



State-of-the-Art Review

Intensive lipid lowering agents and coronary atherosclerosis: Insights from intravascular imaging

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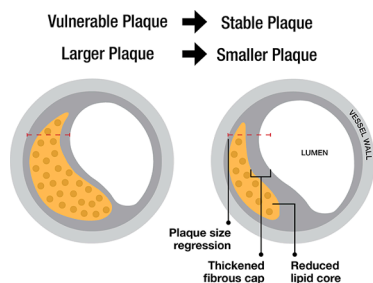
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ABSTRACT

Advances in intravascular imaging have permitted comprehensive evaluation of coronary atherosclerotic plaque from the perspective of its burden and individual components. These advances have been integrated in clinical trials that have evaluated the impact of intensive lipid lowering regimens. These trials have demonstrated that intensive lipid lowering, using high dose statins as monotherapy and in combination with new lipid lowering agents, produce favorable effects on coronary atheroma, resulting in regression and stabilization. These findings provide important biological insights to understand how intensive lipid lowering may reduce cardiovascular risk. This review aims to provide the reader with a contemporary overview of the findings of these studies and to propose the potential clinical implications for management of higher risk patients with atherosclerotic coronary artery disease.

Central Illustration



Impact of intensive lipid lowering on atherosclerotic plaque results in a combination of regression and stabilization as characterized by a reduction in lipid core and thickening of the fibrous cap.

1. Introduction

Substantial data from a range of studies have established the important role that low-density lipoprotein cholesterol (LDL-C) plays in atherosclerotic cardiovascular disease. Genetic studies have directly implicated apolipoprotein (apo) B and LDL-C in the causality of atherosclerosis and are supported by preclinical observations of a range of deleterious effects exerted by LDL particles within the artery wall [1]. It is therefore not surprising that randomized clinical trials have demonstrated that agents that lower LDL-C reduce the risk of cardiovascular events in both primary and secondary prevention, with the benefit directly proportional to the degree of lipid lowering [2]. These findings have influenced successive updates to treatment guidelines which advocate increasingly intensive lipid lowering for those individuals deemed to be at high cardiovascular risk. Early serial imaging studies that employed coronary angiography [3,4] and carotid intima-medial thickness [5–7] demonstrated that lipid lowering had a favorable impact on disease progression, providing a biological rationale underscoring their benefit on cardiovascular events. In more recent years, the use of a range of intravascular imaging modalities have permitted investigation of the impact of intensive lipid lowering on coronary atherosclerosis. With emerging data from more recent intravascular imaging studies, the opportunity presents itself to examine all

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of the data in the context of what it means for lipid management of patients with atherosclerotic coronary artery disease given that the data have clinical implications for intensive lipid management and promotion of medication adherence following acute ischemic syndromes (Table 1 and 2).

2. Development of intravascular imaging modalities

While coronary angiography and carotid intima-medial thickness have been widely employed to study the effects of medical therapies on vascular disease, they are limited in the information that they can provide. Angiography generates a two-dimensional silhouette of the arterial lumen and does not directly image the vessel wall, the site in which atherosclerotic plaques reside. Similarly, carotid intima-medial thickening reflects changes in the normal layers of the artery wall and while it correlates with cardiovascular risk it does not directly image atherosclerotic plaque. The placement of imaging probes on the tips of intravascular catheters have permitted direct visualization of atherosclerosis within the coronary arteries with the opportunity to characterize the burden and individual components of atheroma.

Intravascular ultrasound generates high resolution images of the full thickness of the coronary artery wall and permits quantitation of the volumetric burden of atherosclerosis in a vascular segment. Advances in

Table 1
Intravascular imaging trials of intensive lipid lowering.

