Author’s response to reviews

Title: Prescribing of diabetes medications to people with type 2 diabetes and chronic kidney disease: a national cross-sectional study

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Prof Shlomo Vinker
Editor, BMC Family Practice

Dear Prof Vinker,

Re: FAMP-D-18-00287

Prescribing of diabetes medications to people with type 2 diabetes and chronic kidney disease: a national cross-sectional study

Thank you for reviewing our study, and to the reviewers for their helpful input. I have responded to each of their comments below.

Sandra Vezmar Kovacevic (Reviewer 3)
Comment: Prescribing of diabetes medications to people with type 2 diabetes and chronic kidney disease: a national cross-sectional study is an interesting and well written manuscript. The data are worth publishing since the investigated cohort is large.

Response: Thank you for your comments.

Comment: 1) the use of eGFR and Cockroft-Gault may not be adequate for obese patients and a large proportion of the included patients are obese. Could you please comment on how the eGFR and CLcr took into account obesity?

Response: We utilised eGFR readings that were provided by pathology laboratories; we did not calculate them ourselves. In Australia, eGFR is calculated by pathology laboratories using the CKD-EPI formula (1). It has been recommended that eGFR measurements be adjusted for patient size, but the method to do this is debatable and it is not clear whether this is done in practice. Lemoine et al (2) have specifically explored the performance of eGFR CKD-EPI in obese patients, and concluded that the CKD-EPI equation is validated in the obese population up to a BMI range of 40 kg/m2, specifically for GFR levels <60 ml/min. They also commented that it can be difficult to calculate ideal weight because, for example, older people with chronic diseases may become obese without a proportional increase in muscle mass. For these reasons, obesity wasn’t specifically taken into account for the eGFR readings we utilised.

We used Cockcroft-Gault equation to calculation the CrCl. CrCl is not routinely provided to referring GPs by pathology companies. We calculated the CrCl using recorded weight as opposed to calculating it using lean body weight. As you mention, this may underestimate the CrCl. We have added this as a limitation in the Strengths and Limitation section, page 15, last sentence of first paragraph:

Finally, we calculated CrCl using actual body weight not lean body weight and this means we may have overestimated CrCl and renal function amongst people who were obese.

Comment: 2) Dosage of metformin impacted the results of the study in a large extent. However, ADS guidelines seem to be consistent with the Summary of Product Characteristics for metformin. Nevertheless, common practice, as also discussed by authors, is that metformin dose is adjusted when eGFR or CLcr are lower than 45. This should be pointed out more clearly.

Response: Thank you for your comment. The aim of our study was to explore the prescription of diabetes medications for people with different levels of eGFR.

As illustrated in Table 2, we found that 702/1909 (36.8%) people with eGFR 45-59ml/min/1.73m2 were prescribed metformin at a dose not consistent with guidelines, and this proportion increased for people with an eGFR 30-44ml/min/1.73m2 (762/1261 (60.4%)). As a result, we did not find that it was common practice for metformin dose to be reduced when eGFR was reduced below 45ml/min/1.73m2 and so have not made any changes to the manuscript on this point.
Comment: 3) The most interesting results in my opinion are the differences among prescribing practices in CKD stages. The number of "mistakes" decreased linearly with eGFR and CLcr. This may be because patients advanced CKD are on dialysis and nephrologists are included in their care?? Patients with eGFR and CLcr 45-59 usually have less clinical symptoms of CKD and doctors may be less aware of their condition and need for dose adjustment.

Response: Thank you for your comment.

The number of patients prescribed medications that are not consistent with dosing guidelines did reduce with lower eGFR and CrCl. However, as shown in Table 2, this is likely a reflection of lower numbers of people in lower eGFR categories. In fact, for the metformin group, as eGFR reduced from 45-59 to 30-44, the proportion of people with a dose not consistent with guidelines increased from 36.8% to 60.4%. The proportion of people prescribed metformin with a dose not consistent with guidelines in the eGFR<30 group (40.9%) was similar to that for 45-59 group.

As a result, we are unable to comment as to the contribution of specialist nephrology care, and this data was not available in our dataset. If we take prescription of an erythropoietin agonist as a proxy for nephrologist care or requirement for dialysis, there were very small numbers in this study; only 12 in a cohort of 3505 people.

4) I am not sure I understand footnote 3. Does such classification lead to bias if a DLP-4 inhibitor was not consistent with the guidelines but this reflected to biguanides? The purpose of the stratification by drug class was to understand the factors associated with inconsistent prescribing of any diabetic medication for those who were on a particular drug. For example, the association between factors and inconsistent prescribing of any diabetes medication for those on biguanides. The results from the stratification analysis is still the odds of at least one inappropriate prescription. However, it is presented for different drug classes. For example, the odds of at least one inappropriate prescription for those who are taking a biguanide. It does not mean the inappropriate prescription/s is due to that particular drug class.

Comment: 5) A technical remark - you use the word finally in two consecutive paragraphs on page 13 and 14

Response: Thank you for alerting us to this. We have removed the word “Finally” in the first sentence of the last paragraph of page 13.

Marija Vrca Botica (Reviewer 4) comments

Comment: It is not evident if patients with other comorbidity (special hard disease) were excluded /included in the study. That clinical status needed the personal approach in prescribed medications beside presence guidelines.

Response: As described in the Study sample section on page 6, the study population consisted of patients with a recorded diagnosis of T2D who were aged 18 years and over in the NPS
MedicineInsight dataset. Patients were excluded if they had no recorded prescription of a non-insulin diabetes medicine between 1st of January 2015 and 30th of June 2017. Patients with a recorded prescription who did not have at least two eGFR measurements prior were also excluded. We did not exclude patients from the study who had co-morbidities.

In Table 1 we do provide some data on people with co-morbidities in the cohort, including heart failure, coronary heart disease and stroke.

We agree that individual patient factors are important to consider and that these might not always be captured by clinical guidelines. We discuss this in the second paragraph of the discussion on page 12 and the first paragraph on page 13.

Comment: HbA1c in CKD with an average eGFR<60ml/min1.73 is unreliable indicator of diabetes control and outcome (low eritropoetin, anemia)

Response: Thank you for your comment. We agree that HbA1c is less useful clinically in people with significant renal impairment and anaemia.

Only 0.3% of people in this cohort were prescribed an erythropoietin agonist, but we did not explore haemoglobin levels in participants. We do not believe that this would have a significant impact on our results, which focussed on prescription by eGFR level.

Thank you for considering our paper for publication and for the helpful suggestions of the reviewers. We look forward to hearing the outcome of our submission.

Best regards,

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References:
