1. The Relationship between Hyper-LDL Cholesterolemia and Cardiovascular Disease in the Elderly

The mortality from cardiovascular disease (CVD) increases with age. In 2009, the annual mortalities from acute myocardial infarction per 100,000 Japanese population were 12.4 and 18.4 in people aged 50 to 54 years and 55 to 59 years, respectively. These rates were 127.8 in people aged ≥65 years and 215.0 in the elderly aged ≥75 years, i.e. 10-fold higher than in people aged 50 to 59 years. The mortalities from cerebral infarction per 100,000 Japanese population were 2.6 and 5.8 in people aged 50 to 54 years and 55 to 59 years, respectively, compared with the remarkably higher values of 242.7 and 460.6, respectively, in people aged ≥65 years and ≥75 years.

Epidemiological studies in Western countries have revealed that hyper-LDL cholesterolemia is a risk factor for coronary artery disease (CAD) in the elderly (primarily the young elderly, aged 65 to 74 years) as well as in adults aged <65 years. The NIPPON DATA80 from the Japanese population revealed that the relative risk of death from CAD increases with increases in the LDL-cholesterol (LDL-C) levels in people aged 30 to 60 years, as well as in elderly men aged ≥61 years. On the other hand, many of the studies in the elderly aged ≥75 years reported that there was no relationship between the LDL-C level and the risk of CAD. A meta-analysis of prospective studies (a total of 61 studies) including about 900,000 adult men and women without preexisting disease conducted in Western Europe and North America showed that cardiovascular deaths (due to ischemic heart disease, cerebrovascular disease and other causes) were observed in 55,000 adults during the observation period. The elderly (aged 70 to 89 years) subjects in this study also showed a significant correlation between the total cholesterol (TC) level at the start of observation and the risk of coronary death, although it was not as strong as in younger adults.

In Western countries, there is controversy regarding the relationship between the LDL-C level and stroke. The NIPPON DATA80 showed no relationship between the mortality from stroke and LDL-C in the elderly. In addition, in elderly Japanese subjects with diabetes mellitus (DM), no relationship between hyper-LDL cholesterolemia and stroke was observed; however, a relationship between hypo-HDL cholesterolemia and stroke was noted in this study.

The cholesterol levels in elderly Japanese tend to increase, and the cholesterol levels in people in their 70s increased from 198.3 to 201.2 mg/dL for men and from 210.5 to 222.0 mg/dL for women during the 10-year period from 1989 to 1998. The medical treatment recipient ratio for dyslipidemia increases with age and peaks in the patients aged 65 to 74 years at a rate of 76.2 per 1,000 people. It has been speculated that many elderly people will maintain the risk factors for atherosclerosis that they developed in middle age due to the Westernization of their lifestyle.

The management of dyslipidemia in the elderly is an increasingly important issue, as demonstrated by the inclusion of a chapter on the elderly in the ESC (European Society of Cardiology)/EAS (European Atherosclerosis Society) Guidelines for the management of dyslipidaemias published in 2011.
2. The Efficacy of LDL-C-Lowering Therapy for Preventing Cardiovascular Disease in the Elderly

1) The Efficacy for Preventing CAD

A sub-analysis of secondary prevention studies in Western countries, such as the 4S23) and CARE24) studies, revealed that statin therapy is effective for preventing CAD in elderly patients with hyper-LDL cholesterolemia. Subsequently, the Heart Protection Study (HPS) in both primary and secondary prevention patients25), the ASCOT-LLA study in primary prevention patients with hypertension26), and a sub-analysis of the JUPITER study in primary prevention patients without a history of DM and with normal LDL-C levels (<130 mg/dL) but high hsCRP levels (≥2 mg/L)27) reported that statin treatment was effective for preventing CAD in the elderly, similar to younger adult patients. A meta-analysis of a primary prevention study (WOSCOPS28) and secondary prevention studies (CARE29) and LIPID30)) showed that statin therapy in the elderly (aged 65 to 75 years) decreased the risk of CAD (death from CAD + nonfatal myocardial infarction) by 26%, which was almost equal to the 21% reported in patients aged 55 to 64 years31).

Many of these sub-analyses of the elderly focused on male patients. However, in the HPS, women accounted for 30% of the patients, and the efficacy of statins for preventing CAD was observed in both elderly men and women. A sub-analysis of the HPS including patients aged ≥70 years found that statins significantly inhibit cardiovascular events. A recently published sub-analysis of the SHARP showed that combination therapy with statins and ezetimibe in patients with chronic kidney disease (CKD) aged ≥70 years inhibited the development of major CVD by 32% compared with placebo treatment32). However, it should be noted that both the JUPITER and SHARP studies were of populations with normal LDL-C levels.