Trial	Patient Population	Treatment Studied	LDL-C Achieved	Coronary Findings
REVERSAL	502 patients with angiographic CAD	Atorvastatin 80 mg vs Pravastatin 40 mg for 18 months	79.0 vs 110.0 mg/dL	Halting progression of coronary atherosclerosis with high dose atorvastatin
ASTEROID	349 patients with angiographic CAD	Rosuvastatin 40 mg for 24 months	60.8 mg/dL	Atheroma regression
SATURN	1039 patients with angiographic CAD	Atorvastatin 80 mg vs Rosuvastatin 40 mg for 24 months	62.6 vs 70.2 mg/dL	Plaque regression with both high intensity statin groups
PRECISE IVUS	202 patients with angiographic CAD	Atorvastatin vs Atorvastatin and ezetimibe for 9–12 months	63.2 vs 73.3 mg/dL	Incremental plaque regression with statin/ezetimibe
GLAGOV	985 Stable CAD treated with statin for >4 weeks	Evolocumab vs Placebo for 18 months	36.0 vs 93.0 mg/dL	Incremental plaque regression with statin/evolocumab
HUYGENS	161 NSTEMI patients treated with maximally tolerated statins	Evolocumab vs Placebo for 12 months	28.1 vs 87.2 mg/dL	Increase in fibrous cap thickness in association with a reduction in plaque lipid and macrophages and plaque regression
PACMAN-AMI	300 AMI patients treated with maximally tolerated statins	Alirocumab vs Placebo for 12 months	23.6 vs 74.4 mg/dL	Plaque regression in association with a reduction in plaque lipids and macrophages and increase in fibrous cap thickness

Major clinical trials that have employed intravascular imaging modalities to evaluate the impact of intensive lipid lowering regimens on coronary atherosclerosis. AMI, acute myocardial infarction; CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction.

Table 2
Lipid lowering medical therapies and coronary atherosclerosis.

Lipid Lowering Agent	Mechanism of Lipid Lowering	Impact on Coronary Plaque
Statins	Inhibit HMG CoA reductase Upregulate LDL receptor expression	Promote plaque regression and stabilization (increase calcification, increase fibrous cap thickness, decrease lipid) in direct association with the degree of lipid lowering
Ezetimibe	Inhibit NPC1L1 Inhibit intestinal cholesterol absorption Upregulate LDL receptor expression	Greater plaque regression when administered in combination with statins
PCSK9 inhibitors	Inhibit PCSK9 Upregulate LDL receptor expression	Monoclonal antibodies promote plaque regression and stabilization (increase calcification, increase fibrous cap thickness, decrease lipid)
Bempedoic acid	Inhibit ATP citrate lyase Upregulate LDL receptor expression	Not yet studied
Evinacumab	Inhibit ANGPTL3 Non-LDL receptor mediated reduction in LDL-C	Not yet studied

Classes of medical lipid lowering therapies, their mechanism of action and impact on coronary atherosclerosis using intravascular imaging modalities. ANGPTL3, angiopoietin like protein; ATP, adenosine triphosphate; HMG CoA, hydroxy methylglutaryl coenzyme reductase A; LDL-C, low density lipoprotein cholesterol; NPC1L1, Neiman Pick C 1L1; PCSK9, proprotein convertase subtilisin kexin type 9.

imaging quality have permitted its use for direct evaluation of atheroma, beyond a role for the interventional cardiologist in guiding their percutaneous procedures. Clinical studies have demonstrated that the burden and progression of coronary atherosclerosis on IVUS associate with prospective cardiovascular risk [8]. These studies demonstrate that patients experiencing a clinical event have a greater increase in percent atheroma volume (PAV) of 0.55% compared with those that remain event free [8] and that therapeutic induced regression of PAV by 1% associates with a 20% reduction in the rate of major adverse cardiovascular events [9]. However, IVUS imaging is limited in its ability to characterize the composition of coronary atherosclerosis, beyond detection of calcium and evidence of echogenicity and attenuation, which have been reported to associate with more vulnerable plaques [10].

