Table 1. Inhibitory Effects of Decreased LDL-C Levels by Statins on Vascular Events (per mmol/L reduction)

End points	Any major coronary events	0.77 (0.74-0.80)
	Hemorrhagic stroke	1.05 (0.78-1.41)
	Presumed ischemic stroke	0.81 (0.74-0.89)

[Modified from Cholesterol Treatment Trialists' Collaborators. Lancet, 2005; 366: 1267-1278]

ease is hypertension, it is important to first control blood pressure. Atrial fibrillation is a major risk factor for cardiogenic embolism, and cerebral aneurysm is a significant risk factor for subarachnoid hemorrhage. Therefore, it is necessary to appropriately manage these risk factors. The management of these risk factors should be performed with reference to the relevant guidelines[39].

In Western countries, according to the results of a meta-analysis of prevention studies, lipid-lowering therapy is recommended to prevent noncardiogenic cerebral infarction[7, 40]. In Japan, based on the fact that (1) the incidence of atherothrombotic cerebral infarction is increasing and (2) the MEGA study showed that statins are effective in preventing cerebral infarction, the lipid levels should be managed in order to prevent cerebral infarction. However, it should be emphasized again that managing other risk factors, such as hypertension and smoking, is more important than managing lipids for preventing cerebrovascular disease. It is also desirable to establish management criteria for the prevention of noncardiogenic cerebral infarction in patients with underlying atherosclerosis according to the management criteria for the prevention of ischemic heart disease.

Footnotes

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Committee Report 15

The Elderly

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

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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[1].

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[2-7]. 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[8]. 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[9-11]. 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[12].

In Western countries, there is controversy regarding the relationship between the LDL-C level and stroke[13-18]. The NIPPON DATA80 showed no relationship between the mortality from stroke and LDL-C in the elderly[8]. 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[19].

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[20]. 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[21]. 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[22].

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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 4S[23] and CARE[24] 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 patients[25], the ASCOT-LLA study in primary prevention patients with hypertension[26], 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 (WOSCOPS[28]) and secondary prevention studies (CARE[29] and LIPID[30]) 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 years[31]. 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 treatment[32]. 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 vary[33].

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 increase[34]. 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 CVD[35]. 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 cholesterolemia[36].

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 years[37]. 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 level[38, 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 levels[40].

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 increase[41]. A meta-analysis of 26 randomized prospective intervention 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[42]. 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[43]. 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[44]. 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)[24]. 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[45]. However, the WOSCOPS, a primary prevention study, showed no significant decrease in the risk of stroke[45]. 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[25]. 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)[33].

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[46]. 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[47]. 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)[36].

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 in 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 cholesterolemia. 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[48]. 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[41], 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 atherosclerotic 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[49, 50]. 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[11, 51]. 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

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Committee Report 16

Women

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

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1. Age-Related Changes in Serum Lipids in Women

Age-related changes in the serum lipid levels significantly differ between men and women. The total cholesterol (TC) and LDL-cholesterol (LDL-C) levels are higher in men than in women until the fourth decade of life; however, these levels are higher in women than in men after the fifth decade of life due to menopause. The HDL-C levels in men decrease during puberty, while in women, these levels remain higher than those observed in men at any age. The triglyceride (TG) levels are lower in women than in men, particularly at younger ages[1].

2. Frequency of Cardiovascular Disease (CVD) in Japanese Women

Epidemiological studies conducted in Okinawa and Shiga have shown that the age-adjusted incidence of myocardial infarction in women 35 to 65 years of age is approximately 20% of that observed in men[2, 3]. In women, the incidence of coronary artery disease (CAD) increases after menopause; however, the risk is still lower than that observed in men. An epidemiological study conducted in 76 workplaces in Japan (the 3M study) found that the incidence of myocardial infarction in women in their 50s is approximately 20% of that observed in men[4]. The Vital Statistics collected by the Ministry of Health, Labour and Welfare also show that mortality from myocardial infarction in women is approximately 22% to 25% among women in their 50s, 25% to 33% among women in their 60s and 41% to 48% among women in their 70s compared with the rates observed in men[5]. Death from CAD in women is delayed by approximately 10 years compared with that observed in men at almost all ages[5, 6]. However, Japanese women live much longer than Japanese men, and the rate of mortality from myocardial infarction is increasing in older women[5]. Therefore, preventing CAD in Japanese women will become important in the near future.

