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Milestone of Cardiac Biomarkers

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ABSTRACT
Cardiovascular diseases (CVD) remain the leading cause of death globally, responsible for over 20 million deaths annually. Myocardial infarction (MI), a key manifestation of CVD, results from myocardial ischemia and has seen a notable rise in prevalence, particularly in developing regions. In 2015, CVD accounted for 17.9 million deaths, with significant regional disparities in mortality rates. In contrast, emerging economies, including Egypt, are witnessing an increase in age-adjusted incidence of CVD. Egypt, with one of the highest rates of CVD mortality, faces a particularly high burden of acute coronary syndrome (ACS). This review underscores the importance of cardiac marker comparing each of them, mentioning advantage, disadvantage, and uses of each. As the implementation of effective, evidence-based medical treatment and revascularization in patients with suspected acute coronary syndrome, a speedy and correct diagnosis is crucial; therefore the correct usage of this marker is a must.

Keywords:
Myocardial Infarction Cardiac Biomarkers, Cardiac, Diagnosis of MI, ideal cardiac biomarker

1. Introduction:

Cardiovascular illnesses are the main cause of death in humans, accounting for over 20 million deaths annually. A heart attack or myocardial infarction (MI) is damage to the heart muscle brought on by myocardial ischemia (Vos et al., 2016). Having 17.9 million deaths worldwide in 2015, cardiovascular (CV) illnesses were the greatest cause of death among non-communicable diseases (H. Wang et al., 2016). This increase hides a considerable variation in trends and in epidemiology for different regions of the world As a general rule, developed regions such as Western Europe, North America, and Australia, New Zealand are considered to be in the fourth (highly advanced) stage of what is known as the "epidemiological transition" of health burden (Yusuf et al., 2004). Epidemiological shift predicts that advanced economies would see a decline in infection-related illnesses such as rheumatic heart disease and dietary deficiency-induced conditions affecting the heart muscle. On the contrary, due to changing lifestyles and longer life expectancies, there is a marked rise in the age-adjusted incidence of non-communicable diseases like CVD in emerging economies (H. Wang et al., 2016). Over the past three or four decades, age-adjusted mortality rates linked to CVD have steadily and significantly decreased in developed nations (Capewell & O'Flaherty, 2008).

Egypt has one of the highest rates of CVD mortality when compared to other regions and the entire world (Ramadan A etal, 2024). A study evaluating the prevalence of common risk factors and mitigation methods for acute coronary syndrome (ACS) Data from 11681 patients with ACS were gathered between November 2015 and August 2017 at 30 coronary care centers covering 11 governorates in Egypt, including the Mediterranean coast, the Nile Delta, and Upper Egypt. The patients were identified by the tests CKMB, Troponin, and ECG. ST-elevation myocardial infarction (STEMI) was the most common myocardial infarction in men (49%), whereas unstable angina and non-ST-elevation myocardial infarction (NSTEMI) were more common in women. Central obesity affected 80% of men and 89% of women, and 32% of both sexes had atherogenic dyslipidemia. 62% of men and 72% of men under 55 reported currently smoking. 53 vs 34% of males had type 2 diabetes, 69 vs 49%

had hypertension, 69 vs 49% had dyslipidemia, and 71 vs 41% of women had obesity (p 0.001 for all). The majority of diagnostic and therapeutic treatments showed no gender differences (Reda et al., 2019). **Compared to European countries, Egyptian STEMI patients were younger (mean age 55.4), more frequently current smokers and diabetics** (Shaheen et al., 2020).

Myocardial infarctions can happen repeatedly in patients with established disease or they might be the initial sign of coronary artery disease. The World Health Organization (WHO) used symptoms, ECG abnormalities, and enzymes to identify myocardial infarction in investigations of disease prevalence. However, the diagnosis of ever-increasing quantities of cardiac necrosis is now possible thanks to the development of more sensitive and precise serological biomarkers and precise imaging techniques detecting even small necrosis (Thygesen, Alpert, & White, 2007).

Major American and European cardiac groups issued a consensus statement in **2007** that provided a common definition of MI. This definition added lab testing and clinical history to the prior terminology. **Blood tests that are sensitive to cardiac muscle injury (troponin I or T) and clinical evidence supporting an AMI diagnosis** as described above were used to define MI as an incident. With this inclusive definition, thrombus in the epicedial artery was not a need for all NSTEMI (Saleh & Ambrose, 2018).

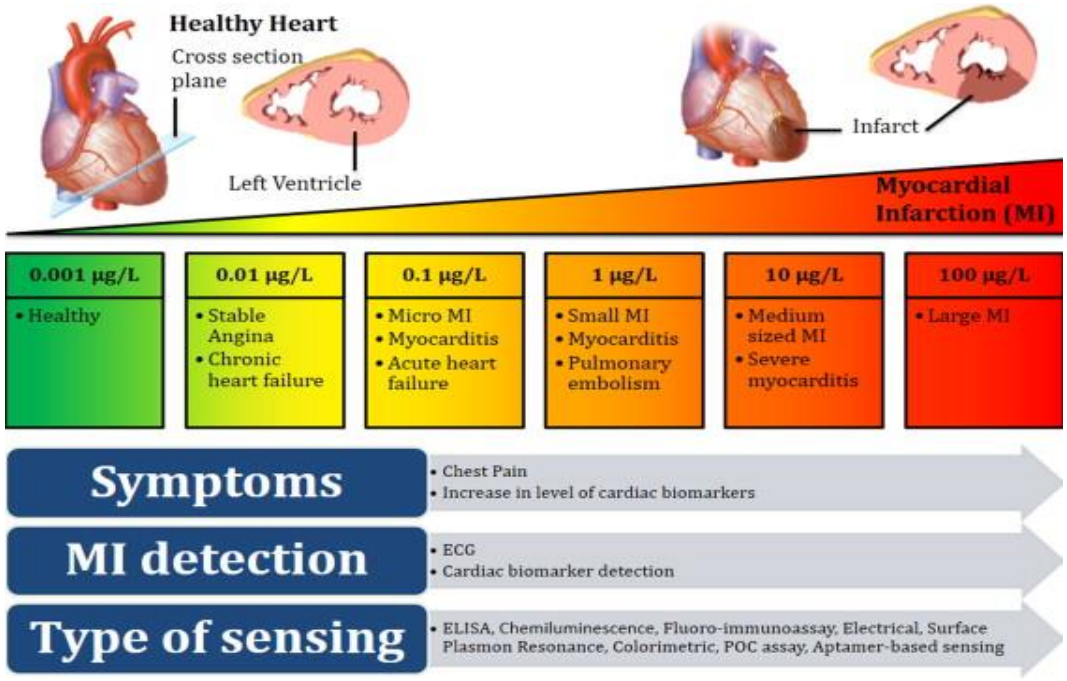

Figure (1): **Diagnostics on myocardial infarction (MI).** Troponin concentration level, symptoms, current methods of MI detection, and methods of cardiac biomarker detection are described (Fathil et al., 2015).

