The Goal of Achieving Atherosclerotic Plaque Regression with Lipid-Lowering Therapy: Insights from IVUS Trials

Hiroyuki Daida, Tomotaka Dohi, Yoshifumi Fukushima, Hirotohi Ohmura and Katsumi Miyauchi

Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

Enormous effort has been put into the prevention of atherosclerosis through risk modification, especially with lipid-lowering therapies. Regression, that is, the reversal of the atherosclerosis process, has long been a goal of atherosclerosis research among basic and clinical investigators. Intravascular ultrasound (IVUS) was developed in the 1990s as an intracoronary imaging technique to observe the details of the vessel walls and to measure the vessel lumen and plaque area with high reproducibility. Compared with the coronary angiogram, IVUS provides far more detailed information on the vessel wall. In this article, we review lipid-lowering trials that have used IVUS and discuss the current understanding of the effectiveness of aggressive lipid-lowering therapy, which inhibits atherosclerotic progression and induces regression and plaque stabilization.

Key words: Lipid-lowering therapy, LDL-C, Plaque regression, IVUS, Statin

Introduction

Atherosclerosis has been classified as the biggest health-care issue around the world¹⁾. Indeed, global health statistics have shown that atherosclerotic cardiovascular disease is the leading cause of death worldwide, and its incidence is increasing in developing countries^{2, 3)}. Enormous effort has been put into the prevention of atherosclerosis through risk modification, especially with lipid-lowering therapies⁴⁻⁶⁾. Regression, that is, the reversal of the atherosclerosis process, has long been a goal of atherosclerosis research among basic and clinical investigators. Substantial effort has been made on plaque regression under lipid-lowering therapy and is still ongoing⁷⁾.

In this article, we review lipid-lowering trials that have used intravascular ultrasound (IVUS) and discuss the current understanding of the effectiveness of aggressive lipid-lowering therapy, which inhibits atherosclerotic progression and induces regression and plaque stabilization.

Mechanism of Atherosclerosis Reversal and Regression

The regression of atherosclerosis by lowering

lipid levels has been a hypothetical goal of therapy since the early 1900s. Several experimental studies have suggested the possibility of plaque regression by showing reduced plaque area with a change from a high-cholesterol to a low-cholesterol diet in animal models^{8, 9)}. Brown *et al.* reported that the improvement of the plaque lipoprotein environment can rapidly correct the macrophage content by reducing the numbers of intraplaque macrophages and forming cells, down-regulating the expression of inflammatory markers and inducing the enrichment with anti-inflammatory markers¹⁰⁾.

Lesion regression is accompanied by potent improvements in the plaque microenvironment, particularly by a strong decrease in plasma levels of apoB-containing lipoproteins and a marked increase in lipid efflux from the plaque¹¹⁾. Plaque shrinkage is a coordinated process that involves the depletion of foam cells and extracellular cholesterol stores, a gradual decline in macrophage numbers through enhanced emigration from the plaque, and the replacement of inflammatory macrophages with anti-inflammatory phagocytes, involved in the removal of necrotic material and tissue healing (Fig. 1).

Consequently, good results of clinical studies using lipid-lowering agents, such as statins, can be

Address for correspondence: Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan E-mail: daida@juntendo.ac.jp

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Fig. 1. Atherosclerosis progression and reversal by enhancing cholesterol efflux and emigration of macrophages from the plaque

