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Nature Review Disease Primers: Atherosclerosis

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Editor's note for peer reviewers: the authors are aware of the new 2018 ACC/AHA Guideline on the Management of Blood Cholesterol released in November 2018, and will update the manuscript to include a brief discussion after peer review.

Abstract

Atherosclerosis, formation of fatty 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 likely 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. Emerging risk factors include inflammation and clonal hematopoiesis. Studies of the cell and molecular biology of atherogenesis have provided considerable insight into the mechanisms that link these risk factors to atheroma development and the clinical manifestations of this disease. We can deploy an array of diagnostic techniques, both invasive and noninvasive, that permit assessment of risk and targeting of therapies for atherosclerosis. We possess an expanding armamentarium of therapies that modify risk factors and confer clinical benefit. We face considerable challenge in providing equitable access to and in maximizing adherence to these treatments. 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.

[H1] Introduction

Atherosclerosis remains a major killer, and has now spread globally. This Primer proposes not to mire the reader in the details of the 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 cardiovascular disease. Each of these topics has witnessed major advances in recent years. Too many individuals still succumb to the acute complications of atherosclerosis out of hospital, despite these 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. This Primer will present illustrations of this remarkable translational pathway.

Despite these successes much remains to be done in applying what we know already more effectively 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 cardiovascular disease. Although most patients survive acute coronary 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.

Atherosclerosis refers to the accumulation of fatty material in the innermost layer of arteries, the tunica media. The term 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. with time, the atheromatous plaque can become more fibrous and accumulate calcified tissue. Advanced atherosclerotic plaques can reduce the arterial lumen impeding blood flow and lead to ischemia of the perfused tissue. Atheromata that do not produce a flow limiting obstruction can disrupt and provoke formation of a thrombus that can include lumen providing a second route, usually more acute, to producing ischemia. Atherosclerosis is a common cause of myocardial infarction, ischemic stroke, and peripheral arterial insufficiency.

[H1] EPIDEMIOLOGY

According to data from the US National Health and Nutrition Examination Survey, the overall population prevalence of high LDL-C did not change significantly 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 those under control more than doubled during the study period, from 14.6% to 33.2%. [1]

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of vascular diseases worldwide. When it affects the coronary circulation it can cause acute coronary syndromes including myocardial infarction and stable angina pectoris. Atheroscelrosis causes many ischemic strokes, and transient cerebral ischemic attacks. It can lead to 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. (Figure 1). Cardiovascular disease (CVD), including coronary heart disease, high blood pressure, and stroke, collectively comprise the number one cause of death globally.[2 3] Heart disease (most commonly due to disease of the coronary arteries) and stroke are the two leading killers in the world; in the United States, heart disease is the first, and stroke the fifth, leading cause of death. Over 17 million people died from CVD in 2015, representing 31% of all global deaths.[2] Of these, an estimated 7.4 million occurred due to coronary heart disease and 6.7 million to stroke. In the United States, among those over the age of 20, 37.4% of men and 35.9% of women have some form of CVD, with men representing 50.6% of deaths from CVD. [3] Of the men with CVD, 37.7% are non-Hispanic whites, 46.0% blacks, and 31.3% Hispanics; in women, these figures are 35.1%, 47.7%, and 33.3%, respectively.

More than 75% of the world's deaths from CVD occur in low-income and middle-income countries.[2] Individuals in such countries who suffer from CVD have less access to effective and equitable health care services, which can delay detection until later in the course of their disease, such that they die younger from CVD and other non-communicable diseases. Cardiovascular disease leads to 18% of disability-adjusted life years (DALYs) lost in high-income countries, and 10% in low-income and middle-income countries, placing a heavy burden on the economies of low/middle income countries.[4]

While ischemic heart disease remains the leading cause of premature adult mortality worldwide, advances since the 1950s have begotten striking declines in mortality in both men and women from heart disease and stroke. Yet, these improvements in cardiovascular health do not apply evenly across all populations. In high-income countries like the United Kingdom, for example, vascular mortality in men aged 35 to 69 decreased from 22% in 1950 to 6% in 2010.[5] The Global Burden of Disease 2010 Study, however, estimated that this decrease does not occur 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 heart disease and stroke likely arise from a number of factors, including changes in behavioral risk factors due to population-based strategies, individual interventions, or both. Changes to individual or combinations of risk factors include tobacco, diet, obesity, physical inactivity, hyperlipidemia, hypertension, and high alcohol use. The increasing epidemic

of obesity, especially in low- or middle income countries, remains a particular threat to a continued decline in CVD.[4] In 2016, the World Health Organization and the United States 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 program will elevate efforts for CVD prevention and control by promoting both population-level interventions to reduce risk factors, including tobacco control and salt reduction, and by strengthening CVD management in primary health care.

[H1] MECHANISMS/PATHOPHYSIOLOGY

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

[H2] Initiation of atherosclerosis

[H3] LDL cholesterol.

Low-density lipoprotein (LDL) causes atherosclerosis. These spheroidal packets of lipids rich in cholesterol, enveloped in a phospholipid coating with apolipoprotein B snaking through its equatorial region, transport water-insoluble cholesterol through the blood. Atherosclerosis probably would not occur in the absence of LDL concentrations in excess of physiologic needs. [8] Phylogenetic, comparative population studies, and pharmacologic intervention investigations suggest that concentrations of LDL in the 20 to 30 mg/dL range (about 0.5-0.8 mM) suffice for good health. [8 9 10 11] Hence, despite recent secular trends toward lower cholesterol levels, the concentrtions of blood cholesterol prevalent in most contemporary human societies exceed by far the biological needs of the organism (on the order of 10-20 mg/dL), and permit the development of atherosclerosis. [12, 13]The cumulative exposure of an artery to LDL over years remains a principle determinant of disease initiation and progression. Patients with familial hypercholesterolemia (FH) will achieve this cumulative LDL-C burden threshold at early ages and will develop premature ASCVD[14]. On the other hand, subjects with PCSK9 loss-of-function mutations with lifelong low LDL-C due to reduced catabolism of the LDL receptors enjoy a greater reduction of coronary events than that afforded by statin treatment alone[15].

How excessive LDL causes atherosclerosis remains unsettled. Many decades of research have supported the concept that oxidatively modified LDL can promote atherogenesis. [16 17] Pathways that can lead to modification of LDL 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 do not drop when cellular cholesterol content rises, as does 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 oxidatively modified forms of LDL as ligands for the scavenger receptors that facilitate foam cell formation

(Figure 2). Constituents of oxidized LDL may incite inflammation and furnish neo-epitopes that stimulate humoral and adaptive immunity. [18]

Despite the wealth of experimental data that support this sequence of events, we still lack rigorous proof that oxidized LDL initiates human atherosclerosis. [19] Perhaps therapeutic interventions that target oxidative pathways have undergone evaluation 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 oxidation, succinobucol, did not reduce cardiovascular events in a large-scale clinical study. [20] Moreover, recent laboratory studies suggest that native LDL rather than oxidized versions of this particle stimulate T cell responses thought to participate in atherogenesis. [21] Thus, while the "oxidized LDL hypothesis" rests on solid experimental evidence, its relevance to human atherosclerosis remains conjectural. From a clinical perspective, LDL oxidation has not yielded an actionable therapy. Nonetheless, strong human genetic evidence, results of observational epidemiologic studies, and pharmacologic interventions (reviewed in detail below) establish LDL as an indubitable causal factor and therapeutic target in atherosclerosis.[22] LDL can deposit in the arterial wall due to impaired barrier function of the endothelium and retention by extracellular matrix macromolecules.[23] An alternative pathway in atherogenesis mediated by aggregated LDL particles has received less attention. When LDL particles accumulate into the subendothelial space they can bind to intimal proteoglycans and form aggregates. These aggregates 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 family members, like scavenger receptors, evade the usual homeostatic mechanisms that reduce expression of the classical LDL receptor under conditions of cholesterol sufficiency. These smooth muscle cells can become engorged with lipid and contribute to lesion progression.[24]

[H3] Inflammation.

Other risk factors implicated causally in atherogenesis include hypertension, cigarette smoking, and the components of the "metabolic syndrome" cluster that encompasses elevated blood pressure, visceral adiposity, insulin resistance, and ultimately full-blown diabetes mellitus. As in the case of LDL, however, the mechanisms that link these risk factors to atherogenesis remain incompletely elucidated. The operation of inflammatory pathways provides a series of host defense mechanisms that could link many if not all of these risk factors to altered behavior of cells that make up the artery wall, and that summon leukocytes to the plaque in a manner that drives atherosclerosis. For example, angiotensin II, implicated in the pathogenesis of hypertension, can also unleash inflammatory pathways such as the master transcriptional regulator nuclear factor kappa B (NFκB).[25] Likewise, recent experimental work implicates adaptive T cell immunity in the pathogenesis of hypertension, providing a common pathogenetic pathway for elevated blood pressure and atherosclerosis.[26] Cigarette smoke can elicit an inflammatory response in the airways and alveoli. Visceral adipose tissue, a common

concomitant of insulin resistance and type 2 diabetes, teams with inflammatory cells and elaborates multiple mediators of inflammation. These remote sites of inflammation can provoke "echoes" in the artery wall, as they release soluble inflammatory mediators such as cytokines that can activate cells in the intima.[27, 28] Biomarkers of inflammation, notably C-reactive protein (measured with a highly sensitive assay, hsCRP) prospectively predict cardiovascular risk and rise in tandem with many established cardiovascular risk factors.[29] 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. [21] Some T cell subtypes promote experimental atherosclerosis (e.g. T helper 1, Th1 cells.) Others appear to mitigate atherogenesis (e.g. regulatory T cells, Treg.)[19, 30] 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. [21 30] These findings, along with study of human plaques and biomarker investigations in human populations, provide support for the contribution of inflammation and immunity in atherosclerosis.

