

review

Acute Coronary Syndrome*

Biochemical Strategies in the Troponin Era

Mauro Panteghini, MD

New biomarkers, such as cardiac troponins, have a major role to play for cost-effective management of individuals with acute chest pain and suspected coronary syndrome, and the laboratory is now poised to assume a vital role in assessing damage and determining prognosis. The redefined biochemical criterion proposed to classify acute coronary syndrome patients presenting with ischemic symptoms as patients with myocardial infarction is heavily predicated on an increased troponin concentration in blood. In an era of evidence-based medicine, we can no longer overlook the diagnostic and prognostic benefits provided by the measurement of these highly sensitive and specific proteins. (CHEST 2002; 122:1428–1435)

Key words: emergency medicine; laboratory diagnosis; myocardial infarction; myoglobin; troponin

Abbreviations: AMI = acute myocardial infarction; CK = creatine kinase; C-SMCD = Committee on Standardization of Markers of Cardiac Damage; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variation; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine; TIMI = Thrombolysis in Myocardial Infarction; URL = upper reference limit.

Proper evaluation of the patient with acute chest pain is a resource-intensive and expensive process.¹ Critical to the effective management of these patients is the early recognition of a cardiac ischemic event and the proper placement of the patient in the risk spectrum of acute coronary syndrome.² With increasing economic pressures on health care, physicians, health plans, and medical centers are interested in improving the efficiency of care for patients with acute chest pain. This interest recently reinforced the need for a better diagnostic approach to patients with suspected acute coronary syndrome and, consequently, the need for a new standard definition of acute myocardial infarction (AMI) and of risk determination.³

For much of the past 3 decades, acute ischemic heart disease has been regarded as a binary phenomenon, AMI or non-AMI, using World Health Organization recommendations that included fulfillment of at least two of the three well-known diagnostic criteria: a history of acute, severe, and prolonged

chest pain; presence of significant changes in ECG; and unequivocal abnormal elevation of traditional enzyme activities in serum.⁴ Chest pain is, however, an unreliable indicator: up to 33% of patients with AMI may have no chest pain and are clinically silent on presentation to the hospital.⁵ The ECG remains the cornerstone for the early diagnosis of acute ischemia, showing ST-segment change within seconds of the ischemic insult in approximately 60% of patients. However, the ECG can be inconclusive in the remaining 40% of cases, therefore showing a globally low sensitivity.⁶ Also well known are the imperfect sensitivity and specificity of the traditional enzymatic markers for the detection of myocardial injury.⁷

In this historical context, the risk of misdiagnosis was therefore relatively high. Several studies estimated that 2 to 8% of patients with AMI were inadvertently sent home from emergency departments because of the diagnostic limitations of the ECG and of measurements of classic enzymes.⁸ Inappropriate early discharge also resulted in significantly higher morbidity and mortality.^{9,10}

THE TROPONIN ERA

Considering these pitfalls in the traditional criteria for diagnosis of AMI and the excellent findings of

*From the Laboratorio Analisi Chimico Cliniche 1, Azienda Ospedaliera 'Spedali Civili,' Brescia, Italy. Manuscript received September 11, 2001; revision accepted January 30, 2002.

Correspondence to: Mauro Panteghini, MD, Laboratorio Analisi Chimico Cliniche 1, Azienda Ospedaliera 'Spedali Civili', 25125 Brescia, Italy; e-mail: panteghi@bshosp.osp.unibs.it

several clinical trials using highly sensitive and specific markers of heart muscle damage that are not themselves enzymes, such as cardiac troponins, the Committee on Standardization of Markers of Cardiac Damage (C-SMCD) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) made in 1999 a recommendation to expand on the enzyme diagnostic criteria for AMI to include cardiac-specific proteins.¹¹ However, the C-SMCD considered that it was the responsibility of cardiology groups, and not laboratorians, to officially redefine the biochemical criterion for diagnosis of AMI. The consensus document¹² recently published by the European Society of Cardiology and the American College of Cardiology is therefore the appropriate next step, making specific new recommendations on the use of biomarkers for the detection of myocardial necrosis. In particular, the document considers as the best biochemical indicator for detecting myocardial necrosis “a concentration of cardiac troponin exceeding the decision limit on at least one occasion during the first 24 h after the onset of clinical event.”¹² The use of creatine kinase (CK)-MB, measured by mass assays, is still considered as an acceptable alternative if cardiac troponin assays are not available.¹² The redefined criterion used to classify acute coronary syndrome patients presenting with ischemic symptoms as AMI patients is therefore heavily predicated on an increased cardiac troponin concentration in blood.

