Committee Report 9

Elderly Patients

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1. Relationship between the Elevated LDL-Cholesterol and Atherosclerotic Diseases in the Elderly

Aging of the Japanese population is accelerating, and elderly people aged 65 or older accounted for 19.5% of the total population according to the national demographic survey in 2004¹⁾. The mortality rate due to atherosclerotic diseases increases with age. The number of deaths due to acute myocardial infarction per 100,000 of the population was 14.7-21.9 in the 50s but was 7 times higher at 89.5-151.3 in the 70s; that due to cerebral infarction increases by more than 20 times from 4.1-7.7 to 105.6-244.0¹⁾.

Epidemiological studies in Western countries showed the importance of elevated LDL-cholesterol level as a risk factor of coronary artery disease (CAD) in the elderly (primarily in those aged 65-74 years) as well as in younger adults²⁻⁷⁾. Study in Japanese subjects (NIPPON DATA80) also showed that the relative risk of death due to CAD increases with increasing of LDL-C level in elderly males aged 61 or older, as in people aged 30-60 years⁸⁾. In contrast, many studies in the subjects in late old age (≥ 75 years) have denied an association between the LDL-C level and risk of CAD⁹⁻¹¹⁾.

The relationship between LDL-C and cerebral infarction is uncertain in Western countries¹²⁻¹⁴⁾, no evaluation restricted to elderly subjects has been conducted. According to NIPPON DATA80, no association was observed between the mortality rate due to stroke and the LDL-C level in elderly Japanese people⁸⁾.

The total cholesterol level in the Japanese elderly is increasing, and that in people in their 70s increased from 198.3 to 201.2 mg/dL in males and from 210.5 to 222.0 mg/dL in females during the past 10 years between 1989 and 1998¹⁵⁾. Proportion of the consultation rate of clinics and hospitals due to dyslipidemia

increases with age and reaches a peak of 76.2 per 1,000 people in those aged 65-74 years¹⁾. With westernization of the lifestyle, many elderly people are considered to retain risk factors of atherosclerosis which acquired in their middle age. Although the management of dyslipidemia in elderly people has become an important issue, diagnostic and therapeutic guideline for the elderly has not been proposed in Japan and in Western countries.

2. Preventive Effect of Statin Therapy on Atherosclerotic Diseases in the Elderly with Elevated LDL-Cholesterol

1) Effect of Statin on CAD

The sub analysis of secondary prevention studies performed in Western countries such as 4S¹⁶⁾ and CARE showed that statin therapy have a preventive effect on CAD in the elderly with elevated LDL-cholesterol level¹⁷⁾. Administration of statin showed a reduction of CAD risk in elderly patients, similar to that in the younger adult patients, by studies such as HPS¹⁸⁾, which included both patients with primary and secondary prevention cases, and ASCOT-LLA¹⁹⁾, in which the subjects were primary prevention cases with hypertension. Meta-analyses of primary (WOSCOPS²⁰⁾) and secondary (CARE²¹⁾, LIPID²²⁾) prevention studies using statins indicated that statin therapy reduces the risk of CAD (fatal CAD + non-fatal myocardial infarction) by 26% in elderly people aged 65-75 years, and that this figure is similar to 21% in those aged 55-64 years²³⁾. Statins have been shown as effective for the prevention of CAD in both males and females with higher LDL-C level. Many of these studies in elderly subjects primarily concerned males, but HPS, in which 30% of the subjects were females, showed that statins are effective for the prevention of CAD in females as well as males.

PROSPER was the first clinical trial of statins for

the elderly alone, and was performed in the subjects aged 70–82 years including with a history of cardiovascular diseases. The LDL-C level decreased by 34%, and the risk of death due to CAD + non-fatal myocardial infarction significantly decreased by 19% after 3-year treatment with pravastatin²⁴. The study clarified that the therapeutic strategy for younger adult can also be applied to elderly patients.

The decrease in the risk of CAD was clear in males than females and in secondary than primary prevention, but these differences were not significant²⁴. Thus, statins are effective for reducing the risk of CAD regardless of gender or age. Studies in Western countries have shown that pravastatin is effective for the primary and secondary prevention of CAD in elderly patients with elevated LDL-cholesterol level in males. Evidence in females is not as well-established as in males.

A therapeutic study using pravastatin was also performed in elderly Japanese patients. In PATE, elderly patients (aged 60 years and older) with moderate higher LDL-cholesterol level were divided into low- and high-dose pravastatin groups and followed up for a mean of 3.9 years. The incidence of cardiovascular events was significantly lower in the high-dose group, which showed a greater decrease in the LDL-C level, and this effect was particularly notable in non-diabetic patients and patients with a history of cardiovascular disorders²⁵. Since females occupied 80% of the PATE subjects, the results may indicate the significance of the management of atherosclerotic diseases in elderly Japanese females with elevated LDL-cholesterol level.

