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

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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 world. 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. 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. Substantial effort has been made on plaque regression under lipid-lowering therapy and is still ongoing.

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. 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 markers.

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 plaque. 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...
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 atherosclerosis. 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. 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.

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 phagocytize 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 (PPARγ), 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 semaphore in 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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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.

**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 lesions. In 2002, Matsuzaki et al. found a significant inhibition and slight regression of atherosclerotic plaques using LDL apheresis in patients with heterozygous familial hypercholesterolemia. 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 IVUS. The landmark study in this field is Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL). 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 rosvastatin at the LDL-C level of 53 mg/dL.

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).

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 ACS. 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 lowering. In the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by IntraVascular Ultrasound) 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 population. 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” theory (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 infiltration. 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. 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-
non-culprit coronary lesions estimated by VH-IVUS. Overall results from tissue IVUS trials have revealed that aggressive LDL-C lowering could reduce the lipid composition with or without reductions in plaque volume. 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 1. Serial intravascular ultrasound studies of plaque progression/regression

| Study       | Year | Design | Treatment                              | N   | Follow-up | LDL-C at baseline | LDL-C at follow-up | IVUS assessment | Serial IVUS results |
|-------------|------|--------|----------------------------------------|-----|-----------|-------------------|-------------------|------------------|---------------------|
| KOBE        | 1997 | RCT    | Pravastatin 10 mg Control              | 13  | 3 years   | 150.2             | 133               | Plaque area     | -7% (p<0.001)       |
|             |      |        | Control                                | 12  |           | 165.4             | 150.2             |                 | +2.7%               |
| GAIN        | 2001 | RCT    | Atorvastatin 20-80 mg Control          | 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 Medication only | 11  | 12 months | 213               | 140               | Plaque area     | -0.69 mm² (p=0.017) |
|             |      |        |                                        | 7   |           | 174               | 181               |                 | +0.88 mm²           |
| ESTABLISH   | 2004 | RCT    | Atorvastatin 20 mg Control              | 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 Pitavastatin 4 mg    | 127 | 10 months | 130.9             | 81.1              | % change in PV  | -18.1% (p=0.5)     |
|             |      |        | Control                                | 125 |           | 133.8             | 84.1              |                 | -16.90%             |
| COSMOS      | 2009 | OBS    | Rosuvastin 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

| Study       | Year | Design | Treatment                              | N   | Follow-up | LDL-C at baseline | LDL-C at follow-up | IVUS assessment | Serial IVUS results |
|-------------|------|--------|----------------------------------------|-----|-----------|-------------------|-------------------|------------------|---------------------|
| REVERSAL    | 2004 | RCT    | Atorvastatin 80 mg Pravastatin 40 mg   | 253 | 18 months | 150.2             | 78.9              | Change in PAV   | -0.4% (p=0.02)      |
|             |      |        | Control                                | 249 |           | 150.2             | 110.4             |                 | 2.70%               |
| ASTEROID    | 2006 | OBS    | Rosuvastin 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 Rosuvastin 40 mg    | 519 | 24 months | 119.9             | 70.2              | Change in PAV   | -0.99% (p=0.17)     |
|             |      |        | Control                                | 520 |           | 120.0             | 62.6              |                 | -1.22%              |

Additional non-statin studies on the top of statin

| Study       | Year | Design | Treatment                              | N   | Follow-up | LDL-C at baseline | LDL-C at follow-up | IVUS assessment | Serial IVUS results |
|-------------|------|--------|----------------------------------------|-----|-----------|-------------------|-------------------|------------------|---------------------|
| ZEUS        | 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 IVUS. 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 system. Nasu et al. also reported a significant reduction of fibro-fatty tissue by fluvastatin, with plaque volume reduction, using virtual histology (VH)-IVUS. Park et al. recently reported that rosuvastatin treatment could change plaque composition and plaque volume in
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

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 trials. 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-up. 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.

Table 2. Serial intravascular ultrasound studies of plaque composition

| Study          | Year | Design | Treatment                  | N  | Follow-up | LDL-C at baseline | LDL-C at follow-up | Tissue characterization | Results                                                                 |
|----------------|------|--------|----------------------------|----|-----------|-------------------|---------------------|------------------------|-------------------------------------------------------------------------|
| **Mild to moderate intensity statin studies** |
| Yokoyama et al. | 2005 | RCT    | Atorvastatin 10 mg         | 20 | 6 months  | 133               | 87                  | IB-IVUS                | LLT reduced plaque volume and changed plaque composition             |
| Kawasaki et al. | 2005 | RCT    | Atorvastatin 20 mg         | 17 | 6 months  | 155               | 95                  | IB-IVUS                | LLT reduced lipid component without changes in plaque volume          |
| Nasu et al.    | 2009 | OBS    | Fluvastatin 60 mg          | 40 | 12 months | 144.9             | 98.1                | VH-IVUS                | LLT reduced plaque volume with reducing fibro-fatty volume           |
| Hong et al.    | 2009 | RCT    | Simvastatin 20 mg          | 50 | 12 months | 119               | 78                  | VH-IVUS                | LLT reduced necrotic core and increased in fibro-fatty volume         |
| T0i et al.     | 2009 | RCT    | Atorvastatin 10 mg         | 80 | 2-3 weeks | 122.0             | 85.3                | IB-IVUS                | LLT with pitavastatin reduced plaque and fibro-fatty volume           |
| Nozue et al.   | 2012 | RCT    | Pitavastatin 4 mg          | 58 | 8 months  | 126               | 74                  | VH-IVUS                | LLT reduced fibro-fatty volume with increasing calcified plaque component |
| Hattori et al. | 2012 | OBS    | Pitavastatin 4 mg          | 26 | 9 months  | 134               | 89                  | IB-IVUS                | LLT reduced plaque and lipid volume                                 |
| **High intensity statin studies** |
| Lee et al.     | 2012 | RCT    | Atorvastatin 40 mg         | 57 | 6 months  | 112.4             | 52.1                | VH-IVUS                | LLT with high-dose statin reduced plaque and fibro-fatty volume       |
| Park et al.    | 2016 | RCT    | Rosuvastatin 40 mg         | 152| 12 months | 105.3             | 59.1                | 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
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 regression. 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 FOU RIER (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. 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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