SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

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Summary

Background The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.

Methods We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes. We searched PubMed and Embase for trials published up to Sept 24, 2018. Data search and extraction were completed with a standardised data form and any discrepancies were resolved by consensus. Efficacy outcomes included major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of renal function.

Findings We included data from three identified trials and 34 322 patients (60·2% with established atherosclerotic cardiovascular disease), with 3342 major adverse cardiovascular events, 2028 cardiovascular deaths or hospitalisation sfor heart failure events, and 766 renal composite outcomes. SGLT2i reduced major adverse cardiovascular events by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014), with benefit only seen in patients with atherosclerotic cardiovascular disease (0·86 [0·80–0·93]) and not in those without (1·00 [0·87–1·16], p for interaction=0·0501). SGLT2i reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (0·77 [0·71–0·84], p<0·0001), with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. SGLT2i reduced the risk of progression of renal disease by 45% (0·55 [0·48–0·64], p<0·0001), with a similar benefit in those with and without atherosclerotic cardiovascular disease. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in hospitalisations for heart failure (p for interaction=0·0073) and lesser reductions in progression of renal disease (p for interaction=0·0258) in patients with more severe kidney disease at baseline.

Interpretation SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that seem confined to patients with established atherosclerotic cardiovascular disease. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.

Funding None.

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have now been studied in several large placebo-controlled cardiovascular outcomes trials[1–3] in patients with type 2 diabetes. These trials were done to satisfy regulatory requirements, specifically to exclude an excess in risk of cardiovascular death, myocardial infarction, or stroke (ie, major adverse cardiovascular events) and to test for efficacy.[4] Data to date suggest this drug class appears to moderately reduce the risk of major adverse cardiovascular events, or at least some components of them. However, the apparent greater benefit of SGLT2i on major adverse cardiovascular events in patients with established atherosclerotic cardiovascular disease than in those with multiple risk factors but without atherosclerotic cardiovascular disease complicates the interpretation of these data. This observation has resulted in European and American diabetes and cardiology society guidelines recommending SGLT2i for patients with atherosclerotic cardiovascular disease but not multiple risk factors.[5,6] However, no single trial has been adequately powered to test for such heterogeneity of cardiovascular efficacy by baseline atherosclerotic cardiovascular disease risk categories because the number of patients and events in those patients with multiple risk factors alone have been

Lancet 2019; 393: 31–39

Published **Online** November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

See **Comment** page 3

This online publication has been corrected. The corrected version first appeared at thelancet.com on January 3, 2019

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Research in context

Evidence before this study

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been studied in large cardiovascular outcome trials in patients with type 2 diabetes and were shown to reduce the risk of cardiovascular events. Both patients with established atherosclerotic cardiovascular disease and those with multiple risk factors but without the disease were studied in these trials. Within individual trials, the magnitude of benefit appeared to be greater on major adverse cardiovascular events in subgroups with established atherosclerotic cardiovascular disease, although formal heterogeneity was not shown. Based on these findings, American and European guidelines recommend use of SGLT2i for patients with type 2 diabetes and atherosclerotic cardiovascular disease, independent of glucose control considerations. However, no single trial has been adequately powered to test for such heterogeneity because the number of patients and events in those patients with multiple risk factors alone have been low. We prospectively planned to meta-analyse cardiovascular outcome results from the dedicated cardiovascular outcome trials stratified by presence or absence of established atherosclerotic cardiovascular disease, once data from the DECLARE-TIMI 58 trial of dapagliflozin versus placebo became available. We searched PubMed and Embase using the Medical Subject Heading terms "diabetes mellitus, type 2", "sodium-glucose-co transporter 2 inhibitor", and "clinical trial" for trials published up to Sept 24, 2018, to find all randomised cardiovascular outcome trials for SGLT2i.

Added value of this study

Incorporating data from the trials EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58, the present meta-analysis of SGLT2i cardiovascular outcome trials showed that the clinical benefit of SGLT2i in reducing the risk of myocardial infarction, stroke, or cardiovascular death was present only in patients with established atherosclerotic cardiovascular disease and not in those with multiple risk factors. Conversely, the reductions in risk of hospitalisation for heart failure or progression of renal disease were robust regardless of the presence of atherosclerotic cardiovascular disease or heart failure at baseline.

