Atherosclerosis

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Abstract | Atherosclerosis, the formation of fibrofatty lesions in the artery wall, causes much morbidity and mortality worldwide, including most myocardial infarctions and many strokes, as well as disabling peripheral artery disease. Development of atherosclerotic lesions probably requires low-density lipoprotein, a particle that carries cholesterol through the blood. Other risk factors for atherosclerosis and its thrombotic complications include hypertension, cigarette smoking and diabetes mellitus. Increasing evidence also points to a role of the immune system, as emerging risk factors include inflammation and clonal haematopoiesis. Studies of the cell and molecular biology of atherogenesis have provided considerable insight into the mechanisms that link all these risk factors to atheroma development and the clinical manifestations of this disease. An array of diagnostic techniques, both invasive (such as selective coronary arteriography) and noninvasive (such as blood biomarkers, stress testing, CT and nuclear scanning), permit assessment of cardiovascular disease risk and targeting of therapies. An expanding armamentarium of therapies that can modify risk factors and confer clinical benefit is available; however, we face considerable challenge in providing equitable access to these treatments and in maximizing adherence. Yet, the clinical application of the fruits of research has advanced preventive strategies, enhanced clinical outcomes in affected individuals, and improved their quality of life. Rapidly accelerating knowledge and continued research promise to provide further progress in combating this common chronic disease.

Atherosclerosis refers to the accumulation of fatty and/or fibrous material in the innermost layer of arteries, the intima. The term atherosclerosis derives from the Greek word for 'gruel' or 'porridge', reflecting the appearance of the lipid material found in the core of the typical atherosclerotic plaque (or atheroma). With time, the atherosclerotic plaque can become more fibrous and accumulate calcium mineral. Advanced atherosclerotic plaques can encroach upon the arterial lumen, impeding blood flow and leading to tissue ischaemia. Atheromata that do not produce a flow-limiting obstruction can disrupt and provoke the formation of a thrombus that can occlude the lumen providing a second route, usually more acute, to ischaemia. Atherosclerotic cardiovascular disease (CVD) remains a leading cause of vascular disease worldwide. When it affects the heart's own circulation, it can cause acute coronary syndromes including myocardial infarction or chronic conditions such as stable angina pectoris (chest pain or discomfort caused by insufficient perfusion of the heart muscle). Atherosclerosis causes many ischaemic strokes and transient cerebral ischaemic attacks. It can lead to the formation of aneurysms including those that form in the abdominal aorta. When it affects the peripheral arteries, it can cause intermittent claudication, ulceration and gangrene that can jeopardize limb viability. Atherosclerosis remains a major killer, and has now spread globally. This Primer proposes not to mire the reader in the details of the pathogenetic pathways that preoccupy the authors in their research work. Rather, it aims to convey the fundamentals of the current concepts of the epidemiology, pathophysiology, risk assessment and management of atherosclerotic CVD. Each of these topics has witnessed major advances in recent years. Too many individuals still die of the acute complications of atherosclerosis out of hospital, despite the improvements in prevention. Yet, if a patient presents to the health-care system with an acute manifestation of atherosclerosis, with our current interventions and management strategies, they overwhelmingly survive. This progress in cardiovascular medicine represents a sterling example of how the clinical application of scientific discoveries can yield benefits for patients.

Despite these successes, much remains to be done in applying what we know already more effectively and equitably in practice. We must also challenge ourselves to confront the remaining unacceptable burden of residual risk. In addition to celebrating our advances, we need to continue to strive to stem the worldwide epidemic of CVD. Although most patients survive acute coronary

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syndromes, they can be left with impaired cardiac function that sets the stage for heart failure, a growing epidemic. This Primer provides a road map for the reader to understand where we are today, and where we should set our sights for the future.

Epidemiology

CVDs, which include coronary heart disease, hypertension and stroke, collectively comprise the number one cause of death globally[1,2] (FIG. 1). Heart disease (most commonly due to atherosclerotic disease of the coronary arteries) and stroke are the two leading causes of death in the world; in the USA, heart disease is the first cause of death, and stroke the fifth[2]. Over 17 million people died from CVD in 2015, representing 31% of all global deaths[1]. Of these, an estimated 7.4 million occurred owing to coronary heart disease and 6.7 million to stroke. In the USA, among individuals of >20 years of age, 37.4% of men and 35.9% of women have some form of CVD, with men representing 50.6% of deaths from CVD[2]. Of the men with CVD, 37.7% are non-Hispanic white, 46.0% black and 31.3% Hispanic; in women, these figures are 35.1%, 47.7% and 33.3%, respectively[2]. According to data from the US National Health and Nutrition Examination Survey, the overall population prevalence of high low-density lipoprotein cholesterol (LDL-C) did not change substantially from 1999–2002 (34.5%) to 2005–2008 (33.5%). However, treatment of high LDL-C increased significantly, from 28.4% in 1999–2002 to 48.1% in 2005–2008. In addition, the prevalence of individuals achieving a degree of LDL lowering more than doubled during the study period, from 14.6% to 33.2%[3].

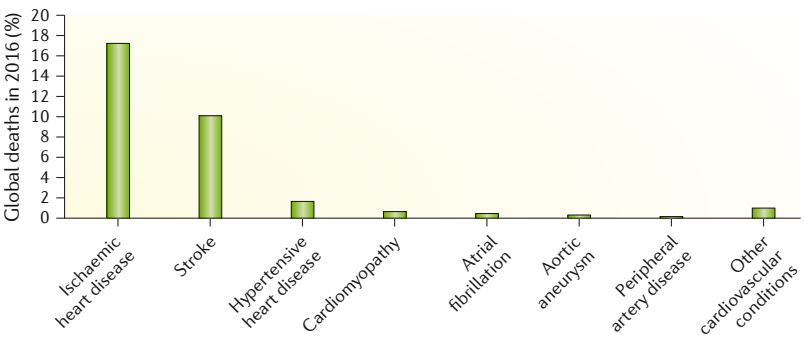

Fig. 1 | **The contribution of cardiovascular diseases to the global burden of death in 2016.** These data convey the importance of atherosclerotic cardiovascular disease worldwide. Of note, many stroke deaths may not result directly from atherosclerotic disease but from hypertension, a highly prevalent cardiovascular risk factor. Similarly, not all cases of cardiomyopathy result from ischaemic damage, and some cases of atrial fibrillation may not be associated with atherosclerosis. Data from the Global Burden of Disease.

Globally, >75% of deaths from CVD occur in low-income and middle-income countries[1]. In these countries, individuals with CVD have limited access to effective and equitable health-care services, a limitation that can delay CVD detection until late in the disease course and increase premature mortality from CVD and other non-communicable diseases. CVD leads to 18% of disability-adjusted life years lost in high-income countries, and 10% in low-income and middle-income countries, placing a heavy burden on the economies of developing countries[4].

Although ischaemic heart disease remains the leading cause of premature adult mortality worldwide, since the 1950s advances in cardiovascular health have led to striking declines in mortality in both men and women from heart disease and stroke. Yet, these improvements do not apply evenly across all populations. For example, in the UK, a high-income country, CVD mortality in men of 35–69 years of age decreased from 22% in 1950 to 6% in 2010[5]. However, the Global Burden of Disease 2010 study estimated that this decrease has not occurred consistently in low-income and middle-income countries[4,6]. Although mortality from stroke has declined, deaths from heart disease have dropped less consistently, with some countries, especially in Eastern Europe and Asia, reporting increases in mortality[4].

Overall declines in cases of heart disease and stroke probably arise from a number of factors, including changes in behavioural risk factors due to population-based or individual interventions, or both. Risk factors include tobacco use, unhealthy diet, obesity, physical inactivity, hyperlipidaemia, hypertension and high alcohol use. Exposure to risk factors has a cumulative effect throughout life (discussed in detail in the Prevention section below). The increasing epidemic of obesity, especially in low-income and middle-income countries, remains a particular threat to a continued decline in CVD[4]. In 2016, the WHO and the US Centers for Disease Control and Prevention launched Global Hearts, a new initiative to reduce the global threat of CVD by 2025, especially in developing countries[7]. This programme will elevate efforts for CVD prevention and control by promoting population-level interventions to reduce risk factors, including reducing tobacco use and dietary salt intake, and strengthening CVD management in primary health care.

Mechanisms/pathophysiology

We can consider conveniently the pathogenesis of atherosclerosis in three phases: initiation, progression and complications.

Initiation of atherosclerosis

LDL cholesterol. LDL particles cause atherosclerosis. These spheroidal packets of lipids rich in cholesterol, enveloped in a phospholipid coating with apolipoprotein B snaking through their equatorial region,

