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Review article

Emerging biomedical and pharmaceutical strategies for the treatment of atherosclerosis: from conventional lipid-lowering therapy to nanomedicine

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Abstract
Atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction and ischemic stroke, is a leading cause of death and disability worldwide and is expected to rise further by 2030. Once limited to industrialized nations, atherosclerosis has become a global issue due to the epidemiological transition from infectious to chronic metabolic diseases. Lipoproteins (chylomicrons, VLDL, LDL, HDL) and apolipoproteins play key roles in lipid metabolism and atherosclerosis development. Macrophages in plaques influence inflammation and plaque stability, with iron homeostasis also impacting disease progression.

Therapies include personalized diets, statins, niacin, omega-3s, fibrates, and antiplatelet agents. Innovative strategies involve natural products and nanotechnology for targeted drug delivery, especially to macrophages and the endothelium, reducing systemic side effects.

In summary, advancing therapies based on molecular insights and patient-specific factors are essential to combat this widespread chronic disease.

Keywords: Atherosclerotic; Atherosclerotic plaque; Lipoproteins; Non-statin therapies; Statins

Highlights:
- Successful prevention and treatment of atherosclerosis require: lipid and blood pressure control, personalized therapy, nutritional education based on nutrigenetics, microRNA modulation and chronopharmacology, use of natural compounds, and RNA therapy.
- Modern methods target inflammation and precise drug delivery. Caution is required with nanotherapeutics. Personalization of diet with omics reduces cardiovascular risk.

Introduction

Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by progressive accumulation of lipids and inflammatory cells within the intima of blood vessels (Falk, 2006). This process leads to the formation of ASCVD plaques that gradually narrow the vascular lumen, restrict blood flow, and may ultimately cause vessel occlusion (Jia et al., 2024; Tasouli-Drakou et al., 2025).

Until recently, atherosclerosis was considered a condition predominantly affecting highly industrialized countries. However, due to the global epidemiological transition – characterized by improved hygiene, vaccination programs and effective management of infectious diseases – the burden of chronic non-communicable diseases, including atherosclerosis, has markedly increased worldwide (Dai et al., 2022; Levenson et al., 2002). As a result, atherosclerosis has become one of the leading causes of mortality globally. Lifestyle changes, including unhealthy dietary patterns and reduced physical activity, further contribute to the growing prevalence of the disease and its occurrence in increasingly younger populations (Fan and Watanabe, 2022; Libby et al., 2019; Liu et al., 2021; Moniz et al., 2011; Riccardi et al., 2022; Sturgeon et al., 2019).

Environmental factors such as smoking, obesity, sedentary lifestyle, and poor diet significantly influence the development and progression of atherosclerosis (Lovren et al., 2015; Poulter, 1999; Wilkins et al., 2012). Epidemiological studies demonstrate that smoking markedly increases the risk of ischemic heart disease and myocardial infarction, with mortality associated with smoking exceeding that caused by lung cancer in some populations (Bays et al., 2021).

Public health interventions such as smoking bans have been shown to significantly reduce the incidence of acute myocardial infarction, highlighting the importance of preventive strategies (Mazonna and Salari, 2018). Although electronic

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cigarettes are sometimes perceived as safer alternatives, evidence suggests that their use may still increase the risk of cardiovascular events compared with non-users (Sharma et al., 2023).

Biomolecular fundamentals of atherosclerosis

Lipoprotein metabolism and lipid accumulation in the arterial wall

Lipids such as cholesterol, phospholipids, and triglycerides are transported in the aqueous environment of blood in association with apolipoproteins, forming macromolecular complexes known as lipoproteins. Apolipoproteins play essential roles in lipid transport and metabolism, including facilitating lipid absorption in the intestine, activating enzymes involved in lipoprotein metabolism, and acting as ligands for lipoprotein receptors located on the surface of hepatocytes and peripheral cells (Frohlich et al., 1989).

Based on their density and composition, plasma lipoproteins are classified into four main fractions: chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). These fractions differ in lipid composition, biological function and metabolic fate (Ahn and Kim, 2016; He and Liu, 2023; Huang and Lee, 2022; Julve et al., 2016).

Chylomicrons are synthesized in the intestinal epithelium during dietary fat absorption and transport triglycerides from the intestine to peripheral tissues. Endothelial lipoprotein lipase hydrolyzes triglycerides within chylomicrons to free fatty acids, which can subsequently be utilized as an energy source or re-esterified in tissues (Ghosh et al., 2022). After triglyceride removal, chylomicron remnants are formed and transported to the liver, where they deliver cholesterol esters (Dash et al., 2015; Ouimet and Marcel, 2012).

VLDL particles, synthesized in the liver, transport endogenous triglycerides. Lipoprotein lipase-mediated hydrolysis gradually converts VLDL into intermediate-density lipoproteins (IDL) and eventually into LDL particles, which are the primary carriers of cholesterol in circulation (Ference et al., 2017; Song et al., 2021; Takahashi, 2017; Varbo and Nordestgaard, 2017).

LDL particles contain apolipoprotein B and transport cholesterol from the liver to peripheral tissues. Cellular uptake occurs via LDL receptor-mediated endocytosis, allowing cholesterol to be used in membrane synthesis or steroid hormone production (Ouimet and Marcel, 2012; Phillips, 2014; Rosenblit, 2019; Sutter et al., 2015; Yancey et al., 2007; Ye et al., 2011). Excess LDL may also be taken up by macrophages through scavenger receptors, leading to intracellular lipid accumulation and foam cell formation, a hallmark of early atherosclerotic lesions (Davidson et al., 2009; Lee et al., 2018).

In contrast, HDL particles – containing apolipoprotein A – play a protective role in lipid metabolism by facilitating reverse cholesterol transport from peripheral tissues to the liver. HDL is highly heterogeneous and contains numerous associated proteins, including enzymes and lipid transfer proteins that influence lipid metabolism and inflammatory processes (Cardoso and Perucha, 2021; Denimal et al., 2015, 2016; Mocciaro et al., 2022; Orsoni et al., 2016; Ouimet and Marcel, 2012; Phillips, 2014; Sutter et al., 2015; Yancey et al., 2007; Ye et al., 2011).

Plasma lipoproteins differ significantly in their physicochemical properties, composition, and biological functions, which determine their role in lipid transport and atherosclerosis development. These differences influence not only their metabolic fate but also their atherogenic or protective potential within the vascular system. A comparative overview of the major classes of plasma lipoproteins is presented in Table 1.

Although dyslipidemia represents a major driver of atherosclerosis, the disease is increasingly recognized as a chronic inflammatory condition involving complex interactions between lipids, immune cells, and vascular tissues (Liberale et al., 2020; Puchner et al., 2014). The pathological process begins when excess LDL infiltrates the arterial wall and undergoes oxidative modification. Oxidized LDL (oxLDL) triggers activation of endothelial cells and promotes the recruitment of circulating monocytes and T lymphocytes to sites of vascular injury (Puchner et al., 2014; Rognoni et al., 2015).

Once inside the intima, monocytes differentiate into macrophages that engulf oxLDL through scavenger receptors, transforming into lipid-laden foam cells. These cells secrete inflammatory cytokines and proteolytic enzymes that contribute to vascular wall damage and plaque progression (Chan et al., 2022; Jougasaki et al., 2010; Neels et al., 2023). Chronic inflammation promotes smooth muscle cell proliferation, extracellular matrix remodeling and deposition of collagen, calcium salts and proteoglycans, resulting in progressive narrowing of the arterial lumen and increased risk of ischemic complications (Csige et al., 2018; Jin and Kim, 2017; Rennenberg et al., 2009).

Macrophages represent key effector cells in atherosclerosis and exhibit remarkable functional plasticity. Depending on environmental signals, macrophages can adopt different activa-

Table 1. Characteristics of plasma lipoproteins (Parthasarathy et al., 2010)

HDL	LDL	VLDL	Chylomicrons	Feature
1.063–1.25	1.019–1.062	0.96–1.019	0.92–0.95	Relative density
About 1400 15	About 1500 35	5 000–10 000 80	10 000–250 000 500	Molecular weight Particle diameter (nm)
54	20	7	1	Composition (% by weight)
6	12	52	87	Apolipoproteins
2	1	1	–	Triglycerides
21	22	19	8	PACS
14	37	14	3	Phospholipids
3	8	7	1	Cholesterol esters
3.5	4.0	1.5	0.05	Serum concentration (g/l)
4 days	3–4 days	6–12 h	12 min	Biological half-life

tion states, most commonly classified as pro-inflammatory M1 and anti-inflammatory M2 phenotypes (De Meyer et al., 2024; Martinez and Gordon, 2014; Momtazi-Borojeni et al., 2019).

