



HAL
open science

Efficacy and safety of SGLT2 inhibitors with and without glucagon-like peptide 1 receptor agonists: a SMART-C collaborative meta-analysis of randomised controlled trials

Ellen Apperloo, Brendon L Neuen, Robert A Fletcher, Niels Jongs, Stefan D Anker, Deepak Bhatt, Javed Butler, David Cherney, William Herrington, Silvio Inzucchi, et al.

► **To cite this version:**

Ellen Apperloo, Brendon L Neuen, Robert A Fletcher, Niels Jongs, Stefan D Anker, et al.. Efficacy and safety of SGLT2 inhibitors with and without glucagon-like peptide 1 receptor agonists: a SMART-C collaborative meta-analysis of randomised controlled trials. *The Lancet. Diabetes & Endocrinology*, 2024, 12 (8), pp.545-557. 10.1016/S2213-8587(24)00155-4. hal-04682483

HAL Id: hal-04682483

<https://hal.univ-lorraine.fr/hal-04682483v1>

Submitted on 30 Aug 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Efficacy and safety of sodium glucose co-transporter 2 inhibitors with and without glucagon-like peptide-1 receptor agonists: A SMART-C collaborative meta-analysis of randomised controlled trials

Ellen Apperloo MD,^{*1} Brendon L Neuen PhD,^{2,3*} Robert A Fletcher MSc², Niels Jongs PhD¹, Prof Stefan D Anker MD,⁴ Prof Deepak L Bhatt MD,⁵ Prof Javed Butler MD,^{6,7} Prof David ZI Cherney PhD,⁸ Prof William G Herrington MD,⁹ Prof Silvio E Inzucchi MD,¹⁰ Prof Meg J Jardine PhD,^{2,11,12} Chih-Chin Liu PhD,¹³ Prof Kenneth W Mahaffey MD,¹⁴ Prof Darren K McGuire MD,¹⁵ Prof John JV McMurray MD,¹⁶ Prof Bruce Neal PhD,² Prof Milton Packer MD,¹⁷ Prof Vlado Perkovic PhD,² Prof Marc S Sabatine MD,^{18,19} Prof Scott D Solomon MD,¹⁹ Natalie Staplin PhD,⁹ Michael Szarek PhD,^{21,22,23} Muthiah Vaduganathan MD,¹⁹ Prof Christoph Wanner MD,²³ Prof David C Wheeler MD,²⁴ Prof Stephen D Wiviott MD,^{18,19} Prof Faiez Zannad MD,²⁵ Prof Hidde J.L. Heerspink PhD^{1,2}

*Contributed equally

Affiliations

1. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands.
2. The George Institute for Global Health, University of New South Wales, Sydney, Australia.
3. Department of Renal Medicine, Royal North Shore Hospital, Sydney, Australia.
4. Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.
5. Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
6. Baylor Scott and White Research Institute, Dallas, TX, USA.
7. Department of Medicine, University of Mississippi School of Medicine, Jackson, MS, USA.
8. Department of Medicine, Division of Nephrology, Toronto General Hospital, Ontario, Canada.
9. Renal Studies Group, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
10. Section of Endocrinology, Yale School of Medicine, New Haven, CT, USA.
11. NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia.
12. Department of Renal Medicine, Concord Repatriation General Hospital, Sydney, Australia
13. Merck & Co., Inc., Rahway, NJ, USA.
14. Stanford Center for Clinical Research (SCCR), Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA.
15. University of Texas Southwestern Medical Center and Parkland Health, Dallas, TX, USA.
16. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom.
17. Baylor University Medical Center, Dallas TX, USA and Imperial College, London United Kingdom.
18. TIMI Study Group.
19. Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
20. Division of Cardiology, University of Colorado School of Medicine, Aurora, CO, USA.

21. CPC Clinical Research, Aurora, CO, USA.
22. State University of New York, Downstate Health Sciences University, Brooklyn, NY, USA
23. Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center (CHFC), University Hospital, Würzburg, Germany.
24. Department of Renal Medicine, University College London, London, United Kingdom
25. Centre d'Investigations Cliniques Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Université de Lorraine, Nancy, France.

Running title: Effects of SGLT2i with and without GLP-1RA

Word count: 3,129

Tables and Figures: 1 table, 5 figures

Keywords: type 2 diabetes mellitus; cardiovascular outcomes; chronic kidney disease; heart failure; clinical trial.

Corresponding author:

Hiddo JL Heerspink
University Medical Center Groningen
Hanzeplein 1
9700 RB Groningen
The Netherlands
Tel: +31 50 3614071
E-mail: H.J.Lambers.Heerspink@umcg.nl

Abstract

Background

Sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) both improve cardiovascular and kidney outcomes in patients with type 2 diabetes. We sought to evaluate whether the benefits of SGLT2i are consistent in patients receiving and not receiving GLP-1RA.

Methods

We conducted a collaborative meta-analysis of trials included in the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, restricted to participants with diabetes.

Treatment effects from individual trials were obtained from Cox regression models and pooled using inverse variance weighted meta-analysis. Outcomes assessed included major adverse cardiovascular events ([MACE] myocardial infarction, stroke or cardiovascular death), hospitalisation for heart failure (HF) or cardiovascular death, CKD progression ($\geq 40\%$ decline in estimated glomerular filtration rate [eGFR], kidney failure or death due to kidney failure), as well as safety outcomes.

Results

Across 12 randomised, double-blind, placebo-controlled trials, 3,065/72,970 (4.0%) participants with diabetes were using GLP-1RA at baseline. SGLT2i reduced the risk of MACE in participants receiving and not receiving GLP-1RA (hazard ratio [HR] 0.81, 95% CI 0.63-1.03 and HR 0.90, 95% CI 0.86-0.94, respectively; P-heterogeneity=0.31). Effects on hospitalisation for HF or cardiovascular death (HR 0.76, 95% CI 0.57-1.01 and HR 0.78, 95% CI 0.74-0.82, respectively; P-heterogeneity=0.90) and CKD progression (HR 0.65, 95% CI 0.46-0.94 and HR 0.67, 95% CI 0.62-0.72, respectively; P-heterogeneity=0.81) were also consistent regardless of GLP-1RA use. Fewer serious adverse events occurred with SGLT2i

compared with placebo, irrespective of GLP-1RA use (relative risk [RR] 0.87, 95% CI 0.79-0.96 and RR 0.91, 95% CI 0.89-0.93; P-heterogeneity=0.41).

Interpretation

The effects of SGLT2i on cardiovascular and kidney outcomes are similar regardless of background use of GLP-1RA. These findings suggest independent effects of these evidence-based therapies and support clinical practice guidelines recommending the use of both these agents in combination to optimise cardiovascular and kidney metabolic outcomes.

Funding

National Health and Medical Research Council of Australia and the Ramaciotti Foundation.