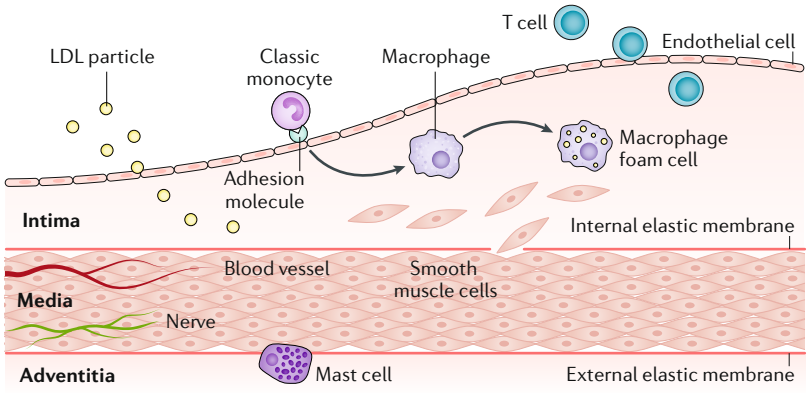

Fig. 2 | **Initiation and progression of atherosclerosis.** The normal artery wall has a trilaminar structure. The outermost layer, the adventitia, contains nerve endings, mast cells, and vasa vasorum, microvessels that nourish the outer layer of the media. The tunica media consists of quiescent smooth muscle cells and a well-organized extracellular matrix comprising elastin, collagen and other macromolecules. The atherosclerotic plaque forms in the innermost layer, the intima. In the early stage of lesion initiation, low-density lipoprotein (LDL) particles accumulate in the intima, where protected from plasma antioxidants, they can undergo oxidative and other modifications that can render them pro-inflammatory and immunogenic. Classic monocytes that exhibit a pro-inflammatory palette of functions then enter the intima. Monocytes circulate in the bloodstream and can bind to adhesion molecules expressed by activated endothelial cells. Chemoattractant cytokines, known as chemokines, can promote the migration of the bound monocytes into the artery wall. Once in the intima, monocytes can mature into macrophages, and attain characteristics associated with the reparative or less pro-inflammatory monocyte/macrophage population. These cells express scavenger receptors that permit them to bind lipoprotein particles and become foam cells. T lymphocytes, although numerically less abundant than monocytes, also enter the intima, and regulate functions of the innate immune cells as well as the endothelial and smooth muscle cells. Smooth muscle cells in the tunica media can migrate into the intima in response to mediators elaborated by the accumulating leukocytes. The smooth muscle cell chemoattractant platelet-derived growth factor arising from macrophages and deposited by activated platelets at sites of endothelial breaches or intraplaque haemorrhage probably participates in this directed migration of medial smooth muscle cells into the intima.

transport water-insoluble cholesterol through the blood. Atherosclerosis probably would not occur in the absence of LDL-C concentrations in excess of physiological needs (on the order of 10–20 mg/dL)[8]. Phylogenetic, comparative population studies and pharmacological intervention investigations suggest that LDL-C concentrations in the 20–30 mg/dL range (about 0.5–0.8 mmol/L) suffice for good health[8–11]. Hence, despite recent secular trends towards lowering cholesterol levels, the concentrations of blood cholesterol prevalent in most contemporary human societies exceed by far the biological needs of the organism, and permit the development of atherosclerosis[12,13]. The cumulative exposure of an artery to LDL-C over years remains a principal determinant of disease initiation and progression[14]. The observation that patients with familial hypercholesterolaemia achieve this cumulative LDL-C burden threshold at early ages and develop premature atherosclerotic CVD supports a causal role of LDL in atherosclerosis[15]. On the other hand, individuals with proprotein convertase subtilisin/kexin type 9 (*PCSK9*) loss-of-function mutations have life-long low LDL-C concentrations due to reduced catabolism of the LDL receptors, and show a greater reduction of coronary events than that afforded by statin treatment alone[16].

How excessive LDL-C causes atherosclerosis remains unsettled. Many decades of research have supported the concept that oxidized LDL particles can promote atherogenesis[17,18]. Pathways that can lead to modification of LDL particles include formation of reactive oxygen species in the intima due to metal ion catalysis (the Fenton reaction), among other sources. The expression of high-capacity scavenger receptors for LDL particles does not drop when cellular cholesterol content rises, as does the expression of the high-affinity LDL receptor. Thus, these scavenger receptors permit overloading of macrophages with cholesteryl ester, generating foam cells, a hallmark of the early atherosclerotic lesion. Most schemata of the initiation of atherosclerosis posit a causal role for oxidized LDL particles as ligands for the scavenger receptors that facilitate foam cell formation (FIG. 2). Constituents of oxidized LDL particles may induce inflammation and furnish neo-epitopes that stimulate humoral and adaptive immunity[19].

Despite the wealth of experimental data that support this sequence of events, we still lack rigorous proof that oxidized LDL particles initiate human atherosclerosis[20]. Perhaps therapeutic interventions that target oxidative pathways are initiated too late in the process, but to date no antioxidant vitamin has forestalled atherosclerotic events in a suitably powered clinical trial. A lipid-soluble antioxidant that effectively blocks LDL particle oxidation, succinobucol, did not reduce cardiovascular events in a large-scale clinical study[21]. Moreover, laboratory studies suggest that native rather than oxidized LDL particles stimulate T cell responses thought to participate in atherogenesis[22]. Thus, although the 'oxidized LDL particle hypothesis' rests on solid experimental evidence, its relevance to human atherosclerosis remains conjectural and, from a clinical perspective, has not yielded an actionable therapy. Nonetheless, strong human genetic evidence, results of observational epidemiological studies, and pharmacological interventions establish LDL-C as an indubitable causal factor and therapeutic target in atherosclerosis (reviewed in detail in REF.[14]).

LDL-C can deposit in the arterial wall owing to impaired barrier function of the endothelium and is retained within the intimal layer by extracellular matrix macromolecules[23]. An alternative pathway in atherogenesis mediated by aggregated LDL particles has received less attention. When LDL particles accumulate in the subendothelial space, they can bind to intimal proteoglycans and form aggregates. These collections can then enter smooth muscle cells through receptors of the LDL receptor-related protein (LRP) superfamily. Cells can accumulate cholesterol in this manner as LRP superfamily members, like scavenger receptors, evade the usual homeostatic mechanisms that reduce expression of the classic LDL receptor under conditions of cholesterol sufficiency. These smooth muscle cells and macrophages can become engorged with lipid and contribute to lesion progression[24].

HDL cholesterol, triglycerides, and lipoprotein(a). High-density lipoprotein cholesterol (HDL-C) concentrations consistently associate inversely with the risk

of atherosclerotic events in observational epidemiological studies. Yet, current human genetic evidence does not support a protective role for HDL-C against atherosclerosis[25]. Moreover, numerous therapies that raise HDL-C have failed to improve cardiovascular outcomes. The disparity with the observational data may be because HDL-C tracks inversely with triglyceride concentrations[26]. Substantial human genetic evidence now supports a causal role for triglyceride-rich lipoproteins in atherosclerosis[27]. In contrast to HDL, convincing human genetic evidence supports the strong observational relationship between lipoprotein(a) (Lp(a)) and atherosclerotic risk[28].

Inflammation. Other risk factors implicated causally in atherogenesis include hypertension, tobacco use and the components of the metabolic syndrome cluster, which include elevated blood pressure, visceral adiposity, insulin resistance and high blood concentrations of triglyceride-rich lipoproteins, and ultimately can lead to full-blown diabetes mellitus. As in the case of LDL-C, however, the mechanisms that link these risk factors to atherogenesis remain incompletely elucidated. But many if not all of these risk factors also participate in the activation of inflammatory pathways. Inflammation in turn can alter the function of the cells of the artery wall in a manner that drives atherosclerosis. For example, angiotensin II, which participates in the pathogenesis of hypertension, can also unleash inflammatory pathways such as those governed by the master transcriptional regulator nuclear factor-κB (NF-κB) pathway[29]. Similarly, recent experimental work implicates adaptive T cell immunity in the pathogenesis of hypertension, providing a common pathogenetic pathway for elevated blood pressure and atherosclerosis[30]. Tobacco use can elicit an inflammatory response in the airways and alveoli. Visceral adipose tissue, a common concomitant of insulin resistance and type 2 diabetes mellitus, contains inflammatory cells and elaborates multiple mediators of inflammation[31,32]. These extravascular sites of inflammation can affect distant artery walls, as they release soluble inflammatory mediators such as cytokines that can activate cells in the intima[33,34]. Biomarkers of inflammation, notably C-reactive protein (CRP; measured with a highly sensitive assay, hsCRP), prospectively predict cardiovascular risk and rise in tandem with many established cardiovascular risk factors[35]. A rich experimental basis has established a role for adaptive immunity in atherogenesis as well. Human atherosclerotic lesions contain T lymphocytes and display markers of adaptive immune activation[22]. Some T cell subtypes (for example, type 1 T helper (T_H1) cells) promote experimental atherosclerosis, whereas others (for example, regulatory T (T_{reg}) cells) seem to mitigate atherogenesis[20,36]. A strong body of laboratory work, mostly conducted in mice, has rigorously demonstrated a causal role for various arms of adaptive immunity in modulating experimental atherosclerosis[22,36]. These findings, along with study of human atherosclerotic plaques and biomarker investigations in human populations, provide support for the contribution of inflammation and immunity in atherosclerosis.

The endothelium. Alterations in the endothelial monolayer, which provides the interface between blood and the arterial intima, the site of atheroma initiation, occur early during atherogenesis. Exposure to atherogenic risk factors, including those considered above, interferes with the production of endogenous vasodilators, such as nitric oxide, by endothelial cells[37]. Consumption of a cholesterol-containing diet can activate the expression of adhesion molecules, such as vascular cell adhesion protein 1, that bind blood leukocytes to the endothelial surface, and of chemoattractants that promote entry of the bound leukocytes into the intima[38,39].

The local haemodynamic environment also affects endothelial functions. Changes to the blood flow are sensed by flow-dependent ion channels or surface structures, such as members of the integrin family of transmembrane proteins. Downstream transcriptional mechanisms that transduce the effects of flow into altered gene expression include Krüppel-like factor 2 (REF.[40]). Such abnormal flow patterns disturb the physiological homeostatic atheroprotective functions of the endothelium, reversing tonic vasodilatation, anti-thrombotic and anti-inflammatory properties, and mechanisms that resist thrombus formation and persistence[41]. Atherosclerotic plaques tend to form at sites of flow disturbance, whereas sites in the arterial tree where laminar shear stress predominates generally resist atheroma formation[42]. Thus, exposure to risk factors for atherosclerosis, or their downstream mediators, in the context of disturbed flow perturbs the homeostatic properties of the endothelial monolayer and promotes some of the initial steps in atherogenesis.