Myocardial infarction has been subdivided in 2008 into 5 subtypes; Type 1 myocardial infarction is caused by the crack, erosion, or rupture of an atherosclerotic plaque, followed by coronary arterial thrombosis. Patients with type 1 myocardial infarctions, which can have a ST elevation or not, are often treated with medication and stenting of the coronary artery lesion that is the cause of the infarction. Ischemia leads to type 2 myocardial infarction, although there hasn't been any fissure, erosion, or disruption of the atherosclerotic plaque. A patient with type 3 myocardial infarction has a traditional myocardial infarction presentation, such as a characteristic ST-elevation ECG, but no troponin blood test was carried out. In nations with strong economies, this circumstance is exceptional. In the context of a percutaneous coronary intervention in the catheterization lab, type 4 myocardial infarction occurs, typically as a result of a procedure-related complication. Similar to type 4, type 5 only happens during coronary bypass surgery (Akbar, Foth, Kahloon, & Mountfort, 2024). Patients with elevated blood troponin levels but without clinical evidence of ischemia are said to have had a myocardial injury, eg. from sternal trauma) is associated with a rising and falling pattern of troponin elevation when serial testing is performed (Babuin & Jaffe, 2005).

The novel class concerning an unusual form of myocardial infarction: **myocardial infarction with non-obstructed coronary arteries (MINOCA).** Clinical research studies of MINOCA have yet to completely reveal the pathophysiology of this syndrome. Several mechanisms, including coronary artery vasospasm, coronary embolism, and a hypercoagulable condition, have been put forth. Many pathophysiological occurrences seem to be able to cause MINOCA (Shamsi, Hasan, Hashmani, Jamal, & Ellaham, 2021).

The 4th Universal Definition of Myocardial Infarction has stimulated considerable debate since its publication in 2018. When patients demonstrate diagnostic ST elevation or not, it is utilized to categorize routine cardiovascular events in those patients. Such patients are nearly always first diagnosed by a troponin concentration over the 99th percentile, which is considered "normal." Myocardial damage is believed to be continuous in all individuals with a cardiac Troponin concentration over the Threshold; in those with a dynamic rise or fall, the damage is considered to be acute/unstable; in those with more static concentrations, the damage is considered to be chronic/stable (Alaour, Liew, & Kaier, 2018).

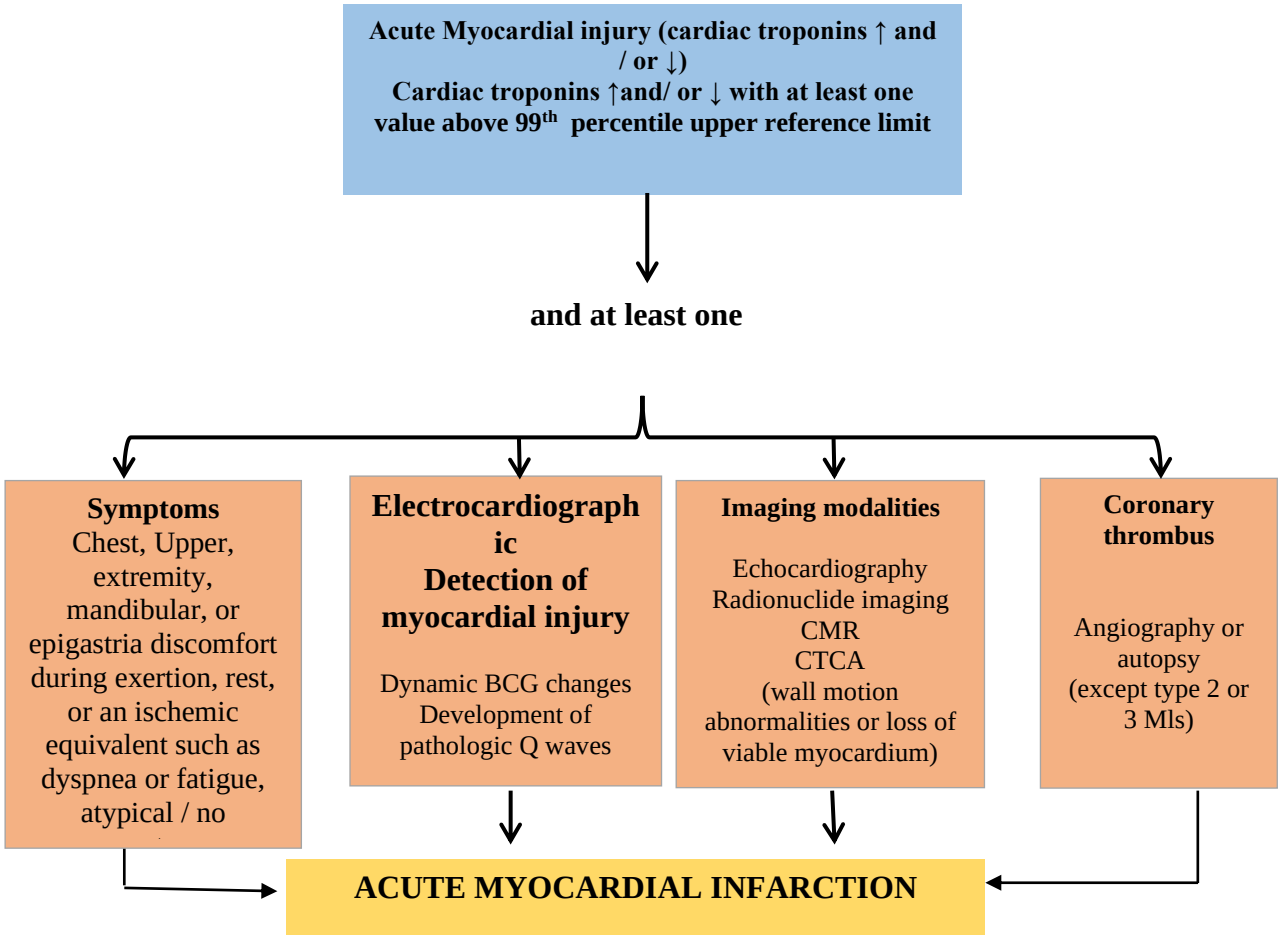

Figure (2): **Schematic diagram of the universal definition of acute myocardial infarction (Collet et al., 2021).** CMR—cardiac magnetic resonance; CTCA—computed tomographic angiography; MI—myocardial infarction; cTn—cardiac troponins

In addition to ECG, echocardiography, coronary angiography, etc., circulating biomarkers are essential for MI diagnosis. The MI circulating biomarkers have gone through a long process from discoveries to clinical applications.

