Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular disease, death and safety outcomes in type 2 diabetes - A systematic review

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Abstract

Aim

Sodium glucose co-transporter 2 (SGLT2) inhibitors appear to protect against increased risks of cardiovascular and kidney disease in patients with type 2 diabetes but also cause some harms. Whether effects are comparable across drug class or specific to individual compounds is unclear. This meta-analysis assessed the class and individual compound effects of SGLT2 inhibition versus control on cardiovascular events, death, kidney disease and safety outcomes in patients with type 2 diabetes.

Methods

MEDLINE, EMBASE, the Cochrane Library and regulatory databases were systematically searched for data from randomized clinical trials that included reporting of cardiovascular events, deaths or safety outcomes. We used fixed effects models and inverse variance weighting to calculate relative risks with the 95% confidence intervals.

Results

The analyses included data from 82 trials, four overviews and six regulatory reports and there were 1,968 major cardiovascular events identified for analysis. Patients randomly assigned to SGLT2 had lower risks of major cardiovascular events (RR 0.85, 95%CI 0.77 ~~to~~ 0.93), heart failure (RR 0.67, 95%CI 0.55 ~~to~~ 0.80), all-cause death (RR 0.79, 95%CI 0.70 ~~to~~ 0.88) and serious decline in kidney function (RR 0.59, 0.49 ~~to~~ 0.71). Significant adverse effects were observed for genital infections (RR 3.06, 95%CI 2.73 ~~to~~ 4.43), volume depletion events (RR 1.24, 95%CI 1.07–1.43) and amputation (RR 1.44 95%CI 1.13–1.83). There was a high likelihood of differences in the associations of the individual compounds with cardiovascular death, hypoglycaemia and amputation (all $I^2 > 80\%$) and a moderate likelihood of differences in the associations with non-fatal stroke, all-cause death, urinary tract infection and fracture (all $I^2 > 30\%$).

Conclusion

There are strong overall associations of SGLT2 inhibition with protection against major cardiovascular events, heart failure, serious decline in kidney function and all-cause death. SGLT2 inhibitors were also associated with infections, volume depletion effects and amputation. Some associations appear to differ between compounds.

Keywords: Diabetes type 2; SGLT2 inhibitors; Cardiovascular disease; Kidney disease; Safety; Amputation; Fracture; Systematic review; Randomised controlled trials

Abbreviations: AKI, Acute kidney impairment; CVD, Cardiovascular disease; MACE, Major macrovascular event; SGLT2, Sodium-glucose cotransporter-2; UTI, Urinary tract infection

1 Background

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been a treatment option for type 2 diabetes since 2013 and the prescription of SGLT2 inhibitors has increased rapidly since the first was marketed. The mechanism of action based upon blockade of the SGLT2 transporter in the proximal renal tubule results in substantial and sustained glycosuria. This is in turn accompanied by improved glycaemia, blood pressure lowering, weight reduction and decreased albuminuria [1] all of which might be anticipated to protect against adverse cardiovascular and renal outcomes. A prior meta-analysis has suggested cardiovascular protection [2] but the results were imprecise and were based mostly on data from one large trial [3].

SGLT2 inhibitors are also associated with increased risks of infections resulting from glycosuria [4] and with side effects resulting from diuresis and blood pressure lowering [2]. Hypoglycaemia is not usually observed [2] but diabetic ketoacidosis can be precipitated in rare cases [5,6] and possible increased risks for bone fracture [7] malignancy [8] and stroke [2,3] have been reported. Most recently, a risk of lower-extremity amputation was also identified [9].

The available data describing the associations of SGLT2 inhibition with cardiovascular outcomes and death was approximately doubled in quantity with the reporting of the CANVAS Program [10]. We sought to make comprehensive new estimates of the associations of SGLT2 inhibitors with clinical efficacy and safety outcomes based upon all available evidence from randomised controlled trials that compared SGLT2 inhibitor treatment to placebo or active control.

