ABSTRACT

Medical management in patients with acute coronary syndrome (ACS) should relieve ischemia and reduce the risk of adverse outcomes. The American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines recommend a variety of pharmacologic interventions to precede invasive treatment for patients with non–ST-elevation myocardial infarction or unstable angina (NSTE-MI/UA). Clinical presentation will determine the appropriate use of medical therapy prior to invasive interventions. For those patients who are good candidates for pharmacologic intervention, the ACC/AHA recommends anti-ischemic agents, antiplatelet agents, and anticoagulants. Although some of these agents—especially aspirin, angiotensin-converting enzyme inhibitors, and beta blockers—may be continued indefinitely in patients who present with ACS, other pharmacologic agents—such as the various formulations of heparin and platelet glycoprotein IIb/IIIa inhibitors—are more appropriate for acute administration. When patients do not respond to appropriate pharmacologic intervention, the choice of an invasive intervention will depend on the extent of coronary disease because the most invasive techniques are reserved for patients at most risk. This article reviews the ACC/AHA Practice Guidelines for the treatment of patients who present with NSTE-MI/UA, including recommendations for pharmacologic and invasive interventions. The treatment implications of recent clinical trials of pharmacologic interventions are also discussed. (Adv Stud Nurs. 2006;4(4):86-94)

INTRODUCTION

For patients who present with non–ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA), medical management has the goals of relieving ischemia and preventing poor outcomes. Figure 1 shows the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines recommended treatment strategy for patients with acute ischemia.1 Following diagnosis of NSTEMI/UA, the treatment strategy recommends anti-ischemia, antiplatelet, and antithrombotic therapies prior to an invasive treatment or further monitoring. High-risk patients or those who do not respond to pharmacologic therapies are candidates for an early invasive intervention. For patients who are not considered high risk, further testing to evaluate left ventricular function and cardiac structure will determine the need for angiography and possible revascularization. For patients who stabilize after initial pharmacologic therapy, patient preference for a definitive therapeutic approach should be considered.1
The treatment approach will be dictated by symptom severity. Patients who have high-risk symptoms, especially cyanosis or respiratory distress, should receive bed rest, continuous electrocardiogram monitoring, and supplemental oxygen while they are being further evaluated (Table 1). Continuous electrocardiogram monitoring of high-risk patients will help identify acute ventricular fibrillation, which is a major cause of preventable death. In addition, it will monitor recurrence or sudden changes in ST deviation, which are useful diagnostic and prognostic indicators.

This article reviews the current ACC/AHA Practice Guidelines for the pharmacologic and invasive treatment of patients who present with NSTEMI/UA. Also, the treatment implications of recent clinical trials in patients with acute coronary syndrome (ACS) will be discussed.

**Pharmacologic Therapy**

**Anti-Ischemic Agents**

Nitroglycerin (NTG) is a vasodilator that affects myocardial oxygen demand and supply. Oxygen demand is reduced through dilation of the venous capacitance vessels, thus reducing venous return to the heart (preload). Myocardial oxygen supply is increased by NTG through coronary vasodilation. NTG therapy promotes dilation of large coronary arteries, collateral flow, and redistribution of blood flow to ischemic muscle. In the absence of a beta blocker, increased heart rate and contractility partially offset the benefits of NTG therapy; therefore, these agents are usually administered concurrently. NTG therapy promotes dilation of large coronary arteries, collateral flow, and redistribution of blood flow to ischemic muscle. Patients whose ischemia is not relieved by sublingual NTG and the addition of an intravenous (IV) beta blocker, in addition to high-risk patients who are not hypotensive, may benefit from IV NTG if no contraindications exist. Intravenous NTG is usually started at a low dose of 10 µg/min and the dose is titrated upward every 3 to 5 minutes based on chest pain, blood pressure, and heart rate.

IV morphine sulfate may benefit patients whose ischemia is not relieved by serial sublingual NTG doses. Morphine sulfate may be administered concurrently with IV NTG to maintain patient comfort. Morphine reduces myocardial oxygen demand by reducing systolic blood pressure, reducing heart rate, and causing venodilation.

