads V2 and V3 is 70% sensitive and 96% specific for an occlusive lesion of the left circumflex artery (19), and should be investigated further with acquisition of posterior lead tracings to rule out a posterior STEMI. While fibrinolytic therapy is considered an “option” for a true posterior STEMI (4), the preferred reperfusion modality is PCI (1). Second, patients with inferior STEMI should be screened for right ventricular (RV) infarction by looking for ST segment elevation in the right precordial lead V4R. Approximately 10–15 % of patients with a RV infarction will have clinically significant hemodynamic abnormalities, and this subgroup is at high risk for a poor outcome (1).

## Reperfusion Therapy

### Options for Reperfusion Therapy

Reperfusion of the infarct-related artery (IRA) is the cornerstone of therapy for STEMI. Fibrinolysis and percutaneous coronary intervention (PCI) are both well established as effective options, but PCI has generally come to be regarded as the treatment of choice. A recent meta-analysis of 23 randomized, controlled trials (RCTs) comparing PCI to fibrinolysis revealed that PCI reduced short-term mortality (7% vs. 9%,  $p=0.0002$ ), non-fatal re-infarction (3% vs. 7%,  $p < 0.0001$ ), and stroke (1% vs. 2%,  $p=0.0004$ ) when compared to fibrinolysis (20). Mortality and re-infarction benefits

**TABLE 3**

*Sgarbossa Criteria for Identifying Acute Myocardial Infarction in Left Bundle Branch Block (16)*

---

ST elevation  $\geq$  1 mm in leads with dominant R waves  
 ST elevation  $\geq$  5 mm in leads with dominant S waves  
 ST depression  $\geq$  1 mm in V1, V2 or V3

---

of PCI in this analysis were maintained through long-term follow-up, and were still significant when trials using the older fibrinolytic streptokinase, and patients with cardiogenic shock were excluded. Despite these results, the issue is still a matter of some debate in the literature, and as noted in the ACC/AHA guidelines, it is not possible to say that one modality is superior for all patients in all settings. There is also concern that outcomes achieved with PCI in the setting of clinical trials may not be reproducible in the "real world," mainly because RCTs usually enroll a select group of patients who are cared for by experts in high-volume centers. Registry data corroborate this argument: Analysis from the NRM1 registry, which included hospitals of various sizes with a wide geographic distribution in the US, revealed that while PCI provided a greater mortality benefit than fibrinolysis in centers with an intermediate or high volume of procedures per year, there was no mortality benefit in low volume centers (fewer than 17 procedures per year) (21). Furthermore, registries consistently reveal significantly longer delays between presentation and invasive treatment than reported in RCTs. For example, the NRM1-2 registry found a median door-to-balloon time of 116 minutes (11). This finding is of concern because door-to-balloon times of over 120 minutes have been correlated with worse outcomes (11), and the current ACC/AHA recommended door-to-balloon time is less than 90 minutes (1).

### Trends in Reperfusion Therapy

Despite the above considerations, PCI is becoming more widely available, and trends in reperfusion therapy reflect an increasing preference for PCI. For example, among patients who presented to hospitals in the US capable of performing coronary artery bypass graft (CABG), the use of fibrinolytic therapy fell from 59.1% in 1994 to 47.9% in 1999, whereas the use of primary PCI increased from 11.8% to 24.4% (both  $p=0.0001$ ) (5). Pooled data from two German registries, the Maximal Individual Therapy in AMI (MITRA) study and Myocardial Infarction Registry (MIR), which also looked at reperfusion trends between 1994 to 1998, found that the proportion of patients receiving PCI increased from 6.3% to 19% (22). Of note, the percentage of patients with STEMI or LBBB presenting within 12 hours of symptom onset who received emergent reperfusion therapy increased only slightly in the US (from 68.8% to 70.0%,  $p=0.0014$ ) during this same time period. This suggests that invasive therapy is being preferentially employed mainly for fibrinolytic-eligible candi-

dates, rather than as a means of reperfusing fibrinolytic-ineligible patients (5).

### Expanding Access to Reperfusion Therapy

There are impediments to the delivery of both pharmacologic and mechanical reperfusion, including ambiguous clinical presentation, perceived risks of therapy, or lack of access to PCI. Fibrinolytic therapy is used less frequently for certain groups of patients. A retrospective European chart review published in 1996 revealed that 37% of fibrinolytic-eligible patients without contraindications did not receive treatment, and regression analysis identified age and female gender as independent risk factors for treatment being withheld (23). A recent systematic review of studies investigating the role of race in health care found that ethnic minorities were also less likely to receive fibrinolysis, even independent of economic status (24). These studies document, but do not explain, these disparities.

