Empagliflozin Reduced the Total Burden of Events Leading to or Prolonging Hospitalisation in EMPA-REG OUTCOME

EMPA-REG OUTCOME®

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Empagliflozin reduces total burden of all-cause mortality and events leading to or prolonging hospitalisation in patients with type 2 diabetes and established cardiovascular disease

What was known

- In the EMPA-REG OUTCOME trial, the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin reduced the risk of total (first plus recurrent) events leading to all-cause hospitalisation (ACH) by 17%, and the composite of all-cause mortality (ACM) and ACH by 19% versus placebo in patients with type 2 diabetes (T2D) and established cardiovascular disease (eCVD).[1]
- A numerically greater empagliflozin treatment effect was observed with recurrent versus first-event analyses.[2]

What's new

- Empagliflozin showed a sizeable reduction in the total burden of ACM and events leading to or prolonging hospitalisation for any cause in patients with T2D and eCVD, with a clinically relevant number of events prevented and a low number needed to treat (NNT).

OBJECTIVE

- We assessed the effect of empagliflozin on the total burden of events leading to or prolonging hospitalisation for any cause (ACH-P; as determined by the investigator), as well as the composite of ACH-P + ACM.

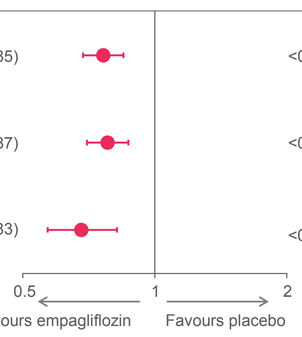
METHODS

- This *post hoc* analysis included participants from the EMPA-REG OUTCOME trial (ClinicalTrials.gov identifier: NCT01131676)[1] with estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2 and glycated haemoglobin (HbA1c) 7.0–9.0% for drug-naïve participants and 7.0–10.0% for those on stable glucose-lowering therapy.
- Participants were randomised to empagliflozin 10 mg, 25 mg, or placebo, in addition to usual care. Empagliflozin dose groups were pooled for comparison versus placebo.
- The rates of total (first plus recurrent) events of ACH-P and the composite of ACH-P + ACM were analysed using a negative binomial regression model that preserves randomisation and accounts for correlation of multiple events within individuals.
  - First events of ACH-P, ACM, and the composite of ACH-P + ACM were analysed using a Poisson regression model.
- Both models included age as linear covariate and treatment, sex, baseline body mass index (BMI) category, baseline HbA1c category, baseline eGFR category, and geographical region as fixed effect(s); log(time to first event) and log(observation time) were used as the offset for the Poisson and negative binomial regression models, respectively.
- Total events of the composite ACH-P + ACM were assessed in a time-to-event analysis using the Wei-Lin-Weissfeld model, which produces estimated relative treatment effects (hazard ratio) for the individual first and recurrent events by the order in which they occur. This model also includes a test of the consistency of the treatment effect estimates across the individual order of sequential events.
- We estimated the number of total (first plus recurrent) events prevented during the trial and the NNT to prevent 1 (first or recurrent) event with empagliflozin versus placebo over 3 years.

RESULTS

Figure 1. The adjusted event rate ratio of total (first plus recurrent) events leading to or prolonging hospitalisation for any cause and the composite with all-cause mortality in pooled empagliflozin versus placebo participants

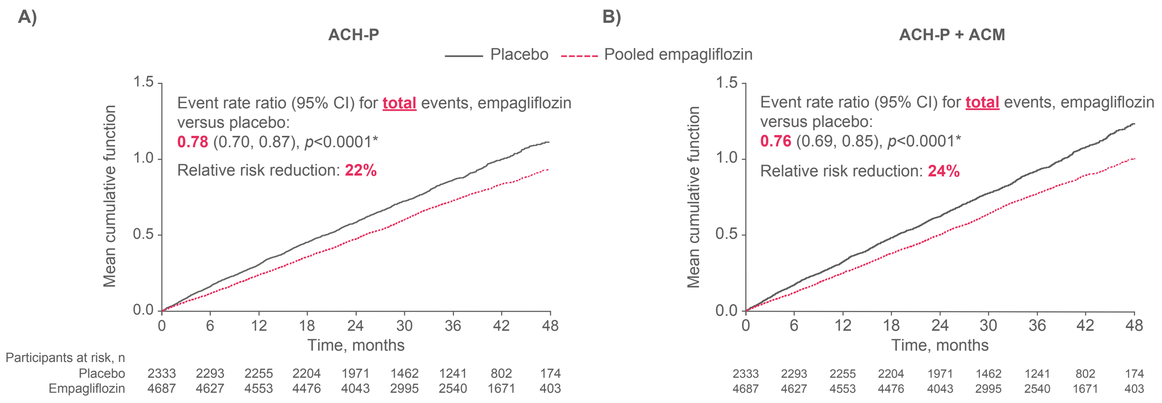
	Pooled empagliflozin (N=4687)	Placebo (N=2333)	Pooled empagliflozin (N=4687)	Placebo (N=2333)	Adjusted event rate ratio (95% CI)*	*p*-value*
	Events, n		Adjusted event rate per 1000 patient years*			
ACH-P + ACM composite*	3513	2104	387.6	508.2	0.76 (0.69, 0.85)	<0.0001
ACH-P*	3302	1954	350.0	448.7	0.78 (0.70, 0.87)	<0.0001
ACM†	269	194	19.6	28.5	0.69 (0.57, 0.83)	<0.0001



