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In the Shadow of the "Statin Festival"

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ABSTRACT

The efficacy of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) for reducing cardiovascular events has been established in large-scaled randomized controlled trials (RCT), and these trials have encompassed both primary and secondary prevention. Also, the safety of statins has been confirmed. Therefore, the market for statins is growing quite rapidly. Despite their proven benefits, a large number of patients who meet the guideline criteria for statin therapy are not receiving these drugs. Various strategies have been used to increase statin therapy in the target populations. However, the number of eligible patients taking statins has remained disappointing. It has been suggested that over-the-counter availability of statins would allow more consumers to use statins and achieve cardiovascular risk reduction. In contrast, those clinical trials have applied selection criteria to protect the internal validity at the expense of reducing the applicability of the trial's findings to the wider population of patients seen in routine clinical practice. Consequently, patients who are prescribed statins in routine clinical practice may systematically differ from those people who received statins in the clinical trials and may have different outcomes from those reported in the trials. This paper will review the efficacy of statins for preventing cardiovascular diseases, and suggest the pitfalls of the randomized controlled trails and the problems in the prescription of statins in the real clinical practice. **(Korean Circulation J 2006;36:77-83)**

KEY WORDS : Hydroxymethylglutaryl-CoA reductase inhibitors ; Randomized controlled trial ; Primary prevention ; Secondary prevention.

Prevention of Cardiovascular Diseases with Lowering Cholesterol Levels

Before the introduction of statins

From the 1950s, the role of high levels of blood cholesterol for the development of atherosclerotic diseases, including coronary heart diseases (CHDs), has been investigated in many cross-sectional, epidemiological and cohort studies. The evidence is now in and it is concrete: a high level of blood cholesterol is an independent risk factor for atherosclerotic diseases.[1)2)]

Since the mid 1960s, a lot of clinical trials have been performed to evaluate the effect of lowering cholesterol on the prevention of coronary heart disease.[2-9)] The trials varied in type of intervention (diet, a variety of drugs, surgery), the degree of cholesterol lowering achieved, the duration of treatment, and the size and the type of study population. Despite their heterogeneity, the trials have fairly consistently shown a reduction in coronary heart disease events with the lowering of cholesterol (Table 1, 2). However, most interventions failed to reduce the cardiovascular or total mortalities before the introduction of statins. A few studies even reported that cholesterol lowering with using fibrate increased total mortality.[8)9)] Attempts have been made to answer questions about the benefits and risks of lowering cholesterol by using meta-analytic techniques. Unfortunately, these meta-analyses have not yielded consistent and/or conclusive results for cause-specific mortality and total mortality. Several analyses have shown significant reductions in coronary heart disease mortality[2)10-12)] and others have not.[13-15)] Therefore, there was continuing debate about the overall benefit of lowering cholesterol until the early 1990s.

After the introduction of statins

Since the introduction of lovastatin in 1987, large scale clinical trials about lowering lipid levels with statins have led to a revolution in the management of atherosclerosis (Table 3).[16)17)] In 1994, the Scandinavian Simvastatin Survival Study (4S) showed that statin not only reduced the major cardiovascular events, but also the cardiovascular mortality and total mortality for the patients suffering with CHDs and high blood cholesterol

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Table 1. Representative clinical trials to evaluate the effect of non-drug methods to lower cholesterol on the prevention of cardiovascular diseases

	Mean TC difference (%)	Duration (years)	All death	CHD death	No. of subjects	Coronary event
Primary prevention						
Goeteborg	0	10	10004/10011	0	0	
MRFIT	2.9	7	6428/6438	0	0	
Minnesota coronary survey	13.8	4.5				
Male			2197/2196	0	0	0
Female			2344/2320	0	0	0
Oslo study	9.1	5	604/628	0	0	+
Finnish	12-18	12				
Male			2276/1902	0	+	
Female			2598/2836	0	0	
Secondary prevention						
Burr (DART), diet	4.0	2	1018/1015	0	0	

+: effective for prevention, 0: ineffective for prevention, TC: total cholesterol, CHD: coronary heart disease, MRFIT: multiple risk factor intervention trial, DART: diet and reinfarction trial

Table 2. Representative clinical trials to evaluate the effect of drugs to lower cholesterol excluding statins on the prevention of cardiovascular diseases