While age, female gender, and race are also associated with a likelihood of not receiving invasive reperfusion (24, 25), the major barrier remains a lack of access to 24-hour interventional catheterization laboratories. One strategy used to expand access to PCI involves transfer of patients from community hospitals to PCI-capable referral centers. This idea was first prospectively investigated in a small feasibility study which found a low incidence of complications during transport (26). Several subsequent randomized controlled trials have also evaluated this approach, the largest of which was DANAMI-2, with more than 1,500 patients (27). Although this study demonstrated that transfer for primary PCI was significantly better than treatment with t-PA in reducing the combined primary endpoint of death, re-infarction, or disabling stroke at 30 days (8.5% vs. 14.5%,  $p=0.002$ ), several points must be addressed before routine implementation of this strategy can be recommended. First, the only component of the combined outcome which achieved statistical significance was a reduction in the rate of re-infarction, yet a majority of patients who failed fibrinolysis or had recurrent ischemia with ST segment elevation were treated with repeat fibrinolysis rather than rescue PCI, even though the latter is the preferred therapy (1, 2). Second, the inter-hospital transfer system was highly organized, with a median presentation-to-transfer delay of only 50 minutes, and a median actual transfer time of 32 minutes, a degree of efficiency that would be difficult to replicate outside of a trial, or in a different geographic setting. Nevertheless, a subsequent meta-analysis of the five

major studies of transfer for PCI, enrolling a total of 2,466 patients, found a significant reduction in mortality with transfer (relative risk 0.69, 95% CI 0.51 to 0.92,  $p=0.01$ ) (28). If these trial conditions can be approximated, transfer for primary PCI appears to be a reasonable option. However, as recent data from the NRMI-4 have noted an average door-to-balloon time for transferred patients of 185 minutes (29), it would appear that considerable improvement is needed before this becomes routine practice.

Rather than centralizing care at referral centers, another option is to increase the availability of PCI at community hospitals. The C-PORT trial, which took place in eleven community hospitals without pre-existing invasive capabilities or cardiovascular surgery back-up, found that after the establishment of PCI programs through a formalized, comprehensive development process, PCI was superior to fibrinolysis in reducing re-infarction (5.3% vs. 10.6%,  $p=0.04$ ) and hospital length of stay (4.5 vs. 6.0 days;  $p=0.02$ ). However, no mortality benefit was demonstrated at 6 weeks or 6 months (30). While this data is encouraging, procedural volume is strongly correlated to patient outcomes, a concern if the number of PCI programs at low volume hospitals increases.

### Pharmacologic Reperfusion

Due to its universal availability, fibrinolysis remains the mainstay of reperfusion therapy. The development of newer, fibrin-specific fibrinolytics, such as t-PA, reteplase, and tenecteplase, represents a small but significant improvement over the first-generation drugs (i.e., streptokinase and urokinase). The newer agents have the advantage of activating plasminogen to form the clot-lysing enzyme plasmin when they are bound to fibrin in a thrombus, thereby promoting targeted fibrinolysis rather than systemic anticoagulation, and theoretically improving clot lysis while lowering the risk of bleeding. The GUSTO-1 mega-trial, a comparison of streptokinase versus t-PA, confirmed that the accelerated t-PA regimen with unfractionated heparin (UFH) reduces 30-day mortality in comparison with streptokinase plus UFH (6.3% vs. 7.4%,  $p=0.001$ ), with this benefit persisting at one year (31).

Although more efficacious than with older agents, reperfusion following administration of newer, fibrin-specific fibrinolytics still remains imperfect, with 90 minute “patency” rates (thrombolysis in myocardial infarction [TIMI] grade 2 or 3 flow) of 75 to 80% (32–34). Reteplase and tenecteplase, recombinant and genetically engi-

neered derivatives of tissue plasminogen activator (t-PA), offer greater ease of administration via bolus dosing; however, neither has demonstrated a survival benefit (35, 36).

### Risks of Reperfusion Therapy

The benefits of fibrinolytic therapy must be weighed against the risks, the most serious of which is stroke. Analysis of GUSTO-I found that 1.4% of the 41,021 subjects suffered an adverse cerebrovascular event. Hemorrhagic and non-hemorrhagic strokes were most common in the t-PA arm (0.70% and 0.66%, respectively), less common in the streptokinase plus intravenous UFH arm (0.57% and 0.64%), and least common in the streptokinase plus subcutaneous UFH arm (0.46% and 0.56%) (37). The excess of strokes due to t-PA did not negate the overall benefit: a combined end point of death or disabling stroke was significantly lower in the t-PA group than in the streptokinase groups (6.9% vs. 7.8%,  $p=0.006$ ) (31). Because of an increased risk of intracranial bleeding, the ACC and AHA consider any history of intracranial hemorrhage, or ischemic stroke within the past 3 months (but not within the past 3 hours), as an absolute contraindication to fibrinolysis (1).

Bleeding is the other major risk of fibrinolytic therapy. Severe bleeding, causing substantial hemodynamic compromise requiring intervention or treatment, occurred in 1.2% of patients in the GUSTO-I trial (38). It was most commonly procedure-related (associated with coronary artery bypass surgery or PCI), and was more common with streptokinase plus intravenous UFH than with the other fibrinolytic and heparin combinations (38). Of the newest fibrinolytic agents, tenecteplase therapy was found to be complicated by fewer major bleeds and blood transfusions than t-PA (4.66% vs. 5.94%,  $p=0.0002$ ; 4.25% vs. 5.49%,  $p=0.0002$ , respectively) (36).

