Biomarkers, new and old, in the diagnosis of acute myocardial infarction

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ISCHAEMIC HEART DISEASE REGISTERS

Report of the Fifth Working Group
(including a second revision of the operating protocol)

Copenhagen
26-29 April 1971
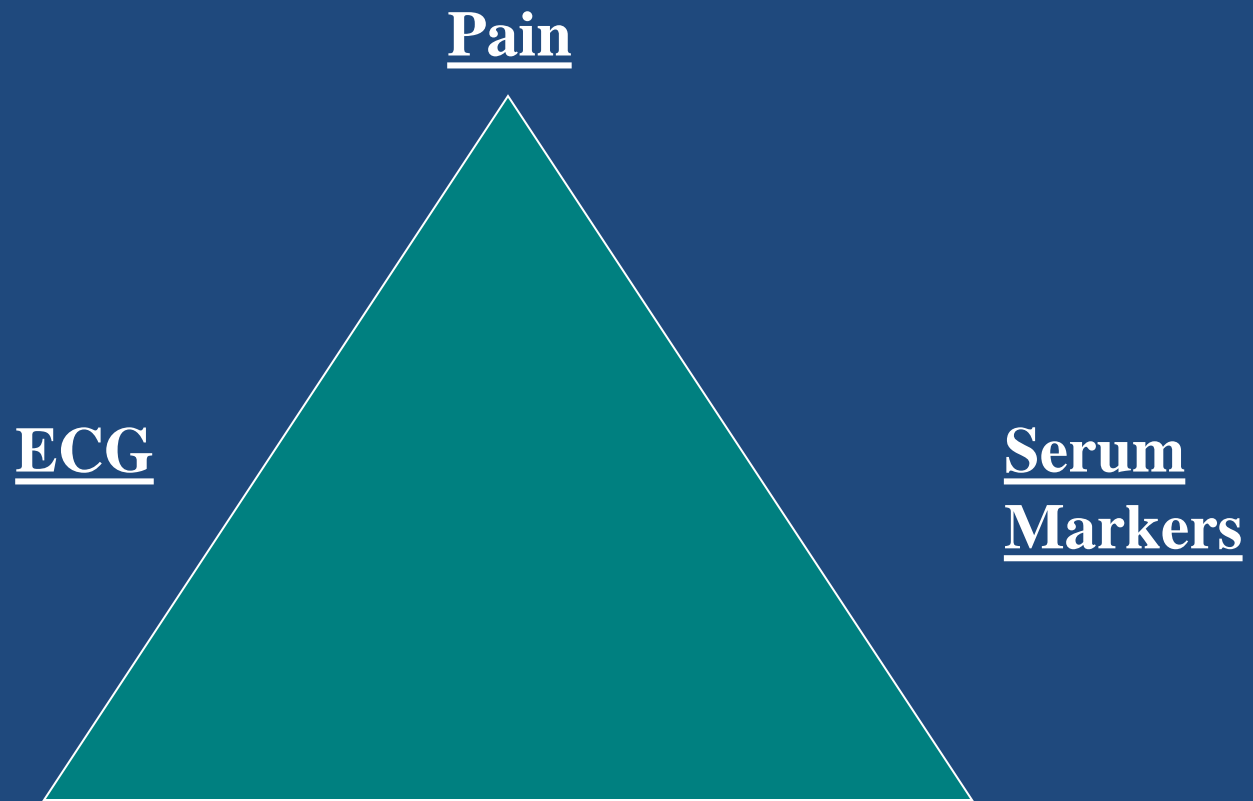

REGIONAL OFFICE FOR EUROPE

World Health Organization

COPENHAGEN

The WHO Definition from the 1970's

- Based on epidemiological principles
- Non-specific
- Did not use biomarkers early on; later biomarker use was not standardized
- Not clinician friendly

The Diagnostic Triad for AMI

Pain

ECG

Serum Markers

The Criteria

The Criteria for the diagnosis of acute MI as established by WHO, included 2 of the following 3:

- **History: Chest discomfort or equivalent**
- **Diagnostic changes on ECG**
- **Elevated cardiac enzymes (or markers)**

WHO MI Definition: Serum Enzymes

"Appropriate enzyme tests will be used whenever possible."

