Cardiac Biomarkers for Better Management of Acute Coronary Syndromes

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Abstract
Acute myocardial infarction (AMI) causes significant mortality and morbidity. Timely diagnosis allows clinicians to risk stratify their patients and select appropriate treatment. Biomarkers have been used to diagnose or rule out AMI. An increasing number of novel biomarkers have been identified to predict the outcome following AMI or acute coronary syndrome (ACS). This may facilitate tailoring of appropriate therapy to high-risk patients. This review focuses on a variety of promising biomarkers which provide diagnostic and prognostic information.

Introduction
Coronary artery disease (CAD) is the leading cause of death among adults and one of the most common reasons for emergency department (ED) visits. Although the standard 12-lead electrocardiogram (ECG) is the single best test to identify patients with acute ST elevation myocardial infarction (STEMI) upon ED presentation, it still has relatively low sensitivity (only 35% to 50%) for detection of acute myocardial infarction (AMI).¹

Cardiac biomarkers are measurable and quantifiable biological parameters which are detected in the blood and serve as indices for physiological and pathophysiological assessments by a specialized immunoassay. In a subject having chest pain along with ECG changes, the elevation of cardiac biomarkers helps to differentiate non-ST segment elevation MI (NSTEMI) from STEMI.² The joint European Society of Cardiology/American College of Cardiology³ has proposed criteria for the diagnosis of AMI as shown in Table 1.

The annual incidence of acute coronary syndromes (ACS) is approximately 3 per 1000 in general population, but varies between countries.⁴ Hospital mortality is higher in patients with STEMI than among those with NSTEMI 7% vs. 35% respectively, but at 6 months the mortality rates are very similar in both conditions 12% and 13% respectively.⁵ Registry data consistently showed that NSTEMI is more frequent than STEMI.⁶ It is estimated that 34% of all ACS events are repeat events, in line with recent data from the Global Registry of Acute Coronary Events (GRACE).⁷ CAD has assumed an epidemic proportion in India. Over 80% of deaths and 85% of disability from cardiovascular disease (CVD) occur in low- and middle-income countries. India is often considered to be the region with highest burden of CVD.⁷

An interesting fact is that CAD affects Indians with greater frequency and at a younger age as compared to the developed countries, as well as many other developing countries. Age-standardized CVD death rates in people between 30-69 years old are 180 per 100,000 in Britain, 280 per 100,000 in China, and 405 per 100,000 in India. Also, 50% of CAD-related deaths in India occur in people <70 years of age, whereas only 22% of CAD-related deaths in Western countries occur in this age group.⁸

Table 1: Criteria for diagnosis of AMI¹

Clinically
Typical rise and gradual fall (troponin [at least value above the 99th percentile of the upper reference limit]) or more rapid rise and fall (creatine kinase-MB) of biochemical markers with at least one of the following:

- Ischemic symptoms
- Development of pathologic Q waves on electrocardiogram
- Electrocardiographic changes indicative of ischemia (ST segment elevation or depression)
- Coronary artery intervention (e.g., coronary angioplasty)

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Received: 21.04.2014; Accepted: 28.05.2014
Why Do We Need Biomarkers for Diagnosis?

ACS is a result of numerous pathophysiological events like (1) plaque rupture with acute thrombosis, (2) progressive mechanical obstruction, (3) inflammation, (4) secondary unstable angina, and (5) dynamic obstruction (coronary vasoconstriction). The cardiac biomarkers now help the physicians to understand the degree of inflammation, myocyte necrosis, vascular damage and hemodynamic stress contributing to ACS. These levels of biomarkers non-invasively demonstrate the pathogenic changes in the heart (Figure 1). As seen in Figure 1, the detection of cardiac troponins in the blood of patients with ACS is indicative of myocardial necrosis with the presence of intracoronary thrombus and distal embolization of platelet microaggregates.9

Though myoglobin is released early in circulation 2-3 hrs after onset of damage to the myocardium, it peaks at 8-12 hours and returns to normal within 24 hours. Though myoglobin can be detected early in the blood it lacks cardiac specificity.2

These sensitive biomarkers (Figure 2) guide the clinician in early management of myocardial ischemia to prevent necrosis with treatments such as fibrinolysis, coronary artery bypass grafting and percutaneous coronary interventions for improving outcomes.10

An ideal biomarker indicative of cardiac necrosis should exhibit cardiac specificity, early and stable release after necrosis, predictable clearance and measurable quantitatively using rapid, cost-effective methodologies and must be available in most of the laboratories. The knowledge of optimal use of cardiac biomarkers is essential to the clinician. For example, biomarkers having high positive-predictive values are suitable for aggressive management of patients at high risk of cardiovascular complications. On the other hand, not all the patients with clinical symptoms suggestive of ACS are likely to have myocardial necrosis, therefore, these highly positive-predictive biomarkers can rule out ACS. Use of combinations of cardiac biomarkers is more effective in diagnosis and stratification ACS.11

Cardiac Troponins

Creatine kinase (CK) and the MB isoenzyme (CK-MB) have been accepted as the best biochemical assays for AMI. However a lack of cardiac specificity (producing false-positives) and a narrow time-window limit their clinical utility. The ongoing search for better biochemical markers of myocardial necrosis has led to the recent development of assays for cardiac-specific troponin proteins. The initial CK-MB rise occurs 4 to 9 hours after the onset of chest pain induced by myocardial injury. The level peaks at 24 hours, and returns to baseline at 48 to 72 hours. One advantage of CK-MB over other markers is that it remains elevated for longer periods and it is easier to detect reinfarction using serial CK-MB measurements.

