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Biomarkers of Atherosclerosis and Acute Coronary Syndromes – A Clinical Perspective

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1. Introduction

Coronary heart disease remains the single biggest killer in the United Kingdom, accounting for around one in five deaths in men and one in six deaths in women (1). In 2003 the total annual cost of coronary heart disease in the United Kingdom was around £3.5 billion (£60 per capita), with the cost of inpatient care accounting for around 79% of these costs (2). Approximately 3% of patients who attend the ED have chest pain that the treating physician suspects may be cardiac in origin (3). 74-88% of these patients are admitted to hospital, making up one in five of all medical admissions (3-5). Ultimately only a quarter of these patients will be diagnosed with an acute coronary syndrome (ACS), which implies that a very cautious approach to the problem has been adopted. Despite this fact, up to 6% of the patients with chest pain who are discharged from the ED actually have myocardial damage that has prognostic significance (6). These patients are up to three times as likely to die as similar patients who were admitted to hospital (7).

2. The pathophysiology of coronary heart disease

Over the past century tremendous advances have been made in our understanding of coronary heart disease and its pathophysiological evolution. In 1910 a Russian physician first described the clinical presentation of acute myocardial infarction (AMI) (8). Two years later, an association was drawn between AMI and acute thrombotic coronary occlusion (9). By 1913 it had been hypothesised that atherosclerosis developed as a result of gradual lipid accumulation within the arterial wall (10). The advent of coronary revascularisation procedures in the latter half of the 20th century allowed the observation that restoring blood flow beyond significant coronary stenotic lesions often led to alleviation of anginal symptoms. This helped to propagate the widespread belief that the greater the coronary

stenosis the greater the risk of a clinically significant event such as AMI or unstable angina pectoris. This axiom underpins much of modern practice in cardiology. Figure 1 illustrates the traditional model of the evolution of coronary atheroma (11).

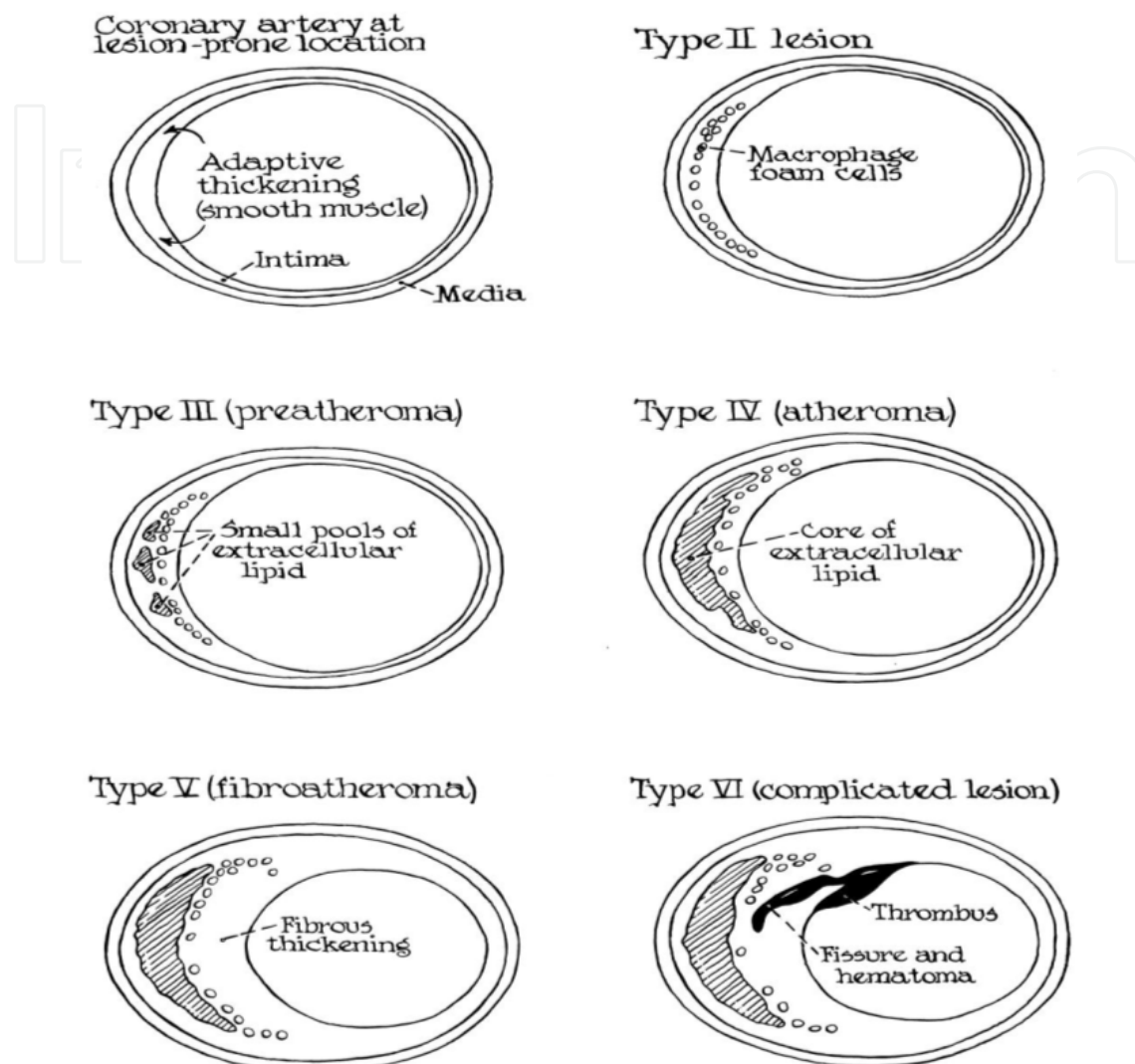


Fig. 1. Drawings of cross sections of the most proximal parts of six left anterior descending coronary arteries, illustrated to depict the traditional concept of the evolution of coronary atheroma. From Stary *et al*, 1995 (11).

In recent years this whole concept has been challenged. Far from a bland disease of cholesterol storage characterised by a passive accumulation of lipid within the vessel wall, a growing body of research and a progression in current thinking suggest that coronary atherosclerosis is in fact a dynamic inflammatory disease, dependent upon complex interactions between the immune, coagulation and humoral systems. It would seem that progression of coronary atherosclerosis is not so much a gradual process as a stepwise one, often characterised by swift and sudden increases in plaque size. Atherosclerotic plaque rupture or endothelial damage may lead to haemorrhage into the plaque or thrombus formation with subsequent organisation. This leads to rapid expansion of the plaque (12). Further, the severity of coronary stenosis on angiography does not predict the development of subsequent AMI (13). Indeed, two thirds of AMIs are provoked by plaques that cause less

than 50% stenosis on angiography (14). The explanation for these phenomena resides in the understanding that there are, in basic terms, two kinds of coronary atheromatous plaques: those which are stable and those which are unstable. While stable plaques may be responsible for stable anginal symptoms (such as exertional chest pain relieved by rest), they are less likely to rupture and cause the clinical manifestations that we recognise as ACS. Meanwhile, unstable plaques are vulnerable and highly likely to rupture with the ensuing risk of developing ACS. There are notable pathological differences between these two types of plaque. Stable plaques are more likely to cause coronary stenosis, presenting a fixed obstruction to blood flow and therefore often being responsible for causing stable anginal symptoms such as exertional chest pain. Unstable plaques, however, may cause little arterial stenosis, thus explaining the observation that the majority of AMIs are caused by lesions that are only mildly stenotic. What is more, they may cause little in the way of clinical symptoms until they rupture, leading to the often dramatic and frequently fatal clinical manifestations of ACS.

Pathologically, stable plaques are likely to be more enriched with smooth muscle cells than those which are prone to rupture. They are likely to contain a dense fibrous cap consisting of collagen and extracellular matrix, which give the plaque tensile strength. On the contrary, plaques that are vulnerable to rupture are likely to have thin, friable fibrous caps, contain abundant inflammatory cells including macrophages and they are rich in extracellular lipid, often with a lipid core containing pro-inflammatory oxygen free radicals, pro-thrombotic material such as tissue factor and necrotic cellular debris (Figure 2) (15;16).

