Committee Report 11

Coronary Artery Disease

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

Tamio Teramoto, Jun Sasaki, Shun Ishibashi, Sadatoshi Birou, Hiroyuki Daida, Seitaro Dohi, Genshi Egusa, Takaumi Hiro, Kazuhiro Hirobe, Mami Iida, Shinji Kihara, Makoto Kinoshita, Chizuko Maruyama, Takao Ohta, Tomonori Okamura, Shizuya Yamashita, Masayuki Yokode and Koutaro Yokote

Committee for Epidemiology and Clinical Management of Atherosclerosis

Epidemiological and interventional studies conducted in Western countries and the results of a meta-analysis have revealed that the incidence of cardiovascular events in patients with coronary artery disease (CAD) is higher than that observed in primary prevention patients. In Japan, the incidence of cardiovascular events in patients who receive dietary therapy was found to be 2.1/1,000 person-years in the MEGA study1, while that in primary prevention patients using statins was found to be 0.9/1,000 person-years in the J-LIT study2. In contrast, the incidence of cardiovascular events in patients with CAD was found to be 4.5/1,000 person-years in the J-LIT study3 and 6.8/1,000 person-years in the JELIS study4. The JCAD5 and CREDO-Kyoto studies6, registry studies of patients with CAD, both reported a high incidence of cardiovascular events of ≥15/1,000 person-years. Moreover, among patients with CAD, those with the conditions listed in Table 1 are at higher risk. It has been reported that such patients have a clearly higher incidence of coronary events, even when the LDL-cholesterol (LDL-C) level is managed to the same extent as in patients without complications.

1. Acute Coronary Syndrome

Patients with acute coronary syndrome (ACS) have a higher risk of recurrence of cardiovascular events than patients with stable CAD. The OACIS-LIPID study investigated the inhibitory effects of early statin treatment on cardiovascular events in Japanese patients with acute myocardial infarction (MI)7. In that study, the incidence of total mortality and nonfatal MI in patients who received lipid-lowering therapy other than statins was 40/1,000 person-years, while that among patients who received statins was 30/1,000 person-years, thus revealing a remarkably high incidence of cardiovascular events.

Meanwhile, it has been reported that the administration of LDL-C-lowering therapy from the early stage of ACS is effective in preventing cardiovascular events8 and that more intensive LDL-C-lowering therapy decreases the incidence of cardiovascular events more significantly than typical LDL-C-lowering therapy9. A meta-analysis of randomized controlled trials (RCTs) of statin treatment started within 14 days after the onset of ACS demonstrated no protective effects on cardiovascular events in a short period of four months10; however, the incidence of cardiovascular events was significantly reduced during an observation period of ≥2 years11. These results suggest that the beneficial effects of providing early, intensive LDL-C-lowering therapy in preventing cardiovascular events are observed from four to 12 months after the onset of ACS.

In Japan, the effectiveness of early LDL-C-lowering therapy in patients with ACS has been investigated by observing coronary artery plaque using intravascu-
lar ultrasonography (IVUS). In the ESTABLISH study, the administration of early, intensive LDL-C-lowering therapy after the onset of ACS decreased the mean LDL-C level to 70 mg/dL after six months, resulting in a decrease in the plaque volume of 13.1% \(^{12}\). The changes in plaque volume were found to be significantly and positively correlated with the LDL-C level after treatment and the rate of decrease in the LDL-C level. The ESTABLISH study followed up (mean: 4.2 years) additional patients and reported that the administration of early, intensive LDL-C-lowering therapy after the onset of ACS significantly decreased cardiovascular events \(^{13}\). Furthermore, the JAPAN-ACS study demonstrated that providing early, intensive LDL-C-lowering therapy using statins in patients with ACS was effective in inhibiting plaque progression \(^{14}\); however, that study found no significant relationships between the changes in the LDL-C level during treatment or the LDL-C level observed after treatment and the rate of plaque regression.

