Current Cardiology Reviews, 2022, *18*, e110422203390

MINI-REVIEW ARTICLE

Synopsis of Biomarkers of Atheromatous Plaque Formation, Rupture and Thrombosis in the Diagnosis of Acute Coronary Syndromes

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ARTICLE HISTORY

Received: August 18, 2021
Revised: December 08, 2021
Accepted: January 15, 2022

DOI:
10.2174/1573403X18666220411113450

Abstract: Acute coronary syndrome is the main cause of mortality and morbidity worldwide and early diagnosis is a challenge for clinicians. Though cardiac Troponin, the most commonly used biomarker, is the gold standard for myocardial necrosis, it is blind for ischemia without necrosis. Therefore, ideal biomarkers are essential in the care of patients presenting with symptoms suggestive of cardiac ischemia.

The ideal biomarker or group of biomarkers of atheromatous plaque formation, rupture and thrombosis for timely and accurate diagnosis of acute coronary syndrome is a current need. Therefore, we discuss the existing understanding and future of biomarkers of atheromatous plaque formation, rupture and thrombosis of acute coronary syndrome in this review.

Keywords were searched from Medline, ISI, IBSS and Google Scholar databases. Further, the authors conducted a manual search of other relevant journals and reference lists of primary articles.

The development of high-sensitivity troponin assays facilitates earlier exclusion of acute coronary syndrome, contributing to a reduced length of stay at the emergency department, and earlier treatment resulting in better outcomes. Although researchers have investigated biomarkers of atheromatous plaque formation, rupture and thrombosis to help early diagnosis of cardiac ischemia, most of them necessitate validation from further analysis. Among these biomarkers, pregnancy-associated plasma protein-A, intercellular adhesion molecule-1, and endothelial cell-specific molecule-1(endocan) have shown promising results in the early diagnosis of acute coronary syndrome but need further evaluation. However, the use of a combination of biomarkers representing varying pathophysiological mechanisms of cardiac ischemia will support risk assessment, diagnosis and prognosis in these patients and this is the way forward.

Keywords: Acute coronary syndrome, myocardial infarction, biological markers, atheromatous plaque formation, plaque rupture, thrombosis.

1. INTRODUCTION

Cardiovascular disease continues to be the leading cause of death worldwide, not only in high-income countries but also increasingly in developing countries. It accounts for 17.9 million deaths annually [1]. Among cardiovascular diseases, ischemic heart disease (IHD) and cerebrovascular disease are predicted to be the main causes of death in the coming decade [1]. Acute coronary syndrome (ACS) is subdivided into two major types depending on the electrocardiogram (ECG) at presentation; those with new ST-segment elevation [(acute ST-elevation myocardial infarction (STEMI)] or new-onset LBBB and those who present with ST-segment depression, T-wave changes or no ECG abnormalities [(non ST-elevation ACS(NSTEACS)]. The latter group (NSTEACS) comprises both unstable angina and non ST-elevation myocardial infarction (NSTEMI). ACS is multifactorial and the type of ACS depends on the degree of obstruction to coronary artery blood flow by atherosclerosis, inflammation, plaque rupture and thrombosis and the presence of collateral blood supply [2, 3].

1.1. Development of Existing Biological Markers and their Limitations

A timely diagnosis of ACS and cardiac ischemia in a patient presenting with chest pain and other suggestive symptoms is a diagnostic challenge for treating clinicians. Biomarkers are essential to the care of patients presenting with symptoms suggestive of ACS in establishing a diagnosis and initiation of effective evidence-based medical management and revascularization [4].

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Acute myocardial infarction (AMI) is defined as evidence of myocardial necrosis in a patient with clinical features of acute myocardial ischemia and represents the 99th percentile of cardiac troponins as the decision value for AMI [5]. Even though ECG is a simple, readily available and principal investigation for the timely diagnosis of ACS, its diagnostic sensitivity may be as low as 50% [6, 7]. Further, the presence of ECG changes does not always indicate coronary pathology as there are other non-coronary cardiac and non-cardiac causes of those changes complicating the differential diagnosis [8]. To overcome this challenge, cardiac biomarkers have been developed, and Aspartate Transaminase (AST) became the first biomarker used in the diagnosis of AMI and was proposed fifty years ago [9]. By the 1970s, lactate dehydrogenase (LDH) and creatine kinase (CK) were developed for the retrospective detection of cardiac damage [10]. Although a lack of specificity limited their value in the diagnosis of acute myocardial ischemia, later on, these markers played a major role in the diagnosis of AMI in the next 20 years and were included in WHO diagnostic criteria in 1979 [11].

