

Can the Cardiovascular Risk Reductions Observed with Empagliflozin in the EMPA-REG OUTCOME Trial be Explained by Concomitant Changes Seen in Conventional Cardiovascular Risk Factor Levels?

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Aim: The EMPA-REG OUTCOME trial demonstrated a significant reduction in cardiovascular (CV) outcomes in patients with type 2 diabetes given empagliflozin, a selective sodium-glucose cotransporter-2 inhibitor. We performed *post-hoc* analyses of this trial examining the degree to which empagliflozin-induced changes in conventional CV risk factors might explain the observed CV benefits.

Materials and methods: We estimated three-year EMPA-REG OUTCOME CV event rates using a type 2 diabetes-specific clinical outcomes simulation model applied to annual patient-level data. Variables included were atrial fibrillation, smoking, albuminuria, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, heart rate, white cell count, haemoglobin, estimated GFR, and prior histories of ischaemic heart disease, heart failure, amputation, blindness, renal failure, stroke, myocardial infarction or diabetic ulcer. Multiple simulations were performed for each participant to minimize uncertainty and optimize confidence interval precision around CV risk point estimates. Observed and simulated cardiovascular relative risk-reductions were compared.

Results: Model-predicted relative risk reductions were smaller than those observed in the trial, with empagliflozin-associated changes in conventional CV risk factor values appearing to explain only 12% of the observed relative risk reduction for all-cause death (4% of 32%), 7% for CV death (3% of 39%) and 15% for heart failure (4% of 29%).

Conclusions: Empagliflozin-associated changes in conventional CV risk factors in EMPA-REG OUTCOME appear to explain only a small proportion of the CV and all-cause death reductions observed. Alternative risk-reduction mechanisms need to be

explored to determine if the observed CV risk changes can be explained by other factors, or possibly by a direct drug-specific effect.

Clinical Trial Registration: <https://clinicaltrials.gov/ct2/show/NCT01131676>

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Keywords: Cardiovascular disease, Empagliflozin, SGLT-2 inhibitors, Type 2 diabetes

Introduction

Individuals with type 2 diabetes are at an increased risk of cardiovascular (CV) disease and premature death compared to the general population.[1] However, those who are able to maintain modifiable CV risk factors in their target ranges have been observed to carry little to no excess risk. [2] Therapies that can improve modifiable risk factors, such as blood pressure, lipid profiles and glycaemia, have been shown to reduce some, but not all, of the excess risk. [3] [4] [5] [6]

In 2008 the U.S. Food and Drug Administration (FDA) issued new guidance for the future development of glucose-lowering drugs for type 2 diabetes focussing specifically on cardiovascular (CV) safety following concerns about a possible increase in CV risk associated with the thiazolidinedione rosiglitazone. [7] Since then, a number of CV outcome trials have been completed, eight of which have shown significant decreases in their primary CV composite endpoint, four with a glucagon-like peptide-1 receptor agonist [8] [9] [10] [11] and four with a sodium-glucose cotransporter 2 inhibitor (SGLT2i). [12] [13] [14] [15]

The EMPA-REG OUTCOME study that evaluated the selective SGLT2i empagliflozin showed a 14% relative risk reduction for the primary CV composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction (MI) or non-fatal stroke ($P=0.04$),[12] driven primarily by a 38% relative risk reduction in CV deaths ($P<0.001$).

To ascertain the degree to which the CV risk reductions observed in EMPA-REG OUTCOME might be explained by concomitant improvements seen in conventional

CV risk factors during the trial, we have used a validated type 2 diabetes specific simulation model to estimate their likely impact on CV event rates.

Materials and methods

The EMPA-REG OUTCOME trial treated 7,020 patients randomized 1:1:1 to empagliflozin 10mg, empagliflozin 25mg, or to placebo between September 2010 and April 2013, with a median follow-up of 3.1 years. [12] We have analysed all participants randomized to empagliflozin as a single cohort as the results obtained with the two doses of empagliflozin did not differ. Selected baseline characteristics for all participants in this CV secondary prevention trial are listed in **Table 1**.

Participants were well treated with respect to CV risk reduction therapies, with 81% taking lipid-lowering and 95% antihypertensive medications at baseline. The primary endpoint of the study was a composite of CV death, non-fatal MI, or non-fatal stroke. Secondary CV outcomes included the occurrence of MI, stroke, CV death, death from any cause and hospitalization for heart failure.

