Current and new Cardiac Markers

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Learning points

- CTn is the preferred cardiac marker to:
  - rule in/out an acute MI
  - risk stratify patients with ACS
  - predicts adverse cardiac events
  - monitor the success of thrombolysis
  - categorize and identify patients who may benefit from invasive (PCI/CABG) therapy or to conservative therapy with LMWHs and/or GIIB/IIIA inhibitors

- A multimarker approach combining BNP, CRP, cTn I has been shown to identify patients with UA/NSTEACS with an increased mortality risk

- CKMB is the marker of choice to monitor re-infarction
  - Many new markers of myocardial ischemia are been studied to assist in the diagnosis of ACS with normal cTn/UA
  - Clinicians and laboratorians to continue supporting a goal for a TAT of 60 min for cardiac markers and to collaborate on setting up diagnostic pathways and algorithms to manage patients with ACS.
Disruption of coronary artery plaque -> platelet activation/aggregation /activation of coagulation cascade -> endothelial vasoconstriction -> intraluminal thrombus/embolisation -> obstruction -> ACS

Severity of coronary vessel obstruction & extent of myocardium involved determines characteristics of clinical presentation either an STEMI, NSTEMI or an UA
Cardiac markers play a pivotal role in the diagnosis, global risk assessment stratification, and management of patients with CVD acute coronary syndromes (ACS).

Biochemical characteristics of an ideal marker of myocardial infarction

1- **Specific:** to myocardial muscle cells (no false positive)

2- **Sensitive:** rapid release at onset of the attack for an early diagnosis, to detect minimal cardiac damage and not to miss positive cases (no false negative)

3- **Prognostic:** relationship between plasma concentration & extent of the cardiac damage

4- **Persists longer:** to diagnose delayed presentation

5- **Simple, inexpensive:** no need for highly qualified personnel

6- **Reliable:** traceable to a scientific evidence

7- **Quick:** short turnaround time

Current Biomarkers for assessment of and diagnosis of atherothrombotic disease/ACS

- Inflammatory cytokines (interleukin-6 (IL-6), IL-8, etc)
- Cellular adhesion molecules such as integrins, selectins, NCAM (neural cell adhesion molecule), VCAM (vascular cellular adhesion molecule), etc.
- Acute-phase reactants C-reactive protein (CRP)
- Plaque destabilization and rupture biomarkers such as Myeloperoxidase (MPO) and possibly matrix metalloproteinase-9 (MMP-9)
- Biomarkers of ischemia such as ischemia modified albumin (IMA)
- Biomarkers of myocardial stretch (BNP)
- Biomarkers of myocardial necrosis (Troponin, CK-MB, Myoglobin)

Apple F S, Clinical Chemistry, March 2005
Acute Coronary Syndromes

- **“ACC/AHA definition”:** A constellation of clinical symptoms that are compatible with acute myocardial ischemia and encompasses a spectrum from MI NSTEMI UA

- **Physiologic definition:** Plaque rupture leading to thrombus formation, and to partial or complete blockage of a coronary artery with or without myocardial necrosis.

- A thrombus that causes a total occlusion and myocardial necrosis shall present with ischemia lasting longer than 30 minutes and elevated cardiac markers and an ECG showing an ST elevation myocardial infarction (STEMI)

- Or a severe (90%) stenosis and myocardial necrosis with elevated cardiac markers and an ECG showing non-ST EMI elevation MI or with ischemia of <20min), no myocardial necrosis, hence, normal cardiac biomarkers and an UA (unstable angina).

Universal Definition of Myocardial Infarction

Kristian Thygesen; Joseph S. Alpert; Harvey D. White;
on behalf of the Joint ESC/ACCF/AHA/WHF Task Force
for the Redefinition of Myocardial Infarction

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial
necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any
one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least
  one value above the 99th percentile of the upper reference limit (URL) together with
  evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle
    branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion
    abnormality.

