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In Search for Novel Biomarkers of Acute Coronary Syndrome

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1. Introduction

Coronary artery disease (CAD) and its one of the severe clinical manifestation, Acute Myocardial Infarction (AMI) continue to be significant cause of morbidity and mortality in both men and women around the world. The extent of myocardial damage after an acute coronary event of atherothrombosis determines the prognosis. The diagnosis of acute coronary syndrome (ACS) encompassing unstable angina, non ST elevated myocardial infarction (NSTEMI) (Bertrand et al., 2002; Braunwald et al., 2000; Hamm et al., 2001) to STEMI (AMI) (Alpert et al., 2000), is based on a combination of symptoms, electrocardiographic changes and biomarkers.

The physical examination can be inadequate in identifying atypical chest pain from chest pain of cardiac origin. On one hand 33% of patients with ACS have no chest pain. On the other hand approximately half of patients with acute chest pain, who have the initial diagnostic findings of ACS and are admitted to the hospital, are later found not to suffer from ACS. In the majority of patients with chest pain, the electrocardiogram (ECG) is the most readily available tool for identifying patients with ACS. However, the ECG is also often not diagnostic for acute chest pain and in fact; the sensitivity of borderline ECG for detecting ACS is only 60% (Canto et al., 2000, Panteghini, 2002).

Over the last 50 years, the contribution of laboratory Medicine to the management of cardiac diseases has become increasingly sophisticated. In 1950s, Karmen et al first reported that enzyme released from necrotic cardiac myocytes could be detected in the serum and could be used in the diagnosis of MI. The ensuing years witnessed progressive improvement in the type of cardiac tissue specific biochemical markers and a corresponding enhancement in the clinical sensitivity and specificity of their use.

1.1 Current practice of diagnostic biomarkers in ACS

Today, markers of myocardial necrosis at the down stream of the pathophysiology of ACS; some specific to myocardial necrosis have gained their mark under routine diagnosis of ACS (Table 1).

1.1.1 Myoglobin

The main advantage of myoglobin is early detection of patients with AMI (Gibler et al., 1987, Roxin et al., 1984). The NACB Laboratory Medicine Practice Guidelines have recommended

myoglobin in addition to cardiac troponins (cTn) for the diagnosis of AMI patients who present within the 6 hours of onset of symptoms (Apple et al., 2007). The serum myoglobin level rises faster than Creatinine Kinase-MB (CK-MB) and cTn, reaching twice the normal values within 2 hours and peaking within 4 hours of symptom onset. The disadvantage of using myoglobin alone is that it has poor specificity for AMI in patients with concurrent trauma or renal failure.

Current Biomarkers
Myoglobin
Creatine Kinase-MB
Troponins
Natriuretic Peptides

Table 1. Current Biomarkers

1.1.2 Creatinine Kinase (CK)

CK-MB, the specific cardiac isoform of CK can be used in the diagnosis of myocardial necrosis (Mair et al., 1991). This was proposed by World Health Organization and was later extended for monitoring trends in cardiac disease (Apple et al., 2007, 2003). Elevation of CK-MB occurs 4 to 6 hours after the onset of acute MI and remains for 24 to 48 hours. CK-MB is relatively sensitive but less specific as it can be elevated in any conditions following acute muscle injury or in patients undergoing any surgical procedure. Furthermore CK is present in skeletal muscle, intestine, diaphragm, uterus and prostate and thus the specificity of CK-MB is impaired in the setting of injury to these organs. Moreover, serial analysis of CK-MB are required for quantitation as well as qualitative assessment of injury to cardiac muscle, therefore, many studies have suggested that a single cTn can be used as a convenient, cost effective and non invasive method for the diagnosis of myocardial necrosis (Apple et al., 1999, De Winter et al., 1995).

1.1.3 Cardiac troponin (cTn)s

Undisputedly troponin (cTnI and cTnT) are the most sensitive and specific biomarker of myocardial injury (Bleier et al., 1998). The kinetics of both the troponins are detectable in the serum within 4 to 12 hours after the onset of acute MI and depending upon the duration of ischemia and reperfusion status, peak values occur 12 to 48 hours from symptom onset (Apple et al., 1999). The tissue specificity and reliable detected concentration of cTn in the peripheral circulation makes it a good indicative of myocardial injury (Bleier et al., 1998). Moreover, several studies have shown that patients presenting with elevated cTns had a poor prognosis compared to those without detectable cTns (Panteghini, 2002). Because both forms of cTn remain in the circulation several days after injury, it allows for diagnosis even in patients who present very late (Apple et al., 2003). However because of long half lives, one of the disadvantages using the cTn is that neither cTnI nor cTnT can be used for detection of reinfarction after an index event. The other disadvantage of cTnT is that it is present in small amounts in skeletal muscle and is re -expressed in diseases that involve skeletal muscle degeneration. Therefore, an elevated cTn without clinical evidence of ACS should prompt for other possible myocardial injuries, including cardiac trauma, cardiac failure, and hypertension (Panteghini, 2002).

1.1.4 Natriuretic peptides

B –Natriuretic peptide (BNP) and its prohormone N-terminal pro BNP (Nt-proBNP) are neurohormones secreted from cardiac ventricles in response to ventricular wall stress (de Bold, 1985, Nakako et al., 1992). BNP, an established biomarker for patients with heart failure, and NT-pro BNP are elevated in ACS and can identify patients at very high risk for adverse cardiovascular events including death (de Lemos &Marrow, 2002, Ishibashi, 2002). The utility of BNP and NT-pro BNP as markers is based on the finding that it increases in the left ventricle during remodeling after a transmural infarction or as a consequence of previous ischemic damage (Lorgis et al., 2007). However these peptides have poor specificity for the diagnosis of ACS since elevated levels can also be seen in patients with renal failure, primary aldosteronism, congestive heart failure and thyroid disease.

Despite the success of these biomarkers, there is still a need for the development of early markers that can reliably rule out ACS in the emergency room at presentation and also detect myocardial ischemia in the absence of reversible myocyte injury. Misdiagnosis has been reported to be the main cause of treatment delays. Undetected infarctions remain a serious public health issue and represent the leading cause of malpractice cases in the emergency settings. These imperfect strategies resulting in costly and inappropriate management decisions have forced us to search new non-invasive quick strategies in identifying the high-risk individuals. One of them is identifying novel cardiac biomarkers.

Biomarkers have multiple uses in the arenas of research and practice. It is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic interventions. In clinical practice, a biomarker may be used to diagnose a medical problem, serve as a tool for staging disease, or provide an indicator of differential prognosis.

1.2 In search for novel cardiac biomarkers of ACS

Recent investigations have been directed towards analyzing components, involved in the pathogenesis of ACS, at upstream from biomarkers of necrosis, such as components released during Ischemia, components of plaque destabilization and rupture, factors of thrombosis, components representing oxidative stress, molecules of inflammation and acute phase reactants for earlier assessment of overall patient risk of adverse event and indexing them under "Biomarkers" (Table 2).

1.2.1 Components released during ischemia

The explicit goal is to maintain micro-circulatory flow to prevent even minor infarctions. Only marker that precedes necrosis and permits prevention of the consequence can meet the clinical need. Identifying markers of ischemia even if necrosis is not present may help in identifying a high risk individual who may in very near future experience the consequences of the infarct. The components that have been studied in this group are Free Fatty Acids unbound to Albumin (FFAu), Choline, Ischemia-Modified albumin (IMA) and Heart type Fatty Acid Binding Protein (H-FABP).

Components Released during Ischemia
Free Fatty Acids unbound to Albumin (FFAu)
Ischemia Modified Albumin (IMA)
Choline
Heart type Fatty acid binding protein (H-FABP)
Thrombotic Factors
Soluble CD40 Ligand (sCD40L)
P-selectin
Tissue Factor (TF)
Plasminogen Activator Inhibitor-1 (PAI-1)
Components involved in Plaque Rupture
Myeloperoxidase (MPO)
Metalloproteinases (MMPs)
Cathepsins
Pregnancy-associated plasma protein-A (PAPP-A)
Components representing oxidative stress
Oxidized LDL (Ox-LDL)
Lectin-like oxidized low density lipoprotein receptor-1 (LOX-1)
Lipoprotein-associated phospholipase A-2 (Lp-PLA-2)
Molecules of Inflammation
Vascular Cell Adhesion Molecule (VCAM-1),
Platelet Endothelial Cell Adhesion Molecule (PECAM-1)
Cystatin C
High-sensitivity C - reactive protein (HsCRP)

Table 2. Emerging Biomarkers

1.2.1.1 Free Fatty Acids unbound to albumin (FFAu)

Increased blood catecholamines in association with ischemia can cause increased FFA by activating lipid hydrolysis within the heart and adipose tissue. Apart from this, reduction of FFA use after ischemia can also cause increased serum concentration of FFA. The observed increase in free fatty acids unbound to albumin (FFAu) in the blood with acute myocardial ischaemia has been evaluated for the early identification of cardiac injury (Kleinfeld et al., 1996). Two groups of investigators have preliminarily studied the sensitivity of this marker at patient presentation to the emergency room and have shown that FFAu was elevated well before other, more traditional, markers of cardiac necrosis and had at admission sensitivity of >90% (Kleifeld et al., 2002, Adams et al., 2002).