The AMI circulating biomarkers can be divided into three categories (Wu et al., 2020)

(1) Biomarkers originated from damaged myocardial tissues and were released into blood circulation

(2) Biomarkers with elevated levels in blood circulation due to systems reactions after the MI events

(3) Biomarkers with abnormal serum levels before the occurrence of MI event

Table (1): Biomarkers with abnormal serum levels before the occurrence of MI event (Saleh & Ambrose, 2018)

Abbreviation	Full name	Characteristics	Remarks
Ils	Interleukins	"Targeting IL-1 could be a novel therapy pericarditis associated with inflammasome activation after MI	IL-IRa may have a predictive effect on MI
IGF-1	Insulin-like growth factor 1	"Reduce adverse cardiac remodeling "improve ventricular arrhythmia	Cannot be used to diagnose MI
VEGE	Vascular endothelial growth factor	"An independent risk fator for adverse clinical outomes after AMI	Different subtypes have various effect
MMPs	Matrix metaloproteinases	Circulating MMP-28, a predictor for short-term prognosis in patients with MI	-

Table (2): Current and Historical Biomarkers originated during Myocardial Infarction (Tilea, Varga, & Serban, 2021)

Biomarker	TFPT	TPL	TRB	Sensitivity	Specificity	PPV(%)*	NPV(%)*
AST	12-24	24-48	10-14 days	75	71	75	71
LDH	6-12	24-72	8-14 days	82	70	76	77
Myoglobin	0.5-2	6-12	12-24 h	79	89	98	60
CK	3-8	12-24	48-72 h	95	68	30	99
CK- MB	4-8	12-24	48-72 h	92	90	98	83
			5-10 days (Tnl)				
cTn	3-6	10-24	10-14 days (TnT)	97-100	94-97	98-99	88-100

TFPT- time to first positive test; h- hours; TPL- time to peak levels; TRB- time to return to baseline PPV- positive predictive value; NPV- negative predictive value; AST- aspartate aminotransferase; CK- creatine kinase; CK-MB- creatine kinase- myocardial band; cTn- Cardiac troponins (i.e., and I); LDH- lactate dehydrogenase. * Data reflect values obtained for serial measurement.

The term **biomarker** is an abbreviation for "biological marker" a phrase first introduced in 1989. In 2001, the definition of biomarker was reined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes or pharmacologic responses and, or pathogenic processes (Atkinson, Colburn, DeGruttola, DeMets, & Gregory, 2001). **Cardiac Biomarkers**

Are intracellular proteins released from a heart muscle, significantly elevated during heart muscle damage. Cardiovascular (CV) illnesses can be addressed by using biomarkers to accurate and robust, guide diagnosis, and estimate prognosis (Morrow & de Lemos, 2007). The term "specificity" often refers to the qualities or characteristics of a single entity. In biology and clinical biochemistry, one must distinguish "analytical specificity," which refers to the ability of an assay to measure a well-defined molecule or substance, i.e. an analyte, rather than others, from "diagnostic specificity," which refers to the statistical percentage of individuals without a given condition who are correctly identified as negative by an assay (Saah & Hoover, 1997). **For the implementation of effective, evidence-based medical treatment and revascularization in patients with suspected acute coronary syndrome, a speedy and correct diagnosis is crucial** (Garg et al., 2017).

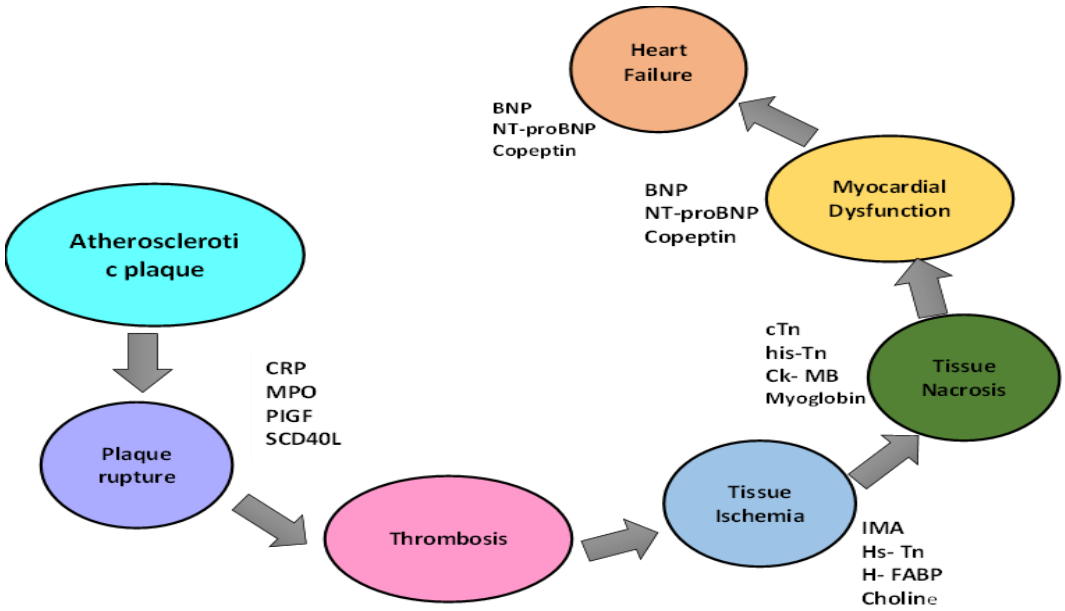

Figure (3): **The Pathogenesis of Schematic of MI and its consequences.** The biomarkers implicated in each process are listed next to the bubble (Ahmad & Sharma, 2012).

Table 3: Characteristics of an ideal cardiac biomarker

High sensitivity
High concentration in myocardium after myocardial injury
Rapid release for early diagnosis
Long half-life in blood for late diagnosis
High specificity
Absent in non-myocardial tissues
Not detectable in blood of non-diseased subjects
Analytical characteristics
Measurable by cost-effective assay
Simple to perform
Rapid turnaround time
Sufficient precision and trueness
Clinical characteristics
Ability to influence therapy
Ability to improve patient outcome

Biomarkers for Acute Myocardial Infarction Diagnosis:

Myocardial necrosis triggers the release of cardiac enzymes into the bloodstream. Hence, myoglobin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and creatine kinase (CK), as well as the idea of delta change, were established as the first biomarkers of AMI (acute myocardial infarction). AST and LDH were historically the first cardiac enzymes utilized to AMI (Parsanathan & Jain, 2020).

