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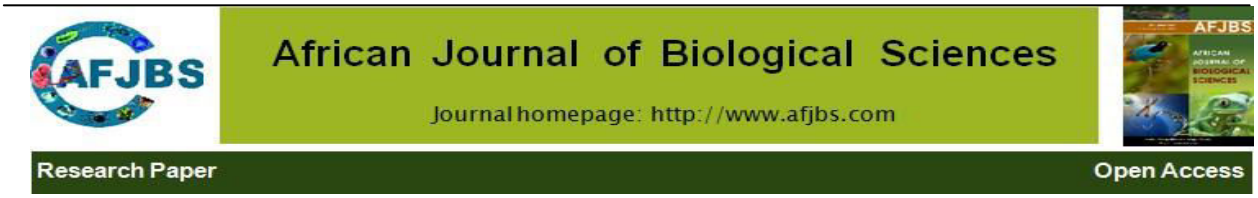

Effect of Lipid Lowering Therapy on Plaque Composition: Current Evidence

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Abstract

Stabilization and regression of coronary atherosclerotic plaques by lipid-lowering therapy plays an important role in the treatment of (CHD). Plaque regression, which includes the removal of lipids and the necrotic core, was shown to restore endothelial function, although the cessation of intravascular smooth muscle cell proliferation is a complex process.

Keywords: Plaque Composition,lipid lowering therapy.

Plaque stabilization by lipid lowering therapy

Stabilization and regression of coronary atherosclerotic plaques by lipid-lowering therapy plays an important role in the treatment of (CHD) (1). Plaque regression, which includes the removal of lipids and the necrotic core, was shown to restore endothelial function, although the cessation of intravascular smooth muscle cell proliferation is a complex process. (2)

Coronary atherosclerotic plaque regression can be detected using various imaging techniques that can measure changes in plaque volume (PV), and IVUS is currently one of the most common of such methods (3). Total atheroma volume (TAV) and percent atheroma volume (PAV) are the indices usually used to evaluate coronary PV. TAV is more sensitive, and PAV is more accurate. (4)

A plaque has regressed when a reduced PV is detected after treatment. Recent studies have indicated that lipid lowering therapy can lead to the regression of a coronary atherosclerotic plaque and reduce the incidence of adverse cardiovascular events (4, 5). A recent meta-regression

analysis by Bhindi et al showed that a 1% reduction in mean PAV was induced by dyslipidemia therapies and was associated with a 20% reduction in the odds of MACE. (6)

Meta-analysis total of 31 studies with 4997 enrolled patients who received lipid lowering therapy for at least 6 months was performed. Changes in coronary PV were measured by IVUS, and the results showed significant coronary plaque regression in patients after receiving lipid lowering therapy, subgroup analysis indicated that TAV was significantly reduced when LDL-C at follow-up was less than 80 mg/dL and high density lipoprotein cholesterol (HDL-C) was greater than or equal to 45 mg/dL, and PAV was significantly decreased when LDL-C at follow-up was less than 90 mg/dL and HDL-C was greater than or equal to 45 mg/dL, these findings were also confirmed by sensitivity analysis. Regression analysis showed that LDL-C levels at follow-up significantly influenced these results. (7)

In previous studies, HDL-C was shown to play an important role in the regression of coronary plaque by reverse cholesterol transport (RCT) (2). HDL-C is mainly synthesized by apoAI and apoAII, which can clear or reuse cholesterol through lipid metabolism pathways, thereby reducing the progressive accumulation of cholesterol in plaque and promoting the regression of plaque (8). A rise in HDL-C levels can reduce the incidence of cardiovascular adverse events. In the latest guideline for the management of dyslipidemias, HDL-C is the class I recommendation for lipid analyses in cardiovascular disease risk estimation (9).

In recent research, a rise in HDL-C level was shown to promote regression of coronary plaque and reduce the occurrence of MACE when LDL-C was greater than or equal to 70 mg/dL in patients receiving statin therapy (10).

