Peer-Reviewed Article | Review Article

Plaque Regression by Lipid-Lowering Therapy

Plaque Characterization Using Intracoronary Imaging: Effects of Lipid-lowering Therapies

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Abstract

Over the past few years, large observational trials have confirmed the consistent association between vulnerable plaques identified by intracoronary imaging and major cardiovascular events in patients with coronary artery disease. Lipid-lowering therapies have reduced the occurrence of cardiovascular events in these patients; however, the exact pathophysiological mechanisms behind their clinical benefits have remained underexplored. Intracoronary imaging modalities, including intravascular ultrasonography, near-infrared spectroscopy, and optical coherence tomography have provided fundamental insight into the biological plausibility of these clinical results. Imaging trials employing serial intravascular ultrasonography have suggested that lipid-lowering therapies can either slow disease progression or promote plaque regression, depending on the degree of lipid lowering achieved. More recently, new randomized trials have added significant insights on the additional beneficial effects of achieving very low low-density lipoprotein cholesterol levels on high-risk plaque features, including fibrous cap thickness, lipid accumulation, and inflammatory cell accumulations. This literature review aimed to summarize current evidence on the clinical usefulness of plaque characterization using contemporary intracoronary imaging and the effects of high-intensity lipid-lowering therapies on vulnerable plaque features.

Keywords: lipid-lowering therapy; vulnerable plaque; plaque stabilization; optical coherence tomography; intravascular ultrasonography

Introduction

Over the past few decades, cardiovascular research has focused on primary and secondary prevention as a central intervention for reducing the burden of cardiovascular disease. However, despite several efforts, coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide, with overwhelming health and economic consequences [1].

To improve the management of patients with CAD, several invasive and noninvasive strategies have been proposed, with the search for myocardial ischemia being the most widely adopted strategy in clinical practice. However, new evidence has questioned the usefulness of this approach in predicting major cardiovascular events, including cardiac death and myocardial infarction (MI) [2, 3]. Conversely, histopathological and in vivo studies have shown a clear relationship between the extent of the coronary disease, its progression rate, and cardiovascular events [4]. More recently, intracoronary imaging (ICI) studies employing new techniques such as high-resolution intravascular ultrasonography (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT) have shed light on the high-precision in vivo assessment of the characterization of the atherosclerotic plaque and showed the clear relationship between plaque size and composition with patient prognosis. Randomized controlled trials using serial ICI evaluations have suggested that high-intensity lipid-lowering therapies can induce beneficial vascular changes in the coronary arteries of patients with MI, providing a solid rationale for the well-established clinical benefits of these pharmacological therapies [5, 6].

This review aimed to summarize current evidence on the clinical usefulness of plaque characterization using contemporary ICI and the effects of high-intensity lipid-lowering therapies on vulnerable plaque features described in prospective studies and randomized clinical trials.

From "Obstructive Lesion" to "Plaque Characterization"

For decades, noninvasive and invasive searche for ischemia was the cornerstone of risk stratification for guiding medical decisions and coronary revascularization of patients with CAD, including endorsement in international guidelines [7]. Landmark randomized trials have suggested that revascularization of flow-limiting coronary lesions reduces adverse cardiovascular events, mainly coronary revascularization. However, the role of ischemia in identifying patients at a higher risk of cardiac death and MI has been subject to a long-term ongoing controversy. In patients with acute coronary syndrome (ACS), risk stratification based on the presence or absence of ischemia-causing lesions has not been proven superior to a strategy with angiography alone [8]. Conversely, the use of surrogates of the extent of myocardial injury including high-sensitivity cardiac troponin T, has improved the mortality risk prediction provided by the Global Registry of Acute Coronary Events (GRACE) risk score [9]. Recently, in the large randomized International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial [2], an initial invasive strategy was not superior to optimal medical therapy in reducing major adverse ischemic events among 5,179 stable patients with moderate ischemia. In this trial, the stratification of patients to undergo or not undergo an initial strategy of invasive management was based on

the presence or absence of moderate ischemia as detected by four different noninvasive testing techniques. The high variability in diagnostic accuracy of these noninvasive techniques may represent a limitation for trial interpretation [2]. Significantly, a subsequent subanalysis highlighted the poor prognostic role of mild-to-moderate ischemia, which showed that the extension of coronary disease (one-, two-, or three-vessel disease) was a much better adverse event predictor than ischemia testing results [3]. Indeed, no correlation between the degree of ischemia and cardiovascular outcomes was observed. Similarly, in a Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial subanalysis, the discriminatory ability of coronary computed tomography angiography (CCTA) for predicting events was higher than that of functional testing [10]. In this study comparing CCTA with noninvasively detected ischemia, when test findings were stratified as mildly, moderately, or severely abnormal, risks for events compared with normal tests proportionally increased for CCTA but not for corresponding functional testing categories (specifically in the no versus low degree of ischemia category) [10]. Of note, in the CCTA group, 54% of events (n = 74/137) occurred in patients with nonobstructive CAD (1–69% stenosis). These findings are consistent with those of previous angiographic studies performed before and after acute MI, which frequently show that at the site of the complete occlusion, the preexisting underlying lesion rarely causes a hemodynamically significant stenosis [11].