Technological developments in the assessment of IVUS imaging have attempted to generate greater insights into the composition of coronary atherosclerosis. Radiofrequency analysis of the ultrasound backscatter has the potential to generate a spectral tissue map or virtual histology (VH-IVUS) distinguishing fibrotic, fibrofatty, calcific and necrotic components. This imaging has been reported to identify patients at greater cardiovascular risk, with evidence that the presence of a thin cap fibroatheroma on VH-IVUS associates with a greater rate of subsequent cardiovascular events [11]. Optical coherence tomography (OCT) uses a light based imaging source, generating imaging with greater resolution but less penetration through the artery wall. This produces imaging with the ability to visualize superficial components of atherosclerosis, such as fibrous cap thickness and accumulation of lipid, macrophages and neovascularization, associated with plaque vulnerability. Registry data from patients undergoing coronary OCT imaging have reported that the presence of a lipid rich plaque, defined by the presence of a thin fibrous cap and large lipid arc, associate with a greater risk of cardiovascular events on long term follow up [12].

Near infrared spectroscopy (NIRS) provides an additional approach to characterizing plaque composition, by virtue of its ability to generate a chemical fingerprint of atheroma in vivo. Early application of coronary

NIRS imaging provides a semi-quantitative determination of plaque lipid content, with evidence of a direct association with prospective cardiovascular risk [13]. As a result, engineering advances have provided a range of intravascular imaging techniques with the potential to provide complementary pieces of information (Table 3). Given the ability to image a matched arterial segment at different time points, they also permit the opportunity to determine the impact of intensive lipid lowering regimens on coronary atherosclerosis. As patients require invasive investigation for these procedures, clinical trials of atheroma utilizing these modalities have traditionally studied patients with a clinical indication for angiography, given the small risk of arterial injury with intravascular imaging catheters. Accordingly, the findings of these trials have immediate implications for higher risk, symptomatic patients.

3. High-Intensity statin therapy

3.1. IVUS studies of plaque burden

Serial IVUS imaging has been employed in clinical trials to determine the impact of more intensive statin therapy on coronary disease. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study compared the effects of treatment with atorvastatin 80 mg or pravastatin 40 mg daily for 18 months in 502 patients with obstructive coronary disease [14]. Achieving a lower LDL-C with atorvastatin (79 vs 110 mg/dL) was associated with favorable effects on coronary plaque burden. While disease progression was observed in the pravastatin group, patients treated with high dose atorvastatin demonstrated no change in plaque burden from baseline. This suggested that intensive statin therapy could arrest progression of coronary disease with evidence of a direct association between both achieved and changes in LDL-C levels and the rate of plaque progression. Subsequent analyses also demonstrated that lowering of the inflammatory marker, high sensitivity C-reactive protein (hsCRP), independently associated with slowing disease progression [15]. This suggested that preclinical observations that statins may possess non-lipid lowering properties may also contribute to their benefit and complemented similar findings of the impact of high dose atorvastatin on clinical events [16].

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) investigated the impact of treatment with rosuvastatin 40 mg daily for 24 months on coronary plaque progression in 349 patients [17]. Lowering LDL-C from 130.4 to 60.8 mg/dL associated with regression of PAV by 0.98%. While there was no comparator group employed in this study, the result represented the first definitive evidence of plaque regression with intensive lipid lowering in a large clinical trial. Subsequent analyses of statin treated patients in serial IVUS trials demonstrated that modest increases in levels of high-density lipoprotein cholesterol (HDL-C) also independently associated with their ability to slow disease

progression [18], although HDL-C raising with specific agents has not yet been shown to reduce cardiovascular risk. This analysis revealed that changes in the ratio of apoB/A-I, reflecting changes in the ratio of atherogenic to protective lipoproteins, most strongly associated with the rate of disease progression [18].

