Chapter

Dyslipidemia and Its Role in the Pathogenesis of Atherosclerotic Cardiovascular Disease: Implications for Evaluation and Targets for Treatment of Dyslipidemia Based on Recent Guidelines

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Abstract

The clinical presentations of atherosclerotic disease are the result of a constellation of diverse metabolic and immunologic mechanisms ultimately set into motion by the formation of fatty acid streaks and the accompanying inflammatory cell activation, endothelial damage, smooth muscle proliferation, vascular fibrosis, and end-organ infarction and necrosis. At the heart of atherosclerosis are the byproducts of lipid metabolism, lipoproteins containing triglycerides, phospholipids, and cholesterol, and the changes they undergo that eventually lead to macrophage activation, foam cell formation, and other downstream atherosclerotic changes. Understanding the functionality of cholesterol, triglycerides, and lipoproteins in the cascade of atherosclerotic pathways has tremendous implications on current guidelines for the evaluation and targets in the management of dyslipidemia, and serves as the foundation for future investigations into targets of atherosclerotic therapies.

Keywords: atherosclerosis, dyslipidemia, cardiovascular disease, guidelines

1. Introduction

Atherosclerosis, the pathogenic process of vascular lipid deposition, arterial luminal narrowing, and plaque expansion and instability, represents the major driver of circulatory morbidity and mortality, including myocardial infarction, ischemic cardiomyopathy, transient ischemic attacks, and ischemic and hemorrhagic stroke [1]. The acute and chronic clinical presentations of atherosclerotic disease are the result of a constellation of diverse metabolic and immunologic mechanisms ultimately set into motion by the formation of fatty acid streaks and the accompanying inflammatory cell activation, endothelial damage, smooth muscle proliferation, vascular fibrosis, and end-organ infarction and necrosis [2].

At the heart of atherosclerosis are the byproducts of lipid metabolism, lipoproteins containing triglycerides, phospholipids, and cholesterol, and the changes they undergo that eventually lead to macrophage activation, foam cell formation, and other downstream atherosclerotic changes [3]. Lipoproteins are distinguished by their lipid content, their position in lipid metabolic pathways, and overall atherogenic risk [4, 5]. This chapter will review the role that the various lipoproteins play in the pathophysiology of atherosclerosis as the fundamental triggers and players in the immunologic, inflammatory, and thrombotic processes that characterize the pathogenesis of atherosclerotic cardiovascular disease. Understanding the functionality of cholesterol, triglycerides, and lipoproteins in the cascade of atherosclerotic pathways has tremendous implications on current guidelines for the evaluation and targets in the management of dyslipidemia, and serves as the foundation for future investigations into targets of atherosclerotic therapies.

2. Lipoproteins and apolipoproteins

Lipoproteins are complex plasma particles containing a core of cholesterol esters and triglycerides surrounded by free cholesterol, phospholipids, and apolipoproteins, and are classified based on size, density, and major lipid and apolipoprotein content [6]. Apolipoproteins, structural proteins that bind triglyceride and cholesterol and enable the formation of lipoproteins, enjoy important roles in lipoprotein structure and metabolism by acting as ligands for lipoprotein receptors and activators or inhibitors of enzymes involved in lipoprotein metabolism [6, 7]. The size, structure, and apolipoprotein content of the lipoproteins, namely chylomicrons (CM), very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein(a) [Lp(a)], crystallize into individualized atherosclerotic risk profiles for the specific lipoprotein [8, 9].

2.1 Chylomicrons and chylomicron remnants

CMs, the largest and least dense of the lipoproteins, are triglyceride rich, released from the intestine, and primarily responsible for delivery of dietary cholesterol and triglycerides to peripheral tissue and the liver [6, 10]. Removal of triglycerides from circulating CMs generates CM remnants that possess a considerably higher cholesterol concentration [6, 11]. CMs and CM remnant size is linked to ingested triglyceride levels and the structure is maintained by multiple apolipoproteins, predominantly apolipoprotein B-48 (Apo B-48) [6]. Apo B-48 is synthesized in the intestine, and represents 48% of the amino acids in the peptide sequence of apolipoprotein B-100 (Apo B-100), the apolipoprotein synthesized by the liver and a major apolipoprotein involved in the atherosclerotic pathophysiology [12].

2.2 Very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL)

Triglyceride consumption by adipose tissue and the resulting cholesterol-rich CM remnants subsequently reach the liver, which reorganizes triglycerides and cholesterol in the form of VLDL that are secreted into circulation and allow for lipoprotein lipase (LPL) mediated absorption of triglycerides by cardiomyocytes, skeletal muscle, and adipose tissue [4, 6]. CMs, CM remnants, and VLDL contain apolipoprotein C (Apo C), specifically Apo C-II, an essential cofactor for LPL, and transposition of triglycerides from circulating lipoproteins to tissue steadily

increases the concentration of cholesterol and overall density of the lipoprotein while simultaneously decreasing the size [6, 13]. The apolipoprotein that plays the most atherogenic role of all the apolipoproteins and distinguishes VLDL from chylomicrons and CM remnants is Apo B-100, a major structural apolipoprotein and LDL receptor (LDLR) ligand [6, 14]. VLDL exists as the bridge between the exogenous and endogenous pathways of lipid metabolism, with the lipid content of CM remnants that reach the liver via gastrointestinal absorption at the beginning of the exogenous pathway being repackaged and secreted by hepatocytes as VLDL to initiate the endogenous pathway. IDLs, considered VLDL remnants, are considerably smaller than the antecedent VLDL and exhibit similar apolipoprotein composition, but they have similar triglyceride and cholesterol contents to the CM remnants [4, 14, 15]. The decreased size and cholesterol along with the appropriate apolipoprotein profile of Apo B-100 and Apo-E, another apolipoprotein ligand for the LDLR, make IDL atherogenic, but the primary atherogenic lipoprotein that sets off the cascade of atherosclerotic lipid, immunologic, and inflammatory pathways remains LDL (**Table 1**).

2.3 Low-density lipoprotein (LDL)

LDL, derived from LPL/Apo C-II-mediated triglyceride removal from VLDL and IDL, is the lipoprotein responsible for cholesterol transport to peripheral tissue and the lipoprotein that has been extensively studied and directly implicated in the development of atherosclerosis [4, 5]. With an average size of 18–25 nm, LDL and the predominant apolipoprotein it contains, Apo B-100, undergo oxidation and other molecular modifications that are responsible for endothelial damage, macrophage chemoattraction, and pathologic arterial changes [1, 6, 16]. Individual LDL particles can vary in size, with decreasing or small dense LDL being noticeably more atherogenic than large LDL particles due to susceptibility to oxidation, ease of extravasation and entrapment in the arterial wall, and avidity for binding with vascular wall proteoglycans [6, 16, 17].

The metabolism of LDL, and thus the circulatory availability and arterial wall extravasation ability of LDL, is determined by the quantity of hepatic LDLR, as the concentration of LDL generated from the metabolism of VLDL and IDL is regulated by the amount of IDL that is absorbed into the liver via the LDLR prior to LPL-mediated triglyceride removal [6, 18]. Hepatic levels of LDLR are primarily modulated by hepatocyte cholesterol levels, with adequate cholesterol levels stimulating

Lipoprotein	Size (nm)	Major lipid content	Apolipoproteins
Chylomicron	>75	Triglyceride	Apo B-48, Apo C, ApoE, Apo A-I, A-II, A-IV
Chylomicron remnants	30–75	Triglyceride, cholesterol	Apo B-48, ApoE
VLDL	30–75	Triglyceride	Apo B-100, Apo C, ApoE
IDL	25–35	Triglyceride, cholesterol	Apo B-100, Apo C, ApoE
LDL	<25	Cholesterol	Apo B-100
Lp(a)	30	Cholesterol	Apo B-100, Apo(a)
HDL	<15	Cholesterol, phospholipids	Apo A-1, A-II Apo C, ApoE

Table 1.
Lipoproteins—size, lipid, and apolipoprotein content.

LDLR targeting for degradation by PCSK9, a protein synthesized by hepatocytes that binds the LDLR and promotes lysosomal LDLR degradation [5, 6, 19].

LDL subfraction sizes and the resulting atherogenicity need to be considered when evaluating patients, as therapeutic regimens (such as niacin) have been known to affect LDL particle size. It is also important to realize that while overall cholesterol panel level changes may occur and appear to be in the right direction, it is actually the atherogenicity of the particles specifically of LDL that drives the pathogenesis of atherosclerosis [20]. Analysis, therefore, of LDL subfractions may be an important component of lipid follow-up in patients with complex lipid disorders on combination pharmacologic therapy.

