



## REVIEW ARTICLE

## Mechanisms, precision therapies, and technological frontiers in coronary atherosclerosis: a comprehensive review

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Coronary atherosclerosis is a leading cause of morbidity and mortality worldwide and is characterized by complex molecular and cellular mechanisms involving lipid dysregulation, endothelial dysfunction, immune-inflammatory processes, and vascular remodeling. Despite advancements in conventional therapies, including statins and antiplatelet agents, significant residual risk persists, particularly in patients with genetic dyslipidemias, persistent inflammation, or limited access to advanced care. Recent breakthroughs in precision medicine, multiomics technologies, and high-resolution imaging are transforming our approach to cardiovascular risk assessment by enabling refined stratification through single-cell transcriptomics, polygenic risk scoring, and artificial intelligence-powered plaque analysis. This review synthesizes the contemporary understanding of disease mechanisms and emerging therapeutic strategies, highlighting novel interventions targeting PCSK, inflammatory pathways, and vascular regeneration through cell-based therapies. We further explored the transformative potential of CRISPR-Cas9 gene editing for durable lipid lowering, nanotechnology-enabled drug delivery, and gut microbiota modulation targeting metabolites such as trimethylamine N-oxide. Although these innovations promise personalized atherosclerosis management, challenges remain in terms of accessibility, health equity, and clinical implementation. The integration of multimodal data analytics with targeted therapeutics heralds a new era of precision cardiology aimed at reducing the global burden of coronary artery disease.

**Keywords:** coronary atherosclerosis; precision medicine; multiomics; inflammation; artificial intelligence; regenerative therapy

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## INTRODUCTION

Coronary atherosclerosis (CAD), which is driven by a complex interplay of endothelial dysfunction, lipid dysregulation, and immune-inflammatory interactions, is a major cause of cardiovascular disease and the leading single cause of death worldwide [1–6]. Epidemiological data suggest that more than 9 million deaths annually are attributed to CAD, with direct and indirect costs exceeding \$1 trillion. Pathological studies indicate that subclinical atherosclerotic changes begin early, sometimes in adolescence, and that a large proportion of acute coronary events occur in previously undiagnosed individuals, underscoring its “silent killer” nature [7, 8].

The past several decades have witnessed remarkable progress in the identification and management of CAD risk factors, with the widespread use of statins, antiplatelet agents, and coronary revascularization strategies [9, 10]. However, these interventions do not fully eliminate cardiovascular risk, particularly among patients with familial or metabolic dyslipidemias, patients with persistent inflammation, or patients with limited access to advanced care [11, 12]. Residual risk may be attributed to genomic, molecular, and environmental determinants insufficiently addressed by conventional approaches [13].

Breakthroughs in molecular biology, imaging, digital health, and engineering have broadened the therapeutic landscape for atherosclerosis. Emerging therapies target not only lipids but also inflammation and metabolic resistance, while advanced diagnostic modalities, including multiomics and artificial intelligence, enable refined risk assessment [14–16]. This review integrates the current understanding of CAD pathobiology, details classical and emerging therapeutic paradigms, and discusses the latest frontiers, including gene- and cell-based therapies, nanotechnology, and implementation challenges in global health [17, 18].

## PATHOPHYSIOLOGICAL MECHANISMS OF CORONARY ATHEROSCLEROSIS

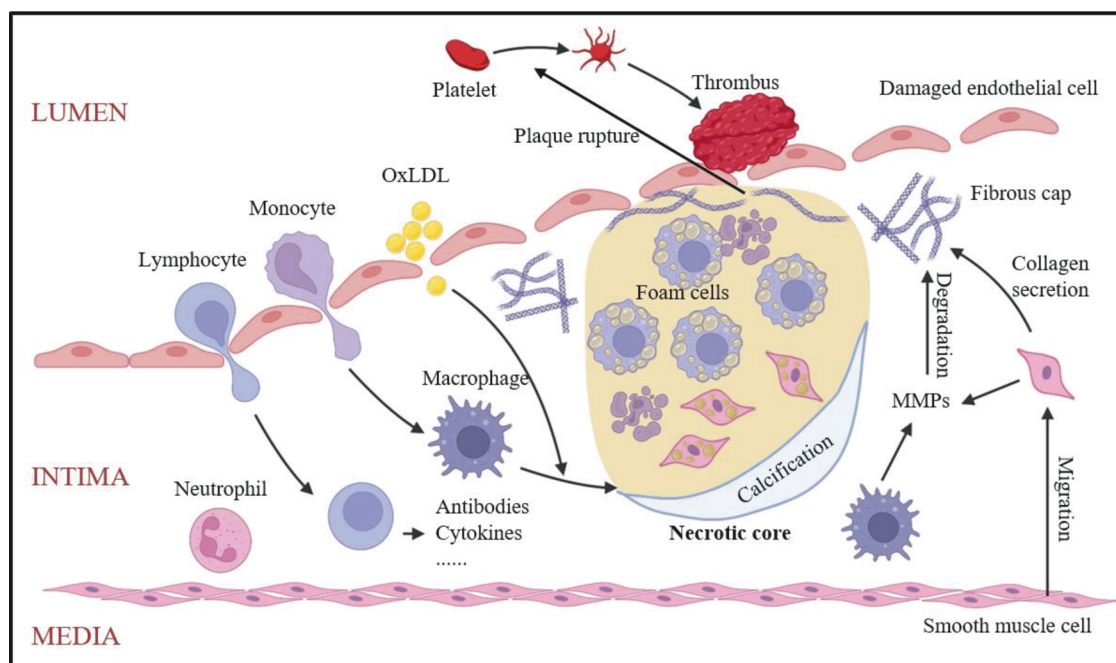
The pathogenesis of coronary atherosclerosis is a dynamic and multifaceted process involving sequential and concurrent events that initiate and propagate atherosclerotic plaque development. These events include the initial endothelial injury; the sub-endothelial accumulation and oxidative modification of lipoproteins; the recruitment of monocytes and their differentiation into macrophage foam cells; and the eventual phenotypic switching

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**Fig. 1 Pathophysiological mechanisms in coronary atherosclerosis.** This figure illustrates the key cellular and molecular events driving atherosclerotic plaque development. The figure depicts endothelial dysfunction with reduced nitric oxide bioavailability and increased oxidative stress, monocyte recruitment and foam cell formation through oxidized LDL uptake, smooth muscle cell phenotypic switching contributing to fibrous cap formation, and eventual plaque destabilization through matrix metalloproteinase activity.

of vascular smooth muscle cells, which contributes to fibrous cap formation and plaque stability (Fig. 1).

#### Endothelial dysfunction and oxidative stress

The vascular endothelium serves as a critical regulatory interface between circulating blood and vascular tissues; it orchestrates vascular homeostasis through the dynamic integration of mechanical and biochemical signals [19]. Under physiological conditions, endothelial cells maintain vascular tone through the balanced production of vasoactive mediators, with nitric oxide (NO) serving as the principal endothelium-derived relaxing factor [20]. However, in atherosclerosis, endothelial dysfunction emerges as a pivotal pathophysiological event characterized by impaired vasodilation, heightened oxidative stress, and a proinflammatory phenotype [21]. This dysfunctional state arises from the complex interplay between hemodynamic disturbances, metabolic dysregulation, and chronic low-grade inflammation, ultimately creating a permissive environment for atherosclerotic plaque formation and progression [22].