RESEARCH IN CONTEXT

Evidence before this study

Multiple large-scale randomised trials have demonstrated that sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce the risk of cardiovascular events and improve chronic kidney disease (CKD) outcomes in patients with type 2 diabetes. Given the different mechanisms of action of these two classes of agents as well as key differences in their effects on a myriad of intermediates of cardiovascular and kidney risk (e.g. substantially greater effects on glycemia and body weight with GLP-1RA compared to SGLT2i), there has been considerable interest in using both SGLT2i and GLP-1RA in combination to reduce cardio-kidney-metabolic risk. Indeed, small, randomised trials of relatively short duration indicate that the combined use of SGLT2i and GLP-1RA improves cardiometabolic risk factors to a greater extent than either alone. However, there are few data on clinical outcomes. Because the event-driven randomised trials of each class of agents were conducted before the benefit of either was confirmed, background use of GLP-1RA in SGLT2i trials was too infrequent in any single trial to evaluate the effects of SGLT2i in patients receiving and not receiving GLP-1RA. To address this evidence gap, we conducted a collaborative meta-analysis of SGLT2i randomised, double-blind, placebo-controlled, event-driven outcome trials within the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. We aimed to assess the effects of SGLT2i on cardiovascular, kidney and safety outcomes in patients with diabetes receiving and not receiving GLP-1RA at baseline.

Added value of this study

With 72,970 participants with diabetes from 12 large-scale randomised trials, including 3,065 receiving GLP-1RA at baseline, this collaborative meta-analysis represents the largest and

most comprehensive assessment of the effects of SGLT2i on cardiovascular, kidney and safety outcomes in people with diabetes receiving and not receiving GLP-1RA.

Compared with placebo, SGLT2i reduced the risk of major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) by 11% and hospitalisation for HF or cardiovascular death by 23%, with consistent effects regardless of GLP-1RA use at baseline. SGLT2i also reduced the risk of CKD progression (defined as $\geq 40\%$ decline in eGFR, kidney failure or death due to kidney failure) by 33% and attenuated the annual rate of decline in kidney function, irrespective of GLP-1RA use at baseline. The effect of SGLT2i on key safety outcomes including serious adverse events, hypoglycaemia and volume depletion did not differ by baseline use of GLP-1RA (all P-heterogeneity > 0.10).

Implications of all the available evidence

Pooled subgroup data from the totality of the worldwide large-scale placebo-controlled SGLT2i trials suggest the effects of SGLT2i on cardiovascular, kidney and safety outcomes are likely to be similar in the types of patients prescribed a GLP-1RA and those not, irrespective of indication for use of the SGLT2i.

Introduction

Sodium glucose cotransporter 2 inhibitors (SGLT2i) reduce the risk of kidney failure, cardiovascular events, and death in patients with diabetes and those with heart failure (HF) or CKD, regardless of diabetes.¹ Consequently, consensus statements from professional diabetes, kidney and cardiovascular organisations recommend that SGLT2i be routinely offered to patients with type 2 diabetes with or at high risk of atherosclerotic cardiovascular disease (ASCVD), HF, or CKD.²⁻⁴ Results from multiple large-scale randomised trials have also shown that glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce the risk of cardiovascular events in people with type 2 diabetes.⁵ Therefore, prevailing type 2 diabetes treatment guidelines and society recommendations endorse an SGLT2i and/or GLP-1RA, independent of glycated haemoglobin considerations, for individuals with type 2 diabetes with or at high risk of ASCVD.⁶

The distinct mechanisms of action of these two classes of agents, their myriad of effects on intermediate markers of cardiometabolic risk that differ between the classes, and the different types of events prevented have led to considerable interest in using SGLT2i and GLP-1RA in combination to further reduce cardiorenal risk. For example, while SGLT2i have substantial benefits on incident or worsening HF and CKD progression, GLP-1RA may yield greater reductions in myocardial infarction and stroke.⁷ Guidelines therefore recognise the potential benefits of the combined use of both classes of agents.⁸

Since clinical trials of SGLT2i and GLP-1RA were conducted during approximately the same time period before the benefits of either therapy had been confirmed, relatively few participants in SGLT2i outcome trials were receiving a GLP-1RA. As a result, individual trials did not have sufficient power to examine the effects of SGLT2i on clinical outcomes in

patients receiving or not receiving GLP-1RA. Accordingly, we conducted a meta-analysis of 12 completed trials enrolling patients with diabetes with or at high risk of ASCVD, HF or CKD to examine and compare the efficacy and safety of SGLT2i with and without use of GLP-1RA at baseline in patients with diabetes.

Methods

The SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) comprises the completed randomised, double-blind, placebo-controlled, event-driven trials that assessed the effects of an SGLT2i (including SGLT1/2i) on a primary clinical outcome in adults (aged ≥ 18 years), restricted to trials with more than 500 participants in each arm and follow-up of at least 6 months. SMART-C is led by an academic steering committee featuring key representatives from each of the collaborating trials. Analyses of interest are conducted independently within each trial dataset by the relevant statistical team using individual participant data, with results pooled across trials using two-stage meta-analysis.

Within the SMART-C framework, we conducted a collaborative meta-analysis using data from trials participating in SMART-C that enrolled patients with diabetes with or at high risk for ASCVD, HF or CKD. These trials were identified through previously published SMART-C systematic reviews and meta-analyses.^{1,9}

Included trials

The present meta-analysis included 12 trials participating in SMART-C with the analysis cohort restricted to trials exclusively enrolling participants diabetes and participants with diabetes enrolled in the HF and CKD trials: EMPA-REG OUTCOME,¹⁰ the CANVAS Program,¹¹ DECLARE-TIMI 58,¹² VERTIS-CV,¹³ CREDENCE,¹⁴ DAPA-CKD,¹⁵

SCORED,¹⁶ EMPA-KIDNEY,¹⁷ DAPA-HF,¹⁸ EMPEROR-Reduced,¹⁹ EMPEROR-Preserved,²⁰ and DELIVER.²¹ All trials excluded participants with type 1 diabetes except for EMPA-KIDNEY, which included 68 of these individuals. We excluded SOLOIST-WHF from this meta-analysis as this trial recruited participants with recent acute decompensated HF followed for a short duration that precluded the assessment of effects on CKD progression.²² All trials were approved by relevant ethics committees, and all participants provided written informed consent for research participation.

Outcomes

The main cardiovascular outcomes assessed were (1) major adverse cardiovascular events, defined as a composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death; and (2) hospitalisation for HF or cardiovascular death. Kidney outcomes assessed included (1) a composite kidney outcome using a standardised definition of percentage decline in eGFR and kidney failure across the trials: $\geq 40\%$ decline in estimated glomerular filtration rate (eGFR), kidney failure (eGFR < 15 mL/min/1.73m², chronic dialysis or kidney transplantation), or death due to kidney failure; and (2) rate of change in eGFR over time (eGFR slope), both total (calculated from the randomisation visit) and chronic (from the first on-treatment eGFR measurement after randomisation).

All cardiovascular outcomes were adjudicated by expert blinded adjudication committees.