Progression of atherosclerosis

Once established, atherosclerotic plaques progress by continued accumulation of lipid and lipid-engorged cells. For many years, most researchers considered macrophages derived from blood monocytes as the precursors of lipid-laden foam cells in atheromata. Recent experimental data suggest that metaplasia of smooth muscle cells may also give rise to foam cells resembling macrophages[43]. The human intima contains resident smooth muscle cells, particularly at sites where atheromata tend to develop. Migration of smooth muscle cells from the media into the intima can contribute to the accumulation of smooth muscle cells in the growing atherosclerotic plaque. These cells can proliferate over the years and elaborate extracellular matrix macromolecules that comprise much of the bulk of an established atherosclerotic plaque[43].

Extracellular matrix of the atherosclerotic plaque. The extracellular matrix of atherosclerotic plaques contains interstitial collagen, elastin, proteoglycans and glycosaminoglycans. Many of these extracellular matrix macromolecules can entrap lipoproteins and promote lipid accumulation within the intima. Inflammatory leukocytes not only arrive in the intima by infiltration but can also proliferate within the lesion[44]. Various retention factors such as semaphorins can retard the egress of these leukocytes and contribute to their

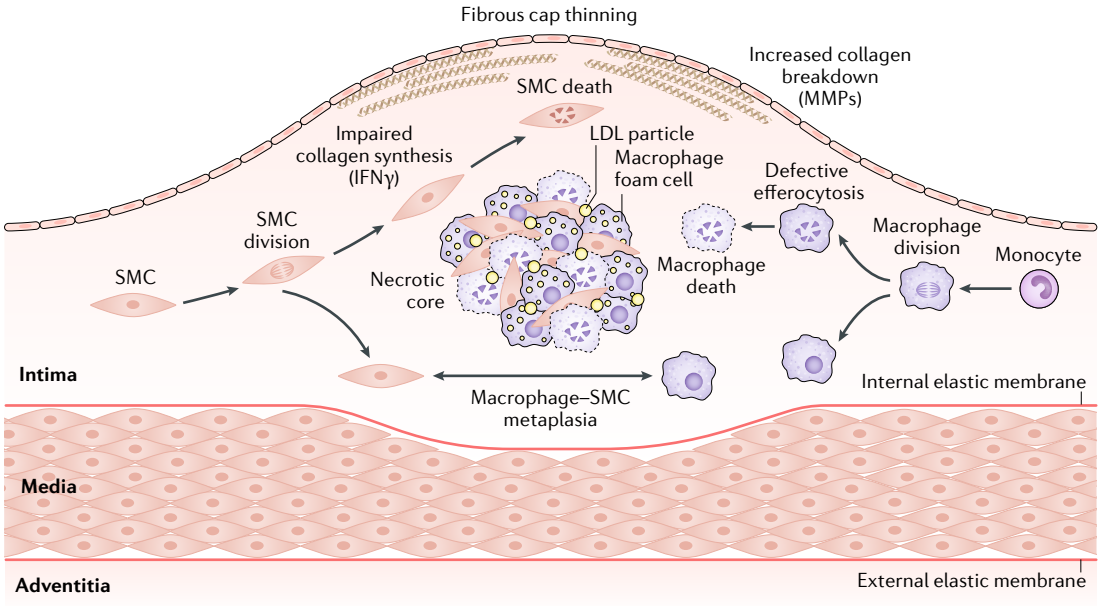

Fig. 3 | **The progression of atherosclerotic lesions: cellular birth and death.** During the evolution of the atherosclerotic plaque, the resident and recruited smooth muscle cells (SMCs) produce extracellular matrix molecules (such as interstitial collagen and elastin, as well as proteoglycans and glycosaminoglycans) that contribute to the thickening of the intimal layer. However, T cell mediators such as IFNγ can impair the ability of the SMC to synthesize interstitial collagen and thereby dampen the ability of these cells to repair and maintain the fibrous cap that overlies the necrotic core. Furthermore, activated macrophages show increased production of enzymes of the matrix metalloproteinases (MMPs) family that degrade the interstitial collagen that lends strength to the fibrous cap. Thinning and structural weakening of the fibrous cap increase the susceptibility of the plaque to rupture. SMCs and macrophages in the evolving lesion can divide. SMCs and the mononuclear phagocytes can also interchange through a process of metaplasia. As the lesion advances, SMCs and macrophages can undergo cell death including by apoptosis. The debris from dead and dying cells accumulates, forming the necrotic, lipid-rich core of the atheroma. Impaired efferocytosis (clearance of dead cells) can contribute to the formation of the necrotic core. LDL, low-density lipoprotein.

persistent presence in the atherosclerotic plaque[45,46]. Although macrophages predominate numerically, T lymphocytes also localize within lesions and may have either positive or negative effects on many aspects of atherosclerotic plaque growth and evolution. T_H1 cells typically elaborate IFNγ that can promote atherosclerosis, whereas T_H2 cells can produce anti-inflammatory cytokines such as IL-10, and T_{reg} cells secrete transforming growth factor β that can limit inflammation and smooth muscle cell proliferation and promote interstitial collagen synthesis[36,47]. Furthermore, atherosclerotic plaque components drain from the lesions and reach adjacent lymph nodes, where they may serve as antigens for T and B cells. Other atherosclerotic plaque components, such as locally produced cytokines, can modulate immune responses in these lymph nodes[48]. In advanced disease, tertiary lymphoid structures (ectopic lymphoid aggregates that form in diseased tissue) may develop adjacent to large arteries. In these structures, B cells differentiating to plasma cells produce large amounts of antibodies against LDL particle components[49].

Macrophages and smooth muscle cells can undergo programmed cell death forming the nidus of a lipid-rich or necrotic core of the advancing atheroma[50,51] (FIG. 3). Impaired clearance of dead cells, known as defective efferocytosis, can also contribute to the formation of the necrotic core[52,53].

Clonal haematopoiesis of indeterminate potential. Recent evidence supports a causal role of myeloid cells that bear mutations associated with the development of myelodysplastic syndromes and acute myelogenous leukaemia in experimental atherogenesis and as a novel important risk factor for human atherosclerosis[54,55]. With age, somatic mutations in bone marrow haematopoietic stem cells that confer a proliferative advantage can give rise to clones of myeloid cells in peripheral blood. Mutations in only a handful of genes (for example, *DNMT3A*, *TET2*, *ASXL1* and *JAK2*) can generate these clones, and over 10% of septuagenarians harbour such clones in the circulation[54,55]. As most persons who have such clones of mutant myeloid cells will never develop leukaemia, this condition is called clonal haematopoiesis of indeterminate potential (CHIP). Individuals with CHIP develop acute leukaemia at a rate of 0.5–1% per year, a transition that is associated with accumulation of successive mutations in the same clone. Carriers of CHIP have a much higher mortality than attributable to haematological malignancy. CVDs, including the complications of atherosclerosis, account for much of the excess mortality in people who have CHIP. Several of the genes mutated in CHIP alter methylation of DNA, and seem to alter the expression of inflammatory genes such as *IL1B* via epigenetic regulation. Mutations in *JAK2* (encoding the tyrosine-protein kinase JAK2) can sensitize leukocytes to form neutrophil extracellular traps

(NETs) that can promote thrombosis (see below)[56]. As the cardiovascular risk associated with CHIP does not depend on traditional CVD-associated risk factors, the pursuit of the mechanisms that connect CVD with CHIP promises to shed new light on pathways that promote atherosclerosis and its complications[57].

Altogether, these findings provide further support for links between leukocytes and atherosclerosis. Some evidence supports the presence of virtually every subtype of leukocyte in the evolving atheroma, although cells with the functional properties of macrophages and various subtypes of T lymphocytes probably predominate in defining the properties of atherosclerotic plaques that give rise to complications[47].

Calcification. During their evolution, many atherosclerotic plaques develop regions of calcification. Far from a passive degenerative process, the accumulation of calcium mineral in atheromata arises from dysregulation of deposition and impaired clearance[58]. Much of the mineralization process in atherosclerotic plaques recapitulates biological processes in bone formation. Microscopic or spotty calcification associates with mechanical instability of plaques, and may promote a tendency to rupture and provoke thrombosis[59]. Larger accumulations of calcium may associate with lower probability of triggering a thrombotic event[60]. PET imaging with $Na^{18}F$ may provide a window on calcification in human atherosclerotic plaques and promises to provide a new tool for research into the pathophysiology of calcification in human atherosclerosis[61].

Complications of atherosclerosis

During much of the disease course of the atherosclerotic plaque, the lesions expand outward radially, in an abluminal (away from the lumen) direction, preserving the calibre of the arterial lumen. Some of the remodelling of the arterial wall that accompanies lesion progression may result from the production by smooth muscle cells of proteinases specialized in degrading constituents of the arterial extracellular matrix, such as matrix metalloproteinase 3 (MMP3, also known as stromelysin 1)[62,63]. Eventually, the growing atherosclerotic plaque begins to encroach upon the arterial lumen, and can lead to the formation of flow-limiting lesions. (FIG. 4). The consequent impairment of coronary arterial perfusion,

