CORRESPONDENCE

Empagliflozin and Major Renal Outcomes in Heart Failure

TO THE EDITOR: Sodium–glucose cotransporter 2 inhibitors reduce the risk of serious adverse renal outcomes in type 2 diabetes, but the renal effects of these drugs in patients with heart failure remain uncertain. Although empagliflozin and dapagliflozin have been reported to slow the rate of decline in the estimated glomerular filtration rate (eGFR),[1,2] changes in the eGFR slope may not predict the effects of these drugs on major renal outcomes.[3]

To investigate the effect of empagliflozin on major renal events in patients with heart failure, we planned a prospective, patient-level, pooled analysis of the results of the EMPEROR-Reduced and EMPEROR-Preserved trials.[4] Both trials had similar protocols, investigative sites, and trial infrastructure, but the EMPEROR-Reduced trial enrolled patients with a baseline ejection fraction of 40% or less, and the EMPEROR-Preserved trial enrolled those who had a value of more than 40%. The enrollment criteria are provided in the Supplementary Appendix (available with the full text of this letter at NEJM.org). In both double-blind trials, patients were randomly assigned to receive empagliflozin at a dose of 10 mg per day or placebo, in addition to usual therapy.

The primary outcome of the pooled analysis was a composite of major adverse renal outcomes (i.e., profound and sustained decreases in eGFR or renal-replacement therapy) (Table S1 in the Supplementary Appendix). A separate statistical analysis plan was used for the pooled analysis (available with the protocol at NEJM.org) and was developed before enrollment in the EMPEROR-Reduced and EMPEROR-Preserved trials had begun. Both trials specified a hierarchical testing procedure, which allowed an alpha level of 0.0496 to be used in the pooled analysis.[4] Heterogeneity of treatment effects across the two trials was assessed to determine whether data pooling would be appropriate.

In the two trials combined, 9718 patients underwent randomization from April 2017 through April 2020 and were included in the pooled analysis. The baseline characteristics were similar between the patients who had received empagliflozin and those who had received placebo (Table S2).

Over a median follow-up of 21 months, 138 of 4860 patients (2.8%) who had received empagliflozin and 170 of 4858 patients (3.5%) who had received placebo had major adverse renal outcomes. There was significant heterogeneity across the two trials ($P=0.016$ for interaction). The hazard ratios for serious renal outcomes were 0.51 (95% confidence interval [CI], 0.33 to 0.79) in the EMPEROR-Reduced trial and 0.95 (95% CI, 0.73 to 1.24) in the EMPEROR-Preserved trial (Fig. 1). In each trial, the effect of empagliflozin was consistent across the components of the primary outcome and across all prespecified subgroups, including patients with and patients without diabetes (Table S3 and Figs. S1 and S2).

In 4111 patients, paired, off-treatment measurements of eGFR were performed at baseline and at approximately 30 days after discontinuation of empagliflozin or placebo, thus enabling an assessment of the long-term effects of empagliflozin

