

A Practical Guide to Understanding the 2002 ACC/AHA Guidelines for the Management of Patients With Non-ST Segment Elevation Acute Coronary Syndromes

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Numerous advances have been made in recent years in the diagnosis and treatment of patients with acute coronary syndromes (ACS). These advances, based on clinical observations, experience, and randomized clinical trials, have led many cardiologists, emergency medicine physicians, and allied healthcare professionals to change their practices. Some physicians, however, have been slow to embrace the new trends. In fact, research shows that a wide gap exists between how evidence suggests patients with ACS should be treated and how these patients actually are treated across the United States.

Since 1980, a joint task force sponsored by the American College of Cardiology (ACC) and the American Heart Association (AHA) has published guidelines for the treatment of various cardiovascular diseases. The guidelines are in-

tended to assist healthcare professionals in making appropriate decisions about the diagnosis and management of specific conditions. The ACC/AHA guidelines for the treatment of patients with unstable angina and non-ST segment elevation ACS (NSTEMI ACS) were first established in 1994 by the Agency for Health Care Policy and Research, now the Agency for Healthcare Research and Quality.

Since the initial publication of the guidelines, angiotensin-converting enzyme (ACE) inhibitors were shown to improve outcomes in patients with coronary artery disease (CAD), platelet glycoprotein (GP) IIb-IIIa inhibitors were shown to reduce the risk of death or nonfatal myocardial infarction (MI) in several large studies, and an early invasive management strategy was shown to reduce long-term mortality. In September 2000, the ACC and AHA jointly published new guidelines for the management of patients with unstable angina or NSTEMI acute MI (NSTEMI), the two conditions that collectively make up NSTEMI ACS.¹ The guidelines were further updated in March 2002, based on new evidence. The treatment of patients with unstable angina or NSTEMI has changed dramatically in the past 6 years, and the changes to the guidelines reflect our growing understanding of the disease.

Unstable angina and NSTEMI are deadly diseases that have major public health implications. The National Center for Health Statistics reported that in 1996 alone there were 1,433,000 hospitalizations for unstable angina and NSTEMI.² Data from the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppres-

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sion Using Integrilin (eptifibatide) Therapy (PURSUIT) trial indicate that unstable angina and NSTEMI pose major health risks.³ At 6 months, of the 10,948 PURSUIT patients who presented with unstable angina or NSTEMI, 20% had either died or had another MI.

In addition, patients with NSTEMI ACS may be at higher risk for death than those with STEMI. Figure 1 shows 6-month mortality rates according to the patient's baseline electrocardiographic (ECG) category in the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial.⁴ Note that patients with ST segment depression (some of whom had NSTEMI) had higher 6-month mortality rates than did those with ST segment elevation.

One reason for the high mortality in ACS patients may be a lack of adherence to guideline-recommended procedures. Ensuring adoption of treatment guidelines remains a major issue in improving patient care; despite educational initiatives that followed publication of the guidelines, beneficial therapies continue to be underused. There is a great need for quality improvement initiatives to improve adherence to the guidelines, thereby improving patient outcomes. Physicians and other healthcare providers should consider changing their practice when evidence from clinical trials suggests that the care of patients can be improved with new treatments or therapies. CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?), a National Quality Improvement Initiative, was designed to promote widespread adherence to the guidelines among physicians and, ultimately, to achieve better care for patients with NSTEMI ACS.

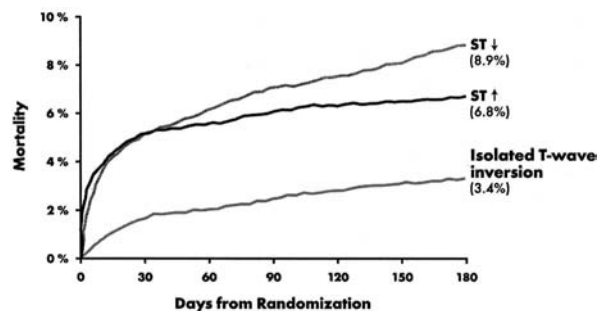


Figure 1. Six-month mortality by electrocardiographic category in GUSTO-IIb. Adapted with permission from JAMA 1999;281:707-13.⁴

THE GUIDELINES

In response to the need to inform physicians of proven therapies for treatment of ACS, the ACC and the AHA developed practice guidelines. Issued in September 2000 and updated in March 2002, the guidelines specifically address the initial evaluation and treatment approaches for patients with unstable angina and NSTEMI.¹

The guidelines have four classes of recommendations (Figure 2). A treatment carrying a Class I recommendation is generally agreed to be useful and effective. Aspirin is a good example of such a treatment. Clinical trial evidence has shown overwhelming efficacy of aspirin in reducing death and MI for people with CAD.⁵

If a treatment carries a Class II designation, then that treatment is generally considered to be effective, but some controversy may exist about the treatment's usefulness. For example, GP IIb-IIIa inhibitors are recommended (Class I) for all patients with ST segment depression or elevated cardiac markers who are undergoing an early invasive treatment strategy, but clinical evidence for the use of these agents in patients not undergoing an early invasive treatment strategy is not as compelling. Thus, the agents receive a Class IIa recommendation in this population.

A Class IIb designation is given for use of GP IIb-IIIa inhibitors in low-risk patients. Because GP IIb-IIIa inhibitors have not been studied in low-risk patients, there is no clear evidence that these agents should be used in this population.

If a treatment has a Class III designation, then the treatment is not recommended because it is not useful or may even be harmful. Generally, this status is reserved for treatments that were once thought to be highly beneficial, but current evidence has shown that this is no longer the

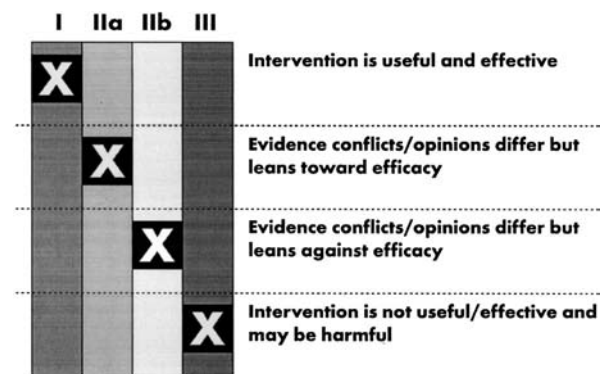


Figure 2. Classes of recommendations in the updated guidelines.

case. For example, abciximab now carries a Class III recommendation because the results of the GUSTO-IV ACS trial showed no efficacy in patients with ACS for whom an early invasive strategy was not planned.⁶

In addition to classes of recommendations, the evidence is also weighted. Grade A evidence results from data from many large randomized trials. Grade B evidence is data from fewer, smaller randomized trials, careful analyses of nonrandomized studies, or observational series. Grade C evidence results from expert consensus.

A Class I recommendation with a grade A level of evidence is therefore the strongest endorsement for any guideline. This intervention has been shown to be useful and effective, and the evidence is based on data from many large, randomized trials.

GUIDELINES RECOMMENDATIONS

Risk Stratification

Each year about 8 million people arrive at emergency departments with symptoms suggestive of ACS; 5 million of these people will be admitted to the hospital. For more than 20 years, the primary focus of physicians when assessing these patients was to “rule out” MI. Only 13% to 15% of this population will have STEMI; however, the remaining 85% will have unstable angina, NSTEMI, or non-ACS chest pain. Now, in addition to ruling out MI, physicians also need to “rule in” the possibility of high-risk NSTEMI ACS. Such patients may need to have early invasive treatment involving catheterization combined with early aggressive antiplatelet therapy. Therefore, the first step in appropriate use of the guidelines is risk stratification.

When patients arrive with chest pain, the goal is to determine whether the pain is of cardiac origin. History and physical examination, electrocardiogram, and serum markers of cardiac injury (creatinine kinase–myocardial band [CK–MB], troponin I and T, myoglobin) are used in the initial evaluation.

HISTORY AND PHYSICAL EXAMINATION

When taking the patient’s history, the physician should focus on the following:

- Characterization of chest discomfort or other possible ischemic signs: frequency, duration, triggers, and severity;

- Demographics and cardiac risk factors: age, sex, prior coronary events, diabetes, hypertension, hyperlipidemia, smoking, family history of CAD, peripheral vascular disease, cocaine use;
- Possible noncardiac explanations for symptoms: gastric ulcer, panic attacks, musculoskeletal disorder, chest trauma; and
- Possible exclusions for reperfusion: major surgery (2 weeks), hemorrhagic stroke, intracranial tumor, head trauma, history of bleeding problems, possible aortic dissection (ripping or tearing pain).

The physical examination, on the other hand, should be used to assess clinical factors that can exacerbate symptoms or drive or complicate treatment:

- Systolic blood pressure >180/100 mm Hg or <90 mm Hg;
- Heart rate: regular or irregular, slow or fast;
- Respiratory rate: check for evidence of respiratory failure;
- Jugular venous pressure;
- Lungs: check for heart failure;
- Heart: assess for gallop, acute murmurs, or rubs;
- Rectal: check for bleeding; and
- Extremities: check perfusion and edema

ELECTROCARDIOGRAPHY

The ECG is one of the best risk-stratification tools available to evaluate a patient with possible ACS. It can independently predict acute cardiac death, even after adjustment for other findings, such as cardiac biomarker levels.

The primary section of the ECG tracing that reflects ischemic changes is the ST segment. This segment can be elevated, depressed, or both (relative to the rest of the horizontal line), and the T wave itself can be inverted. If a patient has transient ST segment changes (>0.5 mm) with symptoms at rest and the changes resolve when the symptoms subside, this strongly suggests acute ischemia and a likelihood of underlying CAD.