The age-adjusted incidence of cerebral infarction in women is also lower than that observed in men. Epidemiological studies conducted in Okinawa and Shiga have shown that the incidence of cerebral infarction in women is approximately 50% of that observed in men[2, 7], while the Hisayama study reported that the incidence of this condition in women is approximately 75% of that observed in men[8]. Therefore, the difference in the incidence of cerebrovascular disease between men and women is smaller than that of myocardial infarction. According to the Vital Statistics compiled by the Ministry of Health, Labour and Welfare, the age-adjusted mortality due to cerebral infarction in women in 2008 was 64% of that observed in men[5]. Given that the incidence of cerebral infarction is higher than that of myocardial infarction in the general Japanese population and that the difference in the incidence of cerebral infarction between men and women is smaller than that of myocardial infarction, the prevention and management of cerebral infarction is also important in women.

3. Lifestyle Factors and CVD in Women

A 14-year follow-up of approximately 84,000 U.S. women (30 to 55 years of age at entry) found that the risk of CAD (nonfatal myocardial infarction + death from CAD) was significantly decreased to 0.4 in the women with three healthy lifestyle factors, including appropriate exercise, a negative history of smoking and proper dietary habits, compared with

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that observed in the women without these healthy lifestyle factors[9]. There are few reports of large-scale studies on lifestyle and CAD in women in Japan; however, the Japanese Acute Coronary Syndrome Study (JACSS), a multicenter study of acute coronary syndrome, revealed that smoking significantly increases the risk of CAD in women and that the odds ratio in women is 8.2, which is much higher than the 4.0 observed in men[10]. The Japan Public Health Center-based Prospective Study (JPHC Study) Cohort I, which included subjects 40 to 59 years of age, also reported that the risk of CAD in female smokers is significantly high, with a value of 3.1, which is comparable to 2.9 observed in male smokers. Among men who quit smoking, the multivariate relative risk of CAD abruptly decreases to 0.1 within two years[11]. Although the effects of smoking cessation in women were not investigated due to a lack of heavy female smokers, the effects of smoking cessation in women are expected to be the same as those observed in men.

Increasing the level of physical activity, promoting healthy dietary habits and encouraging smoking cessation are important measures for preventing CAD not only in men, but also in women.

Lifestyle modification is also important for the prevention and management of cerebrovascular disease. The NIPPON DATA80 study demonstrated that smoking more than two packs of cigarettes a day increases the relative risk of stroke 4-fold in women[12] and that the risk of stroke decreases to the same level as that observed in nonsmokers following smoking cessation[12]. It has been reported that Japanese women who walk and participate in sports tend to have lower rates of mortality from cerebral infarction[13]. The Nurses' Health Study, a prospective study of 71,000 women, showed that women with one or more of five factors (a negative history of smoking, a nonobese status, appropriate exercise habits, moderate alcohol intake and healthy dietary habits) have a lower risk of developing cerebral infarction and that women with all five factors have a significantly lower risk, with a value of 0.2, compared to that observed in women with none of the five factors[14].

Therefore, lifestyle modification is important for the prevention and management of CVD in women and helps individuals avoid the need for excess doses of drugs, while also enhancing the efficacy of drugs.

4. Risk Factors and CVD in Women

A relationship between the TC levels and the risk of CAD has been reported in Japanese women, although it is slightly weaker than that observed in men[15]. The Japan Lipid Intervention Trial (J-LIT), in which women accounted for 68% of the subjects, reported that higher LDL-C levels following simvastatin treatment are associated with an increased relative risk of CAD[16]. On the other hand, the JACSS study showed that the TC level is not a significant risk factor for the development of CAD in women, although hypercholesterolemia is a risk factor for the development of CAD in both men and women <65 years of age[10].

As reported by the NIPPON DATA80 and JACSS studies[10, 17], hypo-HDL cholesterolemia, diabetes mellitus (DM) and hypertension are also important risk factors for CAD in women. Another report found that a high level of TGs also increases the risk of CAD in women[18].