WHO Criteria - 1971

Primordial Biomarkers: Prior to 1980

- **White blood cell count**

- **Body temperature**

- **Blood sedimentation rate**

- **Lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT)**

- **Non-fractionated creatine kinase (CK)**

Biomarkers after the 1980's

- **MB fraction of creatine kinase (CK-MB) – various assays with variable sensitivity and specificity from assay to assay;**

- **Troponin T and I – recently, high sensitivity troponin assays have become widely available.**

The troponin revolution

Definition of MI from 2000, 2007, and 2012: Circulation, Eur Heart Journal, and Journal of the Amer College of Cardiology

- **Based on measurement of highly sensitive and specific troponin in association with:**

    --Clinical evidence of myocardial ischemia from history, ECG, or following a coronary intervention;

    --Non-invasive imaging can assist with the diagnosis;

Definition of Myocardial Infarction

Pathology

Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischemia.

Death of heart tissue due to blocked coronary artery
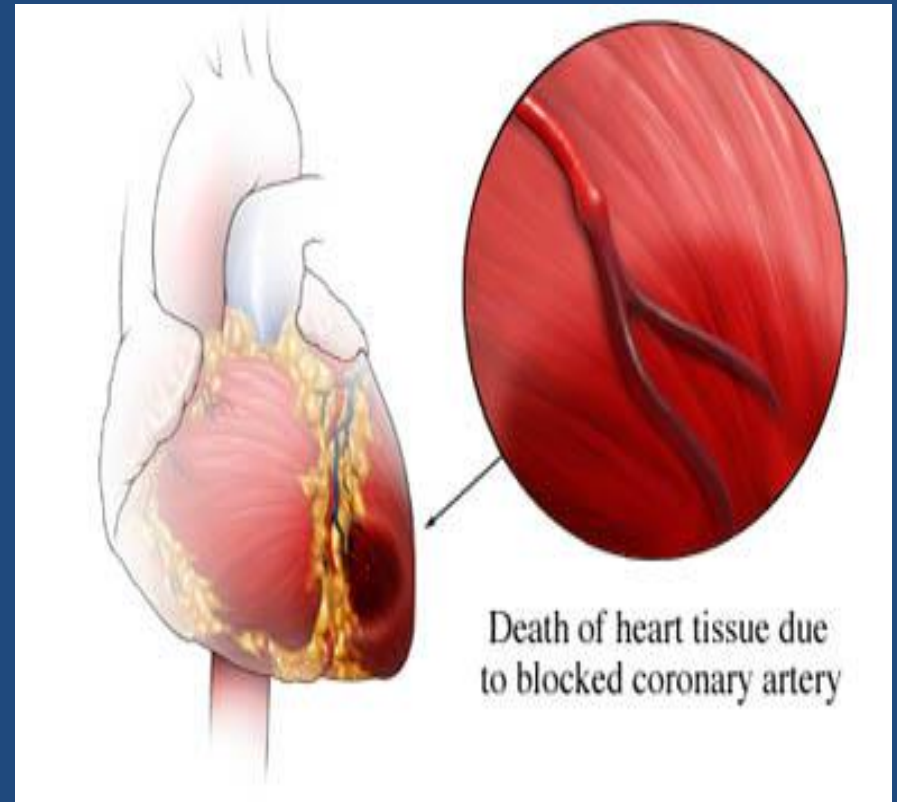
# Biomarkers for Detection of Myocardial Infarction

Preferably

Detection of rise and/or fall of Troponin (I or T) with at least one value above the 99th percentile of the upper reference limit measured with a coefficient of variation ≤ 10%.

When Troponin is not available

Detection of rise and/or fall of CKMB mass with at least one value above the 99th percentile of the upper reference limit measured with a coefficient of variation ≤ 10%.