If patients show persistent ST segment elevation, however, they are having a STEMI and should be referred for immediate reperfusion therapy, if appropriate. There is no need to wait for confirmation by biomarker elevations or other signs.

ST segment depression, the most common ECG abnormality noted in patients presenting

with NSTEMI ACS, is a major predictor of mortality. Patients with ST segment depression have either unstable angina or NSTEMI; the distinction between the two depends on the results of biomarker assays.

ST depression indicates a high likelihood that the patients will have two- or three-vessel disease (66%), resulting in a need for high-risk percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery. Between 40% and 50% of patients with ST depression will develop an MI within hours after presentation to the emergency department. These patients usually present with a high-risk profile, including significantly more diabetes, hypercholesterolemia, congestive heart failure, and prior histories of unstable angina, MI, PCI, or coronary artery bypass graft.⁴

Patients with both ST segment elevation and depression have a significantly worse short- and long-term prognosis than patients with either ST segment elevation or depression alone. This likely reflects their tendency to have larger infarctions, more severe underlying CAD, more congestive heart failure symptoms, and worse left ventricular function.

Although patients with T-wave inversion on the initial ECG have the best prognosis among patients with NSTEMI ACS, up to 5% of such patients will die or have an MI within 30 days. If patients have ischemic chest pain and symmetrical T-wave inversion more than 2.0 mm, this strongly suggests acute ischemia, usually caused by a critical stenosis of the left anterior descending coronary artery.

Patients with a normal ECG may still be having ACS. Although a single normal ECG does not exclude ischemia or infarction, a normal ECG throughout the course of an acute infarct is extremely uncommon. Up to 6% of such patients with a normal ECG will eventually be shown to have had an NSTEMI, and at least 4% are found to have unstable angina.

The ACC/AHA guidelines suggest that serial ECGs increase both sensitivity and specificity. The guidelines do not recommend continuous ST segment monitoring. Mathematical models based on ECG findings are used only to identify low-risk patients and to determine the prognosis of patients with ischemia.

BIOMARKERS OF CARDIAC INJURY

If the initial ECG does not show ST segment elevation, further tests must be used to deter-

mine whether a patient's symptoms relate to myocardial necrosis. Biochemical markers of cardiac injury provide both diagnostic and prognostic information in evaluating patients with suspected ACS.

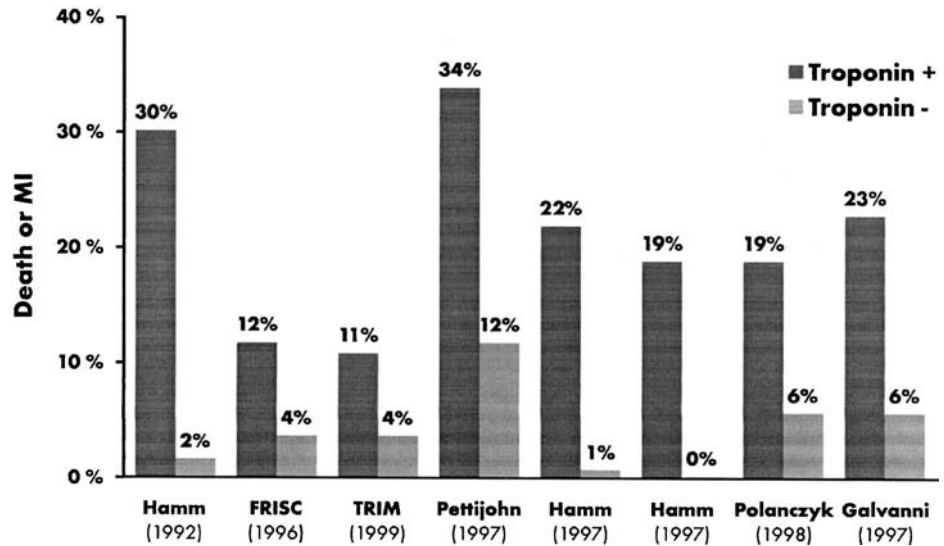
Point-of-care bedside cardiac marker assays can be performed within 15 to 20 minutes of presentation and can accelerate decision-making in the emergency department. Because they help differentiate between unstable angina and NSTEMI, biomarker concentrations serve as a bridge between the initial evaluation and timely management of patients with ACS.

The ACC/AHA guidelines state a preference for a cardiac-specific troponin (troponin I or troponin T), but CK-MB is rated as an acceptable alternative. Until recently, CK-MB was the principal serum marker used to evaluate possible NSTEMI ACS, despite known limitations. One drawback of CK-MB is that low levels of this marker normally may be present in the blood of healthy people. It also can be elevated with severe damage to skeletal muscle.

Troponin is very useful in the diagnosis and prognosis of NSTEMI ACS. Not normally detectable in the blood of healthy individuals, troponin indicates that myocardial cell death (MI) has occurred, and predicts death when elevated, independent of the CK-MB level (Figures 3 and 4).^{7,38} Further, the amount of troponin T or troponin I released relates directly to the risk for death in patients with NSTEMI ACS. Elevated levels of troponin provide prognostic information beyond that supplied by the patient's clinical characteristics, ECG findings, or pre-discharge exercise tests. Patients without troponin elevations still may be at risk for adverse outcomes. In clinical studies, NSTEMI ACS patients with elevated troponin have derived greater benefit from aggressive management with GP IIb-IIIa inhibitors and early diagnostic catheterization.⁷

Myoglobin has limited utility as a biomarker because of its lack of cardiac specificity: skeletal muscle injury will increase the level of myoglobin in the blood. Although myoglobin is not useful to rule in MI, it is useful when ruling out MI. A negative myoglobin suggests that the chest pain is not of cardiac origin. Once patients have been stratified into low-, medium-, and high-risk groups according to history and physical examination, ECG, and cardiac markers, they will

Figure 3. A positive troponin marker is strongly associated with an increased risk for death or MI. Adapted with permission from J Am Coll Cardiol 2001;38:478-85.⁷



need treatment with an early invasive or an early conservative strategy.

Early Invasive Treatment Strategy

The guidelines recommend an early invasive treatment strategy (Class I, level of evidence A) for all high-risk NSTEMI ACS patients. This strategy involves diagnostic catheterization and revascularization within 24 to 48 hours. Patients treated with an early invasive treatment strategy should also receive guidelines-recommended drugs (e.g., aspirin, heparin, and a GP IIb/IIIa inhibitor) as soon as possible. Antithrombotic therapies for patients treated with an early invasive treatment strategy are listed below:

- Aspirin (Class IA);
- Clopidogrel, if aspirin is contraindicated (Class IA);

- Low molecular weight heparins (LMWH) or unfractionated heparin (UFH) (Class IA);
- LMWH is preferable to UFH, unless bypass surgery is planned within 24 hours (Class IIaA);
- GP IIb/IIIa inhibitor, if catheterization or PCI planned (Class IA);
- GP IIb/IIIa inhibitor added to aspirin, heparin, and clopidogrel if catheterization or PCI needed (Class IIaB);
- Clopidogrel, if PCI planned, for at least 1 month (Class IA) and for up to 9 months (Class IB); and
- Withhold clopidogrel for 5 to 7 days if bypass surgery planned (Class IB).

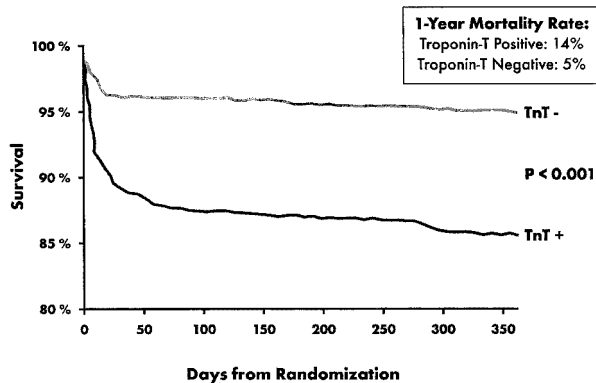


Figure 4. One-year survival in GUSTO-IIa according to troponin status. Adapted with permission from Circulation 1998;98:1853-9.³⁸

Early Conservative Strategy

Low-risk patients should be treated with an early conservative management strategy. This strategy involves medical therapy and continuous monitoring for changes in status (from low-risk to high-risk). Serial ECGs and cardiac markers should be assessed in these patients. If an early conservative strategy is chosen, the patient must be monitored to determine whether they have ischemia at a low level of stress or recurrent angina. Such patients should be switched to the invasive treatment strategy and undergo diagnostic catheterization or revascularization as soon as possible. Antithrombotic therapies include the following:

- Aspirin (Class IA);
- Clopidogrel, if aspirin is contraindicated (Class IA);

- Clopidogrel for at least 1 month (Class IA) and for up to 9 months (Class IB);
- LMWH or UFH (Class IA);
- Eptifibatid or tirofiban in patients with continuing ischemia (Class IIA), elevated troponin I or troponin T (Class IIA), or other high-risk features (Class IIA); and
- Abciximab should not be used unless PCI is planned (Class IIIA).

Thus, rapid-risk stratification is crucial so that high-risk and low-risk patients can receive appropriate treatment as early as possible.

NSTE ACS patients with high-risk features should be treated with early invasive management, which includes diagnostic catheterization and revascularization within 24 to 48 hours. Intermediate-risk patients can be treated with either an early invasive or early conservative strategy. Low-risk patients should be treated with early conservative therapies and monitored for signs of ischemia.

Medications for NSTE ACS

Given that the pathophysiology of NSTE ACS involves a thrombotic response to vessel injury, antithrombotic therapies are the cornerstone to managing patients with NSTE ACS. These therapies include both oral and intravenous antiplatelet agents, as well as intravenous and subcutaneous antithrombin therapies.