1.2.1.2 Ischemia Modified Albumin (IMA)

Due to ischemia the metal binding site on the amino terminus of albumin is damaged. The albumin of patient with myocardial ischemia exhibit lower metal binding capacity for cobalt than that of normal patients (Bar-Or et al., 2001a). IMA gained its importance as it demonstrated a good "negative predictive value." In the assay, Cobalt less bound to albumin reacts with the indicator (Bar-Or et al., 2000). Significant changes in albumin cobalt binding were documented to occur minutes after transient ischemia induced by balloon angioplasty and to return to baseline within 12 hours (Bar-Or et al., 2001b). However its

presence during ischemia of any other organ and in individual with inherent reduced cobalt binding giving false positive results, lost its specificity for routine use in detection of ischemia (Collinson & Gaze, 2008). However correlating with the clinical conditions and other markers may find its use in identifying high risk individuals.

1.2.1.3 Choline

Choline is a biomarker that is released when phospholipids are cleaved, which suggests that perhaps it could be a marker of ischemia and/or necrosis (Danne & Möckel, 2010). Experimental studies have demonstrated that phospholipase D enzyme activation and release of choline in blood are related to major processes of myocardial ischemia. Several studies suggested that the marker might improve prognostication in patients with ACS (Danne et al., 2003). In a study with troponin negative patients, choline detected high-risk unstable angina with a sensitivity and specificity of 86%. Additional studies are however needed to fully investigate the clinical significance of this marker (Apple et al., 2005).

1.2.1.4 Heart type Fatty Acid Binding Protein (H-FABP)

H-FABP is a low molecular weight protein involved in myocardial fatty-acid metabolism (Glatz et al., 1997). This protein is rapidly released immediately after infarction. H-FABP has been shown in mouse studies to be an early marker of ischaemia (Glatz et al., 1988) (before morphological evidence of myocardial necrosis) and can therefore help with diagnosis of MI earlier (Glatz et al., 1988, C. P. Chen et al., 2004, L. Chen et al., 2004). However, studies attempting to use H-FABP alone for early diagnosis of AMI have produced disappointing results. One review of six studies found that the pooled positive predictive value to be 65.8% and pooled negative predictive value to be 82.0% (Body, 2009). Also it still lacks cardiac specificity as it is found in brain, kidney and skeletal tissue and levels can go up in acute ischaemic strokes and intense exercise. Thus its role as biomarker needs further evaluation.

In a recent study, Bhardwaj et al (2011) evaluated an array of established and emerging cardiac biomarkers for ACS among patients with chest discomfort in the emergency department. In their study neither IMA nor H-FABP detected or excluded ACS. Among patients with symptoms suggestive of ACS, results for NT-proBNP, hsTnI or FFA added diagnostic information to cTnT. In the context of hsTnI results, FFA measurement significantly reclassified both false negatives and false positives.

1.2.2 Thrombotic factors

Plaque disruption and thrombus formation in coronary arteries lead to a variable degree of luminal obstruction to the blood flow and can present clinically as unstable angina or AMI and lead to a sudden death. Three major determinants of thrombotic response are (a) the presence of local thrombogenic substances, (b) the local flow disturbances and, (c) the systemic thrombotic propensity. Thus apart from the local thrombogenic potential even systemic pro-coagulant status may determine the severity of the acute event of thrombosis.

1.2.2.1 sCD40 ligand (sCD40L)

The CD40 and CD40 ligand (CD40L) system is expressed on a variety of cell types including activated platelets, vascular endothelial cells, vascular smooth muscle cells, monocytes, and macrophages. CD40L is a trimeric, transmembrane protein (Hennet al., 2001). Following expression on the cell surface, CD40L is partly cleaved by proteases and subsequently

released into the circulation as sCD40L which can be detected in serum and plasma. The main source of circulating sCD40L is platelets (Hennet al., 2001). The binding of CD40L enhances the inflammatory response, acts prothrombotically, leads to plaque destabilization, and inhibits endothelial regeneration. From several clinical studies it has consistently been reported that sCD40L is elevated in patients with ACS and that it provides prognostic information with therapeutic implications independent of established cardiac markers, e.g. cardiac troponins (Heesechen et al., 2003). However, pre-analytical conditions are decisive for the assessment of sCD40L and may preclude routine clinical use (Weber et al., 2006).

1.2.2.2 P-selectin

P-selectin is a cell surface glycoprotein that plays a critical role in the migration of lymphocytes into tissues. It is found constitutively in a preformed state in the Weibel-Palade bodies of endothelial cells and in α-granules of platelets. This stored P-selectin is mobilized to the cell surface within minutes in response to a variety of inflammatory and thrombogenic agents. The mobilized P-selectin is apparently present on the cell surface for only a few minutes after which it is recycled to intracellular space. P-selectin also binds monocytes and neutrophils in addition to activated platelets and is responsible for incorporation of leukocytes into the growing thrombus (Malý et al., 2003). Thus, P-selectin is a marker of platelet activation which in turn is prerequisite for thrombosis (Serebruany et al., 1999a). Fijnheer et al (1997) have concluded that endothelial cell activation is associated with an increased P-selectin concentration per platelet. Elevated levels have been reported not only in AMI and unstable angina but also in stable angina. In our study significant negative correlation of sP-selectin with age in AMI group suggests increased pro-coagulant status in younger AMI patients (Mashru et al., 2010). Its role as biomarker requires extensive clinical evaluations.

1.2.2.3 Tissue Factor (TF)

TF at the upfront of the coagulation pathway plays a crucial role in initiating thrombus formation after plaque rupture in patients with ACS. Tissue injury disrupts vascular endothelium causing its release into circulating blood and hence activation of coagulation cascades. It activates extrinsic pathway of coagulation and act as cofactor for Factor VII (fVII) and initiates cell surface procoagulant activity. It is also known to activate factor X through intrinsic pathway by activating factor IX, leading to thrombin generation and fibrin formation. Since Suefuji et al in 1997 reported the role of TF in AMI, there have been many studies conducted to determine the status of plasma TF and AMI (Kamikura et al., 1997, Nishiyama et al., 1998, Malý et al., 2003, Morange et al., 2007, Xiong et al., 2007) with contradictory findings. We observed increased levels of TF in AMI at presentation (Shalia et al., 2010a). TF exposed from ruptured plaque is the actual trigger but systemic procoagulant status also plays important role. Independent of cellular TF, blood borne soluble TF may play a role in the propagation of thrombosis which also needs monitoring in early atherosclerotic conditions.

1.2.2.4 Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 prevents fibrinolysis and thus accelerates thrombus formation. Immunohistochemical staining of coronary artery specimens (Shindo et al., 2001) and mRNA expression studies (F. Chen et al., 2005) have demonstrated increased expression of PAI. While the evidence of

increased PAI levels before first AMI attack, was given by Thogersen et al (1998). In our study, increased levels of PAI-1 were observed in AMI patients at presentation and were also more associated with younger AMI patients (Shalia et al., 2010). Hamstein et al (1985) have also reported elevated circulating concentrations of PAI-1 in young men at increased risk for recurrent infarction.

1.2.3 Components involved in plaque rupture

A growing understanding of the importance of atherosclerotic plaque rupture in the pathogenesis of coronary events has led to the identification of an expanding array of markers for plaque rupture. The enzymes that have gained importance in this aspect are myeloperoxidase, matrix metalloproteinases, cathepsins, etc.

1.2.3.1 Myeloperoxidase (MPO)

Leucocytes play a central role in atherosclerotic plaque rupture (de Servi et al., 1996). Myeloperoxidase is a degranulation product, secreted by a variety of inflammatory cells, including activated neutrophils, monocytes and macrophages such as those found in atherosclerotic plaques. It possesses proinflammatory properties and may contribute directly to tissue injury (Eiserich et al., 2002). Its systemic levels predicted future cardiovascular event independent of CD40L (Baldus et al., 2003) and gave in-vitro strong support to the role of neutrophil activation as an adjunct pathophysiological event in ACS that is directly different from platelet activation. Collectively the current evidence supports the need for further studies into the actual role of MPO. One of the important roles of Myeloperoxidase in leucocytes is to activate metalloproteinases that bring about plaque rupture (Zhang et al., 2001).