M1 macrophages produce pro-inflammatory cytokines and reactive oxygen species that contribute to tissue damage and plaque instability (Puchner et al., 2014). In contrast, M2 macrophages participate in tissue repair, resolution of inflammation, and clearance of apoptotic cells, processes that may promote plaque stabilization (Bajpai et al., 2018; Duong et al., 2021; Li et al., 2019; Locati et al., 2020; Ma et al., 2019; Song et al., 2022).

Recent studies indicate that macrophages in atherosclerotic lesions form a highly heterogeneous population shaped by local microenvironmental signals (Geissmann et al., 2003; Gordon and Taylor, 2005). Early plaque macrophages are primarily derived from circulating monocytes, whereas in advanced lesions macrophage proliferation within the plaque becomes an important contributor to macrophage accumulation (Jenkins et al., 2011, 2013; Robbins et al., 2013).

Within unstable plaques, macrophages are predominantly polarized toward the M1 phenotype, promoting inflammation and tissue degradation. In contrast, macrophages located in the fibrous cap often display mixed phenotypic characteristics, reflecting the complex regulatory environment within atherosclerotic lesions (Momtazi-Borojeni et al., 2019) – Fig. 1.

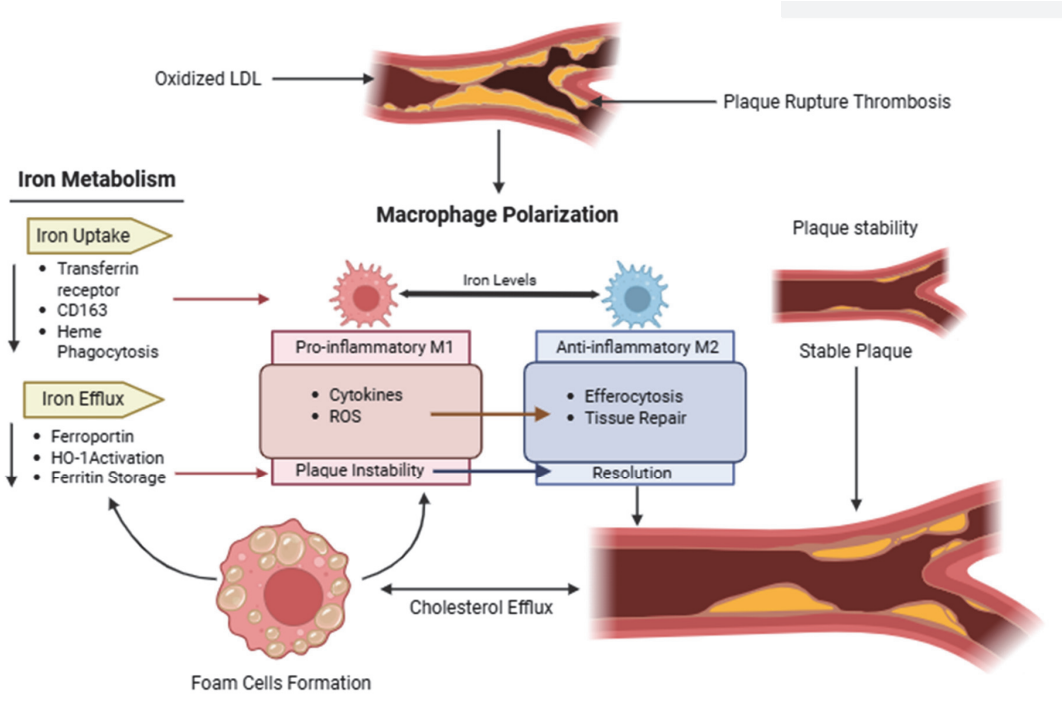


Fig. 1. Schematic representation of the interactions between iron metabolism, macrophage polarization (M1/M2), lipid accumulation, and the progression or stabilization of atherosclerotic plaques. Dysregulation of iron homeostasis promotes pro-inflammatory M1 macrophage activation, foam cell formation, and plaque instability, whereas regulated iron efflux and anti-inflammatory M2 polarization contribute to plaque stabilization and resolution of inflammation.

Recent studies using single-cell sequencing and spatial transcriptomics have shown that macrophages in atherosclerotic plaques form a highly heterogeneous population whose phenotype and activity depend on local microenvironmental signals such as cytokines, lipids, and oxidative stress. It turns out that the classic division into pro-inflammatory M1 and anti-inflammatory M2 is only a simplification, because in reality these cells assume many intermediate and dynamic states of activation that vary depending on the stage and location of the atherosclerotic lesion. This functional complexity of macrophages is crucial for plaque stability, inflammatory processes, and responses to therapeutic interventions, including pharmacological and potentially targeted nanotechnology therapies (Ijaz et al., 2026).

Iron metabolism has emerged as an important factor influencing macrophage function and inflammatory responses in atherosclerosis. Iron is an essential trace element involved in oxygen transport, cellular respiration, and DNA synthesis; however, excessive iron accumulation can promote oxidative stress and tissue damage (Förstermann et al., 2017; Muchowska et al., 2019; Wade et al., 2021; Xia et al., 2021).

Macrophages play a central role in systemic iron homeostasis. They recycle iron from senescent erythrocytes through phagocytosis and regulate intracellular iron levels through membrane transporters and storage proteins such as ferritin (Philpott and Jadhav, 2019; Winn et al., 2020). Iron uptake occurs through receptors including transferrin receptor 1 (TfR1), LRP1 (CD91), and CD163, while intracellular iron can be exported via ferroportin or stored within ferritin complexes.

Following erythrophagocytosis, macrophages activate heme oxygenase-1 (HO-1), which degrades heme into ferrous iron, biliverdin, and carbon monoxide – molecules with anti-inflammatory properties (Fiorelli et al., 2019; Guo et al., 2025; Loboda et al., 2016; Recalcati and Cairo, 2021). However, dysregulated iron metabolism can contribute to oxidative stress through the Fenton reaction, generating highly reactive hydroxyl radicals that damage cellular structures (Cai et al., 2020; Roemhild et al., 2021).

Importantly, intracellular iron levels influence macrophage polarization. Elevated iron levels are generally associated with pro-inflammatory M1 polarization, whereas increased iron efflux may promote anti-inflammatory M2 phenotypes (Guo et al., 2019; Kroner et al., 2014; Wunderer et al., 2020; Zanganeh et al., 2016). Experimental studies demonstrate that iron accumulation in macrophages enhances the production of inflammatory cytokines, while increased iron export mediated by ferroportin or reduced hepcidin signaling may protect against atherosclerosis by promoting M2 polarization (Malhotra et al., 2019; Zhang et al., 2011).

The integration of these mechanisms with lipid disorders and immune processes provides the basis for new therapeutic strategies, including modulation of macrophage polarization, control of iron metabolism, and reduction of oxidative stress, and supports the development of personalized therapies targeting specific metabolic pathways in atherosclerosis.

Current therapeutic strategies

Understanding the interplay between lipid metabolism, macrophage biology, and iron homeostasis provides important insights into potential therapeutic strategies for atherosclerosis. Targeting macrophage polarization, regulating iron metabolism, and modulating inflammatory pathways represent promising approaches for limiting plaque progression and improving plaque stability. For example, therapies aimed at reducing oxidative stress, regulating iron homeostasis or enhancing cholesterol efflux from macrophages may complement traditional lipid-lowering therapies.

Moreover, recent advances in lipidomics have revealed associations between specific lipid species and cardiovascular disease risk, suggesting that lipidomic profiling may provide novel biomarkers for early disease detection and therapeutic monitoring (Chapman et al., 2020; Chen et al., 2017; Cheng et al., 2015; Dang et al., 2016; Di Giorgi et al., 2021; Ding and Rexrode, 2020; Ekroos et al., 2010; Karjalainen et al., 2019; Khan et al., 2018; Kostara et al., 2020; Mantovani et al., 2020; Meikle et al., 2015, 2019; Mocciaro et al., 2022; Poss et al., 2020; Stegemann et al., 2014; Takeda et al., 2020). These findings may ultimately facilitate the development of personalized treatment strategies targeting specific metabolic pathways involved in atherosclerosis.

