COMMENT ON KAUL

Mitigating Cardiovascular Risk in Type 2 Diabetes With Antidiabetes Drugs: A Review of Principal Cardiovascular Outcome Results of EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 Trials. Diabetes Care 2017;40:821–831

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I read with great interest the article by Dr. Kaul in the July 2017 issue of *Diabetes Care* (1), which reviews cardiovascular and microvascular outcomes of the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) trials. While results regarding the progression of diabetic retinopathy (DR) were neutral with liraglutide in the LEADER study, an unexpected higher rate of severe DR complications, mostly among patients with DR at baseline, was detected in patients treated with semaglutide compared with placebo in the SUSTAIN-6 study (hazard ratio 1.76 [95% CI 1.11, 2.78], $P = 0.02$) (2). Considering the beneficial effects of glucagon-like peptide 1 receptor agonists reported in experimental models of DR, these findings are surprising, and the underlying mechanisms are still under discussion. Although a rapid decrease in blood glucose levels in the semaglutide group may have contributed to these negative outcomes, the effect of glucagon-like peptide 1 receptor agonists on DR remains a potential concern, and a direct deleterious effect on the retina cannot be ruled out.

In the same way, ocular safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors, another attractive novel therapeutic option for the treatment of diabetes, is crucial. As mentioned by Kaul (1), no DR composite outcome in the EMPA-REG OUTCOME trial was reported. Nevertheless, some available data, not taken into account in the article, somewhat alter the conclusions of the author. Indeed, details on initiation of laser therapy for DR, vitreous hemorrhage, or diabetes-related blindness were quoted in Table S3 of the Supplementary Appendix of the article by Wanner et al. (3). There were no significant differences in the rates of each ocular event. Additionally, unlike the findings in the SUSTAIN-6 study, a nonsignificant lower rate of laser therapy for DR was observed in patients treated with empagliflozin compared with placebo (hazard ratio 0.69 [95% CI 0.43, 1.12], $P = 0.134$). Pending the results on ocular events in the recent CANVAS (Canagliflozin Cardiovascular Assessment Study) trial comparing canagliflozin to placebo, these reassuring data should be underlined since SGLT2 inhibitors are increasingly used in the treatment of diabetes.

Finally, until more definitive long-term data become available in the ocular drug safety issue, these neutral preliminary findings already have important implications for clinical practice. Nevertheless, clinical trials specifically designed to assess the effects of SGLT2 inhibitors on ocular complications with DR grading at baseline and during follow-up are required to further clarify this important issue and to overcome a possible ocular risk associated with treatment. I would also like to point out an inversion in the Table 3 columns concerning hospitalization for heart failure in the EMPA-REG OUTCOME study (1).

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References

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