In the 1990s, assays were developed to detect cardiac troponins (cTn), highly sensitive and specific biomarkers of myocardial damage [12, 13]. Along with the established value of cTn for diagnosis and guiding therapy, it has a strong relationship with the prognosis [14]. Currently, it is a cornerstone in the diagnosis of ACS.

These are considered to be markers of myocardial necrosis and generally, it occurs following 2-4 hours of ischemia [15]. Hence, they typically do not permit detection of the beginning of myocardial ischemia leading to necrosis in its early stages. Further, it has been identified that maximal sensitivity of these markers is not achieved until six or more hours after the onset of MI [16]. A sampling of blood needs accurate determination of the timing of onset of symptoms which is mostly based on patient reporting and often very challenging to the treating clinician. Moreover, the rise in these markers *e.g.*, cTn, indicates damage to the myocardium but not the mechanism of damage; plaque rupture and acute coronary occlusion leading to AMI (type 1) or the ischemia produced either by increased oxygen demand or decreased supply leading to AMI (type 2) (*e.g.,* coronary artery spasm, coronary embolism, anaemia, arrhythmia, hypertension or hypotension). Even when an upsurge of troponin is consistent with a diagnosis of AMI, other cardiac diseases such as myocarditis, Tako-tsubo cardiomyopathy or anon-cardiac condition such as shock can produce substantial variations of troponin as well [15]. Hence the interpretation of the results is heavily dependent on the clinical context in which it is requested. To overcome these limitations, researchers have been trying to find the ideal cardiac marker to diagnose ACS quickly.

1.2. The Need for Novel Cardiac Markers

As ACS is the main cause of mortality and morbidity worldwide, a rapid test for accurate and timely detection of ACS is essential. To arrive at a definitive diagnosis for individuals admitted with chest pain or other signs suggestive of ACS is often time-consuming, problematic and expensive.

In agreement with the WHO, 'biomarker is defined as any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease' [17,18].

Biomarkers play a pivotal role in the diagnosis and treatment of patients with ACS. At present, there is no validated biomarker to evaluate myocardial ischemia in clinical practice. Though cTn is the gold standard for myocardial necrosis, it is blind for ischemia without necrosis. The beginning of symptomatic ischemia is antedating to myocardial necrosis. Hence, cTn leaves the patient with unstable angina, which by definition indicates myocardial ischemia without necrosis, undiagnosed.

The development of high sensitivity cTn (hs-cTn) aids earlier exclusion of AMI, contributing to a reduced length of stay at ED. Moreover, it facilitates early treatment for AMI, resulting in improved outcomes [19, 20]. Due to the high sensitivity of these assays, the number of patients being admitted for further evaluation to hospital could increase.

Although cTn is the most commonly used diagnostic and prognostic marker in the setting of suspected ACS, perceived limitations of troponin have led to testing newer cardiac biomarkers.

In addition to being readily available and having desirable analytical properties, a cardiac biomarker should be able to detect patients with or at risk of ACS as early as possible with maximum sensitivity and diagnostic accuracy and should be able to give incremental information to existing clinical information. Further, it should be useful for guiding specific treatment algorithms for ACS and must be able to add prognostic information. A faster and more accurate diagnosis or ruling out of ACS can lead to early and optimum management, and reduce stay at the emergency department and hospital costs.

It is therefore essential to evaluate for an ideal biomarker or combination of biomarkers (multimarker approach) reflecting varied pathophysiological entities of ACS which include atherosclerosis, inflammation, oxidative stress, angiogenesis, plaque instability, platelet activation, thrombosis and myocardial ischemia or necrosis to augment the timely and precise diagnosis of ACS [19].

Nearly all regional acute myocardial ischemia is caused by thrombosis developing on a culprit coronary atherosclerotic plaque except in spontaneous coronary artery dissection, coronary arteritis, coronary emboli and coronary spasm [21]. An emergent understanding of the significance of the rupture of atherosclerotic plaque in the pathogenesis of ACS has led to the identification of an expanding array of markers of plaque vulnerability.

The aim of this article is to review the potential cardiac biomarkers of atheromatous plaque formation, rupture and thrombosis in the early and accurate diagnosis of cardiac ischemia before developing necrosis.