2 Methods

This report is a substantive update of a prior systematic review and meta-analysis that included data to end September 2015 [2] and involved four of the current authors (CF, BN, VP, JW). The update uses new database searches covering the period from October 2015 to June 2017 to supplement and expand the prior data.

2.1 Search strategy

We performed a systematic search of the scientific literature according to the PRISMA statement for the conduct of meta-analyses of intervention studies [11] including MEDLINE via Ovid, EMBASE and the Cochrane Library database (Cochrane Central Register of Controlled Trials). The text words and medical subject headings comprised terms relating to ‘randomised trial’, ‘sodium glucose 2 transporter’ and the compound names (Supplementary Appendix 1). The searches were limited to data from randomised controlled trials but without language restriction. In addition, reference lists from included trials, review articles and other relevant reports were manually scanned to identify other data. Submissions made to regulatory agencies [8,12–17] were also identified and searched for applicable data.

2.2 Study selection

The titles and abstracts of all identified articles were screened by two authors for eligibility (KR, MGW) and these authors also assessed the full text of the potentially eligible reports to reach a final decision on inclusion or

exclusion. Review, data extraction and quality assessment were conducted independently in duplicate using a standardized approach. Any disagreement was settled by consultation with a third author (JW, BN). Original papers presenting data on individual randomised clinical trials of any SGLT2 agent in human adults with type 2 diabetes were included, with individual trial report data supplemented or substituted outcome by outcome with information from overviews or regulatory submissions where the data in the overviews or regulatory submissions provided a greater quantity of data or could be used to add data that was clearly identified as not overlapping with that from another report. Duplicate reports, trials which involved compound agents (e.g. SGLT2 in combination with metformin), trials that lasted less than 8 days in duration and trials that did not report on efficacy outcomes of interest (cardiovascular, death or the specified safety outcomes) were excluded. Where there were multiple reports of a single study, the report with longer follow-up was included. Likewise, if different reports on the same trial provided data on different outcomes then maximum non-overlapping data were extracted from each report.

2.3 Data extraction and quality assessment

Data tables used for the prior overview [2] were updated with information for each new data source and outcome that was identified. Standardized data were extracted by one investigator (KR) into the electronic form and checked by another (MGW). Study quality was judged for each included trial (KR) according to evidence of the proper conduct of randomization, concealment of treatment allocation, similarity of treatment groups at baseline, the provision of a description of the eligibility criteria, completeness of follow-up, and use of intention-to-treat analysis as described by the Jadad tool [18].

2.4 Outcomes

There were three broad sets of outcomes grouped as (1) vascular outcomes and death; (2) kidney disease outcomes; and (3) safety outcomes. The primary vascular outcome of interest was the composite of major cardiovascular events comprised of vascular death, non-fatal acute myocardial infarction and non-fatal stroke. The secondary vascular outcomes of interest were vascular death; non-fatal myocardial infarction; non-fatal stroke; hospitalisation for unstable angina and hospitalisation for heart failure. The kidney disease outcomes were progression of albuminuria; and a renal composite outcome describing serious loss of kidney function (defined as major declines in either serum creatinine or glomerular filtration rate or need for renal replacement therapy or renal death). The safety outcomes were urinary tract infection; genital infection; volume depletion; renal adverse events; hypoglycaemia; metabolic acidosis; venous thromboembolism; cancer (total, breast, bladder, kidney); amputation; and bone fracture. Definitions for reported volume depletion events and renal adverse events were particularly difficult to establish for the contributing studies and direct comparability of definitions for most other safety outcomes could not be assured.

