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EDITORIAL COMMENT

Primary and Secondary Prevention, or Subclinical and Clinical Atherosclerosis*

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It is widely accepted that plaque rupture is the basis of most acute coronary events and that the plaques vulnerable to rupture demonstrate distinct morphological signatures that can be identified by various invasive and noninvasive imaging techniques (1). It is not only the plaque characteristics alone, but progressive plaque enlargement, that underlie the fateful lesions. The post-mortem studies have demonstrated that the plaques resulting in fatal events usually carry a large plaque burden and possess large necrotic core volumes. The serial in vivo coronary angiographic, intravascular ultrasound (IVUS) and computed tomography angiography (CTA) studies have informed that the plaques that eventually result in acute events undergo rapid plaque progression before the fateful event (2). In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, the IVUS-verified nonculprit high-risk lesions doubled their size in the interval between the original measurement and the time of event; increment in the plaque size increased the likelihood of an event by more than 4-fold (3). Similarly, a serial invasive coronary angiography study in a small number of patients with intermediate stenosis demonstrated that >70% of lesions with rapid progression over the ensuing 1 year resulted in acute coronary syndromes; no events were observed in patients who sustained a steady plaque progression or whose plaque remained unchanged (4). In a longer CTA-based follow-up, the high-risk plaques with plaque progression over time carried a 28% likelihood of an acute coronary event, whereas the plaques with similarly high-risk morphological features to start, but no interval plaque progression, only infrequently developed acute events up to a 10-year follow-up (5). Therefore, progressive increase in plaque burden and necrotic core enlargement are harbingers of future events over and above the clinical risk factors and high-risk morphological plaque characteristics.

The clinical benefits of lipid-lowering therapy with statins are well known. Through a number of imaging studies utilizing different modalities, it has been demonstrated that aggressive treatment with statins helps reduce total plaque burden predominantly by decreasing necrotic core volume and restricting plaque progression (6,7). Intensive therapy with statins might not always change the degree of luminal stenosis, but rather may reduce plaque volume by replacing lipid-rich cores with fibrous plaque and by producing negative remodeling, and help stabilize lesions (6). An analysis of various invasive coronary angiography and IVUS studies has suggested that the low-density lipoprotein (LDL) levels must be brought down to 70 to 80 mg/dl to achieve a complete elimination of plaque progression (**Table 1**, **Figure 1**). Even lower LDL levels were needed for plaque volume reduction. A serial intracoronary angioscopic and near infrared spectroscopic evaluation demonstrated that the intensity of the yellow score, or lipid core burden index, of the obstructive nonculprit lesions decreased only after significant LDL reduction had been attained (8,9). Similarly, the positron emission tomography-computed tomography imaging-based reduction in carotid inflammation was only observed with intensive statin therapy (10). Plaque-to-myocardium signal intensity ratio on noncontrast T1 mapping by magnetic resonance imaging was shown to decrease by 19% with intensive statin therapy, compared with a 19% increase in plaque-to-myocardium signal intensity ratio in the untreated group (11). One underlying commonality in all of these studies is that the beneficial results of statin therapy are

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TABLE 1 Studies on Plaque Progression

Studies That Demonstrated Reduced Total Atheroma Volume by Statin Therapy

Study/First Author (Ref. #)	Imaging Modality	N	Plaque Feature Studied	Effect on Plaque	Follow-Up
YELLOW (9)	NIRS IVUS FFR	87	LCBI, lesion LCBI $_{4mm}$ max	−69.4% −80.6%	7 weeks
SATURN (12)	IVUS	1039	Percent atheroma volume Total atheroma volume	−1.22% −6.39 mm^3	104 weeks
ASTEROID (13)	IVUS	507	Percent atheroma volume Total atheroma volume	−0.98% −14.7 mm^3	24 months
REVERSAL (14)	IVUS	502	Percent atheroma volume	−0.4%	18 months
AQUAMARINE (11)	MRI	48	PMR	19% reduction in PMR (statin group) 19% increase in PMR (control group)	12 months
Burgstahler et al. (15)	Cardiovascular CTA	46	Noncalcified plaque volume	29% reduction in volume	70 weeks
Inoue et al. (6)	Cardiovascular CTA	32	Total plaque volume	17% reduction	12 months

Studies That Demonstrated Total Atheroma Volume Reduction Through Reduction of Necrotic Core

