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FASTTRACK CLINICAL RESEARCH
Disease management

Relationship between hypoglycaemia, cardiovascular outcomes, and empagliflozin treatment in the EMPA-REG OUTCOME® trial

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Aims Hypoglycaemia, in patients with Type 2 diabetes (T2D) is associated with an increased risk for cardiovascular (CV) events. In EMPA-REG OUTCOME, the sodium-glucose co-transporter-2 inhibitor empagliflozin reduced the risk of CV death by 38% and heart failure hospitalization (HHF) by 35%, while decreasing glycated haemoglobin (HbA1c) without increasing hypoglycaemia. We investigated CV outcomes in patients with hypoglycaemia during the trial and the impact of hypoglycaemia on the treatment effect of empagliflozin.

Methods and results About 7020 patients with T2D (HbA1c 7–10%) were treated with empagliflozin 10 or 25 mg, or placebo and followed for median 3.1 years. The relationship between on-trial hypoglycaemia and CV outcomes, and effects of empagliflozin on outcomes by incident hypoglycaemia [HYPO-broad: symptomatic hypoglycaemia with plasma glucose (PG) ≤70 mg/dL, any hypoglycaemia with PG <54 mg/dL, or severe hypoglycaemia, and HYPO-strict: hypoglycaemia with PG <54 mg/dL, or severe hypoglycaemia] was investigated using adjusted Cox regression models with time-varying covariates for hypoglycaemia and interaction with treatment. HYPO-broad occurred in 28% in each group and HYPO-strict in 19%. In the placebo group, hypoglycaemia was associated with an increased risk of HHF for both HYPO-broad [hazard ratio (HR, 95% confidence interval, CI) 1.91 (1.25–2.93)] and HYPO-strict [1.72 (1.06–2.78)]. HYPO-broad (but not HYPO-strict) was associated with an increased risk of myocardial infarction (MI) [HR 1.56 (1.06–2.29)]. Empagliflozin improved CV outcomes, regardless of occurrence of hypoglycaemia (*P*-for interactions >0.05).

Conclusion In this *post hoc* exploratory analysis, hypoglycaemia was associated with an increased risk of HHF and MI. Hypoglycaemia risk was not increased with empagliflozin and incident hypoglycaemia did not attenuate its cardioprotective effects.

Keywords Type 2 diabetes • Hypoglycaemia • Heart failure • Cardiovascular disease • Hospitalization • Mortality

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Introduction

Hypoglycaemia is a common complication of diabetes treatment, which has been associated with an increased risk for vascular events and mortality, both in a clinical trial setting[1–5] and in population studies.[6–8] Individuals at higher risk include those with advanced disease characteristics, e.g. longstanding Type 2 diabetes (T2D), poor renal function, and on a polypharmaceutical treatment regimen, especially with sulphonylureas and/or insulin. Several potential mechanisms link acute hypoglycaemia with a deleterious impact on the cardiovascular (CV) system, including adrenergic activation, autonomic dysfunction, tachycardia, bradycardia, platelet aggregation, and hypokalaemia. These may increase arrhythmogenicity, promote a pro-thrombotic state, increase myocardial ischaemia, and/or have a detrimental haemodynamic effect.[9,10] Hypoglycaemia is usually associated with increased risk of sudden death and acute vascular events, but less is known about any association between hypoglycaemia and heart failure (HF) events. However, some studies have linked insulin use with HF risk,[11] conceivably through an increase in hypoglycaemia or sodium retention burden. Furthermore, hypoglycaemia has also been associated with prolonged hospitalizations,[12,13] and thus, the range of consequences associated with hypoglycaemia has a major impact on societal healthcare costs.

In the EMPA-REG OUTCOME® trial, the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin, a drug used in T2D to reduce glycated haemoglobin (HbA1c), did not increase the frequency of hypoglycaemic adverse events even when used in combination with insulin.[14] The trial further showed that empagliflozin, in patients with T2D and CV disease, reduced major adverse CV events (MACE) by 14%, CV mortality by 38%, hospitalization for HF (HHF) by 35%, and the composite of CV mortality or HHF by 34%.[14] Notably, this was the first time that a glucose-lowering agent had been shown to reduce adverse CV events in a large CV outcome trial in high-risk patients with T2D and established CV disease.

The purposes of this *post hoc* analysis were to investigate the relationship between CV, mortality, and HHF outcomes with preceding hypoglycaemic events and to assess if hypoglycaemia impacted the cardioprotective effects of empagliflozin.

