An exploration of the heterogeneity in effects of SGLT2 inhibition on cardiovascular and all-cause mortality in the EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, and CREDENCE trials

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Keywords

Cardiovascular mortality; EMPA-REG OUTCOME; CANVAS Program; DECLARE- TIMI 58; SGLT2i

Abstract

Background

Large-scale outcome trials of sodium glucose co-transporter 2 (SGLT2) inhibitors in patients with type 2 diabetes have identified consistent effects on major adverse cardiovascular events, heart failure, and progression of kidney disease. However, the magnitude of effects on cardiovascular and all-cause death appeared to vary between some of the studies.

Methods

We explored the impact of differences in trial methodologies, participant characteristics, types of deaths, follow-up duration, effects on intermediate markers of risk, and drug selectivity for SGLT2 on the magnitude of the protective effect against fatal events achieved in the 4 trials.

Results

The trial populations differed substantively in the proportions with baseline atherosclerotic cardiovascular disease history (99.2% in EMPA-REG OUTCOME to 40.6% in DECLARE-TIMI 58), and macroalbuminuria (88.0% in CREDENCE to 7.6% in the CANVAS Program). Meta-regression analyses identified no clear effect of these (both P >0.09) or other participant characteristics on mortality benefits (all P >0.55). Other differences between the trials (duration, selectivity of the SGLT2 inhibitor, or effects on intermediate markers of risk) also did not explain the heterogeneity in effects on mortality observed (all P >0.30).

Conclusion

No clear explanation for the statistical evidence of heterogeneity in effects of SGLT2 inhibition on fatal outcomes between the trials could be identified. While the analyses had limited statistical power, these results raise the possibility that the observed variations in treatment effects on fatal outcomes between trials may be at least partly due to chance.

Introduction

People with type 2 diabetes mellitus are at substantially increased risk of atherosclerotic cardiovascular disease, heart failure, and kidney failure resulting in an increased risk of premature death [1, 2]. Sodium glucose co-transporter 2 (SGLT2) inhibitors significantly reduce the risk of these events in people with type 2 diabetes [3, 4]. The EMPA-REG OUTCOME trial, the first large-scale study of the SGLT2 inhibitor empagliflozin [5], demonstrated separately significant protection against both cardiovascular death and all-cause mortality. Empagliflozin was subsequently approved by the US Food and Drug Administration with an indication for reduction in cardiovascular mortality. Since then, comparable effects of other SGLT2 inhibitors, including canagliflozin and dapagliflozin, on major adverse cardiovascular events (MACE, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), heart failure, and progression of kidney disease have been reported in 3 more large-scale trials [6-8]. At the same time, the magnitude of the effects on fatal outcomes has varied between studies, with empagliflozin demonstrating a greater effect than that of canagliflozin or dapagliflozin on cardiovascular death (relative risk reduction of CV death: 38% in the EMPA-REG OUTCOME trial versus 13% in the CANVAS Program versus 2% in the DECLARE-TIMI 58 trial versus 22% in the CREDENCE trial) in patients with atherosclerotic cardiovascular disease.

There are some differences in the pharmacological characteristics of each drug [9-12] and there are also differences in the way that each trial was conducted. Further, the compounds differ in their respective selectivity profiles on the basis of in vitro potency [9]. Empagliflozin has the highest selectivity for SGLT-2 over SGLT-1 (>2500-fold), followed by dapagliflozin (>1200-fold), and canagliflozin (>250-fold) . Whether the observed differences in the effects on fatal outcomes between the trials reflect the play of chance, different actions of the compounds on the risk of fatal disease outcomes, or differences in trial methodologies is unclear [3, 13, 14]. Accordingly, we comprehensively investigated each of these aspects in an effort to better understand the likely reasons for the

differences in effects on fatal outcomes observed across the 4 completed large-scale trials of SGLT2 inhibitors in type 2 diabetes.

Methods

We sought to understand the reasons for the observed heterogeneity in effects of different SGLT2 inhibitors on fatal outcomes in the 4 completed large-scale outcome trials by systematically comparing individual properties of each SGLT2 inhibitor (SGLT2 selectivity and inhibitory concentration), trial design, and reported data between each study.