Beta blockers reduce myocardial contractility, sinus node rate, and atrioventricular node conduction velocity by inhibiting the action of catecholamine on beta-adrenergic receptors in the myocardium. These agents reduce systolic blood pressure, myocardial contractility, heart rate, and chest pain, thereby decreasing myocardial oxygen demand. In addition, beta blockers improve coronary flow and collateral flow by increasing the duration of diastole and diastolic pressure-time.

Beta blockers without sympathomimetic activity

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**Figure 1. Treatment Algorithm for Acute Ischemia**

![Figure 1](ImageURL)
are the preferred agents. The choice among these agents is determined by pharmacokinetics and/or side effect profiles. In high-risk patients and in those with ongoing chest pain at rest, beta blockers should be initially administered intravenously followed by oral dosing. Following administration of the IV loading dose, patients who do not experience side effects can be converted to oral administration, with a resting heart rate goal of 50 to 60 beats per minute.1,3 Intermediate- and low-risk patients can be started on oral therapy.1,3

Calcium antagonists cause vasodilation by reducing the cellular uptake of calcium necessary for myocardial and vascular contraction. Some agents also slow atrioventricular node conduction and sinus node impulse formation. The degree of a given effect varies among agents. However, the beneficial effects in patients with ACS are attributed to decreased myocardial oxygen demand and improved myocardial blood flow.4 Calcium antagonists are recommended for patients who experience ongoing or recurrent ischemia despite appropriate treatment with nitrates and beta blockers, or for those patients unable to tolerate effective doses of either of these agents.1,4

Angiotensin-converting enzyme inhibitors have been shown to reduce death rates in patients with acute myocardial infarction and in patients with left ventricular dysfunction who are diabetic or who have had a myocardial infarction (MI).5,9 These agents are recommended in all post-ACS patients.1

### Antiplatelet Agents

Aspirin reduces platelet aggregation by a single mechanism. It prevents the formation of thromboxane A2 by inhibiting cyclooxygenase-1 within platelets. The clinical benefits of aspirin therapy are present at low doses (75–325 mg) and are rapidly established.10,11 In patients with ACS, the first dose of aspirin should be chewed to quicken absorption, and subsequent doses may be swallowed. Aspirin therapy is recommended immediately following the diagnosis or suspicion of ACS, and should be continued indefinitely in patients with NSTEMI/UA or any significant coronary disease.1,5,10,12

The adenosine diphosphate receptor antagonists, ticlopidine and clopidogrel, are approved for antiplatelet therapy. Because their mechanism of action differs from that of aspirin, combination therapy may provide additional benefit. Clopidogrel treatment is recommended over ticlopidine treatment because ticlopidine has a slow onset and less favorable safety profile than clopidogrel.13-15 Clopidogrel in combination with aspirin is the recommended pretreatment in patients undergoing percutaneous coronary intervention (PCI), especially coronary artery stenting.1 Clopidogrel is initially administered in a loading dose and should be continued for up to 12 months after coronary stenting.16

The glycoprotein (GP) IIb/IIIa inhibitors occupy the GP IIb/IIIa receptors that are abundant on the platelet surface. These inhibitors prevent platelet aggregation by preventing interplatelet fibrinogen binding.17,18 It is recommended that GP IIb/IIIa inhibitors be administered in addition to aspirin and heparin in patients who are scheduled for PCI. The GP IIb/IIIa inhibitor may be administered prior to PCI.1

### Anticoagulants

Unfractionated heparin prevents clotting by enhanc-
Unfractionated heparin is a mixture of molecules of widely varying molecular weights (5000–30 000 g) and variable anticoagulant effects, resulting from its nonspecific binding to plasma proteins, blood cells, and endothelial cells. This nonspecific binding translates into a variable anticoagulant response among patients, which necessitates monitoring of the activated partial thromboplastin time to determine the extent of anticoagulant effect. The variable anticoagulant response is exacerbated by differences in patient body weight, age, smoking history, and the presence of diabetes.

