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LETTER

GLP1RAs vs SGLT2is were associated with lower risk of major adverse limb events and similar risks of heart failure hospitalisation and stroke?

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Abbreviations

GLP1RA	Glucagon-like peptide-1 receptor agonist
HFH	Heart failure hospitalisation
MALE	Major adverse limb events
SGLT2i	Sodium–glucose cotransporter 2 inhibitor

To the Editor: Lin and colleagues performed a real-world study [1] aiming to evaluate the risks of major adverse cardiovascular and limb events in people with diabetes treated with glucagon-like peptide-1 receptor agonists (GLP1RAs) vs sodium–glucose cotransporter 2 inhibitors (SGLT2is). The authors concluded that in people with diabetes, GLP1RAs were associated with significantly reduced risks of major adverse limb events (MALE) compared with SGLT2is. Moreover, this relative effectiveness was especially obvious in patients with diabetic neuropathy [1]. These findings are interesting and clinically relevant, but we want to share some additional comments.

First, we advise that care should be taken in the interpretation of results when many statistical tests are performed. In Table 2 of their paper, Lin et al evaluated a total of ten MALE and cardiovascular outcomes, and in Fig. 3 they report a total of ten subgroup analyses [1]. If the Bonferroni method was applied to account for the multiple testing [2], the threshold for significance should be calculated as: $\alpha'=0.05/10=0.005$. Based on this threshold, several of Lin et al's findings would not reach statistical significance. We acknowledge that the authors have clearly specified a primary endpoint for their study (composite outcome for MALE) and therefore strict correction for multiple testing is not necessary [3], but we would still encourage readers to take this into consideration when interpreting these results.

The second noteworthy thing is that the findings regarding the two outcomes of heart failure hospitalisation (HFH) and stroke in Lin et al's article [1] are substantially different to the evidence derived from RCTs and previous observational studies. A traditional meta-analysis based on RCTs [4] showed that GLP1RAs reduced HFH by 11% (HR 0.89; 95% CI 0.82, 0.98) and reduced stroke by 17% (HR 0.83; 95% CI 0.76, 0.92) in patients with type 2 diabetes compared with placebo. Another traditional meta-analysis based on RCTs [5] showed that SGLT2is reduced HFH by 32% (HR 0.68; 95% CI 0.61, 0.76) and yielded similar risk of stroke (HR 0.96; 95% CI 0.87, 1.07) in patients with type 2 diabetes compared with placebo. These two traditional meta-analyses [4, 5] seem to suggest that SGLT2is could reduce more HFH events than GLP1RAs, whereas GLP1RAs could reduce more stroke events than SGLT2is. A network meta-analysis based on RCTs [5] confirmed the aforementioned inference by revealing that SGLT2is significantly reduced risk of HFH (OR 0.74; 95% CI 0.65, 0.85) but significantly increased risk of stroke (OR 1.20; 95% CI 1.03, 1.41) compared with GLP1RAs in patients with type 2 diabetes. Consistent with this network meta-analysis [6], an updated meta-analysis based on large cohort studies [7] identified that SGLT2is vs GLP1RAs were associated with lower risk of HFH (HR 0.79; 95% CI 0.71, 0.88) and higher risk of stroke (HR 1.10; 95% CI 1.01, 1.19) in patients with type 2 diabetes. Taken together,

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the evidence from both RCTs and previous cohort studies support that among patients with type 2 diabetes, SGLT2is are superior to GLP1RAs in reducing HFH risk, whereas GLP1RAs are superior to SGLT2is in reducing stroke risk. However, Lin et al's study [1] showed that GLP1RAs vs SGLT2is had similar risks of HFH (HR 0.81; 95% CI 0.61, 1.09) and stroke (HR 0.93; 95% CI 0.81, 1.07) in patients with diabetes. These discrepancies need further explanation.

Moreover, a commentary study [8] on the basis of a network meta-analysis [6] of 764 RCTs identified that SGLT2is vs GLP1RAs significantly reduced the risk of all-cause death (OR 0.88; 95% CI 0.79, 0.98) in patients with type 2 diabetes. Similarly, a meta-analysis of cohort studies [9] identified that SGLT2is vs GLP1RAs were associated with lower risk of all-cause death (HR 0.92; 95% CI 0.85, 0.99) in patients with type 2 diabetes. On the contrary, in Lin et al's study [1], GLP1RAs were observed to modestly reduce the risk of all-cause death (HR, 0.90; 95% CI 0.80, 1.00) compared with SGLT2is in patients with diabetes. This discrepancy also needs further explanation.

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