2. Smoking

In patients with CAD who continue to smoke, the risk of recurrence of cardiovascular events is higher than that observed in nonsmokers and the risk of fatal cardiovascular events, including total mortality, cardiac death and sudden cardiac death, is significantly increased \(^{15-19}\). In the REACH Registry, a registry study of patients with cardiovascular disease [CAD, cerebrovascular disease and peripheral arterial disease (PAD)] or more than one risk factor for atherosclerosis, the incidence of cardiovascular events in patients who continued to smoke was approximately 1.3-fold higher than that observed in lifelong nonsmokers \(^{20}\). In the OACIS study, even after adjusting for age, sex, diabetes mellitus (DM), hypertension, dyslipidemia, and therapeutic drugs, the risk of total mortality in patients who continued to smoke after the onset of MI was 2.3-fold higher than that observed in lifelong nonsmokers. In contrast, the risk of total mortality in patients who stopped smoking after the onset of MI was as low as that observed in lifelong nonsmokers and was significantly decreased (by 61%) compared with that observed in patients who continued to smoke \(^{21}\). Many epidemiological studies have reported that the risk of recurrence of cardiovascular events decreases after approximately half a year following the cessation of smoking and reaches almost the same level as that observed in lifelong nonsmokers approximately 10 years after smoking cessation, regardless of age and sex \(^{15-22}\).

A subanalysis of the secondary prevention studies, TNT and IDEAL \(^{23}\), showed that the risk of cardiovascular events in continued smokers is higher than that observed in lifelong nonsmokers, even among those receiving intensive LDL-C-lowering therapy with statins. Therefore, providing smoking cessation instructions to patients who continue to smoke is extremely important.

3. Multiple Risk Factors and Metabolic Syndrome

The results of a meta-analysis revealed that patients with CAD complicated by metabolic syndrome have a higher risk of total mortality and cardiovascular events \(^{24}\).

A subanalysis of the TNT study of patients with stable CAD and metabolic syndrome demonstrated the risk of cardiovascular events to increase in association with the presence of each additional component of metabolic syndrome. In particular, patients with three or more major risk factors have a higher incidence of cardiovascular events. However, high-dose statin treatment has been shown to significantly decrease the rate of cardiovascular events (by 29%) compared with usual-dose statin treatment \(^{25}\).

The JCAD, an observational study conducted in Japan, demonstrated that the risk of cardiovascular events in patients with three or more major risk factors is 1.3-fold higher than that observed in patients with two or less risk factors \(^{26}\). In a study in which patients who underwent percutaneous coronary intervention (PCI) were followed up for a long period, the relative risk of cardiovascular events in the patients with metabolic syndrome was 2.1-fold \(^{26}\); however, statin treatment resulted in a significant decrease in total mortality of 44% and coronary death of 47% \(^{27}\).

4. Diabetes Mellitus (DM)

It has been reported that the risk of recurrence of cardiovascular events is increased in the presence of DM in patients with a history of MI \(^{28-31}\). Epidemiological studies of Japanese patients with CAD have also reported that the risk of total mortality and cardiovascular events in patients with DM is high \(^{32-33}\). Moreover, an analysis of patients with CAD in the J-LIT study showed that the relative risk of cardiovascular events is increased approximately 2.5-fold in the presence of DM \(^{3, 7}\).

According to the CTT, a meta-analysis of 14 RCTs of statins, the beneficial effects of statins on cardiovascular events are observed regardless of the presence or absence of DM or CAD \(^{34}\). A subanalysis of the TNT study of patients with CAD and DM showed that high-dose statin treatment significantly decreases cardiovascular and cerebrovascular events by 25% and 31%, respectively, compared with usual-dose...
Statin treatment\textsuperscript{35}.

A meta-analysis of clinical studies using IVUS conducted in Western countries reported that DM is an independent risk factor in patients whose coronary plaque volume is \(\geq 5\%\) despite having a decreased LDL-C level of \(\leq 70\ \text{mg/dL}\) with treatment\textsuperscript{36}. It has also been reported that there is a significant positive relationship between an increase in the coronary plaque volume, as well as the LDL-C level, and the incidence of cardiovascular events after treatment. This suggests that the use of intensive LDL-C-lowering therapy is important in patients with CAD complicated by DM. Furthermore, in a subanalysis of the JAPAN-ACS study conducted in patients with ACS in Japan\textsuperscript{37}, DM was found to be a strong negative risk factor for plaque regression. In addition, although the LDL-C-lowering effects of statins were equivalent to those observed in patients without DM, the effects on plaque volume regression were significantly decreased in patients with DM. However, it has been reported that significant plaque regression effects can be obtained if the LDL-C level is maintained at \(< 75\ \text{mg/dL}\)\textsuperscript{38}.

