Acute coronary syndromes

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Introduction

During the past decade, research in the field of acute coronary syndromes (ACSs) has exploded. The reperfusion era includes not only fibrinolytic therapy but also strategies to open occluded arteries early, to limit infarct size and ventricular remodeling, and to prevent recurrent, major adverse cardiac events including sudden death. These strategies have incorporated the use of aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors; aggressive use of hydroxymethylglutaryl coenzyme A reductase inhibitors; and mechanical and surgical revascularization. Panelists reviewed those topics, which apply to the management of ACSs during the first several hours after an event. Panelists also discussed investigational therapies that may affect the early care of patients with acute myocardial infarction (AMI). Out-of-hospital ECG identifies patients with AMI who will benefit from early reperfusion or rapid transport to an interventional facility. Out-of-hospital fibrinolysis addresses continuing concerns about very early administration of fibrinolytic agents in the field. More aggressive antiplatelet therapy for patients with unstable angina and infarction now involves use of glycoprotein IIb/IIIa (GP IIb/IIIa). The patient groups for which this therapy is most appropriate and the timing of administration of these agents are under intensive study. Metabolic manipulation of the infarct may be important in subgroups of patients with AMI and is assessed as an adjunctive therapy. Finally, the role of percutaneous coronary intervention (PCI) continues to evolve and now includes the use of stents and adjunctive antiplatelet therapy. These new mechanical and combination therapy approaches were also considered.

Topic 1: Out-of-hospital 12-lead ECGs

1992 Guidelines

There is no discussion of out-of-hospital 12-lead ECG diagnostic programs in the 1992 guidelines. The AMI algorithm lists out-of-hospital screening for thrombolytic therapy, 12-lead ECG, computer analysis, and transmission to the emergency department as optional guidelines. (JAMA. 1992;268:2230.)

Proposed addition or change
Out-of-hospital 12-lead ECG diagnostic programs can play a pivotal role in coordinating the medical community's response to patients with AMI and should be performed routinely in urban and suburban emergency medical services (EMS) systems. EMS directors should recognize the importance of out-of-hospital ECG diagnosis and should implement effective methods of communicating the diagnosis to the receiving emergency physician before the patient arrives at the hospital. Recognition of the importance of the out-of-hospital ECG and implementation of strategies to accomplish specific goals can improve out-of-hospital diagnosis, reduce time to treatment in the hospital, identify candidates for fibrinolytic therapy or reperfusion, reduce mortality, and facilitate triage to cardiac or other interventional facilities.

**New science**

A 12-lead ECG transmitted to the hospital speeds diagnosis and shortens time to fibrinolysis. The National Heart Attack Alert Program recommends that EMS systems consider providing out-of-hospital 12-lead ECGs to facilitate early diagnosis of AMI and that all advanced lifesaving vehicles be able to transmit a 12-lead ECG to the hospital.[44A] Hospital EDs should have in place a protocol-driven strategy to immediately assess and treat patients with an ACS. The practice guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society for Cardiology (ESC)/European Resuscitation Council (ERC) recommend a "door-to-needle time" of 30 minutes for administration of fibrinolytic therapy. EMS personnel should triage patients to facilities with this capability. In addition, triage of patients at high risk for complications (eg, congestive heart failure, hypotension, tachycardia, or large anterior wall infarction) to specialists and facilities with cardiac interventional and surgical capabilities should be strongly considered. Specialized care for these patients reduces mortality and improves care.[47D]

The 1996 ACC/AHA guidelines and the ESC/ERC guidelines for management of AMI recommend that out-of-hospital ECGs be obtained when possible (Class IIb). Randomized, controlled clinical trials have demonstrated the benefit of initiating thrombolytic therapy as soon as possible after the onset of ischemic-type chest pain.[48E] In addition, use of an out-of-hospital ECG and a chest pain checklist lead to more rapid out-of-hospital and hospital care.[49F] Out-of-hospital initiation of therapy has been associated with a 17% relative improvement in outcome; improvement is greatest when therapy is started 60 to 90 minutes earlier than it is in the hospital. Although out-of-hospital-initiated thrombolytic therapy results in earlier treatment, the time savings can be offset in most cases by an improved hospital triage with resultant "door-to-needle" time reduced to 30 minutes or less.

The ESC/ERC 1998 guidelines recommend that strategies should be sought that will allow out-of-hospital thrombolysis if the combined journey time and in-hospital delay is more than 60 minutes, or if the journey time is 30 minutes or more.
The primary purpose of out-of-hospital 12-lead ECG diagnostic programs is twofold: early identification of AMI with acute ST-segment elevation and effective communication of the diagnosis to the receiving emergency physician before the patient arrives. Multiple studies have shown the feasibility of obtaining out-of-hospital 12-lead ECGs. Diagnostic-quality ECGs can be obtained and transmitted successfully in ~85% of patients with chest pain who are eligible for 12-lead ECGs. Obtaining an ECG increases the time spent at the scene of an emergency an average of 0 to 4 minutes. Additionally, there is no difference between the information collected in the out-of-hospital setting and that received by cellular transmission at the base station. It has also been demonstrated that use of out-of-hospital 12-lead ECGs improves the accuracy of the out-of-hospital diagnosis of chest pain patients with a final hospital diagnosis of AMI, angina, and nonischemic chest pain. Many studies have demonstrated significant reductions in hospital-based time to treatment with fibrinolytic therapy for patients with AMI identified by an out-of-hospital 12-lead ECG. Time savings in these studies range from 20 to 55 minutes. Patients with AMI who undergo out-of-hospital 12-lead ECG are treated more frequently in the ED than in the coronary care unit (CCU) and tend to be treated more rapidly in both the ED and CCU.

One retrospective study demonstrated a mortality benefit among patients with AMI identified by out-of-hospital 12-lead ECG. Using data from the National Registry of Myocardial Infarction-2 database, Canto et al. evaluated the treatment and outcomes of patients for whom out-of-hospital 12-lead ECGs were and were not obtained. Investigators concluded that the out-of-hospital ECG may influence the treatment of patients with AMI through greater, faster in-hospital utilization of reperfusion strategies and greater use of invasive procedures, factors that may reduce short-term mortality.

Patients with AMI identified by an out-of-hospital 12-lead ECG can be evaluated for fibrinolytic therapy with use of a contraindication checklist. Studies of out-of-hospital fibrinolytic therapy have provided significant experience with this approach. One study evaluated the cost-effectiveness of out-of-hospital 12-lead ECG diagnostic programs. After an initial investment of $2,847 per 50,000 population for equipment, the costs of implementing an out-of-hospital 12-lead ECG diagnostic program in the suburban community studied decreased exponentially over time. Mean cost per year of life saved was $1,613 after 1 year, $737 after 3 years, and $561 after 5 years. The authors concluded that the modest cost per year of life saved shows that an out-of-hospital 12-lead ECG diagnostic program is a relatively inexpensive, life-preserving approach.

