

Biomarkers for the prediction of acute ongoing arterial plaque rupture

Yuan-Lin Guo
Jian-Jun Li

Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

Abstract: Acute coronary syndrome (ACS) is the main cause of mortality for coronary artery disease (CAD). Accordingly, earlier detection and diagnosis might be a key point for reducing the mortality in patients with ACS. One promising strategy is biomarker measurement in patients with ACS. Biomarkers are generally considered to be plasma measurements of molecules, proteins, or enzymes that provide independent diagnostic and prognostic values that can reflect underlying disease state and condition, especially repeated measurements. Nowadays, the most widely used biomarkers to identify or predict ACS are high sensitivity C-reactive protein (hs-CRP) and high sensitivity troponin T/I (hs-TnT/I). The aim of the present review was principally to summarize recent evidence regarding some new biomarkers by which we could directly predict acute ongoing arterial plaque rupture, which may help to identify at-risk patients earlier than hs-CRP or hs-TnT/I.

Keywords: matrix metalloproteinase-9, lipoprotein associated phospholipase A2, myeloperoxidase, soluble lectin-like oxidized low-density lipoprotein receptor-1, pregnancy-associated plasma protein A, placental growth factor, acute coronary syndrome

Introduction

It is well-recognized that the pivotal pathophysiologic mechanism of acute coronary syndrome (ACS) is an unstable atherosclerotic plaque rupture with following thrombosis.¹ However, only by intravascular imaging technology or biopsy/autopsy of atherosclerotic plaques can these processes be directly identified. Additionally, it is often too late to prevent cardiac death at that time. Moreover, many patients with unstable angina were found to have no serious stenosis in coronary artery by angiography. Accordingly, these patients were not suitable to be detected and treated by the method of coronary artery angiography and intervention. For these cases with unstable clinical symptoms, one of the easiest new approaches that could be incorporated into clinical practice would be to test a peripheral blood sample for the presence of a specific atherosclerosis marker. Up to now, the early diagnosis of ACS is still challenging because of its various nonspecific clinical manifestations. However, biomarkers in blood circulation have been gaining cardiologists' interest in recent years.²

An ideal biomarker should be directly related to plaque rupture, appear very early in circulation, and be able to be detected at the bedside quickly and easily. Biomarkers with these characteristics will help us to identify patients at risk of ACS as early as we can. Nowadays, one of the most widely used biomarkers to identify ACS is high sensitivity troponin T/I (hs-TnT/I) and for ACS risk stratification is high sensitivity

Correspondence: Jian-Jun Li
Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, People's Republic of China
Tel +86 10 883 96077
Fax +86 10 683 31730
Email lijn@yaho.com.cn

C-reactive protein (hs-CRP). A rich body of evidence has been produced in the last two decades about the predictable values of hs-TnT/I and hs-CRP for ACS, especially in a repeated measurement manner.^{3,4} There are many other biomarkers reflecting different mechanisms clinically available for predicting adverse cardiovascular events; for example, inflammation-related, hemostasis- and thrombosis-related, oxidative stress-related, myocardial damage- and tissue necrosis-related biomarkers. This review, however, is principally aimed at summarizing recent evidence regarding potential new biomarkers which could directly predict acute ongoing arterial plaque rupture (Table 1).

Matrix metalloproteinase-9

Matrix metalloproteinase-9 (MMP-9) is regarded as a biomarker of plaque rupture or vulnerability, and several studies recently demonstrated that serum MMP-9 level elevation might be a significant new biomarker of ACS.⁵⁻⁹ A study from a Japanese population demonstrated that plasma MMP-9 was an independent predictor of plaque rupture assessed by intravascular ultrasound of culprit lesion in patients with acute myocardial infarction (MI) or unstable angina, even after adjustment for the traditional risk factors.¹⁰ Wang et al¹¹ further revealed that circulating MMP-9 could help differentiate ACS patients with plaques from those without plaques. Because MMP-9 was directly related to atherosclerotic plaque rather than myocardial necrosis, it may have specific high value in the early identification of ruptured plaque. This hypothesis was recently verified in a study performed by Kobayashi et al.¹² They measured MMP-9 and hs-TnT in 200 patients with ST-elevated ACS (115 early ST-elevated ACS; 85 late ST-elevated ACS patients), and 66 patients with non-ST elevated ACS (25 early non-ST elevated ACS; 41 late non-ST elevated ACS patients). An additional 40 patients with stable angina pectoris were enrolled as a control group. The results showed that MMP-9

