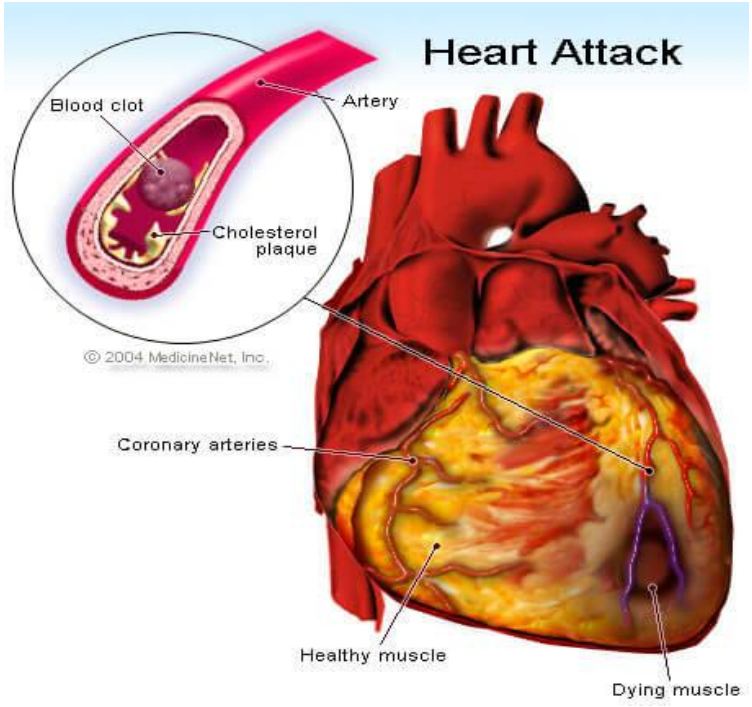
State University of Medicine and Pharmacy "Nicolae Testemitanu"