Cardiac troponin I (cTnI) is more specific than other markers for myocardial injury. Following AMI, cTnI becomes elevated at the same rate as CK-MB, but it remains elevated for 7 to 10 days. Troponin I has a higher specificity (less likely to be false-positive) for myocardial necrosis than CK-MB in selected subsets of patients with ACS, such as patients with recent surgery, cocaine use, chronic renal failure and skeletal muscle disease. Elevations in cTnI predict cardiovascular complications independent of CK-MB and the ECG changes.

Elevations in cTnI and cardiac troponin T (cTnT) can also be used to determine which patients are more likely to benefit from certain adjunct therapies such as treatment with glycoprotein 2b/3a inhibitors and need early invasive therapy.11 The early release kinetics of the troponin proteins is similar to that of CK-MB with its serum half-life being 120 mins but ongoing release from the bound fraction results in
prolonged elevation of troponin levels in the blood, approximately 5 and 12 days for TnI and TnT respectively. Jain and colleagues concluded that cTnT was superior to CK-MB in detecting patients with MI particularly those with multivessel disease.

Advantages of troponin as a cardiac biomarker for ACS diagnosis are mentioned in Table 2. With recent advances high-sensitivity troponin assay has been introduced at the cut-off point of the 99th percentile which is highly sensitive for the diagnosis of AMI by two hours after presentation. This assay is able to identify more patients at risk of future adverse events and its use may therefore influence outcomes. This high-sensitivity (hs) cTnT assay used in routine clinical practice is highly sensitive and specific since it permits measurement of even minor concentrations in blood.

Cut-off Values for Cardiac Troponin

The ESC/ACC global taskforce and NACB guidelines recommend a maximal concentration of cTn exceeding the 99th percentile for a reference control group on at least one occasion during the first 24 hours after the clinical event is indicative of myocardial necrosis consistent with AMI.

Emerging Novel Biomarkers.

B-type natriuretic peptide (BNP); N-terminal pro BNP (NT-proBNP)

BNP has prognostic values across the full spectrum of ACS. A single measurement of BNP obtained in the first few days after the onset of ischemic symptoms provides predictive information in risk stratification in ACS. Evidence has proven that BNP predicts high risk features in ACS such as more severe underlying atherosclerosis, left ventricular dysfunction, left ventricular hypertrophy and the burden of the ischemic insult. When the BNP values are high, it indicates severe hemodynamic insult due to ischemia and the prognosis is worse.

Natriuretic Peptides in Risk Stratification of ACS

Myocardial ischemia releases BNP and the associated diastolic and systolic abnormalities release BNPs as well. In ACS, BNP and NT-proBNP values are powerful prognostic markers. Combination with cTn improves risk stratification in NSTEMI. In patients with ST elevation AMI, BNPs rise rapidly and values are correlative to infarct size and degree of LV dysfunction. Patients with AMI and NT-proBNP concentrations less than 1115 ng/L have a high probability for recovery of LV function. In patients with cardiogenic shock due to AMI, NT-proBNP concentrations more than 12782 ng/L predicted an adverse outcomes despite coronary revascularization.

Cut-Off Values

For convenient clinical use, a decision-limit of 80 pg/ml has been validated for one BNP value and may be useful for clinical use in daily practice.

Optimal Timing for Measurement

When measured at admission, <24 hours after symptom onset, 2 to 5 days after the index event BNP and or NT-proBNP values maintain prognostic performance.

High Sensitive C-Reactive Protein (hs-CRP)

hs-CRP though a non-specific marker of inflammation it directly correlates with acute coronary plaque rupture and also a useful prognostic indicator in patients with ACS. The cut-offs for hs-CRP using standardized assays categorizes patients as follows:

- Low-risk: <1.0 mg/L
- Average risk: 1.0 - 3.0 mg/L
- High-risk: > 3.0 mg/L
- Very high-risk: > 10 mg/L

Levels of hs-CRP greater than 3 mg/L also predict recurrent coronary events, thrombotic complications after angioplasty, poor outcome in the setting of unstable angina, and vascular complications after bypass surgery (CABG). Additionally hs-CRP has prognostic utility in cases of acute ischemia even without troponin level elevation suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture.

Copeptin

Copeptin can rule out AMI earlier in addition to a negative Troponin test. The former has a predictive value in CAD and is of great significance to rapidly rule out of AMI when used in combination with troponin levels.