1.2.3.2 Metalloproteinases (MMPs)

The structural integrity of myocardial Extracellular Matrix (ECM) is dependent on endogenous zinc-dependent endopeptidases known as matrix metalloproteinases (MMP). These enzymes are regulated by tissue inhibitors of metalloproteinases (TIMPs) (Kelly et al., 2008). MMPs may degrade myocardial ECM leading to the development of LV dilatation and heart failure and their inhibition in experimental models of AMI has been associated with reduced LV dilatation and wall stress. Elevated levels of MMP-9 and its major inhibitor TIMP1 have been demonstrated to be associated with cardiovascular death, heart failure or both but not with re-infarction (Kelly et al., 2007). In our study we found that there was significant increase in circulating levels of MMP-9 as well as MMP-8 in AMI at presentation. Moreover the increase in MMP-8 was independent of High sensitive C-reactive protein (HsCRP) and MMP-9 (Shah et al., 2009). MMP-2 is also shown to be elevated post MI (Dhillon et al., 2009) and is associated with poor prognosis (Kelly et al., 2008a). In another study we observed that Serum MMP-3 levels were significantly elevated at presentation of the acute MI as compared to controls (Shalia et al., 2010b) while Kelly et al (2008b) have demonstrated that MMP-3 peaks at 72 hours of MI and plateau levels are associated with increase in LV volume and a lower ejection fraction at follow up. Amongst various MMPs, it has been suggested that MMP-9 may be of value in evaluating patients after acute coronary events (Apple et al, 2005).

1.2.3.3 Cathepsins

Evidence has been obtained for expression in human atherosclerotic lesion of another matrix degrading enzymes cathepsin S, B, K, D and L (Jormsjö et al., 2002). Beside protease function

and vascular effects, protease detection and quantization in peripheral blood may help detect atheromatous disease stages and aid in clinical decision-making (Vivanco et al., 2005). Patients with coronary artery stenosis have demonstrated increased serum cathepsin L levels than those without lesions detectable by quantitative angiography (Liu et al., 2006a). Increased serum cathepsin S has been demonstrated in patients with atherosclerosis and diabetes (Liu et al., 2006b) and increased cathepsin D both in plasma and monocytes of ACS patients. In our study increased peripheral blood levels of cathepsin B and K and decrease in their inhibitor cystatin C at the acute phase of MI were observed (Shalia et al., 2011). Moreover plasma concentration of MMP-9; recently identified as a novel predictor of cardiovascular mortality in patients with CAD and also marker for plaque destabilization and rupture demonstrated strong positive correlation with cathepsin B and negative correlation with cystatin C in AMI group (Shalia et al., 2011).

1.2.3.4 Pregnancy-Associated Plasma Protein-A (PAPP-A)

It is known as high molecular weight (200kDa) glycoprotein synthesized by the syncytio-trophoblast and is typically measured during pregnancy for Down syndrome screening. It is pro-atherosclerotic molecule family of proteins; a member of the insulin-like growth factor (IGF) –dependent IGF binding protein-4 specific metalloproteinase (Bayes-Genis et al., 2000). It is thought to be released when neovascularization occurs and thus may be a marker of incipient plaque rupture which was later confirmed in studies demonstrating its increased expression in unstable plaques and their extracellular matrices (Bayes-Genis et al., 2001) and corresponding increased circulating levels in unstable angina and AMI (Bayes-Genis et al., 2001). Interestingly, it demonstrated increase in risk of cardiovascular death, MI or revascularisation even without a raised Troponin (Lund et al., 2003). Evidence for the use of this biomarker clinically remains scarce but promising. More studies and standardized assays will be needed to improve its clinical utility.

1.2.4 Components representing oxidative stress

Oxidative stress in conjunction with inflammation is the one of the important initiators of atherosclerosis. However they also play important role in increasing the severity of pathogenesis of ACS.

1.2.4.1 Oxidized LDL (Ox-LDL)

Ox LDL is involved at very early critical steps of atherosclerosis. Oxidized LDL as well as its antibody (ox-LDL Ab) have been documented to be elevated in ACS patients including AMI and Unstable Angina and were suggested to be helpful in diagnosis of ACS (Zhou e tal., 2006). Imazu et al (2008) examined the relationship among plasma levels of OxLDL, measured by an enzyme immunoassay using an antibody against OxLDL (FOH1a/DLH3) and apolipoprotein B, at the onset of ACS. Plasma levels of OxLDL were significantly higher in patients with new-onset type ACS than in those with worsening type ACS (2.98 versus 1.53 mg/dL, P = 0.002). In conclusion, plasma levels of OxLDL were demonstrated to be associated with CHD and significantly higher in patients with new-onset ACS. The findings of the study suggested that plasma OxLDL can be a marker of the development of ACS. Oxidized low-density lipoprotein (oxLDL)/beta(2)-glycoprotein I (beta2GPI) complexes implicated in atherogenesis were also demonstrated to be associated with severe coronary artery disease and a 3.5-fold increased risk for adverse outcomes (Greco et al., 2010).

1.2.4.2 Lectin-like Oxidized low density lipoprotein receptor-1 (LOX-1)

LOX-1 is a multi-ligand receptor, whose repertoire of ligands includes oxidized low-density lipoprotein, advanced glycation endproducts, platelets, neutrophils, apoptotic/aged cells and bacteria. Sustained expression of LOX-1 by critical target cells, including endothelial cells, smooth muscle cells and macrophages in proximity to these ligands, sets the stage for chronic cellular activation and tissue damage suggesting the interaction of cellular LOX-1 with its ligands to contribute to the formation and development of atherosclerotic plaques. (Navarra et al, 2010). It was demonstrated to be elevated in ACS patients but not correlating with troponins or CK suggesting it not to be a marker of cardiac injury (Hayashida 2005). Kamezaki (2009) in an another study have shown it to be positively correlating with urinary 8-isoprostane and negatively correlating with superoxide dismutase in ACS patients suggesting that increased serum LOX-1 reflect enhanced oxidative stress in vascular wall.

1.2.4.3 Lipoprotein-associated Phospholipase A-2 (Lp-PLA-2)

Lp-PLA2, also known as the platelet activating factor acetylhydrolase, is a monomeric enzyme that catalyzes the hydrolysis of the sn-2 ester bond, preferentially when short acyl groups are at the sn-2 position, of oxidized phospholipids. The cascade of Lp-PLA2 activity may eventually lead to plaque destabilization, increasing the possibility of rupture and thrombosis (Hsieh et al., 2000). Confirming the same, circulating levels of sPLA2 were found to increase not only in various chronic inflammatory diseases but also independently predicted clinical coronary events in patients with unstable angina and documented coronary artery disease (Kugiyama et al., 1999, 2000).

1.2.5 Molecules of inflammation

Although molecules of inflammation may have its primary role as the indicator of endothelial dysfunction and in development of atherosclerotic plaque, its soluble levels have been implicated in various studies to be associated with ACS.

1.2.5.1 Vascular Cell Adhesion Molecule (VCAM-1)

VCAM-1 is not routinely expressed under physiological conditions. Expression of VCAM-1 occurs only on activated endothelium and vascular smooth muscle cells in developing atherosclerotic lesion (Braun et al., 1999). It was demonstrated to be expressed especially in the intimal neovasculature and largely associated with leukocyte accumulation; promoting the binding of lymphocytes and monocytes which further move by diapedesis which release cytokines and enzymes important for progression of lesion as well as rupture of the plaque (O'Brien et al., 1993, 1996). Literature reports correlation of sVCAM-1 with the extent of coronary atherosclerosis with elevated levels in AMI (Bossowska et al., 2003, G ü ray ü, Erbay et al., 2004). Consistent with this finding we have observed highest levels with AMI patients and unstable angina in decreasing order as compared to controls (Mashru et al., 2010). In our study age matched analysis also demonstrated younger age group (<=40 years) of patients with AMI with highest sVCAM-1 as compared to age matched controls and in unstable angina it was more associated with females than male patients. Above observations suggest VCAM-1 to be also as an indicator towards ACS in patients with low-risk profile for cardiovascular risk factors such as age and gender.

1.2.5.2 Platelet Endothelial Cell Adhesion Molecule (PECAM-1)

PECAM-1 of the immunoglobulin superfamily is with wide variety of functions such as platelet activation, inflammation, cell survival, in the immune response and in transendothelial migration of monocytes (TEM) (Muller et al., 1993). It has also been demonstrated to have role in plaque formation and thrombosis (Newman et al., 1990, Mahooti et al., 2000). In our study (Mashru et al., 2010) there was significant increase in sPECAM-1 in AMI patients at acute event consistent with the finding of Serebruany et al (1999b) and Soeki et al (2003).

