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"Just Make It Lower" Is an Alternative Strategy of Lipid-Lowering Therapy With Statins in Japanese Patients

– LDL-Cholesterol: The Lower, the Better; Is It True for Asians? (Con) –

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It is well known that statins improve the prognosis of cardiovascular diseases (CVD). Recent randomized control trials (RCTs) of statins conducted in Western countries revealed greater avoidance of cardiovascular events if low-density-lipoprotein cholesterol (LDL-C) reached lower levels. However, it is obvious that this evidence cannot be unconditionally extrapolated to Asians because there are great differences between Japanese and Caucasians in the absolute onset rate of CVD. Results of RCTs with Japanese for primary or secondary prevention of cardiovascular events indicate that we could benefit from statins with a relatively higher target LDL-C as compared with Western populations. In this situation, not only strong but also standard statins are still advantageous and the so-called pleiotropic effects of the drugs come to the fore. In this review, we first discuss differences in the absolute event rate in different populations, and then the lack of evidence for recommended LDL-C treatment targets, particularly in Japanese, although there is reliable evidence for reductions in plaque volume in coronary arteries from RCTs recently conducted in Japan with aggressive lipid-lowering therapy with strong statins. Finally, based on recent data, we propose a new concept regarding the secondary prevention of CVD for current Japanese populations. (*Circ J* 2010; **74:** 1731–1741)

Key Words: Cardiovascular diseases; Japanese; Prevention; Statins

Discovery of Statins and the Early Randomized Control Trials

In 1976, the Japanese researcher Akira Endo, who won the Lasker award in 2008, identified a fungal metabolite that blocked cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, resulting in the first "statin", compactin.[1] Since his discovery, quite a few statins have become available and numerous randomized control trials (RCTs) have been conducted to examine if low-density-lipoprotein cholesterol (LDL-C) lowering therapy with statins improves the prognosis of coronary heart disease (CHD). From the results of landmark RCTs such as 4S,[2] WOSCOPS,[3] CARE,[4] LIPID,[5] and AFCAPS/TexCAPS,[6] statins were proved to be effective in preventing cardiovascular events in any type of patient category by the end of 20th century. Therefore, Brown and Goldstein, who are Nobel prize winners for their achievements in LDL receptor discovery, wrote an editorial in *Science* entitled "Heart Attacks: Gone with the Century?"[7] In other words, statins are effective in patients with or without established CHD, and in those with higher or moderate cholesterol levels (**Table 1**).

Epidemiological Side View of CHD

At the beginning of the 20th century, the relationship between hyperlipidemia and atherosclerosis was established by experimental studies.[8] To elucidate if the relationship in human subjects also exists, epidemiological studies were needed and 1 of the most important and oldest one is the famous Framingham Heart Study (FHS) started in 1948.[9] From the FHS, hypercholesterolemia was proved to be a major risk factor of CHD and this result was confirmed as also true in populations living in countries and regions other than North America by the Seven Countries Study (7CS).[10] One of the important messages from the 7CS is the variation in the death rate from CHD by country and region, despite equality of all-cause mortality rates (**Table 2**).[11] As shown in **Table 2**,

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Table 1. Large-Scale Randomized Control Trials in the Early Days After Launching Statins

Patient category	Primary prevention	Secondary prevention
Normocholesterolemia	AFCAPS/TexCAPS[6] (1998)	CARE[4] (1996)
Hypercholesterolemia	WOSCOPS[3] (1995)	4S[2] (1994), LIPID[5] (1998)

Table 2. Age-Adjusted 25-Year Death Rates From CHD and All Causes in the Eight Countries of the 7CS

Nation	n	CHD death per 1,000 in 25 years		All-cause death per 1,000 in 25 years	
		Rate	SE	Rate	SE
USA	2,571	202	8	451	10
Finland	1,677	239	15	549	12
The Netherlands	878	197	13	480	17
Italy	2,480	128	11	456	10
Croatia	1,367	112	12	523	13
Serbia-Yugoslavia	1,565	139	15	456	13
Greece	1,215	67	10	353	14
Japan	1,010	54	10	454	16

CHD, coronary heart disease.
Adopted from Ref 11.