**Evaluation and debate**

Participants supported the proposal to recommend establishment of out-of-hospital 12-lead ECG diagnostic programs; roughly two thirds supported a Class I
recommendation and one third supported a Class IIa recommendation. Dr Kern emphasized that results from studies of out-of-hospital ECG diagnostic programs may be biased because the programs selected for study are generally more established and innovative; he suggested that registry results be interpreted with this potential selection bias in mind, particularly because no data from prospective, randomized clinical trials are available. One participant expressed concern about the costs of implementing and maintaining these programs. Relatively low initial startup costs and preliminary cost-effectiveness data were discussed. It was recognized that EMS systems may contend that they have higher-priority issues and therefore should have the option to invest time and effort in other, more locally appropriate programs. Dr Timerman from Brazil added that logistical problems related to skill maintenance and the different types of providers operating in different countries should be considered.

Two thirds of participants agreed that the recommendation for out-of-hospital ECG programs should be a Class I recommendation. Because of the lack of data from prospective studies, outcome parameters of mortality, quality of life, and cost/benefit ratio were raised. In addition, only a small percentage of patients would actually qualify for intervention. To maximize cost-effectiveness, Dr Ornato suggested that out-of-hospital ECG programs be recommended for busy urban and suburban systems. Dr Smith questioned whether systems with prolonged transport times might also benefit from use of out-of-hospital ECGs because of the delay to arrival at the hospital.

Dr Aufderheide noted that the Class I recommendation was warranted because evidence suggests that the use of out-of-hospital 12-lead ECGs is ultimately linked to reduced mortality caused by AMI, although this has been shown in only 1 large retrospective trial with possible selection bias. The participants who disagreed with the Class I recommendation thought a Class IIa recommendation was more appropriate until additional cost-effectiveness studies and a prospective, randomized trial with mortality as an endpoint are performed. Dr Aufderheide noted that such a trial is unlikely because it would require at least 100,000 patients to be powered appropriately.

The end-of-day summary discussions focused on concerns about the Class I recommendation, which would appear to mandate the use of out-of-hospital ECGs by all providers. One participant stressed that EMS systems may not have the financial resources to implement out-of-hospital ECGs universally. At this time, there is no Medicare reimbursement for the performance or interpretation of out-of-hospital ECGs. Dr Aufderheide clarified cost issues, noting that the equipment costs only $3,000 to $4,000 more than a standard defibrillator. Because no prospective, outcome-based cost-efficacy studies have been performed, many participants believed that a Class IIa recommendation was more appropriate. Dr Aufderheide reviewed the cost data and said that, similar to recommendations for
trauma systems, a recommendation for use of out-of-hospital ECGs as part of a general strategy for early treatment of patients with AMI was appropriately a Class I recommendation. Other participants recommended that the Class I recommendation be clearly specified for urban and suburban EMS systems only. One participant questioned the appropriateness of making a Class I recommendation when training requirements and recurrent educational components have not been clearly determined.

**Proposed guidelines**

Patients with AMI receive an earlier diagnosis and faster treatment with fibrinolytic drugs in the ED when paramedics obtain a 12-lead ECG in the field and transmit the tracing to the receiving emergency physician before the patient arrives at the hospital. Out-of-hospital 12-lead ECG diagnostic programs should be implemented in urban and suburban paramedic systems (Class I).

**Topic 2: Out-of-hospital fibrinolysis**

**1992 Guidelines**

*Out-of-hospital fibrinolysis*

The 1992 guidelines recommend use of fibrinolytic (previously called "thrombolytic") therapy for patients with transmural AMI who present for treatment less than 6 hours after the onset of symptoms (Class I). (JAMA. 1992;268:2230.) The 1996 and 1999 AHA/ACC guidelines state that use of out-of-hospital fibrinolysis is not advocated universally but should be considered if transport time is longer than 90 minutes.[1][2]

*Out-of-hospital triage of patients with AMI*

The 1999 AHA/ACC guidelines make explicit recommendations for initial treatment of certain subsets of AMI patients. For example, insertion of an intra-aortic balloon pump (IABP) is recommended for AMI patients with signs and symptoms of shock that are not quickly reversed by pharmacologic therapy (Class I). The guidelines point out that insertion of an IABP is a stabilizing measure that should be performed before angiography or PCI (Class IIa) and before surgical revascularization in patients with suitable anatomy (Class IIa).

**Proposed addition or change**

Two related proposals were considered: (1) use of out-of-hospital fibrinolytic therapy in busy EMS systems with significant transport delays, and (2) transport of AMI patients with overt heart failure, shock, or both, to a nearby hospital (if
available) with IABP and PCI or coronary artery bypass graft (CABG) revascularization capabilities.

Panelists also considered an additional recommendation to change the nomenclature for the International 2000 Guidelines, replacing the term "thrombolysis" with "fibrinolysis," which more accurately reflects the mechanism of action of this class of agents.

**New science**

**Out-of-hospital fibrinolysis**

Use of fibrinolytic therapy before arrival at the hospital is appealing in light of the strong inverse relationship between the time from AMI symptom onset to reperfusion therapy and the patient's ultimate clinical outcome. For example, Weaver et al\(^{[30]}\) showed that the mortality rate was significantly lower among AMI patients who received recombinant tissue-type plasminogen activator (rtPA) within the first 70 minutes after symptom onset than among those who received rtPA 70 to 180 minutes after symptom onset (1.2% versus 8.7%, respectively; \( P < .009 \)).

Several large (>300 patients), randomized, controlled clinical trials have demonstrated a statistically significant benefit of out-of-hospital fibrinolysis only when the time savings between out-of-hospital and hospital treatment exceeds 60 minutes. These and smaller studies have shown remarkably consistent safety when out-of-hospital fibrinolysis is conducted by physicians or paramedics who have received proper training and who use fibrinolytic protocols and checklists.

Nonetheless, there are several practical problems associated with out-of-hospital fibrinolysis in the United States. First, only 4% to 5% of patients with chest pain (1 of every 200 EMS calls) qualifies for out-of-hospital fibrinolysis. This results in a relatively high cost for an EMS system to use and maintain out-of-hospital fibrinolytic capability. In addition, there has been remarkable improvement in the time from arrival at the ED to initiation of fibrinolytic therapy (door-to-needle time) in the past decade. The latest National Registry of Myocardial Infarction data, obtained from ~1,600 hospitals in the United States, indicates that the current average door-to-needle time is 34 minutes.

**Out-of-hospital triage of AMI patients**

Rates of mortality related to cardiogenic shock are generally high in most reported studies, but in recent years an increasing body of evidence has suggested early hemodynamic stabilization can be achieved with use of IABP pulsation followed by diagnostic cardiac catheterization and (where anatomically appropriate) coronary revascularization with either PCI or CABG.
In large clinical trials randomized for other purposes, the mortality rate of AMI patients with shock was significantly lower in patients who were treated with urgent coronary revascularization than in those treated with fibrinolytic therapy. In the National Registry of Myocardial Infarction, the mortality rate among AMI patients with shock was lower in those treated with a PCI as a primary strategy than in those treated with fibrinolysis. Interestingly, in the same study the mortality rates among AMI patients not in shock were the same regardless of whether PCI or fibrinolysis was the primary treatment.

In a large shock registry, mortality was lower in AMI patients with shock who received early revascularization with either PCI or CABG. Most recently a large, randomized clinical trial showed a significant reduction in 6-month mortality when AMI patients with shock were treated with early revascularization (either PCI or CABG) rather than medical therapy only.