2. METHODS

A literature search using PubMed, Medline, Google Scholar, Science Direct, Cochrane Library, ISI, IBSS and Scopus databases (2000-2020) was carried out to isolate and evaluate all relevant English-language studies of cardiac biomarkers of atheromatous plaque formation, rupture and

thrombosis in the prediction of ACS. The previously published principles were followed when the search strategy was conducted. The following keywords “myocardial infarction”, “acute coronary syndrome”, “cardiac biomarkers”, “atheromatous plaque formation”, “plaquerupture”,“thrombosis” and “troponin” were used. Further, a manual search of bibliographies from the retrieved articles was performed to identify additional studies. Letters, conference abstracts, and editorials were excluded. The chosen articles were further reviewed for relevance and repetition. Selected articles were deeply evaluated and detailed notes were made, impressions were written down and highlighted. The data was then categorised into relevant categories and subcategories after it was identified which pieces of data had values. Finally, data was analyzed in detail and inferences were made.

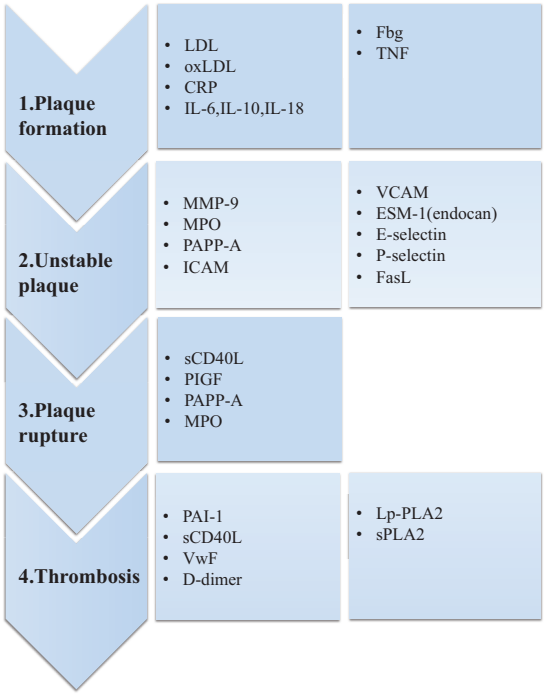

Fig. (1). Biomarkers of atheromatous plaque formation, rupture and thrombosis in the diagnosis of Acute Coronary Syndrome.
CRP: C-Reactive Protein, ESM-1: Endothelial cell-specific molecule, FasL:Fas Ligand, Fbg:Fibrinogen, ICAM: Intercellular Adhesion Molecule, IL-6: Interleukin 6, IL-10: Interleukin-10, IL-18:Interleukin-18,LDL:Low Density Lipoprotein, Lp-PLA2:Lipoprotein Associated Phospholipase A2, MMP:Matrixmetalloproteinases, MPO: Myeloperoxidase, Ox-LDL: Oxidized Low-Density Lipoprotein, PAI-1:Plasminogen Activator Inhibitor-1,PAPP-A: Pregnancy-associated Plasma Protein-A, PIGF: Placenta Growth Factor, sCD40L: soluble CD40 Ligand, sPLA2:secretory Phospholopase A2, TNF :Tumor Necrosis Factor, VCAM: Vascular CcellAdhesion Mmolecule, vWF:vonWillebrand Factor.

3. POTENTIAL BIOMARKERS OF ATHEROMATOUS PLAQUE FORMATION, RUPTURE AND THROMBOSIS IN THE DIAGNOSIS OF ACUTE CORONARY SYNDROMES

ACS is linked with progressive or dynamic obstruction, plaque inflammation, plaque instability and rupture and overlaid thrombosis leading to myocardial ischemia and necrosis [21, 22]. Numerous chemicals are released during this process and can be detected in the peripheral blood. The release of certain markers and enzymes during the phase of plaque formation, development of unstable plaque, plaque rupture and thrombosis are shown in Fig. (**1**) and a few selected markers are discussed in detail.

3.1. Biomarkers of Plaque formation

Atherosclerosis is a systemic arterial disease of consequences of complex endothelial dysfunction persuaded by modified low-density lipoproteins, hypertension, smoking-induced toxins, pathogenic micro-organisms, free radicals, shear stress, and/or a combination of these factors and other causes that points to a compensatory inflammatory reaction [23, 24]. Oxidative stress and inflammation have crucial involvement in plaque formation and various biomarkers are released during this process.