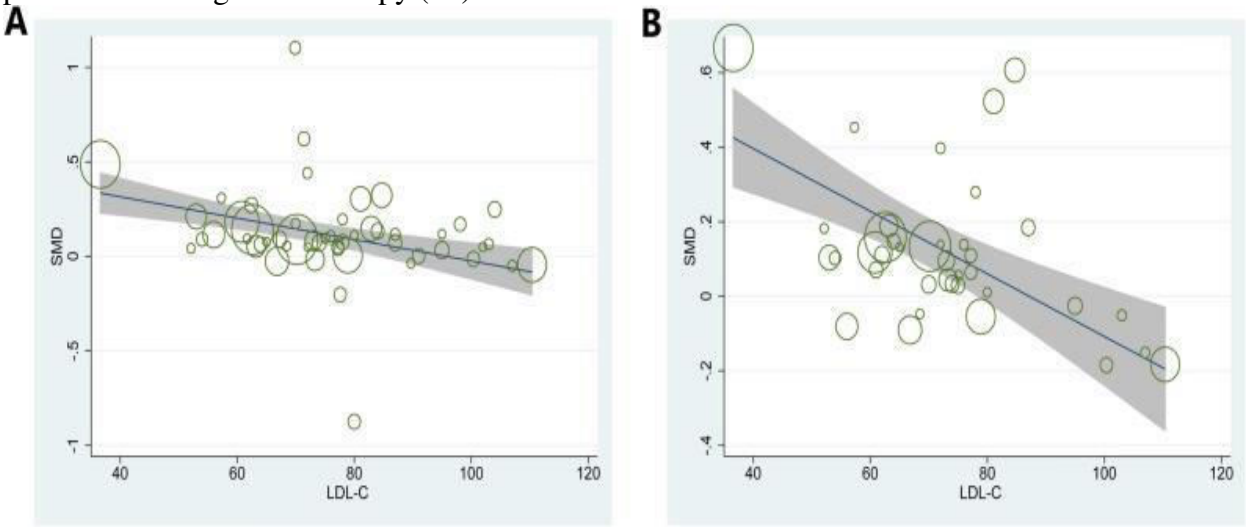

Figure 1. Meta–regression analyses for standardized mean difference (SMD) in plaque volume between patients at baseline and follow-up (7)

(A) effect of LDL-C on TAV; (B) effect of LDL-C on PAV, LDL-C: low density lipoprotein cholesterol, TAV: total atheroma volume, PAV: percent atheroma volume

Multiple randomized trials demonstrated the benefits of statins in reducing mortality and the frequency of myocardial infarctions, ischemic strokes, and coronary revascularizations (11-13). In addition to lowering serum cholesterol levels, statins induce plaque stabilization by reducing inflammation and improving endothelial function (14).

With IVUS, non-obstructive coronary lesions can reduce percentage atheroma volume by 0.9% to 1.2% after long-term administration of high-dose statins, with a trend in reduction in cardiovascular mortality. (4, 15)

Although reduction in atheroma volume has been most commonly reported, plaque composition may play a crucial role in the progression to ACS. (16, 17)

In particular, lipid rich fibroatheromas are at increased risk for plaque rupture and thrombosis (18, 19). Of all plaque components, the lipid core exhibits the highest thrombogenic activity (20). Emerging data using novel in vivo imaging modalities suggest that statins might have a greater impact on modulating lipid content versus plaque volume. (21-24)

Effect of statins and LDL-C reduction on coronary plaques in chronic coronary syndrome (CCS)

The YELLOW trial randomized 87 patients with multivessel CAD undergoing PCI for stable coronary artery disease and at least 1 other severely obstructive (FFR < 0.8) non-target lesion (NTL) to intensive (rosuvastatin 40 mg daily) or standard-of-care lipid-lowering therapy. NTLs were evaluated at baseline and after 7 weeks of therapy with fractional flow reserve (FFR), near infrared spectroscopy (NIRS), and IVUS. The primary endpoint was the change in lipid-core burden index at the 4-mm maximal segment (maxLCBI4mm), wherever this occurred within the lesion. (25)

Median reduction (95% confidence interval) in maximum lipid core burden index (maxLCBI4mm) was significantly greater in the intensive versus standard group (-149.1 [-210.9 to -42.9] vs. 2.4 [-36.1 to 44.7]; p = 0.01). Results remained consistent after adjustment for baseline differences in LCBI between groups and use of change in LCBI across the entire lesion as the dependent outcome. (25)