2.4 High-density lipoprotein (HDL)

HDL differs from VLDL, IDL, and LDL in size, lipid, and apolipoprotein content, role in cholesterol metabolic pathways, and antiatherogenic characteristics. HDL is responsible for peripheral cholesterol uptake and delivery to the liver- and cholesterol-derived hormone-producing organs, and it provides important antioxidant and anti-inflammatory functions that can inhibit atherosclerosis [4, 6, 21]. Devoid of Apo B-100 that contributes to LDL oxidation and subsequent macrophage activation, HDL is associated with multiple subtypes of apolipoprotein A (Apo A) that facilitates cholesterol transfer from peripheral tissue and activates lecithin-cholesterol acyltransferance (LCAT), which allows for cholesterol esterification and movement of cholesterol from the HDL surface to the HDL core [6, 22]. After cholesterol uptake from peripheral tissue and macrophages, HDL facilitates transfer to the liver via scavenger receptor class B type I (SR-B1), where the cholesterol can be converted into bile acids for excretion or be directly secreted into bile [21, 23]. The apolipoprotein profile and receptors involved in cholesterol movement from HDL sheds light on some of the physiologic pathways involved in HDL attenuation of atherosclerosis and conversely the highly atherogenic contents and formulation of LDL.

2.5 Lipoprotein A [Lp(a)]

Lp(a) is the lipoprotein formed of a cholesterol-rich LDL molecule and apolipoprotein a [Apo(a)], with levels that are very fluctuant but are generally dependent on the rates of hepatic production of Apo(a) [6, 24]. The Apo-B100 and the Apo(a) are connected via a disulfide bond, and given its size and cholesterol composition essentially identical to that of LDL, Lp(a) is able to extravasate from plasma into the arterial intima and interact with the extracellular matrix through LDL Apo B-100 and Lp(a) [24–26]. In addition to Lp(a), extracellular matrix interactions that facilitate the trapping of cholesterol that sets the table for macrophage uptake and foam cell formation, Lp(a) disrupts fibrinolysis and enhances coagulation, two functions that promote atherosclerotic plaque instability and rupture [24, 27].

3. Lipoproteins and the atherosclerotic thrombo-inflammatory process

3.1 Endothelial changes and regional plaque distribution

Endothelial cells undergo a series of changes, both connected and unrelated to lipoproteins that contribute to the different pathophysiologic mechanisms at play in atherosclerosis and help to explain the typical regional distributions of atherosclerotic lesions.

While LDL and other small and atherogenic lipoproteins undergo oxidative and structural changes that eventually lead to trapping in the arterial intima that recruit macrophages and other inflammatory cells, access to the intima extracellular matrix is spearheaded by endothelial cell dysfunction and damage from oxidative injury in conditions like smoking and hypertension, advanced glycation end products in diabetes mellitus, and regional hemodynamic forces in particular parts of the arterial tree [1, 28]. Oxidative insults to the endothelium impair production of nitric oxide (NO), the potent modulator of vascular tone and inhibitor of the proliferation of vascular smooth muscle cells (VSMCs), and exhibits important roles in the prevention of LDL oxidation and leukocyte extravasation from the bloodstream to arterial intima [29]. Additional chemical mediators of endothelial dysfunction include endothelin-1 (ET1) that interacts with NO in the regulation of arterial tone, signals changes in endothelial expression of adhesion molecules, and recruits important inflammatory cells such as macrophages while simultaneously regulating extracellular matrix enzymes that contribute to intimal alterations [1, 30].

The endothelial changes that best illuminate the regional pathophysiology of atherosclerosis are not the different levels of NO and other molecular signals, but the regional reorganization of endothelial phenotypes in reaction to local hemodynamic forces. Atherosclerotic plaques generally form at areas of arterial curvature and bifurcation, the locations in the arterial circulation where there are typical patterns of elevated shear stress [31]. Endothelial cells in regions of higher shear stress display a cuboidal morphology, higher cell turnover, and impaired endothelial barrier function that collectively promotes lipoprotein and inflammatory cell migration, in comparison to endothelial cells in arterial beds with more favorable hemodynamics that exhibit ellipsoidal morphology, coaxial alignment, and an endothelial glycocalyx that protects against lipoprotein extravasation [31–33].

While the size, oxidative profiles, and atherogenic risk of the lipoproteins, most significantly LDL and Apo B-100, are the primary drivers of atherosclerosis, critical endothelial changes that further exacerbate the migration of lipoproteins, leukocytes, VSMCs, and fibroblasts are fundamental to the generation of plaques and the clinical consequences of plaque expansion and rupture.

3.2 Initiation of the atherosclerotic plaque: foam cell formation

With continued endothelial compromise in regions of arterial curvature and bifurcation, circulating LDL, and to a lesser degree VLDL and IDL, increasingly migrate from the plasma and are retained in the extracellular matrix of the tunica intima [34, 35]. Subendothelial accumulation of LDL and VLDL remnants precipitates endothelial activation of the nuclear factor kappa B (NF-κB) pathway that enhances endothelial expression of adhesion proteins such as VCAM-1 and P-selection and pro-inflammatory receptors and cytokines that promote monocyte migration [32, 34, 36, 37]. As LDL, VLDL, VLDL remnants, IDL, and Lp(a) collect in the arterial intima, Apo B-100, most significantly in LDL, undergoes oxidation to ox-LDL, a potent ligand of macrophage scavenger receptors [1, 5, 24, 38]. Endothelial activation and upregulation of adhesion molecules enables monocyte rolling, activation, and transendothelial migration where they differentiate from monocytes into macrophages [34, 39]. Retained ox-LDL interacts with two macrophage receptors, class A and B scavenger receptors, and in distinct contrast to cholesterol absorbed via the LDLR by the macrophage, ox-LDL does not cause a negative feedback on scavenger receptor expression, perpetuating continued ox-LDL and cholesterol uptake, resulting in the entrapment of newly formed foam cells in the arterial intima secondary to compromised mobility [1, 34, 39, 40].

Despite the predominance of LDL in the cycle of endothelial damage, macrophage absorption, foam cell formation, and inflammatory transduction, VLDL and Lp(a) play important roles in endothelial activation [4, 24]. Endothelial cell exposure to the triglycerides of VLDL stimulates expression of selectins and other proteins that promote monocyte entry into the arterial intima, and oxidized VLDL increases expression of plasminogen activator inhibitor 1 (PAI-1), a protein that attenuates plasminogen conversion to plasmin and thus plasmin-mediated dismantling of cholesterol aggregates [4, 41, 42]. Lp(a) interactions with certain macrophage surface integrin proteins promote monocyte extravasation and upon macrophage absorption, upregulates expression of IL-1, tumor necrosis factor (TNF) and monocyte chemoattractant protein (MCP-1) that recruits additional macrophages, resulting in formation of more foam cells [24, 43].

3.3 Plaque development: inflammatory cells and smooth muscle cells

In addition to uptake by macrophages, ox-LDL acts as an omnipotent chemokine that induces the activity of multiple immunologic pathways and leads to the migration and activation of additional monocytes and other inflammatory cells and VSMCs [1, 32, 44]. While LDL, VLDL remnants, IDL, and Lp(a) retention leads to foam cell formation as the integral first step in plaque development, subsequent leukocyte adhesion and extravasation promotes clearance of foam cells and apoptotic cell debris from dendritic cells and T cells via a complicated interaction between the innate and adaptive immune systems [33, 45–47]. Atherosclerotic lesion macrophages differentiating into inflammatory M1 macrophages present antigens to T cells, with resulting T cell activation and release of pro-inflammatory cytokines such as IL-1 and IL-6, inducing local lesion inflammation, further foam cell formation, and subsequent foam cell apoptosis and necrosis (**Figure 1**) [1, 48, 49].

In a similar pattern to macrophages, foam cells undergo phagocytosis by dendritic cells, where antigen presentation to T cells promotes release of pro-inflammatory cytokine, and continued phagocytosis compromises dendritic cell mobility resulting in dendritic foam cell formation [45, 50, 51].