Appearance of Biomarkers in Blood After Onset of Myocardial Infarction
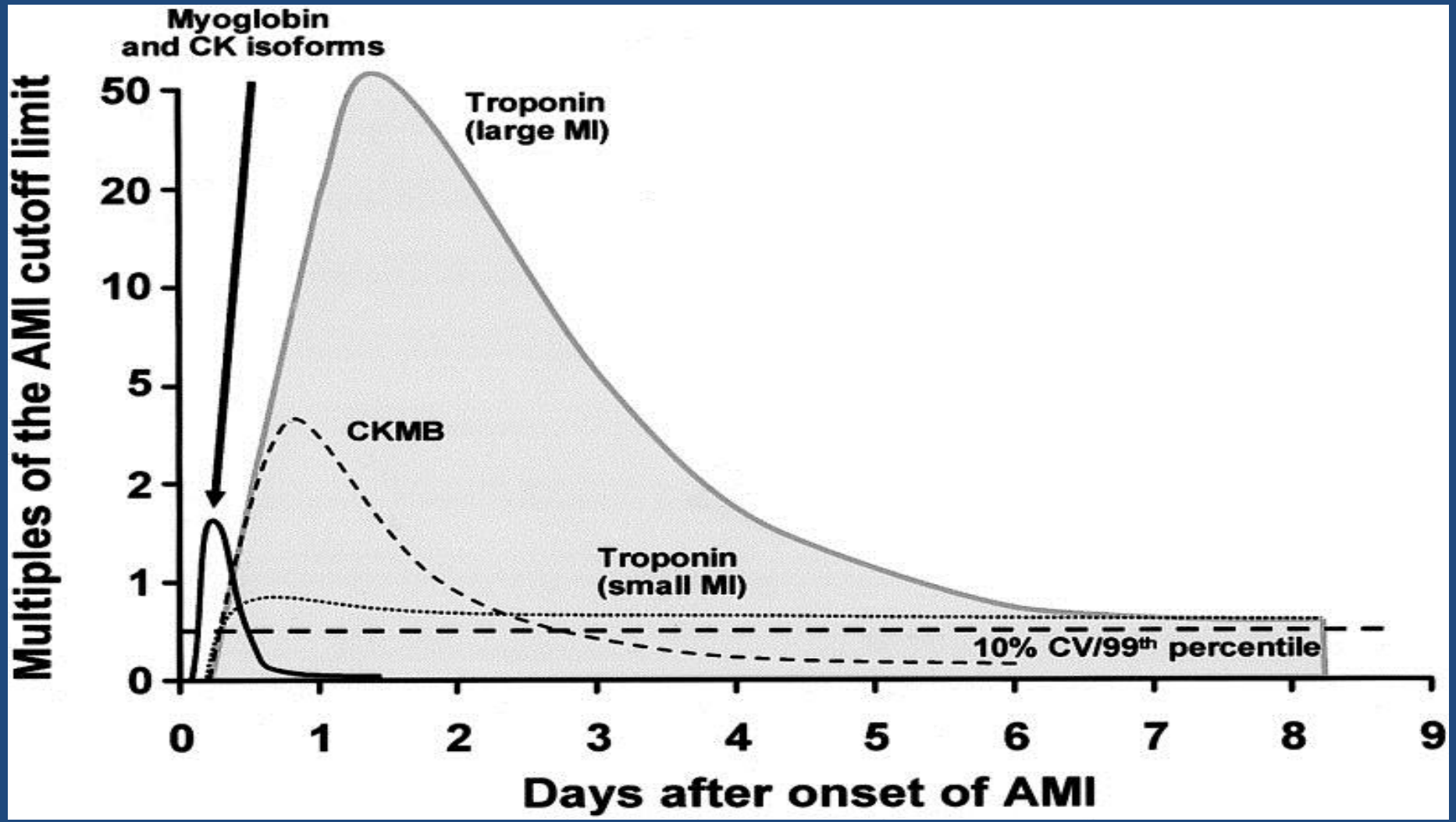
The universal definition for MI is consistent with the pathological definition: The definition seeks to identify the presence of myocardial necrosis in an appropriate clinical setting by measuring highly accurate blood levels of very sensitive and very specific biomarkers of myocardial necrosis.

So, what is wrong with CK-MB?

