Chapter 3

The Diagnostic Value of Biochemical Cardiac Markers in Acute Myocardial Infarction

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Abstract

Cardiovascular disease is the leading cause of death worldwide. The role of cardiac markers in the diagnosis, risk stratification, and treatment of patients with chest pain is vital. Patients with elevated cardiac troponin levels but negative CK-MB who were formerly diagnosed with unstable angina or minor myocardial injury are now reclassified as non–ST-segment elevation MI (NSTEMI) even in the absence of diagnostic ECG changes. CK-MB is both a sensitive and specific marker for myocardial infarction. Cardiac troponin T is a cardio-specific, highly sensitive marker for myocardial damage. Cardiac troponin I is a contractile protein exclusively present in the cardiac muscle. The absolute cardiospecificity of cTnI allows the diagnosis of myocardial infarction distinct from muscle lesions and non-cardiac surgery. In 2000, the European Society of Cardiology and the American College of Cardiology redefined AMI with a particular advocacy on troponin. The 2002/2007 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline Update for the management of these patients strongly recommend to include cTnI. Specifically, with rare exception, the diagnosis cannot be made in the absence of elevated biomarkers of cardiac injury.

Keywords: acute myocardial infarction, unstable angina, CK-MB, cardiac troponin T, cardiac troponin I

1. Introduction

Cardiovascular disease is the foremost cause of death globally, accounting for an estimated 16.7 million deaths per year [1]. The prevalence of coronary artery disease (CAD) varies

between different geographical locations around the world. For example among South Asian populations, Pakistani people have the highest known rate of CAD. According to careful estimates nearly 100,000 individuals suffered from acute myocardial infarction (AMI) in Pakistan, in 2002 [2].

Acute MI is commonly presented with chest pain or discomfort, weakness, sweating, nausea, vomiting, and arrhythmias, sometimes loss of consciousness and syncope. It occurs with the sudden interruption of coronary blood flow and it is a life-threatening medical emergency which requires quick management [3, 4].

2. Pathophysiology

Myocardial ischemia may occur either from increased demand of oxygen by the myocardium, or decreased oxygen supply to the myocardium, or both. During exercise, tachycardia or emotions, myocardial oxygen requirement is increased and if there is coronary obstruction, it will lead to a transitory imbalance. This condition is often termed demand ischemia and is responsible for most episodes of chronic stable angina. In other conditions, this imbalance occurs due to acute decrease of oxygen supply because of increased coronary vascular tone (i.e., coronary vasospasm) or obvious reduction or occlusion of coronary artery as a result of platelet aggregates or thrombi. This condition which is known as supply ischemia may lead to MI and unstable angina (UA). In many conditions, ischemia is a result of both an increase in oxygen demand and a reduction in supply [5–8].

The leading cause of MI, by far, is atherosclerosis, a progressive accumulation of cholesterol and fibrous tissue in plaques present within the arterial wall, spanning over decades [9–12]. Nevertheless atherosclerotic plaques may become unstable, rupture, and form a thrombus that occludes the artery. When a significant plaque rupture occurs in the coronary vessels, it leads to thrombosis and total vascular occlusion which concludes with the occurrence of MI [13, 14].

Total coronary occlusion leading decreased myocardial oxygen supply results with the damage of myocytes [15, 16].

This decreased blood supply has the following consequences:

- After 10–15 min of coronary occlusion necrosis of the myocardial tissue starts and since myocardial cells are strongly differentiated cells they have so weak regenerative abilities. Thus, according the size of the necrotic tissue the heart becomes a permanently weaker pump for the rest of the individual's life;
- The injured myocardial tissue may cause ventricular arrhythmias (e.g. ventricular tachycardias or ventricular fibrillation) by re-entry mechanism. This is the most common underlying mechanism of the sudden cardiac death resulting from MI [17, 18].

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3. Histopathological findings

Examination of the heart shows that there is a well-defined circumscribed area of ischemic necrosis (coagulative necrosis). In the first 12–48 h, myocardial fibers are still well delineated with concentrated eosinophilic cytoplasm, but lose their transversal striations and the nucleus along with red blood cells which infiltrate the interstitial space. Later (5–10 days after the initial event), during healing of the myocardial tissue, the area with coagulative necrosis shows histologically preserved myocardial fibers with intensely eosinophilic cytoplasm, transverse striations and nuclei which are completely lost. The interstitium of the infarcted area is primarily infiltrated with neutrophils, then later with lymphocytes and macrophages to phagocytose the necrotic myocyte debris. The necrotic area is peripherally surrounded and gradually infiltrated by granulation tissue, which ultimately replace the infarct with a fibrous scar [19].

