ABSTRACT

Acute coronary syndrome (ACS) is an important cause of morbidity and mortality in the US population and requires immediate identification and management to prevent the poor outcomes associated with therapeutic delays. Although some patients have the option of either a conservative or invasive strategy to address ACS, invasive percutaneous coronary intervention (PCI) has become an attractive option in many patients. Both medical management and the PCI procedure require the use of antiplatelet agents, as well as antithrombotic therapy, during hospitalization and after discharge to prevent a recurrence of ischemic events. This review will discuss the therapeutic options in ACS for those undergoing medical and invasive management, and will specifically address important issues in the use of antiplatelet agents in these patients. (Adv Stud Med. 2007;7(17):540-545)
events, in part due to the exposure of substances in the plaque to the blood supply, which result in platelet activation, aggregation, and adhesion; thrombin generation; and the development of a thrombus. This thrombus can entirely block the blood supply to the heart and quickly result in myocardial necrosis. This chain of events puts the patient at a significant risk of death, and therefore, it is critical to rapidly identify and manage patients suffering from this syndrome.

Similar to STEMI, a UA/NSTEMI event most typically occurs when a plaque becomes disrupted as a result of arterial inflammation. This event results in a release of platelet aggregates and other substances from the disrupted plaque, but does not usually cause complete occlusion of the artery. Nevertheless, UA/NSTEMI also carries an increased risk of complications and death if not rapidly identified and treated. Although the incidence of STEMI has decreased over the past 2 decades, the incidence of UA/NSTEMI is rising, and efforts are under way to modify UA/NSTEMI risk and improve outcomes in individuals who suffer from these events.

MORBIDITY AND MORTALITY RISK
The high rate of CHD and consequent ACS carries a heavy toll in terms of morbidity and mortality. The long-term consequences of ACS can include a higher risk of heart failure, a recurrence of ACS events, and early mortality. The high risk of poor outcomes in ACS is most striking in patients who do not present with chest pain or other typical symptoms and therefore, receive late treatment or a lack of ideal therapy. An analysis from the Global Registry of Acute Coronary Events (GRACE) found that patients with ACS who did not present with chest pain or other typical symptoms experienced more complications during their hospital stay. Furthermore, almost 20% of patients with STEMI without chest pain died during hospitalization. Overall, CHD was responsible for 1 in 5 US deaths in 2004 and remains the single most common cause of death in men and women. The risk of morbidity and death from ACS due to underlying CHD highlights the importance of early diagnosis and management with the ideal therapeutic strategy in patients presenting with symptoms suggestive of ACS.

THERAPEUTIC OPTIONS
One of the most important aspects of care in ACS is the rapid identification of UA/NSTEMI and STEMI in

PRACTICE RECOMMENDATIONS FOR ACS
• The ACC/AHA guidelines for the management of both UA/NSTEMI and STEMI recommend that patients presenting with suspected ACS receive prompt care that includes ECG and blood marker evaluation.
• The guidelines emphasize risk stratification as an important aspect of the initial evaluation to guide physicians in choosing between medical (drug-based) and invasive (interventional) strategies for care. The TIMI and GRACE risk scoring systems are both recommended as valid tools for stratifying risk in patients with ACS.
• The choice of primary PCI versus fibrinolysis in STEMI should be selected with careful attention to the timing from onset of symptoms to hospital presentation, the immediate availability of catheterization services, and the experience of the personnel and center providing invasive care.
• In UA/NSTEMI, the choice of an invasive versus a conservative strategy is based on the patient’s relative level of risk.
• Patients undergoing PCI should receive pre-PCI administration of antiplatelet therapy with aspirin and a thienopyridine, as well as the periprocedural addition of antithrombotic therapy with unfractionated heparin, low-molecular-weight heparin, or bivalirudin. The addition of a glycoprotein IIb/IIIa inhibitor is also warranted in high-risk patients.

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Strength of Evidence:
Panels composed of experts in the prevention, detection, and management of cardiovascular disease developed the ACC/AHA guidelines for the management of UA/NSTEMI, the ACC/AHA guidelines for the management of STEMI, and the ACC/AHA/Society of Cardiovascular Angiography and Interventions guidelines for PCI. These recommendations are based on the weight of available clinical evidence and are considered to provide a high degree of benefit with a low potential for risk.
patients presenting with suspicious symptoms. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for both UA/NSTEMI and STEMI emphasize that patients with chest pain consistent with ACS, which is generally characterized as severe pain or discomfort over the chest or radiating down the left arm, should be triaged immediately to receive an electrocardiogram (ECG) and evaluation of blood markers of cardiac injury to arrive at a diagnosis of UA/NSTEMI or STEMI.2,3

Once an ACS diagnosis has been established, there are 2 established routes of care. For STEMI, depending on the timing between the onset of symptoms and presentation in the urgent care setting, and the availability of a catheterization facility, physicians decide on a course of either pharmacologic reperfusion (ie, fibrinolysis) or primary percutaneous coronary infusion (PCI). More rapid reperfusion achieved with either strategy is associated with improved outcomes. For UA/NSTEMI, a choice of an invasive strategy, usually within 24 to 48 hours of presentation, or a conservative approach is taken based on the patient's relative degree of risk. Medical management proceeds with an established combination of antiplatelet and antithrombotic drugs, whereas an invasive or interventional strategy also includes a combination of antiplatelet and antithrombotic medications, administered before the procedure, followed by angiography and revascularization with the placement of a stent to prevent future reocclusion of the artery at the location of the atherosclerotic plaque.

