Primary Prevention of Coronary Disease; Management of UA/STEMI; Management of STEMI

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Section 1—Primary Prevention of Coronary Artery Disease

Nehal N. Mehta, MD

CASE: INITIAL PRESENTATION

A 42-year-old man presents to the emergency department with substernal chest pressure and nausea that awoke him from sleep at approximately 5 AM. He had returned home late from work the previous evening and had eaten a meatball sandwich before retiring to bed. The patient has no significant past medical history but has a 15 pack-year smoking history. His electrocardiogram and measurements of cardiac biomarkers are normal, and a stress test the following morning reveals good exercise tolerance with no evidence of ischemia. The patient expresses his concern about his risk of having a myocardial infarction (MI), noting that his brother had his first MI in his late 40s. He is eager to do whatever he can to reduce his personal risk for cardiovascular disease.

INTRODUCTION

Coronary artery disease (CAD) and its associated complications of acute myocardial infarction (AMI) and congestive heart failure continue to be the leading cause of death in the developed world. In less than 20 years, it is projected that CAD will replace infectious diseases as the worldwide leading cause of death. Given the tremendous morbidity and mortality resulting from CAD, major focus has shifted from treatment of CAD to its prevention.

Primary prevention is defined as both the prevention of disease before it occurs and the reduction of its incidence. One of the most important advances in medicine over the past quarter century has been identification of major risk factors for development of CAD. These include elevated low-density lipoprotein cholesterol (LDL), elevated total cholesterol, reduced high-density lipoprotein cholesterol (HDL), hypertension, diabetes, cigarette smoking, family history, and age (Table 1). In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) published a report summarizing these “traditional” risk factors and treatment guidelines for them.

Established Risk Factors for CAD

The NCEP has identified lipid factors that contribute to overall CAD risk and have shown that, if untreated, these significantly contribute to morbidity and mortality associated with CAD. These lipid factors include an elevated LDL and a reduced HDL. Because the majority of circulating cholesterol is LDL, high total cholesterol has also been linked to increasing CAD. LDL elevations alone, as demonstrated by genetic disorders involving defective LDL receptor in familial hypercholesterolemia, accelerate atherosclerosis and increase risk for AMI in the absence of other CAD risk factors.

Abundant data show that lowering of LDL reduces CAD; therefore, LDL is used as a primary marker for those at increased risk of CAD-related events. The ATP III guidelines identify LDL as the primary target of cholesterol-lowering therapy, with LDL goal based on category of risk (Table 2). Of note, diabetes mellitus and...
peripheral vascular disease are considered CAD equivalents in ATP III. New studies suggest that lowering LDL cholesterol with statins to a target of 70 mg/dL in high-risk patients (eg, those with prior acute coronary syndrome or peripheral vascular disease) may be beneficial.\(^7\)

HDL, in contrast to LDL, has the beneficial effects of reverse cholesterol transport, antioxidative properties, and anti-inflammatory properties. Low HDL is associated with increased CAD risk. NCEP ATP III lists low HDL as a major risk factor for CAD, and defines it as less than 40 mg/dL, a change from ATP II (in which low HDL was defined as < 35 mg/dL). In a landmark study showing the importance of elevated HDL, for each 5-mg/dL increase in HDL, there was an 11% reduction in relative risk of a CAD event.\(^8\)

Triglyceride levels have not demonstrated as robust a correlation with CAD as have LDL and HDL. However, hypertriglyceridemia has been shown to be an independent CAD risk factor in certain patient populations (eg, diabetics and postmenopausal women). Much of the data may be confounded, however, because triglyceride elevations may be related to other factors, such as obesity, hypertension, or insulin resistance. Therapy for dyslipidemias is shown in Table 3.

In addition to lipid abnormalities, the ATP III guidelines list nonlipid risk factors, including hypertension, tobacco use, diabetes, sedentary lifestyle, obesity, and a high-fat diet as contributing to CAD (Table 1).

### Table 1. Risk Factors for Cardiovascular Disease in the General Population

#### ESTABLISHED RISK FACTORS

<table>
<thead>
<tr>
<th>Lipid Risk Factors</th>
<th>Nonlipid Risk Factors</th>
<th>Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein (LDL) cholesterol(^a)</td>
<td>Hypertension</td>
<td>Abdominal obesity (men, &gt; 40” waist circumference; women, &gt; 35” waist circumference)</td>
</tr>
<tr>
<td>High-density lipoprotein (HDL) cholesterol</td>
<td>Diabetes</td>
<td>High triglycerides (&gt; 150 mg/dL)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>Overweight/obesity</td>
<td>Low HDL (men, &lt; 40 mg/dL; women, &lt; 50 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Physical inactivity</td>
<td>High blood pressure (≥ 130/≥ 85 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>Atherogenic diet</td>
<td>Elevated fasting glucose (≥ 110 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Tobacco smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonmodifiable (age, sex, family history)</td>
<td></td>
</tr>
</tbody>
</table>

#### EMERGING RISK FACTORS

<table>
<thead>
<tr>
<th>Lipid Risk Factors</th>
<th>Nonlipid Risk Factors</th>
<th>Clinical Signs as Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein remnants</td>
<td>Homocysteine</td>
<td>Carotid intima media thickness</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>Thrombogenic/hemostatic factors (eg, fibrinogen)</td>
<td>Coronary intima media thickness</td>
</tr>
<tr>
<td>Small LDL particles</td>
<td>Inflammatory markers (eg, C-reactive protein)</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>HDL subspecies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoproteins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Primary target of therapy according to National Cholesterol Education Program guidelines.

### Table 2. ATP III Cholesterol Goals by Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal, mg/dL</th>
<th>Non-HDL(^a) Goal, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHD, &lt; 2 risk factors</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
</tr>
<tr>
<td>No CHD, 2+ risk factors</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>CHD or CHD equivalent(^\d)</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease. (Adapted from reference 1. Copyright © 2001, American Medical Association. All rights reserved.)

\(^a\)LDL + VLDL (very low density lipoprotein) cholesterol.
\(^\d\)Diabetes mellitus or peripheral vascular disease.

### CALCULATING RISK

As mentioned, ATP III’s recommended LDL goals are based on a patient’s category of CAD risk. Patients with CAD and CAD risk equivalents are at highest risk. For patients with 2 or more major risk factors (smoking, hypertension, low HDL, family history of premature CAD, and age [men, ≥ 45 years; women, ≥ 55 years]), 10-year risk for CAD using the Framingham risk score should be calculated\(^6\) (www.nhlbi.nih.gov/guidelines/cholesterol/index.htm for an easy to use online calculator). This model, used for patients without known CAD, estimates risk of developing angina pectoris, myocardial infarction, or coronary disease death over the next 10 years. The score is used to categorize patients as low-risk, average-risk, moderately high-risk, and high-risk.
High-risk, average-risk, and low-risk patients are relatively straightforward to manage; it is the patients with a moderately high risk of CAD who pose a clinical challenge. Given the unpredictable rates of CAD-related events in this population, and the fact that only 50% of the risk of atherosclerosis can be explained by traditional risk factors, research has focused on novel risk factors for CAD to help further stratify these patients.

INFLAMMATION, ATHEROSCLEROSIS, AND NOVEL BIOMARKERS

CAD in general and acute coronary syndromes in specific are associated with activation of the inflammatory cascade, both chronically and acutely. Cigarette smoking, glycation products due to diabetes, and elevated blood cholesterol damage endothelium via similar mechanisms. In addition, signal transduction from these stimuli promotes monocyte and lymphocyte recruitment and the creation of further atherogenic particles, such as oxidized LDL. Thus, given this understanding of inflammation and its contribution to ASCVD, inflammatory markers such as CRP and fibrinogen are emerging as candidates for novel CAD risk factors.

HIGH-SENSITIVITY CRP

Recent attention has focused on measurement of CRP as a marker for increased risk of CAD. CRP is produced by the liver as an acute-phase reactant in response to injury or infection. The release is stimulated by proinflammatory cytokines, including interleukin (IL)-1 and IL-6, and CRP levels are a gauge of overall inflammation in the body. Elevated CRP levels measured by high-sensitivity assays (hs-CRP) have been linked to higher rates of stroke, peripheral vascular disease, AMI, and sudden cardiac death. Data from a large study involving more than 27,000 women showed that hs-CRP levels were superior to LDL levels as a marker for future stroke and MI. Even small increases in hs-CRP within the normal range in asymptomatic healthy subjects were predictive of future events in another small study.

Whether hs-CRP is a marker or mediator of inflammation is unclear. Some evidence suggests that CRP may be involved directly in promoting early atherosclerosis, but the utility of hs-CRP as an independent risk factor for CAD has been difficult to assess. CRP is heavily confounded by “traditional” risk factors such as obesity, sedentary lifestyle, and dyslipidemia. Insulin resistance alone is associated with elevated CRP levels, as are other inflammatory states (inflammatory bowel disease, collagen vascular disease, and chronic obstructive pulmonary disease). Also, hs-CRP has largely been studied only in the white population and women, and further studies in broader populations will need to be done prior to making general recommendations.