4. Risk factors

Atherosclerotic risk factors are also the most common risk factors for MI. These risk factors are old age, obesity, smoking, hypertension, hypercholesterolemia more precisely hyperlipoproteinemia particularly high low density lipoprotein (LDL) and low high density lipoprotein (HDL), diabetes mellitus [20–23].

Furthermore, intense exertion, especially if the exertion is unusually more intense as compared to the usual performance, and emotional stress are other risk factors. Recent studies established that quantitatively, the duration of strenuous exercise and following recovery is associated with 6-fold higher MI rate in comparison to the more comfortable time frames for people who are physically more fit. For individuals with poor physical health, the rate differential is over 35-fold higher. Since the increased arterial pulse pressure results in stretching and relaxation of arterial vasculature with each heart beat thereby increasing the mechanical stress on atheromas, hence it significantly enhances the susceptibility of plaque ruptures [16, 24].

Increased spasm/contraction of coronary artery in association with cocaine abuse can also precipitate MI [25–29]. Gender is also another risk factor and male individuals are more prone to suffer from MI [30, 31].

5. Diagnosis

The diagnosis of acute MI depends on both clinical and laboratory findings including electrocardiogram, and cardiac biomarkers for myocyte injury [32]. Biochemical cardiac markers are the signals from the injured myocardium (**Figure 1**) and are released in case of damage at the

cardiac muscle. The most common causes of injury are acute coronary syndromes (MI, non Q-wave MI, unstable angina pectoris) and other conditions affecting cardiac muscle including trauma, cardiac surgery, myocarditis etc. The level of cardiac biomarkers can be detected/measured in blood samples in these cases [33–35].

The role of cardiac biomarkers in the process of diagnosis, risk evaluation, and management of patients with chest pain has continued to evolve. The initial electrocardiogram (ECG) may be non-diagnostic. Although physicians awareness and diagnostic utilities increase the rate of missed MI continues to remain between 1.5 and 2%. Determination of cardiac biomarkers plays an increasingly important role for the evaluation and diagnosis of patients with chest pain. The guidelines for the diagnosis of MI have recently been upgraded and have incorporated the results of cardiac marker estimation in the clinical definition of MI [36–39]. Creatine kinase-MB (CK-MB), cardiac troponin T (cTnT), cardiac troponin I (cTnI), myoglobin, homocysteine and C-reactive protein (CRP) are all used for evaluation of the suspected acute MI. CK-MB, cTnT, and cTnI may also be used to detect and manage high-risk patients [36–39].

In early 1990s, the diagnosis of MI was primarily based on an elevated serum CK-MB level. Though, the introduction of troponin markers significantly increased the sensitivity and specificity for the diagnosis of myocardial injury and for this reason succeeded CK-MB as the gold standard for the diagnosis. A consensus guideline from both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) has redefined acute MI [40]. According to these associations, acute MI is now typically termed as a typical rise and fall of serum biochemical markers (e.g., Troponin, CK-MB), associated with symptoms of ischemic injury, new pathologic Q waves on ECG, ischemic ECG changes (ST-segment elevation or depression), coronary artery intervention or histologic findings of AMI [41, 42].

