EDITORIALS

Optimal Management of Acute Coronary Syndromes

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In the United States, more than a million people are hospitalized annually with unstable angina or myocardial infarction without ST-segment elevation, so-called acute coronary syndromes. For these patients, several treatments have proved to be effective in reducing the incidence of death, infarction or reinfarction, and recurrent ischemia. These treatments include intensive medical therapy and coronary angiography followed by revascularization, if indicated.[1,2] Given the sheer number of medical interventions that are now available for these conditions, knowing which therapy to administer and when to do so is confusing for many physicians. The studies by Giugliano et al.[3] and Mehta et al.[4] in this issue of the *Journal* provide information that physicians can use to further refine their treatment of such patients.

The initial evaluation of patients with acute coronary syndromes should focus on an assessment of the risk of a cardiac ischemic event (death, myocardial infarction, or recurrent ischemia) in the ensuing days, weeks, and months, as well as the risk of a bleeding complication from intensive medical therapy or an invasive cardiac procedure. During the past 10 years, two risk-assessment algorithms have been developed for determining whether a patient is at high risk or at relatively low risk for having an ischemic event. With this information in hand, a treatment strategy can be individually tailored, thereby reducing the occurrence of such an event.

The first of these algorithms, the Thrombolysis in Myocardial Infarction (TIMI) risk score,[5] uses seven easily assessed variables to identify patients with acute coronary syndromes who are at risk for death, myocardial infarction, or recurrent ischemia within 14 days after hospitalization. These variables are an age of more than 65 years, three or more risk factors for atherosclerosis, known coronary artery disease, two or more episodes of anginal chest pain in the 24 hours before hospitalization, the use of aspirin in the 7 days before hospitalization, ST-segment deviation of 0.05 mV or more, and elevated serum markers for myocardial necrosis (troponin or creatine kinase MB). Patients with three or more of the seven variables are considered to be at high risk, whereas those with no more than two of the variables are considered to be at low risk.[6]

The second algorithm, the Global Registry of Acute Coronary Events (GRACE) risk model,[7] uses eight variables to predict whether a patient will die or have a myocardial infarction in the hospital or in the next 6 months. These variables are age, Killip class (a classification of the severity of heart failure with myocardial infarction), systolic arterial pressure, ST-segment deviation, cardiac arrest during presentation, serum creatinine concentration, elevated serum markers for myocardial necrosis, and heart rate. Each variable is assigned a numerical score on the basis of its specific value, and the eight scores are added to yield a total score, which is applied to a reference nomogram to determine the patient's risk. The GRACE application tool is available at www.outcomes-umassmed.org/grace. A comparison of the TIMI and GRACE risk algorithms concluded that either can be used effectively to predict the rates of death or myocardial infarction for a year after hospitalization for acute coronary syndromes.[8]

Although serum markers for myocardial necrosis make up only one of the TIMI or GRACE risk variables, the presence of this variable alone identifies a patient as being high risk.[9] However, although elevated serum markers indicate myocardial necrosis, they provide no insight into its cause. In some patients, myocardial necrosis is caused by disorders other than coronary artery