Methods

Study design

The study design of the EMPA-REG OUTCOME® trial (NCT01131676) has been previously described.[14,15] In summary, the study included patients from 42 countries with T2D (with HbA1c 7.0–9.0% for drug-naïve patients and 7.0–10.0% for those on stable glucose-lowering therapy), established CV disease, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, although intensification was permitted if the patient had a confirmed fasting glucose level of more than 240 mg/dL and a dose reduction or discontinuation of background medication could occur in case of medical necessities. After Week 12 and throughout the trial adjustments of the glucose-lowering therapy was left at the discretion of the investigator according to local guidelines. Investigators were encouraged to monitor blood glucose and HbA1c, and use additional medication for glycaemic control (except SGLT-2 inhibitors) according to applicable standard of care throughout the trial, independent of study treatment assignment that remained masked.

Hypoglycaemic events—categories and definitions

Hypoglycaemic episodes during study follow-up were investigator-reported and for this analysis categorized as either HYPO-broad, defined as a symptomatic hypoglycaemic adverse event with plasma glucose (PG) ≤70 mg/dL, a hypoglycaemic adverse event with PG <54 mg/dL, or a severe hypoglycaemic adverse event; or HYPO-strict defined as a hypoglycaemic adverse event with PG <54 mg/dL, or a severe hypoglycaemic adverse event. A severe hypoglycaemic event was defined as requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Outcomes

The primary outcome of the EMPA REG OUTCOME trial and in the current study was time to first occurrence of 3P-MACE [three-point major adverse CV events; a composite of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke]. Additional outcomes studied were CV death, fatal or non-fatal MI, fatal or non-fatal stroke, all-cause mortality, non-CV mortality, and HHF. Definition of HHF and other outcomes has been reported,[14,16] and all CV outcome events, HF hospitalizations, and CV deaths were prospectively adjudicated by blinded Clinical Events Committees.[14,15]

Statistical analysis

Based on the previously reported consistency of effect,[14,16] analyses were performed on the pooled empagliflozin dose groups vs. placebo. Baseline characteristics were reported as percentages for categorical variables and means and standard deviations for continuous variables.

Time to first hypoglycaemic adverse event (for HYPO-broad and -strict) was analysed with a Cox proportional-hazards model, with study group, age, sex, baseline body mass index, baseline HbA1c level, baseline eGFR, and geographic region as factors. In addition, Kaplan–Meier estimates are presented. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome.

To investigate the relationship between hypoglycaemia and CV outcomes, any hypoglycaemic adverse events prior to a CV event, or respectively censoring for the CV event, were considered. Cox regression models were employed, adjusting for age, gender, baseline body mass index categories, baseline HbA1c categories, baseline eGFR categories, geographical region, treatment, a time-varying covariate for hypoglycaemic events and interaction of treatment, and a time-varying covariate for hypoglycaemic events. An extended Cox regression model also included terms for the following baseline covariates: prior coronary artery disease, prior peripheral artery disease, history of ischaemic/haemorrhagic stroke, baseline albuminuria, time since diagnosis of T2D, insulin at baseline, prior cardiac failure, smoking status at baseline, history of atrial fibrillation, and prior intake of sulfonylurea or glinide. In an attempt to characterize temporal relationship between hypoglycaemia and CV complications, we also defined analysis for HYPO-broad and -strict for CV-, mortality-, and HHF events occurring within a 90-day time-window following the hypoglycaemic event.

All analyses were conducted following a modified intent-to-treat (ITT) approach in patients treated with at least one dose of study drug. Each patient who did not have an event was censored on the last day they were known to be free of the outcome. All analyses were performed on a nominal two-sided $\alpha = 0.05$ without adjustment for multiplicity. Statistical analyses were performed using SAS® version 9.4.

