The Role of Aggressive Lipid Lowering Therapy for Coronary Artery Disease

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Atherosclerotic cardiovascular disease is the leading cause of death worldwide. Among the most promising results of the preventing approach against progression of atherosclerosis derived from lipid lowering therapy especially by statins. Recent clinical trials with statins indicated that aggressive lipid lowering therapy could inhibit the progression of atherosclerosis or even induce the regression of atherosclerotic plaque. It also stabilizes the unstable plaque to stable form and reduces clinical CV events.

Several trials using intravascular ultrasound demonstrated that lowering LDL-C to 70-80 mg/dl by aggressive lipid-lowering treatment with moderately high-dose statins significantly reduced coronary plaque volume, but these studies are vastly underpowered to determine the effects of such lipid-lowering treatment on clinical outcomes. Accordingly, the value of reducing LDL-C levels substantially below 100 mg/dl in patients with CAD, particularly Asian patients, had not been clearly demonstrated, and Japanese guidelines recommended reducing LDL-C only to immediately below 100 mg/dl until recently. HIJ-PROPER and REAL-CAD provided pivotal evidence for the aggressive lipid-lowering in Japanese patients at secondary prevention. The lipid management strategy for secondary prevention is still changing in clinical practice from recent Japanese evidence.

In this article, we will review the history and current understanding of the efficacy of aggressive lipid lowering therapy which inhibits the atherosclerosis progression and induces the regression, and we also will review the recent clinical evidence especially from Japan.

Key words: coronary plaque, statins, lipid-lowering treatment, secondary prevention plaque regression and stabilization

Introduction

Atherosclerotic cardiovascular disease is the leading cause of death worldwide and its incidence is still growing among developing countries although there is a trend of decreasing mortality in some developed countries by their intensive preventive effort against atherosclerosis.¹⁾⁻³⁾ In addition, recent epidemics of obesity and diabetes mellitus raised a serious concern of a resurgence of atherosclerotic CVD over the world.⁴⁾ Atherosclerosis develops through multiple pathways including dyslipidemia, hypertension, smoking, and glucose intolerance, as well as inflammation. Among the

most promising results of the preventing approach against progression of atherosclerosis derived from lipid lowering therapy especially by statins. Recent clinical trials with statins indicated that aggressive lipid lowering therapy could inhibit the progression of atherosclerosis or even induce the regression of atherosclerotic plaque significantly. It also stabilizes the unstable plaque to stable form^{5) 6)} and reduces clinical CV events.^{7) 8)} In this article, we will review the history and current understanding of the efficacy of aggressive lipid lowering therapy which inhibits atherosclerosis progression and induces regression, and we also will review the recent clinical evidence especially from Japan.

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History of research regarding plaque regression and stabilization

The regression of atherosclerotic plaque has been a challenge of researchers since the early 1900s. Epidemiologists and pathologists realized less severe atherosclerosis in the aorta or coronary arteries in subjects with malnutrition or emaciation during World War I or II suggesting modification of diet could reduce the progression of atherosclerosis.^{9) 10)} A similar observation was made in the patients who were suffering from cancer in the post-motive examination by pathologists. In terms of clinical trials, Buchwald started their angiographic trial POSCH in 1974 using partial ileal bypass and found significant suppression of angiographic progression.¹¹⁾ Blackenhorn started using his CLAS in 1975 and reported that aggressive lipid modification could prevent plaque progression and induce some regression in the coronary arteries.¹²⁾ During 1990–2000, there were many angiographic trials conducted around the world using diet modification, exercise and a combination of lipid lowering drugs and later using statins. Overall results of these angiographic trials indicated that aggressive modification of lipids could inhibit atherosclerotic plaque progression and induce regression to some extent.

Familial Atherosclerosis Treatment Study is one of the earliest angiographic trials conducted by Brown *et al*, using their own quantitative coronary angiogram.¹³⁾ Comparing to the control group in which significant progression was observed, the groups with aggressive lipid modification (Lovastatin and colestipol or Niacin and colestipol) showed no progression or even slight regression although the difference between the groups are really small, such as plus minus 0.04 mm in the coronary diameter. In addition, Dr. Brown found significant event reduction in the aggressively treated groups which is hardly explained by the small change of coronary artery lumen. From this observation, he proposed the concept of plaque stabilization in addition to the phenomenon of plaque regression.