Overall, these findings corroborate the concept that ACS is not frequently caused by slow progressive arterial lumen narrowing causing ischemia but rather by sudden blood flow interruption due to plaque disruption and associated lumen thrombosis, with culprit lesions often being nonobstructive before the event. Collectively, these findings suggest that the risk of ACS is not mediated by inducible ischemia itself but by the underlying coronary atherosclerotic burden and composition. This concept also aligns with previous histopathological studies investigating the culprit lesion in patients with fatal coronary events. These studies consistently suggested that in 70% of cases, the cause of an acute coronary event is related to the rupture of a lipid-rich inflamed plaque with a thin-cap fibroatheroma, which was not necessarily obstructive before the lumen thrombosis: the so-called "vulnerable plaque" [12].

The concept of vulnerable plaques has been translated from pathology studies to in vivo detection thanks to the introduction of innovative intravascular imaging modalities capable of characterizing coronary atherosclerosis.

In Vivo Assessment of Atherosclerotic Plaques: The Crucial Role of ICI

Coronary angiography has historically been considered the gold standard for CAD diagnosis. However, coronary angiography generates a two-dimensional reconstruction of the arterial lumen and does not directly show the vessel wall, the site where atherosclerotic plaques reside. Furthermore, the pathological process of coronary atherosclerosis is dynamic and is associated with several processes, including positive remodeling of the arterial wall, which was intuited by Glagov et al. in the late 1980s [13]. In the early stages of atherosclerotic plaque development, usually no luminal changes are observed because the adventitial wall can expand to compensate for disease progression. Glagov et al. first shifted attention to how the luminal area of atherosclerotic coronary arteries could remain constant up to a 40% stenosis rate [13]. According to this phenomenon, which later became known as the "Glagov effect," the size of the coronary lumen is partially preserved by compensatory vessel dilatation until very advanced stages of CAD [13]. Consequently, the luminogram obtained by coronary angiography may be normal or only mildly stenotic in several cases, thereby leading to an underestimation of the disease severity and ignoring the often dangerous intrinsic changes occurring within the vessel wall [13].

The use of contemporary high-precision ICI technologies has emerged as a complement to conventional angiography for characterizing plaque morphology. Different intravascular imaging techniques, including IVUS, NIRS, and OCT, have been introduced for investigating the extension and composition of coronary atherosclerotic plaques, each with different unique characteristics (table 1, fig. 1). Consistent with pathological studies, ICI studies on plaque morphology in culprit lesions of patients with acute MI revealed the frequent presence of a large lipid core with a ruptured thin fibrous cap [14]. Moreover, in four recent large-scale studies including 3,562 patients using either NIRS-IVUS or OCT, patients with lipid-rich plaques (NIRS-IVUS) or thin-cap fibroatheroma (OCT) were associated with an increased risk of future cardiovascular outcomes at 1–5 years [15–18].

IVUS

The IVUS technique based on acoustic sound wave backscattering, was introduced into clinical practice more than 30 years ago in Rotterdam [19] and offers grayscale imaging with an 80–120 µm axial resolution and a penetration depth of 4–8 mm. Therefore, IVUS allows tomographic imaging of the entire coronary vessel wall and accurate quantification of atheroma burden in vivo (fig. 1) [20]. IVUS assessments, performed at baseline and follow-up, have allowed for progression-regression studies of coronary atherosclerosis, which have become crucial for assessing the effects of antiatherosclerotic drugs on plaque burden in

Table 1: Advantages and Disadvantages of the Three Intracoronary Imaging Modalities

Imaging Modality	Pros	Cons	Plaque Features Detected
IVUS	Good spatial resolution, gold-standard for plaque volume assessment	Limited assessment of composition, cannot assess the thickness of the fibrous cap	Plaque burden Calcium (moderate accuracy)
OCT	Very high spatial resolution, gold standard for thin-cap fibroatheroma evaluation	Limited penetration, unable to visualize the entire cross section of the vessel if larger than penetration depth	Thin-cap fibroatheroma, plaque composition (lipids, calcium, fibrotic tissue, inflammatory infiltrates, cholesterol crystals, microvessels, layered plaques)
NIRS	High accuracy for lipid component quantification	No spatial resolution	Lipid content

IVUS: Intravascular ultrasonography; OCT: Optical coherence tomography; NIRS: Near-infrared spectroscopy.

vivo [21–23]. Two IVUS volumetric imaging outcome measures have been established: percent atheroma volume (PAV), which is the percentage of vessel volume occupied by atheroma (the ratio of plaque area divided by vessel area measured at the external elastic lamina), and total atheroma volume (TAV), which is the sum of atheroma area measured in sequential frames.

Prospective data have shown that PAV (known as "plaque burden" in clinical trials) can identify patients at risk for future events. A meta-analysis including 4,137 patients from six clinical trials showed that PAV measurements both at baseline and after a 18–24-month follow-up are independent predictors of major cardiovascular events [24]. Previously, the IVUS modality was implemented with virtual histology, a method based on radiofrequency post-processing ultrasonographic images aimed to identify plaque composition [20]. However, this method did not effectively overcome the intrinsic limitations of IVUS resolution, remained associated with highly sensitive necrotic core detection in the presence of calcium, and was never definitely adopted in clinical practice.