Department of Biochemistry and Clinical Biochemistry

NEW INTERNATIONAL CRITERIA FOR THE DIAGNOSIS OF MYOCARDIAL INFARCTION AND HIGH SENSITIVE CARDIAC MARKERS

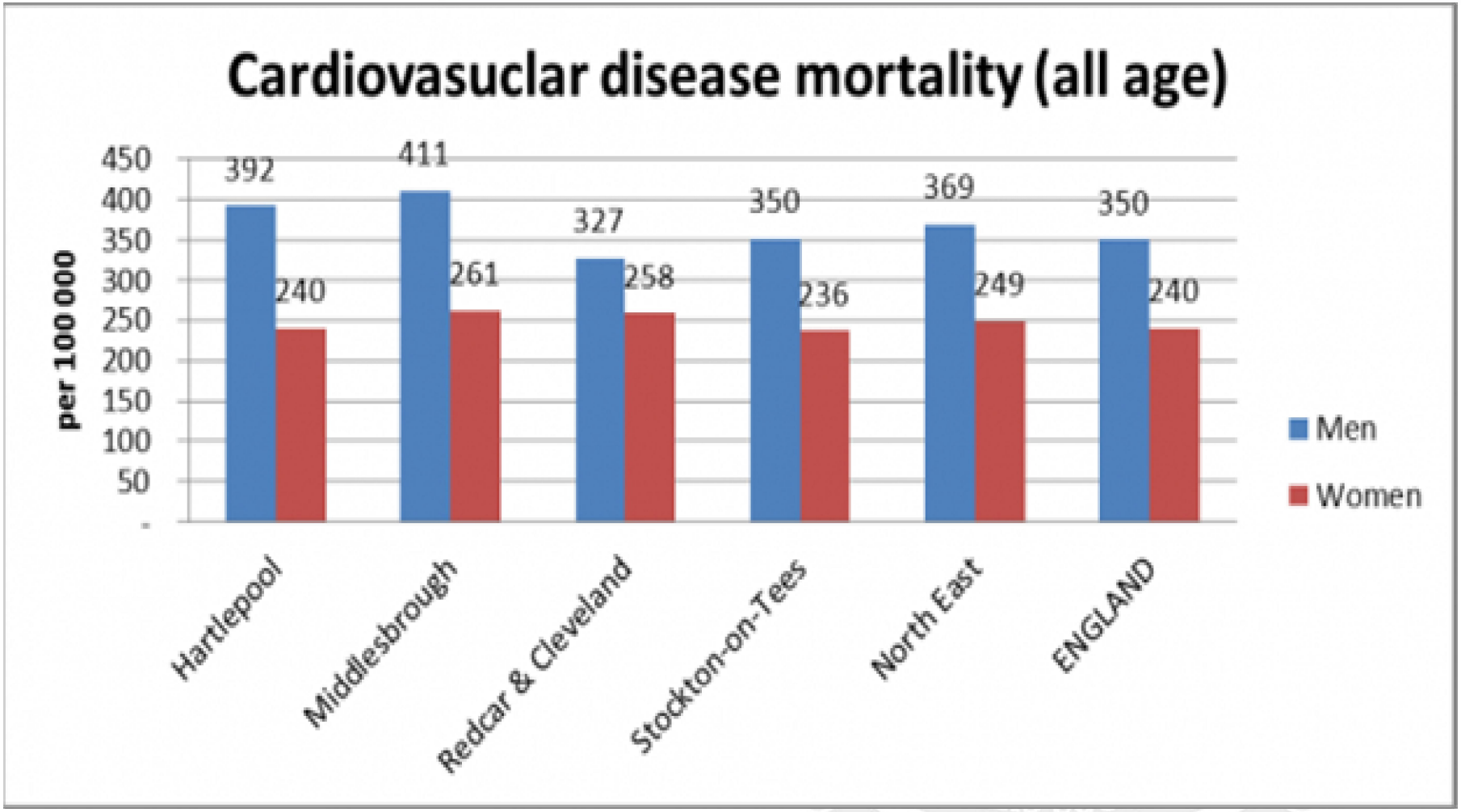


Author: Asla Mohammad, VI year , group M1153

Supervisor: Doctor of Medical Sciences, Assistant Professor Sardari Veronica

The importance of the issue addressed

- Heart disease is the number one cause of death in European countries
- The death rate related to acute MI is approximately three times higher in men than in women.



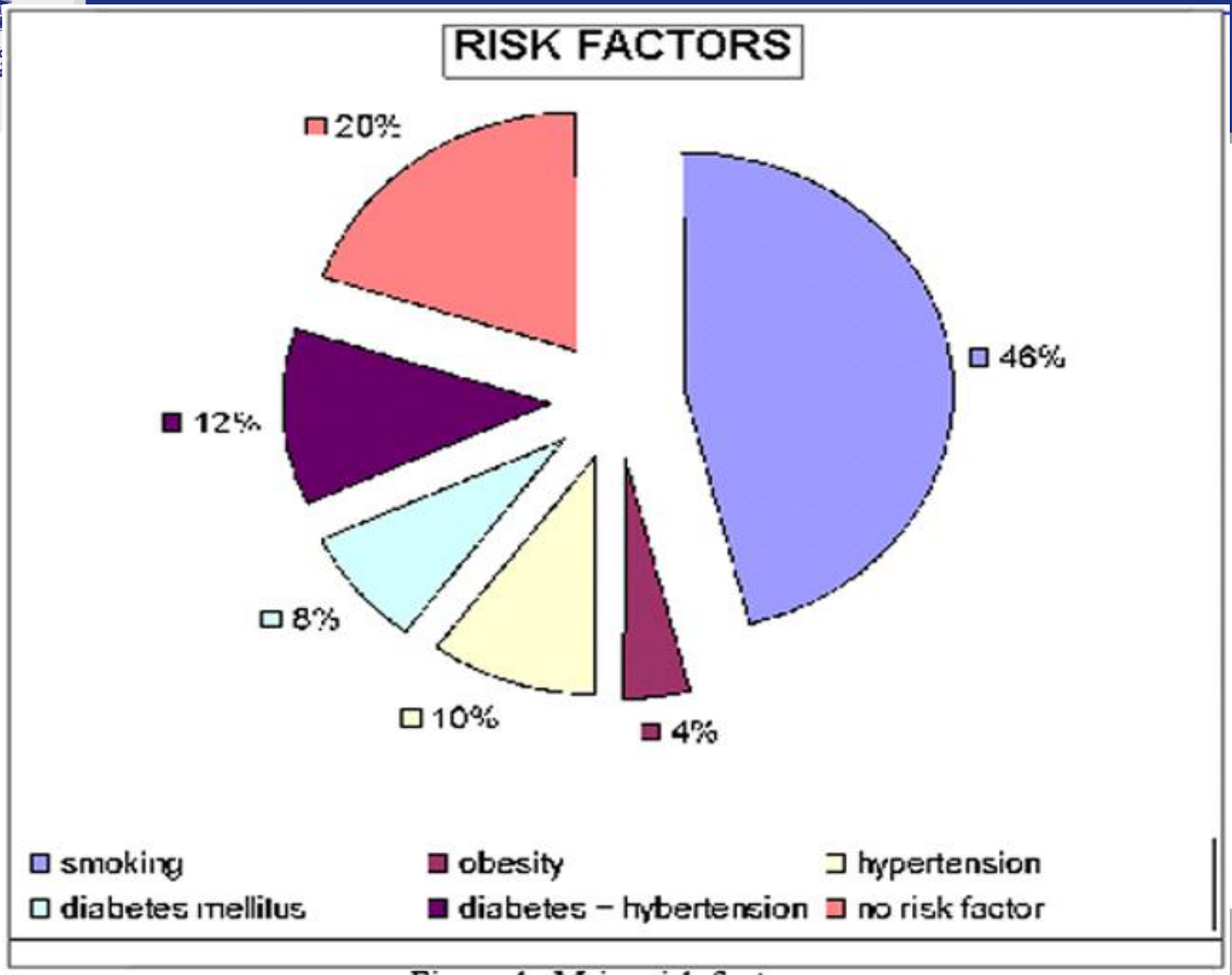
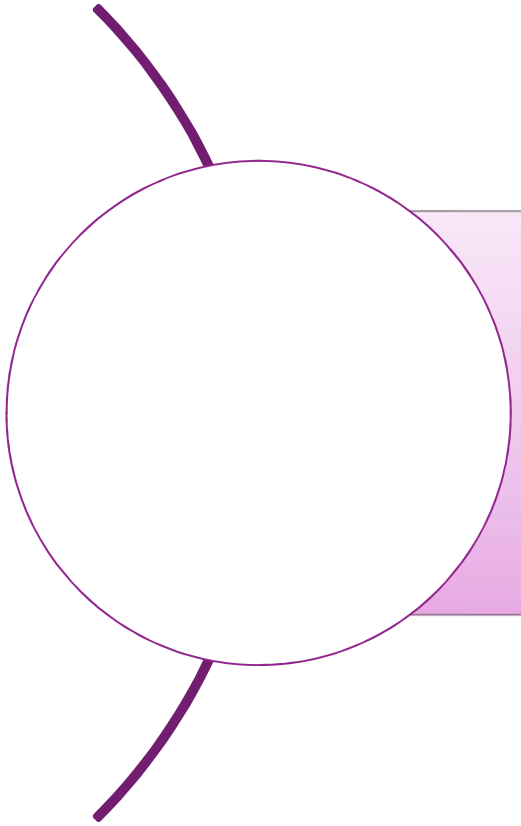