Implications of all the available evidence

These data suggest that SGLT2i should be considered in patients with type 2 diabetes regardless of presence of atherosclerotic cardiovascular disease or history of heart failure, given that SGLT2i safely reduce HbA_{1c} and reduce the risk of hospitalisation for heart failure and progression of renal disease across a broad spectrum of patients with type 2 diabetes. Reductions in major adverse cardiovascular events can also be expected in patients with established atherosclerotic cardiovascular disease.

low. Results from the DECLARE-TIMI 58 trial,[3] which had the highest number of patients with multiple risk factors, now allows more rigorous investigation of this issue. Additionally, these same cardiovascular outcome trials[1,2,7,8] have shown that SGLT2i robustly reduce the risk of hospitalisation for heart failure and progression of kidney disease. However, data from one trial[9] suggested that SGLT2i might reduce the risk of cardiovascular death and hospitalisation for heart failure to a larger extent in patients with a history of heart failure than in those without. Additionally, the glucosuric effects of SGLT2i are dependent on renal function, which raises natural interest in whether the clinical benefit is also related to renal function.[10,11] In terms of safety, SGLT2i might increase the risk of amputations,[2,12] fractures,[2,13] and diabetic ketoacidosis,[14–16] but these events are infrequent, making it difficult to draw meaningful conclusions from individual trials.

The goal of the present meta-analysis was to combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2i to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups.

Methods

Search strategy and selection criteria

For this meta-analysis, we used the methods proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[17–19] This analysis was prespecified in the statistical analysis plan of the DECLARE-TIMI 58 trial.[3] A data search (TAZ, MSS) of all randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i published up to Sept 24, 2018, was done on PubMed and Embase. The search algorithm is presented in detail in the appendix. Data extraction was done by two independent reviewers (TAZ, MSS) for aggregated study-level data.

See Online for appendix

Patients were stratified into those with established atherosclerotic cardiovascular disease versus multiple risk factors (appendix), history of heart failure or not, and by estimated glomerular filtration rate (eGFR; appendix). Efficacy outcomes of interest included: major adverse cardiovascular events (the composite of myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, their individual components, and a standardised composite of renal outcomes including worsening eGFR, end-stage renal disease, or renal death (see appendix for details). Safety endpoints of interest consisted of non-traumatic lower limb amputations, fractures, and diabetic ketoacidosis.

Data analysis

Data were extracted with the use of a standardised data form and any discrepancies were resolved by consensus. We pooled hazard ratios (HRs) with 95% CIs for the effect

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

of randomised treatment allocation on the primary outcomes across trials overall and within the previously mentioned subgroup strata using fixed effects models. We tested for treatment effect modification by subgroup using random effects models, applying the method of residual maximum likelihood and Hartung-Knapp adjustment.[20] All trials met criteria for being well done and had a low risk of bias according to the Cochrane tool for assessing risk of bias in randomised clinical trials (appendix).[21]

We assessed heterogeneity using Cochrane Q statistic, and Higgins and Thompsons' I^2. Heterogeneity was considered to be low if I^2=25%, moderate if I^2=50%, or high if I^2=75%.[22] All reported p values are two-sided and we did no adjustments for multiple testing. We did statistical analyses using R version 3.5.1 (R Core Team, Vienna, Austria) and the R package metafor (version 2.0-0).[23]

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

We identified a total of three trials[1–3] and six secondary analyses[7,9–11,24,25] from the same trials that were eligible for inclusion (appendix). The appendix has an overview of the search and the selection process. In total, data from 34 322 patients were included. The mean age was 63·5 years and 35·1% were women (table). A total of 20 650 (60·2%) patients were known to have atherosclerotic cardiovascular disease and 13 672 (39·8%) had multiple risk factors but without known atherosclerotic cardiovascular disease. The proportion of patients with multiple risk factors differed among the trials, ranging from 0% in the EMPA-REG OUTCOME trial to 34% in the CANVAS Program, and to 59% in DECLARE-TIMI 58 trial. A total of 3891 (11·3%) patients had a history of heart failure, a proportion that was similar across all three trials. Baseline renal function differed among the trials, with the proportion of patients with eGFR <60 ml/min per 1·73 m² ranging from 25·9% in EMPA-REG OUTCOME to 20·1% in CANVAS, and to 7·4% in DECLARE-TIMI 58 (table).

In total, 3342 (9·7%) of 34 322 patients had a major adverse cardiac event in the trials. Of those events, 2588 (77·4%) occurred in the group with established atherosclerotic cardiovascular disease. Overall, SGLT2i reduced the risk of a major adverse cardiac event by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014; appendix). However, this effect was entirely restricted to a 14% reduction in patients with atherosclerotic cardiovascular disease (0·86 [0·80 to 0·93]), whereas no treatment effect was found in patients with multiple risk factors (1·00 [0·87–1·16], p for interaction=0·0501; figure 1).