Thygesen et al. (Circulation, 2007;116:2634-2653.)
The NACB LMPG was produced using a weighted evidence criteria adopted from the AHA/ACC guidelines that were based on relevant published information. Recommendation are designated in classes I, IIa, IIb, and III to describe the indications, and the upper case letters A through C describe the weight of evidence.

NACB recommendations for use of biochemical markers for diagnosis of myocardial infarction (MI)

Class I
Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with ACS (Level of Evidence: C).

Cardiac troponin is the preferred marker for the diagnosis of MI. Creatine kinase MB (CK-MB) by mass assay is an acceptable alternative when cardiac troponin is not available (Level of Evidence: A).

For most patients, blood should be obtained for testing at hospital presentation (baseline) and at 6–9 h (Level of Evidence: C).

Continue with NACB recommendations for use of biochemical markers for diagnosis of myocardial infarction (MI)

In the presence of a clinical history suggestive of ACS, the following are considered indicative of myocardial necrosis consistent with MI (Level of Evidence: C):

a. Maximal concentration of cardiac troponin exceeding the 99th percentile of values of the URL on at least 1 occasion during the first 24 h after the clinical event (observation of a rise and/or fall in values is useful indiscriminating the timing of injury).

b. Maximal concentration of CK-MB exceeding the 99th percentile of values for a sex-specific reference control group on 2 successive samples (values for CK-MB should rise and/or fall).

Class IIb

1. For patients who present within 6 h of the onset of symptoms, an early marker of myocardial necrosis may be considered in addition to a cardiac troponin. Myoglobin is the most extensively studied marker for this purpose (Level of Evidence: B).

Class III

1. Total CK, CK-MB activity, (AST, ALT), -LDH should not be used as biomarkers for the diagnosis of MI (Level of Evidence: C).

2. For patients with diagnostic ECG abnormalities on presentation (e.g., new ST-segment elevation), diagnosis and treatment should not be delayed while awaiting biomarker results (Level of Evidence: C).
Role of the cardiac markers in ACS

Cardiac markers role has evolved largely as the clinical evaluation is limited in many patients by atypical symptoms, and a non-diagnostic ECG

1. Diagnosis or rule in/out an acute MI and distinguishing myocardial damage due to AMI or other cardiac process

2. Risk stratification of patients with UA/NSTEACS

3. Monitor the success of thrombolysis

4. Monitor re-infarction

5. Confirm an old MI (several days)

6. Prognostic markers of:
   - In ACS, pre and post PCI/reperfusion therapy
   - CHF following AMI
When should cardiac markers be measured?

- According to the ACC/AHA/ESC guidelines, management of STEMI is critically time dependent and management of all patients with ACS should start within one hour.

- cTn must be available on a continuous basis, with a target turnaround time of 1 hour or less after patient admission.

- However, Cardiac markers are not necessary for the diagnosis of patients with STEMI, especially since the sensitivity is low in the first 6 hours after symptom onset. These patients are candidates for thrombolytic therapy or PCI within a short timed frame.

Diagnosis and Risk Stratification of ACS

- The current (AHA/ACC) guidelines recommend that five factors should be considered together when assessing the likelihood of an AMI and an ACS:
  - the nature of the symptoms
  - history of ischemic heart disease
  - gender
  - increasing age
  - the presence of traditional cardiovascular risk factors.

- Clinical examination
- Standard ECG and Non-standard ECG leads = STEMI, NSTEMI, UA, other cardiac
- Non-Invasive Studies (Echocardiogram, Exercise testing, Technetium-99m-sestamibi, MR angio, CT angio)
- Cardiac markers

ACS Risk stratification tools:

- It is vital to reliably stratify patients with suspected ACS:
  
  *(a) to assess the* probability that the patient’s symptoms are related to acute coronary ischemia
  
  *(b) to assess the patient’s* risk of recurrent cardiac events, including death and recurrent ischemia

- This can be done using a pretest probability criteria that may include some or all of the below:
  1. Goldman criterion
  2. TIMI risk score
  3. GRACE score
  4. Vancouver CP Rule (more later)
  5. ACI-TIPI: Acute Coronary Insufficiency-Time
NACB recommendations on the use of biochemical markers for early risk stratification in ACS

Class I

1. Patients with suspected ACS should undergo early risk stratification based on an integrated assessment of symptoms, physical exam findings, ECG findings, and biomarkers (Level of Evidence: C).