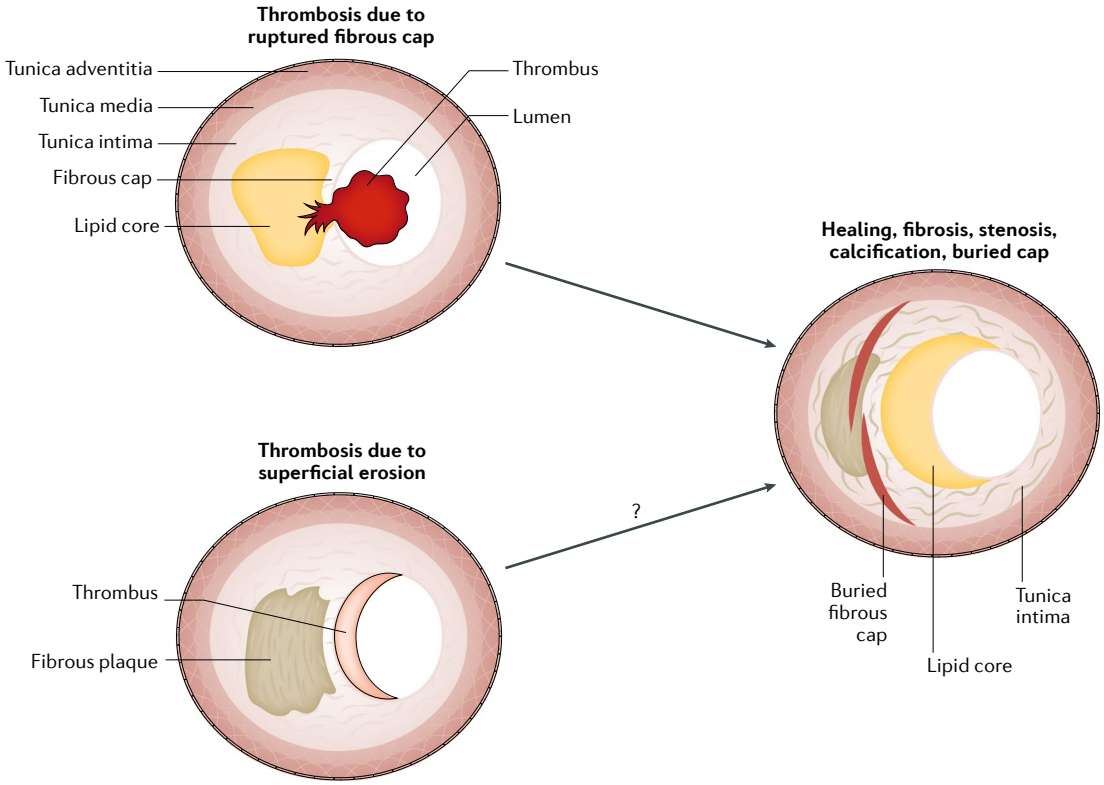

Fig. 4 | **Atheroma complication: disruption and healing.** The fracture of the fibrous cap of the atherosclerotic plaque permits blood coagulation components to access to the core of the plaque. Pro-coagulant substances such as tissue factor can trigger thrombosis, which can cause occlusion of the vessel and lead to an acute ischaemic event. Many mural thrombi may not totally occlude the vessel or may undergo lysis due to endogenous fibrinolytic defences. The resorbing thrombus, a source of transforming growth factor-β (TGFβ) and platelet-derived growth factor elaborated by activated platelets, can stimulate smooth muscle cell migration and extracellular matrix production. These processes lead to increased lesion volume and eventual encroachment upon the arterial lumen. Pathological studies of advanced human atherosclerotic plaques showed 'buried caps' that provide evidence for prior rupture and healing. Plaques that lack a well-defined lipid core and have abundant rather than sparse extracellular matrix can provoke coronary thrombi due to a process known as superficial erosion. The clots associated with superficial erosion have characteristics of platelet-rich 'white' thrombi; by contrast, 'red' thrombi are rich in fibrin and trapped erythrocytes and associate with plaque rupture[184].

particularly when myocardial oxygen demands increase owing to physical effort, can produce ischaemia and the symptoms of angina pectoris.

Plaque rupture. Rupture of atherosclerotic plaques is the most common trigger of acute thrombosis of coronary arteries that causes myocardial infarction[64,65]. Atherosclerotic plaques that have ruptured often have large lipid cores covered by a thin fibrous cap (<60 μm). Lesions with these characteristics have often been termed 'vulnerable plaques'[65]. By contrast, plaques with limited lipid accumulation and thicker fibrous caps are often referred to as 'stable plaques'. This classification oversimplifies considerably the complexity of the mechanisms of atherosclerotic plaque destabilization[66,67], yet has provided a framework for much thought regarding the pathophysiology of acute coronary syndromes for several decades.

Defects in the extracellular matrix that overlies the lipid core of the atherosclerotic plaque can lead to the formation of an overlying fibrous cap, and a fissure can form in this structure. Inflammatory processes can impede synthesis of interstitial collagen by smooth muscle cells in the atherosclerotic plaque, impairing the ability of these cells to maintain the skeleton of the fibrous cap[68,69]. Activated inflammatory cells can also elaborate interstitial collagenases specialized in degrading the key structural components of the fibrous cap of the lesion[70]. Rupture of an atherosclerotic plaque exposes the contents of the interior of the plaque to the blood compartment. Thrombogenic material in the plaque core, notably tissue factor produced by macrophages and smooth muscle cells, can trigger thrombosis, the ultimate and most dreaded complication of atherosclerosis.

Together with locally impaired homeostatic function of the luminal endothelium, persistent and occlusive thrombi can provoke ischaemic insults such as acute coronary syndromes and stroke. Thrombus formation can also contribute to critical ischaemia of the lower extremities and complicate peripheral artery disease. Arterial thrombi that complicate atherosclerotic plaques arise from thrombin-mediated generation of fibrin from fibrinogen. Thrombin also activates platelet aggregation, a process that contributes to clot formation. Recent work has implicated NETs in vascular clotting[71]. NETs consist of strands of DNA that bind leukocyte granular enzymes and proteins such as tissue factor adsorbed from blood and are elaborated by neutrophils that undergo a specialized form of cell death known as NETosis. Thus, blood clots contain fibrin strands, clumps of activated platelets, and NETs that can propagate thrombus formation and amplify intimal injury[72,73].

Under physiological conditions, the arterial endothelium possesses numerous properties that prevent clot formation and promote thrombolysis[41]. Thrombomodulin and heparan sulfate proteoglycans on the endothelial surface and production of nitric oxide and prostacyclin by the endothelial cells contribute to the anticoagulant and antithrombotic properties of the normal endothelial monolayer. Furthermore, the expression of urokinase-type plasminogen activator and tissue-type plasminogen activator combats the persistence of thrombi through promotion of fibrinolysis. Endothelial dysfunction, as occurs in the presence of atherosclerotic risk factors or more acutely during inflammatory activation (for example, due to pro-inflammatory cytokines or pathogen-associated factors, such as bacterial endotoxins), can impair these normal homeostatic properties. Under these circumstances, endothelial cells produce tissue factor, a potent procoagulant molecule, and plasminogen activator inhibitor 1, a key endogenous inhibitor of fibrinolysis[74].

Plaque erosion. Effective anti-atherosclerotic therapy, including measures described below (for example, lipid-lowering therapy, treatment of hypertension and smoking cessation), has shifted the substrate of the thrombotic complications of atherosclerosis. Atherosclerotic plaques have become less inflamed and lipid-laden, and more fibrous, and, therefore, probably less liable to rupture due to fissure of the fibrous cap than in the past[67,75]. Under these circumstances, another mechanism of thrombotic complications of atheroma may account for an increasing proportion of acute coronary syndromes. This alternative thrombotic mechanism, called plaque erosion, seems to arise from lesions with a quite distinct morphology from the typical ruptured plaque (FIG. 4). The lesions complicated by erosion tend to have a rich extracellular matrix without a thin, friable fibrous cap, few inflammatory leukocytes, and little lipid[76]. The mechanisms of plaque erosion have undergone substantially less exploration than those of plaque rupture. Yet, emerging evidence suggests that innate immune activation involving engagement of pattern-recognition receptors, such as Toll-like receptor 2, and the participation of polymorphonuclear leukocytes as amplifiers of the local thrombotic process may contribute to this mode of plaque complication[77,78]. Indeed, NETs may propagate thrombosis during acute coronary syndromes, particularly those caused by intimal erosion[77].

Diagnosis, screening and prevention

Clinical presentation

Atherosclerosis is a diffuse, slowly progressing disease that can affect several arterial beds[79] (FIG. 5). Because of this slow progression, most cases remain asymptomatic for decades. When symptoms do arise, they usually relate to a reduction in blood flow caused by the luminal stenosis (narrowing) or to thrombotic obstruction. Ischaemia due to stenotic, flow-limiting lesions can occur under conditions of increased myocardial oxygen demand, for example during physical exertion, and cause symptoms of angina pectoris. Acute thrombotic occlusion that interrupts myocardial oxygen supply typically results from disruption of atherosclerotic plaques, as described above[64].

The clinical presentation of atherosclerosis can be acute or chronic and varies substantially, depending on the vascular territory involved (FIG. 5). In some arteries, such as renal arteries, the most common presentation is a chronic, long-developing syndrome (for example, progressive renovascular hypertension and/or worsening renal function secondary to renal artery stenosis). In other vascular territories, atherosclerosis most commonly

