Published in final edited form as:

Nat Rev Nephrol. 2014 December ; 10(12): 680–681. doi:10.1038/nrneph.2014.203.

DIABETES:

Statins for microvascular complications—all but the kidney

Kumar Sharma and

Center for Renal Translational Medicine, University of California, San Diego and Veterans Affairs San Diego Healthcare System, Veterans Medical Research Foundation, San Diego, CA 92161

Loki Natarajan

Division of Biostatistics and Bioinformatics, Family and Preventive Medicine, University of California, San Diego, CA 92093, USA

Kumar Sharma: kusharma@ucsd.edu

Abstract

A new study shows that statin therapy before diagnosis of diabetes mellitus is not associated with an increased risk of microvascular disease and might even be beneficial for retinopathy and neuropathy. These data suggest a potential protective effect of statins in specific complications, which should be further investigated in randomized controlled trials.

Treatment with statins is a robust strategy to reduce cardiovascular complications in patients with coronary artery disease, diabetes mellitus and/or chronic kidney disease (CKD).¹ However, a key question remains as to whether statin therapy can prevent the onset, or reduce the progression, of diabetic microvascular complications, including kidney disease. A recent population-based study by Nielsen and Nordestgaard investigated this question in a cohort of Danish residents with incident diabetes.²

Denmark, similar to numerous other countries with well-organized national health care services, has a comprehensive National Registry of inpatient and outpatient hospital records, with uniform data entry and disease classifications.³ Using this database, Nielsen and Nordestgaard identified 202,016 patients aged 40 years who were newly diagnosed with diabetes between 1 January 1996 and 31 December 2009, and showed no evidence of microvascular complications at the time of diagnosis (as documented by annual retinal exams, neurological signs and symptoms, and urinary albumin-to-creatinine ratios [ACRs]).² They randomly selected 15,679 patients who were on statins at the time of diabetes diagnosis and matched them with 47,037 patients who were not on statins. The matching criteria were gender, age at diagnosis of diabetes, year of diagnosis of diabetes, and prior history of cardiovascular disease. The cohort was followed until the end of 2009 for the development of microvascular complications. Patients were monitored annually with

Competing interests

The authors declare no competing interests.

ophthalmologic examinations, assessment of neuropathy and peripheral artery disease, and urine tests for assessment of ACR.

In this well-characterized longitudinal cohort, patients who received statins before the diagnosis of diabetes had a significantly lower cumulative incidence of retinopathy (hazard ratio [HR] = 0.60), neuropathy (HR = 0.66) and gangrene of the foot (HR = 0.88) than those who did not receive statins. These results remained clinically and statistically significant after correction for the usual clinical variables, including duration of diabetes, blood pressure and glycaemic control. Surprisingly, statin use did not protect against the development of diabetic nephropathy (HR = 0.97), as defined by an increase in urinary albumin concentration to the level of microalbuminuria or macroalbuminuria. The authors note, however, that after adjustment for use of antihypertensive agents (including angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers), statin use before diabetes diagnosis was associated with a reduction in the incidence of diabetic nephropathy. In the overall cohort and in subgroup analyses, no detrimental effect of statin use on the development of albuminuria was observed.

The large sample size and stringent statistical approach are strengths of this study. The authors provide unadjusted cumulative incidence graphs as well as covariate-adjusted data from Cox models. Furthermore, they conducted a series of sensitivity analyses to examine potential biases. First, they examined the impact of competing risk of death by estimating subhazard ratios using the Fine and Grey model.⁴ Second, they used propensity scores to match for differences in medical conditions and medication use between users and non-users of statins. Third, they assessed lead-time and ascertainment bias by further matching on the number of physician visits during the 2-year period before diagnosis of diabetes. Fourth, they conducted *post hoc* analyses to adjust for previous use of antihypertensive agents or irregular use of statins. All of these sensitivity analyses produced similar results.

Although the consistent data obtained from the sensitivity and stratified analyses is a positive finding, some questions remain regarding the analytical approach. As the nested study design matched patients by age and gender, why the authors also adjusted for these variables in their models is unclear—this approach could potentially lead to over-adjustment. Whether accounting for use of statins following diagnosis of diabetes would impact the results is also unclear. Modelling statin use as a time-dependent covariate could have addressed this question. Most importantly, residual confounding effects from unmeasured covariates are limitations that are prevalent in all observational studies, including this one. Nevertheless, the large sample size and careful statistical analyses provide evidence that the study findings are robust and likely not attributable to chance alone.

The findings are reassuring on several counts. Importantly, no enhanced risk of worsening diabetic complications with statin use in patients with new-onset diabetes was reported. From a nephropathological perspective, determination of whether changes in estimated glomerular filtration rate (eGFR) differed between the statin and non-statin users in this study would be very useful; however, other recent studies have provided some insight into this question. For example, the Collaborative Atorvastatin Diabetes Study showed a

beneficial effect of atorvastatin on decline in eGFR, but not on the development of albuminuria, in patients with type 2 diabetes.⁵ The Study of Heart and Renal Protection reported no benefit of a combination of simvastatin and ezetimibe on the progression of CKD or worsening of albuminuria in patients with Stage 3–4 CKD owing to multiple aetiologies, including diabetes.⁶ Moreover, the longitudinal Chronic Renal Insufficiency Cohort study found no impact of lipid levels on CKD progression.⁷ These findings, together with the existing clinical data, suggest that a substantial renoprotective effect of statin therapy in patients with CKD is unlikely.

An advantage of the large population-based study by Nielsen and Nordestgaard is that their findings are applicable to the general population; inclusion and/or exclusion criteria that are used for clinical studies, which often limit their applicability to the wider community, are not an issue. Similar population-based studies will be important to determine whether comparable benefits of statin therapy are observed in the USA and in other countries with differing ethnic compositions.

Although causation cannot be inferred from observational studies and regression analyses, interesting hypotheses can be generated for future testing. The new findings suggest that a randomized trial of statin therapy, initiated at the time of diabetes diagnosis or possibly in at-risk patients, for prevention of diabetic retinopathy, neuropathy and peripheral vascular disease could be warranted. An important observation is that treatment with statins at an early stage, before the onset of type 2 diabetes, may be necessary to confer the greatest benefit. Although little additive value likely exists for use of statin therapy to reduce the progression of renal disease, at least within the time frame of the studies discussed above, these agents have established benefits in reducing cardiovascular events. They might also reduce the development of retinopathy and neuropathy when initiated before the onset of diabetes.

References

1. Palmer SC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database of Systematic Reviews. (5) Art. No: CD007784. <http://dx.doi.org/10.1002/14651858.CD007784.pub2>.
2. Nielsen SF, Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. *Lancet Diabetes Endocrinol.* [http://dx.doi.org/10.1016/S2213-8587\(14\)70173-1](http://dx.doi.org/10.1016/S2213-8587(14)70173-1).
3. Andersen TF, Madsen M, Jorgensen J, Mellekjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan. Med. Bull.* 1999; 46:263–268. [PubMed: 10421985]
4. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* 1999; 94:496–509.
5. Colhoun HM, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am. J. Kidney Dis.* 2009; 54:810–819. [PubMed: 19540640]
6. Baigent C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011; 377:2181–2192. [PubMed: 21663949]
7. Rahman M, et al. Relation of serum lipids and lipoproteins with progression of CKD: The CRIC study. *Clin. J. Am. Soc. Nephrol.* 2014; 9:1190–1198. [PubMed: 24832097]