levels were elevated earlier than hs-TnT and also had a higher diagnostic value for early ACS (<4 hours), but not for late ACS.¹² CRP is currently known as an independent risk factor for cardiovascular events. Regarding the relationship between MMP-9 and CRP, a recent study found that the CRP dose dependent-induced expression of MMP-9 in smooth muscle cells in vitro and the local production of CRP in patients with ACS related to an increase in transcoronary MMP-9 levels.¹³ These results indicated that CRP might exert a causative role in plaque complication in vivo through induction and release of MMP-9 in the coronary circulation of ACS patients.

In summary, the elevation of MMP-9 reflects plaque rupture or vulnerability and precedes that of biomarkers for myocardial damage, because plaque rupture or vulnerability precedes myocardial damage in ACS. Recent evidence strongly indicates that the early diagnostic value of MMP-9 might be superior to that of hs-TnT, and the predictive value of MMP-9 might be equal or superior to that of CRP in patients with ACS.

Lipoprotein associated phospholipase A2

The lipoprotein-associated phospholipase A2 (Lp-PLA₂), a 45.4-kDa protein, is a calcium-independent member of the phospholipase A2 family. It is produced mainly by monocytes, macrophages, T-lymphocytes, and mast cells, and has been found to be upregulated in atherosclerotic lesions, especially in complex plaque, as well as in the thin cap coronary lesions prone to rupture. Functionally, Lp-PLA₂ has proatherogenic properties, mainly by promoting oxidation of low-density lipoprotein (LDL).^{14,15} Several studies have found an association between increased concentrations of Lp-PLA₂ and future coronary and cerebrovascular events, independent of a variety of potential confounders.¹⁶⁻¹⁹ A study by Kolodgie et al²⁰ showed that Lp-PLA₂ was strongly expressed within the necrotic core and surrounding

Table 1 Current and potential new biomarkers in ACS

Early stage	Early-to-late stage		Late stage	
Plaque's cell composition-related	Oxidative stress-related	Inflammation-related	Platelet activation-related	Tissue damage-related
Matrix metalloproteinase-9	Myeloperoxidase	hs-CRP	Soluble CD40 ligand	Troponin
Pregnancy-associated plasma protein A	Lipoprotein-associated phospholipase A2	Interleukin-6	Soluble P-selectin	Heart fatty acid-binding protein
Placental growth factor	Soluble lectin-like oxidized low-density lipoprotein receptor-I	Intracellular adhesion molecule I Tumor necrosis factor-α		

Abbreviations: ACS, acute coronary syndrome; hs-CRP, high sensitivity C-reactive protein.

macrophages of vulnerable and ruptured plaques, with relatively weak staining in less-advanced lesions. These findings, together with the association of Lp-PLA₂ in apoptotic macrophages, suggest a potential role in promoting plaque instability. More recently, a study performed by Liu et al²¹ measured plasma Lp-PLA₂ activity in 146 consecutive patients with coronary artery disease (CAD) who underwent clinical-indicated coronary angiography and preinterventional intravascular ultrasound (IVUS). Their results further demonstrated that plasma Lp-PLA₂ activity was associated with plaque rupture, independently of traditional risk factors, such as hs-CRP level and IVUS parameters in patients with CAD. In addition, inhibiting Lp-PLA₂ by its direct inhibitor darapladib could also represent an attractive novel therapeutic target to stabilize atherosclerotic plaque by limiting the progress of its lipid core, which has been demonstrated by a study from Serruys et al.²² So, Lp-PLA₂ may be a reliable risk marker for vulnerable plaque. However, it has been reported that plasma concentration of Lp-PLA₂ is also increased evidently in stable CAD.²³ Hence, its use as a marker of plaque rupture would require more evidence or regularly repeated measurements to define an exact and reliable level for clinical diagnosis or the prediction of unstable plaques rather than stable plaques.