1604 (4·7%) patients had a myocardial infarction (80·5% of which occurred in patients with atherosclerotic cardiovascular disease), 1060 (3·1%) had a stroke (73·1% of which occurred in patients with atherosclerotic cardiovascular disease), and 1256 (3·7%) had cardiovascular death (78·6% of which occurred in patients with the disease). Overall, SGLT2i reduced the risk of myocardial infarction by 11% (HR 0·89 [95% CI 0·80–0·98], p=0·0177) and cardiovascular death by 16% (0·84 [0·75–0·94], p=0·0023, but with high heterogeneity [I^2=79·9%]), whereas SGLT2i had no effect on stroke (0·97 [0·86–1·10], p=0·64; appendix). Analogous to the pattern seen for major adverse cardiovascular events overall, SGLT2i reduced myocardial infarction (0·85 [0·76–0·95]) and cardiovascular death (0·80 [0·71–0·91]) in patients with atherosclerotic cardiovascular disease, whereas no treatment effect was found in patients with multiple risk factors. SGLT2i had no effect on stroke, even in patients with atherosclerotic cardiovascular disease (appendix).

Overall, SGLT2i significantly reduced the risk for the composite of cardiovascular death or hospitalisation for heart failure by 23% (HR 0·77 [95% CI 0·71–0·84], p<0·0001), and hospitalisation for heart failure by 31% (0·69 [0·61–0·79], p<0·0001; appendix). In patients with atherosclerotic cardiovascular disease, the HR for