Hypertension is an important risk factor for cerebrovascular disease in women as well as men. In the NIPPON DATA80 study, women with a systolic blood pressure of ≥ 180 mmHg had a 5.4-fold higher age-adjusted relative risk of stroke[19] compared with women with a systolic blood pressure of < 120 mmHg. Women with DM exhibit an increased risk of cerebral infarction up to 2-fold that observed in women with normal glucose tolerance[20]. The J-LIT study demonstrated that subjects with an LDL-C level of ≥ 160 mg/dL have a ≥ 2-fold higher relative risk of cerebral infarction compared to subjects with an LDL-C level of < 120 mg/dL and that higher TG levels and lower HDL-C levels are associated with an increased risk of cerebral infarction[21]. The risk factors for cerebral infarction in Japanese women are similar to those for CAD.

Hormone replacement therapy (HRT) has been reported to affect the risk of CVD in postmenopausal women. The results of the Heart and Estrogen/progestin Replacement Study (HERS) showed that the use of HRT in women with CAD is not effective in decreasing the risk of CAD or cerebral infarction[22, 23]. In the Women's Health Initiative (WHI), those who received HRT (conjugated estrogen at a dose of 0.625 mg/day + medroxyprogesterone acetate at a dose of 2.5 mg/day) exhibited a relative risk of developing CAD of 1.2 [24] and a relative risk of developing cerebral infarction of 1.4 [25], rates that were significantly higher than those observed in the women treated with a placebo. HRT containing conjugated estrogen alone was found to significantly increase the risk of cerebral infarction 1.6-fold[26].

Based on the results of the WHI, the Japan Society of Obstetrics and Gynecology states that, in order to prevent CVD, the use of HRT with the continuous administration of the above prescription is not recommended in women with risk factors (obesity, hypertension, a smoking habit, etc.)[27]. However, since estrogen is apparently effective in improving lipid metabolism and the vascular function, this recommendation does not deny the efficacy and safety of HRT (the type and dose of hormones used, route of administration, etc.) other than that administered in the WHI. Therefore, these issues require further investigation[27].

5. Primary and Secondary Prevention of CAD and Cerebrovascular Disease in Women

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) found that lipid-lowering therapy containing lovastatin is more effective in inhibiting the development of CAD in women than in men. However, no statistically significant differences were observed due to the low number of events[28].

A subanalysis of women in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, in which postmenopausal women ≤70 years of age accounted for 68% of the subjects, showed that the hazard ratio for CAD in women ≥55 years of age was 0.6 (p=0.10), with no significant differences between the women treated with pravastatin and those treated with dietary therapy alone. However, the hazard ratio for CAD+ cerebral infarction in women ≥55 years of age was 0.6 (p=0.04), with a significantly lower incidence in the pravastatin group[29].

With respect to secondary prevention, the results of a subanalysis of the Scandinavian Simvastatin Survival Study (4S) showed that lipid-lowering therapy is effective in preventing CAD events in women at an equal level to that observed in men[30]. Similarly, the Cholesterol and Recurrent Events Trial (CARE) showed that lipid-lowering therapy with pravastatin is more effective in preventing CAD events in women than in men[31]. Although there were no statistical differences, the relative risk of death from CAD associated with lipid-lowering therapy in women calculated from three studies (the Scottish Society of Physicians, Newcastle upon Tyne and 4S) was 0.4 [32], thus indicating that appropriate treatment is required for secondary prevention in women as well as men.

In Japan, there is little evidence of a risk for CAD among premenopausal women with dyslipidemia. This is because quite a small number of cases of CAD occur in premenopausal women. Previous studies conducted in Japan have shown that even if a diagnosis of CAD is suspected in premenopausal women, no significant stenosis is observed on coronary angiography in many cases and that CAD caused by vasculitis or aortitis due to systemic lupus erythematosus (SLE), not atherosclerosis, may be detected[33].

On the other hand, the results of the Chicago Heart Association Detection Project Industry study conducted in the U.S. found that, among women with no risk factors (a TC level of <200 mg/dL, a blood pressure of <120/80 mmHg and a current non-smoking status), the relative risk of CAD is 0.27, even among middle-aged women 40 to 59 years of age, which is significantly lower than that observed in women with these risk factors, and that total mortality is also significantly decreased[34]. The results of this cohort study showed that even premenopausal women with three healthy lifestyle factors, including proper dietary habits, appropriate exercise habits and a non-smoking status, can decrease their risk of developing CAD to less than half of that observed in women without these habits[9].