1.2.5.3 Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 is a chemokine responsible for the recruitment of monocytes to sites of inflammation that appears to play a critical role in the promotion of plaque instability (Szmitko et al., 2003). In case control studies, plasma MCP-1 concentrations have been shown to be associated with restenosis after coronary angioplasty (Cipollone et al., 2001). However, in a prospective study on a large cohort of ACS patients, the distribution of MCP-1 values in the healthy subjects and the study population overlapped considerably. However, subsequent studies have shown that MCP-1 plasma concentration is associated with different cardiovascular risk factors, and a greater risk of developing a cardiovascular event in the future (de Lemos et al., 2003, Deo et al., 2004).

1.2.5.4 Cystatin C

This biomarker is a low-molecular-weight basic protein (13 kDa) that is freely filtered and metabolized after tubular reabsorption. It seems that it is less influenced by age, gender, and muscle mass than serum creatinine. There is a U.S. Food and Drug Administration-cleared assay that is analytically robust. Some studies suggest that it is useful for prognostication in heart failure (Sarnak et al., 2005, Shlipak et al., 2005), and ACS (Jernberg et al., 2004). This would make sense as it is well accepted that renal function is a critical determinant of prognosis. In our study cystatin C levels did not deviate much from the controls maintaining its normal levels with normal kidney functioning and demonstrated negative correlation with MMP-9 in AMI group (Shalia et al., 2011).

1.2.5.5 Interleukin 6 (IL-6)

As the prototypical acute phase reactants, interleukin-6 (IL-6) has been the focus of investigations for the diagnosis of ACS. The Fragmin and Fast Revascularisation During Instability in Coronary Artery disease II trial (FRISC) study group showed that the circulating level of IL-6 is a strong independent marker of increased mortality among patients with unstable angina and is useful in directing subsequent care. However, the best timing for measurement of IL-6 for diagnosis and risk stratification of ACS remains uncertain (Lindmark et al., 2001). Alwi et al., (2008) concluded that the IL-6 level in ACS were higher than those in CHD. The IL-6 level 4.43 pg/mL could differentiate the acute condition (ACS) and stable condition (non-ACS) with sensitivity of 89.95% and specificity of 77.42%, and ROC of 0.87.

A study by Kavsak et al (2007) demonstrated that IL-6, MCP-1, and a known biomarker, NT-proBNP were independent predictors of long-term risk of death or HF, highlighting the importance of identifying leukocyte activation and recruitment in ACS patients.

1.2.5.6 IL-10

IL-10 is an important anti-inflammatory molecule with so far contradictory findings in ACS patients. On one hand it was shown to demonstrate more favorable prognosis in patients with ACS (Heeschen et al., 2003) while on the other hand it reflected a proinflammatory state in patients with ACS which suggested that IL-10 is as effective biomarker for the risk prediction of future cardiovascular events as other markers of systemic inflammation (Mälarstig et al., 2008). Extensive study may be required to establish its role in the pathogenesis of ACS and its utility as biomarker.

1.2.5.7 IL-18

It is a member of the IL-1 cytokine family, originally identified in macrophages and Kupffer cells as factor able to induce IFN-γ production by T cells which itself is a central proatherogenic factor. Both increased serum levels of IL-18 and reduced concentrations of IL-10 have been shown to have prognostic significance in ACS. Chalikias, et al (2005) sought to assess whether the ratio of serum IL-18/IL-10 levels has higher positive predictive value than the individual measurement of IL-10 and IL-18 in patients admitted to hospital with ACS. Their findings demonstrated that significantly higher odd ratios were found for IL-18/IL-10 ratio (1.74 95% CI 1.09-2.78) compared to individual IL-18 (1.46 95% CI 0.93-2.27) and 1/IL-10 (1.63 95% CI 1.04-2.56) measurements. Recently Hartford et al (2010) demonstrated that IL-18 levels were significantly related to all-cause mortality, even after adjustment for clinical confounders (hazard ratio [HR], 1.19; 95% confidence interval, 1.07 to 1.33; P=0.002). Long-term, cardiovascular mortality was univariately related to IL-18, and the adjusted relation between noncardiovascular mortality and IL-18 was highly significant (HR, 1.36; 95% confidence interval, 1.11 to 1.67; P=0.003). IL-18 independently predicted congestive heart failure, MI, and cardiovascular death/congestive heart failure/MI in both the short and long term. Measurements from day 1 of ACS and 3 months after ACS had a similar power to predict late outcome.

The data from the PRIME Study, a prospective cohort of 9758 asymptomatic middle-aged men recruited in Northern Ireland and France between 1991 and 1993.demonstrated that higher circulating levels of Hs-CRP, intercellular CAM-1 (ICAM-1), IL6 and IL18 to be equally predictive of stable angina and ACS (all P-values of OR comparison >0.05) (Empana et al., 2008).

1.2.5.8 High-sensitivity C-Reactive Protein (HsCRP)

It is thought that one of the driving forces causing atheromatous plaques to rupture or erode, causing a cascade of events leading to coronary artery occlusion, is inflammation in the plaques (Ridker, 2003, Shishehbor et al., 2003). CRP itself mediates atherothrombosis which is supported by a fairly large body of evidence (Pasceri et al., 2000, Nakajima et al., 2002, Nakagomi et al., 2000, Verma et al., 2002, Devaraj et al., 2003). The benefits of HsCRP testing in a primary setting to screen for ischaemic heart disease is very clear, People are risk stratified based on amount of CRP in blood. There are three groups; less than 1mg/l of CRP is low risk group, between 1 – 3mg/l is classified as the moderate risk group and more than 3mg/l is the high risk group (AHA/CDC, 2003). However, its use post-ACS or -MI is less clear. CRP is elevated post-acute coronary syndrome almost exclusively in the setting of myocardial necrosis indicating the level of myocardial inflammation. In a study carried out by us, we observed a three fold increase in the total HsCRP levels in MI patients at presentation; as compared to controls (Shalia et al., 2011).

Elevated peak CRP in the early phase of MI is related to early mechanical complications, including cardiac rupture, ventricular aneurysm and thrombus formation (Anzai et al., 1997). CRP levels post-MI peak at two to four days, then take 8 to 12 weeks to subside to baseline levels. One of the difficulties with CRP is that it is non-specific and also is elevated in the presence of other inflammatory conditions (rheumatoid arthritis, malignancy, vasculitis etc.). A new assay for Human Pentraxin 3 is now available. Human Pentraxin 3 is an isoform which is secreted exclusively in vascular endothelium and therefore may be more specific to the vascular plaque inflammatory activity (Matsui et al., 2010). It remains to be seen if this biomarker can provide incremental information.

2. Conclusion

Thus, non invasive indicators of separate pathobiologically diverse contributors to the progression of ACS, such as molecules of inflammation, components of plaque rupture and thrombosis, could add complementary information in variety of clinical settings. The role of these components in multi-marker testing, in identifying the high-risk individuals, the pathophysiologic stage of the disease and tailoring therapy needs to be established. The future of ACS management would probably shift from single to multi-marker testing leading to better characterization of each individual case by using a combination of both established and new markers for risk assessment and clinical decision making that will substantially improve the outcomes in patients with ACS.

Growing hand in hand with our contemporary fascination are the promises of personalized medicine, the discovery of novel biomarkers in cardiovascular diseases which has been embraced as a major objective of government, private and industry supported research initiatives. More than a decade of advances in our understanding of the complex mechanisms underlying the initiation, progression of atherothrombosis and its complications has stimulated efforts to identify and characterize new markers associated with this processes. In addition newer screening based discovery techniques such as metaloblomics and proteomics have revealed large numbers of candidate metabolites and proteins associated with this disease for which the function or role in pathophysiology has yet to be explained. The clinical application of cardiac biomarkers in ACS is no longer limited to establishing or refuting the diagnosis of myocardial necrosis. Cardiac biomarkers provide a convenient and non invasive means to gain insights into the underlying causes and consequences of ACS that mediate the risk of recurrent events and may be targets for specific therapeutic interventions.

3. Acknowledgement

4. References

Adams, JE.; Kleinfeld, A.; Roe, M.; et al. (2004) Measurement of levels of unbound free fatty acid allows the early identification of patients with acute coronary syndrome. *Circulation*, Vol.106, (Suppl II), p. 532.

AHA/CDC scientific statement on markers of inflammation and cardiovascular disease. (2003) *Circulation,* Vol. 107, No. 3, (January 2003), pp. 499-511.

Alpert, J. & Thygesen, K. (2000), for the Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined–a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *Eur Heart J,* Vol. 21, No. 3, (March 2000), pp. 1502–1513.