Table 1. Treatment Strategies for Patients with Acute Coronary Syndromes.*

Therapy	Initiation	Duration	Reduced Incidence with Drug or Therapy versus Placebo
Low-risk patient			
Antianginal drug[1,2]			
Beta-blocker†	Immediately	During hospitalization, possibly indefinitely	Recurrent ischemia
Nitroglycerin	Immediately	During hospitalization, possibly indefinitely	Not studied
Diltiazem or verapamil†	Immediately	During hospitalization, possibly indefinitely	Myocardial infarction, recurrent ischemia
Lipid-lowering drug[1,2]			
Statin	Before hospital discharge	Indefinitely	Recurrent ischemia
Antiplatelet drug[1,2]			
Aspirin	Immediately	Indefinitely	Death, myocardial infarction
Clopidogrel	Immediately	1–12 mo	Myocardial infarction, recurrent ischemia
Anticoagulant drug[1,2]			
Unfractionated heparin	Immediately	2–5 days	Death or myocardial infarction
High-risk patient			
Antianginal drug[1,2]			
Beta-blocker†	Immediately	During hospitalization, possibly indefinitely	Death, myocardial infarction, recurrent ischemia
Nitroglycerin	Immediately	During hospitalization, possibly indefinitely	Not studied
Diltiazem or verapamil†	Immediately	During hospitalization, possibly indefinitely	Myocardial infarction, recurrent ischemia
Lipid-lowering drug[1,2]			
Statin	Before hospital discharge	Indefinitely	Recurrent ischemia
Antiplatelet drug[1-3,11,12,15]			
Aspirin	Immediately	Indefinitely	Death, myocardial infarction
Clopidogrel	Immediately	≥12 mo	Myocardial infarction, recurrent ischemia
Glycoprotein IIb/IIIa inhibitor (eptifibatide, tirofiban, or abciximab)	At time of PCI	12–24 hr after PCI	Myocardial infarction
Anticoagulant drug[1,2,6,14,15]‡			
Unfractionated heparin	Immediately	2–5 days; discontinue after successful PCI	Death or myocardial infarction
Enoxaparin	Immediately	During hospitalization (up to 8 days); discontinue after successful PCI	Myocardial infarction, recurrent ischemia (as compared with unfractionated heparin)
Bivalirudin	Immediately	Up to 72 hr; discontinue after successful PCI	Bleeding§
Invasive management[1,2,4,13]			
Coronary angiography followed by revascularization (if appropriate)	Up to 36–80 hr after hospitalization; within 24 hr in very high-risk patients		Myocardial infarction, recurrent ischemia

* PCI denotes percutaneous coronary intervention.
† This drug should be avoided in patients with decompensated heart failure, hypotension, or hemodynamic instability.
‡ The choice of unfractionated heparin, enoxaparin, or bivalirudin should be made on the basis of the patient's risk assessment.
§ This benefit assumes that bivalirudin is used as monotherapy, as compared with a combination of heparin and a glycoprotein IIb/IIIa inhibitor.

disease (e.g., pulmonary embolism, decompensated heart failure, severe hypertension or tachycardia, anemia, and sepsis). During evaluation of a patient with a possible acute coronary syndrome, the presence of elevated serum markers should be assessed in conjunction with other variables to provide insight into its most likely cause.

Independent of this initial risk assessment, the patient's general medical and cognitive status, anticipated life expectancy, personal preferences, and risk of treatment-related complications should be evaluated. Since intensive medical therapy and invasive management are associated with bleeding complications, the patient's risk of such events should be assessed before these therapies are administered. Female sex, older age, renal insufficiency, low body weight, tachycardia, high or low systolic arterial pressure, low hematocrit, and a history of diabetes mellitus predict an increased risk of major bleeding, often due to the administration of excessive doses of antiplatelet or anticoagulant agents.[10] The bleeding risk can be estimated with the tool available at www.crusadebleedingscore.org.

Once the risk status of a patient with an acute coronary syndrome is established, treatment is initiated[1,2,11-15] (Table 1). Regardless of the patient's level of risk, antianginal medications, antiplatelet therapy (aspirin and clopidogrel), and a statin should be administered unless contraindicated.[1] Patients who are deemed to be at low risk should receive unfractionated heparin; more intensive (and expensive) antiplatelet or anticoagulant therapy does not further reduce the risk of an ischemic cardiac event but does increase the risk of bleeding.[6] Routine coronary angiography and revascularization are not beneficial in such patients and should be reserved for those with recurrent ischemia despite intensive medical therapy.[12]

In contradistinction, patients who are deemed to be at high risk should receive antianginal medications, antiplatelet therapy (aspirin and clopidogrel), a statin, anticoagulant therapy,[1,5,14] and coronary angiography, followed by revascularization, if indicated (Table 1).[1,6,12] In addition, glycoprotein IIb/IIIa inhibitors, which provide maximal platelet inhibition, reduce ischemic cardiac events in such patients.[1,2,11] The study by Giugliano et al. and other studies[15] demonstrate that glycoprotein IIb/IIIa inhibitors should be initiated at the time of angiography; their routine administration 12 to 24 hours before the procedure carries an increased risk of bleeding and no improvement in outcome.