### Prehospital Fibrinolysis

The benefit of fibrinolysis is greatest when administered early following the onset of symptoms, and declines rapidly after the first several hours (8, 39). In select settings, prehospital fibrinolysis appears to offer a mortality advantage over in-hospital administration. A meta-analysis of 6 trials with 6,434 patients found a reduction in all-cause hospital mortality (odds ratio 0.83, 95% CI 0.70–0.98) with prehospital fibrinolysis (40). All studies included in this meta-analysis enrolled only patients presenting within 4–6 hours of symptom onset, a critical factor considering that

the time saved by prehospital administration (approximately 60 minutes) is probably most beneficial during the early hours of an infarction. The prehospital strategy would seem particularly well suited to rural regions or hospitals with large catchment areas. In a recent prospective, observational cohort study in Scotland, it was indeed shown that “rural” patients who lived further than 10 miles from the study hospital and received prehospital fibrinolysis had the shortest call-to-needle times (median of 52 minutes). This compared favorably with either patients living within 10 miles receiving in-hospital fibrinolysis (median 80 minutes) or the rural patients receiving in-hospital treatment (median 125 minutes) (41). The most recent North American study, ER-TIMI, had a primary outcome measure of time to administration of fibrinolytics, and confirmed a reduction in time to treatment of 32 minutes, from a median of 63 ( $p < 0.0001$ ) (42). Possibly limiting their external validity, a majority of the above trials administered the drug in a mobile intensive care unit with an intensivist on the scene.

### Combined Pharmacological and Mechanical Reperfusion

In an important modification of the usual prehospital strategy, the CAPTIM study group combined prehospital fibrinolysis with transfer to an invasive center for rescue PCI, if needed, and compared this with primary PCI (43). As a result of this approach, 26% in the fibrinolysis group received early angioplasty. Overall, there was no significant difference in the primary composite endpoint of death, non-fatal reinfarction, and non-fatal disabling stroke at 30 days between the two groups, although there was a trend towards benefit in the primary PCI group, with a composite endpoint of 6.2% vs. 8.2% (risk difference 1.96, 95% CI 1.53–5.46). When interpreting these results, one should understand that with only 840 patients, this study was probably underpowered to detect a significant difference.

The role of a combined pharmacological and mechanical approach has been a topic of much discussion, i.e., whether the use of PCI should be driven by evidence of ischemia, or routinely employed. PCI after primary fibrinolysis is clearly indicated for patients who develop cardiogenic shock or pulmonary edema, and is also recommended by the ACC and AHA, albeit with less supporting evidence, for patients with hemodynamic or electrical instability, and/or persistent symptoms (in this case called “rescue PCI”) (1). A more disputed regimen is so-called “facilitated

PCI,” which includes full or partial dose fibrinolytics, alone, or in combination with glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, started prior to early, planned PCI. This strategy is appealing because it combines the immediate availability of fibrinolytics with the higher patency and lower reinfarction rates of PCI, and would seem particularly well suited to patients being transferred from a community hospital to an interventional center.

Most early trials comparing primary PCI with full-dose fibrinolytics prior to immediate PCI found an increase in bleeding and other complications without demonstrating a reduction in adverse cardiovascular events (44, 45). The idea has been revisited, however, with newer pharmacologic agents and interventional techniques. Recent investigative efforts have concentrated on facilitating PCI with a combination of reduced-dose fibrinolytics and GP IIb/IIIa inhibitors (e.g., abciximab). SPEED, a small pilot trial which primarily investigated 60–90 minute angiographic patency rates after abciximab, with or without reteplase, also provided a *post hoc* assessment of facilitated PCI, as 61% of 528 patients received an intervention at the time of angiography (46). While conclusions were limited by the lack of randomization between those who did and did not receive PCI, there was a significantly lower rate of reinfarction and urgent revascularization at 30 days in the facilitated group. Another study, BRAVE, compared two different pharmacologic strategies prior to PCI: abciximab versus abciximab plus half-dose reteplase. Initial TIMI grade 3 flow was more common in the combination arm, and TIMI grade 0 flow more common in the abciximab alone arm. Procedural success was, however, the same, and there was no difference in the primary endpoint of infarct size as measured by SPECT (47). Unfortunately, there was no control group of primary PCI or medical therapy, and therefore the efficacy of facilitated PCI *per se* could not be determined. Upcoming trials include ASSENT-4, ADVANCE MI, and FINESSE, all of which will further assess facilitated PCI with various fibrinolytic and GP IIb/IIIa regimens. The ACC and AHA provide a class IIb recommendation, based on this “conflicting evidence,” that facilitated PCI may be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low (1).

