PCSK9 inhibitors: Studies needed to prove efficacy and safety in chronic kidney disease

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Chronic kidney disease (CKD) is associated with a substantially increased risk for the development of atherosclerotic cardiovascular disease (CVD). Accordingly, cardiovascular mortality is increased even in the earliest stages of CKD. In the general population and in CKD patients, high plasma levels of low-density lipoprotein cholesterol (LDL-

C) are crucially involved in the initiation and progression of atherosclerotic vascular lesions. In addition, it has been documented that LDL accumulating in the vascular wall is prone to be post-translationally modified, for example, by oxidation or carbamylation, which is particularly relevant to patients with CKD.

Lowering LDL-C by use of statins and/or ezetimibe represents the gold standard of lipid-lowering therapy with a great body of evidence from several large clinical trials. Statin therapy reduces cardiovascular events in patients with normal and impaired kidney function alike, while the evidence for patients on maintenance haemodialysis is rather weak. Moreover, reduced kidney function may represent a risk factor for statin-related adverse outcomes such as myopathy.

The inhibition of proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) represents a novel lipid-lowering tool directly modulating hepatic LDL metabolism. PCSK9 protein reduces the expression of LDL-receptor (LDLR) on the surface of liver cells and, thereby, decreases cellular uptake of LDL and thus its clearance from the circulation. Currently, the monoclonal antibodies evolocumab and alirocumab are approved PCSK9 inhibitors. Despite maximum-tolerated statin therapy, they efficiently further reduce LDL-C plasma levels without any major adverse effects.

Moreover, in large clinical outcome trials, both antibodies have been proven to lower cardiovascular events. Notably, the LDL-lowering capacity was independent of baseline kidney function and also efficient in patients with moderate CKD. However, patients with severely impaired kidney function—i.e. the population at the highest cardiovascular risk—have been excluded from those trials. The relevance of the LDL-independent effects of PCSK9 inhibitors such as lowering lipoprotein(a) or ameliorating dyslipidaemia in patients with nephrotic syndrome has to be determined.

"In particular, in patients with advanced CKD, the high annual costs of therapy with PCSK9 inhibitors have to be balanced against weak evidence for a benefit," explains Thimoteus Speer, corresponding author of the review PCSK9 in kidney disease. "Specific studies in CKD patients are mandatory to prove the efficacy and safety of PCSK9 inhibitors and to determine their ability to improve outcomes in these patients."

More information: David Schmit et al, Proprotein convertase subtilisin/kexin type 9 in kidney disease, *Nephrology Dialysis Transplantation* (2019). DOI: 10.1093/ndt/gfz122

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