The cascade of endothelial dysfunction, lipoprotein accumulation, and inflammatory pathways results in dramatic changes in VSMC physiology [32, 52]. Native arterial media VSMCs are activated and undergo proliferation, migration, and phenotypic switching that ultimately plays the most critical roles in atherosclerotic plaque stability or vulnerability [52–54]. VSMC proliferation and migration results in increased production of extracellular matrix components, such as proteoglycans and elastin, that attempts to compensate for the inward architectural distortions caused by subendothelial lipoprotein accumulation, causing outward vascular remodeling [32, 34, 55]. Collagen production by VSMCs is the most critical component in the development of the fibrous cap in atherosclerotic plaques, with TGF-β released from plaque macrophages signaling VSMC proliferation [34, 56, 57].

3.4 HDL and plaque development

The multifaceted pathways of atherosclerotic plaque development and the role LDL and other Apo B-100 lipoproteins serve as a template for the important roles and diverse protective mechanisms and functions of HDL in the pathogenesis of atherosclerosis. Oxidation of Apo-B100 and the resulting accumulation and macrophage phagocytosis of LDL and other lipoproteins can be mitigated by the antioxidant activity of HDL, with its major apolipoproteins, Apo A-I and Apo A-II, and HDL-associated enzymes such as paraoxonase possessing antioxidant activity [21, 58, 59]. Resolving oxidative stress allows HDL to normalize endothelial function

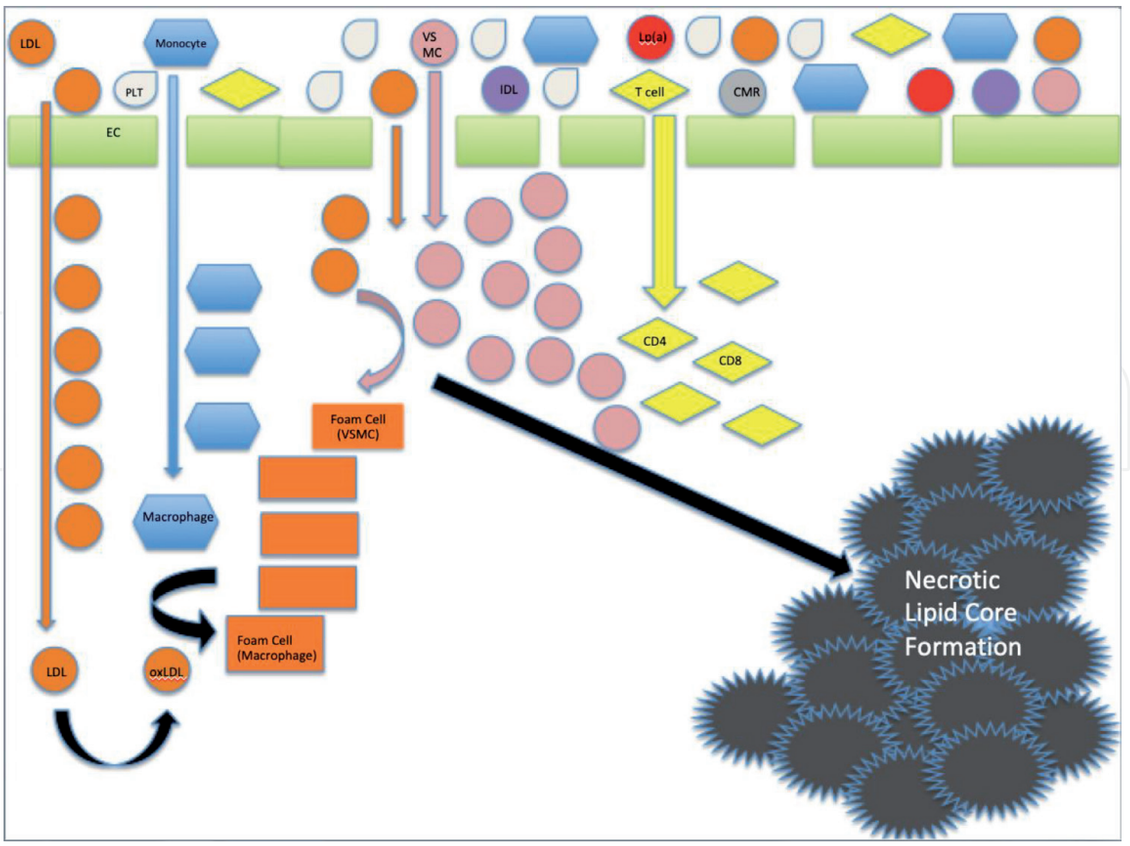

Figure 1.
Small lipoproteins, most prominent LDL, penetrate the dysfunctional endothelial barrier and accumulate in the arterial intima. LDL (Apo B-100 apolipoprotein component) undergoes oxidation to ox-LDL, which triggers inflammatory cascade promoting migration of monocytes, VSMCs, and CD4 and CD8 T cells. ox-LDL undergoes phagocytosis by macrophages (and VSMCs) to generate foam cells. Insufficient clearance of apoptotic foam and inflammatory cells causes steady accumulation of subendothelial lipid necrotic core, which serves as central component of developing atherosclerotic plaque.

by restoring production of NO [23, 60, 61]. HDL disrupts monocyte migration into the arterial intima via inhibition of endothelial cell adhesion protein expression, the fundamental first step in the formation of foam cells [62, 63]. HDL also inhibits VSMC migration and mitigates coagulation system and platelet activation, which come more into play in acute plaque rupture [4, 21, 64].

The major roles of HDL in atherosclerotic plaque development are inhibiting foam cell formation by promoting cholesterol transfer from macrophages and attenuating local lesion inflammation. In a pattern similar to normal reverse cholesterol transport from peripheral tissue to hepatocytes, HDL can remove cholesterol from macrophages and foam cells in the arterial intima via passive aqueous diffusion or cholesterol transporters, such as ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1) and scavenger-receptor BI (SR-BI) that utilize the cholesterol concentration gradient [34, 65, 66]. HDL inhibits the M1 phenotype inflammatory macrophages that dominate in atherosclerotic plaques and present antigens to T cells while promoting M2 anti-inflammatory macrophages and modulating apoptosis of foam cells via antiapoptotic signaling pathways [67–69].

4. Atherosclerotic plaque progression, stability, and acute rupture

4.1 Plaque progression: fibrous cap and necrotic lipid core

Smooth muscle proliferation within the atherosclerotic plaque is characterized by the production of a subendothelial complex extracellular matrix making up the

fibrous cap that acts to wall off the inflammatory and highly thrombotic lesion collection of cholesterol and cell debris that results from immune-mediated apoptosis and destruction of foam cells [1, 70, 71].

As the plaque progresses, the thickening of the intima and the pathologic expansion into the lumen displays areas of distinct cellular and lipid content, with the mature fibroatheroma consisting of an acellular lipid necrotic core of cell debris [71, 76]. The lipid component of the necrotic core consists of foam cells and newly free cholesterol from apoptotic macrophages that have been ineffectively cleared by efferocytosis [1, 71–73]. The necrotic lipid core can undergo steady expansion with resulting plaque enlargement and decreasing arterial lumen caliber due to diminished clearance capacity of cholesterol by VSMCs and advanced plaque macrophages [34, 74].

The steady accumulation of free cholesterol and lipid material alongside necrotic cellular products from apoptosis generates a continuous release of pro-inflammatory stimuli that further promote additional foam cell destruction, a vicious cycle that is contained by the thick collagenous fibrous cap [71, 75]. Vascular remodeling counterbalances this continuous inflammatory process defined by intimal accumulation and lesion expansion, which minimizes protrusion into the lumen and mitigates clinical symptomology over the lifetime of the lesion (**Figure 2**) [34, 71, 76].

4.2 Stable and vulnerable plaques

The structural makeup of the plaque and relationship between fibrous cap thickness, lipid and necrotic core size, inflammatory activity, and overlying endothelial integrity translate to overall atherosclerotic plaque stability and risk of plaque compromise.