Another reperfusion strategy is early PCI, where routine PCI is employed hours to days after fibrinolysis, rather than as soon as possible, as is the case with facilitated PCI. Early PCI would reduce the need for expensive 24-hour catheterization laboratories, and lessen the demand for re-

source consumption by the emergency department (ED), or catheterization laboratory transfer. Although an attractive strategy, the literature regarding its efficacy remains inconclusive. A routine invasive strategy after fibrinolysis (i.e. not symptom driven) was given a class IIb recommendation by the ACC and AHA in the most recent edition of their guidelines. This is in contrast to a class I recommendation for PCI after fibrinolysis in the setting of recurrent MI, provokable ischemia or shock, and weaker than the class IIa recommendation for patients with CHF, an ejection fraction < 40%, or serious arrhythmias (1). Subsequent to the publication of these guidelines, the GRACIA trial was completed; it randomized 500 patients who received accelerated t-PA for STEMI to either routine angiography between 6 and 24 hours after fibrinolysis (with intervention if indicated) or ischemia-driven PCI (48). Patients received guideline-recommended adjunctive therapy (e.g., ASA, beta-blockers, stenting, etc.) as appropriate. Before hospital discharge, 21% (52 of 251) of patients in the ischemia-driven group needed cardiac catheterization for either spontaneous ischemia with ECG changes or stress-induced ischemia. At one year, the primary combined endpoint of death, reinfarction, or ischemia-induced revascularization was significantly less common in the routine angiography group (9% vs. 21%,  $p=0.0008$ ), although the results were largely driven by a reduction in revascularization. Readmission due to ischemia by one year was also reduced from 25% to 15% ( $p=0.006$ ) in the routine angiography group. Limitations of this study include an open design, relatively small sample size, lack of a primary PCI control group, and the inclusion of ischemia-induced revascularization in the combined endpoint (as this was, by definition, part of the treatment strategy for the ischemia-driven group). Nonetheless, this interesting study found no increase in complications and a trend towards reduction in death and reinfarction (49).

### **Patient Characteristics and Choice of Reperfusion Strategy**

There may be utility in “triaging” fibrinolytic-ineligible and high risk patients with evidence of congestive heart failure to emergent PCI, as these are two groups of patients for whom primary PCI is clearly the recommended primary therapy (1). In the absence of these factors, if presentation is within 3 hours of symptom onset, the ACC/AHA guidelines state no preference for either strategy (1). This recommendation is based on emerging evidence that fibrinolysis is as effective as PCI for

patients presenting early. In a subgroup analysis of the PRAGUE-2 trial comparing treatment with streptokinase at a community hospital with transfer for primary PCI, patients randomized within 3 hours of symptom onset had similar 30-day mortality, whereas those presenting later had significant benefit from transfer and an invasive approach (mortality 6.0% vs. 15.3%,  $p<0.02$ ) (50). A subgroup analysis was also performed on data from the above-mentioned CAPTIM trial, which revealed a trend towards benefit of prehospital fibrinolysis over PCI for patients randomized within 2 hours (2.2% vs. 5.7%,  $p=0.058$ ) (51). Registry data support these observations as well: in a retrospective analysis of the MIR/MITRA data, the adjusted mortality was no different for treatment with fibrinolytics and PCI when the prehospital delay was less than 3 hours; however, for patients presenting later, PCI was preferred (52).

### **Adjunctive Therapies**

Reperfusion therapy, while central to the treatment of STEMI, must be accompanied by appropriate adjunctive treatments. PCI actually promotes thrombus formation through iatrogenic vessel injury and stent placement, and platelets may become hyperactive approximately 24 hours after intervention (53). Thus, one of the major early complications of PCI is acute and subacute vessel closure. Anti-platelet agents have proven themselves to be valuable adjuncts to mechanical reperfusion by reducing these early thrombotic complications. Adjunctive therapy is also important following administration of fibrinolytics—it is thought that fibrin-specific agents, while promoting local clot lysis, may actually exert a systemic pro-coagulant effect through increased thrombin activity (54) and possibly via enhanced platelet aggregation (55). Myocardial protective agents, particularly beta-blockers, complement reperfusion therapy. Additionally, the impact of specialized cardiac care units on improved patient outcomes should be acknowledged; some authors consider this to be one of the most important innovations in the care of the patient with STEMI in recent decades (53).

### **Anti-platelet Therapy**

Aspirin plays a critical role in the suppression of platelet function by inhibiting formation of the platelet activator, thromboxane A<sub>2</sub>. It should be given as early as possible to any patient without a true contraindication for the treatment of STEMI, whether in combination with fibrinolysis or PCI

(1). Its benefit was clearly demonstrated in the ISIS 2 trial, which compared ASA and streptokinase, alone and in combination, in 17,187 patients (56). Aspirin mono-therapy resulted in a significant reduction in five-week vascular mortality from 11.8 to 9.4% ( $p < 0.00001$ ). Additionally, aspirin significantly reduced non-fatal reinfarction (1.0% vs. 2.0%) and non-fatal stroke (0.3% vs. 0.6%) compared with placebo, and was not associated with an increase in intracranial hemorrhage or bleeds requiring transfusion.