Data sources

Data were extracted from published reports, trial protocols, endpoint adjudication charters, and the original study datasets for the CANVAS Program and CREDENCE trial, which were available to the investigators. Data describing treatment effects on fatal outcomes were extracted as hazard ratios except for the EMPA-REG OUTCOME trial where some effects were determined from event numbers and estimated as risk ratios.

Trial and drug characteristics evaluated

Trial inclusion criteria – the reported main inclusion criteria for participants in each trial were identified and summarized; *participant characteristics* – a standard set of data describing the baseline demographics, disease history, and clinical management characteristics of participants in each trial were sought and tabulated; m*ethod for adjudication of deaths* – descriptions of the processes were extracted from the respective endpoint adjudication charters. The focus was on the high level assignment of deaths as cardiovascular, noncardiovascular, or undetermined in origin; *proportions of deaths attributed to different causes* – numbers and proportions were obtained from primary trial outcome reports, and data were sought describing all deaths as well as cardiovascular, noncardiovascular, and undetermined causes; e*ffects on intermediate outcomes* – for HbA1c, systolic blood pressure, body weight, and albuminuria were extracted from main trial reports and tabulated; d*uration of follow-up* – the mean and median durations of follow-up were extracted from each of the

main trial reports. In addition, plots of the cumulative event curves for total and cardiovascular mortality were extracted from published reports; and *selectivity of the drug for SGLT2* – with data obtained from external reports [9-11, 15, 16].

Data analysis

We qualitatively compared trial inclusion criteria and methods used to assign cause of death in each of the contributing studies. Participant characteristics and the proportions of deaths attributable to each main cause were also tabulated and compared. Statistical testing was not done to compare baseline characteristics across studies because the large numbers of individuals in each trial would have meant that almost all were statistically different even if the differences were not clinically meaningful. Instead, a qualitative review was undertaken to identify clinically important differences. The same approach was taken for the comparison of effects on the intermediate outcomes. Quantitative estimates of effect on all-cause mortality, and each subset of causes of death, were made by doing fixed effects meta-analysis and calculating *P* values for homogeneity of the individual trial results for each outcome. The evolution of treatment effects over time was explored by visual inspection of the available cumulative event curves and by univariable meta-regression of the mean and median duration of follow-up against the magnitude of the treatment effect for cardiovascular and all-cause mortality. Random effects meta-regressions analyses were used to explore the relationship between the proportion of atherosclerotic cardiovascular disease, the proportion of heart failure, estimated glomerular filtration rate (eGFR) at baseline, follow-up duration, SGLT2 drug selectivity, and the magnitude effect of intermediate markers with the hazard ratio for each trial. Analyses were performed using Stata version 15.1, SAS Enterprise Guide version 7.1, and Review Manager 5.3 by Cochrane.

Results

Data were extracted from 4 protocol documents [6, 7, 17, 18], 4 endpoint adjudication charters [5-8], 10 scientific reports [5-8, 18-23], 1 systematic review [3], and the datasets of the CANVAS Program

and CREDENCE trial. The first trial participant was randomized into EMPA-REG OUTCOME in September 2010 [5, 19] and the last into the CREDENCE trial in May 2017 [7, 24]. The trials completed follow-up in April 2015 (EMPA-REG OUTCOME), February 2017 (CANVAS Program), September 2018 (DECLARE-TIMI 58), and October 2018 (CREDENCE). The CREDENCE trial was stopped early as it met prespecified efficacy criteria at an interim analysis, but each of the others continued until the scheduled number of primary outcome events had been recorded as per the initial trial protocol.

