Should Statins Be Banned from Dialysis?

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The relative decrease in cardiovascular risk by statins diminishes in magnitude as kidney function declines, even after allowing for the smaller reductions in LDL cholesterol obtained in more advanced CKD.1 In patients on maintenance dialysis, several large randomized trials and high-quality meta-analyses revealed that statins have little or no effect on cardiovascular outcome, despite significant LDL cholesterol lowering.1 These counterintuitive findings have been attributed to the poor association of LDL cholesterol with cardiovascular risk in the dialysis population, owing to the predominance of nontraditional risk factors (e.g., mineral and bone metabolism disorder and oxidative stress) and nonatherosclerotic cardiac events (e.g., arrhythmia and heart failure) drowning out classic atherosclerotic disease.2 Overall, about 50% of deaths in patients on dialysis can be attributed to cardiovascular disease. Systematic adjudication reveals that the majority of these deaths are caused by nonatherosclerotic factors (e.g., sudden death is responsible for one quarter of all deaths), whereas acute myocardial infarction accounts for a surprisingly low 4%–5% of deaths.3 However, even typical statin-sensitive outcomes, such as myocardial infarction and stroke, do not seem to be significantly reduced by statins, suggesting a true lack of efficacy in patients on dialysis. The complex lipid abnormalities in CKD (e.g., lipoproteins rendered highly atherogenic by oxidation or carboxylation) may be less affected by statins.2 Furthermore, inflammatory stress activates intracellular cholesterol synthesis, which is not fully inhibited by conventional doses of statins.4 This “statin resistance” leads to intracellular lipid accumulation in the vessel wall, whereas plasma cholesterol may be adequately reduced.4 Other explanations for the disappointing results have been insufficient sample size and duration of the studies in patients on dialysis. However, follow-up for >11 years of patients originally included in the Die Deutsche Diabetes Dialyse Studie (4D Study) endorsed the initial conclusions of the study.5 Taken together, the beneficial effect of statins may be curtailed by the distinct dyslipidemia and pathophysiology of cardiovascular disease in uremia. Whether statins may be advantageous to specific subgroups of patients on dialysis (e.g., those with significantly elevated LDL cholesterol or a history of typical atherosclerotic events) remains to be determined.

The 2013 American College of Cardiology/American Heart Association and the 2014 National Lipid Association Guidelines do not provide any specific recommendations for the treatment of dyslipidemia in patients on dialysis.6 The 2014 Kidney Disease Improving Global Outcomes Lipid Work Group suggests that statins should not be initiated in patients on dialysis, but that statins can be continued in patients already receiving them at the time of dialysis initiation.6 Despite the proven lack of meaningful gains and concerns about costs, polypharmacy, and side effects, statins are currently still widely prescribed to patients on dialysis and viewed as safe and effective agents by most nephrologists.7 However, a new insight may dictate the need to reconsider this attitude.

A recent observational study in patients on RRT revealed that the use of statins correlated with a higher baseline coronary artery calcification (CAC) score, independent of age, sex, and diabetes, as well as a more rapid progression of CAC score in a longitudinal evaluation compared to no treatment with statins.8 Several randomized studies in patients without kidney disease have previously shown that statins cause a progression of CAC, but this was never associated with a greater risk of cardiovascular events.9,10 A classic high-risk atheroma consists of a thin fibrous cap and a lipid-rich core prone to rupture. Statins decrease coronary artery plaque volume and simultaneously replace the lipid core with fibrosis and calcification. This conversion of plaque constituents with an increase in calcium content most likely represents plaque repair, improves plaque stability, and should thus be viewed as a beneficial effect.9,10

However, taking into account the profoundly different pathophysiology of cardiovascular disease in patients on dialysis, the prognostic implications of statin-induced CAC may not be as benign as in the general population. In patients on dialysis, calcium accumulation in the arterial system is highly prevalent. Calcification of the intimal layer, arterial media calcification, and aortic and mitral valve calcification often occur simultaneously. Calcium deposition in the intima
and media with thickening of the vessel wall and obliteration of the lumen impairs blood supply to the tissues. Media calcification induces arterial stiffness, thus contributing to left ventricular hypertrophy and ultimately, heart failure. The myocardial fibrosis that accompanies left ventricular hypertrophy is conductive to conduction abnormalities and eventually, arrhythmic death. Calcific aortic valve sclerosis adds to the risk of left ventricular hypertrophy. Finally, mitral valve calcification may contribute to atrial fibrillation, thromboembolic events, and stroke. Taken together, in a uremic environment, calcification progression induced by statins may thus potentially compound the already severely elevated cardiovascular risk. Although vascular calcifications indisputably and strongly associate with subsequent cardiovascular events, it has been debated whether they are causally related to adverse outcome or merely represent the end stage of vascular inflammation. Positron emission tomography using the combination of $^{18}$F-fluorodeoxyglucose, a validated marker of atherosclerotic inflammation, and $^{18}$F-sodium fluoride, a marker of osteogenesis, holds promise as a new tool to dissect out active remodeling and atherosclerosis from inert calcium masses.\(^{11}\)

The pathophysiology of the procalcifying effects of statins is unknown. Statins exert their lipid-lowering effects by inhibition of hepatic hydroxymethyl glutaryl-CoA reductase, the rate-controlling enzyme of the mevalonate pathway responsible for the production of cholesterol and other isoprenoids. Most of the pleiotropic effects of statins result from inhibition of protein prenylation, affecting crucial cellular signaling pathways.\(^2\) In vitro, statins stimulate vascular smooth muscle cell apoptosis and subsequent calcification,\(^8\) but it is unknown whether this process is at play in vivo. Statins may also exert their procalcifying effects by affecting vitamin K metabolism. The conversion of vitamin K1 derived from dietary vegetables to vitamin K2 in the tissues requires isoprenoids derived from mevalonate.\(^{12}\) In vitro, statins inhibit the synthesis of vitamin K2.\(^8,^{12}\) Vitamin K2 is essential for the activation of proteins responsible for inhibition of vascular calcification, such as matrix-Gla protein and growth arrest–specific protein 6. Vitamin K deficiency is highly prevalent in patients on dialysis and is currently intensively researched as a key player and modifiable risk factor in the development of vascular calcifications in dialysis.\(^{13}\) It is thus tempting to bolster the hypothesis that statins may accelerate vascular calcifications in patients on dialysis by further depleting vascular vitamin K2 levels. This mechanism may thus abrogate the potential favorable effects of LDL cholesterol lowering and be an alternative explanation for the apparent lack of clinical benefits of statins in patients on dialysis.

In conclusion, the evidence supporting a beneficial effect of statins in patients on dialysis is moot, but this has not discouraged physicians to prescribe these drugs. However, the insight that statins potentially accelerate vascular calcifications in patients on dialysis may persuade nephrologists to ban statins from dialysis, pending hard data to supersede these assumptions. As Hippocrates said, make a habit of two things—to help or at least, to do no harm.

**DISCLOSURES**

None.

**REFERENCES**