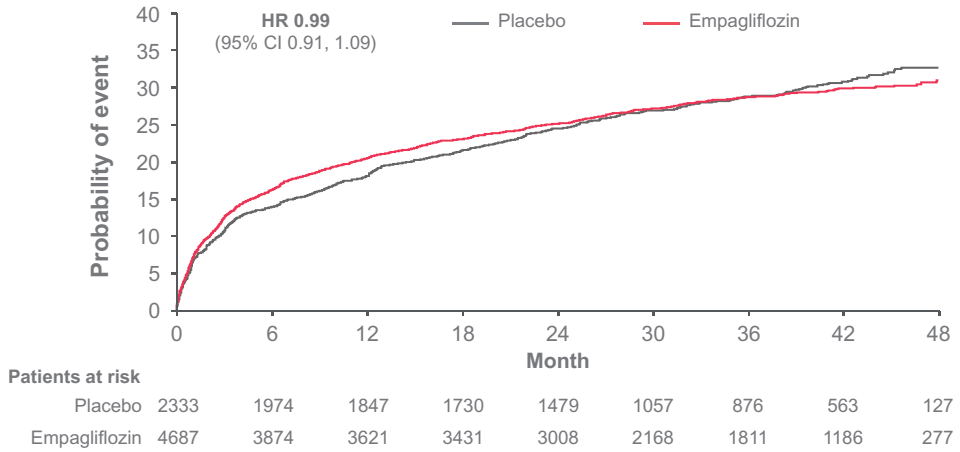


Figure 1 Time to first HYPO-broad: symptomatic hypoglycaemia adverse event with plasma glucose ≤70 mg/dL, or hypoglycaemia adverse event with plasma glucose <54 mg/dL, or severe hypoglycaemia adverse event. Hazard ratio from Cox regression model. Based on Kaplan–Meier estimates; hazard ratio based on a Cox proportional-hazards model, with study group, age, sex, baseline body mass index, baseline glycated haemoglobin level, baseline estimated glomerular filtration rate, and geographic region as factors. HR, hazard ratio.

Results

Study population and effects on glycated haemoglobin and hypoglycaemia

Over the 3.1 years median follow-up, hypoglycaemia rates were comparable between empagliflozin and placebo treatment groups. Out of 7020 participants, 1964 (28.0%), experienced an episode of HYPO-broad [empagliflozin 27.9%, incidence rate (IR) per 100 patient-years 12.3; placebo: 28.2%, IR 12.4; *Figure 1*], whereas 1321 (18.8%) experienced an episode of HYPO-strict (empagliflozin 18.8%, IR 7.5; placebo 18.9%, IR 7.6, Supplementary material online, *Figure S1*). There was no difference between the treatment groups [hazard ratio (HR, 95% confidence interval, CI) 0.99 (0.91–1.09), $P = 0.91$, and HR 0.99 (0.88–1.11), $P = 0.84$, respectively]. This was despite a significant but modest reduction in HbA1c with empagliflozin [after 12 weeks adjusted mean differences (95% CI) vs. placebo in HbA1c were -0.54% (-0.58 to -0.49) with empagliflozin 10 mg and -0.60% (-0.64 to –0.55) with empagliflozin 25 mg; at Week 94, the adjusted mean differences vs. placebo in HbA1c were -0.42% (-0.48 to -0.36) and -0.47% (-0.54 to -0.41), respectively, and at Week 206, they were -0.24% (-0.40 to -0.08) and -0.36% (-0.51 to -0.20). Severe hypoglycaemia, analysed with the modified ITT approach, occurred in 1.8% (43/2333) in the placebo group (6.5 per 1000-patient years at risk) and 1.6% (73/4687) in the empagliflozin group (5.4 per 1000-patient years at risk), respectively, with no between-group differences.

Insulin was used at baseline in 48.2% of patients and sulphonylurea in 42.8% and overall, introduction of post-baseline medication for glycaemic control was more frequent in the placebo group (e.g. sulphonylurea in 7.0% of the placebo group and 3.8% in the empagliflozin group) with also a greater use of insulin (11.5% placebo vs. 5.8% empagliflozin) and larger insulin doses at study end (Supplementary material online, *Tables S1* and *S2*).

Baseline characteristics of patients with and without hypoglycaemia as defined by HYPO-broad or HYPO-strict are provided in *Table 1* and Supplementary material online, *Table S2*. Patients with episodes of hypoglycaemia, had a longer history of T2D, a higher prevalence of albuminuria and retinopathy, and more frequently received insulin (and at higher doses), statins, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. There were no differences in the pattern of baseline characteristics between the empagliflozin and placebo groups by hypoglycaemia identified using either criterion.

Relationship between hypoglycaemia and cardiovascular, mortality, and heart failure hospitalization outcomes in the placebo group

Of all participants with a first 3P-MACE event in the placebo group [$n = 282$ (12.1%)], 69 had a preceding HYPO-broad event to the subsequent 3P-MACE, whereas 213 had 3P-MACE with no preceding hypoglycaemic event (*Figure 2A*). Correspondingly, HYPO-strict preceded 3P-MACE in 41 subjects and there were 241 that had a first 3P-MACE without preceding HYPO-strict (*Figure 2B*). There was no statistically significant increased risk associated with occurrence of 3P-MACE with preceding hypoglycaemia regardless of classification (HYPO-broad or HYPO-strict) [HR vs. no HYPO-broad: 1.18 (0.90–1.55), $P = 0.24$; HR vs. no HYPO-strict: 1.03 (0.74–1.44), $P = 0.87$]. Similar neutral association was observed for stroke and all mortality outcomes. However, preceding hypoglycaemia was associated with an increased risk of HHF using both the HYPO-broad [HR 1.91 (1.25–2.93); $P = 0.003$] (*Figure 2A*) and HYPO-strict [HR 1.72 (1.06–2.78); $P = 0.028$] (*Figure 2B*) definitions, as well as an increased risk of fatal and non-fatal MI using the HYPO-broad definition [HR 1.56 (1.06–2.29); $P = 0.024$] (*Figure 2A*), but not using the HYPO-strict definition (*Figure 2B*). Using the extended model that included additional