Trial inclusion criteria and baseline characteristics of study participants

All trials enrolled patient groups at high cardiovascular risk (**Supplementary Table 2**), with only small differences in definitions of atherosclerotic cardiovascular disease across the trials. The EMPA-REG OUTOME trial required a history of atherosclerotic cardiovascular disease for inclusion whereas each of the other trials also enrolled high-risk primary prevention cohorts with multiple cardiovascular risk factors (**Table 1**). The proportions of primary prevention participants were 34.4% (CANVAS Program), 59.4% (DECLARE-TIMI 58), and 49.6% (CREDENCE). In contrast to the 3 cardiovascular outcome trials, CREDENCE was an event-driven kidney outcome trial in which all participants had type 2 diabetes and urinary albumin: creatinine ratio (UACR) >300 mg/g. As a result, the mean eGFR and median UACR at baseline were markedly different between CREDENCE and the other 3 trials. There was no evidence that the proportions with atherosclerotic cardiovascular disease at baseline (both P >0.09), the proportions with macro-albuminuria at baseline (both P >0.80), the proportions with heart failure at baseline (both P >0.80), or mean eGFR at baseline (both P >0.50) were associated with the magnitude of treatment effect on all-cause or cardiovascular mortality (**Supplementary Figures 2-5**). Neither was there evidence that drug selectivity for SGLT2 was associated with the magnitude of treatment effect on all-cause or cardiovascular mortality (both P >0.30; **Supplementary Figure 6.2**).

In other respects, the baseline characteristics of participants in the 4 trials were much more similar to each other than different. Mean age was highly comparable with a low of 63.0 years in the CREDENCE trial and a high of 64.0 years in the DECLARE-TIMI 58 trial and the proportion of males was greater

than the proportion of females in every study, but the range was limited, extending from 71.5% in EMPA-REG OUTCOME to 62.6% in DECLARE-TIMI 58. Levels of other baseline risk markers were also mostly comparable across the 4 studies as were rates of use of other therapies for the control of diabetes and the prevention of atherosclerotic cardiovascular disease (**Table 1**).

Assignment of causes of death and proportions of deaths attributed to different causes

The 4 trials all adjudicated fatal events using endpoint adjudication committees and prespecified charters that provided explicit definitions to be applied by the committee members (**Supplementary Table 3**) [5-8]. In each study the causes of death were broadly divided into cardiovascular and noncardiovascular causes with all studies except EMPA-REG OUTCOME also including an undetermined category into which deaths that could be assigned as neither cardiovascular nor noncardiovascular were placed. In the EMPA-REG OUTCOME trial such deaths were presumed cardiovascular in cause from the outset and identified as "other cardiovascular cause" A comparable strategy was used for analysis of cardiovascular versus noncardiovascular outcomes in the other trials. Most trials also reported subtypes of cardiovascular deaths, defined using similar criteria, as "sudden cardiac death," "myocardial infarction," "stroke", "heart failure or cardiogenic shock," and "other cardiovascular or undetermined cardiovascular." Additional definitions for more granular subsets of cardiovascular deaths were provided for some studies.

There were 463 deaths in the EMPA-REG OUTCOME trial, 681 in the CANVAS Program, 1099 in the DECLARE-TIMI 58 trial, and 369 in the CREDENCE trial (**Supplementary Table 1**). The proportions of cardiovascular deaths were greater in the EMPA-REG OUTCOME trial (66.7%, n = 309) as compared to the CANVAS Program (54.0%, n = 368), the CREDENCE trial (52.6%, n = 194), and the DECLARE-TIMI 58 trial (44.9%, n = 494). Cardiovascular deaths termed primarily as "other or undetermined" were highest in the EMPA-REG OUTCOME trial (27.9%), reflecting the assignment strategy, but more comparable to the other trials if deaths due to "undetermined cause" were also included. The chance

that the proportion of "other cardiovascular deaths" in the EMPA-REG OUTCOME trial was overestimated due to the adjudication definition is small and unlikely to have affected sufficient numbers of deaths to drive the large variation in effects on mortality observed. This is supported by the fairly consistent proportion of noncardiovascular death seen across the 4 trials (lowest, CREDENCE: 32.2%; highest, DECLARE-TIMI 58: 40.9%). Differences between the proportions of cardiovascular deaths assigned to the main cardiovascular causes were small where data were available. Data describing the main noncardiovascular causes of death were available for only the CANVAS Program and the CREDENCE trial and were comparable.

