Reviewer's report

Title: Association of angiotensin-converting enzyme inhibitor therapy and comorbidity in diabetes: results from the Vermont Diabetes Information System

Version: 2 Date: 30 September 2008

Reviewer: Daniel Hackam

Reviewer's report:

The authors present the results of an interesting and potentially very important cross-sectional analysis in which ACE inhibitors were used less commonly in patients with a history of cancer or peptic ulcer disease. They infer that ACE inhibitors are protective against these two conditions. My interpretation is that patients with common comorbidities are less likely to receive indicated treatment, and this has been documented for many major comorbidities including the ones cited in the report. Potential reasons include polypharmacy, moribund prognosis, poor adherence, and inability to tolerate indicated medications due to comorbid conditions.

Major compulsory revisions

1) ACE inhibitors are indicated in most patients with diabetes based on trial data such as MICRO-HOPE. If these lifesaving medications are being used less optimally in diabetes because of co-existing conditions, then this is potentially very important data for readers. With regard the authors interpretation of potential disease-exposure associations, cross-sectional data such as these lack the following causality elements: time course (i.e. exposure to ACE inhibition preceded the onset - or lack of onset - of the condition - cancer or PUD); randomization (patients were equally likely as not to receive the exposure); dose-response (patients on higher doses of ACE inhibitors were less likely to develop cancer or PUD than patients on lower doses); specificity (ACE inhibitors are protective against some cancers but not others), etc. I believe the current data cannot support the hypothesis that ACE inhibitors are protective against cancer or PUD in the same manner that even a case-control or cohort study can (also observational data). I would like to see this alternate interpretation added to the manuscript (if at all possible) -- see further below, under "In summary".

2) A table with multivariable associations between ACE inhibitors and all of the variables that the authors modelled needs to be added to the manuscript (I only saw the univariate table for ACE inhibitors).

3) Did the authors model any interactions?

4) How did the authors build their logistic model? Was there a Hosmer-Lemeshow goodness of fit test?

5) Was the analysis hypothesis-driven -- i.e. did the authors have an idea that
ACE inhibitors prevent cancer and PUD and then set out to test this concept? Or did they find two statistically significant findings and then build a manuscript around these results?

In summary, this analysis presents important data. Alter and colleagues have termed the phenomenon unmasked here a "treatment-risk paradox" -- essentially, the higher the risk of the patient, the less likely they are to receive treatment (ACE inhibitors). I understand it would require a major rewrite to refashion the manuscript along these lines: essentially that patients who are otherwise good candidates for ACE inhibitors are less likely to receive these lifesaving drugs simply because of comorbidities. That is an important point for both patients and physicians.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.