Atherosclerosis: Pathogenesis, Clinical Features and Treatment

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Atherosclerosis is a chronic inflammatory disease of the inner wall of large- and medium-sized arteries. The condition often begins in infancy, but takes several decades to develop the full-blown cholesterol-rich fibrotic plaques characteristic of the mature disease and worldwide, more people die of the complications of atherosclerosis than of any other cause.

Advanced article

Article Contents

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Introduction

Worldwide, more people die of the complications of a disease that has been a companion of mankind since antiquity than of any other cause. This disease is called atherosclerosis. Macroscopic and microscopic evidence of atherosclerosis has been found in the aortas and the carotid, coronary and femoral arteries of mummies from Egypt, North America and China dating from around 3000 BC to AD 400 (Cullen *et al*., 2005). This is surprising because life expectancy even of the wealthier classes in Egypt was in general only 30–35 years, and even though some meat was consumed, the diet of these people was mainly vegetable. Moreover, tobacco consumption was unknown in ancient Egypt although alcohol was available. It is clear therefore that atherosclerosis is an ancient disease and that its pattern has always been the same irrespective of diet and life style. Nevertheless, industrialization has greatly increased the incidence of atherosclerosis and its complications, and it is accepted that features of the modern life style, in particular cigarette smoking, lack of exercise and a diet rich in animal fats are important risk factors for the disease. **See also**: Atherosclerosis

Historic Background

Leonardo da Vinci (1452–1519) was probably the first to describe the macroscopic appearance of atherosclerotic arteries. When he illustrated the arterial lesions in an elderly man at autopsy, he suggested that the thickening of the vessel wall might be due to 'excessive nourishment' from the blood. In general terms, Leonardo da Vinci's conclusion is still valid today.

The term 'arteriosclerosis', a synonym of the term 'atherosclerosis', was introduced by the German-born French surgeon and pathologist Johann G.C.F.M Lobstein (1777–1835) many years later in 1833. Lobstein considered arteriosclerosis as a hardening of the arterial wall caused by the remodelling of the tissue in response to ageing, metabolic dysfunction and haemodynamic stress.

The German physician Felix J. Marchand (1846–1928) coined the term 'atherosclerosis' (from the Greek words '*athere*' meaning gruel and '*scleros*' meaning hard) to emphasize the macroscopic features of the disease. In the English language, the word 'atherosclerosis' is often used synonymously with arteriosclerosis.

The word 'atheromatosis' was coined by the London surgeon Joseph Hodgson in 1815 to describe the fatty degeneration characteristic of atherosclerotic arteries. This term is still used as a synonym of arteriosclerosis or atherosclerosis.

Rudolf Virchow (1821–1902), a German pathologist and statesman, was the first to introduce the idea of atherosclerosis as an inflammatory process; a concept that is still valid today and is at the time of writing a field of very active research. **See also**: Virchow, Rudolf Carl

Pathophysiology

Atherosclerosis is an inflammatory disease of the inner wall of large- and medium-sized arteries (see **Figure 1**), including the aorta, the carotid arteries, the coronary arteries and the arteries of the lower extremities (Cullen *et al*., 2005). The earliest lesions of atherosclerosis appear during infancy, but it usually takes several decades to develop the full-pronounced atherosclerotic plaque, which is characterized by a large necrotic fatty core covered by a thin fibrous cap consisting of extracellular matrix proteins such as collagen and small numbers of matrix-producing smooth muscle cells.

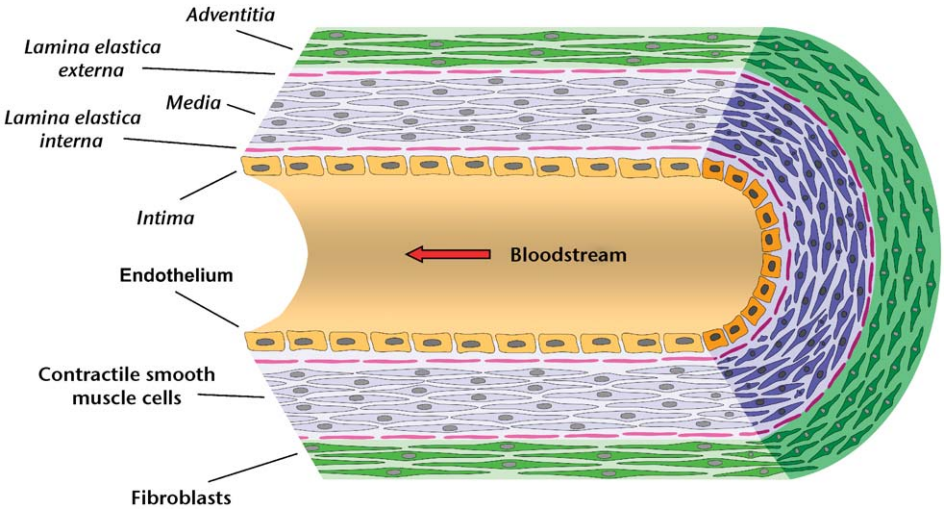

Figure 1 Morphology of a normal artery. A healthy artery consists of three tissue layers: First, the endothelium (orange) which forms a barrier between the subendothelial tissue and the blood. It is a continuous layer covering the complete surface of all arteries. As a selective barrier, it regulates the exchange of compounds between blood and underlying tissues. Second, the media (light blue) consisting of contractile smooth muscle cells which mediate vasoconstriction and vasodilatation to maintain blood pressure. Third, the adventitia (green) which is comprised of mostly fibroblasts. It embeds the artery in the surrounding tissue. The different tissues are separated by elastic laminas termed *lamina elastica interna* and *externa* (pink).