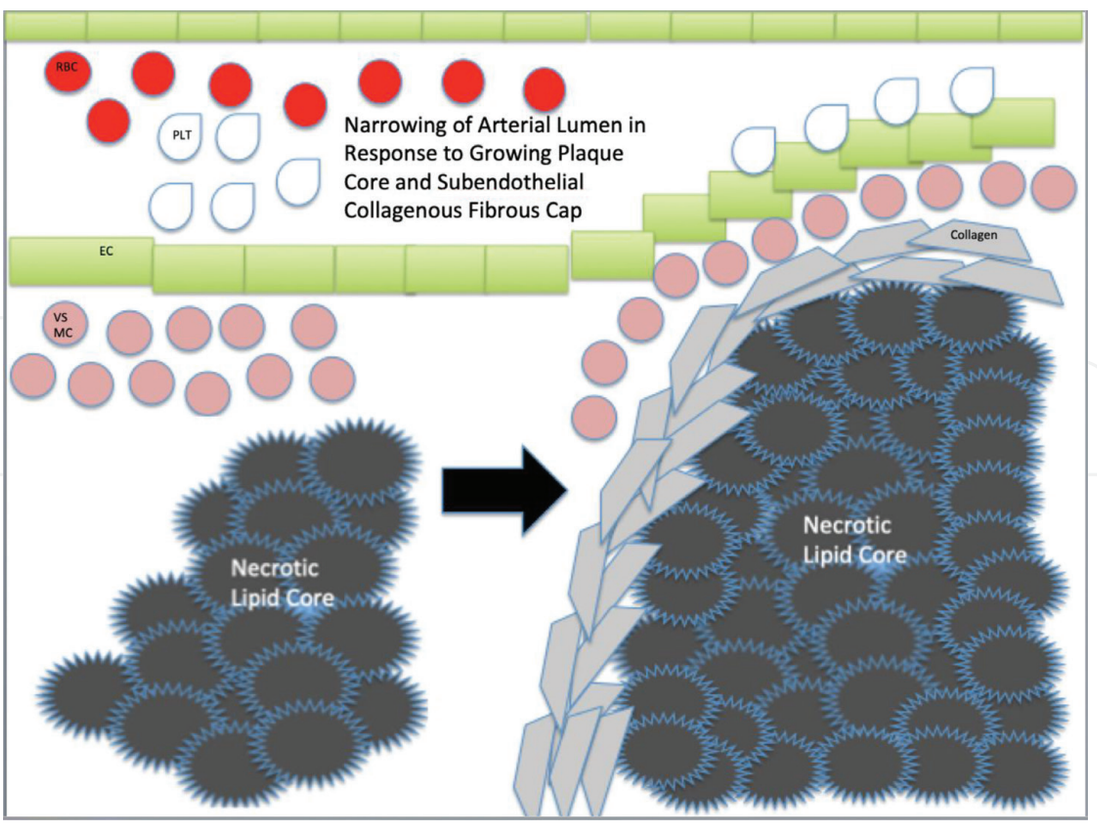

Figure 2.
Steady development of the necrotic lipid core leads to subendothelial expansion, which over time narrows the diameter of the arterial lumen. VSMC migration, proliferation, and activation lead to deposition of fibrous collagenous extracellular matrix material to create the fibrous cap of the atherosclerotic plaque. Overlying dysfunction endothelial changes and breaks in the barrier allow for exposure of the contents of the cap and core to interact with serum cells and proteins, leading to platelet adherence to intact but vulnerable plaques.

In stable atherosclerotic plaques, low-grade inflammation enables VSMC enrichment, which increases the percentage of the plaque that is made up of the collagenous fibrous cap [77, 78]. In general, the lines of demarcation between more stable and more vulnerable plaques tend to center around the ratio between the solid fibrous tissue and the extracellular lipid necrotic tissue, with stable and clinically silent plaques typically displaying thick fibrous caps and minimal to no extracellular lipid and necrotic foam cell debris [77, 79, 80]. While fibrous cap thickness and strength is a critical determinant of overall plaque stability, the fibrous tissue laid down by VSMC in the subendothelial part of the arterial intima is in a constant state of balance between collagen synthesis and degradation mediated by inflammatory cytokines that upregulate the expression of matrix metalloproteinases (MMPs) [1, 78, 81, 82]. MMPs can degrade fibrillar collagen, proteoglycans, and elastin over time, and the resulting thinning and structural compromise of the fibrous cap transitions the stable plaque to a vulnerable and high-risk plaque [77, 78, 83].

In parallel to the changes in the fibrous cap are dynamic swings in inflammatory conditions in the necrotic lipid core, where increasing levels of VSMC and macrophage apoptosis not only decrease the net number of cells that can synthesize collagen and other stabilizing extracellular matrix components but also release additional inflammatory cytokines that can further destabilize the plaque [78, 84]. Similar to the roles played in plaque development, T cells, both T helper CD4 T cells and T cytotoxic CD8 cells, contribute to plaque destabilization via a perpetual loop of macrophage and T cell recruitment, lipid uptake, foam cell formation, antigen presentation, apoptosis, and lipid necrotic core expansion [78, 85, 86].

4.3 Rupture and erosion of vulnerable plaques and acute thrombosis

The nonresolving inflammatory processes of lipoprotein accumulation, foam cell formation, and immunologic activation leads to fibrocellular organization of the plaque, with the plaque becoming increasingly unstable and prone to rupture and acute thrombosis via fibrous cap thinning and lipid necrotic core expansion [34, 77, 87]. The fibrous cap is thinned and weakened by MMPs, and disruption of the collagenous cap and the overlying endothelium leads to exposure of the highly thrombogenic and coagulable lipid necrotic core [1, 88]. Atherosclerotic plaques, prior to any sort of structural compromise, are congregated by platelets that attach to the dysfunctional endothelium of the plaque, and can participate in plaque-associated thrombosis with and without rupture or erosion [88, 89].

Ruptured and eroded plaques trigger a rapid and dramatic thrombotic and coagulation process, with activated platelets adhering to the exposed subendothelial collagen of the thin fibrous cap via interactions between von Willebrand factor (vWF) and glycoprotein (GP) Ib-V-IX, with adherent-activated platelets aggregating via GP IIb/IIIa complexes [90–92]. After adhesion, activated-aggregated platelets release granules containing thromboxane A2, adenosine diphosphate (ADP), and other pro-thrombotic and pro-inflammatory cytokines that recruit inflammatory cells and amplify the platelet response (**Figure 3**) [1, 90, 93].

Alongside platelet activation and thrombus formation is activation of the coagulation system, with tissue factor (TF) receptors in the plaque binding circulating factor VII(a) and triggering the extrinsic coagulation pathway to produce thrombin [90, 94, 95]. Thrombin, a strong platelet agonist via protease-activated receptor (PARs)-1 and 4, converts fibrinogen to fibrin for clot stabilization while simultaneously driving its own positive feedback loops through activation of factor XI and other factors in the intrinsic coagulation pathway [90, 96, 97].

The constellation of plaque rupture, platelet activation and aggregation, and coagulation system stimulation results in the formation of a thrombus on an