Figure-1: Major risk factors

The purpose of the study



To elucidate the high sensitive cardiac markers to improve early diagnosis of MI and monitoring of effectivness of applied treatment .

Objectives

- Awareness and education about myocardial infarction and its diagnosis.
- Researching of the cardiac markers in myocardial infarction.

- Study of each cardiac enzyme and its role in the diagnosis of myocardial infarction.
- Establish the new criteria of diagnosis and the future marker that could be part of criteria for the diagnosis of myocardial infarction.

Research materials and methods:

In order to accomplish the proposed goal, I conducted the literature review between 1989 and 2016. I used the information resources of the Medical Scientific Library of the State University of Medicine and Pharmacy "Nicolae Testemitanu", as well as the publications from the specialized magazines in the PubMed, Medline, MedScape, and Hinari electronic libraries database of search engines, Wikipedia, Harrison internal medicine, robbins and cottran pathology book, using the following key-words: myocardial infarction, cardiac markers, diagnosis, heart .

Myocardial infarction

- Onset of myocardial ischemia is the initial step in the development of MI and results from an imbalance between oxygen supply and demand, which leads to permanent loss of contraction and other complication.

Classification of MI

MI is classified into various types, based on pathological, clinical and prognostic differences, along with different treatment strategies:

- Type 1: Spontaneous myocardial infarction
- Type 2: Myocardial infarction secondary to an ischemic imbalance
- Type 3: Cardiac death due to myocardial infarction
- Type 4 and 5: Myocardial infarction associated with revascularization procedures

Pathological types:

- Transmural AMI
- Subendocardial AMI

The main classes of biomarkers present in cardiovascular diseases are:

1. Markers of Coronary Inflammatory Syndrome: C-reactive protein (CRP), high- sensitive CRP (hs-CRP), Tumor Necrosis Factor alfa (TNF-alfa).
2. Markers of myocardial ischemia/necrosis: Troponins I and T, creatine kinase (CK) isoform MB, myoglobin.
3. Heart failure markers: Brain natriuretic peptide (BNP), pro BNP, atrial natriuretic peptide.

THE IDEAL CARDIAC MARKER

HIGH SENSITIVITY

High concentration in myocardium
Released after myocardial injury:

Rapid release for early diagnosis.

Long half-life in blood for late diagnosis.

HIGH SPECIFICITY

Absent in non-myocardial tissue.

Not detectable in blood of non-diseased subjects.