In recent years, commercial high-throughput proteomics platforms such as Olink and SomaLogic have enabled large-scale epidemiological studies using integrated multi-omics data. Although these technologies have greatly accelerated the discovery of biomarkers in atherosclerotic cardiovascular disease (ASCVD), the quality of the data remains underappreciated in the context of its clinical translation. AI-assisted analyses combined with proteomics can deepen our understanding of the multifactorial causes of ASCVD, taking into account aging processes, and concepts such as “ageotypes” open up the possibility of individualized interventions to slow down aging. At the same time, it has been shown that measurement results across different proteomic platforms are not always consistent, requiring the use of orthogonal verification methods, and platform-specific factors – including epitope effects and cross-reactions – can lead to conflicting results for the same protein, making causal inference difficult. Although tissue proteomics provides valuable complementary information, its use in large trials limits the need for postmortem samples, which carry the risk of protein degradation and reduce the reliability of measurements. Single-cell proteomics and spatial proteomics are also promising areas of research, as they allow for a better understanding of the heterogeneity of atherosclerotic plaques and complement data from aggregate analyses in larger cohorts. Ultimately, for proteomics to fully realize its clinical potential, it will be necessary to use absolute or reliably reconfigurable relative quantitative protein assessment so that the results can directly support therapeutic decisions. In practice, the clinical value of proteomics will be determined more by the quality of measurements than by their quantity (Singh et al., 2026).

Finally, the integration of molecular, metabolic, and immunological insights into the pathogenesis of atherosclerosis may support the development of innovative therapeutic approaches aimed at modulating immune responses, restoring lipid homeostasis and improving vascular health.

The review focuses mainly on studies published in the last 20 years.

Statin lipid-lowering therapies

Advances in understanding lipid metabolism enable therapeutic targeting of multiple pathogenic pathways in atherosclerosis. However, the primary treatment is diet and strict weight control. Pharmacological agents are reached for after failing to achieve satisfactory results of diet, or when factors with an increased risk of coronary artery disease appear (Rustemeijer et al., 1997).

Fig. 2 shows the main factors determining atherosclerosis, including lifestyle and diet, highlights dietary interventions such as omega-3 fatty acids and traditional pharmacological treatment, and illustrates therapeutic strategies based on nanotechnology (Ruisinger et al., 2015).

Statins remain the cornerstone of pharmacological therapy for atherosclerosis due to their well-established lipid-lowering and cardioprotective effects (Chester and El Guindy, 2021; Grundy et al., 2019; Jukema et al., 1995; Mach et al., 2020; Sadowska et al., 2023; Takeda et al., 2020; Tsujita et al., 1986; Visseren et al., 2021; Weber et al., 1997). Their primary mechanism of action involves inhibition of hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase), which leads to reduced endogenous cholesterol synthesis and upregulation of low-density lipoprotein receptors (LDLr), thereby increasing hepatic clearance of LDL cholesterol from the circulation (Sirtori, 2014). This process is mediated through apolipoprotein B (ApoB)-dependent uptake of LDL particles (Adams et al., 2023; Lin et al., 2023).

The diversity of statins reflects differences in their chemical structure, pharmacokinetics, and potency, which may impact their clinical efficacy and safety profile (Harborg et al., 2020; Sirtori, 2014). Individual statins differ in their lipophilicity, metabolic pathways, and duration of action, which may influence their tissue distribution and potential for drug interactions. A summary of the major statins and their structural characteristics is provided in Table 2.

Evidence from multiple randomized clinical trials demonstrates that statin therapy significantly reduces circulating LDL cholesterol levels and lowers the risk of cardiovascular events (Arad et al., 2005; Mihaylova et al., 2012; Otto et al., 1995; Zheng et al., 2016). In addition to lipid lowering, statins exhibit pleiotropic effects, including anti-inflammatory activity, improved endothelial function, and stabilization of atherosclerotic plaques (Allen and Mamotte, 2017; Chruściel et al., 2016; Clim et al., 2024; Essig et al., 1998; Harborg et al., 2020; Ishikawa et al., 2014; Kounatidis et al., 2024; Nenna et al., 2021; Patti et al., 2006; Sahebkar et al., 2015; Storino Farina et al., 2015; Zhu et al., 2017). These effects are partly associated with inhibition of isoprenoid intermediates within the cholesterol biosynthesis pathway, which alters post-transla-

tional modification of intracellular signaling proteins involved in vascular inflammation and smooth muscle cell proliferation (German and Liao, 2023; Harborg et al., 2020; Oesterle et al., 2017; Schwartz et al., 2001; Sirtori, 2014; Storino Farina et al., 2015; Yuzhik et al., 2022).

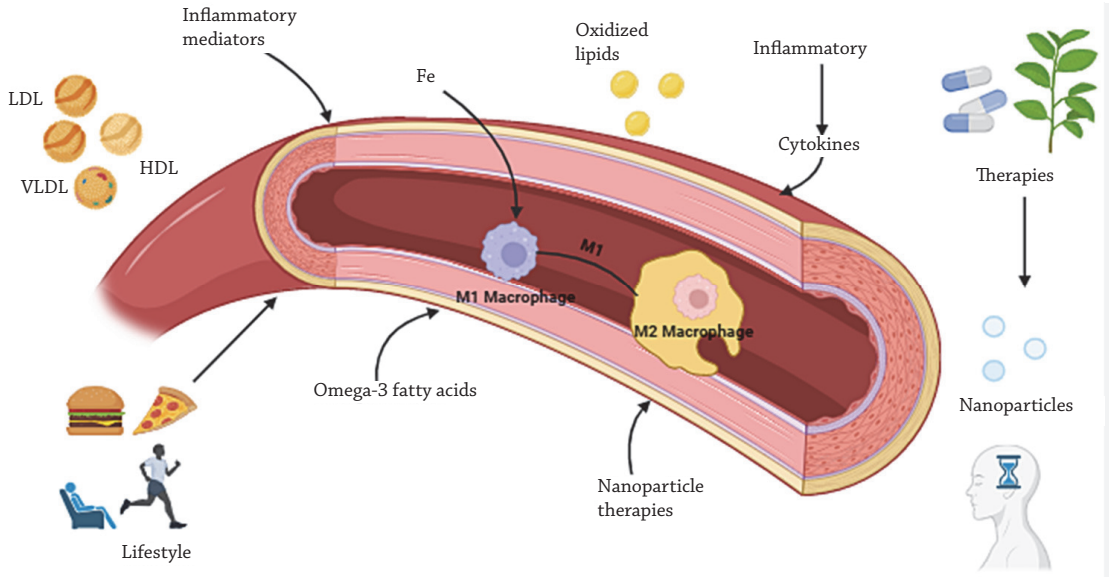


Fig. 2. Overview of major determinants and therapeutic approaches in atherosclerosis, including lifestyle factors, dietary interventions (omega-3 fatty acids), pharmacological treatment, and emerging nanotechnology-based therapies.

Large randomized clinical trials, including the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), and HOPE-3 (Heart Outcomes Prevention Evaluation) trials, demonstrated substantial reductions in C-reactive protein (CRP) levels, in some cases by up to 83%, in addition to lowering LDL cholesterol (Oesterle et al., 2017; Schwartz et al., 2001; Zheng et al., 2016). However, it remains unclear whether the reduction in inflammatory markers is solely a consequence of LDL reduction or reflects additional pleiotropic mechanisms.

Although statins are generally well tolerated, long-term pharmacological therapy may be associated with adverse effects, including hepatotoxicity, gastrointestinal bleeding, myopathy, and cardiac arrhythmias (Newman et al., 2019). In cases of advanced vascular obstruction or severe stenosis, pharmacological therapy may need to be complemented with surgical interventions such as endarterectomy, balloon angioplasty, or stent implantation (Kuhn et al., 2015; Lawton et al., 2022; Lewicki et al., 2015; Wang et al., 2015) – Fig. 3.

Combination therapy: statins and ezetimibe

Ezetimibe represents one of the most widely used adjunctive lipid-lowering agents. Its mechanism of action involves inhibition of the Niemann–Pick C1-like 1 (NPC1L1) receptor in the intestinal epithelium, thereby reducing intestinal cholesterol absorption and lowering circulating LDL cholesterol levels.

