Committee Report 5

Cardiovascular Disease Risk Factors Other than Dyslipidemia

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. Hypertension

Hypertension is an important risk factor for atherosclerotic cardiovascular diseases (CVDs), such as cerebrovascular disease, coronary artery disease (CAD), heart failure and chronic kidney disease (CKD). Among them, it especially exhibits a strong association with cerebrovascular disease^{1, 2)}. Hypertension is a stronger risk factor for cerebral hemorrhage than for cerebral infarction and the incidences of both cerebral hemorrhage and infarction increase in association with in the blood pressure category^{3, 4)}. The Hisayama study demonstrated that the incidence of cerebral infarction significantly increased in patients with grade 1 hypertension (140 to 159/90 to 99 mmHg) compared with that observed in patients with an optimal blood pressure (<120/80 mmHg)⁵⁾. According to “Health Japan 21” report, an increase in systolic blood pressure of 10 mmHg is associated with an increased risk of morbidity and mortality from cerebrovascular disease of 20% in men and approximately 15% in women⁶⁾.

Hypertension is also involved in the development of CAD, although the relationship is weaker than that observed with cerebrovascular disease. It has been reported that an increase in systolic blood pressure of 10 mmHg is associated with a greater risk of morbidity and mortality from CAD of approximately 15% in men⁶⁾. Furthermore, in the 19-year follow-up period in the NIPPON DATA80 study, the hazard ratio for CVD mortality significantly increased in association with a rise in blood pressure in subjects 30 to 64 and 65 to 74 years of age, as well as in the elderly ≥ 75

years of age³⁾. In the J-LIT study, the relative risk of developing CAD in primary prevention patients with hypertension was 2.5-fold for women and 2.3-fold for men compared with that observed in patients without hypertension⁷⁾.

Although blood pressure is usually measured in the office (in a medical environment), it has been reported that home blood pressure and 24-hour ambulatory blood pressure monitoring (ABPM) are more accurate in predicting the development of cardiovascular events than office blood pressure measurements⁸⁻¹⁰⁾.

The reference values for hypertension differ for office blood pressure, 24-hour ABPM and home blood pressure. Hypertension is defined as an office blood pressure of $\geq 140/90$ mmHg, a home blood pressure of $\geq 135/85$ mmHg and a 24-hour ABPM of $\geq 130/80$ mmHg¹¹⁾.

2. Diabetes Mellitus (DM)

DM is an important risk factor for CVD¹²⁻¹⁴⁾. In the Hisayama study, the relative risks of developing CAD and cerebral infarction in patients with DM were higher, with values of 2.6 and 3.2, respectively, than those observed in subjects with normal glucose tolerance¹⁵⁾. The relative risks are the same as those seen in Western patients with DM¹⁶⁾, while the absolute risks are lower than those observed in Westerners by approximately 30% to 70%^{17, 18)}. The increased risk of developing CAD due to DM is higher in women than in men¹⁹⁾. Patients with DM also have an increased risk of developing peripheral arterial disease (PAD)²⁰⁾. The risk of developing CVD increases from the onset of impaired glucose tolerance (IGT) before the development of DM^{21, 22)}; however, it is unclear

whether patients with IGT are at the same risk level as those with DM.

3. Smoking

Many reports, including the Framingham, MRFIT and Honolulu Heart Program studies, have stated that smoking is a risk factor for CAD and cerebrovascular disease²³⁻³⁰. In Japan, this finding has been reported in large-scale cohort studies, including the Hisayama³¹, Hiroshima/Nagasaki³², NIPPON DATA80 (Figs. 1 and 2)³³, JACC³⁴ and JPHC^{35, 36} studies. Smoking is also a well-known risk factor for PAD³⁷⁻⁴⁰.

Meanwhile, a meta-analysis demonstrated that even short-term passive smoking affects the platelet and vascular endothelial functions and the development of atherosclerosis and oxidative stress at levels of approximately 80% to 90% of those observed with chronic active smoking and that the relative risk of developing CAD in passive smokers is 1.3 (95% CI: 1.2 to 1.4)⁴¹. It has also been shown that passive smoking is a risk factor for stroke^{42, 43}.