NIRS

More recently, the IVUS assessment has been improved with a new technique that can automatically assess lipid accumulation in coronary arteries, NIRS. This method combines both IVUS and NIRS in a single multimodal catheter: while IVUS allows plaque images and measures plaque burden, the spectroscopic signal of NIRS accurately identifies the lipid component (fig. 1) and allows its quantification by detecting the spectroscopic signal of lipid molecules in the coronary artery wall. Previous studies mainly conducted in Rotterdam showed a high prevalence of NIRS-derived lipid-rich plaques at culprit lesion sites in most patients with ST-segment elevation myocardial infarction (STEMI) [25]. To quantify intracoronary lipid accumulation, two main NIRS measures have been described. First, the total lipid core burden index (LCBI) represents the fraction of yellow pixels throughout the studied segment obtained from the chemogram, an image map derived from NIRS measurements multiplied by 1,000. The presence of a high LCBI in a non-infarct-related artery (non-IRA) at the time of image acquisition has been associated with up to a four-fold increased risk of developing future adverse cardiovascular events [26]. The second measure is the maximum LCBI in each 4 mm segment of the investigated vessel (maxLCBI4mm), which is the most commonly used NIRS outcome measure. Previous studies validated the maxLCBI4mm as a reliable measure of plaque vulnerability and showed the presence of a high maxLCBI4mm (≥400) in lesions responsible for MI and future cardiovascular event-associated non-culprit lesions [17, 27]. In the recently conducted large PROSPECT II study, the upper quartile of maxLCBI4mm detected by NIRS was used to define lipid-rich plaques, along with IVUS assessment, to identify vulnerable plaques responsible for coronary events at follow-up [16].

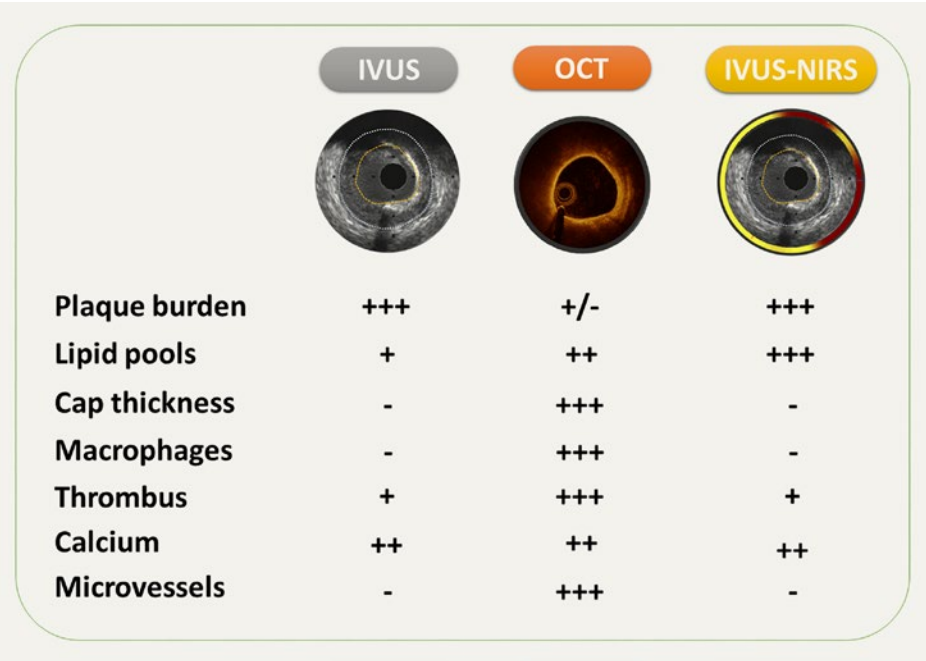

Figure 1: Very high (+++), high (++), good (+), intermediate (+/–), or low (–) accuracy of intracoronary imaging techniques for investigating different plaque characteristics: intravascular ultrasonography (IVUS), optical coherence tomography (OCT), and intravascular ultrasonography-near-infrared spectroscopy (IVUS-NIRS).

OCT

Revolutionary in this field was the introduction of the OCT technique. With its particular near-infrared wavelength, differentiating lipid, calcific, and fibrotic compositions of coronary plaques is possible, which offers new perspectives [28]. Among currently available ICI modalities, OCT has the highest resolution (axial 10–20 µm; lateral 20–90 µm), being approximately 10-fold greater than IVUS at the expense of a lower penetration depth (OCT 1–2 vs IVUS 5–6 mm) [20]. The detection of vulnerable plaque features using OCT, such as thin fibrous caps, large lipid arcs, and the presence of macrophage clusters (fig. 1), was recently associated with a higher cardiovascular event incidence at follow-up [18].

The three techniques are complementary to each other. An example of a vulnerable plaque imaged using the three techniques is depicted in figure 1. A high plaque burden is shown in the IVUS image (>70%), NIRS evaluation detected a large lipid core (maxLCBI4mm >400), and OCT identified a thin-cap fibroatheroma.