Evidence from randomized clinical trials indicates that the addition of ezetimibe to statin therapy provides additional cardiovascular benefits. The IMPROVE-IT trial demonstrated that combination therapy significantly reduced LDL cholesterol levels and the incidence of cardiovascular events compared with statin monotherapy, particularly in elderly patients (Cannon et al., 2015). Similarly, the RACING trial reported that moderate-intensity statin therapy combined with ezetimibe achieved lipid-lowering efficacy comparable to high-intensity statin monotherapy while reducing treatment intolerance (Kim et al., 2022; Lee et al., 2023).

Overall, current evidence suggests that combination therapy may improve lipid control and treatment adherence, although further long-term randomized clinical trials are required to confirm its superiority over high-dose statin therapy in specific patient populations (Bach et al., 2019; Khan et al., 2022; Sydhom et al., 2024).

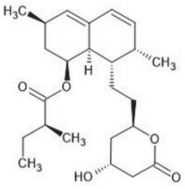
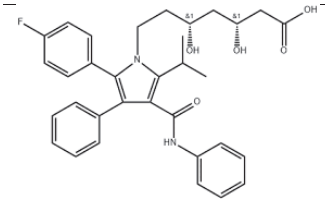
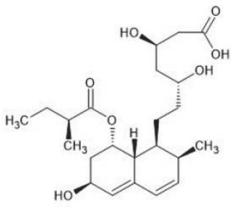
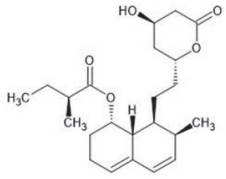
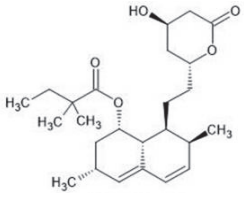
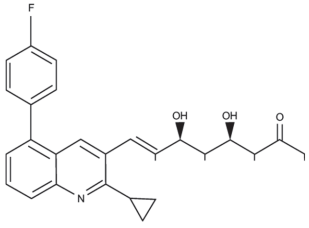
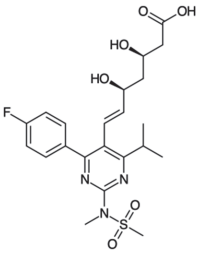
PCSK9-targeted therapies

Recent advances in lipid-lowering therapy have focused on inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of LDL receptor degradation. Monoclonal antibodies such as evolocumab and alirocumab bind circulating PCSK9, preventing its interaction with LDL receptors and increasing hepatic LDL clearance. These agents have been shown to reduce LDL cholesterol levels by approximately 50–60% in high-risk patients (Garwood et al., 2025).

In addition to monoclonal antibodies, RNA-based therapies targeting PCSK9 have recently been introduced. Inclisiran, a small interfering RNA (siRNA) therapy, inhibits intracellular synthesis of PCSK9 by blocking translation of its mRNA, resulting in prolonged reductions in LDL cholesterol levels (Corsini et al., 2025).

Preclinical studies have also explored next-generation antibody constructs targeting PCSK9. For example, Li et al. (2024b) developed a biparatopic antibody (B11-H2-Fc) demonstrating significantly higher binding affinity and more than 95% inhibition of PCSK9 activity in experimental models, highlighting the potential for improved therapeutic strategies targeting this pathway.

Table 2. Types of statins and their formulas (Barrios-González and Miranda, 2010)

Structure	Statin
	Lovastatin
	Atorvastatin
	Pravastatin
	Compactin
	Simvastatin
	Pitavastatin
	Rosuvastatin

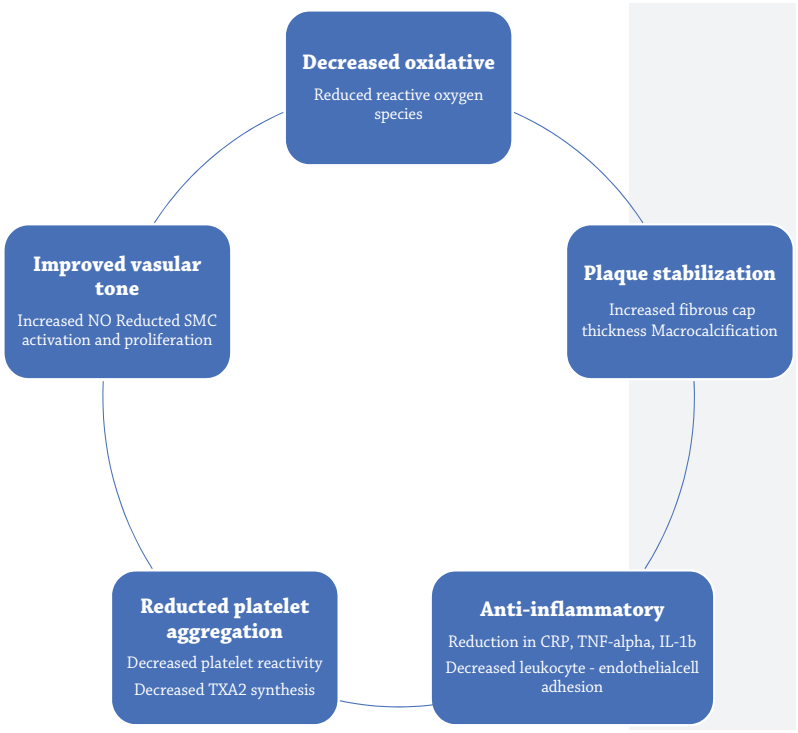


Fig. 3. Comprehensive effects of statin therapy on atherosclerosis: from LDL-C reduction and plaque stabilization to modulation of inflammation and vascular remodeling

The rapid development of novel lipid-lowering and antiatherosclerotic therapies has expanded the spectrum of available pharmacological strategies beyond conventional treatments. In particular, advances in RNA-based technologies, monoclonal antibodies, and small-molecule inhibitors have led to the development of innovative drugs targeting key pathways involved in lipid metabolism and inflammation (Menon and Bril, 2022). A summary of selected new drugs, their mechanisms of action, and the current status of clinical trials is presented in Table 3.

Non-statin lipid-lowering therapies

Niacin

Niacin (nicotinic acid) has historically been used as a lipid-modifying agent due to its ability to inhibit diacylglycerol-2-acyltransferase, thereby reducing hepatic triglyceride synthesis and lowering circulating LDL-C levels. In addition, niacin decreases hepatic catabolism of HDL-C, leading to increased HDL concentrations (Kamanna and Kashyap, 2008). Clinical studies have reported reductions in LDL-C ranging from 5–25% and triglyceride reductions of 20–50%, while HDL-C levels may increase significantly during therapy (National Cholesterol Education Program /NCEP/ Expert Panel..., 2002).

Despite these favorable lipid profile changes, evidence from randomized clinical trials indicates limited cardiovascular benefit when niacin is added to statin therapy (HPS2-THRIVE..., 2014). The AIM-HIGH trial evaluated whether niacin combined with statin therapy could further reduce cardiovascular risk in patients with established cardiovascular disease and dyslipidemia.

Although improvements in lipid parameters were observed – including increased HDL-C and reduced LDL-C and triglyceride levels – the study was terminated early due to a lack of benefit regarding the primary cardiovascular endpoint (AIM-HIGH Investigators et al., 2011; Meyer-Ficca and Kirkland, 2016). Furthermore, a non-significant trend toward increased ischemic stroke risk was observed, although subsequent multivariate analysis did not confirm an association between niacin use and stroke incidence (Goldie et al., 2016; Teo et al., 2013).

Omega-3 fatty acids

Omega-3 fatty acids – including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid (ALA) – represent another class of lipid-modifying agents investigated in the context of atherosclerosis (Mu et al., 2024). Their primary mechanism of action involves inhibition of hepatic triglyceride synthesis, reduced production of very-low-density lipoprotein cholesterol (VLDL-C), and enhanced metabolism of circulating triglyceride-rich lipoproteins (Bradberry and Hilleman, 2013; Padro et al., 2015).

In addition to lipid-lowering effects, omega-3 fatty acids exhibit anti-inflammatory, antiarrhythmic, antithrombotic, and endothelial-protective properties, and may contribute to blood pressure reduction (Lavie et al., 2009). Consequently, they are commonly recommended for patients with hypertriglyceridemia or elevated cardiovascular risk (Gagnon and Ashraf, 2024; Jacobson et al., 2014; Stone et al., 2014; Williams et al., 2012).