Endothelial cells exhibit remarkable phenotypic plasticity in response to their mechanical microenvironment. Laminar shear stress that exceeds 15 dyn/cm<sup>2</sup> promotes an atheroprotective phenotype by upregulating the expression of transcription factors such as Krüppel-like factor 2 (KLF2) and nuclear factor erythroid 2-related factor 2 (Nrf2), which increase endothelial nitric oxide synthase (eNOS) expression and simultaneously suppress proinflammatory pathways [23]. In contrast, regions experiencing disturbed flow patterns, particularly at arterial bifurcations and curvatures, demonstrate preferential activation of nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1). This activation leads to the increased expression of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [24]. This spatial heterogeneity in the endothelial phenotype creates distinct zones of susceptibility to atherosclerotic lesion development, with flow-disturbed regions exhibiting enhanced monocyte recruitment and subendothelial accumulation [25].

The endothelial glycocalyx, a delicate meshwork of proteoglycans, glycosaminoglycans, and plasma proteins that coats the luminal surface, serves as both a mechanosensor and a protective barrier against leukocyte adhesion [26]. Under atherosclerotic conditions, oxidative stress and inflammatory mediators degrade key glycocalyx components such as hyaluronan and heparan sulfate, exposing underlying adhesion molecules and facilitating leukocyte–endothelial interactions [27]. Advanced single-cell transcriptomic analyses have revealed remarkable heterogeneity within the endothelial compartment and have identified distinct subpopulations, including proinflammatory EC1 (characterized by ACKR1 and SELE expression) and reparative EC3 (marked by SULF1 and EDN1 expression) subsets [28]. The spatial distribution of these subpopulations within atherosclerotic lesions suggests a dynamic interplay between inflammatory and protective endothelial phenotypes during disease progression [29].

At the core of endothelial dysfunction lies the dysregulation of NO signaling, a fundamental pathway that governs vascular homeostasis [30]. NO, synthesized by eNOS through the conversion of L-arginine to L-citrulline, has potent vasodilatory, anti-inflammatory, and antithrombotic effects [31]. The atherosclerotic milieu disrupts NO bioavailability through multiple mechanisms, beginning with eNOS uncoupling, a pathological state in which eNOS transitions from producing NO to generating superoxide anions (O<sub>2</sub><sup>-</sup>) [32]. This phenomenon occurs when critical cofactors such as tetrahydrobiopterin (BH4) become oxidized or depleted or with the accumulation of the endogenous eNOS inhibitor asymmetric dimethylarginine (ADMA) [33]. The resulting oxidative environment further exacerbates NO deficiency through the rapid reaction of NO with superoxide to form peroxynitrite (ONOO<sup>-</sup>), a potent oxidant that nitrosylates proteins and damages cellular components [34]. Downstream signaling defects compound this problem: soluble guanylate cyclase (sGC) and protein kinase G (PKG) become desensitized under atherosclerotic conditions, while phosphodiesterase-5 (PDE5) overexpression accelerates cyclic guanosine monophosphate (cGMP) degradation, collectively impairing NO-mediated vasodilation [35].

Mitochondrial dysfunction represents another critical axis of endothelial impairment in atherosclerosis, contributing significantly to oxidative stress and metabolic dysregulation [36]. The electron transport chain, particularly complexes I and III, becomes a major source of reactive oxygen species (ROS) production under pathological conditions [37]. Exposure to pro-atherogenic factors such as trimethylamine N-oxide (TMAO) reduces the expression of complex I subunits while increasing oxidative modifications of complex III components, severely compromising mitochondrial respiratory capacity [38]. This metabolic crisis triggers a compensatory shift toward glycolysis that is mediated by the stabilization of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) and the upregulation of key glycolytic enzymes, despite adequate oxygen availability, a phenomenon reminiscent of the Warburg effect observed in cancer cells [39]. Concurrent defects in mitochondrial quality control mechanisms, including impaired mitophagy and excessive mitochondrial fission, lead to the accumulation of damaged, ROS-generating mitochondria, further exacerbating endothelial dysfunction [40].

Emerging therapeutic strategies aim to restore endothelial function through targeted interventions at multiple levels of these pathological pathways [41]. In addition to their lipid-lowering effects, statins improve NO bioavailability by reducing eNOS uncoupling and increasing BH4 stability [42]. Novel approaches targeting oxidative stress include the use of NADPH oxidase inhibitors and mitochondria-directed antioxidants, whereas metabolic modulators seek to restore mitochondrial function and redox balance [43]. These interventions, particularly when combined with lifestyle modifications addressing traditional cardiovascular risk factors, hold promise for overcoming the vicious cycle of endothelial dysfunction and atherosclerotic progression [13].

The intricate interplay between endothelial dysfunction, oxidative stress, and metabolic reprogramming underscores the complexity of atherosclerotic pathogenesis [22]. Recent advances in single-cell technologies and spatial omics are providing unprecedented resolution of endothelial heterogeneity within atherosclerotic lesions, offering new insights into disease mechanisms and potential therapeutic targets [44]. As our understanding of these molecular pathways deepens, the development of precision medicine approaches targeting specific aspects of endothelial dysfunction may revolutionize the prevention and treatment of atherosclerosis [45].

#### Lipoprotein metabolic abnormalities

Dysregulation of lipid metabolism occurs at the heart of atherosclerotic plaque development and progression [46, 47]. Low-density lipoprotein (LDL) particles, particularly small, dense LDLs (sdLDLs), exhibit enhanced arterial wall penetration and are prone to oxidative modification [48]. The atherogenicity of sdLDLs is due to both its susceptibility to subendothelial retention and its longer plasma half-life, resulting in a chronic inflammatory stimulus [49]. Once in the intima, LDL particles are oxidized by local ROS, perpetuating endothelial activation and monocyte recruitment [50]. Scavenger receptors on macrophages mediate the uptake of modified LDL, leading to the formation of foam cells, one of the earliest visible signs of atherosclerosis [28, 51]. Moreover, oxidized phospholipid (OxPL) signaling triggers downstream inflammatory cascades (such as NF- $\kappa$ B activation) and increased cytokine production [52, 53].

Conversely, high-density lipoprotein (HDL) facilitates reverse cholesterol transport and exerts antioxidant and anti-inflammatory effects [54]. However, HDL can become dysfunctional in diabetes, metabolic syndrome, or in the context of acute and chronic system inflammation, resulting in the loss of cholesterol efflux and antioxidative capacity [55]. Key players in HDL function loss include alterations in apolipoprotein A-I (apoA-I) and the activity of cholesterol transporters such as ABCA1 and

ABCG1 [48, 56]. Genomic studies have revealed mutations and variants in genes that encode the LDL receptor (LDLR), apolipoprotein B, PCSK9, and others that lead to familial hypercholesterolemia and polygenic dyslipidemia [57, 58]. The advent of high-throughput genotyping and polygenic risk scores offers a framework for more nuanced risk stratification [14].

In recent years, ceramide and homocysteine have attracted widespread attention as novel lipid mediators in cardiovascular diseases. Recent studies [59] have shown that these metabolites not only are involved in traditional processes such as endothelial dysfunction and oxidative stress but can also affect vascular regeneration and plaque stability by regulating the posttranslational modification of proteins (such as O-linked N-acetylglucosamine modification and O-GlcNAcylation).

During vascular repair, the transdifferentiation of fibroblasts into endothelial cells (angiogenic transdifferentiation) requires significant metabolic reprogramming. Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), the key substrate of O-GlcNAcylation, is significantly upregulated during this process. Ceramide can affect the generation of UDP-GlcNAc by regulating the sphingolipid metabolic network, whereas homocysteine can indirectly regulate this pathway by interfering with the methylation cycle. Experimental evidence has shown that enhancing the activity of the O-GlcNAcylation pathway can increase the efficiency of transdifferentiation, whereas inhibiting this pathway has the opposite effect.