The result of a meta-analysis of 25 prospective cohort studies, including four Japanese studies, that evaluated the relationship between active smoking and the incidence of type 2 DM, showed a risk of 1.4 (95% CI: 1.3 to 1.6)⁴⁴. A meta-analysis of 54 cross-sectional studies, including two Japanese studies, revealed that the HDL-C levels are significantly lower (by 5.7%) in smokers than in nonsmokers in a dose-dependent manner⁴⁵. Furthermore, it was shown that the HDL-C levels in smokers increase to those observed in nonsmokers following smoking cessation⁴⁶; thus, smoking directly affects lipid metabolism. In Japan, a cross-sectional study reported that the risk of developing metabolic syndrome in smokers increases in association with increases in the number of cigarettes smoked, while the risks observed in ex-smokers decrease in association with increases in the duration of smoking cessation⁴⁷. Moreover, a cohort study reported that the risk of developing metabolic syndrome rises in accordance with the number of cigarettes smoked⁴⁸. Among smokers with metabolic syndrome, atherosclerosis progresses and the risk of developing CAD and/or cerebral infarction increases^{49, 50}. Smoking is by itself a risk factor for CVD; it increases the risk of developing DM, dyslipidemia and metabolic syndrome and is associated with an increased risk of CVD.

4. Age and Sex

Age is a strong risk factor for CVD in Japan as well as Western countries^{51, 52}. Regarding CAD, the U.S. data⁵³, NIPPON DATA80⁵⁴, "Annual Statistical Report of National Health Conditions"⁵⁵, Hiroshima/Nagasaki³², 3M study in workplaces⁵⁶ and Takashima study in Shiga prefecture⁵⁷ studies demonstrated that the mortality and incidence of CAD increase starting from age 45 for men and age 55 for women and that the risk of CVD markedly increases in association with increases in age class.

The incidence and mortality of CAD in women are lower than those observed in men in all age classes. Considering the increased risk associated with age, the increase in the risk of CAD in women occurs more slowly, by approximately 10 years, than that observed in men^{27, 55}. In epidemiological studies conducted in Okinawa and Shiga prefectures, the age-adjusted incidence of myocardial infarction in women 35 to 65 years of age was found to be markedly lower than that observed in men^{2, 57}. The vital statistics prepared by the Ministry of Health, Labour and Welfare reported that the mortality of myocardial infarction in women is 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 to that observed in men⁵⁵. In women, the postmenopausal period is considered to reflect the point at which the risk of CAD increases. Patients who have undergone bilateral oophorectomy should be considered to be at risk of developing CAD, even if they are <55 years of age.

5. Family History

In Western countries, it has been reported since the 1970s that a family history of CAD is a risk factor for the disease⁵⁹⁻⁶⁶. A family history of CAD, especially that in a first-degree relative (parent, child, brother or sister), and a family history of premature CAD (age of onset: <55 years for men, <65 years for women) are strong risk factors for CAD.

The Framingham study reported that if at least one parent has CAD, the age-adjusted odds ratio for developing CAD was 2.6 and 2.3 for men and women, respectively, and 2.0 and 1.7 for men and women following adjustment for all variables in a multivariate analysis⁶². In Japan, the J-LIT study showed that a family history of CAD increases the relative risk of developing CAD by approximately three-fold⁷. The recent CREDO-Kyoto study also reported that a family history of CAD contributes to the development of major cardiovascular events at an early

age⁶⁷⁾.

Traditional risk factors (hyper-LDL cholesterolemia, hypo-HDL cholesterolemia, hypertension, DM and smoking) are associated with genetic predispositions and are affected by the habits of the household. In other words, a family history of CAD is considered to include both genetic and environmental risk factors, a fact that is already well known. Lp(a), small dense LDL and homocysteine have recently received attention as other risk factors to consider, all of which are genetically influenced. However, because family history remains a strong risk factor even after adjusting for all traditional risk factors in a multivariate analysis^{58, 60-62, 68)}, it is assumed that a patient's family history includes many unknown genetic factors⁶⁴⁾.

Therefore, most studies of family history have concluded that a family history of CAD is an independent risk factor for CAD, and a family history of premature CAD (age of onset: <55 years for men, <65 years for women), in particular, should be considered a risk factor.

