ASSESSING INFLAMMATORY STATUS IN CARDIOVASCULAR DISEASE

Dimitris Tousoulis, Charalambos Antoniades, Christodoulos Stefanadis

Heart 2007;**93**:1001–1007. doi: 10.1136/hrt.2006.088211

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Growing evidence suggests that the immune system plays a critical role in all the stages of atherogenesis, from lesion formation to plaque rupture.[1] The inflammatory component of atherothrombosis is a topic of intensive research, since it is still unclear whether inflammatory markers measurable in peripheral blood can be useful tools for risk assessment in the general population; it is also unknown whether therapeutic strategies leading to a decrease of these inflammatory markers can modify cardiovascular risk.[w1]

INFLAMMATORY MECHANISMS IN ATHEROSCLEROSIS

Early in the atherogenesis process, resident or circulating leucocytes bind to the site of a developing lesion in response to oxidised low density lipoprotein cholesterol (LDL-C), injury, or infection. Proinflammatory cytokines play a central regulatory role in this early stage of atherogenesis, since they induce the migration of these inflammatory cells to the subendothelial space, both by acting directly on these leucocytes and by upregulating the expression of several adhesion molecules (such as vascular cells adhesion molecules, intercellular adhesion molecules and selectins) which participate in leucocyte adhesion, rolling and subendothelial migration (fig 1).[w2]

As these monocytes accumulate in the subendothelial space, they continue to ingest chemically modified lipids and lipoproteins, they become macrophages and finally develop into foam cells, and initiate fatty streaks. At the same time, other inflammatory cells, such as activated T cells and mast cells, also attach themselves to the endothelium, contributing to the formation of the atheromatous lesion, which consists of a lipid pool covered by a fibrous cap.[w3] During the whole process, smooth muscle cells (SMCs) secrete chemoattracting factors that recruit additional monocytes.[w4] Local stimulation of SMCs in the artery wall can amplify the inflammatory response and promote a local procoagulant effect.[w3] The activation of all these immune cells and SMCs leads to the release of additional mediators, including cytokines, chemokines and growth factors, molecules which lead to further immune activation and trigger further steps in atherogenesis.[w5]

Interleukin-6 (IL-6), interleukin 1b (IL-1b) and tumour necrosis factor α (TNFα) are the principal pro-atherogenic cytokines,[1] which are also produced in tissues other than the vascular wall and immune system, such as adipose tissue, myocardium, intestine, etc.[1] They upregulate the expression of adhesion molecules on vascular endothelium,[w2] depress nitric oxide synthesis[w6] and promote the subendothelial migration of leucocytes. Further to their local regulatory role at a vascular level, these cytokines induce the liver-derived synthesis of acute phase proteins, such as fibrinogen, plasminogen, C-reactive protein (CRP) and serum amyloid α (SAA), which amplify inflammatory and pro-coagulant responses.[w7 w8]

Although the role of inflammation is critical in all the stages of atherogenesis, from plaque formation to plaque rupture and the development of acute coronary syndromes (ACS), it is unclear whether measurement of circulating levels of inflammatory molecules can be useful in risk assessment or even in the design of therapeutic approaches against the development and/or progression of coronary atherosclerosis. In this review we examine the clinical importance of the most widely known inflammatory markers, in the assessment of cardiovascular risk.

See end of article for authors' affiliations

Correspondence to:
Dr Dimitris Tousoulis, Vasilissis Sofias 114, 115 28, Athens, Greece; drtousoulis@hotmail.com

PROINFLAMMATORY CYTOKINES AS PREDICTORS FOR CARDIOVASCULAR DISEASE

Initial evidence suggested that IL-6 may be a better predictor of coronary artery disease than CRP,[w9 w10] while its effect on the risk for stroke was particularly strong (relative risk (RR) 3.7, 95% confidence interval (CI) 1.67 to 8.21). However, it seems that IL-6 is also elevated in the presence of subclinical atherosclerosis, and it is hard to distinguish between patients with advanced and subclinical atherosclerosis.[w11] The association between subclinical disease and IL-6 is consistent with data from