Mechanistically, O-GlcNAcylation modifies the histone chaperone HIRA, promotes the de novo deposition of the noncanonical histone variant H3.3, and subsequently mediates chromatin remodeling and transcriptional activation. This metabolic–epigenetic coupling mechanism has been verified in *in vivo* lineage tracing and conditional knockout mouse models. Notably, the activation of ceramide receptors (such as sphingosine-1-phosphate receptors) can synergistically increase the activity of this pathway, whereas the endoplasmic reticulum stress induced by homocysteine can disrupt the homeostasis of UDP-GlcNAc.

These findings provide a new perspective for the treatment of atherosclerosis: targeting the ceramide/O-GlcNAcylation axis may improve vascular regenerative capacity and stabilize vulnerable plaques, thus exerting a cardioprotective effect. Future research should focus on exploring how to reprogram the plaque microenvironment by regulating this metabolic–epigenetic network.

#### Immune–inflammatory crosstalk

Atherosclerosis is now considered a chronic inflammatory disease [41]. The recruitment, activation, and differentiation of monocytes to macrophages within the vascular wall represents a central process in plaque development [60]. These macrophages undergo further polarization along a spectrum from classical M1 (proinflammatory) to alternative M2 (anti-inflammatory), as well as more recently described subsets characterized by single-cell ‘omics [61, 62]. M1 macrophages express high levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, whereas M2 and regulatory macrophages secrete anti-inflammatory cytokines such as IL-10, contributing to plaque stability [63]. Foam cell formation is a hallmark of plaque vulnerability, with the accumulation of cholesterol-laden macrophages creating a necrotic core prone to rupture [64]. ABCA1 deficiency exacerbates this process by impairing cholesterol efflux and disrupting cellular metabolism, particularly mitochondrial OXPHOS [65].

Lymphocytes add further complexity: CD4<sup>+</sup> T-helper (Th1) cells promote inflammation via IFN- $\gamma$ , while regulatory T cells (Tregs) exert protective, anti-inflammatory effects. B cells also modulate atherosclerosis, with some subsets (B1a cells, which produce natural IgM) providing protective functions and others (B2 cells) potentially promoting disease. B cells play complex dual regulatory roles in atherosclerosis, with their functional

heterogeneity being increasingly elucidated [28]. Protective B1a cells play a crucial role by secreting natural IgM antibodies (e.g., the oxidation-specific E06 antibody), which not only neutralize oxidized low-density LDL (oxLDL) and reduce macrophage foam cell formation but also secrete the anti-inflammatory cytokine IL-10 to maintain plaque microenvironment homeostasis. In contrast, pathogenic B2 cells activate Th1 cells through antigen presentation, promoting the secretion of proinflammatory IFN- $\gamma$  and exacerbating plaque inflammation [66]. Recent studies have identified a unique T-bet<sup>+</sup> B cell subset characterized by CD11c and CXCR3 expression that produces proatherogenic IgG2c antibodies and sustains chronic inflammation through the formation of tertiary lymphoid structures [67]. Clinical evidence indicates that an imbalance in the B1a/B2 cell ratio within atherosclerotic plaques is closely associated with plaque stability, whereas elevated circulating T-bet<sup>+</sup> B cell levels may predict an increased risk of cardiovascular events [68]. These findings deepen our understanding of B cell involvement in atherosclerosis and provide novel insights for developing immunomodulatory therapies targeting specific B cell subsets.

Recent single-cell studies have revealed remarkable cellular heterogeneity in coronary atherosclerosis [28]. Endothelial cells can be distinctly classified into proinflammatory (EC1, ACKR1<sup>+</sup>-SELE<sup>+</sup>) and reparative (EC3, SULF1<sup>+</sup>EDN1<sup>+</sup>) subpopulations, with EC1 increasing by 40% and EC3 decreasing by 35% in lesion areas [29]. Macrophages transcend the traditional M1/M2 dichotomy, revealing proinflammatory (M $\phi$ 1, CCL3<sup>+</sup>CCL4<sup>+</sup>), reparative (M $\phi$ 2, AREG<sup>+</sup>EREG<sup>+</sup>), and proliferative (M $\phi$ 4, MKI67<sup>+</sup>TOP2A<sup>+</sup>) subsets, with M $\phi$ 1 accounting for 63% of plaque macrophages [61]. Vascular smooth muscle cells exhibit dynamic phenotypic switching from contractile (VSMC2) to synthetic (VSMC1) and proliferative (VSMC4, FABP4<sup>+</sup>MT1A<sup>+</sup>) phenotypes; conversely, compared with quiescent cells, VSMC4 cells exhibit 2.5-fold higher mitochondrial ROS levels ( $P < 0.001$ ) [44]. This imbalance in cellular subpopulations constitutes the fundamental cellular basis for atherosclerotic progression.

#### Vascular remodeling and plaque complications

Vascular remodeling, encompassing both adaptive and maladaptive responses, plays a crucial role in determining plaque fate [69]. The degeneration of the fibrous cap due to heightened MMP and ADAMTS-7 activity leads to cap thinning and an increased risk of plaque rupture, the chief cause of acute coronary events [70]. The interplay of smooth muscle cells (SMCs), which transition from a contractile to a synthetic phenotype under pathological cues, is integral to matrix remodeling and repair [71, 72].

Vascular calcification, a critical complication of atherosclerosis, occurs through the transdifferentiation of smooth muscle cells into osteoblast-like cells, a process that is precisely regulated by a hierarchical signaling network. The BMP-2/4-Smad1/5/8 axis and Runx2/Osterix transcriptional cascade [73, 74] form the core regulatory modules that coordinately activate the expression of osteogenic markers such as alkaline phosphatase and osteocalcin. In the pathological microenvironment, Wnt3a/7b- $\beta$ -catenin signaling promotes matrix remodeling [75, 76], and Notch-Jagged1 interactions increase Runx2 transcriptional activity, whereas inflammatory pathways [77, 78], including IL-6/STAT3 and TNF- $\alpha$ /NF- $\kappa$ B establish positive feedback loops that tightly link vascular inflammation with the calcification process. Concurrently, metabolic reprogramming driven by HIF-1 $\alpha$  stabilization and SIRT1 inactivation [78] can alter cellular energy metabolism and epigenetic regulation, further exacerbating this phenotypic transformation. The resulting microcalcifications are highly vulnerable because of localized mechanical stress [79] from hydroxyapatite crystals, hypoxic inflammation aggravated by insufficient neovascularization, and metabolic imbalance arising from increased glycolytic demand. This multilayered pathogenic mechanism explains why calcified plaques often progress despite

targeted therapies, underscoring the need for combinatorial strategies that simultaneously address both mineralization processes and microenvironmental stressors [80].

Beyond the mechanical factors of vascular remodeling, recent studies have revealed significant effects of chronobiological characteristics on the occurrence of plaque complications. In the ISCHEMIA trial, Stone et al. [81] demonstrated that the incidence of acute coronary events exhibits distinct diurnal fluctuations, with a nearly 40% higher risk during the early morning hours (6:00–12:00) than during other time periods. This phenomenon is closely associated with sympathetic nervous system activation, oscillations in endothelial function, and circadian regulation of inflammatory responses. Enhanced sympathetic tone in the early morning leads to a morning blood pressure surge and altered vascular shear stress, whereas the peak secretion of catecholamines promotes smooth muscle cell contraction and the release of matrix-degrading enzymes via  $\beta$ -adrenergic receptor pathways, collectively compromising the structural integrity of the fibrous cap [82, 83].