We used the UKPDS Outcomes Model version 2 (UKPDS-OM2) [16], a computer simulation model (<http://www.dtu.ox.ac.uk/outcomesmodel/>) that calculates yearly estimates of the total diabetes disease burden over a projected lifetime, to simulate MI, stroke, CV death, heart failure and all-cause mortality rates for EMPA-REG OUTCOME trial participants. This validated lifetime simulation model also provides risk estimates for microvascular complications, which are not reported here. For the purposes of these analyses, the model was used to simulate the lifetime of the study (three years). Trial baseline participant-level data were entered for age, sex, race, diabetes duration, weight, and height, as well as any prior history of ischaemic heart disease, heart failure, amputation, blindness, renal failure, stroke, MI or diabetic

ulcer. Diabetes duration was calculated using the midpoint of the duration categories recorded at baseline, which had upper and lower bounds. *e.g.*, <1 year = 0.5 years, 1–5 years = 3 years *etc.* All those with >10 years duration were set to 12.5 years. Also entered were baseline and annual follow-up data for HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, smoking status, heart rate, white cell count, haemoglobin, estimated glomerular filtration rate, as well as presence of atrial fibrillation, peripheral vascular disease and albuminuria. All variables required for inclusion by the model were available in the EMPA-REG OUTCOME trial.

Cases where baseline data required were missing for CV and fatal event model equations were excluded from the analysis. Data missing at yearly follow-up visits were imputed using the last observation carried forward method. To assess the potential impact of these missing data assumptions on our results, additional simulations were performed using only those patients with complete case data. Monte Carlo simulation error was reduced by averaging 10,000 simulations (loops) per participant. Confidence intervals, reflecting parameter uncertainty, were estimated within the model by using 500 sets of bootstrapped values for the coefficients in the regression equations predicting clinical events. The simulated absolute event rates produced by the model in the empagliflozin and placebo groups were then used to derive estimated relative risk reductions (RRRs) for each event type. Summary data are expressed as means (SD), median (IQR) or N (%) as appropriate.

All data used in these analyses were collected and made available by the original investigators of the EMPA-REG OUTCOME trial to which all participants gave informed consent.

Results

Of the 7,020 patients treated in the EMPA-REG OUTCOME trial, 6663 (95%) with all baseline data available were included in this analysis. Their baseline characteristics are listed in **Table 1**. The CV risk factor differences observed at one year in the empagliflozin group, compared with the placebo group, in the 89% of participants with data available at this time point were a 4.8 mmol/mol (0.44%) lower HbA_{1c}, a 2.7 mmHg lower systolic blood pressure, a 1.7kg lower body weight, and an 0.11 mmol/L higher LDL-cholesterol.

The observed numbers of participants experiencing each prespecified event type during the trial, and the number of each event type simulated by the model, are shown in **Table 2**. In the placebo group the simulated absolute event numbers were similar to those observed for CV death, non-fatal MI and non-fatal stroke, but were higher for death from all causes (14.9% versus 8.5%) and lower for heart failure (2.0% versus 6.3%) with increasing disagreement over time (**Figure 1**). In the empagliflozin group the differences between simulated and observed numbers of deaths from all causes was larger (14.3% versus 5.8%), as was the difference for MI (7.6% versus 4.8% respectively), whereas the results were more similar for heart failure and stroke (**Figure 1**).

Comparing the simulated and observed relative risk reductions for each event type showed that the observed changes in CV risk factor levels during the trial appeared to contribute to only a small proportion of the impact of empagliflozin on the observed outcomes (**Table 2, Figure 2**). The proportions of the observed statistically significant

relative risk reductions potentially explained by the combined impact of conventional risk factors were 12% for all-cause death (4% of 32%), 7% for CV death (3% of 39%) and 15% for heart failure (4% of 29%). The proportions of the observed non-significant relative risk reductions potentially explained were 17% for MI (2% of 12%), while for stroke the observed numerical 23% increase compared with a simulated 6% reduction.