This led to the design of the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) which compared the effects of treatment with atorvastatin 80 mg or rosuvastatin 40 mg daily for 24 months in 1039 patients with coronary disease [19]. Rosuvastatin treated patients achieved lower levels of LDL-C (62.6 vs 70.2 mg/dL) and higher levels of HDL-C (50.4 vs 48.6 mg/dL). While greater regression of PAV was observed in the rosuvastatin group (1.22 vs 0.99%), the difference between the groups did not achieve statistical significance. This resulted in the majority of individual patients demonstrating some degree of plaque regression (68.5 vs 63.2% in the rosuvastatin and atorvastatin treated patients, respectively). This finding suggested that treatment of patients with high intensity statin therapy could not only achieve guideline mandated LDL-C goals, but could result in regression of coronary disease in the majority of patients. The finding that one-third of patients demonstrated ongoing plaque progression, despite use of high intensity statin therapy, is important and reflects the ongoing residual risk in statin treated patients. Subsequent analyses demonstrated that this risk of ongoing progression associated with the presence of diabetes, higher blood pressure, lower levels of HDL-C and higher levels of apoB [20]. This finding reflects not only the multiple risk factor nature of atherosclerosis, but the importance of higher levels of apoB in patients with lower LDL-C levels suggests ongoing risk related to atherogenic lipoproteins. This highlights the potential to target additional lipid lowering in statin-treated patients.

The majority of patients enrolled in these clinical trials had stable forms of atherosclerotic disease. Subgroup analysis of SATURN demonstrated that patients recruited in the setting of an acute coronary syndrome had a greater PAV at baseline (37.3 vs 35.9%) and greater PAV regression (1.46 vs 0.89%) on serial evaluation compared with patients with stable disease [21]. This supported findings from an early, small, single center study which compared the effects of atorvastatin 20 mg daily or placebo for 6 months in 70 patients with an acute coronary syndrome. This study demonstrated that lowering LDL-C by 41.7% associated with a 13% reduction in plaque burden in the atorvastatin group, while LDL-C increased by 0.7% and plaque burden increased by 8.7% in the placebo group [22]. The Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) study of 252 patients with serial IVUS imaging at baseline and after 8–12 months of treatment with pitavastatin 4 mg or atorvastatin 20 mg daily demonstrated a similar degree of regression by 16.9% and 18.1% compared with baseline in the pitavastatin and atorvastatin groups, respectively [23]. These findings, collectively, suggest that the benefits of intensive statin therapy on coronary atheroma are likely to be greater

Table 3
Intravascular imaging modalities and endpoints.

Imaging Modality	Mechanism of Imaging	Imaging Endpoints	Clinical Correlation
Intravascular ultrasound	Ultrasound	<ul style="list-style-type: none"> Percent atheroma volume: percentage of outer vessel wall volume occupied by plaque Total atheroma volume: volume of plaque within the vessel wall Plaque calcification reported as extent of circumference of vessel with a calcium arc and loss of imaging artifact 	Measures of plaque burden and progression associate with prospective risk of cardiovascular events
Virtual histology	Radiofrequency analysis of ultrasound backscatter	<ul style="list-style-type: none"> Area and percentage of plaque occupied by fibrotic, fibrofatty, calcific and necrotic components 	Presence of a thin cap fibroatheroma independently associates with prospective risk of cardiovascular events
Optical coherence tomography	Light	<ul style="list-style-type: none"> Minimum fibrous cap thickness Lipid arc Macrophage accumulation arc 	Presence of a lipid rich plaque (thin fibrous cap, large lipid arc) associates with prospective risk of cardiovascular events
Near infrared spectroscopy	Near infrared	<ul style="list-style-type: none"> Lipid core burden index 	Presence of a high lipid core burden index associates with prospective risk of cardiovascular events

Main intravascular imaging modalities, their mechanism of imaging, main measurement endpoints and correlation with clinical cardiovascular events.

in patients with a recent acute coronary syndrome and provide a biological rationale for the finding that intensive statin therapy reduces the rate of cardiovascular events in patients with acute coronary syndromes [24,25].