ANALYTICAL CHARACTERISTICS

Measurable by cost-effective method

Simple to perform

Rapid turnaround time

Sufficient precision & accuracy

CLINICAL CHARACTERISTICS

Ability to influence therapy

Ability to improve patient outcome

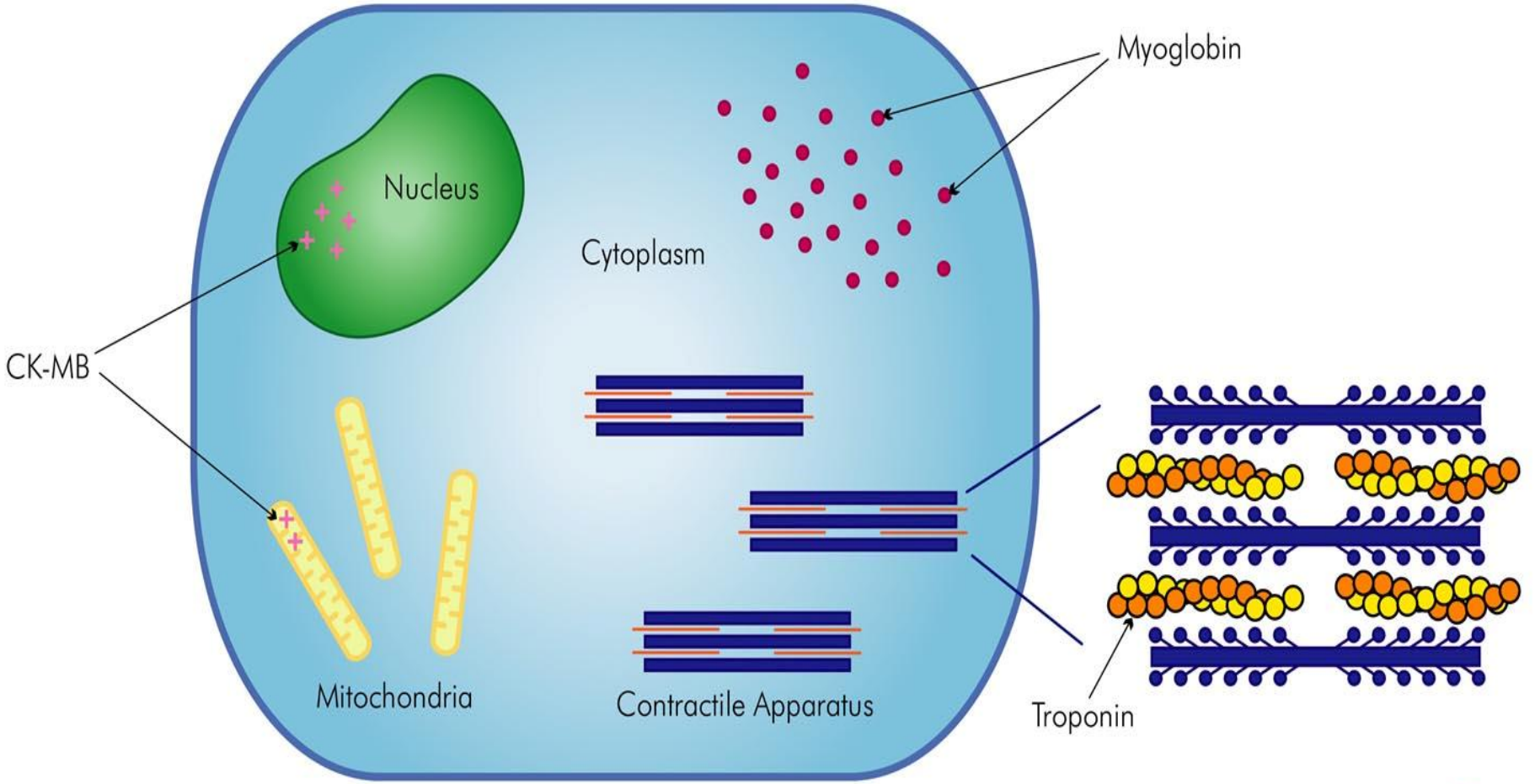
Cardiac marker

- Troponins are the most sensitive and specific test for myocardial damage. Because it has increased specificity compared with CK-MB, troponin is a superior marker for myocardial injury.
- If cardiac troponin assays are not available, the best alternative is creatine kinase-MB (CK-MB) mass assay. This is less tissue-specific than cardiac troponin, but the data documenting its clinical specificity for irreversible injury are more robust.
- Measurement of total CK is not recommended for the routine diagnosis of acute MI, because of the wide tissue distribution of this enzyme.

Cardiac marker

- Total CK, ASAT (aspartate amino transferase), lactate dehydrogenase total and lactate dehydrogenase isoenzymes should not be used to diagnose cardiac damage, due to their low specificity.
- ASAT was the first used. It is not specific for heart damage, and it is also one of the liver function tests.

CARDIAC MUSCLE CELL



Cardiac troponins

- The troponin complex is found on the thin filament (actin) of all types of striated muscle (fast, slow, and cardiac). Its function is to regulate calcium dependent contraction of muscles.
- After myocyte injury, troponin is released in 6 hours and persists for up to 7-10 days.
- Determination of TnT and TnI was proposed as the gold standard for AMI diagnosis.

