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Review Article

The clinical relevance of the reversal of coronary atherosclerotic plaque

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of death globally despite advances in preventive therapies. Understanding of the initiation and progression of atherosclerosis, the interplay between lipoproteins, endothelial dysfunction, inflammation, and immune responses is critical to treating this disease. The development of vulnerable coronary plaques prone to thrombosis, can lead to acute coronary syndromes, for these reasons, the potential plaque stabilization and regression through pharmacological interventions, particularly lipid-lowering agents like statins and PCSK9 inhibitors is crucial. The imaging techniques such as intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT) play a key role in assessing plaque composition and guiding interventional therapeutic strategies. Clinical evidence supports the efficacy of intensive lipid-lowering therapy in inducing plaque regression, with studies demonstrating reductions in plaque volume and improvements in plaque morphology assessed by IVUS, OCT and NIRS.

While pharmacological interventions show promise in promoting plaque regression and stabilization, their impact on long-term cardiovascular events requires further investigation. Multimodality imaging and comprehensive outcome trials are proposed as essential tools for elucidating the relationship between plaque modification and clinical benefit in coronary atherosclerosis. The stabilization or regression of atherosclerotic plaque might serve as the phenomenon linking the reduction in LDL-C levels to the decrease in cardiovascular events. Overall, this review emphasizes the ongoing efforts to advance our understanding of ASCVD pathophysiology and optimize therapeutic approaches for improving patient outcomes.

1. Introduction

Despite tremendous progress in study of the pathophysiological mechanisms underlying atherosclerosis and the subsequent development of innovative preventive therapies, atherosclerotic cardiovascular disease (ASCVD) continues to be the leading cause of death and disability worldwide [1]. In 2019, the Global Burden of Disease Collaboration [1] provided a concerning picture regarding the burden of cardiovascular disease (CVD) on the world's population: globally, CVD affects >523 million individuals and causes approximately 1.8 million deaths each year, of which >85 % are due to ASCVD. This global spread highlights the pressing necessity to comprehend how it originates, make progress in its control, and explore therapeutic possibilities for reducing its impact [2]. Thus, this article explores the evolving knowledge of the pathophysiology of atherosclerotic disease and its potential treatment strategies based on new insights into the underlying causes.

2. The cellular mechanism of atherosclerotic plaque progression and regression

Emerging discoveries derived from translational science have triggered a substantial change in the understanding of the pathophysiology of atherosclerosis, which has challenged many established concepts. Atherosclerosis is a chronic inflammatory disease of the arterial wall in which different cell populations interact with each other and promote subclinical disease progression to cardiovascular (CV) events. Advances in single-cell biology are shedding light on the identification of new cell communities and the molecular pathways involved in the development

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of ASCVD [3].

Arterial walls are formed by three concentric layers characterized by different features and structure. The innermost tunica intima is composed of a monolayer of endothelial cells that separates the circulating blood flow from the vascular wall tissue. The central tunica media is composed of smooth muscle cells that withstand hemodynamic wall stress and are inaccessible to inflammatory cells because they are bounded by a hydrophobic inner and outer elastic lamina. Finally, the outermost tunica adventitia is composed of a dense network of connective tissues including fibroblasts, collagen fibers, the vasa vasorum, nerve endings, and quiescent resident inflammatory cells that are all involved in arterial wall homeostasis [4].

3. Initiation and progression of atherosclerosis

The natural history of atherosclerotic plaque formation involves apolipoprotein B-containing lipoproteins, in particular low-density lipoprotein cholesterol (LDL-C), which is considered the main causal risk factor of ASCVD [5,6]. LDL-C influences four main types of cell populations (endothelial cells (ECs), smooth muscle cells (SMCs), macrophages, and T cells) that communicate with each other. This communication leads to morphological and structural changes among the three layers of the arterial wall.

Chronic exposure to pro-inflammatory atherogenic stimuli related to traditional cardiovascular risk factors (e.g., lipids, smoking, hyperglycemia, hypertension, obesity, physical inactivity, familial history of CVD, and kidney disease) and non-traditional cardiovascular risk factors (e.g., air pollution [7,8], gut microbiota [9,10], mental stress, and sleep disturbance [11,12]) results in endothelial dysfunction and subsequent increased endothelial permeability that promotes the transcytosis of LDL-C particles across the endothelium and their extracellular retention and oxidation into the tunica intima of the arterial vessel. Although the molecular mechanisms that control this process are still not fully understood, this step is considered the primum movens of lesion formation. Oxidated LDL elicits the release of pro-inflammatory cytokines, which drive the recruitment of leukocytes (e.g., monocytes and T cells) by inducing the endothelial cells to express a leukocyte adhesion molecule, such as VCAM-1.

The entry of monocytes and T cells into the tunica intima defines the beginning of an intensive interaction between the innate and adaptive immune responses. That is, monocyte-derived macrophages engulf the lipids and become foam cells, namely, a pro-inflammatory, pro-thrombotic cellular phenotype rich in cholesterol ester droplets. On the other hand, the T cells release a variety of inflammatory mediators to orchestrate innate immune cell function [2,13]. Communication between the different cellular components of innate and adaptive immunity boosts the release of pro-inflammatory cytokines that sustain and amplify the local inflammatory response. Foam cells represent the basic cellular unit of “fatty streaks,” which constitute the earliest macroscopic lesion of atherosclerotic plaque’s life cycle.