The 'response-to-injury hypothesis', first proposed by the Viennese pathologist Karl von Rokitansky (1804–1878) in the mid nineteenth century and rediscovered in 1973 by the American pathologists Russell Ross (1929–1999) and John A. Glomset, is the model that is most widely used at present to explain the appearance of atherosclerosis. According to this hypothesis, atherosclerosis begins with injury to the layer of cells lining the artery (the endothelium) caused by chemical, mechanical or immunological toxins. More recent work, however, emphasizes a dysfunction rather than an injury of the endothelium as being the trigger of atherosclerosis (**Figure 2a**). It is thought that such endothelial dysfunction may be caused by modified fat/protein complexes (lipoproteins) from the blood, free radicals, toxic substances, high blood pressure, diabetes mellitus, infectious agents such as herpes viruses or *Chlamydia pneumonia*, or by a combination of these factors. **See also**: Chlamydiae; Endothelial Cells: Immunological Aspects; Herpesviruses (Human); Lipoprotein Metabolism: Structure and Function; Lipoproteins: Genetic Disorders

Whatever its cause, endothelial dysfunction is characterized by a loss of endothelial-derived vasodilation, endothelial activation and increased permeability of the endothelial barrier. The impairment of vasodilatation is a consequence of a reduced bioavailability of vasodilators, in particular nitric oxide, and an increase in endothelium-derived vasoconstrictors such as endothelin. Activation of the endothelium is characterized by a pro-inflammatory, proliferative and procoagulatory state, which is accompanied by an increased expression of adhesive glycoproteins such as P- and E-selectin and adhesion molecules such as vascular cell-adhesion molecule 1 (VCAM-1) and intracellular cell-adhesion molecule 1 (ICAM-1), which in turn promote the adhesion of leucocytes (in particular monocytes and T lymphocytes) to the arterial wall (**Figure 2b**). **See also**: Cells of the Immune System; Immunological Adhesion and Homing Molecules; Lymphocytes

As a consequence, adherent monocytes migrate into the subendothelial space by a process called diapedesis under the influence of inflammatory and chemoattractant molecules, in particular the chemokine macrophage chemoattractant protein-1 (MCP-1) and other mediators such as interleukin 8 (**Figure 2c**). Under the control of several cytokines, these monocytes differentiate into macrophages, which accumulate within the subendothelial tissue. Macrophages constitute an ancient part of our immune system and express a number of scavenger receptors such as scavenger receptor A, scavenger receptor B1 (SR-B1), cluster of differentiation (CD) 36 and CD68 on their surface. These proteins recognize polyanionic macromolecules and may have physiological functions in the recognition and clearance of pathogens and apoptotic cells. **See also**: Macrophages

Owing to the increased permeability of dysfunctional endothelium, lipoproteins – in particular low-density lipoproteins (LDL) – from the blood enter the subendothelial tissue, where they are retained as components of the extracellular matrix. Following retention, these lipoproteins are modified either by chemical means (in particular, through oxidation) or by enzymatic activity. Macrophages, endothelial cells and smooth muscle cells, which are present within the endothelial space, have been shown to promote the oxidation and enzymatic modification of

LDL *in vitro*. Macrophages, for example, produce lipoxygenases, myeloperoxidase, inducible nitric oxide synthase and nicotinamide-adenine dinucleotide phosphate reduced (NADPH) oxidases, all enzymes that can oxidize LDL and that are expressed within the human atherosclerotic plaque.

In addition to their role in the immune system alluded to above, macrophage scavenger receptors are thought to play an important role in the development of atherosclerosis by binding and taking up modified LDL by a process called receptor-mediated endocytosis. In contrast to the physiological uptake of nonmodified native LDL by the