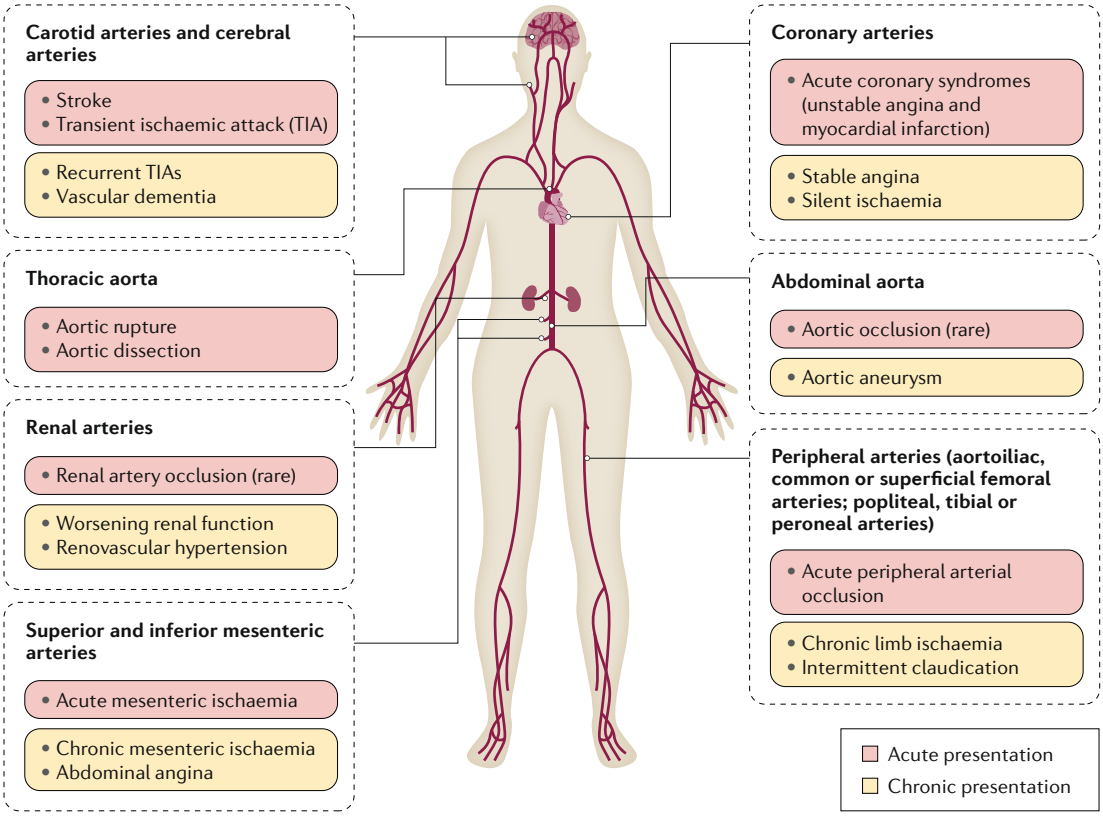

Fig. 5 | **Clinical manifestations of atherosclerosis.** Atherosclerosis is a systemic disease that may involve multiple vessels. Consequently, the clinical manifestations vary widely according to the vascular territory involved. Despite the systemic nature of many risk factors such as hypercholesterolaemia, hypertension, diabetes mellitus and smoking, atherosclerosis tends to involve primarily specific regions of the arterial tree. Arterial areas subjected to either disturbed flow or low shear stress have particular susceptibility to atheroma formation[41]. These conditions prevail at branch points in the arterial tree.

manifests with acute and sudden presentations, such as acute ischaemic stroke due to atherosclerosis. In the coronary arteries, both acute coronary syndromes and chronic presentations (that is, stable angina pectoris) commonly arise.

The definitive diagnosis of the clinical syndromes caused by atherosclerosis usually depends on imaging tests for direct visualization of atherosclerosis or the documentation of target organ ischaemia (TABLE 1). Each imaging method addresses a specific clinical scenario. Whereas ultrasonography and CT angiography are typically used for non-invasive investigation of atherosclerosis in various vascular territories, other more invasive procedures, such as invasive angiography, intravascular ultrasonography or optical coherence tomography, serve mainly to guide interventional therapies. Technologies such as PET and MRI tend to be restricted to use in research on the evaluation of atherosclerosis. Multiple guidelines from various jurisdictions address appropriate use of cardiovascular imaging modalities[80].

Once a definitive diagnosis of clinically significant (see below) atherosclerosis is established, risk stratification of the atherosclerotic disease informs management. Although most individuals with clinically significant atherosclerosis require medical management with lipid-lowering medication (for example, statins) and aggressive management of other risk factors, the extent, severity, location and plaque characteristics of the atherosclerotic disease (as assessed by the aforementioned imaging methods) determine additional medical, catheter-based or surgical interventions to reduce ischaemic symptoms or risk of acute events.

Clinical significance

Since the initial demonstration by invasive angiography of the association between ischaemic symptoms and narrowing of the arterial lumen, the degree of luminal stenosis assesses the clinical significance of atherosclerosis. Classic studies suggest that thresholds of 50% to 75% luminal narrowing associate with physiological limitations in coronary flow at stress and at rest[81]. Thus, patients usually start experiencing symptoms initially under conditions of increased oxygen demand such as physical or emotional stress, when stenosis exceeds a threshold of 50–75%[81] (FIG. 6). Until recently, these results traditionally helped to define the clinically significant atherosclerotic plaque[82]. More recently, studies have used fractional flow reserve (FFR) to assess the severity of atherosclerotic disease in the coronary arteries. This method evaluates the intra-coronary pressure to determine if a luminal reduction is limiting flow, by comparing the pressure upstream and downstream of the lesion after administration of a vasodilator such as adenosine to augment flow. FFR measurements have

demonstrated that the relationship between luminal narrowing and flow is far from linear. Other plaque characteristics such as length, eccentricity (indicated by a plaque volume three times larger on one side than on the other) and positive remodelling (an outward compensatory remodelling of the arterial wall to maintain a lumen diameter), as well as limitations associated with estimation of luminal narrowing on invasive angiography, may all influence the functional consequences of any stenosis[83]. As a result, functional assessments such as with FFR can help to define the clinical significance of a coronary atherosclerotic lesion[84].

Over the last decade, studies have also challenged the concept that luminal narrowing or downstream ischaemia determines the clinical significance of atherosclerotic disease. Studies have shown that the risk of plaque rupture and a subsequent acute event associates more strongly with the propensity of an atherosclerotic plaque to rupture and with systemic patient characteristics, such as inflammation, rather than the degree of focal stenosis[85]. This concept has received further support from evidence that overall plaque burden (measured by CT or by invasive angiography), irrespective of the luminal narrowing, remains the strongest anatomical predictor of incident myocardial infarction or cardiovascular death. The risk portended by more extensive non-obstructive disease resembles that associated with obstructive disease[86,87]. Thus, we need to redefine the criteria for clinical significance of atherosclerotic lesions. We propose a practical, clinically oriented definition of atherosclerotic disease, which extends generally to virtually any arterial bed affected by atherosclerosis (FIG. 5). Atherosclerosis should be considered clinically significant if it leads to the development of documented downstream ischaemia, has already led to an acute vascular event (for example, an acute coronary syndrome) or entails a large documented atherosclerotic burden (for example, a coronary artery calcium (CAC) score, which quantifies the degree of calcification, of >200) or individual plaques that display high-risk characteristics such as high lipid content, compensatory enlargement or spotty calcification. Although overall plaque burden may not be associated with symptoms or flow reduction, this classification has clinical utility, as an increased risk of future cardiovascular events should prompt consideration of changes in clinical management. As this definition of clinically significant atherosclerosis includes asymptomatic disease, the identification of individuals at risk requires a screening strategy.

Screening

Atherosclerosis meets several of the traditional Wilson's criteria[88] that define a disease amenable to screening, such as: the condition is an important health problem (that is, it has a high prevalence), treatment exists for the condition, there is a long latent and/or asymptomatic stage,

Table 1 | **Diagnostic tests for atherosclerosis**

Test	Imaging characteristics	Advantages	Limitations	Routine clinical applications
Direct atherosclerotic plaque visualization				
Ultrasonography or Doppler ultrasonography	Enables differentiation of some plaque components	Non-invasive and no radiation exposure required	Can only be used in large-calibre and superficial vessels	Carotid arteries, intracerebral arteries (with transcranial Doppler ultrasonography), abdominal aorta, lower extremity vessels
CT angiography	Enables differentiation between calcified and non-calcified plaque	Non-invasive	Iodinated contrast agent needed; radiation exposure required	Most vascular territories
MRI	No evaluation of plaque components	Non-invasive and no radiation exposure required	Limited to large-calibre vessels; potentially useful in selected cases of smaller-calibre vessels such as coronary arteries	Carotid artery and aorta
Intravascular ultrasonography	Plaque tissue characterization by analysis of radiofrequency backscatter from the ultrasound signal: 'virtual histology'	Excellent for evaluation of plaque burden and composition	Invasive; radiation exposure and iodinated contrast agent (for catheter positioning) required; limited availability	Selected cases of coronary artery evaluation
Optical coherence tomography	High-resolution imaging for plaque characteristics	Excellent near-field resolution permitting visualization of the intimal morphology in detail	Invasive; radiation exposure and iodinated contrast agent (for catheter positioning) required; limited availability and limited penetration, limiting the evaluation of deeper areas of the plaque	Routine clinical application restricted to very selected cases of coronary artery evaluation
No direct atherosclerotic plaque visualization				
PET	Identifies glucose uptake by inflammatory and other cells in plaques	Evaluates plaque metabolism	Radiation exposure required; can only be used in large-calibre vessels	Applications restricted to research
Invasive angiography	Classic reference standard for the evaluation of luminal stenosis	Widely available; good visualization of the lumen	Invasive; radiation exposure and iodinated contrast agent required; does not visualize the plaque directly	Most vascular territories

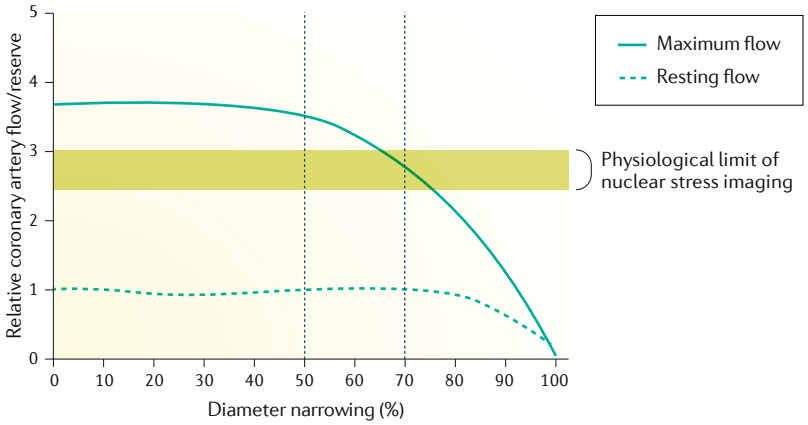

Fig. 6 | **Relationship between luminal diameter narrowing and relative coronary artery flow/reserve at rest and under stress conditions.** Both resting and maximum coronary flows remain unchanged with stenosis of up to 50% luminal obstruction. Above this threshold coronary flow decreases substantially with increased luminal obstruction. The highlighted range is the limit of detection for regular SPECT stress perfusion imaging. The maximum coronary flow was calculated as a fraction of the resting coronary flow, and the values on the *y* axis are relative to the resting flow with no stenosis. Adapted with permission from REF.[81], Elsevier.

and the natural history is adequately understood. Yet, the policy regarding the appropriate screening strategy for atherosclerosis detection and the prevention of its complications remains variable across different guidelines[89–91]. Despite the disagreements, virtually all guidelines recommend the initial evaluation of individual risk of future CVD events based on clinically evident risk factors[89,91,92]. Interestingly, the individual risk scores that serve as screening tools do not involve the actual detection of atherosclerosis but rather the factors discussed above that increase the individual risk of future CVD events.

