

The changing landscape of atherosclerosis

<https://doi.org/10.1038/s41586-021-03392-8>

Peter Libby^{1,2}✉

Received: 29 May 2020

Accepted: 24 February 2021

Published online: 21 April 2021

 Check for updates

Emerging evidence has spurred a considerable evolution of concepts relating to atherosclerosis, and has called into question many previous notions. Here I review this evidence, and discuss its implications for understanding of atherosclerosis. The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case. The risk factor profile has shifted as levels of low-density lipoprotein (LDL) cholesterol, blood pressure and smoking have decreased. Recent research has challenged the protective effects of high-density lipoprotein, and now focuses on triglyceride-rich lipoproteins in addition to low-density lipoprotein as causal in atherosclerosis. Non-traditional drivers of atherosclerosis—such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress—have also gained attention. Inflammatory pathways and leukocytes link traditional and emerging risk factors alike to the altered behaviour of arterial wall cells. Probing the pathogenesis of atherosclerosis has highlighted the role of the bone marrow: somatic mutations in stem cells can cause clonal haematopoiesis, which represents a previously unrecognized but common and potent age-related contributor to the risk of developing cardiovascular disease. Characterizations of the mechanisms that underpin thrombotic complications of atherosclerosis have evolved beyond the ‘vulnerable plaque’ concept. These advances in our understanding of the biology of atherosclerosis have opened avenues to therapeutic interventions that promise to improve the prevention and treatment of now-ubiquitous atherosclerotic diseases.

Although atherosclerotic cardiovascular disease was previously considered a problem that was concentrated in the industrialized world, it now spans the globe. We have witnessed an ‘epidemiological transition’^{1,2}. Increased sanitation, vaccination and the treatment of acute infections have diminished the prevalence of communicable diseases in developing countries, and more individuals now survive to experience chronic diseases such as atherosclerosis (see ref. ³ for an introduction to the fundamental concepts of atherosclerosis). The adoption of less healthy dietary patterns may also have contributed to this trend. Many people now live longer only to suffer the consequences of atherosclerosis, including myocardial infarction, ischaemic cardiomyopathy (which is the commonest cause of heart failure), strokes (which often rob people of their independence, mobility, cognition or ability to communicate) and peripheral arterial disease, which limits activity and jeopardizes limbs. These conditions contribute to ‘morbidity extension’ in the developing world such that, although many individuals escape early death, they must bear the burden not only of chronic cardiovascular diseases but also of arthritis, depression and other long-term impediments to a healthy life. Today, the major pool of risk for developing cardiovascular disease occurs not in Western countries but in the more populous developing world. Atherosclerotic cardiovascular disease now accounts for the majority of mortality worldwide. This global spread creates an urgent need to understand the genesis of this malady, advance in its management and develop prospects for alleviating its

burden. This Review addresses the evolving concepts of atherogenesis and the opportunities for preventing and treating atherosclerosis afforded by new insights into its pathogenesis.

The changing face of atherosclerosis

The classic candidate for heart attack was a middle-aged, white man with hypertension and hypercholesterolaemia, who smoked cigarettes. This picture has evolved considerably in recent decades. We now possess effective therapies for the treatment of high blood pressure and lipid disorders, and control of hypertension and hypercholesterolaemia has improved⁴. A reduction in smoking, accompanied by a decrease in second-hand smoke, has gained a foothold in many societies. We have further witnessed a vast change in people with cardiovascular risk and those who suffer from acute coronary syndromes. Although individuals in mid-life do not evade risk, coronary artery disease now affects an increased number of younger women, and—with the ageing of the population in many countries—the very old now account for an increasing proportion of patients with cardiac conditions^{4–6}.

An epidemic of obesity has swept across the world^{7,8}. Excess adiposity (especially that accumulated in the abdomen) and a fatty liver drive insulin resistance, which sets the stage for diabetes, and shows links with hypertension. From a metabolic perspective, individuals of some ethnicities often tolerate the accumulation of visceral adipose tissue

¹Division of Cardiovascular Medicine, Brigham and Women’s Hospital, Boston, MA, USA. ²Harvard Medical School, Boston, MA, USA. ✉e-mail: plibby@bwh.harvard.edu

particularly poorly⁹. Asian and South Asian individuals, as well as people of some ethnicities in Central and South America, can develop dysmetabolism manifested as glucose intolerance at lower abdominal girths than white individuals. Given the large populations in Asia and Central and South America, increased prosperity—with attendant shifts from traditional dietary habits—and continuing tobacco use, as well as the growing burden of obesity and diabetes (often accompanied by hypertension) presents an enormous public health challenge and is a contributor to regional risks of atherosclerotic cardiovascular disease.

Rather than elevated low-density lipoprotein (LDL) cholesterol, an elevation in triglyceride-rich lipoproteins (TGRL) and low high-density lipoprotein (HDL) now comprise the major pattern of lipid abnormality in many patients who are treated for atherosclerotic cardiovascular disease¹⁰. Highly effective and now-inexpensive therapies for lowering LDL have contributed to an overall drop in LDL, whereas obesity, its attendant insulin resistance and a high-carbohydrate diet favour a rise in the prevalence of the cluster of conditions referred to as the ‘metabolic syndrome’, which is characterized in part by an elevation in TGRL. The prevalence of this cluster—which also includes increased waist circumference, low HDL cholesterol, high blood pressure and raised fasting blood glucose—rose by 35% from 1988–1994 to 2007–2012 in the USA¹¹. Women, members of minoritized groups and populations in developing countries thus bear an increasing burden of atherosclerotic cardiovascular disease. Indeed, despite advances in controlling risk factors in many high-income countries, atherosclerotic cardiovascular disease now predominates in lower-income areas. The Global Burden of Disease study shows that world prevalence of ischaemic heart disease has increased from about 100 million in 1990 to over 180 million cases in 2019⁸. In some regions of the USA and UK, the decline in prevalence of ischaemic heart disease—attributed to controlling risk factor—has slowed or halted in the period 2014 to 2019⁸. Atherosclerotic cardiovascular disease has become a global concern, and we may be losing ground in prevention even in higher-income countries.

A reassessment of the lipid risk factors

LDL, a particle encircled by its signature apolipoprotein B component, causes atherosclerosis^{12,13}. If the entire population maintained LDL concentrations akin to those of a neonate (or to those of adults of most other animal species), atherosclerosis might well be an orphan disease¹⁴. The duration and extent of exposure to above-ideal concentrations of LDL associate with atherosclerotic disease^{13,15}. However, the treatment of children and adolescents with cholesterol-lowering drugs presents many challenges, and lifelong elevated concentrations of LDL cholesterol have already sown the seeds of atherosclerosis in millions of people, increasing their risk for cardiovascular disease. Despite effective interventions for the control of LDL, blood pressure and other traditional risk factors, a considerable residual risk remains for atherosclerotic cardiovascular disease¹⁶. For example, recent clinical trials of novel cardiovascular agents performed in subjects optimally treated with standard-of-care background therapy found that about 1 in 20 will have a recurrent ischaemic event in the year after an acute coronary syndrome^{17,18}. One in ten individuals who survive an acute myocardial infarction in the USA will require readmission within one month, at considerable personal and societal cost¹⁹. Moreover, in addition to obesity and its associated insulin resistance, rises in air pollution, transitions from traditional diets towards those that may aggravate cardiovascular risk and other exposures under intense investigation (ranging from environmental noise to impaired sleep) may mitigate some of the advances that have been made in prevention^{20–22}. Chief among readily remedied shifts towards unhealthy diets, the consumption of sugar-sweetened beverages, often high in fructose content, may contribute to obesity and its adverse metabolic consequences^{23,24}. Indeed, modifiable risk factors contribute enormously to the global burden of ischaemic heart disease².

Large-scale cohort investigations, such as the Framingham study, revealed risk factors for atherosclerosis that we now regard as ‘traditional’²⁵. However, long-term trends have modified risk factors such that these traditional factors no longer capture the contemporary reality of atherosclerosis. Genetic risk scores have undergone continuing refinement and incorporate increasingly expanded numbers of inherited variants that influence atherosclerotic events. As these genetic panels can predict risk from birth, they may inform the early targeted allocation of preventive measures in younger individuals who have an augmented genetic predilection to develop atherosclerotic disease²⁶. Indeed, lifestyle measures appear to mitigate risk of cardiovascular events across the spectrum of estimated genetic risk. Yet, the ability of even the latest generation of genetic risk scores to improve prediction of atherosclerotic events over more traditional algorithms remains controversial^{27,28}.