2.5 Data synthesis and analysis

Analyses were done for all SGLT2 inhibitors combined versus any comparator (placebo or active control) and separately for each individual SGLT2 inhibitor versus any comparator. Relative risks (and 95% confidence intervals) were sought for each outcome with the number of patients randomised used as the denominator and the number of events as the numerator. Where only hazard ratios and 95% confidence intervals were available these were used as substitutes for relative risks [19]. Wherever possible trial level data were used for the meta-analyses but if reported summary estimates including data for several trials for a compound provided more data, then the summary measures of the effect estimate and uncertainty interval were used. Where summary data from another report were included we sought, in order of preference, to use the hazard ratios and 95% confidence interval, or the incidence rate ratio and 95% confidence interval (based upon events/participant years) or the relative risk (based upon events/participant number). Meta-analysis was done using fixed effects models and inverse variance weighting [20] since the effects of different SGLT2 inhibitors on outcomes were *a priori* considered likely to be consistent. The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I^2 statistic and also by calculating the p-value for heterogeneity. An I^2 statistic of 0-25% was considered to reflect a low likelihood, 26-75% a moderate likelihood and 76-100% a high likelihood of differences beyond chance. A p-value of <0.05 for heterogeneity was also deemed likely to reflect a high likelihood of differences beyond chance. A 95% confidence interval that did not span unity indicated a statistically significant result for an outcome. Statistical analyses were performed with Stata, version 14.2 (Stata, College Station, Texas).

3 Findings

Seven SGLT2 inhibitors with data were identified: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin. The updated search from 2015 to June 2017 rendered 1336 additional potentially eligible studies out of which 28 trials and three overviews met the inclusion criteria (Fig. 1) [10,21-50]. The largest addition was from the CANVAS-program which contributed 10,142 participants [10]. Seven of the 28 trials were updates of studies included in the prior analysis [2]; two providing additional results from a randomised double blinded extension period [25,30], one full text update [47] and four for which prior conference abstracts had been replaced or updated by full reports [44-46,51]. There were no new regulatory submissions identified. Most trials were of high quality according to the Jadad tool (Supplementary Appendix). Supplementary data were provided by direct contact with the authors of one paper [40].

Fig. 1 Flow chart. (¹Many participants contributed to both the safety and the efficacy outcomes; DM = diabetes mellitus; RCT = randomised controlled trial; SGLT2 = sodium-glucose cotransporter-2; FDA = United States Food and Drug Administration; CVD = cardiovascular disease).

Data were derived from 82 trial reports, four overviews and six regulatory reports. There were data for 32,893 unique individuals that contributed to the analyses of major cardiovascular events, 30,210 for the analyses of mortality and between 22,762 and 52,305 for the analyses of safety outcomes. Most comparisons were against placebo with just 4009 participants in 14 trials assigned to an active comparator. The median study durations ranged between 1.3 and 188.2 weeks, the mean age of participants in the trials between 48.1 and 68.4 years and the proportions male between 44.2 and 89.5 percent. Funnel plots and Begg's tests done for outcomes with multiple data points for individual trial outcomes showed no evidence of publication bias ([Supplementary Appendix](#)). The risk of bias was assessed as low for all analyses, with all data deriving from studies that were randomised and almost all from trials

that were explicitly described as double-blind.

3.1 Effects of SGLT2 inhibitors on cardiovascular outcomes

For the primary outcome of interest, major cardiovascular events, there were four SGLT2 inhibitors that reported data and there were in total 1968 events recorded. For the analyses of specific cardiovascular outcomes there were 766 cardiovascular deaths, 727 non-fatal myocardial infarctions, 494 non-fatal strokes, 243 hospitalisations for unstable angina and 464 hospitalisations for heart failure. Data for these outcomes were available for only two compounds. In addition, there were 1221 deaths from any cause. In every case the outcomes were dominated by data from two large trial reports [3,10].

Overall, use of SGLT2 inhibition was associated with favourable effects on major cardiovascular events, non-fatal myocardial infarction, hospitalisation for heart failure and all-cause death (Fig. 2). The I^2 statistic indicated a high likelihood of differences between compounds beyond chance for cardiovascular death ($I^2 = 80\%$) and a corresponding moderate likelihood of differences beyond chance for all-cause death ($I^2 = 55\%$). There was no association of SGLT2 inhibition detected for hospitalisation for unstable angina or stroke but for the latter there was a moderate likelihood of differences between compounds beyond chance ($I^2 = 61\%$).

