

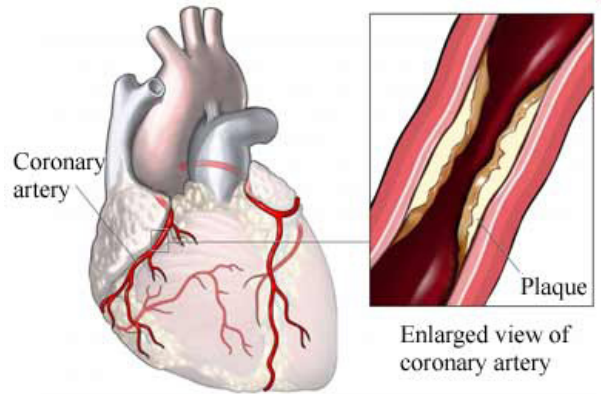
Key to diagnostic excellence

Cardiac Markers in Acute Coronary Syndromes

Cardiac profile (Tro p I, CP K, CKMB) 4,950/= TAT <2hrs
Trop T quantitative 2,950/= TAT <2hrs
CKMB 1,750/= TAT <2hrs
hsCRP 1,700/= TAT <2hrs
Pro-BNP 4,950/= TAT <2hrs
Myoglobin 2,250/= TAT <5hrs

In April 2007, the NACB* updated their 1999 guidelines for the use of markers in Acute Coronary Syndromes (ACS). These were developed utilizing the best available evidence from numerous publications and with input from acknowledged experts and professional organizations, thus representing the current best practice for the utilization of biochemical markers in ACS. In November 2007, a joint ESC, ACCF, AHA and WHF taskforce published their expert consensus document "Universal Definition of Myocardial infarction". See points emphasized below.

*NACB = National Academy of Clinical Biochemistry,



CURRENT RECOMMENDED CARDIAC MARKER PROFILE FOR MANAGEMENT OF ACS - LANCET GROUP

- Diagnosis of AMI:
 1. cTn (I or T)
 2. CKMB (Myoglobin-if early presentation)
 - Diagnosis of Re-infarction:
 1. cTn (I or T)
 2. CKMB mass and Myoglobin (serial measurements)
 - Risk Stratification:
 1. cTn (I or T)
 2. hsCRP
 3. BNP (or NT-proBNP)
- * AST, LDH and CK MB Activity should not be used in the diagnosis of Acute Myocardial infarction (AMI).



Both Trop T and Trop I have similar specificity/value especially when analysed on 3rd generation platforms (contrary to the old notion that one may be superior to the other in certain clinical conditions). Troponin complex consists of TnT, TnI and TnC. TnC is both expressed in Cardiac and Skeletal muscle. TnT and TnI are products of heart-specific genes. The Combined American Academy of Cardiology and American Heart Association Clinical Practice Guidelines as well as National Academy of Clinical Biochemistry Guidelines on the Use of Cardiac Markers in Coronary Artery Diseases recommend the use of Cardiac Troponins (TnT or TnI and NEVER BOTH).

NB: Clinical guidelines are an embodiment of the best practice evidence-based knowledge available at the time written.

The following points are emphasized:

1. Cardiac Troponin (cTn) - T or I - remains the eminent marker of myocardial necrosis and risk stratification, and must be measured in all patients with suspected ACS. Troponin T and Troponin I are of similar value. CK MB Mass is an alternative marker of myocardial necrosis.
2. Myocardial Infarction is diagnosed when the levels of these biomarkers are elevated in the clinical setting of acute myocardial ischaemia.
3. AST, LDH and CK MB Activity should not be used in the diagnosis of Acute Myocardial Infarction (AMI).
4. Importance is placed on finding out why the cTn is elevated. A raised level indicates myocardial necrosis but not the mechanism of the necrosis. Thus in the absence of clinical evidence of ischaemia, a raised cTn should prompt a search for other causes

of myocardial necrosis e.g. Myocarditis, pulmonary embolus, CCF, chest trauma etc. Regardless, Tn elevation, even in the absence of ACS, predicts a worse short- and long-term survival.