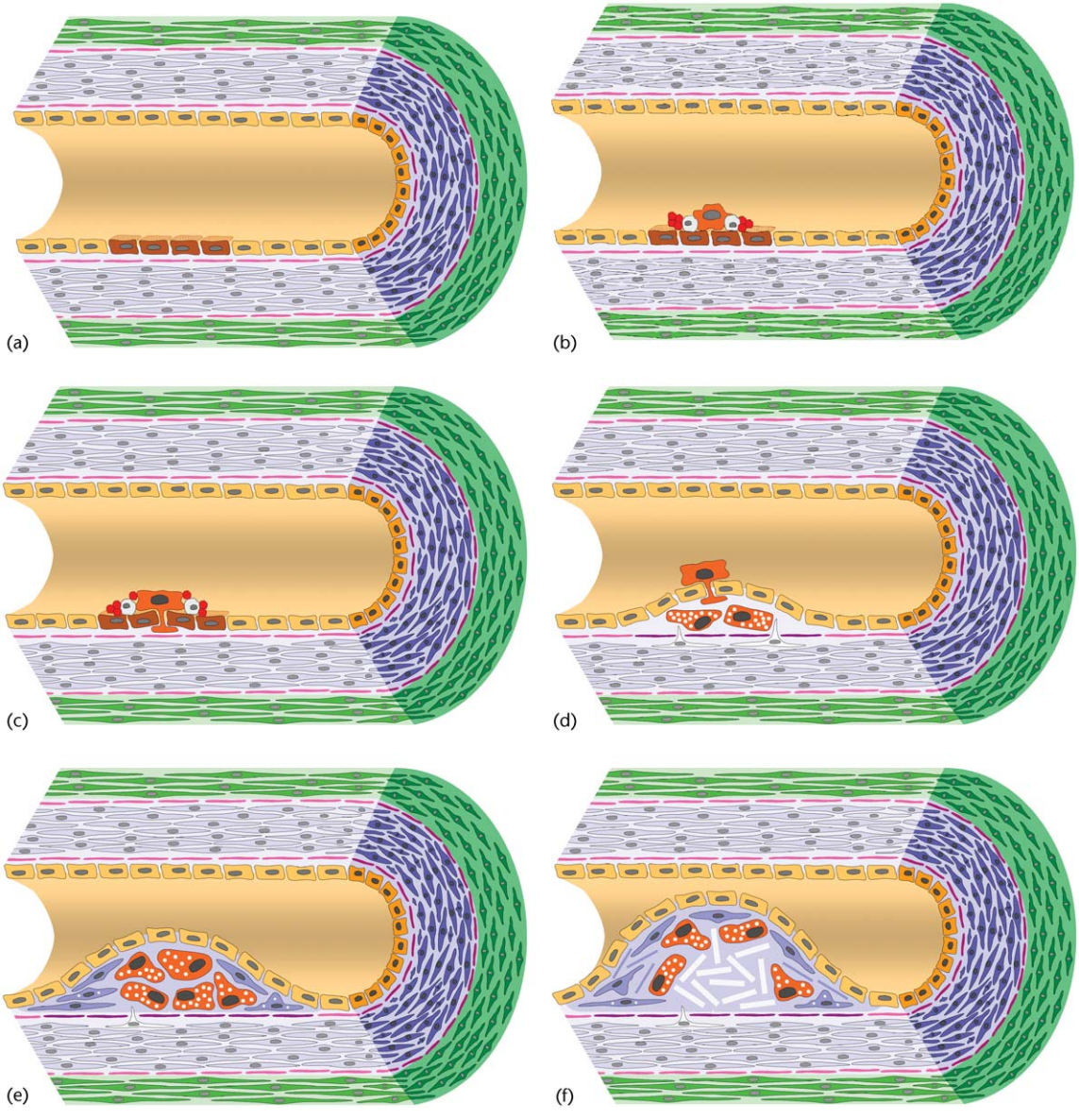

Figure 2 Pathogenesis of atherosclerosis. (a) Endothelial dysfunction (brown). (b) Adhesion of blood leucocytes (T lymphocytes, white; monocytes, orange) and thrombocytes (red). (c) Immigration of adhered monocytes into subendothelial areas (diapedesis). (d) Immigration of smooth muscle cells (white) from the media (light blue) into subendothelial tissues (adaptive intimal thickening) and foam cell formation (formation of an atheroma). The immigration of smooth muscle cells is accompanied by a switch to a synthetic phenotype (purple). Hence, subendothelial deposition of extracellular matrix material (purple) is increased. (e) Thickening of the lesion by enhanced foam cell formation (white spots within the cells), immigration of smooth muscle cells and further deposition of extracellular matrix proteins (purple). (f) Formation of a fibrous cap (purple) and a necrotic lipid core (white). The latter appears because of the death of foamy macrophages. (g) Due to the synthesis of proteases by macrophages, the fibrous cap covering the lipid core is thinned. (h) Plaque rupture or erosion of the endothelium occurs. (i) The contact of blood with the subendothelial tissue activates the clotting cascade and a thrombus (red) is formed. The same colours as in **Figure 1** were used to distinguish between intima, media and adventitia.

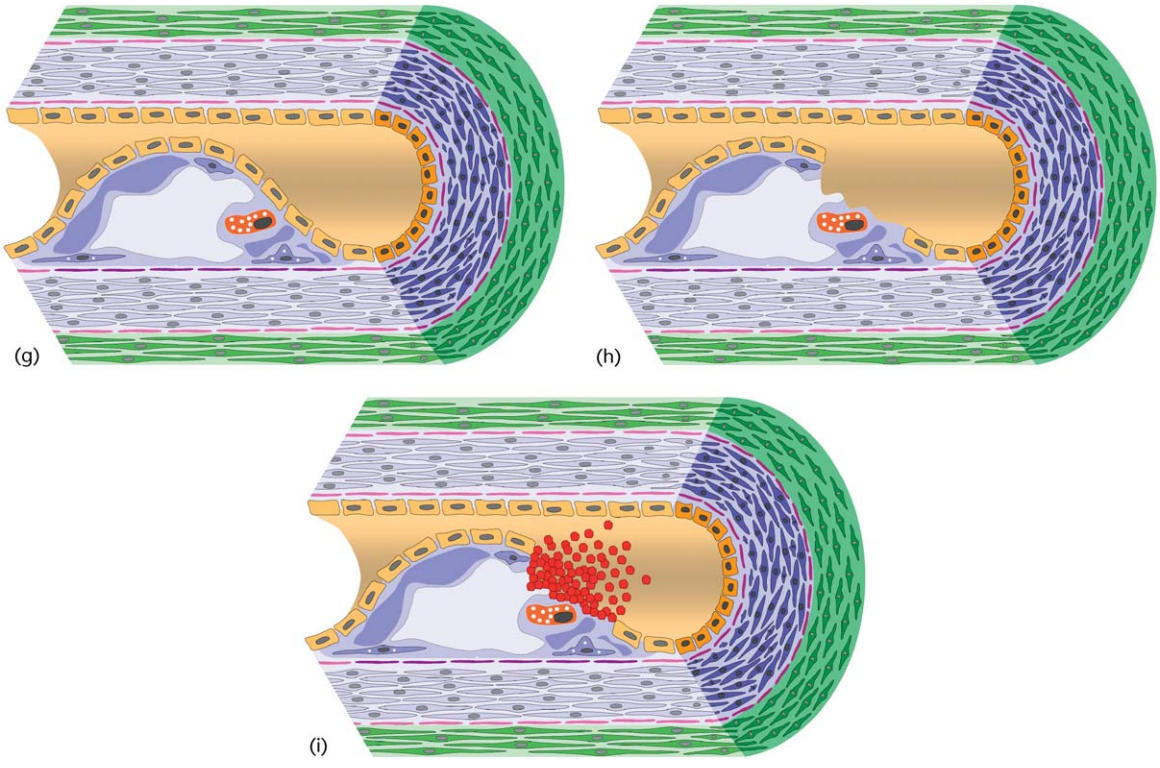

Figure 2 (*continued*)

