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Original Article

Effect of atorvastatin, cholesterol ester transfer protein inhibition, and diabetes mellitus on circulating proprotein subtilisin kexin type 9 and lipoprotein(a) levels in patients at high cardiovascular risk

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KEYWORDS:
Atorvastatin;
Diabetes mellitus;
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PCSK9;
CETP

BACKGROUND: Proprotein subtilisin kexin type 9 (PCSK9) and lipoprotein (a) [Lp(a)] levels are causative risk factors for coronary heart disease.

OBJECTIVES: The objective of the study was to determine the impact of lipid-lowering treatments on circulating PCSK9 and Lp(a).

METHODS: We measured PCSK9 and Lp(a) levels in plasma samples from Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events trial patients with coronary heart disease and/or type II diabetes (T2D) mellitus. Patients received atorvastatin, which was titrated (10, 20, 40, or 80 mg/d) to achieve low-density lipoprotein cholesterol levels <100 mg/dL (baseline) and were subsequently randomized either to atorvastatin + torcetrapib, a cholesterol ester transfer protein inhibitor, or to atorvastatin + placebo.

Clinical Trial Registration: NCT00134264.

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RESULTS: At baseline, both plasma PCSK9 and Lp(a) were dose-dependently increased with increasing atorvastatin doses. Compared with patients without T2D, those with T2D had higher PCSK9 (357 ± 123 vs 338 ± 115 ng/mL, $P = .0012$) and lower Lp(a) levels (28 ± 32 vs 32 ± 33 mg/dL, $P = .0005$). Plasma PCSK9 levels significantly increased in patients treated with torcetrapib (+13.1 ± 125.3 ng/mL [+3.7%], $P = .005$), but not in patients treated with placebo (+2.6 ± 127.9 ng/mL [+0.7%], $P = .39$). Plasma Lp(a) levels significantly decreased in patients treated with torcetrapib (−3.4 ± 10.7 mg/dL [−11.1%], $P < .0001$), but not in patients treated with placebo (+0.3 ± 9.4 mg/dL [+0.1%], $P = .92$).

CONCLUSION: In patients at high cardiovascular disease risk, PCSK9 and Lp(a) are positively and dose-dependently correlated with atorvastatin dosage, whereas the presence of T2D is associated with higher PCSK9 but lower Lp(a) levels. Cholesterol ester transfer protein inhibition with torcetrapib slightly increases PCSK9 levels and decreases Lp(a) levels.

Introduction

Statin therapy decreases low-density lipoprotein (LDL) cholesterol levels and thereby reduces cardiovascular disease (CVD) risk.[1] By inhibiting intracellular cholesterol synthesis, statins increase the expression of the LDL receptor (LDLR), thus promoting an enhanced clearance of LDL particles. However, statins also increase the expression of proprotein convertase subtilisin kexin type 9 (PCSK9), a natural circulating inhibitor of the LDLR.[2] PCSK9 binds to the LDLR and after endocytosis targets the LDLR that normally recycles back to the cell surface, for lysosomal degradation. The efficacy of statins in reducing LDL cholesterol levels appears to be partially offset by a concomitant rise in PCSK9.[3,4] Pharmacologic inhibition of PCSK9 with monoclonal antibodies lowers circulating LDL cholesterol further in patients at high CVD risk and not at LDL cholesterol therapeutic goals despite aggressive statin treatment.[5,6] It is therefore important to determine whether and to what extent statins dose-dependently increase circulating PCSK9 levels in such patients.

In contrast to statins, anti-PCSK9 monoclonal antibodies promote an unexplained 25% to 30% reduction in circulating lipoprotein (a) [Lp(a)] levels.[7] Lp(a) is a lipoprotein subfraction analogous to LDL, where a unique protein homologous to plasminogen, apolipoprotein (a) [apo(a)], is covalently tethered to apolipoprotein B100 by a unique disulfide bond.[8] Approximately 20% of the Caucasian population have high Lp(a) levels (above 50 mg/dL)[9] and a consequent increased risk of coronary heart disease, stroke, calcific aortic valve stenosis, and heart failure.[10–13] The molecular mechanisms of Lp(a) assembly that likely occurs at the surface of hepatocytes between a newly synthesized apo(a) and apoB100 containing lipoproteins (LpB) remain elusive.[14] Apo(a) is never found associated with triglyceride-rich lipoproteins but rather on cholesterol-rich LDL particles.[15,16] The impact of statin therapy on plasma Lp(a) levels is somewhat controversial with studies documenting slight decreases in Lp(a) while others suggest that statins actually increase Lp(a) levels as well as the amount of oxidized phospholipids carried by Lp(a).[17] Similar to PCSK9, whether statins dose-dependently influence Lp(a) plasma levels and whether this could be dependent on metabolic disturbances is unknown.

To shed light on the metabolic states favoring Lp(a) assembly, and thus elevated Lp(a) levels, in conjunction with the ongoing development of PCSK9 inhibitors, we aimed to determine the impact of different doses of statins, with and without metabolic disturbances of triglyceride-rich lipoproteins (eg, in type II diabetes [T2D]) and with and without modulation of their cholesterol content (eg, by inhibition of the cholesterol ester transfer protein [CETP]) on circulating PCSK9 and Lp(a) levels in patients at high cardiovascular risk.

Methods

Study design

The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial included 15,067 men and women at high cardiovascular risk (Trial Registration Number: NCT00134264). The details of the study population have been previously described.[18] Briefly, men and women aged 45 to 75 years were eligible if they had a prior history of myocardial infarction, stroke, acute coronary syndrome, unstable angina, peripheral vascular disease, or cardiac revascularization within the period of 30 days to 5 years before screening. Patients with T2D who met American Diabetes Association criteria or who were currently on hypoglycemic agents were also eligible. During a run-in period of 4 to 10 weeks, patients received atorvastatin, which was titrated (if needed) at 2-week intervals to achieve LDL cholesterol levels <100 mg/dL with atorvastatin 10, 20, 40, or 80 mg/d. Patients whose LDL cholesterol level met the target were randomly assigned to receive either atorvastatin (at a dose established during the run-in period) plus 60 mg of torcetrapib or atorvastatin