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Review

From Plaque to Phenotype: Rethinking Coronary Artery Disease in the Era of Precision Cardiology

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Abstract

Coronary artery disease (CAD) has traditionally been viewed as the progressive consequence of established cardiovascular risk factors. However, this framework does not capture the substantial biological heterogeneity underlying disease development and manifestation. Our understanding of CAD is shifting toward a more complex and dynamic model involving endothelial dysfunction, disordered lipid metabolism, and immune-mediated inflammation, together with thrombotic and vascular remodeling pathways that govern plaque initiation and progression, lesion stability, and the transition to clinical events. Advances in genomics, epigenetics, and non-coding RNA biology are further refining this perspective; meanwhile, circulating biomarkers, advanced imaging, and artificial intelligence are increasingly enabling phenotype-based risk stratification, underscoring marked interindividual differences in susceptibility to and manifestations of CAD. The limitations of a purely risk factor-based approach are now evident, highlighting the need to move beyond a "one-size-fits-all" model for cardiovascular risk assessment. Mechanistic insights into disease development are increasingly being translated into clinical practice. Plaque characterization, using integrated molecular and imaging approaches, is becoming more accurate, and novel approaches to prevention and therapy, including anti-inflammatory and RNA-based therapeutics, are rapidly emerging. In this review, we examine the mechanisms of CAD in the current era, moving from the traditional risk factor-based approach to a more mechanistic and individualized approach to cardiovascular therapy, while also considering the translational challenges inherent in implementing precision cardiology in routine clinical practice.

Keywords: coronary artery disease; atherosclerosis; endothelial dysfunction; inflammation; lipid metabolism; plaque biology; coronary plaque; artificial intelligence; cardiovascular imaging; precision cardiology

1. Introduction

Cardiovascular disease is a leading cause of mortality and morbidity globally despite significant advances in prevention, diagnosis, and therapy. The conventional understanding of coronary artery disease (CAD) as based on modifiable risk factors fails to explain the complexity and variability in its pathogenesis. A large number of individuals present with coronary atherosclerosis and, in some instances, acute myocardial infarction in the absence of classical modifiable risk factors, suggesting the presence of additional biological drivers of disease [1].

The initiation, progression, and rupture of atherosclerotic lesions represent a dynamic, multifaceted process dependent on the interaction of endothelial dysfunction, chronic inflammation, immune activation, dyslipidemia, and vascular remodeling. This progression to symptomatic coronary disease is now understood as an evolving process driven by multiple molecular events, namely fibrous cap rupture, necrotic core expansion, endothelial erosion, and thrombus formation, rather than simply progressive luminal stenosis [2].

This understanding has led to a paradigm shift in which CAD is increasingly recognized as a biologically heterogeneous process, where pathogenesis is driven by multiple overlapping pathways rather than being the resultant product of individual risk factors. Genetic analysis, polygenic risk scores, molecular profiling, and plaque-based imaging have all indicated substantial variability in individual predisposition to disease and clinical outcomes, thereby undermining "one-size-fits-all" approaches to risk prevention and therapy [1,3].

These findings are now translating into clinical practice, whereby inflammation can be effectively targeted in secondary prevention, and coronary Computed Tomography (CT) angiography and intravascular imaging, complemented by AI-based plaque characterization, enable accurate estimation of individual atherosclerotic burden and its progression. Combined with genetic test-

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ing, RNA-based therapies, and mechanism-guided interventions, these strategies are driving the transition toward precision cardiovascular medicine [2,3]. However, most existing reviews have addressed plaque biology, inflammation, biomarkers, imaging, artificial intelligence (AI) or emerging therapies as partially separate domains, whereas a unified translational framework linking these components to biologically defined CAD phenotypes remains less clearly established.

In this review, we outline the main molecular mechanisms governing CAD and discuss the impact these findings are having on current diagnostic and therapeutic approaches, to reframe CAD not only as a risk factor–based disease but also as a biologically complex and clinically impactful condition. Specifically, we aim to integrate molecular mechanisms, plaque characteristics, circulating biomarkers, imaging phenotypes, AI–supported risk stratification, and emerging therapeutic strategies within a phenotype-based precision cardiology model.

Search Strategy and Selection Criteria

For this narrative review, we searched PubMed, Scopus, and Web of Science for articles published up to 2026 using combinations of the terms "coronary artery disease", "atherosclerosis", "plaque biology", "endothelial dysfunction", "inflammation", "lipoproteins", "biomarkers", "coronary imaging", "artificial intelligence", "machine learning", "precision cardiology", and "targeted therapies". Priority was given to recent translational studies, clinical studies, imaging studies, consensus documents, and high-quality reviews addressing biological mechanisms, plaque phenotyping, risk stratification, and emerging therapies in CAD. Additional relevant references were identified from the reference lists of selected articles. Given the narrative nature of this review, studies were selected according to their relevance to the conceptual framework rather than through formal systematic review criteria.

2. From Risk Factors to Biological Disease

Cardiovascular risk factors progress to overt atherosclerotic disease in a highly organized and multifactorial biologic continuum, transforming systemic influences into localized vascular remodeling and dysfunction. Conventional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, diabetes, and obesity) collectively drive a cascade of molecular and cellular changes that promote gradual loss of vascular homeostasis and development of atherosclerotic disease [4].

An essential element of the healthy-to-diseased arterial continuum is endothelial dysfunction, early characterized by decreased bioavailability of nitric oxide, increased oxidative stress, and activation of pro-inflammatory signal transduction pathways. These cellular processes, augmented by abnormal hemodynamics such as low or oscillatory wall shear stress at arterial bifurcations, induce increased expression of adhesion molecules such as VCAM-1 and ICAM-1, leading to increased leukocyte adhesion and transendothelial migration into the artery wall, particularly at sites prone to lesion development. These recruited monocytes differentiate into macrophages, accumulate oxidized low-density lipoprotein (oxLDL) to become foam cells, and form fatty streaks [5,6].

Disease progresses in a non-resolving inflammatory fashion, with continued cytokine, chemokine, and innate immune mediators recruiting inflammatory cells and fostering ongoing vascular inflammation, with subsequent phenotypic switching of vascular smooth muscle cells from contractile to synthetic type. Migration into the intima, followed by proliferation and deposition of extracellular matrix, leads to the formation of fibroatheromatous plaques comprising a lipid-rich necrotic core encased by a fibrous cap [6].

The extracellular matrix within the fibrous cap requires a balance between anabolic and catabolic processes; inflammatory mediators, including interferon and tumor necrosis factor, inhibit collagen synthesis, induce secretion of MMPs that degrade collagen, and facilitate loss of cap integrity leading to plaque rupture. However, recent data challenge the classical definition of the "vulnerable plaque", in which lesion morphology alone dictates risk [7].

In fact, atherosclerotic disease is dynamic, with repetitive cycles of plaque growth, instability with plaque rupture, and subsequent healing by collagen deposition. Over time, these processes accumulate, contributing to the marked heterogeneity of atherosclerotic lesions and partly explaining the lack of correlation between anatomical stenosis and clinical events [6,7].

Acute atherothrombotic events may result from plaque rupture, plaque erosion, or calcified nodules leading to thrombus formation. Systemic prothrombotic and pro-inflammatory conditions may further amplify this process through enhanced platelet reactivity and impaired fibrinolysis, thereby increasing the likelihood of myocardial infarction or ischemic stroke [7].

A significant residual cardiovascular risk persists even with aggressive risk factor management and lipid-lowering therapy. Mechanisms other than low-density lipoprotein (LDL)-mediated ones contribute to residual cardiovascular risk, including chronic low-grade inflammation, metabolic disorders, and genetically determined elements such as lipoprotein(a) and other non-conventional factors.

Additionally, substantial variability in individual risk of cardiovascular disease indicates biological heterogeneity in pathogenesis beyond conventional risk factors. Individual patients may respond to risk factor modification differently and may follow diverse risk trajectories even with similar clinical profiles, implying the existence of yet-uncharacterized risk determinants [8]. Traditional cardiovascular risk factors should not be viewed as separate from

plaque biology, but as upstream modifiers of a broader biological continuum in which endothelial dysfunction, lipid handling, immune activation, thrombosis, and vascular remodeling converge to determine individual disease expression, plaque behavior, and clinical phenotype.

3. Key Molecular Pathways Driving CAD

3.1 Endothelial Dysfunction

Endothelial dysfunction is among the earliest and most integrative biological events in the onset and progression of CAD and represents a transition in the endothelial phenotype from one of physiological vasoprotection to one of chronic inflammation, oxidation, and thrombosis. The healthy endothelial lining controls vascular homeostasis through regulated secretion of nitric oxide, prostacyclin, endothelin, and other vasoactive signaling molecules that determine vascular tone, platelet activation, leukocyte adhesion, permeability, and smooth muscle cell phenotype. Dyslipidemia, hypertension, diabetes, smoking, obesity, and insulin resistance induce and perpetuate a shift toward endothelial activation in which the vascular lining is no longer a passive barrier but becomes an active contributor to vascular inflammation and remodeling [9,10].