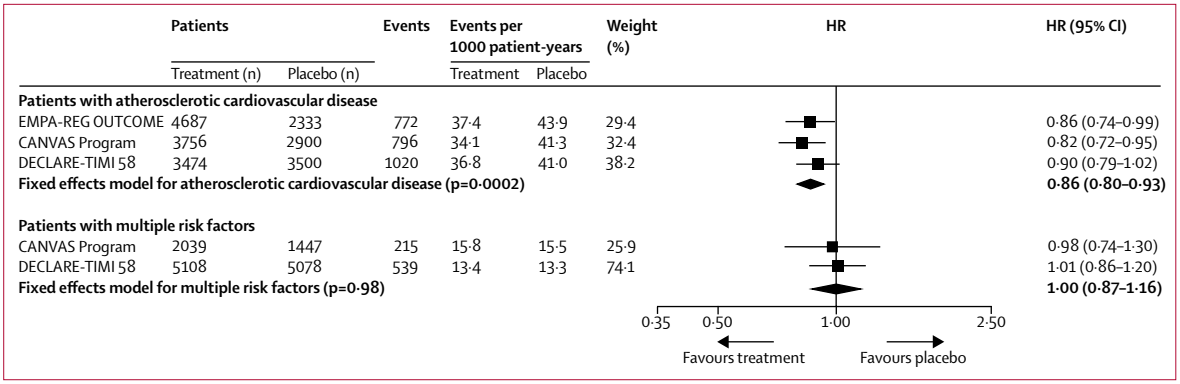

Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

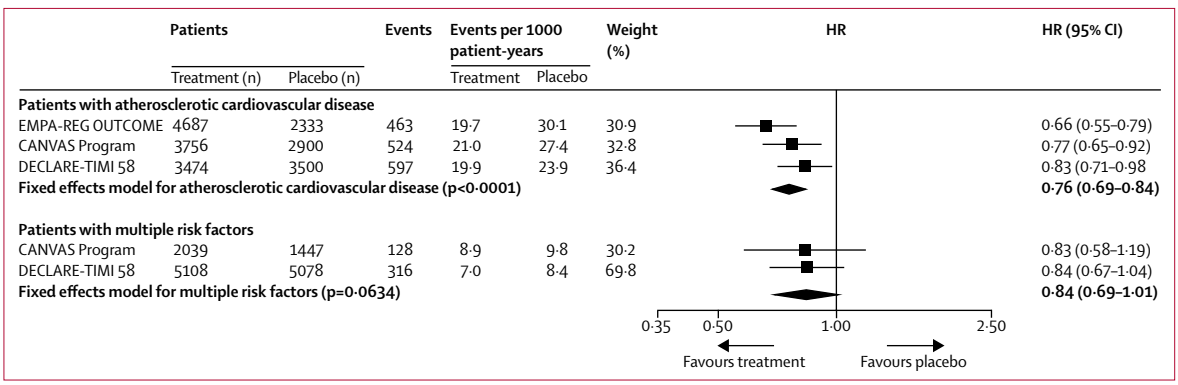

Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

the composite of cardiovascular death or hospitalisation for heart failure was 0·76 (0·69–0·84) and in patients with multiple risk factors it was 0·84 (0·69–1·01, p for interaction=0·41; figure 2). The effect on hospitalisation for heart failure alone was robust, with an approximately 30% reduction in relative risk in both subgroups (appendix). The reduction in the composite of cardiovascular death or hospitalisation for heart failure was not statistically different in patients with (HR 0·71 [95% CI 0·61–0·84]) or without (0·79 [0·71–0·88]) a history of heart failure at baseline (p for interaction=0·51; figure 3), nor were the individual component outcomes (appendix).

Overall, SGLT2i significantly reduced the risk for all-cause death by 15% (HR 0·85 [95% CI 0·78–0·93], p=0·0002), but with high heterogeneity (I^2=75·2%; appendix). In patients with atherosclerotic cardiovascular disease the HR was 0·83 (0·75–0·92) and in those with multiple risk factors it was 0·90 (0·77–1·05, p for interaction=0·69; appendix). Similarly, in patients with a history of heart failure the HR was 0·80 (0·67–0·95) and in those without a history of heart failure it was 0·88 (0·80–0·97, p for interaction=0·63; appendix).

Overall, SGLT2i were renoprotective and reduced the composite of worsening of renal function, end-stage renal disease, or renal death by 45% (HR 0·55 [95% CI 0·48–0·64], p<0·0001). This effect was similarly robust both in patients with atherosclerotic cardiovascular disease (HR 0·56 [95% CI 0·47– 0·67]) and those with multiple risk factors, (0·54 [0·42–0·71], p for interaction=0·71; figure 4; appendix). The reduction in the composite renal endpoint was present across all baseline eGFR levels but was greatest in those with preserved renal function at baseline, with a 33% reduction in patients with an eGFR of less than 60 mL/min per 1·73 m², 44% reduction in patients with an eGFR between 60 and 90 mL/min per 1·73 m², and 56% reduction in patients with an eGFR of 90 mL/min per 1·73 m² or higher (p for interaction=0·0258; figure 5A). Conversely, the reduction in hospitalisation for heart failure was 40% in the lowest group, 31% in the middle group, and a non-significant

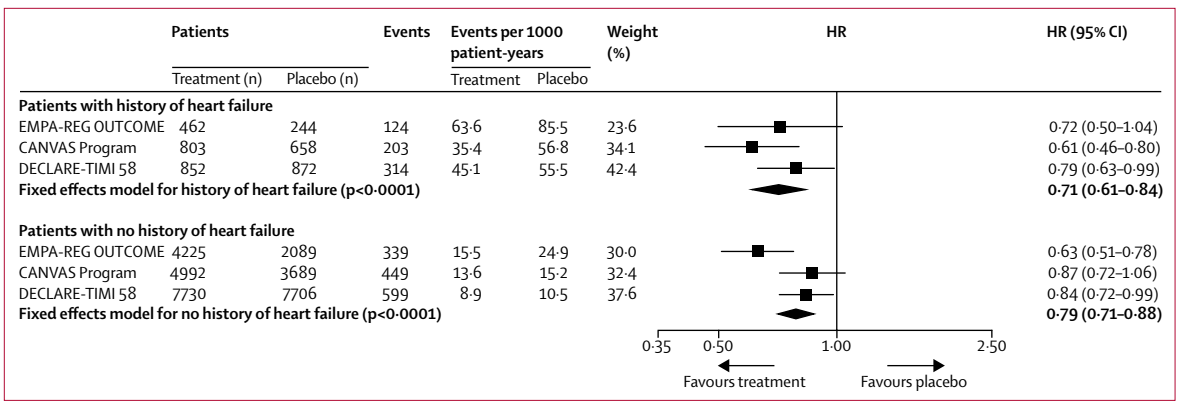

Figure 3: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**
History of heart failure: Q statistic=2·02, p=0·37, I^2=0·8%; no history of heart failure: Q statistic=5·89, p=0·0527, I^2=66%. The p value for subgroup differences was 0·51. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