Evidence from randomized clinical trials has demonstrated mixed outcomes. In the JELIS trial, supplementation with purified EPA (1.8 g/day) significantly reduced the incidence of major coronary events in hypercholesterolemic patients receiving statin therapy (Yokoyama et al., 2007). Similarly, regression of coronary atherosclerotic plaques was observed in the CHERRY study in patients treated with statins combined with EPA supplementation (Watanabe et al., 2017).

Table 3. Latest drugs and clinical trials

	Patents/Protection	Key data and developments	Phase	Mechanism of action	Drug/Therapy
Alradwan et al., 2024	WO 2020/009805A3 – cyclic PCSK9 peptides; protection of enlicitide synthesis process	LDL reduction of ≥50–60%; requires 8 hr fasting	III	First oral PCSK9 inhibitor	Enlicitide (Merck)
Banach et al., 2023; Ray et al., 2025b	Protection on siRNA structure (GalNAc-siRNA)	Lowering of triglycerides and ApoB	I/II	ANGPTL3 inhibitory siRNAs	Solbinsiran (Eli Lilly)
Blais et al., 2023	PCT for anti-IL-6 antibody	Reduction of hsCRP in patients with CKD	II	Anti-IL-6 reduces inflammation	Pacibekitug (Tourmaline Bio)
Brandts and Ray, 2020	Chemical protection and method of application (PCT)	Improvement in HDL, ApoA-I; decrease in MACE, better outcomes in diabetics	II	BET modulator affecting HDL/aero-enhancers	Apabetalone (Resverlogix)
Chen et al., 2024	CID (chemical entity) protection in PCT applications	LDL down to 63%, HDL +165%, Lp(a) reduction; numerous clinical trials	II/III	CETP inhibitor with partnership to statins	Obicetrapib (NewAmsterdam Pharma)
Harbi, 2025	US: patents for chemical structure and GalNAc-siRNA (e.g., US 10,xxx,xxx) – protection for siRNA sequences and formulation; applications in PCT/EU/JP regions	Reduction of Lp(a) by up to ~94%; Phase III studies currently underway	II–III	Lp(a) reduction siRNAs	Lepodisiran (Eli Lilly)
Nicholls et al., 2021	Protection per cyclodextrin structure (PCT/USPCT)	First studied in Australia; target: dissolving plaques	I	Cyclodextrin to remove 7-ketocholesterol	UDP 003 (Cyclarity)
Wilkinson et al., 2024	Protection of GalNAc structure and conjugates (corporate patents, including PCT/US)	Consistent ~50% reduction in LDL for 6–18 months. (ORION-1/10/11/4)	III	siRNA against PCSK9	Inclisiran (Novartis/ Alnylam)

However, other studies evaluating low-dose omega-3 mixtures (EPA/DHA 1 g/day) did not demonstrate significant cardiovascular benefit when added to standard medical therapy (Bowman et al., 2018; Risk and Prevention Study Collaborative Group et al., 2013). These discrepancies may result from differences in formulation, dosage, and biological activity between EPA and DHA, which have been shown to influence oxidative stress, membrane composition, inflammation, and endothelial function (Mason et al., 2016, 2023; Shaikh, 2012).

Fibrates

Fibrates are fibric acid derivatives that function as agonists of the peroxisome proliferator-activated receptor alpha (PPAR-α), which regulates lipid metabolism and inflammation (McPherson et al., 2024). Pharmacologically, fibrates reduce LDL-C by approximately 5–20%, increase HDL-C by 10–20%, and reduce triglyceride levels by 20–50% (Goyal et al., 2014; Jacobson et al., 2014). Currently approved fibrates include fenofibrate, fenofibric acid, and gemfibrozil. When used in combination with statins, fibrates may increase the risk of myopathy, particularly in the case of gemfibrozil, which has been associated with a significantly higher risk compared with fenofibrate (Reiner, 2010).

Meta-analyses and systematic reviews indicate that fibrate therapy may reduce the incidence of major cardiovascular events and non-fatal myocardial infarction; however, most evidence derives from studies evaluating fibrate monotherapy rather than combination therapy (Blais et al., 2021; D'Andrea et al., 2019; Gudzune et al., 2014; Keene et al., 2014; Kim et al., 2024). Importantly, these analyses did not demonstrate a reduction in all-cause mortality among patients treated with fibrates (Blais et al., 2021; Keene et al., 2014; Kim et al., 2024; Saha and Arora, 2010).

Other therapies

Antithrombotic therapies

Antithrombotic therapy plays a critical role in both the primary and secondary prevention of cardiovascular and cerebrovascular events associated with atherosclerosis. Among antiplatelet agents, aspirin remains the most widely used drug in clinical practice (Greco et al., 2023).

Antiplatelet therapy is particularly important in patients with large-artery atherosclerosis and small-vessel disease, while anticoagulant therapy is typically recommended in conditions characterized by blood stasis or hypercoagulability (Greco et al., 2023). Aspirin is commonly used in the management of atherosclerosis affecting the aortic arch, carotid arteries, and intracranial vessels, as well as following carotid artery stenting or endarterectomy (Kleindorfer et al., 2021; Powers et al., 2019).

Some studies suggest that clopidogrel monotherapy may provide greater efficacy compared with aspirin; however, conclusive evidence remains limited (CAPRIE Steering Committee, 1996). In patients undergoing carotid artery stenting, short-term dual antiplatelet therapy (DAPT), typically consisting of aspirin and clopidogrel, represents the standard anticoagulant strategy (American College of Cardiology Foundation et al., 2007).

Natural compounds and phytochemicals

Natural products have long been investigated as potential therapeutic agents due to their structural diversity and biolog-

ical activity (Bai et al., 2019; Han et al., 2022; Lee et al., 2024; Shateri et al., 2022; Song et al., 2021; Witkowski et al., 2020; Yang et al., 2023; Zhao et al., 2021; Zhuang et al., 2019). Increasing evidence suggests that plant-derived compounds may exert protective effects against atherosclerosis through multiple mechanisms, including modulation of lipid metabolism, anti-inflammatory activity, stabilization of atherosclerotic plaques, and regulation of gut microbiota composition (Cheng et al., 2022; Fan and Pedersen, 2021; Han et al., 2022; Karlsson et al., 2012; Song et al., 2021; Yang et al., 2023; Zhao et al., 2021). Several medicinal plants, including *Allium sativum*, *Angelica gigas*, *Artemisia annua*, and *Cinnamomum cassia*, have demonstrated beneficial pharmacological effects in experimental studies (Si et al., 2015; Varshney and Budoff, 2016; Wang et al., 2011; Xing et al., 2015). Bioactive compounds isolated from these plants – including alkaloids, flavonoids, terpenoids, and phenylpropanoids – have shown promising pharmacological activities in cardiovascular disease models (Anwar et al., 2018; Cheng et al., 2017; Han et al. 2022; Jin et al., 2017; Li et al., 2021; Mahmoud et al., 2019; Wang et al., 2011).

Among these compounds, flavonoids represent one of the most extensively studied groups of plant secondary metabolites. These polyphenolic compounds are widely distributed in fruits, vegetables, cereals, and medicinal plants, and exhibit strong antioxidant and anti-inflammatory properties (Al-Khayri et al., 2022; Choy et al., 2019). Mechanistically, flavonoids modulate inflammatory signaling pathways by inhibiting the activity of enzymes such as cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS), while also suppressing the expression of pro-inflammatory cytokines including IL-1β, TNF-α, IL-6, and IL-8 (Chanu et al., 2023; Farzaei et al., 2019).

Other natural compounds, such as phytosterols, reduce cholesterol absorption in the intestine by competing with dietary cholesterol (Köhler et al., 2017; Liu et al., 2024; Nashed et al., 2005; Rysz et al., 2017; Song et al., 2021). Epidemiological studies and meta-analyses have demonstrated that daily intake of approximately 2 g of phytosterols can reduce LDL-C levels by around 10% (Katan et al., 2003; Rysz et al., 2017). Additional studies have shown that combining phytosterol supplementation with statin therapy may enhance lipid-lowering effects compared with increasing the statin dose alone (Cabral and Klein, 2017).