Discussion

Observed changes in conventional CV risk factor values during the EMPA-REG OUTCOME trial appear to explain only a small proportion of the risk reductions observed in key CV outcomes and death from any cause. Our findings suggest that empagliflozin may have only a modest effect over a three-year timescale on atherosclerotic mediated outcomes and that alternative mechanisms need to be explored, as others have suggested, that can more directly explain the cardioprotective benefits observed in the trial. [17] [18] [19] [20] [21] [22]

The first version of the UKPDS Outcomes Model (UKPDS-OM1) [23] was used previously to demonstrate that virtually all of the risk reduction observed in the pre-specified secondary CV outcome of the PROactive trial (a composite endpoint of all-cause mortality, non-fatal myocardial infarction or stroke) [24] could be explained by the observed within-trial pioglitazone-induced changes in conventional CV risk factors. [25] The predictive performance of the UKPDS Outcomes Model has also been validated previously in other populations with type 2 diabetes. Song *et al* [26] showed that all-cause mortality predicted by UKPDS-OM1 was comparable to observed mortality in U.S. National Health and Nutrition Examination Survey participants who had similar characteristics to UKPDS patients; and Pagano *et al* [27]

found that UKPDS-OM1 predictions of all-cause mortality, MI and CHF at 5 and 10 years closely matched the risks observed in the Casale Monferrato Survey in Northern Italy, with poorer predictions for stroke and after 12 years. More recently, UKPDS-OM2, as used in this analysis, was reported by McEwan *et al* to have a high degree of correlation ($R^2 = 0.87$) when predicting 100 validation endpoints across treatment arms of 12 pivotal type 2 diabetes outcome studies. [28] These results suggest that, where observed outcomes are mediated primarily by conventional CV risk factors, the UKPDS Outcomes Model generally simulates comparable rates for predicted outcomes. Therefore, even though the model was developed using a population observed before the common use of statins, the effect of these therapies does not appear to change the risk of CV outcomes over and above that accounted for by their effects on known CV risk factors.

The apparent finding of this study that empagliflozin may have only a modest effect over a three-year timescale on atherosclerotic mediated outcomes is supported by an exploratory mediation analysis of the EMPA-REG OUTCOME trial. [29] This mediation analysis, which used multivariable models incorporating effects of empagliflozin on haematocrit, fasting glucose, uric acid, and urine albumin:creatinine ratio, showed that the most important mediators of the reduction in risk of CV death with empagliflozin, compared with placebo, were changes in markers of plasma volume. Whilst that analytic exercise focussed solely on CV death, it suggests when combined with the results we report here, that the significant reductions in all-cause death, CV death and heart failure seen in EMPA-REG OUTCOME appear to be driven by alternative pathways requiring further investigation. However, it is important to note that haemoglobin is not considered to be an independent risk factor in the estimation of cardiovascular outcomes by the model. The collection of biomarker

data, e.g. NT-proBNP, from large-scale studies may reveal additional associations in future analyses including the impact of SGLT2i treatment on CV outcomes and death.

Limitations to our analysis include the poor prediction of the absolute event rates for all-cause death and heart failure observed in the placebo group, although the performance with respect to CV death, non-fatal MI and non-fatal stroke was considerably better; this suggests that initial calibration of the model to observed placebo event rates – a facility not currently available – could be useful before simulating the effects of specific interventions. In addition, the discriminative ability of the model in this population was poor for non-fatal MI and only adequate for CV death and non-fatal stroke preventing us from making comparisons at an individual participant level. However, the variation observed in risk estimates between those who experienced an event and those who did not does not negate the performance of the overall model estimates, as the model is designed to simulate risk changes at a population rather than an individual level.

The empagliflozin-associated changes in conventional cardiovascular risk factor values recorded in the EMPA-REG OUTCOME trial appear to explain only a small proportion of the actual cardiovascular risk reductions observed for key CV outcomes. Multiple pathways have been hypothesised on how glucose, sodium and water offloading by empagliflozin could lead to beneficial haemodynamic and renal effects. [30], [31] Ongoing studies [32], [33], <https://clinicaltrials.gov/ct2/show/NCT03057977>) will help to determine if the observed changes in risk can be explained by other factors, or possibly by a direct drug-specific effect.

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Duality of interest

Miss Coleman and Dr Gray have no disclosures. Drs Broedl, George, Woerle were employees of Boehringer Ingelheim, Dr Fitchett has received honoraria from Boehringer Ingelheim, Novo Nordisk, AstraZeneca, Sanofi, and Merck & Co, Dr Zinman has received grant support from Astra Zeneca, Novo Nordisk and Boehringer Ingelheim and consulting honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Merck, Sanofi and Janssen Dr Holman has received grants and personal fees from Merck; grants from Bayer, AstraZeneca, and Bristol-Myers Squib; personal fees from AMGEN, Bayer, Intarcia, Novartis, and Novo Nordisk; and other support from GlaxoSmithKline, Jannsen, and Takeda.