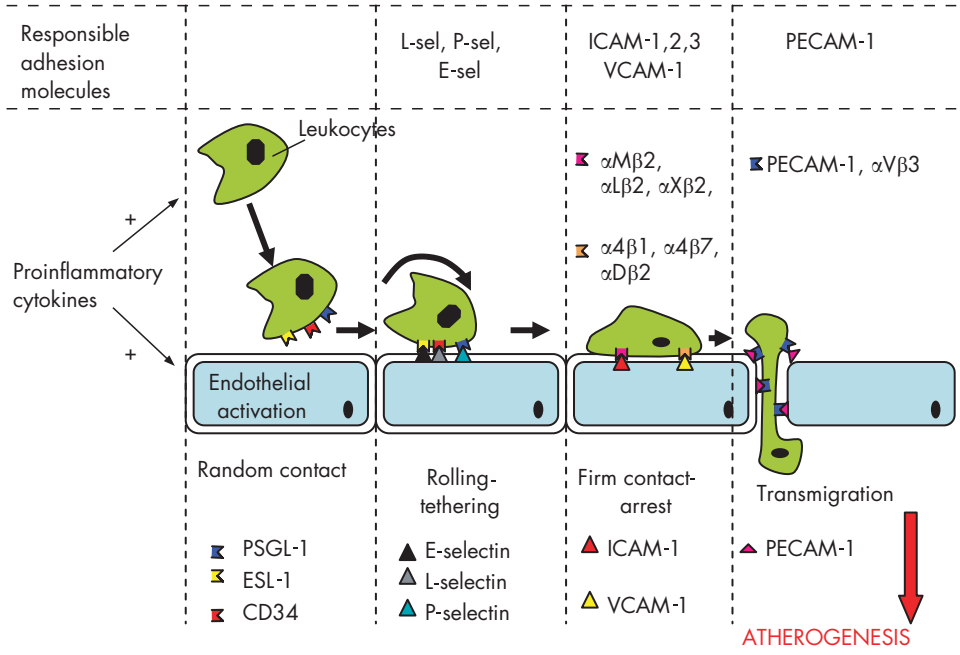

Figure 1 Cytokines and adhesion molecules in the early stages of atherogenesis. Circulating leucocytes are activated by proinflammatory cytokines, and they adhere to vascular endothelium. Adhesion molecules, whose expression is also regulated by proinflammatory cytokines, play a key role in the subendothelial migration of leucocytes. ICAM-1, intercellular adhesion molecule-1; PECAM-1, platelet endothelial cell adhesion molecule; Sel, selectin; VCAM-1, vascular cell adhesion molecule-1.

the Health ABC Study, which showed that both IL-6 and TNFα are higher in older adults with subclinical cardiovascular disease.[w12]

Furthermore, in a study by Ridker *et al*[w13] it was found that apparently healthy subjects with IL-6 at the highest quartile had relative risk for future myocardial infarction, in a 6 year follow up period, 2.3 times higher than those in the lowest quartile (95% CI 1.3 to 4.3), with an increase of risk by 38% for each quartile increase in IL-6.

Although TNFα is directly implicated in atherogenesis, it has not been frequently measured in epidemiologic studies. In the Health ABC Study, it was moderately correlated with IL-6 and weakly correlated with CRP,[w12] while a stronger relationship between TNFα and coronary heart disease (CHD) than with either IL-6 or CRP has been reported.[w9] Additionally, in a nested case–control study, Ridker *et al*[w14] reported a multivariable-adjusted relative risk of recurrent coronary events of 2.5 (95% CI 1.3 to 5.1) among men whose TNFα levels exceeded the 95th centile, as compared with men with lower levels. However, TNFα has a limited half-life and is difficult to measure in large-scale epidemiologic studies,[w15] and this is the main reason for the observed lack of data from prospective studies about the predictive role of TNFα in clinical practice.