Clopidogrel and ticlopidine both cause platelet inhibition via adenosine diphosphate-receptor antagonism, but clopidogrel is preferred to ticlopidine due to a lower risk of serious side effects. There is little outcome data on the benefit of clopidogrel in combination with fibrinolytics. Clopidogrel is recommended, based largely on consensus, for patients receiving fibrinolysis who cannot tolerate aspirin due to allergy (1, 3). For patients undergoing PCI with stenting, combination therapy with ASA and clopidogrel is standard for the reduction of adverse cardiovascular events, including occlusive stent thrombosis. However, these recommendations are largely based on data from trials of patients undergoing elective PCI or PCI for non-STEMI acute coronary syndromes (1). Because clopidogrel should be withheld for 5–7 days prior to CABG, the administration of clopidogrel should generally be delayed until angiography has been performed and the preferred treatment plan (PCI or CABG) has been determined.

Glycoprotein IIb/IIIa inhibitors interfere with the final common pathway in platelet aggregation, namely the cross linking of platelets by fibrinogen. Their utility in reducing recurrent ischemia or infarction after PCI for acute coronary syndromes has been well demonstrated (57). The rationale for the use of GP IIb/IIIa inhibitors in STEMI is similar, but there is considerably less data on this group of patients. The largest and strongest study to date, CADILLAC, enrolled 2,082 stent-eligible patients with STEMI or LBBB to angioplasty alone, angioplasty with abciximab, stenting, or stenting plus abciximab (58). At six months, the composite endpoint of death, reinfarction, stroke, and ischemia-driven revascularization of the IRA had occurred in 20.0% of patients after angioplasty, 16.5% after angioplasty plus abciximab, 11.5% after stenting, and 10.2% after stenting plus abciximab ( $p < 0.001$ ).

The other studies investigating the efficacy of GP IIb/IIIa inhibitors in STEMI also showed a similar, small reduction in urgent ischemia-induced revascularization (59, 60). The ADMIRAL trial was of particular interest because, while a sig-

nificant overall reduction in the combined, 30-day and 6-month endpoints of death, re-infarction, or urgent revascularization was seen, this benefit was only realized in patients who received abciximab in the prehospital setting or in ED (60). The benefit of early administration was further evaluated in a meta-analysis of six randomized trials of early (before transfer to the catheterization laboratory) versus late (at the time of PCI) administration of abciximab or tirofiban in patients with STEMI (61). There was a trend towards mortality benefit (3.4 vs. 4.7%) with early rather than late administration at the longest follow-up period for each study. Thus, with the caveat that their recommendation is based on a relatively small number of patients who received abciximab and PCI for STEMI across several trials, the ACC and AHA suggest that it is reasonable to start abciximab as early as possible prior to primary PCI, with or without stenting, for STEMI (1). The ACCP similarly recommends abciximab for patients undergoing PCI, stating that it should be started prior to balloon inflation when possible (57).

GP IIb/IIIa inhibitors have also been studied as a supplement to full and reduced-dose fibrinolytics, although reduced dosing is now preferred due to concerns about excess risk of bleeding with full dosing. The largest trial to date with clinical outcome measures, GUSTO V, randomized over 16,000 patients in 20 countries to reteplase, or abciximab with half-dose reteplase (62). There was no difference in the primary endpoint of 30-day mortality, although there was a significant reduction in reinfarction and recurrent ischemia in the combined group. While an increase in intracranial hemorrhage (ICH) was not noted with combination therapy, there was a significant increase in other severe bleeding complications compared with reteplase alone. ASSENT 3, the other large trial (6,095 patients) investigating combination therapy, sought to evaluate the role of the low-molecular-weight heparin (LMWH) enoxaparin (see below) as well, comparing (a) full-dose tenecteplase and enoxaparin, (b) half-dose tenecteplase with low-dose heparin and abciximab, against the control regimen of (c) full-dose tenecteplase with weight-adjusted UFH (63). The primary efficacy endpoint, including death, in-hospital reinfarction, or refractory ischemia at 30 days, was lower in groups (a) and (b) than in controls (group [c]) (11.4%, 11.1%, and 15.4% respectively,  $p = 0.0001$ ), with results driven by the reduction in ischemia and reinfarction. There was no difference in the rate of intracranial hemorrhage among the groups, but abciximab was again associated with a greater risk of severe bleeding (4.3%) than either enoxaparin

(3.0%) or UFH (2.2%) ( $p=0.0005$ ). Based on these studies, the ACCP recommends against the combination of abciximab with half-dose reteplase or tenecteplase, and recommends that streptokinase definitely not be combined with a GP IIb/IIIa inhibitor (3). The ESC similarly recommends against combination therapy (2), while the AHA provides a class IIb recommendation, acknowledging conflicting evidence (1).

