Committee Report 6

Other High-Risk Conditions

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. History of Coronary Artery Disease (CAD)

Epidemiological studies and interventional trials conducted in Western countries and the results of a meta-analysis of these studies have revealed that the incidence of cardiovascular events in patients with a history of CAD is higher than that observed in primary prevention patients.

In Japan, the incidence of cardiovascular events in primary prevention subjects in the J-LIT trial was 0.9/1,000 person-years¹⁾, while that in secondary prevention patients was higher, with a value of 4.5/1,000 person-years²⁾. The JCAD³⁾ and CREDO-Kyoto⁴⁾, registration studies of patients with CAD, reported the incidence of cardiovascular events to be $\geq 15/1,000$ person-years. Among secondary prevention patients, there are further high-risk conditions, including acute coronary syndrome, smoking, diabetes mellitus, metabolic syndrome, chronic kidney disease, noncardiogenic cerebral infarction, peripheral artery disease and a constellation of risk factors. It has been reported that these patients clearly have a high incidence of recurrent coronary events, even when the LDL cholesterol (LDL-C) level is managed to the same extent as that in patients without complications.

2. Cerebrovascular Disease

It is well known that patients with a history of cerebrovascular disease are at a high risk for CAD.

It has been reported that the annual incidence of myocardial infarction in stroke patients ranges from 0.40% to 0.45% (4.0 to 4.5 persons/1,000 person-years) in Japan^{5, 6)}. Based on these figures, the incidence of myocardial infarction over 10 years in stroke

patients is approximately 3.9% to 4.4%, suggesting that Japanese stroke patients are also at a high risk of developing CAD. In particular, noncardiogenic cerebral infarctions are derived from atherosclerotic lesions and are therefore a high-risk condition for CAD.

3. Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is defined as the presence of kidney damage and/or a decreased kidney function lasting for ≥ 3 months. The former is determined according to the levels of albuminuria/proteinuria, and the latter is evaluated based on a decreased glomerular filtration rate (GFR). In the Evidence-based Practice Guidelines for the Treatment of CKD 2009 issued by the Japanese Society of Nephrology, CKD is divided into stages 1 to 5, with a therapeutic plan proposed for each stage⁷⁾ (see footnote).

CKD is a high-risk condition for cardiovascular disease (CVD)⁸⁾. Large-scale observational cohort studies conducted in the Japanese general population, including the NIPPON DATA80, Suita study and JALS-ECC trials⁹⁻¹³⁾, have demonstrated that CKD is associated with an approximately 2-fold higher risk of CVD. In a post hoc analysis of the CASE-J trial investigating the effects of antihypertensive agents on CVD in Japanese patients with hypertension¹⁴⁾, the relative risks associated with various risk factors were compared. The analysis showed that CKD exhibits a significant association with cardiovascular risks (relative risk: 2.8) that is comparable to or even stronger than that with a history of cerebrovascular disease (relative risk: 2.2), heart disease (relative risk: 2.2) or type 2 diabetes (relative risk: 2.0).

The exacerbation of classical risk factors associated with CKD, such as blood pressure, the lipid levels and glucose metabolism, contributes to the

increased risk of CVD observed in patients with CKD⁸⁾. Regarding lipids, CKD is a representative cause of secondary hyperlipidemia; nephrotic syndrome¹⁵⁾ is often accompanied by hyper-LDL cholesterolemia, while chronic renal failure¹⁶⁾ is often accompanied by hypertriglyceridemia due to the accumulation of remnant lipoproteins or a high VLDL level and hypo-HDL cholesterolemia. The non HDL cholesterol (HDL-C) level, the sum of the levels of cholesterol in TG-rich lipoproteins and LDL, has been reported to be an independent factor associated with the carotid artery intima-media thickness (IMT)¹⁷⁾ and pulse wave velocity (PWV)¹⁸⁾ in CKD patients. The ARIC¹⁹⁾, an epidemiological study conducted in the US general population, demonstrated that higher total cholesterol (TC) or triglycerides (TG) levels are associated with a higher risk of incident CAD, regardless of the GFR. In contrast, the HDL-C level is not associated with a risk of CAD in patients with a low GFR, suggesting that the non HDL-C level is related to the development of CAD in CKD patients with a low GFR. Therefore, dyslipidemia is closely associated with CVD in patients with CKD.

The risk of CVD is high in the presence of CKD. There is, however, controversy over whether CKD itself is the cause of CVD. It may be that there are common risk factors that adversely affect both CKD and CVD. Meanwhile, in a model adjusted for classical risk factors, the presence or absence of CKD was found to be independently associated with CVD, suggesting the involvement of non-classical risk factors associated with CKD⁸⁾. In any case, CKD should be treated as a high-risk condition for CVD²⁰⁾.

