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The impact of lipid-lowering medications on coronary artery plaque characteristics

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ABSTRACT

Atherosclerosis is the predominant cause of coronary artery disease. The last several decades have witnessed significant advances in lipid-lowering therapies, which comprise a central component of atherosclerotic cardiovascular disease prevention. In addition to cardiovascular risk reduction with dyslipidemia management, some lipid-based therapies show promise at the level of the atherosclerotic plaque itself through mechanisms governing lipid accumulation, plaque stability, local inflammation, endothelial dysfunction, and thrombogenicity. The capacity of lipid-lowering therapies to modify atherosclerotic plaque burden, size, composition, and vulnerability should correlate with their ability to reduce disease progression. This review discusses plaque characteristics, diagnostic modalities to evaluate these characteristics, and how they are altered by current and emerging lipid-lowering therapies, all in human coronary artery disease.

1. Introduction

Ischemic heart disease is the leading cause of death worldwide [1]. It is primarily driven by coronary atherosclerosis, a dynamic intravascular process involving complex interactions between dyslipidemia and pro-inflammatory molecules. This process leads to coronary plaques, the hallmarks of coronary artery disease (CAD) [2]. Coronary atherosclerotic plaque growth can cause myocardial ischemia by narrowing the arterial lumen, whereas plaque rupture or erosion with subsequent thrombus formation and intravascular occlusion causes myocardial infarction. Early diagnosis and timely intervention in patients at increased risk of major adverse cardiovascular events (MACE) stemming from coronary plaque rupture or erosion is a primary goal of cardiovascular disease (CVD) prevention.

The last few decades have witnessed significant advances in lipid-lowering therapies, particularly focused on low-density lipoprotein cholesterol (LDL-C) and residual dyslipidemia management. The convergence of data from large clinical trials has consistently established that these therapies reduce MACE and mortality, especially in patients at increased atherosclerotic cardiovascular disease (ASCVD) risk [3]. Appropriately powered studies have shown lower lipid levels, particularly LDL-C, account for most of the clinical benefit from lipid-lowering medications [4]. Still, some lipid-based therapies show promise in ASCVD prevention beyond their lipid-lowering effects, potentially including tempering effects on inflammation, endothelial dysfunction, and thrombogenicity [5]. Ultimately, however, the non-lipid and lipid-lowering effects of lipid-based therapies converge upon the coronary plaque. Atherosclerotic plaque size, morphology, composition, and fragility, along with overall plaque burden and the hemodynamic consequences of these plaques, govern ASCVD progression and MACE [6].

The natural course and timing of an acute clinical event from CAD can be unpredictable. Whether changes in plaque morphology could predict future events has been a matter of debate. However, understanding plaque features and how they associate with CV risk factors might help develop therapeutic strategies to resolve these abnormalities in disease conditions. For example, patients with non-obstructive calcified or thick-capped plaques might be managed with optimized medical therapy whereas those with thin-capped, rupture-prone lesions could be considered for pre-emptive percutaneous coronary intervention in addition to medical therapy, as long as such an invasive strategy is validated by future clinical trials. Identification of adverse coronary plaque characteristics and how they respond to lipid-based therapies on serial imaging such as with noninvasive angiography may help risk stratification and guide optimization of therapy. For these reasons, we aim to review our current understanding of plaque characteristics, diagnostic modalities to evaluate these characteristics, and how they are altered by current and emerging lipid-lowering therapies.

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2. Atherosclerotic plaque dynamics

Atherosclerosis progression varies from person to person based, in part, on underlying clinical risk factors. Most plaques are asymptomatic (subclinical), some become obstructive, and a few are vulnerable to rupture, subsequently leading to atherothrombotic events. In terms of plaque rupture risk, data on lipid-lowering therapies suggest that qualitative changes in plaque features are more pertinent than luminal diameter changes [6]. Features of rupture-prone lesions include a large, soft lipid-rich necrotic core covered by a thin, inflamed fibrous cap. These changes are associated with expansive remodeling, macrophage infiltration, neovascularization, plaque hemorrhage, adventitial inflammation, and spotty calcifications [7]. Such plaques constitute 10–20% of all atherosclerotic plaques but account for 80–90% of acute clinical events [8,9]. Erosion-prone lesions can similarly promote thrombosis in response to an eroded thin cap. In the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), plaque characteristics of thin-cap fibroatheromas and plaque burden >70% were associated with a 2.5- to 5-fold increased risk of recurrent coronary events in survivors of acute coronary syndromes [10].