Berberine, a plant alkaloid derived from traditional Chinese medicinal plants such as *Coptis chinensis* and *Berberis vulgaris*, has also demonstrated promising cardiometabolic effects. Experimental studies have shown that berberine reduces LDL cholesterol and triglyceride levels, enhances LDL receptor expression, and inhibits PCSK9 activity, thereby improving lipid metabolism and reducing oxidative stress (Fitzgerald et al., 2014, 2017; Hu et al., 2025; Rui et al., 2021).

Treatment with diet

The development and pathogenesis of atherosclerosis is significantly influenced by lifestyle, particularly nutrition (Verhaar et al., 2020). Current developments in science and technology promote personalized nutrition as an effective prevention of atherosclerosis. Nutrition is an environmental factor that constantly has a major impact on the human body (Barrea et al., 2020; Hoefer et al., 2021; Smetneva et al., 2020; Tuttolomondo et al., 2019; Verhaar et al., 2020). Any nutritional disorders, unbalanced diet, emerging vitamin deficiencies, excessive consumption of fatty foods, etc., have a bad effect on the state of the body. The emerging concept of "4Ps" (i.e., personalization, prediction, prevention, and participation) on this topic is based on current advances in "omics" technology, and it addresses the concept of "good nutrition". It is designed to consider personalized nutrition in personalized terms (de Toro-Martín et al., 2017; Grimaldi et al., 2017). Personalized nutrition is characterized by the fact that it takes into account the personal characteristics of the consumer, i.e., the characteristics of the phenotype, genotype, current health status, lifestyle pursued, a number of different psychoemotional, environmental, climatic factors, etc.), which are intended to improve the condition of the body (Di Renzo et al., 2019; Ferguson et al., 2016; Juma et al., 2014; Naureen et al., 2020) – Fig. 4.

Vesnina et al. (2022) showed that in order to accurately analyze the predisposition to atherosclerosis, which is related to nutrition, traits of a genetic nature that affect nutrient metabolism are very important. These traits range from the presence of single nucleotide polymorphisms (SNPs) of genes to factors of an epigenetic nature (Farhud et al., 2010; Gaboon, 2011; International Consortium for Blood Pressure Genome-Wide Association Studies et al., 2011; Tuttolomondo et al., 2019).

Recent research highlights the role of chrono-nutrition and genetic factors in the development of metabolic diseases like atherosclerosis. Nutrigenetic companies use SNP analysis to tailor diets based on genes involved in lipid metabolism, antioxidant defense, and taste preferences (Roy et al., 2009; Tibaut et al., 2019). Key anti-atherosclerotic diets – ketogenic, Mediterranean, and DASH – are rich in antioxidants and low in carbohydrates (Dowis and Banga, 2021; Froyen and Burns-Whitmore, 2020; Keogh et al., 2007), but their accessibility may be limited by regional and economic factors. As an alternative, functional foods and supplements containing biologically active substances like resveratrol, curcumin, and omega-3s show promising anti-atherosclerotic effects (Casas et al., 2018; Minelli and Mortinari, 2019; Verhaar et al., 2020; Xu et al., 2019).

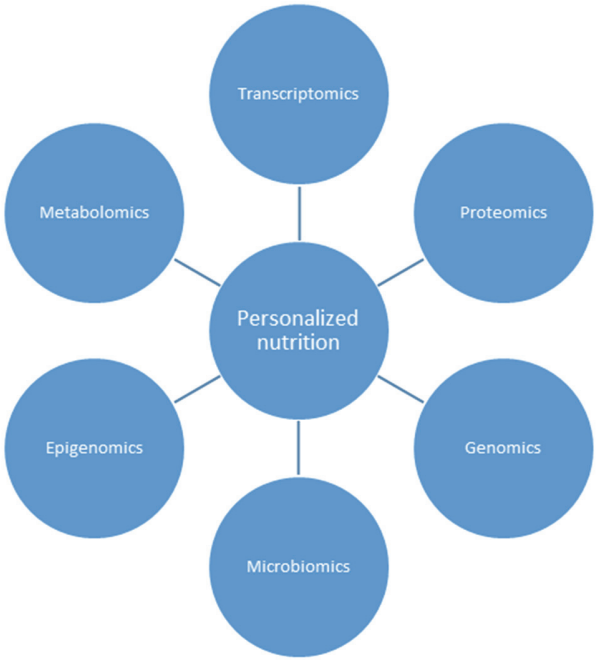


Fig. 4. Components of personalized nutrition: leveraging genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics to guide individualized dietary strategies

Molecular targets in atherosclerosis

Recent advances in molecular biology have identified several new therapeutic targets involved in inflammatory signaling, immune regulation, and lipid metabolism (Luo et al., 2024; Zhang et al., 2025). One of the most extensively studied pathways is the NLRP3 inflammasome, which plays a critical role in linking metabolic stress to inflammatory responses within atherosclerotic plaques (Stitham et al., 2020). Activation of the NLRP3 inflammasome promotes the release of pro-inflammatory cytokines such as IL-1β and IL-18, contributing to macrophage activation, endothelial dysfunction, and plaque instability (Agarwal et al., 2020; Eelen et al., 2015; Liu et al., 2020; Stitham et al., 2020).

Experimental studies have shown that inhibition of NLRP3 signaling can significantly reduce plaque inflammation and necrotic core formation. Anti-inflammatory agents such as colchicine have demonstrated the ability to suppress NLRP3-mediated pathways and modulate NF-κB signaling, thereby reducing vascular inflammation and improving plaque stability. However, the systemic administration of colchicine is associated with dose-dependent toxicity, which limits its long-term use (Stitham et al., 2020; Tang et al., 2023).

Another emerging area of research involves the regulatory role of microRNAs in cardiovascular disease. MicroRNAs function as post-transcriptional regulators of gene expression and influence multiple biological processes involved in atherosclerosis, including endothelial activation, macrophage polarization, and smooth muscle cell proliferation (Huang et al., 2023). Identification of specific microRNA signatures associated with plaque instability may therefore provide both novel diagnostic biomarkers and therapeutic targets.

Beyond inflammasome signaling, increasing attention has been directed toward the role of immune checkpoint pathways and macrophage-mediated clearance mechanisms in the progression of atherosclerosis (Luo et al., 2024). One particularly important pathway involves the interaction between CD47 and signal regulatory protein-α (SIRPα), which functions as a "don't eat me" signal that inhibits macrophage phagocytosis. In atherosclerotic plaques, elevated CD47 expression on apoptotic cells impairs efferocytosis, leading to accumulation of necrotic debris and enlargement of the necrotic core. Experimental studies have demonstrated that blockade of the CD47-SIRPα axis restores macrophage-mediated clearance of apoptotic cells and promotes plaque stabilization, suggesting that modulation of this pathway may represent a promising therapeutic strategy for reducing plaque progression and vulnerability (Kojima et al., 2016; Yurdagul et al., 2018).

Another emerging molecular target involves regulators of cellular cholesterol transport and macrophage lipid handling. Liver X receptors (LXRs) and ATP-binding cassette transporters such as ABCA1 and ABCG1 play essential roles in mediating reverse cholesterol transport and preventing foam cell formation. Activation of LXR signaling enhances cholesterol efflux from macrophages and suppresses inflammatory gene expression, thereby reducing lipid accumulation within the arterial wall. Experimental models have shown that pharmacological activation of LXR pathways can reduce atherosclerotic lesion formation and attenuate inflammatory responses in vascular tissues (Calkin and Tontonoz, 2012; Joseph et al., 2002). These findings highlight the therapeutic potential of targeting cholesterol efflux pathways as a complementary approach to traditional lipid-lowering therapies.

Comparative effectiveness of current therapeutic strategies

Atherosclerosis is a complex and multifactorial disease driven by the interaction between lipid metabolism disorders, chronic inflammation, immune system activation, and endothelial dysfunction. The development and rupture of atherosclerotic plaques remain the main triggers of ischemic cardiovascular events, including myocardial infarction and stroke (Criqui et al., 2014; Joshi et al., 2014; Park et al., 2020). Although dyslipidemia represents a central driver of disease progression, growing evidence indicates that endothelial dysfunction, oxidative stress, and systemic inflammatory processes play equally critical roles in the initiation and destabilization of atherosclerotic lesions (Badimon and Vilakur, 2014; Bahiru et al., 2021; Eelen et al., 2015; Joshi et al., 2014; Li et al., 2024a; Libby, 2021; Libby and Hansson, 2019). Consequently, effective therapeutic strategies must target not only lipid accumulation but also inflammatory signaling pathways and cellular mechanisms responsible for plaque progression.

