Published in final edited form as:

Am J Kidney Dis. 2013 November ; 62(5): 877–879. doi:10.1053/j.ajkd.2013.07.006.

High-Potency Statins and Acute Kidney Injury–Associated Hospitalizations

Colin R. Lenihan, MBBCh and Richard A. Lafayette, MD

Stanford University School of Medicine Stanford, California

Statins have had a dramatic impact on the primary and secondary prevention of cardiovascular disease.^{1–3} In the United States, >10% of the entire population and 40% of those older than 65 years are prescribed an HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor.⁴ The efficacy and relative safety of these agents has led many to argue for universal statin use in everyone older than 50 years.⁵ However, recent concerns about the risks of rhabdomyolysis, diabetes mellitus, and memory impairment have prompted the US Food and Drug Administration (FDA) to issue safety warnings.^{6,7} Now, a new study in the *British Medical Journal* has identified a higher rate of hospitalization with acute kidney injury (AKI) in individuals who use high- versus low-potency statins.⁸

WHAT DOES THIS IMPORTANT STUDY SHOW?

This large retrospective study merged data from several health care databases in Canada, the United Kingdom, and the United States to study the association of high-potency statin use (defined as rosuvastatin, 10 mg, atorvastatin, 20 mg, or simvastatin, 40 mg daily) versus low-potency statin use with the development of AKI. The study required participants to have a 1-year run-in period of enrollment in their respective databases. This allowed them to identify and exclude individuals treated with cholesterol-lowering drugs and extract an extensive array of medical comorbid condition, health care, and prescription data for each participant. The investigators computed propensity scores for high- versus low-potency statin exposure for each participant using 500 covariates. From a pooled population of more than 45 million people, the investigators identified 651,069 patients newly exposed to high-potency statins and 1,356,934 patients newly exposed to low-potency statins between January 1997 and April 2008. The study also identified a subset of patients with chronic kidney disease (CKD), of whom 22,341 and 37,295 were treated with high- and low-potency statins, respectively. The primary end point was hospitalization for AKI identified by diagnosis codes. Each case of AKI was matched with 10 controls by propensity score.

Hospitalization for AKI within 6 months of statin exposure occurred in approximately 3 and 39 per 1,000 patients in the non-CKD and CKD cohorts, respectively. The relative risk of AKI in individuals exposed to high- versus low-potency statins was expressed in terms of duration of exposure: 120 or fewer, more than 120 and up to 365 days; more than 365 and

up to 760 days; and past therapy. High- versus low-potency statin use was associated with a significant increase in hospitalizations for AKI; the adjusted rate ratio was greatest within 120 days of exposure at 1.34 (95% confidence interval [CI], 1.25-1.34) and was attenuated with increased duration of exposure. No significant association between high-potency statin use and AKI in the CKD cohort was identified (adjusted rate ratio, 1.10; 95% CI, 0.99-1.23). The authors estimated that 1,700 patients needed to be treated with a high- versus low-potency statin for 120 days to cause one additional hospitalization with AKI.

This is an interesting and provocative retrospective analysis of statin use and hospital admission for AKI. The analysis is very well conducted and its large size permits the detection of differences in a relatively uncommon outcome that many randomized controlled trials are underpowered to detect. The authors use a number of techniques to minimize confounding by indication, which is by far the greatest threat to the validity of their results. First, the authors chose to compare high- versus low-potency statin use rather than statin versus no statin use, ensuring that all participants had an indication for statin treatment. Second, the authors use propensity score-matched analysis. Propensity scores are used to estimate the probability of a participant receiving one or another intervention, in this case, high- versus low-dose statin therapy. Comparing the outcome of participants with matched propensity scores (an equal probability of receiving high- or low-potency statin) can be helpful in reducing indication bias.⁹ However, even with these precautions, residual confounding by either unmeasured or inaccurately extracted variables and by the remaining imbalance in participants with cardiac failure and baseline hospitalization rates in the propensity-matched intervention groups may still account for some or all of the observed differences in AKI hospitalization rates. The study fails to show a significant increase in AKI hospitalization with high-potency statins in the CKD cohort. Although the CKD cohort size is comparatively small, CKD is a well-established risk factor for nephrotoxin-induced AKI^{10,11} and intuitively would be expected to greatly magnify any effect. The lack of data about mechanisms of hospitalization for AKI also is a weakness. For example, if the majority of hospitalizations were due to rhabdomyolysis, the findings would be lent a certain mechanistic credibility. Finally, the need for acute dialysis, which medical coding usually captures reliably, was not reported.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