Effects of Lipid-Lowering Therapies on Atherosclerotic Coronary Plaques

Reducing low-density lipoprotein cholesterol (LDL-C) plasma levels is the key pharmacological strategy for improving the prognosis of patients with CAD. HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (e.g., statins) were the first lipid-lowering drugs that could positively affect the natural history of patients with CAD. Clinical studies showed how LDL-C reduction achieved by using statins improved the prognosis of patients with CAD, with an additional clinical benefit for each 1.0 mmol/L reduction in LDL-C [29]. Subsequently, the use of potent statins (atorvastatin and rosuvastatin) and, in more recent times, PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors allowed the introduction of a second concept, the proportional link between cholesterol reduction and clinical benefit [30–32]. Consequently, the reduction in cardiovascular events was directly related to the reduction in LDL-C levels, regardless of the drugs used (e.g., ezetimibe). The lower-is-better concept is a significant hallmark of recent guidelines on secondary prevention [33]. Are the beneficial effects on vulnerable plaque characteristics the biological rationale behind the excellent clinical results obtained with LDL-C-lowering drugs? ICI

studies offer unique biological insights in this respect.

Depending on the degree of LDL-C level lowering, prospective studies employing serial IVUS evaluations have consistently shown that lipid-lowering therapies can not only slow disease progression but also induce a reduction in atheroma volume (table 2) [21, 23, 34], with a linear relationship between on-treatment LDL-C levels and reduction in plaque burden [22, 23, 35].

In the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) trial, Nissen et al. compared the effects of treatment with atorvastatin 80 mg/day (intensive regimen) with treatment with pravastatin 40 mg/day (moderate regimen) in patients with angiographically documented CAD [23]. After 18 months, patients treated with atorvastatin 80 mg/day showed no increase in plaque burden, whereas those treated with pravastatin 40 mg/day showed an increase in plaque burden (−0.4 vs 2.7%; p = 0.001). In 2006, the ASTEROID (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden) study demonstrated for the first time that a high-dose statin, rosuvastatin 40 mg/day, could not only slow coronary atherosclerotic plaque progression but also induce significant plaque regression [22]. In 2015, the PRECISE-IVUS (Plaque Regression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by Intravascular Ultrasound) trial evaluated for the first time the effects on plaque regression of combined therapy with ezetimibe and atorvastatin compared with therapy with atorvastatin alone [36]. The results showed that the combination therapy, in addition to obtaining an expected greater reduction in LDL-C levels (63.2±16.3 vs 73.3±20.3 mg/dl; p<0.001), was accompanied by a higher plaque regression incidence intended both as a reduction of PAV (78 vs 58%; p = 0 0.004) and TAV (75 vs 58%; p = 0.02). More recently, the GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was the first randomized double-blind placebo-controlled study designed to evaluate the effects of evolocumab on PAV in patients with angiographically documented CAD [37]. In this trial, 988 patients under optimized statin therapy were randomized to receive either subcutaneous evolocumab 420 mg once a month or placebo. After 78-weeks of treatment, mean LDL-C levels were significantly lower in the PCSK9 inhibitor group (36.6 vs. 93 mg/dl; difference, −56.5 mg/dl [95% confidence interval, −59.7 to −53.4]; p<0.001), with plaque regression occurring in over 60% of patients treated with evolocumab (compared with a percentage below 50% in the standard therapy group) and a greater reduction in both PAV (−0.95 vs. +0.05%; p<0.001) and TAV (−5.8 vs. −0.9 mm^3; p<0.001). Interestingly, a GLAGOV subanalysis revealed an inverse correlation between changes in LDL-C levels and plaque calcification (r = 0.15; p<0.001) [38]. These results were consistent with those of previous studies showing an increase in calcification with lipid-lowering therapies [39, 40].

Table 2: Prospective and Randomized Trials on Coronary Atherosclerotic Plaque Regression Using Intravascular Ultrasonography

Trial	Year	Trial Design	Patient Number	Women (%)	Population	Treatment	Follow-up (weeks)	Mean Change in PAV (%)
REVERSAL [23]	2004	R	502	28	Documented CAD (at least one stenosis ≥20%; target segment with stenosis ≤50% and minimum length 30 mm)	Atorvastatin 80 mg vs Pravastatin 40 mg	72	+0.2 vs +1.6 p<0.001
ASTEROID [22]	2006	P	349	29.8	Documented CAD (at least one stenosis ≥20%; target segment with stenosis ≤50% and minimum length 40 mm)	Rosuvastatin 40 mg	96	−0.79% p<0.001
ILLUSTRATE [35]	2007	R	1188	29.55	Documented CAD (at least one stenosis ≥20%; target segment with stenosis ≤50% and minimum length 40 mm)	Atorvastatin vs Atorvastatin/Torcetrapib 60 mg	96	+0.19% vs +0.12% p=0.72
SATURN [40]	2011	R	1039	26	Documented CAD (at least one vessel with stenosis>20%; target segment with stenosis ≤50%)	Atorvastatin 80 mg vs Rosuvastatin 40 mg	34.8	−0.99% vs −1.22% p=0.17
GLAGOV [37]	2016	R	968	28	Documented CAD (at least one stenosis ≥20%; target segment with stenosis ≤50%) on optimized statin therapy	Evolocumab 420 mg vs Placebo	76	−0.95% vs +0.05% p<0.001
HUYGENS [6]	2021	R	161	28.6	ACS (NSTEMI)	Evolocumab 420 mg vs Placebo	52	−2.29% vs −0.61% p=0.009
PACMAN-AMI [5]	2022	R	300	18.7	ACS (NSTEMI or STEMI)	Alirocumab 150 mg vs Placebo	52	−2.13% vs −0.92% p<0.001

