Review

Contemporary Treatment of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction (Part 1)

Shehzad Sami, MD
James T. Willerson, MD

In this, the 1st part of a 2-part review, we discuss how plaque rupture is the most common underlying pathophysiologic cause of unstable angina and non-ST-segment-elevation myocardial infarction and how early risk stratification is vital in the timely diagnosis and treatment of acute coronary syndrome. Part 2 of this review (to be published in a later issue of this journal) will focus mainly on the various pharmacologic agents and treatment approaches (early invasive vs early conservative) to the management of unstable angina and non-ST-segment-elevation myocardial infarction. ***(Tex Heart Inst J 2010;37(2):141-8)***

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From: *Department of Cardiology, Texas Heart Institute at St. Luke's Episcopal Hospital and The University of Texas Medical School at Houston, Houston, Texas 77030*

Address for reprints: *Shehzad Sami, MD, 6770 Bertner Ave., Suite C550A, Houston, TX 77030*

E-mail: *shehzadsami76@yahoo.com*

Acute coronary syndrome (ACS) refers to the array of clinical signs and symptoms produced by acute myocardial ischemia, including unstable angina (UA), non-ST-segment-elevation myocardial infarction (NSTEMI), and ST-segment-elevation myocardial infarction (STEMI).[1] Each condition shares common pathophysiologic origins related to the instability and rupture of atherosclerotic vulnerable plaques (Fig. 1).[2] Unstable angina and NSTEMI are differentiated one from the other primarily by their severity—whether the ischemia is prolonged enough to lead to structural myocardial damage and to the release of detectable markers of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or creatine kinase (CK)-MB.[3]

Coronary heart disease (CHD) is a major cause of morbidity and death in the United States, affecting approximately 16 million Americans.[4] In fact, someone in this nation experiences a coronary event every 25 seconds, and someone dies from a coronary event every minute. There are more than 1.4 million hospitalizations for ACS in the United States each year, and the direct and indirect costs of CHD are estimated to be more than $165 billion in 2009 alone.[4] As the world's population ages, the incidence of CHD is expected to reach epidemic proportions, especially in developing countries.[5] It is this realization that led to a 20-year effort by the medical community to change the priorities of public healthcare policymakers and to redirect research and capital investment funds toward the field of cardiovascular treatment and care. As a consequence of that effort, the medical literature now contains multiple novel findings from various randomized clinical trials, all of which have helped to establish and refine current evidence-based treatment for ACS.

In this, the 1st part of a 2-part review, we discuss how plaque rupture is the most common underlying pathophysiologic cause of UA/NSTEMI cases and how early risk stratification is vital in the timely diagnosis and treatment of ACS. Part 2 of this review (to be published in a later issue of this journal) will focus mainly on the various pharmacologic agents and treatment approaches (early invasive vs early conservative) to the management of UA and NSTEMI.

Pathophysiology

Unstable angina and NSTEMI result from a disparity between myocardial oxygen delivery and demand, which usually presents as angina occurring with limited physical activity or at rest (a crescendo pattern). The demand-and-delivery mismatch associated with UA/NSTEMI can occur because of dynamic obstruction secondary