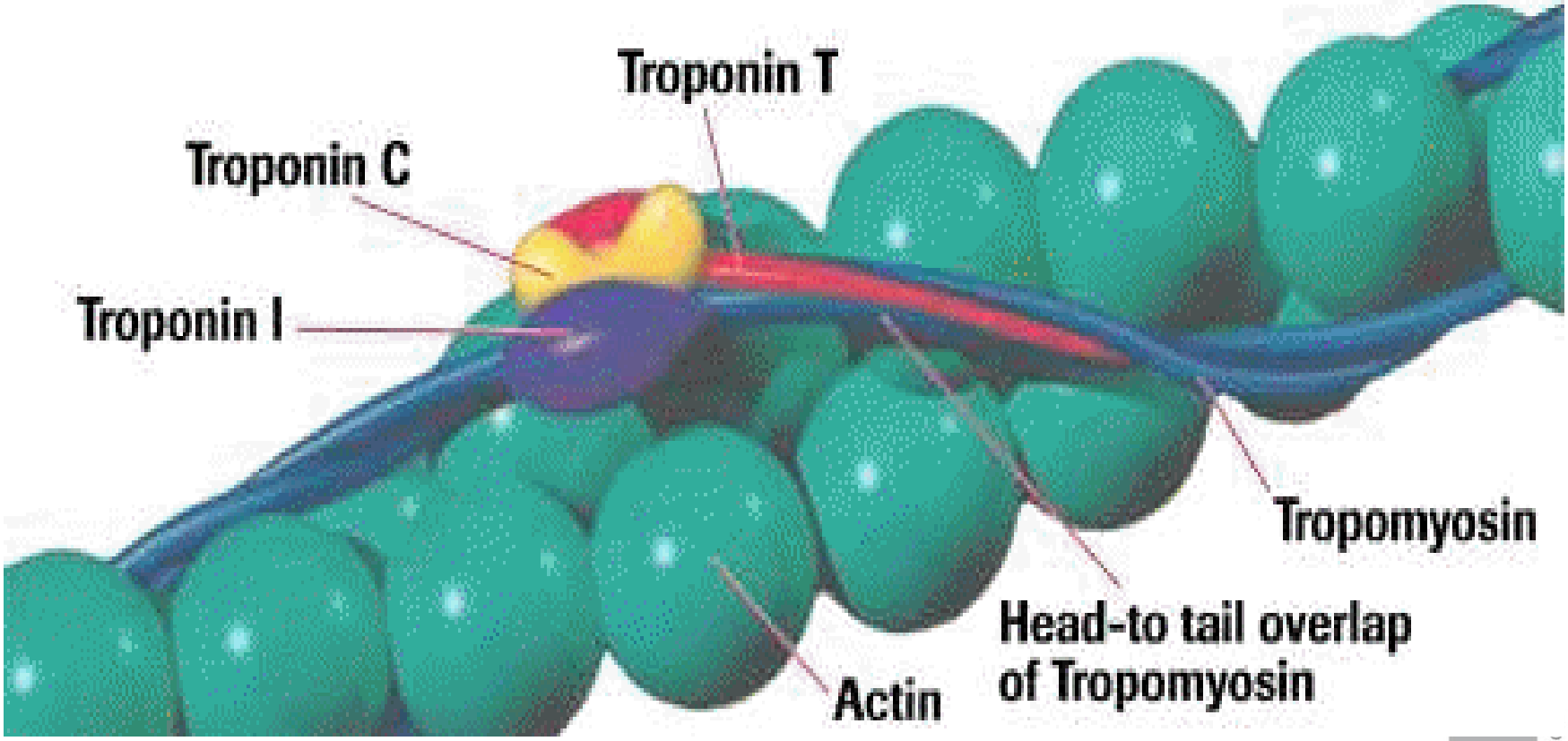
Cardiac troponins

- There are three types of troponins: TnT, TnI and TnC.
- ❑ TnC binds calcium.
- ❑ TnI inhibits the action of the enzyme actomyosin adenosine triphosphatase
- ❑ TnT binds to tropomyosin.
- ❑ Isoforms of the protein, T and I, are specific to myocardium.
- ❑ Troponin T content in cardiomyocytes is doubled comparative to troponin I

