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EDITORIAL

Intensive Lipid-Lowering Therapy With Statins for Primary Prevention

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3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, inhibit conversion of HMG-CoA to mevalonic acid, with subsequent attenuation of synthesis of cholesterol, and thus effectively reduce serum cholesterol levels.[1] It has been well documented that lipid-lowering therapy with statins reduces the risk of death or cardiovascular events in populations with or without a history of coronary artery disease.[2] These benefits are obtained largely irrespective of the initial lipid profile or other presenting characteristics. It has been also demonstrated that intensive statin therapy is more effective than standard statin therapy for patients with established coronary artery disease, comparing a strong statin vs. a standard statin, or high-dose statin vs. standard-dose statin.[3]

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In this issue of the Journal, Nohara et al showed that intensive lipid-lowering therapy with rosuvastatin significantly reduced the rate of mean carotid intima-media thickness (IMT) progression as compared with standard lipid-lowering therapy with pravastatin in Japanese patients.[4] The majority of the study patients (84%) were treated as primary prevention and were mostly in category II or III according to the Japan Atherosclerosis Society (JAS) guideline.[5] This study's results suggest that intensive statin therapy may be more effective than standard statin therapy, even as primary prevention, for Japanese subjects with intermediate to high risk.

Numerous studies have demonstrated the benefits of statin therapy as primary prevention of vascular disease in patients with hypercholesterolemia. The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study showed that pravastatin reduced the incidence of coronary heart disease from 4.8% to 3.3% during 5 years in 7,832 Japanese patients with hypercholesterolemia and no history of coronary heart disease or stroke.[6] In 2007, the JAS proposed a guideline for the diagnosis and prevention of atherosclerotic cardiovascular diseases. To prevent coronary artery disease in future, management goals of low-density lipoprotein cholesterol (LDL-C) range from <160 mg/dl to <120 mg/dl for primary prevention, depending on categories that are determined by the number of risk factors. However, lower LDL-C may be beneficial for patients without coronary artery disease, especially in the presence of additional risk factors. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) randomly assigned 17,802 apparently healthy subjects with LDL-C levels <130 mg/dl and high-sensitivity C-reactive protein levels ≥2.0 mg/L to rosuvastatin (20 mg daily) or placebo.[7] The trial was prematurely stopped after a median follow-up of 1.9 years, because rosuvastatin significantly reduced cardiovascular events by 44%. Because of the differences in lifestyle and the incidences of coronary heart disease and stroke between Japan and other Western countries, it should be verified whether the results of clinical studies done in Western countries can be extrapolated to Japanese patients.[8]

Most cardiovascular events are attributable to healthy individuals with relatively normal cholesterol levels. Importantly, the initial presentation of coronary artery disease in an unignorable number of patients is sudden death. Primary prevention is a major issue of public health interest. However, an enormous sample size is needed to assess the effectiveness of a management approach, because of the very low event rate. Surrogate endpoints are frequently used in primary prevention trails. Most recently, atherosclerosis is often evaluated by imaging techniques. Although intravascular ultrasound and coronary angioscopy provide direct information about coronary atherosclerosis, the use of these intracoronary imaging devices for intervention trials is limited to secondary prevention because of their invasiveness, complexity and expense.[9,10] Carotid IMT is a non-invasive measure commonly used in general practice. It is a combined measurement of the intimal and medial layers of the vessel wall. Although early atherosclerosis is restricted to the intimal layer, the links between carotid IMT and atherosclerosis are well established. Several studies have demonstrated that baseline carotid IMT is associated with the risk of myocardial infarction, stroke, death from coronary artery disease or a combination of these events.[11]

Although a change in IMT has been used as a surrogate endpoint in several trials that investigated the effectiveness of interventions, there is some criticism of using carotid IMT as a surrogate for cardiovascular events. First, it is known that the process of increasing the IMT is a complex phenomenon, not only determined by atherosclerotic risk factors. The multifactorial determinants of IMT may reduce the clinical strength and statistical significance of IMT changes as a surrogate endpoint. Nevertheless, several studies have shown that IMT changes are effectively affected by interventions, including statins, antihypertensive drugs and antidiabetic drugs. The Measuring Effects on Intima-Media Thickness: an Evaluation

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of Rosuvastatin (METEOR) study randomized 984 middle-aged adults with a 10-year Framingham risk score <10%, modest carotid IMT thickening (1.2–3.5 mm), and elevated LDL-C to receive either rosuvastatin (40 mg) or placebo.[12] The change in maximum IMT for the 12 carotid sites increased by 0.0131 mm/year in subjects assigned to placebo, but rosuvastatin reduced it in the rate of progression by –0.0014 mm/year (P<0.001). Second, as atherosclerotic plaques grow longitudinally along the carotid axis more than twice as fast as they thicken, IMT might be a less sensitive measure of plaque evolution. In this issue of the Journal, Nohara et al report on their use of a novel method of measuring carotid IMT. They averaged 60 points of IMT values for mean IMT, which could reflect longitudinal progression or regression of atherosclerosis, and showed that intensive lipid-lowering therapy with rosuvastatin slowed the progression of mean IMT as compared with standard therapy with pravastatin, whereas such difference was not observed in maximum IMT.

Finally, the extent of atherosclerosis differs across vessels such as coronary arteries and carotid arteries. There is still debate whether regression or slowed progression of IMT is associated with a reduced incidence of cardiovascular events. In a meta-analysis of 7 placebo-controlled clinical trials of statins that reported both IMT outcomes and cardiovascular events, Espeland et al showed that carotid IMT progression meets accepted definitions of a surrogate for cardiovascular disease endpoints in statin trials.[13] In contrast, Costanzo et al reviewed 41 trials and reported that, despite a significant reduction in cardiovascular events induced by active treatments, there was no significant relationship between IMT regression and clinical events.[14] In this issue of the Journal, there were only 2 events at 12 months. At present, the Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) (NCT01042730, UMIN000002680), which is planned to compare 3 years' incidence of cardiovascular events in 12,600 patients with stable coronary artery disease randomized to pitavastatin 4 mg and 1 mg, is being carried out in Japan. Such large-scale and longer duration randomized trials focused on clinical events are needed to determine the practice implications of intensive lipid-lowering therapy with statins as primary prevention for subjects with intermediate to high risk.

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