[H3] The endothelium

Alterations in the endothelial monolayer that provides the interface between blood and the arterial intima, the site of atheroma initiation, occur early during atherogenesis. Exposure to atherogenic risk factors, such as those considered above, interfere with the production of endogenous vasodilators such as nitric oxide from endothelial cells.[31] Consumption of a cholesterol-containing diet can evoke the expression of adhesion molecules such as vascular cell adhesion molecule 1, (VCAM-1) that bind blood leukocytes to the endothelial surface and of chemoattractants that beckon the bound white cells to enter the intima. [32, 33]

The sensors of the local hemodynamic environment may include 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 the Krüppel like factors KLF-2 and 4. [34] Such abnormal flow patterns disturb the normal homeostatic "atheroprotective" functions of the endothelium, including tonic vasodilatation, anti-thrombotic and anti-inflammatory properties, and mechanisms that resist thrombus formation.[35] Atherosclerotic plaques tend to form at sites of flow disturbance, whereas sites in the arterial tree that experience laminar shear stress generally resist atheroma formation.[36] Thus, encountering risk factors for atherosclerosis, or their downstream mediators, in the context of disturbed flow perturbs the exquisite homeostatic properties of the endothelial monolayer and promotes some of the initial steps in atherogenesis.

[H2] Progression of atherosclerosis

Once established, atherosclerotic plaques progress by continued accumulation of lipid and lipid-engorged cells. For many years, most 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 give rise to from cells resembling macrophages as well. [37] The human intima contains resident smooth muscle cells, particularly at sites where atheromata tend to develop. Migration of medial smooth muscle cells into the intima can contribute to smooth muscle accumulation in the growing plaque. These cells can proliferate over the years and elaborate extracellular matrix macromolecules that comprise much of the bulk of an established atherosclerotic plaque.[37]

The plaque's extracellular matrix 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. [38]Various retention factors such as semaphorins can retard the egress of these leukocytes and contribute to their persistent presence in the plaque. [39, 40] While macrophages predominate numerically, T lymphocytes also localize within lesions and may orchestrate both positively and negatively many aspects of plaque growth and evolution. Th1 cells typically elaborate interferon gamma that can promote atherosclerosis, while Th2 cells can produce anti-inflammatory cytokines such as IL-10, and Treg secrete transforming growth factor beta that can limit inflammation, smooth muscle cell proliferation, and promote interstitial collagen synthesis.[41] [30]Furthermore, plaque components draining from lesions will reach adjacent lymph nodes, where they may serve as antigens for T and B cells. Other plaque components such as locally produced cytokines, as noted above, can modulate immune responses in these lymph nodes. [42] In advanced disease, tertiary lymphoid structures may develop adjacent to large arteries. In these structures, B cells differentiating to plasma cells produce large amounts of antibodies to LDL components. [43]
Macrophages and smooth muscle cells can undergo programmed cell death forming the nidus of a lipid-rich or "necrotic" core of the advancing atheroma. [44, 45] (Figure 3) Impaired clearance of dead cells, known as defective efferocytosis, can also contribute to formation of the necrotic core. [46, 47]

Recent evidence supports a causal role of myeloid cells that bear mutations associated with the development of myelodysplastic syndromes and acute myelogenous leukemia in experimental atherogenesis and as a novel important risk factor for human atherosclerosis. [48, 49] With age, somatic mutations in bone marrow stem cells that confer a proliferative advantage can give rise to clones of myeloid cells in peripheral blood. Over 10% of septuagenarians harbor such clones of potent leukocytes in the circulation. Mutations in only a handful of genes generate these clones (e.g. DNMT3A, TET2, ASXL1, JAK2.) Individuals who harbor these clones have an over tenfold increase in the risk of developing acute ischemia, associated with accumulation of successive mutations in the same clone. As most persons who have circulating clones of mutant myeloid cells will never develop leukemia, this condition is called clonal hematopoiesis of indeterminate origin (CHIP.) Carriers of these clones have a much higher mortality rate than explained by death due to hematologic malignancy. Cardiovascular disease, 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 appear to alter the expression of inflammatory genes such as interleukin one beta via epigenetic regulation. Mutations in the tyrosine kinase JAK2 to sensitizes leukocytes to formation of neutrophil extracellular traps that can promote thrombosis. [50] As the cardiovascular risk associated with CHIP does not depend on traditional risk factors, the pursuit of the mechanisms that connect cardiovascular disease with this condition promises to shed new light on pathways that promote atherosclerosis and its complications.[51]

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 functionally cells with the properties of macrophages and various subtypes of T lymphocytes likely predominate in defining the properties of plaques that give rise to complications. [41]

Finally, 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. [52] Much of the mineralization process in plaques recapitulates biological processes in bone formation. Microscopic or spotty calcification associates with mechanical instability of plaques, and may promote tendency to rupture and provoke thrombosis.[53] Larger accumulations of calcium may associate with less likelihood triggering a thrombotic event.[54] Imaging with $Na^{18}F$ may provide a window on calcification in human plaques and promises to provide a new tool for research into the pathophysiology of calcification in human atherosclerosis.[55]

[H2] Complication of atherosclerosis

During much of the life history of the atheromatous plaque, the lesions expand outward radially, in an abluminal direction preserving the caliber of the arterial flow channel. Some of the remodeling of the arterial wall that accompanies lesion progression may result from the production of proteinases by smooth muscle cells specialized in degrading constituents of the arterial extracellular matrix such as matrix metalloproteinase (MMP) 3.[56, 57] But eventually, the growing plaque begins to encroach on the arterial lumen, and can lead to the formation of flow-limiting lesions. (Figure 4)The consequent impairment of coronary arterial perfusion, particularly when myocardial oxygen demands increase due to effort, can produce ischemia and the symptoms of angina pectoris.

[H3] Plaque rupture

Rupture of atherosclerotic plaques is the most common trigger acute thrombosis of coronary arteries that cause myocardial infarction. Plaques that have ruptured often have large lipid cores covered by a thin

fibrous cap (less than 60 μm.). Lesions with these characteristics have often been termed "vulnerable plaques."[58] In contrast, many refer to plaques with less lipid accumulation and thicker fibrous caps as "stable." This classification oversimplifies considerably the complexity of the mechanisms of plaque destabilization, [59, 60]yet has provided a framework for much thought regarding the pathophysiology of acute coronary syndromes for several decades

Atherosclerotic plaques that have developed defects in the extracellular matrix that overlies the plaque's lipid core, forming an overlying fibrous cap, can form a fissure in this structure. Inflammatory processes can impede synthesis of interstitial collagen by plaque smooth muscle cells, impairing their ability to maintain the skeleton of the fibrous cap. [61, 62]Activated inflammatory cells can also elaborate interstitial collagenases specialized in breaking down the key structural components of the lesion's fibrous cap. [63] Rupture of an atheromatous plaque exposes the contents of the plaques interior to the blood compartment. Thrombogenic material in the plaque's core, notably tissue factor produced by macrophages and smooth muscle cells, can trigger thrombus formation. Together with locally impaired homeostatic function of the luminal endothelium, persistent and occlusive clots can provoke ischemic insults such as acute coronary syndromes and many strokes. Plaque rupture, arising from lipid-rich plaques with abundant foam cells and with fibrous caps thinned through the action of inflammatory pathways, causes the majority of acute coronary syndromes. [58, 64]

The ultimate and most dreaded complications of atherosclerosis arise from thrombosis. Formation of blood clots causes most acute coronary syndromes including myocardial infarction and many ischemic strokes. Thrombus formation can also contribute to critical ischemia of the lower extremities when complicating peripheral arterial disease. Arterial thrombi that complicate atherosclerotic plaques arise from generation of fibrin from fibrinogen to the action of thrombin. Thrombin also activates platelets to aggregate a process that contributes to clot formation. Recent work has implicated neutrophil extracellular traps (NETs) in vascular clotting.[65] Neutrophils that undergo a specialized form of cell death known as NETosis elaborate these structures that consist of strands of DNA decorated with granular enzymes and proteins such as tissue factor adsorbed from blood. Blood clots thus contain fibrin strands, clumps of activated platelets, and strings of extruded DNA from granulocytes that can propagate thrombus formation and amplify intimal injury.[66, 67]