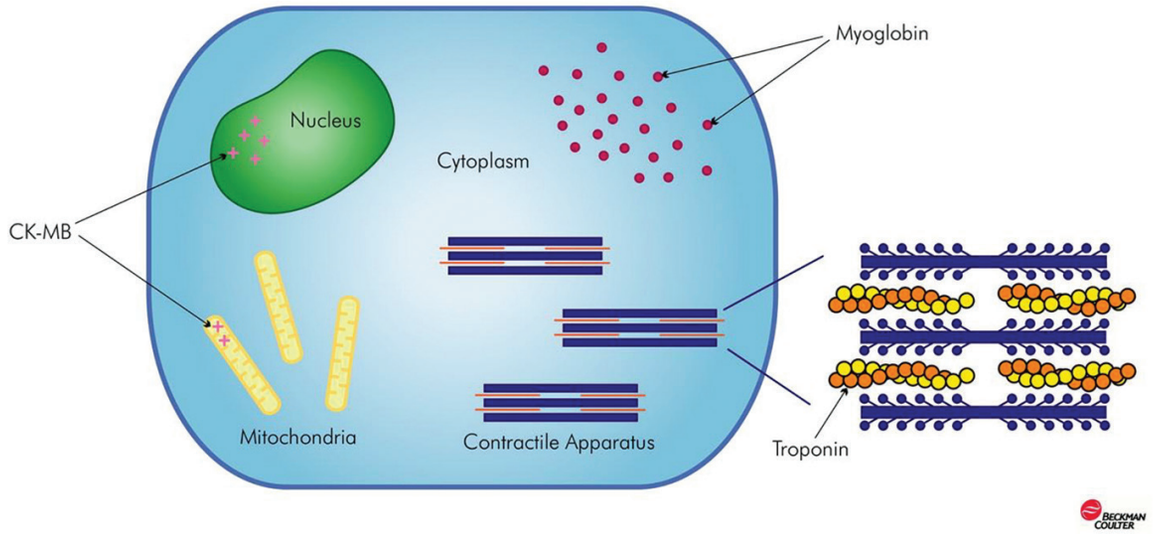

Figure 1. Cardiac muscle cell. Biochemical markers (troponin T, CK-MB, and myoglobin) in myocardium; adopted by Cummins.

Patients with elevated cardiac troponin levels but negative CK-MB who were previously diagnosed as unstable angina or minor myocardial injury are now re-stratified as non–ST-segment elevation MI (NSTEMI) even in the absence of diagnostic ECG changes [43].

5.1. Operational definition for acute myocardial infarction

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. 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 ischemia with at least one of the following:
- Symptoms of ischemia;
- ECG changes indicative of new ischemia (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 [43–46].

5.2. Types of myocardial infarctions

The most recent guidelines recognize five distinct types of MI [43–48].

- Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. This would be the typical ST elevation or non-ST elevation MI.
- Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4: MI associated with percutaneous coronary interventions, and there are two types of this category: one associated with the procedure itself, and one associated with subsequently verified stent thrombosis.
- Type 5: Myocardial infarction associated with CABG [43–48].

6. Biochemical markers of myocardial necrosis

Myocardial cell death can be documented by the appearance in the blood of different proteins released into the blood circulation from the ischemically injured myocytes: including myoglobin, cardiac troponin T and I, CK, LDH, besides many others (e.g. heart fatty acid binding protein). Myocardial infarction is diagnosed when blood levels of sensitive and specific cardiac biomarkers such as cardiac troponin or CK-MB are elevated in the clinical setting of acute myocardial ischemia [33, 49, 50]. Even though elevated biomarkers reflect myocardial damage and necrosis, they do not designate its underlying mechanism. Hence, an elevated value in the absence of clinical findings of ischemia triggers a need to search for other causes of cardiac damage, for example myocarditis [43, 45, 48].

6.1. Creatine kinase and CK-MB isoenzyme

Creatine kinase is a regulator of high-energy phosphate production, that is utilized in contractile tissues [51]. In addition it also has a more general role in shuttling high-energy phosphate bonds via creatine phosphate from the site of ATP production in the mitochondria to the site of utilization within the cytoplasm [51].

Cytoplasmic CK is a dimer, composed of both M and/or B subunits, that produce CK-MM, CK-MB and CK-BB iso-enzymes. CK has also a dimeric mitochondrial form consisting of both sarcomeric and non-sarcomeric subunits [52]. Mitochondrial CK is unstable in human serum, and that's why it is difficult to measure. CK-MM is the main isoenzyme found in striated muscle constituting about 97% of the total CK. CK-MB is found principally in cardiac muscle comprising approximately 15–40% of the total CK activity, with the remainder being CK-BB. CK-BB is the predominant iso-enzyme found in brain, intestinal and urinary systems. The skeletal muscle CK-MB produce 2–3% of the total CK activity; the patients with skeletal muscle injury may have increased CK and CK-MB levels [53].