Effects of SGLT2 inhibition on deaths attributed to different causes

There were separately significant effects of SGLT2 inhibition on total mortality in the EMPA-REG OUTCOME trial (HR 0.68; 95% CI, 0.57–0.82), but while the directions of effect were similar for each of the other trials, the point estimates were less extreme and the confidence intervals crossed unity in every case (**Figure 1**). The same pattern was observed for cardiovascular death. For noncardiovascular death and undetermined death, the point estimates of effect were indicative of benefit rather than harm in every case, but confidence intervals spanned unity for all. There was some evidence of heterogeneity in effects across the four trials for total mortality (I^2*=63.1%; P for interaction* = 0.04) and moderate heterogeneity for cardiovascular death (I^2*=70.7%; P for interaction* = 0.02) driven by the results for cardiovascular mortality in the EMPA-REG OUTCOME trial. For the subtypes of cardiovascular deaths, numbers of events were frequently small and confidence intervals were wide. There was evidence of heterogeneity in the findings between the trials only for death from heart failure or cardiogenic shock (*P* = 0.05), which was driven by a very large protective effect in the CREDENCE trial (HR 0.27; 95% CI, 0.12–0.61).

Evolution of the effects of SGLT2 inhibition over time

Median trial follow-up ranged from a maximum of 218 weeks in the DECLARE-TIMI 58 trial and a minimum of 126 weeks in the CANVAS Program, with the CREDENCE trial (136 weeks) and the EMPA-REG OUTCOME trial (161 weeks) falling in between. Mean follow-up durations were ordered somewhat differently: DECLARE-TIMI 58 trial (182 weeks), CANVAS Program (188 weeks), EMPA-REG OUTCOME trial (140 weeks), and CREDENCE trial (109 weeks). Inspection of the cumulative event curves for the 4 trials (**Figures 2** and **Supplementary Figure 1**) identified that for 3 of the trials, separation of the mortality curves commenced in the first 12 months (DECLARE-TIMI 58 was not included because no separation of the mortality curves was evident). For both total and cardiovascular mortality, the magnitude of the separation accelerated in the EMPA-REG OUTCOME trial from about 18 months onwards with continued progressive separation of the curves during follow-up, but this was not observed in the other trials. Neither the median nor the mean duration of follow-up was associated with the hazard ratio for total mortality or cardiovascular death (all P >0.364; **Supplementary Figure 7**).

Effects of SGLT2 inhibitors on intermediate markers of risk

There were clear positive effects of SGLT2 inhibition on HbA1c, blood pressure, body weight, albuminuria, and haematocrit in all 4 trials (**Table 2**). Differences in the magnitudes of effect were most marked between CREDENCE and the other trials, with CREDENCE recording lesser effects on HbA1c and body weight, but greater effects on albuminuria. There was no evidence that the magnitudes of effect on these intermediate markers of risk were associated with the magnitude of protection afforded by SGLT2 inhibition (all P >0.30; **Supplementary Figures 8-12**).

Discussion

Overall evidence that the effects of SGLT2 inhibitors on major clinical outcomes differ between the 4 large outcome trials is limited. Though there were differences across the 4 trials for all cause death, with EMPA-REG the only trial to report a statistically significant reduction for this outcome (32%), and

statistical heterogeneity for both total mortality (*P* = 0.04) and cardiovascular mortality (*P* = 0.02), these outcomes are not independent of each other, nor are the findings extreme. Indeed, while not statistically significant, in all trials point estimates for total and CV mortality were less than 1. Further, there is no evidence of differences between the trials for other outcomes such as total major adverse cardiovascular events, heart failure, and kidney disease [4, 25]. The strength of evidence supporting a difference in effects on mortality between the trials may weaken as more data from more trials becomes available. It is possible that the very large effect on mortality observed in the EMPA-REG OUTCOME trial may have been a chance overestimate of the effect of empagliflozin, but further data from ongoing trials will provide more insight to analyses that are restricted by the small number of completed studies and the use of summary data from the trials.