5. Noncardiogenic Cerebral Infarction and Peripheral Arterial Disease (PAD)

Cardiovascular diseases, such as CAD, cerebrovascular disease and PAD, which commonly occur in patients with atherosclerosis, interact, leading to a risk of systemic vascular complications. The REACH registry revealed that approximately 16% of patients have two or more cardiovascular diseases\textsuperscript{39}. In a comparison of the results of the CREDO-Kyoto study conducted in Japan with those of a registry study conducted in the U.S.\textsuperscript{33}, the complication rate of cerebrovascular disease was significantly higher in Japan (16.4% vs. 5.0%), while the complication rate of PAD was significantly higher in the U.S.; however, both complications were confirmed to be high risk factors for cardiovascular events in Japan and the U.S.

1) Noncardiogenic Cerebral Infarction

Secondary prevention studies of CAD conducted in Western countries, such as the 4S, LIPID and CARE studies, have reported that patients with CAD with a history of cerebrovascular disease have a high risk of recurrence of cerebrovascular and cardiovascular events, although LDL-C-lowering therapy with statins decreases the risk of recurrence of both cerebrovascular and cardiovascular events\textsuperscript{40-42}.

2) Peripheral Arterial Disease (PAD)

Although patients with PAD with a history of CAD have an extremely high risk of total mortality and fatal cardiovascular events\textsuperscript{43-48}, there are no lipid intervention studies focusing only on patients with PAD complicated by CAD. In a meta-analysis of the effectiveness of lipid intervention in patients with PAD, lipid-lowering therapy was found to decrease the incidence of cardiovascular events by 20% and total mortality by 14\%\textsuperscript{49}. Subanalyses of cohort studies and RCTs have reported the effectiveness of statins in patients with PAD\textsuperscript{50-54}.

A meta-analysis of clinical studies in which the progression of coronary plaque lesions was analyzed using IVUS showed that effects on the inhibition of the progression and regression of plaque are observed when the LDL-C level is maintained at \(< 70\ \text{mg/dL}\), regardless of the presence or absence of PAD, and that plaque regression is related to cardiovascular events\textsuperscript{55}.

6. Chronic Kidney Disease (CKD)

Analyses of long-term observational studies of patients with ACS and those who have undergone PCI stratified according to the estimated glomerular filtration rate (eGFR) have reported that the risk of cardiovascular events, including cerebrovascular disease, cardiac death and total mortality, in patients with mild chronic kidney disease (CKD) increases by 2- to 3-fold compared with patients with a normal renal function, and the risk further increases in association with the severity of renal dysfunction\textsuperscript{56, 57}. The CREDO-Kyoto study reported that, among patients with CKD who have undergone PCI, the risk of cardiovascular death is increased by 2.9-fold and the risk of total mortality is increased by 2.1-fold. In particular, patients \(\leq 55\) years of age were found to have an increased risk of cardiovascular events, including cerebrovascular disease (by 3.7-fold)\textsuperscript{58}. Furthermore, patients with CKD and a serum creatinine level of \(\geq 2.0\ \text{mg/dL}\) were found to have a 7.0-fold increased risk of total mortality. This suggests that patients with CKD who have undergone PCI have an increased risk of cardiovascular events\textsuperscript{33}.

The protective effects of lipid-lowering therapy on cardiovascular events in patients with CKD complicated by CAD have been investigated in a post hoc analysis of early secondary prevention studies using statins. The results showed that statins provide significant beneficial effects on cardiovascular events, but not cerebrovascular disease, in patients with mild CKD and an eGFR of \(< 75\ \text{mL/min/1.73 m}^2\)\textsuperscript{39, 60}. Furthermore, a post hoc analysis of secondary prevention studies reported that high-dose statin treatment significantly decreases the incidence of cardiovascular events by approximately 30% in patients with moderate
CKD compared with usual-dose statin treatment\textsuperscript{61, 62).}

**Footnotes**

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 11) published in Japanese in June 2012.

**Acknowledgements**

We are grateful to the following societies for their collaboration and valuable contributions: Dr. Hitoshi Nakamura (Japan Geriatrics Society), Dr. Kiminori Arakawa (Japanese Society of Physical Fitness and Sports Medicine). We also thank Dr. Manabu Minami, Dr. Tetsuro Hosoda (Japan Society for the Study of Obesity), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Atsunori Kashiwagi (Japan Diabetes Society), Dr. Minoru Takemoto and Dr. Kazuhiwa Tsukamoto for supporting this work.

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