Relationship between hypoglycaemia, outcomes and empagliflozin treatment effect in EMPA-REG OUTCOME

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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Consultin
and CME honoraria from Boehringer Ingelheim, Lilly, Astra Zeneca, Sanofi)
- Others (DSMB chair for Novonordisk)

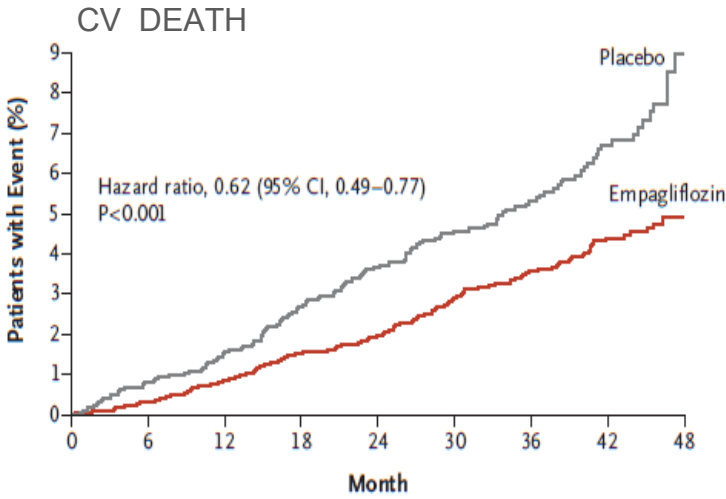
Conflicts of interest

- **David Fitchett**: personal fees from Boehringer Ingelheim, Novo Nordisk, AstraZeneca, Sanofi, and Merck & Co.
- Silvio E Inzucchi: personal fees from Merck & Co, Janssen, Novo Nordisk, Sanofi, Lexicon, vTv Therapeutics, and AstraZeneca; personal fees and non-financial support from Boehringer Ingelheim.
- Christoph Wanner: personal fees from Boehringer-Ingelheim, MSD, Genzyme-Sanofi, Eli Lilly and Company, AstraZeneca and Janssen.
- Bernard Zinman: personal fees from Boehringer Ingelheim, Merck & Co, Novo Nordisk, Sanofi, Eli Lilly and Company, Takeda, AstraZeneca, and Janssen; grants from Boehringer Ingelheim, Merck & Co, and Novo Nordisk.
- Michaela Mattheus, Jyothis T George, Ola Vedin, Odd Erik Johansen: employees of Boehringer Ingelheim.

Objective

In the EMPA-REG OUTCOME® trial, in patients with T2D and CVD, empagliflozin vs placebo added to standard of care[1]:

- ↓ CV death 38%
- ↓ All cause death 32%
- ↓ Heart failure hospitalisation (HHF) 35%
- HbA1C reduced without increase in hypoglycaemia



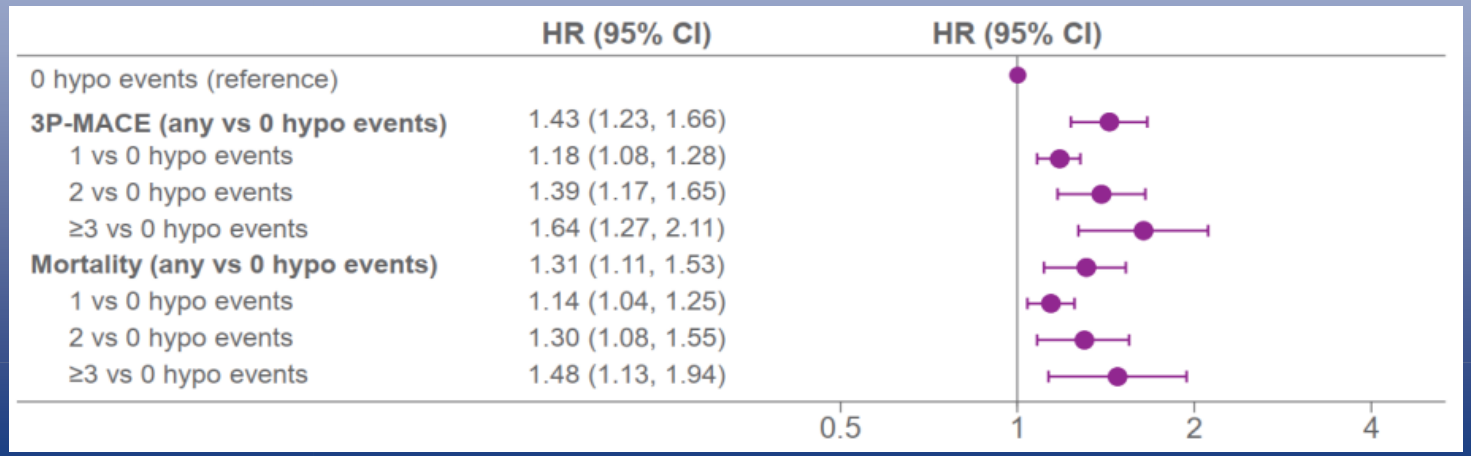
We investigated in the EMPA-REG OUTCOME® trial