The antibodies in turn inhibit M-subunit activity, with remaining enzyme activity being derived from B-subunits only; CK-BB is not detectable by activity measurement in serum, except the patient has suffered a serious cerebrovascular accident, so the residual activity represents CK-MB activity. Although antibodies had been developed to the B- and M-subunits of CK, it was thought that MB did not have its own unique antigenicity. However, specific antibodies were developed in the mid- 1980s, allowing the development of direct immunological assays for CK-MB. Serum total CK activity and CK-MB concentration rise simultaneously following myocardial injury [54, 55].

For CK-MB, two forms of the MB iso-enzyme were eventually recognized and isolated from plasma; the tissue form is designated CK-MB2; removal of the lysine residue from the carboxy terminus of the single M-subunit, catalyzed by the action of carboxypeptidase-N giving rise to the CK-MB1 isoform. Elimination of the lysine residue, which is positively charged, leaves a more negatively charged isoform thereby leaving a basis for isolation of the isoforms by electrophoresis [56]. The B-subunit is not sensitive to enzymic degradation, so only two isoforms of CK-MB exist. In normal plasma, CK-MB isoforms exist with each other in

balance ratio of 1:1. Release of tissue CK-MB2 increases its fraction in plasma; a change in the ratio of CK-MB2:CK-MB1 from 1:1 to 2:1 can be identified using high-voltage gel electrophoresis, even though there is no noticeable change in the plasma concentration of CK-MB [56, 57]. Significant fluctuations in the ratio of both the isoforms in plasma can be detected between 2 and 4 h after myocardial injury. Systematic prospective studies have confirmed that CK-MB isoforms act as an early marker of myocardial injury, and have also established a CK-MB2:CK-MB1 ratio above 1.5:1 as a diagnostic criterion [57–59]. The isoform ratio returns to normal within 18–30 h after injury. It has been proposed that a normal 1:1 isoform ratio in a sample collected at least 6 h after an event effectively excludes a diagnosis of myocardial infarction. The rapid return to normal values makes the CK-MB isoforms the best available laboratory investigation for the confirmation of re-infarction. Unfortunately, the analytical procedure used (high-voltage gel electrophoresis) requires specially designed equipment and a great deal of technical expertise, and is therefore unfeasible for daily/routine use. CK-MB is a sensitive as well as specific marker for myocardial infarction. CK-MB usually becomes abnormal 3–4 h after an event of myocardial infarction, peaks in 10–24 h, and returns to normal within 72 h [60–62].

Besides, skeletal muscle contains trace amounts of CK-MB, so an elevated serum CK-MB may be observed in people with severe skeletal muscle damage and/or renal failure. In such cases, the CK index that is CK-MB divided by total CK is very useful. If the index is lower than 4%, a non-myocardial etiology of a high CK-MB should be suspected [60–62].

6.2. Troponin T

The troponins are regulatory proteins found in both cardiac and skeletal muscles. They have 3 subunits; troponin I (TnI), troponin T (TnT), and troponin C (TnC). The genes that code for the skeletal and cardiac isoforms of troponin C (TnC) are similar. The skeletal and cardiac subforms for troponin I (TnI) and troponin T (TnT) are distinct, and immunoassays have been developed to distinguish subtypes [63, 64]. Skeletal TnI and TnT are structurally diverse. No cross-reactivity arises between skeletal and cardiac TnI and TnT with the current assays [63, 64].

Troponin is adhered to the protein tropomyosin and structurally lies within the groove between actin filaments in muscular tissue. In a relaxed muscle, tropomyosin blocks the site of attachment for the myosin cross-bridge thereby consequently preventing contraction. When the muscle cell is triggered to contract by an action potential, calcium channels get open in the sarcoplasmic reticulum hence releasing calcium into the sarcoplasm. A portion of this calcium gets attach to troponin resulting in conformational change that displaces tropomyosin so that the cross bridges can attach to actin and ensue muscle contraction [63, 64].

Troponin can originate from both skeletal and cardiac muscles, but the specific forms of troponin vary between types of muscle. The main difference is that the TnC in skeletal muscle has four binding sites for calcium ion, whereas in cardiac muscle there are only three. The process of contraction in both cardiac and skeletal muscles is controlled by variation in the intracellular calcium concentration. When calcium level rises the muscles contract, and when calcium drops the muscles relax. Smooth muscle does not contain troponin [65].