**Evaluation and debate**

Dr Smith, representing the American College of Emergency Physicians, disagreed with a Class I recommendation for transport to interventional facilities, noting that EMS systems would have difficulty accessing hospitals with the capability for timely interventional strategies. Dr Chandra-Strobos pointed out that EMS systems need to have experience and recurrent training programs in place before protocols for out-of-hospital fibrinolysis can be implemented. Sue Householder, representing the Council on Cardiovascular Nursing, questioned the rationale for using the term "fibrinolytics." Drs Ornato and Field reviewed the rationale for the change in terminology, which would more accurately reflect the use of these agents in combination with targeted therapy. Dr Rackow, representing the Society of Critical Care Medicine, expressed concern that the trial of Hochman et al failed to achieve the predefined 30-day end point. Dr Ornato noted that the 30-day end point was very early and that long-term follow-up would be necessary. Dr Field noted that the Hochman et al trial reflected the observations in the larger shock registry and emphasized that this trial was not designed to assess fibrinolysis only versus PCI. Patients in the medical strategy group were treated aggressively, with 86% receiving an IABP, an intervention usually not available outside interventional facilities or at least those with cardiac catheterization capability. Dr Kern emphasized that the medical strategy was aggressive and that receiving facilities should have not only IABP capability but also interventional expertise.

Dr Rackow also raised a concern about the definition of heart failure, which has been defined inconsistently in prior clinical trials. Dr Field noted that the 1999 AHA ACLS Handbook included use of the term shock, rales more than halfway up the chest posteriorly, and a combination of hypotension and tachycardia. Consensus was reached that the definition of heart failure should be explored more fully and refined as necessary. Dr Field asked for a show of hands on hospital bypass. Assuming that a timely interventional program was in place and that 70% of the
US population resides within a 45-minute driving radius of a capable center, two thirds of participants indicated that they would favor use of in-hospital bypass for patients in shock.

**Proposed guidelines**

*Out-of-hospital fibrinolysis*

In light of the short door-to-drug times now achieved by many urban and suburban hospitals in the United States, routine use of out-of-hospital fibrinolysis is not recommended at this time (Class III). EMS systems that transport large numbers of eligible AMI patients (≥ 1 per month) and that routinely have transport times of 1 hour or longer should consider use of out-of-hospital fibrinolysis (Class IIb).

*Out-of-hospital triage of AMI patients*

AMI patients with overt heart failure with or without shock should be transported to a nearby hospital (if available) with IABP and PCI or CABG revascularization capabilities (Class I).

**Topic 3: Primary angioplasty and fibrinolytic therapy for AMI with ST-segment elevation**

*1992 Guidelines*

No reference to use of primary angioplasty for management of AMI was made in the 1992 guidelines. At that time, only small randomized studies comparing coronary angioplasty and intracoronary fibrinolysis had been performed. Other reports were from single-center, nonrandomized series analyzed retrospectively.

*Proposed addition or change*

Fibrinolytic therapy has become an inarguable landmark in reperfusion therapy. Randomized trials have demonstrated that primary angioplasty has advantages over fibrinolysis, but some of the data supporting angioplasty are weak and insufficient and thus a cause of concern. Important issues must still be addressed. For example, the long-term results of primary angioplasty, benefits and risk according to clinical indicators of outcome (patient subgroups), clinical effects of the prolonged time delay related to the procedure, applicability in community centers, and cost-effectiveness still need further scientific study. Nevertheless, reproducibility of results obtained in randomized studies, and cost-effectiveness must be resolved before primary angioplasty can be recommended as a better alternative to fibrinolysis.
Participants recommended that primary angioplasty not be advocated as the first therapeutic approach in centers where it is not performed on a regular basis by an expert team and where the results are not validated continuously. Nevertheless, primary angioplasty is preferable to fibrinolysis in selected patients when the necessary standards of quality are guaranteed.

**New science**

In 1993, results of the first multicenter, international, randomized trial comparing primary angioplasty and fibrinolysis and smaller randomized trials were published. A quantitative overview of these initial studies led to the first meta-analysis comparing the effects of primary angioplasty and fibrinolysis. This meta-analysis showed that primary angioplasty resulted in a lower short-term (6-month) mortality rate than fibrinolysis (3.7% versus 6.4%, respectively; odds ratio [OR] 0.56; 95% confidence interval [CI] 0.33 to 0.94). Primary angioplasty also lowered the composite endpoint of mortality and reinfarction (6.1% versus 11%, respectively; OR 0.53; 95% CI 0.35 to 0.80) in 7 combined randomized studies but provided no advantages in improving these 2 individual endpoints in any of 17 trials that tested the effects of angioplasty after lysis, whether it was performed immediately after lysis, soon after lysis, or after a time delay.

The 1996 ACC/AHA guidelines for management of AMI recommended primary angioplasty for the treatment of AMI. Those recommendations were reviewed and adopted by the ACLS Subcommittee in 1997. Use of primary angioplasty as an equivalent alternative to fibrinolysis was recommended only for centers meeting specific quality outcomes, including time delay to balloon insufflation of less than 60 (target) to 90 (maximum) minutes, Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow attained in more than 90% of patients, need for emergency CABG surgery in less than 5% of cases, and a mortality rate below 12%.

The following recommendations for use of primary angioplasty as a reperfusion strategy were made in the 1996 ACC/AHA guidelines: (1) as an alternative to fibrinolytic therapy only if performed in a "timely fashion by individuals skilled in the procedure and supported by experienced personnel in high-volume centers" (Class I), (2) in patients who are candidates for reperfusion but who have a risk of bleeding contraindication to fibrinolytic therapy and in patients in cardiogenic shock (Class IIa), and (3) in patients who do not qualify for fibrinolytic therapy for reasons other than a risk of bleeding (Class IIb).

In 1997, the ACLS Subcommittee made the following recommendations for use of percutaneous transluminal coronary angiography (PTCA) in patients with ST-segment elevation: (1) for patients with signs and symptoms of a large AMI for less than 12 hours who have a risk of bleeding contraindication to fibrinolytic therapy (Class I); (2) for patients with possible "stuttering" infarction with ECG
changes but no clear indications for fibrinolytic therapy, for patients who develop cardiogenic shock or pump failure within 18 hours, and for patients with a history of CABG surgery in whom occlusion of a vein graft may have recently occurred (Class IIa); and (3) for patients with a possible AMI observed in a hospital with rapid access to a catheterization facility and for patients in whom fibrinolytic therapy fails to bring about reperfusion and complete resolution of symptoms (Class IIb).

By 1997, preliminary results of new randomized trials were available, and the quantitative overview of the short-term results of these trials was pooled into a larger meta-analysis by the Primary Coronary Angioplasty and Fibrinolysis (PCAT) Collaborative Group. The advantages of the invasive approach in terms of reduced mortality, mortality, nonfatal reinfarction, and stroke were confirmed in a wide variety of clinical and logistical subsets.