With the limited data available, the Centers for Disease Control and Prevention and the American Heart Association (AHA) published guidelines recommending that hs-CRP levels be assessed only in patients at moderately-high risk as an optional tool to further define coronary risk. These guidelines propose cutoffs of less than 1 mg/dL, 1.0 to 3.0 mg/dL, and greater than 3.0 mg/dL for low, average, and high risk of cardiovascular events, respectively. People in the high-risk group have about a twofold increase in relative risk for cardiovascular disease compared with those in the low-risk group. The AHA does not recommend hs-CRP screening for the entire adult population as a public health measure nor do they suggest using it to track the efficacy of treatment of known CAD.

FIBRINOGEN

Fibrinogen is a glycoprotein cleaved by thrombin
into fibrin as the final step in the coagulation cascade. Soluble fibrin fragments are the most abundant component of blood clots, and epidemiological data support a link between excess fibrinogen levels and an increase in stroke and CAD. Like CRP, fibrinogen is an acute-phase reactant. It has biological functions of vasoconstriction and platelet aggregation and also has an impact on blood viscosity. Recent meta-analyses have shown that patients with fibrinogen levels in the upper tertile had an increase in cardiovascular morbidity and mortality.

In addition to inflammation, smoking has been shown to increase fibrinogen levels, and levels increase as consumption of cigarettes increases. Fibrinogen levels are higher in patients with diabetes, obesity, sedentary lifestyles, and hypertension. Excessive alcohol consumption and estrogen from oral contraception or hormone replacement therapy also increase fibrinogen levels. The exact relationship between fibrinogen levels and these observations remain poorly understood, and in fact, when fibrinogen levels are reduced, there is no impact on morbidity and mortality. In a study evaluating fibrate treatment of peripheral vascular disease, there was no reduction in the incidence of CAD or stroke in that population despite a 13% reduction in fibrinogen levels.

Before fibrinogen gains acceptance as a predictor of CAD-related events, improved understanding is needed of whether fibrinogen has a role in atherogenesis or is merely a marker of preexisting vascular damage. In addition, further trials showing that fibrinogen levels predict CAD events beyond traditional risk factors using a validated scheme need to be undertaken in a patient population without known CAD. The only trial to date that has studied these levels using the Framingham risk score included a high-risk group in which most patients had known CAD and peripheral vascular disease.

HOMOCysteINE

Homocysteine is an amino acid formed as a byproduct when methionine, an essential amino acid, is metabolized. Intracellularly, homocysteine is metabolized via several different pathways that involve different enzymes and cofactors such as vitamin B₆ (pyrodoxine), folate, and vitamin B₁₂ (cobalamin). When these cofactors are absent, such as in B₁₂ or folate deficiency, or when the enzymes are absent, such as in inborn errors of metabolism termed “homozygous homocystinurias,” elevated homocysteine levels predispose individuals to vascular damage and subsequent thromboses. While the mechanism is not fully understood, it had been postulated that homocysteine may induce vascular damage by promoting platelet activation, oxidative stress, endothelial dysfunction, hypercoagulability, and vascular smooth muscle proliferation.

Although hyperhomocysteinemia appears to be an independent risk factor for stroke, peripheral vascular disease, CAD, and venous thromboembolic disease, traditional risk factors appear to be stronger predictors of CAD based on current data.

When homocysteine levels rise to 25% above normal, such as in a gene mutation for MTHFR (5,10-methylenetetrahdrofolate reductase), which is present in 15% of whites, a greater predisposition to vascular disease has been noted. As a result, observational studies in the general population have been conducted to further define the relationship between homocysteine levels and preexisting vascular disease. When other traditional risk factors were controlled for, there was a significant association between CAD and homocysteine levels.

There are no completed primary prevention trials of treatments known to lower homocysteine levels. Trials are underway, but to date there is no clear evidence that supports lowering homocysteine levels in the absence of cardiovascular or thrombotic disease, except in patients who have severe hyperhomocysteinemia. There are also conflicting data with regard to secondary prevention, but at the current time it is recommended that hyperhomocysteinemia be treated in patients with CAD. The exception to this is CAD patients who have received a bare metal stent, in whom therapy for hyperhomocysteinemia should be delayed for 6 months due to a potential increased risk of bare metal stent restenosis with therapy. It is not yet known whether the same risk of restenosis applies to the increasingly more common drug-eluting stents.

Screening recommendations for hyperhomocysteinemia at this time include screening patients with premature CAD who have a paucity of traditional risk factors and patients with otherwise unexplained venous thrombosis. If there is known vascular or coronary disease and the decision to treat is made, folic acid (1 mg/day), vitamin B₆ (10 mg/day), and vitamin B₁₂ (0.4 mg/day) are used. Normalization of the homocysteine concentration has been reported within 2 weeks, with further lowering of homocysteine levels occurring by 6 weeks.

EMERGING HIGH-RISK POPULATIONS

With the improved understanding of lipid and inflammatory risk factors for CAD, 2 populations have emerged over the past decade as having a disproportionate increase in CAD-related events. These include patients with HIV on highly active antiretroviral therapy (HAART) and patients with insulin resistance with or without the metabolic syndrome.
HAART-INDUCED CARDIOVASCULAR RISK

HAART regimens confer a higher risk of cardiovascular disease, which are directly related to effects on serum lipids, damage to vascular endothelium by HAART, and metabolic disorders as well as alterations in the adipose tissue composition. Metabolic disorders, such as fat redistribution, insulin resistance, hyperglycemia, new-onset diabetes mellitus, and exacerbation of preexisting diabetes mellitus, have been reported in patients receiving HAART.26 The pathogenesis of these metabolic disorders may be associated with peripheral and hepatic insulin resistance related to adipose redistribution, and the prevalence appears higher with prolonged exposure to HAART. Thus, the metabolic syndrome and related atherogenic dyslipidemia represent major risk factors for cardiovascular disease in protease inhibitor-based HAART-treated HIV patients.

METABOLIC SYNDROME

The metabolic syndrome is a clustering of atherosclerotic cardiovascular risk factors characterized by visceral adiposity, insulin resistance, atherogenic dyslipidemia (low HDL, elevated triglycerides, small dense LDL), hypertension, and a systemic proinflammatory state.27 In the United States, the metabolic syndrome affects roughly 25% of adults over age 20 years and up to 45% of the population over age 50 years. The clustering of cardiovascular disease risk factors in the metabolic syndrome confers a marked increased risk of developing type 2 diabetes and ASCVD.28,29 Because of this increased risk, some authorities consider metabolic syndrome patients equivalent to diabetics when considering lipid treatment goals. However, an important question that needs to be addressed before guidelines adapt this criteria is the role of insulin resistance in the pathogenesis of vascular lesions associated with the metabolic syndrome. A study recently showed that the NCEP metabolic syndrome definition and measures of insulin resistance were independently and additively associated with burden of subclinical coronary atherosclerosis in an asymptomatic nondiabetic sample, suggesting that promotion of atherosclerosis is a basis, at least in part, for the link to clinical events.30 This finding would suggest that the role of insulin resistance alone might be associated with morbidity and mortality independent of having the metabolic syndrome. This hypothesis is further supported by the fact that the World Health Organization’s definition of the metabolic syndrome includes a measure of insulin resistance in their criteria.30 Further studies will need to be done to stratify CAD-related events in patients with insulin resistance, with or without the metabolic syndrome, prior to changing practice guidelines, but considering these patients as an emerging high-risk group will become important as a public safety measure.

CASE: FOLLOW-UP

As the patient was a smoker and had a family history of MI, he had 2 major risk factors for ASCVD. At his next visit with his primary care physician, a full fasting lipid panel was ordered and his hs-CRP and homocysteine levels were checked. Results revealed an LDL of 188 mg/dL, HDL of 56 mg/dL, triglyceride level of 132 mg/dL, hs-CRP of 1.5, and homocysteine level of 8.9. The patient was instructed on therapeutic lifestyle changes, including a low-fat diet and exercise program, and started on a statin.

REFERENCES


CASE: INITIAL PRESENTATION

A 54-year-old man with a history of hypertension and hypercholesterolemia presents to the emergency department complaining of substernal chest pressure radiating to the left shoulder. The patient has been having chest pain with exertion for a number of months, but this is the first episode that came on with rest. He notes mild dyspnea and nausea but otherwise feels fine. He first felt the chest pain when he awoke from sleep, but it quickly resolved. This latest episode started 20 minutes ago and is gradually improving after receiving sublingual nitroglycerin from the emergency medical services team. His electrocardiogram (ECG) reveals ST depressions in the inferior leads with no reciprocal changes.