We evaluated safety outcomes that could be affected by combination treatment with SGLT2i and GLP-1RA: any serious adverse event, adverse events due to hypoglycaemia, or adverse events due to volume depletion. Because adverse event reporting differed across the trials (i.e. some trials collected serious and non-serious adverse events, whilst others only collected serious events), we primarily focused on serious adverse events, since this outcome was

available in all trials using common serious adverse event criteria for reporting, but also assessed investigator-reported hypoglycaemia and volume depletion as reported in each trial individually.

Data analysis

We undertook a two-stage meta-analysis using harmonised analytical approaches and endpoint definitions across the individual trials as previously described. Investigators from each trial analysed treatment effects and safety events within each trial using individual participant data. In trials that included patients with and without diabetes, analyses were restricted to patients with diabetes, since GLP-1RA were only indicated for use in these individuals at the time the trials were conducted. We compared characteristics of participants receiving and not receiving GLP-1RA at baseline across the three studied populations (diabetes with or at high risk for ASCVD, HF, and CKD). We calculated pooled weighted mean and standard deviations for continuous variables using the weighted inverse variance method and pooled categorical variables across trials by treatment allocation and baseline GLP-1RA use.

Treatment effects on efficacy outcomes by baseline use of GLP-1RA in each trial were obtained from Cox regression models expressed as hazard ratios (HR) with corresponding 95% confidence intervals (CI), with covariate stratification as prespecified in individual trials and without adjustment for differences in characteristics by baseline GLP-1RA use. For safety outcomes, we obtained HR and 95% CI or used risk ratios based on the number of participants experiencing an event where time-to-event data were not available. Summary effect estimates, overall and stratified by trial population and baseline GLP-1RA use, were obtained by pooling log-transformed hazard and risk ratios using inverse-variance weighted

averages. Heterogeneity of treatment effects by baseline use of GLP-1RA was then assessed using p values for heterogeneity obtained from random-effects meta-regression with restricted maximum likelihood.

A two-slope mixed effects linear spline model with unstructured covariance matrix was used for analyses of eGFR slope.^{14,15,17} Chronic and total eGFR slope were defined based on this two-slope model, with a knot generally placed at the first post-randomisation eGFR value in each trial, typically within the first 8 weeks after randomisation. eGFR slope analyses were restricted to on-treatment eGFR values because of the increase in eGFR after SGLT2i discontinuation that could theoretically affect eGFR slope estimates. Models included two-way and three-way interaction terms between randomised treatment, GLP-1RA use, and two-slope linear spline in follow-up time to account for differences between GLP-1RA subgroups in the effect of the treatment on the mean eGFR trajectories. The modelled estimates of total and chronic GFR slope, expressed as the annual rate of change in eGFR (mL/min/1.73m²/year) were then meta-analysed across all trials using the same approach as described above. All trial-level meta-analyses were performed with R version 4.3.1 (R-project, Vienna, Austria).

Results

We included participants from 12 randomised trials of whom 72,970/89,183 (81.8%) had diabetes. Details of these 12 trials are summarised in Table S1, appendix p2. Among the 72,970 participants with diabetes, 3,065 (4.0%) were using GLP-1RA at baseline. GLP-1RA use varied across all trials with a range of 2.8% to 4.4% in the ASCVD trials, 4.2% to 6.0% in the HF trials, and 1.0% to 2.2% in the CKD progression trials (Table S1, appendix p2). Across the studied populations, characteristics of participants receiving and not receiving

GLP-1RA were similar in many aspects (**Table 1**). However, those receiving GLP-1RA were typically more likely to be male, have a higher body mass index, and be receiving insulin (**Table 1**).

Across all 12 trials, 7,187 (9.8%) participants experienced a MACE event, including 268 (8.7%) and 6,919 (9.9%) who were receiving a GLP-1RA at baseline, respectively. The incidence of MACE was highest in the HF trials, driven by cardiovascular death (**Figure 1**). The effect of SGLT2i on MACE (HR 0.89, 95% CI 0.85-0.94) was consistent in participants receiving and not receiving a GLP-1RA (HR 0.81, 95% CI 0.63-1.03 and HR 0.90, 95% CI 0.86-0.94, respectively; P-heterogeneity=0.31; **Figure 1**).

Overall, 6,260 (8.6%) participants were hospitalised for HF or died due to cardiovascular disease, of whom 211 (6.9%) and 6,049 (8.6%) were receiving and not receiving a GLP-1RA at baseline, respectively. The incidence of hospitalisation for HF or cardiovascular death was highest in the HF trials (**Figure 2**). The effect of SGLT2i on hospitalisation for HF or cardiovascular death (HR 0.77, 95% CI 0.74-0.81) was consistent in participants receiving GLP-1RA (HR 0.76, 95% CI 0.57-1.01) and those not receiving GLP-1RA (HR 0.78, 95% CI 0.74-0.82) (P-heterogeneity 0.90; **Figure 2**). The effect of SGLT2i on hospitalisation for HF was similarly consistent regardless of GLP-1RA use at baseline (HR 0.73, 95% CI 0.50-1.06 and HR 0.70, 95% CI 0.65-0.75, respectively; P-heterogeneity=0.83; **Figure 2**) as was the effect on cardiovascular death (HR 0.77, 95% CI 0.50-1.20 and HR 0.86, 95% CI 0.81-0.92, respectively; P-heterogeneity=0.62; **Figure 2**).

The incidence of the composite kidney outcome was highest in the CKD trials, with 3,294 (4.5%) participants experiencing CKD progression, including 130 (4.4%) and 3,164 (4.5%)

who were receiving and not receiving a GLP-1RA at baseline, respectively (**Figure 3**). SGLT2i reduced the risk of CKD progression (HR 0.67, 95% CI 0.62-0.72) in participants receiving and not receiving GLP-1RA (HR 0.65, 95% CI 0.46-0.94 and HR 0.67, 95% CI 0.62-0.72, respectively; P-heterogeneity=0.81; **Figure 3**).

The consistent benefits of SGLT2i on clinical outcomes in participants being prescribed or not being prescribed a GLP-1 RA at baseline were observed across the studied populations. Participants with type 1 diabetes comprised less than 0.1% of the no GLP-1RA subgroup, with none receiving GLP-1RA at baseline. As a result, treatment effects estimates were identical excluding these individuals. Treatment effects on cardiovascular and kidney outcomes by individual trial are summarised in Tables S2-4, appendix p3-6..

SGLT2i attenuated the annual rate of decline in eGFR as measured by chronic and total eGFR slope, regardless of baseline GLP-1RA use (**Figure 4**). Chronic eGFR slope was improved by 1.32 [95% CI 0.98 to 1.66] mL/min/1.73m²/year in participants receiving GLP-1RA and by 1.21 [95% CI 1.14 to 1.28] mL/min/1.73m²/year) in participants not receiving GLP-1RA at baseline (P-heterogeneity=0.55; **Figure 4**). In relative terms, this corresponded to a 57% (95% CI 54-60) improvement in chronic slope, which was observed similarly in participants receiving and not receiving GLP-1RA at baseline (60% [95% CI 45-76] and 57% [95% CI 53-60], respectively; P-heterogeneity=0.43; **Figure 4**). Similar results were observed for total eGFR slope in participants receiving and not receiving GLP-1RA at baseline (absolute difference 0.67 [95% CI 0.41 to 0.94] mL/min/1.73m²/year and 0.66 [95% CI 0.61 to 0.71] mL/min/1.73m²/year, respectively; P-heterogeneity=0.92; **Figure 4**). This translated into a 30% (95% CI 28-32) relative improvement in total slope overall, which was again observed regardless of baseline GLP-1RA use (32% [95% CI 19-44] and 30% [95% CI

28-32], respectively; P-heterogeneity=0.82; **Figure 4**). Treatment effects on eGFR slope in individual trials are summarised in Table S5, appendix p7-8.