The reduction in endothelial Nitric oxide (NO) bioavailability—often as a result of decreased endothelial nitric oxide synthase (eNOS) activity, increased NO oxidation by reactive oxygen species, and eNOS uncoupling—leads to sustained redox imbalance, activation of inflammatory transcriptional programs including NF-κB, increased endothelial expression of VCAM-1, ICAM-1, and E-selectin, and ultimately increased vascular susceptibility to leukocyte adherence and emigration into the arterial wall and early plaque formation [10]. However, endothelial dysfunction is far from being merely an initiating factor and may act as a continuing amplifier of the atherosclerotic cascade: loss of NO and prostacyclin signaling, along with increased endothelin-1 (ET-1) and thromboxane A2 (TxA2) signaling, favor vasoconstriction, thrombosis, and impaired fibrinolysis, whereas persistent endothelial activation favors vascular permeability, endothelial cholesterol transport, inflammatory cell migration, and smooth muscle cell modulation, all of which promote atherogenesis. By doing so, endothelial dysfunction establishes an important linkage between atherosclerosis and thrombosis, thus contributing to the critical role of the vascular and systemic prothrombotic milieu in the occurrence of acute coronary events in patients with coronary plaque disease [10,11].

Endothelial dysfunction is proving to be a biologically heterogeneous systemic process. Cardiometabolic disease, adipokine dysregulation, insulin resistance, and chronic low-grade inflammation may converge on endothelial signaling pathways, whereas vascular aging promotes mitochondrial dysfunction, oxidative stress, cellular senescence, and “inflammaging”, thereby accelerating arterial stiffening and atherosclerotic progression. These observations support the concept that the endothelium may serve as a common biological interface through which metabolic, inflammatory, and aging mechanisms mediate the expression of arterial disease, and that variation in these pathways may contribute to differences in individual susceptibility [11,12,13].

The measurement of endothelial function may indeed hold some value for prognosis, with increased circulating cytokine and adhesion molecule expression as well as microparticles reflecting the activation state of the vasculature. Circulating markers of endothelial activation, including VCAM-1, ICAM-1, E-selectin, endothelial microparticles, and oxidative stress-related markers, may therefore provide indirect information on endothelial phenotype, although their clinical application remains limited by assay variability, lack of standardized thresholds, and incomplete disease specificity. Nonetheless, effective therapies targeted at directly correcting endothelial dysfunction have been disappointing, likely due to the multiple, partially overlapping biological pathways involved, thus emphasizing that the endothelium should be seen not in isolation but as a central player in integrating risk factors, inflammation, lipid handling, thrombosis, aging, and thus the progression of coronary disease to clinically manifest CAD [12,14].

3.2 Lipid and Lipoprotein Biology

Lipid and lipoprotein biology represent a central component in the pathogenesis and progression of coronary artery disease (CAD), not just in the circulating concentrations of atherogenic particles but also in their interaction with endothelial function, inflammation, and thrombosis. Lipoproteins form part of an integrated biological network, with their arterial impact a product of systemic exposure and local arterial events. Of the standard lipid fractions, low-density lipoprotein (LDL)-cholesterol plays a central role in atherogenesis, not only as a consequence of its circulating concentration but also through its interaction with the vessel wall. Modified and oxidized LDL have detrimental effects on endothelial biology: they inhibit nitric oxide generation, induce adhesion molecule expression, and facilitate leukocyte recruitment and plaque development. Conversely, high-density lipoprotein (HDL) cholesterol plays a role in vasculoprotection via activation of endothelial nitric oxide synthase, as an antioxidant and also via suppression of inflammation; however, extremely high levels of HDL-C are not associated with improved endothelial function [15]. This apparent paradox may be partly explained by the distinction between HDL-C concentration and HDL functionality. Under conditions of chronic inflammation, oxidative stress, diabetes, or systemic metabolic dysfunction, HDL particles may undergo structural and proteomic remodeling, losing part of their antioxidant, anti-inflammatory, cholesterol efflux–promoting, and endothelial-protective properties. In this context, HDL may become dysfunctional or even acquire pro-inflammatory features, with reduced ca-

pacity to support nitric oxide bioavailability and vascular homeostasis. Triglyceride-rich lipoproteins contribute to endothelial dysfunction, particularly in states of hypertriglyceridemia and postprandial lipemia [15,16,17].

Beyond conventional lipid fractions, lipoprotein(a) [Lp(a)] is a widely recognized factor associated with residual cardiovascular risk. Lp(a) involves the attachment of apolipoprotein(a) to an LDL-like particle; apolipoprotein(a) is structurally similar to plasminogen and exerts both proatherogenic and antifibrinolytic effects, linking lipid and thrombosis to accelerated atherosclerosis and thrombosis [18,19]. This associated risk may be further enhanced in combination with fibrinogen, a key mediator at the interface of thrombosis and inflammation. Elevated Lp(a) and fibrinogen levels are independently associated with atherosclerotic burden, with evidence of a synergistic interaction between the two biomarkers [19,20].

LDL atherogenicity requires endothelial permeability and transendothelial LDL movement to produce atherogenic plaques. LDL transcytosis across the endothelial barrier is an early and essential process in atherosclerosis pathogenesis. Distinct cellular pathways, including caveolae-mediated transport, SR-B1, and ALK1, facilitate LDL transport across the endothelial cell. Increased endothelial permeability and augmented transcellular LDL transport may provide a mechanistic foundation for arterial lipid retention and lesion initiation, especially in areas exposed to disturbed flow [21].

Recent work using an endothelial cell polygenic risk score (EC-PRS) suggests that endothelial genetic background may identify individuals who are particularly susceptible to LDL-C–mediated vascular disease. Lower LDL-C levels reduce vascular risk, and the majority of vascular benefits are observed in individuals carrying the high endothelial EC-PRS, as seen in trials such as JUPITER and FOURIER [22,23]; these data suggest that endothelial factors modulate lipid-related risk as well as the therapeutic benefit of lowering lipid levels [24].

3.3 Inflammation and Immune Activation

Inflammation and immune activation drive plaque progression and clinical instability in CAD. Lipid deposition initiates the atherosclerotic process, but ongoing immune activation determines the lesion's fate and risk of rupture. Modified and oxidized lipoproteins are central triggers of this immune response, stimulating endothelial activation, subsequent leukocyte recruitment, and a sustained inflammatory milieu within the arterial wall, such that the plaque should be considered an immuno-inflammatory tissue, not just an accumulation of lipid [25].

The initial steps in the formation of an atheroma are largely mediated by the innate immune system. Circulating monocytes are recruited to sites of endothelial activation, differentiate into macrophages, and uptake modified lipoproteins via scavenger receptors, producing lipid-laden foam cells that create a lipid-rich necrotic core. Intracellular inflammatory pathways like the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome amplify this process, leading to the release of interleukin (IL)-1, IL-6, and TNF, which enhance local inflammation, activate systemic inflammatory signaling, and promote matrix degradation via metalloproteinases, weakening the plaque fibrous cap and predisposing it to rupture [26,27]. However, plaque macrophages should not be viewed as a homogeneous cell population. Instead, they display substantial phenotypic plasticity across inflammatory, lipid-handling, reparative, and tissue-remodeling states. Foam cells may also differ in lipid content, inflammatory activity, and capacity for efferocytosis. Impaired efferocytosis favors secondary necrosis, necrotic core expansion, and defective plaque healing, whereas trained immunity may sustain a persistent pro-inflammatory macrophage phenotype even after the initial metabolic or inflammatory stimulus has changed. These mechanisms provide a cellular basis for the heterogeneity of plaque progression, destabilization, and repair [27,28].

Adaptive immune responses also play a critical role in atherosclerotic lesions. A large population of antigen-experienced T cells is found in human coronary atherosclerotic plaques, exhibiting marked activation characteristics. Clonal expansion of T-cell receptors, especially among CD8 T cells, demonstrates the significant impact of T-cell-mediated antigen responses on lesion development and progression [29].

T-cell subsets within the atherosclerotic microenvironment have diverse actions: pro-inflammatory T helper 1 (Th1) cells amplify inflammation and macrophage activation, inhibiting collagen synthesis and thinning the fibrous cap. CD8 T cells directly induce damage to endothelial cells and smooth muscle cells, predisposing to plaque destabilization. Regulatory T cells dampen immune activation and contribute to plaque stability through anti-inflammatory cytokines like interleukin-10 and transforming growth factor-β [25,30]. Accordingly, distinct immune-cell axes may contribute to different CAD endotypes. Monocyte/macrophage–NLRP3 activation and neutrophil-related pathways are more closely linked to innate immune-driven plaque instability, whereas Th1-mediated metaflammation, CD8 T-cell cytotoxicity, regulatory T-cell dysfunction, and potentially natural killer T-cell–mediated pathways may modulate adaptive immune activation, endothelial injury, collagen turnover, and plaque stability [29,30,31].