The most important risk factor for cerebrovascular disease is hypertension, regardless of sex[19, 35], and controlling hypertension is essential for preventing cerebrovascular disease. The NIPPON DATA80 study reported that the estimated decrease in mortality from stroke associated with a decrease in the mean blood pressure of 1 mmHg is 4.3% in men and 2.2% in women[19].

A subanalysis of the MEGA Study revealed that statins are effective in the primary prevention of stroke in Japanese women. In that study, the risk of developing cerebral infarction in women ≥55 years of age in the pravastatin group significantly decreased by 53% compared with that observed in the women who received dietary therapy alone[29]. The effectiveness of high-dose statins in the secondary prevention of stroke was investigated in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. No efficacy was observed in preventing the recurrence of nonfatal cerebral infarction; however, the risk of recurrence of fatal cerebral infarction significantly decreased by 73% in women[36].

The incidence of CAD in women in Japan is much lower than that observed in Western countries[37]. Moreover, controlling hypertension has been reported to decrease the incidence of cerebrovascular disease[37]. On the other hand, new concerns are emerging regarding the increasing risk of CVD due to the Westernization of dietary habits, lack of exercise and a gradual increase in the number of female smokers in their 20s and 30s. Taking into consideration further aging, it is important to introduce healthy lifestyle and control risk factors for the development of atherosclerosis from a younger age, even in women.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 16) published in Japanese in June 2012.

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Committee Report 17

Diagnosis of Atherosclerosis

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

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From the perspective of preventing atherosclerotic cardiovascular disease (CVD), it is essential to determine the presence or absence and degree of atherosclerosis before the development of clinical symptoms and to manage or treat risk factors in order to prevent progression or achieve regression of disease. It is necessary to diagnose whether atherosclerosis is present, and if so, to what extent. The diagnostic techniques for atherosclerosis employed in the primary prevention of CVD should be noninvasive. In secondary prevention, however, the use of invasive diagnostic techniques, including angiography, is necessary. Currently, morphological imaging tests are predominantly used to assess the presence and degree of atherosclerosis.

1. Ultrasonography

Noninvasive imaging tests include body surface ultrasonography (a high-frequency probe of ≥7 MHz), which enables observation of the degree of stenosis and plaque formation (localized atherosclerotic lesions) in the peripheral arteries, such as the carotid arteries and arteries of the lower extremities. In particular, in the carotid arteries, ultrasonography is used to determine the degree of stenosis quantitatively and detect vulnerable plaques that could cause cerebral embolism, thereby assessing the degree of systemic atherosclerosis and/or functioning as an alternative predictor of the presence or development of CVD (e.g., coronary artery disease (CAD), peripheral arterial disease (PAD) or cerebrovascular disease)[1, 2]. The existence of plaques and intima-media complex thickness (IMT) is often used as a measurement index on carotid ultrasonography[3]. Ultrasonography is also useful for making the diagnosis of atherosclerotic renal artery stenosis[4].

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2. Computed Tomography (CT)

Multidetector row CT (MDCT) offers superior imaging speed and spatial resolution and enables visualization of the coronary arteries following the injection of contrast medium into peripheral veins. This technique is starting to replace coronary angiography as a diagnosing test for CAD. In particular, it is superior in specificity[5-8], and if no abnormalities are detected using this technique, the existence of organic coronary stenosis can be almost completely ruled out. In addition, this technique allows for visualization of coronary plaques, and the degree of calcification and fat and fiber content can also be estimated to some extent based on the CT number.

3. Magnetic Resonance Imaging (MRI) and MR Angiography (MRA)

MRA is used to visualize the cerebral/carotid arteries, aorta and renal arteries and enables the visualization of coronary stenotic lesions.

4. Angiography

Invasive diagnostic imaging techniques include angiographic evaluations of the degree of stenosis, which remains a central diagnostic technique for assessing arterial stenosis. The degree of arterial stenosis (the stenosis rate) is represented by the formula $(D-S)/D \times 100\%$, where D is the intravascular luminal diameter at the site proximal to the site of stenosis that appears to be normal and S is the luminal diameter at the site of stenosis. However, because intimal thickening is more or less observed even at sites that appear to be normal, the stenosis rate is underestimated considering the amount of the plaque volume. Because plaques are usually eccentric and the intravascular luminal diameter is therefore not a precise circle, there are limitations in the ability to determine the stenosis rate based on one cross-section. If there is compensatory vascular remodeling, the blood vessel may not be considered to exhibit luminal stenosis even if the plaques are well-formed; thus, there are severe limitations in establishing the plaque volume using this technique.