The onset of a vicious immune-mediated inflammatory cycle in the lesion site triggers the recruitment of SMCs from the tunica media to the intima layer. Here, they undergo metaplasia to convert into a heterogeneous spectrum of extracellular, matrix-producing, macrophage-like cells with gradual changes in their expression profile from a contractile state to a fibroblast- and osteoblast-like state. The proliferation of SMCs and the accumulation of the extracellular matrix within the tunica intima leads to fibrous cap formation above the lipid core and to the conversion of the fatty streak into a fibrofatty lesion [3,14].

Atherosclerotic plaque formation is followed by a period of subclinical atherosclerotic disease progression, which is characterized by plaque morphological changes [15,16]. The death of foam cells and SMCs in the lesion and their ineffective clearance (defective efferocytosis) promote lipid or necrotic core formation. From this stage, activated T cells drive plaque evolution by directing other inflammatory cells toward an atheropromoting or atheroprotective phenotype through a fine balance of pro-atherosclerotic (such as interferon gamma) or anti-atherosclerotic (such as transforming growth factor beta) mediators. The different extents of extracellular matrix synthesis or destruction and the variable rates of apoptosis and necrosis of the macrophagic cells influence the morphological characteristics of the atherosclerotic plaque, which shifts from a thin cap fibroma with a high lipid core to a fibroatheroma with more matrix and less lipids [2,17]

4. Complicated vulnerable coronary plaque

The subclinical progression of coronary atherosclerotic plaque does not advance uniformly over time. Instead, it alternates between phases of relative quiescence and phases of rapid growth. This alternation suggests episodic rather than continuous lesion evolution, in which the plaque acquires unstable characteristics and becomes more prone to thrombosis and subsequent development of acute coronary syndrome (ACS).

In 1989, Muller, Tofler, and Stone pioneered the concept of “vulnerable plaque” to define atherosclerotic plaque with specific anatomical and biological properties at high risk of destabilization and occlusion [18,19]. The three main mechanisms of plaque thrombosis that cause ACS are plaque rupture, plaque erosion, and calcified nodule [20–22]. The most common cause of coronary thrombosis, plaque rupture is caused by a fracture or fissure of the fibrous cap that overlies the necrotic lipid core of the plaque, which results in contact between the blood coagulation factors with thrombogenic material within the plaque [23].

Plaque erosion is the second most frequent cause of ACS. It is caused by a discontinuity in the intimal monolayer due to endothelial injury, which leads to the formation of neutrophil extracellular traps (NETs) that actively contribute to thrombus formation and propagation [24,25]. Finally, plaque with a calcified nodule is the least common of the three causes of ACS. It is caused by heavily calcified plaque with a calcified nodule that protrudes into the lumen-stimulating coronary thrombosis [26].

Advances in imaging techniques have helped to identify the major characteristics of each type of vulnerable plaque before it becomes a culprit lesion. A plaque prone to rupture is an inflamed thin-cap fibroatheroma (TCFA) that is characterized by a thin fibrous cap with macrophages and T cell infiltration. It is further characterized by a decreased SMC content and by a lipid-rich atheromatous core with expansive remodeling [27–29]. On the other hand, a plaque prone to erosion is distinguished by the lack of a lipid or necrotic core and a stronger propensity to be eccentric with constrictive remodeling. Lastly, a plaque with a calcified nodule, even if it is generally free of high levels of inflammation, should be considered high risk if the calcific protrusion causes turbulent blood flow.

It is crucial to emphasize that “complicated plaque” does not necessarily result in CV symptoms and events. Instead, it can complicate with no clinical manifestation and be detected only later in an incidental manner as a “healed plaque.” In fact, the advent of intracoronary imaging and particularly optical coherence tomography (OCT) has allowed us to photograph coronary plaque in great detail, offering us new pathophysiological insights into the natural history of atherosclerosis. It is not uncommon to observe a layer of extracellular matrix with recently deposited collagen overlying the site of a prior disruption with a novel lipid-rich core that develops just above the area where the previous fibrous cap had broken [30,31].

4.1. Intracoronary imaging modalities for the study of atherosclerotic plaque

Atherosclerosis is a dynamic process that involves positive remodeling of the arterial wall (Fig. 2). In the early stages, luminal changes are not apparent as the adventitial wall compensates for disease progression [32]. The “Glagov effect” suggests that the luminal area of

atherosclerotic coronaries remains relatively constant up to a 40 % stenosis, which preserves the coronary lumen through compensatory vascular dilation [33]. This can lead to the underestimation of disease severity in angiograms, ignoring dangerous intrinsic changes within the vessel wall.

Intracoronary imaging techniques, such as intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and OCT, can reveal the extent and composition of atherosclerotic plaques in vivo [34–36] (Fig. 3). IVUS, which was introduced >30 years ago, provides grayscale images with a resolution of 80–120 μm and allows for tomographic imaging of the entire coronary vessel wall as well as accurate quantification of the in vivo atheroma burden. IVUS evaluations, typically conducted at baseline and follow-up, have been crucial for studying the progression-regression of coronary atherosclerosis, which is essential for assessing the effects of anti-atherosclerotic drugs on the plaque burden [34,37]. For this purpose, two volumetric IVUS endpoints, namely the percent atheroma volume (PAV) and the total atheroma volume (TAV), have been established. Prospective data indicate that PAV, also known as the plaque burden in clinical studies, can identify patients at risk of future CV events [37].