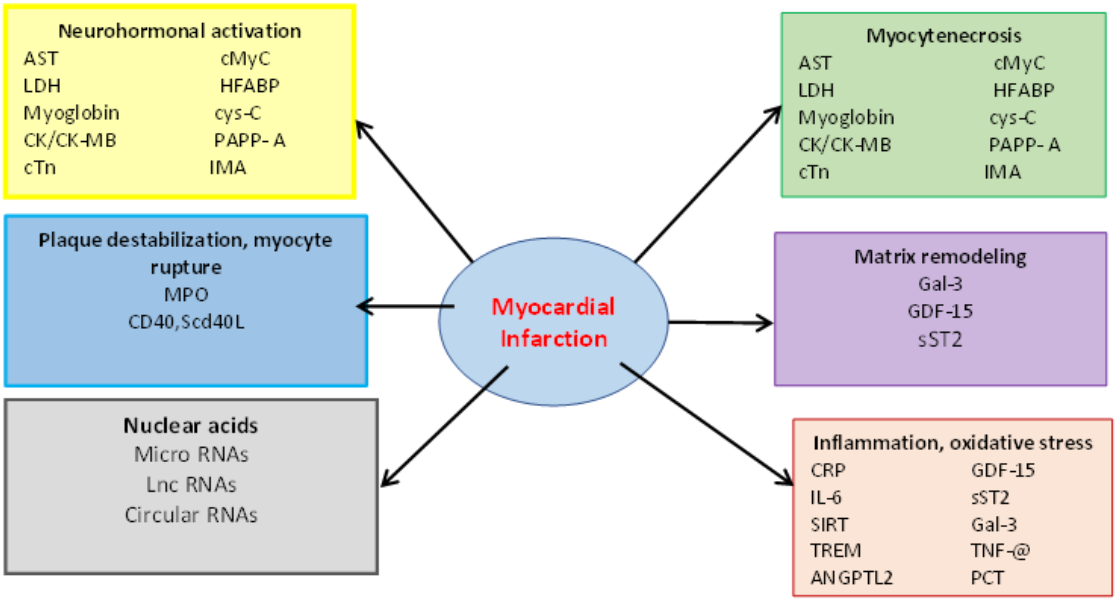

Figure (4): **Pathophysiological pathways in acute myocardial infarction and examples of Biomarkers (Tilea et al., 2021)**. ANGPTL2—angiopoietin-like 2; BNP—B-type natriuretic peptide; CD40—cluster of differentiation 40; cMyC—cardiac myosin-binding protein C; CRP—C-reactive protein; cys-C—cystatin C; Gal-3—galectin-3; GDF-15—growth differentiation factor 15; hFABP—heart-type fatty acid binding protein; IL-6—interleukin 6, IMA—ischemia-modified albumin; LncRNAs—long non-coding ribonucleic acids; MPO—myeloperoxydase; MR-proADM—midregional proadrenomedullin; NT-proBNP—N-terminal fragment of the B-type natriuretic peptide precursor; PAPP-A—pregnancy-associated plasma protein-A; PCT—procalcitonin; RNA—ribonucleic acids; sCD40L—soluble ligand of cluster of differentiation 40; SIRTsirtuins; sST2—soluble suppression of tumorigenicity factor 2; TNF-_—tumor necrosis factor

1. Aspartate Aminotransferase:

Aspartate aminotransferase is a ubiquitous, soluble, intracellular enzyme critical in amino acid metabolism. The largest amounts of AST are expressed in the liver, the myocardium, the kidney, and the skeletal muscle, In 1954, Ladue et al. demonstrated a significant rise in AST 3–4 h after an AMI. The ubiquitous expression of AST in a wide variety of tissues significantly affects its specificity for myocardial injury, limiting its use as a cardiac biomarker. Currently, AST is no longer used for AMI diagnosis (Ladue, Wroblewski, & Karmen, 1954).

2. Lactate Dehydrogenase

LDH was included as a cardiac biomarker only one year after AST. Blood levels of LDH normally rise within 6–12 hours following the onset of AMI, reach a peak within 1–3 days, and return to baseline within 8–14 days. LDH, like AST, is expressed in a wide variety of tissues, including liver, kidney, heart, red blood cells, lung, and especially skeletal muscle, making it a marker with low specificity for cardiac injury. The LDH-1/LDH-2 ratio of >1 has been proposed as a biomarker for AMI, but it did not seem to be a reliable AMI biomarker. Currently, LDH is only used to differentiate between acute and subacute AMI in the late phase of an ischemia event, after other cardiac indicators have returned to normal levels (Rotenberg et al., 1988).

3. Myoglobin:

Myoglobin is an iron- and oxygen-binding protein with a low molecular weight that is highly expressed in the heart and skeletal muscle. Myoglobin is rapidly secreted by myocardial that has been damaged. Myoglobin's blood levels begin to rise 30 minutes to 2 hours after the onset of ischemia, making it a useful marker for the early detection/exclusion of heart damage. Its levels rise over the first 6–10 hours following an AMI, peak 12

hours after the acute episode, and return to baseline 24 hours later. Myoglobin is exclusive to muscle, making it a sensitive marker for acute myocardial infarction (AMI) with a high negative predictive value; hence, it is a valuable test for immed**i**ately ruling out AMI in the emergency room (Malasky & Alpert, 2002).

4. Creatine Kinase

Creatine kinase (CK) activity was considered a better predictor of myocardial injury and an independent indicator of AMI for 20 years (Knudsen, Steenstrup, Byrjalsen, Hildebrandt, & Sørensen, 1989). CK is a dimeric enzyme, consisting of two subunits, M and B, and has three isoenzymes, CK-BB (CK1), CK-MB (CK2), and CK-MM (CK3) (Schlattner, Tokarska-Schlattner, & Wallimann, 2006). Only CK-MB is discovered in the heart, but CK-MB is also recognized in other organs, including the uterus, tongue, etc (Ingwall et al., 1985). When released into the blood, CK-MB can be subdivided into MB1 and MB2 groups. When AMI develops, CK-MB is released into the bloodstream, accompanied by a substantial shift in the MB2:MB1 ratio. A ratio of MB2 to MB1 less than 1.5 is considered indicative of AMI (Aydin, Ugur, Aydin, Sahin, & Yardim, 2019). Ultimately, the correlation between total CK and CK-MB levels and infarct size enables prognostication (Hawkins & Tan, 1999). **CK-MB cannot identify mild myocardial injury**, however. With a sensitivity and specificity of 91% for the diagnosis of AMI during the first 6 h following the beginning of symptoms and a return to baseline within 48–72 h, CK-MB had become a popular emergency department (Keffer, 1996). A new assay known as **CKMB mass (CKMBM)**, in which CKMB was measured in terms of its protein concentration rather than its biological activity. CKMB mass has been measured by electro chemiluminescence technology (Serdar et al., 2005). CKMB mass (CKMBM) is the preferred marker for the detection of re-infarction. The activity of CKMB in the serum can be influenced by light, temperature, pH and prolonged storage (Perry, Doumas, & Jendrzejczak, 1979).