The mechanisms of plaque stabilization were intensively investigated by Aikawa *et al*¹⁴⁾. He found significant reduction of expression of MMP1 and tissue factor as well as adhesion molecule and increase of mature SMC and collagen in the

cholesterol fed rabbit model. Crisby *et al* reported similar observation in humans who underwent carotid endarterectomy. Using pravastatin they have shown significant reduction of the expression of MMP9 and increase of the expression of TIMP-1 as well as collagen.¹⁵⁾ Kajimoto also reported the significant reduction of the expression of JNK, MMP2, the infiltration of macrophages, T lymphocytes and dendritic cells using atorvastatin 20 mg a day in the aorta in patients with AAA (Figure-1A, B).¹⁶⁾

Aggressive LDL-C lowering for plaque regression in patients with CAD: IVUS trials

Intravascular Ultrasound (IVUS) was developed as an intracoronary imaging device which enabled to observe the details of the vessel wall and to measure the plaque volume with high reproducibility.¹⁷⁾ In the field of atherosclerosis research, substantial numbers of trials using IVUS were conducted over the world until now. Among them, the ESTABLISH trial,¹⁸⁾ JAPAN-ACS¹⁹⁾ and COSMOS²⁰⁾ study are the three early major coronary plaque regression studies conducted in Japan. These three studies are designed to clarify the mechanism of the early statin efficacy in secondary CAD prevention and to investigate whether aggressive lipid-lowering therapy could induce a significant reduction in plaque volume.

The ESTABLISH study investigated the efficacy of early aggressive statin therapy in acute coronary syndrome. Early aggressive lipid-lowering therapy by 20 mg of atorvastatin for 6 months significantly reduced the plaque volume in patients with ACS.

After the acute treatment of ACS, the plaque volume of the non-culprit lesions were analyzed using IVUS. Patients were randomly assigned to 20 mg of atorvastatin or diet therapy and followed for 6 months. LDL-C was reduced by 42% down to 70 mg/dl. The plaque volume was significantly decreased by 13% in the atorvastatin group. Percent change in plaque volume showed a significant positive correlation with percent LDL-C reduction, even in patients with low baseline LDL-C.

The JAPAN-ACS study was designed to evaluate whether the regressive effects of aggressive lipid-lowering therapy with atorvastatin on coronary plaque volume in patients with ACS are generalized

B Atorvastatin group

Non-treated group

Figure-1 The significant reduction of the expression of JNK, MMP2, the infiltration of macrophages, T lymphocytes and dendritic cells using atorvastatin 20 mg a day in the aorta in patients with AAA (Kajimoto K, *et al*: Atherosclerosis, 2009; 206: 505-511¹⁶⁾)

Table-1 Early coronary plaque regression study with statin in Japanese CAD patients

study	ESTABLISH ¹⁸⁾ 2004	JAPAN-ACS ¹⁹⁾ 2008	COSMOS ²⁰⁾ 2009
Intervention	Atorvastatin 20 mg vs. Control (n=24/24)	Atorvastatin 20 mg VS. Pitavastatin 4 mg (n=127/125)	Rosuvastatin 2.5 – 20 mg (n=126)
Subjects	ACS Emergent PCI	ACS, HL Emergent PCI	Stable ASHD Scheduled PCI
Follow up	6 month	8 to 12 month	76 weeks
LDL-C levels (% change)	125 → 70 (41.7%)	132 → 84 (36.0%)	140 → 83 (38.6%)
% plaque regression	13.1%	17.5%	5.1%

for other statins in multicenter setting. Patients were randomly assigned to receive either 4 mg/day of pitavastatin or 20 mg/day of atorvastatin and had serial IVUS examinations at baseline and 8 to 12 months' follow-up. The primary end point was the percentage change in non-culprit coronary plaque volume. This study proved non-inferiority of pitavastatin to atorvastatin in terms of plaque regression. Overall, LDL-C was reduced by 36% down to 84 mg/dl and the plaque volume was significantly decreased by 17.5%.

The COSMOS study examined the effect of rosuvastatin on plaque volume in Japanese patients with stable CAD, including those receiving prior lipid-lowering therapy. A 76-week open-label trial was performed at 37 centers in Japan. Eligible patients began treatment with rosuvastatin 2.5 mg/day, which could be increased at 4-week intervals to ≤ 20 mg/day. The change in the serum low-density lipoprotein-cholesterol level from baseline to end of follow-up was -38.6%. The plaque volume, the primary endpoint, was significantly reduced by 5.1%.

Although the regression of atherosclerotic plaque is a surrogate marker of clinical outcome,^{7) 8)} these IVUS trials suggested the efficacy of aggressive LDL-C lowering in Japanese patients with coronary artery disease.