The IVUS-NIRS is a more advanced technique that combines IVUS and NIRS in a single catheter. While IVUS calculates the plaque burden, NIRS accurately identifies and quantifies the lipid component [35]. Relatedly, the Lipid Core Burden Index (LCBI) is an advanced metric used to assess the lipid content in coronary artery plaques, providing valuable insights into the vulnerability of these plaques. LCBI values are particularly crucial in identifying lipid-rich plaques that are prone to rupture, which can lead to future MACE. Studies have shown that a high LCBI, particularly the maximum LCBI over a 4 mm segment (maxLCBI_4 mm), is an independent predictor of future cardiac events [38,39]. The maxLCBI4mm considers the 4 mm segment with the highest LCBI within the studied vessel [35,40]. Studies have validated maxLCBI4mm as a reliable measure of plaque vulnerability, which is associated with both culprit and non-culprit lesions at a higher risk of future coronary events [40].

The introduction of NIRS has significantly enhanced the ability to detect these high-risk plaques, complementing other imaging modalities IVUS and OCT. These techniques together improve the precision in evaluating plaque characteristics and guide therapeutic decisions [41]. For instance, the integration of NIRS with IVUS can simultaneously provide information on both plaque morphology and composition, offering a comprehensive assessment of coronary artery disease [39]. By identifying and quantifying the lipid content in plaques, LCBI plays a crucial role in cardiovascular risk stratification and management, enabling targeted treatments to prevent adverse outcomes in patients with coronary artery disease [38].

Lastly, the introduction of OCT has been a revolution in the field due to its tenfold higher resolution than IVUS. OCT images can meticulously analyze the lipid, calcified, and fibrotic composition of coronary plaques and provide information about the fibrous cap and plaque stability [36].

5. Stabilization and regression of coronary plaque

Fortunately, through the application of ambitious therapeutic targets and the support of intensive lipid-lowering agents, it is possible to reverse the natural history of ASCVD by achieving plaque stabilization and regression. This can be defined not necessarily as an increased luminal diameter measured by coronary angiography but as a morphological plaque change with reduced risk of subsequent CV events. Achieving this ambitious goal means eliminating high-risk plaque features by both the reduction of total plaque volume and the modification of plaque components, in particular, a reduction in lipid and macrophage content and in the inflammatory state and the thickening of the fibrous cap (Fig. 1). Indeed, fibrous cap thickness, necrotic core volume, and positive remodeling have demonstrated their ability to predict the risk of future CV events [42]. However, it is important to clarify that it is not always possible to reverse the life cycle of atherosclerotic plaques. For example, calcific plaques, as opposed to lipid-rich plaques, are very difficult to modify, and this point further emphasizes the need to act pharmacologically as soon as possible while avoiding entering an irreversible phase of the disease.

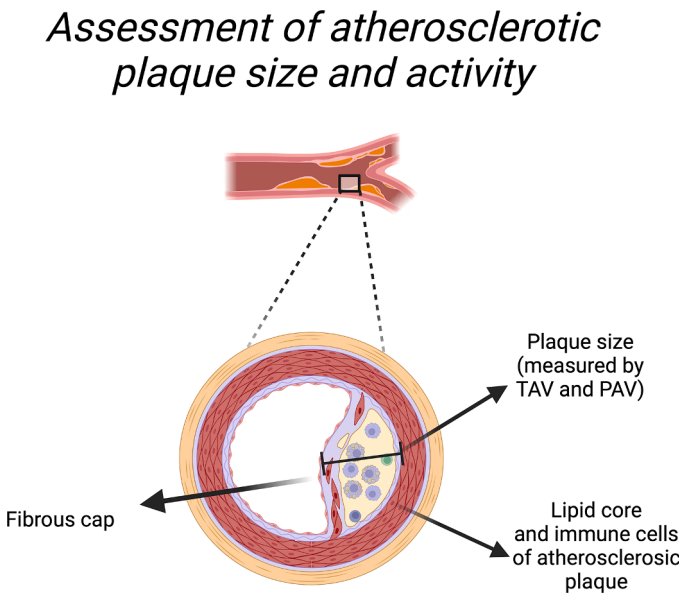

Fig. 1. Details of a vulnerable atherosclerotic plaque.
SMCs: Smooth muscle cells.

5.1. Pharmacological interventions for plaque reversal in coronary atherosclerosis

Effective pharmacological interventions are required for reversing and stabilizing atherosclerotic coronary plaques. Several pharmacological approaches have demonstrated efficacy in plaque reversal, including lipid-lowering agents, anti-inflammatory medications, and novel therapies that target plaque composition.

5.2. Lipid-Lowering agents

Statins are the cornerstone of lipid-lowering therapy. They exert their effects through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme in cholesterol biosynthesis. Aside from their cholesterol-lowering properties, statins also possess pleiotropic effects, including anti-inflammatory and antioxidant activities, which contribute to plaque stabilization and regression [43].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a novel class of medications that effectively reduce LDL cholesterol levels by reducing the degradation of the LDL receptor. These agents have shown remarkable results in promoting plaque regression, particularly in patients with familial hypercholesterolemia and high cardiovascular risk [44].

