PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish National Diabetes Register
AUTHORS	Ekström, Nils; Schiöler, Linus; Svensson, Ann-Marie; Eeg-Olofsson, Katarina; Miao Jonasson, Junmei; Zethelius, Bjorn.; Cederholm, Jan; Eliasson, Björn; Gudbjörnsdottir, Soffia

VERSION 1 - REVIEW

REVIEWER	Pr Ronan Roussel, MD, PhD, Endocrinology Diabetology Nutrition Groupe Hospitalier Bichat - Claude Bernard 46 rue Henri Huchard 75722 Paris Cedex 18 No conflict of interest related to this work.
REVIEW RETURNED	30-Mar-2012

THE STUDY	Very interesting data, but the objective should be focused on safety of metformin according to renal function
RESULTS & CONCLUSIONS	the really original message, safety of metformin in CKD stage 3 is diluted in replicative results.
GENERAL COMMENTS	comments: Actually, I think that some of your data are of tremendous interest, awaited by everyone and especially many health authorities before changing the guidelines of metformin use, but that these major results are diluted in second order ones, just replications of already published data. I mean that the current questions are: "should we decrease the limit of eGFR for metformin use?"; "what will be the cost in terms of lactic acidosis?". You have a part of the answers and the paper should be made concise to deliver these answers very straightforward. Thus, I suggest to modify your objectives to: "to evaluate the safety of metformin use in a large sample of patients with pharmacologically treated type 2 diabetes in clinical practice, according to renal function". In that regard, teh important tables are Table 1, of course, and 6, the other may be supplementary. The title should emphasize this, and include as keywords: "renal function" and "lactic acidosis". data on people excluded for incomplete covariates should be discarded. important information should be described (metformin and other diabetes treatments in excluded patients, age, events rates, etc..). If relevant, this has been to be included in the discussion (limitations) in some way.

	A group of interest and not studied here is defined by an insulin background, plus metformin only or plus other OAD. The insulin requirement should induce a longer duration of diabetes, a major prognostic factor, very different in the current groups. Similar results in this new group would reinforce the conclusions, leaving few space for bias related to duration. Your outcomes are OK, except that lactic acidosis alone should be included as a specific outcome. Indeed, we understand your trouble regarding the low number of events (fortunately), but this is the outcome that people are afraid of. Even if the balance between risks and benefits is good, prescribers do not want to induce severe side effects (they will be considered responsible for them, and not responsible for having avoided myocardial infarctions, for example). Your results will be non significant HRs, and the message clear: no relevant risk associated with metformin. Even if limited to a subgroup of your population, do you have data on metformin dosing? Metformin as monotherapy is not a good comparator group. Indeed, they are much less sick than the other groups; thus, less events occurred. These characteristics lead to a broader approximate of the incidence of the various events. Choosing this group as a comparator, you contaminate all the results with the poor precision you have for them. You may choose other OHA as a reference, this group is more close to the "middle class" of diabetic people. Moreover, presenting this way will allow HR less than 1 for metformin users, more illustrative of the very-likely protective role of metformin. With the same idea, comparing to a common reference the groups insulin+met and insulin+other OHA and insulin only is not very interesting, if we admit that metformin is the drug of interest for this study. I suggest to conduct an analysis in the insulin-treated patients, comparing on top of that insulin background metformin to other OHA to nothing. Please include in the discussion a reference to Lalau's work on lactic acidosis and metformin: he suggested that not only metformin was not associated with lactic acidosis, but was actually asociated with a lower mortality. Your data in some way reinforce this provocative suggestion. Drug Saf. 1999 Apr;20(4):377-84. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Lalau JD, Race JM. minor: in the abstract, not clear what you mean: Metformin"showed"a"reduced"risk"of"any"acidosis/serious"infection,"HR"0.85"(0.74"to"0.97),"and"all-cause"mortality,"0.87"(0.77"to"0.99)"in"patients"with"eGFR"45-60"mL/min/1.73"m2,"and"was"not"associated"with"increased"risk"of"all-cause"mortality,"acidosis/serious"infection"or"CVD"in"patients"with" renal"impairment." the first and the second parts of the sentence seem to describe the same thing. Please clarify.