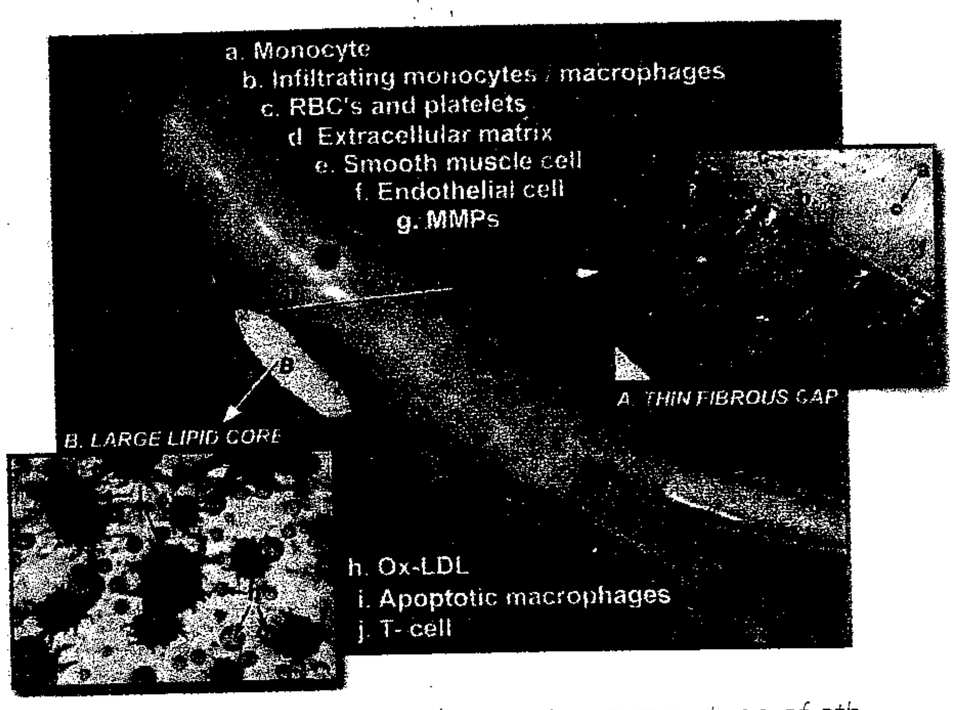

Fig. 1 *Schematic illustrates the most common type of atherosclerotic vulnerable plaque, which is characterized by a thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and a large lipid core—without significant luminal narrowing. Reprinted with permission from: Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108(14):1664-72.*[2]

to intense arterial spasm; because of progressive, severe, flow-limiting atherosclerosis due to intimal hyperplasia or to lipid, calcium, and thrombus deposition, or to fibrointimal hyperplasia after percutaneous coronary intervention (PCI); because of coronary artery dissection; or (in instances of "secondary" UA) because of conditions that alter myocardial oxygen demand or supply, such as intense emotion, tachycardia, or uncontrolled systemic hypertension.[6]

The most frequent mechanism of ischemia during limited physical activity or at rest, however, is a primary reduction of the myocardial oxygen supply due to rupture or ulceration of a vulnerable atherosclerotic plaque, which results in endothelial injury and associated thrombosis and dynamic vasoconstriction.[7,8] Constantinides[9] first described, in 1966, the association between plaque fissure and coronary thrombosis—an association later confirmed in the 1980s by detailed, serial, pathologic studies performed by Davies and Thomas[10] and Falk[11] in fatal cases of UA and myocardial infarction (MI). Buja and Willerson[12,13] also showed the association between thromboses of an infarct-related coronary artery and the development of ACS, using detailed clinicopathologic correlations.

Plaque fissure or rupture exposes the highly thrombogenic subendothelium to circulating platelets and white blood cells, which in turn activates the coagulation cascade. The resultant platelet adhesion and aggregation at the site of plaque disruption leads to transient thrombosis or subtotal coronary artery occlusion with dynamic vasoconstriction. Activated platelets release powerful promoters of vasoconstriction and platelet aggregation, including thromboxane A_2, serotonin, adenosine diphosphate, and platelet-activating factor (Fig. 2).[14]

The involvement of these platelet-derived substances in the pathogenesis of ACS was first demonstrated by Willerson and colleagues[15] nearly 30 years ago. In a study of 60 patients, those with active or rest angina and a recent episode of UA (<24 hr before angiography) had higher transcardiac thromboxane concentration levels than did patients with noncardiac chest pain or patients with significant CAD but a distant history of chest pain (>96 hr before angiography).[15] It was this important finding that led to the discovery of numerous cytokines and therapeutic targets related to the management of ACS. We now know that various other potent cell-derived vasoconstrictors and promoters of platelet aggregation—including activated thrombin, oxygen-derived free radicals, tissue factor, and endothelin—also accumulate locally at the site of plaque ulceration and fissure and contribute to the prothrombotic environment (Fig. 2).[8,15-20]

Plaque rupture can occur in mildly or severely stenosed coronary arteries and often occurs in arteries