The interaction between immune cells and the vascular components exacerbates the disease. Macrophages activate T cells via antigen presentation and cytokine release, while endothelial cells and smooth muscle cells recruit leukocytes through adhesion molecule upregulation in response to inflammation. This continuous crosstalk creates a self-reinforcing inflammatory loop within the plaque, inte-

grating lipid-driven damage, immune activation, and structural remodeling. This immuno-inflammatory axis also influences thrombosis, as cytokine-induced endothelial dysfunction promotes a prothrombotic state, linking inflammation to acute coronary syndromes.

The main biological phenotypes of CAD and their clinical implications are summarized in Table 1 (Ref. [18,19,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55]).

4. Disease Heterogeneity and Molecular Phenotypes

Based on the above mechanistic considerations, CAD can no longer be considered a singular, homogeneous disease entity, but rather a continuum of biologically diverse states triggered by interactions of genetic predisposition, environmental insult, immune dysregulation, metabolic dysfunction, and local vascular processes. Within such a framework, variability in lesion distribution, progression, presentation, and outcomes in patients with ostensibly similar cardiovascular risk factors may be viewed not as a paradox but rather as biologically predictable. CAD can thus be viewed as a disease spectrum rather than a stereotypically evolving pathological process. In such a construct, the widely recognized mismatch between angiographically determined lesion severity, ischemic burden, plaque behavior, and clinical outcome becomes understandable as the result of lesions with fundamentally differing biology rather than mere degrees of lumen narrowing [56].

At a transcriptomic level, evidence supporting this concept is accumulating. Different forms of CAD with similar clinical presentations appear to have been defined by unique inflammatory and cell-death signatures on molecular analysis and distinct biological pathways driving the presentation. For instance, based on clustering with ferroptosis- and necroptosis-related genes, two major phenotypes could be identified: the first driven by innate immune stimulation and neutrophilic inflammation, and the second characterized by gene signatures related to innate and adaptive immune response signaling. These phenotypes showed differential expression of key signaling molecules, *TLR4* and *STAT3*, and had contrasting inflammatory load and disease burden, while alternative gene signatures appeared associated with more stable disease. Pathway analysis revealed neutrophil-related processes to be predominantly represented within the inflammatory cluster, while adaptive immune signaling was dominant in the alternative form [57].

In direct human studies involving coronary plaques, RNA sequencing of plaque samples removed during percutaneous coronary intervention (PCI) has demonstrated that culprit lesions compared to stable plaques show not only differences in transcriptomic signature but also in cellular composition. Acute lesions are enriched in fibroblasts and fibromyocytes, while showing reduced representation of smooth muscle cells, indicating phenotypic modification and plaque instability. Principal component analysis further demonstrated clearly separated clustering of culprit compared to stable lesions and suggests that *in vivo* plaque biology can be distinguished in cellular and transcriptional terms. This could have implications for individualized risk stratification [57,58].

Spatial heterogeneity is also evident. Angiography-based cluster analyses have revealed consistent CAD phenotypes defined by distinct patterns of coronary stenosis distribution. Each pattern is uniquely associated with specific demographics, metabolic parameters, inflammatory burden, and prognostic profiles. The pattern including proximal left anterior descending (LAD) disease with widespread multivessel stenoses is associated with higher inflammation and worse outcomes, while others comprise different combinations of metabolic stress and vulnerability. This suggests that the distribution of atherosclerotic lesions is biologically meaningful and is not merely a consequence of stochastic development [59].

Sex-related differences may further contribute to CAD heterogeneity and should be incorporated into future precision cardiology frameworks. Women more frequently present with non-obstructive CAD, coronary microvascular dysfunction, plaque erosion, and atypical clinical presentations, whereas men more commonly show obstructive epicardial disease and plaque rupture. Differences in endothelial function, inflammatory activation, hormonal status, vascular remodeling, and thrombogenicity may influence plaque phenotype and clinical expression [60,61]. Therefore, sex-specific biological features may represent an additional layer of phenotypic variability relevant to individualized risk stratification and treatment selection.

The phenotype rather than just lumen narrowing defines differences. Distinct phenotypes appear to be driven by combinations of lipid accumulation, inflammation, calcification, cap integrity, intraplaque hemorrhage, and vascular remodeling. Advanced imaging modalities and machine learning algorithms identify features such as lipid index and arc of calcification as key determinants of positive remodeling, a process associated with increased cardiovascular risk. The prevalence of positively remodeled plaques predicts poorer outcomes, indicating the presence of a diffuse vulnerable substrate rather than individual culprit lesions [62].

More broadly, studies integrating proteomics, single-cell transcriptomics, and genomics have elucidated coordinated inflammatory, metabolic, and structural changes during plaque progression and the role of *CD44, TREM2, SMAD3,* and *IL6R* as potential mediators of plaque progression and instability. This appears to be a biologically coordinated process rather than purely anatomical [32].

Within the concept of vulnerable patient phenotypes, the biological processes driving plaque rupture and erosion are mediated by distinct pathways involving inflammation,

Table 1. Biological phenotypes of coronary artery disease and their clinical implications.

Phenotype	Dominant biological axis	Key markers & imaging features	Therapeutic implications (with references)
Lipid-rich phenotype	LDL retention, oxLDL, endothelial permeability	LDL-C, apoB, Lp(a); non-calcified plaque, lipid-rich necrotic core	Intensive lipid lowering, PCSK9 inhibitors, and emerging RNA-based Lp(a)-lowering therapies [18,19,21,22,23,24,39,40,41,42]
Inflammatory phenotype	IL-1β/IL-6/NLRP3 activation	hsCRP, IL-6; plaque inflammation, immune cell infiltration	Anti-inflammatory strategies, including colchicine-sensitive pathways, IL-1β/IL-6 inhibition, and NLRP3-related approaches [25,26,27,28,29,30,43,44,45,46,55]
Thrombo-inflammatory phenotype	Platelet activation, impaired fibrinolysis	Lp(a), fibrinogen; plaque rupture/erosion, thrombosis	Tailored antithrombotic strategies and Lp(a)-targeting approaches in selected lipid-thrombotic phenotypes [18,19,42,52]
Calcific/remodeling phenotype	Plaque healing, micro/ macrocalcification	CAC progression, spotty vs macrocalcification, ^{18}F-NaF uptake	Interpretation of CAC according to treatment context; plaque stabilization and remodeling-oriented strategies [31,34,35,39,47]
Vulnerable patient phenotype	Systemic inflammation + diffuse plaque burden	Multimarker risk, omics signatures; high plaque burden, positive remodeling	Integrated precision approach combining imaging, biomarkers, omics, AI-supported risk stratification, and individualized treatment selection [32,33,36,37,38,48,49,50,51,52,53,54]

LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B; Lp(a), Lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; IL, interleukin; NLRP3, NOD-like receptor family pyrin domain containing 3; hsCRP, high-sensitivity C-reactive protein; CAC, coronary artery calcium; ^{18}F-NaF, fluorine-18 sodium fluoride; AI, artificial intelligence.

endothelial dysfunction, matrix degradation, and thrombosis. Vulnerable plaques display increased interactions among necrotic core expansion, macrophage activity, fibrous cap thinning, microcalcification, neovascularization, and intraplaque hemorrhage, which are not apparent from lumen measurements. Molecular imaging offers the ability to study underlying biological markers of plaque instability, and approaches such as ^{18}F-NaF Positron emission tomography (PET) may move assessment beyond anatomical evaluation toward biologically informed risk stratification [34].

Relevantly, through bioinformatic analysis, advanced and ruptured plaques are characterized by neutrophil degranulation as a key pathway, with genes such as *PLAUR* and *ITGB2* acting as central mediators. Some of these signatures have also been detected in peripheral blood and may reflect a systemic inflammatory substrate underpinning plaque instability, further supporting the existence of distinct molecular states of CAD associated with different clinical profiles [63].

Additional drivers such as clonal hematopoiesis involving *DNMT3A, TET2*, and *JAK2* mutations—recognized as independent risk factors for accelerated atherosclerosis—further highlight the role of immune dysregulation in disease progression [64].

5. Translational Implications: From Mechanisms to Clinical Practice

5.1 Biomarkers

This understanding of CAD as a biologically heterogeneous disease has supported the use of circulating biomarkers not as disease burden indicators but as tools for tracking underlying pathophysiologies. Biomarkers may then be thought of as measures of individual biological axes such as inflammation, lipid metabolism, fibrotic processes, and plaque stability. Accordingly, a phenotype-based interpretation of biomarkers requires their organization according to the dominant biological process they reflect, rather than their use as isolated prognostic variables.

