Committee Report 12

Diabetes Mellitus

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


Committee for Epidemiology and Clinical Management of Atherosclerosis

1. Importance of Diabetes Mellitus as a Risk Factor for Cardiovascular Disease

Diabetes mellitus (DM) is an important risk factor for cardiovascular disease (CVD)\(^1\)-\(^3\). A meta-analysis of data from Western countries showed that the risks of coronary artery disease (CAD) and cerebral infarction due to DM after adjustment for multiple factors, including sex, age and blood pressure, are 2.0 and 2.3, respectively\(^4\). In Japan, the NIPPON DATA80 showed that the risk of death from CAD in patients with DM is 2.8, which is significantly higher than it is for non-DM subjects\(^5\). The Hisayama study showed that the risks of CAD and cerebral infarction after adjustment for multiple factors, including patient sex and age, in patients with DM are 2.6 and 3.2, respectively\(^6\). Although there have been few investigations in Japan, the incidence of CAD in Western patients with type 1 DM is higher\(^9\), especially in patients with nephropathy\(^10\).

CAD in patients with DM is characterized by (1) a higher prevalence of silent myocardial ischemia\(^11\), (2) multivessel lesions, (3) high-grade and diffuse lesions\(^12, 13\) and (4) calcified lesions\(^14\). Cerebral infarction is characterized by increased lacunar infarction and atherothrombotic cerebral infarction\(^15, 16\). The CVD prognosis in diabetic subjects is poor relative to nondiabetic subjects\(^17, 19\), and the recurrence rate of cerebral infarction in patients with DM is higher\(^20, 21\).

Patients with DM are at a higher risk of peripheral arterial disease (PAD), and 20% of patients with PAD symptoms are diabetic. Furthermore, one report found that the risk of intermittent claudication is 2.6-fold higher in patients with DM\(^22\).

Although the risk of CVD in women is lower than in men, women with DM have a higher relative CVD risk than men with DM\(^23, 24\). The results of the Japan Diabetes Complications Study (JDCS) showed that the absolute risks of CAD in Japanese patients with DM were 11.2/1,000 person-years for men and 7.9/1,000 person-years for women, which is still higher in men than in women\(^8\).

The risk of CVD increases after reaching the stage of impaired glucose tolerance (IGT), even before the onset of DM\(^25, 26\). The Hisayama study showed that the relative risk of CVD in patients with IGT compared to normal subjects is 1.9, although it is lower than the risk of 2.6 in diabetic subjects\(^9\). Instead of the fasting blood glucose level, the blood glucose levels at 2 hours after a glucose load have been reported to be significantly associated with the risk of CVD in subjects with IGT\(^27, 28\), showing that postprandial hyperglycemia is a risk factor for atherosclerosis. Thus, patients with IGT have an increased risk of CVD, but it is not obvious whether the degree of risk is equal to that of patients with DM. In this guideline, IGT is distinguished from DM and is considered to be one among many risk factors, such as hypo-high density lipoprotein (HDL) cholesterolemia and a family history of CAD.

2. Cardiovascular Disease Risk Factors and Their Comprehensive Management in Patients with DM

The risk factors for CAD in patients with DM
include hyperglycemia, hypertension, smoking, the male sex, hyper-low density lipoprotein (LDL) cholesterol, hypo-HDL cholesterol, hypertriglyceridemia, and high Lp(a) levels. Diabetic nephropathy and retinopathy are predictors of CAD. The risk factors for cerebral infarction include hypertension, the male sex and atrial fibrillation. The concentration of homocysteine in the blood is also reportedly associated with the severity of PAD.

The comprehensive and early management of risk factors such as hyperglycemia, hypertension and dyslipidemia has been shown to be effective for inhibiting cardiovascular events. Additionally, comprehensive and intensive therapy to mitigate these risk factors has been reported to suppress the progression of CVD in Japan.

The antithrombotic effects of low-dose aspirin and the antioxidant effects of vitamin E for primary prevention in DM patients are not evident.

### 3. Lipid Management in Patients with DM

It is clear that lifestyle modifications, including dietary therapy, increased physical activity and smoking cessation, are fundamental for the management of CVD and these factors contribute to a decrease in disease incidence and mortality. In patients with DM, dietary therapy and exercise decrease the risk of atherosclerosis, hyperglycemia, dyslipidemia and hypertension. Several reports have shown that smoking cessation and increased physical activity decrease the risk of CVD in DM patients.

Patients with DM are likely to have hyper-LDL cholesterol, hypertriglyceridemia and hypo-HDL cholesterolemia. A sub-analysis of the HPS and the CARDS has already shown the effectiveness of statins in preventing CVD in DM patients. A recent meta-analysis of a large-scale clinical trial revealed that statins decreased LDL-cholesterol(C) levels by 38.6 mg/dL, resulting in a decrease in total mortality risk by 9% (p=0.02), death from CAD by 12% (p=0.03), major coronary events [myocardial infarction or death from CAD] by 22% (p<0.0001) and cerebral infarction by 21% (p=0.002); these rates are similar to those in nondiabetic subjects.

