Atherosclerosis has become a global health issue. Despite major advances in health screening and acute management of coronary artery disease, unmet needs exist for more ways to predict cardiovascular risk beyond high blood cholesterol level and conventional risk factors. Although percutaneous coronary intervention (PCI) is highly effective in treating patients with coronary artery stenoses, long-term follow-up data in patients undergoing PCI indicate that major cardiovascular event rates remain substantial. Most of the adverse events, despite successful PCI, occur largely because of atherothrombosis beyond the site of PCI, indicating that merely treating a local blockage is not good enough. Emerging evidence implicating the importance of inflammation, multiple vulnerable coronary plaques and platelet activation in atherothrombosis has largely broadened our vision towards a more long-term, systemic therapy beyond the acute phase and PCI procedure.\textsuperscript{1-10}

Current data suggest that inflammation serves to fuel atherosclerosis and is probably the missing piece of puzzle linking stable chronic atherosclerosis and acute coronary syndrome.\textsuperscript{9,10} Clinical evidence also suggests that elevated inflammatory markers, in particular, C-reactive protein (CRP), predict future adverse cardiovascular events.\textsuperscript{15} Factors such as arterial shear stress, oxidised low-density lipoprotein (LDL), free radicals, etc. can trigger the release of pro-inflammatory cytokines such as Interleukin-1 (IL-1), Tumour Necrosis Factor-\(\alpha\) (TNF-\(\alpha\)), Interleukin-6 (IL-6), etc. Inflammatory cytokines influence the stability and degradation of the fibrous cap, which lead to plaque disruption and subsequent thrombosis.\textsuperscript{9,10}

Acute coronary syndrome, the clinical syndrome that includes unstable angina, non-ST elevation myocardial infarction and ST-elevation myocardial infarction, is caused by thrombosis on the substrate of a disrupted atheromatous plaque. Thus, the physical integrity of the plaque, notably the extracellular matrix of the fibrous caps overlaying the thrombogenic lipid core, governs the most important clinical manifestation of atherosclerosis. A less common form of physical plaque disruption involves a superficial erosion of the atheroma. These areas of endothelial sloughing may arise from local secretion of enzymes such as matrix metalloproteinase (MMPs). These proteolytic enzymes digest away the extra-cellular matrix components that glue the endothelial cells on the basement membrane. In addition, leukocytes within the atheroma can secrete cytokines that sensitise the endothelial cells to apoptosis-programmed cell death. The loss of endothelial integrity in turn leads to platelet activation and subsequent thrombosis. Endothelial erosion is more common in diabetes mellitus, a condition that is also characterised by increased platelet adhesiveness and platelet dysfunction. A more common form of plaque disruption involves the formation of plaque fissure or rupture. Plaque rupture exposes the collagen beneath the atheroma to the circulation and hence activates the platelets and initiates the coagulation cascade.\textsuperscript{9,10}

Plaques that rupture generally have more abundant leukocytic infiltrates than those considered stable. Inflammatory mediators such as cytokines can influence several biologic processes that regulate the stability of the plaque’s fibrous cap and hence resistance to rupture. For instance, \(\gamma\)-interferon, produced by activated T lymphocytes within the atheroma inhibits production of interstitial forms of collagen by human vascular smooth muscle cells. Inflammatory cytokines such as interleukin-1, tumour necrosis factor (TNF), and the cell surface homolog of TNF-\(\alpha\) known as CD40 ligand (a potent pro-inflammatory stimulus) can also elicit the expression by macrophages and smooth muscle cells of enzymes that can weaken the extracellular matrix. Ligation of CD40 on macrophages also elicits the expression of the gene encoding tissue factor, the principal pro-coagulant within the plaque.\textsuperscript{9,10}

Interestingly, the membrane of activated platelets also expresses CD40 ligand, providing yet another link between thrombosis and arterial inflammation. The surface of activated platelet also has increased number of white cell adhesion molecule, P-Selectin. The increased expression of P-Selectin leads to recruitment of leukocytes to the sit of plaque disruption, hence augmenting local inflammation.\textsuperscript{5,15} In experimental model, CD40 Ligand antibody inhibits atherosclerotic lesion progression in LDL receptor knockout mice. CD40 Ligand gene deletion also inhibits lesion progression in Apo-E knockout mice. Soluble form of CD 40L (sCD40L) has been identified and found to be elevated in patients with acute coronary syndrome and after PCI.\textsuperscript{5} Clinical study suggests that statin therapy abrogates the risk of recurrent cardiovascular events associated with high sCD40L during acute coronary syndrome.\textsuperscript{3} Platelet glycoprotein IIb/IIIa receptor antagonists (abciximab, eptifibatide and tirofiban) that block the final common pathway for platelet aggregation have been demonstrated to significantly reduce plasma levels of sCD40L after PCI.\textsuperscript{4,12} Clopidogrel, but not aspirin, has been shown being able to reduce platelet-derived CD40L.\textsuperscript{5,15} Clinical data also showed that
abxicimab could significantly reduce the plasma level of C-reactive protein and cytokines like IL-6 and TNF. Thus, most anti-platelet agents exhibit anti-inflammatory properties.\(^9,10\)