Table 1 Baseline characteristics of participants in EMPA-REG OUTCOME with and without HYPO-broad

	Participants with HYPO-broad		Participants without HYPO-broad	
	Empagliflozin (*n* = 1307)	Placebo (*n* = 657)	Empagliflozin (*n* = 3380)	Placebo (*n* = 1676)
Age (years)	63.5 (8.5)	63.8 (8.3)	63.0 (8.6)	63.0 (9.0)
Male	922 (70.5)	462 (70.3)	2414 (71.4)	1218 (72.7)
eGFR, MDRD (mL/min/1.73 m^2)	71.7 (21.7)	69.2 (20.7)	75.1 (21.5)	75.6 (20.9)
30 to <60	391 (29.9)	234 (35.6)	800 (23.7)	367 (21.9)
<30	6 (0.5)	4 (0.6)	15 (0.4)	2 (0.1)
UACR (mg/g), median (IQR)	21.2 (7.1–90.2)	22.5 (8.0–109.2)	16.8 (6.2–64.5)	16.8 (6.2–62.8)
UACR (mg/g)				
<30	728 (55.7)	357 (54.3)	2061 (61.0)	1025 (61.2)
30–300	392 (30.0)	198 (30.1)	946 (28.0)	477 (28.5)
>300	168 (12.9)	97 (14.8)	341 (10.1)	163 (9.7)
Missing	19 (1.5)	5 (0.8)	32 (0.9)	11 (0.7)
HbA1c (%)	8.1 (0.8)	8.1 (0.8)	8.1 (0.9)	8.1 (0.9)
Diabetes duration (years)				
≤1	9 (0.7)	7 (1.1)	119 (3.5)	45 (2.7)
>1 to 5	84 (6.4)	38 (5.8)	628 (18.6)	333 (19.9)
>5 to 10	254 (19.4)	115 (17.5)	921 (27.2)	456 (27.2)
>10	960 (73.5)	497 (75.6)	1712 (50.7)	842 (50.2)
BMI (kg/m^2)	30.7 (5.4)	30.6 (5.0)	30.6 (5.2)	30.7 (5.3)
SBP/DBP (mmHg)	137 (18)/75 (10)	136 (19)/75 (11)	135 (17)/77 (10)	136 (17)/77 (10)
Background medications				
Insulin	969 (74.1)	483 (73.5)	1283 (38.0)	652 (38.9)
Daily insulin dose	69.4 (49.7)	71.2 (57.2)	62.4 (47.2)	60.3 (44.6)
Metformin	929 (71.1)	452 (68.8)	2530 (74.9)	1282 (76.5)
Sulfonylurea	496 (37.9)	232 (35.3)	1518 (44.9)	760 (45.3)
Any antihypertensives	1249 (95.6)	620 (94.4)	3198 (94.6)	1602 (95.6)
ACE inhibitor/ARB	1087 (83.2)	537 (81.7)	2712 (80.2)	1331 (79.4)
Statins	1070 (81.9)	532 (81.0)	2560 (75.7)	1241 (74.0)
Pre-existing conditions				
Prior stroke	258 (19.7)	138 (21.0)	826 (24.4)	415 (24.8)
Prior MI	572 (43.8)	291 (44.3)	1618 (47.9)	792 (47.3)
Heart failure	116 (8.9)	70 (10.7)	346 (10.2)	174 (10.4)
Retinopathy	403 (30.8)	221 (33.6)	620 (18.3)	302 (18.0)

Data are expressed as *n* (%) and continuous parameters reported as mean (standard deviation) unless otherwise stated. Patients were treated with ≥1 dose of study drug; those with/without a hypoglycaemic AE were determined at the time of CV event/censoring (time at risk not considered).
ACE, angiotensin-converting enzyme; AE, adverse event; ARB, angiotensin-receptor blocker; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HYPO-broad, any symptomatic hypoglycaemic AE with PG ≤70 mg/dL, a hypoglycaemic AE with PG <54 mg/dL, or a severe hypoglycaemic AE (requiring assistance regardless of PG level); IQR, interquartile range; MDRD, modification of diet in renal disease; MI, myocardial infarction; PG, plasma glucose; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

baseline covariates, the increased risk for HHF in the placebo group using the HYPO-broad definition [HR 1.72 (1.11–2.66); $P = 0.015$] remained, whereas others associations were attenuated [e.g. HR for preceding HYPO-broad vs. no HYPO-broad for MI 1.45 (0.98–2.15), $P = 0.06$; Supplementary material online, *Table S4*].