LDL receptor, the uptake of modified LDL by the scavenger receptor is not subject to negative feedback regulation. Since macrophages, like all mammalian cells, are unable to break down cholesterol, this uncontrolled uptake of cholesterol via the scavenger receptor leads to massive accumulation of cholesterol within the cell. This problem is compounded by the fact that macrophages also ingest substantial amounts of cholesterol in the form of necrotic and apoptotic cells and cellular debris. Macrophages possess two mechanisms to counteract the problem of excess cholesterol. First, the cholesterol is stored as cholesteryl esters in cytosolic lipid droplets giving the macrophages a foamy appearance (**Figures 2d, 2e and 3**). Second, macrophages export cholesterol to lipid acceptors such as apolipoprotein A-I, apolipoprotein E or high-density lipoproteins (HDL) as part of a process called reverse cholesterol transport system that redistributes excess cholesterol from peripheral tissues to the liver. **See also**: Cholesterol and Vascular Disease; Clathrin-Coated Vesicles and Receptor-Mediated Endocytosis

If these mechanisms are overwhelmed, cholesterol builds up to toxic levels within the macrophage. This may impair the fluidity of the cell membrane and the function of signal proteins within it. In addition, cholesterol crystals or oxysterols may form within the cell triggering a physiological cell suicide programme called apoptosis or killing the cell in unregulated fashion by necrosis (**Figure 2f**). Although both apoptotic and necrotic macrophages are seen in human atherosclerotic lesions, the exact cause of macrophage death *in vivo* is not clear and may be regulated to other factors in addition to excess intracellular cholesterol. However it occurs, the death of cholesterol-laden macrophages results in the accumulation of large amounts of free cholesterol and cholesteryl esters within the arterial wall. Over the years, the continuous deposition of these lipids results in the formation of the large necrotic lipid core typical of advanced lesions.

Smooth muscle cells within the inner layer of the artery known as the intima also express scavenger receptors and take up modified LDL. Such smooth muscle cell-derived foam cells also contribute to the growth of atherosclerotic lesions, albeit to a much lesser extent than their macrophage-derived counterparts.

The consequences of endothelial activation are not restricted to the formation of foam cells. The activated endothelium also fails to inhibit the proliferation and migration of vascular smooth muscle cells. Together with other factors, this results in an immigration of smooth muscle cells from the muscular middle layer of the artery (media) into the subendothelial space (**Figure 2d**–**2f**). This process is accompanied by a switch in the nature of the smooth muscle cells. In the media, smooth muscle cells exhibit a phenotype characterized by an ability to regulate the vascular tone by contraction and a relatively low rate of