THIS WEEK'S LETTERS

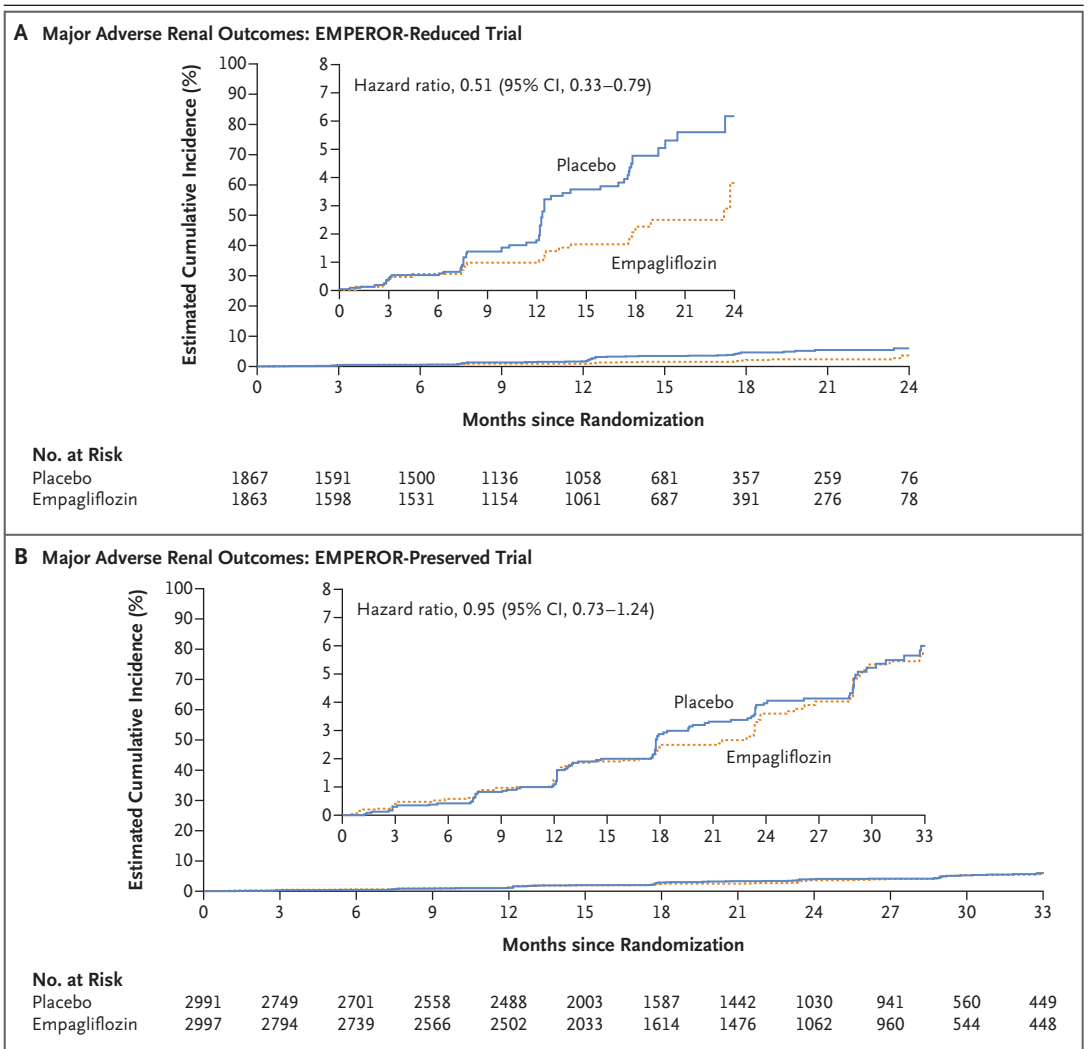

Figure 1. Incidence of Major Adverse Renal Outcomes in the EMPEROR-Reduced and EMPEROR-Preserved Trials.

The primary outcome of the pooled analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials was a composite of major adverse renal outcomes (i.e., profound and sustained decreases in the estimated glomerular filtration rate or renal-replacement therapy) (Table S1 in the Supplementary Appendix, available at NEJM.org). The baseline ejection fraction was 40% or less among patients in the EMPEROR-Reduced trial and more than 40% among patients in the EMPEROR-Preserved trial. Estimates for the composite renal outcome in the EMPEROR-Reduced trial differ slightly from those published previously[2] because the analyses reported here used the pooled data, and covariate adjustment in the pooled analysis differed from that in the individual trials. CI denotes confidence interval.

that was not affected by confounding factors. The annualized decline in eGFR between the paired values was more marked in the placebo group than in the empagliflozin group (Table S3). The adjusted mean difference was nearly twice as great in the EMPEROR-Reduced trial than in the EMPEROR-Preserved trial (1.77 [95% CI, 0.80 to 2.74] vs. 0.94 [95% CI, 0.60 to 1.27] ml per minute per 1.73 m^2), but it was similar between patients who had diabetes and those who did not.

Our finding that ejection fraction influences the effects of empagliflozin on major renal outcomes is noteworthy, given that empagliflozin lowered the incidence of hospitalizations for heart failure to a similar extent in the EMPEROR-Reduced and in the EMPEROR-Preserved trials.[4,5] In the EMPEROR-Preserved trial, the observed lack of benefit with respect to serious renal outcomes contrasts with the finding that empagliflozin slowed the decline in eGFR in that trial,[5] suggesting that eGFR slope analysis has limitations as a surrogate for predicting the ef-

fect of drugs on renal outcomes in patients with heart failure.[3]

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

Data will be made available on request in adherence with transparency conventions in medical research and through requests to the corresponding author. Following execution of prespecified analyses, a full database will be made available in adherence with the transparency policy of the sponsor (available at https://trials.boehringer-ingelheim.com/transparency_policy.html).

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Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion

TO THE EDITOR: Pregnant persons are at risk for severe coronavirus disease 2019 (Covid-19), and infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy is associated with increased risks of preterm birth and other adverse maternal and neonatal outcomes.[1] Although spontaneous abortion (pregnancy loss occurring at less than 20 weeks of gestation) is a common pregnancy outcome affecting 11 to 22% of recognized pregnancies (see Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org),[2-4] data to inform estimates of the risk of spontaneous abortion after receipt of an mRNA Covid-19 vaccine either before conception (30 days before the first day of the last menstrual period through 14 days after) or during pregnancy are limited.

We analyzed data from the Centers for Disease Control and Prevention (CDC) v-safe Covid-19 vaccine pregnancy registry to determine the cumulative risk of spontaneous abortion from 6 to less than 20 weeks of gestation. Participants with a singleton pregnancy who had received at least one dose of an mRNA Covid-19 vaccine either before conception or before 20 weeks of gestation and who did not have a pregnancy loss before 6 weeks of gestation were included in this analysis. Inclusion of pregnant participants at 6 weeks of gestation is consistent with literature estimating the risk of spontaneous abortion in the general population.[2-4] Life table methods were used to calculate the cumulative risk of spontaneous abortion according to gestational week, with appropriate left truncation (i.e., with adjustment for