INTRODUCTION

Initially described as “preinfarctional angina” by Eliaser and Feil in 1937, the syndrome of chest pain associated with severe, transient myocardial ischemia that ultimately results in infarction was termed unstable angina (UA) by Conti and Fowler in 1971. By categorizing the severity and clinical circumstances in which angina occurs, Braunwald further classified UA in 1989 as a means of providing a more uniform working definition of the syndrome in addition to obtaining valuable prognostic and diagnostic information of this common and potentially fatal symptom.

PATHOPHYSIOLOGY

Over the past decade, the term acute coronary syndrome (ACS) has been used to describe the spectrum of diseases that now encompass the heterogeneous manifestations that are associated with myocardial ischemia. Included in this term is a continuum that represents increasing degrees of myocardial ischemia and necrosis ranging from UA, non–ST segment elevation myocardial infarction (NSTEMI) and ultimately ST segment elevation myocardial infarction (STEMI). While all points on this spectrum represent coronary atheromatous plaque rupture, thrombosis, and myocardial ischemia, UA and NSTEMI are unique in that they share similar underlying pathophysiological mechanisms with incomplete coronary artery occlusion and do not present with ST segment elevation or subsequent Q waves on ECG. Consequently, UA/NSTEMI are grouped together. The degree of ischemia and whether it is significant enough to cause myocardial necrosis and release myocardial enzymes (creatine kinase and troponin) represents the primary difference between UA and NSTEMI (Figure).

UA accounts for approximately 1.4 million admissions to U.S. hospitals annually and is the most common reason for cardiac care admissions, a staggering figure that has broad health and economic consequences. By combining information gathered from the medical history, physical examination, ECG, and biochemical cardiac marker measurements at the initial encounter of a patient with chest pain, the evaluating clinician should attempt to answer 2 questions: (1) what is the likelihood that the signs and symptoms represent ACS secondary to obstructive coronary disease, and (2) what is the likelihood of an adverse clinical outcome? Together, these 2 questions assist in establishing an estimation of immediate cardiovascular risk and are further helpful in determining the site of care for the patient (coronary care unit versus telemetry monitoring) in addition to the prompt selection of beneficial therapy.

Braunwald et al constructed a likelihood table illustrating the utilization of the history, physical examination, ECG, and cardiac markers with the likelihood of signs and symptoms representing ACS presentation (Table 1). Once determined that the presenting chest pain is likely of cardiac etiology, it is important to then determine the risk for adverse events. Antman et al developed a 7-point risk score that included age greater than 65 years, more than 3 coronary risk factors, prior angiographic coronary obstruction, ST segment deviation, more than 2 anginal events within 24 hours, use of aspirin within 7 days, and elevated cardiac markers.
Better known as the TIMI risk score, it provides a well-validated,11–14 simple, and rapid estimation of risk for developing an adverse outcome (death, reinfarction, or recurrent severe ischemia that requires revascularization) and provides support for specific therapeutic strategies in patients presenting with UA/NSTEMI. Specifically, an elevated TIMI risk score corresponded to greater benefits with therapy that included low-molecular-weight heparin (LMWH),12 platelet glycoprotein (GP) IIb/IIIa receptor antagonists,13 and an invasive approach versus a conservative strategy.11

MANAGEMENT

The goal of managing patients presenting with UA/NSTEMI is to establish immediate relief of ischemia and to provide rapid therapeutic interventions that have been shown in clinical trials to reduce the incidence of adverse outcomes. The 4 components of therapy for UA/NSTEMI supported by the recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines in 20009 and the 2002 update15 include (1) anti-ischemic therapy; (2) antiplatelet/anticoagulant therapy; (3) invasive therapy, including early catheterization and revascularization for high-risk patients; and (4) risk factor modification. This review will focus on the first 3 aspects of this management approach.

ANTI-ISCHEMIC THERAPY

Simple patient care measures are outlined in the ACC/AHA guidelines and include bedrest for any patient with ongoing ischemia as well as supplemental oxygen. Since it consumes economic resources and the evidence for empiric use is limited, the ACC/AHA guidelines recommend that supplemental oxygen therapy be limited to those patients at risk for hypoxia or with an arterial oxygen saturation less than 90% (as measured by pulse oximetry).9

Nitrates

Nitrates have been shown to limit myocardial infarct size and improve left ventricular function in STEMI.17 Sublingual nitroglycerin should be administered at a dose of 0.4 µg every 5 minutes for a total of 3 doses. In patients that have persistent ischemic pain after 3 sublingual nitroglycerin tablets, intravenous nitroglycerin is started at doses of 10 µg/min and increased by 10 µg/min every 3 to 5 minutes as long as a β blocker has been added (to prevent reflex tachycardia). Nitrates are contraindicated in patients taking phosphodiesterase inhibitors (eg, sildenafil) within 24 hours and should be used with caution in severe hypotension or critical aortic stenosis.18 In addition, nitrate tolerance can develop after 24 hours and providing a 6- to 8-hour nitrate-free interval may be necessary.

Despite physiological benefits discussed above, there are no randomized, placebo-controlled clinical trials that have demonstrated improved clinical outcomes with nitroglycerin in patients with UA/NSTEMI. Instead, the rational use of nitrates in UA/NSTEMI stems from clinical observations and the underlying pathophysiological mechanisms noted above.9,19

Morphine Sulfate

Morphine sulfate possesses potent analgesic and anxiolytic properties that may act to decrease the catecholamine surges associated with ischemic chest pain. In addition, it has the added benefit of inducing vasodilation, decreasing heart rate through vagal tone that together act to decrease MVO₂.9

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beneficial effect in UA/NSTEMI. However, the 2000 ACC/AHA guidelines do recommend administering 1 to 5 mg intravenous morphine sulfate for patients whose anginal symptoms are not relieved with 3 sublingual nitroglycerin tablets. The major adverse reaction to morphine sulfate is hypotension that is typically resolved with intravenous fluids and Trendelenberg positioning. If an allergy exists for morphine sulfate, meperidine hydrochloride may be substituted.

β-Adrenergic Blockers

By inhibiting the effects of elevated catecholamines on myocyte β receptors, β-blocking agents have been shown to decrease myocardial contractility, sino-atrial node rate, and systolic blood pressure, effects that, in summation, act to reduce MVO₂. In addition, by slowing the heart rate, β-blocking agents increase diastolic filling times, and as a consequence increase coronary artery perfusion. While there is clinical trial evidence of the mortality benefit associated with β-blocking agents in acute STEMI, there are less certain benefits and limited clinical trials with β-blocking agents in patients with UA/NSTEMI. However, given the spectrum of the underlying pathophysiological mechanism shared between UA/NSTEMI and STEMI* as well as the mortality benefit observed with β-blocking agents in acute STEMI, the ACC/AHA 2000 guidelines recommended the initiation of β-blocking agents for all patients with UA/NSTEMI except those with contraindications such as severe left ventricular dysfunction, active bronchospasm or severe COPD. β-Blocking agents with intrinsic sympathomimetic activity (metoprolol, propranolol, esmolol) are preferred. By starting β-blocking agents, Yusuf et al. showed a 13% risk reduction in progression to acute myocardial infarction in patients with UA/NSTEMI. Under continuous monitoring, the 2000 ACC/AHA guidelines recommended dosing metoprolol 5 mg intravenously every 5 minutes for a total of 15 mg to achieve a goal heart rate of 50 to 60 bpm, then changing to oral form 25 to 50 mg every 6 hours for 48 hours, and then once-daily dosing.

Calcium Channel Antagonists

There are 2 classes of calcium channel antagonists: nondihydropyridines, which include verapamil and diltiazem, and dihydropyridines, which include nifedipine and amiodipine. The dihydropyridines are capable of peripheral arterial dilation with minimal effect on the atrioventricular or sinus node whereas the nondihydropyridines act more on the atrioventricular node and sinus node, with some small peripheral dilatory effect. The beneficial properties of all calcium channel antagonists results from the ability to decrease myocardial contractility, decrease heart rate, decrease afterload, induce coronary dilation and decrease overall MVO₂—effects similar to those observed with β-blocking agents. There is a trend toward a beneficial effect of the nondihydropyridine group used acutely in patients with ischemic syndromes. The Danish Study Group on Verapamil in MI (DAVIT) trial showed favorable outcomes (fewer deaths or nonfatal myocardial infarctions) in patients that received verapamil versus placebo. The Holland

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Table 1. Likelihood that Signs and Symptoms Represent an Acute Coronary Syndrome Secondary to CAD

