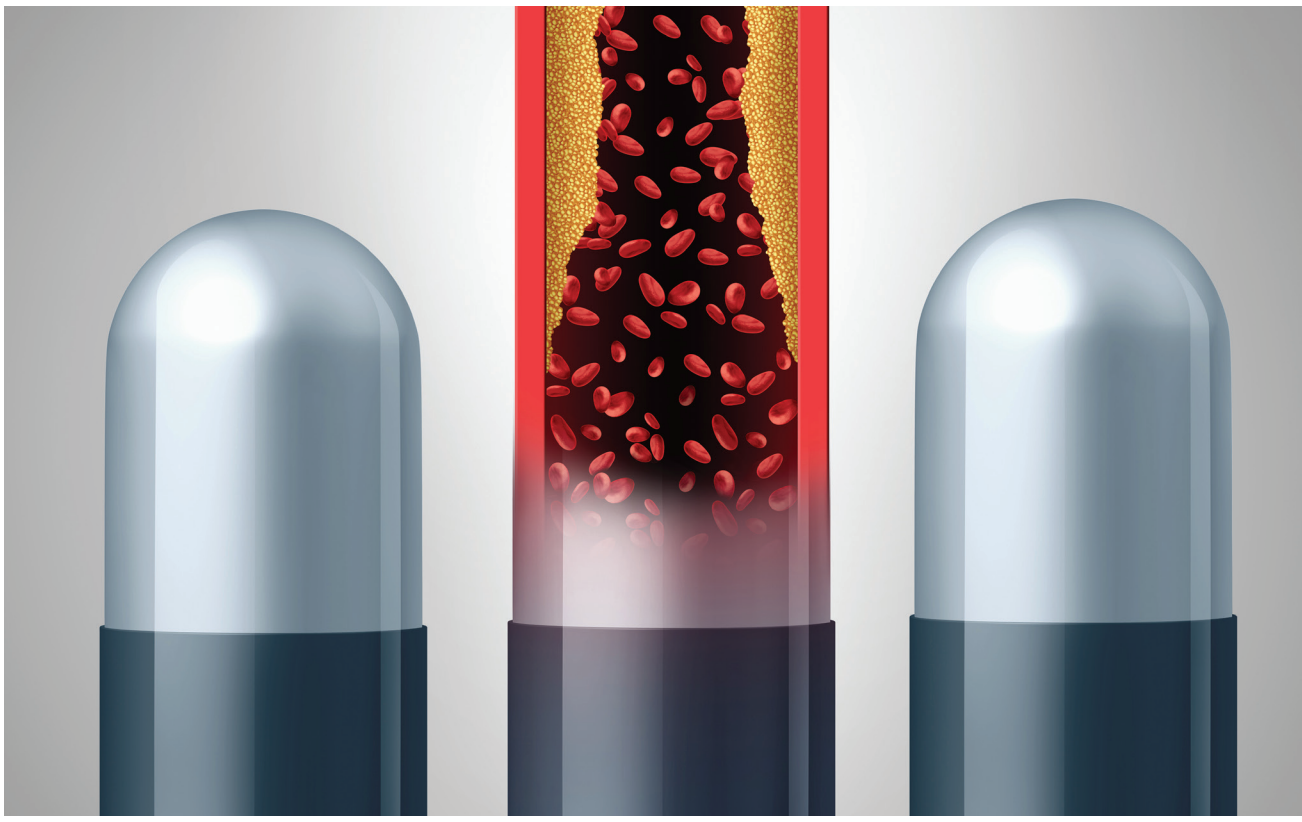
STATIN DRUGS IN CKD AND ESRD: What Is Their Role?

By Yifeng Yang, Mohammed Elsadany, Sonali Gupta, and Joseph Mattana



Dyslipidemia has long been established as a traditional risk factor for cardiovascular disease in the general population. Dyslipidemia, characterized especially by elevated LDL and VLDL, is well known to be associated with higher atherosclerotic cardiovascular disease risk and is a large public health threat.

In patients with chronic kidney disease (CKD) and end stage renal disease (ESRD), cardiovascular disease is accelerated with an even larger impact, compared with the general population. Multiple variables are thought to contribute to this heightened propensity to and accelerated course of cardiovascular disease, including significant alterations in lipoprotein metabolism such as decreased HDL and increased VLDL, vascular damage promoted by uremia-associated inflammation, oxidative stress, and endothelial dysfunction. Microalbuminuria itself, even without diabetes or impaired kidney function, is associated with the development of cardiovascular disease and higher mortality. For patients with ESRD who are using dialysis, their mortality from cardiovascular disease is 10 to 30 times higher than that in the general population.