Alternatively, the soluble forms of TNF receptors 1 (sTNF-R_1) and 2 (sTNF-R_2) levels can be measured; they may be of greater significance than direct measurement of TNFα, and they can be measured with greater sensitivity and reliability.[w15] The soluble TNF receptors may attenuate the bioactivity of TNFα but may also serve as slow-release reservoirs and promote inflammation in the absence of free TNF ligand.[w16] Only a few studies have examined the relationship between levels of sTNF-R_1/sTNFR$_2$ and the risk of CHD.[2 w9 w17] However, recent evidence suggested that measurement of these receptors is a rather weak approach to predicting cardiovascular risk compared to classic inflammatory markers, such as CRP or IL-6.[w18]

Another cytokine with a potential interest for future clinical research, but with limited clinical data currently available, is IL-10. IL-10 is an anti-inflammatory cytokine that inhibits the production of a variety of inflammatory cytokines such as IL-2, TNFα and IFNγ, and it is strongly associated with better prognosis in patients with ACS.[w10 w20] However, IL-10 has not been evaluated in any epidemiologic study, and its clinical use is still obscure.

ACUTE PHASE PROTEINS

C-reactive protein (CRP)

CRP is a widely known acute phase protein, produced by the liver in response to proinflammatory cytokines, and especially IL-6, TNFα and IL-1b.[w8] Although it is a non-specific inflammatory marker, it appears to be a stronger predictor of cardiovascular risk compared to most of the other known circulating inflammatory molecules.[w21]

At a clinical level, measurement of CRP in healthy individuals predicts the future development of coronary artery disease (tables 1 and 2). However, in the Thrombogenic Risk Factor (THROMBO) study, CRP was not a predictor of risk after adjustment for important predictors of prognosis, such as left ventricular ejection fraction and the presence of pulmonary congestion.[w22] The potential association between CRP and cardiovascular prognosis was first illustrated in patients presenting with ACS.[w23] The Thrombolysis In Myocardial Infarction (TIMI) investigators have since shown that the increased risk associated with high CRP values may be evident as early as 14 days after presentation with an ACS.[w24] The CAPTURE[w25] trial investigators found that, although only troponin T was predictive in the initial 72 h period, both CRP and troponin T were independent predictors of risk at 6 months, while the FRISC[w26] investigators reported that the risk associated with elevated CRP values at the time of index event continues to increase for several years. In each of the above studies, the predictive value of CRP was independent of, and additive to, troponin levels. Most importantly, CRP has been found to have prognostic value among patients without evidence of myocyte necrosis; specifically, even among patients

Table 1 Inflammatory markers in coronary atherosclerosis: available meta-analyses of long-term prospective studies in healthy individuals

Marker	Meta-analysis available	Cases	Relative risk (95% CI)
Cytokines/receptors			
IL-6	None available	–	–
TNFα	None available	–	–
TNFα R1	None available	–	–
TNFα R2	None available	–	–
Acute phase proteins			
Fibrinogen	Danesh *et al*[4]	4018	1.8 (1.6 to 2.0)*
	FSC[5]	7213	1.8 (1.6 to 2.0)*
	Danesh *et al*[11]	154211	2.4 (2.2 to 2.6)†
CRP	Danesh *et al*[6]	7068	1.49 (1.37 to 1.62)*
SAA	Danesh *et al*[12]	1057	1.6 (1.1 to 2.2)*
Adhesion molecules			
sVCAM-1	Malik *et al*[7]	1307	1.02 (0.81 to 1.29)*
sICAM-1	Malik *et al*[7]	1192	1.21 (0.95 to 1.55)*
sE-selectin	Malik *et al*[7]	832	1.16 (0.87 to 1.55)*
sP-selectin	Malik *et al*[7]	627	1.18 (0.63 to 2.21)*

CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; SAA, serum amyloid α; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cells adhesion molecule-1; TNFα, tumour necrosis factor α.
*Odds ratio of top third vs bottom third of marker.
†Hazard ratio per 1g/litre increase in usual fibrinogen value.