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Likelihood (Any of the Following)</th>
<th>Intermediate Likelihood (Absence of High-Likelihood Features and Presence of Any of the Following)</th>
<th>Low Likelihood (Absence of High- or Intermediate-Likelihood Features but May Have:)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI</td>
<td>Chest or left arm pain or discomfort as chief symptom Age &gt; 70 years Male sex Diabetes mellitus</td>
<td>Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use</td>
</tr>
<tr>
<td>Physical</td>
<td>Transient MR, hypotension, diaphoresis, pulmonary edema, or rales</td>
<td>Extracardiac vascular disease</td>
<td>Chest discomfort reproduced by palpation</td>
</tr>
<tr>
<td>ECG</td>
<td>New or presumably new transient ST-segment deviation (≥ 0.05 mV) or T-wave inversion (≥ 0.2 mV) with symptoms</td>
<td>Fixed Q waves Abnormal ST segments or T waves not documented to be new</td>
<td>T-wave flattening or inversion in leads with dominant R waves Normal ECG</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Elevated cardiac Tnl, TnT, or CK-MB</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CK-MB = creatine kinase, myocardial bound; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; Tnl = troponin I; TnT = troponin T. (Adapted from reference 10. Copyright © 2000. The American College of Cardiology Foundation and the American Heart Association, Inc.)
Interuniversity Nifedipine/Metoprolol (HINT)\textsuperscript{25} trial showed a 20\% (although not statistically significant) reduction in risk of myocardial infarction or recurrent angina effect of nifedipine when combined with a β-blocker (metoprolol). However, when administered alone, nifedipine had a 16\% increased risk of myocardial infarction versus placebo. As a result of this trial, it is not suggested that the short-acting, rapid-release dihydropropyridines be used in patients with ischemic syndromes unless with a β-blocking agent. In the Diltiazem Reinfarction Study (DRS),\textsuperscript{29} diltiazem was shown to reduce the reinfarction rates as well as refractory angina in 14 days when compared to placebo in patients 24 to 72 hours after a NSTEMI.

As a consequence of the above clinical trial data and the strong trend for a beneficial effect in patients presenting with ACS, the 2000 ACC/AHA guidelines recommend using the nondihydropyridine calcium channel antagonists (verapamil or diltiazem) as an alternative to β-blocking agents when β-blocking agents cannot be used or as additive therapy to a β-blocking agent for refractory anginal symptoms.

**ANTIPLATELET/ANTICOAGULATION THERAPY**

Given the thrombotic and platelet responses to coronary endothelial injury and atheromatous plaque disruption, it is unsurprising that antiplatelet and antithrombotic therapy has become one of the principle players in acute management of ACS. These therapies include oral aspirin, oral adenosine diphosphate receptor antagonists, intravenous GP IIb/IIIa receptor antagonists, and LMWH and unfractionated heparin (UFH).

Aspirin irreversibly inhibits cyclooxygenase-1 in platelets and prevents the formation of thromboxane A\textsubscript{2}. Through this mechanism, aspirin inhibits thromboxane A\textsubscript{2}-dependent platelet aggregation. There are well-documented beneficial effects on mortality with the use of aspirin in patients with suspected STEMI.\textsuperscript{30} Similarly, among all clinical trials of patients presenting with UA/NSTEMI, there has been a consistent benefit in reducing the risk of death from cardiac causes and nonfatal myocardial infarction. The Veterans Administration Cooperative Study,\textsuperscript{31} the Canadian Multicenter Trial,\textsuperscript{32} RISC Study Group,\textsuperscript{33} and the Montreal Heart Institute Study\textsuperscript{34} together demonstrated a 48.8\% risk reduction of fatal and nonfatal myocardial infarction in patients presenting with UA who received aspirin versus placebo.\textsuperscript{35}

Unless contraindications are present (aspirin allergy, active bleeding, hemophilia, severe untreated hypertension, active peptic ulcer disease), all patients presenting with signs or symptoms that are suspicious for ACS should receive 160 to 325 mg of aspirin immediately in the emergency department and 80 to 325 mg thereafter. In order to achieve more rapid absorption and antiplatelet activity, the first dose should be chewed.\textsuperscript{35} While the protective effect of aspirin in clinical trials of unstable angina was up to 2 years, it is reasonable to continue aspirin therapy indefinitely unless adverse gastrointestinal side effects occur.\textsuperscript{36,37}

**Adenosine Diphosphate Receptor Antagonists**

Adenosine diphosphate (ADP) is a potent mediator of platelet thrombosis. By binding the adenosine diphosphate receptor on the platelet surface, ADP induces changes in platelet shape that act to increase platelet surface area and promote platelet activation—all steps that facilitate platelet aggregation.\textsuperscript{36,37} Clopidogrel and ticlopidine are 2 thienopyridine-derivative adenosine diphosphate receptor antagonists that irreversibly inhibit ADP binding to its receptor and are used as therapies to decreased platelet aggregation in patients with ACS. By virtue of their different mechanisms on platelet inhibition, ADP receptor antagonists can act in an additive fashion to aspirin in treating patients with coronary thrombosis. However, the side effects associated with ticlopidine (neutropenia, diarrhea, abdominal pain) have limited its use to patients who cannot tolerate clopidogrel.

In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,\textsuperscript{38} clopidogrel was associated with a 8.7\% relative risk reduction (95\% confidence interval [CI], 0.3–16.5; \(P = 0.043\)) in stroke, myocardial infarction, or death compared with patients randomized to receive aspirin 325 mg/day, with no major differences in safety. The CAPRIE trial demonstrated that clopidogrel is comparable and may have a slight benefit over aspirin in secondary prevention of ischemic stroke or myocardial infarction. However, it did not provide any evidence in the benefit of treating UA/NSTEMI.

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE)\textsuperscript{39} trial investigated the use of clopidogrel in patients presenting with UA/NSTEMI. This multicenter, controlled trial randomized 12,562 patients that presented with UA/NSTEMI within 24 hours of symptoms to clopidogrel (loading dose of 300 mg, followed by 75 mg/day) plus aspirin or placebo plus aspirin. At 3 to 12 months, a composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or stroke was significantly less in the clopidogrel plus aspirin–treated group (9.3\%) versus those patients that received aspirin alone (11.4\%), providing a 0.80 relative risk with clopidogrel compared with placebo (95\% CI, 0.72–0.90; \(P < 0.001\)). The CURE trial provided strong evidence for the use of aspirin with clopidogrel (300 mg
loading, then 75 mg/day) initially with patients presenting with UA/NSTEMI. However, this benefit came at the cost of significantly increased major bleeding events in the clopidogrel plus aspirin group (3.7% versus 2.7%; \( P = 0.005 \)). As a result of the elevated bleeding risk, the 2002 ACC/AHA guideline update recommends using aspirin plus clopidogrel in patients with UA/NSTEMI who are not candidates for revascularization.\(^9\)

Patients with UA/NSTEMI who are given aspirin and are to undergo early aggressive angiography and percutaneous coronary intervention should also receive clopidogrel plus aspirin before the intervention and continue for at least 1 month but likely up to 8 months. This practice is supported by the PCI-CURE trial, a substudy of the CURE trial that recruited 2658 patients from the CURE trial who underwent a percutaneous coronary intervention. A 31% risk reduction in cardiovascular death or myocardial infarction (\( P = 0.002 \)) was demonstrated in patients who received clopidogrel plus aspirin for a median of 10 days before and up to 8 months after the intervention. The Clopidogrel for the Reduction of Events During Observation (CREDO) study\(^{40}\) demonstrated that it is beneficial to pretreat patients with ACS with a loading dose of clopidogrel (300 mg) plus aspirin (325 mg) at least 6 hours prior to percutaneous coronary intervention and continue clopidogrel (75 mg/day) plus aspirin (81–325 mg/day) for 12 months. Doing so provided a 26.9% relative risk reduction (95% CI, 3.9%–44.4%; \( P = 0.02 \)) in the combined risk of death, myocardial infarction, or stroke over aspirin alone.

The ACC/AHA 2002 updated guidelines do not include the recent data from the CREDO trial and the benefit of long-term clopidogrel therapy. Regarding the timing of clopidogrel, the guidelines recommend that clopidogrel not be started if a coronary catheterization can be performed within 24 to 36 hours of admission and it becomes clear that coronary bypass grafting (CABG) surgery is not required. If CABG is not required, the patient can be given a loading dose of clopidogrel on the catheterization table if a percutaneous coronary intervention required. Likewise, clopidogrel can be started if medical management is preferred after cardiac catheterization.\(^9\)

**Heparins**

Due largely to its prominent role as an antithrombotic agent, UFH has been in the forefront in the acute treatment of UA/NSTEMI. UFH is composed of a heterogeneous mixture of glycosaminoglycans with a wide range of molecular weights (3000–30,000).\(^{41,42}\) Through its high affinity with lysine sites on antithrombin,\(^{43}\) UFH inhibits coagulation by accelerating the neutralizing interaction between antithrombin and thrombin in addition to inhibiting factor Xa and factor IXa.\(^9\)