Ezetimibe and bempedoic acid are notable for their roles in the stabilization and regression of atherosclerotic plaques through their cholesterol-lowering effects. Ezetimibe inhibits the Niemann-Pick C1-Like 1 (NPC1L1) protein, reducing intestinal cholesterol absorption. This mechanism has been shown to significantly LDL cholesterol levels when used in combination with statins. Clinical trials, such as the IMPROVE-IT study [45], demonstrated that adding ezetimibe to statin therapy not only lowers LDL-C levels more effectively than statins alone but also leads to a significant reduction in atherosclerotic plaque volume, as evidenced by intravascular ultrasound (IVUS) studies. Meta-analyses have supported these findings, indicating a substantial

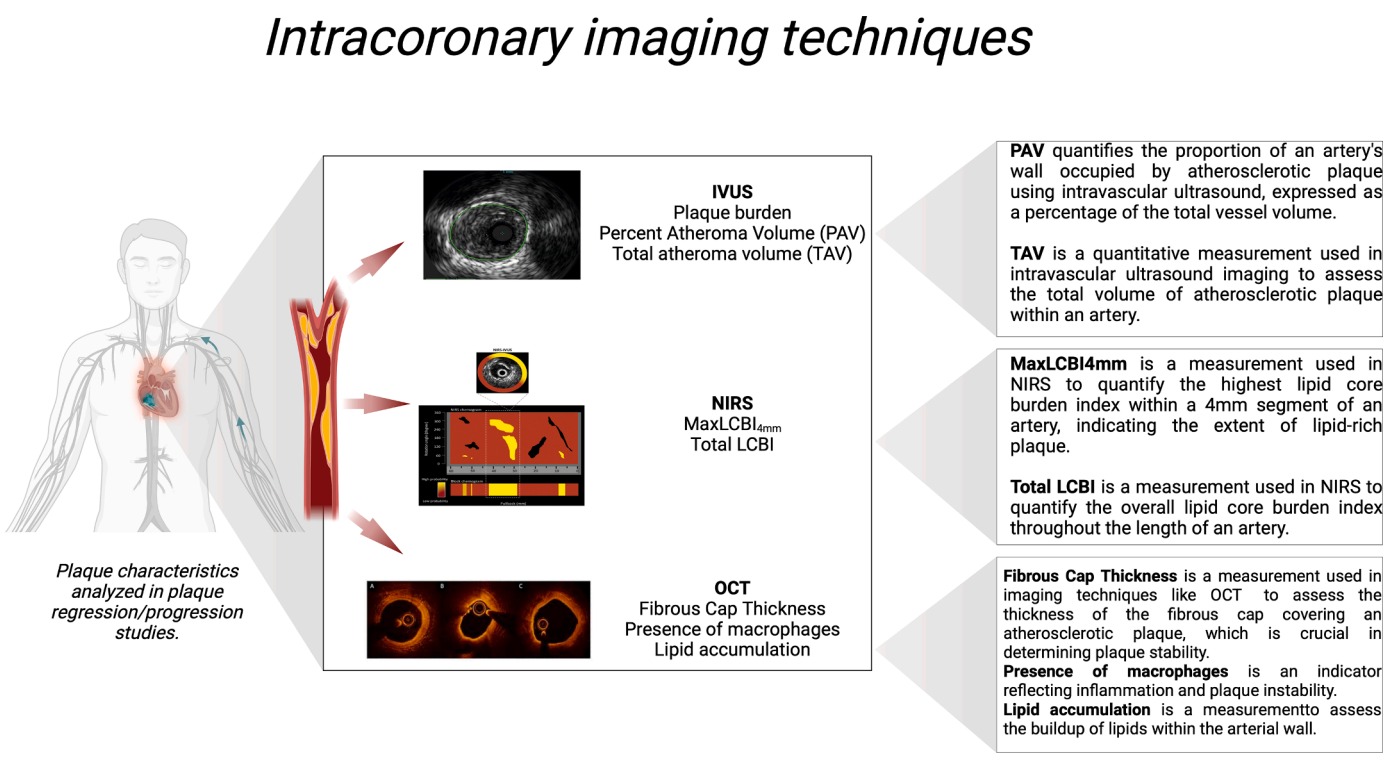

Fig. 2. Parameters evaluated for atherosclerotic plaque size, stability, and activity.
PAV: Percent Atheroma Volume. TAV: Total Atheroma Volume.

decrease in total atheroma volume (TAV) with combined ezetimibe-statin therapy, thereby contributing to plaque stabilization and regression [46,47].

Bempedoic acid, on the other hand, inhibits ATP citrate lyase, an enzyme involved in the hepatic synthesis of cholesterol [48]. This action results in decreased LDL-C levels, complementing the effects of statins and other cholesterol-lowering therapies. Although clinical data on bempedoic acid specifically regarding plaque stabilization and regression are less extensive than for ezetimibe, its LDL-C lowering efficacy suggests it could have similar beneficial effects on atherosclerotic plaques. The CLEAR program demonstrated significant LDL-C reductions in patients treated with bempedoic acid, highlighting its potential role in cardiovascular risk reduction [49]. Additionally, oral non-statin agents, such as bile acid sequestrants, function by binding bile acids in the intestinal lumen. This leads to an increased hepatic uptake of cholesterol and subsequent reduction in LDL cholesterol levels. While their efficacy in inducing plaque regression may be modest compared to statins, they remain a valuable adjunct to lipid-lowering therapy, particularly in patients with statin intolerance [50].

5.3. *Novel therapies for targeting plaque composition*

Acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors represent a promising class of medications that modulate intracellular cholesterol esterification and ultimately reduce the accumulation of cholesterol within macrophages and promote reverse cholesterol transport. Early preclinical studies have demonstrated the potential of ACAT inhibitors to induce plaque regression, which warrants further investigation in clinical settings [51].