The management of patients with NSTE ACS includes two goals: immediate relief of ischemia and prevention of serious adverse outcomes, such as death or (re)infarction. The best approach to achieving these goals includes the use of three types of therapies—antiplatelet agents, anticoagulants, and anti-ischemic drugs—while keeping in mind the bleeding risk that can be associated with these agents.

Antiplatelet therapy involves agents that prevent clotting by inhibiting the activation and aggregation of platelets that lead to thrombus formation. Aspirin and clopidogrel help reduce the activation of platelets by each blocking 1 of 70 platelet agonists. Glycoprotein IIb-IIIa inhibitors block the final common pathway to platelet aggregation, preventing the formation of a thrombus.

Anticoagulants also prevent blood from clotting, but do so by a different mechanism. They serve as blood thinners and should be added to the antiplatelet regimen as soon as possible after identification of an ACS. By partially blocking

thrombin, anticoagulants help prevent the conversion of fibrinogen to fibrin, thus preventing the stabilization of a platelet-rich thrombus. Unfractionated heparin has been the standard in this regard, but LMWH may be used as an alternative to UFH.

Anti-ischemic therapy does not affect the clotting process, but rather acts on the blood vessels to increase blood flow and reduce work for the heart. These therapies include nitrates, morphine sulfate, beta-adrenergic-receptor antagonists (β -blockers), and calcium-channel blockers. Nitrates are vasodilators; they relax the vessels to open and enlarge the lumen. Morphine sulfate is a strong analgesic and relieves the pain of angina. β -Blockers reduce the heart's demand for blood by inhibiting the stimulatory effects of epinephrine (adrenaline). In doing this, β -blockers lower the heart rate and blood pressure. Calcium-channel blockers also lower the heart rate and blood pressure.

Antiplatelet Therapy

Antiplatelet agents block various pathways leading to thrombosis.

Aspirin

Aspirin is effective as an acute treatment for new unstable angina patients and as a preventive medication in CAD patients. By blocking one of the basic activation pathways, aspirin helps prevent the activation of platelets.

Aspirin is the cornerstone of treatment for all ACS. It is inexpensive, has been proven to be effective, and has wide applications in thrombotic disease. Aspirin is given in the hospital to treat and prevent MI, transient ischemic attacks, and angina. Aspirin blocks only one of the pathways to platelet activation: the thromboxane A₂ pathway. Thus, it is a relatively weak antiplatelet agent.

Guideline Recommendations

Aspirin carries a Class IA recommendation in the treatment guidelines for NSTE ACS. Antiplatelet therapy should be started promptly in these patients, and aspirin is the first choice. It is given as soon as possible after the patient arrives in the emergency department and is continued indefinitely.

Contraindications

Few contraindications are associated with aspirin, but some patients cannot tolerate the drug. Contraindications to aspirin include severe intolerance or true allergy. True aspirin allergy, although rare in the general population, can be accompanied by asthma, rhinitis, hives, and anaphylactic shock. Other contraindications include active bleeding, hemophilia, severe untreated hypertension, active peptic ulcer, or other significant sources of gastrointestinal or genitourinary bleeding.

Clinical Trials

The evidence for the beneficial effects of aspirin is overwhelming. Aspirin reduced early deaths by 25% in the International Study of Infarct Survival (ISIS-2) trial.⁸ In the Antiplatelet Trialists Collaboration, a meta-analysis of randomized trials of antiplatelet therapy, a clear benefit was shown when comparing aspirin with placebo for the reduction of adverse ischemic events after MI, unstable angina, or stroke.⁹ In four randomized trials of aspirin versus placebo in patients with unstable angina, there was an approximate 51% reduction in the risk of death after at least 30 days and a 47% reduction in the risk of death or MI with aspirin (Figure 5).¹ Despite its prominence in guidelines recommendations, however, up to 25% of patients with known CAD do not receive aspirin during cardiac hospitalization. Only 78% to 85% are prescribed aspirin therapy at discharge.¹⁰

Clopidogrel and Ticlopidine

Two thienopyridine antiplatelet agents—clopidogrel and ticlopidine—can be considered for patients with NSTEMI ACS. Thienopyridines offer a more potent form of protection for patients with ACS or chronic CAD. By preventing the activation of platelets caused by 1 of 70 agonists called adenosine diphosphate, thienopyridines also help to block platelet activation; however, because these agents are irreversible, bleeding is an issue.

Adenosine diphosphate is 1 of 70 to 100 identified agonists of platelet activation. Adenosine diphosphate is secreted from activated platelets and binds to receptors on the platelet surface called P_2Y_1 and P_2Y_{12} . This binding activates platelets in nearby circulation, resulting in further secretion or release of agonists, in thrombin generation and in expression of GP IIb-IIIa receptors. Ticlopidine and clopidogrel block the P_2Y_{12} receptor, partially blocking the subsequent activation of platelets via the adenosine diphosphate pathway.

The onset of action of these drugs is slow because the drugs need to be metabolized in order to work. In addition, the effect is irreversible, which can lead to bleeding problems.

In February 2002, the U.S. Food and Drug Administration approved the use of clopidogrel with aspirin in patients with NSTEMI ACS, on the basis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial and the Clopidogrel

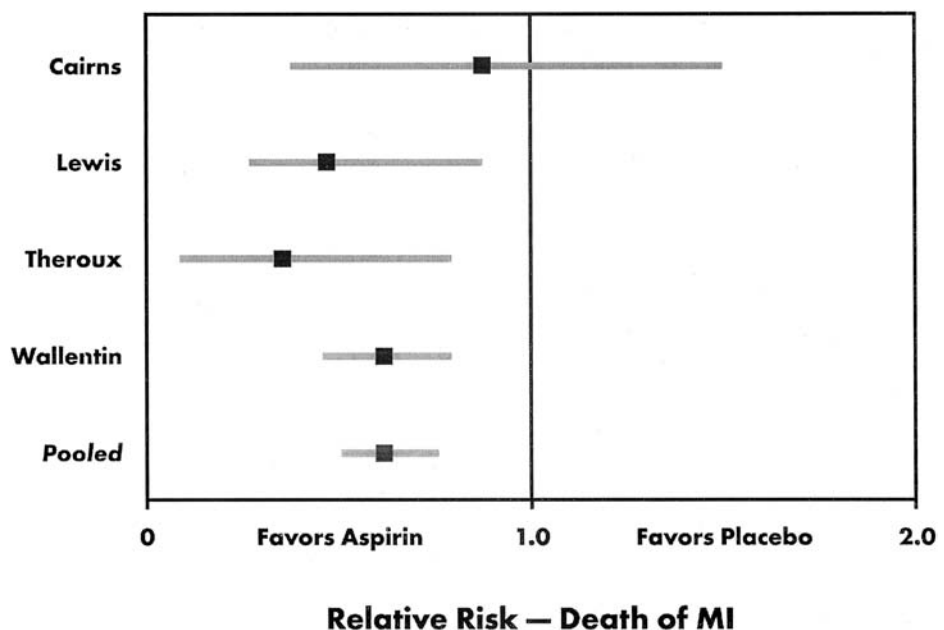


Figure 5. Risk plot showing results of four randomized trials of aspirin versus placebo in acute coronary syndromes. Adapted with permission from *Circulation* 2000;102:1193-209.¹

Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial.^{11,12} Its use was then incorporated in the March 2002 update of the ACC/AHA guidelines for treatment of NSTEMI ACS.

Ticlopidine has been used successfully for secondary prevention of stroke and MI and to prevent stent closure and graft occlusion after coronary artery bypass grafting. Its use is not specifically recommended by the guidelines.

Guideline Recommendations

Clopidogrel should be given to hospitalized patients who cannot tolerate aspirin because of allergy or major gastrointestinal intolerance (Class IA). If no early intervention is planned, clopidogrel should be added to aspirin as soon as possible on admission and given for at least 1 month (Class IA) and for up to 9 months (Class IB). If early PCI is planned, clopidogrel should be started and continued for at least 1 month (Class IA) and continued for up to 9 months if there is no high risk of bleeding (Class IB), and a platelet GP IIb-IIIa antagonist should be given to patients already receiving heparin, aspirin, and clopidogrel (Class IIaB). If bypass surgery is planned, clopidogrel should be withheld for 5 to 7 days beforehand (Class IB).

In most cases, it will not be obvious that early bypass surgery might be required. In high-risk patients managed with an early invasive strategy, it seems reasonable to wait to begin clopidogrel until after diagnostic angiography has been performed and the need for coronary artery

bypass graft surgery has been excluded. Patients who are given clopidogrel still should receive heparin, aspirin, and a GP IIb-IIIa inhibitor because of the delay in antiplatelet activity with clopidogrel.

Contraindications

Contraindications to use of thienopyridines include known prior reactions (such as neutropenia with ticlopidine) and thrombotic thrombocytopenia purpura.