A total of 5,822 (8.0%) participants died during follow up, of whom 160 (5.3%) and 5,662 (8.1%) were receiving and not receiving GLP-1RA at baseline, respectively. The effect of SGLT2i on all-cause mortality (HR 0.89, 95% CI 0.84-0.93) was consistent regardless of GLP-1RA use at baseline (HR 0.82, 95% CI 0.60-1.13 and HR 0.89, 95% CI 0.84-0.94, respectively; P-heterogeneity=0.63; **Figure 5**).

Fewer serious adverse events were observed with SGLT2i compared with placebo, regardless of GLP-1RA use at baseline (RR 0.87, 95% CI 0.79-0.96 and RR 0.91, 95% CI 0.89-0.93; P-heterogeneity=0.41; **Figure 5**). Overall, SGLT2i did not increase the risk of hypoglycaemia (RR 0.96; 95% CI 0.88-1.04), a lack of effect that was consistent by baseline use of GLP-1RA (P-heterogeneity=0.13). SGLT2i increased the risk of volume depletion (RR 1.21, 95% CI 1.10-1.32), an effect which was also consistent irrespective of GLP-1RA use (P-heterogeneity=0.55). Treatment effects on safety outcomes by individual trial are summarised in Table S6, appendix p9.

Discussion

This collaborative meta-analysis of 12 large placebo-controlled outcome trials of SGLT2i involving more than 70,000 participants with diabetes, of whom more than 3,000 were receiving a GLP-1RA at baseline, represents the largest and most comprehensive evaluation of the effects of SGLT2i on clinical outcomes, with and without GLP-1RA use. The smaller proportion of participants receiving GLP-1RA at baseline is reflected in the wider confidence intervals for treatment effects in this subgroup. Notwithstanding the greater imprecision, the

data (including GFR slope) clearly indicate that reductions in cardiovascular, kidney and mortality outcomes with SGLT2i are consistent regardless of GLP-1RA use at baseline. Additionally, the safety and tolerability of SGLT2i appeared consistent in those receiving and not receiving a GLP-1RA. These data provide support for the combined use of SGLT2i and GLP-1RA to optimise cardiovascular and kidney outcomes for patients with type 2 diabetes.

Contemporary guidelines and society consensus recommendations recognise the benefits of combination treatment with SGLT2i and GLP-1RA.^{2,3,6} At the same time, the rationale for their combined use has been largely based on their different mechanisms of action and greater benefits observed on cardiometabolic risk factors observed in small trials of relatively short duration, although results have not always been consistent.²³⁻²⁶ Our findings are consistent with current clinical practice guideline from major diabetes, cardiovascular and nephrology organisations recommending the preferential use of both SGLT2i and GLP-1RA in people with type 2 diabetes having an indication for each therapy.

The consistency of SGLT2i treatment effects by baseline GLP-1RA use across the studied populations is of considerable importance, given the rapidly expanding cardiovascular indications for GLP-1RA therapy, including in people without diabetes. The SELECT and STEP-HF trials reported that the GLP-1RA semaglutide reduces cardiovascular events in individuals with obesity and established cardiovascular disease and improves functional status in patients with HF without diabetes, respectively.^{27,28} Thus, combined use of SGLT2i and GLP-1RA across the spectrum of cardio-kidney-metabolic diseases is likely to increase substantially. Clinicians and patients may therefore be reassured by the finding that SGLT2i appear generally well tolerated in patients receiving and not receiving GLP-1RA across a broad population of underlying cardio-kidney-metabolic diseases.

The cardiovascular and kidney protective effects of SGLT2i and GLP-1RA are likely be explained through distinct mechanistic pathways. Both classes of agents reduce cardiometabolic risk factors such as glycated haemoglobin, body weight, blood pressure, and albuminuria, although the effects of GLP-1RA on glycemia and body weight are substantially greater than SGLT2i. However, these effects are unlikely to fully explain the magnitude of benefit observed on clinical outcomes for either class.^{29,30} While SGLT2i reduce measures of glomerular pressure which may contribute to their kidney protective effects,^{31,32} effects on tubular energy expenditure, nutrient deprivation signalling, autophagy and inflammation are also likely to be important.³³ In contrast, GLP-1RA act to stabilise atherosclerotic plaques as shown in various experimental and clinical studies, and suppresses pro-inflammatory and pro-fibrotic pathways, with the latter potentially contributing to kidney benefits.³⁴ Thus these two classes of agents have distinct domains, clinically and biologically, such that the beneficial cardiovascular and kidney effects are likely to be complementary.

The clear and separate benefit of SGLT2i on the composite kidney endpoint in patients receiving and not receiving GLP-1RA is of particular relevance in the context of the FLOW trial, the only dedicated CKD progression trial of a GLP-1RA in patients with type 2 diabetes. In a company announcement, the FLOW trial reported a statistically significant reduction in kidney disease progression as well as cardiovascular and kidney death of 24% with semaglutide compared to placebo (<https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167028>). Our finding that SGLT2i reduced the risk of the composite kidney endpoint regardless of GLP-1RA use is strengthened by the analyses of eGFR slope, a validated surrogate outcome for CKD progression,³⁵ which provide substantially increased power to examine treatment effects

across subgroups of patients. The consistent benefits on chronic and total slope and the composite kidney endpoint in patients receiving and not receiving GLP-1RA provides the strongest evidence yet for the efficacy of SGLT2i, regardless of GLP-1RA, to reduce the risk of kidney failure in patients with type 2 diabetes.

While the benefits of SGLT2i and GLP-1RA are well established, the uptake of these therapies remains suboptimal across most healthcare settings worldwide.^{36,37} Ensuring equitable access to SGLT2i and GLP-1RA will be important to ensure those who are likely to benefit most from combination cardio-kidney-metabolic therapies are able to receive them, with cost remaining a major barrier to access across many jurisdictions. Economic evaluation of the combined use of SGLT2i and GLP-1RA across different healthcare settings may also provide valuable information. Finally, understanding and addressing barriers to widespread implementation will be critical to realising the full potential of these transformative therapies.