REVIEWER	Prof.dr. Henk JG Bilo, FRCP Department of Internal Medicine Isala Clinics The Netherlands
REVIEW RETURNED	23-Mar-2012

THE STUDY	There is one sentence regarding the inclusion criteria, which needs clarification. At page 5, line 33, it is stated "baseline occurred twelve

	months after the first prescription...", and I think some words have been omitted
GENERAL COMMENTS	The authors analyzed information available in a large database, covering both primary and secondary care, studying 51675 subjects with type 2 diabetes, registered in the Swedish NDR. Their results are partly confirmatory and partly new and remarkable. As it is, most professionals worry about the risk on lactic acidosis in subjects with impaired renal function whilst using metformin, and this despite the findings in a Cochrane analysis, that metformin is a safe drug when used under appropriate conditions. The most remarkable finding is the lack of any association between decreased renal function and such complication; on the contrary, the relationship appears to be in favour of metformin for part of the complications, with a neutral effect in subjects with decreased renal function regarding lactic acidosis and severe infections. Although their conclusions are quite wel validated, one question remained: - when describing the study population, I am confused by the sentence starting with: "baseline occurred twelve months after the first prescription...", and I think some information has inadvertently been omitted. Please clarify the inclusion criteria, since this may have influence on the case mix of study population and - thus - on outcome. As a general remark: some of the tables are difficult to read and interpret. However, I appreciate the difficulties in presenting the large amount of data of this study population.

VERSION 1 – AUTHOR RESPONSE

Dear Mr. Richard Sands, Professor Henk JG Bilo and Professor Ronan Roussel

Thank you for the careful review of our manuscript: bmjopen-2012-001076 “Effectiveness and safety of metformin and other glucose-lowering treatments in 51 675 patients with type 2 diabetes: A cohort study from the Swedish National Diabetes Register (NDR)”, and the opportunity to submit a revised version.

Below you will find our detailed responses to the comments and suggestions made by the reviewers.

We now hope you will find the manuscript acceptable for publication in BMJ Open.

Yours sincerely

Nils Ekström

Reviewer(s)' Comments to Author:

Reviewer: Prof.dr. Henk JG Bilo, FRCP
Department of Internal Medicine
Isala Clinics

The Netherlands

There is one sentence regarding the inclusion criteria, which needs clarification. At page 5, line 33, it is stated "baseline occurred twelve months after the first prescription...", and I think some words have been omitted

Response:
Thank you. We have tried to make this clearer in this revised version of the manuscript. The sentence now reads: “In each patient, baseline was defined as occurring after 12 months of continuous use of the prescribed glucose-lowering medication.”

The authors analyzed information available in a large database, covering both primary and secondary care, studying 51675 subjects with type 2 diabetes, registered in the Swedish NDR.
Their results are partly confirmatory and partly new and remarkable. As it is, most professionals worry about the risk on lactic acidosis in subjects with impaired renal function whilst using metformin, and this despite the findings in a Cochrane analysis, that metformin is a safe drug when used under appropriate conditions. The most remarkable finding is the lack of any association between decreased renal function and such complication; on the contrary, the relationship appears to be in favour of metformin for part of the complications, with a neutral effect in subjects with decreased renal function regarding lactic acidosis and severe infections.
Although their conclusions are quite well validated, one question remained:
when describing the study population, I am confused by the sentence starting with: "baseline occurred twelve months after the first prescription...", and I think some information has inadvertently been omitted. Please clarify the inclusion criteria, since this may have influence on the case mix of study population and - thus - on outcome.

Response:
See above. This part of the Methods has been revised.

As a general remark: some of the tables are difficult to read and interpret. However, I appreciate the difficulties in presenting the large amount of data of this study population.

Reviewer: Pr Ronan Roussel, MD, PhD,

Endocrinology Diabetology Nutrition

Groupe Hospitalier Bichat - Claude Bernard
46 rue Henri Huchard

No conflict of interest related to this work.

Very interesting data, but the objective should be focused on safety of metformin according to renal function

Response:
Thank you. The aim of this revision has been to focus more on metformin (and remove some tables) but also to update the discussion.

comments:

Actually, I think that some of your data are of tremendous interest, awaited by everyone and especially many health authorities before changing the guidelines of metformin use, but that these

major results are diluted in second order ones, just replications of already published data. I mean that the current questions are: "should we decrease the limit of eGFR for metformin use?"; "what will be the cost in terms of lactic acidosis?". You have a part of the answers and the paper should be made concise to deliver these answers very straightforward.

Thus, I suggest to modify your objectives to: "to evaluate the safety of metformin use in a large sample of patients with pharmacologically treated type 2 diabetes in clinical practice, according to renal function". In that regard, teh important tables are Table 1, of course, and 6, the other may be supplementary. The title should emphasize this, and include as keywords: "renal function" and "lactic acidosis".

