Lipid Lowering in Patients With Kidney Disease
– Is It Really That Hard? –

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Increasing interest has focused on the association between chronic kidney disease (CKD) and adverse cardiovascular outcomes, with evidence that a range of renal-associated parameters, from early findings of microalbuminuria through to the setting of reduced glomerular filtration rate (GFR), identify individuals more likely to experience cardiovascular events.1 Although the high cardiovascular risk in these patients is clear, it remains uncertain how best to optimize the approach to disease prevention in these patients. Despite the unequivocal benefit of statins in large, randomized controlled trials,2 there remains considerable debate on the potential benefits of statins and lipid lowering in patients with established renal impairment.

In this issue of the Journal, Ishii and colleagues3 report the findings of their analysis of statin use in the Kumamoto Intervention Conference Study Registry of 5,901 consecutive patients undergoing stent implantation. They observed that use of more potent statin agents reduced cardiovascular events in patients with mild to moderate kidney disease, whereas use of less potent statin agents had no benefit. In patients with severe CKD, statin therapy, regardless of potency, did not reduce cardiovascular events. These are important findings that provide additional information with regard to achieving effective reductions in cardiovascular risk in the setting of CKD.

Although the broad benefits of statin therapy in cardiovascular disease prevention are well established, there remain uncertainties with regard to the ability to extrapolate these findings to patients with kidney disease. Large-scale clinical trials often have abnormality of some form of renal parameter, whether it be GFR or creatinine, as an exclusion criteria. Accordingly, patients with kidney disease are often excluded from such studies, limiting the interpretation of study findings in this patient cohort. Trials performed specifically in patients with CKD have failed to demonstrate a conclusive clinical benefit of statin therapy.4,5 In parallel, variable reports that individual statin agents may have differential effects on renal parameter,6,7 despite no demonstrated evidence of renal parenchymal injury, further dampen the interest of some clinicians in commencing statin therapy in their patients with kidney disease.

A fundamental question that arises in the setting of kidney disease involves understanding the factors that drive the increased risk of cardiovascular events in these patients. The increased prevalence of factors such as hypertension and calcification in kidney disease may reflect factors that underlie these events, yet are potentially less modifiable by lipid-lowering and statin therapies. This particularly appears to be the case in patients with severe CKD. The statin studies were performed predominantly in patients with more severe kidney disease, in whom the modifiability of cardiovascular events is likely to be less influenced by lipid modification. This is further supported by the observation that use of the cholesterol absorption inhibitor, ezetimibe, reduced event rates in patients with kidney disease, but the benefit was not observed in dialysis-treated patients.8 The current analysis provides further support for the concept that milder forms of kidney disease may associate with a cardiovascular risk that continues to be modifiable by interventions that reduce the levels of atherogenic lipoproteins.

What are the implications of these observations for clinical practice? The lack of evidence for benefit of empirical statin use in patients with CKD in attempts to reduce cardiovascular risk suggests that they should not be prescribed to all patients simply on the basis of renal impairment. Rather, the data continues to support the use of tailored risk prediction in individual patients with a view to using statins in those at higher risk. Furthermore, there are no data to support cessation of statin therapy in high-risk patients. Patients who meet the treatment guidelines for statin therapy should continue to be treated accordingly. The presence of CKD continues to be an important factor associated with a greater cardiovascular risk, although the factors that drive this may be different as the degree of renal impairment reaches end stage.

The findings continue to suggest that lipid lowering is likely to be cardioprotective in the patient with milder forms of CKD. The current report supports a potential benefit of using the more potent statins in this setting, which complements similar findings with ezetimibe. These observations support the benefits of lowering the levels of low-density lipoprotein cholesterol. Whether the benefits of potent statin therapy reflect potential pleiotropic effects remains to be determined. Ongoing studies of novel lipid-modifying therapies, including cholesteryl ester transfer protein inhibitors and proprotein convertase subtilisin kexin type 9 inhibitors, are currently evaluating their effects on cardiovascular events. Whether
they will be of benefit in patients with various degrees of CKD remains to be determined.

Ultimately, we continue to learn what drives cardiovascular events in patients with CKD. Although lipid lowering appears to be of benefit in patients with milder forms of renal impairment, there are likely to be many other factors that underscore cardiovascular events. As these factors are identified they will provide novel approaches for risk prediction and therapeutic modification.

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