Renal impairment, cardiovascular disease, and the short-term efficacy and safety of PCSK9 targeted by inclisiran

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Atherosclerotic cardiovascular diseases (CVDs) result in high mortality and morbidity worldwide, especially when concomitant with chronic kidney disease (CKD). A common risk factor for both CVD and CKD is dyslipidemia. In CVD, lowering of atherogenic lipoproteins, reflected in part by reduction of low-density lipoprotein cholesterol (LDL-C), favorably modifies cardiovascular outcomes, lowering both major adverse cardiovascular events and even death. Accordingly, statin therapy is recommended for patients with CVD in the guidelines of the American College of Cardiology and American Heart Association,[1] and the European Society of Cardiology and European Atherosclerosis Society.[2] In CKD, the effects of lipid-lowering therapies are less prominent. A possible explanation is that in CKD patients other mechanisms such as vascular calcifications and inflammation play more important roles than lipoproteins in atherosclerosis. Dyslipidemia can not only cause CKD, but CKD, in turn, can also cause alterations in the lipid profile. These alterations are called the dyslipidemic profile of CKD, which usually exhibits variable (but mostly lower) levels of LDL-C, increased triglycerides, and decreased high-density lipoprotein cholesterol. Furthermore, CKD patients often have a lower tolerance for statins. The Kidney Disease Improving Global Outcomes guidelines[3,4] recommend statin therapy for patients older than 50 years with CKD and an estimated glomerular filtration rate (eGFR) greater than or equal to 60 mL/min per 1.73 m^2 and statin therapy with or without ezetimibe for patients with an eGFR between 30 mL/min per 1.73 m^2 and 60 mL/min per 1.73 m^2. In adult patients younger than 50 years with CKD (without chronic dialysis or kidney transplantation), statin therapy is only suggested in patients with high cardiovascular risk. In dialysis-dependent CKD there is no evidence for a benefit of statin therapy, and lipid-lowering therapy should not be initiated. However, it is suggested that lipid-lowering therapy be continued if patients already receive statin and/or ezetimibe at the time of dialysis initiation.

Among other established and evolving therapies in atherosclerosis, lipid-lowering therapy targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) is on the rise, achieving LDL-C below levels achievable with statin therapy in most patients — such therapy is thus a therapeutic option for high-risk CVD patients, or for patients in whom current treatment is insufficient due to inadequate effect or intolerance for statins. Inhibition of PCSK9 can be obtained via various routes.

First, two fully human monoclonal antibodies that selectively inhibit PCSK9 are already on the market: evolocumab and alirocumab. Evidence for the efficacy and safety of these PCSK9 inhibitors in patients with CKD is still limited. A recent pooled analysis of eight phase III ODYSSEY trials showed that alirocumab significantly improved the lipid profile of CKD patients, without affecting renal function.[5] The FOURIER study group performed a subanalysis comparing the 8077 individuals (16.1%) with preserved renal function (eGFR $\geq$ 90 mL/min per 1.73 m^2), 15,034 (54.6%) with mild impairment/stage 2 CKD (eGFR 60 to $<$ 90 mL/min per 1.73 m^2), and 4443 (29.3%) with stage 3 or higher CKD (eGFR $<$ 60 mL/min per 1.73 m^2). LDL-C lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistently observed across CKD groups.

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However, given the higher event rates of cardiovascular death, myocardial infarction, or stroke at lower eGFRs, the absolute reduction with evolocumab was greater with more advanced CKD. This is most often seen in other high-risk groups, as polyvascular disease or diabetes, making high-risk patients potentially more suitable for PCSK9 inhibiting.[6] However, both trials investigating clinical outcomes using evolocumab (FOURIER)[7] and alirocumab (ODYSSEY OUTCOMES)[8] excluded patients with severe CKD. FOURIER included only patients with an eGFR greater than or equal to 20 mL/min per 1.73 m^2 and ODYSSEY OUTCOMES greater than 30 mL/min per 1.73 m^2, thereby leaving unanswered the effect of PCSK9 in more advanced stages of CKD.

Second, a new promising strategy is the administration of small interfering RNA targeting PCSK9, such as inclisiran, which is currently in development phase II. Presented in this issue of *Mayo Clinic Proceedings* is a combined analysis from the phase 1 ORION-7 renal study and the phase 2 ORION-1 study,[9] investigating the pharmacodynamic properties of inclisiran in subjects with normal renal function, or mild, moderate, or severe renal dysfunction. Wright et al[9] found that the pharmacodynamic effects and safety profile of inclisiran were similar comparing normal with impaired renal function. Although plasma concentrations of inclisiran are increased in parallel with the degree of renal impairment, circulating inclisiran was undetectable 48 hours after injection in all groups, whereas the LDL-C lipid-lowering effect persists for more than 6 months. Therefore, the authors concluded that dose-adjustments of inclisiran are not required in patients with impaired renal function. These findings are of clinical and practical importance, and the authors should be complimented for this valuable and relevant report. However, this combination of phase I and phase II ORION trials is, of course, just the beginning in assessing the efficacy and safety of inclisiran. The current study indicates the short-term renal clearance effects of inclisiran in a relatively small patient group with only seven patients with severe CKD, without addressing the effect on long-term renal function or the effect on clinical outcomes. Currently, larger cohorts of subjects with various degrees of CKD have been enrolled in the ongoing inclisiran phase III LDL-C lowering studies, and another cohort will be enrolled in the first trial investigating the effects of inclisiran on cardiovascular outcomes.

As may be seen in clinical trials, the patients with more severe CKD were probably healthier than patients with comparably severe CKD in the general population. At least patients with worse renal function were younger at baseline compared with those with less severe kidney disease. Safety in older age groups is yet to be determined, in particular because older patients with CKD are prone to multiple comorbidities and are therefore at a higher risk of CVD and other (competing) morbidity and mortality. Furthermore, LDL-C was lower at baseline for patients with lower renal function. As high-density lipoprotein cholesterol and triglycerides were not reported, it is unknown whether this lower LDL-C matches the above-mentioned dyslipidemic profile in CKD.

In general, CKD patients are a heterogeneous population. In this study regarding inclisiran, the underlying etiology of renal impairment is unknown. Effects on both renal function and cardiovascular outcomes may differ between patients who have a predominantly vascular (eg, hypertension or diabetes) or nonvascular etiology (eg, glomerulonephritis or polycystic kidney disease, etc). Patients with vascular CKD may be more responsive to the effects of lipid-lowering therapy than patients with nonvascular CKD, in part because lipid-lowering therapy may exert different effects on lipid metabolism when vascular disease is present. Furthermore, because CKD stage is based on the measurement of only one creatinine level at baseline, it is unclear whether patients had actual CKD, or

reversible acute kidney injury. Whether renal function deteriorated or improved over time is unknown.

In conclusion, as patients with CKD are at high risk of major adverse cardiovascular events and death, there is a need for alternative and more effective lipid-lowering therapies. In the short term, inclisiran seems to be an effective and safe option in patients with reduced renal function. In the long term, the efficacy and safety of inclisiran in the setting of kidney disease are yet to be determined. A potentially important benefit includes the sustained pharmacologic effect of this agent, necessitating injections only once every 6 months. In turn, such infrequent dosing may reduce cost, may be more appealing to patients, and may facilitate medication compliance in a group often in need of multiple medications.

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