Clinical Trials

Most of the information derived from clinical trials about the use of clopidogrel is from the CURE trial.¹¹ In the CURE trial, 12,562 patients with NSTEMI ACS were randomized to receive aspirin with or without clopidogrel for 3 to 12 months. This study included low-risk patients who were not undergoing an invasive procedure. If a participating clinician believed that angiography or revascularization was needed or that a thienopyridine derivative was indicated, the study medication was stopped or open-label clopidogrel or ticlopidine was used. The study excluded patients with contraindications to antithrombotic or antiplatelet therapy, those who were at high risk for bleeding or severe heart failure, those taking oral anticoagulants, and those who had undergone coronary revascularization in the previous 3 months or had received a GP IIb-IIIa inhibitor in the previous 3 days. The

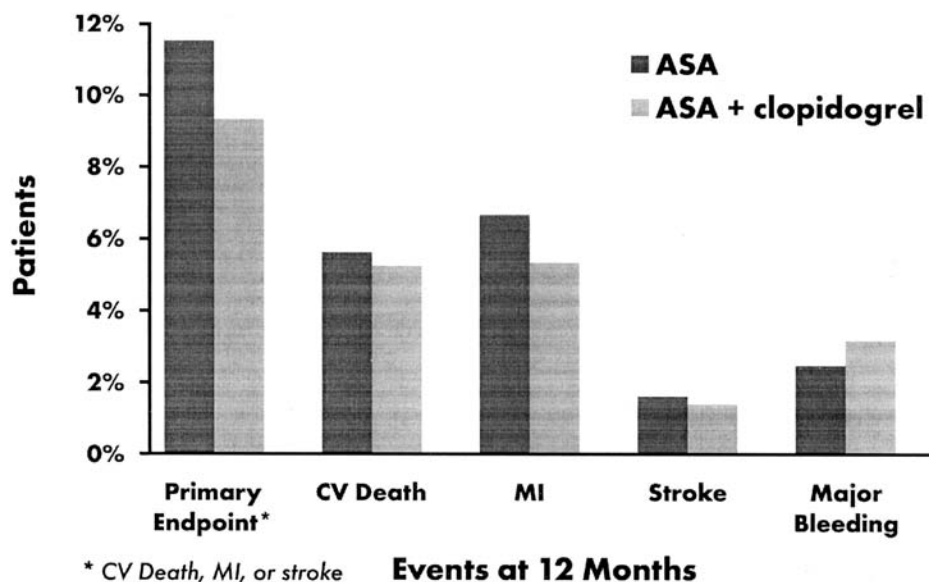


Figure 6. Events at 1 year in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial of aspirin versus aspirin and clopidogrel.

incidence of the primary outcome (cardiac death, MI, or stroke) was reduced by 20% when clopidogrel was added to aspirin (relative risk, 0.80; 95% CI, 0.72–0.90) (Figure 6). The risk of major bleeding was increased by almost 40% among patients treated with clopidogrel (3.7% vs. 2.7%).

Clopidogrel was found to be significantly superior to aspirin in the Antithrombotic Trialists' Collaboration.¹³ Patients who took clopidogrel had fewer gastrointestinal symptoms than did those who took aspirin, and there was a trend toward fewer hemorrhagic strokes.

Intravenous Platelet Glycoprotein IIb-IIIa Inhibitors

Glycoprotein IIb-IIIa inhibitors prevent platelet aggregation. The platelet receptor GP IIb-IIIa is abundant on the platelet surface. When platelets are activated, this receptor is expressed and binds to fibrinogen and other molecules. Regardless of the original stimulus, it is the simultaneous binding of fibrinogen to GP IIb-IIIa receptors on adjacent platelets that is the final common pathway in platelet aggregation. Because GP IIb-IIIa inhibitors occupy the fibrinogen binding site, the pathway is blocked and platelets cannot aggregate. Glycoprotein IIb-IIIa inhibitors also disaggregate thrombus, helping to reduce coronary obstruction. Thus, GP IIb-IIIa inhibitors represent a rational therapeutic choice to prevent thrombotic events.

Consistent benefits seen with GP IIb-IIIa inhibitors have led to recommendations for their use, along with standard treatment (aspirin and heparin), in high-risk patients with NSTEMI ACS in whom early invasive management is recommended.

There are two categories of intravenous GP IIb-IIIa inhibitors: the monoclonal antibody and the small-molecule inhibitors. Three intravenous agents have been approved for use in the United States: eptifibatid and tirofiban (small-molecule agents) and abciximab (a monoclonal antibody fragment). Each agent has very different pharmacokinetic and pharmacodynamic properties. Eptifibatid and tirofiban are more specific for the GP IIb-IIIa receptor and have a much shorter half-life than abciximab. With either tirofiban or eptifibatid, platelet aggregation returns to normal 4 to 8 hours after stopping

therapy, but the effects of abciximab can last for weeks.

Guideline Recommendations

Class IA

A platelet GP IIb-IIIa inhibitor should be given, with aspirin and heparin, to patients for whom catheterization or PCI are planned (level of evidence, A). The GP IIb-IIIa inhibitor also may be given just before PCI if not administered earlier (IA).

The Class IA recommendation indicates strong evidence and general agreement among authors that all patients with ST segment depression, elevated markers, or other high-risk features should undergo early diagnostic catheterization and revascularization, if appropriate. All of these patients should also receive a GP IIb-IIIa inhibitor as early as possible.

Data from the PURSUIT, PRISM-PLUS, and TACTICS trials provide overwhelming support that early use of a GP IIb-IIIa inhibitor combined with an early invasive management strategy has substantial benefit in high-risk NSTEMI ACS patients.^{3,14,15} Therefore, high-risk NSTEMI ACS patients should be quickly identified; treated with aspirin, heparin, clopidogrel, and a GP IIb-IIIa inhibitor; and scheduled for catheterization in a timely manner (within 24–48 hours).

The statement, “also may be given just before PCI,” represents an intention that all high-risk patients receive a GP IIb-IIIa inhibitor during PCI; the guideline authors recognized that not all patients would have received GP IIb-IIIa inhibitor therapy in the emergency department or in transferring hospitals. The Guidelines Acute Ischemia Pathway indicates that the GP IIb-IIIa inhibitor should be given as soon as possible after diagnosis (Figure 7).¹

Class IIa

Eptifibatid or tirofiban should be given, with aspirin and LMWH or UFH, to patients with continuing ischemia, an elevated troponin, or with other high-risk features in whom an invasive management strategy is not planned (level of evidence, A). In addition to strongly recommending that all patients undergoing an early invasive management strategy receive a GP IIb-IIIa inhibitor (IA), this Class IIaA recommendation indicates that all high-risk patients managed conservatively should also receive either eptifibatid or tirofiban upon diagnosis. Thus,

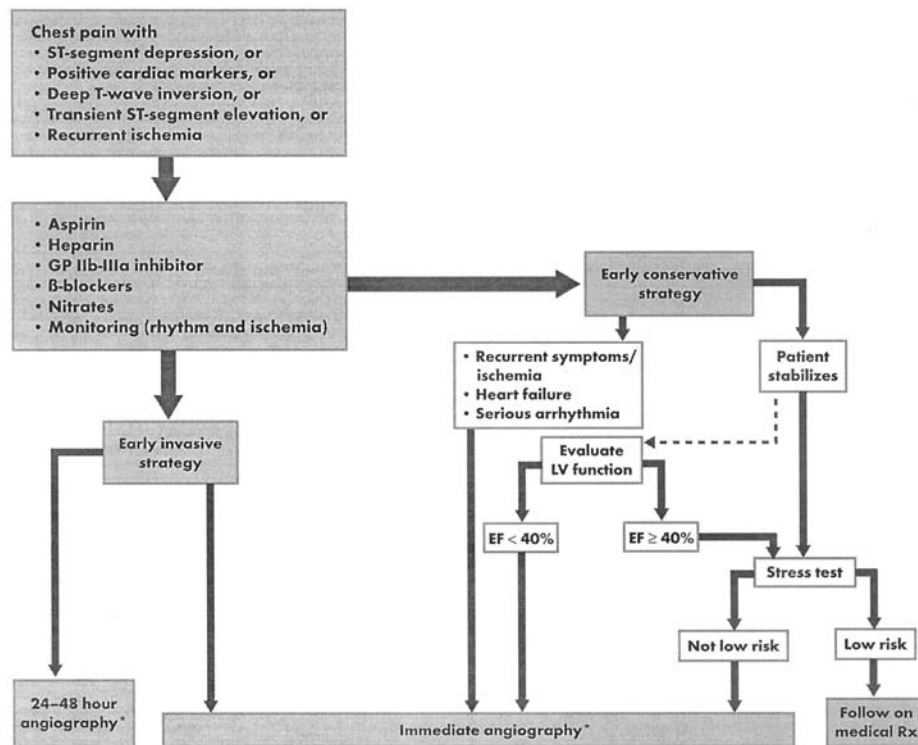


Figure 7. Acute ischemia pathway. Adapted with permission from *Circulation* 2000;102:1193–209.¹

eptifibatide or tirofiban should be used for medical management of high-risk NSTEMI ACS patients who are not scheduled for catheterization or PCI. However, recent evidence suggests that high-risk patients derive greater benefit from an early invasive management strategy.

A platelet GP IIb-IIIa antagonist should be given to patients already receiving clopidogrel in whom catheterization and PCI are planned. The GP IIb-IIIa antagonist may also be given just before PCI (level of evidence, B). Recognizing that the standard of care for PCI includes the use of heparin, clopidogrel, and a GP IIb-IIIa inhibitor, the authors recommend that patients receiving only heparin and clopidogrel (e.g., those failing an early conservative strategy) also receive a GP IIb-IIIa inhibitor before PCI.

Class IIb

Eptifibatide or tirofiban, in addition to aspirin and LMWH or UFH, should be given to patients without continuing ischemia who have no other high-risk features and in whom PCI is not planned (level of evidence, A). Because clinical trials such as PURSUIT and PRISM-PLUS did not include low-risk NSTEMI ACS patients, there is no clear evidence that these agents should be used in low-risk patients being managed conservatively.^{3,14}

Therefore, physicians should quickly identify the high-risk patients who need aggressive antiplatelet therapy and timely catheterization and PCI.

