Despite effective blood pressure and cholesterol-lowering drugs, atherosclerotic cardiovascular disease remains the major morbidity and mortality causation in developed countries. The disease-causing lesions originate from benign-looking, non-occlusive, lipid-laden plaques in childhood (fatty streaks) on the internal surface of arteries. These progress to enlarged plaques (atheromas) characterised by accumulation of lipids, chronic inflammatory cells, connective tissue and an overlying fibrous plaque. Their progression leads to stenosis or occlusion of small and medium-sized arteries.

Atherosclerotic plaques are also described in terms of complexity and resultant instability. Complexity depends on degree of inflammatory cell infiltration, lipid deposition, calcification and intraplaque haemorrhage. Such complex plaques are unstable and prone to rupture. There is therefore an inflammatory mechanism to plaque instability. Plaque rupture exposes the thrombogenic atheromatous core which leads to sudden thrombotic occlusion of small to medium-sized arteries, such as coronary ones, with familiar serious consequences of unstable angina, myocardial infarction, or sudden death. Stable atherosclerotic lesions are slow-growing, less complex and have dense fibrous caps. They allow a collateral circulation time to develop, are less likely to rupture and are therefore less threatening.

Aortic atherosclerotic plaques are mainly confined to its abdominal portion. The aortic lumen is too wide for ruptured plaques to cause aortic thrombotic occlusion, but they may weaken the arterial wall and cause abdominal aortic aneurysm. Intermittent showers of tiny thrombi from ruptured aortic plaques are likely to end up in renal and leg skin arterioles, eventually leading to renal failure and lower limb ischaemic problems.

Atherosclerosis is now recognised to be fundamentally an inflammatory disease. The inciting event is dysfunction of the arterial inner lining cells (endothelium), leading to inflammatory cell infiltration and release of proinflammatory cytokines within the arterial wall. Low density lipoproteins (LDL) are thought to be more likely to be trapped in the lesion when oxidised. Smooth muscle cells of the arterial wall are triggered to migrate into the plaque and to produce a collagen-rich matrix and a fibrous plaque.

Cardiovascular risk factors promote atherosclerosis by damaging the endothelium – the latter is involved in regulating vascular tone, inflammation and thrombosis. Healthy endothelium releases nitric oxide (NO) to induce vasodilatation in response to, say, platelet aggregation. NO also reduces expression of adhesion molecules to prevent macrophage infiltration and damps vascular smooth muscle cell proliferation. These are protective mechanisms against atherosclerosis. Cardiovascular risk factors such as smoking, hypertension, diabetes, obesity and hypercholesterolaemia induce endothelial dysfunction through mechanisms such as free radical oxidation, haemodynamic strain and genetic pathways. Dysfunctional endothelial cells (EC) acquire a

“Hardening of the arteries” and its serious complications have been studied for well over a hundred years. The following is an outline of recent advances in our understanding of its causation, progression, diagnosis and some aspects of management.
proinflammatory phenotype, expressing chemokine receptors, decreasing NO production, and dysregulating cytoskeletal and junctional proteins5-3.

A non-invasive ultrasound-based test of endothelial-dependent vasomotion, termed "flow-mediated dilatation", measures brachial artery diameter change and has been used to detect early endothelial dysfunction2. However, it requires highly trained operators, expensive equipment, and minimisation of environmental and physiological influences.

One can biochemically assess EC dysfunction with use of EC markers. Many candidates, such as NO, inflammatory cytokines, adhesion molecules, thrombosis regulators and markers of endothelial repair have been assessed, but have not proven to be clinically viable2. Endothelial microparticles (EMP), which are small vesicles released during cell activation or injury, are elevated in patients with atherosclerosis5. Since EMPs can be quantified, they are promising candidates for clinical testing.

Lipids within atheromatous plaques are susceptible to oxidation by several enzymes. Oxidised LDLs (oxLDL) are cytotoxic to arterial endothelium. Macrophages migrate from bloodstream towards accumulated lipid in plaques, take up LDLs to degrade them, but oxLDL are resistant to degradation. Diets deficient in antioxidant vitamins and minerals may therefore accelerate oxLDL accumulation in plaques and atheromatous progression.