Alwi, I.; Santoso, T.; Suyono, S.; Sutrisna, B.; Kresno, SB. (2007). The cut-off point of interleukin-6 level in acute coronary syndrome. Acta Med Indones, Vol. 39, No. 4, (Oct-Dec 2007), pp. 174-178.

Anzai, T.; Yoshikawa, T.; Shiraki, H.; Asakura, Y.; Akaishi, M.; Mitamura, H, & Ogawa S. (1977). C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. *Circulation,* Vol. 96, pp. 778–784.

Apple, FS.; Christenson, RH.; Valdes, R.; Andriak, AJ.; Berg A.; Duh, SH.; et al. (1999). Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the Triage cardiac Panel for detection of myocardial infarction. *Clin Chem*, Vol. 45, No. 2 (February 1999), pp. 199-205.

Apple, FS.; Quist, HE.; Doyle, PJ.; Otto, AP. & Murakami, MM. (2003). Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. *Clin Chem*, Vol. 49, No. 8 (August 2003), pp. 1331-1336.

Apple, FS.; Wu, AH.; Mair, J.; Ravkilde, J.; Panteghini, M.; Tate, J.; et al. (2005). Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. *Clin Chem,* Vol. 51: No. 5, (May 2005), pp. 810–824.

Apple, FS.; Jesse, RL.; Kristin Newby, LK.; Wu, AHB. & Christenson, RH. (2007). National academy of clinical biochemistry and IFCC committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: analytical issues for biomarkers of acute coronary syndromes. *Clin Chem*, Vol. 53, No. 4, (March 2007), pp. 547–551.

Baldus, S.; Heeschen, C.; Meinertz, T.; Zeiher, AM.; Eiserich, JP.; Munzel, T. et al. (2003). Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation,* Vol. 108, No. 12, (September 2003), pp. 1440–1445.

Bar-Or, D.; Lau, E. & Winkler, JV. (2000). A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia: a preliminary report. *J Emerg Med*, Vol. 19, No. 4, (November 2000) pp. 311–315.

Bar-Or, D.; Curtis, G.; Rao, N.; Bampos, N. & Lau E. (2001). Characterization of the Co^{2+} and Ni^{2+} binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. *Eur. J. Biochem*, Vol. 268, No. 1 (January 2001), pp. 42–47.

Bar-Or, D.; Winkler, JV.; VanBenthuysen, K.; Harris, L.; Lau, E. & Hetzel, FW. (2001). Reduced albumin-cobalt binding with transient myocardial ischemia after elective percutaneous transluminal coronary angioplasty: a preliminary comparison to

creatine kinase-MB, myoglobin, and troponin I. *Am. Heart J*, Vol. 141, No. 6, (Jun 2001), pp. 985–991.

Bayes-Genis, A.; Conover, CA. & Schwartz RS. (2000). The insulin-like growth factor axis: A review of atherosclerosis and restenosis. *Circ Res*. Vol. 86, No. 2 (February 2000), pp. 125–130.

Bayes-Genis, A.; Conover, CA.; Overgaard, MT.; Bailey, KR.; Christiansen, M.;, Holmes, DR.; Jr, Virmani, R.; Oxvig, C. & Schwartz, RS. (2001). Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. *N Engl J Med*, Vol. 345, No. 14, (October 2001), pp. 1022–1029.

Bertrand, ME.; Simoons, ML.; Fox, KAA.; Wallentin, LC.; Hamm, CW.; McFadden, E. et al. (2002). Management of acute coronary syndromes in patients presenting without persistent ST segment elevation. *Eur Heart J*; Vol. 23, No. 23, (December 2002), pp. 1809–1840.

Bhardwaj, A.; Truo, QA.; Peacock, WF.; Yeo, KT.; Storrow A.; Thomas, S.; et al. (2011). A multicenter comparison of established and emerging cardiac biomarker for the diagnostic evaluation of chest pain in the emergency department. *Am Heart J*. Vol. 162, No. 2, (August 2011), 276-282.e1.

Bleier, J.; Vorderwinkler, KP.; Falkensammer, J.; Mair P.; Dapunt, O.; Puschendorf, B.; et al. (1998). Different intracellular compartmentations of cardiac troponins and myosin heavy chains: a casual connection to their different early release after myocardial damage. *Clin Chem*, Vol. 44, No. 9 (September 1998), pp. 1912-1918.

Body, R. (2009). Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Bet 2. Heart Fatty Acid binding protein for rapid diagnosis of acute myocardial infarction in the emergency department. *Emerg Med J*. Vol. 26, No. 7, (July 2009), pp. 519–522.

Bossowska, A.; Kiersnowska-Rogowska, B.; Bossowski, A.; Galar, B. & Sowiński, P. (2003). Assessment of serum levels of adhesion molecules (sICAM-1, sVCAM-1, sE-selectin) in stable and unstable angina and acute myocardial infarction. *Przegl Lek*, Vol. 60, No. 7, pp. 445-450.

Braun, M.; Pietsch, P.; Schror, K.; Baumnann, G. & Felix, SB. (1999). Cellular adhesion molecules on vascular smooth muscle cells. *Cardiovasc Res*, Vol. 41: No. 2, (February 1999) pp. 395-401.

Braunwald, E.; Antman, EM.; Beasley, JW.; Califf, RM.;, Cheitlin, MD.; Hochman, JS.; et al. (2000). ACC/AHA guidelines for the management of patients with unstable angina and non-STsegment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the management of patients with unstable angina). *J Am Coll Cardiol*; Vol. 36, No. 3, (September 2000), pp. 970–1062.

Canto, JG.; Shlipak, MG.; Rogers, WJ.; Malmgren, JA.; Frederick, PD.; Lambrew, CT. et al. (2000). Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* Vol. 283, No. 24, (Jun 2000), pp. 3223-3229.

Chalikias, GK.; Tziakas, DN.; Kaski, JC.; Hatzinikolaou, EI.; Stakos, DA.; Tentes, IK.; et al. (2005) Interleukin-18: interleukin-10 ratio and in-hospital adverse events in patients with acute coronary syndrome. *Atherosclerosis,* Vol. 182, No. 1, (September 2005), pp.135-143.

Chan, CP.; Sanderson, JE.; Glatz, JF.; Cheng, WS.; Hempel, A. & Renneberg R. (2004). A superior early myocardial infarction marker. Human heart-type fatty acid-binding protein. *Z Kardiol,* Vol. 93, No. 5 (May 2004), pp. 388–397.

Chen, F.; Eriksson, P.; Hansson, GK.; Herzfeld, I.; Klein, M.; Hansson, LO.; et al. (2005). Expression of matrix metalloproteinase 9 and its regulators in the unstable coronary atherosclerotic plaque. *Int J Mol Med,* Vol. 15, No. 1 (Jan 2005), pp. 57-65.

Chen, L.; Guo, X. & Yang, F. (2004). Role of heart-type fatty acid binding protein in early detection of acute myocardial infarction in comparison with cTnI, CK-MB and myoglobin. *J Huazhong Univ Sci Technolog Med Sci, Vol.* 24, No. 5, pp. 449–451.

Cipollone, F.; Marini, M.; Fazia, M.; Pini , B.; Iezzi, A.; Reale, M.; et al. (2001). Elevated circulating levels of monocyte chemoattractant protein-1 in patients with restenosis after coronary angioplasty. *Arterioscler Thromb Vasc Biol*, Vol. 21, No. 3, (March 2001), pp. 327–334.

Collinson, PO. & Gaze DC. (2008). Ischaemia-modified albumin: clinical utility and pitfalls in measurement. *J Clin Pathol* Vol. 61, No. 9, (September 2008), pp. 1025-1028.

Danne, O.; Möckel, M.; Lueders, C.; Mu¨gge, C.; Zschunke, GA.; Lufft, H. et al. (2003). Prognostic implications of elevated whole blood choline levels in acute coronary syndromes. *Am J Cardiol*, Vol. 91, No. 9 (May 2003), pp. 1060–1067.

Danne, O. & Möckel, M. (2010). Choline in acute coronary syndrome: an emerging biomarker with implications for the integrated assessment of plaque vulnerability. *Expert Rev Mol Diagn*, Vol. 10, No. 2, (March 2010), pp. 159-171.

de Bold, AJ. (1985). Atrial natriuretic factor: a hormone produced by the heart. *Science*, Vol. 230, No. 4727, (November 1985), pp. 767–770.

de Lemos, JA. & Morrow, DA. (2002). Brain natriuretic peptide measurement in acute coronary syndromes: ready for clinical application? *Circulation*, Vol. 106, No. 23, (December 2002), pp. 2868–2870.

de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, et al. (2003). Association between plasma levels of monocyte chemoattractant protein-1 and long term clinical outcomes in patients with acute coronary syndromes. *Circulation,* Vol. 107, No. 5, (February 2003), pp.690–695.

de Servi, S.; Mazzone, A.; Ricevuti, G.; Mazzucchelli, I.; Fossati, G.; Angoli, L.; et al: (1996). Expression of neutrophil and monocyte CD11B/CD18 adhesion molecules at different sites of the coronary tree in unstable angina pectoris. *Am J Cardiol*, Vol. 78, No. 5 (September 1996), pp. 564-568.