There are relatively few large-scale data regarding AKI in statin users. The authors cite JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), a randomized controlled trial comparing the effect of rosuvastatin, 20 mg, versus placebo on adverse cardiovascular outcomes in individuals without a history of cardiovascular disease. The authors emphasize that the rosuvastatin group had a nonsignificant increase in AKI (risk ratio, 1.19; 95% CI, 0.61-2.31), which was reported to the FDA. Nonetheless, JUPITER demonstrated an extremely impressive reduction in the primary outcome in participants treated with rosuvastatin.¹² Other data linking statin use with AKI include a large retrospective study of 225,922 statin users registered with general practitioners in the United Kingdom that identified a significant dose-response association between statin use and AKI¹³ and an analysis of the FDA Adverse Event Reports between

2004 and 2009 that identified signals associating pravastatin, simvastatin, atorvastatin, and rosuvastatin use with rhabdomyolysis and AKI.¹⁴

There also has been significant interest in a potential kidney-protective role for statins. Administering statins significantly attenuates renal ischemia-reperfusion injury in experimental rat models,^{15,16} and 3 recent retrospective analyses with a combined population of more than 300,000 patients undergoing major surgery concluded that preoperative statin use is associated with a decrease in risk of postoperative AKI.¹⁷⁻¹⁹ However, similarly designed studies have failed to confirm this kidney-protective effect for statins.^{20,21}

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The results of this study certainly should prompt review of the efficacy and safety of high- versus low-dose statins. Current American Heart Association guidelines suggest statin dosing that “reduces LDL-C [low-density lipoprotein cholesterol] to 100 mg/dL AND achieves at least a 30% lowering of LDL-C” in all patients with cardiovascular disease and an LDL cholesterol target <70 mg/dL in high-risk patients.^{22(p2,433)} However, new guidelines may deemphasize the importance of LDL cholesterol targets and instead advocate statin dosing based on an individual’s overall cardiovascular risk profile.^{23,24}

A number of randomized controlled trials have suggested benefit for high- versus low-potency statins. SAGE (the Study Assessing Goals in the Elderly) compared high- versus low-potency statin in more than 800 elderly patients with a history of myocardial ischemia and showed no difference in the primary end point of absolute change in duration of myocardial ischemia on Holter monitor, but showed a significant reduction in the post hoc end point of death in the high-dose group. There was no difference seen in rhabdomyolysis or major adverse events.²⁵ In the Intensive Versus Moderate Lipid Lowering With Statins After Acute Coronary Syndromes trial, using high- versus low-potency statin treatment after acute coronary syndrome resulted in a 16% reduction in the composite end point of death or major cardiovascular event over a follow-up of 24 months. Rates of major adverse events and creatine kinase level elevation were similar in the 2 groups.²⁶ Statin therapy after ischemic stroke has proven benefits and a recent retrospective study showed that treatment with high- versus low-dose statin therapy poststroke was associated with reduced mortality.^{27,28} However, a meta-analysis of 10 randomized controlled trials comparing high- versus low-/moderate-dose statins found no association with statin intensity and all-cause or cardiovascular death, but showed a reduction in the composite of coronary heart disease death and also found nonfatal myocardial infarction and the composite of fatal and nonfatal stroke to be associated with high-dose statins. The study found no overall increase in the rate of rhabdomyolysis, but noted an increased incidence of creatine kinase level elevation with high-intensity statin treatment in 2 trials.²⁹ The meta-analysis included one trial of high- versus low-dose simvastatin in which all of the 7 reported cases of rhabdomyolysis (in >12,000 study participants) developed in high-dose users.³⁰ Recent analysis of adverse-event reports from the United States and Canada identified more than 800 cases of statin-associated rhabdomyolysis per annum. Rhabdomyolysis was more common with high-dose statin use and was complicated by AKI in nearly 20% of cases.³¹

Statins are extraordinary drugs with a highly impressive benefit to adverse-event profile. Dormuth et al⁸ have associated a significant increase in hospitalization for AKI with high-versus low-potency statin use. Whether this observed difference in this relatively rare event is of clinical significance is uncertain. Further evaluation of statin dosing intensity and adverse outcomes certainly are warranted and physicians should prescribe high-dose statins prudently. However, for now, our enthusiasm for the use of statins to achieve goals and reduce events remains undulled.

Acknowledgments

Support: None.