2. A cardiac troponin is the preferred marker for risk stratification and should be measured in all patients with suspected ACS.

3. In patients with a clinical syndrome consistent with ACS, a maximal (peak) concentration > 99th percentile of values for URL should be considered indicative of increased risk of death and recurrent ischemic events (Level of Evidence: A).

TIMI score, (Thrombolysis In Myocardial) Infarction

- Antman and colleagues developed a simple risk scoring system to identify patients with various responses to treatments for unstable angina and non–ST-elevated myocardial infarction.

- The 7 (TIMI) risk-score–predictor variables are:
  - Aged >65 years,
  - Unstable angina and >3 risk factors for CAD,
  - A prior stenosis of >50%
  - Aspirin in the past 7 days
  - >2 anginal events in the prior 24 hours
  - ST-segment deviation on ECG at presentation
  - Elevated Troponin

- The adverse event rates are significantly increased with a TIMI risk score of $\geq 4$. Hence, based on a TIMI risk score of 6, this combination of features indicates a high-risk patient.

TIMI Risk Score For UA/NSTEMI

- Age ≥65 years
- ≥3CAD Risk Factors
- Prior Stenosis >50%
- ST deviation
- >2 Anginal events ≤24 hours
- ASA in last 7 days
- Elev Cardiac Markers (CK-MB or troponin)

C Statistic=0.65
χ² trend P<.001

Antman EM, et al. JAMA. 2000;284:835-442. (Copyright © 2000 American Medical Association. All rights reserved)
Timing of Release of Various Biomarkers After Acute Myocardial Infarction

Troponins

- Troponin has three subunits, TnC, TnT, and TnI, with Troponin-I solely cardiac, but some Troponin-T is found in the skeletal muscle.

- Troponins rise 2-3 hours after onset of MI and approximately 80% of patients with AMI have positive results at 3 hours.

- Elevations in Troponins may persist for up to 4–7 days for cTnI and 10–14 days for cTnT post MI.

- Laboratory 3rd or 4th Generation assays range definition:
  - Cutoff is set at 99th percentile of a normal reference population, with a CV% < 10%.
  - Troponin levels are virtually undetectable in normal subjects, this 99th percentile corresponds to <0.03 ng/ml (Heparinized samples may produce low values).

1 Am Heart J 113: 1333-44
2 J Mol Cell Cardiol 21: 1349-53
Cardiac Troponin release

Troponins prognostic value

- Troponin level has prognostic value shown by the TIMI IIIB, GUSTO IIa, GUSTO IV ACS, and in the FRISC trial.

- All have demonstrated a direct correlation between TnI/TnT level and ACS in terms of mortality rate, adverse cardiac events, risk stratification and therapeutic decision making.

- Many studies have confirmed that a positive troponin result alone is an independent predictor to label the patient as a high risk patient.

- Therapy with LMWHs and/or GIIB/IIIA inhibitors appears to confer the most benefit on those patients with elevated cardiac troponins levels.


High Troponins risk and treatment benefits

- Large 4 multicentre trials have demonstrated that raised cTN could identify patients that may benefit from therapy with LMWHs and/or GIIb/IIIA inhibitors.

- The PRISM study based on troponin I has shown a significantly reduced short and long term risks of death and a decrease in cardiac events in patients with baseline elevations of troponin treated with Abciximab, compared with patients without an elevated TnI level.

- Bhatt et al., subgroup analysis of the PURSUIT trial, have shown that patients with an elevated troponin level had a better response to the GIIb/IIIA inhibitor eptifibatide therapy than those with a negative result.

