



EMERGING THERAPIES FOR CARDIOVASCULAR DISEASE: PCSK9 Inhibitors and Their Potential Role in Patients with CKD

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Patients with chronic kidney disease (CKD) are at higher risk for premature cardiovascular disease and events in comparison with the general population. This appears to result from a complex interplay of various metabolic and vascular factors. There are some underlying differences in the lipid profile of CKD patients versus individuals without CKD. Among them are an abundance of small, dense, atherogenic LDL particles; elevated concentrations of triglycerides; reduced HDL cholesterol concentrations; altered lipoproteins; and the presence of lipoprotein and chylomicron remnants—findings that are characteristic of the lipid profile in this population. Among other variables that affect the heightened propensity of CKD patients to cardiovascular disease are increased oxidative stress, vascular calcification, and the adverse impact of common comorbid conditions, including diabetes mellitus and hypertension.

Statins and ezetimibe are recognized as the main cholesterol-lowering drugs. Although post hoc analyses of several large clinical trials have shown the efficacy of statins in reducing cardiovascular deaths in the CKD population (not using dialysis) with a magnitude of benefit similar to that in the general population, these trials suffered from under-representation of this subset of the population and the exclusion of patients with advanced kidney disease (1). Moreover, most statins are renally cleared, and the risk of drug–drug interaction in CKD patients limits the use of high-intensity statins in this population subset.

More recently, the newer cholesterol-lowering drugs that are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) have been approved for the control of dyslipidemia in high-risk populations when standard lipid-lowering therapies fail to sufficiently reduce LDL cholesterol levels. PCSK9 binds to the LDL receptor on hepatocytes, resulting in lysosomal degradation of the PCSK9/LDL receptor complex, thereby promoting increased LDL levels and LDL synthesis. Inhibition of PCSK9 results in increased recycling of the LDL receptor to the cell surface, which promotes the removal of LDL cholesterol particles from the circulation, thereby lowering LDL cholesterol concentrations while suppressing LDL synthesis. Of note, PCSK9 is also transiently expressed in the kidneys and is thought to play a role in renal development. Podocyte damage is observed to be associated with high PCSK9 levels, as has been not-

ed in the nephrotic syndrome. Knockout of PCSK9 in a mouse model of nephrotic syndrome was associated with improvement in dyslipidemia, which suggests a potential role of PCSK9 inhibitors in treating nephrotic syndrome–associated dyslipidemia (2).

Although PCSK9 inhibition has recently emerged as a promising therapy in reducing cardiovascular risk by aggressively targeting LDL cholesterol, the utility and efficacy of these agents in patients with CKD has yet to be defined. Pooled analysis of alirocumab efficacy data from eight ODYSSEY phase 3 clinical program trials in 4629 high-cardiovascular-risk patients whose levels of LDL cholesterol were inadequately controlled despite maximally tolerated statin with or without ezetimibe therapy showed that it was well tolerated and resulted in a 61% reduction of LDL cholesterol (3). The reduction in LDL cholesterol was maintained for the duration of therapy (up to 104 weeks). Also, there was a significant reduction in non-HDL cholesterol, apolipoprotein B, and lipoprotein A in contrast to statin therapy. These results were further supported by the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial, which evaluated the clinical efficacy and safety of evolocumab when added to standard statin therapy for patients with clinically evident atherosclerotic cardiovascular disease (4). LDL cholesterol levels were reduced by 59%, and the risk of major cardiovascular events was reduced by 15% in patients receiving evolocumab.

Data on the utility of PCSK9 inhibitors in patients with impaired kidney function are lacking, however. In 2018, Toth et al. (5) presented a subgroup analysis of pooled data from eight ODYSSEY phase 3 trials regarding the lipid-lowering effect and safety of alirocumab, particularly in patients with impaired kidney function (defined as baseline estimated GFR of 30–59 mL/min per 1.73 m²). It was found that alirocumab greatly lowered LDL cholesterol levels, along with apolipoprotein B and lipoprotein A, regardless of kidney function. Also, the reduction in LDL cholesterol did not vary with the level of proteinuria. It was generally well tolerated and did not affect renal function over time, irrespective of baseline renal function. However, patients with severe CKD (estimated GFR <30 mL/min per 1.73 m²) and ESRD were excluded from the initial trials and hence could not be studied.

Whether PCSK9 inhibitors should be prescribed to pa-

tients with kidney disease remains unclear. Although they provide an additional reduction of atherogenic lipids and thereby of cardiovascular risk in patients with relatively preserved kidney function, whether this benefit would be found in patients with advancing kidney disease or ESRD is uncertain. Whether this class of agent would be worthwhile will likely also depend on several factors, including the patient's underlying cardiovascular risk, the cost of the therapy, insurance coverage, and the patient's preference. It is important to keep in mind that the majority of trials excluded patients with progressive CKD, severe kidney impairment, and ESRD. Further research into the role of these and other novel agents in patients with kidney disease, while urgently needed, should be guided by remembering that cardiovascular risk in this population is determined by factors well beyond the basic mechanisms of atherosclerosis in the general population. ■

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