with negative troponin T, an elevated CRP is predictive of future adverse events.[w24–26]

Measuring and evaluating CRP

On the basis of all these data, the US Centers for Disease Control and Prevention and the American Heart Association issued guidelines in 2003 for the use of high sensitivity CRP (hsCRP) in clinical practice (table 3).[3] Subjects are defined as low risk if CRP is <1.0 mg/litre, average risk if CRP is 1.0–3.0 mg/litre, and high risk if CRP is >3.0 mg/litre; however, high CRP values may be associated with an inflammatory disease, and this possibility should be taken into account when evaluating CRP values.

CRP is easily and inexpensively measured, and standardised high sensitivity assays are commercially available.[w27 w28] These assays provide similar results in fresh or frozen plasma, while the predictive value of hsCRP measurement may be further improved by repeating several serial measurements.[w29]

Fibrinogen

Further to its role as an acute phase protein, fibrinogen plays a pivotal role in coagulation mechanisms, as the substrate for thrombin, while there is evidence that it may be involved in multiple mechanisms at all stages of the atherothrombotic process.[w30]

At a clinical level, the first meta-analysis[4] examining the role of plasma fibrinogen as a risk factor for CHD in 4018 subjects, showed a risk of 1.8 for the top third (>350 mg/dl) versus the bottom third (<250 mg/dl), a finding confirmed in another meta-analysis in 7213 cases with CHD (table 1).[5]

Although the direct involvement of acute phase proteins in the progression of coronary atherosclerosis needs to be documented, it is likely that acute phase proteins may be markers reflecting the levels of proinflammatory cytokines, in a more reliable way than the direct measurement of these cytokines in plasma, since they are less variable throughout the day.

Table 2 C-reactive protein (CRP) and cardiovascular risk in healthy individuals

Study	End point	Relative risk (95% CI)
Tracy *et al*[13]	Myocardial infarction	2.67 (1.04 to 6.81)
Ridker *et al*[14]	Myocardial infarction	2.9 (1.8 to 4.6)
Ridker *et al*[14]	Stroke	1.9 (1.1 to 3.3)
Ridker *et al*[15]	Peripheral vascular disease	2.2 (1.1 to 4.8)
Ridker *et al*[16]	Any vascular event	4.8 (2.3 to 10.1)
Ridker *et al*[16]	Myocardial infarction or stroke	7.3 (2.7 to 19.9
Roivainen *et al*[17]	Coronary heart disease	3.56 (1.93 to 6.57)
Ridker *et al*[2]	Cardiovascular events	4.4 (2.2 to 8.9)
Rost *et al*[18]	Stroke	1.9 (1.1 to 3.3)
Lowe *et al*[19]	Ischaemic heart disease	2.73 (1.6 to 4.7)
Ridker *et al*[20]	Cardiovascular disease	3.6 (2.5 to 5.2)
Danesh *et al*[6]	Coronary heart disease	2.13 (1.38 to 3.28)
Boekholdt *et al*[21]	Coronary artery disease	2.49 (2.02 to 3.08)
	Fatal	2.92 (1.83 to 4.67)
	Non-fatal	1.25 (0.93 to 1.66)
Ridker *et al*[22]	Coronary artery disease	2.98 (1.90 to 4.67)

Serum amyloid α (SAA)

SAA is an amphipathic, α-helical apolipoprotein that is transported in the circulation primarily in association with high density lipoprotein (HDL),[w31] and like CRP and fibrinogen, is an acute phase protein. SAA can induce the expression of proteinases thought to degrade extracellular matrix,[w32] which might be important during tissue injury. In several observational and prospective studies, the risk of cardiovascular disease associated with SAA changed in parallel with that seen with CRP,[2 w33] although the absolute level of risk was generally smaller. Moreover, elevated plasma SAA is observed in the presence of risk factors such as obesity,[w34] insulin resistance,[w35] the metabolic syndrome,[w36] and diabetes.[w35] A recent meta-analysis[6] suggests that subjects with SAA at higher tertile have a significant increase in cardiovascular risk up to 1.49 (95% CI 1.37 to1.62), although its use in clinical practice is still controversial. Although additional studies are needed, these observations raise the possibility that SAA may serve as a marker for an increased risk of cardiovascular disease in humans.