**Medical Management**

Current antithrombotic pharmacotherapy consists of treatment with a combination of antiplatelet agents, including aspirin and a thienopyridine (clopidogrel), antithrombotic therapy with unfractionated heparin or low-molecular-weight heparin (or, more recently, a direct thrombin inhibitor or a factor Xa inhibitor), and the addition of a glycoprotein IIb/IIIa inhibitor in high-risk patients and in those undergoing PCI.2,3

In patients diagnosed with STEMI, primary PCI is generally preferred, if available. The ACC/AHA guidelines suggest that fibrinolysis is favored in STEMI when prolonged transport to another facility is anticipated or the time between hospital arrival and the interventional procedure (door-to-balloon time) is anticipated to be greater than 90 minutes.1

In patients with UA/NSTEMI, an invasive strategy is preferred in patients classified as higher risk after an evaluation of symptoms, ECG, cardiac biomarkers, comorbidities, and medical history.2 The Thrombolysis in Myocardial Infarction (TIMI) and GRACE risk stratification tools are both suggested by the guidelines to assess the risk of cardiac events and mortality in ACS, and are used to choose between a conservative and interventional strategy in UA/NSTEMI.2

**Invasive Management**

The decision to proceed with an interventional procedure in many patients with ACS is based on multiple trials that have demonstrated improved outcomes with an invasive strategy.4,5 In patients with STEMI with immediate access to a catheterization facility, primary PCI is often the regimen of choice. However, the ACC/AHA/Society of Cardiovascular Angiography and Interventions guidelines for PCI stress that the value of PCI over medical management has not been established when performed by an operator who performs fewer than 75 cases per year or in low-volume centers (200–400 cases/year).6

The PCI procedure requires the preprocedural administration of antiplatelet therapy with aspirin and a thienopyridine, as well as the periprocedural addition of antithrombotic therapy with unfractionated heparin, low-molecular-weight heparin, or bivalirudin to reduce the risk of further thrombus generation from the ruptured plaque.7,6 The addition of a glycoprotein IIb/IIIa inhibitor is also routinely used to more effectively inhibit platelet aggregation. The direct thrombin inhibitor bivalirudin is an acceptable antithrombotic alternative to heparin therapy, particularly in those who have a contraindication to heparin therapy because of documented heparin-induced thrombocytopenia.2,3,6

Post-PCI antiplatelet management is also critical, particularly in patients whose PCI procedures include the placement of a stent, as antiplatelet therapy is required to reduce to risk of restenosis. Although some debate has surrounded the ideal time frame for pre-PCI initiation of antiplatelet therapy and the length of follow-up therapy after the procedure, data from the PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the CREDO (Clopidogrel for the Reduction of Events During Observation), and the PCI-CLARITY (PCI-Clopidogrel as Adjunctive Reperfusion Therapy) trials...
all revealed that antiplatelet therapy provides the greatest benefit when initiated at least 6 hours before the PCI procedure and continued for a period of 1 year after the procedure. A higher dose of clopidogrel can shorten the pretreatment period to 2 hours to achieve a high level of platelet inhibition. Clinical guidelines now reflect these findings and recommend that ongoing antiplatelet management with both aspirin and a thienopyridine continue for at least 1 month and ideally for up to 1 year after the procedure to reduce the risk of further thrombotic events. For patients with drug-eluting stents, at least 1 year of thienopyridine therapy is recommended.

CURRENT THERAPEUTIC ISSUES

The management of patients with ACS has been considerably advanced with the advent of new pharmacologic therapies in medical and invasive strategies, but important issues still exist with the use of these agents in daily practice.

ANTIPLATELET RESISTANCE

Antiplatelet resistance is increasingly recognized as an important underlying issue that can affect a patient’s response to therapy. The degree of documented antiplatelet resistance often varies considerably between patients and depends on the type of platelet function test used, but a variable response to both aspirin and clopidogrel have been documented in healthy subjects and those undergoing PCI.

Antiplatelet resistance has been identified as a causative factor contributing to the residual risk of periprocedural and postprocedural events that is relatively common in patients undergoing PCI for ACS. In one study that evaluated clopidogrel response in patients with ACS undergoing PCI with a variety of platelet function tests, investigators reported a wide variability in response to clopidogrel therapy, with up to 25% of patients exhibiting clopidogrel resistance. Additionally, 88% of subsequent ischemic events during a 6-month follow-up period occurred in patients who had exhibited clopidogrel resistance, suggesting a link between clopidogrel resistance and a greater risk of postprocedural events. Based on these findings, researchers have suggested that patients undergoing PCI should be evaluated for antiplatelet resistance, at least to assist in risk stratification. In addition, the emergence of new antiplatelet options may help physicians guide therapy when resistance to aspirin and clopidogrel is observed.

