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.

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. 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. 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. Death from CAD in women is delayed by approximately 10 years compared with that observed in men at almost all ages. However, Japanese women live much longer than Japanese men, and the rate of mortality from myocardial infarction is increasing in older women. 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, while the Hisayama study reported that the incidence of this condition in women is approximately 75% of that observed in men. 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. 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...
that observed in the women without these healthy lifestyle factors\textsuperscript{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\textsuperscript{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 women who quit smoking, the multivariate relative risk of CAD abruptly decreases to 0.1 within two years\textsuperscript{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\textsuperscript{12} and that the risk of stroke decreases to the same level as that observed in nonsmokers following smoking cessation\textsuperscript{12}. It has been reported that Japanese women who walk and participate in sports tend to have lower rates of mortality from cerebral infarction\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{10}.

As reported by the NIPPON DATA80 and JACSS studies\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{24} and a relative risk of developing cerebral infarction of 1.4\textsuperscript{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\textsuperscript{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, hyper-
tension, 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 \(\leq 70\) years of age accounted for 68% of the subjects, showed that the hazard ratio for CAD in women \(\geq 55\) 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 \(\geq 55\) 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 \(< 200 \text{ mg/dL}\), a blood pressure of \(< 120/80 \text{ mmHg}\) 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\(^{37}\).

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 \(\geq 55\) 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.

Acknowledgements

We are grateful to the following societies for their collaboration and valuable contributions: Dr. Hide-nori Arai (The Japan Geriatrics Society), Dr. Kiminori Hosoda (Japan Society for the Study of Obesity), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Atsunori Kashiwagi (Japan Diabetes Society), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Hosoda (Japan Society for the Study of Obesity), Dr. Kiminori Arai (The Japan Geriatrics Society), Dr. Kazuhisa Tsukamoto for supporting this work.

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