Extensive exploration of trial characteristics as potential modifiers of the treatment effects has failed to identify clear differences between the studies that might explain the observed variations in the hazard ratios for mortality. In particular, there was no clear evidence that the hazard ratios for fatal outcomes was determined by the proportion of participants with nephropathy at baseline (*P* >0.84 for macroalbuminuria), or according to baseline eGFR (*P* >0.55) though the statistical power to detect modifying effects was in every case limited. There was some suggestion, though not statistically significant, that a higher proportion of participants with atherosclerotic cardiovascular disease at baseline was associated with a greater reduction in CV death with SGLT2 inhibition (*P* = 0.094). However, neither baseline atherosclerotic cardiovascular disease [26, 27]. nor nephropathy [28-31] have been observed to modify the effects of randomized treatment in subgroup analyses of the individual trials, providing some additional confidence in the findings. Moreover, a recent meta-analysis of these 4 trials did not show significant heterogeneity for the outcome of CV death based on history of atherosclerotic cardiovascular disease at study baseline (*P* for interaction = 0.167) [25]. Future analyses based upon individual participant data from the 4 trials would allow a more robust investigation of possible effect modification by participant characteristics.

Differences in duration of follow-up between trials were only moderate, whether recorded as means or medians, and were not associated with differences in the magnitude of protection provided against total or cardiovascular mortality (all *P* >0.36). Likewise, there were different effects of SGLT2 inhibition compared to placebo on intermediate risk factors (HbA_1C, systolic blood pressure, body weight, urine ACR, haematocrit) between the trials, though the absolute magnitude of the differences were mostly small. Canagliflozin had lesser effects on HbA1c and body weight and greater effect on albuminuria in the CREDENCE trial as compared to the CANVAS Program however this most likely represents differences in the populations being studied. All participants in CREDENCE [5] had chronic kidney disease with eGFR of 30 to 90 ml/min/1.73 m^2 and UACR >300 mg/g, as compared to only 17.5% in the CANVAS Program [6]. Prior analysis demonstrate that SGLT2 inhibition has less effects on intermediate markers of cardiovascular risk, such as HbA1c and body weight among patients with chronic kidney disease [29]. Importantly, however, the relative cardiovascular benefits are the same when compared those with eGFR <60 versus eGFR ≥ 60 ml/min/1.73 m^2, suggesting that the cardiovascular and kidney protective effects produced by SGLT2i are not solely mediated by glucose lowering or body weight effects [25].In no case were the differences in effect on the intermediate markers of risk across the 4 trials systematically associated with the differences in effects on cardiovascular or total mortality (all p>0.30).

The proportions of total deaths attributable to cardiovascular causes did vary between studies, and because SGLT2 inhibition would be expected to avert cardiovascular deaths but not noncardiovascular deaths, this might have provided an explanation for differences in the observed hazards for total mortality. However, differences in the proportions of deaths attributed to different causes between studies were only moderate and differences in effects of SGLT2 inhibition compared to placebo persisted when analyses were restricted to cardiovascular mortality. Furthermore, there was limited evidence that randomized treatment produced different protection against one form of

cardiovascular death compared to another. While significant heterogeneity was observed for heart failure death (P = 0.05), this was likely a chance finding driven by an extreme benefit in a single trial (CREDENCE) based upon a small number of events.

These analyses were strengthened by the high standard to which each of the contributing trials were performed and the reasonably standardized methods used for reporting key metrics of interest. The chief limitation is that there are data from only 4 studies, and while this has not limited speculation about possible differences in effects of the drugs between trials, it does seriously restrict the capacity to robustly test for such differences using statistical approaches.

Conclusion

In the context of highly consistent effects across the 4 trials for total major adverse cardiovascular events and most other key cardiovascular outcomes, there is no strong rationale for expecting differences in fatal outcomes. Thus, while it remains possible that the result from the EMPA-REG OUTCOME trial indicates a truly greater effect of SGLT2 inhibition on mortality in that trial, it is also quite possible that this was a chance observation. The completion of further ongoing large trials of SGLT2 inhibitors should provide additional insight over the next few years.

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Declaration of interests

J. Yu, J. Li, B. Neal and C. Arnott are employees of the George Institute. Z. Zhou reports receiving a Scientia PhD Scholarship from the University of New South Wales, Sydney.is a full-time employee of the George Institute for Global Health. K.W. Mahaffey has received research support from Afferent,

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Supplemental Materials

- Online Tables 1-3
- Online Figures 1-13

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