	Mean TC difference (%)	Duration (years)	No. of subjects	All death	CHD death	Coronary event
Primary prevention						
LRC-CPPT, cholestyramine	9	7.4	1906/1900	0	0	+
Helsinki Heart Study gemflbrozil	9.9	5	2051/2030	0	0	+
WHO, clofibrate	9	5.3	5331/5296	-	0	+
Follow-up		9.6		0	0	
Dorr, colestipol	9.8	2	1149/1129			
Male			548/546	0	+	
Female			601/583	0	0	
Secondary prevention						
Stockholm, flbrate & niacin	13	5	279/276	+	+	
Coronary drug project	9.9	6.2	1119/2789	0	0	+
Nicotinic acid		15		+	+	
Clofibrate	6.5	6.2	1103/2789	0	0	0
		15		0		
Newcastle, clofibrate	11	12	244/253		0	
POSCH, operation	23.3	9.7	420/417	0	0	+
VA-HIT, gemfibrozil	4	5.1	1267/1264	0	0	+

+: effective for prevention, 0: ineffective for prevention, -: harmful, TC: total cholesterol, CHD: coronary heart disease, LRC-CPPT: lipid research clinics coronary primary prevention trial, WHO: world health organization, POSCH: program on the surgical control of hyperlipidemias, VA-HIT: veterans' affairs high-density lipoprotein intervention trial

levels.[18] In following year, the West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated that statin reduced major cardiovascular event, CHD mortality and cardiovascular mortality for the patients with high blood cholesterol levels, but who were without CHDs. A trend with borderline significance was also noted for decreasing the total mortality.[19]

The cardioprotective effects of statin were also demonstrated for the patients with myocardial infarction and average cholesterol levels (Cholesterol and Recurrent Events, CARE),[20] for the patients with a broad range of initial cholesterol levels but without CHDs (Air Force/Texas Coronary Atherosclerosis Prevention Study, AFCAPS/TexCAPS),[21] and for the patients with average cholesterol levels and CHDs (Long-Term Intervention with Pravastatin in Ischaemic Disease Study, LIPID).[22] Although statin reduced the major cardiovascular events for patients with high or average cholesterol levels irrespective of the presence of CHDs, the mortality from CHDs or cardiovascular diseases was decreased only for patients with high blood cholesterol levels.

Based on these findings, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]), published in 2001, provided evidence-based recommendations on the management of patients with high blood cholesterol.[17]

Table 3. Representative clinical trials to evaluate the effect of statins on the prevention of cardiovascular diseases

	No of patients M/F	Total mortality	CVD mortality	CAD mortality	CVD event
Primary prevention					
WOSCOPS	6595/0	±	+	+	+
AFCAPS/TexCAPS	5608/997	0	0	0	+
Secondary prevention					
4S	3617/827	+	+	+	+
CARE	3583/576	0	0	0	+
LIPID	7498/1516	+	+	+	+

+: effective for prevention, 0: ineffective for prevention, ±: borderline significance, CVD: cardiovascular disease, CAD: coronary artery disease, WOSCOPS: west of Scotland coronary prevention study group, AFCAPS/TexCAPS: air force/Texas coronary atherosclerosis prevention study, 4S: Scandinavian simvastatin survival study, CARE: cholesterol and recurrent events, LIPID: long-term intervention with pravastatin in ischaemic disease

Table 4. LDL-C goals and cutpoints for non-drug and drug therapy in different risk categories in ATP III guidelines

Risk category	LDL-C goal	Initiate non-drug therapy	Consider drug therapy
High risk:			
CHD* or CHD risk equivalents	<100 mg/dL	≥100 mg/dL	≥130 mg/dL
Moderately high risk: 2 or more risk factors			
10-year risk 10% to 20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
10-year risk <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL

LDL-C: low density lipoprotein cholesterol, CHD: coronary heart disease

According to the ATP III, persons are categorized into 3 risk categories: 1) established coronary heart disease (CHD) and CHD risk equivalents, 2) 2 or more risk factors, and 3) 0 or 1 risk factor (Table 4). The goal for LDL-lowering therapy for persons with CHD or CHD risk equivalents is an LDL-C level <100 mg/dL. LDL-lowering dietary therapy should be initiated for patients with LDL-C levels ≥100 mg/dL. When the baseline LDL-C is ≥130 mg/dL, an LDL-lowering drug should be started simultaneously with dietary therapy. However, LDL-lowering drugs are not mandated if the baseline LDL-C level is in the range of 100 to 129 mg/dL (Table 4).

The goal for LDL-lowering therapy for persons with 2 or more risk factors is dependent upon the Framingham risk scoring system. Persons with a 10-year risk >20% are categorized to CHD risk equivalent and were managed as patients with CHD. For persons with 2 or more risk factors and a 10-year risk ≤20%, the LDL-C goal is <130 mg/dL and LDL-lowering dietary therapy should be initiated for the patients with an LDL-C level above the goal level. If the 10-year risk is 10% to 20%, drug therapy should be considered if the LDL-C level is above the goal level after a trial of dietary therapy. When 10-year risk is <10%, an LDL-lowering drug can be considered if the LDL-C level is ≥160 mg/dL on maximal dietary therapy.