De Winter, RJ.; Koster, RW.; Sturk A. & Sanders, GT. (1995). Value of myoglobin, troponin T, and CK-MB mass in ruling out an acute myocardial infarction in the emergency room. *Circulation* Vol. 92, No. 12, (December 1995) pp. 3401-3407.

Deo, R.; Khera.; A, McGuire.; DK, Murphy SA.; Meo Neto Jde, P.; Morrow, DA.; et al, (2004). Association among plasma levels of monocyte chemoattractant protein-1,

traditional cardiovascular risk factors, and subclinical atherosclerosis. *J Am Coll Cardiol*. Vol. 44, No. 9, (November 2004), pp.1812-1818.

Devaraj, S.; Xu, DY. & Jialal I. (2003). C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. *Circulation*, Vol. 107, No. 3, (January 2003), pp. 398–404.

Dhillon, OS.; Khan, SQ.; Narayan, HK.; Ng, KH.; Mohammed, N.; Quinn, PA.; et al. (2009). Matrix metalloproteinase-2 predicts mortality inpatients with acute coronary syndrome. *Clin Sci (Lond)*, Vol. 118, No. 4 (November 2009), pp. 249-257.

Eiserich, JP.; Baldus, S.; Brennan, ML.; et al. (2002). Myeloperoxidase, a leukocyte-derived vascular NO oxidase. *Scienc,e* Vol. 296 pp. 2391–2394.

Empana, JP.; Canoui-Poitrine, F.; Luc, G.; Juhan-Vague, I.; Morange, P.; Arveiler, D.; et al. PRIME Study Group.(2008). Contribution of novel biomarkers to incident stable angina and acute coronary syndrome: the PRIME Study. *Eur Heart J*, Vol. 29, No. 16 (August 2008), pp. 1966-1974.

Fijnheer, R.; Frijns, CJ.; Korteweg, J.; Rommes, H.; Peters, JH.; Sixma, JJ.; et al. (1997). The origin of P-selectin as a circulating plasma protein. *Thromb Haemost*, Vol. 77, No. 6, (Jun 1997), pp. 1081-1085.

Gibler, WB.; Gibler, CD.; Weinshenker, E.; Abbottsmith, C.; Hedges, JR.; Barsan, WG.; et al. (1987). Myoglobin as an early indicator of acute myocardal infarction. *Ann Emerg Med*, Vol 16, No. 8, (August 1987), pp. 851-856.

Glatz, JF.; van Bilsen, M.; Paulussen, RJ.; Veerkamp, JH.; van der Vusse, GJ. & Reneman, RS. (1988). Release of fatty acid-binding protein from isolated rat heart subjected to ischemia and reperfusion or to the calcium paradox. *Biochim Biophys Acta*, Vol. 961, No. 1, (July 1988), pp.148–152.

Glatz, JF.; Luiken, JJ.; van Nieuwenhoven, FA. & Van der Vusse GJ. (1997). Molecular mechanism of cellular uptake and intracellular translocation of fatty acids. Prostaglandins *Leukot Essent Fatty Acids*, Vol. 57, No. 1 (July 1997), pp. 3–9.

Greco, TP.; Conti-Kelly, AM.; Anthony, JR.; Greco, T.; Jr, Doyle, R.; Boisen, M.; et al. (2010). Oxidized-LDL/beta(2)-glycoprotein I complexes are associated with disease severity and increased risk for adverse outcomes in patients with acute coronary syndromes. *Am J Clin Pathol.* Vol. 133, No. 5, (May 2010), pp. 737-743.

G ö ray, ö.; Erbay, AR.; Guray, Y.; Yilmaz, MB.; Boyaci, AA.; Sasmaz, H.; et al. (2004). Levels of soluble adhesion molecules in various clinical presentation of coronary atherosclerosis. *Int, J. of Cardiol*, Vol. 96, No. 2 (August 2004), pp. 235-240.

Hamm, CW.; Bertrand, M. & Braunwald E. (2001). Acute coronary syndrome without ST elevation: implementation of new guidelines. *Lancet*, Vol. 358, No. 9292 (November 2001), pp. 1533–1538.

Hamstein, A.; Wiman, B.; de Faire, U. & Blomback, M. (1985). Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. *N Engl J Med*, Vol. 313: No. 25, (December 1985),pp. 1557-1563.

Hartford, M.; Wiklund, O.; Hultén, LM.; Persson, A.; Karlsson, T.; Herlitz, J.; et al . (2010). Interleukin-18 as a predictor of future events in patients with acute coronary syndromes. *Arterioscler Thromb Vasc Biol*, Vol. 30, No. 10, pp. 2039-2046.

Hayashida, K.; Kume, N.; Murase, T.; Minami, M.; Nak-agawa, D.; Inada, T.; et al. (2005). Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are elevated in acute coronary syndrome: a novel marker for early diagnosis. *Circulation,* Vol. 112, No. 6, (August 2005), pp. 812-818.

Heeschen, C.; Dimmeler, S.; Hamm, CW.; van den Brand, MJ.; Boersma, E.; Zeiher, AM.; et al. (2003). Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med*, Vol. 348, No. 12, (March 2003), pp. 1104- 1011.

Heeschen, C.; Dimmeler, S.; Hamm, CW.; Fichtlscherer, S.; Boersma, E.; Simoons, ML.; Zeiher, AM.; CAPTURE Study Investigators. (2003). Serum level of the antiinflammatory cytokine interleukin-10 is an important prognostic determinant in patients with acute coronary syndromes. *Circulation*, Vol. 107, No. 16, (April 2003), pp. 2109-2114.

Henn, V.; Steinbach, S.; Buchner, K.; Presek, P. & Kroczek, RA. (2001). The inflammatory action of CD40 ligand (CD154) expressed on activated human platelets is temporally limited by coexpressed CD40. *Blood,* Vol. 98, No. 4, (August 2001), pp. 1047-1054.

Hsieh, CC.; Yen, MH.; Liu, HW.; Lau, YT. (2000). Lysophosphatidylcholine induces apoptotic and non-apoptotic death in vascular smooth muscle cells: in comparison with oxidized LDL. *Atherosclerosis.* Vol. 151, No. 2, (August 2000), pp. 481–491.

Imazu, M.; Ono, K.; Tadehara, F.; Kajiwara, K.; Yamamoto, H.; Sumii, K.; et al.(2008). Plasma levels of oxidized low density lipoprotein are associated with stable angina pectoris and modalities of acute coronary syndrome. *Int Heart J*, Vol. 49, No. 5, (September 2008), pp. 515-524.

Ishibashi, Y. (2002). New insights into the mechanism of the elevation of plasma brain natriuretic polypeptide levels in patients with left ventricular hypertrophy. *Can J Cardiol* , Vol. 18, No. 12, (December 2002), pp. 1294–1300.

Jernberg, T.; Lindahl, B.; James, S.; Larsson, A.; Hansson, LO. & Wallentin L. (2004). Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation,* Vol. 110, No. 16, (October 2004), pp. 2342–2348.

Jormsjö, S.; Wuttge, DM.; Sirsjö, A.; Whatling, C.; Hamsten, A.; Stemme, S. et al. (2002). Differential expression of cysteine and aspartic protease during progression of atherosclerosis in apolipoprotein E-defieicient mice, *Am J Pathol*, Vol. 161, No. 3, (September 2002), pp. 939-945.

Kamezaki, F.; Yamashita, K.; Tasaki, H.; Kume, N.; Mitsuoka, H.; Kita, T.; et al. (2009). Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 correlates with oxidative stress markers in stable coronary artery disease. *Int J Cardiol,* Vol. 134, No. 2, (May 2009), pp. 285-287.

Kamikura, Y.; Wada, H.; Yamada, A.; Shimura, M.; Hivoyama, K.; Shiku H.; et al. (1997). Increased tissue factor pathway inhibitor in patients with acute myocardial infarction. *Am J Hematol*, Vol 55, No. 4 (August 1997), pp. 183-187.

Karmen, A.; Wroblewski, F. & LaDue, JS. (1955). Transaminase activity in human blood. *J. Clin. Invest*, Vol. 34, No. 1, (January 1955), pp. 126– 133.