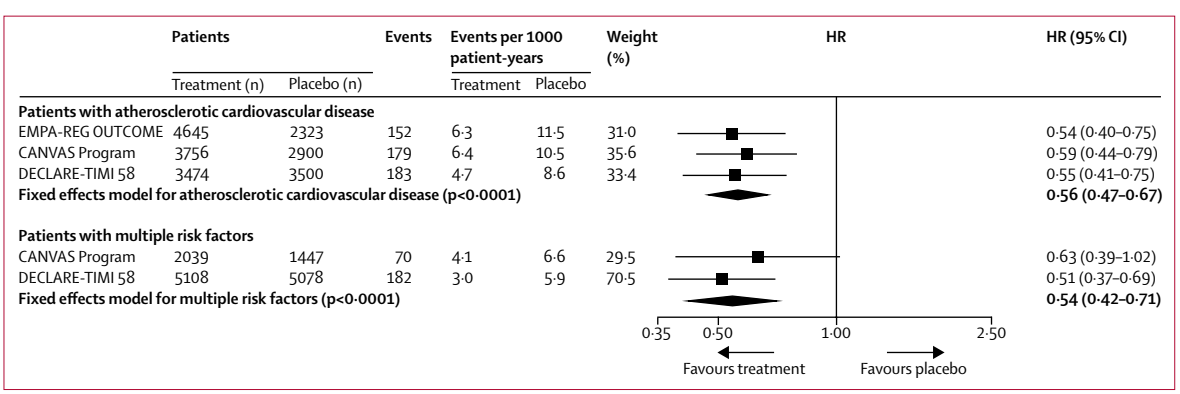

Figure 4: **Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease**
Atherosclerotic cardiovascular disease: Q statistic=0·19, p=0·91, I^2=0%; multiple risk factors: Q statistic=0·52, p=0·47, I^2=0%. The p value for subgroup differences was 0·71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

12% in the highest group (p for interaction=0·0073; figure 5B). A directionally similar but non-significant trend was found for effect modification for major adverse cardiovascular events, with an 18% reduction in the lowest eGFR group, a 9% reduction in the middle group, and a non-significant 6% reduction in the highest group (p for interaction=0·23; figure 5C).

For safety outcomes, an increased risk of amputations and fractures was observed only in one trial (appendix), resulting in moderate to high percentages of total variation across studies that was due to heterogeneity (I^2=79·1% for amputation and I^2=42·1% for fracture). Diabetic ketoacidosis showed a consistent increased risk of almost two times higher in patients given SGLT2i than those given placebo (2·20 [1·25–3·87], p=0·0060), but the event rates were low (<one per 1000 patient-years; appendix).

Discussion

The present meta-analysis of SGLT2i cardiovascular outcome trials substantially expands on previous meta-analyses,[26] and the totality of these data now makes several patterns clear. First, SGLT2i have their greatest and most consistent effect on reducing the relative risk of hospitalisation for heart failure (31%) and of progression of renal disease (45%). Their effect on the composite atherosclerotic outcome of myocardial infarction, stroke, or cardiovascular death (major adverse cardiac events), originally a safety outcome stemming from regulatory guidance, was more modest but still significant with 11% reduction in relative risk. Second, for particular outcomes the clinical effects of SGLT2i depend on the patient population in which they are used. The reduction in major adverse cardiac events was apparent only in patients with established atherosclerotic cardiovascular disease, whereas no effect was observed in patients without atherosclerotic cardiovascular disease. Conversely, the reduction in hospitalisation for heart failure was robust and of similar magnitude regardless of the presence of established atherosclerotic cardiovascular disease or a history of heart failure. The reduction in

