

September 29th, 2020

Re: Manuscript No. 58684

Dear Editor,

thank you for your letter and the possibility of resubmitting our revised manuscript titled "**GLP 1RA and SGLT-2i combination - are we exploiting their full potential in a real life setting**" for consideration for publication in the *World Journal of Diabetes*.

We have carefully considered the reviewers' comments, and we have revised the manuscript accordingly. The changes are marked **in red** in the revised version of the manuscript. Please find the answers to specific reviewers' comments below:

Response to the Reviewer# 05040445

The author aim was to investigate the efficacy of simultaneous versus sequential initiation approach of GLP-1RA and SGLT-2i combination in real world setting. It is kind of interesting, however, much has to be done to make the manu more readable.

1. *If the author want to compare the efficacy of simultaneous versus sequential initiation approach of GLP-1RA and SGLT-2i, then, Table 1 should be comparison of the baseline characteristics of the three group, including HbA1c, FBG,PPG, blood lipids, eGFR, blood pressure, diabetic duration, BMI etc.*

Thank you for your comment. We have performed analysis of all observed parameters, however we have presented only those parameters that were statistically significantly different. This was inserted in the Result section. Significant differences in baseline parameters between three therapy groups are presented in Table 2.

2. *Because of many patients has a long duration, so what about anti-diabetic drugs did those patients use before the initiation of GLP-1RA and SGLT-2i?*

Thank you for your comment. The following text was inserted in the Result section: An average duration of diabetes was over 10 years and majority of patients were treated with metformin, however insulin therapy comes into second place (36% of patients), while only around 15% of patients were treated with sulphonylurea and other OADs. Interestingly, groups treated with monotherapy had less insulin users than simultaneous therapy group. It is shown that there are most insulin patient in GLP-1 group ($p=0.006$), and metformin patients in both SGLT-2i and GLP-1 ($p=0.002$). For SU and other therapies differences were not statistically significant ($p>0.05$). In addition, Table 3 was added with information regarding other antihyperglycemic therapy used in three therapy groups.

3. *. Did they have other complications?*

Thank you for your comment. We have investigated macrovascular complications as an outcome of this study, data on microvascular complications were not collected since this was not an objective of this study. As was stated in a Result section cardiovascular disease was present in 44 (22.1%) prior to inclusion as a macrovascular complication.

4. *Except for ANOVA test, what about the differences between any two groups?*

Thank you for your comment. We have used several statistical analyses which are described in Method section to confirm validity of our data. The ANOVA analysis was chosen since it allows a comparison of more than two groups at the same time to determine whether a relationship exists between them. One-way ANOVA was used to calculate differences between three therapy groups at baseline (in case Levene's test showed significant deviation in homogeneity of variances, Kruskal-Wallis was used). Repeated-measures two-way ANCOVA for three points of measurements (with Bonferroni correction for multiple comparisons) was used, with therapy group as an independent factor, with adjustment for age, sex, duration of diabetes and duration of treatment. In addition, two-way ANOVA without adjustment for age, sex, duration of diabetes and treatment was performed and results were the same as after the adjustment for confounding factors. This was added to the Method and Result section.

5. *Did they use anti-hypertensive drugs or anti- hyperlipidemia drugs? what about the ratio in each group? did they have any differences?*

Thank you for your comment. Majority of patients had hypertension (85.5%) and hyperlipidemia (77.4%) as was already stated in a Result section, with no significant differences between groups. This was added in Result section.

6. *What about the adverse effects of the drugs in each group? What about the changes of blood pressure?*

Thank you for your comment. As was stated in a Discussion section the main limitation of this study is non- interventional observational design and disposal of routine data from everyday clinical settings. Therefore changes in blood pressure were not reported as well as adverse effects of drugs, and data were insufficient for us to perform the analysis. This was added in a Discussion section.

We corrected several typos and additionally revised the manuscript for grammar and language, which now hopefully meets the language requirements.

We are grateful to the reviewer for the valuable comments and suggestions. We hope that we have improved the consistency, clarity and interpretation of data in the manuscript and that the revised version will meet the reviewer's requirements and be suitable for publication in the World Journal of Diabetes.

Thank you again for the privilege of submitting our work to World Journal of Diabetes.

Sincerely,

Anna Mrzljak, MD, PhD