Response:
Thank you. We certainly agree with you that the question regarding benefits and risks (in terms of lactic acidosis) with metformin use in patients with different levels of renal function is central and deserves focus in this manuscript. To emphasize this, we have revised the title and objectives based on your suggestions. However, as described below there only were very few cases of lactic acidosis. Therefore we did not find it suitable to highlight lactic acidosis in the title. The title now reads: “Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish National Diabetes Register” and the objectives reads: “to evaluate the effectiveness and safety of metformin use in a large sample of patients with type 2 diabetes and different levels of renal function in clinical practice”. We hope you find this acceptable.

Metformin is first-line glucose-lowering treatment in obese patients with type 2 diabetes. This recommendation is primarily based on the results of the UKPDS metformin sub-study (a 14 years old study where only 342 patients were treated with metformin). Since metformin is an old agent, approved as a glucose-lowering drug in 1957, it is unlikely that further RCTs investigating the effects of metformin will be done. Even when it comes to observational data the evidence is limited. REACH (Roussel R, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med. 2010;170:1892-9) showed a reduced risk of all-cause mortality in 19 691 patients with type 2 diabetes and cardiovascular disease compared to all other glucose-lowering agents. However, the follow up was only 2 years. Furthermore, they only analysed all-cause mortality (not CVD) and did not adjust for important covariates such as diabetes duration and HbA1c.

Considering the scarce data supporting metformin as first-line treatment we think our analyses, comparing metformin to other commonly used glucose-lowering medications in a large sample of type 2 diabetes patients, which is balanced in regard to a large number of important covariates by propensity score stratified and adjusted analyses, constitute very important information concerning the effectiveness and safety of metformin. Furthermore, our sample is representative of a typical type 2 diabetes population, with approximately one fourth of the patients with a history of cardiovascular disease. Our results also show that metformin is associated with a reduced risk of CVD, which is of clinical importance. Against this background, we would like to keep tables 3 and 5 in the manuscript, and have revised the introduction and discussion in order to emphasise the importance of these results. Tables 2 and 4 have now been changed to supplementary material.

Data on people excluded for incomplete covariates should be discarded. Important information should be described (metformin and other diabetes treatments in excluded patients, age, events rates, etc..). If relevant, this has been to be included in the discussion (limitations) in some way.

Response:
Around 40 % were excluded due to missing data for one or some of the covariates. However, this is not a cross-sectional study with the need to be representative of a population with full data. It is a longitudinal observation study applying prospective analyses, including patients over time for

outcomes, also with regard to relevant covariates. Most important for an observational study is that the number of included patients is reasonably large, as also underlined by STROBE (an international summary giving recommendations for observational studies). More than 50.000 Swedish patients included makes this a very large national study, also in comparison with other international prospective studies on patients with type 2 diabetes. For instance, the ACCORD trial included only 10.000 of all patients in the US, and ADVANCE 10.000 patients from all over the world, and UKPDS only 4.000 of all patients in UK, when prospectively analysing risk factors for CVD. It is worth remembering that the UKPDS study, when comparing diabetes treatments for risk of total mortality in obese patients, included only 342 patients with metformin and 941 patients with other treatments.

This study is based on a register (the NDR), and clinical registers always have missing data for one or a few variables in some patients as also RCTs well may have. The same has been seen for instance in register data from Harvard based on electronic data journals. However, there is no need to suspect bias due to these missing register data in our study, as reporting clinics had no intention to selectively exclude certain data. Missing occurred sometimes by chance, as these variables happened not to be measured in such patients at a special time when reporting to the NDR. Lost to follow-up concerning endpoints is common in many register studies as well as in RCTs. In this study, however, applying national patient and cause of death registries have almost complete follow-up.

However, We made a comparative analysis of means and frequencies for covariates between included patients and patients with missing data, and found no significant differences, except for slightly higher age in missing patients. This should be no problem for our study, as mean age is as high as 65±10 years among included patients, there was no intention by reporting units to exclude somewhat older patients per se, and age is always adjusted for as covariate in Cox regression analyses. Since the included cohort thus has been verified representative, we chose not to include these data in the manuscript.

A group of interest and not studied here is defined by an insulin background, plus metformin only or plus other OAD. The insulin requirement should induce a longer duration of diabetes, a major prognostic factor, very different in the current groups. Similar results in this new group would reinforce the conclusions, leaving few space for bias related to duration.