In addition, therapies that target the extracellular matrix within atherosclerotic plaques, such as the inhibitors of matrix metalloproteinases (MMPs) and agents that promote collagen synthesis, have emerged as potential strategies for stabilizing vulnerable plaques and preventing rupture. These interventions aim to enhance the fibrous cap thickness of plaque and reduce the risk of thrombotic complications [52]. Moreover, novel agents that promote cholesterol efflux from macrophage foam cells, such as liver X receptor (LXR) agonists and apolipoprotein A-I (apoA-I) mimetics, have shown promising results in preclinical models of atherosclerosis. By enhancing the efflux of cholesterol from plaques, these agents contribute to plaque regression and stabilization and offer new avenues for therapeutic intervention [53]. One notable study in this context is the AEGIS-II trial, which investigated CSL 112, a formulation of apolipoprotein A-I (apoA-I), the main protein component of high-density lipoprotein (HDL). ApoA-I plays a pivotal role in reverse cholesterol transport by promoting cholesterol efflux from macrophages in atherosclerotic plaques to HDL particles, which then transport cholesterol to the liver for elimination. The AEGIS-II trial was a large, multicenter, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of CSL112 in patients with ACS. Treatment with CSL112 significantly enhanced cholesterol efflux capacity [54]. This suggests that CSL 112 can effectively increase the mobilization of cholesterol from atherosclerotic plaques, potentially reducing plaque burden and stabilizing existing plaques. However, the AEGIS-II trial failed to show that CSL112 apoA-1 infusion reduces adverse CV outcomes after AMI [55].

Finally, pharmacological interventions play a crucial role in the management of coronary atherosclerosis, with numerous agents demonstrating efficacy in promoting plaque regression and stabilization. While the emergence of novel plaque-modifying therapies provides additional opportunities for improving clinical outcomes, lipid-lowering therapies (LLT) remain central to the treatment of atherosclerosis. For this reason, the focus of pharmacological interventions in this review is on LLT.

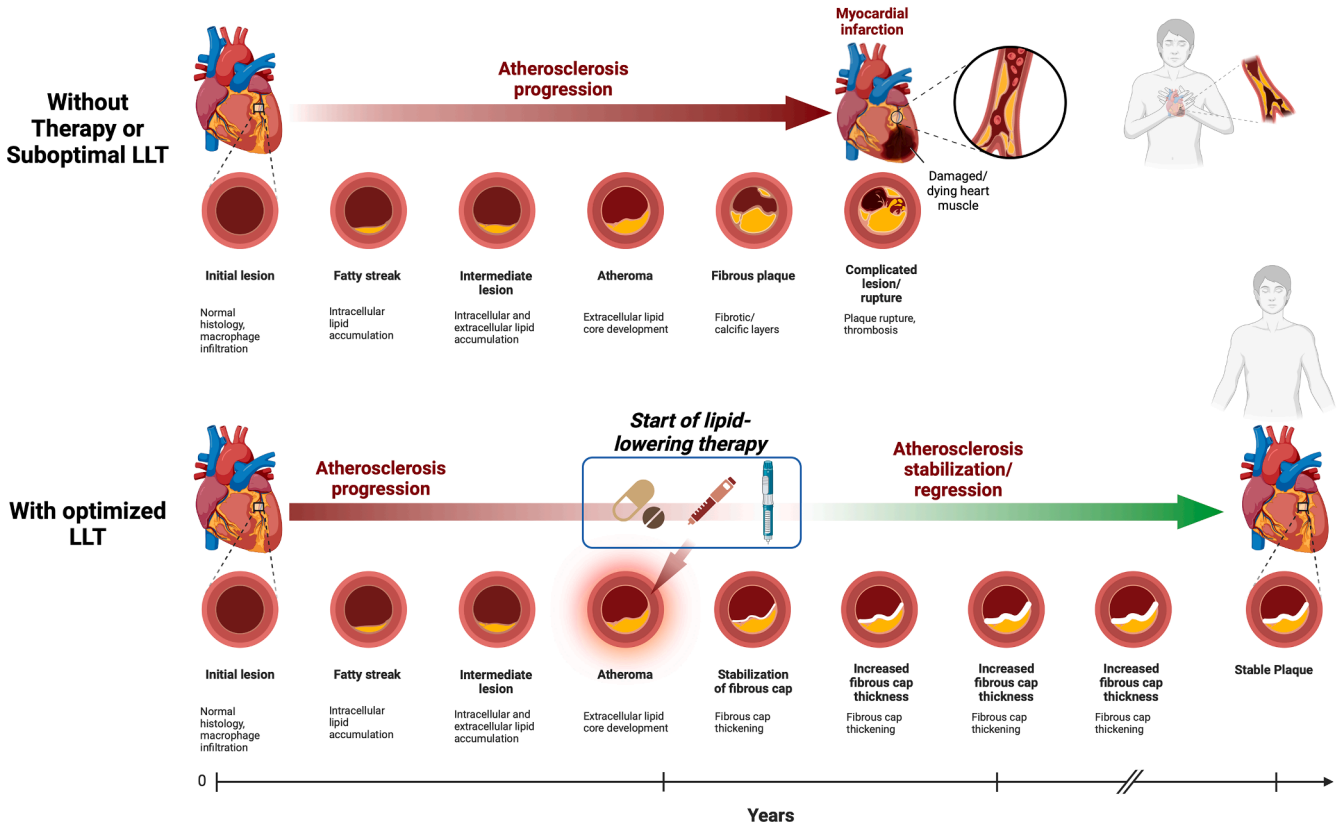

Fig. 3. Intracoronary imaging techniques.
IVUS: IntraVascular UltraSound. LCBI: Lipid Core Burden Index. NIRS: Near Infrared Spectroscopy. OCT: Optical Oherence Tomography. PAV: Percent Atheroma Volume. TAV: Total Atheroma Volume.
The clinical relevance of the reversal of coronary atherosclerotic plaque
LLT: Lipid Lowering Therapy.