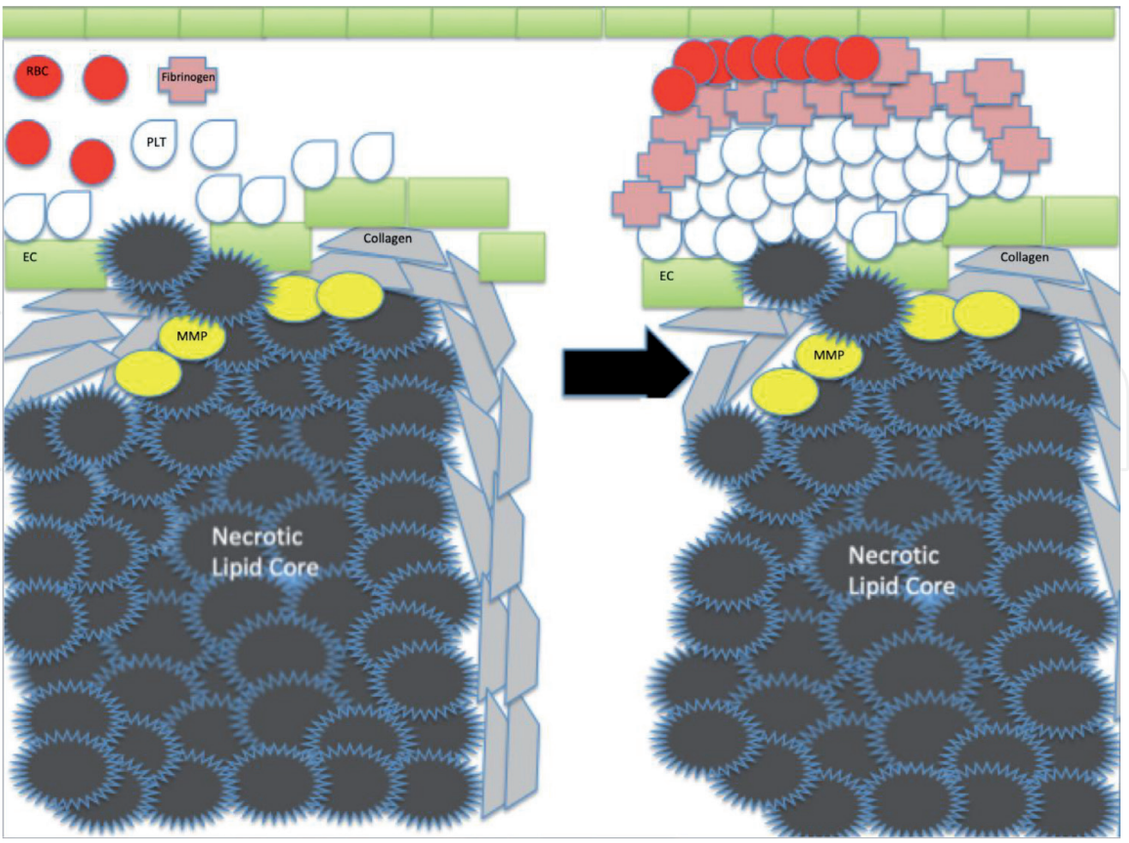

Figure 3.
Rupture or erosion of the plaque's fibrous cap enables exposure of highly thrombogenic and coagulable necrotic lipid core content to circulating platelets and coagulation factors. Acute atherothrombosis results with dramatic aggregation and activation of platelets and coagulation factors, resulting in acute occlusion of the implicated arterial tree and downstream tissue ischemia and necrosis.

atherosclerotic plaque, causing partial to complete obstruction of the arterial lumen, which has already been narrowed steadily over time by plaque progression [1, 34, 90]. Postmortem pathological examination of these atherosclerotic plaque thrombi show a directional morphology that highlights the stepwise process of thrombus formation, with white platelet-rich heads adjacent to the focus of plaque rupture, with red extensions from the white platelet head to the distal arterial wall encompassing the fibrin and red blood cells that accumulate secondary to diminished blood flow from the obstructive thrombus [90, 98, 99].

5. Atherosclerotic cardiovascular disease: presentation, evaluation, and management

5.1 Atherosclerotic cardiovascular disease (ASCVD)

ASCVD is the clinical manifestation of atherosclerosis and atherothrombosis, the resulting symptomology and physical findings of acute and chronic end-organ ischemia and infarction from the pathophysiologic thrombo-inflammatory process of atherogenesis initiated by cholesterol and lipoprotein accumulation in the arterial intima. Public health appreciation and scientific evidence for the role of dyslipidemia in the progression of ASCVD has served as the impetus for organizations throughout the United States, Canada, and Europe to develop guidelines for evaluation and management of dyslipidemia and ASCVD [100–102]. Furthermore, the severity and associated morbidity and mortality of the clinical manifestations of ASCVD, including ischemic heart disease, such as stable angina, unstable angina,

non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), peripheral artery disease (PAD), and cerebrovascular disease, both intracranial and extracranial, have prompted the development of condition specific guidelines for primary prevention, acute management, and secondary prevention [103–114]. Guidelines for management of dyslipidemia in the context of ASCVD are centered on the presence of pre-existing ASCVD, age, and underlying comorbidities, most prominently diabetes.

5.2 Coronary artery disease/ischemic heart disease

In the context of ASCVD, coronary artery disease (CAD), also referred to as ischemic heart disease (IHD), covers a spectrum of acute and chronic conditions resulting from myocardial oxygen demand and supply mismatch, generally caused by atherosclerotic disease of native coronary arteries, both fixed lesions and acute atherothrombosis [107, 115, 116].

Stable angina pectoris is a syndrome of recurrent and intermittent episodes of chest pain during instances of increased myocardial oxygen demand and insufficient oxygen supply from flow-limiting atherosclerotic coronary lesions [116, 117]. Stable angina is the initial clinical manifestation of nearly half of all patients with CAD, and given the high rates of myocardial infarction in patients with stable angina, extensive guidelines on workup and management, including stress testing, coronary calcium scoring by computed tomography, and cardiac catheterization and revascularization, to mitigate the risk of future major cardiovascular events [107, 117, 118].

Acute coronary syndrome (ACS), the acute manifestations of CAD, include unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) are distinguished primarily by the absence of presence of electrocardiographic (EKG) changes and troponin elevation [115, 119]. The pathophysiology that differentiates stable angina from ACS is acute plaque rupture or erosion that results in the acute worsening of coronary artery flow, with subsequent symptomatic, electrocardiographic, and biochemical clinical findings ranging from moderate to severe chest pain all the way to acute cardiogenic shock and cardiac arrest [120, 121]. Myocardial infarction (MI), both NSTEMI and STEMI, caused by acute atherothrombotic disease of an eroded or ruptured plaque, is classified as a type I MI [115, 122]. It is distinguished from other etiologies of cardiomyocyte damage, troponin elevation, and EKG changes such as other acute stressors such as anemia, sepsis, or tachyarrhythmia that cause oxygen demand-supply mismatch (type 2 MI), sudden cardiac death with symptoms suggestive of MI but no blood specimen available for troponin analysis (type 3 MI), type 4 MI as a complication of percutaneous coronary intervention (PCI), and type 5 MI as a complication of coronary artery bypass grafting (CABG) [115, 122–124]. The severity of clinical presentation, along with the acute and long-term risk after adequate management of ACS, has led to countless clinical trials and guideline recommendations on the acute management, involving antiplatelet and anticoagulation therapy, thrombolysis, PCI, and CABG [104–106, 125–127].

5.3 Cerebrovascular disease

Intracranial and extracranial atherosclerotic disease, the drivers of ischemic cerebrovascular accident (CVA/stroke), can be the initial manifestation of atherosclerotic cardiovascular disease or can present concurrently with atherosclerotic disease in other arterial beds, including CAD or PAD [111, 112, 128]. Stroke is classified as either hemorrhagic or ischemic, with hemorrhagic stroke accounting for less than 20% of all strokes, with pathophysiology centered upon ruptured cerebral vessels that have been

damaged secondary to longstanding hypertension and amyloid angiopathy [129, 130]. While acute ischemic stroke can be caused by thromboembolic disease, particularly in the setting of atrial fibrillation, acute ischemic stroke is generally caused by acute thrombosis at the site of a cerebral atherosclerotic lesion, with neurologic motor and sensory manifestations in the anatomical distributions innervated by the affected region of the brain [112, 128, 131, 132]. In similar patterns to coronary artery disease, atherosclerotic cerebrovascular disease carries severely high rates of morbidity and mortality, with extensive evidence from clinical trials and guidelines directing highly time sensitive interventions, including thrombolysis and thrombectomy, and the general recommendations for primary and secondary prevention, including stroke-related treatment of dyslipidemia [112, 113, 131, 133, 134].

5.4 Peripheral artery disease

While clinicians classically associated peripheral artery disease (PAD) with lower extremity atherosclerotic disease, PAD, also referred to as peripheral vascular disease (PVD), encompasses atherosclerotic symptoms and disease of all non-coronary and non-cerebrovascular arterial trees, including the upper and lower extremities, renal, mesenteric, and aneurysms of the abdominal aorta and its branching vessels [103, 108, 135]. The pathophysiology and the clinical presentation of PAD are directly related to the organ system or extremity perfused by the affected arterial tree, and similar to the contrast in stable angina versus acute coronary syndrome, the symptomology can be both acute and chronic.

Lower extremity PAD can manifest in different ways, with the classical symptom of claudication affecting a very small to large portion of the lower extremity, with the affected area directly related to chronic arterial lumen narrowing from local atherosclerotic lesions and the proximal or distal positioning of the plaque [103, 136]. The most acute presentation of PAD is acute limb ischemia, the sudden loss of limb perfusion with associated symptoms typically of severe pain, can be caused by thromboembolism but more commonly is secondary to acute atherothrombosis from a ruptured or eroded atherosclerotic plaque [137–139]. Acute limb ischemia is distinct from critical limb ischemia (CLI), with CLI being classified alongside chronic PAD as CLI progresses over several weeks to months, with clinical symptoms of ischemic extremity pain at rest and/or development of ischemic tissue loss such as non-healing ulcers or gangrene [140–142]. The diagnosis and management, both in the acute and chronic setting, involves assessing pulse and blood pressure differences between upper and lower extremities using the ankle-brachial index, vascular imaging, and revascularization, including thrombolysis, endovascular repair, or open surgical correction [103, 108, 143–145].