- the relationship between hypoglycaemia with CV events and HHF outcomes in a *post hoc* analysis
- whether the treatment effect of empagliflozin in the risk of CV and HHF events is the same among those with or without hypoglycaemia

1. Zinman B, et al. N Engl J Med 2015;373:2117-28

Severe Hypoglycemia and Cardiovascular Disease: Systematic Review and Meta-Analysis[1]

CARMELINA[2]: 1.3 fold increase risk for all-cause mortality associated with non-severe hypoglycaemia



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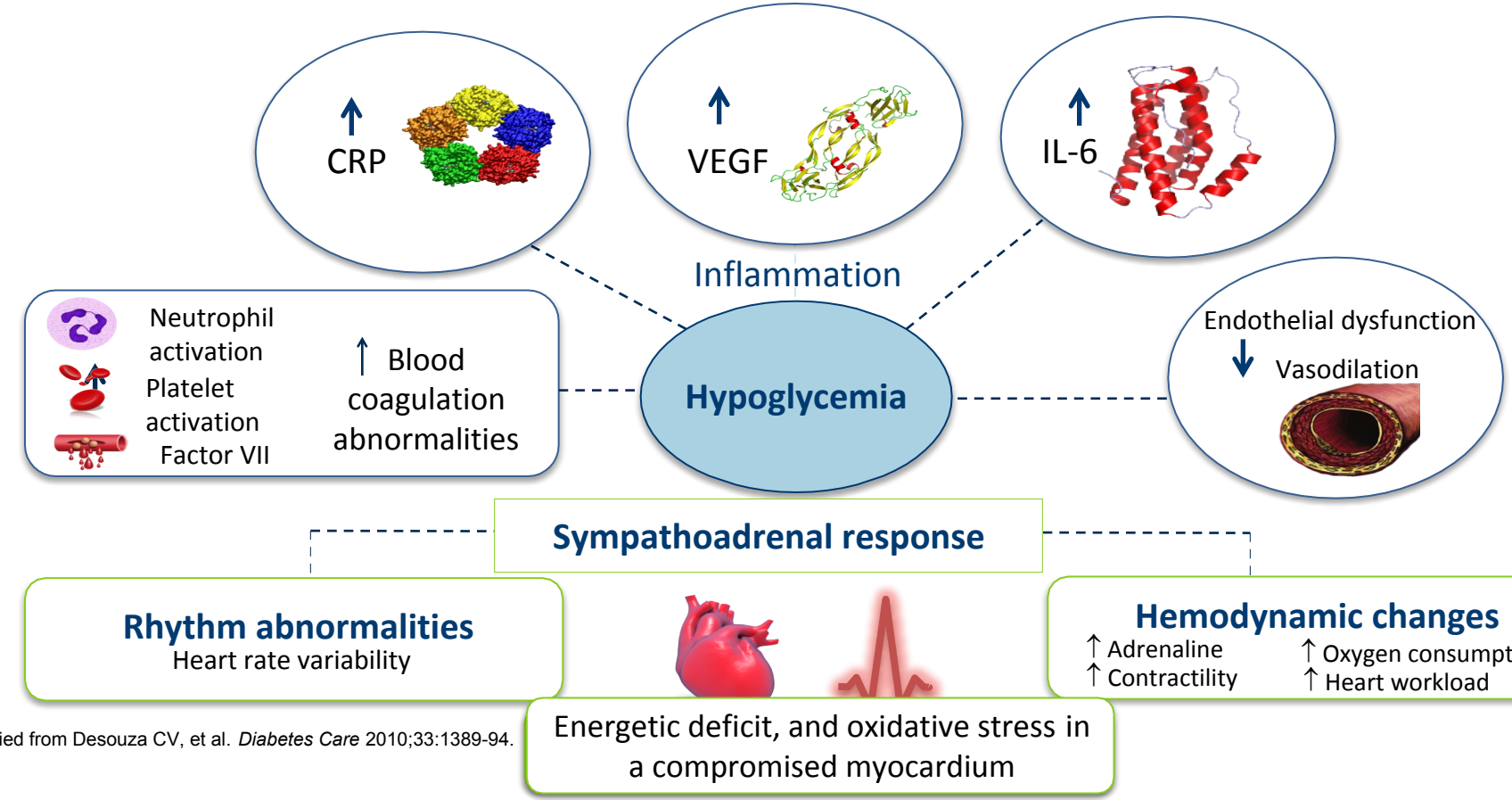
Relative risk of CV event