The goal for LDL-lowering therapy for persons with 0 to 1 risk factor and a 10-year risk <10% is an LDL-C concentration to <160 mg/dL. Dietary therapy is recommended when the LDL-C level is ≥160 mg/dL. If the LDL-C is ≥190 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding a cholesterol-lowering drug. When the serum LDL-C level ranges from 160 to 189 mg/dL, introduction of a cholesterol-lowering drug is a therapeutic option in appropriate circumstances.

Statins for patients with average or low cholesterol levels in the new millennium

Since the publication of ATP III, 5 major clinical trials have been done with using statin therapy and the clinical end points have been published. These include the Heart Protection Study (HPS),[23] the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),[24] the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial (ALLHAT-LLT),[25] the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA),[26] and the Treating to New Targets (TNT).[27] These studies have provided new insight into the preventive effects of statins.

Until recently, cholesterol-lowering clinical trials in high-risk patients have failed to demonstrate the preventive effects of statin for patients with the lower ranges of LDL-C, i.e., below 125 mg/dL.[20][28] This lack of hard evidence has made it impossible for the ATP III to make unequivocal recommendations on LDL-lowering therapy for persons with lower levels of serum LDL-C. Therefore, drug therapy was recommended for the high-risk patients with LDL-C levels ≥130 mg/dL.[17]

The HPS and the TNT trials help to confirm the benefit from further reducing already low LDL-C concentrations in the high-risk patients (Fig. 1). The HPS

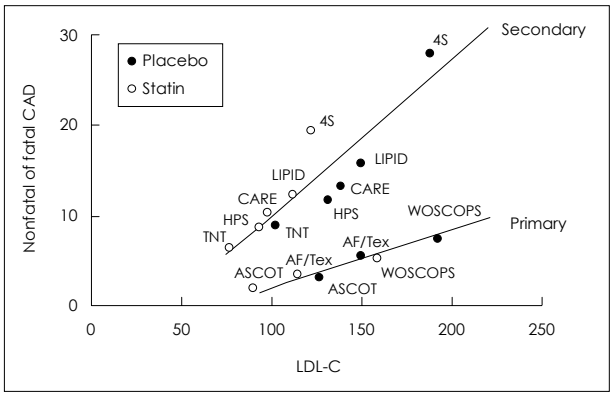

Fig. 1. Relation between LDL-C levels and the incidence of nonfatal and fatal coronary artery diseases in large scale randomized controlled trials of statins for the primary and secondary prevention. LDL-C: low density lipoprotein cholesterol, CAD: coronary artery disease, 4S: Scandinavian simvastatin survival study, AF/Tex: air force/Texas, TNT: treating to new targets, CARE: cholesterol and recurrent events, LIPID: long-term intervention with pravastatin in ischaemic disease, WOSCOPS: west of Scotland coronary prevention study group, ASCOT: Anglo-Scandinavian cardiac outcomes trial, HPS: heart protection study.

was carried out on 20,536 high risk patients with coronary disease, other occlusive arterial disease, or diabetes.[23] Statin therapy produced similar reductions in the relative risk regardless of the baseline levels of LDL-C, including in the subgroups with baseline LDL-C levels <116 mg/dL or <100 mg/dL. The TNT was carried out with 10,001 patients with clinically evident CHD and LDL-C levels <130 mg/dL.[27] Intensive lipid-lowering therapy with 80 mg of atorvastatin per day decreased the mean LDL-C levels to 77 mg/dL as usual therapy with 10 mg of atorvastatin per day to 101 mg/dL. And, Intensive therapy provided a significant clinical benefit by 22% beyond that afforded by the usual treatment. Based on these findings, the NCEP suggested in 2004 that an LDL-C goal of 70 mg/dL is a therapeutic option, i.e., a reasonable clinical strategy for the patients at a very high risk, and this therapeutic option also extends to the patients at a very high risk who have a baseline LDL-C <100 mg/dL.[29]

In ASCOT-LLA, 10,305 hypertensive patients with at least three other cardiovascular risk factors and average or lower-than-average cholesterol concentrations (nonfasting total cholesterol concentrations of 6.5 mmol/L or less) were randomly assigned for receiving atorvastatin 10 mg or placebo.[25] Atorvastatin therapy reduced the non-fatal MI plus fatal CHD by 36% compared with the control group, and this benefit emerged in the first year of follow-up. Based on this finding, NCEP suggested in 2004 that for moderately high-risk persons (2 risk factors and a 10-year risk of 10% to 20%), the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal <100 mg/dL is a therapeutic option. The latter option also extends to moderately high-risk persons with a baseline LDL-C of 100 to 129 mg/dL.[29]