### Anti-thrombin Agents

Complementing the anti-platelet agents are the anti-thrombins, another commonly used adjunctive therapy for both PCI and fibrinolysis. Unfractionated heparin inhibits the activation of various clotting factors, most notably factor Xa and thrombin. There is relatively little evidence confirming a significant additive benefit of heparin over ASA in combination with streptokinase, and recommendations for its use range from no adjunctive treatment with UFH, to subcutaneous or intravenous administration at various doses (1–3). After having demonstrated superiority to streptokinase in GUSTO-I, fibrin-selective fibrinolytics have been used in combination with intravenous UFH in almost all subsequent trials, and guidelines are unanimous in recommending intravenous administration of a bolus dose followed by a maintenance dose adjusted to keep the activated partial thromboplastin time (aPTT) at 1.5–2 times control (50–70 seconds) for 24–48 hours (1, 2).

There has been considerable interest in using enoxaparin (an LMWH) instead of UFH with fibrinolytics, in part because of its ease of administration and the predictability of its anticoagulant effect. The difficulty in achieving the recommended aPTT with UFH was demonstrated in a trial comparing UFH with enoxaparin, when only 30% of the patients were appropriately anticoagulated between 6 and 12 hours after beginning therapy (64). Furthermore, enoxaparin appears to be superior to UFH in reducing reinfarction or revascularization in patients with unstable angina or non-STEMI (64).

There is also evidence for the benefit of LMWH in STEMI. In patients with STEMI, the ASSENT-3 trial found that in combination with tenecteplase, enoxaparin was a better anti-thrombotic agent than UFH, resulting in a reduction of the primary combined endpoint of death, in-hospital re-infarction, and refractory ischemia from 15.4% to 11.4% ( $p<0.001$ ) (63). Subsequently, however, ASSENT-PLUS revealed a significantly increased risk of intracranial hemorrhage with the administration of tenecteplase with enoxaparin, as

opposed to UFH, in patients over the age of 75 (65). As a result of uncertainties raised by ASSENT-PLUS involving bleeding risk, the use of enoxaparin is only recommended as an alternative to UFH in patients < 75 years of age, and even in the non-elderly patients, the recommendation is based on conflicting evidence or opinion (1, 3). The ESC does not make a recommendation regarding its use, citing the need for further investigations (2).

UFH is also recommended for use during primary PCI with weight-adjusted boluses, and was given the highest level recommendation by the ACC and AHA based mainly on the opinion of experts (1). The specific role of LMWH in the invasive management of STEMI is less established. Most trials which have investigated the role of LMWH during PCI have looked at patients undergoing elective angioplasty or PCI for unstable angina or non-STEMI, finding comparable safety and outcomes, but there is a lack of evidence to support replacing UFH with LMWH in STEMI.

### Other Ancillary Medications

There are other medications that provide benefit in the setting of STEMI via mechanisms other than reperfusion, or prevention of reocclusion, of the infarct-related artery. Beta-blockers, for one, are thought to be “protective,” reducing infarct size and reinfarction when co-administered with fibrinolytics, and reducing mortality when continued long term after AMI. The ACC and AHA provide a class I recommendation for the administration of oral beta-blockers early in the course of an STEMI, with a slightly less robust endorsement of the early use of IV beta-blockers because of conflicting evidence (1). The ESC recommends early IV beta-blockers for particular indications, including tachycardia or hypertension, noting that in most cases, oral administration is sufficient. Enthusiasm for routine, early IV administration was tempered by a meta-analysis which did not show an advantage to early IV over oral administration (66). Nonetheless, beta-blockers improve outcomes and should be administered in a timely fashion, as only 42 patients need to be treated for two years in order to prevent one death. Only fibrinolysis with ASA provide a greater benefit(66).

ACE-inhibitors limit ventricular dilatation and remodeling by interruption of the renin-angiotensin-aldosterone system, and it is well established that oral ACE-inhibitors should be given within the first 24 hours post-infarct to patients who have experienced symptoms of heart failure or are known to have a subnormal ejection fraction

---

### Pearls and Pitfalls

---

1. STEMI may present without chest pain. The most common symptoms of an “atypical” presentation are dyspnea, diaphoresis, nausea or vomiting, and syncope. Older patients, females, and diabetics are more likely to present atypically. Do not neglect to obtain an early ECG from patients with these symptoms.
  2. Bundle branch blocks complicate the electrocardiographic diagnosis of a myocardial infarction. In the setting of ischemic symptoms, a new or presumed new LBBB is an accepted indication for fibrinolytics or PCI, but even patients with old or non-left BBB should be considered for reperfusion therapy.
  3. Certain groups of patients are less likely to be offered reperfusion therapy, including women, ethnic minorities, and the elderly, despite demonstrated benefit from intervention. Be particularly vigilant when evaluating these groups for possible ACS.
  4. While oral ACE-inhibitors reduce short-term mortality after AMI in patients with impaired ejection fraction or signs of heart failure, early IV administration is contraindicated because of the significant risk of hypotension.
  5. There is no evidence that nitrates reduce mortality in the setting of STEMI. They should be used for specific indications, including ongoing ischemia or pulmonary edema, rather than given routinely.
- 