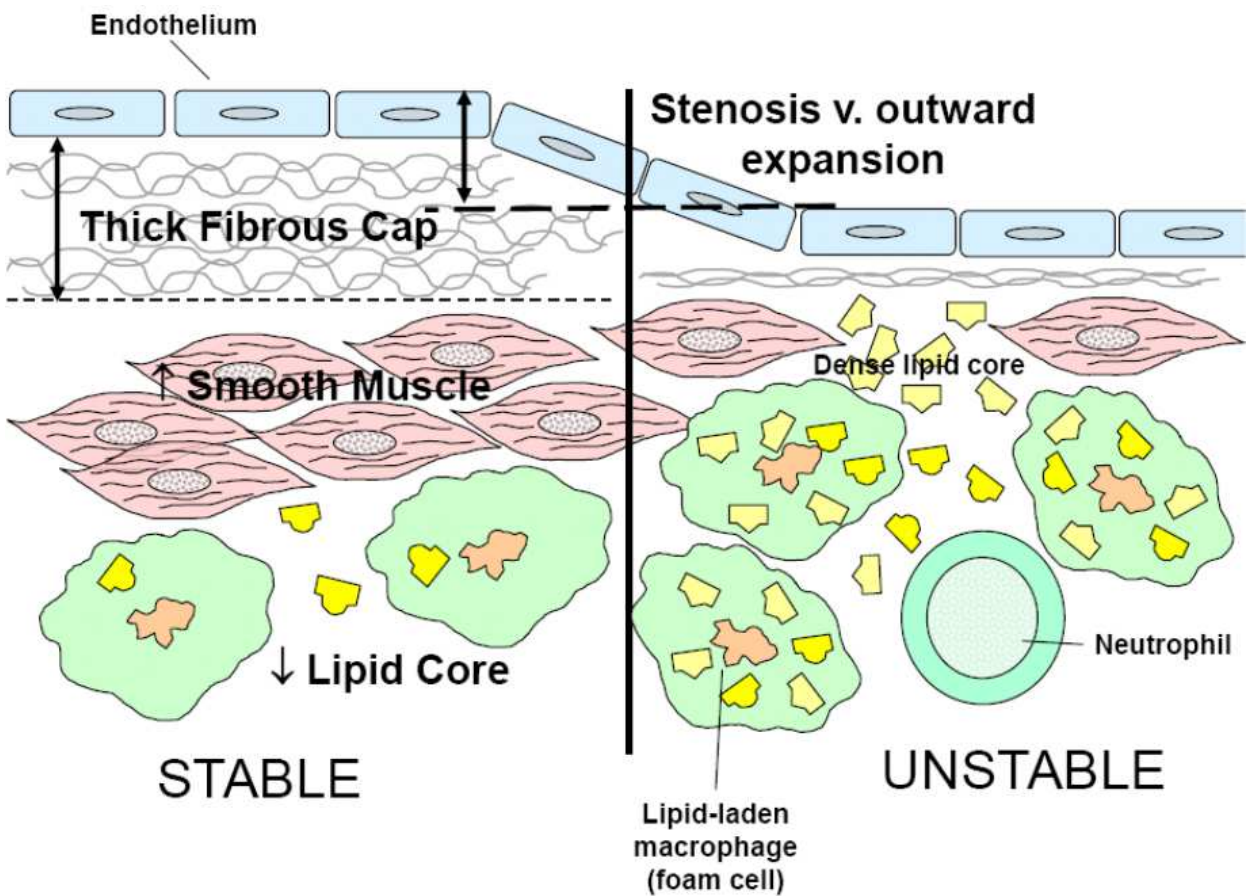


Fig. 2. Stability and instability: The two varieties of coronary atheroma.

While an unstable plaque often causes little or no arterial stenosis, it does not follow that unstable plaques are necessarily smaller in size than their stable counterparts. It has become apparent that the arterial wall is not a static and rigid structure but rather is capable of so-called 'outward remodelling', increasing its external diameter without narrowing the lumen. An unstable plaque may therefore be comparatively large in size while causing little arterial stenosis (15;17-21).

2.1 The pathophysiological evolution of an acute coronary syndrome

In order to fully comprehend the limitations to current diagnostic strategies and to attempt the development of effective new strategies for the diagnosis of ACS it is important to have a reasonable understanding of the initiation and progression of the disease from a molecular level upwards. If we can recognise the precise disease processes we are trying to accurately identify, we stand a much better chance of understanding our current problems and of developing effective novel diagnostic strategies that can be applied in clinical practice.

Coronary atherosclerosis is an inflammatory disease whose origins can only be adequately understood through a sound appreciation of vascular biology (17;22-27). We no longer regard the blood vessel wall as simply an inert tubular conduit for flowing blood but rather as a complex living structure that plays a pivotal role in maintaining vascular homeostasis and integrity. Of particular importance in this regard is the endothelium, a monolayer of cells forming a barrier between flowing blood and tissue. The human endothelium has a total surface area of approximately 1000m² (16) and constitutes around 16% of the myocardium (28). It plays a key role in modulating vascular tone, responding to neural, humoral and mechanical stimuli by synthesising and releasing vasoactive substances. By sending activating signals to circulating inflammatory cells, the endothelium orchestrates complex fluid and cellular movements designed to neutralise and eliminate foreign elements. While these mechanisms are usually beneficial, under certain circumstances these processes can become extreme and counter-productive (29;30).

The endothelium is an active player in the protection against and development of coronary disease, being the guardian of the integrity of the vessel wall. A functional endothelium produces a healthy balance of vascular constricting and relaxing factors. In this respect, the role of endothelium-derived nitric oxide is particularly crucial. In addition to its important vasodilator effect, nitric oxide protects against vascular injury, inflammation and thrombosis. It inhibits leukocyte adhesion to the endothelium, smooth muscle cell proliferation and migration and platelet aggregation (31-34). In the presence of traditional cardiac risk factors such as hyperlipidaemia, smoking, diabetes and hypertension and where there is local or systemic inflammation or reduced shear stress (such as at the branch points of coronary arteries), nitric oxide production is inhibited and its degradation enhanced (Figure 3) (23). Under these conditions, many of the protective inhibitory effects of nitric oxide are lost. Cell adhesion molecules (CAMs) including P-selectin and E-selectin are expressed by the endothelium, where they mediate leukocyte binding. P-selectin and E-selectin bind to carbohydrates that are constitutively expressed on the surface of circulating leukocytes, causing the leukocytes to bind loosely to the endothelial surface and to literally roll across it, scanning the endothelium for further activating signals. Chemoattractant cytokines or chemokines that are also expressed by activated endothelial cells can then induce a conformational change in integrin molecules expressed at the leukocyte cell

surface, changing them from a low-affinity to a high-affinity state (35). These activated integrins may then bind firmly to two further adhesion molecules that are expressed by activated endothelium: intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1). This strong adhesion brings the rolling leukocytes to a halt.

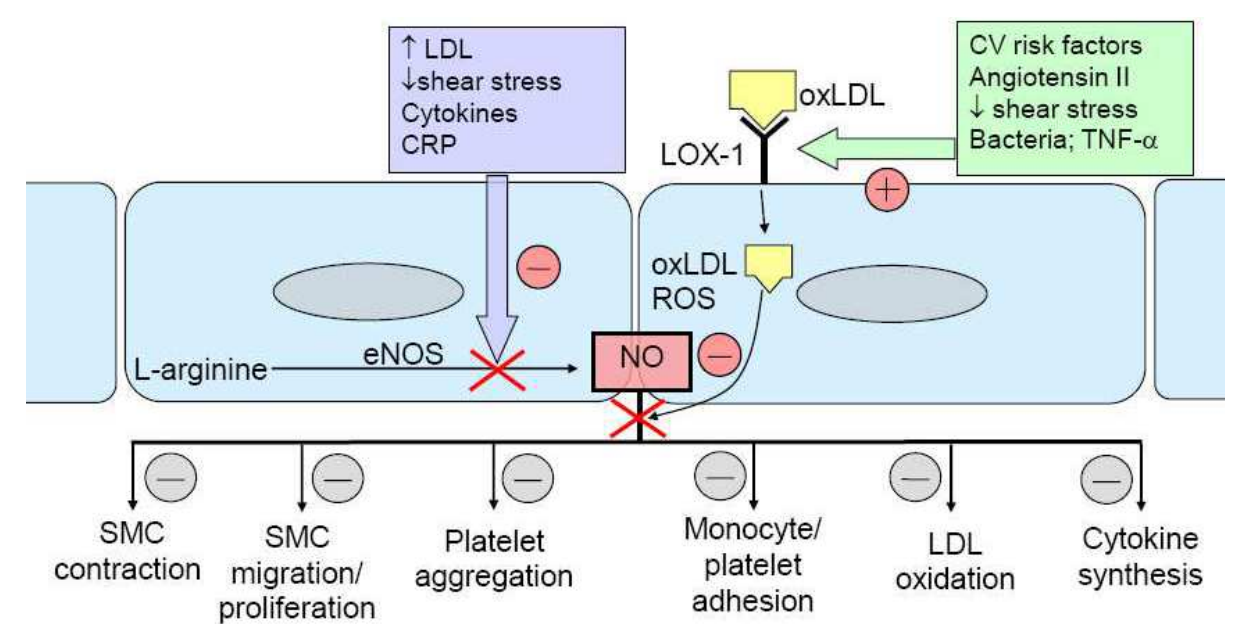


Fig. 3. The pivotal anti-atherogenic role of nitric oxide on a molecular level. Abbreviations: LDL, low density lipoprotein; CRP, C-reactive protein; CV, cardiovascular; TNF- α , tumour necrosis factor α ; oxLDL, oxidised LDL; ROS, reactive oxygen species; SMC, smooth muscle cell; NO, nitric oxide; LOX-1, oxidised LDL receptor-1; eNOS, endothelial nitric oxide synthase.