3.2. IVUS studies of plaque composition

Subsequent analyses of the serial IVUS trials of intensive statin therapy have provided some insights into their effects on plaque composition. While limited in the composition that can be derived from standard IVUS imaging, these trials have demonstrated that the regression observed with intensive statin therapy associates with an increase in plaque calcification [26]. VH-IVUS analysis of SATURN demonstrated that the regression observed with high intensity statin therapy was also accompanied by small proportional reductions in fibrous and fibrofatty components, no change in necrotic material and a larger proportional increase in dense calcium [27]. The Integrated Biomarker and Imaging Studies (IBIS 3 and 4) also failed to demonstrate any change in necrotic core on VH-IVUS associated with plaque regression observed with treatment with rosuvastatin 40 mg daily [28,29]. These observations have been confirmed by a meta-analysis of 9 studies of statin treatment involving 830 patients, which found the most profound impact was on fibrous and calcific components of coronary atheroma [30]. The finding of statin induced plaque calcification has been explored further with computed tomography coronary angiography, which has revealed that the pattern of calcification with statin therapy is more dense in nature, consistent with plaque stabilization [31].

3.3. OCT studies of plaque phenotype

With increasing use of OCT in the catheterization laboratory, this technique has been increasingly employed in clinical trials of coronary atheroma. Observational studies reported that higher LDL-C levels associated with features of plaque vulnerability, as evidenced by thin fibrous caps and large lipid arcs [32]. In contrast, use of more intensive statin therapy associated with less vulnerable disease, with thicker fibrous caps and less evidence of neovascularization [33]. A number of clinical trials at Japanese centers demonstrated features of plaque stabilization on serial OCT imaging with statin therapy [33–39]. The largest of those studies, Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography (EASY-FIT), compared the effects of treatment with atorvastatin 5 or 20 mg daily with serial OCT imaging at baseline and 12 month follow up in 70 patients. The higher dose group achieved lower LDL-C levels (69 vs 78 mg/dL) and greater absolute increases in fibrous cap thickness and decreases in the size of the lipid arc. The increase in fibrous cap thickness correlated directly with the degree of lowering of both LDL-C, hsCRP and macrophage accumulation [37]. Meta-regression analysis of these trials revealed a direct relationship between the extent of lipid lowering and the annual increase in fibrous cap thickness [40].

3.4. NIRS studies of plaque lipid content

The impact of intensive statin therapy on changes in plaque lipid on NIRS imaging has been less extensively studied. The Reduction in Yellow Plaque by Aggressive Lipid Lowering Therapy (YELLOW) study compared the effect of standard lipid lowering therapy with more intensive treatment with rosuvastatin 40 mg daily on plaque lipid with serial NIRS imaging at baseline and 7 week follow up. The more intensively treated patients demonstrated a favorable change in the lipid core burden index within the 4-mm maximal segment ($LCBI_{4mm}$: -149.1 vs $+2.4$) consistent with early reductions in plaque lipid [41]. These early changes were observed without changes in plaque burden and, predictably, only observed in patients with evidence of lipid rich plaques at baseline [42]. The subgroup of patients within IBIS-3 who underwent

serial NIRS imaging did not demonstrate any reduction in $LCBI_{4mm}$ with rosuvastatin therapy, although a trend towards benefit was observed in those with the highest baseline lipid content [28]. While these findings are of interest, the NIRS field has lacked large, definitive studies to provide comprehensive data to understand the impact of intensive statin therapy on plaque lipid.