The cardioprotective effects of statins were also proved for old age persons (PROSPER).[24] In contrast to these studies, ALLHAT-LLT reported that statins were ineffective to prevent cardiovascular diseases in 10,355 older hypertensive persons with moderate hypercholesterolemia and at least one additional CHD risk factor.[25] However, crossover of the usual-care participants to the lipid-lowering drugs was high (32% of the usual-care participants with CHD and 29% of the usual-care participants without CHD). The follow-up of the patients for the lipid results was not complete. Among a nonrandom subset of participants who were tested, their total cholesterol levels were reduced by 17% with using pravastatin versus 8% with using the usual care at 4 years. The authors speculated that the failure to detect a significant reduction for the risk in hypertensive patients treated with pravastatin might be due to the modest differential in the total cholesterol (9.6%) between pravastatin and the usual care.

Issues to be Considered or Solved in Real Clinical Practice

High risk patients with low cholesterol levels

In 1996, the CARE trial showed that statins were ineffective for treating patients with CHDs and LDL-C levels <125 mg/dL.[20] In this new millennium, the HPS and the TNT trials have demonstrated the benefit from further reducing already low LDL-C concentrations in the high-risk patients.[23][27]

The HPS study has several issues to be noted before applying the results to clinical practice. First, the HPS enrolled heterogeneous study populations, i.e. patients with coronary disease, other occlusive arterial disease, or diabetes. Therefore, the proportion of diabetic patients was higher (29%) in this study than in the previous RCTs (1-9%). In clinical practice, diabetic patients with multiple complications and low cholesterol levels are not uncommon, and they are prone to suffer from repetitive coronary events during follow-up. For these patients, statins might be effective to prevent the occurrence or the recurrence of cardiac events. The characteristics of the low-LDL subgroups, i.e., what portions had diabetes, or what portions were free of CVD, was not made available.[29] The problems for the management of diabetic patients will be discussed in the following section.

Second, baseline lipids were determined from nonfasting samples, and the levels of LDL-C were measured by the direct LDL method in the HPS study. Therefore, the estimations of the baseline fasting LDL-C, if calculated by the Friedewald equation, would likely have been about 15% higher than the baseline LDL-C that was calculated by the direct method. If this difference between direct and calculated LDL-C levels holds at low LDL-C levels, a direct LDL-C level of 100 mg/dL would

correspond to a calculated LDL-C of 115 mg/dL.[29]

In the TNT study, intensive lipid-lowering therapy with 80 mg of atorvastatin reduced the major cardiovascular events by 22%, as compared with administering the usual therapy with 10 mg of atorvastatin for the patients with clinically evident CHD and a LCL-C level <130 mg/dL.[27] There was a trend with borderline significance of lowering death from CHD by 20%. However, the total mortality was quite similar between the two groups. This finding implies that non-CHD mortality might show the trend to be higher with intensive lipid-lowering therapy. The details of the non-CHD mortality were unavailable. Like the HPS study, the proportion of diabetic patients was higher in the TNT study (15%). However, the subgroup analyses were not made available.

Therefore, it isn't certain whether statins should be prescribed for all the high risk patients with low cholesterol levels or for only selected persons such as diabetic patients with complications. These qualifying issues must be kept in mind when generalizing the findings of the HPS and TNT studies to all the high-risk patients with low baseline LDL-C levels.

Moderate risk patients with average cholesterol levels

In the ASCOT-LLA, the authors insisted that lowering cholesterol by administering atorvastatin 10 mg in the hypertensive patients with at least three other cardiovascular risk factors and with average or lower-than-average cholesterol concentrations conferred a 36% reduction for fatal CHD and non-fatal myocardial infarction, as compared with placebo.[25] Thus, the ASCOT-LLA supports the use of an LDL-lowering drug in persons with a 10-year risk of 10% to 20% and an LDL-C level of 100 to 129 mg/dL so as to achieve an LDL-C level <100 mg/dL. Although the patients with CHDs were excluded, the ASCOT-LLA study included patients with CHD risk equivalents, diabetes mellitus in 25%, peripheral vascular disease in 5%, and stroke in 9.6%. In addition, the 10 year risk for CHD according to the Framingham point scores calculated from the mean values of the risk factors was 16% or over, and a significant proportion of patients might have 10 year risk for CHD >20%. So, the cardioprotective effect noted in the ASCOT-LLA was mainly derived from the rather high risk patients with diabetes mellitus, peripheral vascular disease, stroke, and 10 year risk for CHD >20%. Therefore, the finding of ASCOT-LLA cannot be applied to patients with a moderate risk and average cholesterol levels who are frequently encountered in real clinical practice.