Recent research has challenged and expanded on the traditional risk factors. With global trends towards a decrease in LDL and the introduction of highly effective therapies for lowering LDL, as well as inexpensive and efficacious antihypertensive therapies, these drivers of chronic risk contribute less today than in previous years. Most markedly and despite decades of belief that HDL protected from atherosclerosis, recent human genetic studies—and the failure of several independent pharmacological measures to raise HDL to reduce atherosclerotic events—have called into question the protective effect of HDL²⁹. Mendelian randomization studies that have corrected for pleiotropy have, however, provided some support for the protective effect of HDL³⁰. Moreover, functional attributes of HDL fractions that are not captured by steady-state measurements of total HDL cholesterol concentrations (such as the capacity to mediate cholesterol efflux or anti-inflammatory actions) may yet exert anti-atherosclerotic effects^{31,32}.

The risk of plasma triglyceride concentration (a biomarker of a class of lipoproteins that include the TGRL) was passed over for many years, as the belief in the protective effect of HDL rendered it logical to adjust triglycerides for HDL—a precaution that attenuated the risk attributed to TGRL³³. Triglycerides and HDL tend to vary inversely, and a recent ranking^{34,35} of the relevant risk factors demotes HDL as a protective factor and points to TGRL as a potent predictor of cardiovascular risk. Moreover, in contrast to the situation with HDL, contemporary and concordant human genetic studies strongly support a causal role for TGRL in atherosclerosis and its complications³⁶. A variety of inherited sequence variations that affect lipoprotein lipase, or factors that modulate the activity of this enzyme, alter the rate of atherosclerotic events, and these findings furnish strong human genetic evidence for the causal role of TGRL in their pathogenesis. Apolipoprotein CIII, ANGPTL3 and ANGPTL4 inhibit the ability of lipoprotein lipase to hydrolyse triglycerides in TGRL, and thus cause accumulation of these particles. By contrast, apolipoprotein V augments the activity of lipoprotein lipase and enhances TGRL clearance^{37,38}. The activity of lipoprotein lipase thus regulates plasma triglyceride concentrations. Gain- or loss-of-function variants in this pathway that raise TGRL track with increased numbers of atherosclerotic events, and those that lower TGRL correlate with improved outcomes. The triglyceride component of TGRL does not appear to account for their atherogenicity¹⁰. TGRL, as with LDL, bear apolipoprotein B; they also contain cholesterol, and can deliver it effectively to macrophages in the atheroma. TGRL provoke inflammation, in part owing to their apolipoprotein CIII content. TGRL concentrations correlate better with inflammatory status than does LDL itself^{39,40}. This refocusing on TGRL as a causal risk factor, and lack of actionability of altering HDL thus far, has notable therapeutic implications.

Observational epidemiological studies have long associated a special form of LDL, lipoprotein(a), with atherothrombotic risk⁴¹. Lipoprotein(a) consists of an LDL particle, the signature apolipoprotein (apolipoprotein B) of which has bound covalently to apolipoprotein(a). Lipoprotein(a) carries oxidized lipids and may inhibit fibrinolysis owing to a structural similarity with plasminogen. Concordant human genetic

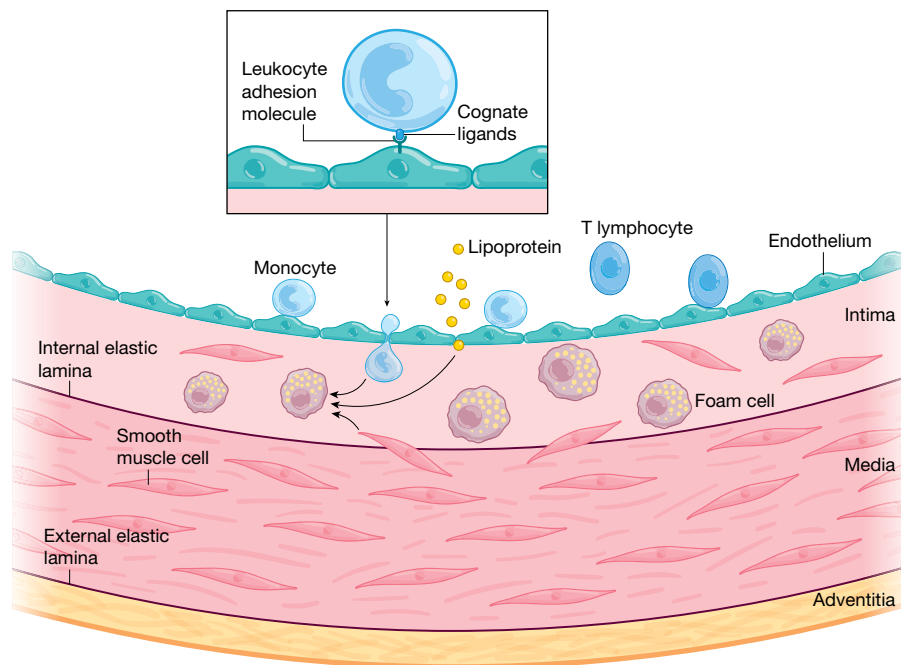


Fig. 1 | Initiation of atherosclerosis. The normal artery comprises three layers: the innermost intima (in close contact with the bloodstream), the tunica media, and the outer coat and adventitia. Under homeostatic conditions, the endothelial monolayer that lines the intima does not gather blood leukocytes. When activated by proinflammatory cytokines or other irritative stimuli related to cardiovascular risk factors, endothelial cells can express a leukocyte adhesion molecule (such as VCAM-1) that interacts with its cognate ligands (VLA4) to promote the rolling, and eventually adherence, of blood monocytes and lymphocytes to the endothelial layer. Chemoattractant cytokines can direct the migration of these bound leukocytes into the intima. Within the intima, foam cells form by uptake of lipids. Some of these lipid-laden foam cells

arise from blood monocytes that have matured into macrophages. Recent evidence¹⁴⁶ in mice indicates that smooth muscle cells can undergo metaplasia, and give rise to foam cells that bear markers in common with those of macrophages. T lymphocytes—although fewer in number than the foam cells—produce mediators that orchestrate many functions of these innate immune cells. In humans (but not in many of the small animals that are often used experimentally), the intima contains resident smooth muscle cells. Other smooth muscle cells (that are usually located in the media) can penetrate into the intima, where they join resident smooth muscle cells to promote the accumulation of extracellular matrix that these cells synthesize within the expanding intima.

studies provide persuasive evidence for the causality of elevated lipoprotein(a) not only in atherosclerosis but also in calcific aortic valve disease^{42–45}.

Inflammation drives atherosclerosis

Beyond dyslipidaemia, a convincing body of experimental and clinical data now indicates that inflammation participates fundamentally in atherogenesis and in the pathophysiology of ischaemic events⁴⁶. Inflammation does not supplant or demote lipid risk; rather, inflammatory responses provide a series of pathways that link lipids and other traditional risk factors to atherosclerosis. For example, concentrations of remnant lipoprotein show links with levels of C-reactive protein, a biomarker of inflammation⁴⁰. A large body of evidence implicates inflammation in hypertension⁴⁷. Experimental investigations have pinpointed the participation of innate and adaptive immunity in atherosclerosis (Figs. 1, 2). Human biomarker studies have shown that indicators of inflammation predict risk of cardiovascular disease in a broad swath of individuals with or without manifest cardiovascular disease, and independently of all traditional risk factors⁴⁸. The acute phase reactant (C-reactive protein), which can be measured with a highly sensitive assay (known as hsCRP), is a validated and clinically useful gauge of the overall innate immune status of an individual in relation to atherosclerotic risk⁴⁹.

In addition to innate immunity (which depends largely on cytokines and macrophages), the adaptive arm of the immune response operates during atherogenesis. T lymphocytes primarily aggravate atherogenesis, but T-helper 2 and regulatory T cells can mute this process, at least

in mice^{46,50}. Candidate antigens include forms of LDL as discussed in ‘Oxidized LDL and the initiation of lesions’. B lymphocytes also can exert a dual role in atherogenesis. Natural IgM antibodies encoded in the germline and produced by B1 cells mitigate experimental atherosclerosis^{51,52}. B2 cells can produce antibodies that may drive this process. One candidate antigen, the mitochondrial enzyme ALDH4A1, emerged from analysis of B cells isolated from mouse atheromata⁵³.

An increased number of links between inflammation, immunity and intermediary metabolism have recently emerged. Inflammatory activation of mononuclear phagocytes and endothelial cells tends to shift their metabolism towards glycolytic pathways^{54–56}. Altered tryptophan metabolism has also garnered considerable interest in atherosclerosis. Cytokines induce indoleamine dioxygenase (the rate-limiting step in tryptophan catabolism), which lowers intracellular tryptophan stores and augments the production of kynurenine and its metabolites; this latter pathway may have a counter-regulatory function by muting inflammation and the cellular immune response^{57–59}.