Clinical Evidence of Aggressive lipid lowering in Secondary prevention from Japan: HIJ-PROPER and REAL-CAD

The results of IVUS trials suggested the role of aggressive LDL-C lowering in patients with coronary artery disease; however, the real importance of this strategy should be proven by large scale clinical trials. Recently two major outcome

trials were reported from Japan. The HIJ-PROPER²¹⁾ study is a prospective, randomized, open-label trial to assess whether intensive LDL-C lowering with standard-dose pitavastatin plus ezetimibe reduces cardiovascular events more than standard LDL-C lowering with pitavastatin monotherapy in patients with ACS and dyslipidaemia. Patients were randomized to intensive lowering (target LDL-C < 70 mg/dl); pitavastatin plus ezetimibe) or standard lowering (target LDL-C 90 mg/dl to 100 mg/dl); pitavastatin monotherapy). The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischaemia-driven revascularization. 1,734 patients were enrolled at 19 hospitals in Japan. Patients were followed for at least 36 months. Mean follow-up LDL-C level was 65.1 mg/dl for pitavastatin plus ezetimibe and 84.6 mg/dl for pitavastatin monotherapy (Table-2). Intensive lipid lowering with standard pitavastatin plus ezetimibe showed no more cardiovascular benefit than statin alone in ACS patients with dyslipidaemia. However, statin plus ezetimibe had a positive effect on clinical outcomes in patients with higher cholesterol absorption (HR 0.71, 95% CI 0.56–0.91). Thus statin plus ezetimibe may be more effective than statin monotherapy in patients with higher cholesterol absorption; however, further confirmation is needed.

In REAL-CAD,²²⁾ a prospective, multicenter, randomized, open-label, blinded end point study, 13,054 Japanese patients with stable coronary artery disease who achieved LDL-C < 120 mg/dl during a run-in period (pitavastatin 1 mg/d) were randomized in a 1-to-1 fashion to high-dose (pitavastatin 4 mg/d; n=6,526) or low-dose (pitavastatin 1 mg/d; n=6,528) statin therapy. The primary end point was a composite of cardiovascular

Table-2 Clinical Evidence of Aggressive lipid lowering in Secondary prevention from Japan: HIJ proper and REAL-CAD

	HIJ-PROPER ²¹⁾	REAL-CAD ²²⁾
Intervention	Pitavastatin 2 mg vs Pitavastatin 2 mg / Ezetimibe 10 mg	Pitavastatin 1 mg vs Pitavastatin 4 mg
Subjects	ACS patients with dyslipidemia	Stable CAD
Sample size (n)	857 vs 864	6,214 vs 6,199
Primary endpoint	All-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, ischaemia-driven revascularization	Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization
Median Follow up	3.86 years	3.9 years
LDL-C level (mg/dl)	84.6 vs 65.1 (p<0.001)	89.4 vs 73.7 (p<0.001)
Event rate	36.9% vs 32.8%	334 (5.4%) vs 266 (4.3%)
Primary endpoint	(HR 0.89; 95% CI 0.76–1.04, p=0.152)	(HR 0.81; 95% CI 0.69–0.95, p=0.01)

death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization. During the entire course of follow-up, LDL-C in the high-dose group was lower by 14.7 mg/dl than in the low-dose group (p<0.001). With a median follow-up of 3.9 years, high-dose as compared with low-dose pitavastatin significantly reduced the risk of the primary end point (hazard ratio, 0.81; 95% confidence interval, 0.69–0.95; p=0.01). High-dose compared with low-dose pitavastatin therapy significantly reduced cardiovascular events in Japanese patients with stable coronary artery disease. Based on the results of REAL-CAD, aggressive LDL-C lowering with high-dose statin appears to be the standard therapy for secondary prevention of coronary artery disease even in the Japanese population.

Summary

It is important to confirm the benefits of statin therapy in the Asian population, because the CV event rate in Asians is much lower than that in Western countries. Several trials using intravascular ultrasound demonstrated that lowering LDL-C to 70–80 mg/dl by aggressive lipid-lowering treatment with moderately high-dose statins significantly reduced coronary plaque volume, but these studies are vastly underpowered to determine the effects of such lipid-lowering treatment on clinical outcomes. Accordingly, the value of reducing LDL-C levels substantially below 100 mg/dl in patients with CAD, particularly Asian patients, had not been clearly demonstrated, and Japanese guidelines recommended reducing LDL-C only to immediately below 100 mg/dl until recently. HIJ-PROPER and

REAL-CAD provided pivotal evidence for the aggressive lipid-lowering in Japanese patients at secondary prevention. In line with these results, newly revised 2017 JAS guidelines recommend target LDL-C levels of < 70 mg/dl in CAD patients with very high CV-risk. In addition, PCSK9 inhibitors are currently available as optional therapy for insufficient LDL-C management on top of maximal tolerated dose of statins with or without ezetimibe, so this approach may provide us new opportunities to obtain plaque regression and consequent CV event prevention from significant LDL-C reduction. The lipid management strategy for secondary prevention is still changing in clinical practice from recent Japanese evidence.

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