Editorial

Management of Acute Coronary Syndromes Based on Risk Stratification by Biochemical Markers

An Idea Whose Time Has Come

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The watchword for modern health care has become cost-effectiveness. This is as true in cardiovascular disease as in any other area of medicine. Hospitalization has been identified as a cost source, and efforts at reducing hospitalizations, length of stay, and unnecessary procedures occupy practitioners and administrators alike. The goal of cost reduction must be balanced with the imperative to provide high-quality patient care. It is ironic that medicine is entering an era with emphasis on cost-effective delivery, while simultaneously, molecular genetics and recombinant DNA techniques are promising a new and exciting paradigm shift to diagnosis, risk stratification, and preventive treatment based on genotyping.1,2 Despite the random coincident timing of these 2 trends, 1 from medical economics and the other from inventive technology, it is hoped that one will not be at the expense of the other. Although the merger will be difficult, it must not lower the quality of health care but rather provide for the implementation of future advances that would better the health of the nation. A major problem for the nation is the $120 billion cost of cardiovascular disease. Unnecessary admission to the hospital of patients with chest pain is estimated to cost more than $12 billion.3 It is hoped that some of these advances can provide high-quality health care and help to contain cost. The cause of chest pain in most patients presenting to the Emergency Department and the most appropriate therapy cannot be reliably ascertained with the conventional clinical armamentarium; this has represented a dilemma for several decades. The use of recombinant DNA techniques to generate recombinant creatine kinase (CK)-MB subforms provided the standards for the development and routine use of the rapid CK-MB subform assay, which excludes or confirms myocardial infarction (MI) within 6 hours of onset of symptoms.4,5 Assays have been developed for 2 new and highly specific markers derived from genes expressed in the fetal and adult heart. These markers, cardiac troponin T6 and cardiac troponin I7 are essential structural proteins of the cardiac muscle sarcomere and are released into the blood to provide a reliable diagnosis within 14 to 16 hours of onset of symptoms. In addition to these quantitative tests performed in the laboratory, qualitative tests that are convenient and rapidly performed at the bedside are also available for troponin T, troponin I, and myoglobin. Thus, simple, rapid, and convenient tests are now available to provide the necessary diagnostic and prognostic information. All of the improved assays (CK-MB, CK-MB subforms, myoglobin, and cardiac troponin I and T) have an assay time of only 20 to 30 minutes and can be performed in any community or larger medical center. Results of a study in this issue of Circulation by the GUSTO II investigators represent an attempt to direct resources such that high-quality care is administered appropriately to all subgroups.8 Improved therapies are emerging in most of the acute coronary syndrome, but their selection and implementation based on triaging with these markers have yet to be evaluated in appropriate large-scale prospective clinical trials.

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Patients presenting to the emergency department with chest pain represent a clinical problem and an opportunity in that the armamentarium now exists to decrease the cost and provide high-quality care. It is estimated that 5 million patients present annually to the emergency room with chest pain and that only a small fraction of these will ultimately be diagnosed with MI. Indeed, from the recently completed multicenter, prospective Diagnostic Marker Cooperative Study of 955 consecutive patients with chest pain, fewer than one third of patients presenting with chest pain were diagnosed as having an acute coronary syndrome (10% with acute MI and 20% with unstable angina).9,10 Although there have been marked advances in the management of patients with acute MI presenting with ST-segment elevation, such advances have not been available for non–Q-wave MI and unstable angina. The proportion with non–Q-wave MI has been steadily increasing, with more than half of all infarctions now classified as non–Q-wave.11,12 ST-segment elevation on the ECG or new left bundle-branch block is highly reliable in identification of patients with MI, because ≥95% will develop infarction. In contrast, ST-segment depression and T-wave inversion (ECG findings in 90% of non–Q-wave MI) are nonspecific and evolve into non–Q-wave MI in <15%, with another 20% having unstable angina and the remainder having either stable angina or non–cardiac-related events.13 This means that the ECG provides a specific diagnosis in ≥40% of patients with acute MI and a specific diagnosis in only ≈5% of all patients presenting with chest pain to the emergency room14; thus the diagnostic dilemma. The thera-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 1998;98:1831-1833.)

