Concerns regarding the reliability of subgroup effects

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Alhassane Diallo and colleagues conducted an interesting and meaningful meta-analysis.[1] In the study, authors assessed the subgroup effects of glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) on major adverse cardiovascular event (MACE) by sex, age, body mass index, race, and duration of diabetes. Accordingly, they concluded: a greater benefit of GLP-1RAs on MACE was found in elderly patients and in Asian patients, and that of SGLT2i in patients with a long diabetes duration. However, the reliability of these findings might be adversely influenced by the following issues.

First, the multiple testing issue seemed not to be correctly considered. In the article, authors in total calculated 12 important P values for subgroup differences ($P_{interaction}$): **Figs. 2–4** report 4 $P_{interaction}$, respectively. According to the Bonferroni method,[2] the corrected significance threshold should be calculated: $0.05 \div 12 = 0.0042$. According to this threshold, three subgroup effects stated in the Conclusion (For SGLT2i: long-term versus short duration, $P_{interaction} = 0.03$. For GLP-1RAs: Asian versus White, $P_{interaction} = 0.07$; ≥75 versus <75 years, $P_{interaction} = 0.37$) would be far from statistical significance. If $P_{interaction}$ calculated in **Figs. S3 and S4** was additionally considered, the subgroup effects proposed by authors would be further from corrected significance. Since the Bonferroni correction

frequently is too strict and sacrifices power,[3] authors should identify a more appropriate method to address the multiple testing issue.

Second, **Fig. 4** in a secondary analysis article[4] of the CREDENCE trial reports all of the subgroup data of interest for this meta-analysis.[1] However, authors did not include them.

Declaration of interests
All authors declare no competing interests.

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