Diurnal variations in endothelial function further exacerbate plaque instability. Studies have shown that eNOS activity and NO bioavailability [84, 85] are significantly reduced in the early morning, while the levels of oxidative stress markers (e.g., superoxide anions) are elevated. This activity is directly linked to the circadian regulation of endothelial cell (EC) function by clock genes (e.g., CLOCK/BMAL1). Additionally, the rhythmic upregulation of adhesion molecules [86] (VCAM-1 and ICAM-1) promotes the localized recruitment of monocytes to plaque sites, accelerating inflammatory progression.

From a clinical perspective, subgroup analyses of the ISCHEMIA trial revealed that although the severity of ischemia was not significantly associated with plaque rupture risk, the extent of coronary artery disease (e.g., three-vessel disease or proximal LAD stenosis) was strongly correlated with the morning peak in events. These findings suggest that anatomically high-risk plaques may be more susceptible to circadian stressors. Notably, adjusting the timing of antiplatelet therapy [87] (e.g., administering P2Y12 inhibitors at bedtime) may reduce risk by suppressing the morning peak in platelet activity, although this hypothesis requires further validation through randomized trials.

These mechanisms are summarized in Table 1.

#### Gut microbiota-derived metabolites in atherosclerosis

The role of gut microbiota-derived metabolites in the pathogenesis of atherosclerosis has garnered increasing attention in recent years. As key mediators of host–microbiome interactions, these metabolites regulate cardiovascular homeostasis through complex molecular networks. Among them, TMAO represents the most extensively studied microbial metabolite with well-characterized pathophysiological mechanisms.

The biosynthesis of TMAO is initiated by the microbial metabolism of dietary nutrients such as choline and *L*-carnitine. Specific bacterial taxa expressing CutC/D lyases [17] convert these precursors into trimethylamine (TMA), which is subsequently oxidized by hepatic flavin monooxygenase 3 (FMO3) to form TMAO. This process is modulated by both host genetic factors and gut microenvironmental conditions. Notably, patients with renal impairment often exhibit TMAO accumulation due to impaired excretion, creating a unique “gut–liver–kidney” metabolic axis dysfunction. Multiple population studies [88] have demonstrated significant positive associations between plasma TMAO levels and atherosclerotic burden, which persist after adjustment for traditional risk factors.

At the molecular level, TMAO promotes atherosclerosis progression through multiple pathways. Its disruption of cholesterol metabolism manifests as dual effects: the inhibition of CYP7A1-mediated bile acid synthesis [17, 89] and the downregulation of hepatic LDL receptor expression; these processes

**Table 1.** Molecular and cellular mechanisms in coronary atherosclerosis.

Pathological Process	Key Features & Cells	Representative Biomarkers/ Genes	Clinical Relevance
Endothelial Dysfunction	↓NO, ↑VCAM-1/ICAM-1, eNOS uncoupling, increased ROS; Endothelial cells	NO, eNOS, BH4, VCAM-1, ICAM-1	Initiation of atherogenesis, plaque formation
Lipid Dysregulation	↑LDL/sdLDL infiltration, ↓HDL efflux, OxPL production; SMCs, macrophages	LDL-C, sdLDL, oxLDL, HDL, ApoA-I, ABCA1/G1	Plaque progression, vulnerability
Immune-Inflammatory Activation	Monocyte recruitment, M1/M2 imbalance, foam cell formation, T/B cell involvement	TNF- $\alpha$ , IL-1 $\beta$ , IL-6, hs-CRP, ABCA1, NLRP3	Chronic inflammation, plaque instability
Vascular Remodeling, Calcification	SMC phenotype switch, matrix degradation, neointimal hyperplasia, microcalcification	MMP-9, ADAMTS-7, BMP-2, Runx2	Plaque rupture, acute coronary events

*NO* nitric oxide, *ROS* reactive oxygen species, *eNOS* endothelial nitric oxide synthase, *OxPL* oxidized phospholipids, *SMCs* smooth muscle cells, *LDL-C* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein, *ApoA-I* apolipoprotein A-I, *MMP* matrix metalloproteinase.

collectively increase circulating cholesterol levels. Within the vascular wall, TMAO alters the balance between the ABCA1/G1 and CD36/SR-A1 pathways, impairing macrophage cholesterol efflux while increasing oxidized LDL uptake, thereby accelerating foam cell formation. Endothelial dysfunction represents another critical mechanism. TMAO reduces NO bioavailability by modulating eNOS phosphorylation patterns and inducing oxidative stress [90] while also upregulating the expression of adhesion molecules to promote monocyte recruitment. Furthermore, TMAO enhances platelet aggregability by activating calcium signaling pathways [91], providing a pathological substrate for thrombus formation.

These mechanistic insights have inspired novel therapeutic strategies targeting the gut microbiota. Dietary modifications (e.g., a Mediterranean diet) can significantly reduce TMAO levels by reshaping microbial composition and metabolic output [92]. Probiotic colonization [91] not only inhibits TMA production but also enhances gut barrier integrity. In drug development, emerging compounds such as FMO3 inhibitors and bile acid receptor modulators have demonstrated promising cardioprotective effects in preclinical studies. These advances open new avenues for precision medicine in atherosclerosis prevention and treatment.

## CLASSIC THERAPEUTIC STRATEGIES FOR CORONARY ATHEROSCLEROSIS

### Lipid-lowering therapies

Statins (HMG-CoA reductase inhibitors) form the backbone of dyslipidemia management; they can substantially reduce LDL-C levels and the risk of cardiovascular events in diverse populations [93, 94]. Their pleiotropic effects, including anti-inflammatory and endothelial-stabilizing properties, reinforce their clinical value [95]. However, the use of statins alone may be insufficient in many patients, familial hypercholesterolemia is associated with only a partial LDL-C response, and up to 10%–20% of patients experience side effects or resistance [96]. Ezetimibe offers modest (~18% additional) LDL-C reduction by inhibiting intestinal cholesterol absorption and has shown additive event reduction, as evidenced by the IMPROVE-IT trial. Bile acid sequestrants, niacin, and fibrates serve as adjuncts but are limited by tolerability and inconsistent efficacy in terms of event reduction [97].

The introduction of PCSK9 inhibitors (alirocumab and evolocumab) marked a paradigm shift [98]. These monoclonal antibodies promote hepatic LDLR recycling, resulting in an additional 50%–60% reduction in LDL-C levels compared with statin therapy [99]. Real-world use is affected by high drug costs, injection requirements, and insurance barriers, particularly in resource-constrained settings [100]. Inclisiran, a long-acting siRNA against PCSK9, promises twice-annual dosing with robust efficacy, potentially increasing patient compliance [101].

### Antiplatelet and anticoagulant agents

Antiplatelet therapy is indispensable for secondary prevention after acute coronary syndrome or revascularization [102]. Standard dual antiplatelet therapy (DAPT) combines aspirin with a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor [103]. Ticagrelor and prasugrel offer superior event reduction compared with clopidogrel but are associated with increased bleeding risk [104]. Individual patient metabolism and pharmacogenomics (e.g., CYP2C19 loss-of-function alleles) significantly influence the response, particularly in East Asian populations, prompting the emergence of genotype-guided therapy algorithms [105].

Direct oral anticoagulants (DOACs), including rivaroxaban and apixaban, have shown efficacy in select populations, notably in the secondary prevention of peripheral artery disease, as per the COMPASS trial, although with a tradeoff in bleeding rates [106, 107].

On the basis of the two pivotal REDUCE-IT and EVAPORATE-FFRCT studies, the role of icosapent ethyl (IPE) in cardiovascular risk management has expanded from demonstrating clinical endpoint benefits to providing validation at the physiological mechanism level. The REDUCE-IT trial demonstrated that IPE, when added to statin therapy, significantly reduced the risk of the primary composite endpoint (cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization) in patients with hypertriglyceridemia [108]. The concordance between investigator-reported and centrally adjudicated events was remarkably high ( $\kappa = 0.89\text{--}0.90$ ), confirming the robustness of these findings [109].