4. Ezetimibe

Addition of the cholesterol absorption inhibitor, ezetimibe, to statin therapy has the potential to achieve greater lowering of LDL-C by up to 20% and greater hsCRP lowering. The Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study randomized 202 patients to treatment with atorvastatin monotherapy uptitrated to achieve a LDL-C less than 70 mg/dL by itself or in combination with ezetimibe 10 mg daily with serial IVUS imaging at baseline and 9–12 months. Patients treated with the combination of atorvastatin and ezetimibe achieved a lower LDL-C level (63.2 vs 73.3 mg/dL), which associated with greater PAV regression (1.4 vs 0.3%) and a greater percentage of patients demonstrating any degree of regression (78 vs 58%) [43]. This finding supported results of clinical trials that demonstrated a favorable effect of adding ezetimibe to statin therapy on cardiovascular events in patients with an acute coronary syndrome [44]. While addition of ezetimibe to low or moderate intensity statin therapy may be better tolerated and produce greater lipid lowering than high intensity statin alone [45], further studies are required to evaluate the impact of these strategies on coronary atheroma.

5. PCSK9 inhibitors

Proprotein convertase subtilisin kexin type 9 (PCSK9) plays an important role in the regulation of LDL metabolism. Development of PCSK9 inhibitory monoclonal antibodies resulted in significant reductions in PCSK9, upregulation of LDL receptor expression on the hepatocyte surface and dose dependent lowering of LDL-C by up to 60% [46]. Use of these agents were demonstrated to produce reductions in major adverse cardiovascular events when used in combination with statin therapy in patients with stable and unstable ischemic syndromes [47,48]. The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) compared the effects of treatment with evolocumab 420 mg or placebo administered monthly for 18 months in 968 patients with obstructive coronary disease, who had been treated with a stable dose of statin therapy for at least 4 weeks [49]. The evolocumab treated patients achieved lower LDL-C levels (36.6 vs 93.0 mg/dL). This associated with PAV regression in the evolocumab treated patients by 0.95% and an increase in PAV by 0.05% in the placebo group. As observed in the statin trials, a greater percentage of evolocumab treated patients demonstrated any degree of regression (64.3 vs 47.3%), although a similar cohort remained that continued to demonstrate plaque progression. A direct relationship between achieved LDL-C levels and changes in plaque burden continued to be observed, extending this correlation to levels as low as 20 mg/dL. The findings were important in that they not only demonstrated a benefit by adding a PCSK9 inhibitor to background statin therapy, but they also failed to identify a low LDL-C level below which incremental benefit was not observed.

Recent findings of new clinical trials have provided additional insights into the impact of PCSK9 inhibition on atheroma burden in patients with acute coronary syndromes. The Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction (PACMAN-AMI) compared the effects of alirocumab 150 mg or placebo every two weeks on serial plaque imaging at baseline and 52 weeks in 300 patients treated with rosuvastatin 20 mg daily following a myocardial infarction [50]. The alirocumab treated patients achieved lower LDL-C levels (23.6 vs 74.4 mg/dL). The decrease

in PAV (-2.1 vs -0.9% in alirocumab and placebo groups, respectively) in the PCSK9 inhibitor group was greater than that observed in the more stable patients in GLAGOV. A similar finding was observed in the High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS), in which the PAV regression observed with evolocumab was much greater than its effects in GLAGOV (-2.29 vs -0.95%) [51]. The consistent finding of greater plaque regression in acute coronary syndrome patients was observed in the setting of greater plaque burden at baseline. These findings also contribute to a growing body of evidence that demonstrates the relationship between achieved LDL-C levels and plaque progression with more intensive lipid lowering regimens (Fig. 1).

Additional analyses from intravascular imaging have begun to elucidate potential effects of PCSK9 inhibition on plaque composition. The subgroup of patients within GLAGOV that underwent serial VH-IVUS imaging demonstrated similar plaque composition changes as observed with high intensity statins in SATURN, with the most dominant effect being a large proportional increase in plaque calcification, which complemented findings from standard IVUS imaging [52]. A direct relationship was observed between the degree of lipid lowering and extent of plaque calcification. Since this finding is now observed with both statins and PCSK9 inhibitors, they suggest a lipid lowering effect, as opposed to a pleiotropic property of statins.