Lipid-lowering therapy remains the cornerstone of atherosclerosis management. Statins are currently the most widely used pharmacological agents due to their ability to inhibit HMG-CoA reductase, thereby reducing hepatic cholesterol synthesis and circulating LDL-C levels. In addition to lipid-lowering effects, statins exhibit pleiotropic properties, including improvement of endothelial function, reduction of oxidative stress, and modulation of inflammatory pathways (Galis and Khatri, 2002; Komukai et al., 2014; Luan et al., 2003; Rezaie-Majd et al., 2002). Imaging studies using intravascular ultrasound have demonstrated that intensive statin therapy can stabilize plaques and slow disease progression when LDL-C levels are reduced to approximately 1.8 mmol/l (70 mg/dl) (Cannon et al., 2017; Chhatriwalla et al., 2009; Du et al., 2016; Izoe et al., 2022; Joshi et al., 2014; Pitt et al., 1995).

Despite these benefits, residual cardiovascular risk persists even in patients receiving optimal statin therapy (Houslay et al., 2006). This residual risk is partly attributed to persistent vascular inflammation and elevated concentrations of other atherogenic lipoproteins such as lipoprotein(a) (Nissen et al., 2023; Thau et al., 2024). Consequently, additional therapeutic strategies have been developed to target alternative lipid pathways. PCSK9 inhibitors and RNA-based therapies such as inclisiran significantly reduce LDL-C levels by enhancing LDL receptor recycling in hepatocytes. Clinical trials have demonstrated that PCSK9 inhibition can reduce cardiovascular events by approximately 15–20% when combined with statin therapy (Ray et al., 2019).

RNA-targeting therapies directed against apolipoprotein(a), including pelacarsen, olpasiran, and SLN360, represent another promising approach for reducing lipoprotein(a) levels, which are strongly associated with increased cardiovascular risk (Jean-Gilles and Gencer, 2025; Nissen et al., 2023). These therapies may play an important role in patients with genetically elevated lipoprotein(a), a population that currently lacks effective treatment options.

In addition to lipid-modifying therapies, anti-inflammatory strategies have gained increasing attention. Clinical trials such as CANTOS demonstrated that inhibition of IL-1β with canakinumab significantly reduced recurrent cardiovascular events independently of lipid levels, providing direct evidence that inflammation represents a key therapeutic target in atherosclerosis. Similarly, low-dose colchicine has shown

beneficial effects in the LoDoCo and COLCOT trials by reducing inflammatory signaling pathways associated with plaque destabilization.

However, not all lipid-modifying interventions have produced favorable outcomes. Therapies such as CETP inhibitors, niacin, and fibrates have shown limited or inconsistent cardiovascular benefits in large randomized clinical trials when added to statin therapy (ACCORD Study Group et al., 2010; Bétrisey et al., 2024; HPS2-THRIVE Collaborative Group, 2013; Lincoff et al., 2017; Takaeko et al., 2020; Wu et al., 2021). These findings emphasize that future therapeutic strategies must target multiple biological mechanisms simultaneously rather than focusing exclusively on cholesterol reduction.

Beyond statins and PCSK9-targeted therapies, additional lipid-lowering agents have been developed to address residual cardiovascular risk. One such strategy involves inhibition of ATP-citrate lyase (ACL), an enzyme located upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Bempedoic acid has emerged as a promising therapy, particularly for patients who are statin-intolerant or require further LDL-C reduction despite optimal therapy. The CLEAR Outcomes trial demonstrated that treatment with bempedoic acid significantly reduced LDL-C concentrations and was associated with a reduction in major adverse cardiovascular events in high-risk patients (Nissen et al., 2023). Earlier clinical trials also confirmed its lipid-lowering efficacy and safety profile in patients with hypercholesterolemia (Ray et al., 2019; Sinnaeve et al., 2020). Importantly, because bempedoic acid is activated primarily in the liver and not in skeletal muscle, it may reduce the risk of statin-associated myopathy, making it a valuable option for patients unable to tolerate high-intensity statin therapy.

Another therapeutic strategy focuses on triglyceride-rich lipoproteins and remnant cholesterol, which are increasingly recognized as important contributors to ASCVD. Icosapent ethyl, a purified eicosapentaenoic acid (EPA) derivative, demonstrated substantial cardiovascular benefits in the REDUCE-IT trial, where therapy reduced the risk of major cardiovascular events by approximately 25% in patients with elevated triglyceride levels receiving statin treatment (Bhatt et al., 2018). The protective effects of EPA appear to extend beyond triglyceride reduction and may include anti-inflammatory effects, stabilization of atherosclerotic plaques, improved endothelial function, and reduced oxidative stress (Mason et al., 2020; Nicholls et al., 2021; Sahebkar et al., 2015). Nevertheless, other large trials evaluating mixed omega-3 fatty acid formulations, such as the STRENGTH trial, did not demonstrate similar cardiovascular benefits, suggesting that therapeutic efficacy may depend on formulation, dosage, and patient selection (Nicholls et al., 2021).

More recently, therapies targeting angiopoietin-like proteins, particularly ANGPTL3, have emerged as promising strategies for regulating lipid metabolism. ANGPTL3 plays a key role in inhibiting lipoprotein lipase and endothelial lipase, thereby influencing plasma triglyceride and LDL-C levels (Ray et al., 2025a). Inhibition of ANGPTL3 using monoclonal antibodies such as evinacumab has shown substantial reductions in LDL-C concentrations even in patients with homozygous familial hypercholesterolemia who respond poorly to conventional lipid-lowering therapies (Raal et al., 2020). Additional genetic and mechanistic studies have demonstrated that loss-of-function mutations in ANGPTL3 are associated with reduced plasma lipid levels and lower cardiovascular risk, supporting the therapeutic potential of this pathway (Rosenson et al., 2020). These findings suggest that targeting ANGPTL3 may represent an important complementary strategy to existing treatments, particularly in genetically predisposed populations with severe dyslipidemia.

Studies have shown that persistent inflammation of the vessel walls may persist even in patients treated with statins, especially in cases of low plasma omega-3 levels (Jun et al., 2020; Ridker, 2016). Clinical intervention trials indicate that adding high-purity EPA (ethyl eicosapentaenoic acid) to standard statin therapy significantly reduces the incidence of cardiovascular events, suggesting a synergistic effect in modulating inflammatory processes and stabilizing atherosclerotic plaques (Boden et al., 2020). However, the effect of other omega-3 preparations and lower purity supplementation on inflammatory biomarker levels is less consistent, highlighting the need for careful selection of the form and dose of fatty acids in the context of the individual patient profile. The combined results of the studies suggest that targeted omega-3 supplementation should be considered as an adjunct to statin therapy to reduce residual vascular inflammation, especially in individuals with low serum levels of these acids (Hoang and Kim., 2020; Nikolic Turnic et al., 2019). In addition, the integration of lipidomics data allows for better identification of patients who could benefit most from such intervention, as well as monitoring the effects of therapy at the metabolic and molecular level, which supports the development of personalized treatment strategies for atherosclerosis.

Nanoparticle-based drug delivery systems: potential and limitations

Nanomedicine has emerged as a promising strategy for improving the treatment of atherosclerosis through targeted drug delivery and controlled release of therapeutic agents (Chen et al., 2020; Duivenvoorden et al., 2019; Talev and Kanwar, 2020). Nanoparticles possess several advantages over conventional drug formulations, including increased bioavailability, prolonged circulation time, and enhanced accumulation at sites of vascular inflammation (Aili et al., 2024; Gu et al., 2024; Panda et al., 2019; Shi et al., 2024; Wang et al., 2018). Surface modification with targeting ligands, peptides, or cell membranes enables nanoparticles to selectively bind to molecules expressed in inflamed endothelium, such as VCAM-1, thereby improving drug localization within atherosclerotic plaques (Gu et al., 2024; Lameijer et al., 2018).

In addition, biomimetic nanoparticle systems derived from monocyte or macrophage membranes have been developed to enhance immune evasion and facilitate targeted delivery to inflamed vascular tissues (Gu et al., 2024; Li et al., 2023; Sha et al., 2022; Yaman et al., 2020). Experimental studies have demonstrated that nanoparticle-encapsulated drugs can inhibit foam cell formation, reduce plaque inflammation, and improve plaque stability while reducing systemic toxicity (Fredman et al., 2015; Gu et al., 2024; Karami et al., 2023; Tao et al., 2020; Tomaszewska et al., 2025).