The EVAPORATE-FFRCT study provided the first evidence using coronary computed tomography angiography-derived fractional flow reserve (FFRCT) that IPE improves coronary physiology. After 18 months of treatment, distal segment FFRCT values were significantly better in the IPE group than in the placebo group ( $-0.01 \pm 0.09$  vs.  $-0.09 \pm 0.12$ ,  $P = 0.03$ ), with trans-lesional FFRCT ( $\Delta$ FFRCT) also showing improvement ( $P = 0.054$ ) [110]. These discoveries offer new insights into the anti-ischemic mechanisms of IPE, suggesting that it stabilizes plaques and improves hemodynamics, thereby early and sustainably delaying the deterioration of coronary function [108, 110].

FFRCT, as a noninvasive physiological assessment tool, was employed here for the first time to evaluate drug efficacy, establishing a new paradigm for future cardiovascular drug development. In summary, IPE not only exerts pleiotropic effects through triglyceride reduction and plaque burden modification, but it also has beneficial effects on coronary physiology, further reinforcing its clinical value in the management of atherosclerosis [108, 110].

### Anti-inflammatory therapies

The anti-inflammatory actions of statins, while beneficial, may not fully address the inflammatory burden in high-risk individuals. The

**Table 2.** Contemporary and emerging therapies for coronary atherosclerosis.

Therapy/class	Molecular target/mechanism	Key trials	Main efficacy outcomes	Limitations/notes
Statins	HMG-CoA reductase (cholesterol synthesis)	JUPITER, WOSCOPS	↓LDL-C 25%–50%, ↓MACE	Myopathy, residual risk
PCSK9 inhibitors (Alirocumab)	PCSK9, ↓LDL receptor recycling	FOURIER, ODYSSEY	↓LDL-C ~ 60%, ↓Events	High cost, injection
Inclisiran (siRNA)	PCSK9 gene silencing	ORION	↓LDL-C ~ 50%	Long-term safety in progress
ANGPTL3 inhibitors	Triglyceride and LDL reduction	ELIPSE HoFH	↓LDL-C, ↓TG in HoFH	Specialty use
Canakinumab	IL-1 $\beta$ (inflammation)	CANTOS	↓hs-CRP, ↓recurrent MI	Infection risk, cost
Colchicine	Anti-inflammation (NLRP3)	COLCOT, LoDoCo2	↓MACE	GI intolerance, rare myopathy
SGLT2 inhibitors	Renal glucose excretion, anti-inflammatory	EMPA-REG, DECLARE	↓CV events, ↓HF hospitalization	Genital infections, rare DKA
GLP-1 RAs	GLP-1 receptor, metabolic modulation	LEADER, SUSTAIN	↓CV events, weight loss	GI symptoms, injection
Gene therapies (CRISPR, ASOs)	Genetic editing/silencing	Early clinical	Durable LDL/TG lowering	Long-term safety unproven
<i>LDL-C</i> low-density lipoprotein cholesterol, <i>MACE</i> major adverse cardiovascular events, <i>HoFH</i> homozygous familial hypercholesterolemia, <i>MI</i> myocardial infarction, <i>TG</i> triglycerides, <i>hs-CRP</i> high-sensitivity C-reactive protein, <i>DKA</i> diabetic ketoacidosis, <i>RA</i> receptor agonist.				

CANTOS trial highlighted IL-1 $\beta$  inhibition (canakinumab) as effective for reducing secondary events in patients with persistently elevated inflammatory markers [111]. Cost, infection risk, and the absence of LDL-C-lowering abilities limit widespread application [13]. Emerging agents targeting the IL-6 pathway (ziltivekimab) and the NLRP3 inflammasome (MCC950) are in late-phase clinical development, with preclinical data supporting robust modulation of vascular inflammation [112, 113]. Several natural compounds, such as andrographolide, have been shown to have anti-inflammatory, antioxidative, and lipid-lowering effects in both preclinical and clinical studies, suggesting their potential as adjunctive or alternative therapies for atherosclerosis [114].

In recent years, RNA-based therapies targeting apolipoprotein C-III (APOC3) have emerged as novel strategies for regulating the metabolism of triglyceride-rich lipoproteins (TRLs). The core mechanism of these therapies involves the use of antisense oligonucleotides (ASOs) or small interfering RNAs (siRNAs) to mediate mRNA degradation, achieving specific inhibition of hepatic APOC3 synthesis, with reductions of more than 80%. This targeted suppression disrupts the inhibitory effect of APOC3 on lipoprotein lipase (LPL), the key enzyme responsible for hydrolyzing TRLs, thereby accelerating the clearance of chylomicrons and low-density lipoprotein (VLDL) remnants [115, 116].

Clinical studies have demonstrated the efficacy of APOC3 RNA therapy in improving lipid profiles. For example, the use of volanesorsen, a second-generation ASO, reduced plasma triglyceride levels by 70%–80% in patients with severe hypertriglyceridemia. Additionally, the therapy significantly decreased the levels of oxidized phospholipids (OxPLs) in LDL particles, a class of pro-atherogenic lipids associated with increased cardiovascular risk [117].

Single-cell RNA sequencing has further elucidated the immunomodulatory effects of APOC3 ASOs. In atherosclerotic plaques, these therapies selectively downregulate the expression of proinflammatory M1 macrophages (CD80<sup>+</sup>CD86<sup>+</sup> subsets) while preserving reparative TREM2<sup>+</sup> macrophage populations. This selective regulation of macrophage polarization represents a unique advantage over traditional lipid-lowering drugs, which often lack direct immunomodulatory effects [28].

Notably, APOC3 inhibition is associated with a gene-dose-dependent response. Patients carrying loss-of-function variants in the APOC3 gene exhibit greater cardiovascular benefits from therapy, highlighting the importance of genetic background in treatment efficacy [118].

Despite these advances, current APOC3 RNA therapies face limitations. Injection-site reactions occur in 15%–20% of patients, and the need for hepatic-targeted delivery systems remains critical to minimize off-target effects. To address these challenges, next-generation GalNAc-conjugated ASOs have been developed. These conjugates enhance liver-specific uptake by targeting asialoglycoprotein receptors on hepatocytes, enabling monthly dosing regimens and improving treatment convenience [119]. These developments position APOC3 RNA therapy as a promising option for patients with familial chylomicronemia syndrome or severe hypertriglyceridemia, offering a precision medicine approach to modulating TRL metabolism and reducing cardiovascular risk.

## DIAGNOSTIC AND THERAPEUTIC INNOVATIONS IN CORONARY ATHEROSCLEROSIS

Multi-modal imaging biomarkers for early detection

The accurate detection and characterization of atherosclerotic plaques has advanced remarkably in the past decade, driven by new imaging technologies and integrated biomarker approaches. Coronary computed tomography angiography (CCTA) and cardiac magnetic resonance imaging (CMR) now enable the

comprehensive visualization of plaque burden, composition, and vascular remodeling [120, 121].

Importantly, CCTA can noninvasively identify high-risk features such as a low attenuation core, positive remodeling, and spotty calcification, which are predictive of future adverse cardiovascular events [122]. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) provide ultrahigh-resolution images of the arterial wall, allowing the direct measurement of fibrous cap thickness and lipid pool size, the primary determinants of plaque vulnerability [122, 123]. OCT, in particular, can detect features such as thin-cap fibroatheromas and microcalcifications [124, 125], which are closely associated with plaque rupture and thrombosis.