Marwah et al, compared clinical and analytical CKMB enzyme activity (CKMBE) and the CKMBM concentration in patients with acute coronary syndrome. The correlation between the methods initially was fair, while it was good at the peak levels i.e. at 12–24 h but at 48–72 h it was poor (Marwah, Shah, Chauhan, Trivedi, & Haridas, 2014).

5. Cardiac Troponin:

Elevated serum cardiac troponin (cTn) concentration is the definitive gold standard for AMI. Combining alterations in cTn with clinical symptoms and ECG could initially diagnose AMI in the early stage following the start of chest discomfort, thereby considerably reducing mortality. Troponin exists as a hetero-trimer consisting of troponin I (TnI), T (TnT), and C (TnC) subunits in the myocardium. As part of the thin filaments of the cardiac sarcomere, the troponin complex interacts with tropomyosin, controlling the calcium-dependent interaction of actin and myosin in response to cytosolic calcium fluctuations. TnC is also present in striated muscle, rendering it unsuitable for AMI diagnosis, but TnT and TnI are heart-specific and are hence referred to be "cardiac troponins." troponin I and troponin T are both proteins, not enzymes, as should be noted. Troponin I is the most specific of these biomarkers for myocardial necrosis. Troponin I and troponin T (both conventional and high sensitivity) are currently the most common diagnostic tests for AMI. High sensitive (hs)-cTn assays measure cTn concentrations that are five to one hundred times lower than standard tests. Anda et al. proposed that the application of risk stratification thresholds for hs-cTnl could identify patients with suspected acute coronary syndrome and at least 2 h of symptoms as being at low risk at presentation, regardless of age or gender. More over one percent of the individuals arriving to emergency departments had a cTn concentration above the 99th percentile URL even when they were stable, outside of the hospital, and going about their everyday lives. This is due to their advanced age and increased cardiovascular risk factors. It is consequently crucial to differentiate between those with chronic/stable cTn elevations and those with transient elevations. A variation in concentration over time can also be used to distinguish the two groups (Valgimigli, Patrono, Collet, Mueller, & Roffi, 2016). Researchers and medical professionals should also be aware of the several factors (fibrin clots, heterophilic antibodies, rheumatoid factor, alkaline phosphatase, and cross-reactions of diagnostic antibodies (anti-cTn) with skeletal troponin molecules) that induce false-positive elevations in cTns (Chaulin, 2022). In average, the amount of cTn per gram of myocardium is 13–15-fold higher than that of CK-MB, explaining the higher sensitivity of cTn in detecting early and/or minor myocardial damage (Aydin et al., 2019). Compared to the traditional troponin (cTn) test, the highly sensitive troponin T (hsTnT) was found to have superior diagnostic performance due to its high sensitivity and negative predictive values (Zhu, Han, & Duan, 2016).

Point-of-care tests (POCTs) for cTnI with diagnostic sensitivity comparable to that of fundamental laboratory testing are now available, allowing for significantly improved turnaround times and immediate results,

as well as enhanced therapeutic decision making, patient flow and experience, and decreased costs (Collinson, 2020). Interestingly, participants treated with statins whose high-sensitivity troponin levels decreased significantly in response to treatment had the highest reduction in non-fatal MI and death from coronary artery disease, indicating a role for high-sensitivity troponin in treatment monitoring (Ford et al., 2016).

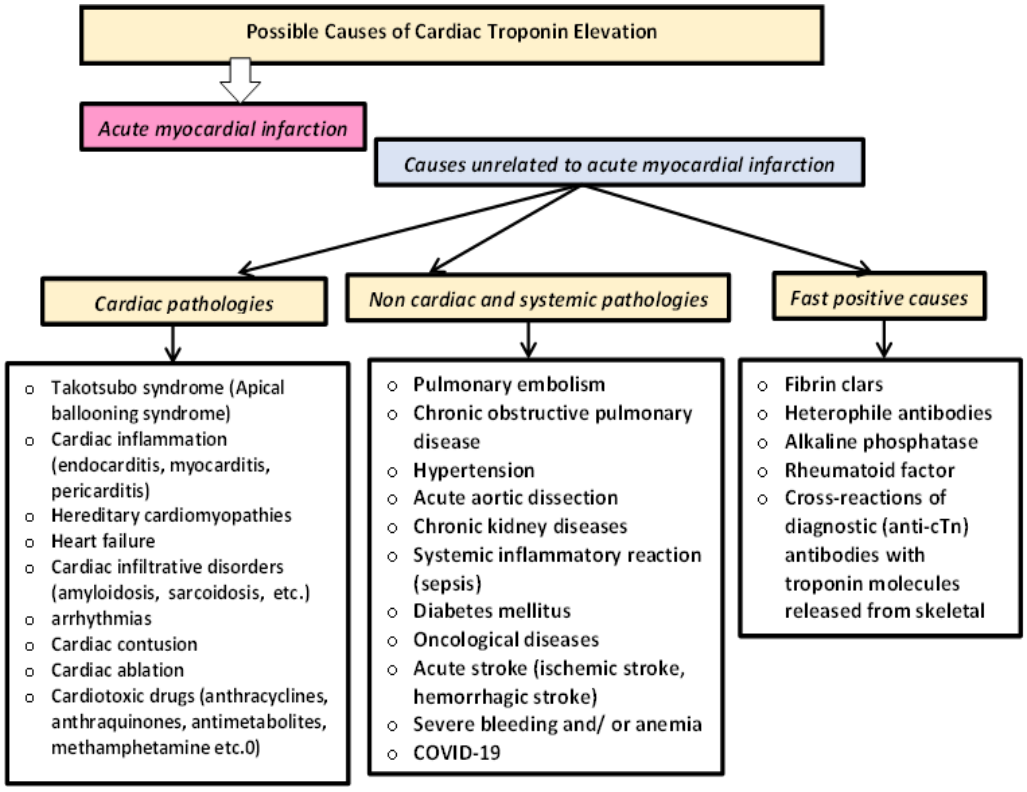

Figure (5): Possible causes of Cardiac Troponin Elevation (Rotenberg et al., 1988).