3.1.1. Tumour Necrosis Factor

Tumour necrosis factor (TNF) was described in 1975 formed by activated macrophages, lymphocytes, endothelial, epithelial cells, smooth muscle cells and cardiac myocytes [25]. TNF exerts its biological effects through two cell surface receptors: TNFR1 and TNFR2 and these receptors show polymorphisms [26, 27]. The involvement of TNF-α in the cardiovascular system includes the influence on endothelial function, inflammatory cells, vasodilatation, smooth muscle cell physiology, cardiac myocytes function and glucose homeostasis [25]. Due to the effect of vascular endothelial cells, TNF-α can cause inflammatory gene induction, leukocytes recruitment, cytoskeleton reorganization, proliferation of endothelial cells, migration and apoptosis [25, 28]. Due to its influence on cardiac myocytes, TNF-α can induce apoptosis, inflammatory gene expression, and hypertrophy and reduce myocytes' contractility. The vascular smooth muscle proliferation, migration, constriction, inflammatory gene expression and apoptosis could be persuaded by TNF-α [25]. Selective inhibition of TNF receptors with specific antibodies, antagonists or siRNAs can counter balance the proinflammatory, proatherogenic effects of TNF-α while maintaining cardioprotective effect [25].

3.2. Biomarkers of Unstable/Vulnerable plaque

Vulnerable plaques have an increased number of macrophages which release lytic enzymes like metalloproteinases and are accompanied with a reduced number of smooth muscles, presence of low-grade stenosis and a thin fibrous cap [29]

3.2.1. Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) belong to the family of endopeptidases which are produced by numerous inflammatory and tumour cells as zymogens which are activated subsequently by proteinases. MMPs oppose the intimal thickening and also destroy the extracellular matrix leading to plaque rupture [30, 31]. MMPs are divided into interstitial collagenases (MMP-1,-8,-13 and -14), gelatinases (MMP-2 and -9), stromelysins (MMP-3,-7,-10 and -11) and macrophage elastase (MMP-12) [30, 32]. MMP-2, MMP-8 and MMP-9 are recognized as proteases involved in atherosclerotic plaque rupture and clinical outcome by degenerating plaque matrix [30, 33-35].

3.2.2. Myeloperoxidase

Myeloperoxidase (MPO) belongs to the haem peroxidizes family. During inflammatory conditions, MPO is formed by polymorphonuclear leukocytes, neutrophils and monocytes. MPO can activate MMPs and induces LDL oxidation [30, 36]. MPO is recognized as a major contributor to the development and rupture of plaque. According to researchers, there is a significant inverse correlation of the level of MPO with paraoxonase-1 bound to HDL [37]. The MPO enzyme is predominantly secreted by activated neutrophils and characterized by strong pro-oxidative and proinflammatory properties. MPO is abundant in ruptured plaque and can be quantified in peripheral blood. This haemprotein enzyme is largely stored in azurophilic granules of polymorphonuclear neutrophils and in macrophages. Recently MPO has been suggested both as a valuable risk indicator and a diagnostic tool in patients with ACS. As an indicator of inflammation and oxidative stress, MPO has been consistently proved to be raised in ACS [38]. It is also important to note that increased MPO is not always specific to cardiac illnesses as stimulation of neutrophils and macrophages could take place in any other infection, inflammation or infiltrative process [38]. MPO shows potent proatherogenic properties. MPO can oxidize cholesterol, enhancing uptake by macrophages and stimulating foam cell formation. MPO activates metalloproteinases and stimulates destabilization and the atherosclerotic plaque surface rupture and also reduce nitric oxide bioavailability impairing vasodilatation and anti-inflammatory functions [39]. Baldus *et al.* concluded that MPO is a potent forecaster of adverse outcome of ACS. According to their study, MPO identified patients at risk for forthcoming cardiovascular incidents better than Tns [39]. Systematic review and meta-analysis conducted by Kolodziej *et al.* showed that MPO is a powerful prognostic marker for clinical outcomes of ACS patients [40]. Calmarza *et al.* showed marked elevation of MPO within the first two hours of symptoms onset in people with myocardial infarction or in individuals with ACS presenting within 3-12 hours of their last episode of chest pain. The same study showed a progressive increase of MPO with the increase in severity of CAD from stable CAD to NSTE-ACS [41]. Studies have identified MPO as an independent and prevailing predictor of cardiac risk at both 30 days and follow-up [41-43].

3.2.3. Pregnancy-associated Plasma Protein-A

Pregnancy-associated plasma protein-A (PAPP-A) is a zinc-binding matrix metalloproteinase and was first recognized in pregnant women. It induces the insulin-derived growth factor-1 (IGF-1) activation, which in turn triggers inflammation and lipid uptake contributing to atherogenesis and plaque instability [30]. According to clinical studies, PAPP-P is linked with recurrent ischaemic and cardiovascular events in patients with acute and chronic CAD [30, 44, 45]. In addition, to be a promising marker of risk categorization of ACS, PAPP-P is a useful serum biomarker to predict increased coronary thin-cap fibroatheromatous burden and plaque instability [30, 46]. Some studies show that PAPP-A was not associated with elevation of biomarkers of cardiac necrosis, indicating that PAPP-A may have a diagnostic value in detecting patients with ACS without myocardial necrosis [47].