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The therapeutic dilemma is perhaps best illustrated by the results of the TIMI IIIB trial, in which administration of a thrombolytic to patients with unstable angina led to an increased incidence of death and infarction and provided no demonstrable benefit to patients with non–Q-wave MI.15 We are currently on the eve of improved therapies for unstable angina and perhaps non–Q-wave MI. Platelet IIb/IIIa inhibitors have recently been demonstrated to improve outcome in patients with unstable angina in 4 clinical trials (PARAGON, PRISM, PRISM PLUS, and PURSUIT).16 Furthermore, the FDA has just approved their use in unstable angina. Whether similar or different strategies might benefit non–Q-wave MI remains to be demonstrated. However, given the clear negative impact of thrombolysis in unstable angina and the possibility that outcomes from non–Q-wave MI may be improved by different treatments than unstable angina, it becomes even more important to distinguish unstable angina from infarction in patients as quickly as possible after presentation to the emergency department.

Coincident with improvements in treatment, developments in diagnostic testing and risk stratification have occurred. For 2 decades, the standard biochemical marker for confirming the diagnosis of MI has been the MB fraction of CK, which reliably excludes or includes MI at ≥12 hours after symptom onset. New diagnostic markers like myoglobin, CK-MB subforms, and the cardiac-specific troponins (I and T) offer the promise of improved diagnosis and risk stratification of patients with chest pain. Several clinical trials have demonstrated a worse prognosis for patients with chest pain and positive markers.17 One of the largest series published to date was that of the GUSTO IIA troponin substudy.18 Increased levels of troponin T in patients with unstable angina and nonspecific ECG changes were shown to be highly predictive of cardiac events at 30 days. Of 801 patients with unstable angina, troponin T was increased in 36% on admission, and the 30-day mortality for those patients with a positive baseline was 11.8%, compared with 3.9% for those patients negative for troponin T. In this issue of Circulation, the GUSTO IIA investigators report1 the added prognostic value from measurements of troponin T beyond the initial presentation in the same patient population with acute coronary syndromes. There were 734 patients who presented within 12 hours of onset of suspected ischemic symptoms with ECG changes of ST-segment elevation, depression, or T-wave inversion who underwent serial troponin T sampling and were followed up for the incidence of infarction, congestive heart failure, shock, and revascularization. In this study, samples obtained at 8 and 16 hours after presentation detected a cumulative total of 75% of patients positive for troponin T. At baseline, 264 patients were positive for cardiac troponin T, whereas by 16 hours after presentation, an additional 323 patients became positive and 151 remained negative. The mortality at 30 days was highest in the baseline-positive group (10%), followed by a mortality of 5% in the late-positive patients and a mortality of 0% in those persistently negative. After adjustment for baseline characteristics, an increased level of cardiac troponin T was found to be strongly predictive of mortality at 30 days. Most of the mortality difference between cardiac troponin T–positive and –negative patients occurred within the first 30 days. The authors note that patients positive at baseline or at 16 hours had a longer duration of symptoms than those who became positive only at 16 hours or remained persistently negative. In addition, those patients who were positive at baseline tended to be older. Patients with ST-segment elevation were most likely to ultimately develop a positive troponin, whereas patients with T-wave inversion or normal ECGs were least likely to be positive. In the recent 6-month follow-up of the Diagnostic Marker Cooperative Study, all of the markers of cardiac injury (troponin T, troponin I, myoglobin, CK-MB subforms, CK-MB mass, and CK-MB activity) were compared for risk stratification, and all were shown to be highly predictive of adverse events and mortality at 6 months after entry.9 Samples obtained for CK-MB subforms and myoglobin within the first hour of presentation to the emergency room confirmed the diagnosis in 80% and 68%, respectively, of patients with MI and were highly predictive of clinical events in the subsequent 6 months.9