	Imaging Modality	N	Plaque Feature Studied	Effect on Plaque	Follow-Up
YELLOW (9)	NIRS IVUS FFR	87	%Attenuated plaque volume	−19%	7 weeks
Kawasaki et al. (16)	IVUS	52	Angiographic stenosis Fibrous volume Mixed lesion volume Lipid core volume	Unchanged +15% +13% −25%	6 months
Hattori et al. (7)	OCT IVUS	42	% Total plaque volume %Lipid volume index Fibrous cap thickness	−6.5% −20% 140 μm → 189 μm 35% increase in thickness	9 months
Takano et al. (8)	Angioscopy	31 patients/145 plaques	Yellow score on angioscopy (range 0–3)	2.03 ± 0.45 → 1.13 ± 0.33 −44%	12 months
Inoue et al. (6)	Cardiovascular CTA	32	Total plaque volume LAP volume Lumen volume	−17% −73% No significant change	12 months

Studies That Demonstrated Halting Plaque Progression Only With Intensive Lipid-Lowering Therapy by Statin

	Imaging Modality	N	Plaque Feature Studied	Effect on Plaque	LDL Target Achieved	Follow-Up
YELLOW (9)	NIRS IVUS FFR	87	LCBI, lesion LCBI $_{4mm}$ max Attenuated plaque %	−69.4% −80.6% −19%	58 mg/dl	7 weeks
SATURN (12)	IVUS	1039	Percent atheroma volume Total atheroma volume	−1.22% −6.39 mm^3	63 mg/dl	104 weeks
ASTEROID (13)	IVUS	507	Percent atheroma volume Total atheroma volume	−0.98% −14.7 mm^3	61 mg/dl	24 months
AQUAMARINE (11)	MRI	48	PMR	19% reduction in PMR (statin group)	70 mg/dl	12 months

AQUAMARINE = Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Noncontrast T1-weighted Technique; ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CTA = computed tomography angiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; NIRS = near infrared spectroscopy; OCT = optical coherence tomography; PMR = plaque to myocardium signal intensity ratio; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering; SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin; YELLOW = Reduction in YEllow Plaque by Aggressive Lipid LOWering Therapy.

pronounced in the intensive treatment arms that achieved LDL levels of <70 mg/dl compared with more lenient therapeutic approaches.

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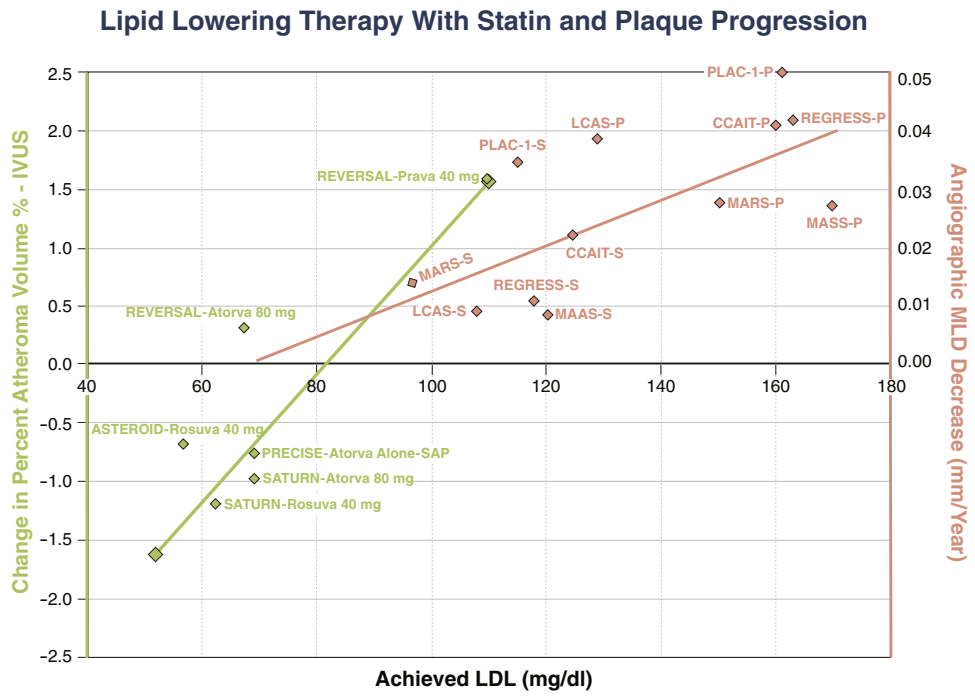
The study by Shin et al. (19), published in this issue of *iJACC*, prospectively compared the effect of statin therapy with strict LDL target (<70 mg/dl) to more lenient LDL target on plaque progression detected by serial coronary CTA. This report demonstrated that the aggressive statin therapy substantially retarded plaque progression. Although there was no other significant difference in the risk factor or clinical profiles between the 2 groups, patients with LDL of <70 mg/dl demonstrated almost a 70% decrease in the annual rate of progression of plaque burden compared with those with LDL >70 mg/dl (4.6 ± 15.0 mm^3 vs. 14.5 ± 22.0 mm^3, respectively). This study adds to the abundant amount of published imaging literature (Table 1) that has demonstrated the need for significant lowering of LDL levels to translate into halting the plaque progression—the feature critically