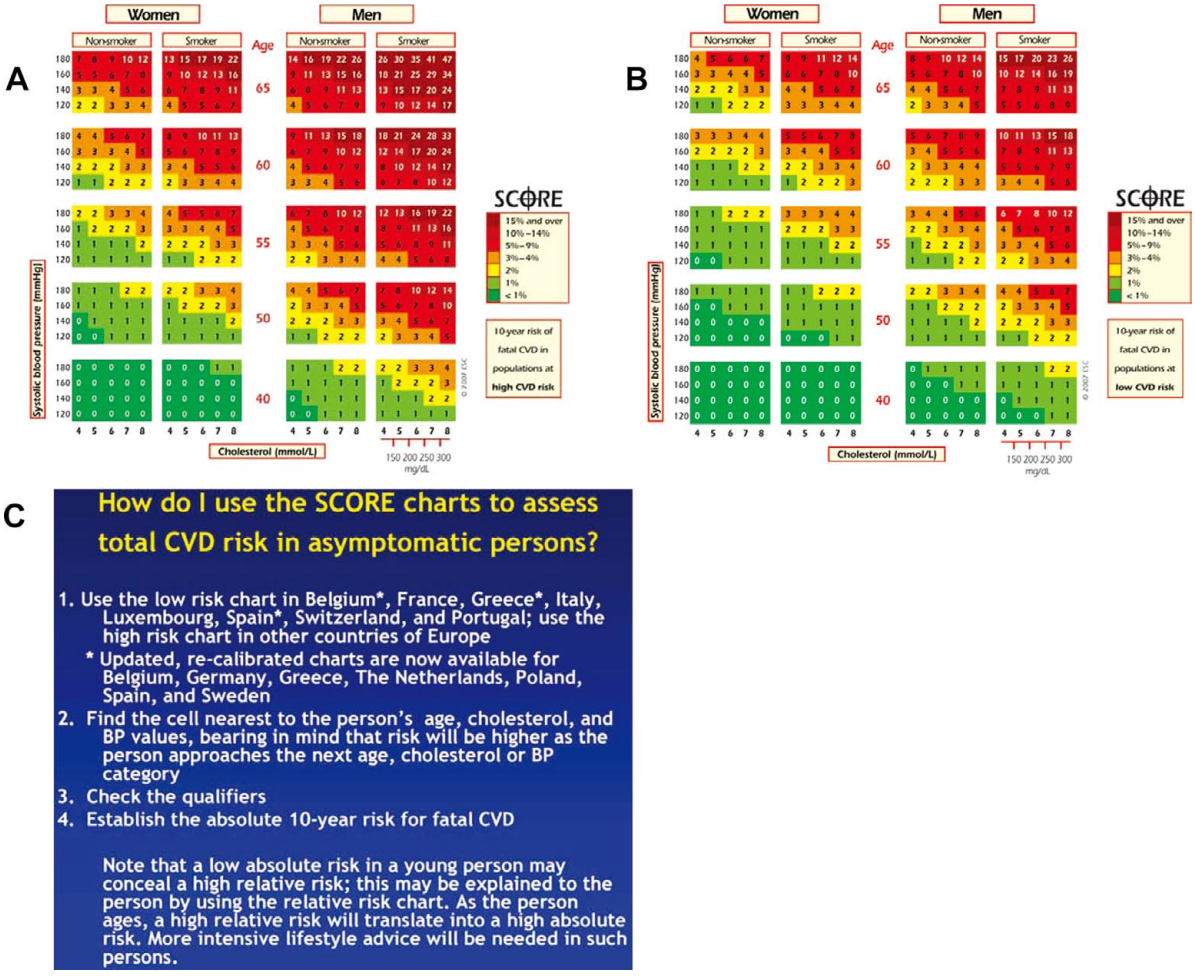

Figure 1. European guidelines on cardiovascular disease prevention in clinical practice. These guidelines recommend using the SCORE system, which estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other. They provide 2 different charts for populations at high (**A**) and low (**B**) cardiovascular disease risk. Both charts are suggested to be used separately in different nations (**C**). Adopted and modified from Ref 12.

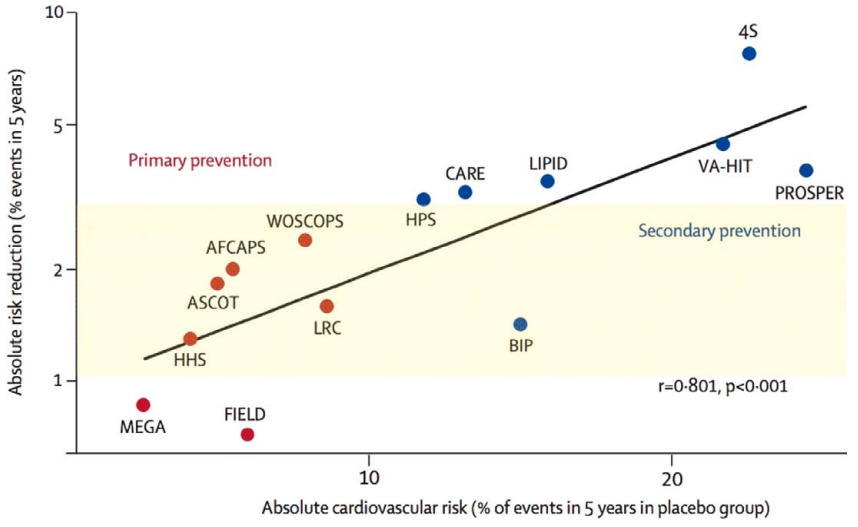

Figure 2. Relationship between absolute cardiovascular risk in placebo groups and absolute risk reduction in major randomized control trials for primary and secondary cardiovascular prevention. The yellow band indicates the range of the occurrence of liver dysfunction from standard (1.1% by pravastatin 40 mg) to aggressive (3.3% by atorvastatin 80 mg) lipid-lowering therapy in PROVE-IT.[22] Adopted and modified from Ref 24.

the rates of death from CHD in Japan and Greece were almost one-quarter of those in the north European and American countries, which clearly shows that the lipid-lowering strategy based on the RCTs done in those countries are not applicable in countries with a relatively low cardiovascular risk such as Japan and Greece. In fact, the European guidelines recommend different lipid-lowering strategies for northern and southern European countries[12] (Figure 1).

Japanese Guidelines for Atherosclerotic Cardiovascular Diseases (CVD)

In 2007, the Japan Atherosclerosis Society (JAS) published *The JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007*.[13] Results from Japanese studies such as J-LIT,[14] KLIS,[15] MEGA,[16] PATE,[17] and JELIS[18] were incorporated in the guidelines. Furthermore, results from a 19-year epidemiologic study, NIPPON DATA 80,[19] were also available in the guidelines. Those studies revealed that there was also a close relationship between hyperlipidemia and CHD in Japanese populations and that drug interventions for hyperlipidemia were effective in preventing atherosclerotic CVD. A meta-analysis of early RCTs with standard statins, as well as those with strong statins, in Western countries showed that statins were effective in reducing the 5-year incidence of major coronary events, coronary revascularization, and stroke, largely irrespective of the initial lipid profile or other presenting characteristics.[20] From the results of all the Japanese randomized studies and that meta-analysis, the Japanese guidelines settled the target LDL-C level as <100 mg/dl for secondary prevention and as <120, <140 and <160 mg/dl for primary prevention in low-, moderate- and high-risk patients, respectively.[13] However, there are no specific studies of Japanese to provide definite therapeutic target LDL-C levels for primary and secondary prevention of CVD, so the Japanese guidelines have cited mainly the NCEP ATP III guidelines.[21] For example, in the US guidelines, the target LDL-C level is defined as <100 mg/dl for secondary prevention, which is the same LDL-C level for the similar patient category in the Japanese guidelines, and there is an assumption that the cardiovascular risk of the patients in that category is >20% for 10 years. However, the recurrence rate of myocardial infarction (MI) for Japanese is less than 10% in the J-LIT patient cohort.[14] Furthermore, in the NCEP ATP III guidelines, therapeutic lifestyle changes are recommended for patients with <10% cardiovascular risk. Therefore, absolute cardiovascular risk should be considered when lipid-lowering therapy with statins is commenced.