Table 3 Statement from the US Centers for Disease Control and Prevention/American Heart Association (CDC/AHA) on the measurement of C-reactive protein, 2003[3]

1. hsCRP assay is the assay of choice and should be performed in metabolically stable persons without obvious inflammatory or infectious diseases
2. The results should be expressed in mg/litre and two assays, averaged, fasting or non-fasting, 2 weeks apart (in this way, they represent the inflammatory status better)
3. The adult population should be stratified in three tertiles, at different cardiovascular risk
4. Subjects at the highest tertile have about a twofold increased risk of future cardiovascular disease compared with those in the lower tertile
5. Subjects with moderate risk (10–20% risk of CHD over 10 years) may benefit from measurement of CRP in addition to traditional cardiovascular risk factors

CHD, coronary heart disease; hsCRP: high sensitivity C-reactive protein.

Table 4 Adhesion molecules in atherosclerosis[w2]

Adhesion molecule	Ligands	Role	Comments	Clinical predictive value of soluble form
Selectins				
P-selectin	CD24, PSGL-1, Lewis X	Rolling and tethering	Present on endothelial cells and platelets. ELISA kits for soluble forms commercially available	Weak predictor in healthy individuals, high risk patients and patients with CAD, moderate predictor for patients with acute coronary events
E-selectin	L-set, PSGL-1, ESL-1, Lewis X	Rolling and tethering	Present in endothelial cells. ELISA kits for soluble form commercially available	Weak predictor in healthy individuals, high-risk subjects, and patients with CAD or ACS
L-selectin	CD34, PSGL-1, Lewis X, GlyCAM	Rolling and tethering	Present in leucocytes. ELISA kit for soluble form commercially available	–
Immunoglobulin-like molecules				
ICAM-1	αMβ2, αLβ2, αXβ2 Firm adhesion		Present in endothelial cells and leucocytes. ELISA kits for soluble-form commercially available	Moderate predictor for healthy individuals, high-risk subjects and CAD patients. Weak predictive value for ACS
ICAM-2	αMβ2, αLβ2	Firm adhesion	Present in endothelial cells, leucocytes and platelets. ELISA kits for soluble form commercially available	–
ICAM-3	αLβ2, αDβ2, DC-SIGN	Firm adhesion	Present in endothelial cells and leucocytes. ELISA kits for soluble form commercially available	–
VCAM-1	α4β1, α4β7, α Dβ2	Firm adhesion	Present in endothelial cells. ELISA kits for soluble form commercially available	No predictive value for healthy individuals. Strong predictor for high risk subjects, CAD patients and patients with ACS
PECAM-1	PECAM1, αVβ3	Leucocyte extravasation	Maintains endothelial integrity. Present in endothelial cells, leucocytes and platelets. ELISA kits for soluble forms commercially available	–

ACS, acute coronary syndromes; CAD, coronary artery disease; ELISA, enzyme-linked immunosorbent assay; ICAM, intercellular adhesion molecule; PECAM, platelet endothelial cell adhesion molecule; VCAM, vascular cells adhesion molecule.

SOLUBLE FORMS OF ADHESION MOLECULES

Cellular adhesion molecules are molecules expressed on the surface of cells that mediate the adhesion of the cell to other cells or to the extracellular matrix.[w2] A number of adhesion molecules expressed mainly on endothelial cells, leucocytes and platelets are actively involved in atherogenesis (table 4). The expression of these molecules is upregulated on the surface of these cells under the stimulatory effect of proinflammatory cytokines,[w2] and they play a key role in atherogenesis (fig 1).