Besides reducing LDL concentrations by blocking cholesterol synthesis, statins also inhibit inflammatory pathways and increase NO production, which enhance endothelial protection4. They also lower cytokine production and inhibit recruitment, migration and cell adhesion to endothelium4.

The role of high density lipoproteins (HDL) on atherosclerosis has received attention. Torcetrapib, a cholesteryl ester transfer protein inhibitor, increases HDL and decreases LDL cholesterol levels but does not significantly reduce coronary atheroma volume4. Another recent approach involves synthesizing fusion proteins of oxLDL binding receptors and the Fc domains of immunoglobulins5. Zeibig et al (2011) created a soluble dimeric fusion protein Fc-CD68 capable of specific high-affinity binding with oxLDL in atherosclerotic plaques, reducing oxLDL uptake. This compound reduced lipid deposition by one third and aortic plaque extension by nearly 50%6.

Some American cardiologists have produced clinical evidence that atherosclerotic progression can be halted, and to some extent reversed, by dietary modification and lifestyle changes (exercise and stress management) alone, and suggested that up to 90% of cardiac surgical interventions may potentially be unnecessary7. Many patients, however, will not modify their diet and change their lifestyle. The quest for more effective and safer anti-atheromatous drugs will therefore remain clinically and commercially important, not least because current statins are associated with side-effects in 10-15% of patients. They inhibit production of coenzyme Q10, which may increase risk of heart failure, and some American cardiologists recommend coQ10 supplements with statins8.

Inflammation is a complex immune response to pathogens or other tissue damage. Clinicopathological and experimental studies have shown that a large variety of inflammatory cells and cytokines are involved at all stages of atherosclerosis. There have also been recent claims of an association between poor oral hygiene with risk for atherosclerotic cardiovascular disease, possibly because bacteria (or bacterial proteins), released into the bloodstream from inflamed gums might promote inflammation within atherosclerotic lesions9.

Despite our greater understanding of atherosclerosis pathogenesis, many challenges remain in its diagnosis and management. Coronary angiography is still the gold standard for identifying risk lesions, although detection of subtle but significant plaques is problematic. Novel imaging modalities have the potential to provide valuable information about extent of lesions in a relatively non-invasive manner. These include intravascular ultrasonography, thermal imaging, and high-resolution magnetic resonance imaging10,11. Magnetic resonance and nuclear imaging that harness molecular mediators of atherogenic inflammation as targets have generated considerable interest12. However, these modalities are not yet ready for clinical application.

Besides elevated LDL, high glucose13 and triglycerides14 (and low HDL15) are associated with sharply higher atherosclerotic disease risks. Low DHEA (dehydroepiandrosterone-sulfate) blood levels are also associated with higher rates of endothelial dysfunction and heart attack16.

Biomarkers are measurable parameters which can serve in diagnosis, treatment follow-up, and prediction of disease progress. Due to the pivotal role of inflammation in atherosclerosis, C-reactive protein (CRP), measured by a highly sensitive assay (hsCRP), has gained attention17. In a study reported in 2002, women with elevated hsCRP were twice as likely to suffer a heart attack or stroke compared to women with high LDL levels18. Another study demonstrated that individuals with an elevated hsCRP have high vascular risk, even when cholesterol levels are considered within normal range19. However, elevated hsCRP is also a marker of cancer. Many other biomarkers associated with progressive atherosclerosis have been investigated – lipoprotein-associated phospholipase A2 (PLAC Test) is the only one currently approved by the FDA14. However, It will not distinguish between unstable plaque in coronary, carotid or aortic locations. Although none of these biomarkers have become routine in clinical practice, they have the potential of becoming so, because around 50% of heart attacks and most strokes occur in people with cholesterol levels within normal limits.

A region on chromosome 9 has been identified as being associated with cardiovascular diseases and genetics may therefore play a role in predicting atherosclerosis risk12. Considerable investigative effort in years to come is still necessary, and clinicians need improved, preferably non-invasive, tools to identify and manage patients with clinically significant atherosclerosis. 

References from thesynapse.net