The applicability to humans of experimental evidence that implicated inflammation in atherosclerosis has engendered considerable controversy^{60,61}. However, recent clinical trials have shown that targeting inflammation can reduce cardiovascular events even in individuals who have already been treated with a full panel of effective standard therapies. The ‘Canakinumab Anti-inflammatory Thrombosis Outcomes Study’ (CANTOS) allocated randomly an antibody that neutralizes the proinflammatory cytokine IL-1 β to patients with stable coronary artery disease at least one month after a qualifying myocardial infarction⁶². The enrolled population had signs of inflammation despite standard-of-care medical therapy, as mandated by prevailing

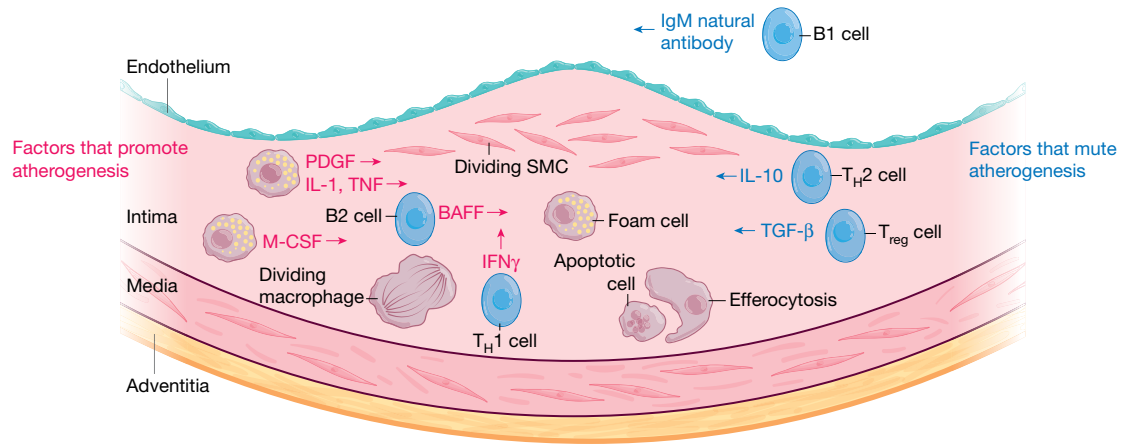


Fig. 2 | The progression of atherosclerosis reflects and interplay between factors that promote or mitigate atherogenesis. This diagram summarizes results from experimental studies in mice, and observations on human atherosclerotic plaques. Pathways thought to promote lesion formation (factors in red) are shown on the left, and mechanisms that may moderate atherogenesis (factors in blue) are on the right. Smooth muscle cells and macrophages can proliferate as the intimal lesion grows. PDGF promotes the migration and replication of smooth muscle cells, and then production of extracellular matrix. All cells in the atheromatous plaque can secrete cytokines, examples of which include IL-1, TNF and M-CSF (also known as CSF1). Activated T-helper 1 (T_H1) lymphocytes produce $IFN\gamma$, which can stimulate mononuclear phagocytes and aggravate atherosclerosis. Other types of cell produce countervailing mediators. B1 lymphocytes can secrete IgM natural antibody; T-helper 2 (T_H2) lymphocytes produce the anti-inflammatory

cytokine IL-10; and regulatory T (T_{reg}) cells can secrete $TGF\beta$. These mediators can antagonize cellular proliferation, promote extracellular matrix synthesis and quell inflammation. Mononuclear phagocytes can engulf dying or dead cells that arise through apoptosis, through a process known as efferocytosis. Inefficient efferocytosis favours the accumulation of debris from dead or dying cells, and promotes formation of the central lipid core of the atherosclerotic plaque. B2 lymphocytes secrete mediators (such as BAFF, a member of the TNF family) that can aggravate atherogenesis. This diagram shows only a subset of the mediators that have been implicated in promoting or antagonizing aspects of atherogenesis. Current research suggests an ongoing struggle between proliferation and death, involving proinflammatory, anti-inflammatory and proresolving mediators—generally through a prolonged course of many years in the evolution of the human atherosclerotic plaque.

guidelines (gauged by an hsCRP above 2 mg l^{-1}). The participants had a baseline LDL of approximately 2 mM (81 mg dl^{-1}). The anti-inflammatory therapy yielded a 15% relative reduction in risk for recurrent myocardial infarction, stroke or cardiac death. In an on-treatment analysis, individuals who responded to the IL-1 β neutralization by achieving a greater-than-median reduction in hsCRP had a 26% reduction in the primary end point, and a decrease in all-cause mortality. As IL-1 β participates in host defences, it was not surprising that CANTOS showed a small but statistically significant increase in infections (including fatal infections) in patients randomized to canakinumab. A highly significant reduction in incident and fatal lung cancer noted in exploratory analyses counterbalanced this risk of infection⁶³.

The natural product colchicine has served as an anti-inflammatory therapy for many years, and its use has become standard-of-care in the treatment of pericarditis. Two recent large-scale outcome trials have indicated efficacy in reducing recurrent cardiovascular events after the development of acute coronary syndromes. The ‘Colchicine Cardiovascular Outcomes Trial’ (COLCOT) showed a 23% reduction in the composite primary end point, driven primarily by fewer revascularizations in patients treated in the early phase after developing an acute coronary syndrome (4–30 days)⁶⁴. The incidence of pneumonia more than doubled in the group who were treated with colchicine. The ‘Low Dose Colchicine 2’ (LoDoCo2) study administered colchicine (5 mg d^{-1}) to individuals with stable coronary artery disease, and reported a reduction in recurrent events similar to that seen in the COLCOT⁶⁵.

These recent large-scale clinical outcome trials have bolstered the clinical applicability of decades of fundamental research into inflammatory pathways in the pathogenesis of atherosclerosis. The increase in infections noted with canakinumab and colchicine indicate an opportunity for the refinement of anti-inflammatory therapy for atherosclerosis that retains efficacy in limiting adverse outcomes, while interfering less

with host defence. But not all anti-inflammatory interventions have yielded clinical benefit⁶⁶. For example, a trial with low-dose weekly methotrexate did not improve cardiovascular outcomes nor did it exert an anti-inflammatory effect in the population studied⁶⁷.

Obesity and its attendant dysmetabolism, often manifested by insulin resistance and diabetes, now drives an increasing proportion of cardiovascular disease risk worldwide. Adipose tissue abounds with inflammatory cells, produces proinflammatory mediators and inflammation contributes mechanistically to the link between obesity, insulin resistance and atherosclerotic risk⁶⁸. Moreover, environmental factors, such as air pollution, noise, disturbed sleep and other stressors have gained increasing recognition as contributors to the risk of atherosclerotic events in part through the activation of inflammatory pathways^{20,21}.

An additional aspect of risk allied with inflammation has recently emerged. With age, we accumulate somatic mutations in haematopoietic stem cells in the bone marrow in genes that drive the development of acute leukaemia^{69,70}. Investigators seeking the origins of leukaemia found that individuals who are apparently well and do not have haematological malignancies can generate clones of leukocytes that circulate in peripheral blood and that bear mutations in a handful of the known driver genes for leukaemia. The prevalence of this condition in individuals aged 70 exceeds 10%, and this burden increases with further ageing. As the population ages, the number of individuals who bear these clones will increase. As expected, those who have this condition—known as clonal haematopoiesis of indeterminate potential (CHIP)—have a risk of developing acute leukaemia of more than tenfold that of unaffected individuals. However, the increase in total mortality in individuals with CHIP by far exceeds that attributable to transformation to acute leukaemia.

Cardiovascular disease accounts for this gap in mortality⁷¹. Fully adjusted for all traditional risk factors, CHIP confers a risk for

Review

myocardial infarction and stroke equal to or greater than previously recognized contributors to cardiovascular risk, save for age itself. The qualification ‘indeterminant potential’ reflects the lack of symptoms or consistent laboratory findings in bearers of these mutant clones of peripheral leukocytes and our current inability to predict which individuals with CHIP will develop leukaemia or cardiovascular disease. Indeed, many carriers of CHIP will never know that they have this condition^{72,73}.

The connection between CHIP and inflammation arises from experimental work that demonstrated that mice engineered to simulate CHIP with mutations in *Dnmt3a* or *Tet2* have accelerated atherosclerosis, and demonstrate increased activity of the NLRP inflammasome IL-1 β –IL-6 proinflammatory pathway^{71,74}. Mice with myeloid cells that bear *Jak2*^{V617F} (another mutation associated with CHIP) show activation of the AIM2 inflammasome⁷⁵. Concentrations of the marker of inflammation hsCRP do not rise consistently in individuals with CHIP. This observation indicates the existence of aspects of inflammation that mark augmented cardiovascular risk but that are not captured by measurements of hsCRP.