Class III

Abciximab should be given to patients in whom PCI is not planned (level of evidence, A). The Class IIIA designation indicates that there is strong evidence and consensus that abciximab should not be used unless PCI is planned, based on the GUSTO-IV ACS trial.⁶ The guidelines state that the current dose of abciximab is inappropriate for the medical management of patients with NSTEMI ACS.

Contraindications

Use of GP IIb-IIIa inhibitors is contraindicated in patients with bleeding diathesis, acute abnormal bleeding in the past 30 days, severe hypertension not controlled by antihypertensives, major surgery within the preceding 6 weeks, history of stroke within 30 days, any history of hemorrhagic stroke, platelet count less than 100,000/mm³, or dependency on renal dialysis.

Clinical Trials

The TACTICS study investigated NSTEMI ACS patients treated with an early invasive treatment

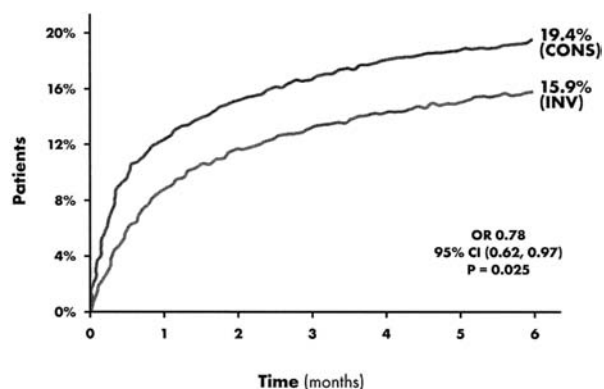


Figure 8. Death, MI, and rehospitalization at 6 months in the TACTICS-TIMI 18 trial of invasive versus conservative treatment strategies. Adapted with permission from N Engl J Med 2001;344:1879–87.¹⁵

strategy (Figure 8).¹⁵ All patients received aspirin, heparin, and the GP IIb-IIIa inhibitor tirofiban. The investigators found that use of an early invasive strategy combined with GP IIb-IIIa inhibitor therapy significantly reduced the incidence of major cardiac events. Based on these findings, the guidelines support a policy of broader use of early GP IIb-IIIa inhibition in combination with an early invasive strategy in such patients. The PURSUIT data (Figure 9)³⁹ also indicate that an early invasive strategy combined with early treatment with the GP IIb-IIIa inhibitor eptifibatide can reduce death or MI.³

Six moderate to large, placebo-controlled trials of GP IIb-IIIa inhibitors have been conducted in patients with NSTEMI ACS.¹⁶ In these trials, platelet GP IIb-IIIa inhibitors, when given with aspirin and heparin, reduced ischemic complications, including MI and death (Figure 10).¹⁶

The six trials differed in study design; making direct comparisons between them is potentially misleading. In the five trials that studied the small-molecular, reversible agents, eptifibatide or tirofiban, the estimate of the effects of the drugs always favored the platelet inhibitor; the only trial that did not favor the platelet inhibitor was the GUSTO IV ACS trial with the monoclonal antibody, abciximab.⁶

Anticoagulant/Antithrombin Therapies

Antithrombin therapies block the production of fibrin, which is crucial for the stabilization of a thrombus.

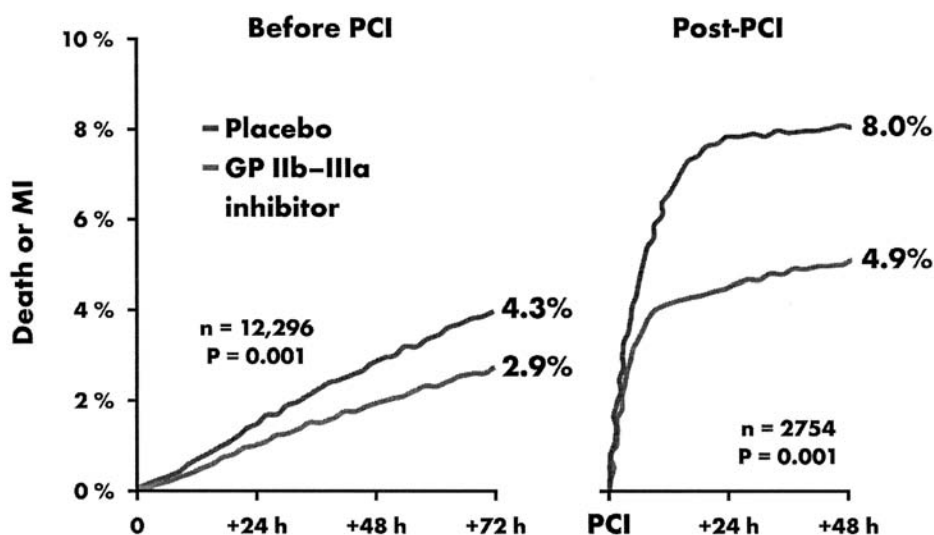
Unfractionated Heparin

Heparin is a key component in the antithrombotic management of patients with ACS. Used intravenously, heparin blocks thrombin formation by accelerating the action of circulating antithrombin, an enzyme that inactivates various factors needed in the production of thrombin. The benefit of heparin is limited, however, because it also binds to other proteins and cells. This nonspecific binding results in reduced amounts of the drug able to exert an effect (that is, poor bioavailability) and marked variations in anticoagulant response among patients.

Guidelines Recommendations

Intravenous heparin should be given to patients with ACS, along with antiplatelet agents (Class IA). Although patients treated with heparin generally fared better, a meta-analysis of six small randomized trials showed a strong (but not

Figure 9. Likelihood of death or MI at 30 days in eptifibatide or placebo patients having early (<72 hours) percutaneous intervention. Adapted with permission from Circulation 2000;101:751–7.³⁹



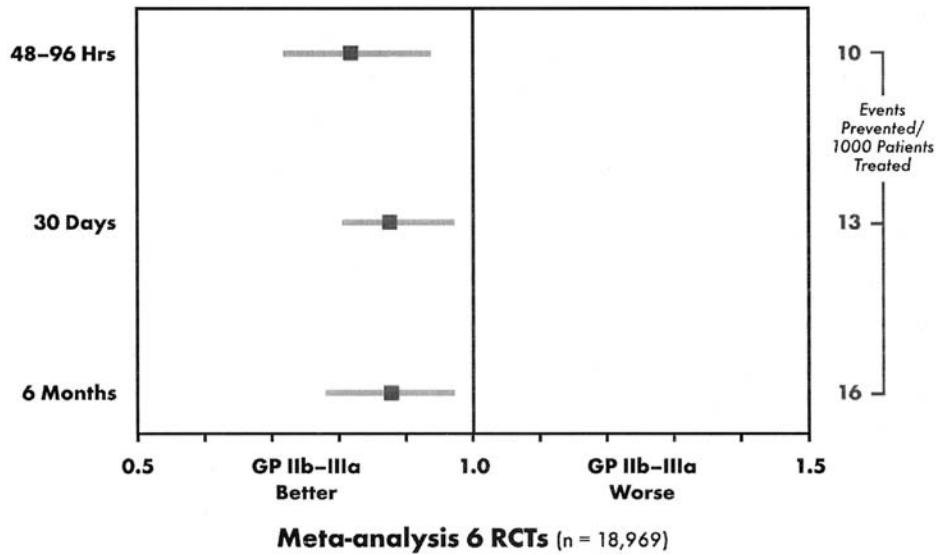


Figure 10. Effect of glycoprotein IIb/IIIa inhibitors on death or (re)infarction in a meta-analysis of six randomized trials. Adapted with permission from *Circulation* 1998;98:2829-35.¹⁶

statistically significant) trend toward benefit with UFH plus aspirin versus aspirin alone.¹⁷

Contraindications

Contraindications to heparin use include hypersensitivity, previous heparin-induced thrombocytopenia, severe current thrombocytopenia, inability to monitor platelet counts, and uncontrollable active bleeding.

Clinical Trials

Clinical trials of studies comparing aspirin and UFH versus aspirin alone have shown consistent reductions in death or MI. A meta-analysis of trials comparing aspirin plus heparin to aspirin alone showed a trend toward a reduction in death or MI, but was not significant (Figure 11).¹⁷

Low Molecular Weight Heparins

Low molecular weight heparins have a smaller molecular structure than do UFH; they have different pharmacologic properties as well. The general advantages of LMWHs over UFH include a longer half-life, which results in more predictable and sustained anticoagulation, and once- or twice-daily subcutaneous administration. Another major advantage of LMWHs is that they typically do not require laboratory monitoring of activity.