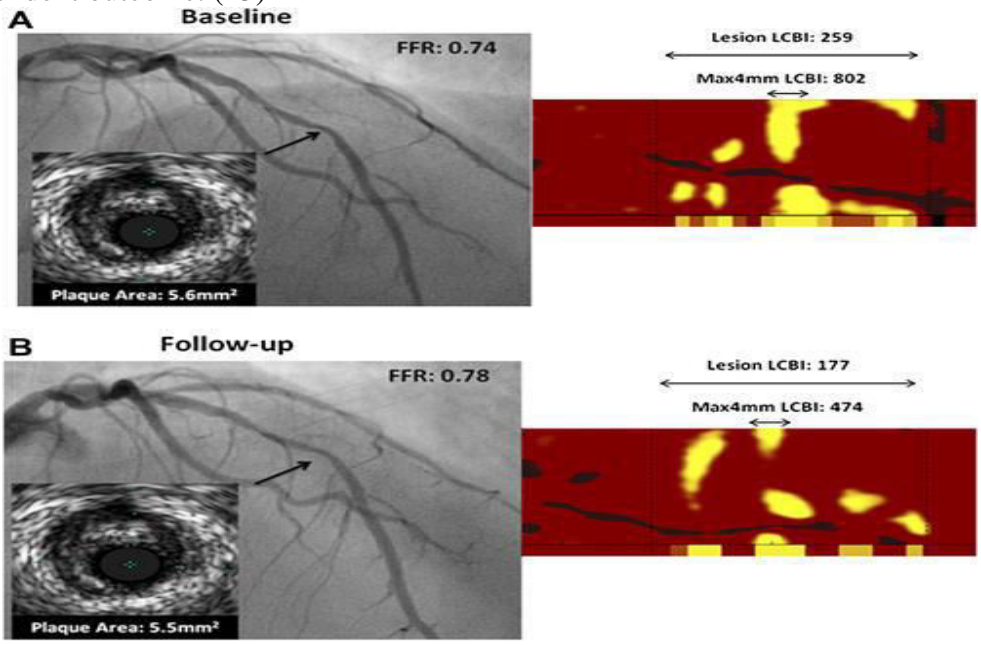

Figure 2. Examples of Angiography, FFR, IVUS, and NIRS in an Individual Case at Baseline (A) and Follow-Up (B) (25)
FFR: fractional flow reserve, IVUS: intravascular ultrasound, NIRS: near infrared spectroscopy

Results of the pilot YELLOW trial suggest changes in plaque composition with short-term intensive statin therapy in severely obstructive CAD. (25)

Previous randomized trials successfully used high-dose statins in patients with acute coronary syndrome and showed significant improvements in clinical events (26, 27)

Improvements in FFR were characterized by a larger reduction in maxLCBI4mm. This preliminary observation suggests that short-term, intensive reductions in LCBI may modulate coronary flow physiology, especially in plaques with large lipid cores. Given the small sample size and post hoc nature of these comparisons; however, these observations exclusively in non-culprit lesions with large lipid cores can only be considered hypothesis generating and require prospective confirmation. (25)

Insights from intracoronary imaging studies suggest that statins result in atheroma regression in patients with stable, non-obstructive coronary artery disease. (15, 28)

Effect of statins and LDL-C reduction on coronary plaques in STEMI

Patients with STEMI are at high risk for recurrent atherothrombotic events, which is related to multifocal disease with a high prevalence of vulnerable plaques, (29) typically extending beyond the culprit site due to widespread inflammation in other plaques including increased protease activity. (30)

In IBIS-4 study, serial intracoronary imaging revealed that high-intensity lipid-lowering therapy like rosuvastatin therapy (40 mg daily) resulted in regression of coronary atherosclerosis in the proximal segments of non-infarct related artery (IRA) in STEMI patients within 13 months. (31)

In this trial, PAV of the non-IRA decreased by -0.9% (95% CI: -1.56 to -0.25, p = 0.007). Patients with regression in at least one non-IRA were more common (74%) than those without (26%). Of note, atheroma burden in the present study was in average higher (≐10%) than previous similar studies in patients with stable, non-obstructive CAD reflecting the higher risk population. Despite the exclusion of patients with obstructive CAD of non-IRA, this observation underscores the high atherosclerotic disease burden observed in the proximal segments of non-IRA among STEMI patients. (31)

Statin therapy has been reported to reduce lipid content, oxidized LDL-C, and inflammatory cells in tissue extracted by means of atherectomy. (32)