CV, cardiovascular

1: Goto A, et al. *BMJ* 2013;347:f4533; 2: Rosenstock J et al. ADA 2019;

Mechanisms by Which Hypoglycaemia May Increase the Risk for Cardiovascular Events



Modified from Desouza CV, et al. *Diabetes Care* 2010;33:1389-94.

Methods

Trial design and patients

- Participants aged ≥18 years in the EMPA-REG OUTCOME® trial had T2D with HbA1c 7.0–10.0%, established CVD and an eGFR of ≥30 ml/min/1.73 m^2 at baseline[1]
- Patients were randomised to receive empagliflozin 10 mg, empagliflozin 25 mg or placebo, once-daily in addition to standard of care[1]
- Background glucose-lowering therapy remained unchanged for 12 weeks, then could be adjusted at the investigator's discretion to achieve glycaemic control according to local guidelines[1]

Analyses

- 2 definitions of hypoglycaemia were used, including all events until the end of follow-up:
  - **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
- Analyses were performed using Cox regression models adjusting for age, sex, baseline body mass index categories, baseline HbA1c categories, baseline eGFR categories, geographical region, treatment, a time-varying covariate for hypoglycaemic AEs (broad or strict), and interaction of treatment and a time-varying covariate for hypoglycaemic AEs (broad or strict)

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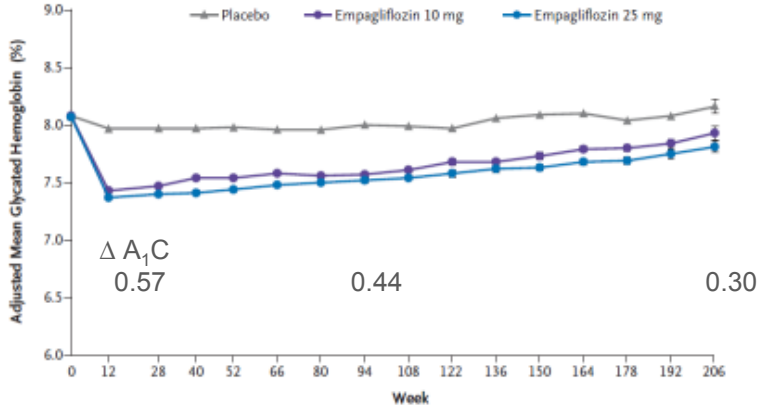
PG, plasma glucose