Because the level of anticoagulant activity cannot be easily measured, controversy exists about the substitution of LMWH for UFH during PCI. However, studies have shown that PCI can be performed safely with LMWH (enoxaparin)

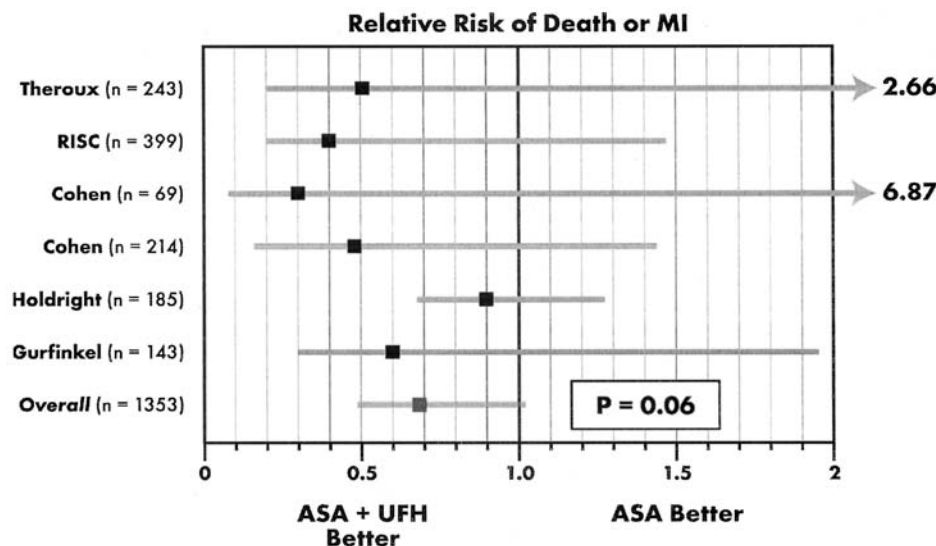
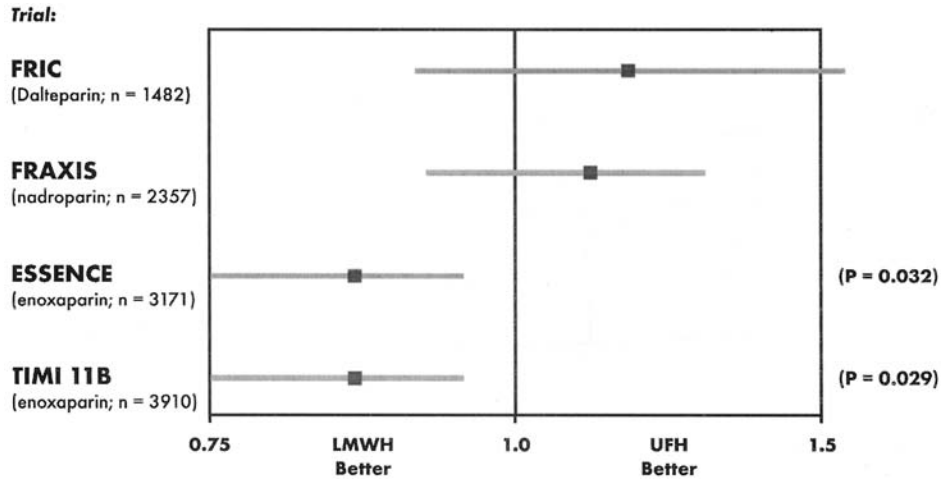


Figure 11. Evidence for use of unfractionated heparin plus aspirin versus aspirin alone. Adapted with permission from *JAMA* 1996;276:811-5.¹⁷

Figure 12. Effect of low-molecular-weight heparin on death, MI, and recurrent ischemia in four trials. Adapted with permission from *Circulation* 2000;102:1193–209.¹



and that bleeding rates between LMWH and UFH are comparable.

Guidelines Recommendations

Anticoagulation with subcutaneous LMWH (enoxaparin) should be added to antiplatelet therapy (Class IA). The guidelines state that enoxaparin is preferable to UFH as an anticoagulant, unless bypass surgery is planned within 24 hours (Class IIaA). A number of studies have examined the use of LMWH with GP IIb-IIIa inhibitors, and none suggested that the combination would lead to excess bleeding, whether or not the patient was scheduled to undergo PCI.¹⁸ Therefore, although the data are not definitive, it does appear that LMWH can be used safely in combination with GP IIb-IIIa inhibitors. Contraindications to use of LMWHs are similar to those with UFH.

Clinical Trials

In ACS, LMWHs have been shown to be superior to UFH, but results with different LMWHs have been inconsistent (Figure 12).¹ Two landmark trials compared the efficacy of subcutaneous enoxaparin with UFH in patients with NSTEMI ACS: the Thrombolysis in Myocardial Infarction (TIMI) 11B and the Efficacy and Safety of Subcutaneous LMWH in Non-Q-wave Coronary Events (ESSENCE) trials.¹⁹ Both showed that LMWH offered improved efficacy over UFH in preventing death and cardiac ischemic events. In a meta-analysis of the two trials, there was a significant 20% reduction in the short-term risk of death or serious cardiac ischemic events (Figure 13).¹⁹

Direct Antithrombin Agents

Direct antithrombin agents, unlike the heparins, inhibit thrombin directly, providing reliable, predictable anticoagulation. They have no structural similarities with the heparins and thus pose no risk of cross-reactivity in patients who have an allergic contraindication to heparins. Because of the lack of clinical evidence, current guidelines do not make recommendations about the direct thrombin inhibitors.

Hirudin (lepirudin, desirudin) is the prototypical direct thrombin inhibitor. It has been studied in three large trials of ACS (n = 16,285): one for prevention of restenosis after angioplasty,²⁰ one as an adjunct to fibrinolysis for STEMI,²¹ and one across the spectrum of patients with ACS, including a primary angioplasty substudy for acute MI.^{22,23} Desirudin showed a modest, nonsignificant advantage over heparin in the primary endpoints of these trials, although it was associated with significantly fewer early adverse events in both trials that included PCI and more consistent anticoagulant effects when compared with heparin.

Hirudin (lepirudin) is currently approved only for anticoagulation in patients with heparin-induced thrombocytopenia and to prevent deep-vein thrombosis in patients undergoing hip-replacement surgery. Bivalirudin has been approved for use in patients with unstable angina undergoing balloon angioplasty.

Anti-ischemic Therapies

Anti-ischemic therapies act on the blood vessels or other structures of the body, reducing oxygen demand, increasing the blood supply, or otherwise

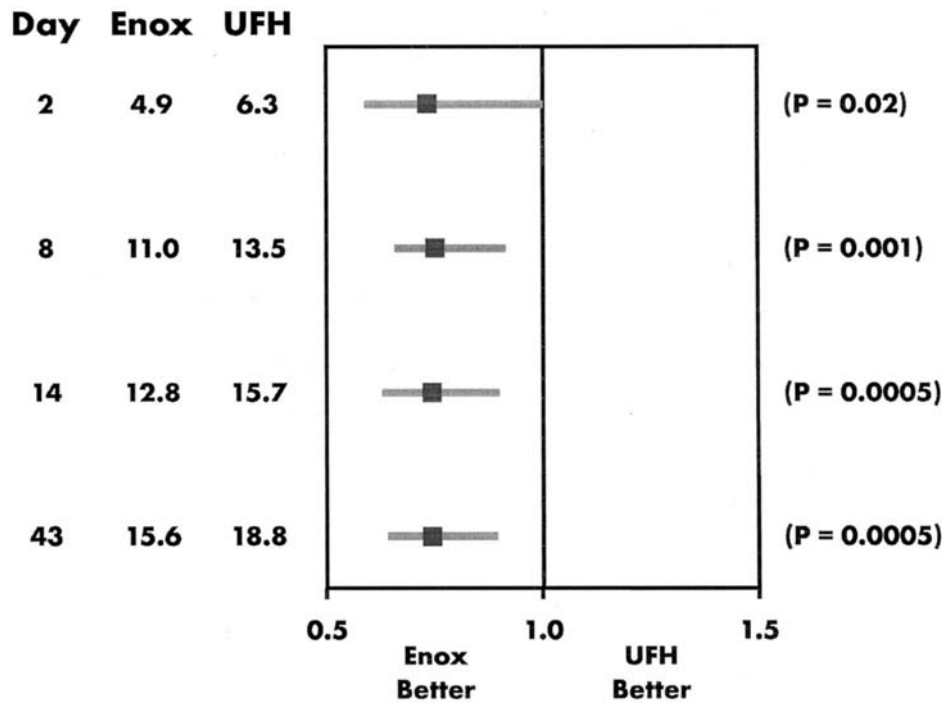


Figure 13. Effect of enoxaparin on death, MI, or urgent revascularization in a meta-analysis of the TIMI-11b and ESSENCE trials. Adapted with permission from *Circulation* 1999;100:1602-8.¹⁹

easing the strain on the heart. Many of these treatments have not been evaluated in randomized trials of patients with ACS, but consensus groups still believe these therapies are valuable.

The guidelines recommend bedrest, oxygen if needed, continuous ECG monitoring, and nitrates, morphine sulfate, β -blockers, and ACE inhibitors (certain patients only). There is some reservation about the use of calcium-channel blockers because of their side effects.

Nitrates

Nitrates, typically nitroglycerin given under the tongue or as a spray, reduce the demand for oxygen by the myocardial cells while increasing the delivery of oxygen to the cells. They do this by dilating both coronary and peripheral blood vessels, thereby reducing the workload of the heart.

Guidelines Recommendations

It is recommended that nitroglycerin, sublingual tablet or spray, be followed by intravenous administration, for the immediate relief of ischemia and associated symptoms (Class IC).

Contraindications

Intravenous nitroglycerin is contraindicated for patients who have taken sildenafil within the past 24 hours. In this case, vasodilation would

be markedly exaggerated and prolonged, and such use has been associated with severe hypotension, MI, and even death.

Clinical Trials

The rationale for using nitrates in NSTEMI ACS is derived from pathophysiologic principles and extensive, but uncontrolled, clinical observations.^{24,25} There have been no randomized, placebo-controlled trials of nitrates for symptom relief or effects on cardiac events. Most studies, which have been conducted in patients with MI, have been confounded by the use of nitrates in the control groups. Abrupt discontinuation of intravenous nitroglycerin has been linked to increased ischemic changes on the ECG; thus, the dose should be tapered slowly before discontinuation.

Morphine

Morphine sulfate is a potent painkiller. It also relieves anxiety and has hemodynamic effects that can be beneficial in NSTEMI ACS. Morphine dilates blood vessels and can reduce the heart rate and blood pressure, reducing myocardial oxygen demand.

Guidelines Recommendations

Intravenous morphine sulfate should be administered if symptoms are not immediately relieved

with nitrates or if the patient has acute pulmonary congestion or severe agitation (Class IC).