The PROSPER, a large-scale clinical study performed only on the elderly, showed that three-year statin treatment in patients aged 70 to 82 years, including secondary prevention patients, decreased the risk of death from CAD + nonfatal myocardial infarction by 19%, clearly demonstrating that intervention with statins may be indicated for the elderly. A decreased risk of CAD was more clearly observed in men than in women, and in secondary prevention patients compared to primary prevention patients, but the results of the interaction analysis were not significant, and the efficacy did not differ significantly by sex or age, although the extent of the decrease in the risk of CAD did vary33).

An analysis of two groups of patients, one receiving statin treatment at the time of discharge, while the other did not, involving a total of 14,907 patients aged ≥80 years who were diagnosed with acute myocardial infarction in Sweden from 1999 through 2003, indicated that patients who received statin treatment showed significant decreases in both total mortality (relative risk ratio: 0.55; 95% CI 0.51 to 0.59) and death from cardiovascular events (relative risk ratio: 0.55; 95% CI 0.51 to 0.60), while the cancer mortality did not increase34). Although this was not a randomized prospective study, this study supports the efficacy of statins for secondary prevention in patients aged ≥80 years.

In the PATE study, a therapeutic study performed on the elderly in Japan, elderly patients with moderate hyper-LDL cholesterolemia (aged ≥60 years) were divided into two groups of patients who received either low-dose statins or high-dose statins, and were followed up for a mean of 3.9 years. The results showed that the incidence of cardiovascular events was significantly lower in patients who received high-dose statins with lower LDL-C levels, and that the efficacy was greater in patients without DM and with a history of CVD35). In the PATE study, women accounted for 80% of patients, and the results suggest the significance of the management of CVD in elderly Japanese women with hyper-LDL cholesterolemia. The MEGA study showed that the hazard ratio for the risk of CAD was 0.50 (p=0.016) and the hazard ratio for the risk of CAD + cerebral infarction was 0.50 (p=0.003) in women aged ≥60 years, and that statin therapy is effective in elderly Japanese women with hyper-LDL cholesterolemia36).

The KLIS study reported that higher LDL-C levels after treatment are associated with an increased relative risk of CAD in the elderly aged ≥65 years37). A sub-analysis of the J-LIT in the elderly (aged 65 to 70 years), 80% of whom were women, showed that higher LDL-C levels after statin therapy were associated with an increased relative risk of the initial development of CAD, and that the absolute risk is higher than that in younger adults at any LDL-C level38, 39). Although no large-scale secondary prevention study in elderly Japanese has been conducted, a small-scale observational study reported that statins are effective for preventing recurrence even in elderly patients with CAD without high LDL-C levels40).

A meta-analysis of 52,351 elderly patients who received intervention with statins alone showed that the total mortality, death from CAD, fatal/nonfatal myocardial infarction and fatal/nonfatal stroke rates were decreased respectively by 15%, 23%, 26% and 24%, while the incidence of cancer did not increase41.

A meta-analysis of 26 randomized prospective inter-
vention studies in 170,000 primary and secondary prevention patients showed that statins were effective for preventing cardiovascular events in both patients aged 65 to 74 years and patients aged ≥75 years. A meta-analysis of the risk of death from CAD in a secondary prevention lipid-intervention study including the elderly aged ≥65 years showed that the efficacy of secondary prevention in the elderly was greater than that estimated from the results of younger adults. Meanwhile, a meta-analysis restricted to primary prevention studies showed no difference between patients who received statin treatment and those who did not in terms of the total mortality, major cardiovascular events and major cerebrovascular events in patients aged ≥65 years. These findings indicate that statin therapy appears to be effective for primary prevention in younger elderly Japanese men and women, but further global evidence should be accumulated in the future to confirm these findings.

2) Efficacy for Preventing Cerebrovascular Disease
A sub-analysis of the elderly in the CARE study in patients with a history of CAD showed that statin treatment decreased the risk of stroke by 40% (p = 0.03). A sub-analysis of the combined data from the WOSCOPS, CARE and LIPID studies also showed that statin treatment significantly decreased the risk of stroke in elderly patients aged ≥62 years. However, the WOSCOPS, a primary prevention study, showed no significant decrease in the risk of stroke. These studies primarily included men, and did not investigate the effectiveness in elderly women. In contrast, in the HPS, women accounted for 30% of patients, and statin treatment significantly decreased the risk of stroke (especially cerebral infarction). This was also clear in the elderly aged ≥70 years and was observed in both men and women. Meanwhile, the PROSPER study showed that statin treatment significantly inhibited the risk of transient ischemic attack (TIA) in the elderly, but was not effective against stroke as investigated by sex or by type of prevention (primary and secondary).