In the presence of further activating signals from within the arterial intima, the leukocytes may subsequently undergo a cytoskeletal change, enabling them to squeeze between the tight cell-cell junctions of the endothelium via interactions with the PECAM-1 (CD31) receptor. Again, under normal circumstances PECAM-1 binds endothelial cells strongly together, preventing leukocyte migration into the arterial intima. However, substances such as thrombin and histamine that are expressed during periods of localised inflammation loosen this binding, promoting cellular retraction and vascular permeability. This enables glycoproteins on the cell surface of the activated leukocytes to bind to PECAM-1, allowing them to pass through the endothelial layer into the arterial intima in a process labelled diapedesis (29;36). Within the arterial intima, activated leukocytes will then migrate towards chemokines (including monocyte chemotactic protein, MCP-1) expressed within foci of inflammation where they participate in inflammatory processes (Figure 4) (29;37;38).

Circulating low-density lipoprotein (LDL) cholesterol can also bind to endothelial receptors and is subsequently modified or oxidised by the endothelial cells. Within the arterial intima, oxidised LDL acts as a strong stimulus for further migration and localisation of inflammatory cells (16). Following migration, monocytes mature into macrophages and, via scavenger receptors, ingest oxidised LDL to become foam cells (24). Together with T lymphocytes and activated endothelial cells, these cells secrete an array of pro-inflammatory cytokines, forming a positive feedback loop which enhances the inflammatory reaction within the arterial intima. If the inflammatory stimuli are not removed or neutralised, this process will continue indefinitely (27).

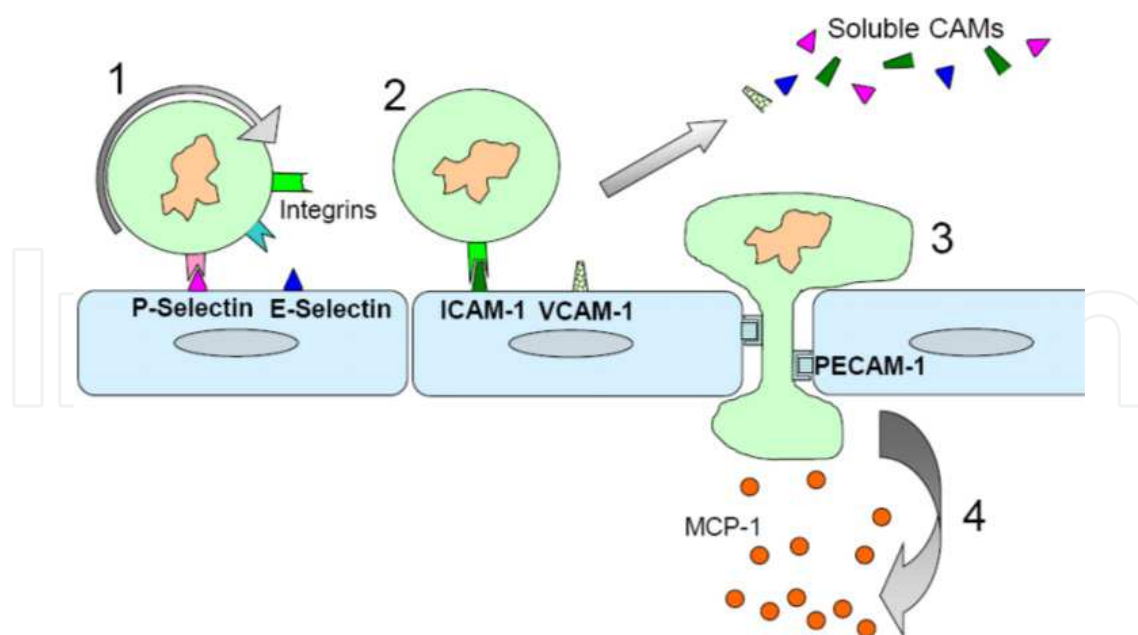


Fig. 4. The multistep model of leukocyte migration. 1. Leukocytes bind to selectins expressed by activated endothelium, causing them to roll, scanning the endothelium for activating signals. 2. In the presence of activating signals, integrins on the cell surface of the leukocyte undergo a structural change and can bind firmly to ICAM-1 and VCAM-1. 3. Leukocytes can then migrate through to the arterial intima by binding to PECAM-1 at the cell junction. 4. Leukocytes migrate along a chemokine gradient (illustrated as MCP-1), which helps to localise the inflammatory response within the intima. Cell adhesion molecules are subsequently released into the circulation in soluble form.

In addition to enhancing inflammation, cytokines stimulate differentiation and migration of smooth muscle cells from the arterial media into the intima (39). While this may ultimately lead to mechanical expansion of the plaque, smooth muscle cells actually play a vital role in maintaining the stability of the atherosclerotic plaque by secreting a dense, fibrous extracellular matrix and substances that prevent its degradation (tissue inhibitors of metalloproteinases, TIMPs) (16) (Figure 5).

Enhanced inflammatory activity within the plaque ultimately renders the plaque vulnerable to rupture by destabilising this fibrous cap. Activated macrophages and neutrophils within atheroma secrete myeloperoxidase (MPO), an enzyme which enhances consumption of nitric oxide, generating highly reactive and pro-inflammatory oxygen free radicals and oxidised LDL, thus perpetuating and enhancing both endothelial dysfunction and the formation of foam cells (40;41). MPO inactivates TIMPs, paving the way for degradation of the fibrous cap. Further, MPO activates matrix metalloproteinases (MMPs), enzymes responsible for actively degrading the fibrous cap (42) (Figure 6) (43).

Atheroma is rendered even more vulnerable to rupture by interactions between the CD40 receptor (which is expressed by endothelial cells, monocytes and B lymphocytes) and its ligand CD40L, which is expressed by activated T helper cells, smooth muscle cells, macrophages, basophils and activated platelets (44;45). This interaction leads to the formation of another positive feedback loop that enhances endothelial dysfunction and inflammation within the plaque and stimulates the release of both the procoagulant tissue factor and MMPs into the lipid core (46-50). The latter further enhance degradation of the fibrous cap (Figure 6).

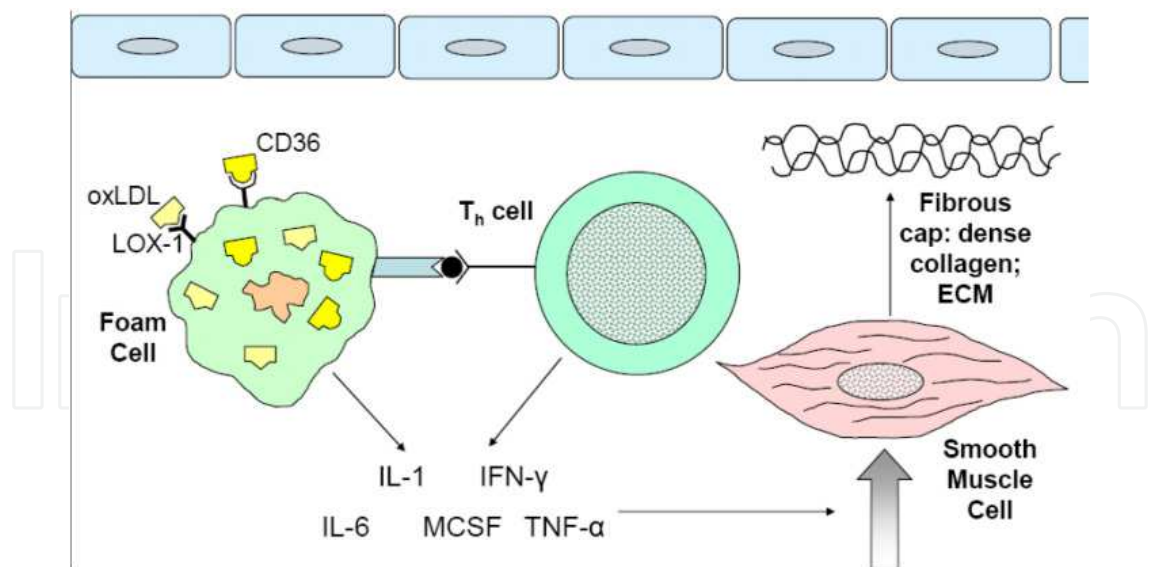


Fig. 5. Progression to organised atheroma. Following migration into the arterial intima, monocytes mature into tissue macrophages and, via receptors including LOX-1 and CD36, take up extracellular lipid including oxidised LDL cholesterol (oxLDL) to become foam cells. Together with T helper cells (Th), foam cells secrete an array of pro-inflammatory cytokines (interleukin-1 (IL-1), interferon- γ (IFN- γ), interleukin-6 (IL-6), monocyte colony stimulating factor (MCSF), tumour necrosis factor- α (TNF- α)), which lead to migration of vascular smooth muscle cells from the arterial media. Following migration, these smooth muscle cells secrete a dense extracellular matrix (ECM) and collagen fibres, which form a tough fibrous cap.