Myeloperoxidase

Oxidative stress participates in all stages of atherosclerosis, from lipoprotein modification to plaque rupture; biomarkers of oxidative stress, such as myeloperoxidase (MPO), may predict the vulnerability of atherosclerotic plaque.

MPO is an enzyme found primarily in neutrophils and monocytes. It is identified in large quantities in human vulnerable atherosclerotic plaque and exerts potent proatherogenic and proinflammatory effects.²⁴ MPO leads to plaque rupture through several pathways, including lipid oxidation, endothelial dysfunction, MMP activation, and collagen layer degradation, etc.²⁵

Many studies have found evidence of elevated MPO levels in ACS patients. The C7e3 fab AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) trial² investigators demonstrated that serum MPO levels were associated with prognosis of cardiovascular death or recurrent MI in a sample of 1090 patients with an ACS event. MPO was the strongest predictor (hazard ratio [HR]: 2.11) of adverse events in a 6-month follow-up period compared to troponin, CRP, vascular endothelial growth factor (VEGF), or soluble CD40 ligand (CD40 L) and was especially capable of predicting such events in the cohort of troponin-negative

patients (HR: 7.48).^{2,26} Recently, another study further suggested the predictive value of MPO among patients without troponin elevation. That study showed that a single measurement of the plasma MPO concentration could help identify patients with a higher risk of having significant coronary stenoses and high-risk angiographic features.²⁷ In addition, MPO may offer a long-term predictive value for cardiovascular risks. To make sure of this result, Heslop et al²⁸ measured MPO, nitrotyrosine, oxidized low-density lipoprotein, and antioxidant capacity in a prospective cohort of 885 selective coronary angiography patients, and followed up for >13 years for cardiovascular mortality. The results showed MPO accurately predicted cardiovascular mortality risk in coronary angiography patients. Accordingly, combination MPO and CRP together may improve long-term risk assessment and CAD patient outcomes.²⁸ Moreover, some studies reported that MPO levels were elevated only among ACS patients. In contrast, CRP levels increased in both ACS and stable patients,²⁹ suggesting that MPO may be more correlated to ongoing plaque rupture while CRP may be more useful for predicting long-term cardiac events among those who recently presented with stable angina.^{23,29} In other words, elevated MPO levels among the ACS patients suggest that this marker may participate in plaque vulnerability and the instability process, whereas higher CRP levels were predictive of cardiac events only among the stable angina patients.

The above data suggest that MPO might be a promising biomarker for the detection of ongoing ruptured plaque and myocardial ischemia, as well as for the risk stratification in patients with ACS. However, MPO determination currently lacks standardized analytical and preanalytical methods. Additionally, therapeutic doses of heparin could interfere to the plasma MPO values measured. These issues may limit the clinical application of MPO in everyday practice.

Soluble lectin-like oxidized low-density lipoprotein receptor-I

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a receptor for atherogenic oxidized low-density lipoprotein (ox-LDL).³⁰ Previous pathological study showed that LOX-1 was prominently expressed by intimal smooth muscle cells and lipid-laden macrophages in human advanced atherosclerotic plaques.³¹ It has already been demonstrated that LOX-1 expression was associated with the instability of atherosclerotic plaques in a hypercholesterolemic animal model.³² As is known, ox-LDL affects plaque vulnerability through apoptosis of vascular

endothelial and smooth muscle cells and production of MMP. However, in this process, in which it is directly linked to plaque rupture, LOX-1 plays an important and imperative role.^{33,34} The above data suggest that LOX-1 may affect atherosclerotic progression and plaque vulnerability through several mechanisms.