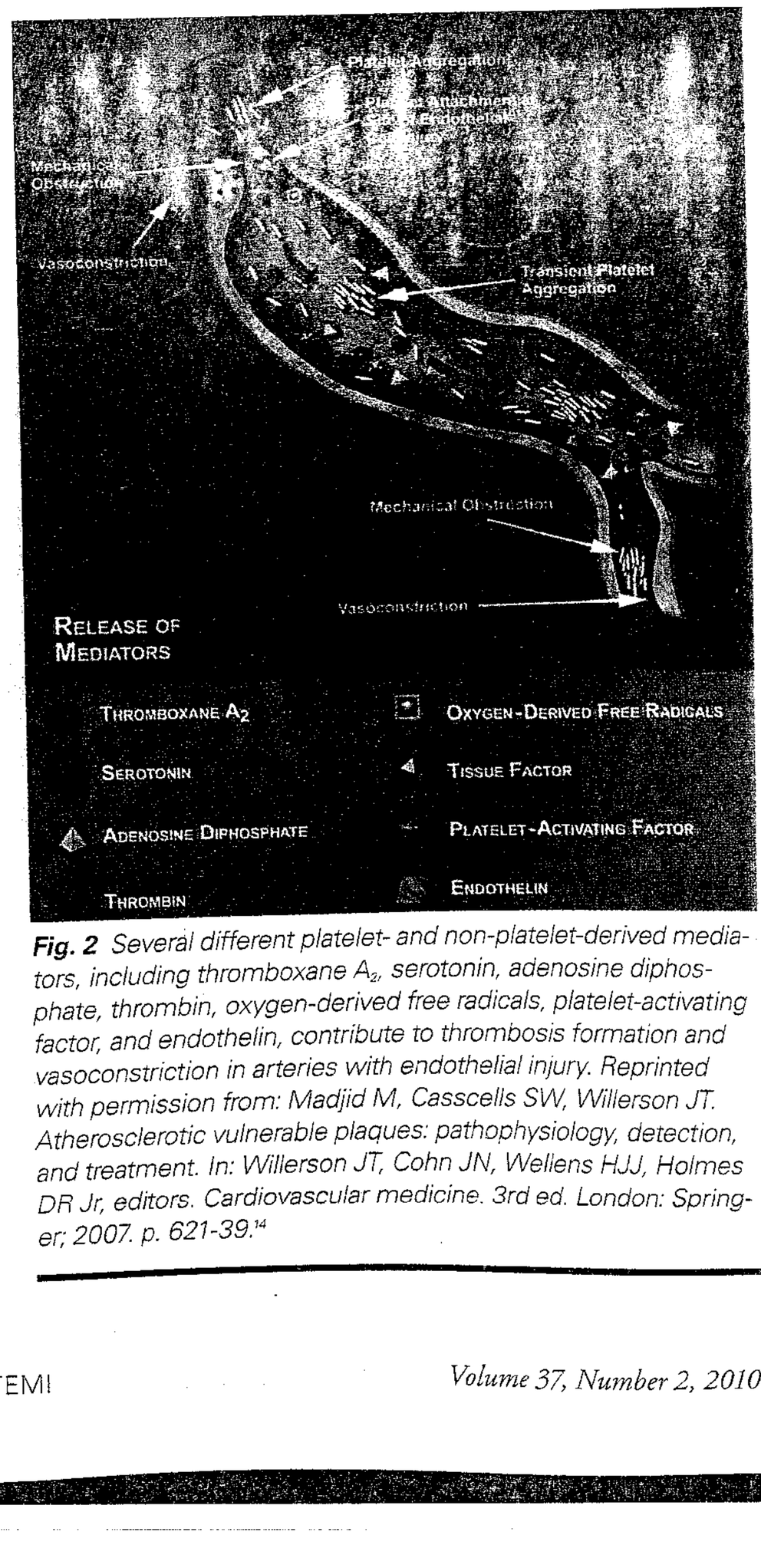

Fig. 2 *Several different platelet- and non-platelet-derived mediators, including thromboxane A_2, serotonin, adenosine diphosphate, thrombin, oxygen-derived free radicals, platelet-activating factor, and endothelin, contribute to thrombosis formation and vasoconstriction in arteries with endothelial injury. Reprinted with permission from: Madjid M, Casscells SW, Willerson JT. Atherosclerotic vulnerable plaques: pathophysiology, detection, and treatment. In: Willerson JT, Cohn JN, Wellens HJJ, Holmes DR Jr, editors. Cardiovascular medicine. 3rd ed. London: Springer; 2007. p. 621-39.*[14]