High-risk patients with acute coronary syndromes benefit from coronary angiography and revascularization (if appropriate), in that the incidence of subsequent ischemic cardiac events is reduced.[1,2,13] The question arises: Should angiography be performed within hours after presentation or can it be delayed for several days to allow medical therapy to stabilize the recently ruptured arterial plaque, thereby reducing the risk of procedure-related complications? According to the study by Mehta et al., in most patients, the use of early invasive therapy (within 24 hours after hospitalization) is no better at preventing death, myocardial infarction, or stroke than delayed invasive therapy (median time, 50 hours), although early therapy is associated with a modest decrease in the occurrence of recurrent ischemia. In contrast, in the third of patients who were considered to be at very high risk (GRACE risk score, >140, which corresponds to an estimated incidence of in-hospital death or myocardial infarction of >20%), an early invasive strategy was superior to a delayed strategy in reducing the incidence of death, myocardial infarction, or stroke.

The treatment of patients with acute coronary syndromes is optimal when the intensity of therapy, both medical and nonmedical (coronary angiography and revascularization), is tailored to the patient's risk of an ischemic cardiac event or a treatment-related complication. In patients who are considered to be at high risk, optimal therapy results in a substantial decrease in rates of myocardial infarction and recurrent ischemia (by 20 to 40%) and a modest decrease in the rate of death (by approximately 10%). The magnitude of benefit correlates with the patient's level of risk.

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Antiplatelet Therapy and Vascular-Access Patency

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Current predictions estimate that by the year 2020, more than 750,000 people in the United States alone will have end-stage renal disease and over 500,000 will require hemodialysis.[1] The success of hemodialysis depends on a well-functioning vascular access, which may be considered the patient's lifeline. However, creating and maintaining a vascular access are challenging and costly. In the first year of hemodialysis, care of the vascular access represents the leading cause of hospitalizations; overall costs are over $1 billion annually.[2,3]

The Dialysis Access Consortium (DAC) Study Group has taken the lead in advancing clinical knowledge of dialysis access dysfunction and clinical approaches to its management.[4,5] In this issue of the *Journal,* Dixon et al.,[5] of the DAC Study Group, report the results from a randomized, placebo-controlled trial of the effect of twice-daily extended-release dipyridamole (200 mg) and aspirin (25 mg) on graft patency in 649 patients undergoing hemodialysis. The primary study outcome was the loss of primary unassisted graft patency, defined as the first occurrence of graft thrombosis or performance of a radiologic or surgical procedure to facilitate graft patency. Patients who received dipyridamole plus aspirin had an absolute risk reduction of 5 percentage points (with an adjusted relative risk reduction of 18%) in the rate of loss of primary unassisted graft patency (adjusted hazard ratio for active treatment vs. placebo, 0.82; 95% confidence interval [CI], 0.68 to 0.98). The median cumulative (overall) graft patency was 22.5 months (95% CI, 20.0 to 28.2) in the placebo group and did not differ significantly in the active-treatment group, nor were there any significant differences between the two groups in the rate of bleeding or any other adverse events. This large and rigorous study evaluating graft outcomes has several important implications.

The preferred vascular access for hemodialysis is an autogenous fistula, typically created at the wrist (radiocephalic fistula) or elbow (brachiocephalic or brachiobasilic fistula). Although functioning fistulas are associated with superior pa-