Hepatic hydroxymethyl glutaryl-CoA reductase inhibitors, known as statins, are among the most commonly prescribed drugs in the world. Scientists studying microorganism host defense first identified statins in the 1970s. They were eventually shown in large randomized trials, such as the Scandinavian Simvastatin Survival Study and the West of Scotland Coronary Prevention Study, to confer substantial clinical benefits over placebo in individuals with hypercholesterolemia. Statins are now a cornerstone for both primary and secondary prevention of coronary heart disease. A number of noncardiovascular benefits—such as in dementia, sepsis, and cancer—have also been proposed, largely on the basis of observational data.

In this issue of JASN, Molnar et al. report the results of an observational study on the association between statin use and decreased incidence of perioperative acute kidney injury (AKI) and mortality. The population-based cohort contained data on 213,347 Ontario Drug Benefits Plan recipients who were aged ≥66 years and underwent elective cardiac, thoracic, vascular, abdominal, or retroperitoneal surgery between 1995 and 2008. As anticipated, those who received statins tended to have more comorbid atherosclerotic disease, hypertension, diabetes, and congestive heart failure; to be treated with a greater number of total and cardiovascular-related medications; to have undergone more extensive cardiovascular diagnostic evaluations and procedures; and more likely to be undergoing cardiac and vascular surgery. On this basis, unadjusted analyses demonstrated an increased risk in perioperative AKI and dialysis use among statin users. However, upon multivariable and propensity score adjustment, statin use was associated with a 14 to 17% reduction in these outcomes. Curiously, unadjusted mortality was 27% lower in the statin group despite greater comorbid disease burden; mortality risk remained 15 to 21% lower after statistical adjustment. Analyses that appropriately accounted for healthier adherer bias and dose-response trends yielded corroborative findings. The population-based cohort design promotes generalizability, although, in fairness, only to elderly patients undergoing elective surgery.

As with all research on humans, internal validity of findings is contingent on accurate characterization of events and conditions. Absent available laboratory data, AKI was characterized solely on the basis of diagnostic codes. Considering the cohort’s era, the majority of hospitalizations would have been coded using the International Classification of Diseases, Ninth Revision classification system, which has only 28.3% sensitivity for AKI. Moreover, chronic kidney disease (CKD)—arguably the most important covariate—was assessed with only 22.9% sensitivity and 87.5% specificity (Appendix D-2). Thus, both the outcome and a critical covariate had substantial error rates.

An often-repeated mantra in epidemiologic research is that nondifferential misclassification biases toward the null hypothesis. In other words, if information on AKI or CKD or other covariates were inaccurate but randomly so, then a study would tend to find no association even if an association existed and would therefore not account for the protective association seen in this study. However, this is an oversimplification for at least two reasons. First, if errors in diagnostic codes were correlated—that is, errors in AKI codes were more common in those with errors in CKD codes, such as might occur for patients with limited medical follow-up—then measures of association could be biased in either direction. Second, we previously showed that AKI diagnostic codes in fact suffer from relevant nondifferential misclassification: codes have higher sensitivity in men than in women, in the elderly, and in those who die in-hospital. To the extent that statin use in the Ontario cohort differed by race, gender, and mortality, misclassification bias cannot be ignored.

As with any observational study, the potential for causal inference must also be interpreted in light of the underlying biological basis and literature precedent. Studies of animal models demonstrated that statin use is associated with a decreased risk for ischemia-reperfusion kidney injury. Proposed mechanisms include favorable effects on oxidative metabolism involving heme oxygenase 1, NF-κB, activator protein 1, mevalonate, and nitric oxide. However, animal data do not invariably translate to clinical practice. For example, N-acetyl cysteine showed similar promise in preclinical models yet demonstrated little to no clinical efficacy in preventing perioperative AKI.

In addition, any cogent attempt to rationalize the study’s findings as causal should account for the graded trend toward incrementally better outcomes among patients exposed to statins for shorter periods (adjusted odds ratios 0.86, 0.77, and 0.61 for statin use >90, 30 to 90, and <30 days, respectively),
which does not follow intuitively on the basis of the proposed mechanism and may instead signal residual confounding.

The plausibility of the magnitude of the observed benefits also needs to be considered in light of previous studies. Molnar et al. report a striking 21% lower odds of death, which is comparable to—or greater than—effects sizes seen in placebo-controlled trials of statins in patients at cardiovascular risk; that is, those with hypercholesterolemia and previous coronary heart disease. It is hard to imagine that the mortality benefit of statins in this population-based study could equal or exceed that seen in populations with high cardiovascular risk.

Notwithstanding these issues, let us consider the therapeutic implications of the study’s findings assuming that estimates are both unbiased and causal. Perioperative AKI was observed in 1.9% of patients. Using the most favorable estimate for the effect of statins (odds ratio 0.84), 1000 patients would need to be treated to avert three instances of AKI. This number treated would avert fewer than one episode of dialysis-requiring AKI. At the same time, estimates from the literature suggest that such treatment would result in approximately four cases of aminotransferase elevation,11 as well as a heightened risk for myalgias, myopathy, and rhabdomyolysis.12 Furthermore, informed assessment of the net health benefits of perioperative statin renal prophylaxis would require simultaneous consideration of permanent renal injury; that is, residual CKD or ESRD and sequelae thereof. Although the article does not address this specifically, absence of association between statin use and reduced dialysis dependence 90 to 120 days postoperatively may be cause for pessimism vis-à-vis long-term renal benefit.

