Retinopathy Outcomes With Empagliflozin Versus Placebo in the EMPA-REG OUTCOME Trial

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce cardiovascular (CV) events in CV outcome trials in patients with type 2 diabetes and CV disease. In BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the SGLT2 inhibitor empagliflozin reduced the risk of 3-point major adverse CV events (3P-MACE; composite of CV death, nonfatal myocardial infarction, or nonfatal stroke) by 14% versus placebo, driven primarily by a 38% reduction in the risk of CV death (1). Empagliflozin also reduced the risk of a prespecified microvascular outcome (composite of time to first initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or incident/worsening nephropathy) by 38% versus placebo, driven by a reduction in kidney outcomes (2). Similarly, in Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), the glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide reduced the risk of 3P-MACE versus placebo (hazard ratio [HR] 0.74 [95% CI 0.58, 0.95]; $P < 0.001$), but was associated with a 76% increase in the risk of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) (1.49 vs. 0.86 events/100 patient-years, respectively; HR 1.76 [95% CI 1.11, 2.78]; $P = 0.02$]) (3). The reason for the increased risk of retinopathy in SUSTAIN-6 is unknown but has been hypothesized to be a consequence of rapid glucose lowering (4). In Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), the GLP-1 RA liraglutide reduced the risk of 3P-MACE versus placebo (HR 0.87 [95% CI 0.78, 0.97]; $P < 0.001$). The incidence of retinopathy events with liraglutide versus placebo was 0.6 vs. 0.5 events/100 patient-years, respectively (HR 1.15 [95% CI 0.87, 1.52]; $P = 0.33$) (5). In response to questions generated by SUSTAIN-6, we report further analyses of retinopathy data from EMPA-REG OUTCOME.

In EMPA-REG OUTCOME, patients were randomized to empagliflozin 10 mg, 25 mg, or placebo in addition to standard of care. Background glucose-lowering therapy remained unchanged for 12 weeks and was then adjusted at the investigator's discretion to achieve glycemic control. Post hoc, we analyzed the composite of time to first initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or administration of intravitreal agents. Differences in risk between the pooled empagliflozin and placebo groups were assessed using a Cox proportional hazards model in patients treated with ≥1 dose of study drug. To assess the potential impact of glucose lowering on retinopathy, we calculated the risk of this outcome after week 12 in subgroups by reductions in HbA_{1c} of ≥1% and <1% at week 12.

Overall, 7,020 patients received ≥1 dose of the study drug. At baseline, mean ± SD age was 63.1 ± 8.6 years, HbA_{1c} was 8.07 ± 0.85%, 57% had a diagnosis of type 2 diabetes for >10 years, 48% were using insulin, 32% had prevalent kidney disease (macroalbuminuria and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2), and 22% had a history of retinopathy. The median observation time was 3.1 years.

The composite retinopathy outcome occurred in 76 patients (1.6%) in the empagliflozin group and 48 patients (2.1%) in the placebo group, with incidence rates of 5.6 and 7.3/1,000 patient-years, respectively (HR 0.78 [95% CI 0.54, 1.12]; $P = 0.1732$) (Fig. 1). The incidence of the composite retinopathy