### Key Concepts

---

1. All patients who present with STEMI within 12 hours of symptom onset should be evaluated for emergent reperfusion therapy. Patients who would likely benefit more from PCI than from fibrinolysis include those with signs of heart failure, those who present more than three hours after symptom onset, and those who are at increased risk of bleeding complications from fibrinolytics.
  2. The fibrin-specific fibrinolytic t-PA offers a small but significant mortality benefit over streptokinase. The newer fibrin-specific agents, e.g., reteplase and tenecteplase, are no more efficacious than t-PA, but offer the advantage of bolus dosing.
  3. The role of “facilitated PCI,” using various combinations of fibrinolytics and glycoprotein IIb/IIIa inhibitors prior to planned PCI, remains under investigation. To date, there is no convincing evidence of benefit from such an approach.
  4. Abciximab is the best studied of glycoprotein IIb/IIIa inhibitors in STEMI, and there is evidence that its use in patients undergoing PCI reduces the need for short- and mid-term ischemia-induced revascularization. This benefit may be greater if abciximab is started before arrival in the catheterization laboratory.
  5. Oral beta-blockers, when initiated promptly after AMI and continued long-term, reduce mortality. The additional benefit of early IV administration is not significant, although hypertension and tachycardia are accepted indications.
- 

(2) (the ACC and AHA also consider an anterior MI a class I indication (1)). ACE-inhibitors should not be administered in the setting of absolute or relative hypotension, and intravenous administration is contraindicated because of the risk of inducing hypotension.

Nitrates, while commonly used, have not demonstrated an outcome benefit in the setting of STEMI. Nitrates might be expected to reduce infarct size and improve outcome, as they diminish preload, thereby decreasing wall stress and myocardial oxygen demand. Additionally,

there is direct vasodilatation of coronary arteries, potentially increasing collateral blood flow to ischemic myocardium. Despite these theoretical advantages, the GISSI-3 and ISIS-4 megatrials (with a combined total of more than 77,000 patients) did not reveal a 4–6 week mortality benefit for nitrates initiated in the acute phase of AMI (either oral or IV) and continued for 4–6 weeks (67, 68). They do, however, appear to be safe in the absence of hypotension, and while there is not a role for routine administration, nitrates are recommended for ongoing ischemia, pulmonary edema, or hypertension (1, 2). Significantly, nitrates should be used only with extreme caution in the setting of RV infarct, as they reduce RV preload, and may therefore have very adverse hemodynamic consequences (1).

### Conclusions

Efforts to improve the outcome of STEMI continue, with much of the recent work focusing on strategies to increase the availability of reperfusion therapy. Research also continues on optimizing fibrinolytic agents, PCI techniques, and adjunctive therapy. With such a large volume of data published on the topic, clinical practice guidelines become an important source of information and direction for the clinician, promoting the application of current evidence to the bedside care of these patients.

### References

(References 1-4 contain relevant practice guidelines)

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110:e82–e292.
2. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003; 24(1):28–66.
3. Menon V, Harrington RA, Hochman JS, et al. Thrombolysis and adjunctive therapy in acute myocardial infarction: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:549S–575S.
4. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. American College of Emergency Physicians. *Ann Emerg Med* 2000; 35(5):521–525.
5. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol* 2000; 36:2056–2063.
6. American Heart Association. Heart Disease and Stroke Statistics—2004 Update. Dallas, Texas: American Heart Association; 2003.
7. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36:959–969.
8. 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(8893):311–322; erratum in: *Lancet* 1994; 343(8899):742.
9. Brieger D, Eagle KA, Goodman SG, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; 126:461–469.
10. Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000; 283:3223–3229.
11. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000; 283:2941–2947.
12. Angeja BG, Gibson CM, Chin R, et al. Predictors of door-to-balloon delay in primary angioplasty. *Am J Cardiol* 2002; 89:1156–1161.
13. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986; 1:397–402.
14. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. (Second International Study of Infarct Survival) Collaborative Group. *J Am Coll Cardiol* 1988; 12:3A–13A.
15. Wellens HJ. Acute myocardial infarction and left bundle-branch block—can we lift the veil? *N Engl J Med* 1996; 334:528–529.
16. Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996; 334:481–487.
17. Gula LJ, Dick A, Massel D. Diagnosing acute myocardial infarction in the setting of left bundle branch block: prevalence and observer variability from a large community study. *Coron Artery Dis* 2003; 14:387–393.
18. Sokolove PE, Sgarbossa EB, Amsterdam EA, et al. Interobserver agreement in the electrocardiographic diagnosis of acute myocardial infarction in patients with left bundle branch block. *Ann Emerg Med* 2000; 36:566–571.
19. Shah A, Wagner GS, Green CL, et al. Electrocardiographic differentiation of the ST-segment depression of acute myocardial injury due to the left circumflex artery occlusion from that of myocardial ischemia of nonocclusive etiologies. *Am J Cardiol* 1997; 80:512–513.
20. 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.
21. Magid DJ, Calonge BN, Rumsfeld JS, et al. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* 2000; 284:3131–3138.