Contribution statement

RLC and RRH designed the study. RLC performed the analyses and wrote the first draft of the manuscript. AMG, UCB, DF, JTG, HJW, BZ and RRH contributed to the design and editing of the manuscript. All authors gave final approval of the version to be published. RRH is the guarantor of this work.

Data availability

Boehringer Ingelheim publicly registers all sponsored clinical studies and discloses the results. Furthermore, to benefit patients, public health, and to foster scientific discovery, Boehringer Ingelheim is committed to responsible sharing of clinical study reports (CSRs), related clinical documents, and patient-level clinical study data after drug approval or after termination of the drug development program.

https://trials.boehringer-ingelheim.com/transparency_policy.html

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Figure legends

Figure 1

Observed and simulated probabilities of time to first event in the EMPA-REG OUTCOME trial placebo and empagliflozin groups. [Placebo (a) - CV death, (b) - myocardial infarction, (c) - stroke, (d) - all-cause death, (e) - heart failure], [empagliflozin (f) - CV death, (g) - myocardial infarction, (h) - stroke, (i) - all-cause death, (j) - heart failure] Shaded area = observed 95% CI, ♦ = simulated point estimate.

Figure 2

Proportions of observed risk reductions attributable to changes in conventional risk factors

Table 1: Participant baseline characteristics. Summary statistics are mean (SD), median (IQR) or n (%)

	Summary statistics
N	6,663
Ethnicity (White Caucasian / Black / Asian)	4847 (73%) / 341 (5%) / 1475 (22%),
Female	1901 (29%)
Age (years)	63 (8.6)
Diabetes duration (years)	12.5 (7.5 – 12.5)
Body Mass Index (kg/m ²)	30.6 (5.2)
Height (m)	1.67 (0.10)
Atrial Fibrillation	372 (6%)
Peripheral Vascular Disease	1365 (20%)
Smoker (current)	872 (13%)
Albuminuria*	2674 (40%)
HDL-cholesterol (mmol/l)	1.14 (0.30)
LDL-cholesterol (mmol/l)	2.05 (1.55, 2.69)
Systolic blood pressure (mmHg)	135 (17)
HbA _{1c} (mmol/mol)	65 (9.3)
HbA _{1c} (%)	8.1 (0.85)
Heart rate (bpm)	69 (12)
White blood cell count (x10 ⁹ /l)	7.4 (1.9)
Estimated GFR (ml/min/1.73m ²)	74 (21)
Prior ischemic heart disease	5055 (76%)
Prior heart failure	675 (10%)
Prior amputation	117 (2%)
Prior blindness	26 (0.4%)
Prior stroke	1554 (23%)
Prior myocardial infarction	3129 (47%)
Prior ulcer	387 (6%)

* albuminuria defined as presence of micro- or macro-albuminuria

Table 2: Observed and simulated empagliflozin and placebo events with their corresponding relative risks

Outcome	Empagliflozin events		Placebo events		Observed	Simulated	Model
	Observed	Simulated	Observed	Simulated	relative risk	relative risk	discrimination
	(n=4,439)	(n=4,439)	(n=2,224)	(n=2,224)	(95% CI)	(95% CI)	C-statistic
Cardiovascular death	162 (3.6%)	311 (7.0%)	133 (6.0%)	160 (7.2%)	0.61 (0.48, 0.76)	0.97 (0.97, 0.98)	0.62
Myocardial infarction	214 (4.8%)	338 (7.6%)	122 (5.5%)	173 (7.8%)	0.88 (0.71, 1.09)	0.98 (0.98, 0.98)	0.59
Stroke	157 (3.5%)	183 (4.1%)	64 (2.9%)	98 (4.4%)	1.23 (0.92, 1.64)	0.94 (0.93, 0.94)	0.63
Heart Failure	197 (4.4%)	86 (1.9%)	139 (6.3%)	45 (2.0%)	0.71 (0.58, 0.88)	0.96 (0.95, 0.96)	0.71
All-cause death	256 (5.8%)	637 (14.3%)	189 (8.5%)	332 (14.9%)	0.68 (0.57, 0.81)	0.96 (0.96, 0.97)	0.66

Baseline variables included in the model are: age, sex, race, diabetes duration, body mass index, prior (ischaemic heart disease, heart failure, amputation, renal failure, stroke, MI or diabetic ulcer), HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA1c, smoking status, heart rate, white cell count, estimated glomerular filtration rate, atrial fibrillation, peripheral vascular disease and albuminuria. Annually assessed variables included in the model are: HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA1c, smoking status, heart rate, white cell count, estimated glomerular filtration rate, atrial fibrillation, peripheral vascular disease and albuminuria.