The normal arterial endothelium possesses numerous properties that prevent clot formation and promote thrombolysis. [35] Surface thrombomodulin, heparan sulfate proteoglycans, and production of nitric oxide and prostacyclin contribute to the anticoagulant and antithrombotic properties of the normal endothelial monolayer. The expression of urokinase and tissue-type plasminogen activators combat the persistence of thrombi through fibrinolysis. Endothelial dysfunction, as occurs in the presence of atherosclerotic risk factors, or more acutely during inflammatory activation (for example due to pathogen associated factors such as bacterial endotoxin or proinflammatory cytokines), can impair these normal homeostatic properties. Under

these circumstances, endothelial cells produce tissue factor, potent procoagulant molecule, and plasminogen activator inhibitor 1 (PAI – 1), a key endogenous inhibitor of fibrinolysis.[68]

[H3] Plaque erosion

In the current era, effective anti-atherosclerotic therapy, including measures described below, (e.g. lipid-lowering, treatment of hypertension, and smoking cessation) has shifted the substrate of the thrombotic complications of atherosclerosis. Plaques have become less inflamed, less lipid-laden, and thus likely less liable to rupture than in previous eras. [60, 69] Under these circumstances, another mechanism of thrombotic complications of atheroma may increase as a proportional cause of acute coronary syndromes. This alternative thrombotic mechanism, called plaque erosion, appears to arise from lesions with a quite distinct morphology from the typical ruptured plaque. The lesions complicated by erosion tend to have a rich extracellular matrix without a thin fibrous cap, few inflammatory leukocytes, and little lipid. [70] 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 (TLR-2) and the participation of polymorphonuclear leukocytes as amplifiers of the local thrombotic process may contribute to this mode of plaque complication. [71, 72] Indeed, DNA extruded by dying granulocytes that bear a number of pathogenic mediators known as neutrophil extracellular traps (NETs) may propagate thrombosis during acute coronary syndromes, particularly those cause by intimal erosion. [71]

In conclusion, excess LDL appears permissive for human atherosclerosis. The definition of "excess" has shifted to lower and lower levels as we gain evidence from clinical trials of lipid-lowering agents (as summarized below) and as experience with humans living with LDL concentrations considered ultra-low in the past increases confidence in the safety of such levels. [11] The pathways of inflammation and immunity have gained ascendancy as mechanisms that link traditional risk factors to the initiation, progression, and complication of atherosclerosis. Our therapeutic gains appear to be modifying human atherosclerosis in the current era, and we must continuously reset our sights to deal with today and tomorrow's disease rather than that of yesteryear.

[H1] Diagnosis, Screening and Prevention

[H2] Clinical Presentation

Atherosclerosis is a diffuse, slow-progressing disease, typically involving several arterial vascular beds (Figure 5),[73] and 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 narrowing. Ischemia due to stenotic, flow-limiting lesions can occur under conditions of increased myocardial oxygen demand, for example during physical exertion, and cause symptoms of episodic chest discomfort called *angina pectoris*. Acute thrombotic

occlusion that interrupts myocardial oxygen supply typically results from disruption of atherosclerotic plaques.[74]

Due to its diffuseness, the clinical presentation of atherosclerosis remains highly variable, depending on the vascular territory involved (Figure 5) and the disease onset, chronic or acute. In some territories, such as renal arteries, the most common presentation is a chronic, long-developing syndrome (e.g. progressive hypertension and/or worsening renal function secondary to renal artery stenosis.) In other territories, atherosclerosis most commonly manifests with acute and sudden presentations, such as acute ischemic stroke due to atherosclerosis. In the coronary arteries, both acute (i. e. acute coronary syndromes) and chronic (i. e. stable angina) presentations commonly arise.

The definitive diagnosis of those clinical syndromes caused by atherosclerosis usually depends on additional testing. This undertaking usually involves the direct visualization of atherosclerosis or the documentation of target organ ischemia. Table 1 presents a short summary of imaging methods for the visualisation of atherosclerosis. Each imaging methods is directed to specific clinical scenario. While ultrasound and computed tomography angiography are usually used for non-invasive investigation of atherosclerosis in various vascular territories, other more invasive procedures such as invasive angiography, IVUS or OCT are mostly used to guide interventional therapies, whereas technologies such as PET and magnetic resonance tend to be restricted to research purposes on the evaluation of atherosclerosis. Multiple guidelines from various jurisdictions offer guidance on appropriate use of cardiovascular imaging modalities.[75]

Once a definitive diagnosis of clinically relevant atherosclerosis has occurred, risk stratification of the atherosclerotic disease will define treatment. While most individuals with relevant atherosclerosis require medical management with lipid-lowering medication (e.g. statins) and aggressive management of other risk factors, the extent, severity, location, and plaque characteristics of the atherosclerotic disease determines additional medical, catheter-based or surgical interventions to reduce ischemic symptoms or risk of acute events. This additional and necessary information routinely emerges from similar imaging methods used for direct atherosclerosis visualisation or ischemia detection, as described above.

[H2] Clinical significance

Since the initial demonstration of the association between symptoms and luminal narrowing by invasive angiography, the clinical significance of atherosclerosis has undergone assessment by the degree of luminal narrowing. Classical studies suggest that thresholds of 50 to 75 percent diameter-narrowing associate with physiological limitations in coronary flow at stress and at rest. Thus, usually patients start experiencing chronic symptoms initially under conditions of increased oxygen demands such as physical or emotional stress, when stenoses exceed 70 percent (Figure 6).[76] These results have helped define the clinically "significant" atherosclerotic plaque, and until recently, the absence of such luminal reduction indicated a "normal"

angiogram.[77] More recently studies have used fractional flow-reserve (FFR.) This method evaluates the intra-coronary pressure to define if a luminal reduction limits flow by comparing the pressure before and after 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 are far from linear. Other plaque characteristics such as length, eccentricity, positive remodelling, as well as limitations associated with luminal narrowing estimation on invasive angiography may all influence the functional implications of any stenosis.[78] As a result, functional assessments such as with FFR should define assessment of the clinical "significance" of a coronary atherosclerotic lesion.[79]

Over the last decade, studies have also challenged the concept that luminal narrowing or downstream ischemia determines the clinical significance of coronary atherosclerotic disease. Studies have shown that the risk of plaque rupture and a subsequent acute event more strongly associates with plaque vulnerability and systemic patient characteristics, such as inflammation, rather than the degree of focal stenosis.[80] This concept has garnered further support by recent evidence that overall plaque burden measured by coronary computed tomography or invasive angiography, irrespective of the luminal narrowing, remains the strongest anatomical predictor of incident cardiovascular events of myocardial infarction or cardiovascular death associated with more extensive non-obstructive disease is comparable to the risk associated with obstructive[81, 82]. We therefore need to redefine the criteria for clinical "significance" of atherosclerotic lesions. Box 1 shows a practical, clinically oriented definition of coronary artery disease (CAD). While the first two aspects of the definition likely associate with symptoms and flow reduction, the third does not. Yet, this classification still holds significance from a clinical standpoint, as the higher risk of future cardiovascular events should prompt changes in clinical management. This definition generally extends to virtually any vascular territory where atherosclerosis may develop (Figure 5); the presence of symptoms, a previous acute vascular event or the presence of plaque with characteristics associated with increased risk of complications, should all define atherosclerosis clinically and prompt changes in medical management. Since this approach includes asymptomatic individuals, the identification of subjects "at risk" requires a screening strategy.

[H2] Screening

Atherosclerosis meets several of the traditional Wilson's criteria[83] that define a disease amenable for screening, such as: A. The condition is an important health problem (i.e. high prevalence); B. Treatment exists for the condition; C. There is a long latent/asymptomatic stage; D. The natural history is adequately understood. Yet, the policy regarding treatment remains variable across different guidelines, as does the appropriate screening strategy for atherosclerosis detection and the prevention of its complications.[84-86]

Despite the disagreements, virtually all guidelines recommend the initial evaluation of individual risk of future cardiovascular events based on clinical risk factors.[87-89] Interestingly, risk assessment using individual risk scores as a "screening" tool derives not from the actual detection of atherosclerosis, but rather on the identification of individuals with an increased risk of future events.

Additional tests can prove invaluable for the identification of atherosclerosis in several vascular beds, such as carotid ultrasound, coronary calcium score measurement measured by computed tomography, and coronary computed tomography angiography. Current data, however, 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 tool for additional risk stratification by most guidelines, particularly for intermediate risk individuals for whom treatment decisions are unclear.[90] Other additional tests may provide prognostic value for risk stratification of future 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 advanced testing for screening and risk stratification has encountered restrictions at least in part due to the limited medical interventions used in the primary prevention setting (i.e. statins and aspirin). Recent data on other lipid-lowering medication,[91] anti-inflammatory drugs,[92] and newer anti-thrombotic drugs[93] leading to a reduction in future CVD events, will likely spur an increase in the role of testing to identify better candidates for those new therapies among individuals in settings of both the primary (no prior event) and secondary prevention (prior event). 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 allow for a sustainable use of healthcare resources.