Newer Biomarkers for Laboratory Diagnosis of Acute Myocardial Infarction

6- Ischemia modified albumin (IMA):

IMA is a biomarker for acute Ischemia When exposed to ischemic conditions, the N-terminus of albumin is damaged, which makes it unable to bind metals and capable of being measured by an albumin cobalt-binding test (R. Sharma et al., 2007). IMA has been implicated in the detection of acute ischemia prior to necrosis because its levels in the blood rise within minutes of the onset of ischemia and return to normal within 6–12 hours. IMA has been proposed as an early biomarker for a number of diseases associated with ischemia and oxidative stress, such as myocardial infarction and cerebrovascular accidents, diabetes and renal failure, and hypothyroidism and hyperthyroidism (Reddy et al., 2017). Evaluation of serum IMA is advised not only for early detection of myocardial ischemia but also as an indicator of disease severity. Compared to patients with elevated troponin, those with a higher IMA exhibited a longer length of hospitalization and a greater number of readmissions. However, high-level IMA did not predict adverse cardiovascular events during hospitalization, while the cTnT test more frequently predicted arrhythmia than the Albumin Cobalt Binding (ACB) test (Nepal et al., 2017).

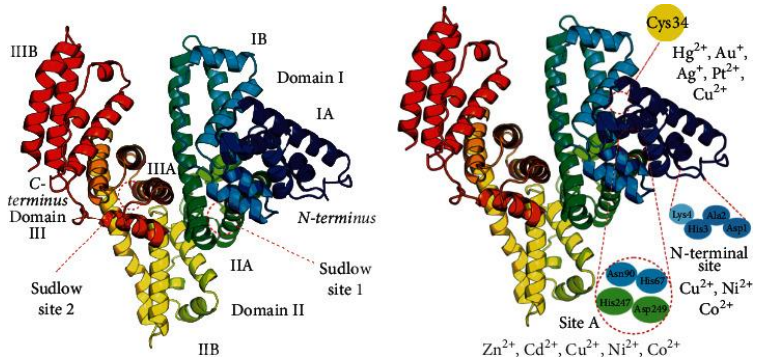

Figure (6): **Structure of human serum albumin.** The albumin structure comprises three homologous domains: I, marked in blue and cyan; II, green and yellow; III, orange and red. Each domain contains two subdomains, A and B, and two sites to bind hydrophobic molecules. Sites for binding transition metal ions: N-terminal site, Cys34, and site A (multimetal binding site). Site B is not shown because its exact position is unknown (Shevtsova, Gordiienko, Tkachenko, & Ushakova, 2021).

Methods for Measuring IMA

Ischemia Technologies Incorporated (Denver, Colorado) used these findings to develop the Albumin Cobalt Binding (ACB) test, which was approved by the U.S. Food and Drug Administration (FDA) in 2003 as a novel method for ruling out myocardial infarction. In principle, a serum sample containing a known number of cobalt ions binds to normal albumin but not to IMA. Upon addition of dithiothreitol as a colouring reagent, the remaining free cobalt ions react with it to form coloured complexes that can be quantified spectrophotometrically. The IMA concentration is directly proportional to the coloured complex concentration and, consequently, the colour intensity (Bar-Or, Curtis, Rao, Bampos, & Lau, 2001). Chawla et al. found IMA's sensitivity and specificity for detecting ACS to be 78.0% and 82.7%, respectively, compared to 58.0% and 60.0% for the CK-MB assay (Chawla, Goyal, Calton, & Goyal, 2006). Lee et al. obtained other results, finding the sensitivity and specificity of IMA for identifying ACS to be 93% and 35.6%, respectively, and the negative and positive predictive values to be 91.8% and 39.6%, respectively (Lee et al., 2007). IMA measurements allow for ACS speculations in the absence of changes in the electrocardiogram and unchanged cardiac markers (Bhakthavatsala Reddy, Cyriac, & Desle, 2014). Comparing results of the ACB test in three categories of ACS (STEMI, NSTEMI, and unstable angina) revealed that IMA tended to increase in the more severe disease, but the difference between the three groups was not statistically significant (Mishra et al., 2018). Evaluation of serum IMA is recommended not only for early detection of myocardial ischemia but also as a prognostic indicator of the disease severity. People with higher IMA showed longer hospitalization days and had more readmissions as compared to patients with high troponin. However, top high-level IMA did not predict negative cardiovascular events during the hospital stay, while the cTnT test predicted arrhythmia more often (Ford et al., 2016).

IMA's advantage over other biomarkers, despite its lack of specificity, is its capacity to recognize ischemic conditions at an earlier stage. It is possible to stratify patients and determine risk groups for adverse events after a stroke, heart attack, traumatic brain injury, and spinal injury, as well as to assess the state of patients with neurological disorders, diabetes, pregnancy complications, and with gynaecological and other ischemic-associated pathologies due to the simplicity and accessibility of the techniques for its determination (Malasky & Alpert, 2002).

Table (4): Change of IMA content in serum of patients with cardiovascular (R. Sharma et al., 2007)

Pathology		Age, years	No of examined	IMA value Control	Patients	Combination with other markers and sensitivity
Acute coronary syndrome	NSTEMI STEMI UA	62.32 ± 16.63	$n = 50$	0.410 ± 0.081 ABSU	0.925 ± 0.094 ABSU 0.843 ± 0.146 ABSU 0.783 ± 0.221 ABSU	cTnI, CK-MB, ECG 92-94%
	NSTEMI STEMI UA	—	$n = 135$	54.70 ± 17.29 U/mL	87.31 ± 5.95 U/mL 92.10 ± 10.60 U/mL 88.90 ± 6.16 U/mL	cTnI, CK-MB 88%
Acute aortic dissection		53 ± 7	$n = 98$	0.62 ± 0.18 ABSU	0.70 ± 0.13 ABSU	cTnT, CK-MB 84.7%*
		52.99 ± 12.17	$n = 731$	—	74.66 ± 20.84 U/mL	IMA–independent forecaster for in-hospital mortality
Chronic heart failure		68 ± 7	$n = 59$	0.379 ± 0.08 ABSU	0.894 ± 0.23 ABSU	cTnI, NT-proBNP 92.9%*
		70 ± 11	$n = 55$	0.470 ± 0.1 ABSU	0.669 ± 0.2 ABSU	Total antioxidant status, total oxidant status, oxidative stress index–not correlation
Dilated cardiomyopathy		46 ± 14	$n = 42$	93.9 ± 9.9 (76-122) kU/L	89.9 ± 13.1 (71-117) kU/L	cTnI, CK-MB, CPK, NT-proBNP, total protein, albumin Not significance
		56 (range 35-68)	$n = 152$	Prechemotherapy 59.2 ± 10.9 U/mL	After the sixth cycle of chemotherapy 140.1 ± 14.8 U/mL	cTnT, CK-MB 92%

IMA was measured in serum by ACB assay. ∗ = sensitivity for IMA alone; ABSU: absorbance units; U: units; CPK: creatine phosphokinase; CK-MB: creatine kinase MB; cTn: cardiac troponin; ECG: electrocardiogram; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; UA: unstable angina.