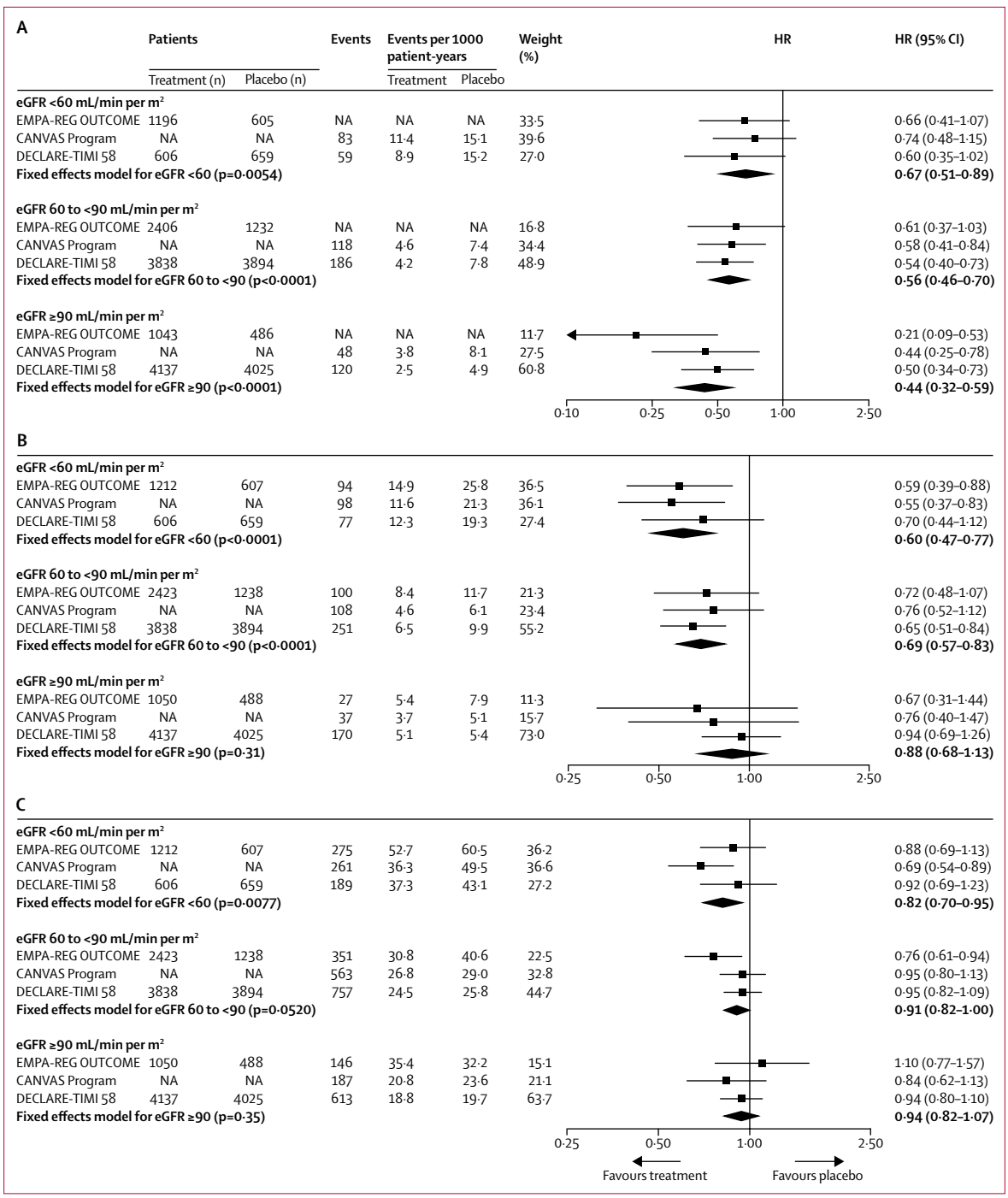

Figure 5: **Meta-analysis of SGLT2i trials on the composite of worsening of renal function, end-stage renal disease, or renal death (A), hospitalisation for heart failure (B), and major adverse cardiovascular events stratified by the eGFR levels (C)**

(A) eGFR <60 mL/min per 1·73 m²: Q statistic=0·36, p=0·84, I^2=0%; eGFR 60 to <90 mL/min per 1·73 m²: Q statistic=0·19, p=0·91, I^2=0%; eGFR ≥90 mL/min per 1·73 m²: Q statistic=3·24, p=0·20, I^2= 38·2%. The p value for risk reduction trend across subgroups was 0·0258. (B) eGFR <60 mL/min per 1·73 m²: Q statistic=0·60, p=0·74, I^2=0%; eGFR 60 to <90 mL/min per 1·73 m²: Q statistic=0·51, p=0·78, I^2=0%; eGFR ≥90 mL/min per 1·73 m²: Q statistic=0·86, p=0·65, I^2=0%. The p value for risk reduction trend across subgroups was 0·0073. (C) eGFR <60 mL/min per 1·73 m²: Q statistic=2·76, p=0·25, I^2=27·5%; eGFR 60 to <90 mL/min per 1·73 m²: Q statistic=3·25, p=0·20, I^2=38·5%; eGFR ≥90 mL/min per 1·73 m²: Q statistic=1·29, p=0·53, I^2=0%. The p value for risk reduction trend across subgroups was 0·23. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. eGFR=estimated glomerular filtration rate. HR=hazard ratio. NA=not available. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

progression of renal disease was also equally robust in patients with and without atherosclerotic cardiovascular disease. However, an interaction between baseline renal function and the clinical benefit of SGLT2 inhibition was seen. Specifically, there was a lesser reduction in progression of renal disease but a greater reduction in hospitalisation for heart failure with SGLT2 inhibition in patients with worse baseline renal function.