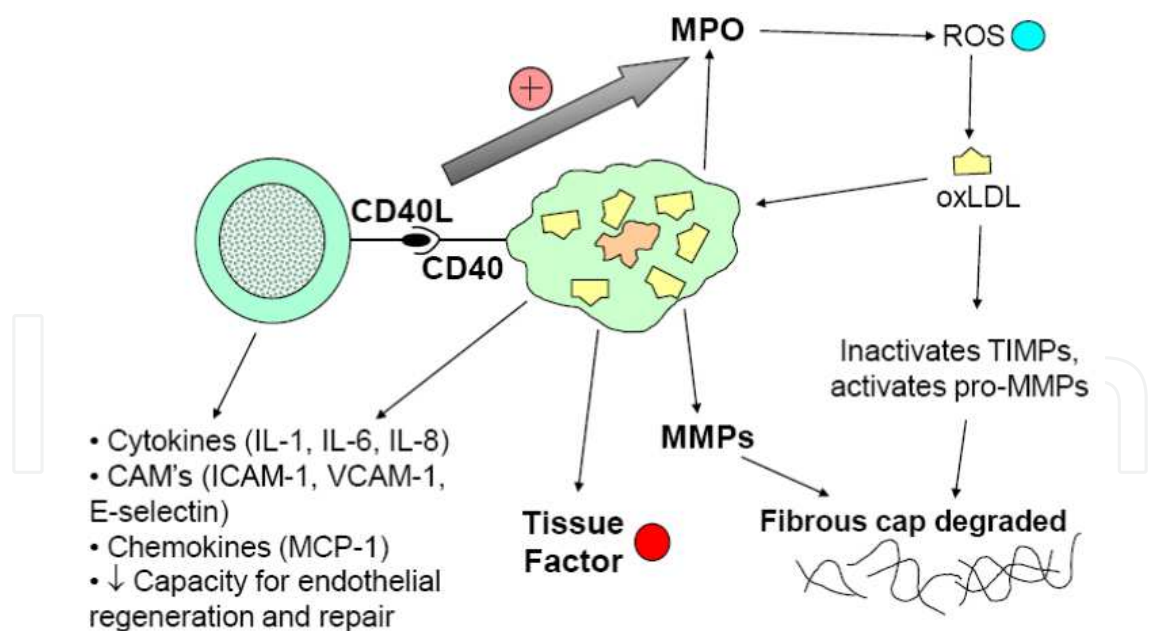


Fig. 6. CD40/L interactions within coronary atheroma. CD40/40L interactions lead to enhanced inflammation, impaired capacity for endothelial repair and regeneration, secretion of pro-coagulant tissue factor, MMPs and upregulation of myeloperoxidase (MPO) secretion. MPO produces reactive oxygen species (ROS) and oxidised LDL (oxLDL), enhancing upregulation and leading to degradation of the fibrous cap by activating the precursors of MMPs (pro-MMPS) and inhibiting tissue inhibitors of metalloproteinases (TIMPs).

Where there is abundant intimal inflammation, pro-inflammatory cytokines may prime cells within the plaque for apoptotic death upon engagement with activated T lymphocytes (22;51). Stimulated apoptosis of smooth muscle cells impedes maintenance of the fibrous cap, favouring its breakdown. Apoptosis of endothelial cells may lead to erosions of the endothelial layer, enabling circulating blood to come into contact with the pro-thrombotic contents of the plaque (Figure 7). Circulating platelets are activated upon contact, binding to the arterial wall and to each other (52). When these areas of endothelial erosion are small, this platelet aggregation occurs only on a microscopic level and is clinically insignificant, serving only to stimulate endothelial regeneration and smooth muscle growth. The new endothelial cells may be dysfunctional, however, predisposing to vasoconstriction (15).

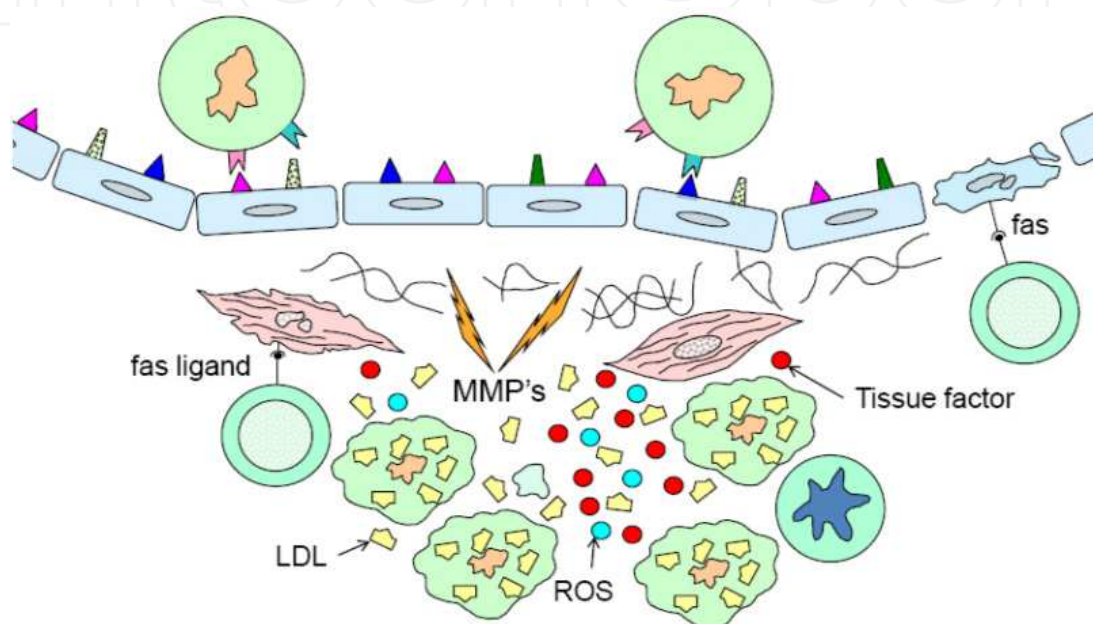


Fig. 7. Positive feedback loops within unstable coronary atheroma and processes leading to endothelial erosion.

In the presence of larger endothelial erosions there may be a rapid increase in intimal inflammation (53) and sufficient platelet aggregation and subsequent fibrin deposition to produce a large thrombus with symptomatic luminal obstruction (15;17;54;55). In itself, this process accounts for approximately 25% of all major thrombi that lead to acute coronary syndromes (56) and may have even greater importance in women and young people (57). Of even greater importance, however, is the high tensile stress that a vulnerable plaque must withstand. As the lipid core is soft and deformable, it cannot bear circumferential stress. This stress is therefore borne by the fibrous cap, made of tough collagen and extracellular matrix. Depending upon the shape of the plaque and its position within the artery, the fibrous cap must withstand focal concentrations of load up to seven or eight times normal systolic wall stress (58;59). This is particularly significant in unstable plaques where the fibrous cap may be thin and friable.

Ultimately, this may lead to sudden rupture of the plaque with endothelial disruption, causing haemorrhage of circulating blood into the core of the plaque (Figure 8). This may be particularly likely to occur following a trigger such as unaccustomed physical activity or emotional stress, which leads to a rapid increase in systolic blood pressure and thus increased circumferential stress on an already vulnerable plaque (60).