Adhesion molecules and risk prediction in coronary atherosclerosis

Since the expression of both acute phase proteins and adhesion molecules is largely regulated by proinflammatory cytokines, it is expected that the soluble forms of adhesion molecules (such as sICAM-l) correlate with acute phase reactants like CRP, and they may provide similar predictive information to CRP in settings of primary prevention.[w37] In large prospective studies, sICAM-l, but not sVCAM-1, has been consistently related to incident coronary artery disease (CAD), at least in healthy populations (table 1).[w37–40] Similarly, data from the Women's Health Study indicated an association between sICAM-1 values and a combined cardiovascular end point,[2] although after controlling for classical risk factors and other inflammatory biomarkers such as CRP, IL-6, and SAA, this association lost significance. Therefore, sICAM-l appears to be a general marker of pro-inflammatory status, and it is expressed in healthy individuals under stable clinical conditions.

Several studies have assessed the prognostic role of soluble adhesion molecules in a setting of secondary prevention. In the AtheroGene study, a prospective cohort of patients with established CAD, sVCAM-1 was identified as a strong independent predictor of future fatal cardiovascular events, independently of most potential confounders, especially other inflammatory markers including hsCRP.[w41] In the Bezafibrate Infarction Prevention (BIP) study based on patients with CAD, baseline sICAM-1 concentration was an independent predictor for future coronary events[w42] and stroke.[w43] Similarly, in CAD patients and high-risk subjects (for example, diabetic patients), sVCAM-1 appears to be a strong predictor of cardiovascular mortality.[w44]

Only few data are available about the relationship between selectin levels and extent of atherosclerosis or their use for cardiovascular risk assessment. The first evidence, summarised in a recent meta-analysis,[7] suggests that soluble selectin values may be predictors of cardiovascular disease in healthy populations; however, these data are based on small numbers of patients, and further studies are needed to establish their role in risk assessment in the general population.

OTHER NEW INFLAMMATORY MARKERS

sCD40L

CD40 ligand is a transmembrane protein related to TNFα.[w45] A variety of cells involved in atherosclerosis, such as endothelial cells, smooth muscle cells, macrophages, T lymphocytes and platelets, express CD40L.[w46] Evidence suggests that sCD40L is a strong predictor for clinical outcome in patients with ACS,[w20 w47 w48] while high sCD40L was correlated with late restenosis after coronary angioplasty. [w49] Although the first results from risk assessment studies were promising, there is still lack of sufficient data about the clinical importance of sCD40L as a predictive marker for coronary atherosclerosis, and further studies are needed to establish its role in the clinical setting.

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Lp-PLA2 is an enzyme distinct from secretory PLA2 and is transported primarily in LDL.[w50] Lp-PLA2 is secreted by cells of the monocyte–macrophage series, T lymphocytes and mast

Table 5 Lp-PLA2 and cardiovascular risk

Study	Measure	Relative risk (95% CI)
Kardys *et al*[23]	Measures of extracoronary atherosclerosis	1.86 (1.01 to 3.43) in men 1.60 (1.08 to 2.37) in women
Ballantyne *et al*[24]	Ischaemic stroke	1.91 (1.15 to 3.18)†
Khuseyinova *et al*[25]	Coronary artery disease	2.04 (1.19 to 3.48)*
Oei *et al*[26]	CHD Stroke	1.97 (1.28 to 3.02)* 1.97 (1.03 to 3.79)*
Packard *et al*[8]	CHD, death, myocardial infarction, revascularisation	1.18 (1.05 to 1.33)‡
Blake *et al*[9]	CHD, death, myocardial infarction, stroke	1.17 (0.45 to 3.05)*
Koening *et al*[27]	CHD, death, myocardial infarction	1.21 (1.01 to 1.45)‡
Ballantyne *et al*[10]	CHD, death, myocardial infarction, revascularisation	1.15 (0.81 to 1.63)†

CHD, coronary heart disease.
*Lowest quartile as reference; †lowest tertile as reference; ‡increase by 1SD of Lp-PLA2 activity.

cells,[w51] and hydrolyses oxidised phospholipids, generating lysophosphatidylcholine which upregulates adhesion molecule expression.[w51] Recent evidence[w52] suggests that Lp-PLA2 is associated with coronary endothelial dysfunction, implying that it could be used as a predictor for cardiovascular risk.