Biomarkers of inflammation are among the most studied. High-sensitivity C-reactive protein (hsCRP) and IL-6 are some of the best-validated circulating biomarkers. hsCRP represents an indicator of downstream inflammatory processes, whereas IL-6 represents an indicator of upstream inflammatory processes. Levels of either hsCRP or IL-6 have been repeatedly correlated with increased risk of future CV events and CV outcomes. hsCRP is an indicator of overall inflammation, whereas evidence suggests IL-6 signaling itself causes atherosclerosis and cardiovascular disease [65]. Additional inflammatory mediators, including IL-1β, TNF, and NLRP3-related signaling markers, may further characterize inflammasome-driven and cytokine-mediated CAD phenotypes, although their routine clinical implementation remains limited [66].

The integration of inflammatory and lipid-related biomarkers further refines risk stratification. Lp(a), a genetically determined pro-atherogenic and pro-thrombotic lipoprotein, has been independently associated with cardiovascular risk. Importantly, the combined elevation of Lp(a) and hsCRP identifies a subgroup of patients at particularly high risk of cardiovascular mortality, suggesting that concurrent activation of inflammatory and lipid pathways confers additive or synergistic risk [66,67]. Similarly, thrombotic and thrombo-inflammatory biomarkers, such as fibrinogen, D-dimer, platelet activation markers, and markers of impaired fibrinolysis, may help identify patients in whom plaque vulnerability is accompanied by a systemic prothrombotic milieu.

Markers of endothelial dysfunction represent another relevant biomarker category within a phenotype-based CAD framework. Circulating adhesion molecules such as VCAM-1, ICAM-1, and E-selectin, together with endothelial microparticles and oxidative stress-related markers, may reflect endothelial activation, vascular permeability, and leukocyte recruitment. However, their clinical applicability remains constrained by limited standardization, biological variability, and incomplete specificity for coronary plaque activity [68,69].

Further novel biomarkers relating to myocardial stress, fibrosis, and immune activation have also been shown to have prognostic importance. Growth differentiation factor-15 (GDF-15), soluble suppression of tumorigenicity-2 (sST2), and galectin-3 are among a number of novel biomarkers of adverse outcomes in a variety of conditions from heart failure to ischemic heart disease [70].

They are complementary to known markers of cardiovascular disease, and their utility in routine clinical practice is not yet established. Novel molecular markers are providing a further dimension to understanding the heterogeneity of cardiovascular disease. A role for microRNAs has been found in the regulation of endothelial function, inflammation, and plaque stability, and they may represent non-invasive markers of plaque biology. Evidence has shown an association of particular microRNA signatures such as higher expression levels of miR-10b and miR-92a with vulnerable plaque phenotype and an unstable clinical picture, helping identify individuals at high risk of clinical instability [71].

In addition, the wider context of multi-omics approaches combining proteomic, transcriptomic, and metabolomic data is increasing the number of candidate biomarkers for atherosclerotic progression and plaque destabilization. The goal of such approaches is to develop multi-biomarker signatures that more accurately capture the complexity of CAD [32,71].

Despite these advances, significant limitations remain. Most candidate markers are non-specific for particular disease endotypes, and their addition to conventional clinical models has provided only minimal incremental prognos-

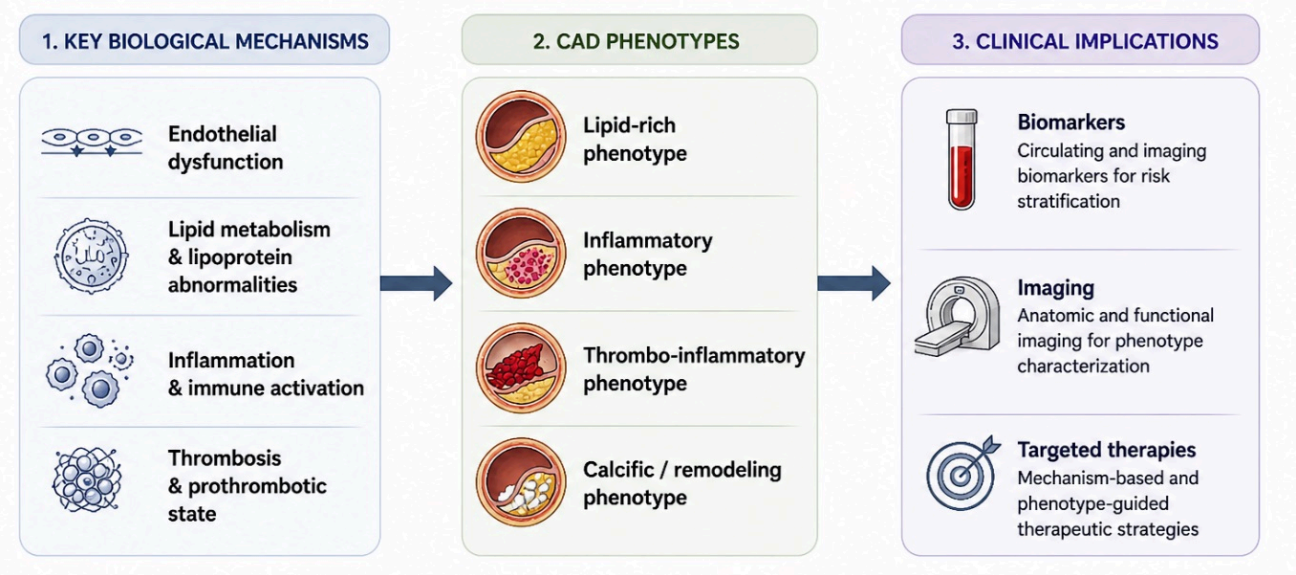


Fig. 1. A simplified framework of coronary artery disease from biological mechanisms to clinical phenotypes. The figure illustrates how endothelial dysfunction, lipid and lipoprotein abnormalities, inflammation, immune activation, thrombosis, and vascular remodeling interact to generate distinct but overlapping CAD phenotypes. These biological phenotypes may be characterized through circulating biomarkers, advanced imaging, and AI-supported risk stratification, ultimately supporting more individualized preventive and therapeutic strategies.

tic value. Difficulties with standardization, reproducibility, and definition of thresholds remain a constraint on clinical practice. Therefore, biomarkers should be interpreted as complementary components of an integrated precision cardiology framework, rather than as stand-alone tools for diagnosis or therapeutic selection.

The integration of these biological mechanisms into clinical practice is illustrated in Fig. 1.

5.2 Imaging

A revolutionary change has occurred in the field of cardiovascular imaging, transitioning from a discipline concerned solely with lumen stenoses to a multidimensional tool enabling interrogation of the biologic processes active within atherosclerotic lesions. The observation that anatomic occlusion is an imperfect surrogate marker of risk and that the majority of acute coronary events arise from non-stenotic yet active plaque lesions has led to changes in the imaging paradigm, where "plaque characterization, not ischemia, is paramount", with a transition towards biologically mediated risk assessment [72].

Within such a scheme, imaging may be seen as a spatially resolved biomarker. It offers the unique ability to reflect the heterogeneity of atherosclerosis on a lesion-by-lesion basis, bridging the gap between circulating markers, which are systemically diluted, and discrete plaque activity.

With respect to quantitative metrics derived from imaging, plaque burden appears to be the strongest predictor of risk. Quantitative coronary computed tomography angiography (CCTA) allows for volumetrically accurate assessment of coronary atherosclerosis across the entire coronary tree with AI-driven algorithms for improved plaque characterization. Interestingly, it has been shown that relatively minor changes in plaque burden translate to a substantial risk increase: in a study of 2839 patients from two independent CCTA cohorts, a PAV threshold of ≥2.6% identified patients at significantly higher risk of ACS, whereas PAV <2.6% was associated with a very low event rate, offering a near-perfect negative predictive value and suggesting that the entirety of coronary plaque burden represents the necessary substrate for clinical events [33].

Crucially, advanced plaque quantification appears to provide prognostic information that is independent of—and in some cases superior to—both traditional risk factors and lumen stenosis severity. In the multicenter CAPIRE study, Andreini et al. [73] demonstrated that quantitative CCTA-derived plaque features, particularly non-calcified plaque volume, were independently associated with cardiovascular events, even after adjustment for clinical risk profiles and multivessel disease. Notably, patients with low non-calcified plaque burden exhibited similar outcomes regardless of anatomical disease extent, whereas those with high non-calcified plaque volume experienced significantly higher event rates. These findings strongly support the concept that plaque composition, rather than stenosis severity alone, drives clinical risk, challenging the long-standing paradigm centered on luminal narrowing [73].