Despite extensive exploratory analyses, the exact mechanisms of the salutary effects of SGLT2i remain unclear.[27] The reduction in glycated haemoglobin (HbA_{1c}) is 0·5–0·6%[28,29] and the data to date suggest that glucose control itself more clearly translates into reduction of microvascular rather than macrovascular complications.[30] Our data suggest that the renoprotective effects of SGLT2i coupled with the natriuresis they induce might largely explain the reduction in hospitalisation for heart failure.[31,32] Patients with lower eGFR at baseline are at an increased risk of hospitalisation for heart failure. Therefore, reno-protection and natriuresis induced by SGLT2i could be of particular benefit in this susceptible population. Reductions in both the progression of kidney disease and hospitalisation for heart failure and their attendant interventions and downstream complications might then reduce the risk of both cardiovascular and all-cause death. The beneficial effect on myocardial infarction remains a topic of active investigation.[27]

By and large the results were consistent between the three different trials of SGTL2i when analysed within similar patient subgroups. However, in patients with atherosclerotic cardiovascular disease, the effect of empagliflozin on cardiovascular death was more pronounced than that of canagliflozin or dapagliflozin, and an increased risk of amputations and fractures was only seen with canagliflozin. Although it is theoretically possible that drug-specific differences in effects exist within this class, other possibilities should be considered. Multiple differences were found in the patient characteristics in each trial that might explain the observed variations with regard to cardiovascular death, and subgroup analyses by one variable might not fully capture other important differences. For example, even within the subgroup of patients with atherosclerotic cardiovascular disease the rates of cardiovascular death ranged two-fold across the placebo groups of the three trials. A greater reduction in cardiovascular death might be seen in higher risk patients. With only data from one trial for each drug, play of chance is also possible. Additional trials and head-to-head comparisons would shed further light on this issue.

Overall, SGLT2i are well tolerated and generally safe drugs, although patients have an increased risk of mycotic genital infections,[33,34] which are usually easily managed and uncommonly recur.[35] SGLT2i do appear to increase the risk of diabetic ketoacidosis, but the rates were very low and risk can be reduced with proper patient education and vigilance.[36,37] Also, initial concerns about safety signals for stroke[38] were not supported in the present meta-analysis. An increased risk of amputation and fracture was seen only in one trial.[2]

These data suggest that SGLT2i should be considered in patients with type 2 diabetes regardless of presence of atherosclerotic cardiovascular disease or history of heart failure, given that they safely reduce HbA_{1c} and reduce the risk of hospitalisation for heart failure and progression of renal disease broadly across the spectrum of these patients. The reductions in risk of hospitalisation for heart failure and progression of renal disease will differ in magnitude based on baseline renal function, but are present throughout the range of renal function. Reductions in major adverse cardiovascular events and cardiovascular death can also be expected in patients with existing atherosclerotic cardiovascular disease. Patients with diabetes are a particularly susceptible patient cohort at increased risk of heart failure and renal disease.[39,40] Ongoing trials in populations with heart failure or kidney disease will clarify whether SGLT2i also exhibit beneficial effects in patients without type 2 diabetes.

We acknowledge several limitations of our study. We used aggregated study-level data rather than individual participant data. Additionally, the exact inclusion criteria and definitions of endpoints varied among the included trials, but only slightly. Lastly, baseline presence of established atherosclerotic cardiovascular disease and heart failure was investigator-reported in all trials and some patients might have had undiagnosed atherosclerotic cardiovascular disease or heart failure at baseline. It is also important to note for external generalisability that even patients with multiple risk factors in the included trials represent patients with typically long-standing type 2 diabetes.

In conclusion, SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that appear confined to patients with established atherosclerotic cardiovascular disease. However, robust reductions in hospitalisation for heart failure and progression of renal disease are seen regardless of baseline atherosclerotic risk category or a history of heart failure.