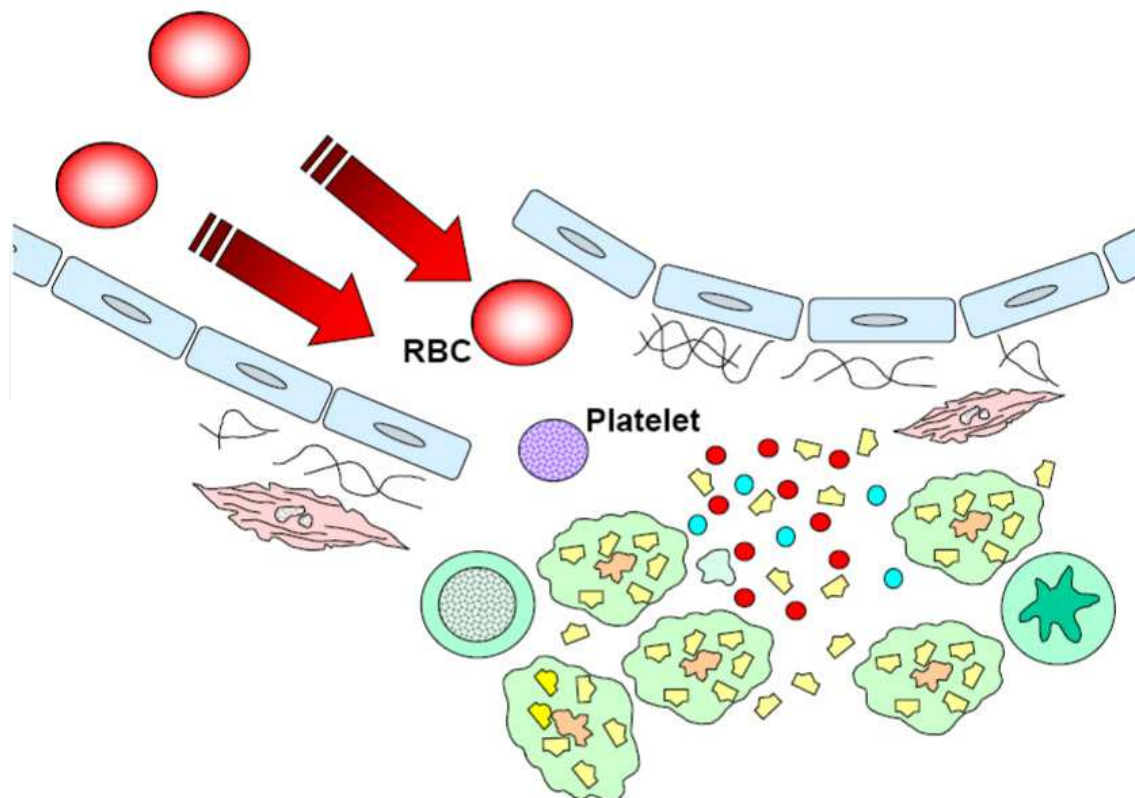


Fig. 8. Plaque rupture. There is haemorrhage into the plaque, causing rapid expansion and, as the contents of the lipid core are highly prothrombotic, thrombus formation ensues. Abbreviations: RBC, red blood cell.

Circulating blood is exposed to the prothrombotic lipid core. Tissue factor activates factor VIIa, which ultimately leads to the cleavage of thrombin from prothrombin and further activation of the coagulation cascade (61). Several substances from within the plaque, including thrombin, CD40L and P-selectin, activate circulating platelets by inducing a conformational change in the glycoprotein receptors and enabling cross-linking or adhesion via fibrinogen and other adhesive ligands. During this process, activated platelets themselves express P-selectin and CD40L, which appear to be necessary for the formation of a stable arterial thrombus (62-64). Both P-selectin and CD40L are later enzymatically cleaved from the platelet surface and released into the circulation in soluble form (65;66).

When plaque rupture is small, intraplaque haemorrhage may lead to rapid expansion with platelet activation and adhesion but the thrombus does not extend into the arterial lumen (12). The thrombus subsequently undergoes organisation, the endothelial layer regenerates and the episode is clinically silent. Among patients with coronary atheroma who died of non-vascular causes such as motor vehicle accidents and subsequently underwent post-mortem examination, up to 8% were noted to have had a recent plaque disruption with intra-plaque thrombi (67). Indeed, in pathological studies of subjects who died of ischaemic heart disease each patient had on average two to three plaque disruptions, although in each case one culprit thrombus was identified that was apparently responsible for causing death (68-70). In the presence of a large plaque rupture or, indeed, when the rupture is not large but the patient is in a pro-thrombotic state (for example during periods of stress or systemic

infection), platelet activation and aggregation may extend into the arterial lumen. Activation of the coagulation cascade leads to fibrin deposition, which increases the size of the thrombus. Again, thrombus formation may be arrested without causing significant luminal stenosis. However, as the thrombus is exposed to flowing blood distal emboli may occur, potentially causing myocardial necrosis on a microscopic level and recognisable symptoms. As activated platelets aggregate to form a platelet-rich arterial thrombus, they release mediators such as serotonin and thromboxane A₂, which cause vasoconstriction. This may lead to localised coronary arterial spasm, which even in the absence of an obstructive coronary thrombus, may lead to transmural myocardial ischaemia and a clinically apparent ACS (71). When thrombus formation continues unchecked, total arterial occlusion may occur. If such occlusion occurs suddenly in a previously uncompromised artery without a well-developed collateral circulation, significant downstream myocardial necrosis will occur with the clinically recognisable signs of acute myocardial infarction (AMI). The cell membranes of the necrosed myocytes are breached and their intracellular constituents are washed out into the circulation. These constituents include myoglobin, creatine kinase, the cardiac troponins and human fatty acid binding protein.

3. Biomarkers of unstable coronary disease

Current diagnostic strategies incorporate biomarkers of myocardial necrosis, the end-point in the pathophysiological evolution of ACS. The measurement of cardiac troponins in the bloodstream has revolutionised the diagnosis of AMI in this regard, enabling the detection of microscopic amounts of myocardial necrosis that could not have previously been identified (72). As described in detail earlier in this chapter, however, a whole host of pathophysiological processes have occurred before myocardial necrosis, none of which are detectable using current diagnostic technology. In fact myocardial necrosis is merely a surrogate marker of the disease process, which occurs within the coronary artery and not the cardiac myocyte. As it is possible to use biomarkers to detect myocardial necrosis with high sensitivity and specificity this raises the additional possibility that other biomarkers may be able to detect evidence of the disease process itself within the coronary arteries. A number of novel biomarkers have been investigated in this regard in recent years.

3.1 Soluble cell adhesion molecules

Cell adhesion molecules (CAMs) mediate the interactions between the endothelium and blood cells, enabling the localised inflammatory response that is essential for the initiation and propagation of coronary atherosclerosis. Their upregulation enhances this inflammatory response, which ultimately renders the atherosclerotic plaque vulnerable to rupture. Following their expression, CAMs are shed from the cell surface. As these soluble CAMs are detectable in peripheral blood, they are promising candidates for use as early markers of vascular activation (37). CAMs that have attracted interest as potential biomarkers of ACS include the molecules P-selectin, E-selectin, ICAM-1 and VCAM-1.

3.1.1 P-selectin

P-selectin mediates the interaction of platelets and endothelial cells with neutrophils and monocytes (65). It is expressed by endothelial cells in atherosclerotic, but not normal, vessels

(73,74), with expression being particularly marked in patients with unstable angina (75). P-selectin is also expressed by activated platelets and has been used as a marker of platelet activation (76). Several investigators have demonstrated significantly raised soluble P-selectin levels in patients with AMI (77-84), unstable angina (85-88) and cohorts of patients with any ACS (89,90). However conflicting results have also been reported, with two reports that P-selectin does not help to predict adverse events in patients with ACS and two studies that did not detect any elevation of plasma P-selectin levels in patients with ACS compared with controls (91-93).

Five studies have investigated the utility of P-selectin for diagnosis of ACS in the ED population. One small study of 44 patients found no difference in plasma soluble P-selectin levels between patients diagnosed with ACS and non-cardiac pain (94). Although the same group also reported that P-selectin was not an independent predictor for a diagnosis of ACS (95), another group reported that P-selectin was an independent predictor for the occurrence of serious cardiac events within three months of presentation to the ED with chest pain (96). Other groups have reported sensitivities of 35 and 55.8% and NPVs of 53 and 71% for the diagnosis of ACS (97-98). The data suggests that the use of soluble P-selectin as a sole rule-out strategy for ACS in the ED is likely to lead to an unacceptably high false negative rate. Our own data however in 713 patients presenting to the ED with suspected cardiac chest pain demonstrated P-selectin had early diagnostic value for AMI and prognostic significance independent of troponin T and ECG findings (99).