The Lower, the Better

The concept of "the lower, the better" was basically established by PROVE-IT[22] and TNT,[23] which proved that an aggressive lipid-lowering strategy with high doses of strong statins was effective in reducing major cardiovascular events in acute coronary syndromes (ACS) and chronic ischemic heart diseases. In those trials, it is worth mentioning that adverse events, such as increasing levels of transaminase, were observed 3–6-fold more frequently in the aggressive strategy arm than in the standard one. Therefore, to accomplish "the lower, the better" with high doses of strong statins, patients and clinicians have to be prepared for the adverse effects of statins. Such is the case for people with a low cardiovascular risk, such as Japanese, treated with statins. Generally, the net benefit of medicines depends on the balance between the adverse reactions and efficacy of the drug. Furthermore, the effects of statins are more significant if the absolute cardiovascular risk is higher[24] (Figure 2). Therefore, the concept of "the lower, the better" will have less impact in Japanese as compared with Caucasians.

Statins as a Plaque Volume Reducer and Plaque Stabilizer

It is well known that statins can not only stop the increase in plaque volume but also reduce it in patients with ACS[25,26] and stable coronary artery disease.[27,28] This effect could be specific to the so-called strong statins, which have been proven effective in improving long-term prognosis.[22,23] However, there are no studies that prove a direct relationship between plaque volume reduction and hard-endpoint events.[29,30] By reducing plaque volume, aggressive lipid-lowering treatment with statins and other optimal medical therapy can be used first to reduce both angina symptoms and the need for revas-

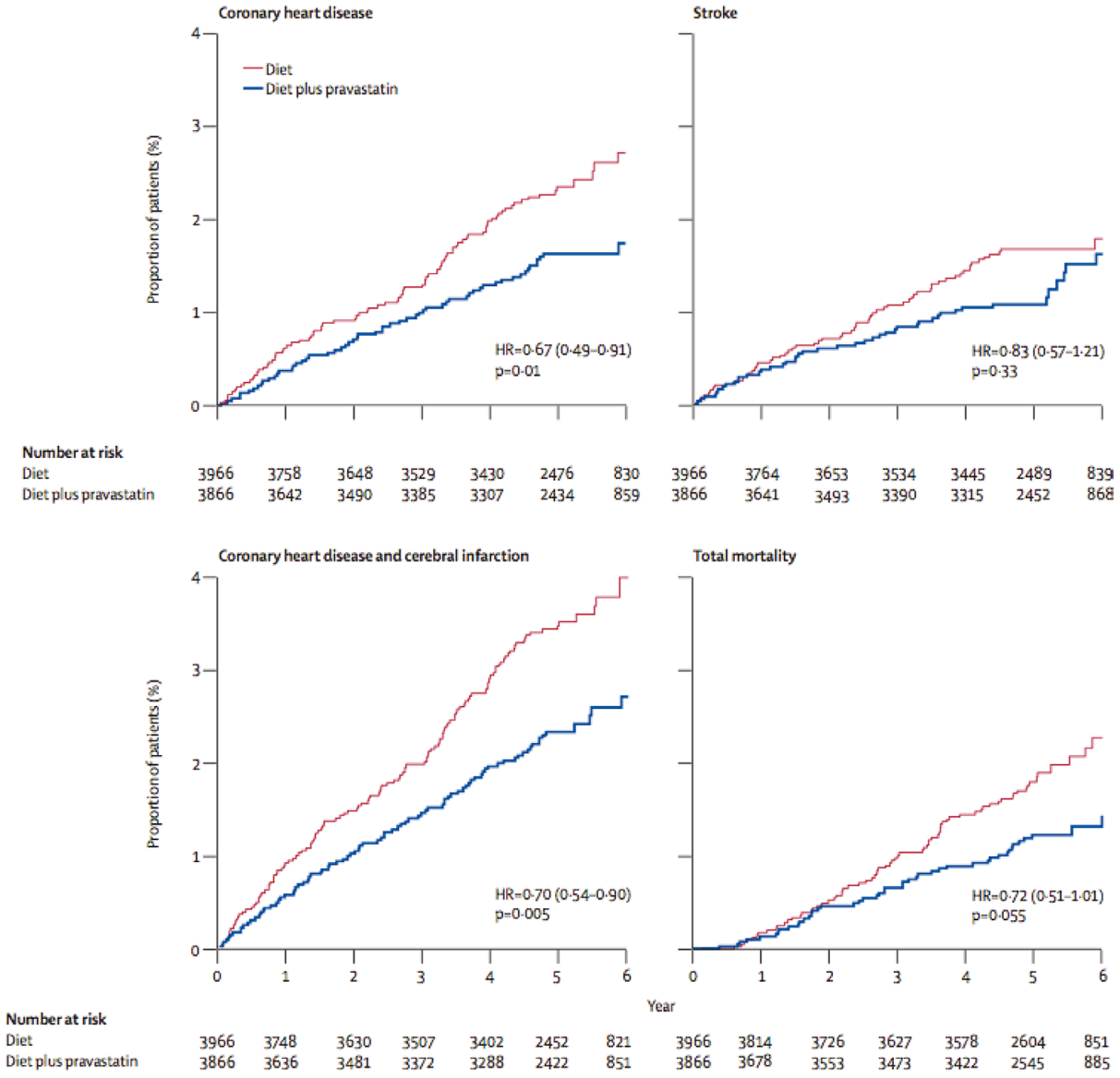

Figure 3. Kaplan-Meier curves for the primary and secondary endpoints of the MEGA study. Diet plus pravastatin was effective in preventing the onset of coronary heart disease and coronary heart disease plus cerebral infarction, but not stroke and total mortality while the tendency of the superiority of the treatment existed. Adopted from Ref 16.

cularization therapy such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting.[31,32] Simultaneously, or even before plaque volume reduction, qualitative changes in the plaque itself[33,34] and modification of the environment surrounding the plaque emerge with statin therapy, what are known as the "pleiotropic" effects of the drug, including anti-inflammation,[35] antioxidation,[36] antithrombosis[37] and improving endothelial function.[38] Generally, it takes a much shorter time for the pleiotropic effects to occur as compared with plaque volume reduction. In the MIRACL study, statin therapy improved prognosis of non-ST-elevation ACS in as short as 16 weeks,[39] which would not be long enough for plaque regression. On the other hand, in some statin trials there was no relationship between LDL-C reduction and event suppression.[3,40] After considering all these findings, in some situations it is possible that not the LDL-C reduction ability but rather the pleiotropic effects of statins comes to the fore in reducing cardiovascular events. In those situations, "the lower, the better" is not be the case.