There have been 6 randomized, placebo-controlled clinical trials involving intravenous UFH in patients with UA/NSTEMI.\(^9\) Overall, these trials have demonstrated a beneficial trend towards reducing the risk of composite death or myocardial infarction by combining aspirin plus UFH in patients with ACS. A meta-analysis performed by Oler et al\(^{44}\) determined there was a 33% overall risk reduction of myocardial infarction or death at 2 to 12 weeks in patients with UA with aspirin plus UFH treatment compared with patients treated with aspirin alone. As a result, the 2002 AHA/ACC guidelines provide a class I recommendation for the use of UFH plus aspirin for patients with UA/NSTEMI.\(^9\) The guidelines recommend using a weight-based dosing regimen of an initial bolus of 60 to 70 U/kg (maximum, 5000 U) followed by an intravenous infusion of 12 to 15 U/kg/hr (maximum, 1000 U/hr), with a goal partial thromboplastin time of 1.5 to 2.5 times control. Despite the consistent overall benefit observed in UFH plus aspirin in patients with UA/NSTEMI, the use of UFH poses some limitations. UFH is highly bound to plasma proteins, endothelial cells, blood cells, and acute phase reactant found in the blood of patients with ACS.\(^{43}\) As a result, UFH has unpredictable pharmacokinetics with a very narrow therapeutic range that necessitates frequent blood monitoring. In addition, daily platelet count and hemoglobin assessments must be followed to detect heparin-induced thrombocytopenia or bleeding. The rare (< 0.2% incidence) immune-related form of heparin-induced thrombocytopenia can actually promote thrombosis, which is obviously an unwelcomed consequence in any patient presenting with an ACS.

Conversely, LMWH, a depolymerized form of UFH, possesses more potent inhibition of factor Xa compared to UFH, has more predictable pharmacokinetics, and less interaction with plasma proteins and blood cells, thus providing a more predictable and sustained level of anticoagulation that does not require laboratory monitoring and can be administered as once- or twice-daily subcutaneous injections.\(^{43}\) Four large clinical trials have investigated the benefit of UFH versus LMWH in patients presenting with ACS. Two of these trials have shown benefit of the LMWH enoxaparin over UFH in the acute treatment of ACS. The Enoxaparin Prevents Death and Cardiac Ischemic Events in Unstable Angina/Non-Q Wave Myocardial Infarction (TIMI 11B)\(^{45}\) trial showed a statistically significant decrease in the number of deaths, myocardial infarctions or need for urgent revascularization at 43 days in the enoxaparin-treated group compared with the UFH group (19.7% versus 17.3%; odds ratio [OR], 0.85 [95%
CI, 0.72–1.00]; \( P = 0.048 \) without an increase in the rate of major bleeding. Similarly, in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events Study Group (ESSENCE) trial, the composite endpoint of myocardial infarction, death, or recurrent angina at 30 days was significantly lower in the enoxaparin-treated group (19.8% versus 23.3%; \( P = 0.016 \)). While only 46% of the patients receiving UFH achieved a therapeutic partial thromboplastin time within 12 to 24 hours, this trial demonstrated the beneficial effects of enoxaparin over UFH in acute management of ACS as well as a cost-saving benefit. In addition, a meta-analysis of the ESSENCE and TIMI 11B trials showed a 20% statistically significant risk reduction in the rate of death, myocardial infarction, or urgent revascularization at 2, 8, 14, and 43 days for UFH in reducing 30- and 50-day incidence of nonfatal myocardial infarction observed with UFH. Enoxaparin has been demonstrated to be safe in a small group of patients undergoing percutaneous coronary interventions. Nonetheless, the 2002 updated ACC/AHA guidelines recommend withholding the dose of enoxaparin on the morning of the procedure and using UFH for patients planning to undergo CABG within 24 hours.

**Direct Thrombin Inhibitors**

Direct thrombin inhibitors (hirudin and bivalirudin) are alternative anticoagulation agents to UFH that are capable of inactivating both free thrombin and fibrin-bound thrombin directly. In a recent meta-analysis involving 35,970 patients with ACS from 11 randomized clinical trials, direct thrombin inhibitors decreased the overall incidence of myocardial infarction compared with heparin at 30 days (4.3% versus 5.1%; OR, 0.85 [95% CI, 0.77–0.94]; \( P = 0.001 \)). Of note, the decreased incidence of myocardial infarction observed with hirudin was at the cost of an increased incidence of major bleeding but less major bleeding risk than with bivalirudin. In the Hirulog and Early Reperfusion/Occlusion (HERO-2) trial, bivalirudin was significantly more effective than UFH in reducing 96-hour and 30-day postmyocardial infarction death rates. In addition, a meta-analysis showed that bivalirudin was significantly more effective than UFH in reducing 30- and 50-day incidence of nonfatal myocardial infarction when used in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for ACS. While the data from direct thrombin inhibitors are promising, their exact role in routine ACS therapy and percutaneous interventions remains to be determined and are not currently recommended for the acute management of UA/NSTEMI unless there is a history of heparin-induced thrombocytopenia.

**GP IIb/IIIa Receptor Antagonists**

Upon activation by humoral mediators in plasma and from other cells, the GP IIb/IIIa receptor complex located on the platelet surface membrane avidly binds and cross-links fibrinogen, which promotes platelet aggregation. Representing the common final pathway of platelet adhesion, activation, and aggregation, the GP IIb/IIIa receptor complex is a logical site for pharmacologic intervention as a way to prevent platelet aggregation and thrombus formation. The GP IIb/IIIa receptor antagonists prevent fibrinogen binding and exist in the form of a monoclonal antibody (abciximab), synthetic nonpeptide antagonists (tirofiban), or synthetic peptide antagonist (eptifibatide). In a large meta-analysis involving 31,402 patients presenting with UA/NSTEMI who were determined not to undergo coronary revascularization, a 9% relative risk reduction in death and myocardial infarction at 30 days was attributed to GP IIb/IIIa inhibitors compared with placebo (10.8% versus 11.8%; OR, 0.91 [95% CI, 0.84–0.91]; \( P = 0.015 \)). In further subset analysis, those patients with elevated troponin gained the most benefit from GP IIb/IIIa inhibitors. These data are reflected as a class I recommendation for the use of eptifibatide or tirofiban in addition to aspirin and heparin for conservative management in patients with elevated cardiac biomarkers, continued ischemia, or TIMI score greater than 4. In addition, 5847 (19%) of these patients actually proceeded to early revascularization, and this subgroup of early revascularized patients that received GP IIb/IIIa antagonists had a 21% reduction in death compared with placebo. Therefore, either eptifibatide or tirofiban (not abciximab) may be used 1 to 2 days prior to and shortly after cardiac catheterization.

In the Global Utilization of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndromes (GUSTO IV–ACS) trial, a bolus followed by 24- or 48-hour infusion of abciximab was associated with a lack of benefit and a nonstatistically significant trend toward increased myocardial infarction at 30 days in patients not undergoing an invasive strategy. As a result, abciximab should be avoided in patients where a percutaneous coronary intervention is not planned.

**ACE INHIBITORS**

There have been no randomized controlled clinical trials involving the use of angiotensin-converting enzyme (ACE) inhibitors in patients with UA/NSTEMI. However, the use of this class of medications as secondary prevention measure is well supported in patients with cardiovascular disease or cardiovascular disease risk factors from both the European Trial With Perindopril in Stable Coronary Artery Disease (EUROPA) and the
Heart Outcomes Prevention Evaluation (HOPE) trial.\textsuperscript{56} As a result, patients at high risk for cardiovascular disease should be treated with an ACE inhibitor.\textsuperscript{57}

**LIPID-LOWERING THERAPY**

HMG coenzyme A reductase inhibitors or “statins” have gained an enormous amount of publicity over the past decade. A large part of this attention has focused on the tremendous effect this class of drugs has had on reducing many clinical events, including myocardial infarction, stroke, and cardiovascular death, in large secondary prevention trials.\textsuperscript{58–60} In these large, multicenter clinical trials, statin drugs were administered to patients 3 to 6 months after an acute myocardial infarction. However, it is now becoming clear that the immediate period that follows an ACS represents a vulnerable time (up to 2–6 times higher risk) for recurrent cardiovascular events,\textsuperscript{61} and residual ischemia in this period is related to adverse clinical outcomes.\textsuperscript{62} When administered during the early period after an ACS, statins exert additional beneficial “pleotropic” effects (mediation of vascular inflammation, thrombogenesis, and arterial-vasomotor properties)\textsuperscript{57,60} that go beyond their cholesterol-lowering effect. To date, there are 4 prospective clinical trials that have investigated the acute initiation of statin therapy in patients with ACS. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial\textsuperscript{64} randomized 3086 patients with similar lipid profiles to receive either atorvastatin or placebo 24 to 96 hours after admission for UA or NSTEMI. Those patients who received atorvastatin had a 16% relative risk reduction at 16 weeks (14.8% versus 17.4%; 95% CI, 0.70–1.00; \(P = 0.048\)) in the primary combined endpoint of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence that required emergent hospitalization.