Alternatively, it is possible that perioperative renal prophylaxis with statins could be targeted to patients at high risk for perioperative AKI, for whom the risk-benefit ratio might be more favorable. However, the data at hand cannot provide supportive evidence for such a paradigm given that subgroup analyses restricted to those at highest risk— for example, patients with diabetes and those with pre-existing CKD—were not performed.

As the authors note, sample size requirements likely preclude the possibility that a dedicated, hard end point, randomized trial will ever be conducted. Considering residual uncertainties, we wonder whether a smaller randomized trial using kidney injury biomarker surrogate end points might be warranted. Would the finding of lower kidney injury biomarker levels postoperatively in patients randomly assigned to statins versus placebo provide sufficient evidence to justify widespread use of statins overall or in high-risk patients? Possibly, but consider the instructive story of torcetrapib, which increased HDL levels but also increased the risk for death in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerosis Events (ILLUMINATE) trial. Approval of torcetrapib on the basis of improvement in a biologically plausible but untested surrogate end point would have been a catastrophic failure.14 Although the U.S. Food and Drug Administration and other international regulatory agencies have qualified several kidney injury biomarkers for preclinical nephrotoxicity monitoring,15 it remains unclear whether and in which contexts novel biomarkers may be acceptable surrogate end points for AKI trials. At the very least, follow-up observational studies using cohorts with available laboratory data are needed before clinical adoption.

To summarize, Molnar et al. have produced a careful analysis of a large data set suggesting an association between statin use and lower risk for postoperative AKI. Unfortunately, potentially insurmountable limitations related to confounding by indication and differential misclassification of exposure and outcome status render the findings insufficiently persuasive to warrant adoption into clinical practice despite the rigor of the authors’ analytic approach. Barring corroborative findings in other studies, this analysis may be relegated to be yet another footnote in the long, sad saga of failed AKI therapeutics.

DISCLOSURES
None.

REFERENCES
10. Adabag AS, Ishani A, Bloomfield HE, Ngo AK, Wilt TJ: Efficacy of
New Insights to Fibroblast Growth Factor 23 in Kidney Transplant

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Some abnormalities in mineral metabolism are evident even at very early stages of chronic kidney disease (CKD) and are important determinants of subsequent bone and cardiovascular disease.1,2 A decade ago, fibroblast growth factor 23 (FGF23) was recognized by a few as the protein responsible for several rare inherited and acquired syndromes of osteomalacia and rickets.3,4 Only recently have studies demonstrated the significance of FGF23 in mineral metabolism in the larger population of patients with CKD and ESRD.5–7 In 2007, Fliser et al.8 reported that higher FGF23 levels were strongly associated with progression of non diabetic CKD. The next year, Gutierrez et al.9 published that incident hemodialysis patients with higher FGF23 levels were at substantially greater risk for all-cause mortality. These and other studies generated considerable interest in the role of FGF23 in mineral metabolism homeostasis in CKD.

Recent reports extend these findings by showing that FGF23 levels are elevated at very early stages of CKD,2 and the associations of FGF23 with all-cause mortality or cardiovascular disease extend to patients with stages 3 to 4 CKD,10 and even to individuals with ostensibly normal kidney function.11 In this issue of JASN, Wolf et al.12 report that higher FGF23 levels associate with the composite outcome of all-cause mortality or kidney allograft loss among 984 stable transplant recipients. Most of the participants were several years after transplantation. This finding is significant for several reasons. First, in conjunction with other literature, this study demonstrates that higher FGF23 levels identify patients at increased risk for adverse outcomes across the spectrum of CKD. Second, because most kidney transplant recipients have survived an extended period on dialysis before receiving an allograft and often have a high burden of vascular disease, the study demonstrates that FGF23 continues to provide risk information in this late stage of disease. Last, given the pattern of other mineral metabolism abnormalities observed in kidney transplant recipients, the study provides new insights into potential mechanisms, as described further next.

With these discoveries come new challenges. Among the most pressing is a better understanding of mechanisms responsible for the link of FGF23 with adverse outcomes.7 Several possibilities require special consideration. A main biological function of FGF23 is to increase urine phosphorus excretion.4,13 A wealth of data spanning from the laboratory to population-based studies implicates hyperphosphatemia as a key factor inducing and promoting arterial calcification.14–16 Thus, perhaps high FGF23 levels are linked with mortality through alterations in phosphorus homeostasis. Several studies have investigated this possibility. Consistently and observed again in the article by Wolf et al.12 in this issue, statistical adjustment for serum phosphorus levels measured concurrently with FGF23 does not attenuate its relationship with outcomes.8–12 However, phosphorus may remain an important intermediary nonetheless. Contemporary clinical laboratories precisely measure serum phosphorus levels, typically with coefficients of variation <3%. However, there is considerable biological variability in serum phosphorus levels within individuals over time.17 This is analogous to serum glucose, for which one can precisely determine the blood level at a given moment, but it gives a mere snapshot of average glucose levels over time. Thus,