Fig. 2 Associations of SGLT2 inhibitors with cardiovascular outcomes and death, overall and for each compound (Hazard ratios were used as approximators for relative risks where relative risks could not be estimated. SGLT2 = sodium -glucose cotransporter-2. Note: relative risks may not be estimable directly from event numbers and totals randomised because of different follow-up durations and randomisation ratios across contributing trials).

3.2 Effects of SGLT2 inhibitors on kidney disease outcomes

There were just two compounds with data describing effects on the renal outcomes of interest [10,47] and there were strong associations of SGLT2 inhibition with protection against progression of albuminuria and the renal composite outcome (Fig. 3).

Fig. 3 Associations of SGLT2 inhibitors with renal outcomes, overall and for each compound (*Progression of albuminuria was a change from normo-albuminuria to micro-albuminuria or macro-albuminuria, or micro-albuminuria or macro-albuminuria; the renal composite outcome describing serious loss of kidney function defined by major declines in either serum creatinine or glomerular filtration rate or need for renal replacement therapy or renal death).

3.3 Effects of SGLT2 inhibitors on safety outcomes

There were several safety outcomes for which clear associations were noted and several for which a moderate to high likelihood of differences beyond chance were identified. There was the anticipated overall increased risk of genital mycotic infections but an I² value of 74% indicated a moderate likelihood of differences between compounds beyond chance (Fig. 4). For three compounds with substantive data there were approximate three times increased risks but estimates for four others with sparse data were variable. There was no overall association with urinary tract infection but a moderate likelihood of differences between compounds beyond chance (I² = 30%) (Fig. 4). An association of SGLT2 inhibition with the risk of volume depletion adverse events was also observed but with no evidence of differences between agents. There was no association with renal adverse events and a low likelihood of differences between compounds beyond chance (I² = 16%). There was no overall effect on hypoglycaemia but a high likelihood of differences between compounds beyond chance (I² = 87%) (Fig. 4). There were 59 placebo-controlled trials, four trials with an active comparator, and six trials with both a placebo and an active comparator that reported data for hypoglycaemia. The heterogeneity for hypoglycaemia was reduced in analyses restricted to placebo-controlled studies only (I² = 50.3%; appendix p 30).

Fig. 4 Associations of SGLT2 inhibitors with infections, volume depletion, renal and hypoglycaemia adverse events.

No associations of SGLT2 inhibition were observed for acidosis, thromboembolism or cancer (total or site-specific). For the two compounds with data about lower extremity amputation there was an overall association indicating an increased risk but a high likelihood of differences between compounds beyond chance ($I^2 = 86\%$) (Fig. 5) with the amputation risk apparent for only one compound. Overall fracture risk was not increased across the four compounds for which data were available but there was a moderate likelihood of differences between the compounds beyond chance ($I^2 = 65\%$) and a separately significant increase in fracture risk for one.

Fig. 5 Associations of SGLT2 inhibitors with acidosis, thromboembolism, cancer, amputation and fracture.

4 Interpretation

These data for patients with type 2 diabetes show strong associations of SGLT2 inhibition with protection against cardiovascular and renal outcomes as well as all-cause death. There were also clearly increased risks of adverse outcomes including infections, volume depletion events and amputations. On balance, however, the cardiovascular benefits associated with SGLT2 inhibitor treatment are likely to outweigh the risks of adverse events for many patients with type 2 diabetes.

For some of the benefits and some of the harms there is uncertainty about whether the observed associations are consistent across the drug class or whether they differ between compounds. Because many comparisons have been made and because data are sparse for some compounds and for some outcomes, it is possible that differences have arisen by chance. For others, however, the findings are indicative of real differences and there is a need for additional data to better understand why these differences might have arisen.

Evidence of differences in protective effects was strongest for the outcome cardiovascular death, where empagliflozin appeared to provide a greater magnitude of protection. There was a corresponding, though less strong, finding for all-cause death that was probably driven by the effect on cardiovascular death. There is no established mechanism to explain these differences or the other possible difference observed for stroke. Most differences found were, however, moderate in magnitude and whether they reflect real differences or chance findings is not clear. For the remaining cardiovascular and renal efficacy outcomes, there were no substantive differences observed between compounds.