where the atherosclerotic lesions previously had caused only mild-to-moderate obstruction.[21,22] The duration of ischemia caused by the platelet-fibrin thrombi and severe dynamic vasoconstriction determines the overall clinical picture. If ischemia is neither severe nor prolonged (usually <20 min) and often recurs at rest, patients are given a diagnosis of UA. However, if ischemia lasts longer than 30 minutes (usually 1–2 hr) and is associated with elevated cardiac markers, a diagnosis of MI is made. Further classification as STEMI or NSTEMI is made on the basis of electrocardiographic findings.[7,8,12,17] Patients with UA/NSTEMI remain at high risk for a new infarction and its sequelae, including sudden cardiac death, until the endothelial injury is repaired. Willerson and colleagues[7,8] were the first to suggest that UA, NSTEMI, and STEMI represent a pathophysiologic continuum. This concept has led to the development of effective pharmacologic therapies that, used in conjunction with careful and rapid risk-assessment strategies and catheter-based therapies, improve outcomes in UA/NSTEMI patients.

Progressive in nature, atherosclerosis is a chronic inflammatory and multifocal disease involving medium- and large-sized arteries. It may begin in the subendothelium as early as in the 1st decade of life,[23] and it usually develops in lesion-prone vascular areas that exhibit underlying endothelial dysfunction as a response to chronic, multifactorial injury to the arterial wall. Various causes of endothelial injury include flow shear stress, hypertension, immune-complex deposition and complement activation, smoking, diabetes mellitus, aging, substance abuse, infection, and mechanical injury to the endothelium, such as that which may occur consequent to coronary angioplasty, stent placement, or heart transplantation.[24] Endothelial dysfunction refers to a process widely regarded as a precursor to the development of vascular disease, including hypertension, heart failure, and atherosclerosis.[25] It is characterized by disruption of vessel-wall homeostasis, which is signified by decreased vasodilation, increased vasoconstriction, increased oxidative stress and inflammation, deregulation of thrombosis and fibrinolysis, abnormal smooth-muscle-cell proliferation, and a deficient repair mechanism. Nitric oxide (NO) released from the terminal guanidine group of L-arginine by endothelial NO synthase (eNOS) and prostacyclin (PGI_2) derived by the action of cyclooxygenase (COX) and prostacyclin synthase play key roles in the maintenance of endothelial homeostasis; however, both are reduced in endothelial cells in which endothelial injury has occurred and in which atherosclerosis develops.

Traditional cardiovascular disease risk factors, such as hypertension, dyslipidemia, diabetes, and smoking, induce oxidative stress that results in the overproduction of reactive oxygen species, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$). Reactive oxygen species accelerate the degradation of NO and activate redox-sensitive transcription factors, such as nuclear factor (NF)-kappa B.[26] This results in the up-regulation of redox-sensitive genes, including adhesion molecules (for example, vascular-cell-adhesion molecules [VCAMs] and intercellular adhesion molecules [ICAMs]), cytokines (for example, tumor necrosis factor-α [TNF-α] and interleukin-1β [IL-1β]), and chemokines (for example, monocyte chemoattractant protein-1 [MCP-1]), which participate in the recruitment and infiltration of inflammatory cells into the vascular wall.[27,28] Once inside the vascular wall, monocytes differentiate into macrophages, which later change into foam cells. Smooth muscle cells also migrate from the tunica media to the intima. Together, these cells proliferate and secrete a rich and complex extracellular matrix and matrix metalloproteinase (MMP). The strength of the fibrous atherosclerotic cap depends on a dynamic balance of collagen synthesis and degradation. Inflammatory cytokines and inflammatory mediators inhibit de novo synthesis of interstitial collagen and increase the production of MMPs, which degrade the fibrous cap and make the atherosclerotic plaque vulnerable to rupture.[29] In asymptomatic patients, testing for various markers of inflammation, including high-sensitivity C-reactive protein (hs-CRP), has been shown to improve risk stratification and prognostication.[30]