In contrast, there was no reduction in RF-IVUS defined lipid-rich tissue (fibro-fatty or necrotic core) but rather an increase in calcium in IBIS-4, (31) An increase in calcium was previously noted independent of statin dose using investigation by coronary computed tomography and RF-IVUS performed at 12 months. (32-34)

PCSK9 inhibitors, a new hope

Proprotein convertase subtilisin kexin type 9 (PCSK9) reduces LDL-C receptor recycling to the hepatic surface, thereby limiting removal of LDL-C particles from the circulation.(35-37) Monoclonal antibodies against PCSK9 reduce LDL-C levels when administered alone or in combination with statins.(38,39) Initial studies have demonstrated the feasibility of using the combination of statins and PCSK9 inhibitors to achieve LDL-C levels much lower than achieved previously.(38,39)

The GLAGOV trial demonstrated that addition of the PCSK9 inhibitor evolocumab in patients treated with moderate- or high- intensity statin therapy had a favorable effect on progression of

coronary atherosclerosis as measured by IVUS. Both the primary and secondary IVUS efficacy measures showed atherosclerosis regression during 18 months of therapy in patients treated with the combination of evolocumab and statins and absence of regression in patients treated with a statin alone. Compared with baseline, for the primary IVUS end point, PAV, patients in the placebo treatment group demonstrated no decrease in atheroma burden (0.05%, p =0.78), whereas patients in the evolocumab group showed a significant reduction in PAV (−0.95%, p < .001), for a between-group difference of −1.01% (p < .001). Similar results were observed for the principal secondary end point, TAV (between-group difference, −4.9mm3; p < .001). (40)

These findings provide evidence that PCSK9 inhibition produces incremental benefits on coronary disease progression in statin-treated patients. This trial also evaluated the percentage of patients demonstrating regression of coronary atherosclerosis, defined as any change in PAV or TAV less than zero. Using this definition, for the primary end point, PAV, approximately 47% of patients in the placebo group experienced regression, compared with 64% of the treatment group receiving the combination of a statin and PCSK9 inhibitor (between-group difference, 17.0%; p < .001). Similar results were observed for TAV, with more patients achieving regression with combination therapy (between-group difference, 12.5%; p < .001) (40)

The PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction) randomized trial sought to determine the effect of early administration of the PCSK9 inhibitor alirocumab on coronary atherosclerosis, assessed by serial, 2-vessel, multimodality intracoronary imaging (IVUS, NIRS, and OCT) of the non-IRAs in patients presenting with AMI. (41)

Favorable effects of intensive lipid-modifying therapies on coronary atherosclerosis would be of particular relevance for patients with AMI, because the heightened risk of recurrent events is largely attributable to frequent coexistence of multiple non-obstructive lesions with high-risk characteristics in the non-IRAs of these patients. (42)

Addition of the PCSK9 inhibitor alirocumab to high-intensity statin therapy in patients presenting with AMI resulted in favorable effects on coronary atherosclerosis, assessed by 2-vessel imaging applying a combination of 3 intracoronary imaging modalities. (43)

The primary IVUS efficacy end point showed significantly greater PAV regression during 52 weeks of therapy in patients treated with the combination of alirocumab and high-intensity statin therapy compared with statin monotherapy. (43)

The extent of PAV regression (2.13%) in the active treatment group of this trial was larger than observed on previous reports and the mean LDL-C levels achieved (23.6 mg/dL) were lower compared with previous IVUS trials of statins (15, 28) and the GLAGOV trial assessing the PCSK9 inhibitor evolocumab.(41, 43)

OCT is the only imaging modality with sufficient spatial resolution to quantify fibrous cap thickening (FCT) in vivo. (44, 45)

This trial found a significantly greater increase in minimal FCT with alirocumab vs placebo. These findings build on previous evidence of FCT increase from smaller, serial OCT studies with statins (46, 47) and are consistent with the findings of the HUYGENS trial, demonstrating a

mean increase in minimal FCT of 29.8 μm with placebo and 62.3 μm with evolocumab among 135 patients with NSTEMI.(48) The CLIMA study showed that the presence of 4 OCT markers of presumed plaque vulnerability was associated with increased risk of subsequent ischemic cardiovascular events; among these markers, minimal FCT less than 75 μm showed the strongest correlation with clinical prognosis.(49)