Macrophages mediate intra-plaque inflammation and play a crucial role in plaque progression [5]. Most plaque macrophages take up inflammatory lipoproteins, become foam cells, and subsequently stoke more inflammation through cytokine release, enzyme secretion, and cell death. In contrast, some macrophages within the plaque can be regulatory or anti-inflammatory. One important regulatory macrophage function is efferocytosis, the process of clearance of necrotic or apoptotic cells by macrophages to maintain tissue homeostasis [11]. In advanced atherosclerotic plaques, necrotic cores from the death of lipid-rich macrophages and defective efferocytosis can increase inflammation to cause plaque progression and instability [5]. Improvement in plaque microenvironment, especially a substantial decrease in lipid levels, can lead to downregulation of inflammation and reduction in macrophage content [9]. Altering the plaque phenotype from a rupture- or erosion-prone lesion to a stable and less inflammatory lesion would be an optimal result of lipid-lowering therapies. These plaque changes could occur regardless of plaque regression, which, while appealing as a potential goal, is not central to current strategies of CVD risk reduction.

3. Imaging modalities to evaluate coronary artery plaque features

Patients with cardiac symptoms or risk factors concerning for underlying CAD are often investigated by anatomic imaging, functional assessment, and/or biomarkers to detect the CAD and estimate future MACE risk. Anatomic imaging provides structural information of the coronary arteries and can help assess atherosclerotic lesion burden and plaque characteristics. This evaluation can facilitate risk stratification and identify individuals who may benefit from intensification of therapy [12]. Such coronary artery atherosclerotic plaque assessment can be done by invasive or non-invasive techniques [13,14]. The benefits and limitations of various imaging techniques to evaluate coronary artery plaque are shown in **Table 1**.

Non-invasive imaging techniques include computed tomography (CT), coronary CT angiography (CCTA), and cardiac magnetic resonance angiography (coronary MRA). CT (without an angiogram) can provide a direct quantitative assessment of coronary artery calcium (CAC). A positive CAC has a sensitivity of 98% and a negative predictive value of 93% for detecting significant CAD on coronary angiography [15]. Importantly, while CAC can identify calcified CAD, it cannot identify the non-calcified lesions that can be more prone to rupture and lead to MACE. Additionally, CAC cannot be used to quantify the degree of coronary stenosis. Recent clinical guidelines favor initiating lipid-lowering therapy in patients with a non-zero CAC score [16]. Patients with even a minimal CAC score (1–10 Agatston units) showed a 3-fold increased risk for incident CAD relative to those with zero CAC [17]. While a CAC score of zero suggests a low risk for CAD, that might not be the case in patients with diabetes, family history of premature CAD, or tobacco smoking. Other limitations of CAC scoring include radiation exposure, albeit relatively low, and the potential for incidental findings.

Unlike the CAC score, CCTA can be used to detect both obstructive and non-obstructive CAD, including non-calcified lesions. The performance of CCTA for detecting CAD varies by study, with 82–97% sensitivity and 78–92% specificity [18]. Positive and negative predictive values for diagnosing obstructive CAD are above 90% [19]. In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II) trials, high-risk plaque characteristics on CCTA (positive remodeling, low CT attenuation suggestive of a lipid-rich necrotic core, napkin-ring sign) were associated with increased risk of future CVD events among patients with chest pain, independent of cardiovascular (CV) risk factor burden [20,21]. In a post-hoc analysis of the SCOT-HEART trial (Scottish Computed Tomography of the HEART), among patients with suspected CAD, both obstructive disease and adverse plaque characteristics on CCTA were associated with higher rates of CAD death or nonfatal myocardial infarction as compared to patients with normal coronary arteries (HR: 11.50; 95% CI: 3.39 to 39.04; $p < 0.001$) [12]. The limitations of CCTA include radiation exposure, contrast use, the potential for incidental findings, and decreased accuracy in patients with extensive calcified plaque or obesity.

Coronary MRA is less commonly used in clinical practice. When operating at field strengths 1.5 or 3.0 Tesla, it has reasonable sensitivity for diagnosing significant CAD [22, 23]. However, limitations of coronary MRA include high cost and time, along with lower spatial resolution than CCTA.

Invasive intracoronary imaging includes coronary angiography (ICA), coronary angioscopy, intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS) [24]. These techniques allow the direct visualization of the arterial lumen and wall with a quantitative and qualitative assessment of atherosclerotic plaques. ICA is the gold standard for the diagnosis of CAD. Compared to pathological analysis of coronary arteries, ICA can identify stable atheromas, disrupted atheromas, and thrombi with 74%, 73%, and 100% specificity, respectively [25]. ICA comes with the risks associated with an invasive vascular procedure, as well as radiation and iodinated contrast exposure. Another limitation of ICA is its poor ability to evaluate the plaque below the surface. Although quantitative assessment of ICA provides crucial details on coronary artery stenosis, it may not accurately capture the physiological significance of lesions, especially in patients with stable CAD [26].