6. Intensive LDL-C lowering therapy: Plaque stabilization and regression

6.1. The imaging truth: Key findings of clinical evidence for plaque reversal

In terms of plaque removal through the above-mentioned methods, we should consider not only the reduction of plaque volume but also differentiation with respect to the effects of a) the reduction of atherosclerosis progression, b) the regression of atherosclerotic plaque, and c) a third change that we can consider plaque stabilization. For example, the inaugural trial that utilized IVUS in 1997 showcased a significant reduction in atheroma volume over 36 months with pravastatin (10 mg once daily) compared to a placebo (7 % reduction versus a 41 % increase; $p < 0.01$) [56]. This pioneering study set the stage for subsequent investigations that encompassed diverse trial designs, such as IVUS and coronary computed tomography angiography (CCTA).

Observational studies, notably the ASTEROID (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden) study in 2006, substantiated the potential of statin therapy to reduce plaque and revealed a 6.1 % reduction in total atheroma volume at 24 months among patients taking 40 mg once daily rosuvastatin measured by IVUS [57]. Intriguingly, the impact of comorbidities, particularly diabetes mellitus, emerged as a crucial factor that influenced statin efficacy in achieving plaque regression. Further, a sub-study of the The Prediction of Extent and Risk Profile of Coronary Atherosclerosis and Their Changes During Lipid-lowering Therapy Based on Non-invasive Techniques (PREDICT) trial, which evaluated 61 stable angina patients, disclosed that individuals with diabetes experienced a significantly greater increase in plaque volume, which implied a potential blunting of statin effectiveness [58] (Table 1).

At the same time, trials have consistently demonstrated the superiority of high-intensity statin therapy for plaque regression compared to low-intensity statins. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial in 2004, which compared atorvastatin (80 mg once daily) with pravastatin (40 mg once daily), identified a greater reduction in total atheroma volume at 18 months with atorvastatin (−0.4 % versus 2.7 %; $p < 0.05$) [59]. Similarly, The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) trial showed reductions in total atheroma volume (−4.8 % versus −3.2 %; $p < 0.05$) among patients treated with rosuvastatin (40 mg once daily) compared with atorvastatin (80 mg once daily) over 24 months, although this difference did not reach significance for the primary endpoint (PAV) [60].

Plaque composition alterations under statin influence have been scrutinized through various imaging techniques. Statin therapy has generally been shown to induce favorable changes, including increased fibrous and calcified plaque volumes and reductions in fibrofatty volume, necrotic core, and noncalcified plaque volumes. Moreover, fibrous cap thickness has been shown to increase, while a decrease in lipid

Table 1
Prospective, randomized studies on coronary atherosclerotic plaque regression at IVUS, OCT, and NIRS.

Study	Year	Therapy	No. of patients	Population	Imaging	Outcome	Outcome change	Ref.
ASTEROID	2006	Rosuvastatin 40 mg	349	Documented coronary artery disease (at least one stenosis ≥20 %; target segment with stenosis ≤50 % and minimum length 40 mm)	IVUS	Change in PAV	−0.79 % ($p < 0.01$)	[57]
IBIS-4	2015	Rosuvastatin 40 mg	103	ACS (STEMI)	IVUS	Change in PAV	−0.9 (−1.56 to −0.25) ($p = 0.007$)	[64]
REVERSAL	2004	Atorvastatin 80 mg vs Pravastatin 40 mg	502	Documented coronary artery disease (at least one stenosis ≥20 %; target segment with stenosis ≤50 % and minimum length 30 mm)	IVUS	Change in PAV	+0.2 vs +1.6 ($p < 0.001$)	[59]
SATURN	2011	Atorvastatin 80 mg vs rosuvastatin 40 mg	1039	Documented coronary artery disease (at least one vessel with stenosis >20 %; target segment with stenosis ≤50 %)	IVUS	Change in PAV	−0.99 % vs −1.22 % ($p = 0.17$)	[60]
YELLOW	2013	Rosuvastatin 40 mg vs standard therapy	87	Multivessel stable coronary artery disease (at least two vessels with stenosis ≥ 70 %)	NIRS	Change in $LCBI_{4mm}$ max	2.4 vs −149.1 ($p < 0.01$)	[61]
GLAGOV	2016	Evolocumab 420 mg monthly vs placebo	968	Documented coronary artery disease (at least one stenosis ≥20 %; target segment with stenosis ≤50 %) on optimized statin therapy	IVUS	Change in PAV	−0.95 % vs +0.05 % ($p < 0.001$)	[68]
HUYGENS	2022	Evolocumab 420 mg monthly vs placebo	161	ACS (NSTEMI)	OCT	Fibrous cap thickness	+42.7 μm vs +21.5 μm ($p = 0.015$)	[69]
PACMAN-AMI	2022	Alirocumab 150 mg/2 weeks	300	ACS (STEMI and NSTEMI)	IVUS OCT NIRS	Change in PAV; Fibrous cap thickness; Change in $LCBI_{4mm}$ max	IVUS: −2.13 % vs −0.92 % ($p = 0.001$) OCT: +62.67 μm vs +33.19 μm ($p = 0.001$) NIRS: −79.42 vs −37.60 ($p = 0.006$)	[70]

ACS: Acute Coronary Syndrome. IVUS: IntraVascular UltraSound. LCBI: Lipid Core Burden Index. NIRS: Near Infrared Spectroscopy. NSTEMI: Non-ST Elevation Myocardial Infaction. OCT: Optical Oherence Tomography. PAV: Percent Atheroma Volume. STEMI: ST Elevation Myocardial Infaction. TAV: Total Atheroma Volume.

content has been demonstrated. Observational studies, such as Reduction in YEllow Plaque by Aggressive Lipid LOWering Therapy (YELLOW) study and Integrated biomarker imaging study (IBIS-4), have provided nuanced insights into the impact of statins on lipid content and inflammation [61,62].