5. Intravascular Ultrasound (IVUS)

IVUS is a technique used to observe the arterial wall from the arterial lumen using an ultrasound device. It enables the evaluation of both the plaque volume and the properties of the plaques.

6. Angioscopy

Angioscopy is a technique used to observe the color of the plaque surface and estimate the properties of plaques.

7. Physiological Tests

Diagnostic techniques other than morphological tests include physiological tests, such as the brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI). Although these parameters are easily determined by measuring the pulse wave in the extremities using a dedicated device, it should be noted that the values function as indices of artery stiffness and do not always reflect the presence of atherosclerosis. The ankle-brachial blood pressure index (ABI), can be used to diagnose PAD in the lower extremities (<0.9 or ≥ 1.3). The techniques used to measure the vascular endothelial function impaired in the early stage of atherosclerosis include flow-mediated vasodilation (FMD), which measures and calculates changes in the vascular diameter following ischemic reactive hyperemia of the extremities using ultrasound, and strain gauge plethysmography, which electrically observes and measures changes in the volume of the arterial blood flow in the extremities as changes in the circumference using a strain gauge. However, the use of these techniques is quite limited in general practice.

If a diagnosis of CAD, particularly effort angina, is suspected, the following noninvasive tests are useful.

8. Exercise Electrocardiography

Exercise electrocardiography has been shown to have a sensitivity of approximately 70% and a specificity of approximately 75% for detecting significant coronary stenosis[9], neither of which are superior; however, since the procedure can be easily performed at a low cost, it is widely used. Because myocardial ischemia can be induced, it is important to keep in mind the risk of possible cardiac events, including ventricular fibrillation and sudden death, when performing this technique.

9. Myocardial Perfusion Scintigraphy

This technique is widely used in the diagnosis of CAD to assess disease severity, myocardial viability and the prognosis and aids in decision making concerning therapeutic strategies. It is also used to screen for significant coronary stenosis, is relatively minimally invasive and may be a useful monitoring test for preventing atherosclerosis. Stressors include exercise stress, dipyridamole stress and adenosine stress. This technique has been shown to have a sensitivity of 80% to 90% and a specificity of 70% to 95% for detecting significant coronary stenosis[10].

At present, ultrasonography is a minimally invasive, simple and easy-to-use test for diagnosing atherosclerosis. Coronary CT, exercise electrocardiography and myocardial perfusion scintigraphy are noninvasive and useful diagnostic techniques in cases in which a diagnosis of CAD is suspected.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 17) published in Japanese in June 2012.

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Committee Report Appendix

Statements

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Committee for Epidemiology and Clinical Management of Atherosclerosis

J Atheroscler Thromb, 2014; 21:299-303.

Comprehensive Risk Management for the Prevention of Cardiovascular Disease

J Atheroscler Thromb, 2013; 20:603-615.

1. In order to prevent cardiovascular disease (CVD), major risk factors, including dyslipidemia, hypertension and diabetes mellitus (DM), should be managed comprehensively from the initial stage of the disease.
2. Lifestyle modification, such as encouraging healthy dietary habits, exercise and the cessation of smoking, constitutes the basis for preventing CVD. It is important to continue to provide guidance on lifestyle modification after initiating drug therapy.

Diagnostic Criteria for Dyslipidemia

J Atheroscler Thromb, 2013; 20:655-660.

1. The incidence of coronary artery disease (CAD) increases in association with increases in LDL-C.
2. The incidence of CAD increases in association with decreases in HDL-C.
3. The incidence of CAD increases in association with increases in TG.
4. The incidence of CAD increases in association with increases in non HDL-C.

Absolute Risk of Cardiovascular Disease and Lipid Management Targets

J Atheroscler Thromb, 2013; 20:689-697.