Because of their antioxidative properties, vitamins C and E in high doses have been shown in animal studies to be of modest benefit in reversing endothelial dysfunction and in preventing the initiation or progression of atherosclerosis.[31-34] However, results from the Physicians' Health Study II,[35] a randomized, double-blind, placebo-controlled factorial trial, suggest that there is no benefit in taking vitamins C and E for the prevention of cardiovascular disease. The 10-year American study included 14,641 male physicians (ages, ≥50 yr) who received individual supplements of vitamin E (400 IU, every other day) and/or vitamin C (500 mg, daily). Neither vitamin E (hazard ratio, 1.07 [95% confidence interval, 0.97–1.18]; $P=0.15$) nor vitamin C (hazard ratio, 1.07 [95% confidence interval, 0.97–1.18]; $P=0.16$) had a significant effect on total death or cardiovascular events.[35]

Diagnosis and Risk Stratification

Early risk stratification is vital in the timely diagnosis and treatment of ACS. Assessment of patients with suspected ACS should include a clinical history, a physical examination, 12-lead electrocardiography (ECG), biochemical marker measurement, and noninvasive risk stratification.

Clinical History

A thorough clinical history is of utmost importance in the initial evaluation and treatment of patients with suspected ACS. Typical symptoms of ACS include chest

pain or discomfort that may or may not radiate to the arm, back, neck, jaw, or epigastrium. Women and elderly patients are more likely to present with atypical features, such as shortness of breath, weakness, diaphoresis, nausea, and lightheadedness.[36] Table I shows the 3 principal presentations of UA.[37]

Physical Examination

Findings from the physical examination of patients with suspected ACS are often normal. Attention must be paid to the presence of complications of ACS, including acute left ventricular failure secondary to ischemia, hypotension, an S_3 gallop, new or worsening mitral regurgitation, and pulmonary edema. In many patients with CHD, the S_4 is audible.

Electrocardiography

Electrocardiography plays an important role in initial assessment, emergency treatment, prognostication, and subsequent decision-making regarding the definitive treatment of patients with suspected ACS. Because it has high specificity for diagnosing STEMI, electrocardiography remains the test of 1st choice. Complete (>90%) occlusion of the coronary arteries alters the electrical potentials of the epicardial surface and usually manifests itself as ST-segment elevation in 2 or more adjacent leads. Although ST-segment depression—especially an up-sloping ST-segment depression—may be considered the baseline (and stable), ST-segment depression associated with UA/NSTEMI is transient and dynamic. Its appearance is usually flat or down-sloping. Concurrent T-wave inversion may or may not be present.

Patients with suspected ACS must have an ECG performed and interpreted within 10 minutes of their arrival at an emergency department,[38,39] because delays are associated with adverse prognoses and outcomes.[40] Patients found to have ST-segment elevation should be treated according to the American College of Cardiology/American Heart Association (ACC/AHA) STEMI Treatment Guidelines[41] and evaluated for an emergency revascularization procedure. Patients with ST-segment depression, T-wave inversion, nonspecific ST-T-segment abnormalities, or normal electrocardiographic results should be further evaluated according to the ACC/AHA UA/NSTEMI Treatment Guidelines.[38]

TABLE I. Classification of Unstable Angina

Class	Presentation
Rest angina*	Angina occurring at rest; usually prolonged, lasting longer than 20 minutes
New-onset angina	New-onset (within the past 2 months) angina; at least a CCS class III in severity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increasing by 1 or more CCS classes to at least a CCS class III in severity)

CCS = Canadian Cardiovascular Society

*Patients with non-ST-segment-elevated myocardial infarction usually present with angina at rest.

Adapted with permission from: Braunwald E. Unstable angina: a classification. Circulation 1989;80(2):410-4.[37]

Biochemical Markers

When ischemia is prolonged enough to produce myocardial necrosis, the integrity of the myocytic membrane is lost. Cardiac enzymes and other substances then leak into the peripheral blood, and their elevated levels in the bloodstream are indicative of acute myocardial infarction (AMI).