- These studies confirm that a positive troponin result alone is an independent predictor of high risk mortality and morbidity.
cTn guides ACS management

- Patients with ↑cTn are more likely to have complex thrombotic coronary lesions, but, they benefit from more aggressive anticoagulant, anti-platelet, and invasive therapies.

- As such, patients with suspected ACS and abnormal troponin results should be treated in accordance with the ACC/AHA/ESC guidelines for the management of high-risk patients with NSTEACS.

- Numerous studies involving over 7,000 patients have now consistently demonstrated that a strategy of early cardiac catheterization and revascularization in appropriately selected patients with NSTEACS leads to fewer adverse cardiac events than an initial strategy of medical therapy alone.
Troponin I Levels and Mortality in Patients with NSTE-ACS

Prognostic Value of Troponin in ACS: A Meta-Analysis

- RR 3.9 (2.9-5.3)
- RR 3.8 (2.6-5.5)
- Neg
- Pos (Trop I + T)

Conservative vs Invasive Strategy for UA/NSTEMI

2003

VANQWISH
MATE
TIMI IIIB

Invasive

ISAR-COOL
RITA-3
VINO
TRUCS
TACTICS-TIMI 18
FRISC II

UA indicates unstable angina, NSTEMI, non–ST-segment myocardial infarction; ISAR, Intracoronary Stenting and Antithrombic Regimen Trial; RITA, Randomized Intervention Treatment of Angina; VANQWISH, Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital study; MATE, Medicine vs Angioplasty for Thrombolytic Exclusions trial; TACTICS-TIMI 18, Treat Angina with Aggrastat® and Determine Cost of Therapy with Invasive or Conservative Strategy; and FRISC, Fragmin during Instability in Coronary artery disease.

Slide reproduced with permission from Cannon CP. Atherothrombosis slide compendium. Available at: www.theheart.org.
Δ Troponin change

- Recurrent infarction is diagnosed if there is a 20% increase of the Troponin concentration in the second sample.

- Troponin concentrations may be considered to coincide with re-infarction if they are different by 3 SDs of the assay CV% (5–7%)

- A change of cTnI >30% may improve the diagnostic clinical specificity for ruling out AMI and could improve risk stratification

- Thus, a 20% change exceeding the 99th percentile URL should be considered significant, as long as it is not expected from analytical variability itself.

“high sensitivity” Troponins

- Studies have confirmed that hs-cTn assay provides a greater clinical sensitivity and MI diagnostic accuracy with an earlier detection after onset of symptoms, thus, enhancing risk stratification of ACS.

- Most of new hs cTn assays are capable of achieving a CV < 10% at the 99th percentile of the reference population, to meet with the requirements of the ACC/ESC and NACB/AACC* definition of MI.

- Elevation of cTN measured with hs assay is likely to identify patients with significant heart disease and a higher risk of adverse outcome, irrespective of the presence or absence of ACS.


“high sensitivity” Troponins

- The major limitation of conventional troponin assays is the low sensitivity (cut off 0.03 ng/L) where by diagnosis of AMI requires prolonged monitoring over a period of 6 to 12 hours and serial blood sampling.

- In contrast, Hs -cTn can measure very low concentrations of troponin (0.003 ng/L) with CV% fulfilling the ACC/AHA/ESC guidelines criteria and have little variability between measurements when performed on blood samples obtained at the time of presentation.


CK-MB

- When cardiac troponin is not available, the next best alternative is CK-MB (measured by mass assay).
- Assays for CK-MB mass offer superior analytical and diagnostic performance and thus are strongly preferred to assays for CK-MB activity.
- The myocardium has CK-MM at 70% and CK-MB at ~30%.
- CK-MB begins to rise 4-6 hours after onset of infarction, Peaks at about 12 hrs and returns to baseline at 24-36 hrs.
- The upper limit of normal for CK-MB (mass assay) is 3-6% of total CK.
- A single assay in the ED/ER has a 34% sensitivity for MI. A normal level in the ED/ER does not exclude the possibility of MI.