Non-lower extremity PAD, including renal artery disease, mesenteric arterial disease, and aortic and branching vessel aneurysms represent additional manifestations of atherosclerotic cardiovascular disease with similar presentations of the acute and chronic natures.

Atherosclerotic renal arterial disease classically manifests as chronic renal disease, primarily presenting as a common cause of secondary hypertension from increased activation of the renin-angiotensin-aldosterone system [108, 146, 147]. Additionally, atherosclerotic renal arterial disease can appear as ischemic nephropathy with renal parenchymal disease and manifestations of renal failure from chronic hypoperfusion, microvascular damage, and tubulointerstitial injury [146, 148]. Atherosclerotic renal arterial disease should be considered in patients with accelerated, resistant, or malignant hypertension with new onset acute renal failure or congestive heart failure, evaluated with renovascular imaging such as duplex ultrasonography and angiography, and appropriately managed with either medical therapy or

revascularization, both endovascular and surgical [108, 149–151]. Mesenteric ischemia can likewise present with chronic and acute symptoms, with chronic symptoms of abdominal pain with eating, classically referred to as intestinal or postprandial angina and representative of oxygen supply demand mismatch secondary to increased intestinal metabolic activity and diminished mesenteric arterial perfusion from underlying atherosclerosis flow-limiting lesions [108, 152]. Acute obstructive intestinal ischemia can be secondary to thromboembolism or to acute thrombosis of a ruptured or eroded atherosclerotic plaque, presenting classically with severe abdominal pain out of proportion to the physical exam, a critical condition that can result in bowel necrosis and acute abdomen [153, 154]. Given the associated morbidity and mortality, particularly of acute mesenteric ischemia, rapid general and vascular surgery consultation, with prompt diagnostic imaging and intervention is critical for appropriate evaluation and management [108, 155, 156].

Important components of the pathophysiology that promotes arterial lumen narrowing in atherosclerosis, namely chronic inflammation and extracellular matrix degradation initiated by oxidized lipoprotein accumulation, are critical processes that contribute to development of abdominal aortic aneurysms (AAA) [157]. While the precise mechanism of atherosclerosis and its relationship to the development of aneurysms of the abdominal aorta and its branch vessels is yet unclear, the high overlap of risk factors and similar pathophysiologic processes between the two conditions has prompted development of guidelines for monitoring and management of dyslipidemia in patients with known AAA, along with appropriate surveillance imaging for assessment of aneurysmal diameter [108, 158].

6. Evaluation, management, and prevention of dyslipidemia and atherosclerosis

6.1 Cholesterol monitoring, LDL, and evolution of dyslipidemia cardiovascular risk algorithms

While the Apo B-100 cholesterol carrying lipoproteins all play roles in the pathogenesis of atherosclerosis through the critical initiating steps of arterial intima lipid accumulation and foam cell formation, cholesterol monitoring and assessment of atherosclerotic cardiovascular risk has centered around surveillance and management of serum LDL and LDL-cholesterol (LDL-C) levels based on the abundant evidence available from epidemiologic and genetic hypercholesterolemia studies, and randomized controlled trials [5, 159]. IDL, Lp(a), small VLDL, and VLDL remnants all possess the requisite diameter (<70 nm) and apolipoprotein profile (Apo B-100) to freely enter the arterial intima, undergo oxidation, and trigger macrophage phagocytosis, but LDL and LDL-C have been demonstrated to be the most atherogenic of the lipoproteins, with probability of LDL retention and risk of progressive plaque development increasing in parallel with LDL and LDL-C levels in dose-dependent manners [5, 35, 159]. Genetic studies of patients with familial hypercholesterolemia (FH), a spectrum of autosomal co-dominant disorders with different loss or gain of function mutations involving genes involved in LDL metabolism, most commonly presenting as a loss of function mutation of the LDLR, carries a markedly increased risk for ASCVD in heterozygous FH patients, with the rare patients who are homozygous FH developing ASCVD as early as childhood and adolescence [5, 160, 161]. Large epidemiologic studies and meta-analyses have also demonstrated linear associations between LDL-C levels and risk of CAD death [5, 162]. The most compelling evidence for the association between LDL-C and ASCVD comes from the library of evidence from randomized

controlled clinical trials showing risk reduction of major cardiovascular events and progression of atherosclerotic plaques proportional to the decrease in LDL-C levels from statin and non-statin therapies [5, 163, 164]. Additionally, LDL subfraction sizes and the resulting atherogenicity need to be considered when evaluated patients, as studies have shown that while overall cholesterol panel levels may be ameliorated with therapy, it is the atherogenicity of the particles, specifically of LDL, that drives the pathogenesis of atherosclerosis [20]. Analysis, therefore, of LDL subfractions is likely an important component of lipid panel monitoring in these patients.

In parallel to the clinical studies and trials demonstrating the relationship between LDL, LDL-C, and ASCVD were the development of algorithms for the appropriate assessment and stratification of cardiovascular risk based on serum lipid profiles and other modifiable and non-modifiable cardiovascular risk factors, including age, gender, family history, smoking, obesity, and hypertension [165, 166]. Multiple ASCVD risk algorithms exist both in the US and Europe, and include the Framingham Risk Score (FRS), the Reynolds Risk Score (RRS), the Systematic Coronary Risk Evaluation (SCORE), the QRisk2, and the American College of Cardiology/American Heart Association arteriosclerotic cardiovascular disease risk estimator (AC/AHA-ASCVD) which has become the benchmark for risk stratification and clinical decision-making on cholesterol therapies [167].

Prior to the assessment of ASCVD risk and decisions on dyslipidemia therapy guidelines and recommendations for screening of cholesterol levels in adult patients who are asymptomatic and without history of ASCVD are employed. Differences exist in screening recommendations in the American, Canadian, and European dyslipidemia guidelines that were published in 2018, 2016, and 2016, respectively [100–102]. Canadian and European guidelines propose that dyslipidemia screening be considered for men at or older than 40 years of age, but diverge on the initial age for women, with Canadian guidelines recommending at or older than 40 years of age, and European guidelines recommending at or older than 50 years of age [100, 102]. According to American guidelines, as recommended in the recently published "2018 AHA/ACC/ACCVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol," screening for LDL-C and non LDL-C can begin in adults as early as 20 years of age, or childhood or adolescence for patients with a history of FH [101].

6.2 Dyslipidemia: primary prevention of ASCVD

Compared to prior US cholesterol guidelines, the new 2018 ACC/AHA [101] guideline allows for more personalized targeted care for patients. By providing a guided approach to treatment for clinicians, they and their patients are given the tools necessary to understand and manage their risk related to cholesterol. Additionally, these revised guidelines highlight the importance of the "clinician-patient discussion." This patient risk discussion should include a review of risk enhancers to arrive at an appropriate share decision-making approach that addresses the patient's values in terms of cost, potential for benefit, adverse effects, and drug-drug interactions.

The 2018 ACC/AHA guideline recommends that primary management of dyslipidemia for the primary prevention of ASCVD be considered for adult patients based on LDL-C levels and specific high-risk patient characteristics, most prominently a comorbid diagnosis of DM.

Anticholesterol therapy is indicated for adult patients with LDL-C greater than 190 mg/dL or for selected patients with moderately high LDL-C levels greater than

160 mg/dL and a family history of premature ASCVD such as MI or CVA before 55 years of age in a first-degree male relative or before 65 years of age in a first-degree female relative (**Figure 4**).

Patients without LDL-C > 190 mg/dL or without LDL-C > 160 mg/dL and significant family history of premature ASCVD are categorized based on the presence of DM and their 10-year ASCVD risk as estimated by their ASCVD score.

Special attention is paid to DM in the context of the primary prevention of ASCVD as DM is a major risk factor for ASCVD and contributes to and accelerates the pathogenesis of atherosclerosis through multiple and diverse mechanisms [168, 169]. DM amplifies the immune response of key inflammatory cells, most critically macrophages, into the arterial intima in response to lipoprotein accumulation, and promotes the instability of atherosclerotic plaques by increasing the size of the necrotic lipid cores [169–171]. For adult patients, age 40–75 years, with DM, current guidelines recommend initiation of moderate-intensity statin therapy with consideration for possible high-intensity statin therapy depending on patient's individualized risk assessment.