For selected populations, the screening strategy might incorporate a more aggressive treatment strategy or use of other specific testing. For example, individuals with familial hypercholesterolaemia merit special interest because of life-long exposure to high LDL-C levels, which increase overall risk for CVD events. This genetic condition typically remains underdiagnosed and undertreated. Its genetic basis supports cascade testing of first-degree family members of individuals with familial hypercholesterolaemia. Even in those without recognized mutations, a family history of early onset of coronary heart disease or CVD (at <60 years of age) also increases the risk of events.

Additional tests (such as carotid ultrasonography, CAC score measurement assessed by CT, and coronary CT angiography) can identify atherosclerosis non-invasively. However, current data do not support their use as the sole method of screening for atherosclerosis with the aim of primary prevention, though some of the tools have robust prognostic value and can act as an alternative approach to additional risk stratification according to most guidelines, particularly for individuals with intermediate risk for whom treatment decisions are unclear[93]. Other tests, such as brachial artery flow-mediated dilation and ankle–brachial index, may provide prognostic value for risk stratification for future CVD events, although they do not focus on the direct detection of disease, and their routine clinical use for screening has its limits.

To date, the role of the additional testing mentioned above for screening and risk stratification is restricted at least in part owing to the limited number of medical interventions that have documented benefit (for example, statins) when used in the primary prevention setting. Recent data on other lipid-lowering medications[94], anti-inflammatory drugs[95] and new anti-thrombotic drugs[96] leading to a reduction in future CVD events will probably spur an increase in the research on the role of testing to identify suitable candidates for new therapies in both the primary and secondary prevention settings. This strategy will provide asymptomatic patients with enough data to remain engaged in shared decision-making for treatment, as well as promote the use of cost-effective strategies to enable a sustainable use of health-care resources.

Prevention

The increasing focus on CVD prevention stems from an appreciation that the improved treatment of patients cannot alone address the enormous global burden of CVD, which experts predict will increase substantially, particularly in low-income and middle-income countries[97]. New insights into the importance of lifetime risk management of CVD has spurred the current interest in prevention, with an emphasis placed on young age groups, and on new opportunities derived from the digital health revolution. Addressing these opportunities should embrace a fundamental shift in approach with a focus on 'wellness maintenance' and not just 'disease treatment'.

Economics. The direct cost of treating CVD in the USA currently exceeds US$300 billion per year, and predictions put both direct and indirect costs to almost a trillion US dollars by 2030 (REF.[98]). Most countries cannot sustain such costs. The adoption of a healthy lifestyle from early life should markedly reduce the atherosclerosis burden and its complications, and widespread use of currently recommended preventive therapies such as statins for primary prevention in at-risk individuals will probably demonstrate high cost-effectiveness from a societal perspective[99].

Effects of lifetime exposure to risk factors. Atherosclerosis begins decades before the appearance of its clinical consequences. Several studies (first by autopsy, then using in vivo imaging) show that subclinical atherosclerosis increases progressively from the first decade of life, and in the PESA cohort (asymptomatic employees in a Spanish bank) was present in 63% of the population (71% of men and 48% of women) by 40–54 years of age[79]. This preclinical disease relates to levels of classic CVD risk factors even in children and adolescents in a cumulative manner. Exposure to risk factors during early life relates to incidence of future cardiovascular events[100] as well as evidence of worse mid-life cognitive performance. Unhealthy behaviour begins early, and habits acquired in childhood probably persist into adulthood. The global epidemic of childhood obesity continues to

affect enormously population health, as does tobacco use and a sedentary lifestyle in teenagers and adults. Clinical studies have demonstrated that the cardiometabolic changes measured in overweight and obese adults already exist across the normal weight profile of children even before puberty[101]. Risk factors such as blood pressure and lipids vary continuously across the weight spectrum of pre-pubertal children in the UK. Children from economically disadvantaged backgrounds may have particular vulnerability[102]. Studies in children have also shown that weight reduction can improve the level of risk factors and vascular wall function[103]. Managing childhood adiposity to delay and/or prevent atherosclerosis is a key public health challenge that will require a broad approach, educating not only the children, but also their families as well as managing their social and living environments[104].

Risk-factor exposure during early life relates to incidence of future CVD events[100] and cognitive impairment. Prospective randomized clinical trials to evaluate the benefit of early control of risk factors on future CVD events encounter obvious obstacles, but genetic studies using Mendelian randomization support the potential benefit of lowering lifetime exposure to risk factors. In a pooled analysis of 102,774 individuals who sustained 14,368 events, even modestly lower levels of blood pressure and LDL-C as a result of favourable genetic variants translated to a 46% clinical event reduction[105]. Sustained lifestyle improvements may yield similar benefits. Prospective clinical trials using risk profiles and arterial function tests support the concept that CVD may be largely preventable if lifetime exposure to risk factors can be reduced[106,107]. Although the entire population would benefit from early sustained CVD risk-factor lowering, achievable by lifestyle changes and reduction in environmental exposures, certain subgroups have a greatly increased risk for future CVD and, therefore, require additional treatment. Examples include individuals with monogenic disorders such as familial hypercholesterolaemia and those with other medical conditions such as type 1 or type 2 diabetes mellitus, kidney disease and chronic inflammatory diseases (for example, rheumatoid arthritis). Periodontitis, the most common cause of chronic systemic inflammation, has a causal relationship with arterial wall changes, metabolic control and future CVD events[108–111].

Patient engagement. Effective adherence to long-term prevention strategies requires that the public and patients be empowered to take responsibility for their cardiovascular health. Communication should focus on both risk and opportunities with emphasis on the benefits gained from early and sustained risk-factor lowering. Ten-year risk prediction models, which are used to guide treatment, have much less value for prevention over a lifetime. Few individuals of ≤50 years of age, even with multiple modifiable risk factors, have a 10-year absolute risk of >7.5%, which is the threshold currently recommended for statin prescription in the USA[112]. The MESA/CARDIA studies showed that individuals of ≤50 years of age with a low 10-year risk but a high lifetime risk already exhibit evidence of subclinical atherosclerosis, with increased carotid intima–media thickness or coronary artery calcification[113]. Estimates show that >50% of the US adult population have a 10-year risk of <10% but a lifetime risk of ≥39%[112]. The Joint British Societies for the prevention of cardiovascular disease (JBS3) introduced a risk calculator, adopted in the UK, that utilizes understandable metrics such as 'heart age'[114] to encourage and engage patients. This approach has shown very promising results for effective communication with patients and resulting behavioural change[115,116].

The shared biology between CVD and other diseases of ageing provides opportunities for broad health gains from early risk-factor intervention. Of note, the cluster of risk factors that increase the risk of CVD (for example, blood pressure, tobacco use, obesity, sedentary lifestyle and diabetes mellitus) also associate with cognitive decline and dementia[117]. The burden of these potentially modifiable risk factors from childhood and middle age have a stronger relationship to brain function than levels in later life, supporting a similar 'lifetime exposure model' for CVD and cognitive function[118,119]. Numerous intervention trials examining the effect of lowering multiple cardiovascular risk factors on cognitive outcomes are underway, following the FINGER trial, which showed improved cognitive performance with a multifactorial intervention. Communication of the benefits of early reduction in CVD risk factors on multiple diseases, including future CVD and dementia, delivers a powerful message on the importance of prevention and supports behavioural change[120].

Digital health. The revolution in digital health provides a new opportunity for CVD prevention. The public currently demonstrates increased interest in their cardiovascular health, as shown with the adoption of wearable devices that track exercise, heart rhythm, diet and sleep, and the use of online risk calculators[114,121]. Continuous monitoring of health-related parameters during normal daily life reinforces positive behaviour patterns, and the analysis of such extensive real-life data will probably substantially refine risk prediction models. As these tracking devices become increasingly sophisticated, the data collected will provide epidemiological insights, refine safety and end points in clinical trials, inform clinical care, and change the culture of CVD prevention.

Management

Because of the multifactorial nature of atherosclerosis, its management should target all known treatable risk factors. Ideally, primary prevention starts by adopting a healthy lifestyle from childhood (primordial prevention), but risk-factor modification to prevent or even reverse the progression of the atherosclerotic process can provide benefit at any stage of atherosclerotic disease, even in the context of secondary prevention. Although the reduction in cholesterol levels, blood pressure and tobacco use has substantially decreased CVD mortality in many populations[122], an increase in other lifestyle-related risk factors such as obesity, type 2 diabetes mellitus, sedentary behaviour and psychosocial stress, challenge these positive results[123]. Whereas lifestyle

modification remains pertinent for all individuals, the use of lipid-lowering medication depends on the estimated risk of incident CVD events. Some studies also recommend anti-platelet therapy after individual assessment of risk and benefit, though this treatment option remains highly debated in the literature[124–126]. Indeed, current data do not support a favourable risk:benefit balance for aspirin therapy in primary prevention[127,128]. If atherosclerotic disease has progressed to a stage causing symptomatic ischaemia, revascularization therapy can often relieve symptoms, and possibly increase survival, a conjecture currently under intense study[89].