Intracoronary instrumentation can provide an even closer view of the plaque. Coronary angioscopy is rarely done but facilitates direct visualization of the coronary artery lumen and can provide information on plaque morphology. Plaques that appear yellow on angioscopy (yellow plaques) represent thin-cap atheromas with a higher incidence of disruption and thrombus formation [27]. Coronary angioscopy is more sensitive than ICA for detecting small intimal dissections and thrombi [28]. As for IVUS, there are multiple modalities – grayscale IVUS, virtual histology IVUS (VH-IVUS), integrated backscatter IVUS, and iMAP-IVUS [29]. Grayscale IVUS can provide precise lumen area, plaque size, and distribution, while virtual histology IVUS can differentiate plaque composition. The sensitivity of grayscale IVUS was 78% to identify a stable atheroma, 81% for a disrupted atheroma, and 57% for a thrombus [25]. Drawbacks of IVUS include limited axial resolution and poor reliability in evaluating non-left main lesions. VH-IVUS has a poor ability to assess heavily calcified plaque. When IVUS and ICA were concordant, there was a 92% agreement with atheroma histology [25]. In the ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis-IVUS) study, among patients undergoing ICA, the presence of VH-IVUS-detected thin-cap fi-

Table 1
Imaging techniques to evaluate coronary artery plaque.

Method to evaluate coronary plaque	Benefits	Limitations
Non-invasive		
Computed tomography for coronary artery calcium (CAC)	• Quantitative assessment of coronary artery calcium • Robust data on risk stratification	• Cannot identify non-calcified plaque • Cannot evaluate the degree of coronary stenosis • Radiation exposure (although relatively low) • Incidental findings
Coronary computed tomography angiography (CCTA)	• Can detect non-calcified lesions • Can identify both obstructive and non-obstructive coronary artery lesions non-invasively	• Radiation exposure • Contrast use • Incidental findings • Decreased accuracy in patients with extensive calcified plaque or obesity
Coronary magnetic resonance angiography (MRA)	• No exposure to ionizing radiation • Detailed evaluation of cardiac anatomy • Can detect flow-limiting lesions, including non-calcified lesions • Can identify both obstructive and non-obstructive coronary artery lesions	• High cost and time • Lower spatial resolution than CCTA • Limited clinical use currently
Invasive		
Invasive coronary angiography (ICA)	• Can identify stable atheromas, disrupted atheromas, and thrombi • Can provide details on the degree of coronary artery stenosis • Coronary intervention could be performed at same time	• Poor ability to evaluate the plaque below the surface • Radiation exposure and contrast use • May not always capture the physiological impact of the coronary lesion • Risks of invasive vascular procedure
Coronary angioscopy	• Direct visualization of the coronary luminal surface • Can provide information on plaque morphology	• Poor ability to evaluate plaque features below the surface • Risks of intracoronary instrumentation • Not part of routine clinical care
Intravascular ultrasound (IVUS)	• Grayscale intravascular ultrasound can provide precise lumen area, plaque size, and distribution • Virtual histology intravascular ultrasound can characterize plaque composition.	• Limited axial resolution • Poor ability to assess heavily calcified plaque • Risks of intracoronary instrumentation
Optical coherence tomography (OCT)	• High axial resolution • Ability to assess fibrous cap thickness and macrophage content	• Low tissue penetration • Risks of intracoronary instrumentation • Uses contrast to clear blood
Near-infrared spectroscopy (NIRS)	• Chemical characterization of tissues within atherosclerotic plaques	• Lacks robust clinical data

broatheroma lesions was predictive of MACE within one year [30]. OCT imaging uses near-infrared light to provide high axial resolution to assess fibrous cap thickness and macrophage content. The sensitivity and specificity of OCT-minimal luminal diameter to detect significant stenosis was 0.74 (0.69–0.78) and 0.70 (0.68–0.73), respectively [31]. Limitations of OCT include the need for contrast and low tissue penetration. NIRS allows the chemical characterization of tissues within atherosclerotic plaques. The sensitivity and specificity of NIRS to detect lipid components of the plaque were 90% and 93%, respectively [29]. Despite these promising results, the use of NIRS is limited by the lack of more robust data at this early stage.

4. Impact of lipid-lowering agents on coronary plaque characteristics

Multiple investigations on lipid-lowering therapies have included assessments of the impact of those agents on coronary plaque characteristics, as measured by either non-invasive or invasive imaging techniques described above. Herein, we summarize the main findings for each class of medication.