1. Much less accurate with assays not as standardized as troponin assays;

2. Much less sensitive: Misses many small infarcts;

3. Tremendous variation from hospital to hospital;

4. Definite **FALSE POSITIVES** that can confuse clinicians.

Elevations of Cardiac Troponin Values because of Myocardial Injury

➤ **Injury related to primary myocardial ischemia (MI type 1)**

➤ **Injury related to supply/demand imbalance of myocardial ischemia (MI type 2)**

➤ **Injury not related to myocardial ischemia**

➤ **Multifactorial or indeterminate myocardial injury**

**Third Universal Definition of Myocardial Infarction**

Prognostic implications of troponin measurements
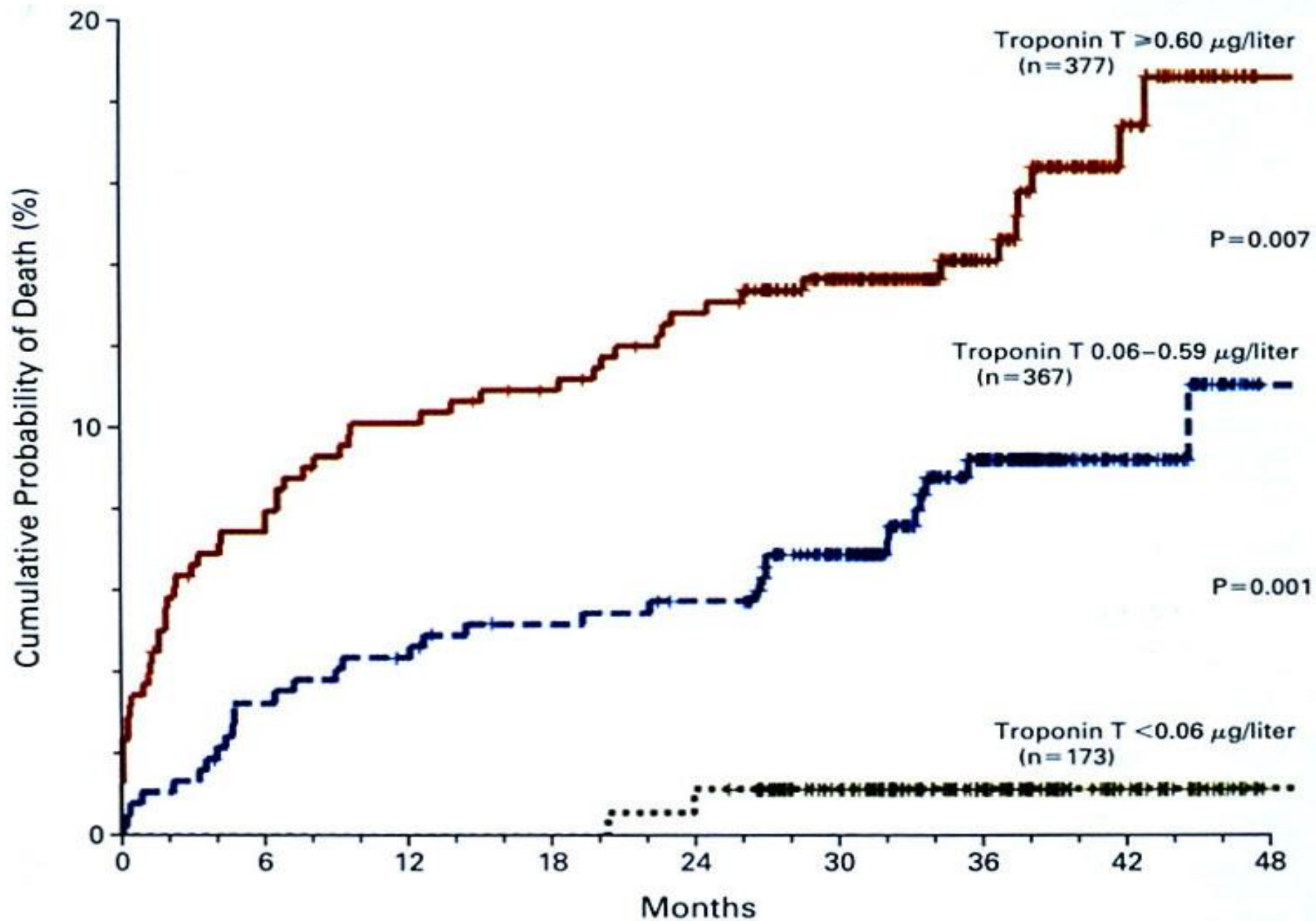
Significance of Myonecrosis on Outcomes after PCI

- **Retrospective, single center analysis (n=5487, Mayo Clinic)**

- **Three groups:**

- **1) Increased cTnT pre-PCI (i.e., NSTEMI or recent MI)**

- **2) Normal cTnT pre-PCI, elevated cTnT post-PCI**

- **3) Normal cTnT pre-PCI and post-PCI**

Prasad A. Circ Intv 2008; 1:10-19.