[H2] Prevention

As discussed above, atherosclerosis remains a leading cause of cardiovascular events and mortality across the globe. The increasing focus on cardiovascular disease prevention stems from an appreciation that the better treatment of patients cannot alone address the enormous global burden of cardiovascular disease, which experts predict will increase substantially, particularly in low- and middle-income countries.[94] Current interest in prevention is based on economic imperatives and novel insights on the importance of lifetime risk management of cardiovascular disease, with an emphasis placed on much younger age groups as well as from new opportunities derived from the digital health revolution.

[H3] Economics

The direct cost of treating cardiovascular disease in the United States currently exceeds USD 300 billion per year, and predictions put both direct and indirect costs to almost a trillion USD by 2030.[95] Most countries cannot sustain these cost burdens. The adoption of a healthier lifestyle

from early life should markedly reduce the atherosclerosis burden and its complications, while wider use of currently recommended preventative therapies such as statins will likely demonstrate high cost-effectiveness from a societal perspective.[96]

[H3] Effects of lifetime exposure to risk factors

Atherosclerosis begins decades before the appearance of its clinical consequences. Early autopsy studies, followed by *in vivo* imaging, show that subclinical atherosclerosis increases progressively from the first decade of life, and is present in the majority (63% of population; 71% of men and 48% of women) by age 40-54 years.[73] This preclinical disease relates to levels of classical cardiovascular risk factors even in children and adolescents in a familiar cumulative manner. Risk factor exposure during early life relates to incidence of future cardiovascular events[97] as well as rate of cognitive decline. Children remain key to future cardiovascular disease risk reduction in the population. Unhealthy behaviour begins early, and habits acquired in this phase likely transition into adulthood. The global epidemic of childhood obesity continues to impact enormously population health, as does cigarette smoking and a sedentary lifestyle in teenagers and adults. Clinical studies have demonstrated that the familiar cardiometabolic changes seen in overweight and obese adults exist across the normal weight profile of children even before puberty.[98] Children from economically disadvantaged backgrounds may endure specific vulnerability.[99] Studies have also shown that weight reduction can improve risk factor level and improve vascular wall function.[100] This key public health issue will require a broad approach, educating not only the child, but also their families as well as managing their social and living environments.[101]

Risk factor exposure during early life relates to incidence of future cardiovascular events.[97] and cognitive impairment (box 2) Prospective randomised clinical trials to evaluate the benefit of early risk-factor control on future cardiovascular events are challenging, but genetic studies using Mendelian randomisation have shown clearly the potential benefit of lower lifetime risk factor exposure. In a pooled analysis of 102,774 subjects who sustained 14,368 events, even modestly lower levels of blood pressure and LDL-cholesterol as a result of genetic variation translated to a 46 percent clinical event reduction.[102] Sustained lifestyle improvements may yield similar benefits. Prospective clinical trials using risk profiles and functional arterial tests support the concept that cardiovascular disease may be largely preventable if lifetime exposure to risk factors can be reduced.[103, 104] While the entire population would benefit from early sustained cardiovascular risk factor lowering, achievable by lifestyle change and reduction in environmental exposures, certain subgroups have a greatly increased risk for future cardiovascular disease and therefore require additional treatment. These populations include patients with co-morbidities such as diabetes (Type 1 and Type 2), chronic inflammatory diseases such as rheumatoid arthritis, and chronic kidney disease, as well as those with monogenic disorders. For example, familial hypercholesterolemia (FH) illustrates how lifetime

exposure to elevated cholesterol levels leads to premature cardiovascular disease, and provides strong evidence for the leveraged gains from early cholesterol reduction.

Recent evidence has shown the importance of inflammation in the pathophysiology of atherosclerosis; these host-defense mechanisms may represent a common pathway for mediating the adverse effects of diverse risk factors. Inflammatory diseases such as rheumatoid arthritis associate with increased cardiovascular risk while periodontitis, the most common form of chronic systemic inflammation, causally relates to arterial wall changes as well as to future cardiovascular events.[105] [106] Benefits from anti-inflammatory drug treatment shown in the CANTOS trial should encourage further research clinical e.g. strategies to limit inflammation.[92]

[H3] Communication of Risk

Current 10-year risk prediction models, which serve to communicate with patients and to guide treatments, have much less value for prevention during a lifetime. Few individuals <=50 years have a 10-year absolute risk of >7.5%, even with multiple modifiable risk factors.[107] The MESA/CARDIA studies showed that individuals with low 10-year risk but high lifetime risk already exhibit evidence of atherosclerosis with increased carotid intima-media thickness and coronary artery calcification.[108] Estimates put >50% of the USA adult population at a 10-year risk of <10% but a lifetime risk ≥39%.[107] For effective adherence to longer-term prevention strategies, communication with patients and the public requires a focus not only on short-term risk but also on lifetime risk, with emphasis on the opportunities for personal gain by early-sustained risk factor lowering. Many individuals can achieve this by lifestyle changes but a significant proportion of individuals will benefit from additional pharmacological treatment. The Joint British Societies recommendations on the prevention of Cardiovascular Disease (JBS3) score, adopted in the UK, utilizes understandable metrics such as "Heart Age"[109] to empower patients; this approach has shown very promising results for effective communication with patients.[110, 111]

The same cluster of risk factors (blood pressure, smoking, obesity, diabetes, and atrial fibrillation) for the development of cardiovascular disease may also accelerate cognitive decline and dementia.[112] The pattern of risk exposure has several similarities, with greater impact from high levels and multiple risk factors. Furthermore, accumulating evidence suggests that early life levels, e.g. blood pressure in middle age, have greater predictability than those at older ages, supporting a similar "exposure model" for brain and cardiovascular disease.[113] Recent evidence has linked risk factors in childhood to cognitive performance in middle age.[114] Numerous intervention trials examining the impact of multiple cardiovascular risk-factor lowering on cognitive outcomes are underway following the recent positive FINGER trial.[115] This study showed how a multifactorial intervention can improve cognitive performance. The potential to benefit both future cardiovascular disease and dementia will deliver a powerful prevention

message to the public. The shared biology between cardiovascular and other diseases may reveal other opportunities for clinical benefit from early intervention.

The revolution in digital health provides a new opportunity for cardiovascular disease prevention. Continuous monitoring during normal daily life reinforces "good behaviour," and consideration of such extensive real-life data will likely significantly refine risk prediction models. The public currently demonstrates enormous interest in their cardiovascular health, as shown with the adoption of wearable devices and the use of online risk calculators.[109] As these devices become more sophisticated, the data collected will provide epidemiological insights, refine safety and endpoints in clinical trials, inform clinical care, and change the culture of cardiovascular disease prevention.

Cardiovascular disease prevention remains the key to future population health. It will require a fundamental shift in thinking with a focus on "wellness maintenance," not merely "disease treatment." Doctors will need to play a leading role and there will need to be changes in medical training and funding allocation. The involvement of allied professionals and shared decision making with patients has growing importance. A "lifetime approach," starting in childhood, aiming to change behaviour and intervene early when needed, should transform the cardiovascular health of future generations and must be a worldwide priority.

[H1] Management

Because of the multifactorial nature of the atherosclerotic process, its management should modify all known treatable risk factors. A discussed above, the optimum path involves primary prevention by adopting a healthy lifestyle from childhood. Yet, risk factor modification to prevent or even reverse the progression of the atherosclerotic process can occur at any stage of atherosclerotic vascular disease, even after an acute coronary syndrome. As reviewed above, cardiovascular mortality has decreased significantly in many populations, due to the reduction in cholesterol, blood pressure levels, and smoking[116]. Unfortunately, an increase in other risk factors attributable to a modern lifestyle such as obesity, type 2 diabetes, sedentary behavior, and psychosocial stress challenge these gains[117]. While lifestyle modification remains pertinent for all individuals, the use of lipid-lowering medication depends on the estimated risk of incident coronary heart disease events or cardiovascular events. Some also recommend anti-platelet therapy after individual assessment of risk and benefit, though this treatment remains highly debatable in the literature.[118 119, 120]

[H2] Lifestyle interventions

Lifestyle interventions are integral to therapy, and have the advantage of targeting multiple risk factors all at once. The emphasis on diet, physical activity, and abstinence from smoking in the prevention of atherosclerotic vascular disease remains essential[121]. Recent evidence shows that a

healthy diet not only influences lipid and risk-factor profile favorably while decreasing obesity, but also affects gut microbiota that may produce metabolites harmful to the vasculature[122]. Therefore, a healthy lifestyle holds great importance to everyone at all stages of atherosclerotic vascular disease.