3.1.2 E-selectin

E-selectin has also been investigated in this regard. Plasma levels of E-selectin have been shown to correlate with the severity of coronary atherosclerosis (87,100). A number of studies have reported elevated plasma E-selectin levels in patients with AMI (101-108). E-selectin elevations have also been reported in patients with unstable angina (85,109). Other studies have reported raised E-selectin in all ACS (80,82,110-112). Plasma E-selectin levels in patients with AMI may be higher among patients who experienced a prodrome of unstable angina (105). Raised E-selectin levels have also been reported following attacks of variant angina (113), although there may be no difference in E-selectin levels during episodes of stable angina (114). A reduction in plasma E-selectin levels has been described in patients with AMI following successful reperfusion (101,108). Further, plasma E-selectin levels may be useful for predicting the risk of death among patients with AMI (103). However not all reports have been consistent. Three groups have failed to find elevated E-selectin levels in ACS (115-117). There is no clear explanation for the discrepancy in the results, although one group measured E-selectin in serum rather than plasma, which may have introduced an important bias. Only one study has investigated E-selectin levels in the ED population with undifferentiated chest pain (118). This study failed to demonstrate a difference in E-selectin levels between patients with AMI, unstable angina and controls. However, the study had significant limitations, including small numbers, suboptimal gold standards and no clinical follow-up. The study was not designed to appraise the performance of E-selectin as a diagnostic test for use in the ED. The available research suggests that E-selectin has promising characteristics for use as a marker of ACS. A large prospective observational cohort study is necessary to evaluate its performance as a diagnostic test. Incorporation into

a multimarker strategy with markers that may reflect other aspects of the pathophysiological evolution of ACS may be necessary to obtain sufficient sensitivity.

3.1.3 Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1)

ICAM-1 and VCAM-1 are responsible for mediating firm adhesion of leukocytes to the endothelium, enabling their subsequent migration. ICAM-1 (but not VCAM-1) levels have been shown to predict adverse cardiac events in apparently healthy men (119-121) and women (122) and may help to predict the development (121,123) and progression of coronary atherosclerosis (124). In addition, ICAM-1 (but not VCAM-1) levels are raised in patients with stable angina and levels may correlate with disease severity (125-127). Levels of both VCAM-1 and ICAM-1 have been shown to be elevated in patients with ACS (128-129), although conflicting results have also been reported (130). Interestingly, levels of VCAM-1 and ICAM-1 in patients with unstable angina who had demonstrable ruptured plaque on coronary intravascular ultrasound were significantly higher than in patients with stable angina who had no evidence of plaque rupture, although neither biomarker was an independent predictor of plaque rupture on multivariate analysis (131). Finally, VCAM-1 and ICAM-1 levels have both been shown to predict prognosis and complications in patients with confirmed ACS (91,103,128,132-137). Evidence for the use of ICAM-1 and VCAM-1 in the ED population with undifferentiated chest pain is disappointing, however. A study of 241 men who presented to the ED with chest pain failed to find a significant difference in ICAM-1 and VCAM-1 levels between patients with AMI and patients with (presumed) non-cardiac chest pain, although the gold standards for diagnosis of non-cardiac pain were suboptimal (138). Other studies have demonstrated no correlation between ICAM-1 and VCAM-1 levels and the occurrence of adverse events within three months of presentation (96,139). One study demonstrated that ICAM-1 predicted in-hospital adverse events with a sensitivity of 63.3%, a specificity of 47.2% and a NPV of 79.3%, which is clearly not sufficient for ICAM-1 to be used in the clinical environment (140).

3.1.4 Soluble CD40 Ligand (sCD40L)

As described earlier in this chapter sCD40L plays a pivotal role in mediating interactions between inflammatory cells within coronary atheroma that ultimately render the plaque vulnerable to rupture. In addition, sCD40L is expressed by activated platelets and plasma levels have been shown to correlate with platelet activation (141). Case control studies have consistently demonstrated elevated levels of sCD40L in patients with ACS when compared with controls (48;141-151). sCD40L levels have also been shown to stratify patients with confirmed ACS according to their risk of developing adverse events (152), although conflicting results have also been reported (153,154). An analysis of data from 1088 patients with confirmed ACS who had been enrolled in a randomised controlled trial (the c7E3 Fab antiplatelet therapy in unstable refractory angina (CAPTURE) trial) and 626 patients who were admitted to hospital with acute chest pain, found that sCD40L was a powerful independent predictor of adverse events at 72 hours, 30 days and six months. Levels correlated poorly with troponin T and may thus identify a separate at-risk group. However sCD40L may be more useful for prognostication than diagnosis. Using the 97.5th percentile

upper reference limit as a diagnostic cut-off sCD40L had a sensitivity of only 56.5% for the diagnosis of ACS in the patients with acute chest pain (141).

3.2 Myeloperoxidase (MPO)

MPO is an enzyme secreted by phagocytic cells. It utilises hydrogen peroxidise to generate oxygen free radicals. In health this leads to the generation of hypochlorous acid, which has bactericidal and viricidal properties (155). Neutrophils and foam cells within coronary atheroma also produce MPO, where the generation of highly reactive oxygen free radicals leads to the generation of oxidised LDL cholesterol, which enhances the formation of foam cells propagating inflammation (156). It also perpetuates the endothelial dysfunction by enhancing the breakdown of nitric oxide (155). Further, MPO activates MMPs from their precursors and inactivates their physiological inhibitors, TIMPS (42). This enables breakdown of the fibrous cap, rendering the plaque vulnerable to rupture. MPO is abundantly expressed by macrophages in eroded or ruptured coronary plaques, although it has not been identified in fatty streaks (43). While expression is enhanced in unstable angina and AMI, it is not enhanced in variant angina or in response to ischaemia in chronic stable angina (157). These findings suggest that increased MPO expression is associated with the ongoing inflammatory process rather than indicating reperfusion injury or a tissue response to ischaemia. Blood levels of MPO have been shown to correlate strongly with the presence of coronary artery disease. When divided into quartiles, patients with MPO levels in the fourth quartile had an adjusted odds ratio for the presence of coronary artery disease of 20.4 compared to patients in the first quartile. MPO levels were more predictive of risk of coronary artery disease than Framingham risk score (158).

A case control study involving 874 patients demonstrated elevated MPO levels in patients with ACS compared with controls who had normal coronary angiograms (159). Two separate analyses of data from randomised controlled trials, involving a total of 2,614 patients, have reported that MPO levels help to predict the occurrence of adverse events in patients with confirmed ACS. Interestingly MPO was found to add additional prognostic information to cardiac troponins. However the rate of major adverse events within 30 days in patients with MPO levels below selected cut-offs remained around 5% in both studies (160,161). Other studies have also demonstrated that MPO levels in patients with confirmed ACS help to predict prognosis (162-165), although one study reported that MPO levels did not help to predict mortality among 325 male patients who had been admitted to hospital with chest pain and were awaiting coronary angiography (166). Several studies have investigated the use of MPO in the ED population. The largest study, of 604 consecutive patients presenting to the ED with suspected cardiac chest pain, found that MPO levels predicted a diagnosis of ACS with sensitivity 65.7%, specificity 60.7%, PPV 53.3%, and NPV 72.2%. MPO levels also predicted adverse events, although 14.8% of patients with normal MPO and troponin levels still had a major adverse event within 30 days (167). A second study of 414 low risk patients who presented to the ED with suspected ACS found that MPO had a sensitivity of 71%, specificity 32% and negative likelihood ratio 0.89 (95% CI 0.26 – 2.05), suggesting that MPO was not a useful diagnostic test for AMI. However the study was underpowered as only seven patients were diagnosed with ACS (168). Among 140 consecutive ED patients with chest pain, MPO helped to diagnose AMI with sensitivity 92.3% (CI 95% 66.7% - 99.6%), specificity 40.2% (CI 95% 32.0% - 48.9%), PPV 13.6% (CI 95%

8.0% - 22.3%) and NPV 98.1% (CI 95% 89.9% - 99.9%). Again, however, the study was underpowered, with only 13 patients being diagnosed with AMI (169). Finally, MPO levels measured in 148 ED patients with chest pain were found to be significantly higher among those diagnosed with AMI. However MPO was both insensitive (13.9% of patients with MPO levels in the bottom quartile had AMI) and non-specific as a diagnostic marker for AMI (only 38.4% of patients with values in the highest quartile had AMI). MPO levels were found to be significant predictors of adverse events within 30 days (167). The available data suggest that MPO is unlikely to have sufficient sensitivity or specificity to be useful as an early diagnostic marker of ACS in the ED. However it may have a role for risk stratification and prediction of prognosis, particularly in troponin negative patients.