The latest update of the ACC/AHA guidelines for management of AMI, published in September 1999, cited additional evidence to support the quality standards required to perform primary angioplasty announced in 1996 with slight modifications. The following new recommendations were made. (1) Primary angioplasty was recommended for patients younger than 75 years old who present within 36 hours after the onset of AMI symptoms, who develop cardiogenic shock, and who can be treated within 18 hours of onset of shock (Class I). It was also recommended as an alternative to lysis for patients with ST-segment elevation or new or presumably new left bundle branch block who can undergo angioplasty of the infarct-related artery (IRA) within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist (Class I). (2) Primary angioplasty was recommended (Class IIa) as a reperfusion strategy in candidates for reperfusion who have a contraindication to fibrinolytic therapy. (3) Primary angioplasty was a Class IIb recommendation for patients with AMI who do not present with ST-segment elevation but who have reduced (<TIMI grade 2) flow of the IRA and when angioplasty can be performed within 12 hours of onset of symptoms. (4) Primary angioplasty was not recommended (Class III) for patients with AMI who undergo elective angioplasty of a non-IRA at the time of AMI, are beyond 12 hours after the onset of symptoms and have no evidence of myocardial ischemia, have received fibrinolytic therapy and have no symptoms of myocardial ischemia, are eligible for thrombolysis and are undergoing primary angioplasty performed by a low-volume operator in a laboratory without surgical capability.

The ESC/ERC 1998 guidelines emphasize that delays in achieving coronary reperfusion following drug therapy may be circumvented by the use of primary angioplasty, which may also be used for patients in whom thrombolytic therapy is contraindicated. Primary angioplasty yields higher coronary patency rates than thrombolytic therapy, and full patency is achieved immediately when the angioplasty balloon is deflated following successful dilatation. But primary
angioplasty is clearly a hospital procedure, and there is an unavoidable preliminary "door-to-balloon" time. Clinical trials comparing primary angioplasty with hospital thrombolysis are encouraging, but the full benefits of angioplasty may not be well sustained. To date, the only available evidence comparing out-of-hospital thrombolysis with primary angioplasty has not shown any advantage with the interventionalist strategy and there are no randomized trials. Early "rescue" angioplasty has a role where reperfusion by thrombolysis has failed, but it is often unsuccessful. In localities where both out-of-hospital thrombolysis and angioplasty are available, local policies for the early management of patients with acute myocardial infarction should be followed.

Evidence-based evaluation of the available results of primary angioplasty demonstrated that this procedure provides a wide array of advantages and has many potential indications. Nevertheless, several issues must be resolved before primary angioplasty can be recommended as a better alternative to fibrinolysis, including long-term outcome of primary angioplasty, benefits and risk according to clinical indicators of outcome (patient subgroups), clinical effects of the prolonged time delay related to the procedure, applicability in community centers, reproducibility of results obtained in randomized studies, and cost-effectiveness.

**Long-term results**

The short-term benefits associated with primary angioplasty were recently confirmed in a population of 2,635 randomized patients of the PCAT study analyzed at 6 months. Angioplasty, as compared with fibrinolysis, resulted in a lower risk of death (6.1% versus 8.1%, OR 0.73, P=.055), reinfarction (4.4% versus 9.7%, OR 0.43, P=.0001), and both end points combined (6.8% versus 13.4%, OR 0.47, P<.0001). The reduction in these 2 major end points was greatest in certain subgroups treated with primary angioplasty, particularly diabetic patients (9.2% versus 19.3%, P<.05) and those older than 70 years old (9.3% versus 17.0%, P<.02). The sustained benefits of primary angioplasty over fibrinolysis were also demonstrated in the Primary Angioplasty in Myocardial Infarction (PAMI) trial; analysis of the 2-year follow-up data showed that primary angioplasty resulted in lower rates of the following major end points: combined mortality and reinfarction (14.9% versus 23%, P=.034), recurrence of ischemia (36.4% versus 48%, P=.026), and need for repeated target-vessel revascularization (TVR) (18.5% versus 43%, P<.0001). Similar results have been observed in other nonrandomized series. Even more striking benefits of angioplasty at 5±2 years of follow-up were recently reported by Zijlstra et al. The mortality rate was 13% in the angioplasty group and 24% in the fibrinolysis group (relative risk [RR] 0.54, 95% CI 0.36 to 0.87); nonfatal reinfarction occurred in 6% and 22%, respectively (RR 0.27, 95% CI 0.15 to 0.52); and the combined incidence of death and nonfatal reinfarction was lower in the angioplasty group (RR 0.13, 95% CI 0.05 to 0.37).
Primary angioplasty is a demanding technique that requires very high standards of organization, technology, and medical care. Its application to selected candidates in whom the invasive approach is likely to offer the greatest advantages over fibrinolysis may prove a rational approach.

Primary angioplasty, as compared with lysis, reduced the incidence of stroke, recurrent ischemia, and need for repeated TVR after AMI in all randomized trials, even in low-risk patients. In certain cases, it yielded better left ventricular functioning and was of benefit in patients with anterior AMI even 24 hours after symptom onset. The effects on mortality and reinfarction are more significant among high-risk patients, particularly those with hemodynamic failure. For example, in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial, which was designed to compare emergency revascularization (ERV) with initial medical stabilization (IMS) and delayed revascularization of patients in cardiogenic shock, the 30-day mortality rate was 46.7% among patients treated with ERV and 56% among those treated with IMS in the whole population (95% CI -20 to 1.9, P=.11) and 41.4% and 56.8%, respectively, in patients younger than 75 years (P<.01). At 6 months, the mortality rate was significantly lower in the ERV group (whole population 50.3% versus 63.1%, P=.027; patients <75 years 45% versus 65%, P=.0002). Preliminary data from the 12-month follow-up examination confirmed a significantly lower mortality rate in the ERV group regardless of age (55% versus 70%, P=.008). Other indicators of improved mortality have been identified by analysis of patients included in randomized trials, and a stratification of risks to improve selection of patients who will benefit from angioplasty in terms of mortality has been proposed by Weaver. Age older than 70 years is an indicator of high risk per se. Among younger patients, concomitant occurrence of an anterior AMI or previous MI with a heart rate more than 75 beats/min or blood pressure below 115 mm Hg on arrival at the hospital has been associated with higher mortality in patients treated with fibrinolytic therapy.

Another group of patients at higher risk of death includes those with an inferior AMI and right ventricular involvement, an association observed in nearly one third of patients with inferior AMI. Low cardiac output syndrome resulting from right ventricular AMI may reduce the efficacy of fibrinolytic agents, and indirect data suggest that the mechanical approach may be a better alternative to fibrinolysis in patients with this condition. A similar line of reasoning could be applied to patients with AMI caused by occlusion of a saphenous vein graft. Both the low blood flow status and the large thrombotic burden create a less favorable environment for effective recanalization of the conduit by means of fibrinolytic agents. Furthermore, patients who have previously undergone CABG surgery are generally older and more likely to have a history of AMI, multivessel disease,
diabetes, and lower mean left ventricular ejection fraction,[41] all of which are associated with increased mortality. Despite the lack of conclusive evidence from randomized trials, primary angioplasty is a rational alternative for the treatment of such patients and is often preferred to fibrinolysis when available.[42] [43]

Patients in whom reperfusion does not occur after fibrinolysis, especially those with anterior AMI, [31] [74] are also at high risk.[75] Despite initial reluctance based on the results of early experiences, rescue angioplasty is a helpful therapeutic option and should be indicated in patients with high-risk baseline characteristics. Appropriate selection of patients will optimize the benefits of an aggressive approach.