5. Detection of a rise and/or fall in the measurement of the marker is essential to the diagnosis of AMI. Thus a repeat sample 4-8 hours later is necessary to confirm or rule out MI. Some patients may need additional sample 12-24 hours later, if earlier results were normal but clinical suspicion of AMI remains high. The rising or falling pattern is necessary to distinguish "background" elevated cTn levels from increases secondary to AMI. cTn levels rise within 3-4 hours of the onset of myocardial injury and remain elevated for up to 10-14 days for cTnT, and 4-7 days for cTnI.

6. Once the diagnosis of AMI is made, repeat marker testing at a reduced frequency (e.g. 6-10 hrs X3), is valuable to qualitatively estimate the size of the infarct and to detect complications such as reinfarction. The value of these markers to discriminate very early reinfarction, during a time when the concentration of the marker is still increasing from the initial event, is obviously limited.

7. For detection of reinfarction CK MB Mass is traditionally the preferred marker (although recent data suggests cTn can provide similar information). If reinfarction is clinically suspected, a sample should be drawn immediately for the relevant marker and repeated 3-6 hours later.

8. Reinfarction is diagnosed if there is a > 20% increase in the level of the marker in the second sample.

9. For patients with diagnostic ECG abnormalities at presentation, the diagnosis and management should obviously not be delayed while awaiting biomarker results. If necessary, for patients who present within 6

hours of the onset of symptoms, myoglobin can also be requested as part of a "Rule-Out" strategy. Myoglobin is a non-specific cardiac marker which starts to rise 2 - 4 hours after myocardial infarction, peaks at 4 - 12 hours, and generally returns to normal in 24 - 36 hours. It is therefore useful as an early, non-specific marker, and to rule out MI, provided that the specimen is collected within the appropriate time frame. Its rapid return to normal also makes it suitable as a possible marker of re-infarction at a time when the other cardiac markers are still elevated following the primary event.

10. Accumulating evidence indicates that a multimarker strategy adds to the traditional biomarkers of necrosis for risk stratification in ACS. Data from multiple studies indicate that increased concentrations of hsCRP and BNP or NT-proBNP at presentation, identifies patients who are at a higher risk of mortality, irrespective of whether there is detectable elevation of troponin. Regarding CK MB: • Like Total CK, CKMB begins to rise 3 to 4 hours after the onset of myocardial injury and falls to the normal range by 48 to 72 hours.

11. Ischaemic injury may be present with elevated CKMB and normal Total CK.

12. Reference ranges are different for men and women and levels exceeding these (the 99th percentile), suggests infarction. (a rise and/or fall in level must be shown to indicate an acute event).

13. CKMB Mass constitutes 1 to 3% of the total CK in skeletal muscle, and is present in minor quantities in the intestine, diaphragm, uterus and prostate. Therefore in the setting of major injuries to these organs, especially skeletal muscle, the specificity of CKMB maybe impaired. (i.e. there may be false positives) Thus requesting CKMB as a single test for ACS is not advised - serial levels should be done, and the lack of specificity

considered.

14. CKMB as a percentage of total CK has been proposed to distinguish skeletal from cardiac muscle damage [2,5 to 5%] This may improve specificity, but has limitations in certain clinical settings (patients with both skeletal and cardiac injury and patients with chronic skeletal muscle disease etc.)

15. In MI, the magnitude and temporal course of CKMB elevation and decline has been shown to correlate strongly with infarct size. The evidence for troponin providing similar information is still limited.

Other Markers on the Horizon

The most promising appear to be

- Ischaemia Modified Albumin (IMA) - rules out ischaemia well, but the meaning of a positive value is less certain.
- Myeloperoxidase (MPO) - appears to reflect plaque instability.
- CD40 ligand - a marker of platelet activation. Possible participation in plaque destabilization.
- Whole blood choline - possible indicator of 30-day mortality in patients presenting with chest pain. Despite the promise of many cardiac markers in the management of ACS, cTn remains the most powerful and gives both diagnostic and prognostic information that positively influences the delivery of cardiac care.

REFERENCES: Circulation.2007; 115: e356-e375; Circulation.2007; 116: 2634-2653

Compiled by Dr Ahmed Kalebi MBChB (Nbi) MMed Path (Nbi) FCPATH SA, from the Lancet SA July 2008 Newsletter - Department of Chemistry
Images used in this Newsletter have been obtained from various internet sources