There were a total of 5031 events of ACH, 225 events prolonging hospitalisation, and 5256 events of ACH-P.
*Negative binomial model including age as a linear covariate and treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category and geographical region as fixed effects; log(observation time) was used as offset.
†Poisson model with same adjustment.
ACH, all-cause hospitalisation; ACH-P, events leading to or prolonging hospitalisation for any cause; ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

- There were 2666 patients with at least 1 event leading to ACH-P. The event rate ratio (95% confidence interval [CI]) of empagliflozin versus placebo for first events was 0.88 (0.81, 0.95), *p*=0.0018 corresponding to a relative risk reduction of 12%.
- There were 5256 total (first plus recurrent) events leading to ACH-P.
  - The event rate ratio (95% CI) for empagliflozin versus placebo for total ACH-P events was 0.78 (0.70, 0.87) (**Figure 1**)
  - Empagliflozin reduced the relative risk of total events of ACH-P by 22% compared with placebo (**Figure 2A**).
- There were 2844 patients with at least 1 event for the composite of ACH-P + ACM. The event rate ratio (95% CI) of empagliflozin versus placebo for first events was 0.86 (0.80, 0.93), *p*=0.0001 corresponding to a relative risk reduction of 14%.
- There were 5617 total (first plus recurrent) events leading to the composite of ACH-P + ACM.
  - The event rate ratio (95% CI) for empagliflozin versus placebo for total composite of ACH-P + ACM events was 0.76 (0.69, 0.85) (**Figure 1**)
  - Empagliflozin reduced the risk of total events of ACH-P + ACM by 24% compared with placebo (**Figure 2B**).
- The number of ACH-P events prevented with empagliflozin versus placebo was 55.9 per 1000 patient years. The NNT (95% CI) over 3 years to prevent 1 such event was 6.0 (4.1, 11.1).
- The number of ACH-P + ACM events prevented with empagliflozin versus placebo was 67.7 per 1000 patient years. The NNT (95% CI) over the 3 years to prevent 1 such event was 4.9 (3.5, 8.4).

Figure 2. Total (first plus recurrent) events (A) leading to or prolonging hospitalisation for any cause and (B) the composite of events leading to or prolonging hospitalisation for any cause and all-cause mortality

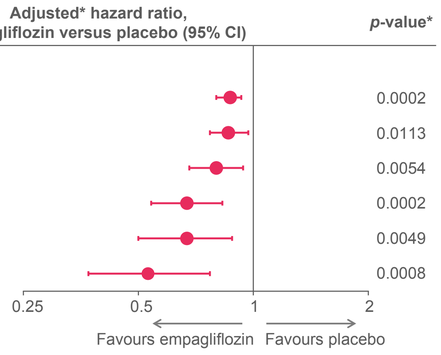


*Negative binomial model including age as linear covariate and treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region as fixed effect(s); log(observation time [days]) was used as offset.
The cumulative mean function shows the population cumulative mean number of events up to time *t*.
ACH-P, events leading to or prolonging hospitalisation for any cause; ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

- Time-to-event analyses of the ACH-P + ACM composite by order of event (1 to ≥6 events) yielded a numerically larger risk reduction with empagliflozin versus placebo with higher order of events, although the test for consistency was not significant (**Figure 3**).