6. Other Risk Factors or Markers to Consider

Aside from the established risk factors described above, the other parameters listed in **Table 1** have been proposed to be risk factors or markers for CVD. It should be noted that these parameters include not only factors that are true risk factors for the development of atherosclerosis, but also factors that are simply markers of atherosclerosis.

1) Lp(a)

Lp(a) is a class of LDL in which apo(a) is attached to apo B-100 by a disulfide bond. It has been reported that the plasma levels of Lp(a) as well as the size of apo(a) are independent risk factors for CAD and strokes⁶⁹⁻⁷⁶⁾. Several atherogenic properties of Lp(a) have been clarified^{78, 79)}. For example, apo(a) proteins are highly homologous to plasminogen⁷⁷⁾, promote thrombus formation by interfering with plasminogen^{80, 81)}, easily bind to oxidized phospholipids⁷⁸⁾ and tend to be anchored to the arterial wall⁸²⁾.

2) Remnant Lipoproteins

Remnant lipoproteins, which are commonly observed in patients with postprandial hyperlipidemia, have been proposed to play a pivotal role in the development of CAD⁸³⁾. Remnant lipoproteins are intermediate lipoproteins that are produced during the metabolism of chylomicrons and VLDLs and are deposited in the vascular intima, leading to the development of atherosclerosis⁸⁴⁾. The pathophysiological

conditions under which the amount of remnant lipoproteins is increased include familial combined hyperlipidemia, familial type III hyperlipidemia, DM and metabolic syndrome.

3) Small Dense LDL

Small dense LDL particles^{85, 86)} are subfractions of LDL particles that are small in size and high in density. Many reports have shown that increased levels of small dense LDL are related to CAD⁸⁷⁻⁹¹⁾ and associated with PAD and aneurysm formation^{92, 93)}. The proposed mechanisms underlying the strong atherogenicity of small dense LDL include the following: small dense LDL particles are easily oxidized⁹⁴⁾ and processed by pathways other than those for LDL receptors⁹⁵⁾; and the particles are easily incorporated into the arterial wall⁹⁶⁾ where they tend to bind to the matrix⁹⁷⁾. The presence of small dense LDL is closely associated with hypertriglyceridemia and hypo-HDL cholesterolemia⁹⁸⁾. An increase in the level of small dense LDL is found in conditions such as type 2 DM, metabolic syndrome and insulin resistance⁹⁹⁾.

4) Oxidized LDL and MDA-LDL

Oxidized LDL, in which lipids (e.g., phospholipids) and apolipoproteins are oxidatively modified, is involved in a broad range of processes related to atherosclerosis, such as vascular endothelial cell injury, enhancement of infiltration of monocytes into the vessel walls and foam cell formation. Assays to measure the level of MDA-LDL, a class of oxidized LDL in which apoB-100 is modified by malondialdehyde (MDA), are commercially available.

5) Apo B

Apo B is an apolipoprotein contained in atherogenic lipoprotein particles, such as LDL and remnant lipoproteins. Because there is one apo B molecule per lipoprotein particle, the apo B level is proportionate to the number of atherogenic lipoprotein particles. Therefore, even if the LDL-C level remains constant, an increase in the number of LDL particles caused, for instance, by the existence of small dense LDL particles will result in a higher level of apo B. A meta-analysis of epidemiological studies revealed that the apo B level is a stronger marker of cardiovascular events than the levels of LDL-C and HDL-C¹⁰⁰⁾.

6) Ratios of Lipids and Apoproteins

The lipid levels, such as those of LDL-C and HDL-C, are strong risk factors for the development of CVD; however, several studies have proposed that the proportion of cholesterol in each lipoprotein or the

ratio of apolipoproteins, i.e., the TC/HDL-C ratio, the non HDL-C/HDL-C ratio, the LDL-C/HDL-C ratio and the apo B/AI ratio, may be stronger markers of CVD than the lipid or apolipoprotein levels themselves¹⁰¹⁻¹⁰⁴). It should be noted that most of these data are derived from Western countries; thus, in Japan, the current management goals should be evaluated using the absolute value of each lipid level.