**Time delay**

Primary angioplasty requires more preparation time than simple intravenous administration of a fibrinolytic drug. The rationale for delaying the treatment of a patient with an ongoing MI is twofold: first, the rate of TIMI grade 3 coronary flow achieved (as assessed by angiography) is higher with primary angioplasty, and second, the total time needed to achieve reperfusion with a lytic drug is never less than 60 minutes even with the most recent and effective regimen.[76] Therefore, the total time delay from hospital arrival to reperfusion of the 2 procedures may be almost equivalent provided that angioplasty is performed within 60 minutes.

The longer time delay associated with primary angioplasty results in a larger infarct and reduced left ventricular functioning,[77] [78] but it does not affect the patency rate and the 6-month clinical outcome.[76] Although some data suggest that the 30-day mortality rate is lower among patients treated very early (within 2 hours of symptom onset), mortality is independent of time to reperfusion for patients presenting after 2 hours.[76] Indeed, the in-hospital mortality rate associated with angioplasty is low and consistent in patients treated within 12 hours of symptom onset who do not present with cardiogenic shock,[77] [78] probably because TIMI grade 3 flow can usually be established (in >90% of cases) despite the time delay.[79] With fibrinolytic treatment, however, the reperfusion rate decreases and the mortality rate increases with increasing time, particularly beyond the third or fourth hour after symptom onset.[79] [80] [81] [82]

Outcomes of interventions performed in the community setting are not identical to those achieved in centers operating under the specific requirements of a randomized study,[83] a point demonstrated by large national registries[84] [85] [86] and the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) study,[47] a randomized trial designed to address this particular issue. The advantages of angioplasty are, however, sustained in patients with hemodynamic impairment at hospital presentation.

The results obtained by analysis of data from large registries illustrate the importance of high-quality standards for primary angioplasty; therefore, primary
angioplasty should not be preferred to fibrinolysis in centers where such standards cannot be guaranteed. Initial results from small studies suggest that transport of patients to high-volume tertiary centers is a safe and valuable therapeutic alternative, and, at least in theory, transport may be a more rational option than development of a more widespread network of low-volume centers. This approach is being investigated in large randomized studies in both the United States (AIR-PAMI) and Europe (Danish Trial in Acute Myocardial Infarction [DANAMI-2]).

Growing evidence demonstrates that primary angioplasty is a cost-saving alternative to fibrinolysis over the long term despite an initially higher procedural cost. This cost savings is mainly a result of the lower incidence of in-hospital reinfarction, recurrent ischemia, and stroke and a shorter hospital stay among patients treated with primary angioplasty. Also, patients treated with angioplasty have a significantly lower need for new revascularization procedures after discharge. These benefits are especially important in countries with high rates of mechanical coronary revascularization after AMI, expensive pharmaceuticals, and an increasingly cost-conscious health care environment.

**Evaluation and debate**

There was a unanimous consensus that primary angioplasty is an equivalent reperfusion strategy and alternative to fibrinolysis. There was also agreement that PCI is a superior reperfusion strategy when IRA patency and short-term mortality are objective end points, assuming that the procedures are performed by experienced individuals in high-volume centers. Dr Smith, representing the American College of Cardiology, expressed concern that triage to centers with interventional capability would likely prevent timely intervention. Dr Field noted that these strategies would require an EMS system to interact closely with a cardiac center. A center offering primary angioplasty would be expected to achieve a door-to-balloon inflation time of 60 to 90 minutes. Dr Chandra-Strobos pointed out that the registry data provided a good reflection of practice in the community, noting that a number of community hospitals have transport balloon capability. Dr Chandra-Strobos thought that a strong case could be made for transporting a patient to the nearest hospital and then transferring to a larger center.

Dr Field then asked participants whether angioplasty should be recommended as a preferred strategy for patients in shock. Although there was consensus that angioplasty should be a preferred strategy, there was disagreement about the class of recommendation. Half thought a Class I recommendation was most appropriate, and half thought a Class IIa recommendation was most appropriate. It was noted that the most recent ACC/AHA guidelines list angioplasty for patients in shock as a Class I recommendation. Most discussion centered on the definition of shock in the field. A majority of participants thought patients with clear clinical shock should be transferred to an interventional facility. Dr Chandra-Strobos
suggested exclusion of patients with volume-responsive shock. There was less consensus on anterior wall infarction, blood pressure less than 100 mm Hg and heart rate more than 100 beats/min, and rales over lower 1/3 of the lungs posteriorly.

Primary angioplasty results in a higher rate of TIMI grade 3 coronary flow and a lower incidence of undesirable effects compared with fibrinolysis. These effects may be associated with better myocardial preservation, improved survival, and lower morbidity. Compared with fibrinolysis, primary angioplasty reduces short- and long-term mortality in patients with hemodynamic impairment\cite{34,60,61} and in subgroups of high-risk patients.\cite{62} It also reduces the risk of bleeding, the recurrence of ischemia, and the need for new TVR procedures over both the short and long terms.\cite{39,41,43,47,50,53,55} These advantages are obtained despite the longer time delay associated with this procedure.\cite{80} Results differ, however, according to the level of organization, experience, and expertise of the center, and the guidelines should not recommend primary angioplasty in hospitals where the procedure is not performed routinely according to ACC/AHA standards and where continuous assessment of the immediate and long-term results is not guaranteed.

**Proposed guidelines**

In addition to the standards of quality recommended in the ACC/AHA guidelines for management of AMI, panelists recommend the following. (1) Not only the interventional cardiologist but also the nursing and technical staff of the catheterization laboratory must be experienced in the treatment of acutely ill patients and must be stable components of the interventional team. Furthermore, the team must provide on-call service 24 hours a day, 7 days a week. (2) Postintervention monitoring and management are crucial components of care and must be optimized according to a well-defined profile of risk to identify actual or potential complications (eg, hemodynamic, renal, or respiratory impairment; recurrence of ischemia; enzymatic release; and risk of bleeding) as early as possible. Early identification of complications leads to rapid treatment and may prevent more severe complications. Postintervention management should be aimed at early discharge from the hospital whenever possible. (3) An ongoing program of outcome analysis and periodic case review, with particular attention to evaluation of the patient's clinical status after discharge and long-term outcome, must be established.

In addition, the following recommendations for selection of patients were made.

**Class I**

Primary angioplasty is recommended for patients who develop cardiogenic shock or pump failure and can be treated within 18 hours of onset of shock; patients considered at high risk who have a contraindication to fibrinolysis; patients
considered at high risk after unsuccessful fibrinolysis; and as an alternative to fibrinolysis in patients with ST-segment elevation or new (or presumably new) left bundle branch block who can undergo angioplasty of the IRA within 12 hours after the onset of symptoms or after more than 12 hours if ischemic symptoms persist.\[^{[51]}\]

**Class IIa**

Primary angioplasty is also recommended for patients considered at high risk who present to the hospital more than 4 hours after symptom onset; patients with a possible "stuttering" infarction with ECG changes but no clear indication for fibrinolytic therapy; and patients with a history of CABG surgery in whom occlusion of a vein graft may have recently occurred.\[^{[45]}\]

**Class IIb**

Primary angioplasty may be helpful and is probably not harmful in patients not at high risk (regardless of whether they are suitable for fibrinolysis or have a contraindication to it); patients at high risk presenting within the first 2 hours after symptom onset; and patients not at high risk after unsuccessful fibrinolysis.