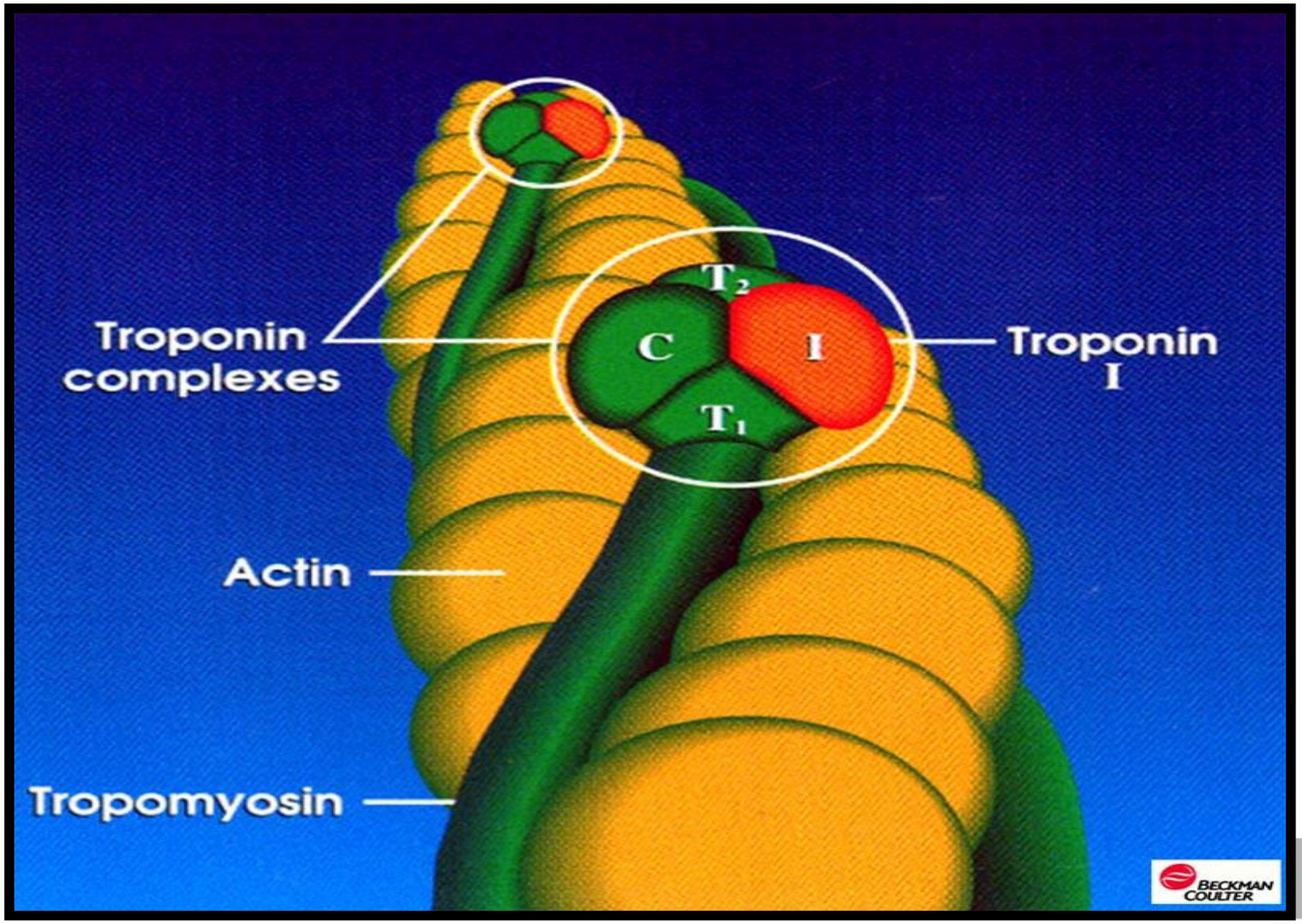
THE TROPONIN REGULATORY COMPLEX

TROPONIN T

A regulatory protein released when cardiac cell necrosis occurs.



THE TROPONIN REGULATORY COMPLEX



Creatine kinase

- Creatine kinase is an enzyme composed of two subunits, M and/or B. Three different pairs of these units combine to give rise to three different isoenzymes, CK-BB, CK-MB and CK-MM.
- CK-MB is the heart specific isoenzyme, represents 20– 30% of total CK .

Creatine kinase and acute myocardial infarction

- It is one of the oldest markers in this field, it has a clinical sensitivity for the diagnosis of AMI of 90%.
- It is released within 4-6 hours, peaks in serum at 24-36 hours, and returns to normal in 48-72 hours.
- As a result of these release kinetics, measurement of total CK is not suitable for the early diagnosis of AMI. CK as a marker is also unsuitable for the detection of myocardial damage.
- CK-MB mass is more sensitive than measurement of activity.