Smoking cessation remains the most clinically- and cost-effective strategy for the prevention of atherosclerotic vascular disease[123]. Blood pressure control with lifestyle intervention, as well as medications when necessary, also remain vital depending on the level of blood pressure and the risk of the patient[124]. The management of diabetes reduces the risk of microvascular complications and, with newer agents, macrovascular disease, and improves cardiovascular outcomes in these patients[125]. Lifestyle modifications to reduce LDL cholesterol and lipid levels should accompany recommendations to all patients. If goals are not met, pharmacological therapy should be considered.

[H2] Pharmacological therapy

[H3] LDL-cholesterol lowering therapy

Lipid-lowering therapy remains the cornerstone of the management of atherosclerotic vascular disease. Evidence from epidemiologic, genetic, and Mendelian randomization studies and randomized clinical trials involving more than 2 million participants and more than 20 million person-years of follow-up have shown that LDL-C acts not only as a risk factor but as a causal factor[126]. Therefore, early control of LDL-C holds great importance. Randomized trials have consistently demonstrated that lowering LDL cholesterol reduces the risk of CV events proportional to the absolute fall in LDL cholesterol independent of other risk factors[127]. These findings support the current concept that therapy should target primarily LDL-C.

Although some differences exist in the approach to LDL-C lowering in various guidelines, the principals remain the same. The intensity of treatment should be proportional to the risk of the patient. Risk is defined on the basis of known disease or by various risk scores in those without clinical cardiovascular disease.. Treatment intensifies as risk increases. However, mendelian randomization trials have shown us that having a lower cholesterol load throughout life prevents cardiovascular events to a greater extent than shown in 2-5 year intervention trials of pharmacologic lipid lowering. Therefore early intervention before cardiovascular disease manifests itself should prove more effective that later institution of therapy. [128, 129]

The European Guidelines, which take into account all published evidence, recommend that specific treatment goals for LDL-C should be targeted according to the risk of the patient[130] (Table 2). Setting goals tailors therapy taking into account individual variability in response to drugs and increases adherence to medication. Pharmacologic treatment should start with a statin. Compelling evidence from randomized clinical trials (RCTs) shows that reducing LDL-C with statins decreases CV 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 cardiovascular events per mmol/L reduction in LDL-C.[131] Statin prescriptions should reach the highest recommended or tolerated dose to attain the goal. If the goal still remains unmet, combination therapy may prove successful.

On the other hand, the ACC/AHA 2013 guidelines, which are based solely on RCT evidence, recommend universal use of statins in all high-risk subjects[132]. They define the following groups of patients who should be given high or moderate dose statin therapy: Individuals with clinical ASCVD, primary elevations of LDL–C >190 mg/dL, diabetes aged 40 to 75 years with LDL– C 70 to 189 mg/dL and without clinical ASCVD, or without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk measured by Pooled Cohort Equation >7.5%.

All guidelines agree that statins should remain the first choice in initiating pharmacological therapy due to its ample supporting evidence. Depending on the potency and dose of statin used, a 30-50 percent reduction in LDL-C levels may prove possible depending on the type and dose of statin. Yet, extremely high-risk and FH patients may not achieve their goals, and may therefore require further LDL-C reduction with combination therapy. People with FH merit special interest because of lifelong exposure to high LDL-C levels. This genetic condition typically remains underdiagnosed and undertreated. Because these patients harbor a higher risk than others with same levels of LDL-C, the clinician should rule out FH with clinical criteria. Achieving targets can prove challenging, especially in patients with FH and those with statin intolerance who warrant a non-statin drug.

[H3] Other LDL-cholesterol lowering drugs

The cholesterol-absorption inhibitor ezetimibe 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%. The IMPROVE-IT Study showed that in patients with acute coronary syndrome, adding ezetimibe to a statin associated with a 6.5% proportional reduction in major cardiovascular events.[133]

Earlier clinical trials have shown that bile-acid sequestrants also lower LDL-C and decrease CV events. Yet, gastrointestinal side effects, drug interactions, and elevation triglyceride levels limit their widespread use[134].

PCSK9 inhibitors are a new class of drugs that can be used in combination with statins in selected patients with high risk. PCSK9 chaperones LDL receptors to destruction, and inhibiting PCSK9 can decrease LDL-C significantly. Studies with monoclonal antibodies inhibiting PCSK9 have shown that LDL-C can decrease up to 60% with their use[135, 136]. Clinical trials have tested the fully human antibodies evolocumab and alirocumab as well as the humanized antibody

bococizumab in over 10,000 patients. The GLAGOV intracoronary ultrasound study showed that decreasing LDL-C levels with evolocumab even further on top of statin therapy could reverse coronary atherosclerosis on IVUS[137]. The more recent FOURIER and ODYSSEY clinical outcome trials showed that inhibition of PCSK9 with evolocumab or with alirocumab on a background of statin therapy lowered LDL cholesterol levels substantially (in FOURIER to a median of 30 mg per dL, 0.78 mmol per liter) and reduced the risk of cardiovascular events with a good safety profile[138]. In the SPIRE study, adding the incompletely humanized PCSK9 inhibitor bococizumab to statins decreased cardiovascular outcomes in high-risk patients with a baseline LDL-C over 100 mg/dL, but the development of antidrug antibodies in 15-20 percent of patients attenuated the substantial reduction in LDL-C[139]. Small interfering RNAs like inclisiran, furnish another way to inhibit PCSK9 with impressive durability, and are currently under clinical investigation[140].

Evidence from recent trials with combination therapy using ezetimibe and PCSK9 inhibitors show that greater CVD benefit derives from much lower LDL-C than previously achievable: concentrations that fall below 70 mg/dL down to 25 mg/dl. [141] The EAS/ESC published a consensus paper to help identify patients likely to derive the most potential benefit from this novel therapy, while also taking into account the financial constraints of one's healthcare budget[142]. This consensus recommends consideration of treatment with a PCSK9 monoclonal antibody in very high-risk patients with atherosclerotic vascular disease or in patients with severe FH without ASCVD 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. Recent post-hoc analysis from trials are suggesting that certain subgroups of patients such as those with CABG, multivessel disease and recent MI may derive greater benefit from aggressive LDL-C lowering with combination therapy.

[H3] Non-HDL-cholesterol lowering therapy

Non-HDL-C (total cholesterol minus HDL concentration) represents the cholesterol in all atherogenic particles. Although usually concordant with LDL-C, some discordance between LDL-C and Non-HDL-C may exist in insulin resistant states in which case non-HDL may be a better predictor of disease. Once the desired LDL-C goal is reached non-HDL-C should serve as a secondary target for treatment especially in diabetic individuals. The goals for non-HDL-C in European guidelines are less than 100, 130, 145 mg/dL (2.6, 3.4, 3.8 mmol/L) for very high-, high- and moderate- risk patients, respectively[130].

Fibrates lower triglycerides and triglyceride-rich remnant particles, which augment atherogenesis. Yet, prospective RCTs in combination with statins have not met their primary endpoints of improving cardiovascular outcomes. In several such studies, the subgroups with low HDL-C and high triglycerides did derive benefit.[143] The European guidelines recommend statins

as the first choice to reduce risk in patients with hypertriglyceridemia, but consider the use of fibrates in combination to reach non-HDL goals, especially in the high-risk diabetic patient.[89]

[H3] Antiplatelet drugs

Platelets play a critical role in the pathogenesis of atherothrombotic processes. Antiplatelet therapy does not fall under routine recommendations in primary prevention due to the increased risk of major bleeding. In secondary prevention, however, the benefits of aspirin exceed the bleeding hazards[144]. P2Y12 inhibitors further inhibit platelet aggregation by irreversibly blocking the adenosine diphosphate P2Y12 receptor. These agents should be used in addition to aspirin in acute coronary syndromes or in the setting of percutaneous coronary intervention.[145].

[H3] Anti-inflammatory drugs

The inflammatory component of atherosclerotic vascular disease has recently gained momentum as a therapy target because of several clinical trials to test anti-inflammatory agents. The anti-interleukin 1 beta antibody canakinumab (150 mg every 3 months subcutaneously) reduces major adverse cardiovascular events (MACE) significantly (by 15%) in post-MI patients with hsCRP > 2 mg/L. [92] In the responders, who achieved concentrations of hsCRP below 2 mg/L after the first dose of canakinumab, MACE was reduced 25%, and total and cardiovascular mortality by more than 30%. [146] Fatal lung cancer fell by 77% in those treated with canakinumab 300 mg every 3 months, in an exploratory analysis. [147] Large secondary prevention studies are evaluating colchicine and methotrexate as alternate anti-inflammatory agents. [148]

Non-steroidal anti-inflammatory agents (NSAIDs), drugs that inhibit prostaglandin synthesis, are commonly used anti-inflammatory drugs in a variety of conditions. They may, theoretically exert beneficial effects on vascular inflammation, however, their capacity to inhibit production of prostacyclin, a prostaglandin that inhibits platelet aggregation may counterbalance such effects. Cyclooxygenase-2 selective inhibitors (Coxibs) that inhibit prostacyclin without interfering with production of the proaggregatory prostaglandin, thromboxane A2 can increase cardiovascular events. [149, 150]

[H3] Therapeutic challenges

As noted above, the challenges we face today include nonadherence to lifestyle and lipid-lowering therapy, with most patients not achieving or maintaining their goal. The benefits we see in randomized trials will only replicate in "real world" situations if patients adhere to treatment. Studies show that nearly half of patients discontinue statin use within the first year after the initial prescription, with higher discontinuation rates after two years[151]. Discontinuation associates with increased risk for cardiovascular events and death[152]. Statin-associated muscle symptoms remain the most frequent reason for nonadherence. Although there are no objective criteria for definitive diagnosis, these patients should be managed carefully with statin rechallenges. Recent evidence shows that persistence remains important in high-risk patients,

and continued statin use even after an adverse reaction associates with a lower incidence of death and cardiovascular events[153].