The Fluvastatin on Risk Diminishing after MI Trial (FLORIDA)\textsuperscript{62} compared fluvastatin 40 mg twice daily versus placebo in 540 patients with acute myocardial ischemia symptoms given within 24 hours. In contrast to the MIRACL trial,\textsuperscript{64} there was no statistically significant difference in clinical events (cardiovascular death or recurrent myocardial infarction) at 1 year between those patients that received fluvastatin versus placebo.

In the PROVE-IT trial,\textsuperscript{65} patients who were randomized to receive intensive and early statin initiation with atorvastatin 80 mg daily within 10 days of hospitalization had a 16% reduction in the hazard ratio of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days, after randomization), and stroke compared with pravastatin 40 mg daily (95% CI, 5%–26%; \(P = 0.005\)). In addition, this effect was observed within 30 days, and the mortality and morbidity benefit coincided with a reduction in low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) levels. As a result, it is thought that the beneficial effect of early aggressive statin therapy may not be a consequence of the degree of LDL reduction but rather due to the drug’s anti-inflammatory influences.\textsuperscript{66} This theory is further supported in the Z phase of the recent A to Z trial where there was smaller decrease in the CRP levels (16.7%) compared with those observed at trial completion in both the MIRACL (34%) and PROVE-IT trials (38%).\textsuperscript{57,67} In the Z phase of the A to Z trial, aggressive early therapy with simvastatin 40 mg daily for 1 month followed by 80 mg daily thereafter resulted in a favorable trend in major cardiovascular events but failed to show any significant benefit in early aggressive statin therapy compared to less aggressive therapy and, in fact, was associated with a significant increase in myopathy.\textsuperscript{68}

By supporting the early and aggressive approach to statin therapy in patients who present with ACS, the data obtained from MIRACL, PROVE-IT, and A to Z trials have given clinicians new ammunition to help prevent adverse outcomes in this patient population. This recent evidence is now reflected in the 2004 update of the National Cholesterol Education Program Adult Treatment Panel III guidelines, where it is recommended that intensive statin therapy be initiated for all patients admitted with ACS with an LDL goal of less than 70 mg/dL.\textsuperscript{69}

**EARLY INVASIVE VERSUS CONSERVATIVE MEDICAL MANAGEMENT**

Before the era of potent antiplatelet GP IIb/IIIa antagonists and coronary stenting, 2 clinical trials showed that a conservative or early invasive catheterization-based therapeutic approach to treating patients with UA/NSTEMI was equivalent. As a result, early UA guidelines supported either modality in treating patients with UA/NSTEMI.\textsuperscript{9} In addition to determining worse outcomes in treating UA/NSTEMI with thrombolytic therapy, the TIMI IIIb trial\textsuperscript{70} demonstrated that there was no statistically significant difference in outcomes of death, myocardial infarction, or an unsatisfactory symptom-limited exercise stress test at 6 weeks between an early invasive strategy versus a more conservative approach. Later, the Veterans Affairs Non-Q Wave Infarction Strategies in Hospital (VANQWISH) trial\textsuperscript{71} showed more outcomes (death, myocardial infarction) associated with an invasive (< 72 hours) regimen compared with a more
conservative approach at the time of hospital discharge. However, the overall mortality at cumulative long-term follow up did not differ between strategies.

More recently, 3 clinical trials that were performed during the era of GP IIb/IIIa antagonists and coronary angiography with stenting all showed improved outcomes with an early invasive management strategy. Both the FRISC-II and TACTICS-TIMI 18 clinical trials showed superiority of an invasive approach over a more conservative therapy. The TACTICS-TIMI 18 trial randomized 2220 patients with UA/NSTEMI to receive either an early invasive strategy with catheterization and revascularization within 4 to 48 hours or a more conservative approach with selective catheterization for recurrent symptoms. All patients received aspirin, heparin, and tirofiban. At 6 months, the invasive arm demonstrated superiority to the conservative approach in terms of composite of death, nonfatal myocardial infarction, or recurrent ACS (15.9% versus 19.5%). Moreover, the patients identified as intermediate or high risk by the TIMI risk score derived the most benefit from early invasive therapy.14 As a result, the ACC/AHA 2002 guidelines include a class I recommendation for the use of an early invasive strategy in patients with UA/NSTEMI who have the following risk factors: recurrent angina/ischemia at rest, elevated troponin T or I, new ST segment depression, recurrent ischemia with congestive heart failure symptoms, S, gallop, pulmonary edema, worsening rales or new or worsening mitral regur-
gitation, diminished left ventricular ejection fraction (< 40%), hemodynamic instability, sustained ventricular tachycardia, percutaneous coronary intervention within 6 months, or prior CABG.15 There was no statistically significant difference in outcomes between an invasive or conservative approach in low-risk patients.

**CASE: FOLLOW-UP**

The patient was given an aspirin to chew and assessed for further pain. He continued to note mild discomfort and was given a second sublingual nitroglycerin tablet, which resolved the pain. Metoprolol 5 mg IV was provided every 5 minutes for 3 doses after which his heart rate reduced to 65 bpm. LMWH was given. The patient was pain-free on transfer to the critical care unit. His admission orders included oral metoprolol, nitroglycerin as needed, aspirin, and LMWH. Clopidogrel was held until catheterization. After evaluation in the critical care unit by the cardiologist on call, it was decided that coronary intervention was likely and this was subsequently confirmed when the patient’s second troponin value came back mildly elevated. An eptifibatide infusion was then initiated.

**CONCLUSION**

UA accounts for more than 1 million hospital admissions annually and there is a high incidence of mortality and morbidity associated with the condition (15% rate of death or infarction in 30 days).13 Early recognition of cardiac ischemia manifesting as UA or NSTEMI and prompt risk stratification can help guide therapeutic decision making in hopes of reducing the mortality and morbidity associated patients presenting with ACS.

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Section 3—Management of ST Elevation Myocardial Infarction

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CASE: INITIAL PRESENTATION

A 56-year-old man with a history of hypertension and obesity presents to the emergency department with the acute onset of “crushing” substernal chest pain radiating to his left shoulder associated with both diaphoresis and nausea. He was driving to work when it came on and had to pull to side of the road where he was then able to call 911. He presents 45 minutes after the pain began. His blood pressure is 110/70 mm Hg and heart rate is 106 with an O₂ saturation of 92% on room air. Cardiopulmonary examination reveals absent jugular venous distension, clear lung fields, and a normal S₁ and S₂ with no S₄. Electrocardiogram shows 3-mm ST elevations in the inferior leads with reciprocal ST depressions in leads V₁ to V₃. Within 10 minutes of his presentation to the hospital, the emergency department physician concludes that the patient is experiencing an acute ST elevation myocardial infarction (STEMI).

MANAGEMENT

INITIAL MANAGEMENT

STEMI represents the acute occlusion of a coronary artery, most often from the rupture of a previously nonocclusive atherosclerotic plaque. As opposed to unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI), the occlusion is complete and myocardial infarction is occurring, as evidenced by the eventual release (within 4 hours) of the biomarkers of myocardial injury (creatine phosphokinase and troponin).

The immediate management of patients with an acute STEMI is the same as previously outlined for UA/NSTEMI. Oxygen should be provided, particularly if the O₂ saturation is below 90%. Unless the patient has recently ingested a phosphodiesterase inhibitor or blood pressure is less than 90/30 mm Hg, nitroglycerin should be initially given sublingually, up to three 0.4-mg tablets every 5 minutes, and then a nitroglycerin drip started. Morphine (2–4 mg IV repeated every 5–15 minutes) is indicated if nitroglycerin fails to completely relieve the pain. The simple and effective intervention of providing a chewable aspirin at a dose of at least 162 mg remains a high priority in STEMI.

Life-threatening ventricular arrhythmias require aggressive management per advanced cardiac life support protocol, and rapid supraventricular tachycardias need immediate attention because of the excess demand they place on the myocardial tissue. A β blocker (eg, metoprolol) given in 5-mg increments every 5 minutes for 3 doses can quickly slow any tachycardia, with calcium channel blockers as a secondary option if there is an absolute contraindication to β blockade. In any case, an oral β blocker should be considered if the patient’s blood pressure is at an acceptable level. Once these initial steps have been taken, a plan should be in place for rapid revascularization of the occluded artery with either fibrinolysis of percutaneous coronary intervention (PCI).

FIBRINOLYSIS

Systemic thrombolytic therapy in STEMI was first considered in the early 1980s and tested in 2 landmark trials (GISSI-1 and ISIS-2). GISSI-1 demonstrated that an infusion of streptokinase could reduce overall hospital mortality at 21 days by 2.3% (number needed to treat [NNT], 43) with a relative risk reduction of 18%. GISSI-1 also found a time-dependent relationship between the effectiveness of thrombolytic therapy and the initiation of the patient’s symptoms. Therapy was progressively less effective with time and was ineffective and possibly harmful if given after 9 hours from the onset of symptoms. Clear benefit was present only if given within a 6-hour window (though later studies have suggested effectiveness up to 24 hours). ISIS-2 confirmed the results of GISSI-1 and also clearly demonstrated the effectiveness of aspirin therapy, which acted synergistically with streptokinase to reduce mortality.