Footnote

CKD is currently classified based on the cause, GFR category and albuminuria (or proteinuria) category (CGA), as proposed by the 'KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease' and the 'Clinical Practice Guidebook for the Diagnosis and Treatment of Chronic Kidney Disease 2012' issued by the Japanese Society of Nephrology.

4. Peripheral Arterial Disease (PAD) and Abdominal Aortic Aneurysm (AAA)

Peripheral arterial disease was traditionally called ASO (arteriosclerosis obliterans) in Japan; however, in these guidelines, the term PAD²¹⁾ is used and the disease is defined as the presence of stenotic/obstructive lesions caused by atherosclerosis of the arteries in the extremities. PAD is characterized by symptoms such

as coldness of the lower extremities, intermittent claudication, ulcers and necrosis. Abdominal aortic aneurysm (AAA) is a condition involving plaque formation and ulceration in the luminal face, as well as external saccular aneurysm formation due to atherosclerosis of the abdominal aorta. These atherosclerotic diseases (including carotid artery stenosis and renal artery stenosis) require treatments such as revascularization; however, managing the causative risk factors is also important. It should also be noted that the primary cause of death in patients with these diseases is CAD or cerebrovascular disease. Although epidemiological studies conducted in Western countries revealed long ago that these diseases are high-risk conditions for CVD, this has only recently been reported in Japan.

The REACH registry, a prospective epidemiological study, reported that the incidence of CVD per year in 603 patients with coexisting PAD among 5,193 Japanese patients entered until 2004 was 1.25% for all deaths, 0.55% for cardiovascular death, 0.77% for nonfatal myocardial infarction, 1.56% for nonfatal stroke, 3.08% for cardiovascular death + nonfatal myocardial infarction + nonfatal stroke and 10.52% for cardiovascular death + nonfatal myocardial infarction + nonfatal stroke + hospitalization⁵⁾. These values are comparable to those for patients with coexisting CAD. Furthermore, in a prospective observational study of 557 patients with PAD, Shigematsu *et al.* reported that the incidence of CVD over three years was 6.3% for cardiovascular death, 11.3% for heart disease, 7.0% for brain disease and 16.9% for lower extremity events²²⁾.

Regarding AAA, Kioka *et al.* performed preoperative coronary angiography in 94 Japanese patients who underwent elective surgery for AAA (81 men; mean age: 71.7 ± 6.4 years) and reported that complications of CAD were observed in 45.7% of the patients²³⁾. Similarly, Takigawa *et al.* reported that the complication rate for asymptomatic CAD detected on coronary angiography in 201 Japanese patients who underwent elective surgery for AAA (161 men; mean age 73.1 ± 7.7 years) was 29.4%²⁴⁾. Hirose *et al.* performed ATP-loading myocardial single-photon emission computed tomography (SPECT) in a total of 788 Japanese patients, including 500 patients with aortic aneurysms, 183 patients with lower extremity PAD and 105 patients with combined aortic aneurysms and lower extremity PAD, who had not been diagnosed with CAD and reported that myocardial ischemia was observed in 77% of the patients with combined aortic aneurysms and PAD, 55% of the patients with PAD and 37% of the patients with aortic aneurysms²⁵⁾. These reports demonstrate that the existence of PAD

and AAA is also an important high-risk condition for CVD in Japanese patients.

Atherosclerotic findings in the carotid artery are independent risk factors for CVD^{26, 27}. Thickening of the common carotid artery IMT on ultrasonography is associated with an increased incidence of CVD. In addition, the existence of plaque and its characteristics (e.g., low-intensity features and the formation of ulcers) is involved in the development of CVD^{28, 29}. In Japan, it has been reported that IMT is an independent significant predictive factor for CAD as well as cerebral infarction³⁰⁻³². In several reports, the extent of IMT has been found to be significantly correlated with the extent of coronary atherosclerosis^{33, 34}. Shimada *et al.* reported that 37% of patients with carotid artery stenosis who underwent carotid endarterectomy presented with coronary lesions on preoperative coronary angiography, half of whom presented with triple-vessel disease or left main CAD³⁵.

Atherosclerotic renal artery stenosis is a cause of renovascular hypertension. It has been reported that 5% to 22% of elderly patients with CKD have coexisting renal artery stenosis. Renal artery stenosis is also a risk factor for CVD, and the complication rate for atherosclerotic disease in other organs is high^{7, 36-38}. In the primary prevention of CVD, carotid artery findings and renal artery stenosis should be noted.

As noted above, it has been reported that AAA, carotid artery lesions and renal artery stenosis are associated with CVD; however, it is difficult to say that sufficient results of prospective studies in Japan have been accumulated. Therefore, these guidelines include only PAD as a high-risk condition.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 6) published in Japanese in June 2012.

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