3.2.4. Intercellular Adhesion Molecule-1

Intercellular adhesion molecule-1(ICAM-1) is a type 1 glycoprotein and is a member of the immunoglobulin superfamily with molecular weight ranges between 80-114kDa [48, 49]. The key role of ICAM-1 is to facilitate firm adhesion helping leukocytes transendothelial migration into the vascular subendothelial space and antigen presentation. ICAM-1 correlates with the development and expansion of atheroma [48, 50, 51]. ICAM-1 is hardly expressed under physiological conditions, but under inflammatory conditions, due to the activation of inflammatory factors, it is expressed widely [49]. A circulating type of ICAM-1 is soluble ICAM-1(sICAM-1) and is present in serum, cerebrospinal fluid, synovial fluid, sputum, urine and bronchoalveolar fluid. Raised levels of sICAM-1 are present in people with cardiovascular disease [48]. Gross *et al.* showed that the concentration of sICAM-1 might be an initial marker indicating alterations in the arterial wall that is associated with atherosclerosis and the existence of advanced plaque in the carotid and coronary arteries [50]. Data suggests that in individuals with stable CHD, increased levels of sICAM-1 are linked with the risk of forthcoming cardiac death or non-fatal acute MI [52]. Association of sICAM-1 and cardiovascular condition is also seen in prospective epidemiological studies, including Women's Health Study, Physicians Health Study, ARIC Study and the British Regional Heart Study of mature adults [50, 53].

3.2.5. Vascular Adhesion Molecule-1

Vascular Adhesion Molecule-1 (VCAM-1) belongs to the immunoglobulin superfamily. It is a transmembrane glycoprotein that presents on the cell surface and mediates cell interaction and adhesion to other cells and the extracellular matrix [54-56]. VCAM-1 is not routinely expressed under physiological conditions, but with appropriate pro-inflammatory stimuli like exposure to inflammatory cytokines like TNF-α or IL-1β it can be activated and expressed by the vascular endothelium [56] and bound to VLA-4 expressed in monocytes and lymphocytes leading to transmigration of inflammatory cells [57]. Studies showed that the presence of VCAM-1 in initial atherosclerotic lesions and the shoulder region of established atheroma plays a vital role in mononuclear cell adhesion and accumulation [58]. Also, soluble-VCAM-1 can reflect the inflammatory process in the endothelium and is related to the magnitude of coronary lesions [59].

3.2.6. E-Selectin

Selectins consist of three carbohydrate-binding proteins and belong to the C-type lectin family [60, 61]. E-selectin (Endothelial-leukocyte adhesion molecule) is found on activated endothelial cells, P-selectin is expressed on activated platelets and endothelial cells and L-selectin are expressed on leukocytes. E-selectin was first reported by Bevilacqua and the team in the 1980s. Its expression on inflamed endothelium is stimulated by cytokines (TNFα, IL-1β or platelet factor 4) [54, 60]. E-selectin is regarded as the key selectin for transferring cells to inflammatory sites in humans and it mediates leukocytes rolling on stimulated endothelium at inflammatory sites [59-66]. E-selectin and P-selectin are together known as "Vascular selectins". As E-selectin is found only in the activated endothelium, its presence in the blood reflects conclusive evidence of endothelial activation [67].

3.2.7. P-Selectin (Granule Membrane Protein-140)

P-selectin was introduced in 1984 by McEver and co-workers and Furie and co-workers. It is kept in α-granules of circulating platelets and Weibel-Palade bodies of endothelial cells. It is the largest of the selectins, with a mass of 140kDa [68]. Following pro-inflammatory stimulus by histamine or thrombin, P-selectin is rapidly translocated from the granules to the surface of the cell [60, 62]. Though P-selectin is spotted on the atherosclerotic endothelium of active plaque, it is not found on the normal/non-inflamed endothelium. Elevation of expression of P-selectin is considered the first and primary event at the beginning of atherosclerosis [54]. P and E-selectin on an activated endothelium trap leukocytes from the circulation and allow them to roll along the endothelium [68, 69]. P-selectin is partly accountable for the binding of platelets and certain leukocytes to the endothelium [68, 69]. It is considered that P and E-selectin function in leukocytes adhesion is overlapping and it is hypothesized that there might be a combined effect of these selectins on the formation of atheroma [66]. Soluble P-selectin in plasma can exert procoagulant activity and might have a main role in thrombosis and acute coronary incidence [70]. Hence, P-selecin is a possible therapeutic target.