Clinical evidence suggests that elevated Lp-PLA2 values are associated with increased risk of CHD and stroke, independently of lipid values (table 5).[8 9 w50] This association was shown in men enrolled in the West of Scotland Coronary Prevention Study (WOSCOPS), among whom Lp-PLA_2 values in the highest quintile were independently associated with a twofold increase in risk compared with those in the lowest quintile.[8] In the Women's Health Study, the baseline Lp-PLA_2 value was significantly higher in women who had a cardiovascular event during a mean 3 year follow up (1.20 mg/litre vs 1.05 mg/litre in controls); however, after adjustment for other cardiovascular risk factors, the relative risk in the highest versus the lowest quartile of Lp-PLA_2 was not statistically

Table 6 Comparison of common inflammatory markers in cardiovascular risk assessment

Marker	Advantage	Disadvantage
Cytokines		
IL-6	Direct implication in atherogenesis. It presents rapid variations during acute coronary events	Large daily/seasonal variability. Measurement relatively expensive Hard to distinguish between patients with advanced and subclinical atherosclerosis
TNFα	Direct involvement in atherogenesis. Probably stronger association with coronary artery disease than IL-6	Limited half-life, difficult to measure in large-scale epidemiologic studies. Not routinely measured in prospective studies. Lack of sufficient epidemiologic data about its role. Expensive to measure
sTNF-R1 and sTNF-R2	Alternative measures to TNFα. Measured with greater sensitivity and reliability than TNFα	Very few data about their predictive role. The first reports show that they are weaker predictors for cardiovascular disease than IL-6 or CRP. Expensive to measure
Acute phase proteins		
CRP	Easy and cheap to measure. Probably the most well established inflammatory marker in cardiovascular risk assessment. Long half-life, therefore less circadian variability than IL-6 and less seasonal variability that fibrinogen	Its direct involvement in atherogenesis is not clear. It reflects cytokine expression only in the presence of sufficient liver biosynthetic activity. It is a non-specific marker of inflammation
Fibrinogen	Direct involvement in atherothrombosis. Predictive value comparable to that of CRP. Relatively cheap to measure on a routine basis	Relatively high seasonal variability. Affected by liver biosynthetic ability. It is a non-specific marker of inflammation
SAA	Its variation is in parallel with that of CRP. Elevated in the presence of risk factors such as obesity, insulin resistance, metabolic syndrome and diabetes	No specific advantage over CRP or fibrinogen. The absolute level of risk for subjects with high SAA is generally smaller that that of CRP
Adhesion molecules		
sICAM-1	Good predictor for healthy individuals, high-risk subjects and CAD patients. Value comparable to that of CRP. Direct involvement in atherogenesis	Weak predictive value for ACS. Expensive to measure. Not enough data from large population-based studies
sVCAM-1	Strong predictor for high risk subjects, CAD patients and patients with ACS. Direct involvement in atherogenesis	No predictive value for healthy individuals. Expensive to measure. Not enough data from large population-based studies
sP-selectin	Direct involvement in atherothrombosis. Marker of platelet activation. Rapidly increased in ACS	Not enough data for its role as cardiovascular risk factor. Expensive to measure
sE-selectin	Direct involvement in atherogenesis. Marker of endothelial function	Not enough data for its role as cardiovascular risk factor. Expensive to measure
Others		
sCD40L	Important pathophysiologic role. Strong predictor for clinical outcome in patients with ACS. High sCD40L is correlated with late restenosis after PTCA. Marker of platelet activation	Relatively new marker. Not enough data for its clinical significance
Lp-PLA2	Direct involvement in atherogenesis. Useful to identify patients at increased risk for stroke or CHD, including those who have "normal" LDL-C (<130 mg/dl, <3.4 mmol/l) and are not targeted for drug treatment by the current guidelines. In healthy subjects with moderately raised total cholesterol, Lp-PLA2 and CRP seem to have additive role in their ability to predict risk of CHD. Very promising marker, when combined with measurement of CRP	Further studies are needed to establish its role, especially in combination with CRP
MPO	Role in LDL oxidation. Increased in CAD	No evidence for its role in cardiovascular risk assessment

