Regarding the comments about our article1 from Koh, we agree that the results from recent randomized clinical trials of several glucose-lowering compounds (including sodium-glucose cotransporter-2 inhibitors [SGLT-2i] and glucagon-like peptide-1 receptor agonists), complemented by large observational studies, such as CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors), should drive a paradigm shift in the management of type 2 diabetes mellitus, from a narrow focus on hemoglobin A1c, to a broader focus on reducing the risk of adverse cardiovascular events (including heart failure), especially for those with established cardiovascular disease. As evidenced by the recent Standards of Care for Diabetes,2 just released by the American Diabetes Association, this shift is already occurring, and is likely to accelerate in the near future. We would also caution against overinterpretation of hazard ratios generated by the subgroup analyses from the EMPA-REG OUTCOME trial (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Specifically, in regard to the impact of empagliflozin and canagliflozin on cardiovascular outcomes across racial subgroups, the interaction P values were nonsignificant in both studies, indicating consistent effects with no significant heterogeneity.3,4

Regarding the comments from Jin-shan and Xue-bin: first, the CVD-REAL study was not designed to explore the mechanisms behind the cardiovascular benefits associated with SGLT-2i. Nevertheless, it is unlikely that these are directly related to their glucose-lowering properties. Several possible mechanisms have been proposed,5–7 including reduction in plasma volume,8 and a number of mechanistic studies are under way and should offer further insights in the near future. Second, we have recently reported that lower risk of heart failure, death, and a composite of heart failure or death associated with initiation of SGLT-2i versus other glucose-lowering agents was similar in patients both with and without established cardiovascular disease at baseline.9 Recent subgroup analyses from the CANVAS Program also show directionally consistent results for heart failure hospitalization and all-cause death in patients with and without established cardiovascular disease.10 Collectively, these data suggest that the cardiovascular effects of SGLT-2i (at least as they apply to the end points of heart failure hospitalization and all-cause mortality) may be similar across the cardiovascular risk continuum. The DECLARE-TIMI 58 Trial (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; ClinicalTrials.gov. Unique identifier: NCT01730534) will provide additional important information in terms of potential cardiovascular benefits of SGLT-2i in patients without established cardiovascular disease. Third, we focused on the cardiovascular outcomes associated with SGLT-2i use in the CVD-REAL study, and did not examine glycemic end points. However, our group and others have separately reported lower risk of severe hypoglycemia associated with the initiation of SGLT-2i versus other glucose-lowering agents.11–13

With regard to the comments by Taegtmeyer and Karlstaedt, we appreciate the authors’ mechanistic insights. As previously mentioned, the CVD-REAL study did not address the underlying mechanisms behind the associations we observed. Many mechanistic investigations are currently under way, and may support or refute some of the hypotheses that have been suggested. Second, it is important to continue evaluating long-term safety of SGLT-2i (and other glucose-lowering agents). This is being addressed by ongoing pharmacovigilance programs; the DECLARE-TIMI 58 Trial will also provide additional important information in this regard.

In regard to the comments by Tampaki et al: first, we believe that large, international, methodologically rigorous comparative effectiveness studies, such as CVD-REAL, offer important, complementary insights to the data generated from randomized clinical trials. As an example, our recently reported data on the rates of heart failure and all-cause death in patients with and without established cardiovascular disease suggests that, despite the drastic difference in absolute event rates between these 2 subgroups, the lower relative risk of these outcomes associated with initiation of SGLT-2i versus other agents is similar across the cardiovascular risk continuum. Furthermore, it is important to point out that the annualized event rates of heart failure and all-cause death observed among patients without established cardiovascular disease in the CVD-REAL study were quite low. Given the large number of patients in our study, we were still able to provide a meaningful inference into the relationship of SGLT-2i (versus other agents) with these important outcomes. However, it is highly unlikely that a randomized clinical trial of patients with type 2 diabetes mellitus who have very low risk, such as those in the primary prevention cohort of the CVD-REAL study, would be feasible.14 Second, we did not evaluate the outcome of myocardial infarction (including silent myocardial infarction) in the CVD-REAL study. Finally, we respectfully disagree with the authors in regard to the relative risk-benefit balance of SGLT-2i. Although careful consideration in regard to the safety and tolerability of these agents, and the individualization of care remain important (as is the case for all patient-centered clinical decisions), we believe that the cardiovascular benefits of this class outweigh the potential risks in many patient groups, especially as it applies to persons with type 2 diabetes mellitus and established cardiovascular disease, who have the highest absolute risk of cardiovascular complications.

Disclosures

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Footnotes

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