Although not getting to goal is a very important determinant of residual risk, events still continue in optimally treated patients at LDL-C goal. It has been possible to lower events even further by pushing LDL-C levels to below guideline recommended levels by combination therapy. Other risk factors beside LDL-C also contribute to residual risk and all known risk factors in a patient such as smoking, diabetes, hypertension, obesity should be treated. Remnant lipoproteins, Lp(a) , inflammation are other factors that contribute to the residual risk and their relevance is being tested in studies.

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 persistence of treatment following existing guidelines for our patients. If atherosclerotic vascular disease has progressed to a stage causing symptomatic ischemia, revascularization can often relieve symptoms, and possibly increase survival, a conjecture currently under intense study. [154]

[H1] QUALITY OF LIFE

Health-related quality of life (HRQL) 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.[155] It is the final pathway of a complex construct that links biological variables to symptom burden, functional capacity/exercise capacity, and psychological well-being; these are collectively referred to as patient-reported outcomes.[156] Given the improved survival of patients with atherosclerosis (and thus total lifetime burden), research into HRQL of these patients has increased.

Patients with atherosclerosis have an HRQL worse than age-matched healthy patients, yet the individual responses of these patients are quite variable.[157] Progressive atherosclerosis often leads to increased angina, fatigue, dyspnea, and exercise intolerance. Complex treatment regimens and healthcare utilization may additionally lead to a negative impact on HRQL by affecting a patient's psychological and social well-being[158], related to anxiety due to prognosis and future events, depression, sleep disturbances, and side effects. The occurrence of acute coronary syndromes compounds these perceptions, often associated with lower HRQL.[158] Patients with atherosclerosis often have comorbid conditions (e.g., diabetes, peripheral arterial disease, and obesity) that may further worsen their HRQL, while the development of heart failure diminishes HRQL. Other predictors of impaired HRQL include a younger age, female gender, poor/inadequate emotional support, racial minorities, lower socioeconomic status, and disease severity. These all present future targets for improving HRQL.

Three types of instruments remain paramount in measuring HRQL in atherosclerosis: generic, disease-specific for atherosclerosis, and disease-specific for ancillary disease conditions germane to the individual. Generic instruments, such as Short Form-36 and EQ5D, allow for comparison of HRQL to other patients and to measure changes in overall health state beyond atherosclerosis. Thus, headaches produced by nitrates may counterbalance improvements in angina, with the magnitude being driven by the importance to the patient and the severity of each symptom. Common disease-specific instruments used to measure HRQL include the Seattle Angina Questionnaire (SAQ) and the Myocardial Infarction Dimension Assessment Scale (MIDAS)[159]. These instruments remain more responsive to change and can measure efficacy of an intervention or track changes over time. Numerous instruments provided ancillary understanding on conditions and common disease states, including functional capacity (e.g., DASI)[160] and depression (e.g., PHQ-9).[161]

Revascularization remains the cornerstone for improving HRQL in atherosclerosis patients with multi-vessel disease. Compared to surgery, percutaneous coronary intervention (PCI) patients have better quality of life improvement by one month and less physical limitations[162]; however by six months and beyond, surgical revascularization patients have greater anginal improvements and improved overall HRQL. High-intensity interval training versus moderate exercise training have had similar benefits on HRQL.[163] Nursing-led secondary prevention efforts, including education and behavioral counseling/support, and patient lifestyle changes result in improvements in HRQL[164, 165]; however, the details on key elements that translate into improved outcomes remain limited. As we continue to make progress in the management of acute and chronic atherosclerosis, we must also develop strategies to maximize HRQL.

[H1] Outlook

The very advances in managing the complications of atherosclerosis have extended life, but leave many with impaired cardiac function contributing to an epidemic of heart failure due to ischemic cardiomyopathy. Beyond its intolerable human costs, the burden of heart failure creates a major strain on healthcare 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, depend on increasingly complex technologies. Arrhythmias and heart failure most often arise because of atherosclerosis. Treatment of these conditions, when advanced, often also involve highly technological interventions such as pacemakers, cardiac resynchronization, and mechanical circulatory support. Lewis Thomas referred to such solutions as "halfway technologies." [166] 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 behavioral or societal changes. Our ability to deploy adoption of healthy diets, regular physical activity, smoking 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 target novel pathways and address unmet needs rather than exhausting well-mined targets. In our clinical practices, we should strive to implement what we already know in an evidence-based manner, and never allow guidelines and practice algorithms to replace our bond with individual patients and our judgement and experience regarding that individuals particular circumstances, needs, and preferences. As a society, we need to combat unhealthy lifestyles and provide a healthy environment to limit the spread of cardiovascular disease in the future.

Box 1. Definition of clinically significant coronary atherosclerotic disease.

Coronary atherosclerosis should be considered clinically relevant if any of the characteristics below is present
1. It leads to the development of documents downstream ischemia; 2. It has already led to an acute vascular event (e.g. an acute coronary syndrome); or 3. The documented atherosclerotic burden (extent and severity) or individual plaque characteristics have been associated with worse outcomes in large population studies.

Figure Legends

Figure 1: The contribution of cardiovascular diseases to the global burden of death in 2016.

These data, collected from the global burden of disease website (https://vizhub.healthdata.org/gbd-), convey the importance of atherosclerotic cardiovascular

disease worldwide. Many stroke deaths may not result directly from atherosclerotic disease but from hypertension, and a highly prevalent cardiovascular risk factor. Likewise, not all cases of cardiomyopathy are ischemic in origin, and some cases of atrial fibrillation may not associate with atherosclerosis.

Figure 2. Initiation and progression of atherosclerosis

The normal artery wall has a tri-laminar structure. The atherosclerotic plaque forms in the innermost layer, the intima. The tunica media normally consists of resting smooth muscle cells and a well-organized extracellular matrix comprised of elastin, collagen, and other macromolecules. The outermost layer, the adventitia, contains nerve endings, mast cells, and gives rise to vaso vasorum, microvessels that nourish the outer layer of the media. The normal human intimal layer contains some smooth muscle cells. In the early stage of lesion initiation, low density lipoprotein (LDL) particles accumulate in the intima. There, protected from plasma anti-oxidants, the lipid and protein constituents of atherogenic lipoproteins can undergo oxidative and other modifications that can render them potentially pro-inflammatory and immunogenic. Early in atherogenesis, “classical”, pro-inflammatory, monocytes enter the intima. Their traversal through the bloodstream slows when they encounter adhesion molecules expressed by activated endothelial cells on the intimal surface. Chemoattractant cytokines known as chemokines can beckon the bound leukocytes to enter the artery wall. T lymphocytes, while numerically less abundant than monocytes, also enter the intima early during lesion formation. Although fewer in number, they may exert regulatory roles that are decisive in regulating the innate immune cells and intrinsic arterial cells: the endothelium and smooth muscle cells. The monocytes that congregate in the nascent intimal lesion express scavenger receptors that permit them to bind lipoprotein particles and become engorged with cholesterol forming foam cells. The “classical”

974 monocytes, once resident in the intima, can mature into macrophages, and attain characteristics
975 associated with the reparative or less inflammatory monocyte/macrophage population. Smooth
976 muscle cells, usually quiescent in the tunica media, can migrate into the intima in response to
977 mediators elaborated by the accumulating leukocytes. The smooth muscle cell chemoattractant
978 platelet-derived growth factor (PDGF) likely participates in this directed migration of medial
979 smooth muscle cells into the intima.