"Time Integral of LDL-C" Hypothesis

As mentioned before, atherosclerotic plaque is basically formed in the hyperlipidemic state,[7] so it is reasonable that the longer the arterial vessel wall is exposed to hyperlipidemia, the more the lesion develops. In this way, the volume of atherosclerotic plaque at a particular time point might be calculated mathematically by the integration of LDL-C with respect to the time from birth to that point. The higher the LDL-C level and the longer the time of exposure, the larger

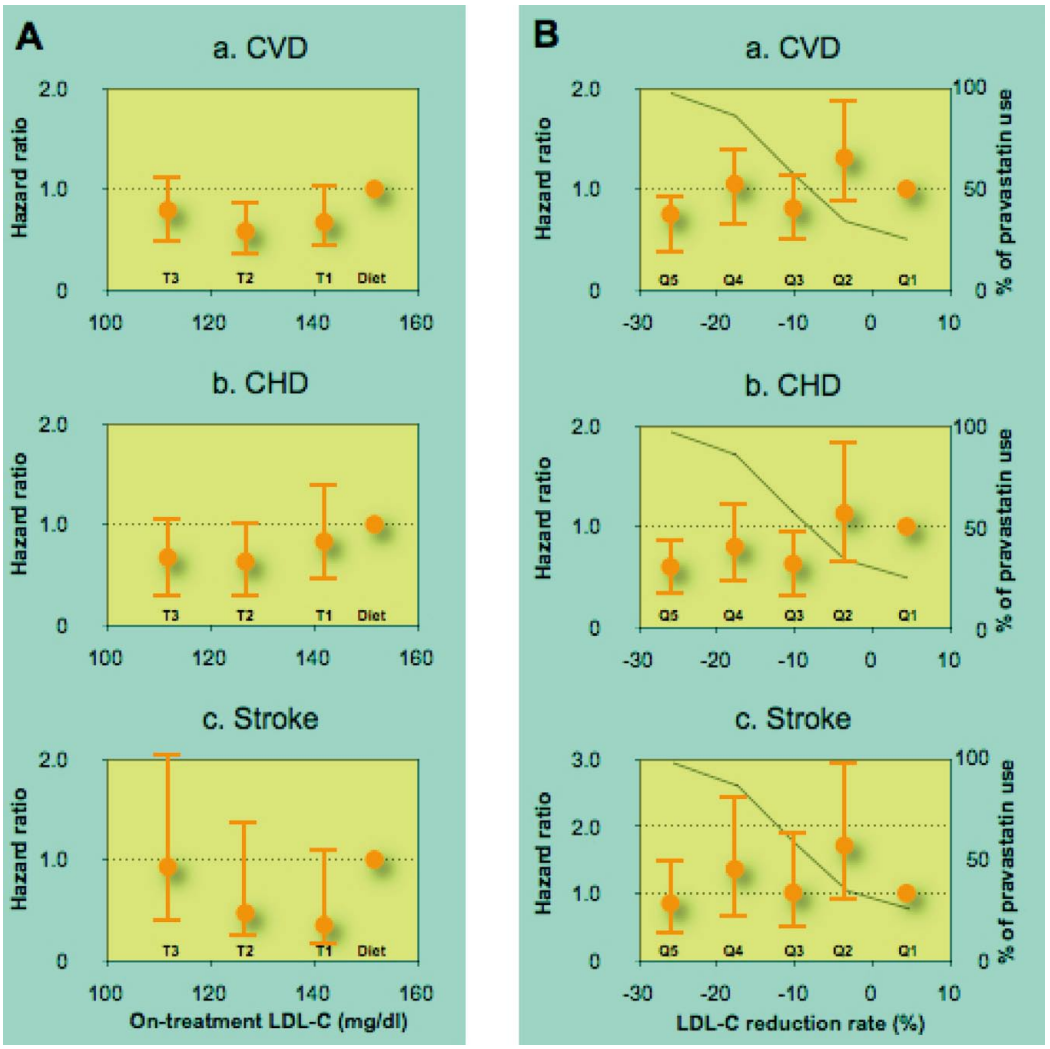

Figure 4. (**A**) Incidence of cardiovascular disease (CVD), coronary heart disease (CHD), and stroke according to tertiles of on-treatment low-density lipoprotein cholesterol (LDL-C) level in the diet plus pravastatin group in the MEGA study. There were no significant differences in event rates in the comparison with the diet only group according to the on-treatment LDL-C level except T2 in CVD incidence. (**B**) Incidence of CVD, CHD, and stroke according to quintiles of LDL-C reduction in the total population of the MEGA study. The LDL-C level for each quintile was based on mean LDL-C reduction. The percentage of patients in each quintile of LDL concentration in the diet plus pravastatin group is indicated by the solid line, corresponding to the right vertical axis. There was no linear relationship between the LDL reduction rate and the incidences of CVD, CHD, and stroke in the total study group, including the diet only group. Adopted and modified from Ref 41.

and more firm will be the atherosclerotic plaque that could be formed. In those patients, long-term use of strong statin could be effective in reducing plaque volume and even improve prognosis. In contrast, patients with modest LDL-C levels and a relatively short clinical history, the pleiotropic effects of statins not their lipid-lowering effect should be highlighted. In this situation, it is possible that even the standard statins could play a significant role in both primary and secondary prevention of cardiovascular events. It can be assumed that most of the current Japanese population who grew up in the relatively poor post-war days belong to such a cohort of patients. However, future Japanese patients with ischemic heart disease who have been living in luxury (high-caloric diet) in recent years will need more potent statins, similar to the Western countries, to effectively prevent cardiovascular events.