Despite these promising findings, several limitations currently hinder the clinical translation of nanoparticle-based therapies (Chen et al., 2023; Guo et al., 2021). First, the majority of studies remain at the preclinical stage, with relatively few nanomedicine formulations evaluated in human clinical trials. To date, only a limited number of nanoparticle-based systems – such as liposomal prednisolone or paclitaxel-associated nanoemulsions – have entered early-phase clinical testing (Cheng et al., 2023). Second, concerns remain regarding the long-term safety of nanoparticles, including potential cardiotoxicity, oxidative stress induction, mitochondrial dysfunction, and inflammatory responses (Guo et al., 2021; Niżnik et

al., 2024). These toxicological mechanisms may lead to myocardial damage or vascular dysfunction if nanoparticle formulations are not carefully optimized (Guo et al., 2021; Herrera-Rodríguez et al. 2023).

Additional barriers to clinical implementation include variability in nanoparticle physicochemical properties, difficulties in large-scale manufacturing, regulatory challenges, and incomplete understanding of nanoparticle interactions with biological systems. The formation of a protein corona around nanoparticles, for example, can alter their biodistribution and targeting ability, potentially reducing therapeutic efficacy. Standardization of nanoparticle parameters such as size, surface charge, and composition is therefore essential to ensure reproducibility and safety in clinical applications.

The efficacy of nanoparticle-based drug delivery systems in the diagnosis and treatment of atherosclerosis has been extensively studied in animal models, which have shown promising results in imaging, plaque stabilization, and targeted drug delivery. For example, macrophage-mimicking NPs have been designed to target inflamed areas of blood vessels, delivering anti-inflammatory drugs and sequestering pro-inflammatory cytokines, resulting in reduced plaque inflammation in preclinical studies (Chen et al., 2022; Cheng et al., 2021). One example is long-circulating liposomal prednisolone phosphate nanoparticles (L-PLP), which were effectively delivered to macrophages in atherosclerotic lesions in animal models (Jiang et al., 2020; Patel et al., 2026; Zhang et al., 2019).

Personalized medicine and integration of omics technologies

Advances in genomics, transcriptomics, metabolomics, and microbiome research are transforming the understanding of cardiovascular disease and enabling the development of personalized therapeutic strategies. Nutritional genetics – including nutrigenetics and nutrigenomics – has demonstrated that genetic variability influences individual responses to dietary factors and lipid-lowering interventions (Barrea et al., 2020; Ferguson et al., 2016; Naureen et al., 2020; Vesnina et al., 2022). Integration of omics technologies may therefore facilitate individualized dietary and pharmacological interventions aimed at reducing cardiovascular risk.

Chronopharmacology represents another emerging concept in personalized medicine. Studies have shown that the expression of many genes involved in inflammation, lipid metabolism, and vascular function follows circadian rhythms. For example, oscillations in the CCL2-CCR2 signaling pathway regulate the rhythmic recruitment of inflammatory cells to vascular tissues, thereby influencing the progression of atherosclerosis (Lu et al., 2018). Therapeutic strategies aligned with biological rhythms may therefore enhance treatment efficacy while minimizing adverse effects.

Parallel to advances in proteomics, recent studies in lipidomics indicate that atherosclerosis and associated chronic inflammation of the arterial wall lead to significant disturbances in fatty acid metabolism, which is reflected in changes in plasma lipid composition (Padro et al., 2015). Studies comparing patients with carotid atherosclerosis and healthy controls have shown that traditional lipid markers, such as the omega-6 to omega-3 ratio or EPA and DHA status, have limited ability to distinguish between groups, and their diagnostic value is further reduced in populations treated with statins. In response to these limitations, new, more complex lipidomic indicators have been introduced, including the PUFA n-6/n-3 balance index (Omega-6/3 Balance Index, O6/3-BI), the ratio of saturated to monounsaturated fatty acids (SFA/MUFA, C18:0/C18:1n-9), and a logit function combining these indices. The new indices showed a significant improvement in distinguishing patients with atherosclerosis from healthy individuals, both in untreated populations and in groups taking statins, with AUC values reaching 0.88 and a strong prognostic effect (Cliff's $\Delta = 0.76$), surpassing individual classic indices. These results highlight the potential of modern lipidomic markers in improving diagnosis, risk stratification, and monitoring of treatment effects in atherosclerosis, providing a natural complement to proteomic data and other multi-omics approaches toward personalized cardiovascular medicine (Eroshchenko et al., 2026; Meikle et al., 2015).

Future directions and perspectives

Future research should focus on integrating advances in molecular biology, nanotechnology, and precision medicine to develop more effective therapeutic strategies for atherosclerosis (Luo et al., 2024; Stitham et al., 2020). Several key priorities can be identified. First, further optimization of nanoparticle-based drug delivery systems is required to improve plaque-specific targeting and reduce systemic toxicity. Second, large-scale clinical trials are needed to evaluate the long-term safety and efficacy of RNA-based therapies and nanomedicine approaches. Third, integration of omics technologies with clinical data may facilitate the identification of patient subgroups most likely to benefit from specific therapeutic interventions. Finally, combination therapies targeting multiple pathogenic pathways – including lipid metabolism, inflammation, and immune regulation – may represent the most effective strategy for reducing cardiovascular risk. Continued translational research bridging basic science discoveries with clinical applications will therefore be essential for improving the prevention and treatment of atherosclerosis (Chan and Huang, 2021).

Another promising direction for translational research involves a deeper understanding of immunometabolic mechanisms driving atherosclerosis. Increasing evidence suggests that metabolic reprogramming of immune cells, particularly macrophages and T lymphocytes, plays a crucial role in plaque development and progression. Alterations in cellular metabolism – including glycolysis, fatty acid oxidation, and mitochondrial function – can influence inflammatory signaling pathways and determine macrophage polarization within atherosclerotic lesions. Recent studies indicate that targeting immunometabolic pathways may represent a novel therapeutic strategy for modulating vascular inflammation and improving plaque stability (Bäck et al., 2019; O'Neill et al., 2016; Pomeyie et al., 2025). In particular, modulation of macrophage metabolism and inflammatory lipid mediators has emerged as a potential approach to limit chronic vascular inflammation and promote resolution of atherosclerotic lesions.

In addition, advances in computational biology and artificial intelligence are increasingly being applied to cardiovascular research. Integration of large-scale datasets generated from genomics, proteomics, metabolomics, and imaging studies allows for the identification of complex molecular networks underlying atherosclerosis. Machine learning approaches may facilitate the discovery of novel biomarkers and improve risk prediction models by integrating genetic, metabolic, and clinical variables. Recent studies have demonstrated that AI-based analysis of multi-omics data can identify previously unrecognized pathways involved in cardiovascular disease and may support the development of personalized treatment strategies tailored to individual patient profiles (Khera et al., 2018; Leopold and Loscalzo, 2018). The combination of advanced computational tools with experimental and clinical

research will therefore play an increasingly important role in translating molecular discoveries into effective therapeutic interventions.

Conclusion

Effective prevention and treatment of atherosclerosis require an integrated approach, including lipid and blood pressure control, individualized therapy, and nutritional education based on the principles of nutrigenetics and nutrigenomics. Contemporary therapeutic strategies focus on inflammation modulation, precision drug delivery, microRNA expression regulation, and chronopharmacology. Natural bioactive compounds such as flavonoids and salidroside, which have anti-inflammatory and anti-atherosclerotic properties, are also playing an increasingly important role.

Modern therapies, including breakthrough RNA interventions and oral PCSK9 inhibitors, allow for long-term and specific control of cardiovascular risk factors. At the same time, the safety of nanomedicine delivery systems requires further research and regulation due to the potential risk of myocardial damage and induction of oxidative stress. It also remains crucial to determine whether the observed reductions in biomarkers such as LDL-C, Lp(a), and inflammatory markers will translate into a real reduction in cardiovascular events and exceed the effects of standard therapies.

As a result, future therapeutic approaches should combine innovative pharmaceutical technologies with individualized treatment and nutritional strategies to achieve maximum effectiveness in the prevention and treatment of atherosclerosis.

Ethical aspects and conflict of interest

The authors have no conflict of interest to declare.

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