980 **Figure 3. The Progression of Atherosclerotic Lesions: Cellular Birth and Death**

981 During the evolution of the atherosclerotic plaque the resident and recruited smooth muscle cells
982 can undergo division as indicated by the mitotic figures. The smooth muscle cell produces
983 extracellular matrix molecules such as interstitial collagen and elastin as well as proteoglycans
984 and glycosaminoglycans that contribute to the thickening of the intimal layer during lesion
985 formation. T cell mediators such as gamma interferon (IFN-γ can impair the ability of the smooth
986 muscle cell to make interstitial collagen impairing the ability of these cells to repair and maintain
987 the fibrous cap which overlies the necrotic core of the typical atherosclerotic plaque. The
988 mononuclear phagocytes in the evolving lesion also can divide. Evidence from experimental
989 atherosclerosis in mice show that mononuclear phagocyte accumulation in the later phases of
990 atherogenesis involve more replication than recruitment. As the lesion advances, smooth muscle
991 cells and macrophages alike can undergo cell death including programmed cell death by
992 apoptosis. The debris from dead and dying cells accumulates forming the “necrotic” or lipid-rich
993 core of the atheroma. Impaired clearance of dead cells, a phenomenon known as defective
994 efferocytosis, can contribute to the formation of the necrotic core. Activate macrophages boost
995 their production of enzymes that are specialized in breakdown of extracellular matrix
996 macromolecules including interstitial collagen. Many of these enzymes belong to the matrix

metalloproteinases (MMP) family. These enzymes attack the interstitial collagen that lends strength to the plaque's fibrous cap leading to a thinning and structural weakening of this structure that protects the plaque from rupture. Current evidence suggests that smooth muscle cells and the mononuclear phagocytes can interchange through a process of metaplasia. Experimental evidence suggests that many of the macrophages in the advanced mouse atherosclerotic plaque bear markers of smooth muscle lineage.

Figure 4. Atheroma Complication: Disruption and Healing

Occasionally plaques that have undergone thinning and weakening of the fibrous cap due to impaired repair by smooth muscle cells and increased degradation by macrophage-derived degrading enzymes can rupture. The fracture of the plaque's fibrous cap permits blood coagulation components access to the core of the plaque. Pro-coagulant substances such as tissue factor in the core of the plaque can trigger thrombosis that when sustained and occlusive can cause an acute coronary event. Many mural thrombi may not totally occlude the vessel or may undergo lysis due to endogenous fibrinolytic defenses. The resorbing thrombus, a source of platelet-derived transforming growth factor beta (PDGF-β) and PDGF can stimulate a round of smooth muscle cell migration and extracellular matrix production. These processes lead to increased lesion volume and eventual encroachment on the arterial lumen. Pathological studies of complicated human atherosclerotic plaques disclose "buried caps." These provide evidence for prior rupture and healing as described above. 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 versus the fibrin and trapped erythrocyte-rich "red" thrombi

associated with plaque rupture. Whether or not healing of eroded plaques occurs as in the case of plaque rupture remains unknown.

Figure 5: Clinical manifestations of atherosclerosis

Atherosclerosis is a systemic disease that may involve multiple vessels. Consequently, the clinical manifestations are also widely variable according to the territory involved Despite the systemic nature of many risk factors such as hypercholesterolemia, hypertension, diabetes, and smoking, atherosclerosis tends to involve particularly specific regions of the arterial tree primarily. Arterial areas subjected to either disturbed flow or low-shear stress have particular susceptibility to atheroma formation. [35] These conditions prevail at branch points or flow dividers in the arterial tree.

Figure 6. Relationship between luminal diameter narrowing and coronary artery flow / reserve at rest and stress. Both resting and maximum coronary flows remain unchanged with stenosis of up to 50% luminal obstruction. Above this threshold there is a substantial decrease in coronary flow with increased luminal obstruction. From Gould, K. L. & Lipscomb, K. Effects of coronary stenoses on coronary flow reserve and resistance. *The American journal of cardiology* **34**, 48-55 (1974).

1038 # Tables

1039 Table 1. Diagnostic testing for atherosclerosis.

Test	Imaging characteristics	Limitations	Advantages	Routine Clinical applications
Ultrasound (±doppler)	Direct plaque visualization Allows differentiation of some plaque components	Can only be used in large calibre and superficial vessels	Non-invasive No radiation	Carotid arteries Intracerebral arteries (transcranial doppler) Abdominal aorta Lower extremity vessels
Coronary computed tomography angiography	Direct plaque visualization Allows partial evaluation of plaque composition (calcified vs. non-calcified)	Iodine contrast needed Uses radiation	Non-invasive	Most vascular territories
Magnetic resonance	Direct plaque visualisation No evaluation of plaque components	Limited to large calibre vessels Potentially useful in selected cases of smaller calibre vessels such as coronary	Non-invasive No radiation	Carotid, aorta
Positron emission tomography	No direct plaque visualisation, identifies inflammatory plaque activity	Radiation Can only be used in large calibre vessels	Evaluates pathophysiology of the plaque	Applications restricted to research
Invasive angiography	Classic reference standard for the evaluation of luminal stenosis No direct plaque visualization	Invasive Radiation Iodine contrast needed Visualisation of stenosis, not plaque		Most vascular territories

Intravascular Ultrasound	Direct plaque visualisation Potential "virtual histology" plaque characterisation Excellent for plaque burden and composition evaluation	Invasive Radiation Contrast (for catheter positioning) Limited availability		Routine clinical application limited to selected cases of coronary artery evaluation
Optical coherence tomography	Direct plaque visualisation High resolution imaging for plaque characteristics	Invasive Radiation Contrast (for catheter positioning) Limited availability Limited penetration, only allows the evaluation of plaque closer to the endothelium		Routine clinical application restricted to very selected cases of coronary artery evaluation

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Table 2:

Risk factor goals and target levels for important cardiovascular risk factors

Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg[a]
Lipids[b] LDL[c] is the primary target	**Very high-risk: <1.8 mmol/L (<70 mg/dL),** or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)[d] **High-risk: <2.6mmol/L (<100 mg/dL)**, or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) **Low to moderate risk: <3.0 mmol/L (<115 mg/dL).**
HDL-C	No target but >1.0 mmol/L (>40mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c <7%. (<53 mmol/mol)

BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol.

[a]Blood pressure <140/90 mmHg is the general target. The target can be higher in frail elderly, or lower in most patients with DM (see chapter 3.a.8) and in some (very) high-risk patients without DM who can tolerate multiple blood pressure lowering drugs (see chapter 3.a.9).

[b]Non-HDL-C is a reasonable and practical alternative target because it does not require fasting. Non HDL-C secondary targets of <2.6, <3.3 and <3.8 mmol/L (<100, <130 and <145 mg/dL) are recommended for very high, high and low to moderate risk subjects, respectively. See section 3a.7.10 for more details.

[c]A view was expressed that primary care physicians might prefer a single general LDL-C goal of 2.6 mmol/L (100 mg/dL). While accepting the simplicity of this approach and that it could be useful in some settings, there is better scientific support for the three targets matched to level of risk.

[d]This is the general recommendation for those at very high-risk. It should be noted that the evidence for patients with CKD is less strong.

Adapted from Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM and Authors/Task Force M. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37:2315-2381.

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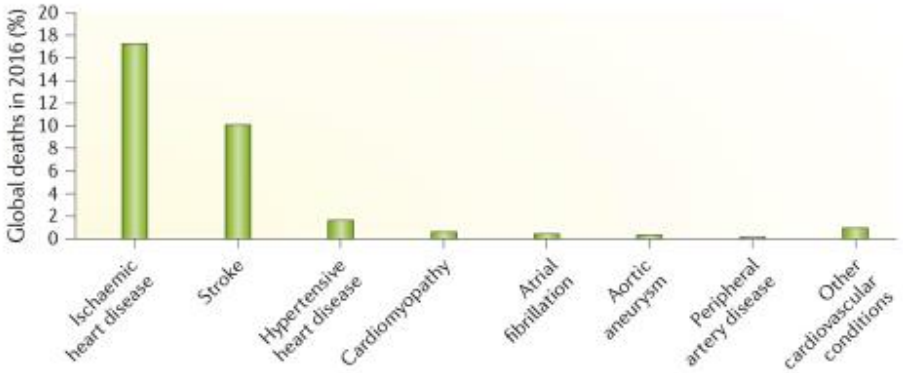

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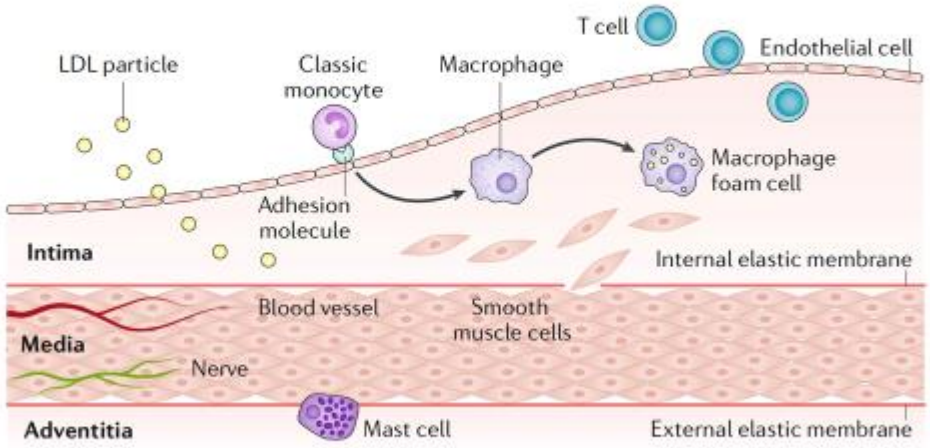