Previously, elevated levels of CK and its cardiac-specific isoform myocardial isoenzyme CK-MB were used to make a diagnosis of AMI. However, a more specific and sensitive immunoassay of cardiac troponins has been developed,[42] and, in the past 10 years, it has been validated and refined through many large clinical trials. Currently, cardiac troponins are the gold standard of biomarkers for establishing a diagnosis of AMI. Any elevation in the circulating levels of these biomarkers also may provide a clinical distinction between UA and NSTEMI.[1]

Cardiac troponins are subunits of the thin-filament–associated troponin-tropomyosin complex, which help regulate muscle contraction. Troponins T and I within cardiac and skeletal muscle are encoded by tissue-specific genes that enable the development of monoclonal antibodies to cardiac troponins.[43] Cardiac troponins are also excellent independent markers of short-term and long-term prognoses.[44] Risk of death within the first 42 days is directly proportional to cardiac troponin levels, and the prognostic information is independent of other clinical and electrocardiographic risk factors (Fig. 3).[45] Therefore, in addition to their significant therapeutic implications (which will be discussed later, in part 2 of this review), they are an invaluable tool in the initial risk stratification of patients with ACS.[28] The glycoprotein (GP) IIb/IIIa inhibitors abciximab and tirofiban have been shown to reduce rates of death and nonfatal MI when given to moderate-to-high-risk UA/NSTEMI patients with elevated cardiac troponin levels. However, patients without elevated troponin levels might not benefit from administration of GPIIb/IIIa inhibitors and can even experience deleterious effects.[46-48]

The release kinetics of troponins T and I are similar—both are detectable in the serum 4 to 12 hours after onset of myocardial necrosis, and both peak 12 to 48 hours from symptom onset. Therefore, serial sampling, including the acquisition of a baseline sample and

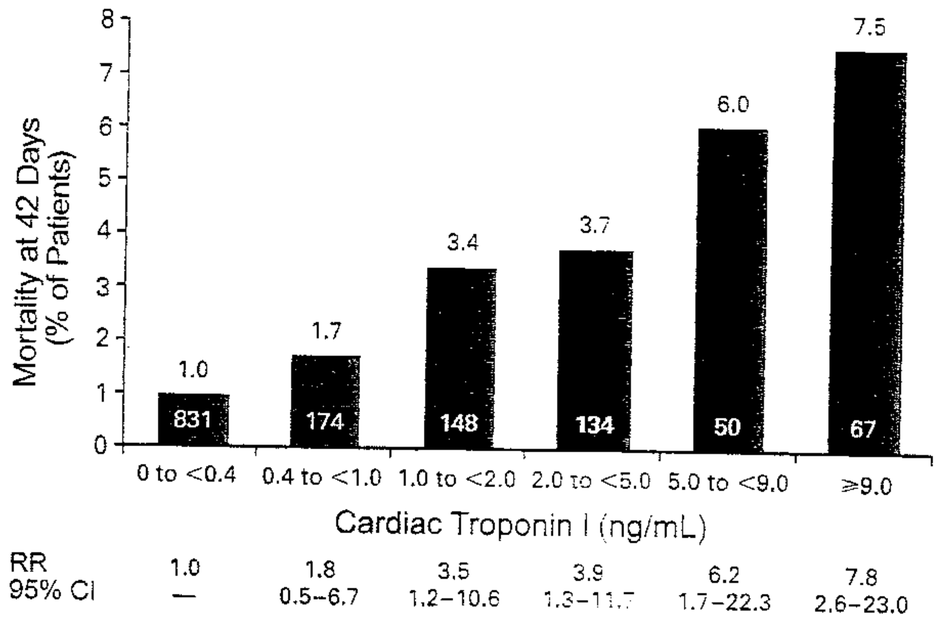

Fig. 3 *Cardiac troponin I levels are an accurate tool for predicting mortality risk in patients with acute coronary syndromes. The number within each bar is the number of patients who had cardiac troponin I levels within each range. The number at the top of each bar is the percentage of patients within each range who died within 42 days. Reprinted with permission from: Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335(18):1342-9.*[45]

CI = confidence interval; RR = risk ratio

a follow-up sample 8 to 12 hours after symptom onset, is recommended. Keep in mind, however, that elevated levels of cardiac troponin signify that ischemia was sufficient to cause myocardial necrosis and that ACS is a continuum of the disease process (plaque rupture and subsequent thrombosis of varying degrees). Heidenreich and colleagues[49] showed in a meta-analysis of 11,963 patients that even in patients without elevated troponin levels, there was a 1.6% incidence of death and a 5.9% incidence of death or AMI at 12 weeks' follow-up.[49]

