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Letter to the Editor

Letter by Awadhesh Kumar Singh Regarding Article, "Cardiovascular Outcomes Comparison of Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylurea as Add-on Therapy for Type 2 Diabetes Mellitus: A Meta-Analysis"

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See the article "Cardiovascular Outcomes Comparison of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylurea as Add-on Therapy for Type 2 Diabetes Mellitus: a Meta-Analysis" in volume 10 on page 210.

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Conflict of Interest
The authors have no conflicts of interest to declare.

To the Editor,

We read the manuscript by Jeon et al.[1] on "Cardiovascular Outcomes Comparison of Dipeptidyl Peptidase-4 Inhibitors versus Sulfonylurea as Add-on Therapy for Type 2 Diabetes Mellitus: a Meta-Analysis" published in your esteemed journal with great interest and applaud the authors for conducting such a high-quality meta-analysis. However, we noticed few major errors in this meta-analysis that need correction, in order to assist the conclusion. First, regarding the interpretation of ischemic stroke or transient ischemic attack (TIA) outcome between DPP-4 inhibitors (DPP-4Is) and sulfonylureas (SUs)—while authors have reported that DPP-4Is were associated with a higher risk of ischemic stroke or TIA (random-effect risk ratio [RR], 2.78; 95% confidence interval [CI], 1.06–7.30; p=0.065; I^2=51.9%) when compared to SUs from the analysis of 6 studies (5 randomized controlled trials [RCTs] and 1 prospective study), after the adjustment through the trim and fill method (excluding one small study that showed bias in ischemic stroke analysis) there was no significant difference in ischemic stroke between SUs and DPP4-Is (random-effect RR, 1.28; 95% CI, 0.50–3.29; p=0.612). Intriguingly, while title of this meta-analysis suggests a comparison of cardiovascular outcomes with DPP-4Is vs. SUs as an add-on therapy for type 2 diabetes mellitus, all analysis were done in reverse order i.e., SUs vs. DPP-4Is. In fact, the forest plot made by the authors itself suggests a rather 2.8-fold increase in relative risk of ischemic stroke or TIA in SUs recipients compared to DPP-4Is not the vice versa, as interpreted by the authors. Although reversing the order may not change the final results of any outcome, interpretations would be mistaken and funnel plot could be misleading, as in this case. Indeed, when we re-analyzed the ischemic stroke or TIA data from the same selected six studies (having exactly the same number of events and patients) using Comprehensive meta-analysis software version 3, Biostat Inc. Englewood, NJ, USA, we found a significantly 63% lesser relative risk amongst DPP-4Is recipients (random-effect RR, 0.37; 95% CI, 0.14–0.95; p=0.039) compared to SUs, with a similar insignificant albeit moderate heterogeneity (I^2= 51.4%; p=0.068) (**Fig. 1**). Interestingly, in our analysis, funnel plot found no publication bias, and the Trim and Fill method computed the same result (**Supplementary Fig. 1**). These findings do suggest

Author Contributions

Conceptualization: Singh AK; Data curation: Singh AK, Singh R; Formal analysis: Singh AK, Singh R; Writing - original draft: Singh AK; Writing - review & editing: Singh AK, Singh R.

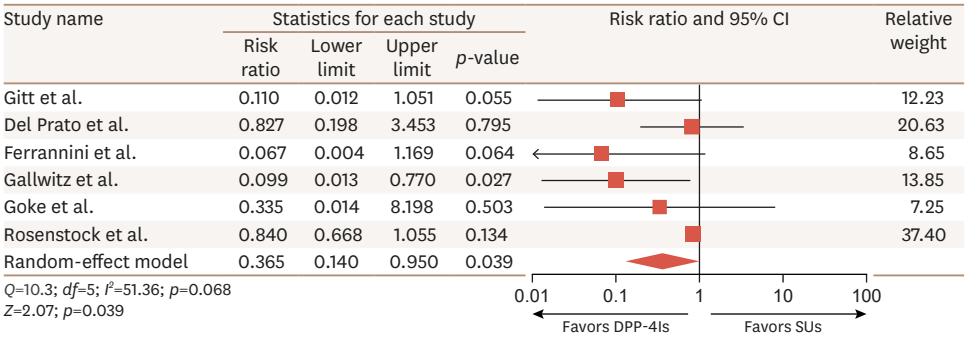

Fig. 1. Ischemic stroke or TIAs between DPP-4Is and SUs.
TIA, transient ischemic attack; DPP-4Is, DPP-4 inhibitors; SUs, sulfonylureas; CI, confidence interval.

DPP-4Is were associated with a significantly lesser risk of ischemic stroke or TIA compared to SUs. In a previous meta-analysis of 5 RCTs, Bain et al.[2] also reported a significant relative risk of increase in stroke (hazard ratio [HR], 9.40; 95% CI, 3.27–41.9; *p*=not reported) in SUs users compared to DPP-4Is. However, no significant difference in stroke or TIA outcome was observed in a dedicated, large (n=6,042), double-blind, randomized, cardiovascular outcome trial (CAROLINA) comparing DPP-4I (linagliptin) to SU (glimepiride). CAROLINA demonstrated no statistical difference in TIA (HR, 0.75; 95% CI, 0.45–1.26, *p*=0.28), non-fatal stroke (HR, 0.87; 95% CI, 0.66–1.15; *p*=0.34), and fatal or non-fatal stroke (HR, 0.86; 95% CI, 0.66–1.12; *p*=0.27) outcomes with linagliptin compared to glimepiride, although a reduced trend is noted with the former compared to later.[3] Second, authors have put p value for heterogeneity (I^2) instead of p value of overall effects (Z) against all the outcomes studied across the manuscript, surprisingly. This could be confusing and misleading at a time for the readers. Third, it should be noted that amongst all the hard end-points outcomes assessed in Jeon et al.[1] meta-analysis, only ischemic stroke or TIA outcomes were significantly (*p*=0.039) different between 2 antidiabetic agent that was mistakenly interpreted. Finally, we also noticed few other minor errors in the manuscript. For example—"all-cause mortality data was achieved from 13 studies while Rosenstock et al. (Ref. 31) reported no mortality events during follow-up and thus was excluded in the analysis"—It should be recalled that CAROLINA trial by Rosenstock et al. (Ref. 31) did report all-cause mortality and we believe authors meant exclusion of Rosenstock et al. (Ref. 27) instead. Similarly, the study by "Baptist Galhwitch" et al. should have been spelt "Baptist Gallwitch" instead, across all the tables and figures in the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Funnel plot for publication bias and Trim & Fill computation.

Click here to view

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