REFERENCES

1. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012; 380:581–590. [PubMed: 22607822]
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994; 344:1383–1389. [PubMed: 7968073]
3. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med*. 2009; 169:260–268. [PubMed: 19204217]
4. National Center for Health Statistics. [Accessed May 15, 2013] Health, United States. 2011. <http://www.cdc.gov/nchs/data/hsr/hsr11.pdf>
5. Ebrahim S, Casas JP. Statins for all by the age of 50 years? *Lancet*. 2011; 380:545–547. [PubMed: 22607823]
6. FDA Drug Safety Communication. [Accessed May 15, 2013] Important safety label changes to cholesterol-lowering statin drugs. 2012. <http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm>
7. FDA Drug Safety Communication. [Accessed May 15, 2013] New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>
8. Dormuth CR, Hemmelgarn BR, Paterson JM, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ*. 2013; 346:f880. [PubMed: 23511950]
9. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health*. 2000; 21:121–145. [PubMed: 10884949]
10. Oliveira JF, Silva CA, Barbieri CD, Oliveira GM, Zanetta DM, Burdmann EA. Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother*. 2009; 53:2887–2891. [PubMed: 19364846]
11. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002; 105:2259–2264. [PubMed: 12010907]
12. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359:2195–2207. [PubMed: 18997196]
13. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010; 340:c2197. [PubMed: 20488911]
14. Sakaeda T, Kadoyama K, Okuno Y. Statin-associated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. *PLoS One*. 2011; 6:e28124. [PubMed: 22205938]

15. Sabbatini M, Pisani A, Uccello F, et al. Atorvastatin improves the course of ischemic acute renal failure in aging rats. *J Am Soc Nephrol*. 2004; 15:901–909. [PubMed: 15034092]
16. Gueler F, Park JK, Rong S, et al. Statins attenuate ischemiareperfusion injury by inducing heme oxygenase-1 in infiltrating macrophages. *Am J Pathol*. 2007; 170:1192–1199. [PubMed: 17392159]
17. Brunelli SM, Waikar SS, Bateman BT, et al. Preoperative statin use and postoperative acute kidney injury. *Am J Med*. 2012; 125:1195–1204. [PubMed: 23062398]
18. Molnar AO, Coca SG, Devereaux PJ, et al. Statin use associates with a lower incidence of acute kidney injury after major elective surgery. *J Am Soc Nephrol*. 2011; 22:939–946. [PubMed: 21493769]
19. Layton JB, Kshirsagar AV, Simpson RJ Jr, et al. Effect of statin use on acute kidney injury risk following coronary artery bypass grafting. *Am J Cardiol*. 2013; 111:823–828. [PubMed: 23273532]
20. Kuhn EW, Liakopoulos OJ, Stange S, et al. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90 000 patients [published online ahead of print April 5, 2013]. *Eur J Cardiothorac Surg*. doi:10.1093/ejcts/ezt181.
21. Mithani S, Kuskowski M, Slinin Y, Ishani A, McFalls E, Adabag S. Dose-dependent effect of statins on the incidence of acute kidney injury after cardiac surgery. *Ann Thorac Surg*. 2011; 91:520–525. [PubMed: 21256305]
22. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011; 58:2432–2446. [PubMed: 22055990]
23. Ledford H. Cholesterol limits lose their lustre. *Nature*. 2013; 494:410–411. [PubMed: 23446392]
24. Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. *Circ Cardiovasc Qual Outcomes*. 2011; 5:2–5. [PubMed: 22253366]
25. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007; 115:700–707. [PubMed: 17283260]
26. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004; 350:1495–1504. [PubMed: 15007110]
27. Amarenco P, Bogousslavsky J, Callahan A III, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006; 355:549–559. [PubMed: 16899775]
28. Flint AC, Kamel H, Navi BB, et al. Statin use during ischemic stroke hospitalization is strongly associated with improved poststroke survival. *Stroke*. 2012; 43:147–154. [PubMed: 22020026]
29. Mills EJ, O'Regan C, Eyawo O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J*. 2011; 32:1409–1415. [PubMed: 21385791]
30. Armitage J, Bowman L, Wallendszus K, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010; 376:1658–1669. [PubMed: 21067805]
31. Holbrook A, Wright M, Sung M, Ribic C, Baker S. Statin-associated rhabdomyolysis: is there a dose-response relationship? *Can J Cardiol*. 2011; 27:146–151. [PubMed: 21459261]