4.1. LDL-C lowering therapies

As the mainstay of CAD therapy, LDL-C lowering therapies have the most robust evidence for CV risk reduction and, concordantly, have the most data for beneficial effects on coronary plaque size and composition.

4.1.1. Statins

Statins are inhibitors of HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Statin-mediated inhibition results in reduced intracellular cholesterol, which in turn causes a compensatory increase in LDL receptor expression on the cell membrane to promote uptake of circulating LDL-C. Statins are the most used lipid-lowering therapy with strong evidence of safety and efficacy in primary and secondary CVD prevention. They can lead to a 22–63% reduction in LDL-C and may exert additional CV protective effects independent of LDL-C lowering, so-called pleiotropic effects [32]. Non-lipid lowering effects of statins in CVD include reducing inflammatory cytokines, reducing oxidation-sensitive inflammatory pathways, and modulating leukocyte-endothelial cell interactions [33].

The relationship between statin therapy and coronary plaque characteristics has varied across studies and has been subject to debate, but when the data is considered together, some common themes emerge.

First, statin treatment tends to correlate with an increase in plaque calcification, likely allowing for less vulnerability [34]. In a study involving long-term statin users (mean 4.7 years of therapy) assessed by CCTA and CAC, despite the progression of plaque volume, there was a reduction in the number of soft unstable plaques and an increase in calcified plaques [35]. In another study of patients with type 2 diabetes mellitus and advanced atherosclerosis, the progression of CAC was found to be significantly higher in patients who reported higher adherence to statins (95%) than those who reported lower adherence (14%) [36]. In a multicenter, prospective observational MESA study (Multi-Ethnic Study of Atherosclerosis) involving 3398 participants (20% were statin users), after accounting for CAC volume, CAC density while on statin was inversely associated with ASCVD risk [37]. Likewise, in the CONFIRM (CCTA for clinical outcomes: an international multicenter registry) study involving 6673 participants without known CAD undergoing CCTA, statin use was associated with coronary plaques that contained more calcification [38]. Statin therapy is also associated with reduced progression of more susceptible low-attenuation plaques (< 30 Hounsfield units) and non-calcified plaques [39].

Multiple studies involving differing modalities for plaque assessment have given finer detail on plaque composition beyond calcification. By angioscopy, pitavastatin reduced yellow, vulnerable plaques [40]. By IVUS, long-term maximally intensive statin therapy significantly reduced vulnerable fibro-fatty plaque [41]. Using ICA, atorvastatin-driven LDL-C reduction correlated well with a reduction in plaque vulnerability [42]. Plaque regression, sometimes considered an idealized goal of CAD treatment, has also been documented with statins in certain cases. In patients with ST-elevation myocardial infarction, high-intensity rosuvastatin over 13 months was associated with regression of coronary atherosclerosis in non-infarct-related arteries, although without changes in necrotic core or plaque phenotype, as measured by IVUS [43].

Meta-analyses of multiple trials have supported these effects. In eight prospective randomized trials involving 3495 participants (1545 on high-intensity statin, 1726 on low-intensity statin, 224 not on statin) assessed by serial coronary IVUS, statins promoted plaque calcification with a stabilizing effect [44]. In another analysis of 830 participants assessed with VH-IVUS, statins significantly reduced plaque volume ($p = 0.023$) and increased dense calcium volume ($p = 0.043$) without impacting lumen volume [45]. By OCT in participants with CAD, intensive statin therapy was associated with less vulnerable plaque features, including greater fibrous cap thickness, and this occurred independently of other coronary risk factors or medications [46,47]. Similar findings occurred in studies that combined OCT and IVUS [48]. Coronary lesions with a large lipid-rich plaque detected by NIRS also had a large plaque burden on IVUS, and a reduction in this plaque was seen in patients receiving intensive statin therapy ($p = 0.004$) [49]. Hinting at a pleiotropic effect, in a meta-analysis of 1623 participants, high-intensity statin therapy correlated with significant plaque regression irrespective of reaching an LDL-C target ≤70 mg/dL [50]. Other studies support regression being more likely at LDL-C ≤ 70 mg/dL or even lower [35,51,52].

Considering all the studies, the overall effects of statins on coronary plaques include a decrease in lipid content, borderline plaque regression, increase in calcification, increase in fibrous cap thickness, attenuation of inflammation, all likely to yield plaque stabilization, but without significant changes in necrotic core. These effects appear enhanced with high-intensity statins and in patients who reach a low LDL-C target, and such plaque stabilization by statins matches well with their well-documented ability to reduce the risk of acute coronary events [53].