Beyond global burden, imaging provides refined characterization of plaque phenotype, enabling identification of high-risk morphological features such as lipid-rich necrotic

core, positive remodeling, spotty calcifications, and thin fibrous cap. Invasive intracoronary imaging modalities—including IVUS, OCT, and near-infrared spectroscopy—have been instrumental in validating these features *in vivo*, effectively functioning as an "optical biopsy" of the arterial wall. These approaches have demonstrated that plaque vulnerability is not a binary condition but rather a continuum of structural and inflammatory states, reflecting complex interactions between lipid accumulation, immune activation, and extracellular matrix degradation [33,74].

More recently, attention has shifted toward the assessment of plaque biological activity, capturing dynamic processes such as inflammation and microcalcification. Hybrid PET-CT imaging with tracers such as ^{18}F-sodium fluoride enables visualization of active calcification, a process closely linked to necrotic core expansion and inflammatory signaling. In a large prospective cohort of patients with recent myocardial infarction, increased coronary plaque activity assessed by fluorine-18 sodium fluoride (^{18}F-NaF) uptake was associated with higher rates of cardiac death or recurrent myocardial infarction, independently of traditional risk factors and anatomical disease severity. These findings position molecular imaging as a functional biomarker of plaque instability, capable of identifying high-risk disease states beyond structural characterization alone [34].

A central and exciting emerging concept is that the risk of plaque, like disease, is not static, but rather evolving. Baseline plaque features have failed to discriminate between lesions destined to cause or not cause ACS in longitudinal imaging studies, and changes over time are therefore of the greatest significance. In a serial CCTA study, the development of increases in necrotic core and luminal stenosis and remodeling index, along with changes in the CT-derived fractional flow reserve (CT-FFR), had a significantly greater predictive capability for subsequent ACS events than did baseline parameters. The incorporation of a temporal element may encourage imaging to be viewed not as a static descriptor, but a reflection of the biological process [34,75].

Simultaneously, machine learning techniques have enabled the integration of multiple imaging domains into more comprehensive models of plaque biology. The value of these approaches does not lie only in higher predictive accuracy, but in their ability to translate heterogeneous imaging data into reproducible quantitative phenotypes. In this regard, anatomical plaque burden from CCTA, compositional information from OCT or IVUS, functional assessment with CT-FFR, and molecular or perfusion data from hybrid PET-based imaging may capture complementary dimensions of CAD, including plaque volume, vulnerability features, hemodynamic relevance, microvascular dysfunction, and biological plaque activity. In one study, plaque volume, remodeling index, CT-FFR, and necrotic core features entered into an XGBoost model predicted ACS with high accuracy (AUC 0.918), outperforming individual parameters [75]. More broadly, recent multimodal imaging literature and consensus recommendations suggest that AI-supported plaque quantification may help move coronary imaging from descriptive assessment toward individualized risk stratification, monitoring of treatment response, and potentially treatment escalation based on total plaque volume and patient-specific risk profiles [36,37,38]. However, the clinical value of these models will depend on external validation, reproducibility across scanners and populations, standardized acquisition protocols, model interpretability, and integration with clinical and biomarker data rather than on algorithmic performance alone.

5.3 Targeted Therapies

Lipid-lowering treatments, particularly high-intensity statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, predictably induce a shift in plaque phenotype, characterized by reduced lipid content, fibrous cap thickening, and increased calcified burden [39,40]. Importantly, treatment-related increases in calcification may occur alongside reductions in atheroma volume and cardiovascular events, suggesting that coronary artery calcium (CAC) progression during intensive lipid lowering may reflect favorable plaque remodeling rather than disease progression per se. From this perspective, calcium deposition may represent the terminal stage of a stabilization cascade, whereby an active, high-risk plaque is transformed into a more inert mineralized scar. This concept is consistent with the clinical outcome benefits observed in major PCSK9 inhibitor trials, including FOURIER and ODYSSEY OUTCOMES, and with dedicated coronary imaging studies demonstrating regression of atheroma, reduction in lipid-rich plaque components, and features of plaque stabilization with intensive lipid lowering [23,41,76]. Thus, CAC may serve less as a purely quantitative marker of treatment response and more as a qualitative indicator of plaque remodeling.

In parallel, emerging RNA-based therapies targeting lipoprotein(a), including antisense oligonucleotides and small interfering RNA approaches, represent a particularly relevant example of mechanism-guided prevention for genetically determined residual risk. By directly lowering Lp(a), these agents may allow more precise treatment of lipid-thrombotic phenotypes in which conventional LDL-C lowering alone does not fully address the dominant biological driver of risk [42].

The addition of targeted anti-inflammatory therapies introduces a further dimension to this concept. In CANTOS, reduction in cardiovascular events through IL-1β inhibition occurred independently of lipid lowering, firmly establishing the clinical relevance of residual inflammatory risk [55]. Similarly, IL-6 and IL-1 receptor blockade has been shown to reduce myocardial injury and systemic inflammation in the setting of ACS [43,44,45]. Other

approaches, including colchicine-sensitive inflammatory pathways and strategies directed toward the NLRP3/IL-1β/IL-6 axis, may further refine the treatment of inflammatory CAD phenotypes [46].

Mechanistically, these therapies may act upstream of overt calcium deposition. This suggests an important distinction: whereas lipid-lowering therapies may promote plaque stabilization through consolidation of calcium into macrocalcification, anti-inflammatory therapies may prevent the formation of high-risk microcalcifications by attenuating apoptosis, extracellular vesicle release, and local inflammatory signaling. Although direct evidence linking specific therapies to distinct CAC trajectories remains limited, available data support the hypothesis that different therapeutic strategies may generate different CAC signatures, reflecting discrete pathways of plaque remodeling [34,77].

From a clinical standpoint, this evolving framework challenges traditional interpretations of CAC progression. An increase in CAC under optimal therapy should not be considered a failure of treatment, but rather a potential biomarker of effective plaque transformation. Conversely, stable or low CAC in untreated or poorly controlled patients may mask the persistence of lipid-rich, non-calcified, and potentially high-risk plaques. Therefore, the clinical meaning of CAC becomes context-dependent, requiring integration with treatment status, lipid levels, inflammatory burden, and complementary imaging findings.

Emerging therapeutic strategies further expand this concept. Nanomedicine and targeted delivery systems are being developed to directly modulate the plaque microenvironment, enabling site-specific reduction of inflammation, promotion of cholesterol efflux, and enhancement of fibrous cap integrity [78,79]. These approaches may allow a more precise orchestration of plaque healing processes, potentially influencing not only the extent but also the spatial distribution and morphology of calcification. In this scenario, CAC may evolve from a global burden metric into a fingerprint of localized therapeutic effects within the arterial wall.

Taken together, these observations support a paradigm shift in which CAC is no longer interpreted solely as a measure of cumulative atherosclerotic burden, but as a readout of the balance between injury and repair under therapy. Looking forward, the integration of CAC with advanced imaging modalities, molecular biomarkers, and computational approaches may enable a more refined characterization of treatment response. Rather than asking whether CAC increases or decreases, future strategies should aim to determine what type of calcium is forming, in which biological context, and under which therapeutic pressure. Such an approach would reposition CAC as a dynamic biomarker within a multidimensional framework of precision cardiovascular medicine [47,48].

6. Future Directions and Precision Cardiology

Moving from isolated stenotic lesion identification toward a multidimensional view of CAD as a dynamic, biologically heterogeneous, and patient-specific process will be central to the evolution of precision cardiology. This transition requires integrated strategies for risk stratification, surveillance, and therapeutic selection, combining anatomical, functional, biological, and computational domains. AI-supported coronary imaging represents one of the most important recent developments in this field.

Beyond improving the speed and reproducibility of image analysis, AI may help transform heterogeneous imaging data into quantitative plaque and patient phenotypes. AI-based CCTA can estimate total plaque burden and composition with strong concordance with expert readers, while comparisons with invasive imaging such as optical coherence tomography have shown good agreement between noninvasive and invasive plaque quantification [49]. More broadly, AI-driven CCTA plaque analysis may support reproducible quantification of plaque burden and composition, helping to translate anatomical imaging into individualized risk assessment [50].

However, future progress will depend less on isolated plaque markers and more on integrated models combining imaging, biomarkers, clinical data, and treatment response. This reflects the shift from the vulnerable plaque to the vulnerable phenotype, in which plaque characteristics are interpreted within a broader system shaped by inflammation, hemodynamics, immune activation, thrombosis, and diffuse plaque burden [51]. This concept is further supported by the recognition that plaque erosion represents a distinct pathway in ACS and may provide a gateway to more personalized therapeutic strategies [52]. AI may support this transition by connecting anatomical plaque burden, functional assessment, biomarker profiles, and clinical risk into individualized prediction frameworks [50,53].

A further key direction is the recognition of atherosclerosis as a dynamic disease. Serial imaging suggests that changes in plaque characteristics over time may be more informative than static baseline measures. Systems biology and mathematical modeling may strengthen this approach by describing CAD as a network process and by identifying patient-specific trajectories of progression, stabilization, or residual risk.