1. Zinman B, et al. N Engl J Med 2015;373:2117-28

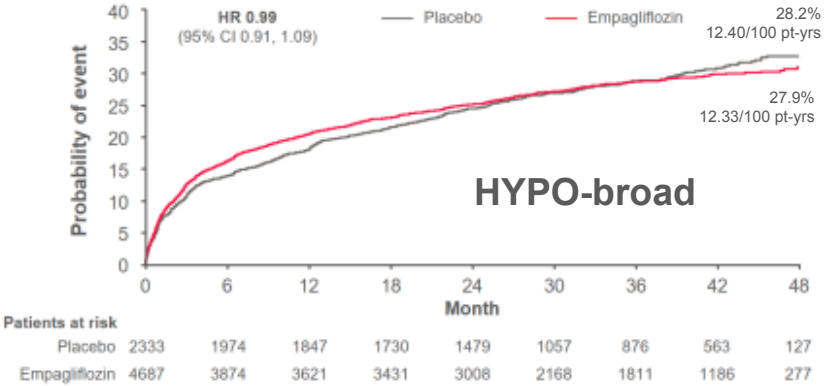
Results

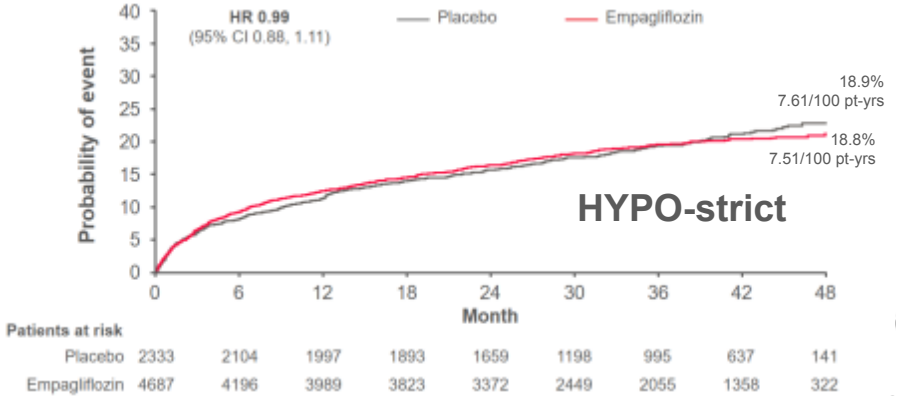
- A total of 7020 patients received ≥1 dose of the study drug and were observed for a median of 3.1 years
- HbA1c was significantly reduced with empagliflozin



Incidence of hypoglycaemia:

- HYPO-broad 28.2% and 27.9%, in the placebo and empagliflozin groups
- HYPO-strict 18.9% and 18.8%,





Baseline characteristics occurring more frequently with HYPO-broad:

Lower eGFR, more albuminuria, longer history of T2D, more receiving insulin, more retinopathy

	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)
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)
HbA1c, %	8.1 (0.8)	8.1 (0.8)	8.1 (0.9)	8.1 (0.9)
Diabetes duration, >10 years	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 (U)	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)
Sulphonylurea (SU)	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)

Similar pattern observed for HYPO-strict

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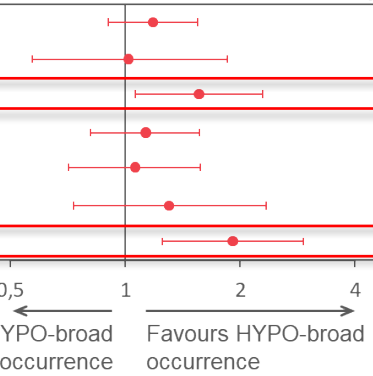
Hypoglycaemic AEs associated with an increased risk of HHF and MI