**Targeted therapies: precision breakthroughs from molecular mechanisms to clinical translation**

Recent breakthroughs in single-cell transcriptomics have revolutionized targeted therapeutic strategies for coronary atherosclerosis. This seminal work [126] systematically characterized >105,000 cells from human cardiac arteries, identifying 10 major cell types with 25 functionally distinct subpopulations. Vascular smooth muscle cells (VSMCs), which constitute the predominant arterial wall population (31.0%–33.7%), exhibited four transcriptionally defined subsets: VSMC1 (FN1<sup>+</sup>VCAN<sup>+</sup>, coronary artery-specific synthetic phenotype), VSMC2 (CNN1<sup>+</sup>DES<sup>+</sup>, contractile phenotype), VSMC3 (CYLT1<sup>+</sup>DPT<sup>+</sup>, large artery-specific synthetic phenotype), and VSMC4 (FABP4<sup>+</sup>MT1A<sup>+</sup>, proliferative/migratory phenotype) [29]. This refined classification elucidates artery-specific pathophysiology, exemplified by the 2.1-fold expansion of αSMA<sup>+</sup>FABP4<sup>+</sup> VSMC4 cells in atherosclerotic coronary arteries [44]; this characteristic highlights their potential as therapeutic targets for vascular remodeling.

The inflammatory landscape reveals remarkable macrophage heterogeneity. Single-cell RNA sequencing revealed four macrophage subsets, with Mφ1 (CCL3<sup>+</sup>CCL4<sup>+</sup>) and Mφ2 (AREG<sup>+</sup>EREG<sup>+</sup>) demonstrating potent proinflammatory properties, while Mφ3 (TXNIP<sup>+</sup>CD14<sup>+</sup>) maintained a quiescent state [13]. Notably, Mφ1/Mφ2 populations expanded to 58% of lesional macrophages in inflammatory coronary disease and were strongly correlated with intraplaque IL-1β levels ( $r = 0.72$ ,  $P < 0.001$ ) [61]. These findings mechanistically explain the differential treatment effects observed in the CANTOS trial, where canakinumab specifically benefited patients with elevated hs-CRP levels by selectively depleting inflammatory macrophage subsets [13].

EC heterogeneity emerges as another critical determinant of disease progression. Four EC subpopulations were identified, with EC1 (ACKR1<sup>+</sup>CCL14<sup>+</sup>) displaying the most atherogenic profile through ICAM1/VCAM1-ITGB2-mediated monocyte recruitment. Clinical specimens demonstrated a 37% increase in EC1 and a 52% reduction in protective EC3 (SULF1<sup>+</sup>EDN1<sup>+</sup>) in atherosclerotic lesions, which correlated with impaired endothelial barrier function (64% decrease in transendothelial electrical resistance) [19]. This imbalance suggests that restoring EC subpopulation homeostasis may represent a novel therapeutic paradigm.

These discoveries have catalyzed a paradigm shift from pancellular to subset-specific interventions. In lipid management, PCSK9 inhibitors not only reduce LDL-C but also decrease VSMC4 proportions from 15.3% to 9.8% according to scRNA-seq analysis [11]. Similarly, anti-ICAM1 monoclonal antibodies (e.g., alicaforsen) reduced plaque inflammation by 12.7% in phase II trials. Most promisingly, FABP4-targeted siRNA nanoparticles achieved 41% plaque regression in animal models while sparing normal VSMC subsets, as confirmed by single-cell tracking [127].

These contemporary and emerging therapies are summarized in Table 2.

**Gene- and cell-based therapies**

Stem cell therapy represents a promising regenerative approach for atherosclerotic regression that aims to restore endothelial

integrity, promote neovascularization, modulate immune-inflammatory responses, and facilitate plaque stabilization. The most extensively investigated cell types include endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cell (iPSC)-derived vascular cells, each of which contribute to vascular repair through distinct mechanisms.

Stem cells mediate atherosclerotic regression through multiple coordinated mechanisms. EPCs and iPSC-derived endothelial cells enhance reendothelialization and restore nitric oxide bioavailability, thereby improving endothelial function and reducing plaque vulnerability. MSCs exert potent immunomodulatory effects by suppressing proinflammatory macrophage polarization and promoting regulatory T cell expansion, as revealed by single-cell RNA sequencing studies [28]. Additionally, stem cells secrete paracrine factors that inhibit smooth muscle cell apoptosis, reduce matrix metalloproteinase activity, and increase fibrous cap thickness [44]. Furthermore, engineered stem cells can increase cholesterol efflux from foam cells through upregulating the expression of ABCA1 and ABCG1 transporters, which reduces lipid accumulation in atherosclerotic plaques.

Preclinical studies have demonstrated significant therapeutic potential. Intravenous or local delivery of MSCs or EPCs attenuates plaque progression and induces regression in atherogenic mouse models, with MSC transplantation reducing plaque size by up to 40% and increasing collagen content in ApoE<sup>-/-</sup> mice [128]. Clinical trials have shown that autologous EPC infusion improves endothelial function and reduces ischemic symptoms in patients with advanced atherosclerosis [29]. However, challenges remain regarding cell engraftment, survival, and potential maldifferentiation.

**Nanotechnology and biomaterials**

Innovations in nanotechnology and biomaterials are revolutionizing both drug delivery and vascular intervention. Nanoparticles, functionalized with targeting ligands or antibodies, can be used to deliver statins, siRNAs, or anti-inflammatory agents directly to plaque-resident macrophages, reducing off-target effects and increasing local efficacy [129, 130]. Liposomal delivery vehicles provide a platform for the sustained, controlled release of therapeutics [131].

Bioresorbable scaffolds (e.g., magnesium-based stents) and hydrogel matrices have been introduced to combine the mechanical benefits of vascular scaffolding with the promotion of native endothelialization, the inhibition of neointimal hyperplasia, and the release of bioactive factors supporting tissue healing. Current research is focused on optimizing scaffold composition, degradation kinetics, and immune responses to minimize adverse events such as late thrombosis [131].

Rotational atherectomy (RA) serves as a crucial adjunctive technique for managing severely calcified coronary lesions that are resistant to conventional balloon angioplasty. By utilizing a high-speed diamond-coated burr rotating at 140,000–180,000 rpm, RA employs the principle of “differential cutting” to selectively ablate rigid calcific plaques while preserving elastic vascular tissue, thereby improving vessel compliance and facilitating subsequent stent deployment [132].

This technique is particularly valuable in cases of circumferential calcification (grade IV), balloon-uncrossable or balloon-undilatable lesions, and challenging anatomies, including ostial and angulated segments [133]. Clinical evidence has demonstrated that RA significantly improves procedural success rates in complex calcified lesions, although long-term outcomes remain variable across studies. Meta-analytical data from Kato et al. demonstrated that CT-derived extracellular volume (ECV) quantification provides valuable insights into myocardial fibrosis patterns associated with calcific coronary disease, with pooled ECV values significantly elevated in aortic stenosis (31.9% [95% CI: 30.2%–33.8%]) and cardiac amyloidosis (48.9% [95% CI: 44.5%–53.3%]) cohorts

**Table 3.** Diagnostic modalities in coronary atherosclerosis.

Modality	Information provided	Sensitivity/specificity	Typical clinical use
CCTA	Non-invasive anatomic plaque imaging	High/High	Screening, risk stratification
IVUS	Plaque burden, composition	Very high/Very high	Interventional planning, research
OCT	Cap thickness, lipid arc, microcalcification	High/Excellent	Plaque assessment, PCI guidance
PET (18F-FDG/NaF)	Inflammation, microcalcification	High/Moderate	Research, risk prediction
AI/ML-based image analysis	Automated risk prediction	Increasing	Screening, phenotyping

*CCTA* coronary computed tomography angiography, *IVUS* intravascular ultrasound, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention, *PET* positron emission tomography, *ML* machine learning.

compared with controls (28.5% [95% CI: 27.3%–29.7%]) [134]. This advanced imaging capability enhances patient selection for RA by identifying concomitant myocardial pathology that may influence procedural outcomes.