Cardiac troponins are correctly regarded as the most cardiac-specific of currently available biochemical markers for the diagnosis of myocardial injury.¹³ In particular, cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have been identified. These proteins are associated with specific amino acid sequences encoded by genes different from those encoding skeletal muscle isoforms. While cTnI has been shown to have complete specificity for cardiac muscle, cTnT is present in small amounts in skeletal muscle during human fetal development and is reexpressed during diseases that involve skeletal muscle regeneration (*eg*, Duchenne muscular dystrophy).¹⁴ The cumulative data indicate that troponins appear in the serum relatively early after AMI onset (4 to 10 h), peak at 12 to 48 h, and remain abnormal for 4 to 10 days (Fig 1). These release kinetics can be accounted for by examining the distribution of the proteins within the myocardial cell. The great majority of both cTnI and cTnT is bound to the myofibril (94 to 97%), and a relatively small amount (approximately 3% for cTnI and 6% for cTnT, respectively) is free in the cytoplasm. After a cardiac cell is injured and the free cytoplasmic pool is immediately released, there is slow continuous release of the myofibril-bound proteins, which re-

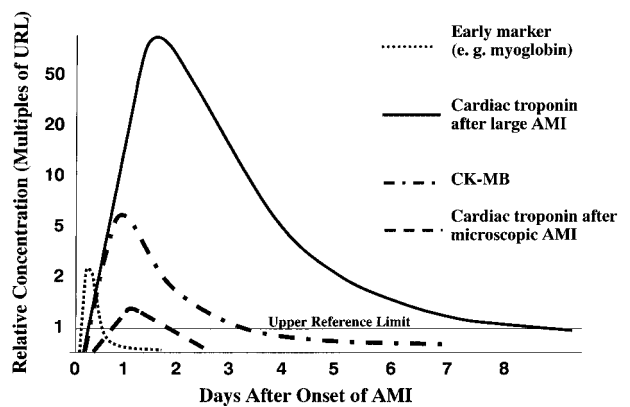


FIGURE 1. Time course of release of cardiac proteins in blood after AMI. “Large” and “microscopic” AMI are definitions derived from Alpert et al.¹²

sults in the observed prolonged troponin elevations noted before.⁷ Although cTnI and cTnT exhibit a similar clinical performance, there are some differences in analytical, biochemical, and clinical characteristics of these proteins (Table 1).¹⁵ Finally, it should be remembered that cardiac troponins reflect myocardial damage but do not indicate its mechanism.¹² Thus, an elevated value in the absence of clinical evidence of ischemic heart disease should prompt a search for situations in which various degrees of myocardial injury may be present (Table 2).

In the foreseeable future, cardiac troponins will largely replace CK-MB testing as the “gold standard,” especially in any setting where the specificity of CK-MB is in doubt, as in any cause of acute or chronic muscle injury or in patients undergoing surgical procedures.¹⁶ Some cardiologists however still express concerns about totally replacing CK-MB.¹⁷ Many physicians use the peak serum concentration of this isoenzyme to qualitatively estimate infarct size. Others have questioned the use of serial troponin measurements for monitoring reinfarction

Table 1—Comparison of cTnT and cTnI

cTnT	All assays marketed by one manufacturer; good standardization
	Earlier detection and longer permanence in blood after myocardial infarction
	More clinical validation studies performed with the same assay
	Possibility of false-positive results in patients with myopathies
cTnI	Assays manufactured by several companies
	Lack of standardization between assays; impossible to compare results obtained with different assays
	Analytical performance of different assays not comparable
	No increase observed in patients with skeletal muscle myopathy

Table 2—Elevation of Cardiac Troponins in Patients Without Overt Ischemic Heart Disease

Cardiac trauma (including contusion, ablation, pacing, firing, cardioversion, cardiac surgery)
Congestive heart failure
Hypertension
Hypotension, often with arrhythmias
Postoperative noncardiac surgery
Chronic renal failure
Critically ill patients, especially with diabetes
Hypothyroidism
Myocarditis
Pulmonary embolism
Sepsis
Amyloidosis
Cardiotoxicity from cancer therapy