Lifestyle interventions

Lifestyle interventions furnish the foundation of therapy, have the advantage of targeting multiple risk factors, and hold great importance to all with any stage of atherosclerotic disease. The emphasis on diet, physical activity and abstinence from tobacco use in the prevention of atherosclerotic disease remains essential[89]. A healthy diet not only influences lipid and risk-factor profile favourably while decreasing obesity, but also affects gut microbiota that may produce metabolites harmful to the vasculature[129]. Smoking cessation remains the most clinically effective and cost-effective strategy for the prevention of atherosclerotic disease[130]. Blood pressure control (with lifestyle intervention as well as medication when necessary) also remains vital depending on the level of blood pressure and the risk profile of the patient[131]. The management of diabetes mellitus reduces the risk of microvascular complications and, with certain newer agents, macrovascular disease, and improves cardiovascular outcomes in these patients[132]. Lifestyle modifications to reduce LDL-C and lipid levels should accompany recommendations to all patients, and should accompany guideline-directed pharmacological therapy.

Lipid-lowering pharmacological therapy

Lipid-lowering therapy remains the cornerstone of the management of atherosclerotic disease. Evidence from epidemiological, genetic and Mendelian randomization studies and from randomized clinical trials involving >2 million participants and >20 million person-years of follow-up have shown that LDL-C acts as a causal risk factor[14]. Thus, early control of LDL-C holds great importance. Randomized clinical trials have consistently demonstrated that lowering LDL-C reduces the risk of CVD events proportionate to the absolute fall in LDL-C independent of other risk factors[133]. A substantial overall record of safety has been amassed for the use of statins, with rare serious complications, although some individuals do not or will not tolerate statin therapy for various reasons, primarily myalgia (muscle aches)[134]. These findings support the current concept that lipid-lowering therapy should target primarily LDL-C.

Although some differences exist in the approach to LDL-C lowering in various guidelines, the principles remain the same. The intensity of treatment reflects the risk profile of the patient, defined on the basis of known disease or by various risk scores in those without clinical CVD. However, Mendelian randomization analyses have shown that having lifetime low cholesterol levels reduces the probability of CVD events to a greater extent than 2–5 years of pharmacological lipid-lowering therapy[14]. Thus, early intervention before CVD manifests should prove more effective than initiating therapy after CVD onset[135,136]. The 2016 European guidelines and the 2018 US cholesterol clinical practice guidelines[137] recommend that treatment goals for LDL-C depend on the risk profile of the patient[89,137]. Pharmacological treatment should start with a statin.

Non-HDL-C (total cholesterol concentration minus HDL concentration) represents the cholesterol in all atherogenic particles. Although usually concordant with LDL-C, some discordance between LDL-C concentration and non-HDL-C concentration may exist in insulin-resistant states, in which non-HDL-C may better predict disease than LDL-C[138]. Thus, having reached the desired LDL-C goal, non-HDL-C should serve as a secondary target for treatment, especially in individuals with diabetes mellitus. In the 2016 European guidelines, the goals for non-HDL-C are <100 mg/dL (2.6 mmol/L) for very-high-risk patients, <130 mg/dL (3.4 mmol/L) for high-risk patients and <145 mg/dL (3.8 mmol/L) for moderate-risk patients[89]. As detailed below, the 2018 US guidelines recommend treatment of those with established atherosclerosis with high-intensity or maximally tolerated statin therapy, and allocation of statins to other groups depending on risk stratum[137] defined by clinical characteristics or a risk calculator.

Fibrates (which are weak agonists of a widely expressed nuclear receptor protein that regulates lipid metabolism) lower the levels of triglyceride-rich lipoprotein particles, which augment atherogenesis. Yet, prospective randomized controlled trials of fibrates in combination with statins have not met their primary end points of improving cardiovascular outcomes. In several of these studies, the subgroups with low HDL-C and high triglyceride levels did derive benefit from combination therapy[139]. The European guidelines recommend statins as the first choice to reduce risk in patients with hypertriglyceridaemia, but suggest the consideration of the use of fibrates in combination with statins to reach non-HDL-C goals, especially in the high-risk patient with diabetes mellitus[89]. The FDA has withdrawn approval of fenofibrate in combination with statins[140]. Gemfibrozil should never be combined with statins owing to a strong drug–drug interaction.

Statins. Statins inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoAR), the rate-limiting enzyme in the synthesis of cholesterol. Compelling evidence from randomized clinical trials shows that reducing LDL-C with statins decreases CVD events. In a large meta-analysis from statin trials, treatment with a statin associated with a log-linear 22% reduction in the risk of major CVD events per millimole per litre reduction in LDL-C[141]. Statin prescriptions should reach the highest recommended or tolerated dose to attain the treatment goal. If the goal still remains unmet, combination therapy with a statin and a non-statin drug may prove successful.

On the other hand, the American College of Cardiology/American Heart Association 2018 guidelines

recommend universal use of statins in all high-risk individuals[142]. According to these guidelines, the following groups of patients should receive high-dose or moderate-dose statin therapy: individuals with clinical atherosclerotic CVD; individuals with LDL-C >190 mg/dL; and individuals of 40 to 75 years of age with diabetes mellitus and LDL-C in the range 70–189 mg/dL but without clinical atherosclerotic CVD. In adults 40 to 75 years of age evaluated for primary atherosclerotic CVD prevention, a clinician–patient risk discussion should precede the start of statin therapy. The risk discussion should include a review of major risk factors, the presence of risk-enhancing factors (such as a high CAC score or CRP), the potential benefits of lifestyle and statin therapies, the potential for adverse effects and drug–drug interactions, consideration of costs of statin therapy, and patient preferences and values in shared decision-making.

All guidelines agree that statins should remain the first choice in initiating pharmacological therapy owing to the ample evidence supporting their efficacy. Depending on the type, potency and dose of statin used, a 30–50% reduction in LDL-C levels may prove possible. Yet, achieving treatment targets can be challenging, especially in some patient groups, for example, individuals with familial hypercholesterolaemia and those with statin intolerance, and, therefore, may require combination therapy for further LDL-C reduction.

Non-statin lipid-lowering drugs. Early clinical trials have shown that bile-acid sequestrants also lower LDL-C and decrease CVD events. Yet, gastrointestinal adverse effects, drug interactions and elevation of triglyceride levels limit their widespread use[143]. Ezetimibe inhibits cholesterol absorption by enterocytes and augments expression of liver LDL receptors, and has proven useful in combination therapy. Ezetimibe, when added to statins, further reduces LDL-C by 15–20%[144]. The IMPROVE-IT study showed that in patients who survived an acute coronary syndrome, adding ezetimibe to a statin associated with a 6.5% proportional reduction in major CVD events[145].

PCSK9 binds to LDL receptors and promotes their intracellular degradation, and inhibiting PCSK9 can decrease LDL-C substantially. PCSK9 inhibitors, a newer class of drugs, can be used in combination with statins in selected high-risk patients. Studies with anti-PCSK9 monoclonal antibodies have shown that they can decrease LDL-C up to 60%[146,147]. Clinical trials have tested the fully human antibodies evolocumab and alirocumab as well as the humanized antibody bococizumab in >10,000 patients. The GLAGOV study showed that, on a background of statin therapy, decreasing LDL-C levels with evolocumab even further could reverse coronary atherosclerosis (assessed with coronary ultrasonography)[148]. The FOURIER and ODYSSEY clinical outcome trials showed that inhibition of PCSK9 with evolocumab or alirocumab in addition to statin therapy lowered LDL-C levels substantially and reduced the risk of CVD events with a good safety profile over the duration of the studies[149]. In the SPIRE trials, adding bococizumab to statins decreased adverse cardiovascular outcomes in high-risk patients with a baseline LDL-C of >100 mg/dL, but the development of anti-bococizumab antibodies in 15–20% of patients attenuated the substantial reduction in LDL-C[150]. Small interfering RNAs such as inclisiran provide another way to inhibit PCSK9 with impressive durability, and have entered clinical investigation[151].

Evidence from trials with combination therapy using ezetimibe and PCSK9 inhibitors in addition to statins show that this therapy enables the achievement of much lower LDL-C levels than was previously possible (from 70 mg/dL to lower), and this further reduction conferred greater CVD benefit[152]. The European Atherosclerosis Society/European Society of Cardiology published a consensus paper to help to identify patients who would derive the most potential benefit from this new therapy, while also taking into account the financial constraints of health-care budgets, given current costs of PCSK9 inhibition therapy[153,154].

This consensus recommends consideration of treatment with a PCSK9 monoclonal antibody in very-high-risk patients with atherosclerotic disease or in patients with severe familial hypercholesterolaemia without atherosclerotic CVD with substantially elevated LDL-C levels despite maximal statin–ezetimibe therapy. Patients in these groups with verified statin intolerance also merit consideration for PCSK9 inhibition therapy. A cost-effective approach to the use of PCSK9 inhibitor therapies targets the individuals at highest risk[154]. Post-hoc analyses from trials suggest that certain subgroups of patients, such as those with coronary artery bypass graft surgery, multivessel atherosclerotic disease and recent myocardial infarction, may derive great benefit from aggressive LDL-C lowering with combination therapy[155].

The use of omega-3 fatty acid supplements to prevent CVD have yielded controversial results in the past. However, a recent trial showed that among statin-treated patients with elevated triglyceride levels the risk of ischaemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo[156].

Non-lipid-lowering therapy

Antiplatelet drugs. Platelets play a crucial part in the pathogenesis of atherosclerosis-associated thrombotic processes. Antiplatelet therapy does not fall under routine recommendations in primary prevention of atherosclerosis, owing to the increased risk of bleeding. However, in secondary prevention settings, the benefits of aspirin generally exceed the bleeding hazards[157,158]. Inhibitors of the P2Y purinergic receptor 12 (P2Y12, an adenosine diphosphate receptor expressed by platelets) further inhibit platelet aggregation. These agents should be used in addition to aspirin in acute coronary syndromes or in the setting of percutaneous coronary intervention[159]. A recent study has shown that among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone[96].

