Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial

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Diabetes Care 2018;41:e4–e5 | https://doi.org/10.2337/dc17-1551

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are oral glucose-lowering agents indicated for the treatment of type 2 diabetes. In the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, the SGLT2 inhibitor canagliflozin was associated with an increased risk for lower-limb amputation (LLA) (including minor and major amputation) versus placebo (hazard ratio [HR] 1.97 [95% CI 1.41, 2.75]) in patients with type 2 diabetes and high cardiovascular risk (1). In the EMPA-REG OUTCOME trial in patients with type 2 diabetes and established cardiovascular disease (2), the proportion of patients with LLA was similar between those treated with empagliflozin and placebo (3). We report further analyses of LLA in the EMPA-REG OUTCOME trial.

Any hospital admission during the EMPA-REG OUTCOME trial was to be reported as a serious adverse event. Investigators were asked to provide a detailed narrative with additional medical information for each serious adverse event. From the EMPA-REG OUTCOME trial database, we identified LLA via a systematic search of serious adverse event narratives, from events reported as adverse events, and from those reported as a "medical procedure" under "concomitant therapy" in electronic case report forms or in investigator comments describing adverse events. All cases identified were medically reviewed to confirm an LLA event. Time to first LLA was analyzed using a Cox proportional hazards model and Kaplan-Meier estimates are presented. Frequencies, incidence rates, and incidence rate ratios were calculated in all patients and in subgroups by baseline characteristics based on established risk factors for amputation (4).

A total of 7,020 patients were treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in addition to standard of care. At baseline, 71% of patients were male, mean (SD) age was 63.1 (8.6) years, BMI was 30.6 (5.3) kg/m^2, HbA_{1c} was 8.1% (0.9%), 57% had a diagnosis of type 2 diabetes for >10 years, 48% were taking insulin, and 22% had a history of peripheral artery occlusive disease. The median observation time was 3.1 years. During the trial, LLAs were reported in 131 patients: 88 patients (1.9%) treated with empagliflozin and 43 (1.8%) treated with placebo. The incidence rate was 6.5 per 1,000 patient-years in both groups. In the analysis of time to first event, the risk of LLA was similar between empagliflozin pooled and placebo (HR 1.00 [95% CI 0.70, 1.44]) (Fig. 1*A*). Results were similar with empagliflozin 10 mg (HR 0.96 [95% CI 0.63, 1.47]) and empagliflozin 25 mg (HR 1.04 [95% CI 0.69, 1.58]). The findings were consistent across subgroups by established risk factors for amputation (Fig. 1*B*).

We acknowledge the inherent limitations of manually identifying LLA and performing post hoc analyses. A dedicated case report form was not used in the EMPA-REG OUTCOME trial as there was no concern regarding an increased risk of amputation with empagliflozin before or during the trial. We are confident that the reporting and systematic retrieval processes employed were thorough. Using our comprehensive search strategy based on three independent categories of event, we identified 116 of 131 (88.5%) patients with LLA in more than one source, providing confidence in the completeness of reporting and retrieval. In addition, the patient subgroups with higher incidences of LLA were consistent with known risk factors for LLA (4). We acknowledge that our manual retrieval strategy may not account for investigator subjectivity in ascertainment, but such instances would be balanced through randomization.

In conclusion, the SGLT2 inhibitor empagliflozin was not associated with

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Received 27 July 2017 and accepted 11 October 2017.