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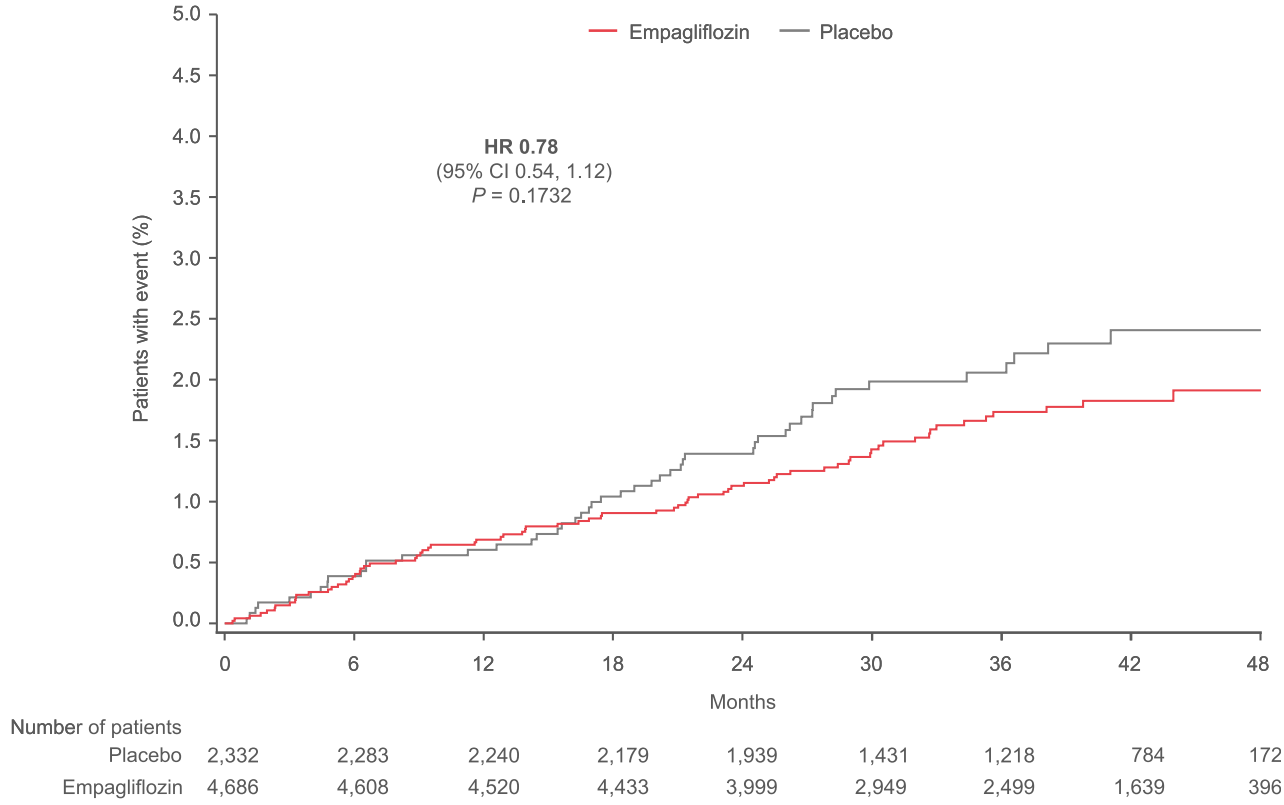

Figure 1—Cumulative incidence of a composite retinopathy outcome (initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or administration of intravitreal agents). HR is based on Cox regression analysis. Data are from patients treated with ≥1 dose of study drug. The outcome could not be assessed in two patients.

outcome for empagliflozin and placebo was higher in patients with diabetic retinopathy at baseline (13.6 and 18.2 events/1,000 patient-years, respectively) (HR 0.73 [95% CI 0.44, 1.20]; $P = 0.2187$) than in patients without diabetic retinopathy at baseline (3.6 and 4.2/1,000 patient-years, respectively) (HR 0.84 [95% CI 0.50, 1.42]; $P = 0.5214$) ($P = 0.7018$ for treatment by retinopathy at baseline interaction). Initiation of retinal photocoagulation occurred in 41 patients (0.9%) in the empagliflozin group and 29 (1.2%) in the placebo group (3.0 and 4.4/1,000 patient-years, respectively) (HR 0.69 [95% CI 0.43, 1.12]). Vitreous hemorrhage occurred in 30 patients (0.6%) in the empagliflozin group and 16 (0.7%) in the placebo group (2.2 and 2.4/1,000 patient-years, respectively) (HR 0.93 [95% CI 0.51, 1.71]). Administration of intravitreal agents occurred in 10 patients (0.2%) in the empagliflozin group and 7 (0.3%) in the placebo group (0.7 and 1.0/1,000 patient-years, respectively) (HR 0.70 [95% CI 0.27, 1.85]). Diabetes-related blindness occurred in 4 patients treated with empagliflozin and 2 treated with placebo; an HR was not calculated as the number of patients with events was <14. There was no difference in the risk of composite retinopathy for empagliflozin 10 mg (HR 0.74 [95% CI 0.48, 1.14]; $P = 0.1683$) or empagliflozin 25 mg (HR 0.82 [95% CI 0.54, 1.24]; $P = 0.3472$) versus placebo. The risk of the composite retinopathy outcome with empagliflozin versus placebo after week 12 was also consistent whether patients had a reduction in HbA_{1c} at week 12 of <1% (HR 0.87 [95% CI 0.58, 1.31]) or ≥1% (HR 0.41 [95% CI 0.14, 1.16]) ($P = 0.1866$ for treatment by subgroup interaction). We acknowledge the inherent limitations of post hoc analyses. While retinopathy at baseline was coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 18.0), the nature and severity of retinopathy was not collected. Additionally, retinal evaluations and photography were not performed routinely but were captured as adverse events during each study visit or if the patient notified the study site between visits.

In conclusion, in the EMPA-REG OUTCOME trial in patients with type 2 diabetes and CV disease, empagliflozin was not associated with an increased risk of retinopathy compared with placebo.

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