Lessons From the MEGA Study, a Japanese Primary Prevention Study

MEGA is a landmark RCT for primary prevention in Japanese. In this study 7,832 hypercholesterolemic patients (men aged 40–70 years and postmenopausal women aged less than 70 years with total cholesterol levels 220–270 mg/dl and any cardiovascular disease), were randomized to standard diet therapy or diet plus pravastatin 10–20 mg/day.[16] Of the study patients, almost 70% were women, more than 40% had hypertension and 20% had diabetes. The high-density lipoprotein-cholesterol level at baseline was 57.5 mg/dl, which was much higher than in other RCTs, suggesting that the study

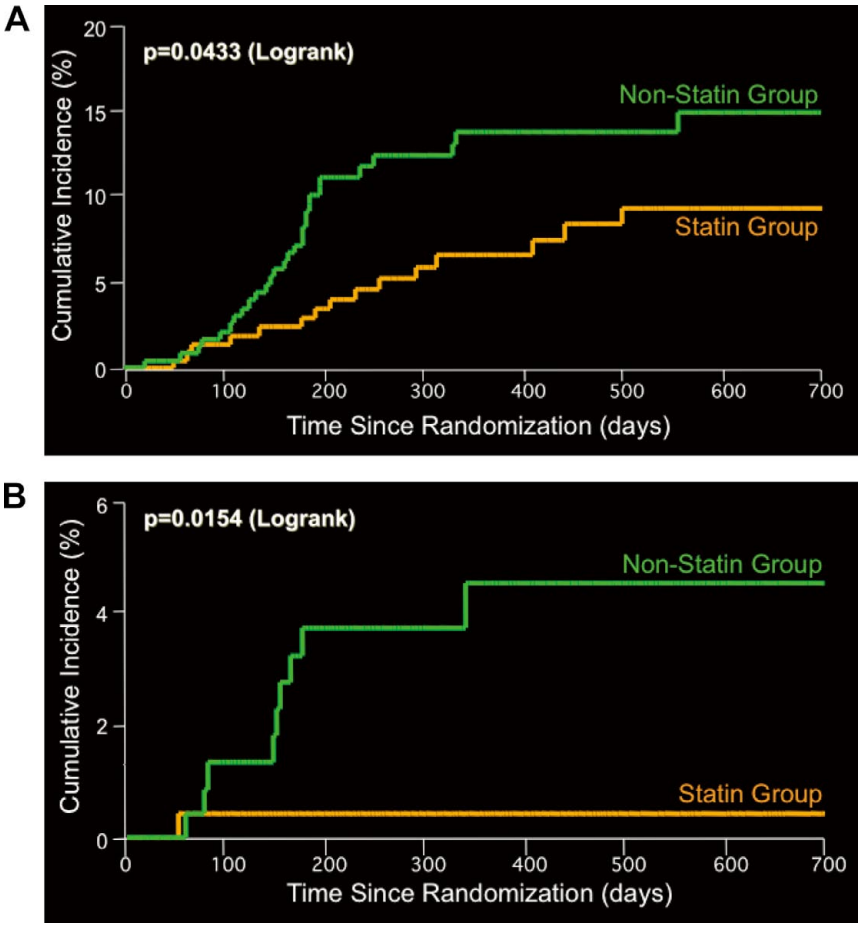

Figure 5. Kaplan-Meier estimates of combined primary outcomes (**A**) and onset of congestive heart failure requiring emergency rehospitalization (**B**) in MUSASHI-AMI. Statin therapy reduced cardiovascular events significantly as compared with standard therapy without statins in patients with AMI. Of all the primary endpoint events, symptoms of congestive heart failure were strikingly suppressed by statin treatment. AMI, acute myocardial infarction.

population in the MEGA study had a low cardiovascular risk. Pravastatin reduced LDL-C levels by 18%, whereas diet did by only 3.2%. At a mean follow-up of 5.3 years, the onset of CHD defined as fatal or non-fatal MI, sudden death, angina pectoris and coronary revascularization therapy was reduced by 33% (P=0.010; 3.3/1,000 patient years in the diet plus pravastatin group vs 5.0/1,000 patient years in the diet group), and the number-needed-to-treat was 119 (**Figure 3**). No clinically significant difference was found between the 2 groups with severe adverse events or cancer. These results demonstrated that only 10–20 mg pravastatin reduced the CHD risk even in low-risk populations such as Japanese, as compared with the RCT with 40 mg pravastatin of the Western populations.[3]

Recently, in a noteworthy subanalysis published by the MEGA study group,[41] the relationship between changes in LDL-C and reduction in the incidence of CVD was evaluated. Regarding the incidence of CVD among tertiles in the diet plus pravastatin group, a significant risk reduction was observed in the second tertiles with the lowest hazard ratio (0.57, P=0.01) among the groups. Furthermore, CHD in total and the stroke rate were totally equal among the groups (**Figure 4A**). A definite relationship was not observed between achieved LDL-C levels and event rates, which was the case for all the study subjects, whether diet only or diet plus pravastatin. Specifically, after dividing the total study group in 5 patient groups according to the achieved LDL-C level, there were no linear relation between the levels and cardiovascular event rates (**Figure 4B**). The authors discussed that based on these results, the "the lower, the better" hypothesis in studies conducted with moderately-high and high-risk patients could not be extrapolated to a low-risk population, such as the Japanese patients with mild to moderate hypercholesterolemic studied in MEGA.