CAD, coronary artery disease; CRP, C-reactive protein; IL-6, interleukin-6; LDL, low density lipoprotein; Lp-PLA2, lipoprotein-associated phospholipase A2; MPO, myeloperoxidase; SAA, serum amyloid α; sCD40L, soluble CD40-ligand; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; TNFα, tumour necrosis factor α.

Inflammatory markers in atherosclerosis: key points

- Inflammation is a key element of atherogenesis
- Proinflammatory cytokines, adhesion molecules and acute phase proteins are the main inflammatory markers measured in humans
- C-reactive protein is the strongest inflammatory predictor for atherosclerosis
- Fibrinogen and serum amyloid α have been associated with atherosclerosis, but their predictive role is still controversial
- Among adhesion molecules, the soluble form of sICAM-1 is a predictor of cardiovascular risk in healthy individuals, and sVCAM-1 in high-risk patients
- Lp-PLA2 and sCD40L are new promising inflammatory markers with predictive value in cardiovascular disease, but their clinical usefulness is still under investigation

significant.[9] Recent evidence also suggests that Lp-PLA2 and CRP have additive effects to increase risk for cardiovascular events. In the ARIC study[w53] which included 12 819 men and women free of CHD at baseline, both Lp-PLA2 and CRP were associated with increased risk for CHD over a 6 year follow up period. In the presence of low LDL-C, CHD risk was three times greater for individuals with both Lp-PLA2 and hsCRP in the highest versus the lowest category.[10] [w28]

Myeloperoxidase (MPO)

MPO is an abundant enzyme stored in the primary granules of neutrophils and monocytes. MPO has been demonstrated in human atherosclerotic lesions and has been implicated as a catalyst for LDL oxidation, leading to increased uptake and foam cell formation,[w21] and may also contribute to endothelial dysfunction. MPO values may be elevated among individuals with CAD.[w53] Increasing concentrations of leucocyte-MPO and blood-MPO were significant predictors of the risk for CAD.[11] After adjustment for white blood cell count and Framingham risk score, individuals in the highest quartile of blood-MPO had a 20-fold higher risk of CAD than individuals in the lowest quartile.[w53] However, further to these initial reports, there is a lack of prospective studies examining its long-term predictive value in cardiovascular risk.

CONCLUSIONS

The role of inflammation in atherogenesis is now well established. Although a large variety of inflammatory markers participating at several stages of atherogenesis can be measured in plasma or serum, only some of them seem to be clinically important (table 6). The acute phase proteins such as CRP and fibrinogen as well as SAA are the most well studied inflammatory markers, which can be used for cardiovascular risk assessment in the general population. Among the soluble forms of adhesion molecules, sICAM-1 is a promising inflammatory marker which can predict cardiovascular risk in healthy individuals, while measurement of sVCAM-1 is more useful for risk assessment in high-risk subjects and in patients with advanced atherosclerosis. Newer inflammatory markers such as sCD40L, Lp-PLA2, or MPO also seem promising for the prediction of cardiovascular risk, but further studies are needed to establish their role in cardiovascular disease.

Additional references appear on the *Heart* website— http://heart.bmj.com/supplemental

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Authors' affiliations
Dimitris Tousoulis, Charalambos Antoniades, Christodoulos Stefanadis, Athens University Medical School, A' Cardiology Department, Athens, Greece

In compliance with EBAC/EACCME guidelines, all authors participating in Education in *Heart* have disclosed potential conflicts of interest that might cause a bias in the article

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