When LOX-1 is proteolytically cleaved at its membrane proximal extracellular domain, it will be released in a soluble form, as soluble LOX-1 (sLOX-1). Several studies have showed circulating sLOX-1 levels are dramatically elevated in patients with ACS. Data from Hayashida et al³⁵ showed the excellent sensitivity and specificity of sLOX-1 for early identification of ACS. In this study, they examined serum sLOX-1 levels in 521 patients, including 80 patients with ACS, 173 symptomatic patients with CAD, 122 patients with significant coronary stenosis without ischemia, and 52 patients without apparent coronary atherosclerosis, plus 34 patients with noncardiac acute illness and 60 patients with noncardiac chronic illness.

Time-dependent changes in sLOX-1 and TnT levels were analyzed in an additional 40 ACS patients. The results showed serum sLOX-1 levels were significantly higher in ACS than that of other groups, and sLOX-1 levels were associated with ACS, as shown by multivariable logistic regression analyses. Moreover, the sensitivity and specificity of sLOX-1 were much higher compared with hs-CRP and TnT. Also, peak values of sLOX-1 in ACS were observed earlier than those of TnT. These results indicated sLOX-1 might be a more useful novel biomarker for early diagnosis of ACS, especially for early detection for those without Q wave and those without significant elevation of TnT levels at the time of visit.³⁵ Recently, another study from Kume et al³⁶ further demonstrated that the sensitivity and specificity of sLOX-1 for diagnosis of ACS were superior to those of TnT. In this study, the investigators compared the diagnostic value of sLOX-1 for ACS with those of TnT and heart-type fatty acid-binding protein (H-FABP) in 107 patients who underwent coronary angiography, including 18 ACS and 89 non-ACS. The results suggest that circulating sLOX-1 level is a biomarker more sensitive and specific for ACS than TnT and H-FABP, and provides additional diagnostic values when measured in combination with TnT.

In addition, a pilot study performed by Kume et al³⁷ followed up 94 ACS patients undergoing emergency percutaneous coronary intervention for a median time of 29 months. The results showed that besides its good diagnostic value, sLOX-1 also predicted ACS recurrence or death well.

In summary, because sLOX-1 is directly linked to plaque instability, it may be a more useful marker than those biomarkers linked to myocardial ischemia or necrosis for diagnosing ACS at the earliest stage.

Pregnancy-associated plasma protein-A

The pregnancy-associated plasma protein-A (PAPP-A) is a high molecular mass metalloproteinase. It is so named because of its special use as a prenatal screening test for the detection of trisomy 21 (Down syndrome) during the first trimester of pregnancy.³⁸ Previous studies showed that PAPP-A might be produced by different activated cells in unstable atherosclerotic plaques, released into the extracellular matrix in the artery wall, and circulated in a form of a heterotetrameric complex. Using specific monoclonal antibodies, PAPP-A was found to be abundantly expressed in both eroded and ruptured coronary and carotid plaques, mainly in monocyte/macrophages present in the cap and shoulder region in vulnerable plaque.³⁹ Functionally, PAPP-A is considered to be participating in many local proliferative processes, including the healing of atherosclerotic plaque which thus affects the vulnerability of plaques. However, it is still uncertain whether PAPP-A can directly degrade extracellular matrix.

A large number of studies have suggested that circulating PAPP-A levels were significantly higher in patients with ACS and that its high value of predicting cardiac events was independent of troponin.^{40–45} Of those, the most representative one was the CAPTURE trial that showed that high PAPP-A levels were related to an increased risk of death and MI, in both patients with troponin negative or positive tests. In multivariable analyses, PAPP-A, soluble CD40 ligand (sCD40L), interleukin 10 (IL-10), and VEGF were independent predictors of outcome.⁴⁵ A recent study which enrolled ACS patients with elevated cardiac enzyme levels ($n = 105$) and with normal cardiac enzyme profiles ($n = 62$) showed similar efficacies of CRP and PAPP-A levels in their ability to detect unstable plaques. The results highlight the utility of both CRP and PAPP-A levels as determinants of plaque instability.⁴⁶

It seemed that PAPP-A might be a very attractive novel biomarker for identifying plaque rupture before a detectable increasing in cardiac troponin T and for predicting future outcome in patients with acute chest pain. However, further studies are needed to make PAPP-A easy and accurate enough to be used clinically at emergency departments.