FIGURE 1 **Effect of Intensive Lipid-Lowering Therapy on Plaque Progression Demonstrated by Clinical Studies With ICA or IVUS**



Atherosclerotic plaque progression or regression is directly related to the low-density lipoprotein (LDL) levels and the intensive lipid-lowering therapy. This graph presents 2 regression lines demonstrating the relationship of plaque progression to the LDL level. The **pink regression line** ($r^2 = 0.6116$), adapted from O'Keefe et al. (17), shows that invasive coronary angiography (ICA)-verified lesions do not progress when LDL reaches <70 mg/dl. The **pink symbols** represent LDL levels achieved in randomized placebo-controlled trials and respective decrease in minimal luminal diameter (i.e., extent of stenosis) per year. The **green regression line** ($r^2 = 0.926$) and **symbols**, adapted from Tsujita et al. (18), represents intravascular ultrasound (IVUS) studies demonstrating the effect of statin therapy and LDL level on plaque progression, measured by change in percent atheroma volume (PAV). IVUS studies demonstrate that PAV shows plaque regression when target LDL reaches below 80 mg/dl. ASTEROID = A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; Atorva = atorvastatin; CCAIT = Canadian Coronary Atherosclerosis Intervention Trial; DPAV = absolute change in percent atheroma volume; LCAS = Lipoprotein and Coronary Atherosclerosis Study; MAAS = Multicentre Anti-Atheroma Study; MARS = Monitored Atherosclerosis Regression Study; MLD = mean luminal diameter; P = placebo; PLAC = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; Prava = pravastatin; PRECISE = Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention; RE-GRESS = Regression Growth Evaluation Statin Study; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering; S = statin; SAP = stable angina pectoris; SATURN = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin.

important for its association with likelihood of a future event.

The study by Shin et al. (19), however, disappointingly indicated that the presence of atherosclerosis on CTA did not persuade many clinicians to initiate intensive statin therapy. Among 147 patients who were identified to have coronary atherosclerosis by CTA, only 37 (25%) achieved an LDL target of <70 mg/dl, whereas 110 (75%) patients had an LDL ≥70 mg/dl, with an average LDL level of 104 mg/dl. Of the 90 patients who were not on statin before CTA, the revelation of coronary atherosclerosis on CTA led to initiation of statin therapy in only 50 (56%) patients. The remaining 40 patients (44%) who were not initiated on statins comprised the component of the group that demonstrated the highest rate of plaque progression.

Although the effectiveness of statins in reducing death and myocardial infarction in both primary and secondary prevention has been firmly established, there are no clear guidelines as to how aggressively patients should be treated upon detection of subclinical atherosclerosis. As shown in the study in context, only 56% of the statin-naive patients with documented atherosclerosis on CTA were started on a statin, of whom only 25% attained the progression-defying LDL target of <70 mg/dl (19). These findings call for a need for more relevant guidelines than the

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prevalent cholesterol guideline, which may recommend cholesterol reduction rather than specifying a goal of <70 md/dl. With the ever-increasing clinical use of imaging modalities such as CTA, coronary calcium scoring, or carotid ultrasound that allow for detection of subclinical atherosclerosis, how should a patient with such findings and no history of previous cardiovascular events be treated? Knowing that plaque progression is likely an important step before the incident event, and only intensive statin therapy can halt the plaque progression, how aggressively should we treat the patients upon finding subclinical atherosclerosis? Has the time come to re-evaluate the concept of primary versus secondary prevention, vis-à-vis detection of subclinical atherosclerosis?

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