3.2.8. Endothelial Cell-specific Molecule-1(endocan)

Endothelial cell-specific molecule-1 (ESM-1) is an immunoregulatory glycoprotein which is released by vascular endothelial cells and has an extensive role in a number of processes, including cell proliferation, migration and neovascularisation [71-73]. ESM-1 has a crucial involvement in endothelial dysfunction and inflammatory reaction [71,74] Vascular endothelial dysfunction shows an important role in the advancement of atherosclerosis and endocan promotes endothelial cells to produce inflammatory cytokines, leukocytes migration, and increases vascular permeability, smooth muscle cells migration and proliferation [71, 75]. Lassalle *et al.* found that endocan was highly expressed in atheromatous plaque suggesting its vital function in the pathogenesis of atherosclerosis [71,76]. An increased level of serum endocan is an independent risk factor for ACS and increased serum ESM-1 is found in individuals with ACS [71]. Circulating endocan levels were positively linked to the severity of CAD [76].

3.2.9. Fas Ligand

FasLigand (FasL) is a type II membrane protein that triggers apoptosis in Fas-bearing cells [77]. The death receptor Fas and FasL are found in advanced atherosclerotic plaques in humans and are implicated in cellular apoptosis in atherosclerotic lesions. FasL-mediated apoptosis eliminates cells from atheroma and thereby attenuates the advancement of atherosclerosis [77,78]. Stimulation of the Fas/FasL pathway of apoptosis has been associated with atheroma remodelling [79]. In the atherosclerotic plaque, FasL is expressed on T cells, macrophages and endothelial layer covering fibrous cap and plaque. Fas receptor is expressed on smooth muscle cells, macrophages and endothelial cells [79]. Soluble forms of Fas (sFas) and FasL (sFasL) are spotted in plasma and readily considered as indicators of apoptosis. With regards to cardiovascular disease, increased levels of sFasL represent a profile of low cardiovascular risk [80].

3.3. Biomarkers of Plaque Rupture

Currently, it is well known that inflammation and oxidative stress have a key role during every step of the pathogenesis of atherosclerosis until the final pathophysiological outcomes like plaque destabilization and eventually plaque rupture [81]. Various cells classic for atherosclerotic plaque, like monocytes derived macrophages and T-lymphocytes are capable to form and release such mediators like chemokines, cytokines, growth factors, enzymes and disintegrins, which leads to activation of endothelial cells, lesion progression and ultimately weakening of a susceptible plaque by matrix degradation, thinning and rupture of fibrous cap [81-83]. Rupture of plaque is linked with the discharge of soluble CD40 ligand, placental growth factor, pregnancy-associated plasma protein-A and adhesion molecules [83].

3.4. Biomarkers of Thrombosis

Superimposed thrombosis is a manifest as rising levels of D-dimer, P-selectin, CD-40 ligand, plasminogen activator inhibitor-1 and von Willebrand factor [29].

3.4.1. Soluble CD40 Ligand

This soluble CD40 ligand (sCD40L) biomarker is a member of the tumor necrosis factor superfamily. It is found in various types of cells comprising immune cells (like lymphocytes, dendritic cells, neutrophils and macrophages) and non-immune cells (such as epithelial cells, vascular smooth muscle cells and endothelial cells) [84]. The binding of CD40L with its receptor CD40 is particularly important for immunomodulating properties. CD40L can also fix receptors in the platelet surface, leading to its activation and release of soluble types of mediators and production of reactive oxygen species [82]. CD40L may function in an autocrine loop to promote platelet-platelet aggregates by interaction with a major platelet integrin and /CD40 receptor [85].

3.4.2. Lipoprotein-associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2), **a**lso called as platelet-activating factor acetylhydrolase belongs to the phospholipase A2 superfamily. Lp-PLA2 is mainly produced by monocytes and macrophages and it modifies the surface of LDL, increasing susceptibility to oxidation [30, 86]. Following LDL oxidation, Lp-PLA2 causes the secretion of lyso-phosphatidylcholine and oxidized fatty acids, which trigger the inflammatory cascade.

3.4.3. Secretory Phospholipase A2

The secretory phospholipase A2 (sPLA2) family consists often of disulfide-rich isoenzymes, which have a function in a variety of biological processes [86]. These enzymes have a role in atherogenesis and inflammation by facilitating lipoprotein retention with vascular proteoglycans, inducing platelet activation through the prostanoid pathway activation, and facilitating LDL oxidation [87, 88].

