

Dear Sir/Madam:

Thank you for your patience. We have revised our manuscript. Our replies are as followings:

Editorial Office ' s comments: Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

Answer: Thank you for your comments. We have corrected the issues.

Reviewer #1:

Specific Comments To Authors:

This systematic review and meta-analysis concentrates on the efficacy and safety of endothelin receptor blockers in diabetic kidney disease. This is an interesting and current topic. The meta-analysis was performed at high methodological level; the research methodology is described in details. From my point of view, the manuscript can be published after some major revisions.

1. The title: I recommend replacing "antagonist" with "antagonists", as this is not a single drug.

Answer: Thank you for your comments. We have corrected the word.

2. Materials and methods: When describing studies included in the meta-analysis, it is useful to highlight the differences in their design, primary and secondary endpoints.

Answer: Thank you for your comments. We have add these details on Page7 according to your suggestions.

3. Results. It would be great to present the dynamics of clinically significant parameters, such as albuminuria, eGFR, and blood pressure, not only in the form of statistical differences between the group, but also in absolute numbers (if it's possible).

Answer: Yes, I agree with your advice. However, we can't extract the enough information to present the dynamics of clinically significant parameters. That is a pity.

4. Discussion.

(1) It should be emphasized that the SONAR study was the largest one in terms of the number of participants and duration of follow-up. Specific details of the SONAR study design, such as assessment of antialbuminuric response before randomization, should be indicated.

Answer: Thank you for your comments. We have add these details on Page14 according to your suggestions.

(2) A premature termination of the Mann 's study with avosentan due to excess of cardiovascular events also need to mention.

Answer: Thank you for your comments. We have add these details on Page14 according to your suggestions.

(3) It is advisable to briefly discuss the possible mechanisms of the side effects, such as fluid retention, anemia and hypoglycemia.

Answer: Thank you for your comments. We have added these details on Page 12 according to your suggestions.

5. The conclusion, in my opinion, could have been more cautious.

(1) It should be specified that the renal protective effect of the endothelin receptor antagonists was demonstrated in patients with a combination of elevated albuminuria and decreased eGFR only.

Answer: Yes, that is an important point. We corrected the conclusion part. The renal protective effect of the endothelin receptor antagonists was demonstrated in patients with diabetic nephropathy. Diabetic nephropathy was diagnosed with albuminuria or/and decreased eGFR in subjects with DM. We should emphasize the renoprotection effect of ER antagonists on DN patients with decreased eGFR.

(2) It is advisable to identify tasks for future research, based on the results of the study. The ongoing trials in this area are also worth mentioning.

Answer: Thank you for your comments. We have added some sentences in implications for policymakers and clinicians part of discussion.

Reviewer #2:

Specific Comments To Authors (File):

This appears to be a well done meta analysis.

1. ABSTRACT - Conclusion - The ER reduce albuminuria but not eGFR. Do not say that they reduced renal function decline.

Answer: Yes, this sentence is not clearly elucidated. I rewrite the sentence.

2. You can remove the first 2 sentences of the INTRO. Start with "Studies show.." ... In the 2nd paragraph of INTRO remove "sufficient"

Answer: We have removed the first 2 sentences according to your suggestion.

3. METHODS - "...with $P < 0.1$ and $I^2 > 50\%$ indicated existing statistical significance [13]" Not clear as written.

Answer: We have reedited the sentences according to your suggestion.

4. RESULTS - Study Quality - substitute "good" for "great"

Answer: Thank you for your comments. We have corrected the word.

5. DISCUSSION - 1st paragraph- "Thus, ER antagonists largely prevent the development of proteinuria, renal vasoconstriction, renal hypertrophy, and structural injury [18-21]." You show no evidence for preventing vasoconstriction, renal hypertrophy and injury. All you demonstrate is lower albuminuria.

Answer: Thank you for your comments. We have rewritten the sentences.

6. DISCUSSION - "Nevertheless, ER antagonists will be confronted by formidable competitors, for instance, inhibitors of glucagon-like peptide-1 receptor antagonists and sodium-glucose co-transporter 2 (SGLT2), " but because SGLT protect the kidneys does not preclude use of ET blockers. Rewrite.

Answer: Thank you for your comments. We have rewritten the sentences.

7. CONCLUSION - ET blockers prevent proteinuria not eGFR decline.

Answer: Thank you for your comments. I rewrote the sentence. However, according to our subgroup analysis, in the middle-dosage subgroup, the ER antagonist group exhibited lesser eGFR reduction than the control group. Thus ER antagonists of optimal dosage (middle-dosage) could delay renal function progression.

Reviewer #3:

Specific Comments To Authors: The submitted metanalysis deals with the interesting topic of new therapeutic interventions against diabetic nephropathy. The authors followed a right methodology and described their findings in a well-written and compact manuscript. The study provides several interesting results with some of them, such as the effect of ETA-R blockers dose on eGFR, being new, and suggest the need for further RCTs. For all these reasons, I suggest accepting the manuscript as is.

All changed parts were highlighted in red. Thank you very much for your help!

Yours !

Guang Chen.