Risk Stratification

Clinical features, ECG, and cardiac troponin levels are fairly insensitive for immediately ruling out ACS. Given the large number of patients with suspected ACS who are seen every day in emergency departments, it is important to reliably stratify patients who are at high or low risk of an MI and who are likely to have adverse events in the near future. Clinicians' risk assessments of patients begin with 1st contact and continue throughout the hospital stay. It also should guide therapy before hospital discharge, to improve the long-term prognosis. Early risk stratification upon hospital admission also is essential for tailoring the therapeutic plan.

Various risk-stratification algorithms and scores have been developed from results of large clinical trials and registries, many of which have been validated independently in large cohort studies. Perhaps, the 3 most important and widely known risk scores are the Thrombolysis in Myocardial Infarction (TIMI) score,[50] the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) score,[51] and the Global Registry of Acute Coronary Events (GRACE) score.[52] All use a set of variables to identify high-risk patients who may benefit from early revascularization procedures and to predict major adverse cardiac events up to 1 year.

The TIMI risk score for UA/NSTEMI was developed using a derivation cohort consisting of 1,957 patients who were randomly assigned to the unfractionated heparin (UFH) arm of the TIMI IIB trial, which was a phase III, international, randomized, double-blind trial comparing the effects of UFH with those of the low-molecular-weight heparin (LMWH) enoxaparin.[50] The primary endpoint was the composite of all-cause death, new or recurrent MI, or severe recurrent ischemia that prompts urgent revascularization by day 14. It is a simple 7-point score that can be calculated easily at the bedside (Table II).[50]

The TIMI risk score has been used and validated through large clinical trials and has been found helpful not only for initial prognostication, but also for guiding the use of specific therapies, including medical therapy (LMWH and GPIIb/IIIa inhibitors) and early invasive procedures. In fact, patients with higher TIMI risk scores appear to benefit from all 3 therapies. In the TIMI IIB and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial,[53] there was no significant difference in adverse cardiac events occurring in patients with low TIMI scores who were randomized to receive either UFH or enoxaparin. However, as TIMI risk scores increased, so did the absolute and relative risk reduction

TABLE II. The TIMI Risk Score*

Age ≥65 years
At least 3 risk factors for CAD, including a family history, hypercholesterolemia, diabetes, or being a current smoker
Significant coronary artery stenosis (e.g., previous coronary stenosis ≥50%)
ST-segment deviation
Severe angina symptoms (e.g., 2 or more events in the past 24 hours)
Use of aspirin within the past 7 days
Elevated serum cardiac markers

CAD = coronary artery disease; TIMI = Thrombolysis in Myocardial Infarction

*The 7 clinical variables for calculating the TIMI risk score. Each variable is given 1 point, for a total score ranging from 0–7.

Adapted with permission from: Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284(7):835-42.[50]

in adverse cardiac events.[53] Results from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI) trial showed that intermediate- and high-risk patients benefited from a routine early-invasive treatment plan with regard to a composite primary endpoint of death, nonfatal MI, or rehospitalization for ACS.[54]

The GRACE score[52] was derived from the GRACE registry, which includes 94 hospitals of varying sizes located in 14 countries throughout Europe, North America, South America, Australia, and New Zealand. It incorporates 8 independent clinical variables for calculating outcomes, as well as predictive scores for in-hospital deaths and post-discharge deaths at 6 months. The GRACE score is unique in that it includes a variable for renal function within its algorithm. The high prevalence of impaired renal function in older ACS patients makes this feature relevant in daily clinical practice. One drawback of the GRACE score, however, is that it requires the use of a computer program to calculate its rather complex and unequally weighted variables.

In addition to the TIMI risk score and the GRACE score, many other risk scores have been developed, and comparison in clinical trials[55] shows that all have "fair to good" predictive accuracy with regard to death and MI. However, none of these risk scores and algorithms should be used alone to guide the disposition of ACS patients in the emergency department. Even in patients with low TIMI risk scores (0–2), there is still a 5% risk of their having a significant adverse cardiac event within 30 days.[56]

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