GUIDELINE ADHERENCE

It is also important to note that a failure to follow established evidence-based guidelines for the management of patients with ACS who are undergoing PCI, especially with respect to the length of follow-up antiplatelet therapy, also may impact outcomes and result in excessive thrombotic risk. Although physicians should carefully evaluate patients for bleeding risk, it is important to consider up to 1 year of antiplatelet therapy with a thienopyridine, such as clopidogrel, in patients who have undergone PCI.

OPPORTUNITIES TO IMPROVE OUTCOMES

There is no doubt that therapeutic options in ACS have greatly expanded in the past decade with the introduction of agents such as low-molecular-weight heparins and other anticoagulants, glycoprotein IIb/IIIa inhibitors, and clopidogrel. The wealth of research in ACS and PCI continues to bring new concepts to light for improving outcomes and reducing the residual risk that is still observed after patients receive interventional procedures.

LIPID LOWERING IN ACS

Although lipid reduction with the use of statin agents has traditionally been considered a long-term management strategy, it is now becoming clear that the use of statin therapy in the acute setting may improve outcomes in ACS due to effective reductions in low-density lipoprotein cholesterol (LDL-C) and C-reactive protein, a marker of systemic inflammation.

The MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study randomized 3086 patients with NSTEMI to begin atorvastatin 80 mg or placebo within 24 to 96 hours of hospital admission. During a follow-up period of 4 months, patients receiving atorvastatin had a 16% lower risk of the primary composite endpoint of death, nonfatal acute MI, cardiac arrest requiring resuscitation, or recurrent symptomatic myocardial ischemia requiring emergency rehospitalization (P = .048). Patients receiving atorvastatin experienced a 42% reduction in mean LDL-C, declining from 124 mg/dL to 72 mg/dL during treatment.
The PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) TIMI-22 trial investigated the use of either standard-dose statin therapy (pravastatin 40 mg/day) or high-dose statin therapy (atorvastatin 80 mg/day) in 4162 patients with ACS who were randomized within 10 days of hospitalization for ACS and were followed for a period of up to 2 years. Those receiving the intensive statin regimen had a 16% reduction in the composite endpoint of all-cause mortality, MI, recurrent angina requiring hospitalization, revascularization (≥30 days after randomization), and stroke (P = .005).17 The A to Z (Aggrastat to Zocor) trial likewise reported a benefit with intensive statin therapy after 4 months posthospitalization, but failed to demonstrate an early benefit.17 However, an analysis of data from the PROVE-IT and A to Z trials concluded that the results of both studies demonstrate the benefit of early intensive statin therapy.18 The administration of intensive statin therapy has a favorable safety profile17,18 and is an attractive therapeutic option in ACS.

**NEW ANTIPLATELET OPTIONS**

New antiplatelet therapies have the potential to further expand treatment options, especially in light of the problems encountered with resistance to aspirin and clopidogrel. The effects of prasugrel, a novel thienopyridine, were recently evaluated in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) TIMI-38 trial. A population of 13,608 patients with ACS (UA/NSTEMI and STEMI) scheduled for PCI was randomized to receive either clopidogrel (300-mg loading dose followed by 75-mg/day maintenance dose) or prasugrel (60-mg loading dose followed by 10-mg/day maintenance dose). All patients received aspirin therapy in addition to the thienopyridine. Over a median treatment period of 12 months, those receiving prasugrel had a significantly lower rate of the primary composite endpoint of cardiovascular death, MI, or stroke compared with those receiving clopidogrel (12.1% vs 9.9%, P = .0004). In addition, a greater than 50% reduction in stent thrombosis was observed. However, prasugrel was associated with a significantly higher rate of major bleeds (2.4% vs 1.8%, P = .03; Figure),19 and investigators suggested that prasugrel should not be used in patients with a history of cerebrovascular accidents or transient ischemic attack.19

**CONCLUSIONS**

Patients presenting with ACS benefit from recent advances in management strategies, including the advent of thienopyridine antiplatelet drugs that reduce the risk of periprocedural events during PCI and improve long-term outcomes after hospital discharge. Although challenges remain in identifying patients who may exhibit antiplatelet resistance, new therapeutic options are emerging that may represent viable alternatives in patients who exhibit resistance. Overall, antiplatelet agents, along with antithrombotic agents and glycoprotein IIb/IIIa inhibitors, have greatly improved outcomes when used in accordance with ACS guidelines. The high risk of poor outcomes and mortality in unrecognized or undertreated ACS highlights the continuing need to emphasize early identification and effective management of ACS in daily practice.

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**Figure. Efficacy and Safety Findings in the TRITON TIMI-38 Trial**

CABG = coronary artery bypass graft; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; TIMI = Thrombolysis in Myocardial Infarction; TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.

REFERENCES