Lessons From the MUSASHI Project, a Japanese Secondary Prevention Study

Regarding secondary prevention in the Japanese population, data from a multicenter study for aggressive lipid-lowering strategy by HMG-CoA reductase inhibitors in patients with acute myocardial infarction (MUSASHI-AMI) are available. MUSASHI-AMI was conducted in 54 hospitals in 28 prefectures in Japan and included 486 consecutive patients with AMI.[42] Within 96 h of symptom onset, patients were assigned to receive conventional therapy without statins or plus open-label statin treatment with one of the following statins available in Japan at that time: pravastatin, atorvastatin, simvastatin, fluvastatin or pitavastatin. Almost half of the study patients were treated with pravastatin and two-thirds with standard statins. The mean follow-up period was 416± 11 days. The primary endpoint was a composite of cardiovascular death, nonfatal MI, recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization, congestive heart failure requiring emergency rehospitalization, and nonfatal stroke. LDL-C

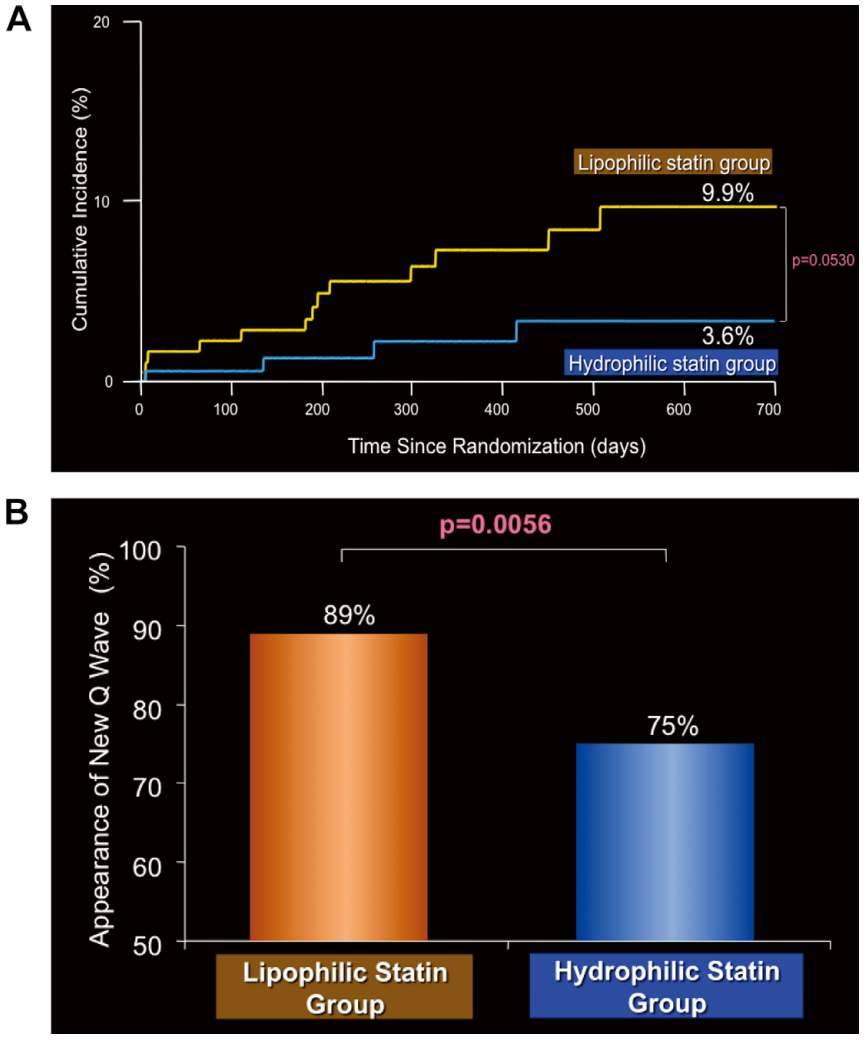

Figure 6. Kaplan-Meier estimates of acute coronary syndrome incidence rates in the lipophilic statin and hydrophilic statin groups in MUSASHI-AMI (**A**). Hydrophilic pravastatin has a tendency to prevent cardiovascular events as compared with lipophilic statins, despite less ability to reduce low-density lipoprotein-cholesterol. (**B**) Incidence of newly appearing Q-waves in the lipophilic statin and hydrophilic statin groups in MUSASHI-AMI. Abnormal Q-waves were observed less frequently in patients treated with hydrophilic pravastatin as compared with those taking the lipophilic satins. AMI, acute myocardial infarction.

levels were reduced by 23% (134–103 mg/dl) after 2 years' treatment. As shown in **Figure 5A**, the risk of the primary combined endpoint was markedly decreased in the statin group during the follow-up period. Of each primary endpoint event, the prevention by statin therapy of congestive heart failure requiring emergency rehospitalization became prominent after 6 months of treatment (**Figure 5B**). As mentioned before, several statins were used at physicians' discretion in the MUSASHI-AMI trial, consequently enabling a unique subanalysis; namely, comparison of the event rate according to the statins' lipophilicity.[43] In normocholesterolemic Japanese patients after acute MI, hydrophilic pravastatin could be superior to lipophilic statins in reducing cardiovascular events (**Figure 6A**) and preventing new Q-wave appearance (**Figure 6B**), although the LDL-C reduction rate was higher in the lipophilic statins group as compared with the hydrophilic one (−34% vs −19%). In animal experimental models, pravastatin has proven to be effective in preserving left-ventricular function and it could be its hydrophilic property that contributes a great deal to this protective effect.[44] Furthermore, 10 mg daily of pravastatin increased plasma adiponectin levels and improved glucose tolerance.[45,46] In the other arm of the MUSASHI trial, or MUSASHI-PCI, it has been reported that standard-dose statin therapy provided incremental benefits in diabetic patients compared with non-diabetic patients.[47] Therefore, as observed in the primary prevention trial MEGA, statins were also effective in secondary prevention, in particular for diabetic patients and with hydrophilic pravastatin. One of the reasons why relatively modest statin therapy succeeded in secondary prevention after acute MI in the MUSASHI-AMI study cohort could be the superior breakdown of pravastatin usage to other lipophilic statins.