Individual subunits play different roles:

- Troponin C binds to calcium ions to create a conformational change in TnI
- Troponin T binds to tropomyosin, interlocking them to constitute a troponin-tropomyosin complex
- Troponin I binds to actin in thin myofilaments in order to hold the troponin-tropomyosin complex in place [66].

Cardiac troponin T (cTnT) is a cardio-specific, highly sensitive marker for myocardial injury. Cardiac troponin T rises approximately 3–4 h after acute myocardial infarction (AMI) and may continue up to 2 weeks thereafter [65, 66]. In comparison to ST-elevation myocardial infarction (STEMI), the diagnosis of non-ST elevation myocardial infarction (NSTEMI) mainly relies upon level of cardiac troponin T [66]. The diagnosis of MI can be made when blood levels of cTnT are above the 99th percentile of the accepted limit along with an evidence of myocardial ischemia [67]. Cardiac troponin T is an independent prognostic marker which can forecast the near-, mid-, and even long- term outcome of events in patients with acute coronary syndrome (ACS). Cardiac troponin T is also ideal marker of myocardial injury in the diagnosis and management of non-ST elevation acute coronary syndromes [43, 68] (**Figure 2**).

6.3. Cardiac troponin I

Cardiac troponin I is the contractile part and it is only present inside the myocardium [69, 70]. It is a part of the troponin complex (I, T, C) that along with the tropomyosin is bound to actin within the thin myofibril filament. cTnI is acquired as free TnI, as well as intricated with troponin C with troponin T termed as binary IT or with both the troponin C and troponin T where it is called as ternary ITC. Its physiological function is to hinder the ATPase activity of the actin-myosin complex during lack of calcium, and thus, to avert muscular contraction [71].

Three types of tissue isoforms are found. Fast and slow troponin I (19,800 Da) participating in fast and slow twitch skeletal muscle fibers and cTnI (24,000 Da). All the three isoforms of troponin I are encoded by the different genes. The human cTnI reveals merely 54 and 52% amino acid sequence homology with human slow and fast skeletal troponin I, respectively [72]. cTnI specific monoclonal antibody pair is selected. Moreover it is found that skeletal muscles do not express cTnI, neither during development nor in response to a stimuli [72]. cTnIs can differentiate cardiac and skeletal muscle injuries, and facilitates the diagnosis of MI discrete from the skeletal muscle injuries (e.g. rhabdomyolysis, polytraumatism or from the non-cardiac surgery) [72–75]. Increased troponin I levels are also determined in unstable angina [76] and congestive cardiac failure [77]. In acute MI serum concentrations of both cTnI and CK-MB show similar increase and decrease patterns. It is recommended that at least three blood samples should be collected during the early triage period [78]. In the cardiac muscles the level of cTnI is 13 times more than that of CK-MB. Moreover cTnI does not circulate in the

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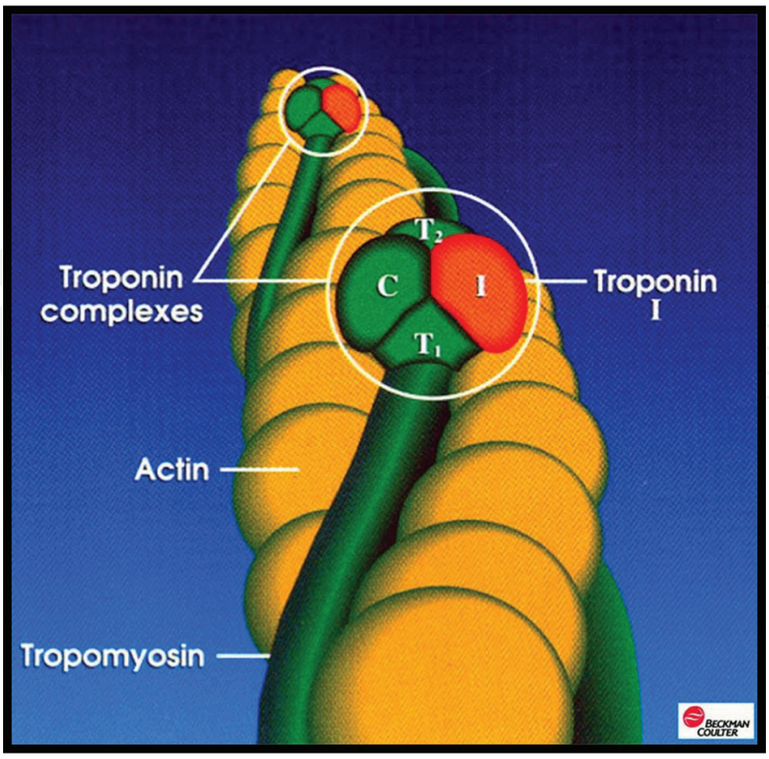