The propagation of platelet activation and inflammatory status critically determine the clinical consequences of a given plaque disruption. Pathological studies reveal that plaque disruptions occur quite frequently but seldom produce symptoms. Limited mural thrombi very often heal and resolve by virtue of endogenous fibrinolysis. Local thrombin generation at the sites of clinically silent plaque disruption can stimulate smooth muscle cell proliferation. Release of platelet-derived growth factor and transforming growth factor from platelets degranulating at these sites can augment smooth muscle migration and collagen gene expression. In this manner, thrombosis in situ can promote the evolution of a plaque from an earlier lipid-rich lesion to a more advanced fibrous plaque. Plaque ruptures may have fewer propensities to rupture and cause thrombosis than the atheromatous lipid-rich lesion. However, these fibrous plaques formed as a result of disruption and healing (“wear and tear”) may have a greater tendency to evolve into flow-limiting stenoses over time. In this model, anti-thrombotic therapies may prevent progression of atheroma.\(^9,10\) Therefore, a combination of lipid-lowering and anti-thrombotic therapies may not only reduce the risk of acute complications of atherosclerosis, but also slow the evolution of lesions from fatty streaks to those that cause flow-limiting stenoses.

On the other hand, if the platelet thrombus propagates, it can lead to acute narrowing or subtotal occlusion of the lumen resulting in myocardial ischemia. Platelet or atheromatous debris embolisation may in turn lead to myocardial necrosis as reflected by elevation of cardiac enzymes. Clinically, it would manifest itself as unstable angina or non-ST elevation myocardial infarction. If the platelet activation is more sustained and totally occlusive, ST-elevation or trans-mural myocardial infarction may ensue.\(^9,10\)

High-sensitivity C-reactive protein (hs-CRP) is the most widely studied inflammatory biomarker with relevance to atherothrombosis. It is a strong predictor of adverse cardiovascular events including first-ever stroke, independent of conventional risk factors and Framingham risk score.\(^1,2\) The hs-CRP level should be measured twice (averaging results) 2 weeks apart, in metabolically stable patients. If the hs-CRP is >10 mg/L, the assay should be repeated and sources of infection/systemic inflammation ruled in. Patients with hs-CRP>3 mg/L are categorized as high risk. Pharmacological therapies with aspirin, clopidogrel, statins or rosiglitazone have been associated with reduction in hs-CRP levels.\(^3,4,6,7,12\)

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an emerging biomarker of coronary artery disease.\(^11\) It is produced predominantly by macrophages and highly up-regulated in atherosclerotic plaques. It plays a crucial role in LDL oxidation. Lp-PLA2 may be the “missing link” between circulating LDL and plaque formation. Clinical studies have demonstrated that levels of Lp-PLA2 are independently associated with incident coronary events, even after adjustment for conventional risk factors and CRP. It is more vascular-specific than CRP. Lipid-lowering therapies have shown significant reductions in Lp-PLA2 levels. It may become the major contender of hs-CRP in cardiovascular risk prediction and target for pharmacological intervention.\(^11\)

The concept of “vulnerable plaque” has generated much interest in interventional cardiology. Various imaging modalities have emerged to detect vulnerable plaques, which include magnetic resonance imaging (MRI), optical coherence tomography (OCT), intravascular ultrasound (IVUS) with virtual histology, thermography, etc.\(^1,2,3,6,7\) However, growing evidence suggests that the inflammatory process underlying lesion instability is usually more widespread than what we used to think, and it is not uncommon to find multiple vulnerable plaques simultaneously in the coronary arteries.\(^1,2,3,5\) “Stenting” all unstable non-flow limiting lesions would seem a bit impractical and may do more harm than good. A more rational approach should be combining intensive anti-platelet and lipid-lowering therapy with interventional strategies to prevent not only local complications arising from the target lesion but also limit the sequel to bystander lesions’ vulnerability.\(^9,10\) It is high time we target both conventional risk factors and inflammatory biomarkers in managing patients with coronary artery disease.

References