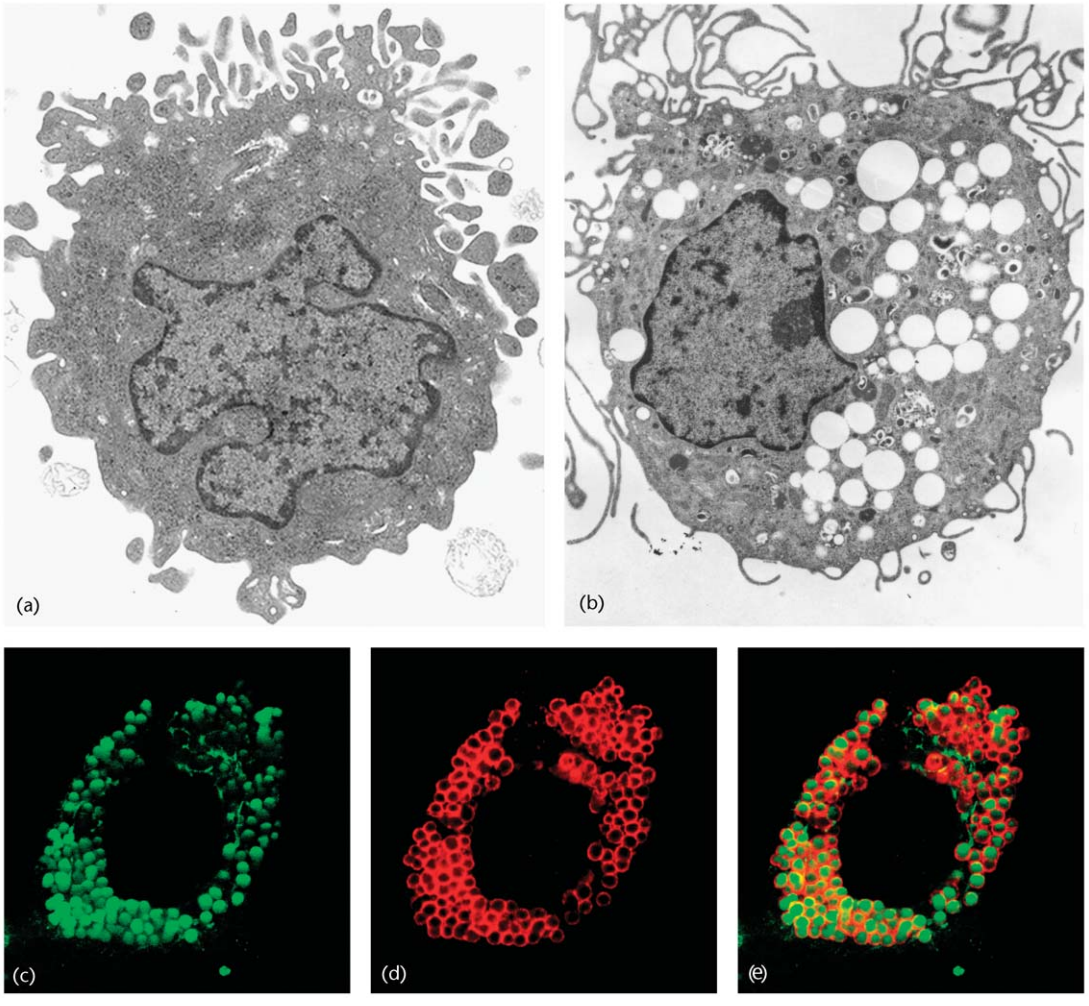

Figure 3 Foam cell formation of macrophages. (a) Transmission electron microscopic picture of a cultured primary human monocyte-derived macrophage. (b) Transmission electron microscopic picture of a cultured primary human macrophage-derived foam cell. The monocyte-derived macrophage was cultured in the presence of chemically modified LDL to induce foam cell formation. Lipid droplets appear white in the cytoplasm. The pictures were kindly prepared by Dr. Oliver Hofnagel and Prof. Dr. Horst Robenek (Leibniz Institute of Arteriosclerosis Research, Münster, Germany). (c) Fluorescence confocal laser-scanning microscopic picture of a human THP-1 macrophage-derived foam cell. The cell was cultured in the presence of chemically modified LDL. Left-hand-side: Green staining of neutral lipids using the dye BODIPY. Centre: Red staining of adipophilin, a protein that covers and pervades lipid droplets, using specific antibodies. Right-hand side: Merged picture of the BODIPY staining (green) and the adipophilin staining (red). These pictures are adapted from Robenek *et al.* (2005). Reproduced by permission of American Society for Biochemistry & Molecular Biology.

production of extracellular matrix proteins (contractile phenotype). The smooth muscle cells of the intima, by contrast, are characterized by a high rate of proliferation and by the synthesis of large amounts of extracellular matrix proteins such as collagens. Both processes – the immigration of smooth muscle cells into the subendothelial area and the synthesis of extracellular matrix proteins – are triggered by cytokines secreted by macrophages and foam cells within the lesion.

To sum up, the atherosclerotic thickening of the arterial wall is the result of two processes (**Figure 2g**): First, smooth muscle cells immigrate from the media into the intima where they start to proliferate and to produce extracellular matrix proteins which are deposited within the lesion. A subset of the intimal smooth muscle cells engulfs modified LDL forming foam cells. Second, monocytes infiltrate and mature into macrophages, which take up massive amounts of modified LDL. The death of the resulting foam cells leads to the accumulation of lipids and the formation of the necrotic lipid core. At a later stage of plaque progression another process may further contribute to lesion size. Rupture of the lesion occurs and results in the formation of a thrombus by activation of the clotting process. In some cases such thrombi may be reorganized and integrated into the lesion. **See also**: Blood Coagulation

However, the complications of atherosclerosis are not limited to the reduced lumen or the occlusion of arteries due to an increasing size of the lesions. In many cases, endothelial erosion or rupture of the atherosclerotic plaque occurs (**Figure 2h**). A consequence of endothelial erosion or plaque rupture is the formation of a thrombus, which is formed due to the activation of the clotting cascade when subendothelial tissue comes into contact with the circulating blood (**Figure 2i**). Thrombi may occlude the artery at the site of rupture or erosion, or they may float with the bloodstream into arteries with a smaller lumen than that of the artery where the thrombus was formed, which they may occlude either partially or completely. Such an occlusion reduces the supply of nutrients and oxygen to downstream tissues and will lead to their death if the process is severe and prolonged enough. In the case of coronary or cerebral arteries such occlusion leads to myocardial infarction and stroke respectively. **See also**: Stroke

It is not completely understood why rupture of the atherosclerotic plaque occurs, although it is thought to be at least partly due to macrophages within it producing large amounts of proteases which digest the extracellular matrix of the fibrous cap, causing it to tear.

Frequency and Clinical Importance

Atherosclerosis is a partly inflammatory, partly degenerative condition affecting the large- and medium-sized arteries. Most, perhaps even all adults develop atherosclerosis to some degree, so that the disease may be regarded as ubiquitous. The important question, therefore, is not its absolute prevalence, but the degree to which it causes clinically significant disease. This in turn is related not so much to the atherosclerotic process *per se* but to the complications it causes either by reducing the blood flow in the affected artery, a process termed ischaemia, or by provoking clotting of the blood in the affected vessel. These clots may remain at the site of their formation and are then called thrombi. Alternatively, they may break off in whole or in part and be carried with the blood flow to cause blockage at some distant location. Such moving blood clots are called emboli (plural of embolus). If a thrombus is not large enough to block the artery completely, it may cause no symptoms and gradually be incorporated into the atherosclerotic plaque. Indeed, many older atherosclerotic lesions show histological evidence of incorporated thrombi, so that this is probably the more likely fate of thrombi. However, if a thrombus is of sufficient size it may completely block (occlude) the artery in which it forms, cutting off blood flow in the affected vessel. If this is an end vessel exclusively supplying an area of tissue, then this area of tissue will be completely starved of oxygen and die in a process called infarction.

About 40% of all deaths in developed countries are due to cardiovascular disease, and most of these cardiovascular deaths are due to complications of atherosclerosis (see **Table 1** for data from Germany as an example of a Western developed country). In Germany, for example, about 250 000 people suffer a myocardial infarction every year. Despite great improvements in intensive care, about half of all persons suffering a first myocardial infarction will die within 4 weeks. A main reason for this is that in up to a half of all cases, a first myocardial infarction occurs 'out of the blue' without any warning symptoms whatsoever. These stark statistics underline the need for measures to prevent myocardial infarction from occurring in the first place. These include refraining from smoking, eating a balanced diet, taking regular exercise and avoiding being overweight. Treatment of other risk factors, in particular high cholesterol levels, high blood pressure or diabetes mellitus are also very important in reducing heart attack risk. As the world's population ages, and as many countries improve economically, the impact of atherosclerosis worldwide is set to increase dramatically in the next 30 years. A measure of this is that in 2003, infectious disease was for the first time in the history of mankind supplanted as the number one killer. This dubious distinction now goes to atherosclerosis.

Table 1 Ten most common causes of death in Germany in 2002, in percent, according to the Statistisches Bundesamt

Cause of death	Total
Chronic ischaemic heart disease	10.3[a]
Acute myocardial infarction	7.5[b]
Heart failure	5.9
Carcinoma of the lung	4.9
Stroke	3.9[c]
Colon carcinoma	2.4
Chronic obstructive lung disease	2.4
Pneumonia	2.2
Breast cancer	2.2
Diabetes mellitus	1.9

[a]Men: 9.3%; women: 11.1%.
[b]Men: 8.7%; women: 6.5%.
[c]Men: 2.9%; women: 4.8%.