3.4.4. Plasminogen Activator Inhibitor-1

MI is usually secondary to thrombosis at the place of ruptured/ fissured atherosclerotic plaque. The dynamic balance between coagulation and fibrinolysis governs the thrombotic response. Fibrinolysis is primarily controlled by Plasminogen Activator Inhibitor-1 (PAI-I). PAI-I, a serine

protein inhibitor, has multifunction properties and is the main determinant of endogenous fibrinolysis. It blocks both tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) and inhibits fibrinolysis [89-93]. Overexpression of PAI-I promotes the development of weak plaque with thin fibrous caps. Hence, increased PAI-I influences the development of MI by affecting both atheroma and thrombosis. In large epidemiological studies, elevated levels of plasma PAI-I have been spotted as a predictor of MI [94]. The regulation of PAI-I is multifactorial including environmental factors and genetic control [89]. A study done by Gray *et al.* presented that diabetic patients have higher PAI-I than non-diabetic patients. Raised PAI-I activity may predispose diabetic patients to MI and poor outcomes [95].

3.4.5. Von Willebrand Factor

Von Willebrand factor (vWF); multimeric glycoprotein is formed virtually by endothelium and is a useful marker of endothelial dysfunction. After synthesis, vWF is stored in both megakaryocytes/platelets (α-granules) and endothelial cells (Weibel-Palade bodies) [96, 97]. The soluble form of vWF found in plasma is predominantly of endothelial origin and plasma vWF is considered a surrogate indicator of activation of the endothelium [98]. Under high shear conditions, vWF has a vital role in platelet adhesion and aggregation. VWF supports the clotting factor activation by carrying and stabilizing factor VIII. VWF is a well-recognized marker of cardiovascular risk and its levels in plasma are raised in patients with ACS and considered one of the risk factors for acute MI [96, 97]. A meta-analysis carried out by Wang *et al.* revealed that plasma level of vWF was significantly higher in acute MI patients than healthy volunteers or non-ACS patients. They demonstrated that high plasma vWF levels persisted for one week [94]. The plasma levels decreased to baseline at two weeks after MI [99]. The most common inherited bleeding disorder is Von Willebrand disease (VWD) and is due to either quantitative or qualitative defects in vWF. Case series analysis conducted by Hassan *et al.* showed that CAD is uncommon in patients with VWD [100]. A cross-sectional study performed by Sanders *et al.* also demonstrated a decreased prevalence of thrombosis in arteries in VWD patients [101].

3.4.6. D-dimer

D-Dimer, a high-weight molecule of the fibrinogen derivative, was discovered in the 1970s, and it was first used in patients with suspected venous thromboembolism or disseminated intravascular coagulation [102, 103]. High D-Dimer level is identified in diseases like acute venous thromboembolism, IHD and cancer. D-dimer concentrations are highly sensitive to determine thrombus formation [103]. Bayes-Genis *et al.* claimed that normal D-dimer levels might be useful in excluding ischemia and adverse cardiovascular incidences in patients presented with chest pain. Moss *et al.* stated that the presence of elevated D-dimer levels after two months of MI was linked to recurrent coronary events. Akgul *et al.* showed that MI patients with high D-dimer had a high incidence of all-cause mortality and cardiovascular mortality compared to the low D-dimer group [103]. Measurement of D-dimer levels is simple and easy and can be utilized as a risk stratification tool in ACS. Orak *et al.* discovered that D-dimer had a sensitivity of 83.7 percent and a specificity of 95.4 percent for ACS in patients admitted with chest pain in an emergency department, suggesting that D-dimer is a good biomarker in the emergency department [104]. A study conducted by Reihani *et al.* concluded that the measuring serum D-dimer level is a useful marker with high sensitivity and relatively high specificity for differentiating MI from UA in patients with suspected ACS [105].

CONCLUSION

A timely diagnosis of ACS and cardiac ischemia in a patient presenting with chest pain and other suggestive symptoms is a diagnostic challenge for treating clinicians. To overcome this challenge, cardiac biomarkers have been developed. Though cTn is the gold standard for myocardial necrosis it is blind for ischemia without necrosis. In addition to being readily available and having desirable analytical properties, a cardiac biomarker should be able to detect patients with or at risk of ACS as early as possible with maximum sensitivity and specificity. However, the clinical use of cardiac biomarkers in ACS is no longer restricted to establishing or disproving the diagnosis. It also provides a convenient and noninvasive way to increase understanding of the primary causes and consequences of ACS that facilitate the risk of recurrent events, prognosis and may be a guide for specific therapeutic interventions.