Placebo group
HYPO-Broad criteria

	n with CV event/ n with HYPO-broad (%)	n with CV event/ n without HYPO-broad (%)	HR (95% CI)	*p*-value
3P-MACE	69/642 (10.7)	213/1691 (12.6)	1.18 (0.90, 1.55)	0.24
Fatal/non-fatal stroke	14/653 (2.1)	55/1680 (3.3)	1.02 (0.57, 1.85)	0.94
Fatal/non-fatal MI	38/648 (5.9)	88/1685 (5.2)	1.56 (1.06, 2.29)	0.024
All-cause mortality	50/659 (7.6)	144/1674 (8.6)	1.13 (0.81, 1.56)	0.48
CV death	34/659 (5.2)	103/1674 (6.2)	1.06 (0.71, 1.57)	0.78
Non-CV death	16/659 (2.4)	41/1674 (2.4)	1.30 (0.73, 2.34)	0.37
HHF	34/650 (5.2)	61/1683 (3.6)	1.91 (1.25, 2.93)	0.003



In an extended model that included 10 additional baseline covariates, the increased HHF risk with preceding HYPO-broad remained (HR 1.72 (1.11, 2.66); p=0.015), whereas others associations were attenuated (e.g., MI 1.45 (0.98, 2.15), p=0.06)

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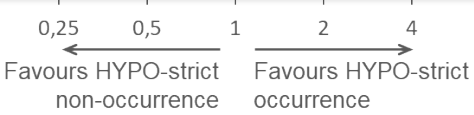
Hypoglycaemic AEs were associated with an increased risk of HHF

Placebo group
HYPO Strict criteria

	n with CV event/ n with HYPO-strict (%)	n with CV event/ n without HYPO-strict (%)	HR (95% CI)	HR (95% CI)	*p*-value
3P-MACE	41/428 (9.6)	241/1905 (12.7)	1.03 (0.74, 1.44)		0.87
Fatal/non-fatal stroke	9/437 (2.1)	60/1896 (3.2)	1.00 (0.49, 2.01)		0.99
Fatal/non-fatal MI	21/431 (4.9)	105/1902 (5.5)	1.20 (0.75, 1.93)		0.45
All-cause mortality	33/440 (7.5)	161/1893 (8.5)	1.09 (0.75, 1.60)		0.64
CV death	22/440 (5.0)	115/1893 (6.1)	1.01 (0.64, 1.60)		0.96
Non-CV death	11/440 (2.5)	46/1893 (2.4)	1.30 (0.67, 2.53)		0.44
HHF	22/436 (5.0)	73/1897 (3.8)	1.72 (1.06, 2.78)		0.028



In an extended model that included 10 additional baseline covariates, the increased HHF risk with preceding HYPO-strict was attenuated (HR 1.40 (0.86, 2.30), p=0.18).

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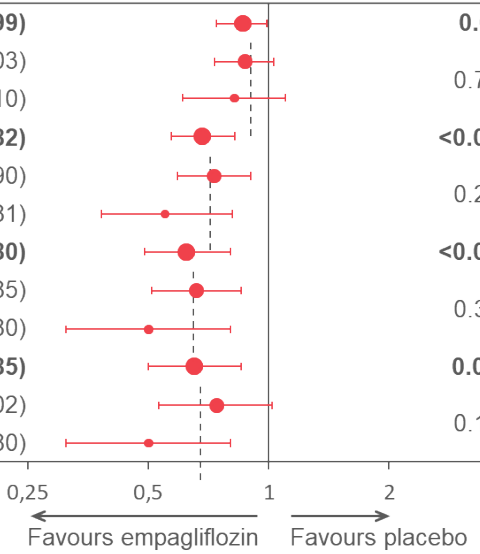
Empagliflozin reduced 3P-MACE, CV death, all-cause mortality, and HHF, regardless of occurrence of HYPO-broad

	Empagliflozin n with CV event/ n analysed (%)	Placebo n with CV event/ n analysed (%)	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)	