(because of the prolonged release pattern) and suggest a continuing role for CK-MB for this purpose. With regard to the first point, it was recently showed that a single measurement of plasma cTnT concentrations performed at the time corresponding to the slow continuous release after AMI, regardless of the kinetic of marker appearance in blood, can be used as a convenient and cost-effective, noninvasive estimate of infarct size, revealing a similar reliability as peak CK-MB measurement (requiring repetitive sampling) or nuclear imaging (too expensive to be routinely used).¹⁸ If the major concern about totally replacing CK-MB with cardiac troponins in hospital institutions is the lack of evidence on the ability of troponins to estimate the infarct size, these findings may thus support the definitive implementation of cardiac troponin testing and the replacement of CK-MB in the laboratory cardiac panel.

It may also be appropriate to monitor the continuing decline of CK-MB daily to show an extension of the infarct. In an experience, only 3% of patients with AMI had a reinfarction during the stay in coronary care unit.¹⁹ Consequently, the standard monitoring of this marker to obtain this information could not be cost-effective. Anyway, if laboratories have to retain CK-MB for this use, the recommendation is to use the mass assays, which have been shown to be clearly superior to activity-based assays (such as immunoinhibition or electrophoresis).²⁰

THE BIOCHEMICAL STRATEGY

An important point concerns the selection of the most appropriate strategy for the use of new markers and the suggested sample frequency in patients with chest pain and without ECG evidence of AMI at hospital admission. In fact, the excitement of new

applications in the use of biomarkers to improve routine patient care can be offset by angst regarding the appropriate selection and utilization of currently available and new assays.

Two strategies have competed in this area. The first relies on the use of a combination of two markers—a rapid rising marker, such as myoglobin, and a marker that takes longer to rise but is more specific, such as cardiac troponin—to enable detection of AMI in patients who present early and late after symptom onset.^{11,17} As demonstrated in a systematic review of literature, myoglobin is the marker that currently most effectively fits the role as an early marker.²¹ Myoglobin is detectable in blood as early as 2 to 3 h after onset. Its concentration appears to peak quickly, reaching the maximum level between 6 h and 12 h after the onset of symptoms. It then falls to normal levels over the next 24 h, rapidly cleared from the serum by the kidneys (Fig 1). Measurement of myoglobin has the merit of a robust scientific evidence, with > 30 studies published on the use of this protein as an early sensitive marker for excluding AMI.²¹ Myoglobin has therefore potential utility as test for excluding early AMI in patients presenting to the emergency department with chest pain. The negative predictive value of this marker for excluding early infarction 4 h after hospital admission is virtually 100%.²²

This two-marker strategy is predicated on the assumption that early diagnosis of AMI will change care by providing the ability to discharge patients earlier, thus improving flow within the emergency department setting, and by facilitating identification of patients who may be candidates for aggressive interventions and, more generally, facilitating the triage of patients who are admitted to various parts of the hospital. Zaninotto et al²³ clearly documented the high performance of the two-marker approach, showing that the combination of myoglobin and troponin significantly improves the clinical predictive values of standard CK-MB alone irrespective of the disease prevalence. More recently, Caragher et al²⁴ reported their experience in the use of the two-marker protocol for diagnosis of chest pain at a midsize community hospital in the suburbs of Chicago. Considering acute coronary syndrome-negative patients, the percentage of patients discharged in < 1 day rose from 28% in the control group using traditional enzymatic approach to 50% in the group evaluated by the two-marker protocol.²⁴ Patients discharged in less than half a day also rose from 22% in the control group to 37% in the test group.²⁴ The diagnostic information provided by the two-marker strategy significantly improved the accuracy and

timeliness of diagnosis of acute coronary syndrome while reducing length of stay and patient episode cost.²⁴

The second strategy suggests that the urgency is less critical than suggested by the first strategy. The tactic involved is simply to measure cardiac troponin, with the understanding that definitive exclusion or inclusion of AMI will take longer.¹¹⁻¹³ The logic of this strategy insists that for those hospitals who do not have an area for rapid rule-out of patients with chest pain, and therefore patient triage decisions are not made within the first few hours after hospital admission, the use of an early marker is unnecessary. In this case, only measurement of cardiac troponin is suggested with a sampling frequency of admission, 6 h, and 12 h. Once again, if compared with the traditional enzymatic approach, this protocol is markedly effective in altering patient management by enabling early discharge of patients, resulting in significant cost savings and increasing bed availability without compromising patient outcome.²⁵