The temporal relationship analysis was limited by few number of hypoglycaemic events followed by an outcome event within 90 days which precluded robust outcome-association analysis, but generally the pattern remained as observed in the primary analysis, e.g. HR for preceding HYPO-broad for HHF 1.71 (0.96–3.04), $P = 0.07$ and HR for preceding HYPO-strict for MI 1.91 (1.02–3.57), $P = 0.04$ (Supplementary material online, *Table S5*).

Empagliflozin treatment effects on cardiovascular, mortality, and heart failure hospitalization outcomes by occurrence of hypoglycaemia

There were no differences in proportion of individuals that experienced hypoglycaemia (HYPO-broad or HYPO-strict) between the

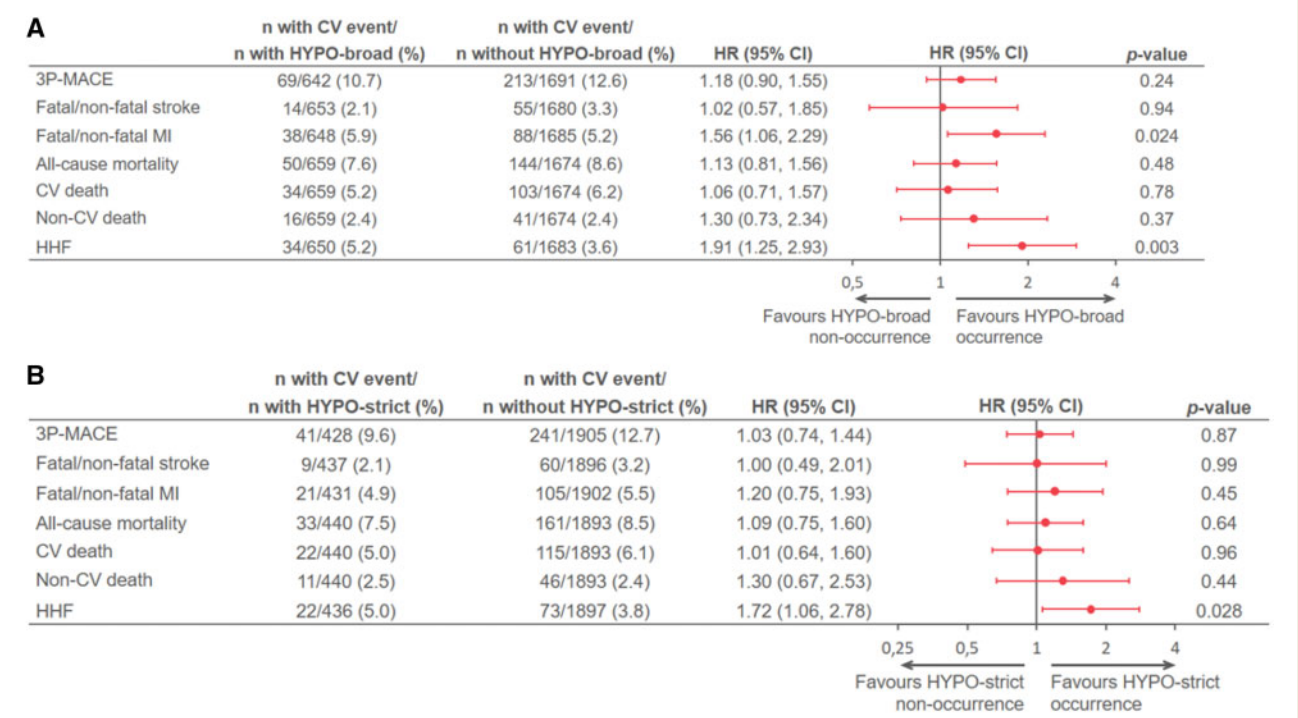


Figure 2 (*A*) Relationship between occurrence vs. non-occurrence of HYPO-broad and outcomes in the *placebo* group of EMPA-REG OUTCOME. (*B*) Relationship between occurrence vs. non-occurrence of HYPO-strict and outcomes in the *placebo* group of EMPA-REG OUTCOME. Based on a Cox regression model with terms for age, sex, baseline body mass index categories, baseline HbA1c categories, baseline estimated glomerular filtration rate categories, geographical region, treatment, time-varying covariate of HYPO-broad or HYPO-strict, interaction of treatment, and time-varying covariate of HYPO-broad or HYPO-strict. Patients were treated with ≥1 dose of study drug; only for presentation of patient numbers, those with/without HYPO-broad or HYPO-strict were determined at the time of CV event/censoring. **P* value for interaction. 3P-MACE, three-point major adverse cardiovascular event (CV death, non-fatal MI, or non-fatal stroke); AE, adverse event; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalization for heart failure; HYPO-broad: time to first symptomatic hypoglycaemic AE with PG ≤70 mg/dL, any hypoglycaemic AE with PG <54 mg/dL, or a severe hypoglycaemic AE (requiring assistance regardless of PG level); HYPO-strict, any hypoglycaemic AE with PG <54 mg/dL, or a severe hypoglycaemic AE (requiring assistance regardless of PG level); MI, myocardial infarction; PG, plasma glucose.

treatment groups. Empagliflozin treatment, however, significantly reduced 3P-MACE, CV death, all-cause mortality, and HHF, all consistent with the previously reported magnitude of effects,[14,15] regardless of the occurrence or severity of the hypoglycaemia (*P*-values for all interactions >0.05) (*Figure 3A* and *B*).

