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Roles of HDL and Cholesteryl Ester Transfer Protein in the Prevention of Atherosclerosis: Lesson from the Development of CETP Inhibitors and Subjects with CETP Deficiency

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High density lipoprotein (HDL) has been recognized to be anti-atherogenic lipoprotein since HDL plays a crucial role in reverse cholesterol transport.

A numbers of epidemiological studies reported that low plasma levels of HDL"cholesterol", a clinical marker of HDL levels, correlate to increased prevalence of cardiovascular disease. On the contrary, it has been generally believed that the subjects with high HDLcholesterol levels can escape from atherosclerotic diseases. According to this HDL hypothesis, 5 pharmaceutical industries attempted to develop the drugs which may increase plasma levels of HDL-cholesterol by the inhibition of cholesteryl ester transfer protein, CETP which serves in the transfer of cholesteryl ester from HDL to apoB- containing lipoproteins such as LDL and VLDL. However, none of five companies succeeded the development CETP inhibitors for therapeutic use, although these CETP inhibitors could raise plasma HDL "cholesterol" levels remarkably.

In this presentation. I would like to discuss about the reason why CETP inhibitors could not have anti-atherogenic effect in spite of the function for raising HDL cholesterol by showing the lipoprotein metabolism in the subjects with genetic CETP deficiency which we had discovered more than 30 years ago and have analyzed atherogenisity of the deficiency.

Finally we will show the importance of CETP in the reverse cholesterol transfer system, which is considered to be a protective system of plaque formation by transporting excess cholesteryl ester in vascular cells to the liver through HDL particles.