**Class III**

Primary angioplasty is not recommended for patients treated with elective angioplasty of a non-IRA at the time of AMI; patients who have received fibrinolytic therapy and have no symptoms of myocardial ischemia; patients eligible for fibrinolysis who are being treated at a center with a low volume of primary angioplasties and no surgical capability; and patients with spontaneous complete reperfusion at the moment of emergency angiography (ie, relief of chest pain, spontaneous and sustained achievement of TIMI grade 3 coronary flow of the IRA, and a reduction of ST-segment elevation of <50% compared with the initial ECG).

**Class Indeterminate**

The available data are insufficient to recommend use of primary angioplasty in patients with inferior AMI and right ventricular involvement and in patients at high risk presenting more than 12 hours after symptom onset without evidence of ongoing ischemia or hemodynamic impairment.

**Topic 4: Use of GP IIb/IIIa Inhibitors in non-ST-segment elevation MI and unstable angina**

**1992 Guidelines**

None.
Proposed addition or change

A GP IIb/IIIa inhibitor should be administered in the hospital to patients with unstable angina or non-ST-segment elevation MI who are at high risk for adverse cardiovascular events, especially in conjunction with PCI. Use of a GP IIb/IIIa inhibitor should be considered for patients with an ACS who are not at high risk for adverse cardiovascular events.

New science

ACSs affect a heterogeneous population of patients who can be placed on a continuum of increasing risk from unstable angina to non-ST-segment elevation and ST-segment elevation AMI. The severity of ACSs and the associated risk of death vary widely, with ST-segment elevation AMI posing the highest risk of death. After plaque rupture in the coronary artery, tissue factor in the lipid-rich core is exposed and forms a complex with factor VIIa, and the tissue factor-factor VIIa complex promotes generation of factor Xa. In the coagulation cascade, relatively low concentrations of factor Xa lead to production of large amounts of thrombin, with deposition of fibrin strands and activation of platelets.[95] Platelet adhesion, activation, and aggregation may result in arterial thrombus formation and are pivotal in the pathophysiology of ACSs.[96] Optimal management of unstable angina and non-ST-segment elevation MI is rapidly evolving. The integrin GP IIb/IIIa receptor is considered the final common pathway to platelet aggregation, leading to the binding of circulating adhesive macromolecules such as fibrinogen and von Willebrand factor, which cross-link on adjacent platelets, allowing platelet aggregation. Administration of a GP IIb/IIIa receptor antagonist (inhibitor) is one method to reduce acute ischemic complications after plaque fissuring or rupture.

Research in the administration of GP IIb/IIIa receptor inhibitors for ACSs is quite extensive and initially was conducted in patients undergoing PCI.[97][100] More than 30,000 patients with an ACS without ST-segment elevation have been enrolled in clinical trials evaluating multiple therapeutic agents to block the IIb/IIIa receptor.[101][107] Our initial literature review included all human GP IIb/IIIa inhibitor trials, but the final review of relevant literature included 1 meta-analysis and 6 randomized, controlled trials involving patients with an ACS treated initially with medical management without planned PCI.[101][107] Although the GP IIb/IIIa inhibitors have an impressive ability to reduce adverse cardiac events such as MI and death, another class of drugs, the low molecular weight heparins, also reduce death and nonfatal MI in patients with unstable angina or non-ST-segment elevation AMI.

A total of 10,948 patients were enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial, a multicenter, randomized placebo-controlled trial. Investigators hypothesized that inhibition of platelet aggregation with eptifibatide would have an incremental
benefit beyond that of heparin and aspirin in reducing the frequency of adverse outcomes in patients with an ACS who did not have persistent ST-segment elevation. The primary end points were death from any cause and nonfatal MI at 30 days. Patients were enrolled a median of 11 hours after the onset of symptoms, and the drug was infused for a median time of 72 hours. Treatment with eptifibatide resulted in a significant reduction in the incidence of death or MI at each time point. There was a 1.5% absolute reduction in the frequency of the composite end point by 96 hours, and this reduction was maintained for 30 days. The early divergence of the Kaplan-Meier curves was maintained throughout the study. PTCA was performed in 23.3% of patients in the eptifibatide group and in 24.8% of patients in the placebo group. The low-dose trial of eptifibatide was discontinued after randomization of 3,218 patients as specified in the protocol.

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) and PRISM-PLUS (Patients Limited by Unstable Signs and Symptoms) trials used tirofiban for the management of unstable angina or non-ST-segment elevation MI. In PRISM, investigators hypothesized that inhibition of the final common pathway for platelet aggregation with tirofiban, a nonpeptide GP IIb/IIIa receptor antagonist, would improve clinical outcome in patients with unstable angina or non-ST-segment elevation MI. A total of 3,232 patients were randomly assigned to receive tirofiban, aspirin, and placebo heparin or aspirin and heparin. The primary endpoint was a composite of death, MI, or refractory ischemia at 7 days. The composite end point at 7 days was 10.3% for the tirofiban group and 11.2% for the heparin group. The difference was not statistically significant. Although the difference in the primary end point was not statistically significant, the Kaplan-Meier curves for 30-day mortality showed an early divergence and a significant difference in mortality at 30 days. The early 48-hour time frame during administration of tirofiban showed a reduction in the composite end point, but this reduction was not maintained to 7 or 30 days. PRISM-PLUS continued to evaluate tirofiban in the treatment of unstable angina and non-Q-wave MI. A total of 1,915 patients were enrolled to evaluate (1) tirofiban in combination with placebo heparin, (2) tirofiban and heparin, and (3) placebo tirofiban and heparin. The trial testing tirofiban with placebo heparin was discontinued early because of excess mortality at 7 days. The primary end point was a composite of death from any cause, new MI, or refractory ischemia within 7 days after randomization. Tirofiban provided additional benefit when added to standard therapy with heparin and aspirin at 7 days. There was an early divergence of the Kaplan-Meier curves at 48 hours before implementation of PCI in many patients. Table 1 provides an overview of selected end points in PURSUIT, PRISM, and PRISM-PLUS.

Table 1. Clinical end points among patients with a non-ST-segment elevation acute coronary syndrome at various time points.