CK-MB

- In the presence of a clinical history suggestive of ACS, a maximum concentration of CK-MB exceeding the 99th percentile of values for a sex-specific is considered indicative of myocardial necrosis consistent with MI (Level of Evidence: C)

- Desirable imprecision (expressed as %CV) of CK-MB mass assay has been defined as < 10% CV at the 99th percentile reference limit

- The CKMB measurements should be recorded at the time of the first assessment of the patient and 6–9 h later in order to demonstrate the rise and/or fall exceeding the 99th percentile URL for the diagnosis of myocardial infarction.


CK-MB and Re-infarction

- CK-MB is the marker of choice for diagnosis of re-infarction in patients with STEMI, who have undergone a PCI, or CABG

- The ACC/AHA definition of re-infarction includes both
  - re-elevation of CK-MB
  - supporting criteria including ECG changes, pain or hemodynamic instability

- CK:CK-MB Ratio improves the specificity of CKMB to reflect MI, where ratios of 2.5-5 are still used in some parts of the world: relative index- RI (% MB as of CK)
  - CKMB <7 and RI <4% :negative
  - CKMB <7 and RI >4% :equivocal
  - CKMB >=7 and RI <4% :equivocal
  - CKMB >=7 and RI >4% :positive

- However, it is could be misleading in the setting of hypothyroidism, renal failure, and chronic skeletal muscle diseases

Total Creatine Kinase  CK

- Total CK and CKMB and the Relative Index (RI) can be used as an acceptable alternative with improved myocardial tissue specificity where cTn or CK-MB mass assays are not available or feasible.

- Increases 4-6 hours after the onset of MI, Peak activity is at 18 to 24 hours, Usually returns to baseline levels by 36 hours.

- Although they are of historical significance, total CK, LDH and AST should no longer be used for the diagnosis of MI because they have low specificity for cardiac injury and more specific alternative biomarkers of necrosis are available.

Biochemical markers of ischemia

- Approximately 40%–60% of patients with definite ACS present with an initial troponin concentration **below the clinical decision-limit for the assay**:
  1. Due to early presentation post onset of symptoms for which cTnI/T is not yet detectable by serum/plasma testing
  2. Or as acute myocardial ischemia without necrosis (i.e. unstable angina).

- Discriminating these 2 groups from patients with non ACS chest pain is a major clinical challenge.
- Hence, a biomarker that can reliably detects myocardial ischemia in the absence of necrosis, and/or before cardiac troponin is increased, has the potential to add substantially to available clinical tools
1. Myoglobin

- Myoglobin, is a low-molecular-weight heme protein found in the cardiac and skeletal muscle, and is released from infarcted myocardium as early as 1 h after the onset of myocyte damage and returns to normal within 12–24 h post MI.

- Myoglobin levels, although highly sensitive, are not cardio-specific.

- Many studies have shown that the combined use of myoglobin and cardiac troponin or CKMB may be useful for the early exclusion of MI.

- Multimarker strategies that include myoglobin have been shown to identify patients with MI more rapidly than laboratory-based determination of a single marker.

2. Placental Growth Factor (PlGF)

- Is a member of the vascular endothelial growth factor family (VEGF)
- It is up-regulated in atherosclerotic plaques in ACS patients with the subsequent platelet aggregation and systematic thrombosis

- PLGF levels measured at 12 hours of symptom onset and 30 days later may independently predict fatal outcome and adverse cardiac events in patients with NSTEACS

- Plaque instability, represented by PlGF elevation, has an important role in the pathogenesis of future coronary events.


Clinical Inflammatory Biomarkers in Acute Coronary Syndromes, Part III: Biomarkers of Oxidative Stress and Angiogenic Growth Factors
3. Whole blood/Plasma choline

- Choline is the major enzymatic product of phospholipase D that plays a role in the pathophysiological evolution of atherosclerotic plaque destabilization.