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

PAPP-A is a matrix metalloproteinase (MMP), one of a family of at least 25 proteases, of which 14 have been characterised in vascular cells. They are secreted by a variety of cells that are involved in the atherosclerotic process including foam cells, endothelial cells, T lymphocytes, mast cells and smooth muscle cells (170). They are upregulated in atherosclerotic plaque and play a pivotal role in the degradation of the fibrous cap that renders the plaque vulnerable to rupture (171,172). PAPP-A was originally detected in the serum in late pregnancy and has been used in first trimester screening for Down's syndrome (173). It is also abundantly expressed in unstable but not stable atherosclerotic plaques (54) and raised levels have been shown to correlate with complex coronary stenoses on angiography (174). A small case control study involving a total of 69 patients found that PAPP-A levels were significantly higher in patients with AMI or unstable angina compared to patients with stable angina and healthy controls without coronary disease (54). PAPP-A has been investigated as a potential early marker of AMI, with mixed results. A study of 346 patients who presented to the ED with chest pain found that PAPP-A levels were significantly higher in those patients who were diagnosed with AMI (175). In a second study that included 415 patients admitted to a cardiology unit with suspected ACS, PAPP-A levels were also found to be significantly higher in those patients with AMI although the AUC was only 0.56, suggesting that PAPP-A is unlikely to be useful as a lone diagnostic investigation for AMI (176). Further, a case control study found no significant difference in PAPP-A levels between 80 patients with STEMI and 80 healthy controls (177). Finally, among 59 patients who presented to the ED with suspected ACS and were deemed to be at intermediate risk for having a significant coronary event, PAPP-A was found to be an independent predictor of a diagnosis of ACS (odds ratio 2.09), following adjustment for other clinical factors (178).

When tested at the time of presentation in the ED population, PAPP-A may help to predict cardiac events in the near future. In a subgroup of a large study involving 626 ED patients with chest pain, Heeschen et al found that PAPP-A predicted adverse events with an adjusted odds ratio of 2.32 (179). In an ED population of 136 patients with suspected ACS but negative troponin I, Lund et al found PAPP-A to be an independent predictor of adverse cardiac events at six months, albeit with a sensitivity of only 54%, specificity 75%, PPV 30% and NPV 15% (180). In a study of 364 ED patients with suspected ACS, Laterza et al reported that PAPP-A predicted adverse events at 30 days with a sensitivity of 66.7%, specificity 51.5%, PPV 12.6% and NPV 93.6%. Thus for every 100 patients discharged and reassured on the basis of a negative PAPP-A level, three would have an adverse cardiac

events within 30 days (175). Finally, among 422 patients who presented to the ED with chest pain but had neither troponin elevations nor ECG abnormalities, PAPP-A was found to be a significant predictor of adverse events after a median of 60 weeks follow up, although this was not significant once other factors had been taken into account (including a clinical risk score, exercise tolerance testing and plasma levels of other biomarkers) (181). The available evidence suggests that PAPP-A levels alone are unlikely to be sufficient to enable early diagnosis of AMI in the ED or to accurately identify a population of patients who are at sufficiently low risk of adverse events to affect clinical practice.

3.4 Coagulation markers

3.4.1 D-dimer

D-dimer is a degradation product of cross-linked fibrin. Its presence indicates both thrombus formation and subsequent endogenous fibrinolysis, thus confirming that both thrombin and plasmin have been generated (182). It is a sensitive tool for exclusion of venous thromboembolism in the low risk group (183). In ACS plaque rupture or erosion is followed by exposure of the procoagulant lipid core to circulating blood with ensuing thrombus formation. As coronary thrombus precedes myocardial necrosis, it is possible that coagulation markers such as D-dimer are sensitive markers of ACS, potentially rising earlier than markers of myocardial necrosis including troponins. Elevated D-dimer levels in apparently healthy males have been shown to predict the future occurrence of AMI, ACS and coronary heart disease (121,184,185). Further, patients in whom the first presentation of coronary heart disease is with AMI may have higher D-dimer levels than patients who first present with stable angina (186). A weak but statistically significant correlation has been demonstrated between plasma D-dimer levels and severity of coronary disease on angiography in patients with unstable angina (187,188). In a cohort of 54 patients who were diagnosed with unstable angina and underwent coronary angiography, D-dimer levels (cut-off 270ng/ml) predicted significant coronary disease on angiography with sensitivity 70%, specificity 50%, PPV 86%, NPV 72%. By lowering the cut-off to 200ng/ml sensitivity increased to 95% but specificity dropped to 20% (189).

Several studies have demonstrated that patients with ACS have elevated levels of D-dimer when compared to controls with stable angina or no coronary disease (139,190,193). Plasma D-dimer level has also been shown to be a significant predictor of long-term mortality (after a median of 29 months follow up) in 320 patients with a diagnosis of NSTEMI-ACS (194), although a separate study of 358 patients with NSTEMI-ACS found that D-dimer did not predict the occurrence of adverse events (death, AMI, revascularisation or hospital admission for acute heart failure) within six months (hazard ratio 1.26, 95% CI 0.79 – 2.02) (195). Among 257 patients D-dimer levels (cut-off 500ng/l) at the time of admission (mean 160 minutes from symptom onset) diagnosed AMI with sensitivity 65%, specificity 80%, PPV 36% and NPV 93%, although the study utilised an outdated gold standard (incorporating CK-MB levels) for the diagnosis of AMI. D-dimer levels were found to be significantly higher in patients who were diagnosed with ischaemic pain, AMI and unstable angina (196). Another study of 184 patients who presented to the ED with suspected cardiac chest pain showed that D-dimer levels taken at the time of presentation were on average 111% higher in patients who were diagnosed with ACS compared to those who were not. D-dimer (at a cut-off of 1mg/l) had a sensitivity of 18% in order to achieve a set specificity of

92%, although the implications of accepted a more conventional, lower D-dimer cut-off were not evaluated (197). In 102 patients who presented to a Brazilian ED, D-dimer levels at the time of ED presentation were significantly higher in patients who had a troponin T $>0.01\text{ng/ml}$ at the time of presentation compared with patients whose troponin T was $<0.01\text{ng/ml}$. Unfortunately the results of 12-hour troponin testing were not available for analysis in this study, precluding evaluation of true diagnostic performance for AMI (198). The largest study to have investigated the use of D-dimer for the diagnosis of AMI in ED patients included a total of 741 patients who presented to the ED with suspected AMI. In that study, plasma D-dimer levels measured 12-24 hours after arrival at the ED had an AUC of 0.734 (95% CI 0.715 – 0.753) for predicting a troponin T result of $>0.03\text{ng/ml}$. At a cut-off of $500\mu\text{g/l}$ D-dimer had a sensitivity of 95%, specificity 27%, PPV 92% and NPV 41% (199). Finally, in a study of 432 patients who presented to the ED with suspected ACS D-dimer levels measured at the time of ED presentation did not help to predict the occurrence of adverse events (death, AMI, revascularisation, recurrent ACS or hospital admission with congestive heart failure) after 42 days of follow up (odds ratio 1.3, 95% CI 0.4 – 4.5, at a cut-off of $500\mu\text{g/l}$).

The evidence suggests that D-dimer is unlikely to be useful as an early marker of AMI when used alone in the ED population and at present the evidence for the use of D-dimer as a prognostic marker is also sparse. Future research into this biomarker must focus upon evaluating its potential value as part of a multimarker strategy.

3.5 Markers of ventricular stress

3.5.1 Brain Natriuretic Peptide (BNP)

BNP was first isolated from porcine brains but it has since been recognised as a cardiac hormone synthesised predominantly by the ventricles in response to ventricular wall stress. Together with atrial natriuretic peptide, which is secreted primarily by the atria, BNP belongs to the natriuretic peptide family that is involved in cardiac homeostasis. Biological effects include diuresis, vasodilatation, inhibition of the renin-aldosterone system and of cardiac and vascular myocyte growth (200). BNP is known to be a marker of acute and chronic left ventricular dysfunction and may be useful for the ED diagnosis of the former (201,202). It has been used as a marker of left ventricular systolic dysfunction following AMI, where it provides prognostic information (203). BNP is also expressed in ischaemic human myocardium and plasma levels may rise during periods of ischaemia (204-208). A number of studies, that together have included a total of 5159 patients, have demonstrated that BNP level acts as a strong predictor of mortality at seven days, 30 days, six months and 10 months in patients with confirmed ACS (208-214). Other studies have shown that BNP levels help to predict all adverse cardiac events, both during the index hospital admission and at follow up after up to 1 year (215-217). BNP levels have also been shown to help predict the development of congestive heart failure when measured in patients with both STEMI and NSTEMI-ACS (218-219). In addition to having prognostic value, there is evidence that BNP may assist in the diagnosis of ACS. Several small case control studies have demonstrated higher BNP levels in patients with AMI (220-222) and unstable angina (223,224) when compared with controls. There is some evidence to suggest that BNP levels may, in fact, correlate with infarct size (225). However, among 1676 patients with confirmed NSTEMI-ACS only 15.6% of patients had BNP levels above 80pg/ml . Indeed only 25.2% of

patients with NSTEMI had BNP levels above 80pg/ml, suggesting that BNP, at least at the stated diagnostic cut-off, may have limited sensitivity for these diagnoses (211).