Diabetes mellitus

The ATP III guidelines recommended that diabetic patients are to be classified as a high risk group (CHD risk equivalents) and that the goal for LDL-lowering therapy in these patients is an LDL-C level <100 mg/dL. When the baseline LDL-C is ≥130 mg/dL, a LDL-lowering drug should be started along with dietary therapy.

In a combined analysis of the two secondary prevention trials with pravastatin, Cholesterol And Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) as a part of the Prospective Pravastatin Pooling Project, statin did not reduced cardiovascular events in 2607 patients with low pretreatment LDL-C levels (<125 mg/dL).[28] On the subgroup analysis, cardiovascular events were decreased by 43% in the diabetic patients with LDL-C levels <125 mg/dL, but not in the non-diabetic patients with low LDL-C levels. Those patients with LDL-C levels <125, as compared with patients with LDL-C levels ≥125 mg/dL, were more likely to be diabetic (15% versus 9%), and they had higher triglyceride levels (169 versus 154 mg/dL) and lower HDL-C levels (36.5 versus 38 mg/dL). HDL-C and triglyceride levels were both significantly stronger predictors of recurrent CHD events for the participants with LDL-C levels <125 than for the participants with LDL-C levels ≥125 mg/dL. Therefore, statin may be helpful for diabetic patients with high risk and low cholesterol levels, although the mechanisms that are responsible for this are unclear, i.e., a reduction of LDL-C levels, a reduction of triglyceride levels, and/or an elevation of the HDL-C levels.

In the HPS study, statins were effective for the prevention of cardiovascular events in both the diabetic and non-diabetic patients irrespective of their baseline LDL-C levels.[23] However, the relationships of the characteristics of the enrolled diabetic patients such as complications or the duration of diabetes mellitus, the cholesterol levels and the risk of the patients were not demonstrated. In addition, the HPS study had problems, as was stated above.

In summary, statin is an effective treatment for diabetic patients with high risk irrespective of their cholesterol levels. However, until now, there has been no evidence that statin is effective for the patients with uncomplicated diabetes mellitus and who are otherwise at low risk. Therefore, it is unclear whether the ATP III guideline must be applied to all or only a portion of diabetic patients.

Safety

The usual doses of statins are safe and patient compliance is generally good, except for cerivastatin. Hepatic toxicity (more than 3 times the upper normal limit) is less than 1% and muscular toxicity (more than 3 times the upper normal limit) is rare. Severe complication such as rhabdomyolysis is extremely rare.[16] However, adverse effects increase with high doses of statins. In the TNT study, hepatic toxicity was found in 0.2% of patients with using 10 mg atorvastatin and in 1.2% of patients with

using 80 mg atorvastatin.[27] There were no differences in muscular toxicity and rhabdomyolysis between the doses. When considering the hepatic toxicity, high doses of statin must be reserved for the patients who will achieve definite benefit with the therapy.

In most studies performed on middle age individuals or individuals with a wide range of age, the incidence of cancer was not increased with statin therapy. However, in the PROSPER study, which was a study of older age people, new cancer was diagnosed 25% more frequently when statins were administered than when placebo was administered.[24] Therefore, statin needed to be administered cautiously in old patients balancing the risk of cancers and the benefit from reducing CHDs.

Cerivastatin has been withdrawn from the market, and it has been reported that the pharmacokinetics and side effects are different among the different kinds of statins. Additionally, for a kind of statins, increased drug levels were observed for Asians as compared with Caucasians.[30] This finding means the initial dose of this statin must be halved for Asian patients. As a higher dose of this statin increases the side effects, the maximal recommended dose is limited to the initial dose for high risk patients.

Summary

Statins are very effective in preventing cardiovascular diseases for the high risk patients who have high or average cholesterol levels, and for moderate risk patients with high cholesterol levels. Statins may be effective even for high risk patients with low cholesterol levels and for moderate risk patients with average cholesterol levels. However, further research is needed to elucidate whether statins are effective for all patients or only a part of patients in these groups.

In real clinical practice, statin should be prescribed based on the estimated risk for the individual patient. For example, medications are indicated for the diabetic patients with low cholesterol and a high risk status such as CHD, and for the patient without CHDs but with average cholesterol levels and high risk. Yet, medications are not indicated for the uncomplicated diabetic patients with low cholesterol and a low risk status, and for the patients without CHDs and with average cholesterol levels and moderate risk.

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