Coming back to the sampling protocol for detection of AMI using the strategy employing early and late markers, the IFCC C-SMCD recommends specimen collection at hospital admission, and 4 h, 8 h, and 12 h later.¹¹ This approach enables association of the high predictability of myoglobin in excluding AMI within 4 h after hospital admission and the diagnostic power of a single positive result for troponin that would trigger a diagnosis of myocardial necrosis, without the need for completing the necessary sequence of blood samples at every time point.²⁶ The question of whether zero time in the protocol should be assigned to the onset of chest pain or to presentation to the hospital is debatable.²⁷ Patients with large infarcts tend to have a clear-cut start to the symptoms and to present early, but normally these are not the patients in whom there is any doubt about the need for hospital admission. In the patients with no ECG changes and possible small myocardial damage, the symptoms may have a stuttering start and undergo a waxing-and-waning time course that mirrors the waxing-and-waning myocardial ischemia. It is not uncommon for these patients to report multiple episodes of chest pain over the hours and days prior to hospital admission. Studying a consecutive series of approximately 250 patients with AMI, Bholasingh et al²⁸ showed an inaccurate estimation of time interval between onset of symptoms and admission in about 15% of them. The suggestion is therefore that, for routine clinical practice, blood collections should be referenced relative to the time of presentation to the hospital: the use of the recommended early and late marker combination will permit infarct timing in any case.¹¹

SELECTION OF DECISION LIMITS FOR TROPONIN USE

One of the most important problems in the practical use of the cardiac-specific troponins is the right definition of decision limits. The basic question is, "How much necrosis is needed to make the diagnosis of AMI?"²⁹ In the purest physiologic sense, the answer is that any detectable necrosis is an AMI. Consequently, even small elevations of specific markers of myocardial damage, such as cardiac troponins, should be acknowledged as indicative of significant injury, reflecting the incremental risk associated with increasing concentrations of the marker, consistent with the continuous injury concept of acute coronary syndrome.¹² From a clinical perspective, there is clear evidence that any amount of detectable cardiac troponin release is associated with an increased risk of new adverse cardiac events. Currently available data demonstrate no threshold below which elevations of troponin are harmless and without negative implications for prognosis. For cTnT, the original Fragmin During Instability in Coronary Artery Disease study already showed the continuous relation between marker concentrations and the risk of clinical events.^{30,31} More recently, the second Fragmin During Instability in Coronary Artery Disease study confirmed that optimal risk stratification in patients with acute coronary syndrome can be achieved with use of a cutoff concentration around the detection limit of the cTnT assay (*ie*, 0.03 $\mu\text{g/L}$) instead of the suggested higher cutoff of the manufacturer (*ie*, 0.10 $\mu\text{g/L}$).³² Similar results were originally demonstrated for cTnI in the Thrombolysis in Myocardial Infarction (TIMI)-IIIB trial and more recently confirmed in TIMI-11B substudy, where use of the upper reference limit (URL) concentrations produced significant odds ratios with the three cTnI assays employed.^{33,34}

On the basis of all these evidences, the cardiologists' consensus document quoted earlier defines myocardial necrosis as an increase of cardiac troponin values exceeding the upper limit of the normal healthy population, set at the 99th percentile of value distribution to limit the number of false-positive designations of myocardial injury.¹² Pragmatically, the use of this approach as a diagnostic criterion for AMI will lead to an increase of the numbers of infarct patients in the acute coronary syndrome population from 15 to 30%.³⁵⁻³⁷ However, the document emphasizes that in applying the proposed new diagnostic criteria to clinical practice, patients should not be labeled simply as "myocardial infarction," but rather as patients with coronary artery disease in whom the extent of myocardial necrosis should be clearly defined as microscopic, small, medium or

large and possibly related to the current left ventricular function.¹² However, increasing diagnostic sensitivity for AMI can have a positive impact on society, resulting in more cases identified, thereby allowing appropriate secondary prevention and hopefully reducing health care costs in the future. In a recent study,³⁶ the patients who had an AMI diagnosis made solely on the basis of a positive troponin value experienced a threefold increase in short-term mortality when compared to normal troponin group.