The HUYGENS trial primarily aimed to employ serial OCT imaging to evaluate the impact of PCSK9 inhibition on features of plaque vulnerability. In this study, 161 patients with a myocardial infarction and evidence of vulnerable plaque features in a non-culprit vessel were randomized to treatment with evolocumab 420 mg or placebo monthly for 52 weeks, in addition to background statin therapy. Approximately 24% of patients had been treated with a statin prior to their index acute coronary syndrome. During the course of the trial more than 95% of patients were treated with a statin, of which more than 80% was high intensity in accordance with treatment guidelines. LDL-C levels decreased from approximately 140 mg/dL at baseline to 87.2 mg/dL in the statin monotherapy and 28.1 mg/dL in the statin and evolocumab groups. Evolocumab treated patients demonstrated greater increases in minimum fibrous cap thickness ($+42.7$ vs $+21.5$ μm) and decreases in maximum lipid arc (-57.5 vs -31.4°) and macrophage index (-3.35 vs -1.43). Less evolocumab treated patients had evidence of an image with a minimum fibrous cap thickness less than 65 μm at the end of the study (12.5 vs 30.2%). Similar effects were observed throughout the length of

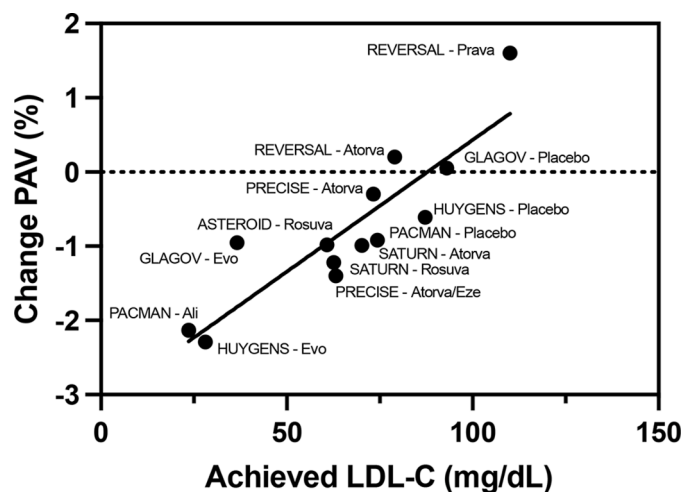


Fig. 1. LDL-C v plaque in IVUS trials

Association between achieved levels of low-density lipoprotein cholesterol (LDL-C) and change in percent atheroma volume (PAV) in clinical trials using serial intravascular ultrasound imaging of coronary atherosclerosis. Ali, alirocumab; atorva, atorvastatin; evo, evolocumab; eze, ezetimibe; rosuva, rosuvastatin.

the vessel and in prespecified lipid rich regions. A direct relationship was observed between changes in fibrous cap thickness and both achieved and changes in levels of LDL-C [51]. Similar findings were observed on serial OCT in PACMAN-AMI, in which alirocumab treated patients demonstrated a greater increase in fibrous cap thickness ($+62.7$ vs $+33.2$ μm) and decrease in macrophage arc (-26 vs -16°) [50]. At a trial level, a direct association is demonstrated between achieved LDL-C levels and changes in fibrous cap thickness (Fig. 2). A small non-randomized, observational study from Japan revealed that the OCT detected improvements in fibrous cap thickness and lipid arc begin to be evident as early as 4 weeks [53], suggesting that early administration of a PCSK9 inhibitor in acute coronary syndrome patients can produce rapid changes in the artery wall that are sustained for up to 12 months in patients adhering to intensive lipid lowering.

In addition to IVUS and OCT imaging, patients participating in PACMAN-AMI also underwent serial NIRS evaluation of coronary plaque. Alirocumab treated patients demonstrated a greater reduction in $\text{LCBI}_{4\text{mm}}$ (-79.4 vs -37.6) [50]. This represents the first large scale trial demonstrating definitive evidence of a reduction in plaque lipid on NIRS imaging with intensive lipid lowering and contributes to understanding the biological effects that will result from reducing LDL-C to very low levels. A dedicated serial NIRS imaging study is ongoing to evaluate the effect of evolocumab on plaque lipid content [54].