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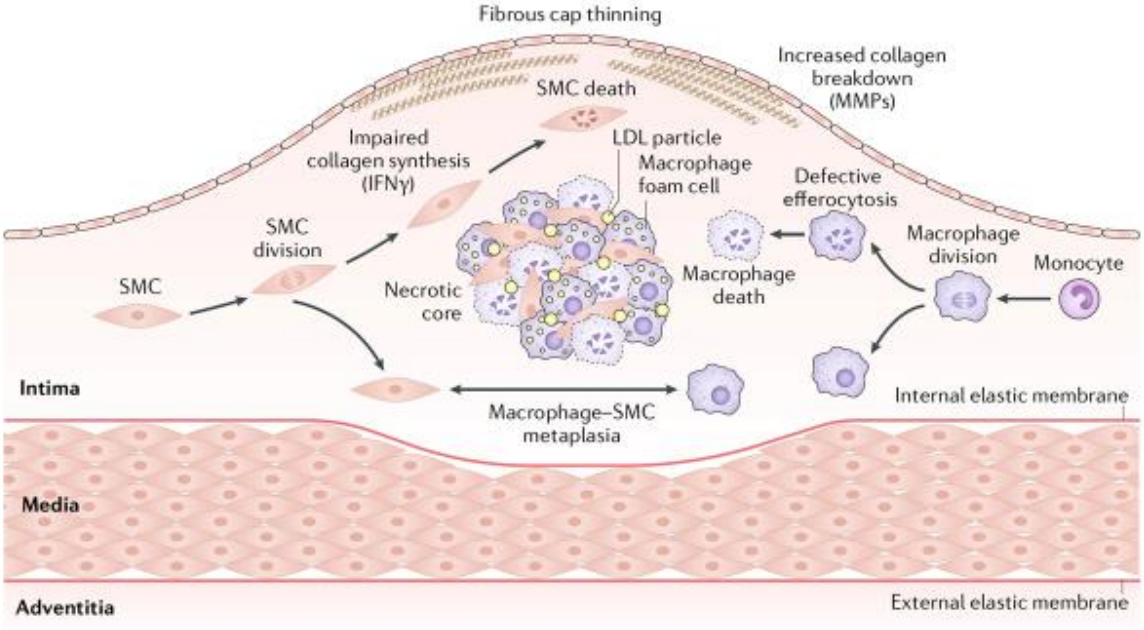
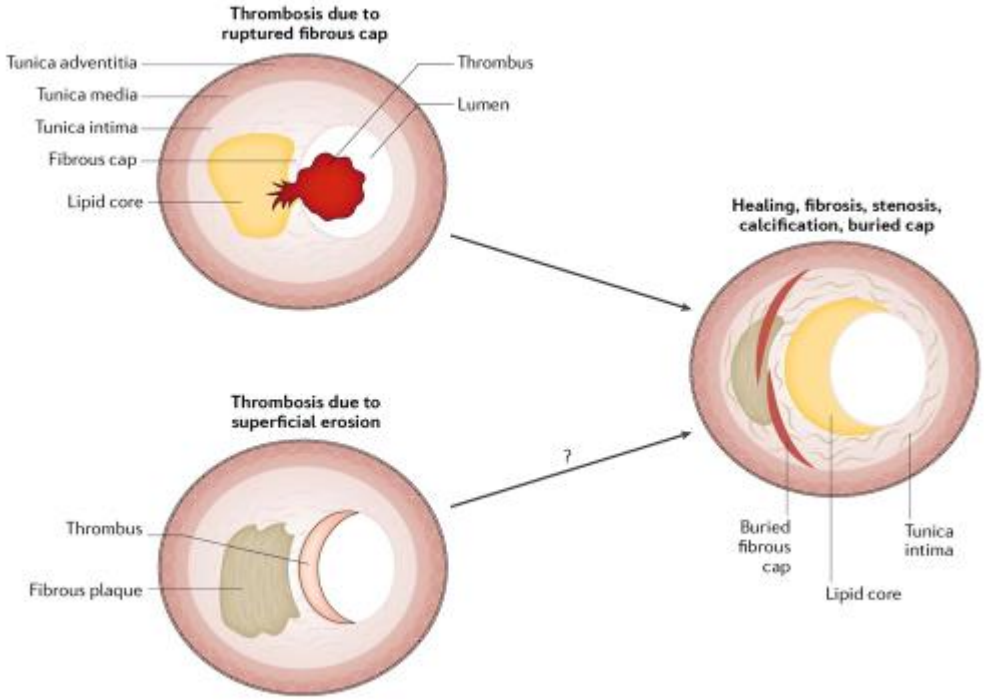
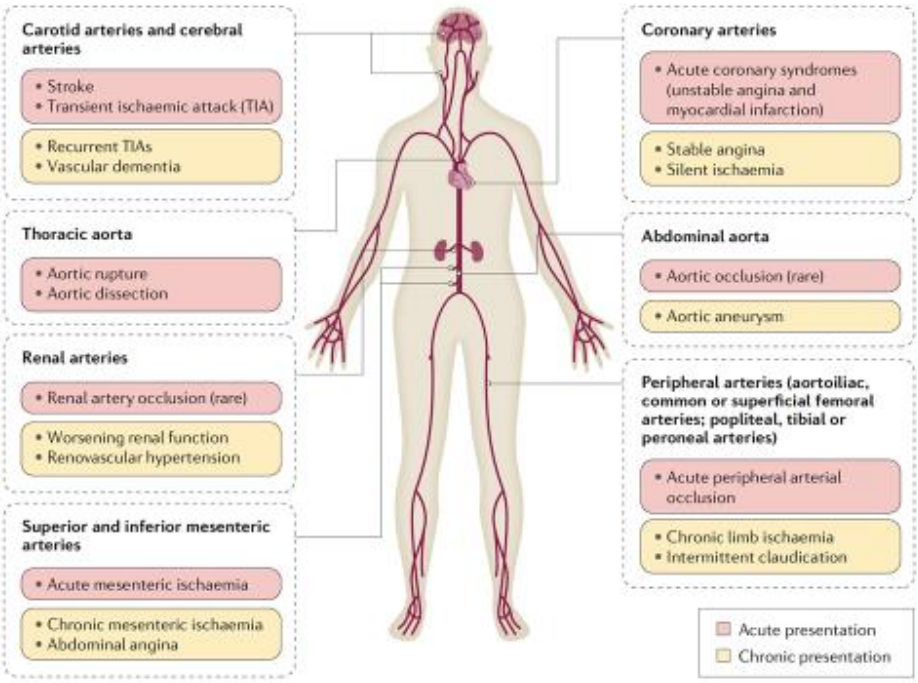

Fibrous cap thinning
Increased collagen breakdown (MMPs)
SMC death
Impaired collagen synthesis (IFNγ)
LDL particle
Macrophage foam cell
Defective efferocytosis
SMC division
SMC
Necrotic core
Macrophage death
Macrophage division
Monocyte
Intima
Internal elastic membrane
Macrophage–SMC metaplasia
Media
Adventitia
External elastic membrane


Thrombosis due to ruptured fibrous cap
Tunica adventitia
Tunica media
Tunica intima
Fibrous cap
Lipid core
Thrombus
Lumen
Healing, fibrosis, stenosis, calcification, buried cap
Thrombosis due to superficial erosion
?
Thrombus
Fibrous plaque
Buried fibrous cap
Tunica intima
Lipid core



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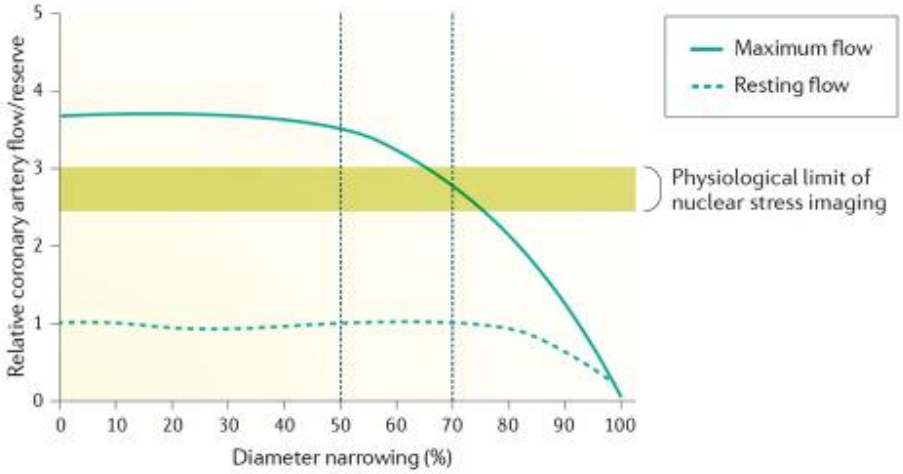

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