

Cardiovascular Outcomes and Safety of Empagliflozin in Patients With Type 2 Diabetes Mellitus and Peripheral Artery Disease

A Subanalysis of EMPA-REG OUTCOME

Peripheral artery disease (PAD) is one of the most common cardiovascular complications in patients with type 2 diabetes mellitus (T2DM)¹ and is a predictor of cardiovascular death.² Interventions that reduce cardiovascular complications in this patient population are urgently required. In the EMPA-REG OUTCOME trial, the sodium glucose cotransporter 2 inhibitor empagliflozin reduced the risk of cardiovascular death by 38% (hazard ratio [HR], 0.62; 95% confidence interval [CI] 0.49–0.77) and hospitalization for heart failure (HHF) by 35% (HR, 0.65; 95% CI, 0.50–0.85) versus placebo when given in addition to standard of care.³ We report analyses of the effects of empagliflozin on cardiovascular outcomes, mortality, and renal outcomes in patients with and without PAD at baseline in the EMPA-REG OUTCOME trial.

Patients in EMPA-REG OUTCOME had T2DM (hemoglobin A_{1c}, 7%–10%), established cardiovascular disease, and estimated glomerular filtration rate ≥ 30 mL·min⁻¹·1.73 m⁻² at baseline. PAD at inclusion was defined as the presence of any of the following: limb angioplasty, stenting, or bypass surgery; limb or foot amputation resulting from circulatory insufficiency; evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via noninvasive methods) in ≥ 1 limb; and ankle brachial index <0.9 in ≥ 1 ankle. Patients were randomized 1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, or placebo in addition to standard of care. Cardiovascular outcome events and deaths were prospectively adjudicated by Clinical Events committees. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. Patients provided informed consent before study entry.

In subgroups by PAD at baseline (yes/no), we assessed the risk of cardiovascular death, 3-point major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), 4-point MACE (3-point MACE plus hospitalization for unstable angina), all-cause mortality, HHF, the composite of HHF or cardiovascular death, and incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death caused by renal disease) with empagliflozin pooled versus placebo using a Cox proportional hazards model. The model included factors for age, sex, baseline body mass index, hemoglobin A_{1c}, estimated glomerular filtration rate, region, treatment, PAD, and treatment-by-PAD interaction. *P* values for the treatment-by-subgroup interaction were obtained from tests of homogeneity of treatment group differences among subgroups with no adjustment for multiple testing. Kaplan-Meier estimates are presented for cardiovascular death. Lower limb amputation (LLA) was identified via a systematic search of serious adverse event (AE) narratives, from events reported as AEs, and from those reported as a medical procedure under concomitant therapy in electronic case report forms or in investigator comments describing AEs, and analyzed using a Cox proportional hazards model. Minor LLA was defined as any resection through or distal to the

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articulation of the ankle.⁴ Minor LLA, major LLA, and other AEs were assessed descriptively.

Of 7020 patients treated, 1461 (20.8%) had PAD at baseline (982 treated with empagliflozin, 479 treated with placebo). In this group, baseline mean±SD age was 64.0±8.5 years, body mass index was 30.7±5.3 kg/m², hemoglobin A_{1c} was 8.12±0.86%, 69% were male, 10% had a history of HF, 67% were current or ex-smokers, 30% had estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻², 92% were on antihypertensive therapy, 75% were on lipid-lowering therapy, and 85% were on antiplatelet/anticoagulant therapy. In patients without PAD, the mean±SD age was 62.9±8.7 years, body mass index was 30.6±5.3 kg/m², hemoglobin A_{1c} was 8.06±0.84%, 72% were male, 10% had a history of HF, 57% were current or ex-smokers, 25% had estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻², 96% were on antihypertensive therapy, 83% were on lipid-lowering therapy, and 90% were on antiplatelet/anticoagulant therapy.

In patients with PAD at baseline, empagliflozin reduced cardiovascular death by 43% (HR, 0.57; 95% CI, 0.37–0.88), all-cause mortality by 38% (HR, 0.62; 95% CI, 0.44–0.88), 3-point MACE by 16% (HR, 0.84; 95% CI, 0.62–1.14), 4-point MACE by 7% (HR, 0.93; 95% CI, 0.70–1.24), HHF by 44% (HR, 0.56; 95% CI, 0.35–0.92), and incident or worsening nephropathy by 46% (HR, 0.54; 95% CI, 0.41–0.71) versus placebo, consistent with findings in patients without PAD (Figure, A). The reductions in cardiovascular death appeared early and persisted for the duration of the trial (Figure, B). In general, overall AEs and serious AEs were balanced between the empagliflozin and placebo groups in patients with and without PAD. In patients with PAD, LLA occurred in 54 of 982 (5.5%) treated with empagliflozin and 30 of 479 (6.3%) treated with placebo (HR, 0.84; 95% CI, 0.54–1.32). In patients without PAD, LLA occurred in 34 of 3704 (0.9%) treated with empagliflozin and 13/1853 (0.7%) treated with placebo (HR, 1.30; 95% CI, 0.69–2.46; Figure, A). In patients with PAD, major LLA occurred in 13 of 982 (1.3%) and 16 of 479 (3.3%) patients in the empagliflozin and placebo groups, respectively, and in patients without PAD, major LLA occurred in 5 of 3704 (0.1%) and 2 of 1853 (0.1%) in the empagliflozin and placebo groups, respectively. In patients with PAD, minor LLA occurred in 41 of 982 (4.2%) and 14 of 479 (2.9%) patients in the empagliflozin and placebo groups, respectively, and in patients without PAD, minor LLA occurred in 29 of 3704 (0.8%) and 11 of 1853 (0.6%) in the empagliflozin and placebo groups, respectively.