Low–molecular-weight heparins are a mixture of molecules that vary in molecular weight from 4200 g to 6000 g. The low–molecular-weight heparins have less binding affinity for plasma proteins and endothelial cells, a longer half-life, and dose-dependent clearance. Therefore, these preparations have predictable and long-acting effects that can be sustained with once- or twice-daily subcutaneous injection. However, the level of anticoagulant effect cannot easily be measured for low–molecular-weight heparins. It is recommended that patients be switched from low–molecular-weight heparins to unfractionated heparin prior to coronary artery bypass graft (CABG) surgery so the level of anticoagulation activity can be accurately measured during surgery.

Hirudin is a direct thrombin inhibitor that is currently indicated only for patients with heparin-induced thrombocytopenia. Similarly, warfarin should only be used in patients with NSTEMI/UA who have other indications for warfarin, such as atrial fibrillation or mechanical heart valves.

**INVASIVE THERAPY**

Coronary angiography can define the coronary artery anatomy in patients with NSTEMI/UA and identify those patients who would benefit from early revascularization. Angiography provides detailed coronary structural information that is helpful in determining prognosis. Left ventricular angiography also allows the assessment of left ventricular function. An early invasive approach that incorporates coronary angiography within 24 hours is indicated for patients with NSTEMI/UA who have symptoms of ischemia despite appropriate pharmacologic therapy.
logic treatment or those who have high-risk clinical symptoms (Table 2). Figure 2 shows the ACC/AHA recommended strategy for proceeding from coronary angiography to revascularization. The decision to move to revascularization is influenced by coronary anatomy and other factors, such as age, ventricular function, comorbid conditions, physical function, symptom severity, and amount of myocardium at risk.3,24

The choice of revascularization procedure primarily depends on the extent of coronary disease (Table 3).1 PCI refers to a group of revascularization techniques, including balloon angioplasty, placement of an intracoronary stent, and atheroablation. Balloon angioplasty followed by stent placement, usually with drug-eluting stents, constitutes the bulk of PCIs today. The efficacy and safety of PCI techniques have been increased by the addition of GP IIb/IIIa inhibitors to standard antithrombotic regimens.1 CABG surgery is the recommended revascularization procedure for high-risk patients, especially those with multivessel disease and left ventricular dysfunction. CABG surgery provides modest long-term benefit to low-risk patients compared with the benefit to high-risk patients. However, low-risk patients whose symptoms are severe or impair their physical function may elect to undergo revascularization to improve their quality of life.6 Because the ACC/AHA guidelines were developed approximately 4 years ago, it is important to note that our understanding of the benefits and risks of PCI versus CABG in specific patient groups is constantly evolving. As such, in today’s clinical practice, the number of patients undergoing PCI is rapidly increasing compared with those undergoing CABG surgery.

SEX DIFFERENCES AND NSTEMI/UA TREATMENT

Although women are more likely than men to have chest pain that is not caused by coronary artery disease (eg, noncardiac pain, coronary vasospasm), women still represent a significant percentage of patients with NSTEMI/UA.25-26 Because women develop coronary artery disease later in life than men, they tend to be older and have more comorbid conditions when they present with ACS.27-29 Despite the considerable incidence of ACS in both sexes, differences in treatment patterns have been observed. For example, aspirin and other antithrombotics are consistently prescribed for fewer women with ACS compared with men.30 In the case of invasive procedures, successful PCI and outcomes are similar in both sexes, although women may have early complications more frequently and generally undergo angiography less frequently.1 In older studies of women undergoing CABG surgery, women had higher death rates, fewer complete revascularizations, and a lower likelihood of receiving an internal mammary artery.1 Fortunately, more recent studies show a normalization of these trends.23,26