The FIELD study investigated the effects of fibrates on CVD in patients with DM and mild dyslipidemia and showed a decrease in coronary events (nonfatal myocardial infarction or death from CAD) as a consequence of primary prevention. A sub-analysis of the ACCORD trial demonstrated that combination therapy of statins with fibrates in patients with hypertriglyceridemia and hypo-HDL cholesterolemia may significantly reduce the risk of cardiovascular events even after statin treatment. It was also reported that adding eicosapentaenoic acid (EPA) treatment for patients with impaired glucose metabolism complicated by hypercholesterolemia and already under statin treatment can reduce coronary events by 22% (the JELIS study) and that combination therapy with statins and ezetimibe in patients with DM complicated by chronic kidney disease (CKD) decreases the development of cardiovascular events by 22% compared to a placebo treatment (the SHARP study).

In previous guidelines, a TG <150 mg/dL and HDL-C ≥40 mg/dL have been recommended as target values regardless of the presence or absence of DM. This new guideline adopts non HDL-C as a secondary management target if hypertriglyceridemia is present after controlling LDL-C. It has been reported that increased non HDL-C levels are significantly associated with the risk of death from CVD in patients with DM.

### 4. LDL-C Management for the Prevention of CAD

DM is considered to be a “coronary risk equivalent” by the NCEP-ATP III, and an LDL-C level of <100 mg/dL is the recommended target. These concepts were introduced by ADA clinical practice recommendations. The ESC/EAS guidelines also recommend that LDL-C levels of <100 mg/dL should be the primary goal in all patients with type 2 DM.

In Japan, the J-LIT chart was used to investigate the incidence of CAD by stratifying the presence of risk factors in patients with DM. This chart shows that the risk of CAD in patients with DM alone is clearly lower than the risk of recurrence in secondary prevention patients without DM for both men and women, indicating that there is an insufficient rationale for considering DM alone as a “coronary risk equivalent” among the Japanese. However, a sub-analysis of the J-LIT study showed that even if the number of subjects with newly diagnosed CAD does not differ between diabetic and nondiabetic patient groups, the LDL-C levels are lower by approximately 30 to 40 mg/dL in diabetic subjects. This result suggests that stricter management of LDL-C is needed in diabetic patients.

DM conditions vary for each patient. It is practical to find patients who are at high risk of CAD, and then attempt to strictly control their risk factors. Previous reports revealed that patients at a high risk of CAD or death from CAD are characterized by conditions including (1) microangiopathy (e.g., retinopathy, nephropathy), (2) persistently poor glycemic control, (3) smoking, and (4) noncardiogenic
cerebral infarction/PAD\textsuperscript{75}, (5) metabolic syndrome\textsuperscript{76} and (6) more than one major risk factor (Table \ref{tab:1})\textsuperscript{65,66,74}.

All patients with DM should aim for LDL-C levels of <120 mg/dL as part of their primary CAD prevention. In patients with the previous characteristics, it is essential to follow intensive and strict management measures to reach the target values. Patients with DM who have more than one of these characteristics are expected to be at an extremely high risk of CAD, and the secondary prevention target values could be considered.

Lipid management in secondary prevention patients with DM is described in Chapter 11 of “Coronary Artery Disease.”

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 12) published in Japanese in June 2012.

Acknowledgements

We are grateful to the following people and societies for their collaboration and valuable contributions: Dr. Hidenori 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. Masayasu Matsumoto (The Japan Stroke Society), Dr. Tetsuho Shoji (Japanese Society of Nephrology) and Dr. Hiroaki Tanaka (Japanese Society of Physical Fitness and Sports Medicine). We also thank Dr. Shinji Koba, Dr. Manabu Minami, Dr. Tetsuro Miyazaki, Dr. Hirotoshi Ohmura, Dr. Mariko Harada-Shiba, Dr. Hideaki Shima, Dr. Daisuke Sugiyama, Dr. Minoru Takemoto and Dr. Kazuhisa Tsukamoto for supporting this work.

Table \ref{tab:1}. Diabetic Patients with a Higher Risk of Developing CAD

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>• Microangiopathy (retinopathy, nephropathy, etc.)</td>
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<tr>
<td>• Persistent poor glycemic control\textsuperscript{*}</td>
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<tr>
<td>• Smoking</td>
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<tr>
<td>• Non-cardiogenic cerebral infarction/PAD</td>
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<tr>
<td>• Metabolic syndrome</td>
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<tr>
<td>• More than one major risk factor \textsuperscript{*}</td>
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\textsuperscript{*}: HbA1c $\geq$ 8.4\% (NGSP)

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