How Early After Treatment Initiation are the CV Benefits of Empagliflozin Apparent? A Post hoc Observation from the EMPA-REG OUTCOME® Trial

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Presenter Disclosure

Subodh Verma

• Holds Tier 1 Canada Research Chair in Cardiovascular Surgery

• Received grants and personal fees for speaker honoraria and advisory board participation
  – Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group.

• Serves as President of the Canadian Medical and Surgical Knowledge Translation Research Group

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Introduction

• Timely reduction of CV risk in T2D remains a priority of pharmacological therapies

• In EMPA-REG OUTCOME®, in patients with T2D and atherosclerotic CV disease, empagliflozin compared with placebo reduced the relative risk of CV death by 38%, hospitalization for heart failure (HHF) by 35%, and the composite of HHF or CV death by 34%.

• Reduction in risk of CV and HF outcomes appeared to occur early after treatment initiation but the timing of when the benefit reached significance has not been explored

• Therefore this post hoc analysis explored the time point after randomization at which the benefits of empagliflozin became statistically significant

CV, cardiovascular; HF, heart failure, HHF, hospitalization for heart failure; T2D, type 2 diabetes.
Methods

- EMPA-REG OUTCOME® enrolled patients with T2D, atherosclerotic CV disease and an eGFR ≥30 ml/min/1.73 m²
  - Adult patients were randomized (1:1:1) to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care
- Time trajectories were expressed for the effect of pooled empagliflozin versus placebo on time to CV death, first HHF, and the composite of first HHF or CV death (excluding fatal stroke)
- HRs were calculated each day following randomization until the last day of observation, using a Cox proportional hazards model that included terms for treatment, age, sex, baseline BMI, baseline eGFR, baseline HbA1c, and geographical region
- Timing was assessed for when treatment effect first reached statistical significance (p<0.05)

BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HHF, hospitalization for heart failure; T2D, type 2 diabetes.
Time to CV death
Time to CV death

Cox regression for time to CV death, pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set. CV, cardiovascular.

Overall

HR 0.62
(95% CI 0.49, 0.77)

$p<0.0001$

Focusing on first 360 days...
Cox regression for time to CV death, pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set.
CV, cardiovascular.
Time to first HHF
Cox regression for time to first HHF, pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set.

HHF, hospitalization for heart failure.
Cox regression for time to first HHF, pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set.

HHF, hospitalization for heart failure.

Time to first HHF or CV death
Time to first HHF or CV death

Cox regression for time to first HHF or CV death (excluding fatal stroke), pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set.

CV, cardiovascular; HHF, hospitalization for heart failure.
Cox regression for time to first HHF or CV death (excluding fatal stroke), pooled empagliflozin versus placebo. Hazard ratios and 95% confidence intervals (CI) are shown in relation to time point of censoring – treated set. CV, cardiovascular; HHF, hospitalization for heart failure.
Conclusions

• Treatments that reduce risk of CV and HF outcomes expeditiously are important in the management of patients with T2D and atherosclerotic CV disease

• In this post hoc analysis, we demonstrate that empagliflozin exerts clinically and statistically significant CV benefits within weeks of treatment initiation

• The earliest effect appears to be on HHF at day 17

• These findings demonstrate the rapidity of benefit of empagliflozin in reducing the risk of CV and HF outcomes

CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; T2D, type 2 diabetes.