<table>
<thead>
<tr>
<th>Trial and Results (%)</th>
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<tbody>
<tr>
<td></td>
<td>48-96 h</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
</tr>
<tr>
<td><strong>PURSUIT</strong></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.9</td>
</tr>
<tr>
<td>MI</td>
<td>7.1</td>
</tr>
<tr>
<td>Death or nonfatal MI</td>
<td>7.6 †</td>
</tr>
<tr>
<td><strong>PRISM (tirofiban without heparin)</strong></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.4</td>
</tr>
<tr>
<td>MI</td>
<td>0.9</td>
</tr>
<tr>
<td>Death or MI</td>
<td>1.2</td>
</tr>
<tr>
<td>Death, MI, or refractory ischemia</td>
<td>3.8 †</td>
</tr>
<tr>
<td><strong>PRISM-PLUS (tirofiban with heparin)</strong></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.1</td>
</tr>
<tr>
<td>MI</td>
<td>0.8 †</td>
</tr>
<tr>
<td>Death or MI</td>
<td>0.9 †</td>
</tr>
<tr>
<td>Death, MI, or refractory ischemia</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**MI**, Myocardial infarction; **PURSUIT**, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trial; **PRISM**, Platelet Receptor Inhibition in Ischemic Syndrome Management trial; **PRISM-PLUS**, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms.

* Treatments were as follows: PURSUIT, eptifibatide; PRISM, tirofiban; and PRISM-PLUS, tirofiban.
Neutral or opposing evidence was provided by the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) study of lamifiban. PARAGON had a partial factorial design with patients randomly assigned to receive low or high doses of lamifiban and heparin or no heparin. Aspirin was administered to all patients. The primary end point was a composite of all-cause mortality and nonfatal MI at 30 days. There was no significant difference between groups at 30 days, but divergence of the end points occurred at 6 months. At 6 months, there was a significant (23%) reduction of death or nonfatal MI in the low-dose lamifiban group with or without heparin.

Kong et al conducted a meta-analysis of the GP IIb/IIIa receptor antagonist clinical trials. The meta-analysis reviewed death, MI, and revascularization in 16 controlled trials of GP IIb/IIIa inhibitors using a Bayesian random-effects model to describe the combined outcomes in 32,134 patients. For the combined end point of death or nonfatal MI, there was a highly significant benefit of GP IIb/IIIa inhibitors at every time point (48 to 96 hours, 30 days, and 6 months). The use of GP IIb/IIIa inhibitors in the ACS trials resulted in no significant differences in mortality at any endpoint, but a significant benefit of GP IIb/IIIa inhibitors for the combined endpoint of death or nonfatal MI was observed early and at 30 days. For the composite end point of death, MI, or revascularization in the ACS trials, there was a highly significant benefit of GP IIb/IIIa inhibitors at all time intervals (48 to 96 hours, 30 days, and 6 months).

Inclusion criteria and end point definitions in the GP IIb/IIIa inhibitor trials varied widely (eg, there were differences in definitions of high-risk unstable angina, abnormal levels of cardiac markers, recurrent and new MI, and refractory ischemia; differences in ECG criteria for inclusion; and differences in the timing of randomization from 12 to 24 hours after the index event). Table 2 provides a brief overview of the differences in selected high-risk characteristics from the trials.

### Table 1. Clinical end points among patients with a non-ST-segment elevation acute coronary syndrome at various time points.

<table>
<thead>
<tr>
<th>Trial and End Point</th>
<th>Results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48-96 h</td>
</tr>
<tr>
<td>Treatment* Placebo</td>
<td>Treatment* Placebo</td>
</tr>
</tbody>
</table>

† P<.05.
Table 2. High-risk characteristics in patients with a non-ST-segment elevation acute coronary syndrome.

<table>
<thead>
<tr>
<th>Trial and Treatment Group</th>
<th>Characteristic</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior MI (%)</td>
<td>Age* (y)</td>
<td>ST-Segment Depression (%)</td>
<td>T-Wave Inversion (%)</td>
</tr>
<tr>
<td><strong>PURSUIT</strong></td>
<td>32</td>
<td>64</td>
<td>49.8</td>
<td>51.6</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>32.9</td>
<td>64</td>
<td>50.2</td>
<td>50.0</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRISM</strong></td>
<td>46.8</td>
<td>62.5</td>
<td>31.5</td>
<td>51.4</td>
</tr>
<tr>
<td>Tirofiban only</td>
<td>47.1</td>
<td>62.4</td>
<td>31.5</td>
<td>51.4</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRISM-PLUS</strong></td>
<td>45</td>
<td>63</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>Tirofiban with heparin</td>
<td>39</td>
<td>63</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Age in PURSUIT trial was median; age in PRISM and PRISM-PLUS trials was mean.

MI, Myocardial infarction; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy trial; PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management trial; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial.

Aspirin therapy was administered during all trials, but administration of heparin, heparin dosing, and activated partial thromboplastin times varied. None of the trials used troponin as a predictor of high risk. Risk stratification of patients with unstable angina also varied among trials.

In addition to administration of GP IIb/IIIa inhibitors, there has been much interest in developing new antithrombins that can be administered during the persistent activation of the coagulation cascade that occurs for several weeks to months after the index event in ACSs. The TIMI-IIB trial studied enoxaparin in 3,910 patients.
with high-risk unstable angina or non-Q-wave MI. Inclusion criteria were modified after enrollment of 1,800 patients to recruit higher-risk patients by requiring either ST-segment deviation or elevated levels of cardiac markers. The primary end point was a composite of all-cause mortality, recurrent MI, or urgent revascularization at 8 days and 43 days for outpatient therapy. At 8 days, the primary end point was observed in 14.5% of patients receiving unfractionated heparin and in 12.4% of patients receiving enoxaparin (OR 0.83, 95% CI 0.69 to 1.00, \( P = .048 \)). The composite end point of death or MI was reduced from 5.9% in the unfractionated heparin group and 4.6% in the enoxaparin group (\( P = \text{NS} \)). The Kaplan-Meier plots remained parallel, suggesting no additional relative treatment benefit with an additional 35 days of enoxaparin therapy.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study was a prospective, randomized, double-blind, parallel-group, multicenter trial. A total of 3,171 patients were enrolled in this study, which included patients with recent-onset angina (occurring within 24 hours before randomization). The primary end point was death, MI, or recurrent angina at 14 days. The risk of death, MI, or recurrent angina was significantly lower in the enoxaparin group than in the unfractionated heparin group (16.6% versus 19.8%, respectively; OR 0.80, 95% CI interval 0.67 to 0.96; \( P = .019 \)). This benefit was maintained over 30 days.

**Evaluation and debate**

GP IIb/IIIa inhibitors provide additional benefit in reducing adverse events over aspirin and heparin. There was an early divergence in the Kaplan-Meier curves in the PRISM, PURSUIT, and PRISM-PLUS trials in the GP IIb/IIIa inhibitor arms. These results suggest that there is additional benefit of early treatment with GP IIb/IIIa inhibitors in the high-risk AMI population. Direct comparisons of the GP IIb/IIIa inhibitors are not available, so the specific choice of agent remains speculative.