Response:
We certainly agree with you that diabetes duration is a major prognostic factor. Diabetes duration was included as a covariate in our analyses and by performing propensity analyses the different groups were balanced in regard to the covariates including diabetes duration (see Appendix table 1). However, as suggested by the reviewer, we have performed an “on-top analysis” comparing patients on insulin only to patients on insulin in combination with metformin and patients on insulin in combination with other OHA. The results from this analysis are now presented in the results section and in Appendix Table 6.

Your outcomes are OK, except that lactic acidosis alone should be included as a specific outcome. Indeed, we understand your trouble regarding the low number of events (fortunately), but this is the outcome that people are afraid of. Even if the balance between risks and benefits is good, prescribers do not want to induce severe side effects (they will be considered responsible for them, and not responsible for having avoided myocardial infarctions, for example). Your results will be non significant HRs, and the message clear: no relevant risk associated with metformin.

Response:
We are aware that lactic acidosis is the event physicians are afraid of when prescribing metformin to patients with reduced renal function, and optimally our analyses would include lactic acidosis as a separate outcome. However, during the study period (with more than 200 000 patient-years at risk)

only 8 cases of lactic acidosis occurred (4 in metformin only, 2 in metformin + insulin and 2 in insulin only). We are convinced that there are more cases, but, in the eyes of the clinicians reporting the DRG codes in the medical record files, other diagnoses were more important. This is the cause for creating a composite endpoint with severe infections and different types of acidosis. An analysis based on the eight cases of lactic acidosis would not provide any valuable information. Instead we have added information about the exact number of lactic acidosis cases and also the 5 most common outcomes (diagnoses) included in the composite endpoint acidosis/serious infection. This information can be found in the discussion section, limitations.

Even if limited to a subgroup of your population, do you have data on metformin dosing?

Response:
Yes, we have calculated mean doses of metformin in each treatment group at baseline. This information is now included in the results section.

Metformin as monotherapy is not a good comparator group. Indeed, they are much less sick than the other groups; thus, less events occurred. These characteristics lead to a broader approximate of the incidence of the various events. Choosing this group as a comparator, you contaminate all the results with the poor precision you have for them. You may choose other OHA as a reference, this group is more close to the "middle class" of diabetic people. Moreover, presenting this way will allow HR less than 1 for metformin users, more illustrative of the very-likely protective role of metformin.
With the same idea, comparing to a common reference the groups insulin+met and insulin+other OHA and insulin only is not very interesting, if we admit that metformin is the drug of interest for this study. I suggest to conduct an analysis in the insulin-treated patients, comparing on top of that insulin background metformin to other OHA to nothing.

Response:
Thank you for these suggestions. We agree with you that metformin is the drug of interest, and we would therefore like to keep the focus on metformin in this study. A change of reference group to other OHA, however, would, e.g., make the comparison between metformin and insulin impossible. Therefore we have chosen to keep metformin only as the reference group in the analysis in the manuscript. However, we did the analysis with other OHA as reference as well. These results are presented in Appendix Table 4 and shortly described in the results section. As described above, we also did the “on top of insulin”- analysis.

Please include in the discussion a reference to Lalau's work on lactic acidosis and metformin: he suggested that not only metformin was not associated with lactic acidosis, but was actually asociated with a lower mortality. Your data in some way reinforce this provocative suggestion.
Drug Saf. 1999 Apr;20(4):377-84.
Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Lalau JD, Race JM.

Response:
Thank you. We have now included the reference in the discussion.

minor:
in the abstract, not clear what you mean:
Metformin"showed"a"reduced"risk"of"any"acidosis/serious"infection,"HR"0.85"(0.74"to"0.97),"and"all-cause"mortality,"0.87"(0.77"to"0.99)"in"patients"with"eGFR"45-60"mL/min/1.73"m2,"and"was"not"associated"with"increased"risk"of"all-cause"mortality,"acidosis/serious"infection"or"CVD"in"patients"with" renal"impairment."
the first and the second parts of the sentence seem to describe the same thing. Please clarify.

Response:
Thank you. We have revised the sentence in order to clarify, and it now reads: Metformin showed a reduced risk of any acidosis/serious infection, HR 0.85 (0.74 to 0.97), and all-cause mortality, 0.87 (0.77 to 0.99) in patients with eGFR 45-60 mL/min/1.73 m2, and was not associated with increased risk of all-cause mortality, acidosis/serious infection or CVD in patients with eGFR 30-45 mL/min/1.73 m2.