ACS: Acute coronary syndrome; CAD: Coronary artery disease; NSTEMI: Non-ST-segment elevation myocardial infarction; P: Prospective; PAV: Percent atheroma volume; R: Randomized; STEMI: ST-segment elevation myocardial infarction.

Notably, a clear correlation exists between atherosclerosis regression and the clinical benefit of the investigated drug. Torcetrapib, a cholesterol ester transfer protein inhibitor that increases high-density lipoprotein levels, showed to increase the incidence of cardiovascular events and total mortality. Consistently, torcetrapib failed to show any atheroma reduction [35]. Similarly, the ACAT (acyl-coenzyme A:cholesterol acyltransferase) inhibitor pactimibe was not associated with a clinical benefit and did not lead to any reduction in the atheroma burden compared with placebo in the ACTIVATE (ACAT Intravascular Atherosclerosis Treatment Evaluation) trial [41, 42].

Two randomized trials investigated the effect of statins on plaque compositional rather than plaque volume aspects using methods other than IVUS (table 3) [5, 6].

In the YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) study, obstructive coronary lesions from 87 patients were analyzed using the NIRS-IVUS technique at baseline and after the 7-week rosuvastatin 40 mg/day therapy [43]. The study suggested that aggressive short-term statin therapy can decrease the lipid content in obstructive lesions, with participants on rosuvastatin therapy having a larger median percentage reduction in maxLCBI4mm than those on standard therapy (32 vs 0.6%; p = 0.02). However, the small sample size of the enrolled population prevented any definitive conclusions.

In the EASY-FIT (Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography) trial investigating 70 patients with ACS, atorvastatin therapy 20 mg/day resulted in a greater increase in fibrous cap thickness than that obtained with atorvastatin 5 mg/day [44].

The Integrated Biomarker Imaging Study-4 was a pioneering observational study investigating the effects of statins using multimodality imaging in more than one coronary segment for the first time. Overall, 103 patients underwent IVUS and OCT evaluation in two non-IRAs in the acute phase of a STEMI. At the 13-month follow-up, high-dose rosuvastatin resulted not only in a significant reduction in plaque burden but also in plaque stabilization by increasing fibrous cap thickness of +24.4 µm (p = 0.008) and reducing macrophage accumulations [45]. In the OCTIVUS (Optical Coherence Tomography versus Intravascular Ultrasound-Guided Percutaneous Coronary Intervention) substudy on 87 patients with STEMI without any prior statin treatment, treatment with ezetimibe in addition to atorvastatin 80 mg showed additional changes in plaque composition assessed by OCT compared with the control group (atorvastatin 80 mg alone) owing to an increase in fibrous cap thickness and a reduction in lipid content and macrophage infiltration [46]. However, no power calculation was performed in these studies and the small number of patients limited the interpretation of the results.

The first data with adequate sample size and statistical power to assess changes in plaque compositions recently came from two randomized trials, namely the PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction) [5] and HUYGENS (High-resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) [6] trials, which investigated the additional vascular benefits of PCSK9 inhibitor treatment in addition to high-intensity statin therapy in patients with ACS (tables 2 and 3).

In the PACMAN-AMI trial [5], non-IRAs of 300 patients were investigated using IVUS, NIRS, and OCT evaluations at admission and after 52 weeks. Compared with the group undergoing high-intensity statin treatment alone, patients also treated with alirocumab showed significantly lower on-treatment LDL-C levels (alirocumab group, 23.6 mg/dl vs placebo group, 74.4 mg/dl; p<0.001) and a greater reduction in PAV in non-IRAs (primary efficacy endpoint) (−2.13 vs −0.92%; p<0.001). Moreover, the addition of alirocumab therapy was associated with a greater reduction in plaque lipid content (mean change in maxLCBI4mm

Table 3: Prospective and Randomized Trials on Plaque Stabilization using Optical Coherence Tomography (OCT) (changes in fibrous cap thickness and lipid arc) or Near-infrared Spectroscopy (NIRS) (changes in lipid core burden index)