The proinflammatory recruitment of monocytes is followed by their subendothelial trafficking to the arterial intima, where monocytes differentiate into proinflammatory macrophages. The macrophages phagocytose proatherogenic low-density lipoprotein (LDL), oxidized LDL (oxLDL), and very low-density lipoprotein enriched with cholesterol. The accumulation of lipids in macrophages leads to their loss of mobility, retention in the vascular wall, and transformation to foam cells. Foam cells contribute to the formation of the intraplaque lipid pool and then the necrotic core. The increased production of matrix metalloproteinases (MMPs) by foam cells and plaque macrophages leads to plaque destabilization and rupture. Potent improvements in plasma lipoprotein levels by lowering LDL cholesterol and increasing high-density lipoprotein cholesterol can induce plaque regression, characterized by the enhancement of the reverse cholesterol transport, reduction of foam cell numbers, macrophage emigration, and phenotypic switch of retained macrophages from proinflammatory cells to anti-inflammatory cells that deal with the clearance of necrotic debris and plaque material and tissue repair. The increased mobility of macrophages is associated with up-regulation of liver X receptor and peroxisome proliferator-activated receptor gamma (PPAR γ), which mediate cholesterol efflux in macrophages, activation of anti-inflammatory genes and cell mobility genes such as C-C chemokine receptor 7 (CCR7), and down-regulation of genes that inhibit cell migration such as semaphorin 3E and netrin 1.

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ECM, extracellular matrix; LPL, lipoprotein lipase; PC, phosphatidylcholine; SR-B1, scavenger receptor.

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attributed primarily to the induction of stability of small vulnerable plaques by reducing intraplaque macrophage numbers, an important signature of lesion vulnerability¹². These plaques contain a large lipid core and dense clusters of intimal macrophages. Such lesions constitute only 10–20% of the entire plaque population, but account for 80–90% of acute clinical events.

History of Atherosclerosis Regression Studies and Development of IVUS

Epidemiologists and pathologists recognized less severe atherosclerosis in the aorta or coronary arteries in subjects with malnutrition or emaciation during

World Wars I and II, suggesting that dietary modification could reduce the progression of atherosclerosis¹³. Angiographic trials were enthusiastically conducted from 1980 to 2000, and the overall results indicated that the aggressive modification of lipid profiles could inhibit plaque progression and induce some degree of regression^{14–17}. The introduction of IVUS further stimulated research into the progression and regression of atherosclerosis. This modality enabled us to observe and measure atherosclerotic plaques quantitatively as well as qualitatively¹⁸.

IVUS was developed in the 1990s as an intracoronary imaging technique to observe the details of the vessel walls and to measure the vessel lumen and plaque area with high reproducibility¹⁸. Compared

with the coronary angiogram, IVUS provides far more detailed information on the vessel wall, including the size and location of atheromatous plaques, plaque tissue characteristics, and vessel remodeling. After the introduction of the auto-pullback system, IVUS took its place as the principal imaging tool in atherosclerotic progression/regression trials instead of the quantitative coronary angiogram, because of its ability to precisely measure plaque volume and also provide quantitative measurements of plaque morphology and tissue characteristics^{19, 20}.

Aggressive LDL-C Lowering for Plaque Regression in Patients with Coronary Artery Disease; IVUS Trials

The first IVUS trial in the field of atherosclerotic progression/regression was reported from Kobe, Japan, using pravastatin. Takagi *et al.* found a significant inhibition of atherosclerotic progression, although they only investigated the cross-sectional area of target lesions²¹. In 2002, Matsuzaki *et al.* found a significant inhibition and slight regression of atherosclerotic plaques using LDL apheresis in patients with heterozygous familial hypercholesterolemia²². They also measured the cross-sectional areas of targeted plaques in their trial. The very first trial with the application of volumetric analysis was the German Atorvastatin Intravascular Ultrasound Study (GAIN) trial in which the investigators measured plaque volume as well as plaque characteristics with gray-scale IVUS. Although they could not identify any significant regression of plaques, they did find increased plaque intensity on gray-scale IVUS²³. The landmark study in this field is Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)²⁴. In this trial, Nissen *et al.* compared changes in plaque volume between 40 mg of pravastatin and 80 mg of atorvastatin in patients with chronic coronary artery disease and found a small but significant rate of progression in the pravastatin group, but no progression in the atorvastatin group at the LDL-C level of 80 mg/dL. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) demonstrated significant plaque regression in patients with stable coronary artery disease using rosuvastatin at the LDL-C level of 53 mg/dL²⁵.