4.1.2. Ezetimibe

Ezetimibe inhibits the absorption of cholesterol at the brush border of the small intestine via the sterol transporter named Niemann–Pick C1-like intracellular cholesterol transporter 1 (NPC1L1). Ezetimibe monotherapy can yield an 18–20% reduction in LDL-C with good safety and tolerability [32]. Angioscopy and IVUS in stable CAD patients receiving elective percutaneous coronary intervention (PCI) noted significant plaque volume reduction with the addition of ezetimibe 10 mg/day to background statin therapy [54]. In another study utilizing IVUS and involving patients who underwent PCI, the use of ezetimibe in combination with background statin showed a greater reduction in LDL-C ($p < 0.001$) and coronary plaque regression (78% vs. 58%; $p = 0.004$) than those on statin alone [55]. Statin therapy combined with ezetimibe also showed a significant increase in fibrous cap thickness compared to intensive statin monotherapy in multiple studies [56,57].

4.1.3. PCSK9 inhibitors

The Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors are fully-humanized monoclonal antibodies that bind and inhibit free plasma PCSK9 protein. PCSK9 normally binds to the LDL receptor to promote its degradation, so PCSK9 inhibition allows more receptors to remain intact on the cell surface. The LDL receptors bind and internalize LDL-C to lower its circulating level. The U.S. FDA has approved two PCSK9 inhibitors: evolocumab and alirocumab. PCSK9 inhibitor monotherapy can cause a 43–64% reduction in LDL-C with good safety and tolerability [32]. In the ATHEROREMO-IVUS (the European collaborative project on inflammation and vascular wall remodeling in atherosclerosis-IVUS) study, 581 participants underwent ICA for acute coronary syndrome or stable angina, and PCSK9 inhibition was associated with smaller necrotic cores by VH-IVUS, independent of statin use [58]. In the GLAGOV trial (Global Assessment of Plaque regression with a PCSK9 antibody as measured by IVUS), 968 statin-treated participants with angiographic coronary disease were randomized to receive 420 mg evolocumab monthly or placebo for 76 weeks [59]. Evolocumab resulted in a greater decrease in LDL-C (93.0 vs. 36.6 mg/dL, $p<0.001$) and atheroma volume than placebo. Using serial OCT in ACS patients, the addition of evolocumab (140 mg every 2 weeks) to background rosuvastatin 5 mg daily yielded a statistically significant reduction in LDL-C, increase in fibrous-cap thickness, and regression of the lipid-rich plaque [60].

4.1.4. Bempedoic acid

Bempedoic acid is a relatively novel lipid-lowering medication. It is a potent inhibitor of ATP-citrate lyase, an essential enzyme in fatty acid biosynthesis. It is used as monotherapy or as adjuvant therapy in patients who do not attain adequate LDL-C lowering with maximally tolerated statin therapy and in statin-intolerant patients at risk for CVD. In a systematic review and meta-analysis of phase II and III randomized controlled trials, bempedoic acid significantly reduced lipid parameters with attenuation of inflammation and an acceptable safety profile [61]. While preclinical studies have suggested bempedoic acid could increase fibrous cap thickness and reduce necrotic cores [62], its impact on human coronary plaque composition is not yet documented.

4.2. Lipid therapies that target non-LDL-C components

LDL-C lowering therapies are the backbone of CAD therapy, and their impact on the plaque milieu can vary, as described above. Still, they generally trend toward reduced vulnerable plaque volume and increased calcification and fibrous cap development, particularly for statins, ezetimibe, and PCSK9 inhibitors. However, CAD risk also correlates with elevated circulating triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C). Some of the lipid therapies that modulate these components have data on their impact on plaque composition.

4.2.1. Fibrates

Fibrates are peroxisome proliferator-activated receptor alpha (PPAR alpha) agonists that reduce TG by 25–50% and increase HDL-C by 5–20% [64]. Fenofibrate has been shown to have non-lipid pleiotropic effects such as improving flow-mediated dilation and reducing fibrinogen, C-reactive protein, and other pro-inflammatory markers [65]. Despite the lack of consistent improvements in fenofibrate's CV outcomes, it remains a useful option in patients with dyslipidemia, particularly

characterized by high TG and low HDL-C levels [65]. While preclinical evidence suggest reduced plaque thrombogenicity and increased plaque stability [66], there is currently no rigorously documented effect of fibrates on human plaque composition.