An emergent understanding of the significance of the rupture of atherosclerotic plaque in the pathogenesis of ACS has led to the identification of an expanding array of markers of plaque vulnerability. Although there is a large number of biomarkers of atheromatous plaque formation, rupture and thrombosis in the diagnosis ofACS have been investigated, most need to be validated in further studies. Moreover, studies are needed to identify biomarkers which can be used as a point of care testing to augment early diagnosis prior to developing ischemia and necrosis and to reduce the length of stay at ED.

Pathophysiology of cardiac ischemia is a complex mechanism and involves different pathways including atherosclerosis, inflammation. oxidative stress, angiogenesis, plaque instability, platelet activation, thrombosis, myocardial ischaemia, or necrosis. Various biomarkers related to these different steps of ACS have been identified and new therapies have been discovered with the advancement of knowledge. However, more efforts are needed to find convenient and accurate methods to measure them in blood as no such methods exist to measure most of these biomarkers in clinical practice. The use of a combination of these biomarkers (multi-marker approach) with both established and new markers for risk assessment, early diagnosis, prediction of prognosis and clinical decision-making will overcome drawbacks in individual biomarkers and is the way forward to improve outcomes in patient with ACS. One such ideal combination would be a marker of unstable/ vulnerable plaque (Myeloperoxidase or PAPP-A) or marker of plaque rupture (circulating T-cell monocyte complexes released from ruptured atherosclerotic plaque) with troponin which point towards ACS due to plaque rupture. Metalloproteinases (that disrupt the integrity of plaque) with soluble CD40 ligand, a marker of platelet activation and thrombosis and troponin will mark the thrombosis causing ACS.

Further, technological advances are needed to incorporate these biomarkers into a single cassette at point of care to offer rapid and convenient multi marker profiles to guide risk assessment, early diagnosis and to therapeutic decision making.

Moreover, studies are needed to prepare validated biochemical tools using a combination of biomarkers of haemodynamic stress, inflammation (high sensitivity CRP), thrombosis and plaque rupture with bio markers of myocardial ischemia and necrosis (troponin) to enhance risk assessment, early diagnosis before developing ischemia or necrosis and predicting prognosis in patients with ACS. Also, these types of tools can be used to direct therapeutic decision-making.

LIST OF ABBREVIATIONS

ACS	=	Acute Coronary Syndrome
AMI	=	Acute Myocardial Infarction
AST	=	Aspartate Transaminase
CK	=	Creatine Kinase
cTn	=	Cardiac Troponins
ECG	=	Electrocardiogram
ED	=	Emergency Department
ESM-1	=	Endothelial Cell-specific Molecule-1
FasL	=	Fas Ligand
hs-cTn	=	High Sensitivity Troponin
ICAM-1	=	Intercellular Adhesion Molecule-1
IHD	=	Ischaemic Heart Disease
Insulin	=	Derived Growth Factor-1
LBBB	=	Left Bundle Branch Block
LDH	=	Lactate Dehydrogenase
Lp-PLA2	=	Lipoprotein Associated Phospholopase A2
MI	=	Myocardial Infarction
MMPs	=	Matrix Metalloproteinases
MPO	=	Myeloperoxidase
NSTEACS	=	Non ST-Elevation ACS
NSTEMI	=	Non ST-elevation Myocardial Infarction
PAI-1	=	Plasminogen Activator Inhibitor-1
PAPP-A	=	Pregnancy-Associated Plasma Protein-A
sCD40L	=	Soluble CD40 Ligand
sPLA2	=	Secretory Phospholipase A2
STEMI	=	ST-Elevation Myocardial Infarction
TNF	=	Tumour Necrosis Factor
VCAM-1	=	Vascular Adhesion Molecule-1
vWF	=	Von Willebrand Factor.
WHO	=	World Health Organization

AUTHORS' CONTRIBUTIONS

UR conceived the research idea and conducted the literature searches, collected and collated articles and drafted this paper. UR and RS commented in detail on drafts and contributed to the final version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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HOW TO CITE:

Ralapanawa Udaya* Ramiah Sivakanesan, "Synopsis of Biomarkers of Atheromatous Plaque Formation, Rupture and Thrombosis in the Diagnosis of Acute Coronary Syndromes", Current Cardiology Reviews 2022; 18(5): e110422203390 https://www.eurekaselect.com/article/122457