Recent assessments using CCTA have corroborated these findings and revealed shifts in plaque composition with statin therapy [63–65]. These changes encompassed increases in calcified plaque and reductions in noncalcified plaque. The intricate relationship between statin treatment and various facets of plaque morphology suggests a multifaceted interplay, with outcomes influenced by factors such as comorbidities and statin intensity.

In addition, the impact on plaque regression of adding ezetimibe 10 mg to optimal medical therapy (OMT) has been studied in several trials using IVUS. The majority of these studies reported significant plaque regression, ranging from 2.9 % to 13.9 %. Masuda et al. [66] observed a substantial reduction in TAV in the ezetimibe group compared to OMT alone (13.2 % versus 3.1 %; $p < 0.05$) at six months for 40 patients. Other larger trials indicated a trend toward greater plaque regression in the ezetimibe-with-OMT group compared to OMT alone, but these differences were not statistically significant. Similarly, Hibi et al. [67] assessed plaque composition using IVUS, which revealed an increased lipid volume and reduced fibrous and calcified plaque volume in the ezetimibe group [67]. However, the observed benefits of adding ezetimibe in terms of inducing plaque regression appear to be modest.

In recent years, monoclonal antibodies targeting PCSK9 have become a common addition to the treatment of coronary artery disease alongside statins and ezetimibe. The GLAGOV trial [68], conducted in 2016, was the first double-blind, randomized controlled trial that evaluated the impact of evolocumab on atherosclerotic plaque in patients with confirmed coronary artery disease. In the trial, 988 patients receiving optimized statin therapy were randomly assigned to receive either evolocumab (at a monthly subcutaneous dosage of 420 mg) or a placebo. After 78 weeks, the study revealed that over 60 % of the patients treated with evolocumab experienced plaque regression, which exceeded the rate observed in the patients receiving standard therapy (below 50 %). Notably, the PCSK9 inhibitor arm showed significantly lower LDL cholesterol levels compared to standard therapy (36.6 versus 93 mg/dl; difference −56.5 mg/dl (95 % confidence interval −59.7 to −53.4); $p < 0.001$). This reduction in LDL cholesterol was associated with a more pronounced decrease in both PAV (−0.95 % versus +0.05 %; $p < 0.001$) and TAV (−5.8 versus −0.9 mm3; $p < 0.001$) [68].

Fascinating insights from OCT observations of plaque in patients undergoing PCSK9 inhibitor therapy emerged from two randomized trials: The High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS) study and Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction (PACMAN-AMI) [69,70]. In the HUYGENS trial, the primary endpoint was the absolute change in minimum fibrous cap thickness, assessed by serialized OCT, from baseline to 50 weeks. Among 135 patients with assessable images, the evolocumab group achieved significantly lower mean LDL cholesterol levels (28.1 versus 87.2 mg/dl; $p < 0.001$). This group exhibited a greater increase in minimal fibrous cap thickness (+42.7 versus +21.5 μm; $p = 0.015$), a decrease in maximal lipid arc (−57.5° versus −31.4°; $p = 0.04$), and a reduction in the macrophage index (−3.17 versus −1.45 mm; $p = 0.04$) in plaques with a lipid component. Additionally, a greater regression of PAV was observed with evolocumab compared to placebo plus OMT

(−2.29 ± 0.47 % versus −0.61 ± 0.46 %; $p = 0.009$) [69].

In the PACMAN-AMI trial, the non-culprit coronary arteries of 300 patients were assessed using IVUS, NIRS, and OCT at admission and after 52 weeks. The patients treated with alirocumab and statins, in comparison to those undergoing high-intensity statin treatment alone, demonstrated a greater reduction in mean PAV change in their non-culprit arteries (−2.13 % versus −0.92 %; $p < 0.001$). The addition of alirocumab was associated with a greater reduction in plaque lipid load (mean change in maximum LCBI within 4 mm was −79.42 with alirocumab and −37.60 with placebo; $p = 0.006$), an increased minimum fibrous cap thickness (mean change 62.67 versus 33.19 μm; $p = 0.001$), and a decreased angular extent of macrophage infiltration ($p < 0.001$). Notably, the substantial reduction in the angular extent of the macrophage infiltration observed in the PACMAN-AMI study was not correlated with a significant decrease in C-reactive protein values, in contrast to studies conducted with statins [70].

6.2. *The clinical truth: Reduction of cardiovascular events and long-term benefits*

Several studies have consistently shown that achieving lower levels of LDL-C is linked to a decrease in major adverse CV events (MACE) [71]. Likewise, as discussed earlier, the extent to which treatments lower LDL-C seems to correspond with the extent of plaque regression. However, there is limited data that evaluates whether plaque regression or its stabilization by reducing LDL-C directly translates to a reduction in CVs [72].

