Clinical Significance of Mild Lipid-Lowering by Statins for Prevention of Cardiovascular Disease in Japanese High-Risk Patients

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Numerous studies have demonstrated that diabetes mellitus (DM) closely correlates with cardiovascular disease mortality. Diabetic patients often have hyperglycemia, dyslipidemia and insulin resistance, all of which cause typical features of coronary artery disease (ie, multivessel disease and long, narrow and complex lesions with calcified plaque). Whether intensive glucose-lowering prevents the development of atherosclerosis in patients with DM remains controversial. In the Heart Protection Study, simvastatin therapy rapidly reduced the incidence of coronary events and ischemic stroke in high-risk patients, including those with DM, and in the Collaborative Atorvastatin Diabetes Study, atorvastatin (10 mg daily) reduced the risk of first cardiovascular events in diabetic patients without high levels of low-density lipoprotein (LDL)-cholesterol. Sub-analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study demonstrated that mild LDL-cholesterol lowering by pravastatin decreased the incidence of cardiovascular diseases in Japanese diabetic subjects. However, whether standard statin therapy is useful for preventing future cardiac events in Japanese diabetic individuals with coronary heart disease (CHD) remains unclear.

In this issue of the Journal, Kojima et al report that standard-dose statin therapy provided incremental clinical benefit in a population of Japanese patients with CHD and DM. They assessed the Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitor in Japanese High-Risk Patients (N=1028), which includes 486 patients with acute myocardial infarction (AMI) and 533 patients with stable angina who underwent percutaneous coronary intervention (PCI). The patients with AMI were randomly assigned within 96h of onset and patients with stable angina were randomly assigned within 48h of PCI to standard therapy with any statin or to standard therapy without statin. Finally, a total of 1,016 patients with CHD were randomized to either a statin group (n=503) or a non-statin group (n=513); this study population consisted of 301 diabetic patients and 715 non-diabetic patients. Statin therapy equally decreased LDL-cholesterol levels to approximately 100mg/dl in both diabetic and non-diabetic patients, and reduced the incidence of major adverse cardiovascular and cerebrovascular events. Interestingly, statin therapy was more effective in diabetic patients (number needed to treat (NNT)=8, relative risk reduction (RRR) 67%) compared with non-diabetic patients (NNT 30, RRR 24%), although it achieved LDL-cholesterol levels of approximately 100mg/dl in both groups, suggesting the efficacy of standard-dose statin treatment. However, there were several biases in the study. The study subjects consisted of 2 different populations who had either experienced AMI or not, and such a heterogeneous population may affect the prognosis of diabetic and non-diabetic groups because previous AMI is a major risk factor for recurrent cardiovascular disease. In addition, the study population was relatively small, which may lead to overestimation of the difference between the statin and non-statin treatment groups.

In a Western population, aggressive lipid-lowering by high-dose atorvastatin therapy further reduced the risk of cardiovascular events in patients with CHD and metabolic syndrome compared with low-dose atorvastatin. In the Japanese population, there are several studies that indicate that aggressive lipid lowering therapy might be beneficial in high-risk patients. In the secondary prevention study by Kojima et al, however, mild lipid-lowering by statins dramatically reduced the risk of cardiac events in high-risk patients and this result urges us to discuss further the adequate level of LDL-cholesterol for preventing recurrence of cardiovascular disease in Japanese high-risk patients. Furthermore, Kojima et al demonstrated that statin treatment only reduced the incidence of unstable angina, defined as recurrent symptomatic ischemia with emergency hospitalization, in both diabetic and non-diabetic groups. Therefore, we need to carefully interpret the huge impact of statin therapy in diabetic patients, because this endpoint was diagnosed on the basis of the physician’s decision and asymptomatic myocardial ischemia occurs often in diabetic patients with cardiac autonomic neuropathy. Nevertheless, these preferable results suggest that standard-dose statin therapy stabilizes so-called vulnerable plaque. Clinical and preclinical studies also suggest that statins have various effects that are independent of LDL-cholesterol lowering (ie, pleiotropic effects). Besides statins suppressing cholesterol biosynthesis by inhib-
Mild Lipid Lowering in Diabetic Patient With CHD

References


Disclosure

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