7- Heart Type Fatty Acid-Binding Protein:

Fatty acid-binding proteins (FABPs) belong to a family of proteins that are responsible for the transportation of fatty acids and lipophilic materials into or out of cells (Chmurzyńska, 2006) In various organs, including the kidneys, myocardium, intestines, and adipose tissues, fatty acid-binding proteins (FABP) are responsible for the cytoplasmic transport of unsaturated fatty acids (Ockner, Manning, Poppenhausen, & Ho, 1972). Various enzyme-based immunoassays for measuring h-FABP demonstrated that its plasma levels peaked earlier than CK-MB and LDH, with elevations detectable 5–10 h after the onset of ACS symptoms (Kleine, Glatz, Van Nieuwenhoven, & Van der Vusse, 1992). The h-FABP concentration reaches its peak 6 h after symptom onset and returns to its baseline level by 24 hr (Gururajan et al., 2010). At present, no formal recommendation exists for a clinically useful threshold level for h-FABP. A cut-off of 4 ug/L (Willemsen et al., 2015). In a recent study by Ho et al., high levels of H-FABP were a distinct risk factor for CV death and acute HF-related hospitalization in 1071 patients with chronic coronary disease (Ho et al., 2018). A H-FABP-troponin ratio may be useful for distinguishing acute ischemia from chronic myocardial damage in patients with decompensated HF when H-FABP is used as a screening tool, for example, during routine health examinations (Rezar et al., 2020) As a strong and independent correlation of H-FABP with individual prognosis was shown in several studies, it may, therefore, be used in mid- to long-term treatment planning (Cabiati et al., 2013).

Biomarkers of Inflammation:

Coronary artery disease is an inflammatory process. Atherosclerotic plaque formation begins with endothelial cell injury thought to be triggered by a range of factors including smoking, diabetes, hypertension, and dyslipidemia (De Servi, Mariani, Mariani, & Mazzone, 2005). A wide variety of pro-inflammatory cytokines have been shown to increase in the setting of AMI and to predict prognosis in this population. This is particularly the case for C-reactive protein (CRP), interleukin- (IL-) 6, and procalcitonin (PCT) (Sproston & Ashworth, 2018).

8- C-reactive protein/Hs -CRP:

CRP is an acute-phase protein produced by the liver that is upregulated in conjunction with the inflammatory response (Chmurzyńska, 2006). Increased CRP levels are associated with the severity of myocardial damage and a worse prognosis in AMI patients. Due to the fact that CRP levels increase in a variety of other contexts, they are not specific enough to qualify as a ranked as the highest of AMI.[18] Other inflammatory biomarkers, such as IL-1_, IL-37, and angiopoietin-like protein 2, have also been shown to increase in AMI patients, but additional research is required to come to an agreement (X. Y. Wang, Zhang, Zhang, Zheng, & Yang, 2020).

9- Markers of plaque destabilization:

Additionally, metalloproteinases are indicators of plaque destabilization. Myeloperoxidase (MPO) is the most abundant metalloproteinase and is an enzyme produced by neutrophils and macrophages with polymorphonuclear nuclei. It produces a variety of reactive oxidants and radical species that contribute to the formation of atheroma and eventual plaque rupture (Eggers et al., 2010). As a prognostic biomarker, MPO has demonstrated some utility in predicting future adverse events. Although MPO can be used to estimate the risk of coronary artery disease in healthy individuals, the association between MPO and CAD is stronger in individuals who have been diagnosed or suspected ACS (Wu et al., 2020).

Understanding the pathobiology of atherosclerosis has revealed inflammation to be a key factor in the onset and progression of atherosclerotic vascular disease. Inflammatory biomarkers may have prognostic value for future cardiovascular risk in individuals with a high cardiovascular disease risk or with proven cardiovascular disease. They may also be useful for identifying apparently healthy individuals without CAD who may be at a higher risk than estimated by conventional risk factors. Lastly, they may aid in the identification of individuals who are not eligible for preventive therapies based on traditional risk factors, but who are at high risk for future cardiovascular events and could benefit the most from these interventions. To date, however, data regarding the optimal biomarker for the diagnosis or prognosis of CAD are contradictory. Likely, a combination of biomarkers will prove suitable for our objective (Zakynthinos & Pappa, 2009).

Biomarkers of Neurohormonal Activation **"Heart Failure (HF) Biomarker"**

10- BNP and pro-BNP

The serum level of ANF (later renamed to atrial natriuretic peptide (ANP)) was found to be elevated in patients with heart failure, and it became a decisive diagnostic and prognostic biomarker (Brandt, Wright, Redfield, & Burnett, 1993). Eventually, after identifying BNP in human heart samples and revealing the ventricles as the primary site of BNP secretion (Mukoyama et al., 1991), it was determined that BNP is primarily secreted by the ventricles. Initial studies revealed that the plasma levels of Neopterin and BNP were elevated in patients with HF and that these levels increased with the severity of the disease. BNP was found to have greater specificity and positive predictive value than ANP for the diagnosis of HF (Cowie et al., 1997). Also released into circulation is the N-terminal fragment N-terminal pro-BNP (NT-proBNP). In patients with a reduced left ventricular ejection fraction, NT-proBNP has been found to be comparable to BNP (Richards et al., 1998). Both BNP and NT-proBNP are detectable using rapid immunoassays, but the potential advantages of NT-proBNP include its greater range of values and longer half-life (Mair, 2008).

11- Neopterin:

Neopterin,2-amino-4-hydroxy-6-(D-erythro-1′,2′,3′-trihydroxypropyl)-pteridine,is biosynthetically derived from guanosine triphosphate (GTP) (Murr, Widner, Wirleitner, & Fuchs, 2002). Neopterin is produced in macrophages after interferon gamma (INF-) induces GTP cyclohydrolase I. Consequently, any condition that can stimulate the production and activation of INF- can also stimulate the production of neopterin. Prior research has established a link between neopterin levels and cardiovascular diseases. demonstrated that neopterin levels are elevated in patients with chronic stable angina and correlate well with adverse coronary events (Avanzas, Arroyo-Espliguero, Quiles, Roy, & Kaski, 2005). Rodriguez et al. demonstrated that high levels of neopterin were associated with cardiac death and decreased ejection fraction (EF) in survivors of AMI Caruso et al. found an association between elevated neopterin levels and the severity of heart failure (HF), the degree of left ventricular remodeling, an increase in cardiac volume, and echocardiography values. Neopterin can be used as an unbiased

biomarker for HF intensity, diagnosis, and prognosis, according to studies (Caruso et al., 2013). Dogheim et al., also demonstrated a correlation between neopterin with heart rate and NT-Pro BNP (Dogheim, Khairat, et al., 2022). The use of neopterin to correlate well with disease and to the severity assess the effectiveness of drug therapy in HF is yet to be further investigated to draw a definitive conclusion (Dogheim, Amralla, & Werida, 2022).