Exercise training and the mediterranean diet: synergistic cardiovascular protection

Exercise training and a Mediterranean diet demonstrate significant synergistic effects on cardiovascular protection, a phenomenon validated by multiple clinical studies. The PREDIMED study, which followed 7447 high-risk individuals over the long term, revealed that a Mediterranean diet supplemented with extra virgin olive oil or nuts reduced the incidence of major cardiovascular events by 28%–31% [135]. This protective effect stems from multilevel complementary mechanisms between exercise-induced physiological adaptations and the diet's bioactive components [136].

In regulating vascular endothelial function, exercise training promotes the expression and activation of eNOS through periodic blood flow shear stress [136], whereas polyphenols in the Mediterranean diet inhibit NADPH oxidase activity, thereby reducing oxidative degradation of nitric oxide [135].

Metabolic regulation highlights another dimension of this synergy: acute exercise activates the AMPK pathway to promote GLUT4 translocation and glucose uptake (a rapid response to energy demands) [136], whereas the Mediterranean diet's monounsaturated fatty acids and polyunsaturated fatty acids regulate PPAR $\gamma$  nuclear receptor activity to improve long-term insulin sensitivity and fat metabolism [135].

Anti-inflammatory mechanisms also reveal complex interactions between exercise, diet, and TCM. Exercise induces the release of muscle-derived cytokines such as IL-6, which exerts anti-inflammatory effects by promoting lipid metabolism and reducing chronic systemic inflammation [136] (a phenomenon known as "exercise-induced anti-inflammation"). Moreover, Mediterranean diet polyphenols regulate the gut microbiota composition and inhibit the NF- $\kappa$ B signaling pathway, further suppressing proinflammatory cytokine production [135].

The integrated traditional Chinese and Western medicine (TCM-WM) approach has also demonstrated favorable outcomes [137] in the treatment of cardiovascular diseases. Western medicine primarily focuses on lipid regulation (statins/PCSK9 inhibitors), anti-inflammatory therapy (e.g., colchicine), and antiplatelet treatment, whereas traditional Chinese medicine adopts syndrome differentiation-based treatments such as promoting blood circulation to remove blood stasis (e.g., Xuefu Zhuyu Decoction) and resolving phlegm to unblock collaterals (e.g., Gualou Xiebia Banxia Decoction) [138].

This synergistic approach improves endothelial function, stabilizes plaques, and reduces cardiovascular events (e.g., Shexiang Baoxin Pills have been shown to lower the risk of major adverse cardiovascular events (MACE) by 26.9%) [137]. Evidence-based studies have indicated that combined TCM-WM therapy significantly improves lipid control rates (e.g., Xuezhikang reduces

LDL-C levels by 20.2%) [139], alleviates angina symptoms (with a 1.25-fold increase in overall efficacy), and maintains a favorable safety profile (with a lower incidence of adverse reactions than statin monotherapy does).

These findings underscore the importance of a holistic, integrated approach to cardiovascular prevention. By combining the structured, evidence-based frameworks of Western lifestyle medicine (exercise and diet) with the personalized, holistic wisdom of TCM (herbs and mind-body practices), we can develop more effective, individualized strategies for reducing cardiovascular risk.

The diagnostic modalities used in coronary atherosclerosis are summarized in Table 3.

## TRANSLATIONAL AND CLINICAL CHALLENGES IN CORONARY ATHEROSCLEROSIS

Realizing the promise of precision medicine

Although molecular profiling and polygenic risk scoring have improved our understanding of individual risk, significant limitations remain. Many genetic variants identified through GWAS account for a small fraction of heritability; the clinical utility of polygenic risk scores (PRS) is hampered by differences in allele frequencies, effect sizes, and linkage disequilibrium across populations [140]. Current PRS models often perform suboptimally in non-European ancestry groups, exacerbating health disparities [140, 141]. Furthermore, most genetic loci associated with CAD have modest effect sizes, making clinical actionability challenging outside extreme outliers [142].

Moreover, the integration of multiomics data, spanning genomics, epigenomics, transcriptomics, proteomics, and metabolomics, into actionable clinical workflows is hampered by analytical complexity, high computational demands, and a lack of standardized thresholds for interpretation [143]. Deep learning and neural networks can extract hidden relationships but often generate "black box" predictions with limited mechanistic explainability, constraining clinical trust and regulatory approval [144].

Clinical practice gaps and health system challenges

The translation of diagnostic and therapeutic advances from evidence-based guidelines into routine clinical practice faces significant hurdles and contributes to persistent residual cardiovascular risk. These challenges primarily manifest in three critical areas: the identification of high-risk phenotypes, the gap between evidence and practice, and the accessibility of innovative therapies.

A foremost challenge in optimizing coronary atherosclerosis management is the precise identification of patients with the "rapid progression" phenotype. These individuals exhibit accelerated plaque growth and increased vulnerability despite controlling standard risk factors [145]. Current risk stratification tools are largely reliant on traditional factors and anatomical stenosis

severity and often fail to capture the dynamic biological processes driving rapid disease advancement. This phenotyping gap impedes the timely initiation of intensive preventive strategies, leading to potential undertreatment of high-risk individuals. The integration of artificial intelligence with multiomics data holds promise for defining dynamic risk trajectories and identifying rapid progressors through biomarkers such as specific proteomic signatures or plaque activity on imaging, enabling preemptive intervention before clinical events occur [146].

A significant chasm persists between established evidence and its application in routine care, undermining the potential benefits of proven therapies. For example, despite strong guideline endorsements for noninvasive functional assessment using CT-derived fractional flow reserve (FFRCT) in patients with stable chest pain [147], its real-world adoption remains limited because of factors such as limited access to technology, reimbursement barriers, and physician familiarity with traditional pathways. Conversely, the overuse of revascularization in patients without demonstrated ischemia, contrary to the findings of trials such as ISCHEMIA [148], highlights the persistence of outdated practice patterns. This evidence-practice gap is exacerbated by delays in updating local protocols and the lack of integrated decision-support systems within electronic health records, ultimately resulting in suboptimal patient outcomes and inefficient resource allocation [148].

The profound disparity in access to high-cost innovative therapies, driven by economic and health care system barriers, represents a major challenge to equitable care. Potent agents such as PCSK9 inhibitors and novel anti-inflammatory biologics face significant accessibility constraints because of their high upfront costs, particularly in resource-constrained settings and for under-insured populations [149]. This creates a “two-tiered” system of cardiovascular care, where life-saving treatments are not equally available to all patients. Furthermore, conventional health economic models often struggle to capture the long-term value of these innovations, leading to restrictive reimbursement policies. The development of sustainable financing mechanisms, such as outcome-based agreements [149] and the implementation of tiered pricing strategies, are crucial steps toward ensuring that scientific breakthroughs can be translated into broad patient benefits without exacerbating global health inequities.

#### Heterogeneity and resistance to therapy

Biological and environmental heterogeneity drive divergent responses to therapy. Statin resistance, for example, can originate from pharmacogenomic factors, such as gene variants, or can be triggered by a variety of factors, such as inflammatory cytokines [150, 151]. Notably, IL-1 $\beta$  interferes with sterol regulatory element-binding protein cleavage-activating protein activity. PCSK9 inhibition nonresponse or partial response may be related to high levels of oxidized lipids, chronic inflammation, or the presence of lipoproteins (a) [152]. The benefit of an IL-1 $\beta$  inhibitor appears to be confined to those with elevated hs-CRP levels, whereas others result in little or no risk reduction and may be exposed to infection risk without clear gain [153].