Figure 3. Time-to-event analyses of the composite of events leading to or prolonging hospitalisation for any cause and all-cause mortality by order of event according to the Wei-Lin-Weissfeld model in pooled empagliflozin versus placebo participants

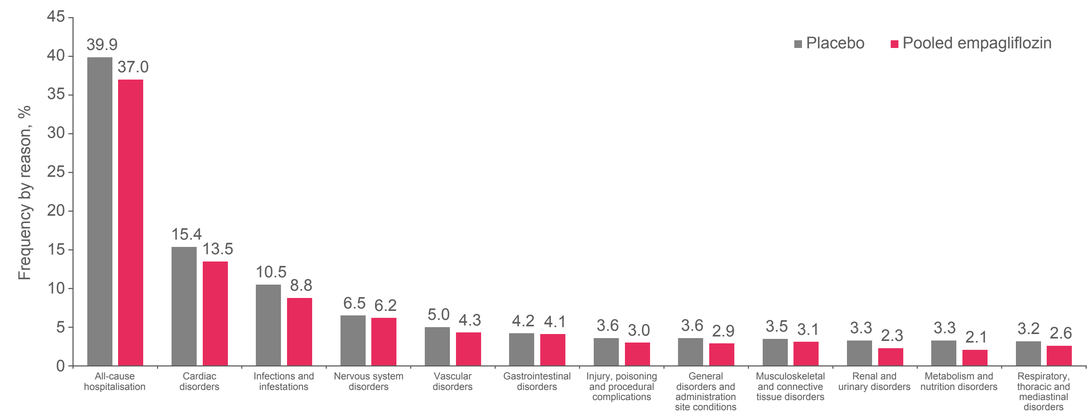
	Pooled empagliflozin (N=4687)	Placebo (N=2333)	Adjusted* hazard ratio, empagliflozin versus placebo (95% CI)	*p*-value*
	Patients, n (%)			
ACH-P + ACM composite				
≥1 event	1836 (39.2)	1008 (43.2)	0.87 (0.80, 0.93)	0.0002
≥2 events	816 (17.4)	460 (19.7)	0.86 (0.77, 0.97)	0.0113
≥3 events	405 (8.6)	246 (10.5)	0.80 (0.68, 0.94)	0.0054
≥4 events	196 (4.2)	144 (6.2)	0.67 (0.54, 0.83)	0.0002
≥5 events	113 (2.4)	84 (3.6)	0.67 (0.50, 0.88)	0.0049
≥6 events	60 (1.3)	56 (2.4)	0.53 (0.37, 0.77)	0.0008
Test for consistency†: *p*=0.1518				



*Analysed as hazard ratio for time to event using a Wei-Lin-Weissfeld model with factors for treatment, age, sex, baseline BMI, baseline HbA1c, baseline estimated glomerular filtration rate, and geographical region.
†Test for consistency (provided as a *p*-value) is the test for equality of ratios of empagliflozin versus placebo over the event count across all orders of events.
A maximum of 10 events per participant were included in the model as <14 participants had higher numbers of events. Data not shown in figure: ≥7 events: HR 0.54 (95% CI 0.34, 0.85), *p*=0.0076; ≥8 events: 0.54 (0.30, 0.96), *p*=0.0354; ≥9 events: 0.37 (0.17, 0.82), *p*=0.0138 and ≥10 events: 0.41 (0.16, 1.06), *p*=0.0644.
ACH-P, events leading to or prolonging hospitalisation for any cause; ACM, all-cause mortality; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

- A summary of the reasons for events leading to or prolonging hospitalisation by system organ class is shown in **Figure 4**.

Figure 4. Reasons for events leading to or prolonging hospitalisation by system organ class occurring in ≥3% of all participants*



*In either pooled empagliflozin or placebo participants.
System organ class refers to MedDRA version 18.0. Numbers shown are percentages of participants with events based on all participants treated. Categories are not mutually exclusive as 1 hospitalisation could be counted in different categories if investigators provided more than 1 reason for a hospitalisation.
MeDRA, Medical Dictionary for Regulatory Activities.

Disclosures

GS is an employee of Boehringer Ingelheim (BI). **SEI** has served as a consultant, speaker, or member of clinical trial steering committees for BI, AstraZeneca (AZ), Novo Nordisk (NN), Sanofi/Lexicon Pharmaceuticals, Merck, vTv Therapeutics and Abbott/Alere. **CW** has received financial support from BI, Eli Lilly and Company (EL), and Janssen. **DHF** has received financial support from Amgen, AZ, BI, EL, Merck & Co., and Sanofi. **BZ** has received financial support from AZ, BI, EL, Janssen, Merck, NN, and Sanofi. **SDA** has received financial support from AZ and BI. **MM**, **OV**, **SH**, and **SSL** are employees of BI. **SSL** owns shares in NN and shares in dynamically traded investment funds, which may own stocks from pharmaceutical companies.

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