In a study of 100 patients who were admitted to a Medical Admissions Unit with suspected cardiac chest pain, BNP (diagnostic cut-off 5pg/ml) helped to diagnose AMI with sensitivity 88.6%, specificity 78.6%, PPV 75%, NPV 89.6% with an AUC of 0.868. BNP was significantly more sensitive but less specific than troponin T when used at the time of admission to the unit. By combining BNP and troponin T performance improved (sensitivity 95.4%, specificity 76.8%). Unfortunately, however, this study had significant weaknesses as the primary outcome (discharge diagnosis of cardiac pain) could not be objectively verified through use of a gold standard, the study was retrospective and no follow up data was provided (226). Several studies have investigated the diagnostic and prognostic value of BNP levels in the ED population. Among 631 consecutive patients who presented to the ED with suspected cardiac chest pain with symptom onset <12 hours, BNP levels at the time of admission were found to be significantly higher among patients who were ultimately diagnosed with AMI (227). For predicting a diagnosis of AMI, BNP had an AUC of 0.710. Using a cut-off of 100pg/ml BNP predicted AMI with sensitivity 70.8%, specificity 68.9%, PPV 22.7%, NPV 94.8%, positive likelihood ratio 2.28 and negative likelihood ratio 0.42. When combined with CK-MB and troponin I, the presence of any raised biomarker for a diagnosis of AMI performed with sensitivity 87.3%, specificity 65.7%, PPV 27.0%, NPV 97.3%, positive likelihood ratio 2.55 and negative likelihood ratio 0.19. This suggests that, had BNP been introduced into clinical practice, this would have enabled the early detection of an additional 22 AMIs that could not otherwise have been recognised at the time of admission. However this would come at a cost of 163 false positive diagnoses (227). In a retrospective analysis of 546 patients who presented to the ED with suspected cardiac chest pain, a point-of-care BNP test was found to have an AUC of 0.755 for a diagnosis of AMI. At a cut-off of 100ng/l, BNP sensitivity was 66.7%, specificity 71.3%, PPV 17.1%, NPV 96.0%, positive likelihood ratio 2.32 and negative likelihood ratio 0.47. However the study had significant weaknesses. Clinicians were not blinded to BNP results, the study was subject to significant verification bias as only a minority of patients with normal point of care tests underwent subsequent gold standard troponin testing and, for those who did undergo troponin testing, an outdated troponin cut-off was used to diagnose AMI (228). Another study prospectively recruited 306 patients who presented to the ED with suspected cardiac chest pain. BNP was measured using two separate assays at the time of admission. The AUC of each assay for a diagnosis of ACS was found to be less than 0.6. BNP levels were found to be significant predictors of adverse events after 30 and 90 days but, again, the AUC was less than 0.7 for each assay (229).

Finally, in another prospective cohort study, 426 patients who presented to the ED with suspected cardiac chest pain had BNP levels measured at the time of presentation. The AUC of BNP for diagnosis of AMI, diagnosis of ACS and occurrence of adverse events (death, AMI or coronary revascularisation) within 30 days was 0.766, 0.691 and 0.675 respectively. The authors incorporated BNP into a multimarker strategy that also included CK-MB, myoglobin and troponin I. Using serial estimations at the time of ED presentation and 90 minutes later, this multimarker panel had a sensitivity of 97.4% (95% CI 86.5 – 100.0%), specificity 47.8% (42.7 – 52.9%), PPV 15.8% (11.5 – 21.1%) and NPV 99.5% (97.0 – 100.0%) for diagnosis of AMI. For a diagnosis of ACS performance was slightly worse, with a sensitivity

of 88.1% and NPV 92.9% and for predicting adverse events within 30 days the panel performed with sensitivity 88.5%, specificity 43.9%, PPV 18.0% and NPV 96.5% (230). The available evidence suggests that BNP may have value as a diagnostic and prognostic marker in patients who present to the ED with suspected ACS. However it is readily apparent that BNP is unsuitable for use as a lone biomarker in this situation. Future research is still necessary in order to define the potential role of BNP as part of a multimarker strategy.

3.6 Novel markers of myocardial necrosis

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

H-FABP is a cytoplasmic protein that is abundantly expressed in human myocardial cells. It is also found in much lower concentration in skeletal muscle, kidney and brain tissue (231). Experimental data first suggested that H-FABP may be a potential novel biomarker of AMI as early as 1988 (232). In 1991 Tanaka et al reported elevated H-FABP levels in patients with AMI, with levels peaking earlier than CK-MB (233). Despite interest in H-FABP as an early marker of AMI for many years it has never gained widespread acceptance for use in clinical practice.

Five studies have investigated the diagnostic utility of H-FABP when used for the diagnosis of AMI at the time of presentation to the ED (234-238). Four of these studies utilised qualitative assays that are available as point of care tests. All five studies had significant weaknesses, with most studies employing now outdated gold standards for AMI diagnosis and being subject to significant verification bias. The data reporting in the small study by Alashemi et al precludes calculation of total sensitivity and specificity (235). If the remainder of the results are pooled this would give H-FABP a total sensitivity of 70.0% (95% CI 66.0 – 73.7%) and a total specificity of 80.7% (78.1 – 83.0). Excluding the study by Ghani et al, in which a quantitative assay was used, the pooled sensitivity is 76.8% (72.6 – 80.5%), pooled specificity 72.5% (68.9 – 75.8%), pooled PPV 65.8% (61.6 – 69.8%) and pooled NPV 82.0% (78.6 – 85.0%). The positive likelihood ratio would be 2.79 and negative likelihood ratio 0.32. It should be acknowledged that pooling results in this manner does not take account of heterogeneity and is inferior to a formal meta-analysis. However, assuming that these statistics are a true reflection of the performance of H-FABP, if we were to apply the test in a typical United Kingdom ED population with suspected cardiac chest pain who have a prevalence of AMI of approximately 18%, the post-test probability of AMI given a normal H-FABP test would be 6.6%. This provides similar predictive value to a normal ECG in this cohort (239) but is still far from excluding the diagnosis.

4. Multimarker strategy

Previous work from our own group, investigating heart fatty acid binding protein (H-FABP), CK-MB, myoglobin, cTnI, BNP, D-dimer, neutrophil gelatinase associated lipocalin (NGAL) and myeloperoxidase, in 705 patients presenting to the emergency department demonstrated that no single biomarker could exclude AMI. However multivariate analysis identified cTnI and H-FABP as an optimal biomarker combination. When combined with clinical risk stratification, the strategy exhibited a sensitivity of 96.9%, specificity of 54% and negative predictive value of 98%. [240].

The utility of a multimarker strategy must also be considered in the light of developments in assays. We have evaluated a high sensitivity troponin T assay in 915 patients, where the results demonstrated a negative predictive value of 99.4%. [241]

5. Conclusion

In recent years there has been substantial and growing interest in a number of novel biomarkers that may facilitate early diagnosis of AMI and enhanced risk stratification of patients who present to the ED with suspected ACS. Promising markers of each step in the pathophysiological evolution of an acute coronary syndrome have been identified, each of which may be detected in the peripheral circulation. Unfortunately it is unlikely that any of these biomarkers will be as cardio-specific as the cardiac troponins and, despite considerable research, there is at present no single biomarker that can be used to confirm or exclude a diagnosis of ACS in the ED. If there is to be a future for novel biomarkers in the ED diagnosis of ACS, therefore, future research must focus on incorporating levels of multiple biomarkers and available clinical information into a risk score or clinical decision rule, in order that the predictive value of individual biomarkers and clinical features may be combined and enhanced.

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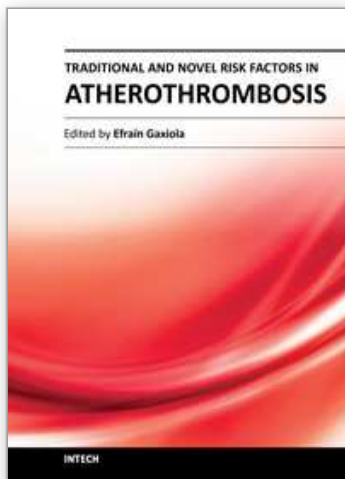
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Atherothrombosis has reached pandemic proportions worldwide. It is the underlying condition that results in events leading to myocardial infarction, ischemic stroke and vascular death. As such, it is the leading cause of death worldwide manifested 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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