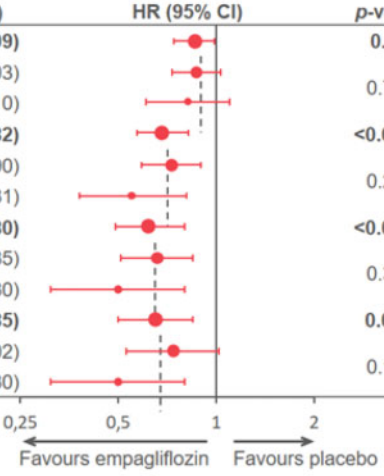
Discussion

In this *post hoc* analysis and exploratory analysis from the EMPA-REG OUTCOME trial, hypoglycaemia was associated with an increased risk of MI and HHF but no other investigated CV outcomes. Furthermore, hypoglycaemia risk was not increased with empagliflozin and incident hypoglycaemia did not attenuate its cardioprotective effects.

The observation of a positive association between preceding hypoglycaemia and CV events (e.g. MACE and mortality) has been observed in population-based studies[6,7] and previous other CV outcome trials involving subjects with T2D and CV disease,[1–4,17–19] although not in all trials.[20] Also, previous reports mainly found an association with severe hypoglycaemia but not non-severe combined with severe hypoglycaemia, which is at variance with the current results, which used a more moderate hypoglycaemia definition. The magnitude of association of effect in our trial for MI, with an HR of 1.56 (1.06–2.29) for the broader hypoglycaemia classification, was, however, far less than, for example, the HR 3.53 (2.41–5.17) that was observed in ADVANCE for mortality.[1] These differences may be attributed to different populations and distinct treatment regimens and approaches tested in the two trials. Since EMPA-REG OUTCOME was not a trial to test intensive glycaemic strategies, together with the inherent low risk of hypoglycaemia with SGLT-2 inhibitors, as also confirmed in CV outcomes trials completed to date,[21] we observed few severe episodes of hypoglycaemia. Consequently, although we could not assess any association between preceding severe hypoglycaemia and CV outcome-events, it is possible the results would have differed in a population more susceptible to hypoglycaemia. Another important consideration that has been debated intensively is whether there is any causality between hypoglycaemia and outcomes events, or whether hypoglycaemia is merely

A

	Empagliflozin n with CV event/ n analysed (%)	Placebo n with CV event/ n analysed (%)	HR (95% CI)	HR (95% CI)	*p*-value
3P-MACE	**490/4687 (10.5)**	**282/2333 (12.1)**	**0.86 (0.74, 0.99)**		**0.04**
No hypoglycaemic AE	369/3412 (10.8)	213/1691 (12.6)	0.87 (0.73, 1.03)		0.75*
Hypoglycaemic AE	121/1275 (9.5)	69/642 (10.7)	0.82 (0.61, 1.10)		
All-cause mortality	**269/4687 (5.7)**	**194/2333 (8.3)**	**0.68 (0.57, 0.82)**		**<0.0001**
No hypoglycaemic AE	211/3380 (6.2)	144/1674 (8.6)	0.73 (0.59, 0.90)		0.21*
Hypoglycaemic AE	58/1307 (4.4)	50/659 (7.6)	0.55 (0.38, 0.81)		
CV death	**172/4687 (3.7)**	**137/2333 (5.9)**	**0.62 (0.49, 0.80)**		**<0.0001**
No hypoglycaemic AE	137/3380 (4.1)	103/1674 (6.2)	0.66 (0.51, 0.85)		0.30*
Hypoglycaemic AE	35/1307 (2.7)	34/659 (5.2)	0.50 (0.31, 0.80)		
HHF	**126/4687 (2.7)**	**95/2333 (4.1)**	**0.65 (0.50, 0.85)**		**0.002**
No hypoglycaemic AE	90/3395 (2.7)	61/1683 (3.6)	0.74 (0.53, 1.02)		0.19*
Hypoglycaemic AE	36/1292 (2.8)	34/650 (5.2)	0.50 (0.31, 0.80)		