Trial	Year	Trial Design	Imaging Modality	Patients (n)	Women (%)	Population	Therapy	Follow-up (weeks)	Mean Change in Fibrous Cap Thickness	Mean Change in Lipid Content
YELLOW [43]	2013	R	NIRS	87	24	Multivessel stable CAD (at least two vessels with stenosis ≥70%)	Rosuvastatin 40 mg vs standard therapy	6.8	–	–149.1 vs 2.4 maxLCBI4mm p = 0.01
EASY-FIT [44]	2014	R	OCT	60	20	Non-treated unstable angina and dyslipidemia	Atorvastatin 20 mg vs 5 mg	48	+73 µm vs +19 µm p = 0.002	–50 vs –10 lipid arc p<0.001
IBIS-4 [45]	2015	P	OCT	103	9.7	ACS (STEMI)	Rosuvastatin 40 mg	52	+24.4 µm p = 0.008	–12.4 lipid arc p = 0.013
HUYGENS [6]	2021	R	OCT	161	28.6	ACS (NSTEMI)	Evolocumab vs placebo	52	+42.7 µm vs +21.5 µm p = 0.015	–57.5 vs –31.4 lipid arc p = 0.04
PACMAN [5]	2022	R	OCT, NIRS	300	18.7	ACS (NSTEMI or STEMI)	Alirocumab vs placebo in addition to Rosuvastatin 20 mg	52	+62.67 µm vs +33.19 µm p = 0.001	–79.42 vs –37.60 maxLCBI4mm p = 0.006

ACS: Acute coronary syndrome; CAD: Coronary artery disease; maxLCBI4mm: Maximum lipid core burden index in each 4 mm segment of the investigated vessel; NSTEMI: Non-ST-segment elevation myocardial infarction; P: Prospective; R: Randomized; STEMI: ST-segment elevation myocardial infarction.

was −79.42 with alirocumab and −37.60 with placebo; p = 0.006), a greater increase in minimum fibrous cap thickness (mean change, 62.67 vs. 33.19 µm; p = 0.001), and a greater reduction in angular extent of macrophage infiltration (p<0.001). A patient from the PACMAN-AMI trial showing atheroma volume regression, reduction in lipid content, and fibrous cap thickening at the 52-week follow-up is shown in figure 2.

In the HUYGENS trial [6], the absolute change in minimum fibrous cap thickness from baseline to week 50 as measured by serial OCT evaluations was the primary efficacy endpoint. Among the 135 enrolled patients with evaluable images at follow-up, the evolocumab group achieved significantly lower mean LDL-C levels (28.1 vs 87.2 mg/dl; p<0.001) and showed a greater increase in minimum fibrous cap thickness (+42.7 vs +21.5 µm; p = 0.015), decrease in maximum lipid arc (−57.5 vs −31.4; p = 0.04), and macrophage index reduction (−3.17 vs −1.45 mm; p = 0.04).

Interrelation between On-treatment LDL-C Levels, Plaque Changes, and Impact on Clinical Outcomes

The different results achieved across trials regarding plaque burden reduction, besides achieving LDL-C levels at follow-up, may rely on several factors. The first factor could be the type of CAD presentation. Trials enrolling patients with stable CAD, such as the GLAGOV [37] and ASTEROID [22] trials, showed a smaller effect of lipid-lowering therapies on plaque burden than trials including patients presenting with acute MI, such as the PACMAN-AMI [5] trial (fig. 3). This is not surprising, as patients with acute MI are more likely to harbor vulnerable plaques, which are more prone to the beneficial effects of lipid-lowering treatment. Furthermore, PAV at baseline, an independent predictor of regression, was larger in the PACMAN-AMI trial than in the GLAGOV trial. Lastly, the GLAGOV trial included patients receiving statin therapy with a median LDL-C level of 92.5 mg/dl at the time of randomization, whereas 88% of the 300 patients enrolled in the PACMAN-AMI trial were statin-naïve.

Despite differences, an overall surprisingly consistent linear relationship was noted between the achieved on-treatment LDL-C levels and the achieved plaque burden reduction in patients with CAD (fig. 3A). Interestingly, plaque regression may be achieved in patients with on-treatment LDL-C levels lower than 2.0 mmol/l. The positive effects of lipid-lowering therapies on plaque burden reduction have been linearly associated with a reduction in cardiovascular events. In a recent meta-analysis encompassing 23 studies and 7,407 patients, atheroma regression by 1% was associated with a 25% reduction in the risk of major adverse cardiovascular events [47]. However, substantial heterogeneity across studies in trial design and outcome definition limits the interpretation of study results. The robust relationship with on-treatment LDL-C levels is not only limited to plaque regression but also includes fibrous cap thickening, although with much fewer observations from randomized controlled trials (fig. 3B). Accordingly, the clinical effects of plaque stabilization along with atheroma regression are also unclear. In a recent PACMAN-AMI trial subanalysis, concomitant favorable changes in coronary atheroma burden and composition, namely triple regression, were observed in one-third of patients with acute MI treated with potent lipid-lowering therapies and associated with favorable cardiovascular outcomes at one year, mainly ischemia-driven revascularizations [48]. However, the PACMAN-AMI trial was not designed for investigating this aspect, and further confirmation by dedicated randomized trials is warranted.

Collectively, the LDL-C level and regression/stabilization effect add convincing arguments to achieve the lowest LDL-C level possible in patients with CAD.

Future Perspectives

After two decades of extensive research, regression trials have yielded a wealth of information on the impact of optimal medical therapy on the natural history of human atherosclerosis. However, several questions remain unanswered. The effects of high-intensity lipid-lowering therapies are now evident; however, their routine application in cardiovascular management warrants several considerations, including cost-effectiveness. In this regard, ICI can help identify patients at a higher risk of adverse events who may benefit more from high-intensity lipid-lowering therapies. In the previously mentioned PACMAN-AMI trial subanalysis, patients with large lipid-rich plaques were those who underwent triple regression more frequently, resulting in a clinical benefit [48]. Although dedicated randomized trials are needed to confirm this hypothesis, these results suggest that using imaging modalities can facilitate the selection of patients for aggressive medical treatment.