4.2.2. Omega-3 fatty acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids that are used in various combinations with 10–50% TG-lowering efficacy [64]. The mechanism of action is not fully known. They potentially lower TG by suppressing lipogenic gene expression, increasing beta-oxidation of fatty acids, and increasing lipoprotein lipase expression [67,68]. At high doses, they have been found to exert additional atheroprotective properties such as T-cell differentiation modulation that promotes the resolution of tissue injury and inflammation [68]. Two recent large randomized controlled trials assessing CV outcomes with omega-3 fatty acids (with EPA and with EPA+DHA) showed divergent results [69]. Due to comparable efficacy in TG-lowering, the observed differences in outcomes may be attributable to achieved plasma EPA levels. Human plaques readily incorporate EPA, which could improve plaque stability [68]. In patients with CAD, a combination EPA with statin therapy significantly reduced coronary plaque volume, as measured by IVUS, compared with statin therapy alone in the CHERRY trial (Combination Therapy of EPA and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography) [70]. In another study using IVUS for 95 patients on intensive statin background therapy for at least 6 months, randomization to EPA 1.8 g/day was associated with reduced lipid volume in coronary plaques and decreased inflammatory cytokines compared to placebo [71]. Finally, among patients with coronary atherosclerosis by CCTA on stable statin therapy with persistently elevated triglycerides, the addition of 4 g/day of icosapent ethyl slowed non-calcified plaque, fibrous plaque, and calcified plaque growth, with no significant change in low-attenuation plaque [72].

4.2.3. Niacin

Niacin is a lipid-lowering medication, now rarely used due to lack of positive CV outcomes and the advent of newer lipid-modulating therapies. It increases HDL-C, decreases TG by 20–50%, and mildly lowers LDL-C [64]. Niacin's effects are thought to be mediated by nicotinic acid receptors to promote intracellular degradation of ApoB-containing lipoproteins, decreased hepatic TG synthesis, and decreased degradation of HDL-C [73]. In a small study of 28 patients with intermediate CAD, those randomized to 1000 mg niacin with 40 mg simvastatin had significantly decreased coronary plaque volume as measured by IVUS (change in normalized total atheroma volume $p = 0.024$, change in percent atheroma volume $p = 0.047$) and attenuated inflammatory response compared to those on the simvastatin alone [74]. However, in another study of older individuals with established atherosclerosis, there was no difference in plaque regression with niacin added to background statin therapy, although this study focused on the internal carotid artery measured by MRI, as opposed to the coronary arteries [75].

While additional lipid-lowering therapies exist, including mipomersen, lomitapide, and bile acid sequestrants, there is insufficient data on their effects on human coronary plaque characteristics, and none are currently in common clinical use.

4.3. Emerging lipid-lowering medications

In addition to the approved LDL-C, HDL-C, and TG-modifying therapies, several agents are in various development and testing stages, and many are now emerging for potential clinical use. Inclisiran is a small interfering RNA that inhibits hepatic translation of PCSK9 protein. In a pooled analysis of ORION-9, ORION-10, and ORION-11 (inclisiran for subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C), twice-yearly inclisiran injections resulted in a 52% LDL-C reduction at 510 days than placebo ($p<0.0001$) with no signs of liver, kidney, or muscle toxicity [76]. Because monoclonal PCSK9 inhibitors have been shown to lead to some coronary plaque regression, there is promise that inclisiran would have a similar effect.

Evinacumab is a fully-humanized monoclonal antibody that inhibits Angiopoietin-like protein 3 (ANGPTL3), a secreted protein that inhibits lipoprotein lipase. In humans, ANGPTL3 deficiency has been associated with a decrease in serum LDL-C. In APOE*3-Leiden.CETP mice (which possess a 'human-like' dyslipidemia profile), triple treatment with atorvastatin, alirocumab, and evinacumab regressed atherosclerotic lesion size in the thoracic aorta by 50% and the aortic root by 36%, decreased macrophage accumulation through reduced proliferation, and abated lesion severity [77].

CRISPR/Cas9 genome editing technology enables the permanent knockout or repair of existing genes. In an animal study, CRISPR/Cas9 targeting of PCSK9 reduced plasma PCSK9 levels, increased hepatic LDL receptor levels, and reduced plasma cholesterol levels by 35–40% [78]. In a recent study in non-human primates, adenine base editing demonstrated a substantial decrease in LDL-C and TG by editing the PCSK9 gene (59% LDL-C reduction) and ANGPTL3 gene (64% reduction in TG and 19% reduction in LDL-C) without evidence of off-target editing [79].

Pemafibrate is a selective PPAR alpha modulator. It has been shown to have better efficacy and safety compared to conventional fibrates [80]. In animal models, pemafibrate was associated with inhibition of inflammatory responses in coronary artery atherosclerosis [81]. Other non-lipid mechanisms of pemafibrate include enhanced expression of ABCA1 and ABCG1 (ATP-binding cassette transporter A1 and G1 respectively) in macrophages and attenuation of proinflammatory genes, including Interleukin-6 [80].