Contributors

TAZ contributed to study design, data collection, statistical analysis, data interpretation, and drafting of the manuscript. SDW and MPB contributed to study design, data collection, data interpretation, and critical review of the manuscript. KI and ELG contributed to statistical analysis and critical review of the manuscript. IR, OM, ETK, AC, RHMF, DLB, LAL, DKM, and JPHW contributed to data interpretation and critical review of the manuscript. MSS contributed to study design, data collection, statistical analysis, data interpretation, and critical review of the manuscript. MSS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

TAZ reports a research grant from Deutsche Forschungsgemeinschaft (ZE 1109/1–1), and grants to his institution from AstraZeneca, and grants from Bristol-Myers Squibb during the conduct of the study. SDW reports grants and personal fees from AstraZeneca and Bristol Myers Squibb during the conduct of the study. SDW also reports grants from Amgen and Sanofi Aventis, grants and personal fees from Arena,

Daiichi Sankyo, Eisai, Eli Lilly, and Janssen, grants, personal fees, and other from Merck, and personal fees from Aegerion, Allergan, Angelmed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, St Jude Medical, and Xoma outside of the submitted work. IR reports personal fees from AstraZeneca and Bristol-Myers Squibb during the conduct of the study. IR also reports personal fees from Boehringer Ingelheim, Concenter BioPharma—Silkim Ltd, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk Inc, Orgenesis, Pfizer, Sanofi, SmartZyme Innovation Ltd, Panaxia, FuturRx Ltd, Insuline Medical, Medial EarlySign Ltd, CameraEyes, Exscopia, Dermal Biomics Inc, Johnson & Johnson, Novartis Pharma AG, Teva, Glucome Ltd, and DarioHealth outside of the submitted work. MPB reports grants from Amgen, AstraZeneca, Merck, and Pfizer, and personal fees from Aralez, Amgen, AstraZeneca, Bayer, Janssen, Pfizer, and Sanofi during the conduct of the study. OM reports grants and personal fees from AstraZeneca and Bristol-Myers Squibb during the conduct of the study. OM also reports grants and personal fees from NovoNordisk and personal fees from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Jansen, and Novartis outside of the submitted work. ETK reports personal fees from AstraZeneca, Ono Pharmaceutical, Daiichi Sankyo, Bristol-Myers Squibb, and Tanabe-Mitsubishi Pharma outside the submitted work. AC reports personal fees from Novo Nordisk, Eli Lilly, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, and Glucome, and grants and personal fees from AstraZeneca outside of the submitted work. RHMF reports grants to his institution from AstraZeneca, DalCor, Boehringer, Pfizer, Jansen, and Sanofi outside the submitted work. DLB is on the Advisory Board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences, is on the Board of Directors for Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft, is the Chair of the American Heart Association Quality Oversight Committee, is on Data Monitoring Committees for Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute, received honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees). DLB reports other positions at Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), and VA CART Research and Publications Committee (Chair). DLB also reports funding from Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Eli Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company, and royalties from Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease). DLB is site co-investigator for Biotronik, Boston Scientific, St Jude Medical (now Abbott), and Svelte, and is a trustee of the American College of Cardiology. DLB also reports unfunded research with FlowCo, Merck, Novo Nordisk, PLx Pharma, and Takeda. LAL reports grants and personal fees from AstraZeneca during the conduct of the study. LAL also reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, personal fees from Servier, and grants from GlaxoSmithKline outside of the submitted work. DKM reports personal fees from AstraZeneca during the conduct of the study. DKM also reports personal fees from Boehringer Ingelheim, Janssen Research and Development LLC, Sanofi US, Merck Sharp and Dohme, Eli Lilly, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai Inc, Esperion, Metavant, and Pfizer outside of the submitted work. JPW reports personal fees and other from Brigham and Women's Hospital during the conduct of the study JPW also reports grants, personal fees, and consultancy fees paid to his institution from AstraZeneca, Novo Nordisk, and Takeda, personal fees and consultancy fees paid to his institution from Boehringer Ingelheim, Lilly, Janssen, Napp, Mundipharma, and Sanofi, and consultancy fees paid to his institution from Wilmington Healthcare outside of the submitted work. MSS reports grants and personal fees from Amgen, AstraZeneca, Intarcia, Janssen Research and Development, The Medicines Company, Medimmune, Merck, and Novartis, grants from Daiichi-Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Takeda, Abbott Laboratories, Bayer, Critical Diagnostics, Genzyme, Gilead, and Roche Diagnostics, and personal fees from Bristol-Myers Squibb, CVS Caremark, Dyrnamix, Esperion, Alnylam, Ionis, and MyoKardia outside of the submitted work. KI and ELG report grants to their institution from Abbott Laboratories, Amgen, AstraZeneca, Bayer, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, Gilead, GlaxoSmithKline, Intarcia, Janssen Research Development, the Medicines Company, MedImmune, Merck, Novartis, Pfizer, Poxel, Roche Diagnostics, and Takeda outside of the submitted work.

Acknowledgments

TAZ was supported by the Deutsche Forschungsgemeinschaft (ZE 1109/1–1).

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