Several issues must be kept in mind when evaluating the evidence from the GP IIb/IIIa inhibitor trials. First, use of heparin in combination with tirofiban varied among the studies of that therapy. Second, the study of lamifiban provided neutral and opposing evidence. Third, inclusion criteria and definitions of end points varied widely among studies, as did the time frame for entry into trials for initial medical management of an ACS (from 12 to 24 hours after the index event), risk stratification of patients with unstable angina, the range of primary end points assessed, and the percentage of ST-segment depression. Fourth, an elevated level of troponin was not used as a criterion to establish high risk among patients with unstable angina. Fifth, protocol requirements for the time frame for use of PCI also varied among trials.
It has been suggested that the GP IIb/IIIa inhibitors may perform better during angioplasty when they are delivered at the time of arterial trauma and platelet aggregation. The lesser benefit observed among patients with ACSs may reflect the delay between the initial index event and the start of therapy. Optimal management of ACSs is evolving. Studies are being conducted to compare the benefits of invasive and conservative management of ACSs and to determine the benefits of administration of other drugs that act on the coagulation cascade in conjunction with or separately from the GP IIb/IIIa inhibitors.

Dr Rackow, representing the Society of Critical Care Medicine, stated that there was insufficient evidence to classify use of GP IIb/IIIa inhibitors as a Class IIa recommendation for all patients with an ACS. Dr Rackow noted that the GP IIb/IIIa inhibitors appear to be helpful if a composite endpoint is evaluated but that they are certainly not helpful if the endpoint is death only. Dr Chandra-Strobos suggested that we not define where to start the drug (ie, in the ED or critical care unit) but when to start the drug (early). Dr Chandra-Strobos also suggested that we expand the guidelines to include more discussion of low molecular weight heparins because the magnitude of benefit observed in the ESSENCE trial was as good as that of the GP IIb/IIIa inhibitors.

Consensus was reached on the classification of GP IIb/IIIa inhibitors as a Class IIa recommendation for patients with non-ST-segment elevation ACS at high risk for adverse cardiovascular events, especially in conjunction with PCI, and as a Class IIb recommendation if the patient is not at high risk for adverse cardiovascular events. For patients not at high risk for adverse cardiovascular events, all available modalities should be considered.

**Proposed guidelines**

Administer a GP IIb/IIIa inhibitor in the hospital to patients with unstable angina or non-ST-segment elevation MI who are at high risk for adverse cardiovascular events, especially in conjunction with PCI (Class IIa). Consider use of a GP IIb/IIIa inhibitor in patients with an ACS who are not at high risk for adverse cardiovascular events (Class IIb).

This guideline change will require an addition to the current ACS algorithm. This addition should include instruction to consider the use of GP IIb/IIIa inhibitors for patients with non-ST-segment elevation ACS who are at high risk for adverse cardiovascular events. It will be important for the guidelines to specify the characteristics of high risk, including elevation of such cardiac markers as myocardial muscle creatine kinase isoenzyme (CK-MB) or troponin, presence of ST-segment depression or ischemic changes on the ECG, and a history suggestive of unstable angina or MI. Other characteristics that place a patient at high risk include increasing age, current absence of beta-blocker therapy, and use of PCIs.
Topic 5: Administration of glucose-insulin-potassium during AMI

1992 Guideline

None.

Proposed addition or change

Glucose-insulin-potassium (GIK) solution should be administered to patients with AMI.

New science

GIK may reduce mortality during AMI through several mechanisms. Exogenous glucose is a more efficient fuel than either free fatty acids (FFAs) or glycogen. FFAs increase during myocardial ischemia and are toxic to the ischemic myocardium because they increase the rate of myocardial ventilation (MVO₂) and depress contractility. It is also believed that FFAs may impair calcium hemostasis and lead to electrical instability. GIK has anti-FFA activity and reduces circulating levels of FFAs as well as myocardial uptake. It also antagonizes the effects of catecholamines and heparin on increased FFAs.

The concept of metabolic modulation to improve myocardial salvage during AMI was first described by Sodi-Pallares et al. in 1962. Results of early experimental and clinical studies were promising, demonstrating a reduction in infarct size, heart failure, and mortality. These small clinical trials had significant variations in research methods, treatment patterns, and the rate of mortality from AMI. These variations have made it difficult to ascertain whether GIK solution should be administered to all patients with AMI. There has been a resurgence of interest in the usefulness of GIK in reducing mortality during AMI, culminating in several recent randomized, controlled clinical trials.

The DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial was a randomized, controlled study of diabetic patients with AMI who were treated with an intravenous infusion of GIK followed by subcutaneous insulin given 4 times a day for 3 months. There was no statistically significant difference between the treatment and control groups at 3 months, but there was a 30% reduction in mortality at 1 year and a 40% reduction in fatal infarction after 1 year in the GIK-subcutaneous insulin group. It is unclear whether this benefit was secondary to the GIK infusion at the time of the infarct or because of slightly better glucose control during the year after infarction. This study reported no significant metabolic alterations precipitated by the administration of GIK in diabetic patients. A large randomized, controlled trial is now under way in Scandinavia to address this issue.
A recent meta-analysis of 9 trials conducted before the era of fibrinolytics found a proportional mortality reduction of 28% to 48% depending on the dosage and timing of GIK administration.[115] The only significant adverse effect was the development of phlebitis in a small percentage of patients in the treatment groups.

The Estudios Cardiologicos Latinoamerica (ECLA)-GIK trial is a large placebo-controlled study that includes patients treated with fibrinolytic therapy and other types of reperfusion therapy.[116] A 57% relative mortality reduction in patients treated with GIK within 12 hours of symptom onset was observed in the pilot study. An even more impressive 66% relative reduction in mortality was observed in the subset of patients treated with a reperfusion strategy, suggesting that restoration of blood flow alone may not fully exhaust the potential for myocardial salvage during AMI.

In the recently reported Polish GIK (Pol-GIK) trial, low-dose GIK infusion was used in the treatment arm. No reduction in mortality was observed in the treatment group, but a non-statistically significant trend of increased noncardiac mortality in treated patients was noted.[117]

**Evaluation and debate**

Consensus was reached that GIK should not be administered routinely to all patients with AMI. Dr Chandra-Strobos reviewed the data from these studies and found problems with study design and subgroup analyses. Particularly bothersome was the high rate of mortality in the control group in the ECLA reperfusion arm, which was not explained. She recommended a conservative approach pending publication of more data from randomized, prospective studies. Dr Weil concurred and noted that interactions between GIK and other therapeutic agents have not been evaluated fully. Dr Weil thought that a very conservative approach should be taken until larger trials that have an ability to evaluate baseline and concomitant treatment therapies are conducted.

Intravenous GIK therapy for patients with AMI seems very promising: it is easily administered, inexpensive, and associated with few adverse effects. Administration through a peripheral vein is associated with a 2% incidence of significant phlebitis and no serious metabolic consequences, even in diabetic patients. In certain subsets of patients (ie, diabetic patients and those treated with reperfusion strategies), the effect on mortality may be different from the effect observed among the general population. Further investigation is needed to determine the definitive mortality effect of intravenous GIK administered during AMI in the general population and in various subsets of patients.

**Proposed guidelines**
Administer GIK solution to patients with AMI (Class IIb). This guideline change will necessitate a revision to the AMI algorithm. Intravenous administration of GIK solution will need to be added as a treatment to consider. A description of the potential mechanisms of action of GIK and its adverse effect profile, along with recommendations on timing, dosing, and route of administration, will need to be added to the text.

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**ADDITIONAL STUDIES ON OUT-OF-HOSPITAL FIBRINOLYSIS**


   Abstract

   Abstract

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