Figure 1

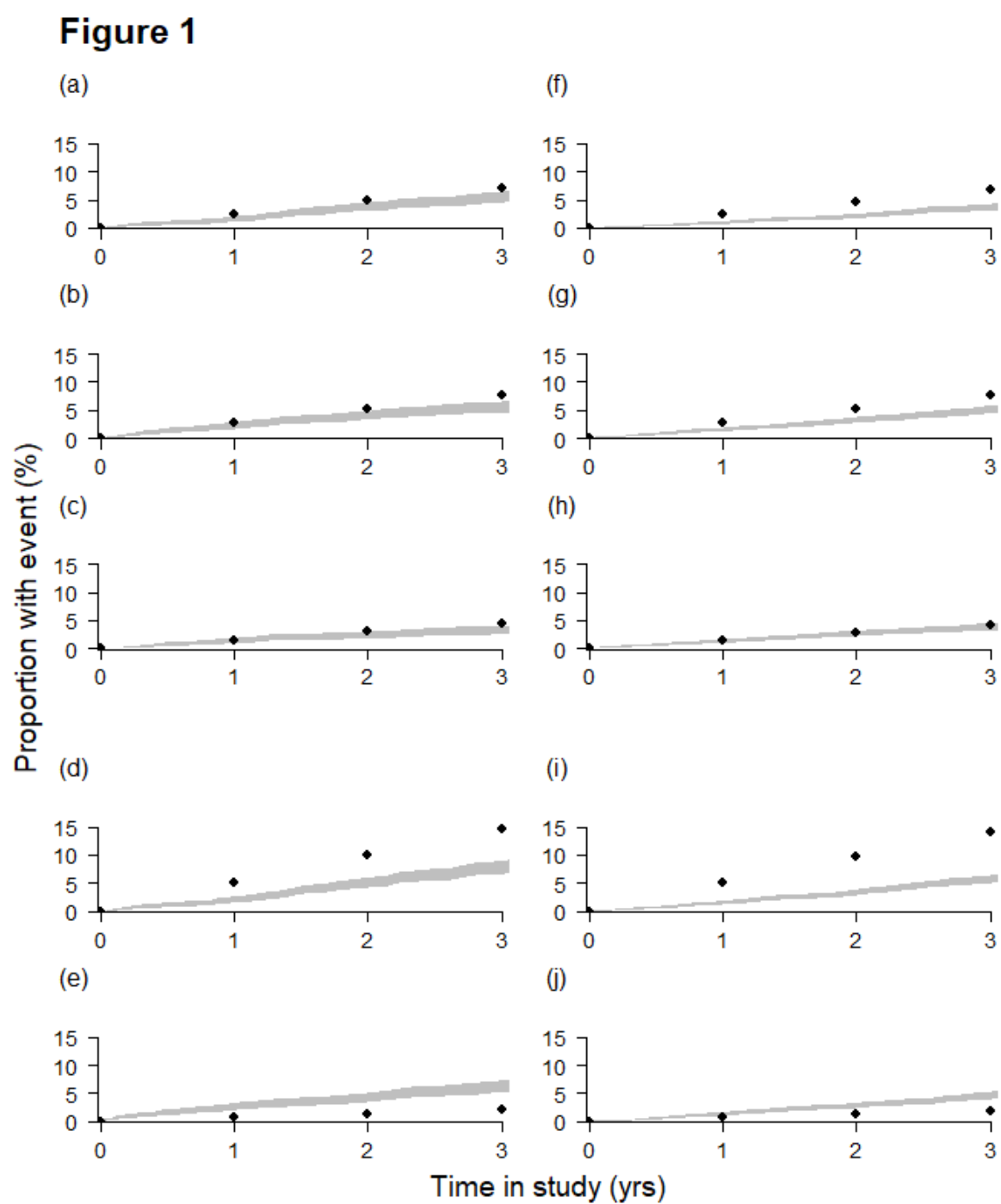


Figure 2