Significantly, despite the high accuracy, the invasive nature of the abovementioned imaging modalities is a major limitation to their use in routine clinical practice. Accordingly, noninvasive serum and imaging markers of atherosclerosis have been investigated

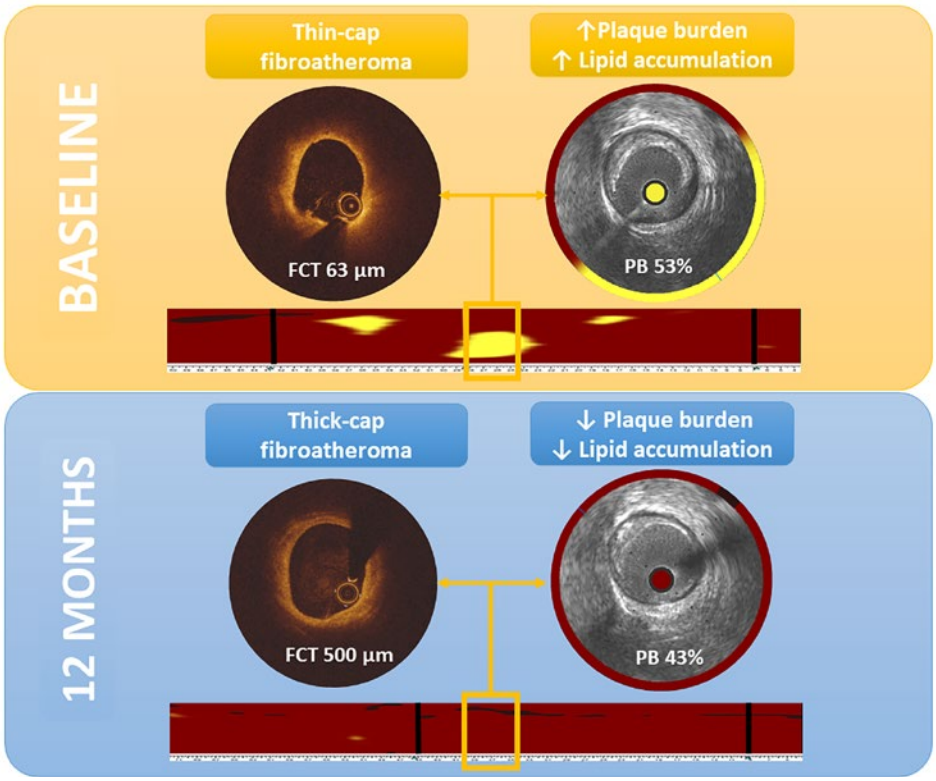

Figure 2: A patient in the PACMAN-AMI trial showing high-risk plaque features at baseline and atheroma volume regression, reduction in lipid content and fibrous cap thickening at the 12-month follow-up. Optical coherence tomography (left) reveals the plaque type and cap thickness; intravascular ultrasonography (right) reveals the plaque burden; and the near-infrared spectroscopy-derived lipid plaque spread-out plot is shown on the bottom.
FCT: Fibrous cap thickness; PB: Plaque burden.