The well-known 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) can effectively reduce serum LDL levels and have been demonstrated to improve major cardiovascular outcomes and reduce mortality, thus providing these drugs with a major role in the prevention of primary and secondary cardiovascular disease (1). Whereas CKD is a risk factor for accelerated atherogenesis and cardiovascular events, the role of statins is well known to be complex. In patients with CKD stages 1–4, many studies have shown that statins can in fact prevent cardiovascular events. In 2011, the Study of Heart and Kidney Protection (SHARP) trial found a 17% reduction in major cardiac events in the statin-treated group than in the group receiving placebo (2). Subsequently, a meta-analysis by Major et al. (3), including six clinical trials with more than 8000 patients, found that statins reduced the risk of cardiovascular disease by 41% in patients with CKD stages 1–3, including mortality, coronary heart disease events, and stroke. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines thus recommend the use of a statin or a statin/ezetimibe combination for patients with CKD who are older than 50 years and do not require dialysis.

As the CKD stage advances, the benefit of statins on cardiovascular outcomes unfortunately appears to decrease. Using a Health Insurance Research Database, Huang et al. (4) studied >14,000 nondiabetic, CKD stage 5 (estimated GFR <15 mL/min per 1.73 m^2), and predialysis patients. Among them, statin users were identified and were matched to non–statin users with propensity scoring. The investigators found that statin therapy did not appear to decrease the risk of de novo major cardiovascular events in patients with advanced kidney disease, although it was associated with reduced all-cause mortality and sepsis-related mortality.

For patients using either hemodialysis or peritoneal dialysis, statins unfortunately do not appear to be beneficial in reducing cardiovascular events. In 2012, Palmer et al. (5) published a meta-analysis incorporating 80 clinical trials with more than 51,000 participants. They found moderate- to high-quality evidence demonstrating that statins had little or no effect on all-cause mortality, cardiovascular mortality, or cardiovascular events in patients using dialysis. Another meta-analysis of 28 trials and more than 180,000 participants showed that smaller relative effects on major vascular events were observed as estimated GFR declined, and little evidence of benefit was found for patients using dialysis (6). Given these data, the KDIGO guidelines state that initiation of statin treatment is not recommended for hemodialysis patients.

Why do the cardiovascular-protective effects of statins grow smaller as the estimated GFR declines in CKD patients? It has been proposed that the progression of cardiovascular disease in this population may be related more to other lipoproteins, for example, intermediate-density lipoprotein. However, statins, specifically pravastatin, can reduce both intermediate-density lipoprotein and LDL cholesterol concentrations to a similar extent, making this theory somewhat less plausible. Others have proposed that other pathophysiologic processes such as inflammation and arterial wall calcification are more dominant than derangements of LDL metabolism itself. Although statins do have well-known anti-inflammatory effects, in the face of multiple variables that can contribute to vascular wall damage, their efficacy may be consequently blunted. An additional hypothesis is that the level of lipids in the blood may be of lesser importance than intracellular accumulation and that altered expression of cholesterol transport genes promoting a lipid-accumulation phenotype in macrophages may be operative (7).

The role of statins in patients with kidney disease extends beyond cardiovascular protection. A meta-analysis by Navaneethan et al. (8) involving 26 studies and more than 25,000 participants showed that in CKD patients not using dialysis, statins may reduce urine protein excretion, although the authors did not find an impact on the rate of decline in kidney function. Chung et al. (9) carried out a retrospective analysis using a National Health Insurance Research Database in Taiwan and found during a follow-up period of approximately 3 years that statin therapy may reduce the risk of development of ESRD in patients with predialysis advanced CKD. An additional study using this same database revealed that statin use may be associated with a decreased risk for the development of atrial fibrillation/flutter in CKD patients, although, as with the prior study, it is at present unclear to what extent these findings may be applicable to other patient populations (10).

In summary, whereas statins appear to have less of an impact on primary prevention of cardiovascular events, with greater declines in GFR, it is critical to remember that they can benefit many patients with earlier-stage CKD. Other potential effects of statins in patients with kidney disease, such as possibly reducing proteinuria, slowing progression, and decreasing atrial tachyarrhythmias, merit further study. ■

Mohammed Elsadany, MD, Yifeng Yang, MD, and Joseph Mattana, MD, are associated with St. Vincent's Medical Center, Bridgeport, Connecticut, and the Quinnipiac University Frank H. Netter MD School of Medicine, North Haven, Connecticut. Sonali Gupta, MD, is associated with the University of Rochester, Rochester, New York.

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