In summary, in the vulnerable subgroup of patients with T2DM and PAD, empagliflozin reduced mortality,

and in patients without PAD, major LLA occurred in 5 of 3704 (0.1%) and 2 of 1853 (0.1%) in the empagliflozin and placebo groups, respectively. In patients with PAD, minor LLA occurred in 41 of 982 (4.2%) and 14 of 479 (2.9%) patients in the empagliflozin and placebo groups, respectively, and in patients without PAD, minor LLA occurred in 29 of 3704 (0.8%) and 11 of 1853 (0.6%) in the empagliflozin and placebo groups, respectively.

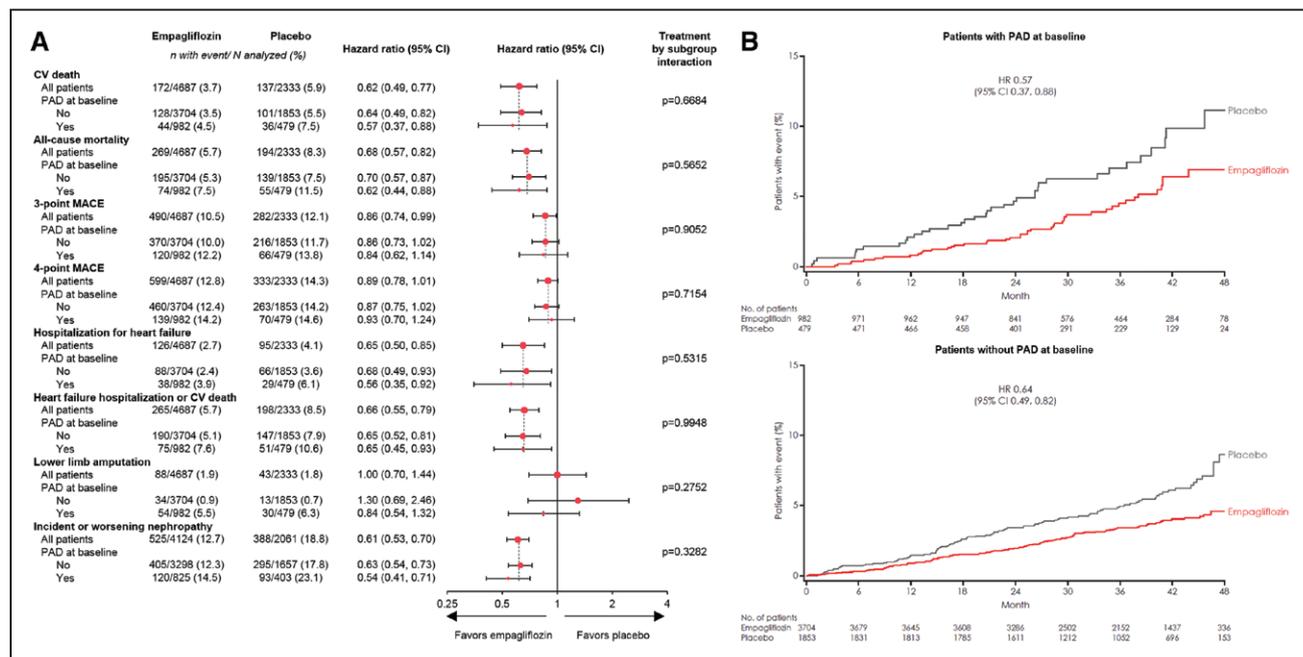


Figure. Cardiovascular outcomes, all-cause mortality, lower limb amputation, and incident or worsening nephropathy by peripheral artery disease (PAD) at baseline.

A, Cardiovascular outcomes, all-cause mortality, lower limb amputation, and incident or worsening nephropathy by PAD at baseline. Cox regression analysis in patients treated with ≥1 dose of study drug. Interaction P value is for test of homogeneity of treatment group difference among subgroups (test for treatment by subgroup interaction) with no adjustment for multiple tests. Information on PAD at baseline was not available for 1 patient in the empagliflozin group and 1 patient in the placebo group. **B**, Time to cardiovascular (CV) death. Kaplan-Meier estimates in patients treated with ≥1 dose of study drug. Hazard ratio (HRs) and 95% confidence intervals (CIs) are based on Cox regression analyses. MACE indicates major adverse cardiovascular event.

HHF, and progression of renal disease with no observed increase in the risk of LLA. The reduction in cardiovascular death with empagliflozin in patients with T2DM and PAD translates to a number needed to treat of 29 patients over 3.1 years to prevent 1 event. These data have important translational implications for risk reduction approaches in patients with T2DM and PAD.

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FOOTNOTES

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