Figure 2. The troponin regulatory complex; adopted by Roger Cummin.

blood in normal circumstances, therefore elevated serum levels of c TnI are more significant for the diagnosis of myocardial necrosis [79]. Data obtained from recent studies specify that the troponin I concentration can be determined within the first 3–6 h after the onset of chest pain. The levels of Troponin I reach the peak level at approximately 12–16 h and remain elevated for 4–9 days after acute MI. The time to attain the peak concentration of cTnI was found to be more among patients who did not underwent thrombolytic therapy [73, 80, 81].

Recent studies have found that in patients after AMI the predominant form of cTnI exhibited in blood is the binary troponin IC complex with slight concentrations of ternary ITC complex, binary IT complex and free cTnI [82–85]. The release pattern of these forms in MI is still under investigation. Commercially available laboratory methods can identify complexed and free cTnI subforms [82, 86, 87]. Some of the assays have the same responses to different forms of cTnI. The second type may result in over or under estimation of troponin I concentrations in complex biological settings. The equimolar binding characterized as the ability to determine both the complexed and free cTnI forms uniformly leads to an unbiased estimation of the total cTnI found in the samples from same subject in MI. The Access AccuTnI assay identifies the binary troponin IC or IT or ternary troponin ITC complexes and free cTnI evenly. The assay detects both the phosphorylated and dephosphorylated forms of cTnI complex [88].

The American College of Cardiology (ACC) and the European Society of Cardiology (ESC) guidelines advocate that the different laboratories define their own reference range and also

an elevated level of cTnI be identified as an amount above the 99th percentile of a normal control group, that is, 99th percentile of the upper reference limit [89, 90].

Conversely in patients with unstable angina and acute MI without the evidence of ST segment elevation (NSTEMI) the expectation of suffering from an adverse event is reported to be quite difficult. The advancement as well as commercialization of more specific and more sensitive cardiac troponin I (cTnI) immunoassays have considerably added to the accurate diagnosis of MI and to the risk stratification of NSTEMI/UA patients.

The definition of MI was formally redefined in 2000 by the European Society of Cardiology and the American College of Cardiology to realign evidence of myocardial injury as defined by biomarkers with a particular advocacy on troponin [32]. The 2000/2002 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline Update evocatively advocate to incorporate the estimation of cTnI for the management of AMI patients and also for the risk stratification of patients presenting with symptoms suggestive of acute coronary syndromes [40, 91]. This definition was updated in 2007 [43] to reflect the progress that had been made in understanding assays. It again relied heavily on a definition based on troponin. Specifically, with rare exception, the diagnosis cannot be made in the absence of elevated biomarkers of cardiac injury [43, 68].

Considering the potential adverse outcomes the estimation of the prognosis should aid clinicians in identification and management of high risk patients. Eventually the evaluation of the prognosis will be helpful in both the identification of site of care as well as in distinguishing patients most likely to get benefit from specific therapeutic interventions.

7. Conclusion

Acute myocardial infarction usually presents with discomfort or chest pain, weakness, sweating, nausea, vomiting, and arrhythmias. Common risk factors include old age, obesity, smoking, hypertension, hypercholesterolemia and diabetes mellitus. Myocardial ischemia may result either from increased demand or decreased supply of oxygen to the myocardium or both.

A consensus guideline from both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) has redefined AMI as a typical rise and fall of serum biochemical markers (e.g., Troponin, CK-MB), associated with symptoms of ischemic injury, new pathologic Q waves on ECG, ischemic ECG changes (ST-segment elevation or depression), coronary artery intervention or histological findings of AMI.

Biochemical cardiac markers include myoglobin, cardiac troponin T, cardiac troponin I, CK-MB, LDH, and many others like ischemia modified albumin, Glycogen phosphorylase BB and fatty acid binding protein. Cardiac markers are vital not only from diagnostic but also from the prognostic viewpoint.

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