Placental growth factor

Placental growth factor (PIGF) is another important novel candidate biomarker of plaque instability. It is a heterodimeric angiogenic protein belonging to the VEGF superfamily. PIGF can be abundantly secreted by various types of cells, such as vascular smooth muscle cells and inflammation-mediated cells, under the condition that cells are activated by different kinds of stresses.⁴⁷ There is evidence that a high-level PIGF plays an important role in plaque development, destabilization, and rupture by increasing proliferation and migration of endothelial cells and vascular smooth muscle cells, chemotactic recruitment of circulating monocytes and macrophages into atherosclerotic lesions, and the upregulation of several cytokines that promote plaque progress.^{48,49}

Also, evidence from several clinical trials indicated that circulating PIGF could be a good biomarker and predictor for ACS. In the CAPTURE trial, elevated concentrations of PIGF at admission significantly distinguished patients with ACS from those with other benign reasons of acute chest pain. The levels were also significantly associated with an increased risk of adverse events (death or nonfatal MI) at both 30 days and 4 years. Furthermore, this association was independent of several other biomarkers, such as troponin, sCD40 L and hs-CRP.^{50,51} Additionally, another study by Apple et al⁵² also demonstrated the promising prognostic value of PIGF in a heterogeneous group of 457 patients presenting with subtle symptoms of ACS. However, Möckel et al,⁵³ using a multimarker strategy, didn't find that PIGF level at admission could predict death and MI at 42 days, in a population of 432 patients admitted for a suspected ACS. The reason for this disparity may be linked to the population studied. It was considered that PIGF would have performed better in a higher risk cohort while their study population was at an overall low risk for mortality. Recently, a study from Glaser et al⁵⁴ demonstrated the high prognostic value of PIGF by combining it with a B-type natriuretic peptide and estimated glomerular filtration rate. They considered that a combination might be the most accurate method in risk-stratifying patients with suspected ACS.

The above data may suggest that PIGF is a potential useful biomarker for the early identification of ACS, by detecting ongoing plaque rupture. Further studies on its mechanism as well as its clinical practice are needed.

Conclusion

The development of promising circulating biomarkers is very attractive for clinicians. However, a single biomarker, even

if it is ideal, is not enough for early identifying of an ACS, due to the complex nature of the disease. In daily clinical practice, it is much better and wiser to combine multiple classical and novel biomarkers as well as other noninvasive or invasive techniques to make a final decision.⁵⁵⁻⁵⁷

Currently, there are lots of biomarkers for predicting ACS under investigation. Biomarkers mentioned in this review are only a part of those directly related to ongoing plaque rupture, which would be released into the circulation prior to markers of myocardial damage, and thus it would be more useful for identifying an ACS at its earliest stage. It is worthy of mention that biomarkers of plaque instability do not seem helpful in the early diagnosis of acute MI, but they do provide high value in the early diagnosis of unstable angina with troponin negative, and in the risk stratification of patients with acute chest pain.⁵⁸ Evidently, it is extremely important to identify patients, prior to the development of acute MI, because it would make a quite different outcome by early guidance to the right therapy strategy. In addition, sLOX-1, PAPP-A, and PIGF are associated with inflammation in general and are not independent predictors of plaque rupture. Their clinical use is highly hypothetical accordingly. As for the other early markers of plaque rupture, only repeated measurements in patients at risk can detect plaque rupture. Further prospective studies are needed to verify the diagnostic and prognostic value of the above potential biomarkers used alone and in combination in the real world clinical practice of cardiovascular medicine.

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Disclosure

The authors report no conflicts of interest in this work.

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