Since these 2 early trials, numerous studies have been performed with other thrombolytic agents.
Appraising the Medical Literature—Articles About Therapy

Over the past decade, perhaps no other area in medicine has seen therapeutic advances come as rapidly as has cardiology. The engine of this progress has been the many well-funded randomized trials addressing care of the cardiac patient. Many of these landmark trials have been discussed in the present manual; thus, it is appropriate to review the critical appraisal of therapy studies here.

A number of guidelines have been published that present a systematic approach to appraising the medical literature. We present a framework based on these guidelines below. We suggest asking 3 basic questions:

1. Does the study possess internal validity?

**Internal Validity**

Internal validity is the degree to which a study minimizes bias and confounding so that the results reflect actual reality. Bias is reduced when study groups are treated in precisely the same way, except for the intervention of interest. Randomization ensures that potential confounders—both known and unknown—are distributed equally between the 2 groups. The adequacy of randomization can be assessed by looking at the comparisons provided in the baseline variables table. Blinding ensures that the parties involved are not influenced, either consciously or unconsciously, by knowledge of the intervention assignment. Triple blinding—patients, providers, and data assessors (if possible)—is now the standard.

A major threat to internal validity after randomization is crossovers and losses to follow-up. Crossovers are patients who were initially assigned to one therapy but who received the other, either in addition to or in place of the therapy initially assigned. An intention to treat analysis reduces the amount of postrandomization bias in that it analyzes patients in the groups to which they were originally assigned regardless of the intervention they received. On the downside, it tends to dilute the difference between the groups (bias towards the null). Losses to follow-up should be minimal. In general, a loss of greater than 20% of the initial study population can lead to a biased study. Less than 5% is ideal, and 10% is tolerable.

2. What are the results?

**Statistical Significance**

The first step in assessing the results of the study is to ask whether the differences in outcomes were statistically significant. Typically, this is expressed as a P value, which is the probability of obtaining the study results by chance if the null hypothesis is true. A P value of less than 0.05 tells you that the likelihood that the difference between the 2 groups occurred by chance alone is less than 5%. Five percent is the arbitrary standard used for setting the level of statistical significance in most studies.

What if the results are not statistically significant? The interpretation of a negative study, (one that does not detect a difference) can sometimes be as interesting as a positive one. A negative study does not necessarily mean that the intervention had no effect. First, most studies assume a false-negative rate of 20% as part of the sample size calculation. Second, finer distinctions between 2 groups require larger study samples. This is intuitive: it would not take a large sample for us to recognize that insulin is a powerful therapy in diabetic ketoacidosis. The difference would be clear after only a few patients. However, the difference between 2 effective antihypertensives in preventing stroke takes a much larger study to detect. This is because the distinction between 2 relatively effective therapies is quite small. Thus, in a negative study, it may be that a difference between 2 groups does indeed exist, but we simply did not study enough patients to detect that difference.

**Effect Size**

Once we have concluded that the results are unlikely to have been the result of chance, we assess the magnitude of the difference in outcome. This is often described in terms of risk relationships. Absolute risk is expressed as the percentage of patients in each group who experienced the bad outcome. For example, assume 6% of patients who received the therapeutic intervention were dead at 1 year; whereas 12% of patients who received placebo died. So the risk of dying at 1 year if nothing is done is 12%. How much did the intervention lower risk? In this case, it was lowered 6 percentage points, for an absolute risk reduction (ARR) of 6%.

Relative risk in this case is obtained by dividing 6% by 12%, which figures out to 0.5—a relative risk reduction of 50%. Relative risk reduction is the more commonly reported result in studies, but it can be deceiving if baseline risk is not taken into account. A 50% reduction (from 12% to 6%) would be considered meaningful to most people. But the relative risk reduction reflected by the absolute risk reduction of 0.000012% to 0.000006% is also 50%, but few would find that difference meaningful. For this reason, it is increasingly common to see outcomes reported as the number needed to treat (“NNT”), which is simply 1/ARR. In our example, the absolute risk reduction was 6% or 0.06. 1/0.06 equals roughly 17, which means that 17 people would need to be treated in order to avoid 1 bad outcome (however it is defined). NNT is an attractive option for outcome reporting because it accounts for baseline risk and also gives us a small number that both patients and clinicians can easily appreciate.

3. Does the study possess external validity?
Tissue plasminogen activator (t-PA; alteplase), which is more fibrin-specific, was the first new agent studied.\textsuperscript{3} The GUSTO-I trial demonstrated that a “front-loaded” t-PA regimen, in which two thirds of the dose was given in the first 30 minutes, produced a 1% mortality improvement (NNT, 100) over the streptokinase regimens. Further trials with “wild-type” variations of t-PA (reteplase, lanetoplasse, and tenectplase) have demonstrated similar results to front-loaded t-PA. Tenecteplase is becoming increasingly popular because it is easy to give as a single bolus injection and appears to carry less risk of noncerebral bleeding. Streptokinase, however, remains the most commonly used thrombolytic agent worldwide. All agents carry a risk of intracranial hemorrhage of approximately 1% to 2%.\textsuperscript{4} By convention, most studies have also utilized unfractionated heparin given as a weight-based regimen and continued for at least 48 hours. Low-molecular-weight heparin may be superior to unfractionated heparin but can only be used in patients without renal dysfunction.\textsuperscript{5} Enoxaparin and tenecteplase, both given as a single dose, is a simple regimen that appears to maximize the effectiveness and minimize the potential side effects of thrombolytic therapy while improving the ease of administration.

As noted, unfractionated or low-molecular-weight heparin should be given following the infusion or bolus of thrombolytics. Glycoprotein (GP) IIb/IIIa in association with half-dose t-PA was studied with initially encouraging results and improvement in the attainment of TIMI 3 flow, but further trials showed no improvement in mortality and an increase in the risk of intracranial bleeding.\textsuperscript{6} Thus, using GP IIb/IIIa inhibitors in this setting cannot be recommended at this time.

In March 2005, the New England Journal of Medicine published the results of the CLARITY TIMI-28 trial,\textsuperscript{7} which evaluated the use of clopidogrel (300 mg loading dose, 75 mg daily) in addition to a standard fibrinolytic regimen that included aspirin in the treatment of STEMI. All patients received angiographic evaluation within 8 days. There was a 36% relative risk reduction (NNT, 16) for the presence of an infarct-related arterial occlusion, with positive results across all major subgroups. A 20% relative risk reduction was found in the combined endpoint of cardiovascular death, myocardial infarction (MI), or recurrent ischemia at 30 days. There was no increase in hemorrhage or stroke. Although the study was not powered to determine a mortality benefit, these early findings suggest a role for the addition of clopidogrel to standard thrombolytic therapy.

Though thrombolytic therapy has been shown to improve mortality, it must be used judiciously. The absolute contraindications to fibrinolysis include any prior history of intracranial hemorrhage, known intracranial malignancy, ischemic stroke within the last 3 months (unless acute), and active bleeding. Relative contraindications are often more relevant and need to be weighed against the therapeutic benefit in the setting of the overall clinical context. They include uncontrolled severe hypertension (> 180/110 mm Hg), recent bleeding, known active peptic ulcer disease, and pregnancy.\textsuperscript{8}

Undue emphasis on the side effects and contraindications of thrombolytic therapy should not obscure its virtues, however. Despite its well-demonstrated benefit and virtually universal availability, fibrinolytic therapy is underutilized, presumably due to concern about side effects or failure to recognize its indication. Less than 50% of patients eligible for fibrinolytics actually receive them. And in those who receive them, only approximately 53% will achieve TIMI 3 flow (normal perfusion).\textsuperscript{6} Thus, in the absence of PCI, in only 25% of patients who present to care for an STEMI is the afflicted myocardium successfully and completely reperfused.

The 2004 ACC/AHA guidelines recommend that “in the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads…and new or presumably new left bundle branch block.”\textsuperscript{9} Consideration
can be given to thrombolytics as far out from symptom onset as 24 hours. “Door-to-needle” time should not exceed 30 minutes, and emergency medical systems should strive to administer thrombolytics to eligible patients within 2 hours of symptom onset.