According to the suggestions of the cardiologists' document, the diagnostic manufacturers must now provide on the package insert sheet the 99th reference limit of the specific troponin assays, based on information available from peer-reviewed literature and obtained using the IFCC recommendations on the theory of reference values.^{38,39} Lacking between-assay standardization, reference limits need to be determined separately for each assay and platform, even if available from the same manufacturer.^{40–42} This information should be available along with the level of analytical imprecision of the assay at this concentration limit.⁴³ Accurate discrimination between “minor” myocardial injury vs analytical noise requires assays that have high precision at low troponin concentrations.⁴⁴ For clinical use, the IFCC C-SMCD recommends for troponin assays a total imprecision, expressed as coefficient of variation (CV), of < 10% at the AMI decision limit.⁴⁵ A failure to reach this goal could increase the risk of reporting misleading results that will either prompt unnecessary confirmatory testing, as in the case of artifactually abnormal concentrations, or lead to clinical inaction when inappropriately low concentrations are reported for patients. This places a large responsibility on the manufacturers of troponin as-

says to ensure that their assays have the necessary precision to permit the use of the proposed cutoff, *ie*, the 99th percentile limit of the reference population. From this point of view, not all the troponin assays presently perform equally well in routine clinical settings, and many commercially available assays cannot indeed meet the 10% CV recommendation at the 99th percentile values (Table 3). Clinical laboratories should therefore consider more carefully the effect of imprecision on clinical decision making when they implement an assay for troponin determination. However, manufacturing industries should carefully consider this critical issue because diagnostic and therapeutic decisions will be based on lower cardiac troponin cutpoints in the future.

From a practical point of view, in the context of clinical practice, for troponin assays that cannot presently meet the 10% CV at the 99th percentile value, a predetermined higher concentration that meets this imprecision goal should be used as cutoff for infarction until the goal of a 10% CV can be achieved at the 99th percentile (Table 4).⁵⁹ Of course, this could decrease the overall clinical sensitivity of the assay.

BIOMARKERS IN ST-SEGMENT ELEVATION OF MYOCARDIAL INFARCTION

As previously stated, since the sensitivity of the initial ECG is only 60% for detecting AMI, the use of the new biochemical markers may significantly contribute to the early diagnosis and become relevant just when ECG is not diagnostic. Conversely, there is no need for the use of any biochemical marker when the clinical diagnosis of AMI is unequivocal. In these

Table 3—Total Imprecision Around the Diagnostic Cutoffs of Commercial Assays for Cardiac Troponin Determination

Company/Platform	Troponin Concentration, µg/L	Total Coefficient of Variation, %	Source
Abbott/AxSYM	2.90	10.0	Apple et al ⁴⁶
Bayer/ACS:180	1.33	4.1	Pagani et al ⁴⁷
Bayer/ACS:Centaur	0.52	13.0	Stiegler et al ⁴⁸
Bayer/Immuno 1	1.00	4.9	Wu ⁴⁹
Beckman/Access second generation	0.09	10.0	Wu et al ⁵⁰
BioMerieux/Vidas	0.27	8.4	Bataillon et al ⁵¹
Biosite/Triage	0.34	19.5	Wu ⁴⁹
Dade/Dimension RxL second generation	0.14	11.4	Kaminski et al ⁵²
Dade/Opus second generation	1.70	25.6	Kao et al ⁵³
Dade/Stratus CS	0.08	14.0	Altinier et al ⁵⁴
DPC/Immulite	1.00	9.8	Kao et al ⁵³
First Medical/Alpha Dx	0.30	7.4	Apple et al ⁵⁵
Ortho-Clinical Diagnostics/Vitros	0.35	10.0	Apple et al ⁵⁶
Roche/Cardiac Reader	0.33	18.0	Muller-Bardorff et al ⁵⁷
Roche/Elecsys third generation	0.11	3.6	Pagani et al ⁵⁸

Table 4—Implication of the Analytical Imprecision of Some Troponin Assays for the Diagnosis of AMI