- A study suggested that whole blood choline is a strong independent predictor of 30-day mortality in patients with chest pain presenting to the Emergency Department. ¹

- Incorporating whole blood choline (WBCHO) and plasma choline (PLCHO) is been proposed as novel cardiac markers for ACS reflecting coronary plaque destabilization and tissue ischemia.

1. Christopher Vaccari, Sameer Nagamia, Ramadan Hammoud Elevations in Serum Isoprostanes and Choline Correlate to 30 Day Outcomes in Patients with Acute Coronary Syndrome; Martin Thoenes²; Bobby V Khan³ (Circulation. 2007;116:II_579.) 2007 American Heart Association, Inc.
4. Myeloperoxidase

- A heme-protein enzyme stored within neutrophils, where activation of leukocytes in patients with ACS initiates secretion of MPO to produce higher levels in than in normal controls.  

- MPO is shown to degrade the protective collagen coating of plaques, causing them to become vulnerable to erosion and rupture.  

- MPO levels have been shown to increase within two hours of ACS symptoms’ onset, much earlier than Troponin and CK-MB.

- Data from the CAPTURE trial showed that ACS patients with MPO levels > 350μg/l were significantly more likely to have an MI or die within six months than those with MPO levels below this threshold.


Clinical Utility of MPO in practice: Patient with Chest pain

Association between MPO and Cardiac event rate
CAPTURE Cohort: Patients with chest pain, n = 547

For the follow up time: (72h, 30 days and 6 month, event rate showed significant differences among MPO tertiles)

Normal Range
- Plasma MPO: 51 - 633 pmol/mL

Stefan Blankenberg, MD; Renate Schnabel, MD; Edith Lubos, MD, et al., Myeloperoxidase Early Indicator of Acute Coronary Syndrome and Predictor of Future Cardiovascular Events 2005
5. Copeptin, a novel cardiac marker

- Copeptin, a 39-amino acid glycopeptide that comprises the C-terminal part of the AVP precursor (CT-proAVP), was found to be a stable and sensitive surrogate marker for AVP release.

- Reichlin *et al.* has demonstrated that Copeptin is significantly elevated in patients with AMI presenting early to the ED and still negative for troponin T.

- The combination of troponin T and Copeptin resulted in a very high diagnostic accuracy of AMI at presentation (AUC = 0.97).

- In this study they have concluded that Copeptin in the context of ACS could rapidly and reliably ruled out AMI at admission in two-thirds of patients, and only the remaining one-third of patients (instead of all patients) would need monitoring and serial blood.

- Copeptin could be a powerful predictor for future CV mortality and events.

Copeptin and Troponin T Levels at Presentation in Relation to Time Since Onset of Symptoms

6. Ischemia modified albumin (IMA)

- In the setting of MI, there are modifications to the amino acids of the N-terminus of the human albumin molecule that prevent its binding of transition metals, such as cobalt.
- IMA increases within minutes of ischemia and remains elevated for 6-12hrs – and disappears by 24hrs with a ~90% negative predictive value.
- IMA has been shown to predict with high sensitivity subsequent elevation in the troponins in the clinical setting\(^1\).
- It has a highly sensitive and has a high negative predictive value.
- The combination of IMA–myoglobin–CK-MB–TnI increases the sensitivity for detecting ischemia to 97%, with a negative predictive value of 92%\(^2\).

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7. Heart- fatty acid binding protein

**H-FABP**

- H-FABP is a 15 kDa protein thought to be involved in myocardial lipid homeostasis, and is present in substantial amounts in the cytoplasm of myocardial tissue, but is also expressed in tissues outside the heart.

- H-FABP can be detected as early as 1 h and peaks at 6-8 h after an acute coronary occlusion and demonstrates a good correlation to infarct size.

- The H-FABP prognostic utility of in long-term A report, on 2287 patients with NSTEMI in the OPUS-TIMI 16 trial reflected H-FABP as a marker of death and major cardiac events among ACS patients. Among these patients, H-FABP was an independent predictor of adverse outcome.