Adaptive resistance can also be seen with long-term metabolic modulators (e.g., increased renin-angiotensin activation after SGLT2 inhibition) and with regenerative cell therapies owing to poor engraftment, immune rejection, or loss of function over time. Addressing these challenges necessitates biomarker-driven patient selection, combination therapy strategies, and longitudinal phenotyping [142].

#### FUTURE DIRECTIONS

**Paradigm shift in myocardial infarction pathology**  
Research on the pathogenesis of myocardial infarction has evolved beyond the macroscopic events of coronary

atherosclerotic plaque rupture and acute thrombosis. Current frontiers are focused on the intricate cellular and systemic interactions underlying the disease process.

A key priority will be to decipher cell–cell communication and the remodeling of the cardiac microenvironment. Research will aim to elucidate how various cell types within the infarct zone, such as cardiomyocytes, immune cells, fibroblasts, and vascular endothelial cells, exchange information via exosomes, cytokines, and metabolites under ischemic stress [154, 155]. Through single-cell multiomics analysis of diseased human hearts and subsequent validation in mouse models, Amrute et al. reported that CCR2<sup>+</sup> macrophages drive cardiac fibrosis by instructing fibroblasts to adopt a pathogenic state via IL-1 $\beta$  signaling, a process that can be therapeutically targeted to alleviate fibrosis and improve heart function [156]. Tombor et al. reported a novel immunoregulatory cardiac EC induced by myocardial infarction that activates T cells via IFN- $\gamma$ . They further demonstrated that blocking this pathway enhances postinfarction cardiac recovery [157]. Li et al. identified a CD248<sup>+</sup> fibroblast subset that drives cardiac fibrosis via an ACKR3-dependent mechanism to retain and activate T cells; this pathological interaction can be targeted with antibodies or CAR-T-cell therapy to improve cardiac function [158].

#### Future perspectives on therapy

Synthetic biological advances are enabling the creation of designer lipoproteins (e.g., sHDL) with vastly increased cholesterol efflux and anti-inflammatory activity, opening a novel therapeutic domain for plaque regression and stabilization [159]. mRNA therapeutics, already validated in vaccine development, are being engineered to induce transient, targeted downregulation of inflammatory cytokines (e.g., IL-1 $\beta$  and IL-6), thus offering the controlled modulation of immune responses with rapid adaptation to population- or variant-specific needs [160].

Regenerative cell therapies stand at the brink of scalability, underpinned by breakthroughs in iPSC differentiation, organoid engineering, and exosome-based paracrine factor delivery [161, 162]. Advances in biomaterials and tissue scaffolding support not only vascular healing postrevascularization but also myocardial repair after infarction [152, 161].

CRISPR-Cas9 technology has gained significant attention in cardiac research and has advanced our understanding of both its physiology and pathology [163–166]. Furthermore, the CRISPR-Cas9-mediated inactivation of PCSK9, ANGPTL3, or Lp(a) in hepatocytes has been demonstrated to decrease long-term LDL-C, triglyceride, and Lp(a) levels in animal models, with early-phase human studies underway [18, 167, 168]. The successful deployment of these “one-and-done” therapies will depend on the development of precise, targeted delivery systems, such as lipid nanoparticles or viral vectors with high liver specificity, capable of minimizing off-target risks [160, 169]. These developments pave the way for its therapeutic application in coronary atherosclerosis and related cardiovascular diseases.

#### Integration of angiography-derived FFR in PCI guidance

Recent advances in computational physiology have facilitated the development of angiography-derived fractional flow reserve (angio-FFR) as a wire- and hyperemia-free tool for physiological assessment [170, 171]. The multicenter randomized FLAVOUR II trial demonstrated that a comprehensive percutaneous coronary intervention (PCI) strategy guided by angio-FFR was noninferior to intravascular ultrasound (IVUS) guidance in terms of the composite endpoint of death, myocardial infarction, or revascularization at 12 months in patients with angiographically significant stenosis [172, 173].

Notably, the angio-FFR group exhibited a significantly lower rate of PCI implementation and reduced stent utilization, highlighting its potential to minimize unnecessary interventions while maintaining noninferior clinical outcomes. These findings support

the integration of angio-FFR into routine catheterization workflows, particularly for noncomplex coronary artery disease, offering a less invasive yet equally effective alternative to conventional IVUS for both revascularization decision-making and procedural optimization. Future studies should focus on validating these results in higher-risk populations and complex lesions, as well as exploring hybrid approaches combining angio-FFR with intravascular imaging for further optimization of PCI outcomes [174, 175].

## DISCUSSION

Despite significant advances in our understanding of coronary atherosclerosis pathogenesis and management, substantial knowledge gaps persist that hinder optimal patient care and outcomes. The transition from stable to vulnerable plaques remains incompletely understood, particularly the precise cellular and molecular triggers that precipitate acute events beyond established inflammatory mechanisms. This represents a critical area for future investigations, as elucidating these mechanisms could enable more targeted interventions to prevent plaque rupture and its devastating consequences. Additionally, the considerable heterogeneity in individual treatment responses highlights our incomplete understanding of personalized disease mechanisms, including the role of genetic polymorphisms, epigenetic modifications, and environmental factors in modifying disease progression and therapeutic efficacy.

Methodological limitations continue to challenge the field, particularly the lack of standardized, validated biomarkers for early disease detection and dynamic risk stratification. While current imaging technologies provide valuable anatomical information, they offer limited insight into the dynamic biological processes driving disease progression. Furthermore, most therapeutic strategies focus on risk factor modification rather than targeting underlying pathophysiological mechanisms, indicating the need for more mechanism-based interventions.

Substantial clinical implementation barriers also warrant attention. The persistent discordance between evidence-based guidelines and real-world practice, particularly in resource-limited settings, continues to compromise patient outcomes. The high cost of innovative therapies creates significant accessibility issues, while inadequate health economic evaluations hinder their widespread adoption. The implementation of precision medicine approaches requires sophisticated infrastructure and interdisciplinary collaboration that may not be universally available, potentially exacerbating existing health care disparities.

Future research should prioritize several promising directions. Advanced imaging technologies combining anatomical and functional assessments are needed to better characterize plaque vulnerability. Large-scale prospective studies integrating multiomics data with clinical outcomes are needed to identify novel biomarkers and therapeutic targets. The development of cost-effective, scalable point-of-care diagnostic tools could revolutionize early detection and monitoring. Research on novel therapeutic approaches, including gene editing, RNA-based therapies, and targeted anti-inflammatory agents, should be accelerated to address unmet clinical needs. Addressing these knowledge gaps through multidisciplinary collaboration and robust research initiatives will be essential for developing more effective prevention strategies, improving risk stratification, and creating personalized treatment approaches that ultimately reduce the global burden of cardiovascular disease.

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## AUTHOR CONTRIBUTIONS

ZXQ: Conceptualization, Literature review, Writing – original draft, Visualization. RYW: Literature review, Data curation, Writing – original draft. YZ: Methodology, Validation, Writing – review & editing. HBH: Writing – review & editing, Visualization. RYH: Writing – review & editing, Funding acquisition. HY: Investigation, Formal analysis, Writing – review & editing. PHL: Resources, Supervision, Writing – review & editing. BY: Methodology, Project administration. ZFX: Supervision, Project administration, Writing – review & editing, Funding acquisition. QJH: Conceptualization, Supervision, Writing – review & editing.

## ADDITIONAL INFORMATION

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