Anti-inflammatory drugs. The inflammatory component of atherosclerotic disease has gained attention as a therapy target because of several clinical trials to test anti-inflammatory agents. The anti-IL-1β antibody canakinumab reduces major adverse cardiovascular events (MACE) by 15% in patients after myocardial infarction with evidence of inflammation gauged by CRP levels above the median[95]. In the responders who achieved a reduction in CRP level greater than the median reduction, MACE fell by 25%, and total and cardiovascular mortality by >30%[96]. In an exploratory analysis, the incidence of fatal lung cancer fell by up to 77% in those treated with canakinumab[160].

Large secondary prevention studies are evaluating colchicine as an alternative anti-inflammatory agent[161]. Methotrexate in a low-dose weekly regimen did not reduce cardiovascular events in the Cardiovascular Inflammation Reduction Trial (CIRT). This treatment did not, however, lower biomarkers of inflammation CRP, IL-1β or IL-6[162], and the participants did not have elevated CRP levels at baseline.

NSAIDs, commonly used in a variety of conditions, inhibit prostaglandin synthesis. Theoretically, they may exert beneficial effects on vascular inflammation; however, their capacity to inhibit production of prostacyclin, a prostaglandin that inhibits platelet aggregation, may counterbalance such effects. Coxibs selectively inhibit cyclooxygenase-2 (COX-2, also known as prostaglandin G/H synthase 2). This enzyme inhibits prostacyclin production without interfering with production of the proaggregatory thromboxane A2. Inhibition of COX-2 might thus increase CVD events[163,164].

Therapeutic challenges

Therapeutic challenges include nonadherence to lifestyle and lipid-lowering therapy, with most patients not achieving or maintaining their goal. The benefits observed in randomized clinical trials will only apply in practice if patients adhere to treatment. Nearly half of patients discontinue statin use within the first year after the initial prescription, with higher discontinuation rates after 2 years[165]. Discontinuation associates with increased risk for CVD events and death[166]. Statin-associated muscle symptoms, such as myalgia, remain the most frequent reason for nonadherence. Although there are no objective criteria for definitive diagnosis of statin intolerance, patients who present with statin-associated symptoms should undergo careful statin re-challenge (that is, the reintroduction of a statin after suspending the treatment for ≥4 weeks, during which time symptoms abate). Evidence shows that adherence to therapy remains important in high-risk patients, and continued statin use even after an adverse reaction is associated with a reduced incidence of death and CVD events[167–169].

Although not achieving the treatment goal is a very important determinant of residual risk, CVD events can still occur in optimally treated patients who have achieved their LDL-C goal. Combination therapy could lower CVD events even further by achieving LDL-C levels below guideline-recommended levels. Other risk factors besides LDL-C also contribute to residual risk and all known risk factors such as tobacco use, diabetes mellitus, hypertension and obesity should be treated. Remnant lipoproteins, Lp(a), and inflammation also contribute to the residual risk, and their management is currently under study.

New developments in imaging technologies will continue to expand and validate personalized risk-assessment and tailored treatment according to patient and plaque characteristics in the future. Awaiting such advances, we must strive to implement and encourage adherence to treatment following existing guidelines.

Quality of life

Health-related quality of life (HRQOL) is a key patient-centric outcome that represents a person's perception of their sense of well-being in the context of their expectations for health[170]. It links biological variables to symptom burden, functional capacity, exercise capacity and psychological well-being; these parameters are collectively referred to as patient-reported outcomes[171]. Given the improved survival of patients with atherosclerosis (and, therefore, the increased total lifetime burden of coexisting with the disease), research into HRQOL of these patients has increased.

Patients with atherosclerosis have an HRQOL worse than that of age-matched healthy individuals, yet the individual responses of these patients are quite variable[172]. Progressive atherosclerosis often leads to increased angina pectoris, fatigue, dyspnoea and exercise intolerance. Complex treatment regimens and healthcare utilization may additionally aggravate HRQOL by affecting a patient's psychological and social well-being[173], which is also impaired by anxiety due to prognosis and fear of future CVD events, depression, sleep disturbances and adverse drug effects. The occurrence of acute coronary syndromes often associates with reduced HRQOL[173]. Other factors that can further impair the HRQOL of patients with atherosclerosis include comorbid conditions (for example, diabetes mellitus, peripheral artery disease and obesity), the development of heart failure, young age, female sex, poor or inadequate emotional support, belonging to a racial minority, low socioeconomic status and disease severity[173–175].

Three types of instruments serve to measure HRQOL in atherosclerosis: generic, disease-specific for atherosclerosis, and disease-specific for ancillary disease conditions relevant to the individual. Generic instruments, such as the Short Form-36 Health Survey and EuroQol 5D, enable comparison of the HRQOL of patients with atherosclerosis to that of other patients and measurement of overall changes in health status; importantly, the adverse effects of a drug may counterbalance the improvements in atherosclerosis-related symptoms, and the weights of both positive and negative effects depend not only on the magnitude of each effect but also on the importance given to it by the patient. Common disease-specific instruments include the Seattle Angina Questionnaire (SAQ) and the Myocardial Infarction Dimension Assessm ent Scale (MIDAS)[176]. These latter instruments more readily respond to change and can measure efficacy of an intervention or track changes over time. Numerous

instruments can measure HRQOL associated with ancillary conditions and common disease states, including functional capacity (for example, the Duke Activity Status Index (DASI))[177] and depression (for example, the Patient Health Questionnaire 9 (PHQ-9))[178].

Revascularization therapy remains the cornerstone for improving HRQOL in patients with multi-vessel atherosclerotic disease. Patients who underwent percutaneous coronary intervention have better quality of life improvement by 1 month and fewer physical limitations than patients who received surgical revascularization[179]; however, after ≥6 months, patients who underwent surgery have greater improvements in angina pectoris and improved overall HRQOL. High-intensity interval training and moderate exercise training have similar benefits on HRQOL[180]. Nurse-led secondary prevention efforts, including education and behavioural counselling and support, and patient-led lifestyle changes result in improvements in HRQOL[181,182]. Yet, understanding how individual elements of these interventions translate into improved outcomes remains limited. As we continue to make progress in the management of acute and chronic atherosclerosis, we must also develop strategies to maximize HRQOL.

Outlook

The very advances in managing the complications of atherosclerosis have extended life, but many individuals are left with impaired cardiac function, contributing to an epidemic of heart failure due to ischaemic cardiomyopathy. Beyond its human costs, the burden of heart failure creates a major strain on health-care systems and resources. We have made much progress in understanding the mechanisms of atherosclerosis. We possess many tools for treating or managing atherosclerosis and its complications. Yet, the job is unfinished. We have only partially mastered atherosclerosis, and much remains to be done. Many of the contemporary interventions that extend life depend highly on expensive and invasive technology or medications. For example, percutaneous and surgical management of coronary and peripheral atherosclerotic disease, albeit often effective, depends on increasingly complex technologies. Arrhythmias and heart failure most often arise because of atherosclerosis. When these conditions are advanced, their treatment often also involves highly technological interventions such as pacemakers, cardiac resynchronization therapy, and mechanical circulatory support. Physician and writer Lewis Thomas referred to such solutions as 'halfway technologies'.[183] We have succeeded in creating a cohort of survivors of atherosclerotic complications who live longer, but experience considerable morbidity and poor quality of life. Some of the simpler solutions to stemming the epidemic of atherosclerosis require behavioural or societal changes. Our ability to deploy adoption of healthy diets, regular physical activity, tobacco cessation and other preventive measures has lagged behind our technological prowess.

We must strive on several fronts to confront the remaining burden of atherosclerotic risk. In the laboratory, we must continue to explore the fundamental causes of this disease, keeping our eye on the 'moving target' of the human disease, and on the limitations of our in vitro and animal experiments. In our translational undertakings, we must develop and test rigorously novel therapeutics that address novel pathways and address unmet needs rather than exhausting well-mined targets. In our clinical practice, we should strive to implement what we already know in an evidence-based manner, and never permit guidelines or practice algorithms to replace our bond with individual patients and our judgement and experience regarding an individual's particular circumstances, needs and preferences. As a society, we need to combat unhealthy lifestyles and provide a healthy environment to limit the spread of CVD in the future.

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Competing interests
P.L. is an unpaid consultant to, or involved in clinical trials for, Amgen, AstraZeneca, Esperion Therapeutics, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Novartis, Pfizer, Sanofi-Regeneron and XBiotech, Inc. P.L. is a member of scientific advisory boards for Amgen, Corvidia Therapeutics, DalCor Pharmaceuticals, IFM, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune and Novartis. P.L.'s laboratory has received research funding in the last 2 years from Novartis. L.B. has performed lectures and advisory board work in 2017 for Sanofi, Amgen and Astrazeneca. L.B. receives research grant support from AstraZeneca and research funding and grants from Fondo de Investigaciones Sanitarias (FIS), Plan Nacional-Retos MINECO and the EU. G.K.H. is the inventor of patents regarding immune therapy in atherosclerosis. G.K.H. is also the recipient of grants for research on immune mechanisms in atherosclerosis from the Swedish Research Council, the Swedish Heart-Lung Foundation and the EU. J.D. has received CME honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk and Bayer. J.D. is a member of a Study Steering Committee for Novo Nordisk and has received research grants from the British Heart Foundation, MRC(UK), NIHR, PHE, MSD, Pfizer, Aegerion, Colgate and Roche. M.S.B. has received research support funding from Sanofi and consulting fees from Boston Scientific. L.T. is a member of the scientific advisory boards for Merck, Abbott, Amgen, Sanofi and Daichi Sankyo. L.T. also performed lectures for Abbott, Astra, Actelion, Merck, Servier, Recordati, Mylan, Amgen, Novartis, Sanofi, Pfizer, Bayer, Novo Nordisk and Sanovel. E.F.L. reports institutional research grant and consulting from Novartis, and institutional research grants from Amgen and Sanofi. J.E.B. declares no competing interests.

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