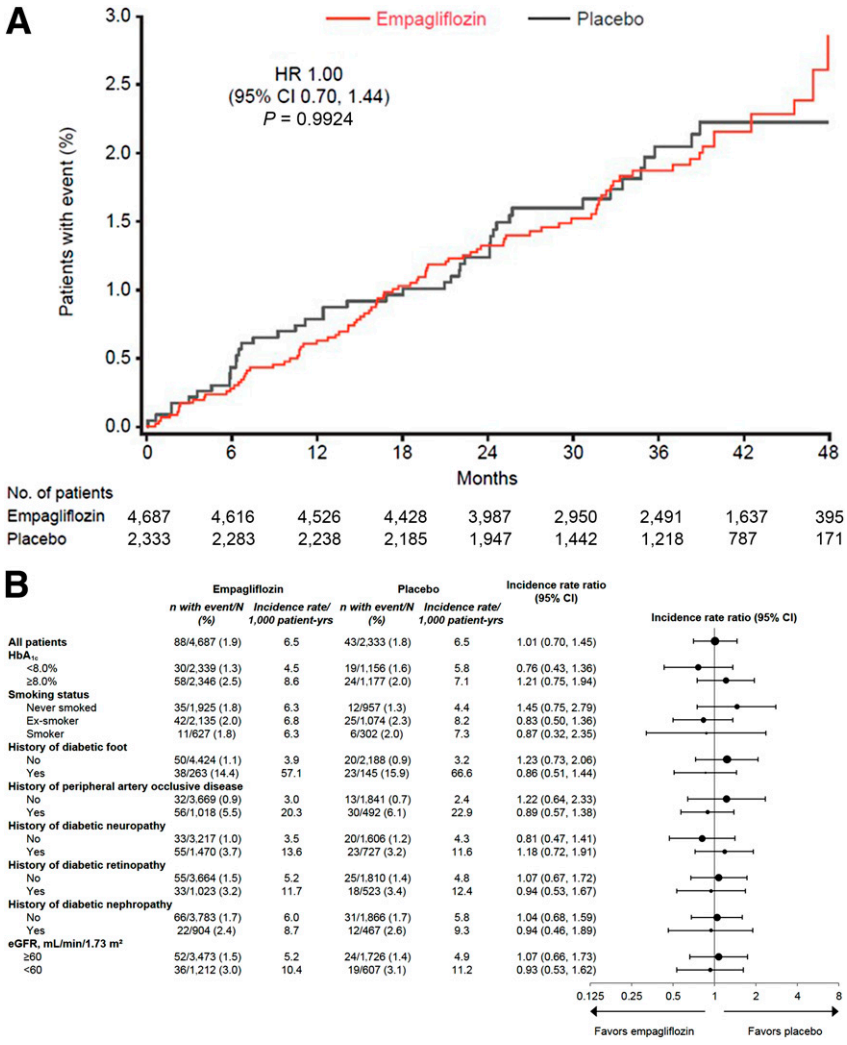

Figure 1—*A*: Kaplan-Meier estimate of time to first LLA. Analyses in patients who received ≥1 dose of the study drug. LLAs were those reported as an adverse event, those reported as a "medical procedure" in electronic clinical report forms or in investigator comments describing adverse events, or those identified from a systematic search of serious adverse event narratives using the search terms "amput," "disarticul," "resect," and "remov." HR and 95% CI were based on a Cox proportional hazards model adjusting for baseline age, sex, BMI, HbA_{1c}, estimated glomerular filtration rate, and region. Patients who did not experience an event were censored on the last study visit. *B*: Subgroup analysis of LLA. Analyses in patients who received ≥1 dose of study drug. Time at risk was derived from the first study drug intake until the last day the patient was known to be free of the outcome or the last visit date. Of patients with LLAs during the trial, 27/88 (31%) in the empagliflozin group and 10/43 (23%) in the placebo group had a history of amputation at baseline. Of all patients treated, 22/4,687 (0.5%) in the empagliflozin group and 9/2,333 (0.4%) in the placebo group had >1 amputation event during the trial. eGFR, estimated glomerular filtration rate based on Modification of Diet in Renal Disease equation.

an increased risk of LLA compared with placebo in the EMPA-REG OUTCOME trial.

Acknowledgments. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Elizabeth Ng of FleishmanHillard Fishburn, London, U.K., during the preparation of the paper.

Duality of Interest. The EMPA-REG OUTCOME trial was funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. S.E.I. has consulted for Boehringer Ingelheim, AstraZeneca, Merck & Co., Intarcia Therapeutics, Inc., Lexicon Pharmaceuticals, Janssen, Sanofi, Novo Nordisk, and vTv Therapeutics. H.I. and E.P. are employees of Boehringer Ingelheim. B.Z. has received research grants from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk and honoraria from Janssen, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Novo Nordisk, and Merck & Co. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.E.I. and B.Z. contributed to the interpretation of data and the development of the manuscript. H.I. and E.P. contributed to the analysis and interpretation of data and the development of the manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of development, and approved the final version. S.E.I. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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