In sum, we have witnessed a considerable change in the ranking of risk factors for atherosclerosis: some factors have receded in importance and relevance given current therapies, and others have rapidly expanded, in part owing to socioeconomic and behavioural factors² (Table 1).

Revised concepts of atherogenesis

Oxidized LDL and the initiation of lesions

Most reviews of the mechanisms of atherosclerosis posit a pivotal role for oxidized LDL as the prime mover of this disease (Fig. 1). Although LDL participates causally in atherogenesis, despite a large body of animal research, scant evidence actually supports the causal role of oxidized LDL in humans. A variety of clinical intervention trials with antioxidant vitamins or one of a highly effective lipophilic antioxidant drug have not reduced atherosclerotic events. Native, rather than oxidized, LDL appears to drive the adaptive immune response in mice⁷⁶. LDL *per se* appears to be a relatively weak stimulus to innate immune activation. Recent work supports the participation of cavelolin-1-dependent LDL transcytosis through the endothelium in experimental atherosclerosis⁷⁷. ALK1 and SRB1 can also participate in LDL transcytosis^{78,79}. Although these results emphasize the causality of LDL in atherogenesis, they do not invoke the participation of oxidized LDL in this process. How LDL causes atherosclerosis is not understood completely, and we should seek explanations beyond the oxidation hypothesis. When oxidized lipid binds to plasminogen, they can activate fibrinolysis⁸⁰. Thus, oxidized lipids may promote atherogenesis but boost thrombolysis—an opposing effect that could contribute to the net lack of benefit in trials of anti-oxidant strategies⁸¹. LDL that aggregates in the intima in association with proteoglycan, or adaptive immune responses to native LDL, provide alternative mechanisms through which this lipoprotein promotes atherogenesis. Macrophages in plaques take up aggregated LDL⁸², and the LDL receptor-related protein can mediate the uptake of aggregated LDL by intimal smooth muscle cells⁸³.

Regardless of the initial trigger or triggers, experimental and human observations agree that the recruitment of blood leukocytes mediated by activation of endothelial cells that line the arterial lumen occurs early in lesion formation (Fig. 1). The resting endothelium resists attachment of blood leukocytes. In an atherogenic environment, endothelial cells can express leukocyte adhesion molecules that mediate the rolling and firm attachment of white blood cells to the intimal surface (Fig. 1). Chemokines direct the migration of the adherent leukocytes into the arterial intima. Mononuclear phagocytes can proliferate within the intimal layer (the site of lesion initiation)⁸⁴. These cells engulf lipids and become foam cells, the hallmark of atherosclerotic lesions. T lymphocytes, which drive the adaptive immune response, interact with innate immune cells within the intima^{85,86}. A proinflammatory

subset of monocytes gives rise to lesional macrophages^{87,88}. Recent lineage-tracking experiments support a smooth muscle origin of many foam cells in mouse atheromata⁸⁹. The cooperation between these cellular constituents of innate and adaptive immunity stimulate the production of proinflammatory cytokines that sustain and amplify the local inflammatory response.

Inexorability of atheroma progression

Many have considered atherosclerosis an inevitable ‘degenerative’ process that progresses continuously over time (Fig. 2), but current evidence supports a much more dynamic and discontinuous evolution of atheromata^{90–92}. Episodes of systemic inflammation or regional inflammation that is remote from the atherosclerotic plaque itself can provoke ‘crises’ in the evolution of the plaque, and stimulate a round of inflammatory activation that can promote cell migration, proliferation, lesion progression and complication (Fig. 2). The concept of ‘trained immunity’ raises the possibility that successive encounters with irritative stimuli elicit exaggerated responses^{93,94}. Arterial smooth muscle cells—which normally reside quiescent in the middle layer of the artery (the tunica media)—enter the intimal layer, where they can proliferate and may undergo metaplasia to become macrophage-like cells⁸⁹. The application of advanced cell-sorting techniques and of single-cell RNA sequencing has disclosed a high degree of heterogeneity in the cellular contributors to atherosclerosis^{95–97}. Sorting out the functional consequences of the newly identified cell types that participate in atherogenesis will require considerable work, and holds promise for advancing the identification of new therapeutic targets.

Atherosclerosis may not proceed continuously, but rather in phases of relative quiescence punctuated by periods of rapid growth. Emerging evidence points to haematopoiesis as a key contributor to lesion evolution and as a link between regional inflammation, environmental stimuli and atherogenesis⁹⁸. Mental stress, sleep disturbance and remote injury or infection can stimulate haematopoiesis in the bone marrow, furnishing leukocytes that can populate the plaque^{98,99}. Extramedullary haematopoiesis, as well as the mobilization of preformed pools of leukocytes in the spleen, furnish further leukocytes that can home in on atheromata under stress situations. Indeed, the work that identified CHIP as a risk factor for atherosclerosis underscores the link between atherosclerosis and haematopoiesis. These observations have opened a window onto the pathogenesis of atherosclerosis, and provide a link between oncogenesis and atherogenesis that was unsuspected only a few years ago. The death of mononuclear phagocytes in the lesion, and their ineffective clearance (defective efferocytosis), promote the formation of the lipid or necrotic core of the atherosclerotic lesion¹⁰⁰. Lesion progression can occur silently over many decades. Indeed, many young or middle-aged individuals contain asymptomatic and subclinical atherosclerotic lesions, as shown by autopsy and imaging studies^{101–103}.

‘Vulnerable plaques’

The acute events such as myocardial infarctions and ischaemic strokes that complicate atherosclerosis arise from thrombosis or formation of blood clots (Fig. 3), a physical disruption of atherosclerotic plaques provokes most acute thromboses. The so-called ‘vulnerable plaque’ has received considerable attention^{104,105}. A fracture of the fibrous cap of the plaque (which overlies the necrotic core) exposes blood and its coagulation proteins to thrombogenic substances (such as tissue factor) within the plaque, triggering acute thrombosis¹⁰⁶ (Fig. 3a). The fibrous cap owes its tensile strength largely to interstitial collagen. The thinning of the fibrous cap arises from an inflammation-related decrease in collagen synthesis and augmented degradation owing to overexpression of collagenases by inflammatory cells¹⁰⁷. Autopsy studies¹⁰⁴ have implicated rupture of the fibrous cap as the cause of the majority of fatal acute coronary syndromes, stimulating focus on the thin-capped fibroatheroma as a possible culprit. Yet, post-mortem

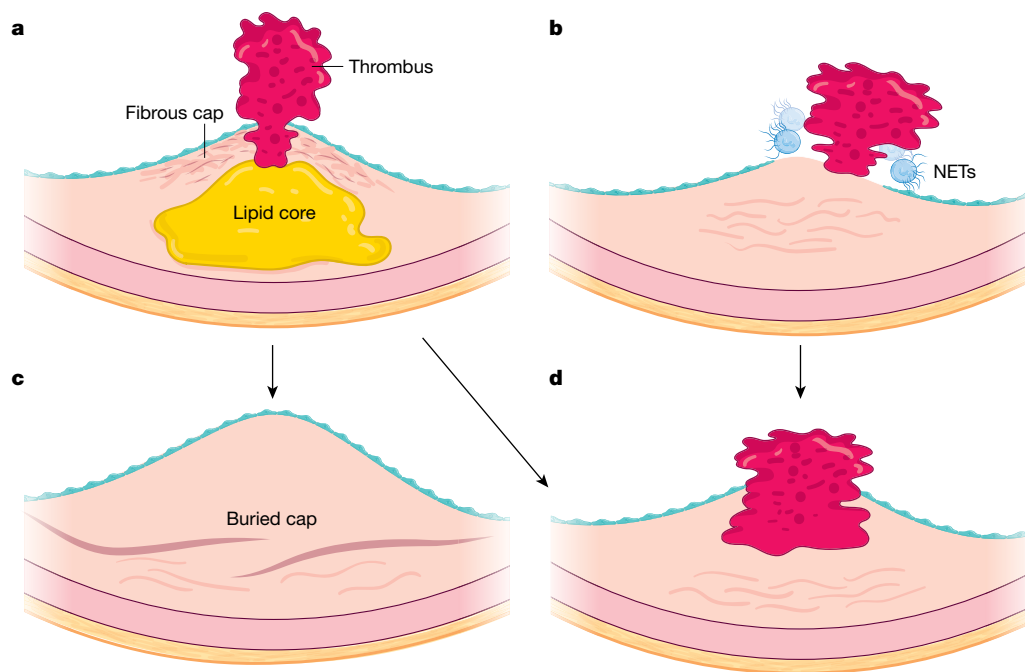


Fig. 3 | Thrombotic complications of atherosclerosis and evolution of the atherosclerotic plaque. **a**, Plaque rupture. This involves a fracture or fissure of the fibrous cap that overlies the lipid core of the plaque. This physical disruption permits contact of blood coagulation factors with thrombogenic material (principally the potent procoagulant tissue factor) within the plaque. The ensuing thrombosis can obstruct blood flow and lead to cardiac ischaemia. This mechanism accounts for about two-thirds of acute myocardial infarction, but appears to be waning; current preventive therapies lead to a reduction in accumulation of lipid within plaques and to the reinforcement of the fibrous cap. **b**, Superficial erosion. This cause of coronary artery clot formation involves a sloughing or desquamation of the endothelial monolayer. Granulocytes trapped in the plaque or adherent to the intimal basement membrane can form neutrophil extracellular traps (NETs). NETs are strands of nuclear DNA that have unwound, present various neutrophil granular proteins and bear other proteins that they bind from the blood, forming a solid-state