A sub-analysis of the KLIS study showed that higher LDL-C levels after treatment were associated with an increased relative risk of cerebral infarction in men aged ≥65 years. A sub-analysis of the J-LIT revealed that male gender, aging and high LDL-C levels were associated with the risk of cerebral infarction in primary prevention patients. A sub-analysis of women in the MEGA study showed that the hazard ratio for the risk of cerebrovascular accident in patients who received statin therapy aged ≥60 years was significantly decreased, with a value of 0.42 (p = 0.012).

As described above, there is controversy over whether statin therapy is effective for preventing stroke in primary and secondary prevention for elderly patients with CAD; however, for elderly Japanese whom stroke frequently occurs, an increasing number of studies have suggested that decreased LDL-C levels resulting from statin therapy are associated with a decreased risk of stroke in both male and female primary prevention patients with hyper-LDL cholesterol. Meanwhile, regarding the prevention of events after stroke or TIA, a sub-analysis of the SPARCL study showed that statins are effective for preventing stroke, TIA and major cardiovascular events in the elderly, similar to non-elderly adults. Although there have been no results indicating that statins are effective for preventing recurrence after cerebrovascular disease in Japanese patients, statin therapy should also be considered in the elderly to prevent the recurrence of cerebral infarction. In any case, a history of cerebral infarction increases the risk of developing cerebral infarction and CAD and vice versa; thus lipid-lowering therapy can help to prevent the development of both cerebral infarction and CAD. Moreover, the therapy is effective for preventing the development of other vascular diseases, such as peripheral arterial disease (PAD).

3. Management of the Elderly
In order to prevent CVD and maintain the QOL in the elderly, it is important to manage their dyslipidemia, especially hyper-LDL cholesterolemia, because it is an important risk factor. As described previously, in elderly Japanese with hyper-LDL cholesterolemia, statin therapy has been shown to be potentially effective in preventing CAD for both men and women. The absolute risk of CAD in the elderly is higher than that in younger adults. Therefore, the efficacy of treatment for hyper-LDL cholesterolemia for preventing CAD in the elderly is considered to be equal to or better than that in younger adults. Cerebrovascular disease, especially cerebral infarction, is a more common cause of death and being bedridden in Japanese people than in Westerners. Treatment for hyper-LDL cholesterolemia in elderly Japanese is therefore also expected to be effective for preventing cerebral infarction in both men and women.

Based on the study results that have been reported to date, including a meta-analysis in foreign countries, it is appropriate to manage dyslipidemia in the younger elderly (aged ≥65 years) using the same criteria as are used for younger adults. The treatment of patients who have been managed from adulthood according to the guidelines for the prevention of ath-
erosclerotic CVD should basically be continued into old age.

4. Points to Consider when Treating the Elderly

When treating the elderly, there are many points to consider, including the presence of multiple other diseases that will affect the prognosis, the latency of organ damage, the atypia of symptoms, decreased organ reserve and decreased drug-metabolizing capacity. In addition, although the basis of the treatment for dyslipidemia is dietary therapy and exercise therapy, in the elderly, strict dietary therapy may worsen the nutritional status and encouragement of exercise therapy may cause orthopedic disorders. Drug therapy should therefore be performed with extreme caution due to the fact that adverse drug reactions are more likely to occur in the elderly due to both their decreased drug-metabolizing capacity and their likelihood of taking multiple medications. Treatment based on the status of each patient is more necessary in elderly patients than in younger adults. It should also be noted that secondary hyperlipidemia due to the presence of hypothyroidism or other conditions frequently occurs in the elderly.

Few studies have been performed on the management of dyslipidemia in the very old. There have been reports that high TC or LDL-C levels are associated with longevity in the oldest old. However, in the very old secondary prevention patients with CAD who are highly engaged in social activities, drug therapy should be considered at the discretion of their attending physician. It is appropriate to consider the condition of each patient and to take a flexible approach at the discretion of the attending physician. The prevention of CVD in the elderly is an important issue in Japan, a country with a high life expectancy, and further studies are warranted.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 15) published in Japanese in June 2012.

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