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Editorial

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Serum HDL-Cholesterol Level Does Not Influence Cardiovascular Event Rate under Sufficient Lowering of LDL-Cholesterol by Pitavatatin in Patients with Stable Coronary Artery Disease

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Numerous epidemiological studies have shown that a low level of high-density lipoprotein cholesterol (HDL-C) is an independent risk factor for atherosclerotic cardiovascular diseases (ASCVD) such as coronary artery disease (CAD). A fasting HDL-C concentration of <40 mg/dl is diagnosed as dyslipidemia associated with an increased risk of atherosclerotic cardiovascular events, and the lower the HDL-C value, the higher the cardiovascular (CV) morbidity. On the contrary, higher HDL-C level of > 80–100 mg/dl was not always associated with lower all-cause and CV mortality[1]. Many drugs have been developed to improve low HDL-C level, however treatments that increase HDL-C levels could not always improve ASCVD morbidity. Recently, a variety of cholesteryl ester transfer protein (CETP) inhibitors have been developed to increase HDL-C levels by suppressing the transfer of cholesteryl ester from HDL to apolipoprotein (apo)B-containing lipoproteins. However, they failed to suppress CV events[2] except for anacetrapib[3], the development of which was terminated because of its persistent accumulation in adipose tissues[4].

Anti-dyslipidemic agents which have properties for increasing HDL-C levels are statins, ezetimibe, nicotinic acids, fibrates, and a selective PPARα modulator (SPPARMα), pemafibrate[5, 6]. Fibrates and pemafibrate can increase serum HDL-C levels (20~30%) more than other drugs such as statins, ezetimibe, and nicotinic acid (10~20%). Fibrates can decrease serum triglyceride (TG) level by 30~40% along with the increase in HDL-C level, however they could not always prove the effectiveness for reducing CV events in patients with hypertriglyceridemia[5]. In the ACCORD-LIPID study, which aimed to evaluate the primary and secondary preventive effects of ischemic heart disease in patients with type 2 diabetes mellitus using simvastatin, the addition of fenofibrate did not significantly suppress CV events in all participants, but significantly attenuated them in a selected patient group whose TG levels were ≥ 204 mg/dL and HDL-C levels <34 mg/dL[7]. When considering therapeutic interventions for high TG levels or low HDL-C level, unlike therapeutic interventions for high low-density lipoprotein cholesterol (LDL-C) levels, it is important to consider the impaired lipoprotein profile in such patients[5].

Statins decrease LDL-C levels by 20 to 40% or more and increase HDL-C levels up to about 20%. Among statins, pravastatin or pitavastatin has a tendency to increase HDL-C levels by 10 to 20% and apoprotein A-1 levels by about 6%[6]. The underlining mechanisms for the increase in HDL-C levels by statins are as follows; 1) the inhibition of HMG-CoA reductase by statins in hepatocyte suppresses Rho signaling and increase apoA-1 through activation of PPARα, and 2) statins elevate hepatic ABCA1 expression via activation of SREBP2 and LXR. Thus, activation of ABCA1 and apoA-1 accelerates the formation of preβHDL particles, leading to an enhanced production of mature spherical HDL particles[6]. There are some reports about the amelioration of CV outcome after the increase in HDL-C level using statins. Coronary plaque regression was observed in patients treated with pravastatin for 6 months[8]. HDL-C and apoA-1 levels significantly increased, while LDL-C level did not significantly change in the plaque regression group compared with the plaque progression group, and the

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change of plaque volume correlated with the changes in HDL-C level. In a retrospective analysis of patients after percutaneous coronary intervention, Maruyama *et al.*[9] showed that treatment with either atorvastatin or pitavastatin significantly reduced LDL-C compared with pravastatin or without statin, whereas only pitavastatin treatment significantly increased HDL-C levels. There was no statistically significant difference in prevention of major adverse cardiovascular events (MACE) among statins, and pitavastatin was the most effective, especially in patients with a baseline low HDL-C level (≤ 45 mg/dl).

High-dose (4 mg/day) compared with low-dose (1 mg/day) pitavastatin therapy has been reported to significantly reduce CV events in Japanese patients with stable CAD (REAL-CAD Study)[10]. Furthermore, in an issue of the Journal of Atherosclerosis and Thrombosis, Omote *et al.*[11] have examined whether baseline HDL-C level or change in HDL-C level after pitavastatin therapy may correlate with MACE in the REAL-CAD study. Patients with stable CAD whose LDL-C levels were ≤ 120 mg/dL on pitavastatin 1 mg/day at any time during the run-in period were randomized to either pitavastatin 1 or 4 mg/day. The primary outcome (a composite of CV MACE after 6 months from randomization) and the secondary outcome (a composite of the primary endpoint event and clinically indicated coronary revascularization) were observed in patients with low (<40 mg/dL), intermediate (40–79 mg/dL), or high (≥ 80 mg/dL, n=240) HDL-C groups. During a median follow-up period of 4.0 (IQR 3.2–4.7) years, there was no significant difference in crude and adjusted cumulative incidence of the primary and secondary outcome and their components among the three groups of HDL-C level at 6 months (Fig. 2A, 2B, 2C and 2D) as well as after the risk adjustment (Fig. 3 and 4). There was a slight increase in CV outcome in the population with the lowest and highest HDL-C levels, but the differences did not reach significance. Moreover, no significant difference was observed when patients attained their HDL-C levels with 10 mg/dL increase or 10% increase from the baseline, regardless of the LDL-C value at that time. Comparing the data of REAL-CAD Study[10] and the CIRCLE Study[9], it can be speculated that higher HDL-C levels after the administration of pitavastatin to patients do not always result in the reduction of MACE. Recent basic studies have shown that HDL particles exert anti-inflammatory, anti-oxidant, anti-thrombotic, endothelial-protective, anti-infective, vasodilatory, anti-apoptotic, and anti-diabetic actions in addition to cholesterol efflux[6]. It is speculated that dysfunctional HDL, which exhibits abnormalities in these functions, is associated with increased atherogenicity[6]. Even though serum HDL-C level is simply raised by interventions, anti-atherogenic properties exerted by HDL particles are not always enhanced[12]. It may be necessary to reduce atherosclerosis by increasing functional HDL particles, not by simply increasing the HDL-C level. Further basic and clinical studies focusing on enhancing HDL function are strongly needed for reducing atherogenicity.

Conflict of Interest

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