The ESTABLISH (Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event) study investigated the efficacy of early, aggressive statin therapy in patients with acute coronary syndrome (ACS)²⁶.

Early, aggressive lipid-lowering therapy with 20 mg of atorvastatin for 6 months significantly reduced the plaque volume by 13% at an LDL-C level of 70 mg/dL in patients with ACS. The percentage change in plaque volume showed a significant positive correlation with percentage reduction in LDL-C, even in patients with low baseline levels of LDL-C.

Since these early trials in the field of atherosclerosis research, a substantial number of clinical trials using IVUS have been conducted all over the world in patients with chronic coronary disease and ACS²⁷⁻²⁹. The observations have been consistent in finding that aggressive lipid modification could reduce atherosclerotic progression and induce plaque regression. In addition, the degree of plaque change was associated with the LDL-C level or the percentage reduction in LDL-C. These changes are more obvious among patients with ACS who have more unstable plaques that appear to be more prone to regress with aggressive LDL-C lowering⁷. In the PRECISE-IVUS (Plaque REgression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by IntraVascular Ultra-Sound) trial, Tsujita *et al.* demonstrated a further reduction in plaque volume using ezetimibe in addition to statin, and confirmed the effectiveness of aggressive LDL-C-lowering therapy among the Japanese population³⁰. They also found a larger response in patients with ACS than in those with stable coronary artery disease. The most recent IVUS trial, GRA-GOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound), reported the effectiveness of the PCSK9 inhibitor compared with statin alone, on plaque regression at the LDL-C level of 36 mg/dL, further confirming “the lower the better” theory³¹ (Table 1).

IVUS Trials Demonstrating Plaque Stabilization by Lipid Lowering

During the process of plaque regression by aggressive lipid-lowering therapy, treatment could also stabilize the unstable plaque and reverse the positive remodeling of the vessel wall. An unstable plaque was characterized by a thin fibrous cap, a large lipid core, and inflammatory cell infiltration³². An unstable plaque is observed frequently in vessel segments with positive remodeling. Lipid-lowering therapy could change these characteristics to thicken the fibrous cap, reduce the lipid core, and decrease inflammatory cell infiltration^{33, 34}. This represents a reversal of the process of positive remodeling of the vessel wall.

Changes in these plaque characteristics were also identified in IVUS trials. As described previously, the GAIN trial first reported changes in plaque character-

Table 1. Serial intravascular ultrasound studies of plaque progression/regression

Study	Year	Design	Treatment	N	Follow-up	LDL-C		IVUS assessment	Serial IVUS results
						at baseline	at follow-up		
Mild to moderate intensity statin studies									
KOBE	1997	RCT	Pravastatin 10 mg	13	3 years	150.2	133	Plaque area	-7% ($p<0.001$)
			Control	12		165.4	150.2		+27%
GAIN	2001	RCT	Atorvastatin 20-80 mg	48	12 months	155	86	% change in PV	+2.5% ($p=0.14$)
			Control	51		166	140		11.80%
LACMART	2002	OBS	Medication plus LDL-apheresis	11	12 months	213	140	Plaque area	-0.69 mm ² ($p=0.017$)
			Medication only	7		174	181		+0.88 mm ²
ESTABLISH	2004	RCT	Atorvastatin 20 mg	24	6 months	124.6	70	% change in PV	-13.1% ($p<0.0001$)
			Control	24		123.9	119.4		+8.7%
JAPAN-ACS	2009	RCT	Atorvastatin 20 mg	127	10 months	130.9	81.1	% change in PV	-18.1% ($p=0.5$)
			Pitavastatin 4 mg	125		133.8	84.1		-16.90%
COSMOS	2009	OBS	Rosuvastatin 2.5-20 mg	126	18 months	140.2	82.9	% change in PV	-5.10% ($p<0.0001$ vs. baseline)
High intensity statin studies									
REVERSAL	2004	RCT	Atorvastatin 80 mg	253	18 months	150.2	78.9	Change in PAV	-0.4% ($p=0.02$)
			Pravastatin 40 mg	249		150.2	110.4		2.70%
ASTEROID	2006	OBS	Rosuvastatin 40 mg	349	24 months	130.4	60.8	Change in PAV	-0.98% ($p=0.001$ vs. baseline)
SATURN	2011	RCT	Atorvastatin 80 mg	519	24 months	119.9	70.2	Change in PAV	-0.99% ($p=0.17$)
			Rosuvastatin 40 mg	520		120.0	62.6		-1.22%
Additional non-statin studies on the top of statin									
ZEUS ⁴⁹	2014	OBS	Atorvastatin plus ezetimibe 10 mg	45	6 months	116.2	56.8	% change in PV	-12.5% ($p=0.06$)
			Atorvastatin alone	50		114.3	70.3		-7.50%
PRECISE-IVUS	2015	RCT	Atorvastatin plus ezetimibe 10 mg	100	10 months	109.8	63.2	Change in PAV	-5.2% ($p<0.001$)
			Atorvastatin alone	102		108.3	73.3		-1.30%
GRAGOV	2016	RCT	Statin + PCSK9i	423	18 months	92.6	36.6	Change in PAV	-0.95% ($p<0.0001$)
			Statin alone	423		92.4	93.0		0.05%