Significance of Peri-procedural Myonecrosis on Outcomes after PCI
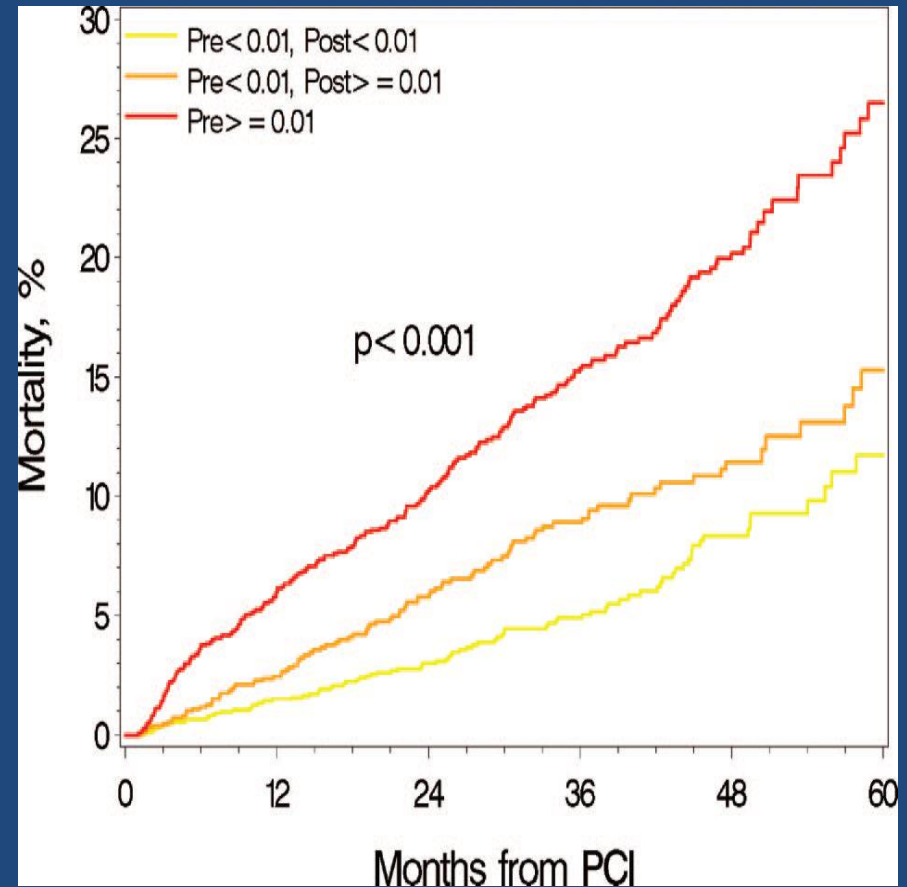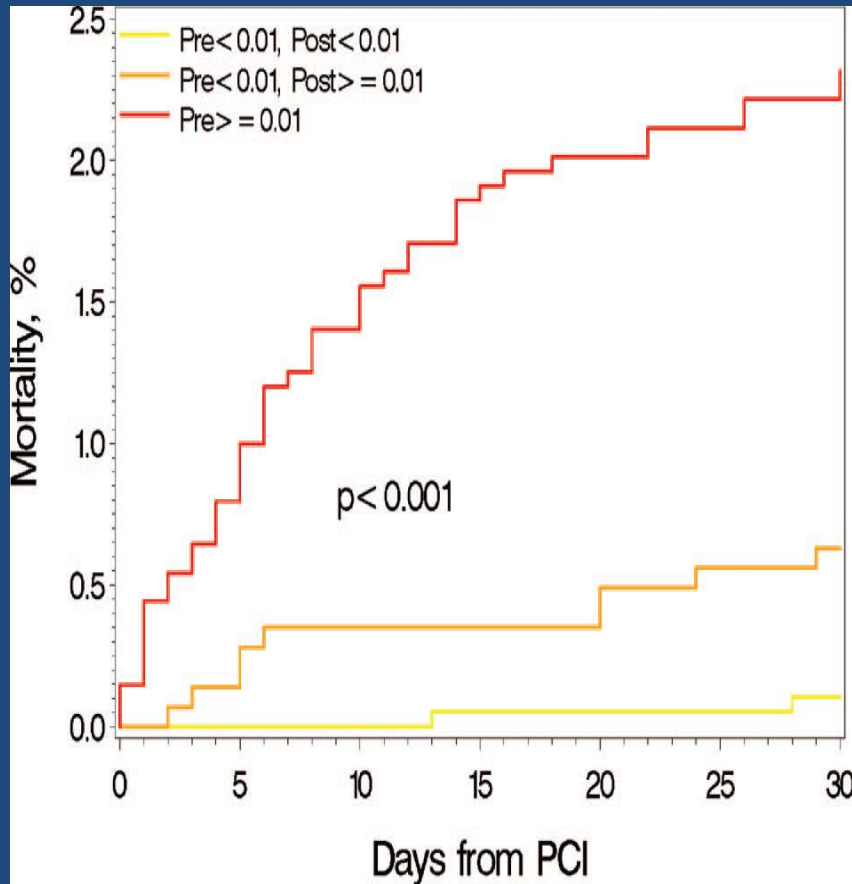
Criteria for Acute Myocardial Infarction