B

	Empagliflozin n with CV event/ n analysed (%)	Placebo n with CV event/ n analysed (%)	HR (95% CI)	HR (95% CI)	*p*-value
3P-MACE	**490/4687 (10.5)**	**282/2333 (12.1)**	**0.86 (0.74, 0.99)**		**0.04**
No hypoglycaemic AE	410/3829 (10.7)	241/1905 (12.7)	0.84 (0.72, 0.99)		0.63*
Hypoglycaemic AE	80/858 (9.3)	41/428 (9.6)	0.93 (0.64, 1.36)		
All-cause mortality	**269/4687 (5.7)**	**194/2333 (8.3)**	**0.68 (0.57, 0.82)**		**<0.0001**
No hypoglycaemic AE	227/3805 (6.0)	161/1893 (8.5)	0.70 (0.57, 0.85)		0.68*
Hypoglycaemic AE	42/882 (4.8)	33/440 (7.5)	0.63 (0.40, 0.99)		
CV death	**172/4683 (3.7)**	**137/2331 (5.9)**	**0.64 (0.51, 0.80)**		**<0.0001**
No hypoglycaemic AE	147/3805 (3.9)	115/1893 (6.1)	0.63 (0.49, 0.80)		0.72*
Hypoglycaemic AE	25/882 (2.8)	22/440 (5.0)	0.56 (0.32, 1.00)		
HHF	**126/4687 (2.7)**	**95/2333 (4.1)**	**0.65 (0.50, 0.85)**		**0.002**
No hypoglycaemic AE	98/3816 (2.6)	73/1897 (3.8)	0.66 (0.49, 0.90)		0.84*
Hypoglycaemic AE	28/871 (3.2)	22/436 (5.0)	0.62 (0.35, 1.08)		

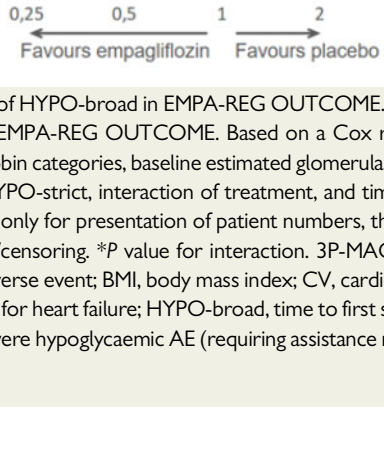
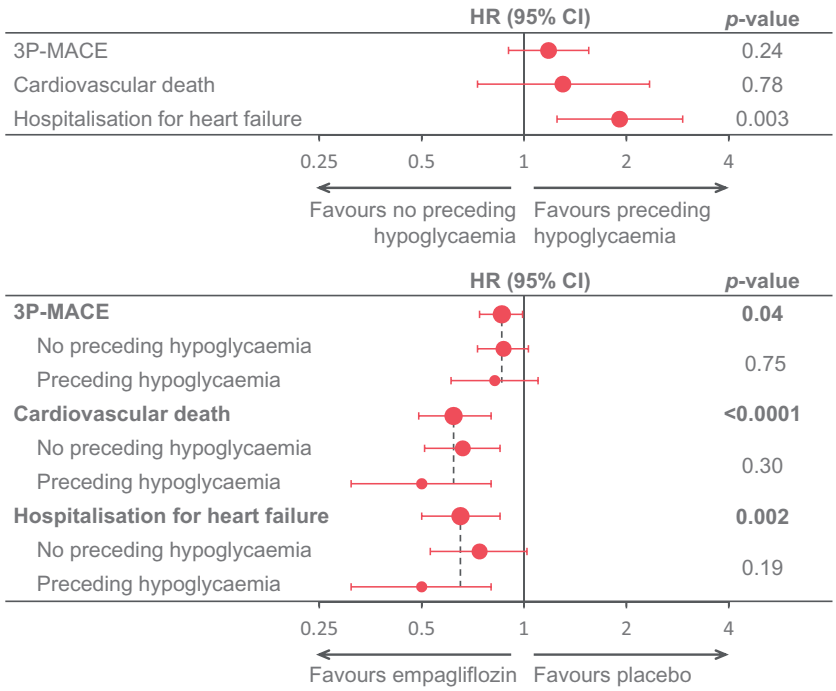


Figure 3 (*A*) Effect of empagliflozin on outcomes in the total population and by occurrence of HYPO-broad in EMPA-REG OUTCOME. (*B*) Effect of empagliflozin on outcomes in the total population and by occurrence of HYPO-strict in EMPA-REG OUTCOME. Based on a Cox regression model with terms for age, sex, baseline body mass index categories, baseline glycated haemoglobin categories, baseline estimated glomerular filtration rate categories, geographical region, treatment, time-varying covariate of HYPO-broad or HYPO-strict, interaction of treatment, and time-varying covariate of HYPO-broad or HYPO-strict. Patients were treated with ≥1 dose of study drug; only for presentation of patient numbers, those with/without HYPO-broad or HYPO-strict were determined at the time of cardiovascular event/censoring. **P* value for interaction. 3P-MACE, three-point major adverse cardiovascular event (CV death, non-fatal MI, or non-fatal stroke); AE, adverse event; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalization for heart failure; HYPO-broad, time to first symptomatic hypoglycaemic AE with PG ≤70 mg/dL, any hypoglycaemic AE with PG <54 mg/dL, or a severe hypoglycaemic AE (requiring assistance regardless of PG level); MI, myocardial infarction; PG, plasma glucose.