Contraindications

Intravenous morphine should not be used in patients with an allergy to morphine or other opiates, acute bronchial asthma, or obstruction of the upper airway. The major adverse effects of morphine are hypotension (especially in patients who are dehydrated or who are receiving vasodilator therapy) and respiratory depression.

Clinical Trials

No randomized trials have specifically assessed the effects of morphine in the initial management of ACS.

β -Blockers

β -Blockers competitively block the β receptors for adrenaline (a stimulant) on the myocardial cell surface. This action reduces the tendency of the muscle cells to contract, thereby reducing the heart rate and contractile changes in response to chest pain or other stimuli. The drugs also reduce systolic blood pressure. The net effect is to reduce cardiac work and myocardial oxygen demand.

Guidelines Recommendations

Intravenous β -blocker is recommended for ongoing chest pain, followed by oral administration, unless there are contraindications (Class IB).

Contraindications

β -Blockers are contraindicated in severe bradycardia (slow heart rate), hypotension (low blood pressure), second- or third-degree atrioventricular heart block, cardiogenic shock, decompensated heart failure, or sick-sinus syndrome (unless the patient has a permanent pacemaker). The drugs should be used with great caution in patients with chronic lung disease (asthma, chronic bronchitis).

Clinical Trials

β -Blockers have been extensively studied in cardiovascular disease, but only a small portion of the evidence pertains to NSTEMI ACS. Initial studies of benefit in ACS were small and uncontrolled. An overview of double-blind, randomized trials in patients with threatened or evolving MI suggests an approximate 13% reduction in the risk of progression to MI, but these trials

were not large enough to assess the effects of β -blockers on mortality in ACS.²⁶ Large randomized trials in other cardiovascular conditions (acute MI, recent MI, stable angina with daily ischemia, and heart failure), however, have all shown reduced mortality or morbidity with these drugs. Thus, the rationale for their use in all forms of coronary disease, including NSTEMI ACS, is compelling. Unless there are contraindications, these drugs should be part of routine care, especially for patients who will undergo cardiac or noncardiac surgery.

Calcium-Channel Blockers

Calcium blockers limit the amount of calcium transported into the cell, thereby inhibiting both myocardial and vascular smooth-muscle contraction. All also dilate blood vessels; some of these agents delay conduction of the electrical signal driving the heart beat.

Because some of these drugs can have harmful effects—including hypotension, worsening heart failure, bradycardia (severely slowed heart beat), and atrioventricular block (disruption of the electrical signal controlling the heart beat)—their use is limited to patients with continuing ischemic symptoms who are already receiving nitrates and β -blockers, those who cannot tolerate one or both of these agents, and those with variant angina. Because calcium-channel blockers tend to slow the heart rate in the same way as β -blockers, the two drugs should not be taken together.

Guidelines Recommendations

In patients with continuing or frequent ischemia for whom β -blockers are contraindicated, a nondihydropyridine calcium antagonist (such as verapamil or diltiazem) should be given as initial therapy if there is no severe left ventricular dysfunction or other contraindication (Class IB). In cases involving left ventricular dysfunction, amlodipine or felodipine may be used. In patients with ACS, nifedipine should be avoided unless there is adequate beta blockade, based on adverse outcomes shown in controlled clinical trials.

Contraindications

Calcium blockers are contraindicated in patients with severe heart failure, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick-sinus syndrome or second- or third-degree atrioventricular block (unless the patient has a permanent pacemaker), atrial flutter or

fibrillation and an accessory bypass tract (such as Wolff-Parkinson-White and Lown-Ganong-Levine syndromes), and known hypersensitivity to calcium blockers.

Clinical Trials

Several randomized trials have assessed the use of calcium antagonists in ACS. Two meta-analyses of all calcium blockers used in NSTEMI ACS trials have suggested no overall effect on outcomes, but effects differ by agent and patient subgroup.^{27,28} For example, although both verapamil and diltiazem appear to provide an overall benefit in ACS patients, their use in patients with suspected MI and left ventricular dysfunction appeared to increase mortality. This is being explored further in ongoing research projects.

Other trials have noted a harmful effect of certain calcium blockers when given without β -blockers. In the Holland Interuniversity Nifedipine/Metoprolol (HINT) trial of 515 patients with ACS, nifedipine alone increased the risk of MI or recurrent angina by 16% compared with placebo, whereas metoprolol (a β -blocker) decreased it by 24%; the combination of these drugs reduced outcomes by 20%.²⁹ These differences were not statistically significant because the study was stopped early out of concern about the use of nifedipine alone. In patients already taking a β -blocker, however, the event rate was significantly reduced.

In conclusion, dihydropyridine calcium antagonists (such as nifedipine) should be reserved as second- or third-line therapy, after treatment begins with nitrates and β -blockers. For verapamil and diltiazem, there is no evidence of harm when given early in ACS, and strong trends suggest a benefit. When β -blockers cannot be used, then, these agents may offer an alternative. When required for refractory symptom control, these agents can be used early during hospitalization, even in patients with mild left ventricular dysfunction, but the combination of β -blockade and calcium blockade may depress left ventricular function.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme is an enzyme that stimulates the conversion of angiotensin I to angiotensin II. Angiotensin-converting enzyme inhibitors prevent this from happening. Angiotensin II constricts blood vessels and stimulates the release of aldosterone, a hormone that in-

creases the retention of salt and fluid in the body, thus raising blood pressure. The ACE inhibitors, therefore, dilate blood vessels, prevent fluid retention, and ease the workload of the heart.

Guidelines Recommendations

Angiotensin-converting enzyme inhibitors should be used when high blood pressure persists after nitroglycerin and β -blocker treatment in patients with left ventricular dysfunction or congestive heart failure and in patients with ACS and diabetes (Class IB).

Contraindications

Patients should not receive ACE inhibitors if they are hypersensitive to these drugs or have severe hypertension. Blood-cell counts may need to be monitored, as well as measures of liver and kidney function.

Clinical Trials

Angiotensin-converting enzyme inhibitors reduce mortality in patients with new or recent MI and left ventricular dysfunction, in patients with diabetes and left ventricular dysfunction, and in a spectrum of patients with high-risk chronic cardiovascular disease.³⁰ Angiotensin-converting enzyme inhibitors should be used in all of these groups and in those whose high blood pressure is not controlled with β -blockers and nitrates. Thus, ACE inhibitors are becoming important in the treatment of patients with hypertension, heart failure, diabetes, and chronic cardiovascular disease. For all ACS patients, ACE inhibitors are classified as IIaB, which may be upgraded as new data become available.

Discharge Interventions and Medications

The guidelines also recommend risk factor modification strategies, such as smoking cessation counseling, dietary counseling, referral for cardiac rehabilitation, hypertension control, and glycemic control in diabetics. One of the goals of discharge therapy is to reevaluate long-term care. The acute event that brought the patient to the hospital is an opportunity to educate the patient on lifestyle and risk factor modification. Aggressive risk factor modification (e.g., smoking cessation, dietary modification, and hypertension control) are the mainstays of the long-term management of stable CAD.

	I	IIa	IIb	III	
A					ASA if not contraindicated
A					β-Blocker if not contraindicated
A					Lipid ↓ agents + diet if LDL > 125 mg/dL
B					Lipid ↓ agents if LDL > 100 mg/dL after diet modification
A					ACE inhibitor if CHF, EF < 40%, or ↑BP
A					Clopidogrel if ASA not used

Figure 14. Recommended discharge medications.

The guidelines recommend that the agents in Figure 14 be given at discharge. Aspirin, β-blockers, ACE inhibitors, and cholesterol-lowering agents have all been shown to have long-term prognostic benefits. The selection of the medical regimen should be individualized to the patient based on the patient's specific needs.

Many patients may still have chronic angina at discharge, and such patients should receive the above-indicated pharmacotherapy. Some observational data suggest that hormone replacement therapy provides a protective effect for coronary events. However, the only randomized trial that has been completed (Heart and Estrogen/Progestin Replacement [HERS] study) showed no beneficial effect.³¹ In addition, there was an excess of death and MI early after hormone replacement therapy initiation. Thus, it is recommended that postmenopausal women who are already receiving hormone replacement therapy should continue receiving it, but hormone replacement therapy should not be initiated for the secondary prevention of coronary events.