6. Future directions

The emergence of a range of imaging tools has enabled study of novel approaches to intensive lipid lowering at the level of the artery wall. A question arises, should we treat the plaque or the LDL-C level? To date, the data from clinical trials suggests that we treat lipids according to the level of clinical risk of the patient. Given that these studies have been performed in patients undergoing a clinically indicated coronary angiogram, the level of risk is typically higher and the studies reinforce the recommendations of guidelines. Whether specifically treating according to different patterns of atherosclerotic disease, beyond a simple assessment of presence or absence, has not yet been studied in clinical trials. Similarly most trials involve patients who predominantly identify as male and Caucasian. Future studies have the opportunity to examine the biological effects of therapies across a broad and diverse range of patients. It remains to be determined whether similar studies will evaluate new LDL-C lowering interventions, such as bempedoic acid, inclisiran or gene editing approaches, but the experience to date can predict the extent of benefit that would be observed. Similarly, new

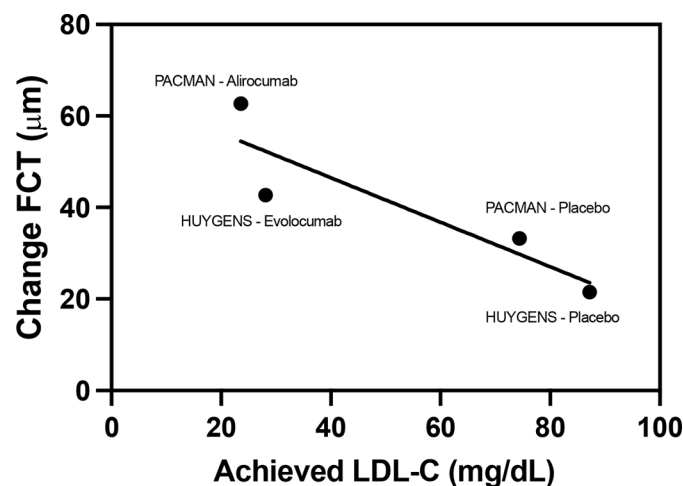


Fig. 2. LDL-C v FCT in OCT trials

Association between achieved levels of low-density lipoprotein cholesterol (LDL-C) and change in fibrous cap thickness (FCT) in clinical trials using serial optical coherence tomography imaging of coronary atherosclerosis.

interventions targeting additional lipid factors such as triglyceride rich lipoproteins or Lp(a) may be studied, with evidence of plaque benefits already demonstrated on intravascular imaging in response to HDL mimetics [55], high dose EPA [56] and the lipid effects of pioglitazone [57]. As the technological advances of non-invasive coronary imaging with computed tomography (CT) have improved, this now provides the opportunity to examine a range of features and to apply it to lower risk patients, avoiding the need for invasive coronary procedures. The application of CT and IVUS imaging of medical therapies has the potential to provide complementary information regarding the impact of these interventions on different aspects of the biology in the artery wall in patients at different levels of cardiovascular risk.

7. Summary

The ability to integrate serial imaging within clinical trials has provided important insights into the biological effects of medical therapies. The relevance of these findings is supported by observations of a relationship between a number of plaque features and cardiovascular events. These studies have demonstrated that increasing intensive lipid lowering, achieved with high intensity statins as monotherapy or in combination with other agents, produce favorable effects on plaque burden and composition. These findings have an important opportunity to maintain long term adherence to these therapies in order to achieve more effective reductions in cardiovascular risk.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Stephen Nicholls reports a relationship with AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron that includes: funding grants. Stephen Nicholls reports a relationship with Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron and Novo Nordisk that includes: consulting or advisory. Stephen Nicholls has patent issued to Amgen.

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