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 together with evidence of ischemia with at least one of the following:

--Symptoms of ischemia

--ECG changes of new ischemia (new ST-T changes or new LBBB)

--Development of pathological Q waves in the ECG

--Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Troponin measurement is the current "gold standard" for identifying myocardial necrosis secondary to ischemia.

Are there new biomarkers that might replace troponin as the best test to identify myocardial necrosis?

1. High sensitivity troponin T (hsTn);
2. B-type naturetic peptide (BNP) – better predictor of prognosis but not accurate at identifying acute phase of MI;
3. Heart fatty acid-binding protein (cytosolic protein in myocytes – H-FABP);
4. Myeloperoxidase (lysosomal protein in neutrophils – MPO).

Inoue et al: Circ J (Japan) 2011; 75: 2813. Haaf et al: Am J Med 2011; 124: 444. Scheven et al: Eur Heart J 2012; 33: 2272. Body et al: JACC 2011; 58: 1332.

Combining troponin (Tn) with B-type naturetic peptide (BNP) gives excellent diagnostic results as well as powerful prediction of longer term prognosis.

Haaf et al: Am J Med 2011; 124: 444; Scirica et al: Eur Heart J 2011; 32: 697.

Other recently suggested biomarkers for identifying myocardial necrosis (1)

- **Placental growth factor (platelet derived protein - PlGF);**

- **Copeptin (c-terminal component of vasopressin);**

- **Soluble fms-like tyrosine kinase-1 (endothelial growth factor);**

- **Circulating microRNAs (multiple cellular roles);**

- **Neutrophil gelatinase-associated lipocalin (neutrophil protein).**

Hochholzer et al: Eur Heart J 2011; 32: 326. Reichlin et al: JACC 2009; 54: 60.
D'Alessandra et al: Eur Heart J 2010; 31: 2765. Lindberg et al: JACC 2012; 60: 339.

Other recently suggested biomarkers for identifying myocardial necrosis (2)

- **Pregnancy-associated plasma protein-A (regulatory protein in cell proliferation);**

- **Metabolomic profiling (assay of multiple small metabolites from bodily fluids).**

- **Many others!!**

Bonaca et al: JACC 2012; 60: 332. Shah SH, Kraus WE, Newgard CB: Circulation 2012; 126: 1110.

High sensitivity troponin assays excellently discriminate between patients with acute myocardial infarction and those with myocardial necrosis from non-ischemic heart injury (area under receiver-operating characteristics curve = 0.94).

Haaf et al: Circulation 2012; 126: 31. Than et al: JACC 2012; 59: 2091.

The
End