RCT: randomized controlled trial; OBS: observational study; PV: plaque volume; PAV: percent atheroma volume; IVUS: intravascular ultrasound

istics using gray-scale IVUS²³). In early 2000, several IVUS systems were developed to investigate plaque characteristics. Kawasaki *et al.* demonstrated a significant reduction in the lipid composition of plaque in the statin-treated group compared with controls using an integrated backscatter-IVUS system³⁵). Nasu *et al.* also reported a significant reduction of fibro-fatty tissue by fluvastatin, with plaque volume reduction, using virtual histology (VH)-IVUS³⁶). Park *et al.* recently reported that rosuvastatin treatment could change plaque composition and plaque volume in

non-culprit coronary lesions estimated by VH-IVUS³⁷). Overall results from tissue IVUS trials have revealed that aggressive LDL-C lowering could reduce the lipid composition with or without reductions in plaque volume³⁸⁻⁴³). The positive remodeling of the vessel wall is also reduced by aggressive LDL-C lowering, appearing as a shrinkage of vessel size. These changes appear to correlate with the degree of LDL-C reduction, further strengthening “the lower the better” theory from this perspective (Table 2).

Table 2. Serial intravascular ultrasound studies of plaque composition

Study	Year	Design	Treatment	N	Follow-up	LDL-C		Tissue char- acterization	Results
						at baseline	at follow- up		
Mild to moderate intensity statin studies									
Yokoyama <i>et al.</i>	2005	RCT	Atorvastatin 10 mg Control	20 22	6 months	133 N/A	87 N/A	IB-IVUS	LLT reduced plaque volume and changed plaque composition
Kawasaki <i>et al.</i>	2005	RCT	Atorvastatin 20 mg Pravastatin 20 mg Control	17 18 17	6 months	155 149 152	95 102 149	IB-IVUS	LLT reduced lipid component without changes in plaque volume
Nasu <i>et al.</i>	2009	OBS	Fluvastatin 60 mg Control	40 39	12 months	144.9 122.3	98.1 121.0	VH-IVUS	LLT reduced plaque volume with reducing fibro-fatty volume
Hong <i>et al.</i>	2009	RCT	Simvastatin 20 mg Rosuvastatin 10 mg	50 50	12 months	119 116	78 64	VH-IVUS	LLT reduced necrotic core and increased in fibro-fatty volume
Toi <i>et al.</i>	2009	RCT	Atorvastatin 10 mg Pitavastatin 2 mg	80 80	2-3 weeks	122.0 114.7	85.3 74.8	IB-IVUS	LLT with pitavastatin reduced plaque and fibro-fatty volume
Nozue <i>et al.</i>	2012	RCT	Pitavastatin 4 mg Pravastatin 20 mg	58 61	8 months	126 137	74 95	VH-IVUS	LLT reduced fibro-fatty volume with increasing calcified plaque component
Hattori <i>et al.</i>	2012	OBS	Pitavastatin 4 mg Control	26 16	9 months	134 122	89 121	IB-IVUS	LLT reduced plaque and lipid volume
High intensity statin studies									
Lee <i>et al.</i>	2012	RCT	Atorvastatin 40 mg Atorvastatin 10 mg	57 54	6 months	112.4 122.4	52.1 68.5	VH-IVUS	LLT with high-dose statin reduced plaque and fibro-fatty volume
Park <i>et al.</i>	2016	RCT	Rosuvastatin 40 mg Rosuvastatin 10 mg	152 73	12 months	105.3 109.3	59.1 78.8	VH-IVUS	LLT reduced plaque and necrotic core volume with decreasing thin-cap fibroatheroma rate