Major Clinical Features and Complications

As noted above, many of the clinical features of atherosclerosis are due to the formation of a thrombus at the site of an atherosclerotic plaque. When this occurs in the heart, the result is a myocardial infarction, which is commonly known in the US as a 'coronary' and in Britain and its former colonies as a 'heart attack'. If the process occurs in the brain, the result is a stroke. More rarely, blockage of an artery supplying a lower limb, a kidney or part of the gut

may occur, resulting in death (necrosis) of these tissues also. A feature of atherosclerosis occurring particularly in the arteries of the neck is that many small emboli may be formed over that shoot into the brain causing temporary blockage of small brain arteries. This may lead to multiple small strokes (transient ischaemic attacks) that recover in a short space of time. Such transient ischaemic attacks require urgent attention, as they are often the harbingers of full-blown stroke. Finally, it has become clear in recent years that many cases of dementia in the elderly are not due to Alzheimer's disease, but due to diffuse atherosclerosis of the arteries of the brain, sometimes accompanied by multiple transient ischaemic attacks. This is termed vascular dementia.

Previously, it was thought that such clotting occurs mainly at the site of advanced disease. However, more recent research has shown that smaller atherosclerotic plaques termed 'culprit lesions' are more often associated with thrombotic events. These culprit lesions are metabolically active and are characterized by a soft lipid core covered by a fibrous cap. In most cases, the event leading to thrombosis appears to be a tear of the fibrous cap in a process called plaque rupture. This exposes the circulating blood to the interior of the atherosclerotic lesion, which triggers the clotting cascade in the blood. In some cases, it appears that thrombosis may occur even without rupture when there is a break in the layer of cells lining the artery at the location of an atherosclerotic plaque. Such a break in this layer of cells is termed superficial erosion.

Other important clinical features of atherosclerosis relate to the ability of some plaques to reduce flow in the affected artery so that the oxygen supply of the downstream tissue is precarious. An oxygen supply that is adequate under resting circumstances may no longer be sufficient when tissue demand rises as, for example, during exercise. This lack of oxygen causes pain in the affected tissue. If this occurs in the heart, the result is angina pectoris, if it occurs in the legs it results in a condition known as intermittent claudication. A further important complication of atherosclerosis concerns the aorta, which is the main artery leading from the heart. Atherosclerosis of the aorta may weaken the wall of this vessel to such an extent that it bulges out. This is called an aortic aneurysm. An aortic aneurysm may bleed, causing pain. Alternatively, and catastrophically, it may burst, leading to massive internal bleeding and sudden death.

Risk Factors

Atherosclerosis is a complex disease that does not occur for a single reason. Epidemiological studies have identified factors that influence both the susceptibility to atherosclerosis and its progression and outcome. Disease mediators that influence the clinical outcome of atherosclerosis are termed 'risk factors' (Von Eckardstein, 2005). Risk factors may be divided into those that can be modified and those that cannot. Nonmodifiable risk factors include age, male sex, certain genetic mutations and a positive family history of early-onset atherosclerosis. The modifiable risk factors for atherosclerosis include smoking, overweight and obesity, lack of exercise, psychological stress, low social status, poor diet, high blood pressure, high LDL, low HDL, high triglycerides, high levels of a lipoprotein called Lp(a) and the presence of diabetes mellitus (**Table 2**). **See also**: Cardiovascular Disease: Epidemiology

Table 2 Importance of the leading 10 risk factors of disease in developed countries in 2000 according to *The World Health Report* 2002, in percent, of disability-adjusted life years (one disability-adjusted life year being equal to the loss of one healthy life year)

Risk factor	%
Tobacco	12.2
Blood pressure	10.9
Alcohol	9.2
Cholesterol	7.6
Overweight	7.4
Low fruit and vegetable intake	3.9
Physical inactivity	3.3
Illicit drugs	1.8
Unsafe sex	0.8
Iron deficiency	0.7

Approaches to Management

Changing life style

The risk of dying due to the complications of atherosclerosis in the industrialized world is higher than in developing countries. This is related in large part to the life style associated with affluence. Thus, the simplest and most inexpensive way to avoid atherosclerosis and its complications is to implement life style changes by stopping smoking, reducing alcohol intake and stress, eating a balanced diet and taking at least 30 min of moderate exercise (e.g. brisk walking, cycling) every day.

Drug therapy

In patients with severe hypercholesterolaemia or hypertriglyceridaemia, in high-risk asymptomatic patients, or in those with established atherosclerosis, it is often not possible to reduce serum levels of risk factors to acceptable levels by life style changes alone. In such persons, treatment with drugs to lower cholesterol, to normalize blood pressure and to treat diabetes mellitus may be necessary.

Drugs to lower blood pressure

High blood pressure (hypertension) is an important risk factor for atherosclerosis and its progression, and is an important contributor to cardiovascular death. Large clinical trials have shown the effectiveness of lowering blood pressure in reducing risk in hypertensive individuals (Kohlman-Trigoboff, 2004). First-line antihypertensive drugs are diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin AT1 receptor antagonists, β-blockers and calcium channel blockers. **See also**: Hypertension

In the class of diuretics, the thiazides are of primary importance. They facilitate the elimination of excess salt and water from the body via the kidney. The important side effects of the thiazides include impairment of glucose and lipid metabolism, impotence and reduced blood potassium levels (hypokalaemia). Because of the latter effect, thiazides are often combined with ACE inhibitors, which have an opposite effect on blood potassium and thus reduce the incidence of hypokalaemia.