Promising Cardiac Biomarker:

12- Growth-differentiation factor-15 (GDF 15)

It is a transforming growth factor beta (TGF-ß) family cytokine found in low concentrations in normal tissue and plasma. Stress and tissue damage upregulate the expression of this marker, which is linked with inflammatory conditions of various organs, including the myocardium (Emmerson, Duffin, Chintharlapalli, & Wu, 2018). It is expressed and secreted in response to oxidative stress, inflammation, and hypoxia. Cardiovascular disease is a major contributor to the creation of GDF-15. Atherosclerotic plaques in the carotid or coronary arteries also express GDF-15. GDF-15 is also upregulated in the heart following an acute myocardial infarction (MI). In chronic nonischemic heart failure patients (HF). As a diagnostic marker, GDF-15 has limited utility, for example in patients with acute chest pain or dyspnea. However, this lack of cardiac specificity may serve as an advantage when predicting CV risk. Based on previous pathophysiological findings, GDF-15 is a marker of underlying, integrated CV disease burden, not acute cardiac instability (Wollert, Kempf, & Wallentin, 2017).

A meta-analysis was conducted using data pooled from eight trials involving 53486 patients with atherosclerotic cardiovascular diseases. The median duration of follow-up was 2.2 years. GDF-15 concentration at baseline was analyzed as a continuous variable using predetermined cut points. GDF-15 was discovered to add prognostic information for CV death and HF. Beyond established clinical factors and biomarkers, it is also a useful marker for MI and stroke in patients with stabilized or stable ASCVD, but not in the acute setting of ACS (W. Wang et al., 2020).

Patients with stable coronary artery disease were the subject of a second meta-analysis examining the relationship between GDF-15 level and adverse outcomes, which yielded conflicting results. Seven studies involving 28,765 patients with stable CAD were identified and analyzed. In addition, consistent GDF-15 values for predicting major adverse cardiovascular events were observed in each subgroup. In stable CAD patients, an elevated GDF-15 blood level is an independent predictor of major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality (Li et al., 2022).

13-Galectin-3:

It is a β-galactoside-binding lectin protein with multiple physiological cellular functions, including cellular growth, proliferation, apoptosis, differentiation, cellular adhesion, and tissue repair. Involvement in inflammation, tissue fibrosis, and angiogenesis are the primary functions of Gal-3 (Blanda, Bracale, Di Taranto, & Fortunato, 2020). There was significant interest in galectin-3 as a biomarker when it was first implicated in HF in 2004, when it was found to be specifically overexpressed in the myocardium of Ren-2 rats that would go on to develop HF (U. C. Sharma et al., 2004). Gal-3 is implicated in fibrosis development, the atherosclerotic process, and inflammation-based diseases in general. As suggested by the international guidelines of the American Heart Association, Gal-3 measurement should be recommended for the prognosis evaluation of HF patients, whereas the predictive value of HF development remains uncertain. Innovative and intriguing therapeutic applications for Gal-3 inhibitors exist, but additional clinical research is required to confirm their potential for CVD prevention (Blanda et al., 2020).

14- Soluble suppression of tumorigenicity factor 2 (sST2):

ST2L is a membrane-bound receptor whose functional ligand is IL-33. Signaling of IL-33/ST2L induces inflammatory gene transcription, resulting in the production of inflammatory cytokines/chemokines and the activation of the immune system. In relation to the heart and HF, IL-33 is thought to exert a cardioprotective effect. Recent evidence implicates the lungs as a significant source of sST2, particularly in relation to type II pneumocytes' alveolar epithelial production (Pascual-Figal et al., 2018). This may help to understand how sST2 correlates with presence and severity of pulmonary congestion in HF, but also with severe inflammatory pulmonary conditions such as acute respiratory distress syndrome (Bajwa et al., 2013). It provides prognostic

information in HF patients independently of, and additive to, other established markers such as cardiac troponins or natriuretic peptide (Meijers et al., 2021). sST2 and galectin-3 have been included in the 2017 ACC/AHA guideline for additive risk stratification in patients with acute and chronic HF (Yancy et al., 2017).

15- Micro RNA

Non-coding RNAs, including microRNAs (miRNAs), circular RNAs, and long noncoding RNAs (lncRNAs), act as strong, tissue- and cell-specific epigenetic regulators of cardiac gene expression, homeostasis, and function, and have recently emerged as promising biomarkers in a wide variety of cardiovascular diseases. Four miRNAs—miR-1, miR-133a/b, miR-208b, and miR-499, the latter two being expressed solely in the cardiac myocytes—have been consistently reported to increase in AMI patients, although controversies still remain regarding the value of individual miRNAs as AMI biomarkers (Kleveland et al., 2016).

Biomarker	AHA/ACC			ESC		
	Recommendation	COR	LOE	Recommendation	COR	LOE
CK-MB	Not recommended for diagnosis of ACS [256]	III	A	Not recommended for diagnosis of ACS [257]	III	
h-FABP	Not in guidelines			Not recommended for diagnosis of ACS [257]	III	B
Troponin	Diagnosis of ACS [256]	I	A	Diagnosis of ACS [257]	I	B
	Additive risk stratification in chronic HF (hscTn) [182]	IIb	B-NR			
sLOX-1	Not in guidelines			Not in guidelines		
BNP and NT-proBNP	Screening for HF [182]	IIa	B-R			
	Diagnosis of HF [182]	I	A	Diagnosis of HF [135]	I	B
	Prognosis or disease severity in chronic HF [182]	I	A			
	Prognosis in ADHF [182]	I	A			
	Pre-discharge for prognosis [182]	IIa	B-NR			
Galectin-3	Additive risk stratification in chronic HF [182]	IIb	B-NR	Not in guidelines		
sST2	Additive risk stratification in chronic HF [182]	IIb	B-NR	Not in guidelines		
hsCRP	As a risk enhancing factor to aid discussion of statin therapy initiation [258]			Not recommended for risk stratification in CVD prevention [259,260]	III	B

Table (5): AHA recommendation in regards to Cardiac Biomarker (Collet et al., 2021)

Biomarkers in Cardio-Oncology

In cardio-oncology, cardiac biomarkers provide a means of detecting toxicity early, ideally prior to the development of irreversible organ damage, and, if elevated, a pathway of care that enables cancer patients to continue treatment safely. Left ventricular damage, dysfunction, and/or HF are the most frequent cardiotoxicities caused by cancer treatments. **The most significant markers of cardiac damage are cardiac troponin and natriuretic peptides, accompanied by cardiac troponin**, while markers of inflammation such as interleukin-6, C-reactive protein, myeloperoxidase, Galectin-3, growth differentiation factor-15 are under investigation for their use in detecting cardiotoxicity early (Ananthan & Lyon, 2020).

Disclosure

The author reports no conflicts of interest in this work.

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