In MEGA, which evaluated the primary preventive effects of dietary therapy and pravastatin on cardiovascular diseases in females after menopause to the age of 70 years and males aged 40–70 years, the hazard ratio of CAD risk was reduced to 0.67 in the pravastatin compared with the dietary therapy group²⁶. In this study, 68% of the subjects were postmenopausal women. In females aged 60 or older, the hazard ratio of CAD risk was reduced to 0.50, and that of CAD + cerebral infarction to 0.50, by pravastatin, indicating the effectiveness of treatment in elderly Japanese females with elevated LDL-cholesterol level²⁷. In KLIS, the primary prevention effects of CAD between pravastatin and other treatments in adult Japanese males were compared. The relative risk of CAD increased with elevations in the LDL-C level after treatment in subjects aged 65 years or older²⁸. Sub analysis of the J-LIT, in which 80% of the elderly subjects (aged 65–70 years) consists of females, showed that the relative risk of the occurrence of the first episode of CAD in-

creased with elevations in the LDL-C level after simvastatin treatment, and that the absolute risk was higher in older subjects than in the younger adult at all LDL-C levels²⁹. No large-scale secondary prevention study has been performed in elderly Japanese subjects. Smaller observational studies, statins was shown to prevent recurrence of CAD in the elderly subject whose the LDL-C was not elevated³⁰.

Thus, the effectiveness of statin treatment on the primary prevention of CAD is being established in elderly Japanese males and female with elevated LDL-C level, but that of secondary prevention remains conclusive.

2) Prevention of Stroke

An elderly sub analysis of CARE, in which the subjects with a history of CAD was examined, pravastatin treatment was shown to reduced the risk of stroke by 40%¹⁷. In sub analysis of the results of WOSCOPS, CARE, and LIPID, the risk of stroke was significantly reduced following pravastatin treatment in the elderly aged 62 or older³¹. However, in WOSCOPS, no significant decrease in the risk of stroke was noted³¹. In these studies, the subjects were primarily males, and the effectiveness of treatment in elderly females was not evaluated.

HPS, in which 30% of the subjects were females, showed a significant decrease in the risk of not only CAD but also stroke (cerebral infarction, in particular) by simvastatin. Such decrease was also clear in the elderly aged 70 years or older and was observed in both males and females¹⁸. On the other hand, in PROSPER, pravastatin significantly reduced the risk of transient ischemic attack in elderly subjects, but the treatment was not effective on the risk of stroke both in males and females irrespective of primary and secondary prevention²⁴.

In KLIS, it was reported that the relative risk of cerebral infarction increased with elevated LDL-C after treatment in males aged 65 or older³². According to J-LIT subanalysis, the male sex, age, and a elevated LDL-C level were related to increased risk of cerebral infarction in subjects with primary prevention of CAD³³. In a MEGA subanalysis on females, the risk hazard ratio of stroke was significantly reduced to 0.42 in the statin-treated group aged 60 or older²⁷.

As described above, in Western countries, no consensus has been obtained as for the primary or secondary preventive effect of statins on stroke in the elderly patients with CAD. However, in Japanese elderly, who are considered to be more susceptible to stroke compared with people in Western countries, evidence is accumulating that LDL-C reduction with statins in

subject with elevated LDL-C without history of CAD leads to a decrease in the risk of stroke in both male and female.

3. Strategies for Treatment of Dyslipidemia in the Elderly

Aging of the Japanese population is advancing rapidly, and elderly people, who have multiple risk factors since middle age, are expected to increase. To prevent atherosclerotic cardiovascular disease and maintain the quality of life in elderly people, the management of dyslipidemia, particularly elevated LDL-C level is important.

As discussed above, it has been suggested that CAD can be prevented with statins in female as well as male elderly Japanese with elevated LDL-C. The absolute risk of CAD is higher in elderly people than in younger adults. Thus, the preventive or beneficial effect of CAD with treatment of elevated LDL-C in the elderly might be equal to, or greater than, that in younger adults. Stroke, particularly cerebral infarction, is more important as a cause of death or severe disability in Japanese than in Western populations. Management of LDL-C in elderly Japanese is also expected to be effective for the prevention of cerebral infarction in both males and females.

According to the research results obtained to date, the strategy for the management of dyslipidemia established in younger adults are considered to be applicable to the subjects in early old age (65-74 years). When the treatment has been initiated at younger age based on the Japanese guidelines for the prevention of atherosclerotic diseases, it must not be discontinued just because the patient became older.

4. The Points of Management in the Elderly Patients with Dyslipidemia

There are many points concerning in treating elderly patients, such as complication of life threatening diseases other than atherosclerotic disease, the presence of subclinical organ damage, and impairment of metabolizing ability. Diet and exercise are the basis of treatment for dyslipidemia also in the elderly, and drug therapy should not be selected as an easy option. However, in the elderly, strict diet therapy may lead to malnutrition and rigorous exercise may cause orthopedic injuries. Drug therapy must be conducted with caution to adverse reactions. Treatment adjusted to the condition of each patients is particularly important in the elderly.

There have been few studies on the management of dyslipidemia in patients in late old age. It has been reported that elevated LDL-C level is associated with

longevity in very old people¹¹⁾. However, in socially active people in late old age with CAD, drug therapy may be continued or initiated. Flexible approaches after sufficient evaluation of each patients are recommended.

The Japanese Research group involved in the "Long-Term Outcome Study of Hyperlipidemia in the Elderly", Comprehensive Scientific Research on Longevity has proposed the following 2 points concerning the management of dyslipidemia in elderly people: (1) In people in early old age, dyslipidemia should be managed based on the same Japanese guidelines for the prevention of atherosclerotic disease as those for younger adults; and (2) in people in late old age, the management should be left to the judgment of attending physicians³⁴⁾.

Prevention of atherosclerotic disease in the elderly is an important issue because of advanced longevity in Japan, and further researches are necessary.

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