For adult patients, age 40–75 years, without DM, decisions on lifestyle modifications and statin therapy are guided by the 10-year ASCVD risk as estimated by

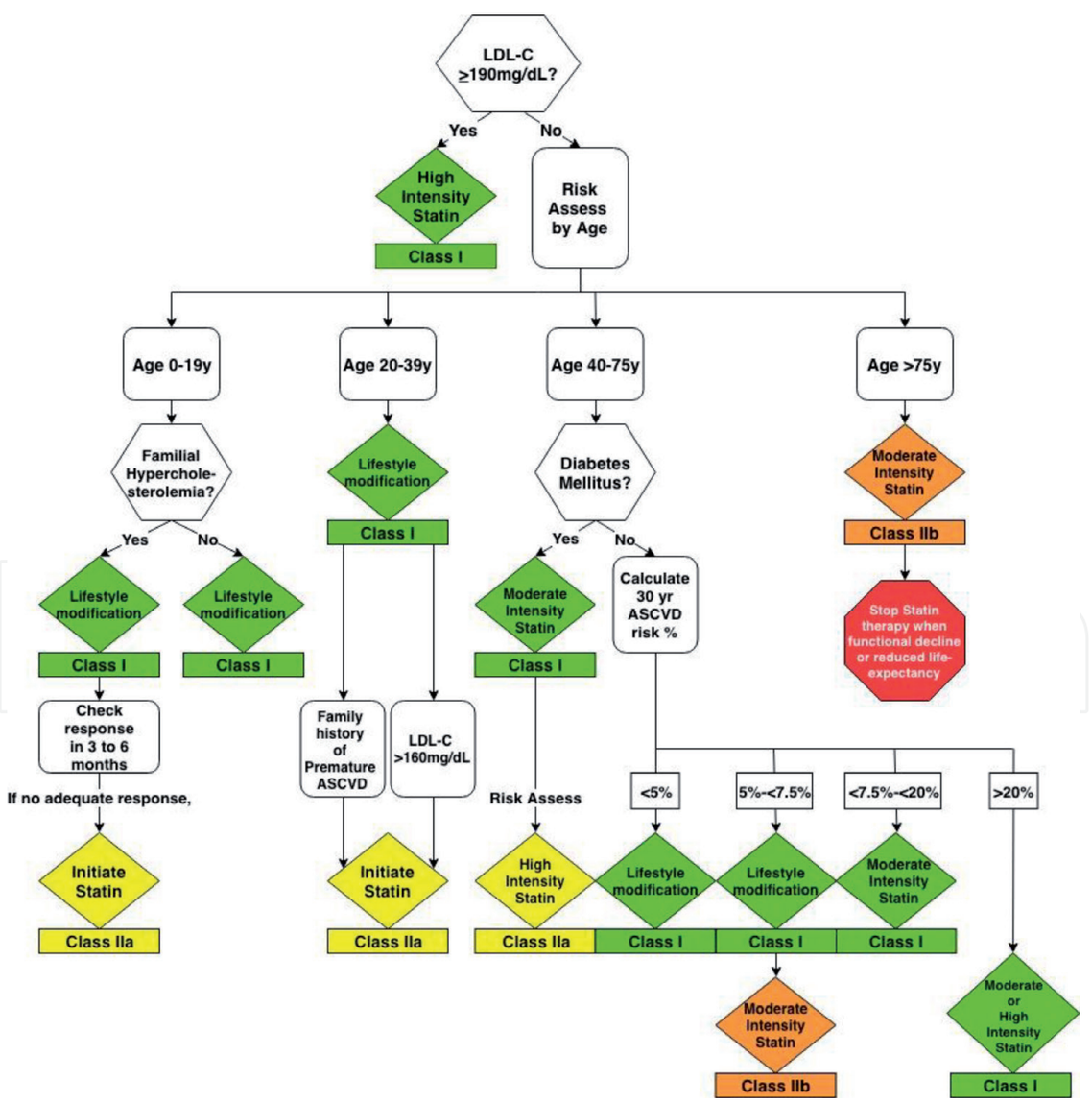

Figure 4.
Management algorithm of dyslipidemia for primary prevention of ASCVD (adapted from 2018 AHA/ACC/ACCVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol).

the patient's ASCVD score, with patients with a 10-year ASCVD risk score >7.5% qualifying for moderate-intensity statin therapy, and for patient' with a 10-year ASCVD risk score >20% qualifying for moderate to high-intensity statin therapy. Beyond the 10-year ASCVD risk score, clinician-patient discussions of dyslipidemia and primary risk prevention should consider multiple factors, including patient preference, likelihood of statin side effects, prospective benefit of intensive lifestyle modifications, and presence or absence of risk-enhancing factors. Important risk-enhancing factors to consider include metabolic syndrome, chronic kidney disease, chronic inflammatory or infectious conditions such as rheumatologic disease or HIV/AIDs, high-risk race or ethnicity, family history of premature ASCVD, and presence of lipid levels or biomarkers associated with increased ASCVD risk such as elevated Lp(a).

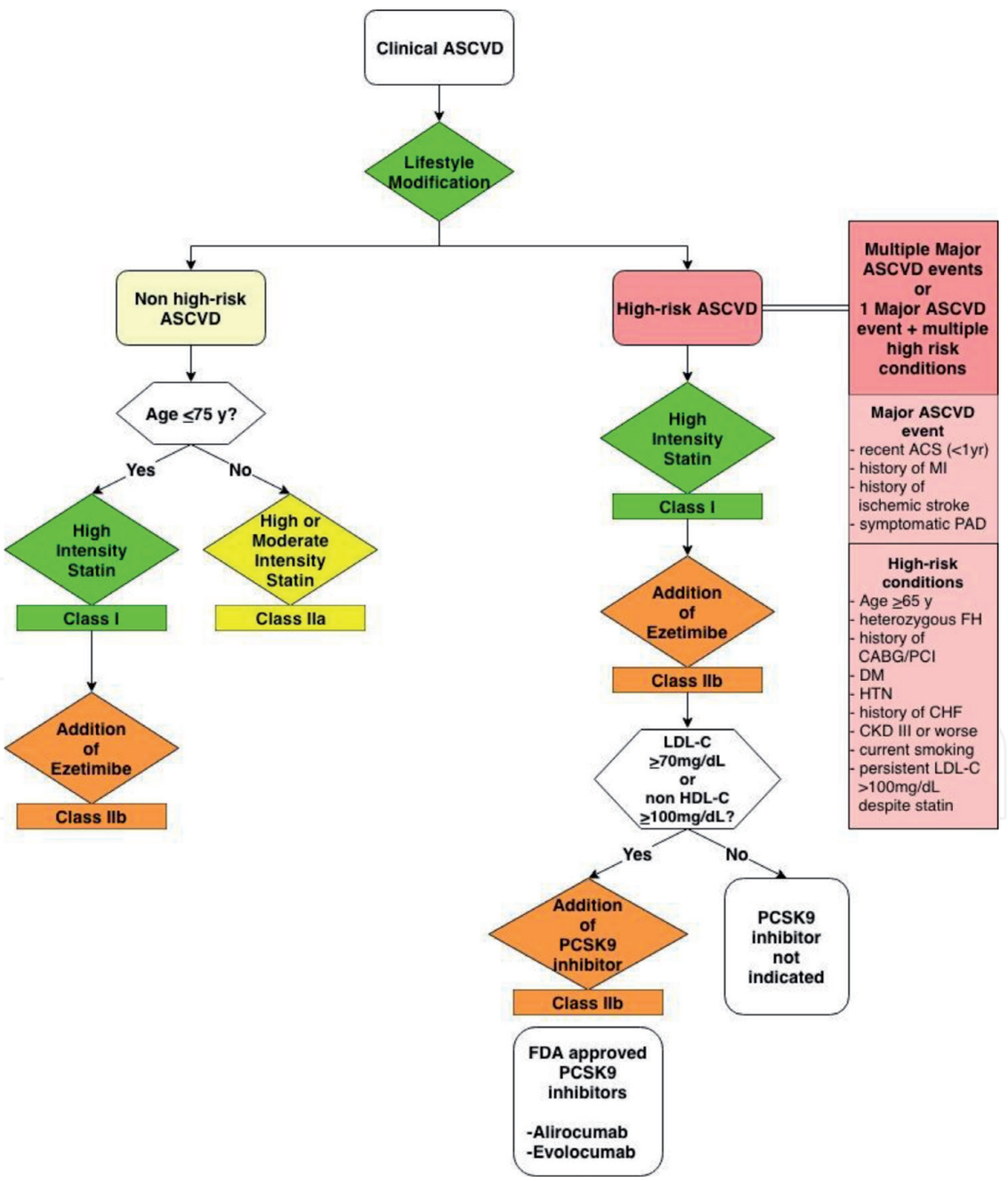

Figure 5.
Management algorithm of dyslipidemia for secondary prevention of ASCVD (adapted from 2018 AHA/ACC/ACCVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol).