The guidelines recommend ACE inhibitors for patients with congestive heart failure, left ventricular dysfunction, hypertension, or diabetes. Angiotensin-converting enzyme inhibitors are traditionally used in patients with low ejection fractions. However, ACE inhibitors may be useful in a broader range of the population. In the Heart Outcomes Prevention Evaluation (HOPE) study,³² ramipril (an ACE inhibitor) significantly reduced the rates of death, MI, and stroke in a broad range of high-risk patients who did not have congestive heart failure or a low ejection fraction (Figure 15).³² Several large clinical trials have examined the hypothesis that reducing total cholesterol or low-density lipoprotein

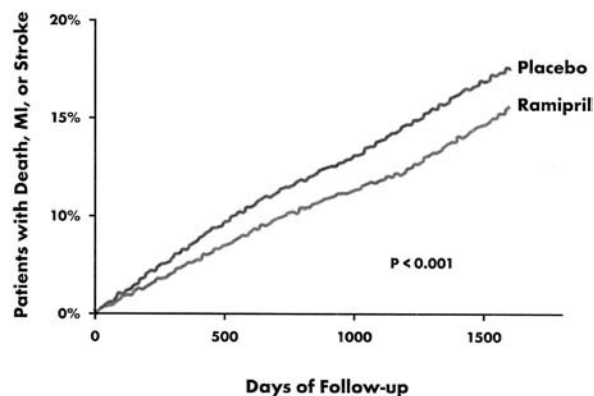


Figure 15. Results of the Heart Outcomes Prevention Evaluation Study, demonstrating a reduction in mortality and vascular events with long-term use of ramipril in patients with coronary artery disease. Adapted with permission from N Engl J Med 2000;342:145-53.³²

cholesterol concentrations would reduce rates of morbidity and mortality from CAD in patients both with and without established atherosclerotic disease.³³

The guidelines recommend a lipid-lowering agent if low-density lipoprotein cholesterol is more than 100 mg/dL after diet modification. The introduction of lipid-lowering agents known as HMG Co-A reductase inhibitors (statins) has yielded lowering of low-density lipoprotein-C of a dimension not previously achievable with medication. Abundant evidence exists that cholesterol-lowering therapy for patients with CAD and hypercholesterolemia, as well as for patients with mild cholesterol elevation after MI or unstable angina reduces vascular events and death (Figure 16).³³

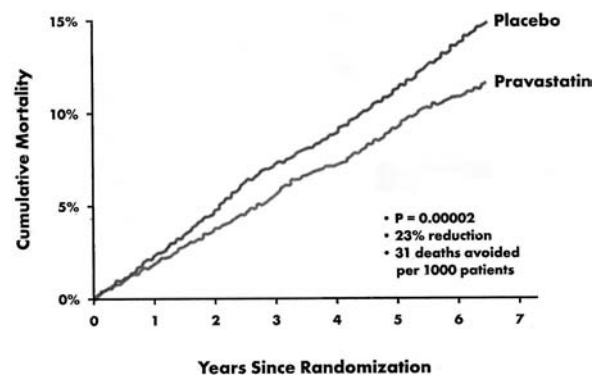


Figure 16. Results of the LIPID trial, showing that long-term use of pravastatin reduced mortality in patients with a history of MI or unstable angina. Adapted with permission from N Engl J Med 1998;339:1349-57.³³

Table 1. Benefits of Evidence-Based Therapies: Data From Non-ST Elevation ACS Patients in GUSTO-IIb

Therapy	Current Use (Ideal Patients)	Additional Lives Saved per 1,000 (Ideal Use)
Aspirin	86%	9
β -Blockers	59%	11
ACE inhibitors	52%	23
CA ⁺⁺ blockers	27%	13*
Total		56

*Number reflects lives not lost because of use when contraindicated.

Adapted with permission from *J Am Coll Cardiol* 1998; 32: 2023–30.³⁴

BENEFITS OF USING EVIDENCE-BASED THERAPIES

The benefits of using evidence-based therapies can be seen in an analysis of patients with NSTEMI ACS from the GUSTO-IIb trial conducted by the DCRI (Table 1).³⁴ If evidence-based therapies were used in all patients with appropriate indications, then outcomes would be improved.

QUALITY IMPROVEMENT PROJECTS FOR THE PROMOTION OF ADHERENCE TO ACC/AHA GUIDELINES

With the overwhelming scientific evidence, the need for a quality improvement initiative has

never been greater. Other quality improvement initiatives have shown great success in changing physician behavior and improving patient outcomes.

Guidelines Applied in Practice

The Guidelines Applied in Practice (GAP) project in southeast Michigan distributed educational tools to caregivers and patients alike on the benefits of the latest recommended therapies.³⁵ The project was the result of a fruitful, multifaceted partnership between academic peer review groups, the ACC, and regional private insurers and healthcare providers.

GAP investigators found that targeted educational interventions significantly increased the use of beneficial medications and nonmedical interventions, such as smoking-cessation counseling for patients with acute MI. Indicators such as cholesterol, biochemical markers, and smoking rates improved after GAP implementation. The GAP tools also significantly improved use of aspirin, β -blockers, and cholesterol-lowering agents (Figure 17).³⁵

Erlanger Project

An observational quality improvement initiative study at Erlanger Medical Center in Chattanooga, Tennessee, yielded similar results.³⁶ More than 2,000 patients with chest

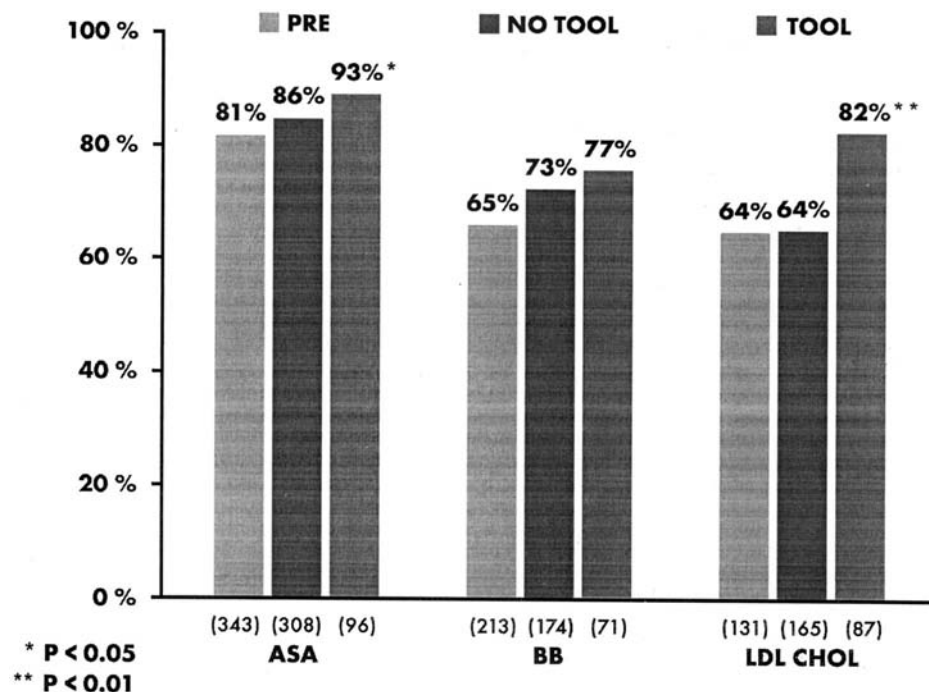


Figure 17. Results of the GAP project, showing the effect of standard admission orders on use of medications. Adapted with permission from *JAMA* 2002;287:1269–76.³⁵

pain were followed over a 1-year period. In addition to other analyses, the use of GP IIb-IIIa inhibitors was evaluated in the high-risk subset of this group. Every 4 months, a different phase of the initiative was implemented. With each escalation in the initiative, the use of GP IIb-IIIa inhibitors increased, from a low of 6.3% without intervention to 45% by the final phase.

Cardiovascular Hospitalization Atherosclerosis Management Program

The UCLA Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP) focused on the in-hospital initiation of aspirin, cholesterol-lowering therapy, β -blockers, and ACE inhibitors.³⁷ CHAMP implemented adherence to treatment guidelines for patients with MI, created standard treatment orders, and tracked and reported medication use rates. Treatment rates and clinical outcomes were compared in patients with acute MI discharged during the 2-year periods before and after CHAMP began (Table 2).

CRUSADE

CRUSADE is a national quality improvement initiative that aims to ensure the adoption of treatment guidelines for the care of patients with NSTEMI ACS. The objectives of CRUSADE are to determine the current state of awareness of and adherence to the ACC/AHA guidelines, to implement quality-improvement initiatives designed to promote the ACC/AHA treatment recommendations for high-risk patients with ACS, and to improve clinical outcomes through early implementation of the guidelines.

A major goal of CRUSADE is to develop a nationwide collaboration between emergency medicine physicians and cardiologists for improved treatment of patients with ACS. Emergency medicine physicians, cardiologists, and data coordinators will be the champions for improving practice. Cross-department collaborative efforts will be a powerful force for effecting change.

Another goal of CRUSADE is to link early risk stratification with the application of guideline-recommended therapies. Early risk stratification will help identify high-risk patients who should receive more aggressive therapies. Combined with educational efforts to emphasize the importance of treating these patients appropriately, CRUSADE will improve adherence to the guidelines from the time the patient enters the emergency department to the time of hospital discharge.

This initiative promises to have a substantial effect on healthcare delivery and outcomes. About 400 to 600 sites throughout the United States will be selected to participate, and CRUSADE will collect blinded, retrospective information about the care given to thousands of NSTEMI ACS patients.

The Duke Clinical Research Institute, the coordinating center for CRUSADE, will provide regular feedback reports to participating sites, as well as educational initiatives designed to improve the understanding and use of guideline-recommended therapies. These reports will include details about the site's treatment of high-risk NSTEMI ACS patients, as well as the use and timing of evidence-based medicines. By being able to track adherence to guidelines recommendations, participating sites will be able to identify areas in which improvement is needed and then implement quality improvement interventions to increase guidelines adherence.

What separates CRUSADE from other initiatives is the elective interventions, or materials, being offered to participating sites to help address areas in which more education regarding treatment guidelines is desired. By providing a wide range of tools, such as guideline-based standing orders, risk stratification tools, continuing education tele-conferences, thought-leader interaction, and online education, CRUSADE will offer sites tailored education to meet the needs of each participating hospital. The ultimate goal of CRUSADE is to improve the outcomes of high-risk NSTEMI ACS patients.

Table 2. Change in Discharge Medication Use Rates Before and After CHAMP

Discharge Therapy	Pre-CHAMP (1992–1993) (n = 256)	Post-CHAMP (1994–1995) (n = 302)	P Value
Aspirin	78	92	<0.001
β -Blockers	12	61	<0.001
Nitrates	62	34	<0.01
Ca ⁺⁺ blockers	68	12	<0.001
ACE inhibitors	4	56	<0.001
Statins	6	86	<0.0001

Adapted with permission from *Am J Cardiol* 2001; 87: 819–22.³⁷

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