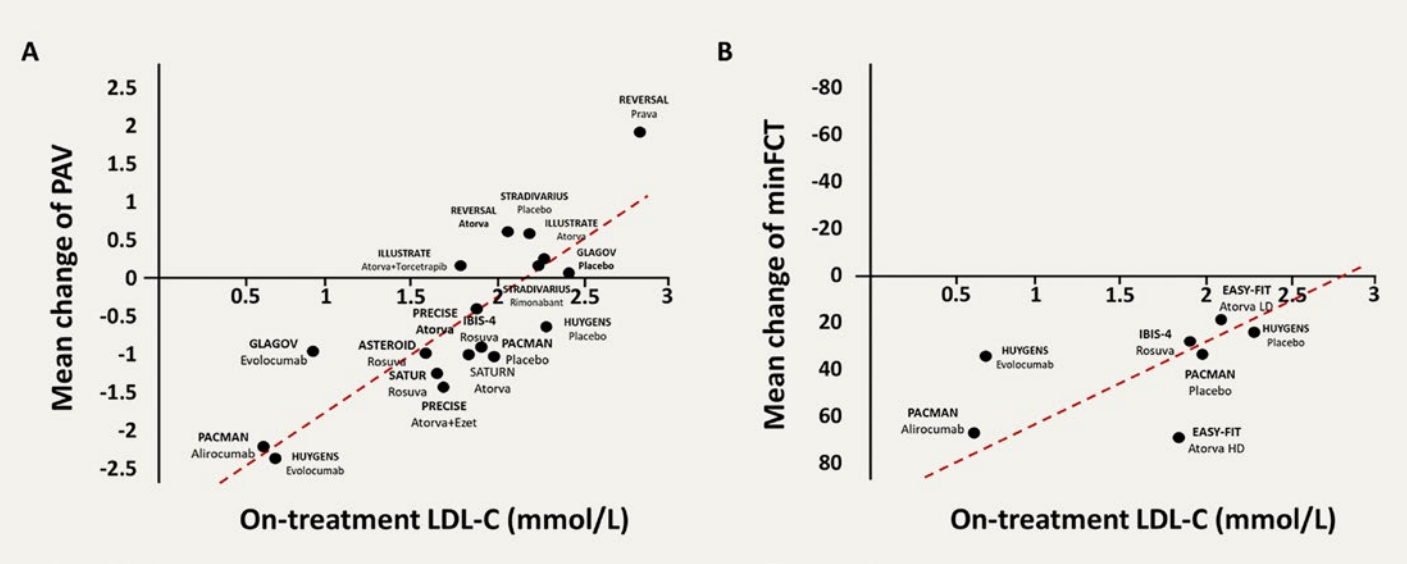

Figure 3: On-treatment low-density lipoprotein cholesterol (LDL-C) levels and changes in plaque burden (intravascular ultrasonography [IVUS] trials) and minimal fibrous cap thickness (minFCT) (optical coherence tomography [OCT] trials). Heterogeneity in results highlights discrepancies in trial design, study treatment, and enrolled population across studies. Trials enrolling patients with acute coronary syndrome (PACMAN-AMI and HUYGENS) show the strongest relationship between changes in atherosclerotic plaque features and on-treatment LDL-C levels. (**A**) Association between achieved LDL-C levels and changes in percent atheroma volume (PAV) in clinical trials using serial IVUS imaging. (**B**) Association between achieved LDL-C levels and changes in minFCT in clinical trials using serial OCT.
Atorva: Atorvastatin; Atorva HD: Atorvastatin high-dose 20 mg; Atorva LD: Atorvastatin low-dose 5 mg; Ezet: Ezetimibe; Prava: Pravastatin; Rosuva: Rosuvastatin.

for years [49, 50]. Recently, increased soluble lectin-like oxidized low-density lipoprotein receptor-1 plasma levels in patients with ACS were correlated with coronary plaque vulnerability and progression [51]. However, to date, robust data on the relationship between serum levels of atherosclerosis-promoting factors and the course of coronary atherosclerosis are lacking. Similarly, to achieve similar results, several noninvasive techniques have been developed. Currently, CCTA is a clinically established imaging technique, allowing for the noninvasive identification and characterization of coronary atherosclerotic disease [52].

Recent studies have demonstrated the ability of CCTA to quantify plaque burden and identify high-risk plaques with a high correlation with OCT images [53]. However, evidence on the use of CCTA in plaque regression/stabilization studies is lacking, but results of ongoing trials such as the GOLDI-LOX-TIMI 69 study (clinicaltrials.gov ID: NCT04610892) are expected. Furthermore, cardiac magnetic resonance (CMR) and positron emission tomography (PET) are other emerging modalities to noninvasively detect coronary atherosclerotic features [54]. However, atherosclerotic changes detected using CMR or PET have not yet been investigated. The suboptimal resolution and coronary vessel motion currently represent significant limitations for their clinical applications.

Lastly, different phenotypic types of coronary atherosclerosis should be considered when evaluating the effects of medical therapy. The use of ICI in patients with ACS has recently shed light on plaque erosion, the second most common pathophysiological mechanism of coronary instability following plaque rupture [55]. However, the effects of lipid-lowering therapies on plaque erosion-prone atherosclerotic arteries remain unknown and warrant further research.

Conclusion

Three ICI techniques available in contemporary catheterization laboratories allow in-depth plaque characterization, including plaque volume (IVUS), lipid content (NIRS), cap thickness and macrophage accumulations (OCT). These plaque features are reportedly associated with future cardiovascular events in large-scale studies and represent a key target for therapeutic interventions. To date, only LDL-C-lowering therapies (e.g., statins and PCSK9 inhibitors) have shown to consistently reduce plaque volume (regression), lipid content and inflammatory cells (macrophage accumulations) and increase fibrous cap thickness (plaque stabilization). These changes occur early following therapy initiation and largely depend on the achieved on-treatment LDL-C levels, reinforcing the lower-is-better concept from a biological point of view.

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Funding Statement

This study was conducted in an independent academic setting funded by the University Hospital of Bern.

Conflict of Interest Statement

FGB has no potential conflict of interest to declare. LR received research grants awarded to the institution (Inselspital, Bern) from Abbott, Biotronik, Boston Scientific, Heartflow, Infraredx, Sanofi, the Swiss National Science Foundation, the Swiss Heart Foundation, and Regeneron and speaker/consultation fees outside the submitted work from Abbott, Amgen, AstraZeneca, Canon, Novo Nordisk, Medtronic, Occlutech, Sanofi and Vifor.

Author Contributions

Concept, F.G.B and L.R.; Writing, Reviewing, Editing, F.G.B and L.R; Supervision, L.R. All authors have read the submitted manuscript and are jointly responsible for all aspects of the work.

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You will find the full list of references online at https://cvm.swisshealthweb.ch/en/article/doi/cvm.2024.1379478206/.