7) CRP and Inflammation-Related Markers

Inflammation plays an important role in the formation of atherosclerotic lesions^{105, 106}. C-reactive protein (CRP) is an acute-phase protein that is usually used as an inflammatory marker. It has recently been reported that the high-sensitivity CRP (hsCRP) level observed under a steady state can be used as a marker for the primary/secondary prevention of CAD¹⁰⁷⁻¹¹². It has also been reported that the CRP level is an independent risk factor for CAD, cerebral infarction and vascular death and is a stronger marker than systolic blood pressure or the non HDL-C level¹¹³. However, an analysis of CRP genotypes in patients with CAD revealed that the genotypes that result in high levels of CRP are not associated with the development of CVD; thus, CVD is considered to be associated with the inflammatory state reflected by the CRP level¹¹⁴.

Similar to CRP, Lp-PLA2, an enzyme produced in atherosclerotic lesions, and amyloid A, an acute-phase protein, have been reported to be markers of CVD^{110, 115, 116}. Infections with organisms such as *Chlamydia pneumoniae* and cytomegalovirus have been proposed to be related to the development of atherosclerosis via the effects of local and/or systemic inflammation¹¹⁷. A recent study also indicated that periodontal disease is associated with atherosclerosis¹¹⁸.

8) Homocysteine

Many reports have indicated that increased plasma levels of homocysteine are a risk factor not only for CAD, but also for strokes and PAD¹¹⁹⁻¹²¹. For example, the Physicians' Health Study showed that increased homocysteine levels are associated with an increased relative risk of myocardial infarction¹²². In addition, a recent analysis suggested that homocysteine is a stronger predictor of cardiovascular events than CRP¹²³. On the other hand, the administration of vitamin supplementation therapy to lower the plasma homocysteine levels fails to reduce the incidence of cardiovascular events¹²⁴. Furthermore, a recent study clarified that there is no relationship between CVD and gene mutations that genetically increase the plasma homocysteine levels¹²⁵. Therefore,

further investigations are warranted to determine whether the plasma levels of homocysteine are simply a marker or a true causal risk factor for CVD.

9) Blood Coagulation and Fibrinolytic Factors

Plaque rupture and subsequent thrombus formation are important events in the pathogenesis of CAD¹²⁶. Fibrinogen, a coagulation factor, has been shown to be a risk marker for CVD since the 1970s¹²⁷. The fibrinogen level is correlated with other risk factors, such as age, the smoking status, the LDL-C level and the physical activity level¹²⁸; however, even when corrected for these factors, the fibrinogen level has been shown to be a marker of CVD¹²⁹⁻¹³². It has also been proposed that fibrinolytic factors, such as t-PA¹²⁹ and PAI-1⁷⁸, are involved in the pathogenesis of CVD. The PAI-1 level is associated with the severity of several conditions, including visceral fat accumulation and insulin resistance^{133, 134}; thus, it has been speculated that the presence of these conditions affects the association observed between the PAI-1 level and the development of CAD. The activities of coagulation and fibrinolytic factors are thought to be linked with each other, thereby contributing to the formation of atherosclerotic lesions¹³⁵.

Footnotes

This is an English version of the guideline from the Japan Atherosclerosis Society (chapter 5) published in Japanese in June, 2012.

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Fig. 1. Relative Risks (with 95% CI) of Death from Cerebrovascular Diseases Associated with Smoking, Follow-up of 51,774 man-years, the NIPPON DATA80.

The data were adjusted for age, systolic blood pressure, BMI, the TC level, alcohol intake and DM.

CI: Confidence interval

*: $p < 0.05$ compared with nonsmoker group

Schematic diagram obtained from Ueshima H et al. Stroke. 35: 1836-1841, 2004

Fig. 2. Relative Risk (with 95% CI) of CAD-related Death Associated with Smoking, Follow-up of 51,774 man-years, the NIPPON DATA80.

The data were adjusted for age, systolic blood pressure, BMI, the TC level, alcohol intake and DM.

CI: Confidence interval

*: $p < 0.05$ compared with nonsmoker group

Schematic diagram obtained from Ueshima H et al. Stroke. 35: 1836-1841, 2004

Table 1. Risk Factors or Markers to Consider

Lipid-related factors/markers	Non-lipid factors/markers
• Lp(a) • Remnant lipoproteins • Small dense LDL • Oxidized LDL and MDA-LDL • Apo B • Ratio of lipids or apoproteins	• C-reactive protein (CRP) • Inflammation-related markers • Homocysteine • Coagulation/fibrinolytic factors

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