The release of various markers of cardiac injury is influenced by a number of factors. Time from onset of symptoms, molecular weight of the marker, site of localization of the marker within the cardiomyocyte (structural protein versus free in the cytosol), and the clearance of the marker may all influence positivity on blood sampling. The temporal characteristics of release of a marker from the myocardium into the plasma are important. Proteins present in the cytosol, such as myoglobin and CK-MB, are released more rapidly after the onset of symptoms than structural proteins. For example, plasma levels of myoglobin are increased to diagnostic levels in the plasma in the majority of patients suffering MI within the first 2 to 4 hours after onset, as is the CK-MB subform. In contrast, the cardiac troponins are structural proteins; they are released more slowly and do not reach diagnostic plasma levels in most patients until 14 to 18 hours. Thus, in contrast to the rapid release of CK-MB subforms or myoglobin, the troponins cannot be used to reliably exclude infarction until at least 12 to 16 hours after symptom onset. This is emphasized in the present study, in which only 36% had increased cardiac troponin T at baseline, and two thirds of the patients who subsequently exhibited increased cardiac troponin T did not do so until 16 hours from onset. For optimal triage and risk stratification in the emergency department, early markers of myocardial injury, ie, CK-MB subforms or myoglobin, appear preferable to avoid unnecessary delays, such as may be required for the cardiac troponin markers.

Whether release of troponin T reflects myonecrosis or may occur in the setting of ischemia without infarction is unclear. In a recent experimental study performed in conscious dogs, irreversible myocardial injury induced by complete coronary occlusion (15 to 20 minutes) and confirmed by electron microscopy 72 hours later was associated with increased serum CK, whereas severe myocardial ischemia (glycogen depletion and cell swelling) induced by shorter duration of coronary occlusion was not associated with elevations of serum CK.19 Although it is a cytosolic protein, CK-MB has a molecular weight of 84 000, which explains its lack of release in ischemia without infarction. Thus, CK-MB release reflects myonecrosis. Despite claims that the troponins may be
released in the setting of ischemia without necrosis, these molecules are structural proteins, and their release most likely reflects myocardial necrosis. The prognostic power of a positive troponin T in the present study was most potent as a predictor of cardiac events occurring in the subsequent first 30 days, an observation consistent with the interpretation that release of cardiac troponins signifies necrosis. In contrast, myoglobin is a small (17 000 MW) cytosolic protein and conceivably could be released after an ischemic reversible insult. Thus, a conundrum of infarction versus ischemia exists and remains to be fully resolved. The clinical implications of this conundrum are not trivial. Although unstable angina and MI exist as part of the spectrum of acute coronary syndromes, their responses to therapeutic strategies may differ.

The elegant demonstration by the GUSTO IIa investigators of the prognostic power of troponin T both at baseline and with serial measurements is in concert with similar studies using troponin I, CK-MB, and CK-MB subforms. The ability of these markers to identify high-risk patients with acute ischemic syndromes provides the opportunity to affect those at greatest risk. These results emphasize the need for large-scale clinical trials to evaluate the hypothesis of early treatment of high-risk patients as identified by diagnostic markers. Although all of the markers appear to be prognostically important, the greatest utility is likely to occur with the use of diagnostic markers released early after symptom onset. Patients at low risk could be assigned to less expensive diagnostic and treatment algorithms without affecting morbidity and mortality, whereas high-risk patients might have improved outcomes from more aggressive therapy. Studies such as the present GUSTO substudy and others have shown that the diagnostic and prognostic dilemma of triaging patients into high- and low-risk categories has essentially been solved. Rapid early triaging on presentation is available with a variety of markers. We look forward to this next step in the application of diagnostic markers and the evolution of appropriate, high-quality, and cost-effective therapy.

References
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Circulation. 1998;98:1831-1833
doi: 10.1161/01.CIR.98.18.1831

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/98/18/1831

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