PCSK9 inhibitors reduce lipoprotein (a) production

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A new study published today in *JACC: Basic to Translational Science* sheds light on PCSK9 inhibitors, a new class of low density lipoprotein (LDL) lowering drugs, and their impact on another risk factor for heart disease, levels of lipoprotein (a).

Efforts to prevent atherosclerotic heart disease to date have focused on lowering LDL concentrations. However, observational and human genetic studies have identified lipoprotein (a) as an important risk factor for atherosclerotic cardiovascular risk, which is independent of LDL. In particular, African Americans tend to have higher lipoprotein (a) levels. Despite the wealth of observational epidemiology and genetic data, the therapeutic targeting of lipoprotein (a) has proven difficult. Most drugs that target lipid metabolism, including statins, have little effect on lipoprotein (a).

PCSK9 inhibitors, antibodies that neutralize proprotein convertase subtilisin/kexin type 9, are the latest FDA approved therapy for treating elevated LDL cholesterol levels. While PCSK9 inhibitors dramatically lower blood cholesterol levels, research evaluating the safety of these agents and their effectiveness in preventing cardiovascular events is underway.

In addition to lowering blood cholesterol levels, PCSK9 inhbitors diminish lipoprotein (a) concentrations, offering hope that PCSK9 inhibitors may also prove beneficial to treat patients with elevated lipoprotein (a) levels.

This new study shows that PCSK9 increases the release of lipoprotein (a) by liver cells, and treatment with a PCSK9 inhibitor reduces the secretion of lipoprotein (a) by liver cells, a mechanism that differs distinctly from the LDL lowering action of these agents.

"There is currently a clear need to understand how, unlike statins, PCSK9 inhibitors reduce the circulating levels of lipoprotein (a) in patients," said Gilles Lambert, Ph.D., senior author of the study. "This could result from an enhanced clearance and/or a reduced production of lipoprotein (a). To answer this question, we have investigated the role of PCSK9 and of the low-density lipoprotein receptor in mediating lipoprotein (a) cellular uptake."

Researchers looked at skin cells from patients with and without familial hypercholesterolemia as well as cultures from liver cells. These cells were treated with PCSK9 and/or alirocumab, a PCSK9 inhibitor, while others were not. Lipoprotein (a) cellular uptake occurred in a low-density lipoprotein receptor-independent manner. Neither PCSK9 nor alirocumab altered the internalization of lipoprotein (a). However, the secretion of apolipoprotein (a) in liver cells sharply increased when treated with PCSK9, but treatment with alirocumab reversed this effect.

"These findings provide a novel mechanism of action to explain why and how PCSK9 inhibitors lower lipoprotein (a) levels," said Douglas L. Mann, M.D., FACC, editor-in-chief of *JACC: Basic to Translational Science*. "PCSK9 inhibitors, currently used only to treat patients with familial hypercholesterolemia, may also have much broader applicability than originally proposed."

"This study raises the optimistic note that further dissection of the molecular mechanisms by which PCSK9 modulates lipoprotein (a) production will not only increase our understanding of the effects of this pleiotropic molecule but also provide potential new areas of development for therapies that can modulate lipoprotein (a)," said Peter Libby, M.D., FACC, in an editorial comment accompanying the study. "Given the dearth of acceptable pharmacological approaches to lowering lipoprotein (a) in our current armamentarium, the advent of the anti-PCSK9 antibodies and the new insight that they lower lipoprotein (a) plasma concentrations by

inhibiting hepatic production rather than by augmenting catabolism, as they do in the case of LDL, has both mechanistic and therapeutic implications for the future."

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