Kavsak, PA.; Ko ,DT.; Newman, AM.; Palomaki, GE.; Lustig, V.; MacRae, AR.; Jaffe, AS. (2007). Risk stratification for heart failure and death in an acute coronary syndrome population using inflammatory cytokines and N-terminal pro-brain natriuretic peptide. Clin Chem, Vol. 53, No. 12, (December 2007), pp. 2112-2118.

Kelly, D.; Cockerill, G.; Ng, LL.; Thompson, M.; Khan, S.; Samani, NJ. et al. (2007). Plasma matrix metalloproteinase-9 and left ventricular remodellingafter acute myocardial infarction in man: a prospective cohort study. *Eur Heart J*, Vol. 28, No. 6, (March 2007), pp. 711-718.

Kelly, D.; Khan, SQ.; Thompson, M.; Cockerill, G.; Ng LL.; Samani, N. & Squire IB. (2008a). Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular remodeling and prognosis after acute myocardial infarction. *Eur Heart J*, Vol. 29, No. 17, (September 2008), pp. 2116-2124.

Kelly, D.; Khan, S.; Cockerill, G.; Ng LL.; Thompson, M.; Samani, NJ. & Squire, IB. (2008b). Circulating stromelysin-1 (MMP-3): a novel predictor of LV dysfunction, remodelling and all-cause mortality after acute myocardial infarction. *Eur J Heart Fail*, Vol. 10, No. 2, (February 2008), pp. 133-139.

Kleinfeld, AM.; Prothro, D.; Brown, DL.; Davis, RC.; Richieri, GV. & DeMaria A. (1996). Increases in serum unbound free fatty acid levels following coronary angioplasty. *Am. J. Cardiol*, Vol. 78, No. 12, (December 1996), pp. 1350–1354.

Kleinfeld, AM.; Kleinfeld, KJ. & Adams JE. (2002). Serum levels of unbound free fatty acids reveal high sensitivity for early detection of acute myocardial infarction in patient samples from the TIMI II trial. *J. Am. Coll. Cardiol*, Vol. 39, pp. 312A.

Kugiyama, K.; Ota, Y.; Sugiyama, S.; Kawano, H.; Doi, H.; Soejima, H.; et al. (2000). Prognostic value of plasma levels of secretory type II phospholipase A2 in patients with unstable angina pectoris. *Am J Cardiol*, Vol. 86, No. 7, (October 2000), pp. 718–722.

Kugiyama, K.; Ota, Y.; Takazoe, K.; Moriyama, Y.; Kawano, H.; Miyao, Y.; et al. (1999). Circulating levels of secretory type II phospholipase A2 predict coronary events in patients with coronary artery disease. *Circulation*, Vol. 100, No. 12, (September 1999), pp.1280–1284.

Lindmark, E.; Diderholm, E.; Wallentin, L.; Siegbahn, A. (2001). Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA*, Vol. 286, No. 17, (November 2001), pp. 2107-2113.

Liu, J.; Sukhova, GK.; Yang, JT.; Sun, J.; Ma, L.; Ren, A. et al. (2006a). Cathepsin L expression and regulation in human abdominal aortic aneurysm, atherosclerosis and vascular cells. *Atherosclerosis*, Vol. 184, pp. No. 2, (February 2006), pp. 302-311.

Liu, J.; Ma, L.; Yang, J.; Ren, A.; Sun, Z.; Yan, G.; et al. (2006b). Increased serum cathepsin S in patients with atherosclerosis and diabetes. *Atherosclerosis*, Vol. 186, No. 2, (Jun 2006), pp.411-419.

Lorgis, L.; Zeller, M.; Dentan, G.; Sicard P.; Jolak, M. & L'Huillier I. (2007). High levels of N-terminal pro B- type natriuretic peptide is associated with ST resolution failure

after reperfusion for acute myocardial infarction. An Int J Med, Vol. 100, No. 4, (April 2007), pp. 211-216.

Lund, J.; Qin, QP.; Ilva, T.; Pettersson, K.; Voipio-Pulkki, LM.; Porela, P.; et al. (2003). Circulating pregnancy-associated plasma protein-A predicts outcome in patients with acute coronary syndrome but no troponin I elevation. *Circulation*, Vol. 108, No. 16, (October 2003), pp. 1924–26.

Mahooti, S.; Graesser, D.; Patil, S.; Newman, P.; Duncan, G.; Mak T.; et al. (2000). PECAM-1 (CD31) expression modulates bleeding time in vivo. *Am J pathol*, Vol. 157, No. 1, (July 2000), pp. 75 -81.

Mair, J.; Artner-Dworzak, E. & Lechlertner, O.(1991). Early detection of acute MI by measurement of CKMB mass. *Am J Cardiol*, Vol. 68, No. 17, (December 1991), pp. 1545-1550.

Mälarstig, A.; Eriksson, P.; Hamsten, A.; Lindahl B,.; Wallentin, L.; Siegbahn A. (2008). Raised interleukin-10 is an indicator of poor outcome and enhanced systemic inflammation in patients with acute coronary syndrome. *Heart*, Vol. 94, No. 6, (June 2008), pp. 724-729.

Malý, M.; Vojácek, J.; Hrabos, V.; Kvasnicka, J.; Salaj P. & Durdil V. (2003). Tissue factor, tissue factor pathway inhibitor and cytoadhesive molecules in patients with an acute coronary syndrome. *Physiol Res*, Vol. 52, No. 6, pp. 719-728.

Mashru, MR.; Shah, VK.; Soneji, SL.; Loya, YS.; Vasvani, JB.; Shalia, KK.; et al. (2010). Soluble Levels of Cell Adhesion Molecules (CAMs) in Coronary Artery Disease. *Ind Heart J*, Vol. 62, No. 1, (Jan-Feb 2010), pp. 57-63.

Matsui, S.; Ishii, J.; Kitagawa, F.; Kuno, A.; Hattori, K.; Ishikawa, M.; et al. (2010). Pentraxin 3 in unstable angina and non-ST-segment elevation myocardial infarction. *Atherosclerosis*, Vol. 210, No. 1, (May 2010), pp. 220–225.

Morange, PE.; Blankenberg, S.; Alessi, MC.; Bickel, C.; Rupprecht, HJ.; Schnabel, S.; et al. (2007). Prognostic value of plasma tissue factor and tissue factor pathway inhibitor for cardiovascular death in patients with coronary arterty disease: The AtheroGene Study. *J Thromb Hemost*, Vol. 5, No. 3, (March 2007), pp. 475-482.

Muller, WA.; Weigl, SA.; Deng, X Philips. (1993). PECAM-1 is required for transendothelial migration of leukocytes. *J Exp Med*, Vol. 178, No. 2, (August 1993), pp. 449-460.

Nakagomi, A.; Freedman, SB. & Geczy CL. (2000). Interferon-gamma and lipopolysaccharide potentiate monocyte tissue factor induction by C-reactive protein: relationship with age, sex, and hormone replacement treatment. *Circulation*, Vol.101, No. 15, (April 2000), 1785–1791.

Nakajima, T.; Schulte, S.; Warrington, KJ.; Kopecky, SL.; Frye, RL.; Goronzy, JJ. & Weyand, CM. (2002). T-cell-mediated lysis of endothelial cells in acute coronary syndromes. *Circulation*, Vol. 105, No. 5, (February 2002), pp. 570–575.

Nakao, K.; Ogawa, Y.; Suga, SI. & Imura, H. (1992). Molecular biology and biochemistry of the natriuretic peptide system. I: Natriuretic peptides. *J Hypertens*, Vol. 10, No. 9, (September 1992), pp. 907–912.

Navarra, T.; Del Turco, S.; Berti, S.; Basta, G. (2010). The Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 and its Soluble Form: Cardiovascular Implications. *J Atheroscler Thromb*, Vol. 17, No. 4: (April 2010), pp. 317-331.

Newman, PJ.; Berndt, MC.; Gorski, J.; White, GC.; 2nd, Lyman, S.; Paddock, C.; et al. (1990). PECAM-1 (CD31) cloning and relation tp adhesion molecules of the immunoglobulin gene supefamily. *Science,* Vol. 247, No. 4947, (March 1990), pp. 1219-222.

Nishiyama, K.; Ogawa, H.; Yasue, H.; Soejima, H.; Misumi, K.; Takazoe, K.; et al. (1998). Simultaneous elevation of the levels of circulating monocyte chemoattractant protein-1 and tissue factor in acute coronary syndromes. *Jpn Circ J,* Vol. 62, No. 9, (September 1998), pp. 710-712.

O'Brien, KD.; Allen, MD.; McDonald, TO.; Chait, A.; Harlan, JM.; Fishbe, D.;, et al. (1993). Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. Implications for the mode of progression of advanced coronary atherosclerosis. *J Clin Invest,* Vol. 92, No. 2, (August 1993) 945-951.