reactor on the intimal surface. NETs can propagate inflammation and thrombosis. **c**, **d**, Plaques can heal, which augments the bulk of the plaque and promotes the formation of flow-limiting stenosis in previously disrupted arteries. During thrombosis, platelets release PDGF and TGF β , which promote the synthesis of extracellular matrix proteins that contribute to fibrosis and plaque growth. **c**, Ruptured plaques that have healed often show morphologic evidence of the rupture underneath a layer of more recently deposited extracellular matrix (a 'buried' fibrous cap). **d**, Plaques can also grow through incorporation of a thrombus. Lesions can also calcify (not shown), in part owing to cell-derived microvesicles that can nucleate this process. Regions of spotty calcification imaged by computed tomography correlate with an increased risk of a thrombotic event. In contrast to smaller deposits of calcium, macroscopic plates of calcium may stabilize plaques from mechanical disruption (rather than create inhomogeneity in stresses that promotes thrombotic complications due to plaque disruption).

studies such as these lack a denominator for how many lesions with the characteristics attributed to vulnerability do not cause acute thrombotic complications. Recent *in vivo* imaging studies in humans have furnished this missing information, and have shown that plaques that thin-capped plaques seldom cause clinical events^{108–110}. Thus, current evidence shows that 'vulnerable plaque' is a misnomer^{111,112}.

In an era of intense lipid lowering, plaques of the classical vulnerable morphology are on the wane¹¹³. Another mechanism of plaque disruption (known as superficial erosion) currently appears to be on the rise and probably has a distinct pathophysiology^{114–116} (Fig. 3b). This trigger to coronary artery stenosis does not involve fissure or rupture of the fibrous cap of the plaque, but rather a discontinuity in the intimal endothelial lining. The application of an intravascular imaging modality known as optical coherence tomography enables identification of plaque rupture, and has led to the development of criteria for the diagnosis of probable or definite erosion in individuals with acute coronary syndromes¹¹⁷. The mechanisms of erosion involve endothelial injury, the participation of polymorphonuclear leukocytes and neutrophil extracellular traps as a local contributor to thrombus formation and propagation^{114,118,119}.

Clinical implications

From a therapeutic perspective, we have reason for optimism in addressing the growing burden of atherosclerotic risk. First, we face

an imperative to encourage healthy lifestyle choices and a public environment that supports them by encouraging physical activity, discouraging sugar-sweetened beverages that contribute to the obesity epidemic and continuing to abate tobacco use. Indeed, a healthy lifestyle can mitigate—in part—genetic risk for atherosclerotic events¹²⁰. Such public health measures include promoting pedestrian zones, bicycle paths and playgrounds, and providing healthy foods in schools. Second, the drug therapy for atherosclerosis has advanced not only in the availability of agents that address an expanded array of causal targets, but also by harnessing biomarkers and genetic information to deploy therapy more precisely^{62,121}. The application of evidence-based interventions that address the established risk factors provides a firm foundation for future advances.

The introduction of statins (agents that are highly effective in lowering LDL and that also quell inflammation independently of effects on lipids) has revolutionized the prevention and treatment of atherosclerosis, a topic that has been well-reviewed in previous publications¹²². The availability of an inhibitor of intestinal absorption of cholesterol that targets the Niemann Pick C 1-like protein 1 yields further reductions in LDL and a further decrement in cardiovascular events¹²³. The identification of mutations in *PCSK9* as a cause of autosomal dominant hypercholesterolaemia led rapidly to the development of therapeutic agents that can improve further cardiovascular outcomes in patients who were already treated with statins^{17,18,124}. *PCSK9* conducts the LDL

receptor to the lysosome, where it undergoes proteolytic degradation. Inhibition of PCSK9 favours the recycling of undegraded LDL receptors to the cell surface, where they can capture and internalize LDL, and thus lowers the plasma concentration of this highly atherogenic lipoprotein¹²⁴. The introduction and recent approval in the USA of bempedoic acid (an inhibitor of ATP citrate lyase, which acts upstream of hydroxymethylglutaryl co-enzyme A (the target of statins)) adds to the range of non-statin agents that lower LDL^{125,126}. The availability of inclisiran (a small interfering RNA that limits the production of PCSK9) provides a notably long duration of action, and could be administered twice a year or even annually¹²⁷. Large-scale clinical trials in progress will evaluate the ability of these newer LDL-lowering treatments to improve cardiovascular outcomes. An antisense RNA agent has entered clinical investigation that targets lipoprotein(a), the highly atherogenic cousin of LDL¹²⁸. Treatment of elevated lipoprotein(a) (which is often familial) has proven an enduring problem in preventive cardiology¹²⁹.

Beyond LDL, a cardiovascular end-point study is evaluating a selective PPAR α agonist in individuals with high triglycerides and low HDL¹³⁰. The 'Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial' revealed that prescription-grade icosapentaenoic acid can reduce events substantially in individuals with hypertriglyceridaemia^{131,132}. Part of this benefit (but probably not all of it) results from a lowering of blood triglycerides; some of the benefit may accrue from an anti-inflammatory action¹³³.

Recent studies targeting IL-1 β (CANTOS) and trials with colchicine (COLCOT and LoDoCO2) have demonstrated the ability of anti-inflammatory therapies that do not lower atherogenic lipids to reduce cardiovascular events in patients who are already receiving a full standard-of-care regimen, including high-dose statins⁶². Beyond affirming the inflammation hypothesis of atherosclerosis, these studies identify colchicine as a readily actionable anti-inflammatory therapeutic agent for atherosclerosis.

There is currently a revolution at the conjunction of diabetes and cardiovascular disease. A 'gluco-centric' view of diabetic complications has long prevailed¹³⁴. Although microvascular complications (such as retinopathy, nephropathy and neuropathy) do respond to glucose lowering, the heightened atherosclerotic risk in people with diabetes had—until recently—proven intractable to traditional hypoglycaemic interventions. Recent studies with SGLT2 inhibitors and GLP1 receptor agonists indicate that the macrovascular complications of diabetes involve mechanisms beyond glucose lowering^{135–141}. These late-generation agents promise to make inroads in the prevention of cardiovascular complications of diabetes (including myocardial infarction, stroke, heart failure, renal disease and premature death). The success of these drugs in forestalling cardiovascular events emphasizes protective mechanisms beyond those of glucose lowering; the investigation of these mechanisms promises to open avenues in the understanding and treatment of atherosclerosis and heart failure, a common complication of coronary artery disease.

Atherosclerosis is a moving target

A conjunction of fundamental research and clinical investigations has markedly altered traditional concepts of atherosclerosis, and has informed improvements in our ability to manage atherosclerotic risk (Table 1). At the same time, the clinical profile of patients with atherosclerosis has evolved considerably from that of classical cohort studies that have long furnished the basis of our thinking about this disease. Research advances have arisen from improvements in human genetics studies enabled by next-generation sequencing and other technological innovations (including bulk and single-cell RNA sequencing), and the ever-evolving toolkit for genetic manipulation of mice including gene-editing and induced pluripotent stem cell methodology^{142,143}. Beyond DNA and mRNA analyses, understanding the functions of

Table 1 | Changing views on atherosclerosis

Past	Present
Atherosclerosis predominantly affects developed countries	Developing countries now bear the greatest burden of atherosclerosis
Coronary thrombosis affects primarily middle-aged white men	Women, younger individuals, individuals from a range of ethnic backgrounds and the very old suffer increasingly from acute coronary syndromes
Atherosclerosis is a lipid storage disease	Inflammation links dyslipidaemia and other risk factors to atherogenesis
Oxidized LDL drives atherosclerosis	Native or aggregated LDL drives atherogenesis
HDL cholesterol protects against atherosclerosis	TGRL participate causally in atherosclerosis
Thin-capped fibroatheromata are vulnerable plaques	The 'vulnerable plaque' is a misnomer; superficial erosion is an increasing cause of arterial thrombosis
Atherosclerosis is an inevitable, steady and degenerative accompaniment to ageing	Atherosclerosis evolves episodically, can regress, and lifestyle and medical measures can modulate the process

non-coding RNAs in atherosclerosis has improved. MicroRNAs and long non-coding RNAs alter the transcription of genes implicated in atherosclerosis^{144,145}. These advances will doubtless lead to therapies to address the unacceptable burden of risk that persists in spite of current interventions.