RECENT STUDIES IN PATIENTS WITH ACS

PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS

Investigators in the CHARISMA trial randomized more than 15 000 patients with symptomatic cardiovascular disease or multiple risk factors for cardiovascular disease to receive low-dose aspirin and either clopidogrel or placebo. Follow-up lasted for 28 months.31 Patients received clopidogrel and low-dose aspirin or placebo. The primary endpoint was a composite of cardiovascular death, MI, or stroke. Overall, dual therapy provided no significant benefit over aspirin alone. Among patients with multiple risk factors but no history of a prior vascular event, dual therapy was associated with increased death rates. However, fewer patients with symptomatic cardiovascular disease who received clopidogrel reached the endpoint compared with patients receiving placebo (6.9% vs 7.9%, P = .046). The risk of moderate bleeding was increased in the clopidogrel group (2.1% vs 1.3%.

Table 3. Mode of Coronary Revascularization Is Dictated by Extent of Disease

<table>
<thead>
<tr>
<th>Extent of Disease</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main disease</td>
<td>No contraindication</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>EF &lt;50%</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>Proximal LAD, EF &lt;50% and treated diabetes</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>EF &gt;50% and no diabetes</td>
</tr>
<tr>
<td>1- or 2-vessel disease</td>
<td>No proximal LAD, with extensive myocardial ischemia or high-risk criteria</td>
</tr>
</tbody>
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CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; LAD = left anterior descending; EF = ejection fraction.

These findings indicate that clopidogrel therapy offers no additional benefit to aspirin in patients at high risk for cardiovascular events.

**Secondary Prevention of Cardiovascular Events**

The CREDO trial enrolled 2116 patients with ACS who were scheduled for PCI or deemed good candidates for PCI. Patients were randomized to receive a 300-mg loading dose of clopidogrel or placebo 3 to 24 hours prior to PCI. All patients received clopidogrel 75 mg per day for 28 days after PCI. On day 29, the group given the loading dose continued to receive clopidogrel 75 mg per day for 12 months, whereas the group given placebo continued to receive placebo. All patients received aspirin throughout the trial. The primary outcome measures were 1-year rates of death, MI, or stroke, and 28-day rates of death, MI, or urgent revascularization.

Long-term clopidogrel therapy was associated with a 27% risk reduction in the primary endpoint (P = .02). Clopidogrel pretreatment did not provide benefit over placebo except in the subpopulation of patients who received clopidogrel treatment at least 6 hours prior to PCI, in which there was a trend toward risk reduction (39%, P = .051). Risk of bleeding was the same between treatment groups.

The CURE trial randomized 12,562 patients with NSTEMI to receive clopidogrel (300 mg, followed by 75 mg once daily) or placebo for 3 to 12 months. All patients received aspirin. The primary endpoint of death, MI, or stroke occurred in 9.3% of patients in the clopidogrel group compared with 11.4% of patients receiving placebo (P < .001). Refractory ischemia or the primary endpoint occurred in 16.5% of patients receiving clopidogrel and 18.8% of patients receiving placebo (P < .001). Clopidogrel therapy was also associated with lower rates of in-hospital refractory or severe ischemia, heart failure, and revascularization, but higher rates of major bleeding.

The CLARITY-TIMI 28 investigators randomized 3491 patients with STEMI to receive clopidogrel (300-mg loading dose, then 75 mg daily) or placebo. Patients received a fibrinolytic agent, aspirin, and heparin as appropriate. All patients were scheduled for angiography 48 to 192 hours after starting the study medication. The primary endpoint was a composite of death, recurrent MI before angiography, or occluded artery on angiography.

Significantly fewer clopidogrel-treated patients reached the endpoint compared with the placebo group (15.0% vs 21.7%, P < .001). By 30 days, combined rates of cardiovascular death, recurrent MI, or urgent revascularization were reduced in the clopidogrel group compared with the placebo group (11.6% vs 14.1%, P = .03). The incidence of major bleeding or intracranial hemorrhages was the same between groups.