In this context, digital twin approaches could eventually integrate imaging, biomarkers, clinical risk factors, genetic background, and treatment exposure to support individualized prediction of plaque evolution and therapeutic response [54].

Despite these advances, important limitations remain. AI models are often developed on specific datasets, limiting generalizability across populations, scanners, and clinical settings. Data bias, limited transparency, workflow integration challenges, privacy requirements, uncertain reim-

bursement, regulatory oversight, and medico-legal responsibility may all complicate implementation. These barriers are particularly relevant in low-resource settings, where unequal access to advanced imaging, biomarker testing, and computational infrastructure may widen disparities in cardiovascular prevention.

Ultimately, the future of precision cardiology will depend on careful integration rather than innovation alone. The most useful tools will be those capable of generating clinically meaningful, reproducible, and actionable information to identify low- and high-risk patients, monitor disease evolution, and guide therapy according to the dominant biological mechanisms driving individual disease processes [50,53,54].

7. Conclusions

A paradigm shift in coronary artery disease thinking is needed, where the condition is not perceived solely as the summation of historical cardiovascular risk factors or as a disease merely characterized by the degree of luminal stenosis, but instead as a process dictated by interactions between endothelial dysfunction, lipid and lipoprotein biology, inflammation and immune activation, thromboinflammatory processes, and vascular remodeling that produce a complex biologically diverse spectrum of disease. Within this framework, patients with identical cardiovascular risk profiles may not necessarily present with similar plaque phenotype, progression, and subsequent clinical outcome.

The translation of this plaque phenotype concept into clinical practice has far-reaching implications for diagnosis, prognosis, and therapeutic strategies. Circulating biomarkers, contemporary coronary imaging modalities, molecular profiling technologies, and AI-based tools have provided increasingly powerful insights into the quantification of atherosclerotic burden, plaque activity, and the intrinsic biology underlying each patient's disease state. Simultaneously, therapy is advancing beyond simple risk factor reduction toward mechanism-guided intervention with novel lipid-lowering, anti-inflammatory, RNA-based, and targeted agents. Future advances in cardiovascular disease prevention and treatment will rely on translating these developments into actionable, reproducible, and clinically useful strategies. Precision cardiology represents not simply a collection of novel technologies but the ability to delineate the primary drivers of disease at an individual patient level, track the temporal evolution of these processes, and make individualized treatment decisions based on their interplay. In this context, CAD should not be considered a single disease to be treated uniformly, but rather a spectrum of biologically individualized and conceptually integrated phenotypes. The clinical value of this approach will depend not only on technological innovation, but also on validation, accessibility, interpretability, and integration into real-world care pathways.

Abbreviations

CAD, coronary artery disease; LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoprotein; apoB, apolipoprotein B; Lp(a), lipoprotein(a); hsCRP, high-sensitivity C-reactive protein; IL, interleukin; NLRP3, NOD-like receptor family pyrin domain containing 3; CAC, coronary artery calcium; ^{18}F-NaF, fluorine-18 sodium fluoride; PCSK9, proprotein convertase subtilisin/kexin type 9; AI, artificial intelligence.

Author Contributions

FAV contributed to conceptualization, literature review, and drafting of the manuscript, as well as critical revision and supervision. FP, FAG, and GSch contributed to literature review and manuscript drafting, with subsequent critical revision. GSam contributed to literature search and to the interpretation of relevant data and evidence for the manuscript, critical revision and intellectual content. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Figtree GA, Vernon ST, Harmer JA, Gray MP, Arnott C, Bachour E, et al. Clinical Pathway for Coronary Atherosclerosis in Patients Without Conventional Modifiable Risk Factors: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2023; 82: 1343–1359. https://doi.org/10.1016/j.jacc.2023.06.045

[2] Cheng WH, Wang Y. Inflammatory Pathways in Coronary Artery Disease: Which Ones to Target for Secondary Prevention? Cells. 2025; 14: 153. https://doi.org/10.3390/cells14030153

[3] Karlsberg RP, Cho GW, Aldana-Bitar J. A Promising Pathway Toward Mitigation and Eradication of Coronary Artery Disease. Cardiology Research. 2024; 15: 415–424. https://doi.org/10.14740/cr1721

[4] Zhang P, Liu X, Feng N, Duan P, Guo Y, Bai C. Risk factors for coronary artery disease progression: A retrospective cohort study of clinical and biochemical predictors. Medicine. 2025; 104: e42706. https://doi.org/10.1097/MD.0000000000042706

[5] Kopych V, Da Costa ADS, Park K. Endothelial Dysfunction in Atherosclerosis: Experimental Models and Therapeutics. Bio-

materials Research. 2025; 29: 0252. https://doi.org/10.34133/bmr.0252
[6] Noothi SK, Ahmed MR, Agrawal DK. Residual risks and evolving atherosclerotic plaques. Molecular and Cellular Biochemistry. 2023; 478: 2629–2643. https://doi.org/10.1007/s11010-023-04689-0
[7] Galli M, Abbate A, Bonaca MP, Crea F, Forte M, Frati G, et al. Residual cardiovascular risk in coronary artery disease: from pathophysiology to established and novel therapies. Nature Reviews. Cardiology. 2026; 23: 500–523. https://doi.org/10.1038/s41569-026-01249-z
[8] Simonetto C, Rospleszcz S, Kaiser JC, Furukawa K. Heterogeneity in coronary heart disease risk. Scientific Reports. 2022; 12: 10131. https://doi.org/10.1038/s41598-022-14013-3
[9] Wang X, He B. Endothelial dysfunction: molecular mechanisms and clinical implications. MedComm. 2024; 5: e651. https://doi.org/10.1002/mco2.651
[10] Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L. Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutical Approaches. International Journal of Molecular Sciences. 2021; 22: 3850. https://doi.org/10.3390/ijms22083850
[11] Młynarska E, Bojdo K, Frankenstein H, Krawiranda K, Kustosik N, Lisińska W, et al. Endothelial Dysfunction as the Common Pathway Linking Obesity, Hypertension and Atherosclerosis. International Journal of Molecular Sciences. 2025; 26: 10096. https://doi.org/10.3390/ijms262010096
[12] De Bartolo A, Angelone T, Rocca C. Elucidating emerging signaling pathways driving endothelial dysfunction in cardiovascular aging. Vascular Pharmacology. 2025; 158: 107462. https://doi.org/10.1016/j.vph.2025.107462
[13] Wang Z, Yang Y, Wang Q, Wang L, Zhao Y, Qian X, et al. Pathological mechanisms and clinical research progress of endothelial dysfunction. Frontiers in Cardiovascular Medicine. 2026; 13: 1749548. https://doi.org/10.3389/fcvm.2026.1749548
[14] Kaur R, Singh V, Kumari P, Singh R, Chopra H, Emran TB. Novel insights on the role of VCAM-1 and ICAM-1: Potential biomarkers for cardiovascular diseases. Annals of Medicine and Surgery (2012). 2022; 84: 104802. https://doi.org/10.1016/j.amsu.2022.104802
[15] Higashi Y. Endothelial Function in Dyslipidemia: Roles of LDL-Cholesterol, HDL-Cholesterol and Triglycerides. Cells. 2023; 12: 1293. https://doi.org/10.3390/cells12091293
[16] Matsuzawa Y, Lerman A. Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment. Coronary Artery Disease. 2014; 25: 713–724. https://doi.org/10.1097/MCA.0000000000000178
[17] Ouyang FW, Chiang HH, Hsu WL, Tsai MH, Huang CY, Remaley AT, et al. Dysfunctional high-density lipoprotein: an updated review. Frontiers in Cardiovascular Medicine. 2025; 12: 1713387. https://doi.org/10.3389/fcvm.2025.1713387
[18] Zhang Y, Jin JL, Cao YX, Liu HH, Zhang HW, Guo YL, et al. Prognostic utility of lipoprotein(a) combined with fibrinogen in patients with stable coronary artery disease: a prospective, large cohort study. Journal of Translational Medicine. 2020; 18: 373. https://doi.org/10.1186/s12967-020-02546-y
[19] Liang D, Liang D, Liu J, Zheng Y, Huang D, Li Z, et al. Impact of lipoprotein(a) and fibrinogen on prognosis in patients with coronary artery disease: A retrospective cohort study. Technology and Health Care: Official Journal of the European Society for Engineering and Medicine. 2024; 32: 3317–3328. https://doi.org/10.3233/THC-240005
[20] Wei M, Liu Z, Wei M, Liu S, Jin M, Zhou Y, et al. Synergistic effects of lipoprotein (a) and fibrinogen on carotid plaque in patients with coronary artery disease. European Journal of Medical Research. 2025; 30: 129. https://doi.org/10.1186/s40001-025-02351-7
[21] Zhang X, Fernández-Hernando C. Transport of LDLs into the arterial wall: impact in atherosclerosis. Current Opinion in Lipidology. 2020; 31: 279–285. https://doi.org/10.1097/MOL.0000000000000701
[22] Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. The New England Journal of Medicine. 2008; 359: 2195–2207. https://doi.org/10.1056/NEJMoa0807646
[23] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England Journal of Medicine. 2017; 376: 1713–1722. https://doi.org/10.1056/NEJMoa1615664
[24] Marston NA, Kamanu FK, Melloni GEM, Schnitzler G, Hakim A, Ma RX, et al. Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering. Nature Medicine. 2025; 31: 963–969. https://doi.org/10.1038/s41591-025-03533-w
[25] Wang H, Liu Z, Shao J, Lin L, Jiang M, Wang L, et al. Immune and Inflammation in Acute Coronary Syndrome: Molecular Mechanisms and Therapeutic Implications. Journal of Immunology Research. 2020; 2020: 4904217. https://doi.org/10.1155/2020/4904217
[26] Guo X, Ma L. Inflammation in coronary artery disease-clinical implications of novel HDL-cholesterol-related inflammatory parameters as predictors. Coronary Artery Disease. 2023; 34: 66–77. https://doi.org/10.1097/MCA.0000000000001198
[27] Deng S, Liu Y, Wang Y, Zhang S, Chen X, Yu Z, et al. Progress in macrophage immune regulation of atherosclerosis. American Journal of Translational Research. 2025; 17: 3261–3275. https://doi.org/10.62347/GMTC2479
[28] Zhang B, Zou Y, Yuan Z, Jiang K, Zhang Z, Chen S, et al. Efferocytosis: the resolution of inflammation in cardiovascular and cerebrovascular disease. Frontiers in Immunology. 2024; 15: 1485222. https://doi.org/10.3389/fimmu.2024.1485222
[29] Chowdhury RR, D'Addabbo J, Huang X, Veizades S, Sasagawa K, Louis DM, et al. Human Coronary Plaque T Cells Are Clonal and Cross-React to Virus and Self. Circulation Research. 2022; 130: 1510–1530. https://doi.org/10.1161/CIRCRESAHA.121.320090
[30] Laera N, Malerba P, Vacanti G, Nardin S, Pagnesi M, Nardin M. Impact of Immunity on Coronary Artery Disease: An Updated Pathogenic Interplay and Potential Therapeutic Strategies. Life (Basel, Switzerland). 2023; 13: 2128. https://doi.org/10.3390/life13112128
[31] Ban X, Li Z, Duan Y, Xu K, Xiong J, Tu Y. Advanced imaging modalities provide new insights into coronary artery calcification. European Journal of Radiology. 2022; 157: 110601. https://doi.org/10.1016/j.ejrad.2022.110601
[32] Wang C, Feng Y, Liu X, Sun H, Guo Z, Shao J, et al. Molecular landscape of atherosclerotic plaque progression: insights from proteomics, single-cell transcriptomics and genomics. BMC Medicine. 2025; 23: 254. https://doi.org/10.1186/s12916-025-04058-2
[33] Bär S, Knuuti J, Saraste A, Klén R, Kero T, Nabeta T, et al. Derivation and validation of an artificial intelligence-based plaque burden safety cut-off for long-term acute coronary syndrome from coronary computed tomography angiography. European Heart Journal. Cardiovascular Imaging. 2025; 26: 1163–1173. https://doi.org/10.1093/ehjci/jeaf121
[34] Moss A, Daghem M, Tzolos E, Meah MN, Wang KL, Bularga A, et al. Coronary Atherosclerotic Plaque Activity and Future Coronary Events. JAMA Cardiology. 2023; 8: 755–764. https:

