Author’s response to reviews

Title: Drug related problems in type 2 diabetes patients with hypertension

Authors:

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Author’s response to reviews: see over
Dear editor,

Please find attached the response to the reviewers in yellow highlight. The manuscript has been proofread by the professional and scientific editor ie Editage. Thank you very much for your kind consideration.

Best regards,

Dr Hasniza Zaman Huri
Corresponding author

Response to comments of reviewer 2

Minor Essential Revisions
1. The text should be revised to correct some mistakes like:--done
Pg. 2 - DPRs must be replaced by DRPs.---done
Pg.4 – Data collection: … presence of comorbidities, concurrent medications, laboratory results and concurrent medications were also collected.---done
Pg. 14 10th line: previders replace by providers---done
28th line: exclude “were” (…domains were are concerned…)---done
2. The study design is not clear. Is it a cross-sectional study or only incident DRPs were considered? –This is a cross-sectional study
3. Based in which parameters was the sample size calculated?—The sample size is calculated based on the prevalence of type 2 diabetes mellitus patients in Malaysia
4. The retrospective nature of the study is recognized as a study limitation in the discussion. But another limitation must be added: the number of studied patients (200) in face of the 535 potentially eligible patients (less than 50%).—has been included in the limitation

Discretionary Revisions
5. I suggest the exclusion of “Aims” since it is included in objectives.---done
6. Only the exclusion criteria #3 and # 5 need to be stated since the others are consequence of the inclusion criteria.---done

Response to comments of reviewer 1

Methods
A retrospective method was used, and you have provided a flow chart (fig 1, see also comment below). This information should be mentioned earlier (e.g. under study population) than under statistical techniques, either as a text, or refer to it
as fig 1. You then screened medical records to patients with T2DM and included those with hypertension as well.--- done

Exclusion criteria - Patient with missing data was excluded. What does this mean? Does this imply that all the required data had to be found in the records for the inclusion in the study? E.g. if data on liver status was not included in the record, the patient would have been excluded?—We exclude patients who we can’t obtain the medical records (as in figure 1)

Furthermore, it should be stated by whom the data was collected. Probably the data collectors are pharmacists since the authors are pharmacists.--- done

You should also describe the hospital better. I would have expected your patients to be older and also I would have thought that in a 948 beds hospital much more than 200 patients with T2DM and hypertension would be admitted during a 2 years period. The prevalence of hospitalised patients with hypertension and T2DM in a medical ward my country is around 15-20%, which mean that in a 1000 bed hospital I would expect to collect 150-200 patients at a much shorter period than 2 year?—the sentence has been rephrased. As in figure 1, initially we have 535 patients. In due to strict inclusion criteria and uncaptured patients medical records at the end we manage to get 200 patients. Nevertheless the number is more than our minimum calculated sample size.

Renal impairment – firstly; how was creatinine clearance calculated? Secondly; a creatinine clearance less than 50, but higher than 35 does not necessarily mean that you have any problem with drug use. I would suggest that you change the definition.—In this case the creatinine clearance of less than 50 is the reference for the clinical characteristic of patients for ‘renal impairment’ based on the reference no. 19. It does not refer to the use of the drugs. For the assessment of creatinine clearance with the use of drugs, it depends on individual drugs with the range of 30-50 ml/min based on the BNF, Lexicomp and other references.

Drug interactions – you have not defined which drug interactions to include. You say later that you on included significant potential interactions, but it should be described in methods as well.--- the definition has been included

Combination of drugs was counted as a single item, except for antidiabetic and antihypertensive drugs. I did not understand this properly – so you should explain it better. Does this mean that if you have a combination drug containing a thiazide + an ACE-inhibitor it was counted as two drugs?—For drugs other than antidiabetes and antihypertensive, if the drug is a combination, we counted it as a single item. However for antidiabetes and antihypertensive, if it were a combination we counted it as a separate entity since the two classes of drugs are our main target drugs.

The identification of DRPs. As I understand it you have used Lexicomp, BNF and Beers criteria to identify DRPs and then classified then according to the PCNE classification. It should be mentioned who identified the DRPs, that is if there were several persons involved and whether it was pharmacists or physician involved in the identification and classification. Since you do this retrospectively
you have the possibility to use two independent researchers to assess each patient record and by doing that controlling that the identification and classification of DRPs are correct. It is a problem that the identification is done retrospectively. The DRPs you identify will be theoretical and what you assess as a DRP could have been prescribed intentionally and fitted to the patient. You have only briefly mentioned this under limitation, however, you should extend the discussion here. --- The authors who are the pharmacists are the one identifying and classifying the DRPs upon discussion with the physicians.

The Beers criteria - Drugs listed on Beers List are drugs used in the US and drugs used in the elderly population. How does this fit with the drugs used in Malaysia? You only used the criteria on those younger than 65 (less than half of your patients) Do you think this will be a bias for your results? You should discuss these two comments in the discussion. --- For Beers criteria, we only considered drugs which are available in Malaysia. In our study population, we use PCNE as a main tool for DRPs assessment. The Beers criteria is a supplement tool for elderly patients for one parameter ie ‘inappropriate selection of drugs’

Result
I recommend to not have sub-headings--- done
Demographics – see comment with regard to the number and the time of collection. Further, I would expected the majority of patients to be older – could you comment on that in discussion?—have included in the discussion section.
Drug use pattern – why do you include this? This is not your aim. I suggest you delete this part – consequently also fig 2, 3. And table 6 and 7. See also below.— has been deleted.
Adverse effects – one problem with your data is that this is retrospective hospital data. They have probably not asked patients for adverse effect, but only noted the ones that are important for the hospital admission. Could you address this limitation further in discussion?---done
Factors found to be associated with DRPs – do you mean cardiovascular disease or cardiovascular event (as defined in methods)? (I would include hypertension in cardiovascular disease, but not in event). This comment applies to table 17 A as well.---all have been changed to cardiovascular event.

Discussion
See several comments above
Renal impairment – See comments under methods. I do not agree that a patient with a creatinine clearance just below 50 ml/min has an impairment important for the use of most drugs. I think most pharmacologists would agree that below 30-35 ml/min would be a better limit.---it has been explained above
Cardiovascular disease – see comments above under results—it has been changed to cardiovascular events
The paragraph regarding limitations of the study should be extended, see comments above.---done
Figures and tables
Fig 1 - The flow sheet is OK, but you could also describe it in the method section. (I would prefer that)--- done
Table 1 - Not necessary, you define that you use the version 5.01 version. It is enough.—it has been deleted
Table 2 - 3 should be merged - Is too large, many of the parameters are too detailed and should be lumped together. Furthermore, I would suggest only including the information you use further in the study. You could, if you want to include it, mention it briefly in the text. For example, you do not use the under groups of BMI and why is it necessary to inform about ethnicity?---done
Table 4 and 5 - Should instead be included as text in the result.---done
Table 6 and 7 – Delete – drug use pattern is not your aim ---done
Table 8, 9, 10, 12, 13 and 14 – Merge into one table---done
Table 11 Not necessary---it has been deleted
Table 16 – could be included in text as a short comment---done
Figure 2-7 Not necessary, could be shortly commented in text. --ok