Transforming these scientific advances in therapies has required large-scale clinical investigations, which—because of the success of standard-of-care therapies—have required increasing ingenuity and investment. Placebo-controlled, randomized clinical trials remain the most reliable tool for validating the application to humans of therapies derived from laboratory discoveries. However, we also need to embrace targeting segments of the larger population of patients to enrich those enrolled in clinical trials for enhanced risk and responsiveness to specific interventions. This approach has revolutionized the management of cancer, but has barely begun in the cardiovascular arena. The application of polygenic risk scores may identify young people who may benefit particularly from early preventive treatments.

On the one hand, we are witnessing a globalization of cardiovascular disease risk that has increased the overall burden of atherosclerotic disease. On the other hand, progress in laboratory and clinical investigation promises to provide us with tools to confront this global epidemic. Ultimately, making inroads in the control of atherosclerosis will require a multidisciplinary partnership of public health measures, applied behavioural psychology, risk factor control, consistent application of existing therapies, and the development and validation of new therapeutic approaches.

- Gaziano, T. A., Prabhakaran, D. & Gaziano, J. M. in *Braunwald's Heart Disease* (eds Zipes, D. P. et al.) 1–18 (Saunders, 2018).
 - Dai, H. et al. Global, regional, and national burden of ischemic heart disease and its attributable risk factors, 1990–2017: results from the global Burden of Disease Study 2017. *Eur. Heart J. Qual. Care Clin. Outcomes*, <https://doi.org/10.1093/ehjqcco/qcaa076> (2020).
 - Libby, P. et al. Atherosclerosis. *Nat. Rev. Dis. Primers* **5**, 56 (2019).
 - Virani, S. S. et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation* **143**, e254–e743 (2021).
 - Arora, S. et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. *Circulation* **139**, 1047–1056 (2019).
 - Towfighi, A., Markovic, D. & Ovbiagele, B. National gender-specific trends in myocardial infarction hospitalization rates among patients aged 35 to 64 years. *Am. J. Cardiol.* **108**, 1102–1107 (2011).
 - Blüher, M. Obesity: global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* **15**, 288–298 (2019).
 - Roth, G. A. et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J. Am. Coll. Cardiol.* **76**, 2982–3021 (2020).
- This compilation provides recent data regarding cardiovascular risk factors in various regions of the world, and their import for cardiovascular diseases.**

9. Després, J.-P. & Lemieux, I. Abdominal obesity and metabolic syndrome. *Nature* **444**, 881–887 (2006).
10. Nordestgaard, B. G. & Varbo, A. Triglycerides and cardiovascular disease. *Lancet* **384**, 626–635 (2014).
11. Moore, J. X., Chaudhary, N. & Akinyemiju, T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination survey, 1988–2012. *Prev. Chronic Dis.* **14**, E24 (2017).
12. Ference, B. A. et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **38**, 2459–2472 (2017).
13. Borén, J. et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **41**, 2313–2330 (2020).
14. Goldstein, J. L. & Brown, M. S. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* **161**, 161–172 (2015).
- A review of the involvement of LDL in atherosclerosis, which represents one of the major advances in cardiovascular science in the past century.**
15. Domanski, M. J. et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J. Am. Coll. Cardiol.* **76**, 1507–1516 (2020).
16. Ridker, P. M. How common is residual inflammatory risk? *Circ. Res.* **120**, 617–619 (2017).
17. Sabatine, M. S. et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Engl. J. Med.* **376**, 1713–1722 (2017).
18. Schwartz, G. G. et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N. Engl. J. Med.* **379**, 2097–2107 (2018).
19. Kwok, C. S. et al. Unplanned hospital readmissions after acute myocardial infarction: a nationwide analysis of rates, trends, predictors and causes in the United States between 2010 and 2014. *Coron. Artery Dis.* **31**, 354–364 (2020).
20. Brook, R. D., Newby, D. E. & Rajagopalan, S. Air pollution and cardiometabolic disease: an update and call for clinical trials. *Am. J. Hypertens.* **31**, 1–10 (2018).
21. Münzel, T. Up in the air: links between the environment and cardiovascular disease. *Cardiovasc. Res.* **115**, e144–e146 (2019).
22. Drager, L. F., McEvoy, R. D., Barbe, F., Lorenzi-Filho, G. & Redline, S. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation* **136**, 1840–1850 (2017).
23. Mozaffarian, D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation* **133**, 187–225 (2016).
24. Malik, V. S. & Hu, F. B. Sugar-sweetened beverages and cardiometabolic health: an update of the evidence. *Nutrients* **11**, 1840 (2019).
25. Andersson, C., Johnson, A. D., Benjamin, E. J., Levy, D. & Vasan, R. S. 70-year legacy of the Framingham Heart Study. *Nat. Rev. Cardiol.* **16**, 687–698 (2019).
26. Aragam, K. G. & Natarajan, P. Polygenic scores to assess atherosclerotic cardiovascular disease risk. *Circ. Res.* **126**, 1159–1177 (2020).
- A recent review of the generation and use of polygenic risk scores for atherosclerosis.**
27. Elliott, J. et al. Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease. *J. Am. Med. Assoc.* **323**, 636–645 (2020).
28. Mosley, J. D. et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. *J. Am. Med. Assoc.* **323**, 627–635 (2020).
29. Siddiqi, H. K., Kiss, D. & Rader, D. HDL-cholesterol and cardiovascular disease: rethinking our approach. *Curr. Opin. Cardiol.* **30**, 536–542 (2015).
30. Thomas, D. G., Wei, Y. & Tall, A. R. Lipid and metabolic syndrome traits in coronary artery disease: a Mendelian randomization study. *J. Lipid Res.*, <https://doi.org/10.1194/jlr.P120001000> (2020).
31. Nazir, S. et al. Interaction between high-density lipoproteins and inflammation: function matters more than concentration! *Adv. Drug Deliv. Rev.* **159**, 94–119 (2020).
32. Shea, S. et al. Cholesterol mass efflux capacity, incident cardiovascular disease, and progression of carotid plaque. *Arterioscler. Thromb. Vasc. Biol.* **39**, 89–96 (2019).
33. Libby, P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur. Heart J.* **36**, 774–776 (2015).
34. Musunuru, K. & Kathiresan, S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. *Circ. Res.* **118**, 579–585 (2016).
35. Voight, B. F. et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* **380**, 572–580 (2012).
36. Do, R. et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat. Genet.* **45**, 1345–1352 (2013).
37. Khera, A. V. et al. Association of rare and common variation in the lipoprotein lipase gene with coronary artery disease. *J. Am. Med. Assoc.* **317**, 937–946 (2017).
38. Lewis, G. F., Xiao, C. & Hegele, R. A. Hypertriglyceridemia in the genomic era: a new paradigm. *Endocr. Rev.* **36**, 131–147 (2015).
39. Varbo, A., Benn, M., Tybjaerg-Hansen, A. & Nordestgaard, B. G. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation* **128**, 1298–1309 (2013).
- This contribution from the Copenhagen group presents evidence that remnant TGRL produce a greater inflammatory response than does LDL.**
40. Hansen, S. E. J., Madsen, C. M., Varbo, A. & Nordestgaard, B. G. Low-grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115000 individuals from the general population. *Clin. Chem.* **65**, 321–332 (2019).
41. Tsimikas, S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J. Am. Coll. Cardiol.* **69**, 692–711 (2017).
42. Tsimikas, S. & Hall, J. L. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. *J. Am. Coll. Cardiol.* **60**, 716–721 (2012).
43. Thanassoulis, G. et al. Genetic associations with valvular calcification and aortic stenosis. *N. Engl. J. Med.* **368**, 503–512 (2013).
- This genome-wide association study pointed to lipoprotein(a) as causal for aortic stenosis, which is a common concomitant of atherosclerosis.**
44. Lee, S.-R. et al. LPA gene, ethnicity, and cardiovascular events. *Circulation* **135**, 251–263 (2017).
45. Tsimikas, S. Potential causality and emerging medical therapies for lipoprotein(a) and its associated oxidized phospholipids in calcific aortic valve stenosis. *Circ. Res.* **124**, 405–415 (2019).
46. Libby, P. & Hansson, G. K. From focal lipid storage to systemic inflammation: JACC review topic of the week. *J. Am. Coll. Cardiol.* **74**, 1594–1607 (2019).
- This review provides an overview of various theories of atherogenesis, culminating in a portrayal of the current view that posits a synthesis that combines elements of many of the previous concepts.**
47. Xiao, L. & Harrison, D. G. Inflammation in hypertension. *Can. J. Cardiol.* **36**, 635–647 (2020).
48. Ridker, P. M., Koenig, W., Kastelein, J. J., Mach, F. & Lüscher, T. F. Has the time finally come to measure hsCRP universally in primary and secondary cardiovascular prevention? *Eur. Heart J.* **39**, 4109–4111 (2018).
49. Ridker, P. M. A test in context: high-sensitivity C-reactive protein. *J. Am. Coll. Cardiol.* **67**, 712–723 (2016).
50. Ketelhuth, D. F. J. & Hansson, G. K. Adaptive response of T and B cells in atherosclerosis. *Circ. Res.* **118**, 668–678 (2016).
51. Que, X. et al. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. *Nature* **558**, 301–306 (2018).
52. Sage, A. P., Tsiantoulas, D., Binder, C. J. & Mallat, Z. The role of B cells in atherosclerosis. *Nat. Rev. Cardiol.* **16**, 180–196 (2019).
53. Lorenzo, C. et al. ALDH4A1 is an atherosclerosis auto-antigen targeted by protective antibodies. *Nature* **589**, 287–292 (2021).
54. Ketelhuth, D. F. J. et al. Immunometabolism and atherosclerosis: perspectives and clinical significance: a position paper from the Working Group on Atherosclerosis and Vascular Biology of the European Society of Cardiology. *Cardiovasc. Res.* **115**, 1385–1392 (2019).
55. Tabas, I. & Bornfeldt, K. E. Intracellular and intercellular aspects of macrophage immunometabolism in atherosclerosis. *Circ. Res.* **126**, 1209–1227 (2020).
56. Rohlenova, K., Veys, K., Miranda-Santos, I., De Bock, K. & Carmeliet, P. Endothelial cell metabolism in health and disease. *Trends Cell Biol.* **28**, 224–236 (2018).
57. Sakash, J. B., Byrne, G. I., Lichtman, A. & Libby, P. Cytokines induce indoleamine 2,3-dioxygenase expression in human atheroma-associated cells: implications for persistent *Chlamydia pneumoniae* infection. *Infect. Immun.* **70**, 3959–3961 (2002).
58. Cuffy, M. C. et al. Induction of indoleamine 2,3-dioxygenase in vascular smooth muscle cells by interferon- γ contributes to medial immunoprivilege. *J. Immunol.* **179**, 5246–5254 (2007).
59. Baumgartner, R., Forteza, M. J. & Ketelhuth, D. F. J. The interplay between cytokines and the kynurenine pathway in inflammation and atherosclerosis. *Cytokine* **122**, 154148 (2019).
60. Hansson, G. K. Inflammation and atherosclerosis: the end of a controversy. *Circulation* **136**, 1875–1877 (2017).
61. Baylis, R. A., Gomez, D., Mallat, Z., Pasterkamp, G. & Owens, G. K. The CANTOS trial: one important step for clinical cardiology but a giant leap for vascular biology. *Arterioscler. Thromb. Vasc. Biol.* **37**, e174–e177 (2017).
62. Ridker, P. M. et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* **377**, 1119–1131 (2017).
- Results of the clinical trial that first established the role of inflammation in human atherosclerosis by showing improved cardiovascular and other outcomes by targeted neutralization of IL-1 β .**
63. Ridker, P. M. et al. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* **390**, 1833–1842 (2017).
64. Tardif, J. C. et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N. Engl. J. Med.* **381**, 2497–2505 (2019).
65. Nidorf, S. M. et al. Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* **383**, 1838–1847 (2020). **Two studies^{64,65} that report the results of large-scale clinical trials, showing that treatment with colchicine can reduce recurrent events in patients with recent myocardial infarction or stable coronary artery disease.**
66. Libby, P. & Everett, B. M. Novel antiatherosclerotic therapies. *Arterioscler. Thromb. Vasc. Biol.* **39**, 538–545 (2019).
67. Ridker, P. M. et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N. Engl. J. Med.* **380**, 752–762 (2019).
68. Ross, R. et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat. Rev. Endocrinol.* **16**, 177–189 (2020).
69. Jaiswal, S. et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med.* **371**, 2488–2498 (2014).
70. Genovesi, G. et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Engl. J. Med.* **371**, 2477–2487 (2014).
71. Jaiswal, S. et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N. Engl. J. Med.* **377**, 111–121 (2017).
- This paper describes a newly recognized, potent, age-related, independent and common risk factor for atherosclerosis.**
72. Steensma, D. P. et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* **126**, 9–16 (2015).
73. Libby, P. et al. Clonal hematopoiesis: crossroads of aging, cardiovascular disease, and cancer: JACC review topic of the week. *J. Am. Coll. Cardiol.* **74**, 567–577 (2019).
74. Fuster, J. J. et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science* **355**, 842–847 (2017).
75. Fidler, T. P. et al. The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis. *Nature*, <https://doi.org/10.1038/s41586-021-03341-5> (2021).

76. Gisterá, A. et al. Low-density lipoprotein-reactive T cells regulate plasma cholesterol levels and development of atherosclerosis in humanized hypercholesterolemic mice. *Circulation* **138**, 2513–2526 (2018).
77. Ramírez, C. M. et al. Caveolin-1 regulates atherogenesis by attenuating low-density lipoprotein transcytosis and vascular inflammation independently of endothelial nitric oxide synthase activation. *Circulation* **140**, 225–239 (2019).
78. Kräehling, J. R. et al. Genome-wide RNAi screen reveals ALK1 mediates LDL uptake and transcytosis in endothelial cells. *Nat. Commun.* **7**, 13516 (2016).
79. Huang, L. et al. SR-B1 drives endothelial cell LDL transcytosis via DOCK4 to promote atherosclerosis. *Nature* **569**, 565–569 (2019).
80. Leibundgut, G. et al. Oxidized phospholipids are present on plasminogen, affect fibrinolysis, and increase following acute myocardial infarction. *J. Am. Coll. Cardiol.* **59**, 1426–1437 (2012).
81. Libby, P. Counterregulation rules in atherothrombosis. *J. Am. Coll. Cardiol.* **59**, 1438–1440 (2012).
82. Kruth, H. S. Sequestration of aggregated low-density lipoproteins by macrophages. *Curr. Opin. Lipidol.* **13**, 483–488 (2002).
83. Llorente-Cortes, V., Martinez-Gonzalez, J. & Badimon, L. LDL receptor-related protein mediates uptake of aggregated LDL in human vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* **20**, 1572–1579 (2000).
84. Robbins, C. S. et al. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. *Nat. Med.* **19**, 1166–1172 (2013).
85. Lichtman, A. H., Binder, C. J., Tsimikas, S. & Witztum, J. L. Adaptive immunity in atherosclerosis: new insights and therapeutic approaches. *J. Clin. Invest.* **123**, 27–36 (2013).
86. Gisterá, A. & Hansson, G. K. The immunology of atherosclerosis. *Nat. Rev. Nephrol.* **13**, 368–380 (2017).
87. Swirski, F. K. et al. Ly-6C^{hi} monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J. Clin. Invest.* **117**, 195–205 (2007).
88. Tacke, F. et al. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J. Clin. Invest.* **117**, 185–194 (2007).
89. Bennett, M. R., Sinha, S. & Owens, G. K. Vascular smooth muscle cells in atherosclerosis. *Circ. Res.* **118**, 692–702 (2016).
90. Kubo, T. et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J. Am. Coll. Cardiol.* **55**, 1590–1597 (2010).
91. Deliangryis, E. N. Intravascular ultrasound virtual histology derived thin cap fibroatheroma now you see it, now you don't. *J. Am. Coll. Cardiol.* **55**, 1598–1599 (2010).
92. Vergallo, R. & Crea, F. Atherosclerotic plaque healing. *N. Engl. J. Med.* **383**, 846–857 (2020).
93. Netea, M. G. et al. Trained immunity: a program of innate immune memory in health and disease. *Science* **352**, aaf1098 (2016).
94. Christ, A. et al. Western diet triggers NLRP3-dependent innate immune reprogramming. *Cell* **172**, 162–175 (2018).
95. Williams, J. W. et al. Single cell RNA sequencing in atherosclerosis research. *Circ. Res.* **126**, 1112–1126 (2020).
96. Kalluri, A. S. et al. Single-cell analysis of the normal mouse aorta reveals functionally distinct endothelial cell populations. *Circulation* **140**, 147–163 (2019).
97. Kalucka, J. et al. Single-cell transcriptome atlas of murine endothelial cells. *Cell* **180**, 764–779 (2020).
98. Schloss, M. J., Swirski, F. K. & Nahrendorf, M. Modifiable cardiovascular risk, hematopoiesis, and innate immunity. *Circ. Res.* **126**, 1242–1259 (2020).
This paper summarizes work that links lifestyle and behavioural variables with alterations in the bone marrow that modify cardiovascular diseases.
99. Libby, P., Nahrendorf, M. & Swirski, F. K. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded “cardiovascular continuum”. *J. Am. Coll. Cardiol.* **67**, 1091–1103 (2016).
This paper summarizes recent data that add the central nervous system and bone marrow to traditional cardiovascular risk schemes.
100. Yurdagul, A., Jr, Doran, A. C., Cai, B., Fredman, G. & Tabas, I. A. Mechanisms and consequences of defective efferocytosis in atherosclerosis. *Front. Cardiovasc. Med.* **4**, 86 (2018).
101. Virmani, R. et al. Coronary artery atherosclerosis revisited in Korean war combat casualties. *Arch. Pathol. Lab. Med.* **111**, 972–976 (1987). https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3307684&dopt=Abstract
102. Tuzcu, E. M. et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation* **103**, 2705–2710 (2001).
103. Fernández-Friera, L. et al. Vascular inflammation in subclinical atherosclerosis detected by hybrid PET/MRI. *J. Am. Coll. Cardiol.* **73**, 1371–1382 (2019).
104. Davies, M. J. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. *Circulation* **94**, 2013–2020 (1996).
105. Waksman, R. et al. The lipid-rich plaque study of vulnerable plaques and vulnerable patients: study design and rationale. *Am. Heart J.* **192**, 98–104 (2017).
106. Libby, P. Mechanisms of acute coronary syndromes and their implications for therapy. *N. Engl. J. Med.* **368**, 2004–2013 (2013).
107. Libby, P. Collagenases and cracks in the plaque. *J. Clin. Invest.* **123**, 3201–3203 (2013).
108. Stone, G. W. et al. A prospective natural-history study of coronary atherosclerosis. *N. Engl. J. Med.* **364**, 226–235 (2011).
109. The SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N. Engl. J. Med.* **379**, 924–933 (2018).
110. Douglas, P. S. et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N. Engl. J. Med.* **372**, 1291–1300 (2015).
111. Libby, P. & Pasterkamp, G. Requiem for the ‘vulnerable plaque’. *Eur. Heart J.* **36**, 2984–2987 (2015).
112. Arbab-Zadeh, A. & Fuster, V. The myth of the “vulnerable plaque”: transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J. Am. Coll. Cardiol.* **65**, 846–855 (2015).
113. Pasterkamp, G., den Ruijter, H. M. & Libby, P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. *Nat. Rev. Cardiol.* **14**, 21–29 (2017).
114. Franck, G. et al. Haemodynamic stress-induced breaches of the arterial intima trigger inflammation and drive atherogenesis. *Eur. Heart J.* **40**, 928–937 (2019).
115. Crea, F. & Libby, P. Acute coronary syndromes. *Circulation* **136**, 1155–1166 (2017).
116. Libby, P., Pasterkamp, G., Crea, F. & Jang, I. K. Reassessing the mechanisms of acute coronary syndromes. *Circ. Res.* **124**, 150–160 (2019).
117. Kolte, D., Libby, P. & Jang, I.-K. New insights into plaque erosion as a mechanism of acute coronary syndromes. *J. Am. Med. Assoc.*, <https://doi.org/10.1001/jama.2021.0069> (2021).
118. Libby, P. Once more unto the breach: endothelial permeability and atherogenesis. *Eur. Heart J.* **40**, 938–940 (2019).
119. Molinaro, R. et al. Targeted delivery of protein arginine deiminase-4 inhibitors to limit arterial intimal NETosis and preserve endothelial integrity. *Cardiovasc. Res.*, <https://doi.org/10.1093/cvr/cvab074> (2012).
120. Khera, A. V. et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N. Engl. J. Med.* **375**, 2349–2358 (2016).
This paper presents data that show that healthy behaviours can modify coronary disease risk that is conferred by inherited factors.
121. Ridker, P. M. et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).
122. Collins, R. et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* **388**, 2532–2561 (2016).
123. Cannon, C. P. et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N. Engl. J. Med.* **372**, 2387–2397 (2015).
124. Abifadel, M. et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **34**, 154–156 (2003).
This paper reports a molecular mechanism that regulates LDL concentrations, and that led to the rapid development of a class of lipid-lowering drugs that lower cardiovascular risk.
125. Preiss, D., Tobert, J. A., Hovingh, G. K. & Reith, C. Lipid-modifying agents, from statins to PCSK9 inhibitors: JACC focus seminar. *J. Am. Coll. Cardiol.* **75**, 1945–1955 (2020).
126. Ray, K. K. et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N. Engl. J. Med.* **380**, 1022–1032 (2019).
127. Ray, K. K. et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N. Engl. J. Med.* **376**, 1430–1440 (2017).
128. Tsimikas, S. et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N. Engl. J. Med.* **382**, 244–255 (2020).
129. Libby, P. Lipoprotein (a): a frustrating final frontier in lipid management? *JACC Basic Transl. Sci.* **1**, 428–431 (2016).
130. Pradhan, A. D. et al. Rationale and design of the pemafrilate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. *Am. Heart J.* **206**, 80–93 (2018).
131. Bhatt, D. L. et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N. Engl. J. Med.* **380**, 11–22 (2019).
132. Bhatt, D. L. et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J. Am. Coll. Cardiol.* **73**, 2791–2802 (2019).
133. Mason, R. P., Libby, P. & Bhatt, D. L. Emerging mechanisms of cardiovascular protection for the omega-3 fatty acid eicosapentaenoic acid. *Arterioscler. Thromb. Vasc. Biol.* **40**, 1135–1147 (2020).
134. Libby, P. & Plutzky, J. Diabetic macrovascular disease: the glucose paradox? *Circulation* **106**, 2760–2763 (2002).
135. Zinman, B. et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128 (2015).
136. Perkovic, V. et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* **380**, 2295–2306 (2019).
137. Neuen, B. L. et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation* **138**, 1537–1550 (2018).
138. Wiviott, S. D. et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **380**, 347–357 (2019).
139. Marso, S. P. et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).
140. Marso, S. P. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **375**, 1834–1844 (2016).
141. Gerstein, H. C. et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* **394**, 121–130 (2019).
142. Seeger, T., Porteus, M. & Wu, J. C. Genome editing in cardiovascular biology. *Circ. Res.* **120**, 778–780 (2017).
143. Karakikes, I., Ameen, M., Termglinchan, V. & Wu, J. C. Human induced pluripotent stem cell-derived cardiomyocytes. *Circ. Res.* **117**, 80–88 (2015).
144. Feinberg, M. W. & Moore, K. J. MicroRNA regulation of atherosclerosis. *Circ. Res.* **118**, 703–720 (2016).
145. Jaé, N. & Dimmeler, S. Noncoding RNAs in vascular diseases. *Circ. Res.* **126**, 1127–1145 (2020).
146. Owsiany, K. M., Alencar, G. F. & Owens, G. K. Revealing the origins of foam cells in atherosclerotic lesions. *Arterioscler. Thromb. Vasc. Biol.* **39**, 836–838 (2019).