//doi.org/10.1001/jamacardio.2023.1729
[35] Khanna S, Nerlekar N, Bhat A. Reconciling Coronary Artery Calcification in the Lipid-Lowering Era. JACC. Advances. 2026; 5: 102506. https://doi.org/10.1016/j.jacadv.2025.102506
[36] Veneziano FA, Gioia FA, Gentile F. Hybrid PET/CT and PET/MR in Coronary Artery Disease: An Update for Clinicians, with Insights into AI-Guided Integration. Journal of Cardiovascular Development and Disease. 2025; 12: 338. https://doi.org/10.3390/jcdd12090338
[37] Pinna A, Boi A, Mannelli L, Balestrieri A, Sanfilippo R, Suri J, et al. Machine Learning for Coronary Plaque Characterization: A Multimodal Review of OCT, IVUS, and CCTA. Diagnostics (Basel, Switzerland). 2025; 15: 1822. https://doi.org/10.3390/diagnostics15141822
[38] Schulze K, Stantien AM, Williams MC, Vassiliou VS, Giannopoulos AA, Nieman K, et al. Coronary CT angiography evaluation with artificial intelligence for individualized medical treatment of atherosclerosis: a Consensus Statement from the QCI Study Group. Nature Reviews. Cardiology. 2026; 23: 100–115. https://doi.org/10.1038/s41569-025-01191-6
[39] Zhang X, Feng H, Han Y, Yuan X, Jiang M, Wang W, et al. Plaque Stabilization and Regression, from Mechanisms to Surveillance and Clinical Strategies. Reviews in Cardiovascular Medicine. 2024; 25: 459. https://doi.org/10.31083/j.rcm2512459
[40] Sabouret P, Angoulvant D, Pathak A. FOURIER to ODYSSEY: the end of the journey for lipid-lowering therapy trials? Lessons from recent clinical trials with anti-PCSK9 antibodies. EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2018; 14: 144–146. https://doi.org/10.4244/EIJY18M04_1
[41] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. The New England Journal of Medicine. 2018; 379: 2097–2107. https://doi.org/10.1056/NEJMoa1801174
[42] Alhomoud IS. Emerging therapies targeting lipoprotein(a): the next frontier in cardiovascular risk reduction. Frontiers in Medicine. 2025; 12: 1727918. https://doi.org/10.3389/fmed.2025.1727918
[43] Galli M, Gurgoglione FL, Sciarretta S, Abbate A. Inhibition of interleukin-1 or -6 after myocardial infarction: pros, cons, and future perspectives. European Heart Journal. Cardiovascular Pharmacotherapy. 2025; 11: 321. https://doi.org/10.1093/ehjcvp/pvaf022
[44] Broch K, Anstensrud AK, Woxholt S, Sharma K, Tøllefsen IM, Bendz B, et al. Randomized Trial of Interleukin-6 Receptor Inhibition in Patients With Acute ST-Segment Elevation Myocardial Infarction. Journal of the American College of Cardiology. 2021; 77: 1845–1855. https://doi.org/10.1016/j.jacc.2021.02.049
[45] Abbate A, Wohlford GF, Del Buono MG, Chiabrando JG, Markley R, Turlington J, et al. Interleukin-1 blockade with anakinra and heart failure following ST-segment elevation myocardial infarction: results from a pooled analysis of the VCUART clinical trials. European Heart Journal. Cardiovascular Pharmacotherapy. 2022; 8: 503–510. https://doi.org/10.1093/ehjcvp/pvab075
[46] Pan Y, Fan F, Jiang J, Zhang Y. Clinical outcomes of anti-inflammatory therapies inhibiting the NLRP3/IL-1β/IL-6/CRP pathway in coronary artery disease patients: a systemic review and meta-analysis of 37,056 individuals from 32 randomized trials. Inflammation Research. 2025; 74: 99. https://doi.org/10.1007/s00011-025-02058-9
[47] Arun AJ, Darji B, Maksymiuk V, Baig M, Frishman WH. Coronary Artery Calcium as a Biological Staging Marker for Atherosclerosis: Aligning Preventive Therapies With Plaque Evolution. Cardiology in Review. 2026. https://doi.org/10.1097/CRD.0000000000001240 (online ahead of print)
[48] Parizad R, Hatwal J, Brar A, Desai R, Batta A, Mohan B. Artificial Intelligence for Cardiovascular Risk Prediction: An Umbrella Review of Applications and Translational Challenges. Vascular Health and Risk Management. 2026; 22: 590502. https://doi.org/10.2147/VHRM.S590502
[49] Li G, Yu W, Wang Z, Chen Y, Chu M, Li Z, et al. Artificial intelligence-powered automatic coronary computed tomography angiography plaque quantification: comparison against optical coherence tomography. European Heart Journal. Digital Health. 2026; 7: ztag024. https://doi.org/10.1093/ehjdh/ztag024
[50] Xia J, Bachour K, Suleiman ARM, Roberts JS, Sayed S, Cho GW. Enhancing coronary artery plaque analysis via artificial intelligence-driven cardiovascular computed tomography. Therapeutic Advances in Cardiovascular Disease. 2024; 18: 17539447241303399. https://doi.org/10.1177/17539447241303399
[51] Sgreva S, Alsubai SE, Bianchini E, Alqahtani F, Del Sole PA, Elzomor H, et al. Plaques Do Not Act Alone: Time to Redefine Coronary Vulnerability from Lesion to Phenotype. Journal of Clinical Medicine. 2025; 14: 7568. https://doi.org/10.3390/jcm14217568
[52] Buonpane A, De Caterina AR, Trimarchi G, Pizzino F, Ciardetti M, Coceani MA, et al. Uncovering Plaque Erosion: A Distinct Pathway in Acute Coronary Syndromes and a Gateway to Personalized Therapy. Journal of Clinical Medicine. 2025; 14: 5456. https://doi.org/10.3390/jcm14155456
[53] Aikawa M, Sonawane AR, Chelvanambi S, Asano T, Halu A, Matamalas JT, et al. Precision cardiovascular medicine: shifting the innovation paradigm. Frontiers in Science. 2025; 3: 1474469. https://doi.org/10.3389/fsci.2025.1474469
[54] Skalidis I, Stalikas N, Collet C, Chatzizisis YS, Samant S, Apostolos A, et al. Digital twins and simulations in transcatheter coronary and structural heart interventions. European Heart Journal. Digital Health. 2026; 7: ztaf129. https://doi.org/10.1093/ehjdh/ztaf129
[55] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. The New England Journal of Medicine. 2017; 377: 1119–1131. https://doi.org/10.1056/NEJMoa1707914
[56] Currie G, Kiat H. Beyond the Lumen: Molecular Imaging to Unmask Vulnerable Coronary Plaques. Journal of Cardiovascular Development and Disease. 2025; 12: 51. https://doi.org/10.3390/jcdd12020051
[57] Liu WP, Li P, Zhan X, Qu LH, Xiong T, Hou FX, et al. Identification of molecular subtypes of coronary artery disease based on ferroptosis- and necroptosis-related genes. Frontiers in Genetics. 2022; 13: 870222. https://doi.org/10.3389/fgene.2022.870222
[58] Widlansky ME, Liu Y, Tumusiime S, Hofeld B, Khan N, Aljadah M, et al. Coronary Plaque Sampling Reveals Molecular Insights Into Coronary Artery Disease. Circulation Research. 2023; 133: 532–534. https://doi.org/10.1161/CIRCRESAHA.123.323022
[59] Krohn JB, Nguyen YN, Akhavanpoor M, Erbel C, Domschke G, Linden F, et al. Identification of Specific Coronary Artery Disease Phenotypes Implicating Differential Pathophysiologies. Frontiers in Cardiovascular Medicine. 2022; 9: 778206. https://doi.org/10.3389/fcvm.2022.778206
[60] Gaudino M, Di Franco A, Cao D, Giustino G, Bairey Merz CN, Fremes SE, et al. Sex-Related Outcomes of Medical, Percutaneous, and Surgical Interventions for Coronary Artery Disease: JACC Focus Seminar 3/7. Journal of the American College of Cardiology. 2022; 79: 1407–1425. https://doi.org/10.1016/j.ja