Myoglobin

- Constitutes 2% of the total cytosolic protein content of cardiac muscle.
- Represents low molecular weight (MW) protein
- Skeletal & cardiac muscle Mb are identical
- Serum levels increase within 2h of muscle damage
- Peaks at 6 – 9h
- Normal by 24 – 36h

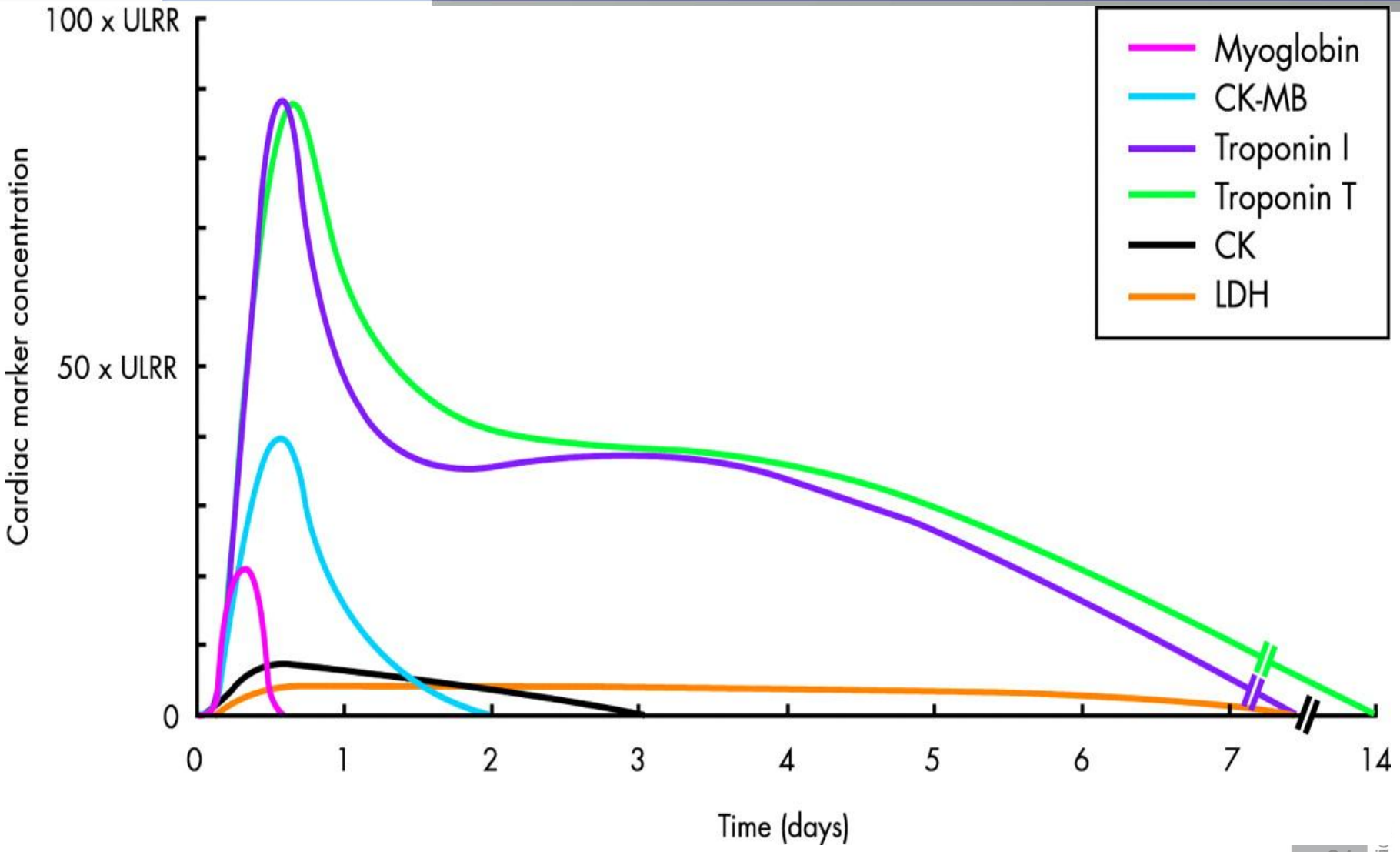
Myoglobin

- Myoglobin is one of the best available early markers of AMI within 2 hours after symptom onset. Rapid myoglobin assays are available, but overall, they have a lack of cardiospecificity.
- Myoglobin is used less than the other markers. It has the advantage of responding very rapidly rising and falling earlier than CK-MB or troponin.
- Small molecules like myoglobin are eliminated very quickly, and large ones like lactate dehydrogenase (LDH) slowly.

Lactate dehydrogenase

- LDH is not as specific as troponin.
- In AMI increased LDH-1 appears in serum after about 10-12 hours, 48-72 hours reaches maximum values, and then returns to normal in 7 to 10 days.
- A high LDH-1 level to LDH-2 suggests MI.

Appearing time of cardiac enzyme in the blood



Ischemia-modified albumin

- Serum albumin is altered by free radicals released from ischaemic tissue.
- IMA can be detected via the albumin cobalt binding (ACB) test, a limited available FDA approved assay. Myocardial ischemia alters the N-terminus of albumin reducing the ability of cobalt to bind to albumin.
- IMA measures ischemia in the blood vessels and thus returns results in minutes rather than traditional markers of necrosis that take hours.