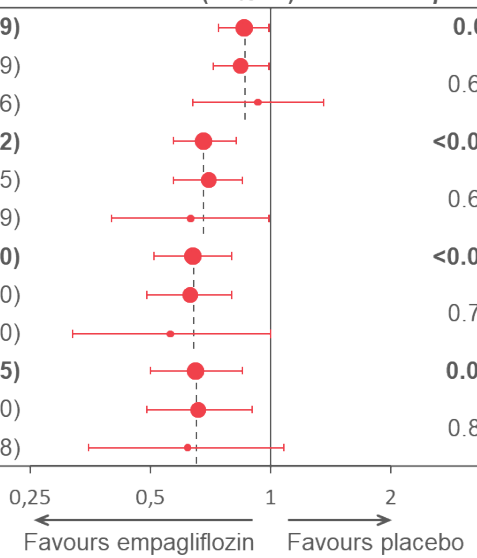


*p-value for interaction.
Patients were treated with ≥1 dose of study drug; only for presentation of patient numbers, those with/without HYPO-broad were determined at the time of CV event/censoring.
3P-MACE, 3-point major adverse cardiovascular event; CV, cardiovascular; HHF, hospitalisation for heart failure; MI, myocardial infarction.

EMPA-REG OUTCOME®

Empagliflozin reduced 3P-MACE, CV death, all-cause mortality, and HHF, regardless of occurrence of HYPO-strict

	Empagliflozin n with CV event/ n analysed (%)	Placebo n with CV event/ n analysed (%)	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)	



*p-value for interaction.
Patients were treated with ≥1 dose of study drug; only for presentation of patient numbers, those with/without HYPO-strict were determined at the time of CV event/censoring.
3P-MACE, 3-point major adverse cardiovascular event; CV, cardiovascular; HHF, hospitalisation for heart failure; MI, myocardial infarction.

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Limitations

- Severe hypoglycaemic events were very infrequent
  - 6.5 per 1000-patient years at risk in the placebo group
  - 5.4 per 1000- patient years at risk in the empagliflozin group

  Associations between serious hypoglycaemia and outcomes could not be assessed

- Difference in insulin dose between study groups at baseline or post-baseline not analysed
  - Cannot address whether observed association between hypoglycaemia and HHF could be linked to insulin therapy [1,2]

1. Cosmi F et al. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. Eur J Heart Fail . 2018;20:888-895; 2. Shen L et al. Insulin treatment and clinical outcomes in patients with diabetes and heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;21:974-984.

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Conclusion

- In this exploratory post-hoc analysis, hypoglycaemia was associated with an increased risk of HHF and MI but no other outcomes in the placebo group
- Hypoglycaemia risk was not increased with empagliflozin, despite a greater reduction in HbA1c
- Hypoglycaemia did not attenuate empagliflozin's cardio-protective effects on CV mortality and HHF in T2D

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CV, cardiovascular; HHF, hospitalisation for heart failure; MI, myocardial infarction; T2D, type 2 diabetes

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ESC European Society of Cardiology

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

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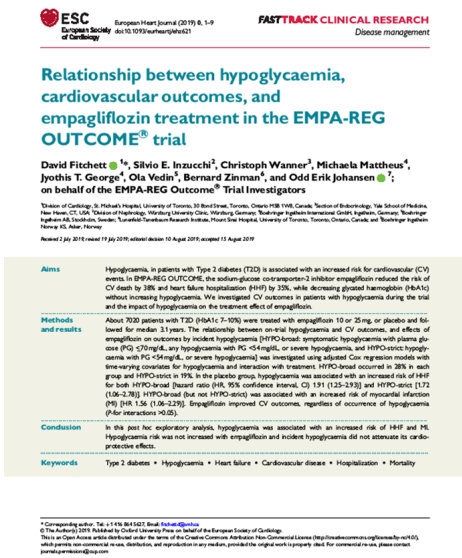

ESC European Society of Cardiology European Heart Journal (2019) 0, 1–9 doi:10.1093/eurheartj/ehz621

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 (1.23–2.93)] 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).

Condusion 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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