22. Zahn R, Schiele R, Schneider S, et al. Decreasing hospital mortality between 1994 and 1998 in patients with acute myocardial infarction treated with primary angioplasty but not in patients treated with intravenous thrombolysis. Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Registry and the Myocardial Infarction Registry (MIR). *J Am Coll Cardiol* 2000; 36:2064–2071.
23. Translation of clinical trials into practice: a European population-based study of the use of thrombolysis for acute myocardial infarction. European Secondary Prevention Study Group. *Lancet* 1996; 347:1203–1207.
24. Lillie-Blanton M, Maddox TM, Rushing O, et al. Disparities in cardiac care: rising to the challenge of Healthy People 2010. *J Am Coll Cardiol* 2004; 44:503–508.
25. Buiatti E, Barchielli A, Marchionni N, et al. Determinants of treatment strategies and survival in acute myocardial infarction: a population-based study in the Florence district, Italy: results of the acute myocardial infarction Florence registry (AMI-Florence). *Eur Heart J* 2003; 24:1195–1203.
26. Vermeer F, Oude Ophuis AJ, vd Berg EJ, et al. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999; 82(4):426–431.
27. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003; 349:733–742.
28. Zijlstra F. Angioplasty vs thrombolysis for acute myocardial infarction: a quantitative overview of the effects of interhospital transportation. *Eur Heart J* 2003; 24:21–23.
29. Jacobs AK. Primary angioplasty for acute myocardial infarction—is it worth the wait? *N Engl J Med* 2003; 349:798–800.
30. 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(15):1943–1951.
31. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993; 329(10):673–682.
32. Carney RJ, Murphy GA, Brandt TR, et al. Randomized angiographic trial of recombinant tissue-type plasminogen activator (alteplase) in myocardial infarction. RAAMI Study Investigators. *J Am Coll Cardiol* 1992; 20:17–23.
33. Bleich SD, Adgey AA, McMechan SR, Love TW. An angiographic assessment of alteplase: double-bolus and front-loaded infusion regimens in myocardial infarction. Double Bolus Lysis Efficacy. *Am Heart J* 1998; 136(4 Pt 1):741–748.
34. Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. *Circulation* 1996; 94:891–898.
35. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med* 1997; 337:1118–1123.
36. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. *Lancet* 1999; 354:716–722.
37. Gore JM, Granger CB, Simoons ML, et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995; 92(10):2811–2818.
38. Berkowitz SD, Granger CB, Pieper KS, et al. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. The Global Utilization of Streptokinase and Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) I Investigators. *Circulation* 1997; 95:2508–2516.
39. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348:771–775.
40. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000; 283:2686–2692.
41. Pedley DK, Bissett K, Connolly EM, et al. Prospective observational cohort study of time saved by prehospital thrombolysis for ST elevation myocardial infarction delivered by paramedics. *BMJ* 2003; 327:22–26.
42. Morrow DA, Antman EM, Sayah A, et al. Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction: results of the Early Reteplase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 trial. *J Am Coll Cardiol* 2002; 40(1):71–77.
43. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002; 360:825–829.
44. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. The TIMI Research Group. *JAMA* 1988; 260:2849–2858.
45. Simoons ML, Arnold AE, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1988; 1:197–203.
46. Herrmann HC, Moliterno DJ, Ohman EM, et al. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) Trial. *J Am Coll Cardiol* 2000; 36:1489–1496.
47. Kastrati A, Mehilli J, Schlotterbeck K, et al. Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2004; 291:947–954.
48. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004; 364(9439):1045–1053.
49. Verheugt FW. Lyse now, stent later: the grace of GRACIA. *Lancet* 2004; 364:1014–1015.
50. 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.
51. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003; 108:2851–2856.
52. Zahn R, Schiele R, Gitt AK, et al. Impact of prehospital delay on mortality in patients with acute myocardial infarction treated with primary angioplasty and intravenous thrombolysis. *Am Heart J* 2001; 142(1):105–111.

53. Braunwald E. Heart disease: a textbook of cardiovascular medicine. 6th ed., W.B. Saunders Company; 2001.
54. Eisenberg PR. Role of heparin in coronary thrombolysis. *Chest* 1992; 101:131S–139S.
55. Gurbel PA, Serebruany VL, Shustov AR, et al. Effects of reteplase and alteplase on platelet aggregation and major receptor expression during the first 24 hours of acute myocardial infarction treatment. GUSTO-III Investigators. Global Use of Strategies to Open Occluded Coronary Arteries. *J Am Coll Cardiol* 1998; 31:1466–1473.
56. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2:349–360.
57. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:576S–599S.
58. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002; 346:957–966.
59. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. *Circulation* 1998; 98:734–741.
60. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001; 344:1895–1903.
61. Montalescot G, Borentain M, Payot L, et al. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004; 292:362–366.
62. Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001; 357:1905–1914.
63. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (Assent)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; 358(9282): 605–613.
64. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997; 337:447–452.
65. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003; 108:135–142.
66. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318:1730–1737.
67. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 1994; 343:1115–1122.
68. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995; 345:669–685.