1. In primary prevention, the management targets for LDL-C should be determined according to categories based on the absolute risk of CAD. [Recommended level IIa, evidence level C]
2. In secondary prevention, an LDL-C level of < 100 mg/dL should be targeted. [Recommended level IIa, evidence level C]
3. The target for the TG level should be < 150 mg/dL. [Recommended level IIa, evidence level C]

4. The target for the HDL-C level should be ≥40 mg/dL. [Recommended level Ⅱa, evidence level C]
5. The target for the non HDL-C level should be < management target for the LDL-C level + 30 mg/dL. [Recommended level Ⅱa, evidence level C]

Cardiovascular Disease Risk Factors Other than Dyslipidemia

J Atheroscler Thromb, 2013; 20:733-742.

1. Hypertension is a risk factor for cerebrovascular disease and CAD.
2. DM is a risk factor for CVD, such as CAD, cerebrovascular disease and peripheral artery disease (PAD).
3. Smoking is a risk factor for CAD, cerebrovascular disease and PAD.
4. Passive smoking is a risk factor for CAD and cerebrovascular disease.
5. Aging is a risk factor for cerebrovascular disease and CAD.
6. A family history of premature CAD is a risk factor for the development of CAD.

Other High-Risk Conditions

J Atheroscler Thromb, 2013; 20:785-789.

1. A history of CAD is a risk factor for CAD and cerebrovascular disease.
2. A history of non-cardiogenic cerebral infarction is a risk factor for cerebrovascular disease and CAD.
3. CKD is a high-risk condition for CAD and cerebrovascular disease.
4. PAD is a high-risk condition for CAD and cerebrovascular disease.

Treatment—Lifestyle Modification

J Atheroscler Thromb, 2013; 20:835-849.

1. Avoid smoking and passive smoking to prevent atherosclerosis. [Recommended level Ⅰ, evidence level B]
2. For the management of obesity, reduce the total energy intake and increase physical activity in order to reduce the body weight to the ideal level. [Recommended level Ⅰ, evidence level B]
3. Increase the intake of vegetables, fruit, unrefined grains, seaweed, soy products, etc. [Recommended level Ⅰ, evidence level B]
4. In order to reduce the LDL-C level, reduce the intake of saturated fatty acids and increase the intake of unsaturated fatty acids. In addition, limit the intake of cholesterol and increase the intake of dietary fiber. [Recommended level Ⅰ, evidence level B]
5. In order to reduce the TG level, reduce the intake of carbohydrates and alcohol and increase the intake of n-3 polyunsaturated fatty acids. [Recommended level Ⅰ, evidence level B]

6. In order to increase the HDL-C level, engage in moderate aerobic exercise, reduce body weight and avoid the intake of trans fatty acids. [Recommended level I, evidence level B]
7. Sustained physical activity or aerobic exercise is effective for preventing atherosclerosis. [Recommended level I, evidence level B]

Treatment—Drug Therapy

J Atheroscler Thromb, 2013; 20:850-860.

1. If a patient cannot achieve the management target for LDL-C after adequate lifestyle modification in the setting of primary prevention, drug therapy should be considered according to the weight of the patient's risk. [Recommended level IIa, evidence level B]
2. If a patient persistently has an LDL-C of ≥ 180 mg/dL in category I, drug therapy should be considered. [Recommended level IIa, evidence level C]
3. Statin therapy is recommended for the treatment of hyper-LDL cholesterolemia. [Recommended level I, evidence level A]
4. In patients with high-risk hyper-LDL cholesterolemia, the use of ezetimibe in combination with a statin should be considered. [Recommended level IIa, evidence level B]
5. In patients with high-risk hyper-LDL cholesterolemia, the use of ethyl icosapentate (EPA) in combination with a statin should be considered. [Recommended level IIa, evidence level A]
6. In patients with hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drug therapy with fibrates or nicotinic acid derivatives should be considered according to the level of the patient's risk. [Recommended level IIa, evidence level B]

Metabolic Syndrome

J Atheroscler Thromb, 2014; 21:1-5.

1. Metabolic syndrome is a high-risk condition for CVD.
2. For the treatment of metabolic syndrome, lifestyle modification is recommended. [Recommended level I, evidence level C]

Familial Hypercholesterolemia

J Atheroscler Thromb, 2014; 21:6-10.

1. Familial hypercholesterolemia is a frequent autosomal dominant disease associated with a high risk of CAD. Early diagnosis and rigorous treatment are recommended. [Recommended level I, evidence level B]
2. For the treatment of heterozygous FH, strict lipid management, primarily with statin