BNP and NT-proBNP

- BNP and NT-proBNP are released from cardiac myocytes in response to increases in ventricular wall stress.
- Patients with STEMI plasma, BNP rises rapidly and peaks at 24 h, with the peak concentration proportional to the size of the MI providing prognostic information complementary to cardiac troponin.
- Patients with unstable angina and NSTEACS, a higher concentration of BNP and NT-proBNP have been shown to predict risk of short- and long-term mortality.
- Death rate had increased from 1% among patients with BNP concentrations in the lowest quartile to 15% in those with a BNP concentration in the highest quartile.
- Patients with negative Troponin T and elevated NT-proBNP levels had risk comparable to TnT-positive patients.

B-type Natriuretic Peptide (BNP) and Mortality in ACS Patients

Mortality (%) vs. Days After Randomization for different quartiles:
- Quartile 1 (n=631)
- Quartile 2 (n=632)
- Quartile 3 (n=632)
- Quartile 4 (n=630)

Statistical significance: P<.001

BNP and Risk of Death in ACS

- **ST ↑ MI**: 825
- **Non-ST ↑ MI**: 565
- **Unstable Angina**: 1133

P-values:
- **P = 0.02**
- **P < 0.0001**
- **P = 0.001**

Reference:
Class IIa

- Measurement of brain-type (B-type) natriuretic peptide (BNP) or N-terminal pro-BNP (NTproBNP) may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS.

- The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A)

CRP vs hs-CRP

- High sensitivity assays detects low grade inflammation to predict vascular risks and events.
- hs-CRP level > 10 mg -15.0 mg/L/l are associated with a notably high risk of adverse cardiac events and death in patients with NSTE-ACS (Class IIa, Evidence C)
- NACB recommends measurement of hs-CRP in addition to a cTn, for risk assessment in patients with a clinical syndrome consistent with ACS.
- The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A).

Clinical Application of hs-CRP for Cardiovascular Risk Prediction

Low Risk

Moderate Risk

High Risk

Acute Phase Response
Ignore Value, Repeat Test in 3 weeks

A recent clinical overview of CRP, the CDC established a set of cut points to be used in routine clinical practice.

CRP levels \(>10 \text{mg/L}\) may indicate an acute phase response and should be remeasured in 2 to 3 weeks.

Values that remain in this range are true positives and again reflect high vascular risk.

Ridker PM. *Circulation* 2003;107:363-9
Predictive Value of hs-CRP for Mortality from ACS in FRISC Substudy

CRP Level Predicts Prevalence of Multiple Coronary Plaques in Patients with Unstable Angina

Patients by CRP Tertile (mg/L)

- Low (0.12-1.0): n=78, 30.8%
- Med (1.1-4.3): n=71, 46.3%
- High (4.5-29.4): n=79, 89.9%

Patients with Multiple Plaques ≥2 (p < 0.001)

Multiple cardiac markers Approach post

- Data from multiple studies indicate that increased concentrations of either of CRP and BNP or NT-proBNP at presentation with cTn enhances risk assessment and identifies patients who are at higher mortality risk irrespective of cTn.

- Moreover, in one study a simple multimarker approach combining each of BNP, CRP, cTnI) identified a 6- to 13-fold gradient of mortality risk between those without elevation of any marker and those in whom all 3 markers were increased.

- The MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in NSTEACS) trial followed up for a mean of 343 days, after including all biomarkers, only NT-proBNP and cTnI were independently associated with CV death, and only cTnI with myocardial infarction (MI).

- Myeloperoxidase and hs-C-reactive protein, while independently associated with some adverse CV outcomes, did not provide substantial incremental prognostic information when evaluated together with cTnI and NT-proBNP.
Multimarker Approach: Troponin I, CRP, and BNP to Predict 30-Day Mortality in ACS

OPUS-TIMI 16

No. of Elevated Biomarkers

30-Day Mortality (%)

P = .014

TACTICS-TIMI 18

No. of Elevated Biomarkers

30-Day Mortality (%)

P = .001