Appearing time of cardiac enzyme in the blood

Marker	Start	Peak	Duration
LDH-1	10 _ 12 h	48 _ 72 h	7 _ 10 days
Total CK	**3** _ 8 h	12 _ 30 h	**3** _ 4 days
CK mass	2 _ **3** h	18 h	**< 24 h**
cTnI	**6** h	24 h	**7** _ 10 days
cTnT	**6 h**	12 _ 48 h	**7** _ 10 days
Myoglobin	**2** h	**6** _ **9** h	24 _ 36 h
IMA	Few minutes	**2** _ **4** h	**6** h

Markers for diagnosis of myocardial infarction.

Recent

- Troponins (T, I)
- CK-MB mass
- Myoglobin

Future

Glycogen phosphorylase isoenzyme BB

Heart-type fatty acid binding protien

Lipoprotein-associated phospholipase A2

Myeloperoxidase

Oxidized Low-Density Lipoprotein

Homocysteine

Superoxide dismutase

Traditional

AST activity

LDH activity

LDH isoenzyme

CK total

CK-MB activity

CK- isoenzyme

Glycogen phosphorylase isoenzyme BB

- Glycogen phosphorylase isoenzyme BB (GPBB) is one of the three isoforms of glycogen phosphorylase. This isoform of the enzyme exists in cardiac and brain tissue.
- The enzyme is one of the "new cardiac markers" which are discussed to improve early diagnosis in acute coronary syndrome. During the process of ischemia, GP-BB is converted into a soluble form and is released into the blood.
- A rapid rise in blood levels can be seen in myocardial infarction and unstable angina.
- GP-BB is elevated 1–3 hours after process of ischemia.
- It is not cardiac specific

Heart-type fatty acid binding protein

- H-FABP is involved in active fatty acid metabolism where it transports fatty acid from cell membrane to mitochondria for oxidation.
- Its small size will facilitate its rapid diffusion through interstitial space.
- appearing as early as 1-3 hrs after onset of MI and peaking within 6 hrs, it returns to normal within 12-24 hrs.
- It has low specificity for myocardial tissue, but 20 time more specific than myoglobin. Its combination with troponin will increase its accuracy.
- In addition to its diagnostic potential, H-FABP also has prognostic value. It was the only cardiac biomarker that proved to be a statistically significant predictor of death or MI at one year.

Lipoprotein-associated phospholipase A2

- Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an enzyme produced by inflammatory cells and hydrolyzes oxidized phospholipids in LDL.
- Lp-PLA_2 is a novel biomarker of vascular-specific inflammation that provides information about atherosclerotic plaque inflammation and stability.
- Elevated levels of serum Lp-PLA_2 are indicative of rupture prone plaque and a strong independent predictor of cardiovascular risk, including coronary artery disease, MI, and stroke.

Myeloperoxidase

- Myeloperoxidase is stored in azurophilic granules of polymorphonuclear neutrophils and macrophages. This enzyme has been implicated in the oxidation of lipids contained within LDL.
- Myeloperoxidase participates in the inflammatory process of ACS, that's why is useful as a marker.

Oxidized Low-Density Lipoproteins

- Oxidized Low-Density Lipoproteins (OxLDL) particles pose a risk for cardiovascular disease when they invade the endothelium and become oxidized, since the oxidized forms are more easily retained by the proteoglycans.
- Circulating OxLDL - specific markers strongly reflect the presence of ACS.

Homocysteine

- A high level of homocysteine (HCys) in the blood makes a person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which in turn may lead to atherogenesis, which can result in ischemic injury.
- Hyperhomocysteinemia (HHCys) is therefore a possible risk factor for coronary artery disease.
- HCys was demonstrated to contribute to the initiation and progression of vascular disease by activating monocytes, resulting in the secretion of cytokines that amplify the inflammatory response.

Superoxide dismutase

- Superoxide dismutase (SOD) is the antioxidant enzyme in response to increased free radicals to prevent vascular damage.
- SOD and the other enzymes may represent a good therapeutic target against reactive oxygen species (ROS), but they are not useful markers for the diagnosis of coronary artery disease (CAD).

Conclusions

- Practical application of traditional cardiac markers of myocardial necrosis in acute coronary syndrome has a number of essential disadvantages due to the low specificity of enzyme markers (ASAT, LDH, total CK and CK-MB) and protein marker – myoglobin.
- Troponins are the most sensitive and specific test for myocardial damage and were proposed as the gold standard for AMI diagnosis, but they havnt 100% specificity, that needs the development of new cardiac markers.
- At the moment, many diagnostic and therapeutic cardiology issues are waiting for their solutions, and we hope that with the rapid development of genomics and proteomics, it will be developed new markers significantly superior in the performance currently available.