O'Brien, KD.; McDonald, TO.; Chait, A.; Allen, MD. & Alpers, CE. (1996). Neovascular expression of E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in human atherosclerosis and their relation to intimal leukocyte content. *Circulation*, Vol. 93, No. 4. (February 1996), pp. 672-682.

Panteghini M. (2002). Acute coronary syndrome: biochemical strategies in the troponin era. *Chest*, Vol. 122, No. 4, (October 2002), pp. 1428-1435.

Pasceri, V.; Willerson, JT. & Yeh, ET. (2000). Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*, Vol. 102, No. 18, (October 2000), pp. 2165–2168.

Ridker PM. (2003). Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*, Vol. 107, No. 3 (January 2003), pp. 363–369.

Roxin, LE.; Culled, I.; Groth, T.; Hallgren, T. & Venge P. (1984). The value of serum myoglobin determinations in the early diagnosis of acute myocardial infarction. *Acta Med Scand,* Vol. 215, No. 5, pp. 417-425.

Sarnak, MJ.; Katz, R.; Stehman-Breen, CO.; Fried, LF.; Jenny, NS.; Pasty, BM.; et al. (2005). Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med,* Vol. 142, No. 7, (April 2005), pp. 497–505.

Serebruany, VL. & Gurbel AP. (1999a). Assessment of platelet activity by measuring platelet derived substances in plasma from patients with acute myocardial infarction: surprising lesions from the GUSTO-III platelet study. *Thromb Res*, Vol. 93, No. 3, (February 1999), pp. 149-150.

Serebruany, VL.; Murugesan, SR.; Pothula, A.; Semaan, H. & Gurbel PA.(1999b). Soluble PECAM-1, but not P-selectin, nor osteonectin identify acute myocardial infarction in patients presenting with chest pain. *Cardiology*, Vol. 91: No. 1, pp. 50-55.

Shah, VK.; Shalia, KK.; Mashru, MR.; Soneji, SL.; Abraham, A.; Kudalkar, KV.; et al. (2009). Role of Matrix Metalloproteinases in Coronary Artery Disease. *Ind Heart J,* Vol. 61, No. 1, (Jan Feb 2009), pp. 44-50.

Shalia, KK.; Shah, VK.; Mashru, MR.; Soneji, SL.; Vasvani, JB.; Payannavar, SS.; et al. (2010). Circulating thrombotic and haemostatic components in patients with coronary artery disease. *Ind J of Clin Biochem*, Vol. 25, No. 1, pp. 20-28.

Shalia, KK.; Shah, VK.; Mashru, MR.; Soneji, SL.; Vasvani, JB.; Payannavar, S.; et al. (2010). Matrix metalloproteinase-3 (MMP-3) -1612 5A/6A promoter polymorphism in

coronary artery disease in Indian population. *Ind J of Clin Biochem,* Vol. 25, No. 2, pp. 133-140.

Shalia, KK.; Mashru, MR.; Shah, VK.; Soneji, SL. & Payannavar, S. (2011). Cathepsins and Coronary Artery Disease. Accepted in Indian Heart Journal (2011).

Shalia, KK., Savant, S., Haldankar, VA., Nandu, T., Pawar, PP., Divekar, SS., Shah, VK., Bhatt, P. (2011) Study of C-Reactive Protein and Myocardial Infarction in the Indian Population. *Ind J. of Clin Biochem*, DOI 10.1007/s12291-011-0164-9.

Shindo, J.; Ishibashi, T.; Kijima, M.; Nakazato, K.; Nagata, K.; Yokoyama, K.; et al. (2001). Increased plasminogen activator inhibitor-1 and apolipoprotein (a) in coronary atherectomy specimens in acute coronary syndromes. *Coron Artery Dis*, Vol. 12, No. 7, (November 2001), pp. 573-579.

Shishehbor, MH.; Bhatt DL. & Topol EJ. Using C-reactive protein to assess cardiovascular disease risk. (2003). *Cleve Clin J Med*, Vol. 70, No. 7, (July 2003), pp. 634–640.

Shlipak, MG.; Katz, R.; Fried, LF.; Jenny, NS.; Stehman-Breen, CO.; Newman, AB.; et al. (2005). Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol.* Vol. 45, No. 2, (January 2005), pp. 268–271.

Soeki, T.; Tamura, Y.; Shinohara, H.; Sakabe, K.; Onose, Y. & Fukuda N. (2003). Increased soluble platelet/endothelial cell adhesion molecule-1 in the early stages of acute coronary syndromes. *Int J Cardiol,* Vol. 90, No. 2-3, (August 2003), pp. 261-268.

Suefuji, H.; Ogawa, H.; Yasue, H.; Kaikita, K.; Soejima, H.; Motoyama, T.; et al. (1997). Increased plasma tissue factor levels in acute myocardial infarction. *Am Heart J,* Vol. 134, No, 2pt1, (August 1997), pp. 253-259.

Szmitko, PE.; Wang, CH.; Weisel, RD.; de Almeida, JR.; Anderson, TJ.; Verma, S. (2003). New markers of inflammation and endothelial cell activation. Part I. *Circulation*, Vol. 108, No.16, (October 2003), pp. 1917–1923.

Thogersen, AM,; Jansson, JH.; Boman, K.; Nilsson, TK.; Wienehall, L.; Huhtasaari F.; et al. (1998). High PAI-1 and tPA levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation*, Vol. 98, No. 21, (Novembro 1998), pp. 2241-2247.

Verma, S.; Wang, CH.; Li, SH.; Dumont, AS.; Fedak, PW.; Badiwala, MV.; et al. (2002). A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation*, Vol. 106, No. 8, (August 2002), pp. 913–919.

Vivanco, F.; Martín-Ventura, JL.; Duran MC.; Barderas MG.; Blanco-Colio L.; et al. (2005). Quest for novel cardiovascular biomarkers by proteomic analysis. *J Proteome Re,* Vol. 4, No. 4, (July-August 2005), pp. 1181-1191.

Weber, M.; Rabenau, B.; Stanisch, M.; Elsaesser, A.; Mitrovic, V.; Heeschen, C. & Hamm C. (2006). Influence of sample type and storage conditions on soluble CD40 ligand assessment. *Clin Chem*, Vol. 52, No. 5, (May 2006), pp. 888-891.

Xiong, SL.; Wang, Q.; Zheng, L.; Li, JL.; Wen, ZB. & He, SL. (2007). Value of plasma tissue factor, tissue factor pathway inhibitor and factor VII assessments in patients with acute myocardial and cerebral infarction. *Nan Fang Yi Ke Da Xue Xue Bao,* Vol. 27, No. 12, (December 2007), pp. 1821- 1823.

Zhang, R.; Brennan, ML.; Fu, X.; Aviles, RJ.; Pearce, GL.; Penn, MS.; et al. (2001). Association between myeloperoxidase levels and risk of coronary artery disease. *JAMA,* Vol. 286, No. 17, (November 2001), pp. 2136–2142.

Zhou, ZX.; Qiang, H.; Ma, AQ.; Chen, H.; Zhou, P. (2006). Measurement peripheral blood index related to inflammation and ox-LDL, ox-LDLAb in patients with coronary heart disease and its clinical significance. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*, Vol. 31, No. 2, (April 2006), pp.258-262.
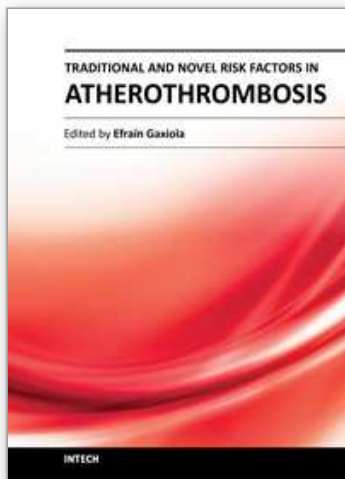
Traditional and Novel Risk Factors in Atherothrombosis

Edited by Dr. Efrain Gaxiola

Atherothrombosis has reached pandemic proportions worldwide. It is the underlying condition that results in events leading to myocardial infarction, ischemic stroke and vascular death. As such, it is the leading cause of death worldwide manifested mainly as cardiovascular/cerebrovascular death. The complex and intimate relationship between atherothrombosis and traditional and novel risk factors is discussed in the following chapters of Traditional and Novel Risk Factors in Atherothrombosis - from basic science to clinical and therapeutic concerns. Beginning with pathology and pathophysiology of atherothrombosis, plaque rupture/disruption, this book continues with molecular, biochemical, inflammatory, cellular aspects and finally analyzes several aspects of clinical pharmacology.

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