ACE inhibitors act by blocking ACE, which catalyses the conversion of angiotensin I to angiotensin II. Angiotensin is a hormone that is produced by the kidney. Its major effects are to increase vascular tone and to increase the secretion of a second hormone, aldosterone, from the cortex of the adrenal glands. Aldosterone acts on the kidney to increase salt retention, and thus increases intravascular volume. Thus, the combined effect of angiotensin II is to raise arterial blood pressure. For this reason, reducing plasma levels of angiotensin II reduces blood pressure.

Angiotensin AT1 receptor antagonists also modulate the renin–angiotensin system, not by inhibiting production of angiotensin II, but by blocking it from binding to the AT1 receptor. Blockade of the AT1 receptor causes vasodilation, reduces secretion of vasopressin and reduces secretion of aldosterone. AT1 receptor antagonists have few side effects and may be combined with diuretics. Their main drawback at the present time is their relatively high cost, although this will fall as generic medications become available over time.

β-Blockers act by inhibiting the sympathetic nervous system. They may be used in combination with other drugs, particularly diuretics or calcium channel blockers. The exact mechanism of their antihypertensive effect is still unclear, but it results at least in part by reducing heart rate and the force of contraction of the heart (negative chronotropic and inotropic effects respectively). Hypertensive patients with coronary heart disease may derive particular benefit from therapy with β-blockers.

Calcium channel blockers are among the most potent antihypertensive agents. They act to block calcium channels within the heart and major blood vessels, thus lowering the heart rate and decreasing the contraction force of the myocardium. In the last few years, reports have appeared on increased mortality when channel blockers are used on their own. However, these drugs still have a place as antihypertensive agents in combination with other blood pressure-lowering drugs.

Lipid and lipid-modifying therapy

Many epidemiological studies have shown a clear relationship between high levels of LDL cholesterol and increased risk of cardiovascular disease. In addition, large numbers of well-performed clinical trials have shown a clear benefit of lowering LDL cholesterol by drugs in reducing the risk of cardiovascular disease in a wide variety of patients. Principally, two classes of drugs with different modes of action called statins and fibrates are used to treat lipid disorders. **See also**: Cholesterol-Lowering Agents and Their Use

LDL cholesterol lowering

Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme (HMG-CoA) reductase, the enzyme that catalyses the rate-limiting step in the cholesterol synthesis pathway (Paoletti *et al*., 2005). Widely used statins are the hydrophilic pravastatin and lipophilic lovastatin, fluvastatin, simvastatin and atorvastatin.

The benefits of statins are mainly due to their LDL-lowering effects. In addition, statins may also have additional benefits on cardiovascular risk over and above their cholesterol-lowering effects. These effects may be due to a reduction in the level of biologically active intermediate products of the cholesterol synthesis pathway. Such so-called 'pleiotropic' effects include an improvement in endothelial function, stabilization of the atherosclerotic plaque and inhibition of inflammation, foam cell formation, smooth muscle cell activation and proliferation, thrombus formation and monocyte adhesion and migration.

Lowering triglycerides levels

Fibrates are fibric acid derivatives, which comprise a widely used class of drugs for treating high blood lipid levels (Robillard *et al*., 2005). They reduce blood triglycerides by 30–50% and increase HDL-cholesterol ('good cholesterol') by about 6%. Some fibrates, such as bezafibrate or fenofibrate, also reduce serum LDL-cholesterol ('bad cholesterol') by 10–20%.

Fibrates act through the activation of peroxisome proliferator-activated receptors (PPARs). Upon activation, these nuclear receptors form heterodimers with the retinoid X-receptor (RXR) and modulate the expression of several genes involved in lipoprotein metabolism. As a result lipoprotein lipase is increased and the clearance of circulating triglyceride-rich lipoproteins is enhanced. Furthermore, the expression of apolipoprotein C-III, an inhibitor of the lipoprotein lipase, is decreased. Increased HDL levels are a consequence of an increased expression of major HDL components, the apolipoproteins A-I and A-II. Fibrates also promote the reverse cholesterol transport by enhancing the expression of the adenosine

triphosphate (ATP)-binding cassette transporter A1 and the scavenger receptor B1. Furthermore, fibrates reduce the ability of LDL to cause atherosclerosis by changing the composition of LDL particles, from the pro-atherogenic small dense variety, to less dangerous larger particles of reduced density. Finally, activation of PPARα by fibrates has an anti-inflammatory effect by reducing the expression of genes encoding pro-inflammatory cell signalling molecules (cytokines) and proteins of the so-called 'acute phase' of inflammation.

In recent years, several reports have appeared of serious and sometimes fatal side effects when statins (in particular cerivastatin) are combined with fibrates. These side effects are related principally to muscle toxicity and led to the worldwide withdrawal of cerivastatin from sale. Nevertheless, in certain cases, a combination of a statin and a fibrate may be appropriate if treatment is closely monitored by a specialist.

Raising HDL cholesterol levels

Patients with low HDL cholesterol serum levels have an increased risk of coronary artery disease, and there are some indications that raising HDL cholesterol levels by drugs may reduce risk (Van der Steeg *et al*., 2005). This is however not proven at the time of writing.

Nicotinic acid (niacin or vitamin B_3) leads to favourable changes of all major lipid fractions and exerts the strongest HDL-increasing effect of all commercially available drugs with increments of up to 30%. Nicotinic acid increases HDL cholesterol probably by decreasing the fractional catabolic rate of apolipoprotein A-I, the major apolipoprotein of HDL. Side effects of nicotinic acid include flushing, skin disorders (itching, rashes, pruritus, dry skin or increased pigmentation), increased urinary frequency, dysuria, hyperuricaemia and hepatic and pancreatic disturbances with high doses.

Cholesterol ester transfer protein (CETP) is a component of HDL that transfers cholesteryl ester from HDL to other lipoprotein particles in exchange for triglyceride. Persons with an inherited defect of CETP have very low HDL cholesterol levels, but seem to be protected from atherosclerosis and have a prolonged life expectancy. This observation has led to the development of inhibitors of CETP as potential antiatherosclerosis drugs. Two such drugs (JTT-705 and torcetrapib) are currently being investigated in clinical trials. Preliminary data indicate that higher doses of torcetrapib may increase blood pressure. Thus, the results of large long-term trials must be awaited before deciding if CETP inhibitors are useful either alone or in combination with statins.