**Success and Failure in Thrombolysis**

There are no perfect criteria to judge the adequacy of reperfusion following the administration of thrombolytics. Assessment is usually based on the timely resolution of the ST-segment elevations to less than 50% of their original elevation, a criterion that has a diagnostic accuracy of 80% to 85%. The presence or absence of chest pain can be misleading and poorly correlates with reperfusion. If the ST segments fail to improve, the patient is usually considered to have failed thrombolysis therapy. At this point, consideration is often given to repeating thrombolysis or performing “rescue PCI” (angioplasty). Repeat thrombolysis has not been well studied in a prospective randomized fashion, but observational studies suggest that it may be useful. The ACC/AHA guidelines make no specific mention of it. Rescue PCI also suffers from a lack of convincing data for its effectiveness and is unlikely to be helpful if offered more than 12 hours after the initiation of symptoms. The ACC/AHA guidelines do recommend rescue PCI in patients younger than 75 years of age who develop shock within 36 hours of an MI.5

**PERCUTANEOUS CORONARY INTERVENTION**

PCI was initially evaluated as a “salvage” option following the administration of thrombolytics but soon gained consideration as a primary option (primary PCI). Compared with thrombolytic therapy, it offers a number of theoretical benefits. Cardiac catheterization allows for a rapid definition of the patient’s coronary anatomy and the culprit vessel involved with the potential for rapid restoration of flow. Patients with multivessel disease can also be referred for coronary artery bypass graft surgery if appropriate. Academic tertiary care centers quickly embraced primary PCI and numerous studies have since been performed comparing primary PCI with thrombolytic therapy. Keeley and colleagues performed a systematic review of the 23 randomized trials in 2003 and reported primary PCI was superior to thrombolytics in reducing short-term death (2% absolute risk reduction; NNT, 50), nonfatal reinfarction (4% absolute risk reduction; NNT, 25), with less risk of stroke (1% versus 2%; NNH, 100). Although the benefit of angioplasty was greatest in comparison with the older streptokinase regimen, the newer fibrin-specific regimens were also inferior to primary PCI. PCI has also been shown to restore TIMI 3 flow in a greater percentage (90%) of patients than thrombolytics with less risk of reocclusion (25% versus 5%). Although time delay remains an important consideration in PCI, and the ACC/AHA guidelines mandate a “door-to-balloon” time of no greater than 90 minutes, studies have also suggested that patients who receive PCI can tolerate greater time delay, even up to 4 hours (door-to-balloon). Furthermore, the benefit of PCI over thrombolytics appears to be greatest in those at highest risk. On the basis of the present data, the ACC/AHA recommends patients undergo primary PCI in lieu of thrombolytics if the door-to-balloon time is less than 90 minutes and, in hospitals that do not have rapid PCI capability, if patients can be transferred to a PCI facility such that the delay to reperfusion is not greater than 1 hour. PCI is also preferred in patients younger than 75 years of age who present with shock, severe congestive heart failure, or late arrivals.

From the above, one can see that all things being equal, primary PCI is preferable to thrombolytic therapy. Commonly, however, all things are not equal. Less than 15% of patients who present to acute care with a STEMI come to facilities with rapid PCI capability. Many of the studies that have demonstrated better outcomes with PCI have also been performed in high-volume centers that have experienced interventional cardiologists and 24-hour coverage. In light of these concerns, 5 trials have been performed comparing thrombolytics with transfer for primary PCI in community settings. PRAGUE-2 randomized 850 patients presenting to community hospitals to thrombolysis or transfer for PCI. It was the only one of the 5 studies powered to detect a mortality difference, and it failed to do so in the total study population. Patients who arrived more than 3 hours after symptoms did, however, have a statistically significant mortality benefit from transfer. The larger DANAMI-2 trial published in the New England Journal of Medicine in 2003. 1572 patients in Denmark were assigned to alteplase or PCI, with patients presenting to noninterventional sites receiving rapid transport for PCI at another facility. The study demonstrated a 5.7% absolute risk reduction (14.2% to 8.5%) in the primary composite endpoint of death, clinical reinfarction, or disabling stroke if patients were transferred, but again it was not powered to detect a mortality difference. Thus, while PCI is the preferred therapy when it can be done promptly with transfers not exceeding 1 hour, thrombolysis should still be considered an effective alternative in the majority of patients who do not live in areas near PCI facilities.
Adjunctive Therapy with PCI

As noted, GP IIb/IIIa inhibitors have not been demonstrated to improve mortality in the setting of thrombolytic therapy. Their use in PCI is more common and studies have shown a nonsignificant trend towards improvement in mortality when given in the setting of STEMI. Clopidogrel is clearly beneficial to prevent in-stent thrombosis and may have a role even when a stent is not necessary. The ACC/AHA guidelines recommend continuing clopidogrel for 1 month following a bare metal stent implantation and for several months after implantation of a drug-eluting stent.

CASE: FOLLOW-UP

The chest pain team at the hospital (which has primary PCI capabilities) evaluates the patient. The GP IIb/IIIa inhibitor abciximab is started in the emergency department, and he is transferred to the catheterization laboratory for immediate percutaneous transluminal coronary angioplasty (PTCA). An obstructive lesion is found in the right coronary artery. Attempts at PTCA produce a small dissection and a stent is deployed with resulting TIMI 3 flow. The patient is given 300 mg of clopidogrel in the catheter laboratory, and he is then transferred to the critical care unit for further management.

The patient is comfortable and chest pain–free following transfer to the critical care unit. Initially, the telemetry monitor shows an idioventricular rhythm suggestive of reperfusion. Over the next 6 to 8 hours, however, he frequently has runs of nonsustained ventricular tachycardia and frequent premature ventricular contractions. Baseline laboratory tests drawn on admission revealed a blood sugar of 301 mg/dL and a hemoglobin of 8.4. His potassium was normal at 4.5 mg/dL, but magnesium was reduced at 0.9 mg/dL. The patient had not been previously aware of either the low hemoglobin or the elevated blood sugars.

ADJUNCTIVE MEDICAL THERAPY

Following attempts at reperfusion in STEMI, patients are usually transferred to an intensive care setting for further stabilization and the institution of medical therapies that have been proven to reduce long-term mortality. This patient has previously unrecognized diabetes as well as anemia. His chronic hyperglycemia has also likely led to an osmotic diuresis with associated magnesium depletion.

Arrhythmia management following STEMI has evolved considerably in the last 20 years. Prophylactic treatment of ventricular ectopy, whether in the form of premature ventricular contractions or nonsustained ventricular tachycardia, is no longer indicated after the routine use of anti-arrhythmics was shown to increase mortality. Sustained mono- or polymorphic ventricular tachycardia should still be treated aggressively with either electric shock or amiodarone. Ventricular fibrillation or significant sustained ventricular tachycardia more than 48 hours following STEMI should be carefully managed. If there is no evidence of residual ischemia, the ACC/AHA guidelines recommend consideration of an implantable cardioverter defibrillator. In any case, magnesium should be repleted.

The care of diabetic patients following an acute MI was altered dramatically by the publication of the DIGAMI study in 1999. Of 620 patients who presented with acute MI, 306 were randomly assigned to an insulin drip with tight glucose control during hospitalization and follow-up (glycosylated hemoglobin < 7) and the remainder were assigned to conventional therapy. After 3.4 years of follow-up, there was an 11% absolute risk reduction (44% to 33%; NNT, 9) in mortality with intensive management. These data are in line with other studies showing the importance of glucose control in critical care settings.

The management of anemia in acute MI and critical care settings is controversial. One study performed in a critical care setting found that a restrictive transfusion strategy (only transfusing when hemoglobin < 7) was preferable, but the subgroup of patients ischemic heart disease had a nonsignificant trend towards increased mortality. A later retrospective study of elderly patients hospitalized for an MI indicated improved 30-day mortality if hemoglobin level was greater than 10 mg/dL. The ACC/AHA guidelines make no specific recommendation regarding blood transfusion in the setting of acute MI.

Other than the issues noted above, the secondary prevention of acute coronary syndrome was discussed in the UA/NSTEMI section of this manual. There is overwhelming evidence for the long-term use of aspirin and β blockers in patients with known coronary artery disease. Angiotensin-converting enzyme (ACE) inhibitors have clearly been shown to benefit patients who suffer an acute MI and have an ejection fraction of less than 40%; the ACC/AHA guidelines recommend oral administration within the first 24 hours in patients with an anterior infarction, congestive heart failure, or an ejection fraction less than 40%. The HOPE trial supports their use in all patients with atherosclerotic heart
A c u t e  M a n a g e m e n t  o f  U n s t a b l e  A n g i n a / N o n–S T  E l e v a t i o n  M I
disease. Patients intolerant of ACE inhibitors should be offered an angiotensin receptor blocker. Further aldo-
sterone blockade with eplerenone or spironolactone is indicated in patients with STEMI and an ejection
fraction less than 40% or symptomatic heart failure, provided the serum creatinine is not greater than
2.5 mg/dL. Finally, virtually all patients should be placed on statin therapy with a goal low-density lipopro-
tein cholesterol level of less than 70 mg/dL. Exercise, diet, smoking cessation, and weight loss counseling
are a vital part of secondary prevention efforts and should not be neglected. Patients are often the most
psychologically open to lifestyle counseling in the immediate post-MI period, and physicians should attempt
to capitalize on this window of opportunity for dramatic lifestyle change.

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