RCT: randomized controlled trial; OBS: observational study; IB-IVUS: integrated backscatter intravascular ultrasound; VH-IVUS: virtual histology intravascular ultrasound; LLT: lipid-lowering therapy

Clinical Significance of Plaque Regression

Whether plaque volume changes could predict future events has been a matter of considerable discussion. Nissen *et al.* found a significantly higher event rate among patients with plaque progression than among patients with plaque regression in their IVUS trials⁴⁴. Dohi *et al.* also found significantly better outcomes in patients with plaque regression than in patients with progression in the Extended ESTABLISH trial after 4 years of follow-up⁴⁵. Although several plaque imaging modalities could not predict clinical outcomes, coronary artery imaging modalities have consistently been reported to offer a sufficient and powerful tool for predicting future clinical events among patients with coronary artery disease.

Summary and Future Directions

The regression of atherosclerosis through lipid lowering has been a goal since the early 1900s. Early experimental and epidemiological studies suggested the possibility of plaque regression. Angiographic trials were conducted from 1980 to 2000 and their overall results indicated that aggressive modification of the lipid profile could inhibit plaque progression and induce some degree of regression. The introduction of IVUS further stimulated research into the progression and regression of atherosclerosis. This modality enabled us to observe and measure atherosclerotic plaques quantitatively as well as qualitatively. Observations have been consistent in suggesting that aggressive lipid profile modification could reduce atherosclerotic progression and induce plaque regression.

In addition, the degree of plaque change was

associated with the level of LDL-C or the percentage reduction in LDL-C. Notably, the LDL-C threshold of 70 mg/dL, which recurs in Japanese, European, and American recommendations, is close to the theoretical inversion point from a condition of coronary atherosclerosis progression to one of regression²⁵). Furthermore, no threshold level below which the LDL-C lowering benefit ceases has been established, and in the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) and the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trials, additional benefits from ezetimibe and evolocumab were found, regardless of LDL-C levels^{46, 47}). The process of plaque regression by aggressive LDL-C lowering therapy could also stabilize the unstable plaque and reverse the positive remodeling of the vessel wall. The pharmacological inhibition of cholesterol absorption (with ezetimibe) and PCSK9 activity (with evolocumab or alirocumab) provides potentially useful approaches for the therapeutic modulation of LDL-C metabolism in statin-treated patients. As combination therapy with a statin and either ezetimibe or PCSK9 inhibitors lowers LDL-C levels beyond that achieved with statin monotherapy, this early dual lipid-lowering treatment strategy may have additional protective cardiovascular effects, reducing coronary disease progression and improving cardiovascular outcomes in selected patients.

The observations available from IVUS appear to offer a powerful tool for predicting future clinical events among patients with coronary artery disease. More recently, other coronary imaging modalities have come into clinical use, such as optical coherence tomography and near-infrared spectroscopy, further accelerating research into atherosclerotic progression and regression, improving our understanding of the mechanisms underpinning atherosclerosis, and opening up new treatment options.

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