Regarding the safety outcomes, sparse data for one or more compounds seem likely to explain the possible between drug differences in risks for genital mycotic infection and urinary tract infection. For the hypoglycaemia outcome, differential use of background therapies and comparison against active control in some studies may account for the variation. Different use of concomitant therapies may also account for differences in volume depletion between compounds but this cannot be quantified based upon the available data. The association between amputation and use of SGLT2 inhibitors is a new finding that appeared to be restricted to canagliflozin. However, only limited

data were available for two compounds [3,10,49,52] and in the absence of an established mechanism specific to canagliflozin the European Medicines Agency currently warns about amputation risk for the SGLT2 class. Since the conduct of the meta-analyses, ertugliflozin has been provided FDA marketing approval. Within the product labelling a risk of amputation is noted (11 active, 1 placebo) which corresponds to a RR of 1.31, (95% CI 1.10–1.55). Inclusion of these data in the meta-analysis of amputation data showed an overall increased risk of amputation RR 1.14 (95% CI 1.04–1.26) with a persisting considerable heterogeneity between compounds ($I^2 = 88.3\%$). For fracture, there was also a separately significant adverse effect observed for canagliflozin that warrants further investigation and requires additional data to better clarify the nature of the risk. The lack of a clear adverse effect for acidosis likely reflects the very few events recorded in the trials and the drug class carries a warning based upon post marketing adverse event findings and the known mechanism by which metabolic acidosis can be caused [48].

The absence of a renal safety signal indicates that early volume-related declines in estimated glomerular filtration do not result in significant harm. While the SGLT2 class has label warnings about the risk of acute kidney injury the risk is clearly manageable with careful administration of therapy and monitoring. Further, the observed associations with renal efficacy outcomes suggest a renoprotection role for SGLT2 inhibition that is currently being assessed by dedicated renal efficacy trials such as The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE). CREDENCE is a randomised, double-blind, event-driven, placebo-controlled trial evaluating clinically important kidney outcomes as well as cardiovascular outcomes for canagliflozin in patients with type 2 diabetes and established kidney disease [53].

This overview benefits from the robust systematic methods used and the comprehensive assessment of all key efficacy and safety outcomes. There are almost double the quantity of efficacy outcomes since the last substantive meta-analysis was reported [2] with significant new insights provided into the likely effects of both individual compounds and the class. The overview also has some weaknesses. There are still relatively few events for some of the outcomes of interest and some of the associations have wide confidence intervals. Outcome definitions were not identical across studies. For example, the albuminuria outcome data for the CANVAS Program included progression to microalbuminuria from normoalbuminuria whereas the data from EMPA-REG OUTCOME did not [9,47]. Likewise, for the composite renal outcome there were differences in the use of serum creatinine versus eGFR, and definitions of kidney related adverse events were uncertain. Trials were done in a range of different settings and in many different population groups with varied prevalence of comorbid conditions and utilisation of background therapies. The use of hazard ratios and incident rate ratios as approximators of relative risks can be an issue if event rates are high. Trials with placebo and active comparators were included to maximise power and while this is unlikely to have impacted upon the estimates of efficacy outcomes, it may have influenced estimates for some safety outcomes [2]. All except four studies [24,54–56] excluded patients with significant kidney disease so little can be concluded about effects of SGLT2 inhibition in patients with significant co-morbid renal disease.

5 Conclusion

There are strong overall associations of SGLT2 inhibition with protection against major cardiovascular events, serious declines in kidney function and all-cause death. SGLT2 inhibitors also cause infections, volume depletion effects and amputation. Some associations appear to differ between compounds.

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Author contributions statement

KR and MGW did the literature search and data extraction. JW did the analyses. KR wrote the first draft of the paper. BN conceived of the project. All authors made substantive contributions to editing and interpretation.

Declaration of interests

GF, KM, BN and VP were investigators on the CANVAS Program.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabres.2018.03.027>.

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Appendix A. Supplementary material

[Multimedia Component 1](#)

Supplementary data 1

[Multimedia Component 2](#)

Supplementary data 2

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