The PCI-CLARITY study was a subanalysis of CLARITY-TIMI 28, in which 1863 patients with STEMI underwent PCI following angiography. The primary endpoint was the composite of death, recurrent MI, or stroke within 30 days of PCI. For the clopidogrel group, significantly fewer deaths, MI, or strokes occurred through 30 days compared with the placebo group (7.5% vs 12.0%, P = .001). No difference in the rates of bleeding was observed between treatment groups.

In the COMMITT/CCS-2 study conducted in China, 45,852 patients with acute myocardial infarction (93% of patients had an STEMI) were enrolled to assess the effects of adding clopidogrel (vs placebo) and early IV followed by oral metoprolol (vs placebo) to aspirin therapy. Clopidogrel was administered at 75 mg daily, and metoprolol was administered intravenously in three 5-mg doses over 15 minutes followed by daily oral doses of up to 200 mg. The primary endpoint was the composite of death, reinfarction, or stroke. In the clopidogrel arm, significantly fewer patients reached the endpoint compared with the control group (9.3% vs 10.1%, P = .002). No difference in the occurrence of major bleeding was observed between treatment groups. In the metoprolol arm, there was no significant reduction in the incidence of the composite endpoint of death, reinfarction, or ventricular fibrillation/cardiac arrest associated with metoprolol treatment; however, there were significant reductions in the risk of reinfarction (P = .001) and ventricular fibrillation (P < .001). Metoprolol treatment was associated with an increased risk of cardiogenic shock (P < .00001), especially during the first day of hospitalization.

In the ISAR-REACT 2 trial, 2022 patients with NSTEMI who were scheduled for PCI were randomized to receive bolus and 12-hour infusion abciximab and heparin (70 U/kg), or placebo and heparin (140 U/kg). All patients were pretreated with clopidogrel 600 mg and aspirin 500 mg. The primary endpoint was death, MI, or urgent revascularization. Overall, abciximab treatment reduced the risk of reaching the endpoint by 25% compared with placebo (8.9% vs 11.9%, P = .03). In patients with elevated troponin levels, abciximab reduced the risk of a poor outcome (13.1% vs 18.3%, P = .002). No benefit was shown for...
patients without elevated troponin levels who received abciximab. No significant difference in the risk of bleeding was observed between the group given abciximab and the group given placebo.

In OASIS-5, 20 078 patients with NSTEMI/UA were randomized within 24 hours of symptom onset to receive either fondaparinux, a selective factor Xa inhibitor, 2.5 mg daily or enoxaparin 1 mg/kg twice daily for 6 days. The primary endpoint was the occurrence of major bleeding, death, MI, refractory ischemia by 9 days, or a combination of these events. There was a trend toward fewer combined events in the fondaparinux group ($P = .13$ at 30 days and $P = .06$ at study end). The rate of major bleeding was lower in the fondaparinux group (2.2% vs 4.1%, $P < .001$), and the incidence of major bleeding in combination with the other endpoints was significantly lower in the fondaparinux group at 9 days (7.3% vs 9.0%, $P < .001$). Fondaparinux treatment was associated with lower mortality than the enoxaparin at 30 days (2.9% vs 3.5%, $P = .02$) and 180 days (5.8% vs 6.5%, $P = .05$).

In OASIS-6, 12 092 patients with STEMI were randomized to receive an 8-day course of fondaparinux 2.5 mg, unfractionated heparin for 48 hours followed by placebo for up to 8 days, or an 8-day course of placebo in patients with contraindication to unfractionated heparin. The primary endpoint was death or reinfarction at 30 days. Significantly fewer patients in the fondaparinux group reached the endpoint compared with the control group (9.7% vs 11.2%, $P = .02$) and 180 days (5.8% vs 6.5%, $P = .05$).

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Collectively, these clinical trials provide important new information about the efficacy and safety of antiplatelet and antithrombotic agents in ACS. However, it is important to remember that bleeding is a significant adverse effect associated with these agents. An analysis of the results of the CRUSADE study pointed out that excessive doses of unfractionated heparin, low–molecular-weight heparin, and glycoprotein IIb/IIIa inhibitors are frequently administered to patients with ACS. Importantly, these excessive doses are associated with increased risk of bleeding.