a marker of frailty and high risk.[20,22,23] Recent studies suggest that there is a temporal association between hypoglycaemia and outcomes with the highest risk of CV events and all-cause mortality occurring early (e.g. during the first weeks and months following a severe hypoglycaemic episode) and that these risks decline during the following months, yet remain higher also in long-term follow-up.[4,7] Owing to the limited number of hypoglycaemic events, the present trial cannot provide robust support for or against this hypothesis.

A novel observation from this analysis that needs further confirmation is the increased risk for HHF associated with preceding hypoglycaemia (*Take home figure*). It is possible, as suggested by others, that acute hypoglycaemia might have a deleterious impact on an already vulnerable myocardium (as a result of autonomic activation, electrophysiological alterations, haemodynamic changes, and/or effects via the coagulation system).[9,10,24] However, another possibility is that greater use of insulin and at higher doses in the placebo



Take home figure The key observations of this article. Upper panel: relationship between occurrence vs. non-occurrence of hypoglycaemia and select outcomes in the placebo group of EMPA-REG OUTCOME. Lower panel: Effect of empagliflozin on select outcomes in the total population and by occurrence of hypoglycaemia in EMPA-REG OUTCOME. Hypoglycaemia defined as symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL, any hypoglycaemia with PG <54 mg/dL, or severe hypoglycaemia.

group over time could be playing a role. Insulin treatment is known to induce weight gain, sodium, and fluid retention,[25] all associated with deleterious vascular effects[26] and in some HF trials, is associated with worse outcomes.[11] While insulin treatment may just be a marker of severity of disease (i.e. confounder by indication), there exist some mechanistic data to suggest that insulin may adversely affect myocardial contractility mediated by β_2-adrenergic receptor activation pathways.[27] Although our expanded analysis that included an adjustment for insulin use at baseline confirmed an association of increased risk of hypoglycaemia with HHF, we did not adjust for the insulin-dose increase in the placebo group over time: this remains to be further explored.

Another area for further research in CV outcome trials not analysed in the present study, given the observation of an association between preceding hypoglycaemia and MI risk, is to test the clinical hypothesis whether it could be an association between hypoglycaemia and coronary revascularization procedures, as shown in registry studies.[28]

The observation of a consistent benefit of empagliflozin on CV, mortality, and HHF outcomes regardless of occurrence of hypoglycaemia is reassuring and is consistent with several other subanalyses.[14,16] The present *post hoc* analysis, confirms its treatment effect on reducing CV mortality and HHF before and after occurrence of hypoglycaemia. These efficacy and safety findings are supportive of the European Society of Cardiology (ESC) HF guideline and other diabetes treatment algorithms,[29,30] suggesting that empagliflozin should be considered in patients with T2D and CV disease. These data also support the treatment algorithm of European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) consensus recommendation for choice of therapies even outside of the context of patients with established CV disease, when there is a compelling need to avoid hypoglycaemia,[31] as well as the ESC/EASD clinical practice guidelines that underscores that attention should be paid to avoidance of hypoglycaemia whilst achieving glycaemic goals in an individualized manner.[32]

In conclusion, in this exploratory *post hoc* analysis, hypoglycaemia was associated with an increased risk of HHF and MI but no other outcomes. Hypoglycaemia risk was not increased with empagliflozin and incident hypoglycaemia did not attenuate its cardio-protective effects.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: D.F. has received personal fees from Boehringer Ingelheim, Novo Nordisk, AstraZeneca, Sanofi, and Merck & Co. S.E.I. has received personal fees from Merck & Co, Janssen, Novo Nordisk, Sanofi, Intarcia, Lexicon, vTv Therapeutics, and AstraZeneca; received personal fees and non-financial support from Boehringer Ingelheim. C.W. has received personal fees from Boehringer-Ingelheim, Genzyme-Sanofi, Eli Lilly and Company, and Janssen. B.Z. has received personal fees from Boehringer Ingelheim, Merck & Co, Novo Nordisk, Sanofi, Eli Lilly and Company, Takeda, AstraZeneca, and Janssen and has received grants from Boehringer Ingelheim, Merck & Co, and Novo Nordisk. O.V., M.M., J.T.G., and O.E.J. are employees of Boehringer Ingelheim.

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