Volanesorsen is a second-generation ASO targeted to reduce apolipoprotein C-III (Apo C-III) mRNA. In a phase III trial, it has been shown to reduce TG to less than 750 mg/dL in 77% of patients with familial chylomicronemia syndrome, which otherwise remains an untreatable disease [82]. Apo C-III primarily synthesized by the liver attenuates TG hydrolysis by inhibiting lipoprotein lipase and hepatic lipase and increasing TG incorporation in TG-rich lipoproteins [83]. Apo C-III has a proinflammatory effect on human monocytes and has been shown to contribute directly to atherogenesis by activating endothelial cells and recruiting monocytes [84].

Lp(a) is a lipoprotein that consists of apolipoprotein(a) bound by a disulfide bond to the ApoB of the LDL-C particle. It is an independent risk factor for CVD and calcific aortic valve stenosis [85]. A study involving 255 CAD patients who underwent OCT imaging of culprit lesions showed a higher Lp(a) level associated with a higher prevalence of thin-cap fibroatheromas, particularly in patients with high LDL-C [86]. Among patients with acute coronary syndrome evaluated by OCT and/or ICA, elevated Lp(a) was associated with increased plaque burden and features of high-risk coronary atherosclerosis [87]. Among over 6000 patients in PCSK9 inhibitor trials, PCSK9 antibodies lowered Lp(a) by about 26 percent compared to placebo [88]. In a phase II trial involving participants with elevated Lp(a), an ASO targeting apolipoprotein(a) reduced Lp(a) by 67–72%, and using a modified ASO that was more selective, Lp(a) was reduced by 92% [89]. Like many of the emerging therapies, the effects of such Lp(a) lowering through these agents on human coronary plaque are not yet known.

4.4. Lipid-lowering therapy, plaque characteristics, and clinical care

Despite a wealth of diverse observations on plaque composition in response to lipid-modifying treatment, how to incorporate this information into clinical care is less certain. Thin-capped or inflamed lesions are more vulnerable and more likely to drive acute coronary syndromes, and many of the imaging modalities discussed here can help identify such lesions. Once identified, these plaques can stabilize in response lipid-lowering therapies, particularly well-documented with statins, through regression, decreased lipid content, increase in calcification, increase in fibrous cap thickness, and attenuation of inflammation. However,

Table 2
The impact of lipid-lowering medications on coronary artery plaque characteristics.