Acknowledgements P.L. receives funding support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund and the Simard Fund.

Author contributions P.L. is entirely responsible for the conception and design of the work; the acquisition, analysis and interpretation of data; and the initial draft of the work and its revision. P.L. approved the previously submitted version and has agreed both to be personally accountable for his own contributions and to ensure that questions related to the accuracy or

integrity of any part of the work are appropriately investigated, resolved and the resolution documented in the literature.

Competing interests P.L. is an unpaid consultant to, or involved in clinical trials for, Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion, Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Merck, Novartis, Pfizer and Sanofi-Regeneron. P.L. is a member of the scientific advisory boards for Amgen, Corvidia Therapeutics, DalCor Pharmaceuticals, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis and XBiotech, Inc. The laboratory of P.L. has received research funding in the past two years from Novartis. P.L. is on the Board of Directors of XBiotech, Inc. P.L. has a financial interest in Xbiotech, a company developing therapeutic human antibodies. The

interests of P.L. were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare, in accordance with their conflict of interest policies.

Additional information

Correspondence and requests for materials should be addressed to P.L.

Peer review information *Nature* thanks Christie Ballantyne, Michael Holmes and Daniel Rader for their contribution to the peer review of this work.

Reprints and permissions information is available at <http://www.nature.com/reprints>.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© Springer Nature Limited 2021