Reviewer’s report

Title: Additive effects of blood glucose lowering drugs, statins and renin-angiotensin system blockers on all-site cancer risk in patients with type 2 diabetes

Version: 2 Date: 17 February 2014

Reviewer: Zachary Bloomgarden

Reviewer’s report:

- Major Compulsory Revisions

The authors present a fascinating analysis of development of cancer in 271 persons among a ~6000-person well-characterized diabetic cohort over a median 5-year follow-up, with the striking finding that they were considerably less likely to have A1c <7% (although this was non-significant in univariate analysis) and to receive a statin, a fibrate, metformin, or a thiazolidinedione (all significant during follow-up in univariate analysis), or a RAS-inhibitor (although this was non-significant in univariate analysis).

The authors are quite cognizant of issues of bias in epidemiologic studies and address prevalent user bias and immortal time bias in their analytic approach. They also consider the use of a propensity score adjustment sufficient to correct for bias by indication, although the striking 9-year difference in mean age may render the use of a linear adjustment on this factor less reliable.

An important issue is that the measured variables used as covariates seem to omit those related to socioeconomic status (educational attainment, income, etc) which would lead to preferential prescription of certain medicines for individuals with some characteristics while those with other characteristics would not have such prescriptions – clearly relevant to the findings the authors describe. This statistical issue, which has been termed “allocation bias,” is the most striking potential limiting factor in the interpretation of the report, and is subtly but importantly different from bias by indication, which indeed should be demonstrable to some extent from the covariates used in the analysis. The extremely high likelihood ratios found for cancer given at the end of the results section lead this reviewer to fear that such a phenomenon underlies the authors’ findings.

- Minor Essential Revisions

none

- Discretionary Revisions

none

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I have received payments for consultations and lectures from BMS, Astra-Zeneca, Jansen, Merck, Novartis, Borhinger Ingelheim, NovoNordisk, Santarus, and am a stockholder in Novartis, Baxter International, CVS Caremark, Roche Holdings, and St Jude Medical, all of which entities might have some financial interest in the medications taken by individuals with diabetes, and hence in the subject of this report. Moreover, I have a large clinical practice taking care patients with diabetes, so the logic of declarations of competing interests would in this regard also be considered relevant to my "interests."