cc.2021.07.066
[61] Taqueti VR. Sex Differences in the Coronary System. Advances in Experimental Medicine and Biology. 2018; 1065: 257–278. https://doi.org/10.1007/978-3-319-77932-4_17
[62] Kinoshita D, Suzuki K, Yuki H, Niida T, Fujimoto D, Minami Y, et al. Coronary plaque phenotype associated with positive remodeling. Journal of Cardiovascular Computed Tomography. 2024; 18: 401–407. https://doi.org/10.1016/j.jcct.2024.04.009
[63] Zhu G, Gao Y, Qian J, Lai Y, Lin H, Liu C, et al. Comprehensive analysis of atherosclerotic plaques reveals crucial genes and molecular mechanisms associated with plaque progression and rupture. Frontiers in Cardiovascular Medicine. 2023; 10: 951242. https://doi.org/10.3389/fcvm.2023.951242
[64] Di Vito L, Di Giusto F, Mazzotta S, Scalone G, Bruscoli F, Silenzi S, et al. Management of vulnerable patient phenotypes and acute coronary syndrome mechanisms. International Journal of Cardiology. 2024; 415: 132365. https://doi.org/10.1016/j.ijcard.2024.132365
[65] Kurt B, Reugels M, Schneider KM, Spiesshoefer J, Milzi A, Gombert A, et al. C-reactive protein and cardiovascular risk in the general population. European Heart Journal. 2026; 47: 1799–1810. https://doi.org/10.1093/eurheartj/ehaf937
[66] Menichelli D, Gatto L, Biccirè FG. Editorial: Prognostic value of inflammatory and thrombotic biomarkers in acute coronary syndrome. Frontiers in Cardiovascular Medicine. 2026; 13: 1814669. https://doi.org/10.3389/fcvm.2026.1814669
[67] Wang Z, Tang J, Shi Q, Fang L, Liu N, Zhang J. Synergistic effect of lipoprotein(a) and high-sensitivity C-reactive protein on the risk of all-cause and cardiovascular death in patients with acute myocardial infarction: a large prospective cohort study. Frontiers in Endocrinology. 2024; 15: 1392859. https://doi.org/10.3389/fendo.2024.1392859
[68] Jaime Garcia D, Chagnot A, Wardlaw JM, Montagne A. A Scoping Review on Biomarkers of Endothelial Dysfunction in Small Vessel Disease: Molecular Insights from Human Studies. International Journal of Molecular Sciences. 2023; 24: 13114. https://doi.org/10.3390/ijms241713114
[69] Santos JCD, Cruz MS, Bortolin RH, Oliveira KMD, Araújo JNGD, Duarte VHR, et al. Relationship between circulating VCAM-1, ICAM-1, E-selectin and MMP9 and the extent of coronary lesions. Clinics (Sao Paulo, Brazil). 2018; 73: e203. https://doi.org/10.6061/clinics/2018/e203
[70] Mittal A, Singhal K, Djoumsie EB, Sharma YP, Batta A. Emerging Novel Biomarkers in Acute Coronary Syndrome Management: Insights and Future Directions. Cardiovascular Innovations and Applications. 2026; 11: 984. https://doi.org/10.15212/CVIA.2026.0001
[71] Kowara M, Kopka M, Kopka K, Głowczyńska R, Mitrzak K, Kim DA, et al. MicroRNA Inhibiting Atheroprotective Proteins in Patients with Unstable Angina Comparing to Chronic Coronary Syndrome. International Journal of Molecular Sciences. 2024; 25: 10621. https://doi.org/10.3390/ijms251910621
[72] Kwiecinski J, Tzolos E, Williams MC, Dey D, Berman D, Slomka P, et al. Noninvasive Coronary Atherosclerotic Plaque Imaging. JACC. Cardiovascular Imaging. 2023; 16: 1608–1622. https://doi.org/10.1016/j.jcmg.2023.08.021
[73] Andreini D, Magnoni M, Conte E, Masson S, Mushtaq S, Berti S, et al. Coronary Plaque Features on CTA Can Identify Patients at Increased Risk of Cardiovascular Events. JACC. Cardiovascular Imaging. 2020; 13: 1704–1717. https://doi.org/10.1016/j.jcmg.2019.06.019
[74] Gurgoglione FL, Denegri A, Russo M, Calvieri C, Benatti G, Niccoli G. Intracoronary Imaging of Coronary Atherosclerotic Plaque: From Assessment of Pathophysiological Mechanisms to Therapeutic Implication. International Journal of Molecular Sciences. 2023; 24: 5155. https://doi.org/10.3390/ijms24065155
[75] Wang Y, Chen H, Sun T, Li A, Wang S, Zhang J, et al. Risk predicting for acute coronary syndrome based on machine learning model with kinetic plaque features from serial coronary computed tomography angiography. European Heart Journal. Cardiovascular Imaging. 2022; 23: 800–810. https://doi.org/10.1093/ehjci/jeab101
[76] Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, et al. Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. JAMA. 2022; 327: 1771–1781. https://doi.org/10.1001/jama.2022.5218
[77] Bora R, Kılıç AT, Toprak B. Atherosclerosis and Inflammation: Are the Rules of the Game Changing with Biological Therapies? Journal of Inflammation Research. 2025; 18: 9811–9822. https://doi.org/10.2147/JIR.S531345
[78] Ren Y, Zhou Y, Xiang B, Li Q, Zhou X. Nanotechnology for atherosclerotic plaque stabilisation: bridging innovation and clinical practice. EBioMedicine. 2026; 123: 106102. https://doi.org/10.1016/j.ebiom.2025.106102
[79] Karami Z, Mehrzad J, Akrami M, Hosseinkhani S. Anti-inflammation-based treatment of atherosclerosis using Gliclazide-loaded biomimetic nanoghosts. Scientific Reports. 2023; 13: 13880. https://doi.org/10.1038/s41598-023-41136-y