Company/Platform	Calculated 99th URL*	Concentration Associated With a 10% Coefficient of Variation†
Abbott/AxSYM	0.50 µg/L‡	2.90 µg/L (5.8 × URL)§
Bayer/ACS:Centaur	0.15 µg/L‡	1.40 µg/L (9.3 × URL)§
Dade/Dimension RxL first generation	0.05 µg/L‡	0.40 µg/L (8 × URL)§
DPC/Immulite	0.40 µg/L‡	1.20 µg/L (3 × URL)§
Ortho-Clinical Diagnostics/Vitros	0.10 µg/L‡	0.35 µg/L (3.5 × URL)§
Roche/Elecsys third generation	0.01 µg/L‡	0.03 µg/L (3 × URL)§

*Troponin cutoff for AMI, as suggested by European Society of Cardiology/American College of Cardiology Committee.¹²

†Troponin cutoff for AMI, as suggested by IFCC C-SMCD.⁴⁵

‡Based on manufacturer information.

§Based on Apple et al,⁴⁶ Stiegler et al,⁴⁸ Kao et al,⁵³ Apple et al,⁵⁶ Hafner et al,⁶⁰ and Hallermayer et al.⁶¹

patients, biochemical marker testing is indeed unnecessary for diagnostic purposes, being the ECG changes, namely ST-segment elevation > 1 mm in two or more contiguous leads, not very sensitive but highly specific.⁶ The ST-segment elevation reflects a transmural myocardial ischemia caused by an occlusive thrombosis in the coronary vessel supplying the corresponding myocardium. The goal of the treatment is to reopen the occluded coronary artery as soon as possible by thrombolysis or acute angioplasty, and the results of measurements of marker proteins must not be awaited before recanalization therapy is initiated.

In this group of patients, biochemical marker testing may be valuable for confirmation of diagnosis, and may be useful to qualitatively estimate the size of the infarction and to stratify the subsequent risk early, to detect the presence of complications such as a reinfarction, and to monitor thrombolytic therapy. Clinical studies have shown that the hospital admission concentration of cardiac troponin may contain prognostic information. In the Global Use of the Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes-IIa study, 30-day mortality was only 5% in AMI patients with a normal troponin level at hospital admission, while the mortality was 13% in patients who presented with an elevated troponin value.⁶² Similar results were observed in the study by Stubbs et al.⁶³ In this trial, infarct with ST-segment elevation and a positive cTnT finding on hospital admission was associated with a threefold higher cardiac event rate than infarct with a negative cTnT hospital admission value, and the observed hazard persisted for up to 3 years of follow-up.⁶³ These data were confirmed in the Global Use of the Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes-III study, where the 30-day mortality rate was 6.2% in patients who were cTnT negative on hospital admis-

sion vs 15.7% in cTnT-positive patients.⁶⁴ The mechanisms behind this difference are not fully elucidated. One possible explanation might be a less successful reperfusion, deriving from a lower efficiency of thrombolytic therapy, in patients with elevated troponin on hospital admission. Whether direct angioplasty can improve the current morbidity in this patient group awaits randomized studies, so that the therapeutic implications of this finding remain speculative.⁶⁵ Two additional studies have found that an elevated troponin level on hospital admission also predicts higher rates of failed primary percutaneous coronary interventions in patients with ST-segment elevation AMI.^{66,67}

A variety of efforts over many years have attempted to diagnose reperfusion predicated on changes in marker proteins. A review of these efforts showed studies involving 460 patients that monitored various cardiac markers following thrombolytic therapy using different evaluation approaches: slopes, ratios, absolute differences, etc.⁶⁸ Unfortunately, even the best data heretofore have been unable to separate TIMI-II from TIMI-III flow in the revascularized coronary artery. Thus, until and unless marker protein analysis can achieve the ability to detect TIMI-III from TIMI-II flow that may still require intervention, it is unlikely to become a routine part of the cardiologist armamentarium for the evaluation of this particular clinical problem.⁶⁹

In conclusion, new biochemical markers are integral to the diagnosis and management of patients in whom acute coronary syndrome is suspected. The role of biochemical testing as a part of a structured decision-making protocol is to provide accurate and timely information that can be used to guide patient management. In this respect, the diagnostic superiority of the new markers of myocardial damage

opens fascinating perspectives for the triage and management of patients with acute myocardial ischemia.

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