6.3 Dyslipidemia: secondary prevention of ASCVD

Management of dyslipidemia for the secondary prevention of ASCVD is centered on encouragement of intensive healthy lifestyle modifications and risk assessment for future ASCVD. Patients with high or very high-risk ASCVD are those with multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. Major ASCVD events include ACS within last 12 months, MI, ischemia CVA, PAD with claudication and ABI < 0.85, and PAD with previous revascularization or amputation. High-risk conditions are similar to the risk-enhancing factors that were considered for the management of dyslipidemia in the context of primary prevention of ASCVD, and include age > 65, history of CABG or PCI outside of the major ASCVD events, DM, hypertension, chronic kidney disease, current smoking status, congestive heart failure, and persistently elevated LDL-C above 100 mg/dL despite maximal tolerate dose of statin therapy and ezetimibe, an anticholesterol drug that decreased small intestine absorption of cholesterol (**Figure 5**).

For patients with the aforementioned high-risk conditions who are on the maximal tolerated dose of statin therapy and ezetimibe with persistently elevated LDL-C > 70 or non HDL-C > 100, the addition of PCSK9 inhibitors can be considered.

7. Current and future therapy targets for dyslipidemia ASCVD

7.1 Statins

Dyslipidemia therapy for the primary and secondary prevention of ASCVD, both current and therapies under investigation for future use, are centered on targeting LDL-C given the extensive evidence demonstrating the relationship between LDL and ASCVD, and no class of medications has been shown to be more effective at lowering LDL-C than statins, the foundation of lipid and cholesterol lowering therapy [101, 172, 173].

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the synthetic pathway of cholesterol, resulting in lowering of tissue cholesterol, most critically intrahepatic cholesterol, and reflex increase in hepatic expression of surface LDLR and accompanying enhancement of receptor-mediated uptake of LDL and other circulating lipoproteins [172, 174]. Beyond the inhibition of hepatic cholesterol synthesis and the resulting reduction in circulating LDL, statins have demonstrated other important benefits in atherosclerotic plaque progression and the risk of acute atherothrombosis [174, 175]. Statins promote plaque stabilization by reducing inflammation and increasing collagen content in atherosclerotic plaques, slow the progression of overall plaque volume, and diminish high-risk or vulnerable plaque features [174–176].

Statin dosing intensity is categorized by expected reduction in LDL-C, with high-intensity statins typically lowering LDL-C by at least 50%, moderate-intensity statins typically lowering LDL-C by 30–49%, and low-intensity statins typically lowering LDL-C by less than 30%.

7.2 Nonstatins

There are different classes of non-statin medications used in the management of dyslipidemia, including bile acid sequestrants (cholestyramine, colestipol, and colesevelam), niacin, and fibrate, with ezetimibe and the PCSK9 inhibitors being the non-statin classes of medications that incorporated into the guidelines for dyslipidemia management in the primary and secondary prevention of ASCVD in combination therapy with statins [100].

Ezetimibe decreases small intestine cholesterol absorption by inhibiting the Niemann-Pick C1-Like 1 (NPC1L1) transporter [172, 177]. While the exact mechanisms of the effect of ezetimibe on atherosclerosis by itself are not as well defined as the effects of statins on atherosclerotic plaque progression and stabilization, the addition of ezetimibe to statins has been shown to regress plaque burden, reduce plaque volume, and promote plaque stabilization [178, 179]. PSCK9 works by interacting in with hepatic LDLR and enhancing the degradation of the receptor by hepatic lysosomes, with PSCK9 inhibitors thus mitigating the PSCK9-mediated turnover of hepatic LDLR and prolonging LDLR lifespan and uptake of circulating LDL-C [180]. PSCK9 inhibitors, namely alirocumab and evolocumab, in combination with statins have been shown to increase plaque calcification (a marker of plaque stability), and promote VSMC and collagen plaque content while simultaneously decreasing the size of the lipid necrotic core [181, 182].

7.3 New and future therapeutic targets and approaches to dyslipidemia and ASCVD

Beyond the dramatic reductions in LDL-C and mechanisms of atherosclerotic plaque stabilization and slowing of progression effected by statins, ezetimibe, and PSCK9 inhibitors and their codification in the management algorithms for dyslipidemia and ASCVD: the other inflammatory, lipoprotein, and metabolic pathways involved in the pathophysiology of atherosclerosis serve as potential targets for therapies in the primary and secondary prevention of dyslipidemia and ASCVD.

The antiatherogenic properties of HDL, both in terms of its antioxidant and cholesterol efflux capacities, have led to investigations for the therapeutic potential of reconstituted HDL and methods to improve endogenous HDL functionality [23, 183]. Apo A-1 and apolipoprotein E (Apo E) are the atheroprotective apolipoprotein components of HDL, but studies involving Apo A-1/HDL mimetic peptides transcriptional upregulators of Apo A-1 did not result in significant regression of coronary atherosclerotic lesions despite the enhanced HDL-C efflux [184]. Apo E consists of three isoforms (Apo E2, Apo E3, and Apo E4) and promotes clearance of circulating TG-rich lipoprotein remnants, cholesterol efflux from macrophages preventing foam cell formation, and diminishes expression of adhesion molecules necessary for macrophage migration into the arterial intima [184–186]. ApoE exerts additional atheroprotective functions via tampering the inflammatory response by inhibiting T cells, lipoprotein oxidation, and resulting proliferation and migration of VSMCs, suppressing platelet aggregation, and restoring endothelial function by promoting release of NO [184, 187–190]. Given ApoE diverse protective properties at various stages of the atherosclerotic thrombo-inflammatory process, studies investigating the potential value of reconstituted HDL with favorable ApoE content or methods to promote increased ApoE profiles among endogenous HDL can serve substantial roles for the future management of dyslipidemia and ASCVD.

Given the extensive inflammatory pathways and processes underlying the pathogenesis of atherosclerosis, considerable work has been and is currently dedicated to anti-inflammatory targets of therapy in dyslipidemia and ASCVD, with drugs in various stages of research and development. The role of lipoprotein oxidation, most significantly LDL to ox-LDL, has prompted the study of therapeutic antioxidants in the management of dyslipidemia, and has shown promising benefits in secondary prevention of ASCVD after ACS within 12 months [191, 192]. The increase of ox-LDL levels due to phospholipase A2 activity which enzymatically generate phospholipids with atherogenic modifications has led to study of the role of phospholipase 2 inhibitors in the prevention of atherosclerosis [193]. Many other inflammatory pathway targets have been investigated for the management of dyslipidemia and ASCVD

including leukotriene pathway inhibitors (promote atherosclerotic plaque development and progression via chemoattraction of macrophages and other inflammatory cells and increasing endothelial permeability), chemokine CC motif ligand 2 (CCL2), also known as MCP1 (chemokine recruiter of plaque destabilizing macrophages), and blockade of potent inflammatory markers TNF and IL-1 [191, 194–196].

8. Conclusion

Atherosclerotic cardiovascular disease encompasses conditions carrying tremendous morbidity and mortality, and is the acute and chronic clinical manifestations of a progressive pathogenic process that is initiated by the inflammatory responses to dyslipidemia. The diverse metabolic and immune mechanisms at play in the thrombo-inflammatory pathophysiology of atherosclerosis are driven by disruptions in the body's native metabolism of cholesterol, triglycerides, and lipoproteins, with comorbid conditions and risk factors such as smoking, hypertension, and obesity promoting critical changes in cholesterol and lipoproteins that initiate a vicious cycle of lipoprotein accumulation, foam cell formation, and inflammatory reaction. The fact that so many immune cell lines and metabolic factors play important roles in the development of atherosclerosis serves as a pool of current and potential future targets for therapies in the primary and secondary prevention of dyslipidemia and ASCVD.

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