Apolipoprotein A-I and lipid-poor HDL particles take up cholesterol avidly from cells including foamy macrophages. Several studies have been performed in which apolipoprotein A-I or reconstituted HDL (discs consisting of apolipoprotein A-I and lecithin) were given intravenously. Animal studies and small preliminary clinical studies have indicated a possible positive effect on this therapy on the atherosclerotic plaque. This therapy is limited by the necessity for intravenous administration. To circumvent this, mimetic apolipoprotein A-I peptides have been tested for oral use. At present, however, this form of treatment must be regarded as experimental.

Lowering blood cholesterol with nonstatins

Beside the class of statins, there are other drugs for lowering serum cholesterol levels: the group of bile acid sequestrants (Ast and Frishman, 1990) and cholesterol absorption inhibitors (Patel, 2004).

Bile acids are essentially modified cholesterol molecules that are made by the liver. Their function is to solubilize, and hence help, in the digestion and absorption of fat and cholesterol in diet. Drugs that bind bile acids (bile acid sequestrants such as cholestyramine and colestipol) and form insoluble complexes, which are excreted in faeces, reduce the absorption of fat and cholesterol, and thus lower the level of cholesterol in the bloodstream.

Ezetimibe is the first representative of the class of cholesterol absorption inhibitors. These are new drugs that act by binding to a protein that is required for cholesterol import, thus reducing cholesterol uptake and blood cholesterol levels. Use of these drugs may be expected to lower LDL cholesterol levels by 10–15%. Since this is often not sufficient, ezetemibe is usually given in combination with statins.

Inhibition of platelet aggregation

People suffering from advanced atherosclerosis such as coronary heart disease, peripheral artery occlusive disease or carotid artery stenosis have an increased risk of thrombosis. In some cases, it may be useful to administer antithrombotic drugs to such patients (Phillips *et al*., 2005). The main drug used for this purpose is acetylsalicylic acid (ACS or 'aspirin®'). Acetylsalicylic acid acts by irreversibly inhibiting the enzyme cyclo-oxygenase, thus blocking the synthesis of prostaglandins. One such prostaglandin is thromboxane A2, which causes platelets to clump together, one of the earliest steps in the formation of a thrombosis.

The main side effect of acetylsalicylic acid is irritation and bleeding in the stomach. For this reason, many patients cannot tolerate the drug. In such patients, ticlopidine or clopidogrel are alternatives that have a similar effect on platelet aggregation, but they are much more expensive. Owing to concerns about serious side effects of ticlopidine (thrombotic thrombocytopenic purpura, neutropenia), most doctors now use clopidogrel.

Invasive treatment

A small group of patients with genetic disorders of cholesterol metabolism may have high LDL cholesterol levels despite maximum treatment with diet and drugs. In such

patients, invasive measures to lower blood cholesterol may be required (Lees *et al*., 1999).

Surgical diversion

Surgical treatment of atherosclerosis is no longer a procedure of choice. Of the four techniques that have been evaluated, two were based on direct alteration of liver cholesterol metabolism. All surgical methods were used to treat patients with a severe genetic disorder of cholesterol metabolism called homozygous familial hypercholesterolaemia. Since the advent of newer drugs to treat high LDL cholesterol, in particular powerful statins and inhibitors of cholesterol absorption, use of surgical treatments has virtually ceased. **See also**: Familial Hypercholesterolaemia

Plasmapheresis and selective LDL apheresis

The second invasive means of lowering LDL cholesterol is to directly remove LDL particles from the circulation by means of selective LDL apheresis. The pioneers of selective LDL removal from plasma were Paul-Joseph Lupien and colleagues in the 1970s. Their method involved withdrawing a unit of blood, which was mixed in a transfusion bag with heparin-agarose beads. Both LDL and very low-density lipoprotein (VLDL) are selectively complexed with heparin-agarose and the blood was reinfused through a transfusion filter that retained the beads. The process is repeated several times per treatment and is both well tolerated and cost-effective, but time-consuming.

In 1981, it was demonstrated that the removal of LDL can also be accomplished by using polyclonal anti-LDL antibody columns in a closed continuous system or by precipitating LDL from plasma with heparin under mildly acidic conditions. However, in the mid-1980s, cost-effective continuous LDL adsorption systems based on LDL binding to polyanionic dextran sulfate were developed. A system utilizing columns of dextran sulfate bonded chemically to a polymeric matrix was approved for use and is generally well tolerated.

In 1997, Bosch and colleagues introduced an apheresis system that treats whole blood, obviating the need for cell separation. The direct adsorption of lipoproteins system removes apolipoprotein B-containing lipoproteins by electrochemical interaction with polyacrylate-coated polyacrylamide.

Several clinical studies have shown that patients, particularly patients with severe, drug-refractory hypercholesterolaemia, benefit from apheresis in terms of LDL cholesterol lowering and long-term coronary heart disease event reduction. However, current apheresis methods remain time-consuming and costly, and their use is therefore limited to the small group of patients with genetic cholesterol disorders and clinical atherosclerosis who fail to respond adequately to maximal treatment with life style and drugs.

Summary

Despite decades of research, we are still far from understanding the pathogenesis of atherosclerosis. In addition, despite great advances in preventive medicine, more people still die of the complications of this condition than of any other cause. With the increase in life-expectancy and affluence worldwide, the importance of atherosclerosis is set to increase rather than decrease in the coming years. Thus, research must still focus on improved risk prediction and on treatment of risk factors. A major, and achievable, area of improvement is a better implementation of known preventive strategies. This will require a concerted effort of government and health care providers. Recent legislation to curb smoking in Europe is a good example of what can be achieved.

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