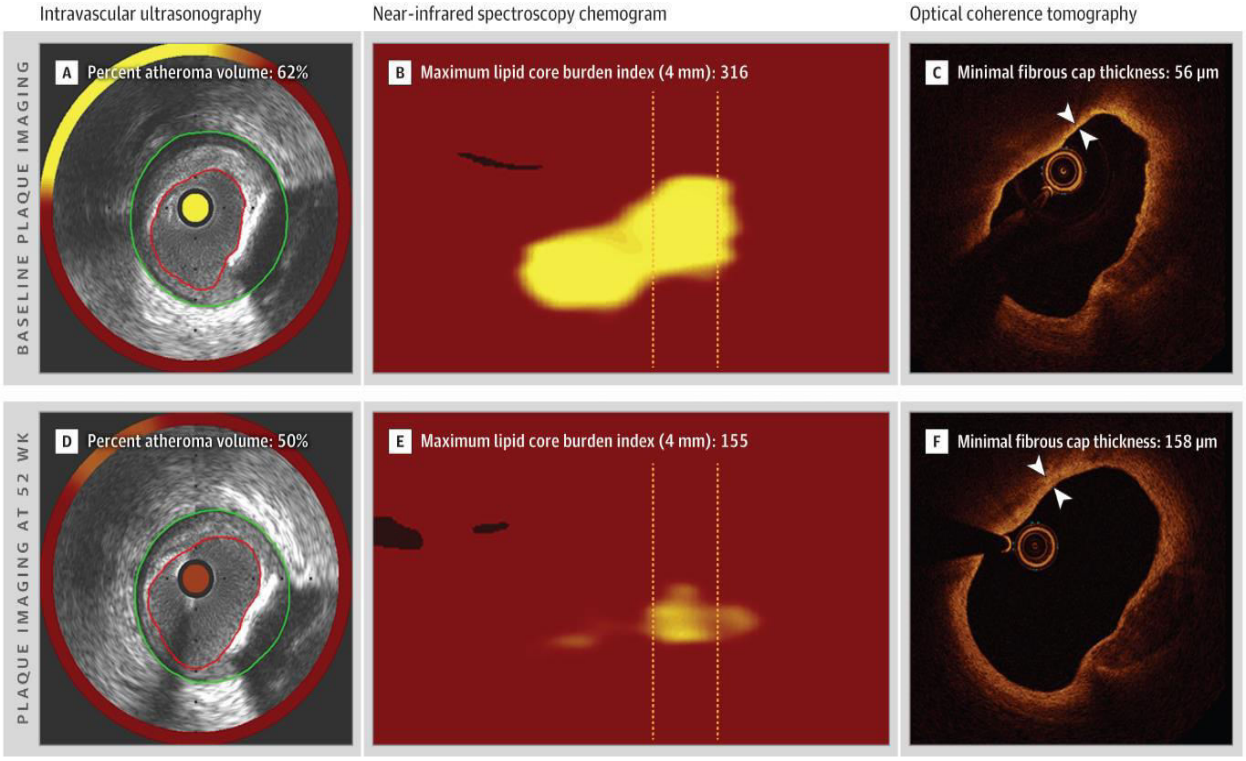

Figure 3. Example of Plaque Regression, Lipid Regression, and Fibrous Cap Thickening in a Trial Patient (43)

To summarize, effects of intensive statin therapy on plaque composition have been well documented in non-culprit lesions in both ACS and CCS in many trials but no studies have assessed effects of short-term intensive statin therapy initiated immediately post ACS on non-culprit plaque composition and its possible effect on hemodynamic significance.

Abbreviations

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CCS	chronic coronary syndrome
CHD	coronary heart disease
FFR	Fractional flow reserve
HDL-C	High density lipoprotein cholesterol
IVUS	Intravascular ultrasound
LDL-C	Low density lipoprotein cholesterol
MACE	Major adverse cardiovascular events

maxLCBI4mm	maximum lipid core burden index
NIRS	Near infrared spectroscopy
NTL	non-target lesion
OCT	Optical coherence tomograpphy
PAV	percent atheroma volume
PCSK9	Proprotein convertase subtilisin kexin type 9
PV	plaque volume
STEMI	ST segment elevation myocardial infarction
TAV	Total atheroma volume

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