In triage of chest pain patients determination of copeptin and troponin improves diagnostic performance early after onset of chest pain. This multimarker panel provides a remarkable negative predictive value virtually independent of onset of chest pain. This aids to rule out ACS early in the ED.

At the time of presentation a copeptin level of <14 pg/mL and a Trop T level of <0.01 could rule out AMI with an area under the curve (AUC) of receiver operating
characteristic curve (ROC) of 0.97 (negative-predictive value of 99.7%), thus obviating the need for monitoring and serial blood tests in majority of patients. 19

There are certain novel biomarkers like tumor necrosis factor α (TNFα), intercellular adhesion molecule-1 (ICAM) and vascular adhesion molecule (VCAM) are being investigated for their value in diagnosis and prognostication of ACS.

Time Schedule for Cardiac Biomarker Testing (Table 3)

When a patient of chest pain arrives in ED, early diagnosis is essential, therefore a blood sample on arrival is important and if it is negative, a repeat sample at 6-9 hrs is useful for diagnosis of ACS. The recent ACC/AHA guidelines2 for the treatment of patients with unstable angina and NSTEMI recommended a baseline sample upon ED arrival and a repeat sample 6-9 hours after presentation. If the patient still continues to have symptoms of ischemia after admission, then serial sampling is necessary within 12 to 24 hours time window. This is considered as a strong recommendation having significance to rule out AMI by ACC/AHA guidelines.2

Biomarker-guided Therapeutic Approach

Numerous diagnostic options are available for ACS patients and at the same time physicians also have wide range of therapeutic regimens for these patients. The treatment regimens range from use of antiplatelets and intravenous glycoprotein IIb/IIIa inhibitors, antithrombotic therapies and invasive management approach like angioplasty. To choose from this array of therapies a simple bedside tool is more likely to help physicians to choose the appropriate antiplatelet and antithrombotic therapy and decide the urgency of invasive coronary procedures. Cardiac biomarkers assist in risk stratification, help in choosing the therapies for ACS and provide prognostic values.15

Multimarker Strategy

The emergence of different biomarkers in ACS provides insight into the varied pathophysiology of this disease. A study reported that the mortality was independently related to each biomarker tested and there was a near-doubling of mortality rate for each additional biomarker that was positive. Similarly, the short term and intermediate cardiac event rates were also strongly related to the number of biomarkers positive at admission. The diagnosis of ACS can be improved with a multi-marker strategy by addition of BNP levels than troponin alone.16

Recommendations for Indian Physicians

The consensus among cardiologists and emergency medicine physicians is that cardiac biomarkers should be available within one hour of specimen collection and optimally within 30 minutes or less called the turnaround time (TAT). To meet this stringent requirement several measures are necessary.

First, the specimen for analysis should be anticoagulated whole blood so that centrifugation and handling is not necessary or plasma should be used to avoid a delay due to the clotting process. Secondly, institutions that cannot consistently deliver cardiac biomarker TAT of approximately one hour should implement point-of-care testing with multimarker panels.

Particularly in India biomarkers are not measured routinely in all patients since the diagnostic cost goes up but it is important to understand that for early and accurate diagnosis this is beneficial. The use of multimarker panels can diagnose or rule out ACS and thereby the patients with non-cardiac chest pain can be discharged on same day from ED. At the same time when these diagnostic panels are supplied in bulk it is likely to reduce the cost. It is recommended that on arrival quantitative troponin is to be measured. If these initial levels are not elevated, then testing to be repeated 6-9 hrs after chest pain. If feasible, use of hs-troponin measurements increases accuracy and additional CK-MB and BNP levels are complimentary. TAT for troponin should be less than 30 min. It is advisable to have panels having troponin (hs-Troponin I) and copeptin to diagnose or rule out AMI in case of chest pain in ED.

ED physicians and cardiologists should routinely use the biomarkers to accurately diagnose, treat and prognosticate a case of chest pain. These biomarkers also let the physicians predict the outcomes. Recently, we published Indian consensus document on cardiac biomarkers pertaining to its application in congestive heart failure.20

In conclusion, the ultimate goal of cardiac diagnostics is the prevention of even a minor infarction and therefore only biomarkers preceding necrosis may satisfy these clinical needs. Diagnostic strategies in patients with acute chest pain have to be reliable and simple. The objective is to reduce mortality and morbidity by timely initiating the best mode of therapy. The ECG allows the exclusion of AMIs requiring immediate therapeutic intervention. Troponins can identify high risk coronary patients that should be treated with glycoprotein IIb/IIIa antagonists and referred for invasive evaluation at the
earliest. Individual cardiac markers when used at the time of ED presentation do not attain sufficient negative-predictive value to safely allow to rule out ACS. However, combinations of two or more cardiac biomarkers increase the predictive value.

Acknowledgments

This project has been made possible through an unrestricted educational grant from Alere Medical Pvt. Ltd, India, Gurgaon.

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