Reviewer's report

Title: Estimated glomerular filtration rate as an independent predictor of atherosclerotic vascular hospitalization in older women

Version: 1 Date: 10 February 2012

Reviewer: Kevan Polkinghorne

Reviewer's report:

Many thanks for asking me to review this paper by Dr Lewis and colleagues entitled "Estimated glomerular filtration rate as an independent predictor of atherosclerotic vascular hospitalization in older women". The paper is interesting, well written and assesses an important issue for the GFR estimating equations where there has been controversy on the utility as a prognostic marker in the elderly age group.

I have some major comments that I think need addressing.

Major Compulsory Revisions

1. A central issue to the study is the standardisation or calibration of the serum creatinine measurements to produce “reliable” eGFR estimates. The authors state that “the serum creatinine analysed using an isotope dilution mass spectrometry (IDMS) traceable Jaffe kinetic assay”. I have to question this statement. The recommendations and technique for creatinine standardisation to a IDMS reference material were published in 2005-2006 (eg Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: A report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5-18), well after the baseline creatinine measurements in 1998. While I don’t doubt that the current Roche assay is IDMS traceable the assay at the time would not have been. Therefore their statement cannot be correct. This becomes very important as standardisation makes a big difference to the creatinine values in the normal range and thus the GFR estimates in the 50 to 60 range. It would likely have a big effect on the eGFR results. I am assuming there is not any stored serum to go back and measure a sub sample in order to standardise the creatinines. If it is not possible to ensure calibrated creatinines then the author should use the old 186 MDRD forumula. CKD-EPI was develop with IDMS creatinines so it will remain a big limitation. This needs to be satted as a clear limitation to the analysis.

2. Statistical Analysis. The authors change the primary outcome (mortality) as it did not obey the proportional hazards assumption. I am assuming by this they are referring to the eGFR results and mortality. This to me is intriguing and I am surprised that is has not been explored in a different way. Did they try stratification? What is the exact issue with the data - is the loss of the proportional hazards present in both males and females? Using logistic
regression is not ideal as it takes away any issue of the time which seems here to be important. This needs to be explored more fully.

3. Figure 1. Using the bar graphs with numbers side by side makes it difficult to compare the two equations. Can they produce a smoothed density plot with both equation on the same plot which makes it easier to compare the two equations.

4. Recent work suggests the the CKD-Epi equation produces lower eGFR values in the elderly compare to MDRD (eg: van den Brand, J. A. J. G., etal .Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population. NDT 2011). This seems at odds to the current data - mean EGF for CKD-Epi is higher (table 1). While this could be related to issue as discussed above, could the authors provide more information of the eGFR distribution in the cohort.

5. Table 2 & 3. Table 2 shows unadjusted HR’s. Can the authors provide the fully adjusted data as well as that is more relevant. I am a little unclear on the table 3 data. Is the HR for the eGFR equations adjusted only by framingham risk score and nothing else? If so they need to be fully adjusted for the other risk factors. While the score will I guess will account got some of the confounders will it account for all.

6. NRI I IDI data. This data is very interesting. Again are the models fully adjusted as per above. Can they provide confidence intervals for the NRI (& IDI) and not just the p values.

**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