**Treatment Implications of Recent Clinical Trials**

As a primary preventive treatment in patients with multiple risk factors but no history of prior vascular events, dual aspirin and clopidogrel therapy provided no benefit compared with aspirin alone. However, in patients with symptomatic cardiovascular disease, dual aspirin and clopidogrel therapy reduced the incidence of cardiovascular events while increasing the risk of bleeding. Therefore, in this high-risk patient population, the addition of clopidogrel to aspirin therapy is not recommended. As secondary preventive treatment, pharmacologic therapy with clopidogrel and aspirin significantly reduced the rates of cardiovascular events, but increased the risk of bleeding. Clopidogrel pre-treatment followed by daily clopidogrel therapy significantly reduced the risk of cardiovascular events in the 30-day period following angiography and subsequent PCI without an increased risk of bleeding. Similarly, long-term clopidogrel therapy following PCI significantly reduced the risk of cardiovascular events without increasing the risk of bleeding. These outcomes suggest that clopidogrel therapy provides significant benefits to patients receiving pharmacologic or invasive intervention. Clopidogrel therapy seems to increase the risk of bleeding only in patients who do not receive invasive intervention.
Additional monitoring will be required in these patients.

Significant short-term reductions in the rates of major bleeding and cardiovascular events were observed in patients receiving fondaparinux treatment compared with those receiving enoxaparin treatment. Thirty-day mortality was also reduced in the fondaparinux group. Similarly, fondaparinux treatment significantly reduced mortality and cardiovascular event rates compared with patients receiving unfractionated heparin. However, there was no observed treatment difference between fondaparinux and unfractionated heparin for those patients who required PCI. These outcomes suggest that fondaparinux therapy was superior to enoxaparin therapy and unfractionated heparin therapy in patients who underwent pharmacologic intervention but not those who required invasive intervention. Fondaparinux therapy does not seem to require additional monitoring for bleeding.

Enoxaparin treatment reduced the rates of mortality and cardiovascular events in patients undergoing fibrinolysis therapy compared with patients receiving unfractionated heparin. Benefits from enoxaparin therapy were also seen in the rates of intracranial hemorrhage. However, the risk of major bleeding was increased in the enoxaparin group. Enoxaparin therapy seems to provide greater benefit than unfractionated heparin as ancillary treatment to fibrinolysis. However, enoxaparin therapy will require additional monitoring for bleeding in this scenario.

Abciximab treatment reduced the risk of mortality and cardiovascular events in patients with elevated troponin levels who underwent PCI compared with those patients who received placebo. Treatment benefits were not observed in patients without elevated troponin levels, and there was no difference in the incidence of bleeding between groups. This study suggests that patients who are at risk for significant myocardial damage, as indicated by elevated troponins, may benefit most from abciximab therapy.

**Conclusions**

The ACC/AHA Practice Guidelines for patients with NSTEMI/UA recommend pharmacologic therapies, including anti-ischemic agents, antiplatelet agents, and anticoagulants. Depending on the clinical presentation and the patient’s level of risk, these agents are recommended prior to an invasive intervention or further observation. Patients who require invasive revascularization will benefit from PCI or CABG, depending on the extent of coronary artery disease and presence of contraindications.

Recent clinical trials of pharmacologic agents have confirmed their therapeutic benefits. Clopidogrel was shown to be an effective agent in pharmacologic therapy and as pretreatment for an invasive intervention. Fondaparinux was superior to enoxaparin and unfractionated heparin for patients receiving pharmacologic treatment alone, and enoxaparin was superior to unfractionated heparin as ancillary treatment to fibrinolysis. Finally, abciximab was shown to benefit patients who have elevated troponins. Although some pharmacologic therapies are associated with an increased risk of bleeding, their appropriate use may help to lower the high mortality attributable to ACS.

**REFERENCES**