Plaque progression is a necessary step in the evolution of atherosclerotic plaque, progressing from a nonobstructive plaque to an acute coronary event [73]. This progression occurs over the course of several weeks to months, during which the plaque progressively enlarges before rupturing and resulting in an acute event. The pathology of these plaques has been investigated by examining thrombosis sites associated with myocardial infarction and cardiac death [74]. Three primary types of underlying lesions prone to thrombosis have been identified. In order of occurrence, they are plaque rupture, plaque erosion, and calcified nodules [75]. Plaque rupture stands out as the most frequent cause of coronary thrombotic events and contributes to approximately 70 % of such occurrences and cardiovascular deaths [76]. Notably, pathology studies indicate that plaque ruptures may happen without accompanying events, and previously healed ruptured plaques are commonly found in patients without clinical heart disease, which serves as a prevalent mechanism in plaque progression [18].

However, it has been suggested that intensive lipid-lowering therapy can halt plaque progression and reduce the risk of acute events. In fact, stabilization/regression of atherosclerotic plaque could be the epiphenomenon that relates LDL-C reduction and reduction of CV events. The crux of the matter is that there is crucial clinical relevance in atherosclerotic plaque reversal: it could be argued that most acute coronary events result from plaque rupture, that rupture is secondary to plaque progression (or necrotic evolution), and that plaque progression is modifiable with LLT. The progression to an atherosclerotic vulnerable plaque, characterized by a thin cap fibroatheroma, a large necrotic core, and the development of micro-vessels within the plaque, is governed by the balance between pro-inflammatory and anti-inflammatory molecules. Moreover, inflammation is a major event in atherosclerosis and plaque progression and is usually related to decreased structural stability [77] (**Graphical Abstract**). Recent findings appear to suggest that the degree of stenosis has little impact on the fate of plaque compared to its structural features. However, controversy surrounding this hypothesis suggests that plaques may alternate between vulnerable and non-vulnerable phenotypes, meaning that non-vulnerable plaques may transition into an unstable morphology and suffer rupture or erosion. A recent meta-regression analysis of 17 prospective studies demonstrated an association between reductions in plaque volume and MACE [78]. This analysis revealed that each 1 % reduction in PAV was associated with a 20 % reduction in the odds of experiencing MACE [78]. Despite this observed association, however, direct evidence linking plaque regression to a reduction in CV events is currently lacking.

Utilizing multimodality imaging trials could enhance the efficiency of drug development by identifying medication candidates that induce regression and stabilization. Such trials could pave the way for more extensive outcome trials. Notably, only one post hoc, pooled analysis encompassing six IVUS progression/regression trials with a total of 4137 patients has explored a direct association between atheroma volume progression and adverse CV events [79].

The recent PACMAN-AMI sub-analysis investigated the rates, determinants, and prognostic value of triple regression in patients with acute myocardial infarction who underwent high-intensity lipid-lowering therapy [80]. Triple regression was defined by the presence of PAV reduction, a maximum LCBI within a 4 mm reduction, and a minimal increase in fibrous cap thickness. The study assessed one-year follow-up clinical outcomes and found that 31.7 % of the 84 patients (40.8 % in the alirocumab group versus 23.0 % in the placebo group) presented triple regression, with statistical significance ($p < 0.002$). Additionally, patients with triple regression had lower on-treatment LDL-C levels compared to patients without regression, with a between-group difference of 27.1 mg/dL ($p < 0.001$). The study concluded that triple regression was independently predicted by alirocumab treatment [Odds Ratio (OR): 2.83; $p < 0.001$)] and a higher baseline maximum LCBI within 4 mm (OR: 1.03; $p < 0.013$) [80]. The patients with triple regression also had a lower frequency of the composite clinical endpoint of death, myocardial infarction, and ischemia-driven revascularization when compared to patients without triple regression (8.3 % versus 18.2 %; $p < 0.04$).

These data showed that triple regression was associated with better clinical outcomes and was independently predictable by alirocumab treatment and a higher baseline maximum LCBI within 4mm [80]. The study's finding of a relatively high proportion of patients experiencing triple regression (31.7 %) was not unexpected. This can be attributed to the remarkably low on-treatment levels of LDL-C attained, with the triple regression group reaching 38.4 mg/dL compared to 55.7 mg/dL in the non-triple regression group. Despite the relatively short follow-up duration, robust anti-atherosclerotic effects were observed, as evidenced by a substantial percentage of subjects exhibiting individual reductions in PAV (75.1 %), lipid levels (64.1 %), and an increase in fibrous cap thickness (64.9 %) [80].

7. Conclusions

The presence of a coronary plaque burden as an imaging indicator of atherosclerotic cardiovascular disease correlates with the likelihood of experiencing CV events. Moreover, the stabilization and regression of coronary atherosclerotic plaque serve as significant biomarkers that indicate the activity of the disease. The development of advanced modalities for plaque imaging could streamline the investigation of both progression and regression, which emphasizes the importance of not only reducing plaque volume but also enhancing plaque stability.

Pharmacological interventions for plaque reversal in coronary atherosclerosis play a pivotal role in managing this dynamic process. Lipid-lowering agents, especially statins and PCSK9 inhibitors, remain central to therapy as they exhibit not only cholesterol-lowering effects but also anti-inflammatory and plaque-stabilizing properties. While plaque regression and stabilization are associated with lower LDL-C levels and improvements in plaque composition, the direct translation of these changes into reduced CV events requires further exploration. The intricate relationships between plaque morphology, inflammation, and clinical outcomes underscore the need for comprehensive studies to evaluate the long-term benefits of pharmacological interventions.

While pharmacological interventions demonstrate efficacy in promoting plaque regression and stabilization, their impact on long-term cardiovascular outcomes warrants further investigation. Multimodality

imaging and comprehensive outcome trials are essential to advance our understanding of the intricate relationship between plaque modification and clinical benefit in coronary atherosclerosis.

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Declaration of competing interests

The authors declare they have no conflict of interest.

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