A similar evaluation to that performed in the MEGA study was also done in the MUSASHI project.[48] In the subanalysis to clarify the optimal lipid-lowering target level for statins in Japanese patients undergoing PCI, the relation between achieved LDL-C level with statins and the cardiovascular events rate was analyzed using the MUSASHI-PCI database. A total of 1,019 patients whose serum total cholesterol levels ranged from 180 to 240 mg/dl were enrolled and randomly assigned to receive any available statin or not. Indications of PCI were stable angina in 54%, ST-elevation ACS in 41% and non-ST-elevation ACS in 5%. In the stain group, the mean LDL-C levels declined from 133 to 96 mg/dl at 2 years, and from 130 to 121 mg/dl in the non-statin group (both $P<0.0001$). The Kaplan-Meier estimate of primary endpoint events was 9.4% in the statin group and 14.7% in the non-statin group for 2 years ($P=0.0228$ by log-rank) (**Figure 7**).

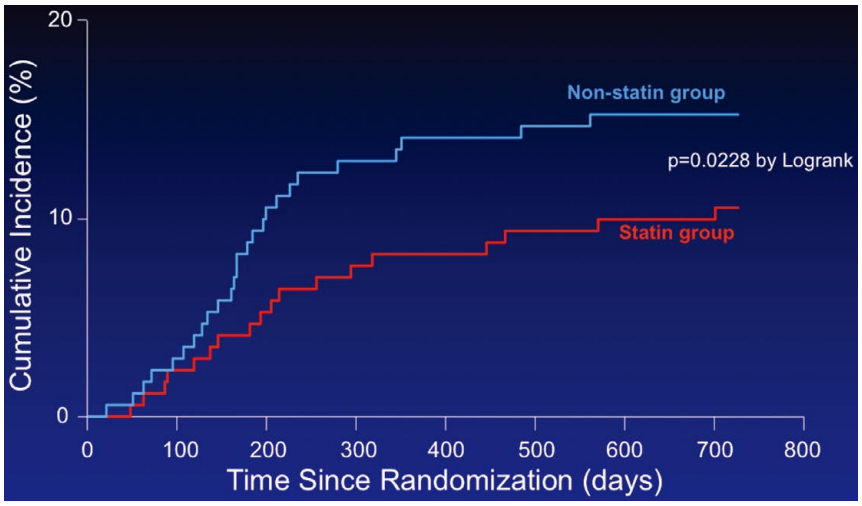

Figure 7. Kaplan-Meier estimates of combined primary outcomes in MUSASHI-PCI. Statin therapy reduced cardiovascular events significantly as compared twith standard therapy without statins in patients undergoing PCI. PCI, percutaneous coronary interventions.

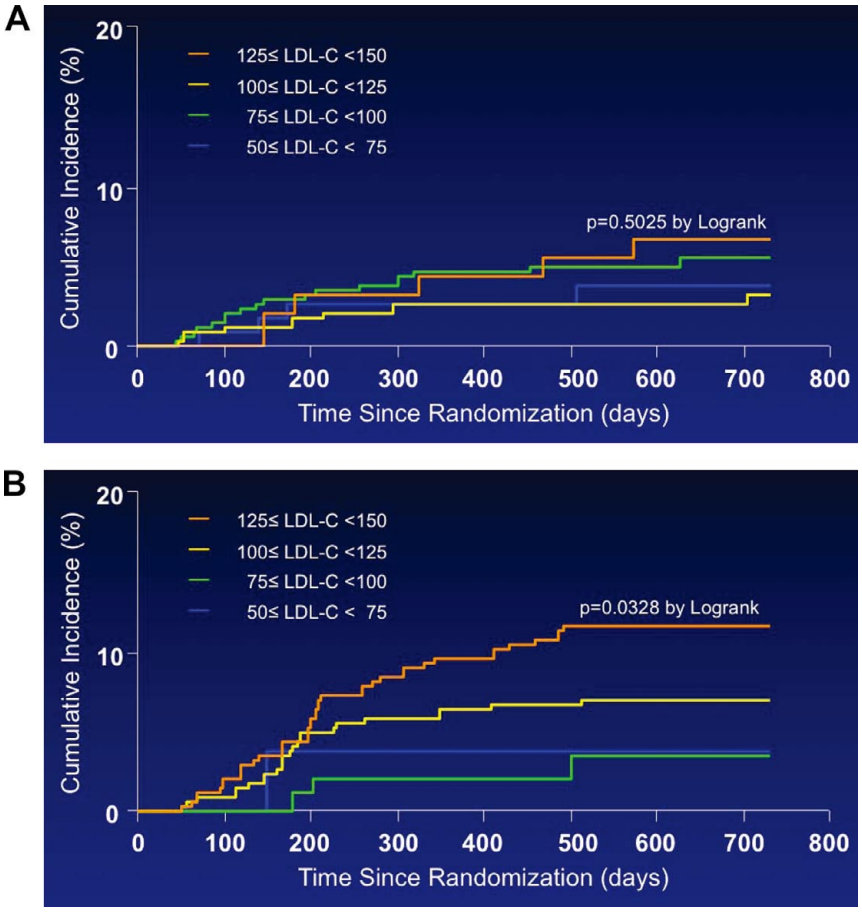

Figure 8. Kaplan-Meier estimate of primary endpoint events according to the achieved LDL-C levels in the statin group (**A**) and the same analysis in the non-statin group (**B**) in MUSASHI-PCI. LDL-C, low-density lipoprotein-cholesterol; PCI, percutaneous coronary interventions.

There were no differences in the incidence of the endpoint event rate among the 4 groups of every 25-mg/dl range of achieved LDL-C levels, or 50–75, 75–100, 100–125 and 125–150 mg/dl in the statin group (P=0.5025 by log-rank) (**Figure 8A**). On the other hand, in the non-statin group the incidence increased according to the achieved LDL-C (P=0.0328 by log-rank) (**Figure 8B**). In this way, statin therapy equalized the cardiovascular event rate after PCI in Japanese, independently of achieved LDL-C levels at least between 50 and 150 mg/dl. These data were basically the same as those observed in the MEGA study. In other words, for primary or secondary prevention of cardiovascular disease in Japanese populations, not setting lower target LDL-C levels and aiming for them by using high-dose strong stains, but rather

using statins per se and reducing the LDL-C level by 20–30% could be as efficient and important for improve the prognosis of patients with a relatively lower cardiovascular risk as compared with Caucasians. Not "the lower, the better" but "just make it lower" could be an applicable strategy in these populations.