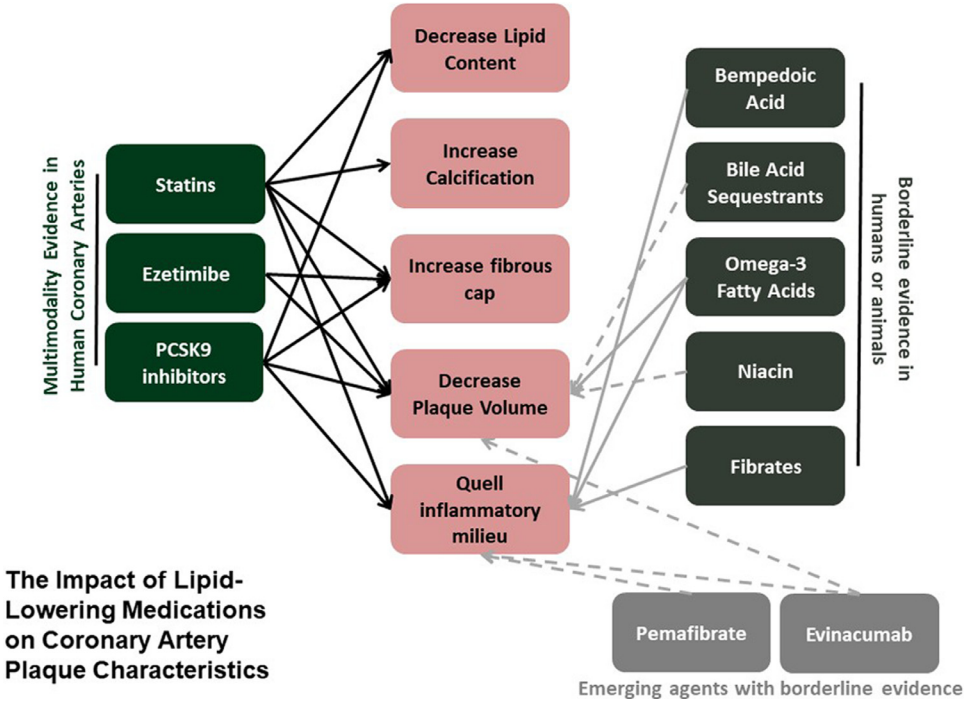
Medication	Mechanism	Abundance of data on plaque effects	Modalities to assess coronary plaque	Most common effects on coronary artery plaque	MACE reduction	References
Effects of current lipid-lowering medications on coronary plaque characteristics						
Statins	HMG-CoA reductase inhibitor	+++	CCTA, CAC, Angioscopy, ICA, IVUS, OCT, NIRS	• Plaque stabilization • Decreased lipid content • Increased dense calcium volume • Increased fibrous cap thickness • Variable change in plaque volume • Decreased inflammatory cytokines • Decreased oxidation-sensitive inflammatory pathways • Altered T-cell differentiation and leukocyte-endothelial cell interaction	Yes	[34–52]
Ezetimibe	NPC1L1 inhibitor	++	ICA, IVUS, OCT	• Plaque volume reduction • Plaque regression • Increased fibrous cap thickness	Yes	[54–57]
PCSK9 inhibitors	monoclonal antibodies to free plasma PCSK9 protein	++	ICA, IVUS, OCT	• Decreased plaque volume • Increased fibrous cap thickness • Regression of lipid-rich plaque • Attenuation of plaque inflammation	Yes	[58–60]
Bempedoic acid	ATP-citrate lyase inhibitor	+	Animal studies only	• Attenuated plaque inflammation • Potential plaque stabilization	Unknown	[61–62]
Bile acid sequestrants	Interrupt enterohepatic homeostasis	+	Animal studies only	• Borderline plaque regression	No	[63]
Fibrates	PPAR alpha agonists	+	Animal studies only	• Reduced plaque thrombogenicity • Decreased fibrinogen and C-reactive protein • Improved flow-mediated dilatation	Variable	[65–66]
Omega-3 fatty acids	Not fully understood; likely multiple effects	+	IVUS, Laboratory and clinical studies	• Modulation of T-cell differentiation • Plaque-stabilization • Reduced coronary plaque volume • Decrease in inflammatory cytokines	Variable	[68,70-71]
Niacin	Likely multiple effects	+	ICA, IVUS	• Anti-inflammatory effects • Protection against endothelial dysfunction • Reduced coronary plaque volume	No	[73–75]
Effects of emerging lipid-lowering medications on coronary plaque characteristics						
Evinacumab	monoclonal antibody to Angiopoietin-like protein 3	+	Animal studies only	• Regression of atherosclerotic lesion size • Decrease in macrophage accumulation	Unknown	[77]
Pemafibrate	Selective PPAR alpha modulator	+	Animal studies only	• Inhibition of inflammation • Enhanced expression of ABCA1 and ABCG1 in macrophages • Attenuation of proinflammatory genes	Unknown	[80–81]

ABC, ATP-binding cassette transporter; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; ICA, coronary angiography; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NIRS, near-infrared spectroscopy; NPC1L1, Niemann-Pick C1-Like 1; OCT, optical coherence tomography, PCSK9, Proprotein convertase subtilisin/Kexin type 9 serine protease; PPAR, peroxisome proliferator-activated receptor-alpha. *Therapies not listed have no clear data yet on plaque characteristics.*

the question of whether using more aggressive lipid-lowering strategies—such as combined statin, ezetimibe, and PCSK9 inhibitor or setting ultra-low LDL-C targets—or even employing earlier thresholds for PCI, driven by findings of plaque vulnerability, deserves dedicated clinical trials. Ultimately, we speculate that such strategies aimed at vulnerable plaque will become part of future cardiovascular care.

5. Conclusion

The effects of lipid-lowering medications on coronary artery plaque characteristics are summarized in Table 2. It is likely that many lipid-lowering therapies beneficially stabilize atherosclerotic plaques. However, the complex mechanisms of atherogenesis and plaque progression, along with the challenges of accurately measuring changes in plaque size and composition in human coronary arteries, have prevented reliable documentation of these beneficial effects. As our understanding of atherosclerosis pathophysiology and our ability to track plaque changes improve, establishing such protective effects on the target lesions should be more feasible. A multitude of non-invasive coronary imaging techniques with improving resolution and specificity will also offer effective and safer alternatives to invasive evaluations. Newer therapies targeting pathways involved in atherogenesis should also expand our approach to CVD risk reduction. Whether it is possible to predict plaque consequences and tailor therapy to its longitudinal effect on the plaque for each patient is unclear. Still, such individualization should remain a goal to maximally reduce CVD for the population.



6. Author contributions

V.P.P. and F.J.A both wrote and edited the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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