"The Lower, the Better" Is Still Mandatory for Selected Japanese Patients

As discussed thus far, at least for most of today's Japanese patients, regular doses of standard statins could be a sufficient therapeutic option to prevent first or recurrent onset of cardiovascular events. However, as shown in several intravascular ultrasound studies of Japanese, strong statins can reduce plaque volume in as little as 6–9 months. This property of strong statins could be shown in patients with a very high risk such as left main trunk disease, 3-vessel disease or diabetes. In the MUSASHI-PCI patient cohort, patients whose LDL-C levels were less than 75 mg/dl had less cardiovascular events as compared with those with 75–125 or >125 mg/dl (Table 3). This result is compatible with those of RCTs of Western populations with high cardiovascular risk. Therefore, "the lower, the better" could be significant for selected cases in current Japanese with a very high cardiovascular risk or maybe for most of the Japanese population in the future. Taken together, for the moment, it is possible that the concept of risk stratification as recommended in the JAS guidelines for primary prevention is also advantageous for secondary prevention. By introducing this idea for secondary prevention of Japanese populations, lipid-lowering therapy with statins could become safer, more efficient and more amenable. Table 4 shows our tentative therapeutic option for secondary prevention with lipid-lowering treatment using statins for modern Japanese patients. In this plan, patients are stratified by both baseline LDL-C level and other risk factors in a 2×2 fashion. Patients with the highest risk conditions (ie, those with higher baseline LDL-C level, with diabetes and so on) should be treated by high-dose strong statins aiming for LDL-C <75 mg/dl. For patients with at least 1 of the aforementioned 2 risk factors, target LDL-C levels less than 100 mg/dl, which meets the current guidelines, could be appropriate. Finally, for patients without any of the risk factors, statin therapy may be successful if a definite therapeutic target is not provided. The fact that statins are casually administered might be important and the concept "just make it lower" is most applicable in this patient category.

Table 3. Cardiovascular Event Rate According to the Achieved LDL-C Level at 6 Months After Statin Treatment in the MUSASHI-PCI Patient Cohort

Response to statin	Good	Moderate	Bad
Achieved LDL-C level (mg/dl)	<75	75–125	>125
Event rate (%)	1.5	10.4	10.6
P value (vs Good)	–	0.021	0.029

LDL-C, low-density lipoprotein-cholesterol; PCI, percutaneous coronary intervention.

Conclusions

It is essential for both primary and secondary prevention of cardiovascular disorders to reduce the patient's LDL-C level. For that purpose, use of statins is strongly advocated, because numerous RCTs have proved that these drugs are effective through not only their LDL-C lowering ability but also because of several pleiotropic effects. So far, there is no established evidence of the LDL-C level that is low enough for Japanese. Because we very occasionally encounter serious side-effects of strong statins in particular, we should weigh the advantages and disadvantages of the drugs in daily practice. Recent data from Japanese trials for primary and secondary prevention revealed that patients treated with statins can equally enjoy the potential to avoid cardiovascular events, whatever the achieved LDL-C level. In other words, using statins per se may bring good news without clearly targeted LDL-C levels. On the other hand, aggressive lipid lowering therapy, with strong statins used in high doses in particular, undoubtedly reduces coronary plaque volume. In this way, there is a certain percentage of patients who are favored with extremely low LDL-C levels, even among contemporary Japanese and maybe more in the future. Therefore, "just make it lower" and "the lower the better" could be complementary therapeutic concepts, at least in modern Japanese patient cohorts. Risk stratification of therapeutic recipients could be useful and practical for lipid lowering therapy with statins in primary and even secondary prevention of CVD and we should change statins according to the patients' cardiovascular risk, tolerance of strong or standard statins, and normal or high doses.

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Table 4. Proposed Therapeutic Option for Secondary Prevention for Modern Japanese Patients by Lipid-Lowering Treatment Using Statins

Pretreatment lipids levels	Coronary risk factors	
	Other than right	DM/Smoker/Obesity/CKD
Mild to moderate (LDL-C ≤160–180 mg/dl)	Normal-dose standard statins without specific target goal	High-dose standard or normal-dose of strong statins aiming for LDL-C <100 mg/dl
Moderate to severe (LDL-C >160–180 mg/dl or HDL-C <40 mg/dl)	High-dose standard or normal-dose of strong statins aiming for LDL-C <100 mg/dl	High-dose strong statins aiming for LDL-C <75 mg/dl

DM, diabetes mellitus; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol. Other abbreviation see in Table 3.

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Authors' Comments on the Pro-Side Authors

In this issue of the Circulation Journal, Miyauchi et al discuss the importance of aggressive lipid-lowering therapy using statins.[49] We agree completely with their opinion in a specific clinical setting, or for patients with higher cardiovascular risk such as Caucasians and Japanese with multiple coronary risk factors. Coronary plaque regression may bring cardiovascular risk reduction by logical or even syllogistic ways of thinking. However, at the present time, there is no definite evidence of statin treatment showing a direct relationship between cardiovascular event reduction and coronary plaque regression, which is the point on which their argument for "the lower, the better" is based. To prove that "the lower, the better" is true for Asians, we need a RCT similar to PROVE-IT[22] or TNT.[23] However, suppose such RCTs are done for Asian populations, whether fruitful results are obtained is debatable because of the relatively low absolute cardiovascular risk in Asians and the certain percentages of side-effects brought about by statins. Furthermore, discussion regarding recommended LDL-C treatment targets is still ongoing, even in Western countries where the RCTs were conducted.[50] For the moment, "the lower, the better" is not always true for Asians.