There are some limitations to acknowledge when interpreting these findings. The number of outcomes among the patients using GLP-1RA was much lower than those not using a GLP-1RA. As a result, the number of composite kidney endpoints in participants receiving a GLP-1RA was modest. However, the use of eGFR slope provided an opportunity to evaluate the consistency of effects on CKD progression, with findings that were entirely consistent with the composite endpoint. The estimated treatment effects were not derived from one-stage meta-analysis. However in lieu of pooled individual participant data, our use of a harmonised analytical approach and outcome definitions within a two-stage meta-analysis framework is consistent with the approach taken with other large cardio-metabolic consortia,^{35,38} and an important strength of this work. We did not evaluate whether the effects of GLP-1RA on clinical outcomes are similar with and without SGLT2i, although subgroup data from two

large GLP-1RA trials suggest that the effects of GLP-1RA are similar regardless of SGLT2i use.³⁹ We only analysed treatment effects by baseline GLP-1RA use without the ability to perform time-updated analyses based on GLP-1RA use at any time point, although such analyses are introduce potential bias by way of post-randomisation subgroups. Our analyses group all GLP-1RA together, however there may be important differences in efficacy and/or safety among different agents within the class. Finally, this work is not a definitive randomised test of whether effects are independent and additive and is unable to address the question of combined initiation of GLP-1RA and SGLT2i. Direct support for additive benefits of combination therapy with both drug classes_would require a dedicated clinical outcome trial.

In summary, the effects of SGLT2i in reducing cardiovascular and kidney outcomes are similar in patients receiving and not receiving GLP-1RA at baseline. These findings suggest independent effects of these evidence-based therapies and support clinical practice guidelines recommending the use of both these agents to optimise cardiovascular and kidney prognosis.

Table 1. Characteristics of participants stratified by study population and use of GLP-1RA at baseline.

	GLP-1RA yes		GLP-1RA no	
	SGLT2i	Placebo	SGLT2i	Placebo
Diabetes at high risk for ASCVD trials				
Participants, n	937	693	23626	17312
Age, years (SD)	63.0 (7.1)	62.8 (6.8)	63.7 (7.8)	63.8 (7.6)
Male, n (%)	668 (71.3)	486 (70.1)	15704 (66.5)	11174 (64.5)
Female, n (%)	269 (28.7)	207 (29.9)	7922 (33.5)	6138 (35.5)
History of CV disease, n (%)	602 (64.2)	410 (59.2)	16784 (71.0)	11044 (63.8)
History of heart failure, n (%)	85 (9.1)	58 (8.4)	3318 (14.0)	2388 (13.8)
Systolic BP, mmHg (SD)	132.8 (15.5)	133.8 (15.2)	135.0 (15.5)	135.1 (15.6)
Body mass index, kg/m ² (SD)	34.9 (5.8)	35.0 (6.8)	31.5 (5.7)	31.5 (5.8)
HbA1c, % (SD), mmol/mol	8.2 (1.0) 66.1	8.1 (1.0) 65.0	8.2 (1.0) 66.1	8.2 (1.1) 66.1
eGFR, mL/min/1.73m ² (SD)	79.3 (20.5)	77.5 (19.8)	79.3 (19.8)	78.9 (19.4)
uACR ≥30 mg/g, n/N (%)	312/925 (33.7)	228/684 (33.3)	8034/23486 (34.2)	5680/17156 (33.1)
RAS blockade use, n (%)	807 (86.1)	583 (84.1)	19063 (80.7)	13977 (80.7)
Insulin use, n (%)	477 (50.9)	349 (50.4)	10788 (45.7)	7781 (44.9)
Chronic kidney disease trials				
Participants, n	635	640	9839	9817
Age, years (SD)	66.0 (8.8)	65.5 (9.1)	66.0 (9.4)	66.3 (9.3)
Male, n (%)	418 (65.8)	406 (63.4)	5954 (60.5)	5944 (60.5)
Female, n (%)	217 (34.2)	234 (36.6)	3885 (39.5)	3873 (39.5)
History of CV disease, n (%)	296 (46.6)	273 (42.7)	4560 (46.3)	4621 (47.1)
History of heart failure, n (%)	116 (18.3)	112 (17.5)	2248 (22.8)	2252 (22.9)
Systolic BP, mmHg (SD)	138.0 (17.2)	137.4 (17.5)	139.1 (16.9)	139.4 (16.9)
Body mass index, kg/m ² (SD)	35.4 (6.8)	35.7 (7.6)	31.2 (6.4)	31.2 (6.3)
HbA1c, % (SD), mmol/mol	8.1 (2.2) 65.0	8.2 (2.0) 66.1	8.2 (2.0) 66.1	8.2 (2.0) 66.1
eGFR, mL/min/1.73m ² (SD)	44.4 (13.5)	43.0 (13.7)	43.8 (14.4)	43.6 (14.4)
uACR ≥30 mg/g, n (%)	477 (75.1)	463 (72.3)	7804 (79.3)	7799 (79.4)
RAS blockade use, n (%)	568 (89.4)	583 (91.1)	9057 (92.1)	8960 (91.3)
Insulin use, n (%)	454 (71.5)	496 (77.5)	6024 (61.2)	5893 (60.0)
Heart failure trials				
Participants, n	88	72	4781	4798
Age, years (SD)	67.7 (8.9)	70.4 (9.1)	69.0 (9.7)	69.0 (9.7)
Male, n (%)	65 (73.9)	44 (61.1)	3166 (66.2)	3125 (65.1)
Female, n (%)	23 (26.1)	28 (38.9)	1615 (33.8)	1673 (34.9)
History of CV disease, n (%)	62 (70.5)	56 (77.8)	3213 (67.2)	3186 (66.4)
History of heart failure, n (%)	88 (100.0)	72 (100.0)	4781 (100.0)	4798 (100.0)
Systolic BP, mmHg (SD)	127.9 (17.4)	126.9 (16.7)	127.4 (16.5)	127.5 (16.6)
Body mass index, kg/m ² (SD)	31.3 (6.8)	31.3 (7.1)	29.9 (6.0)	30.0 (6.0)

HbA1c, % (SD), mmol/mol	8.0 (1.5) 63.9	7.5 (1.7) 58.5	7.4 (1.6) 57.4	7.4 (1.6) 57.4
eGFR, mL/min/1.73m ² (SD)	53.3 (20.3)	56.2 (20.2)	60.8 (20.4)	61.0 (20.4)
uACR ≥30 mg/g, n/N (%)*	26/43 (60.5)	14/35 (40.0)	1223/2350 (52.0)	1201/2366 (50.8)
RAS blockade use, n (%)	67 (76.1)	56 (77.8)	4119 (86.2)	4082 (85.1)
Insulin use, n (%)	53 (60.2)	44 (61.1)	1286 (27.4)	1333 (28.2)

*Only available in EMPEROR-Reduced and EMPEROR-Preserved. GLP-1RA: glucagon-like peptide-1 receptor agonists; SGLT2i: sodium glucose cotransporter 2 inhibitors; ASCVD: atherosclerotic cardiovascular disease; CV: cardiovascular; BP: blood pressure; HbA1c: glycated haemoglobin; eGFR: estimated glomerular filtration rate; uACR: urine albumin:creatinine ratio

FIGURE LEGEND

Figure 1. Effect of SGLT2 inhibitors on major adverse cardiovascular events

(myocardial infarction, stroke or cardiovascular death) with and without use of GLP-1 receptor agonists at baseline.

Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

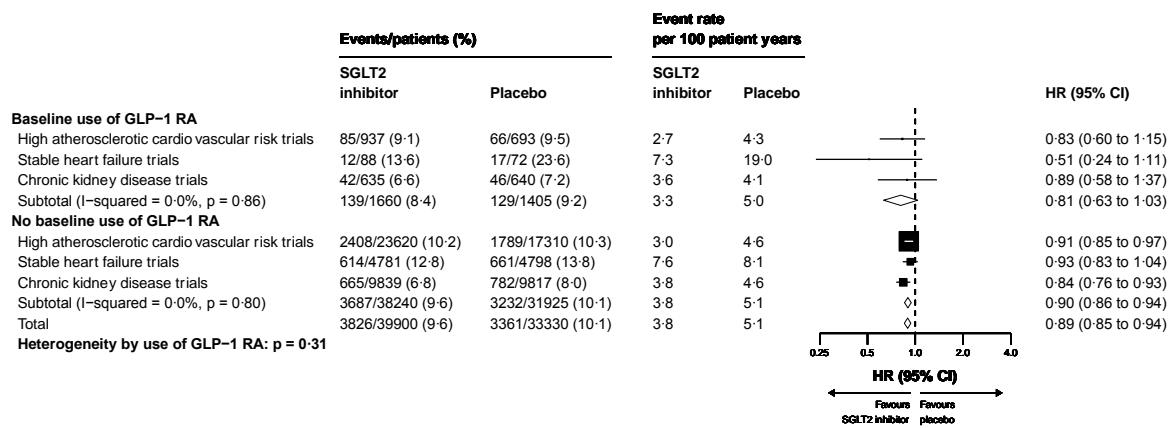


Figure 2. Effect of SGLT2 inhibitors on (A) hospitalisation for heart failure or cardiovascular death, (B) hospitalisation for heart failure and (C) cardiovascular death, with and without use of GLP-1 receptor agonists at baseline.

Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

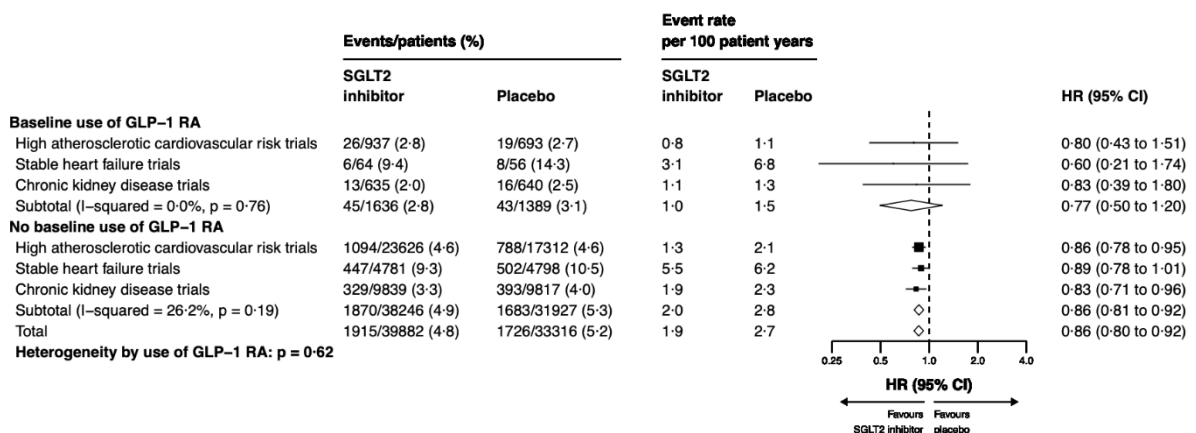
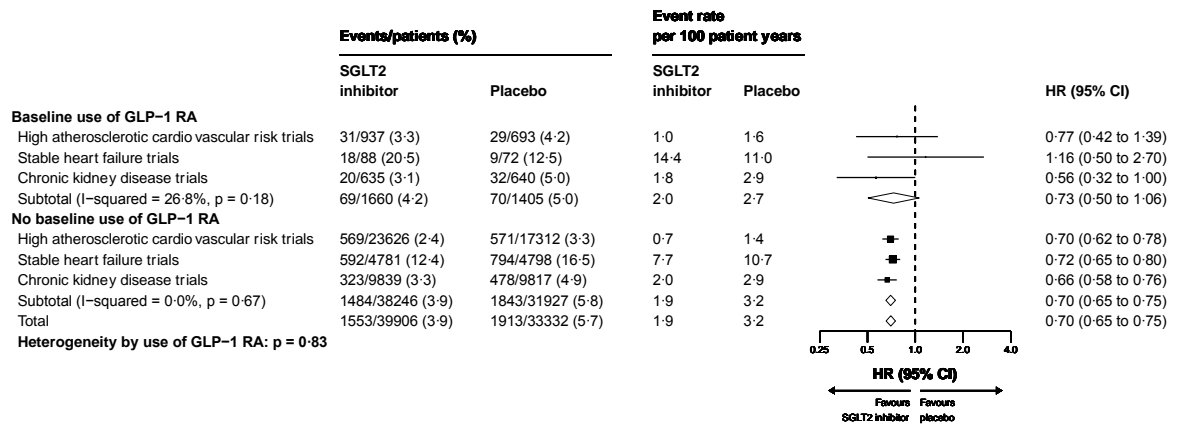
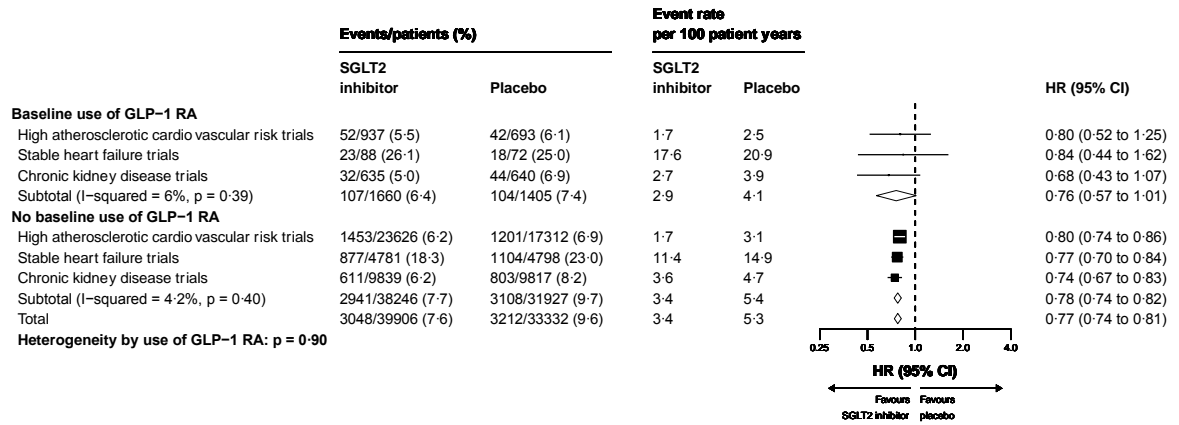


Figure 3. Effect of SGLT2 inhibitors on chronic kidney disease progression ($\geq 40\%$ decline in estimated glomerular filtration rate, kidney failure or death due to kidney failure) with and without use of GLP-1 receptor agonists at baseline.

Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

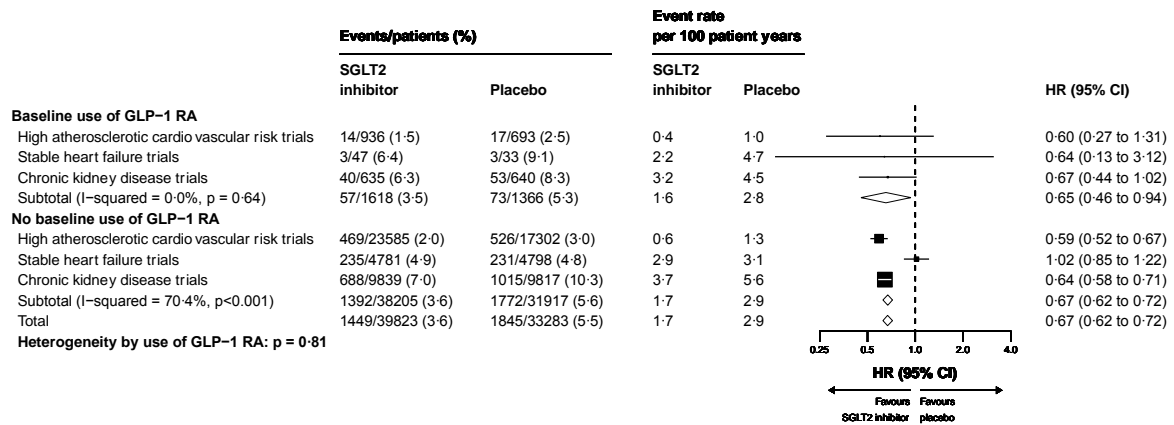


Figure 4. Effects of SGLT2 inhibitors on (A) chronic eGFR slope and (B) total eGFR slope with and without use of GLP-1 receptor agonists at baseline.

Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; eGFR: estimated glomerular filtration rate; CI: confidence interval.

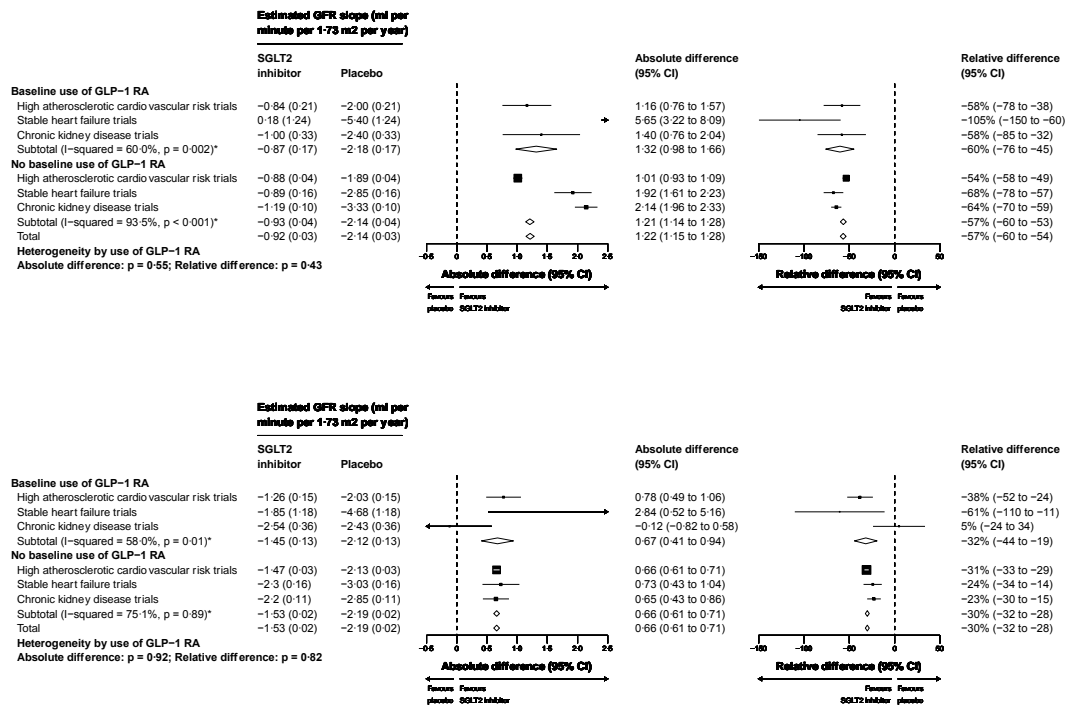
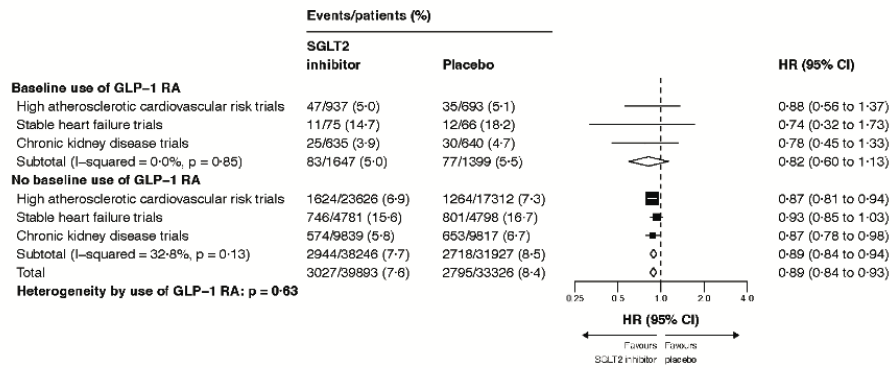


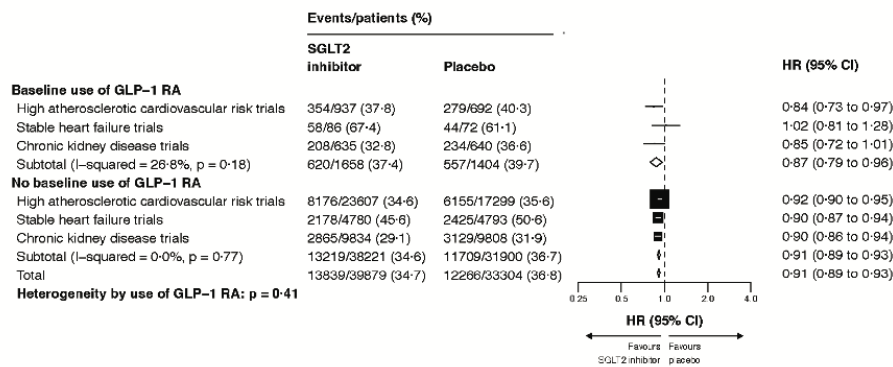
Figure 5. Effects of SGLT2 inhibitors on (A) all-cause mortality. (B) serious adverse events, (C) hypoglycaemia and (D) volume depletion, with and without use of GLP-1 receptor agonists at baseline.

Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

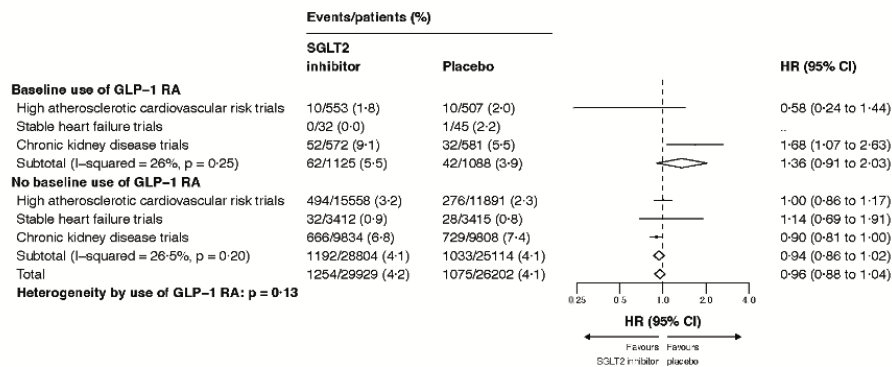
A All-cause mortality



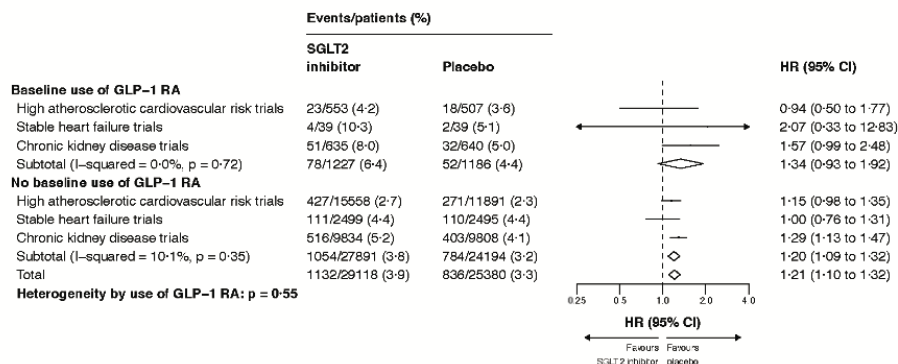
B Serious adverse events



C Hypoglycaemia



D Volume depletion



Acknowledgements

Funding

EMPA-REG Outcome, EMPEROR-Reduced, EMPEROR-Preserved and EMPA-KIDNEY were funded by Boehringer Ingelheim. The CANVAS Program and CREDENCE were funded by Janssen Research & Development, LLC. DECLARE-TIMI 58, DAPA-HF, DAPA-CKD and DELIVER were funded by AstraZeneca. SCORED was funded initially by Sanofi and then by Lexicon Pharmaceuticals. VERTIS CV was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, in collaboration with Pfizer Inc.

SMART-C is partly supported through an Australian National Health and Medical Research Council Emerging Leader Investigator Grant (grant number 2026621) and a Ramaciotti Foundation Health Investment Grant (grant number 2023HIG69), both awarded to Dr Neuen. The funders had no role in the writing of the manuscript or decision to submit for publication.

Prior Presentations

Parts of this work were presented at the American College of Cardiology 73rd Scientific Sessions in Atlanta, USA on 7th April 2024 and the European Renal Association Congress on 24th May 2024.

Contributors

BLN and HJLH conceived the meta-analysis and developed its design with EA, RF, and NJ. SI and CW provided data from EMPA-REG OUTCOME. BN, VP, MJJ and KWM provided data from the CANVAS Program and CREDENCE. SDW and MSS provided data from DECLARE-TIMI 58. DZIC, CCL and DKM and provided data from VERTIS. DCW and HJLH provided data from DAPA-CKD. JJVM provided data from DAPA-HF. DLB and MS

provided data from SCORED. SDA, JB, MP and FZ provided data from EMPEROR-Reduced and EMPEROR-Preserved. SDS and MV provided data from DELIVER. WGH and NS provided data from EMPA-KIDNEY. Data extraction and preparation was performed by EA and RAF. Statistical analyses were done by RAF. EA, BLN and HJLH wrote the first draft of the manuscript. All authors contributed to data interpretation and manuscript revisions. All authors had access to all the data. BLN, EA, RAF and HJLH accessed and verified the data. EA, BLN and HJLH take final responsibility for the decision to submit for publication.

Data sharing

Detailed information on data sharing policies for individual trials included within SMART-C are available in the primary publication of each relevant trial.

Disclosures

Dr. Neuen reports fees for travel support, advisory boards, scientific presentations, and steering committee roles from AstraZeneca, Alexion, Bayer, Boehringer and Ingelheim, Cambridge Healthcare Research, Cornerstone Medical Education, Janssen, the limbic, Medscape, Novo Nordisk and Traverre Therapeutics with all honoraria paid to The George Institute for Global Health.

Mr Fletcher has received studentship awards from the HDR-UK-Turing Wellcome Programme in Health Data Science.

Dr. Anker reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics,

Occlutech, Pfizer, Regeneron, Repairon, Scirent, Sensible Medical, Servier, Vectorious, and V-Wave. Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

Dr. Bhatt discloses the following relationships - Advisory Board: Angiowave, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Stasys; Board of Directors: American Heart Association New York City, Angiowave (stock options), Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock); Consultant: Broadview Ventures, GlaxoSmithKline, Hims, SFJ, Youngene; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering

committees), CSL Behring (AHA lecture), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Alnylam, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Otsuka, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo. Dr. Butler reports consulting fees from Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific,

Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pharmacosmos, Pharmain, Pfizer, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll.

Dr. Cherney has received honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL-Behring, Otsuka, Novartis, Youngene, Lexicon and Novo-Nordisk and received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL-Behring and Novo-Nordisk.

Dr. Herrington reports funding from the UK Medical Research Council, Kidney Research UK and Health Data Research UK; and grants to the University of Oxford from Boehringer Ingelheim and Eli Lilly for the EMPA-KIDNEY trial.

Dr. Inzucchi reports serving as an advisor or consultant to Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Merck, Pfizer, and Bayer, and delivering lectures sponsored by Boehringer Ingelheim and AstraZeneca.

Dr. Jardine is supported by an NHMRC Investigator Grant; is responsible for research projects that have received funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, and MSD; has received fees for advisory, steering committee and/or scientific presentations from Akebia, Amgen, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, Cestas Linx, Chinook, CSL, Janssen, Medscape, MSD, Occuryx, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution.

Dr. Liu is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Dr. Mahaffey has received research support from Afferent, Amgen, Apple Inc, AstraZeneca, Cardiva Medical Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health, Novartis, Sanofi, St. Jude, and Tenax, and has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco.

Dr. McGuire has received honoraria for trial leadership from Boehringer Ingelheim, Pfizer, AstraZeneca, Novo Nordisk, Esperion, Lilly USA, CSL Behring, Eidos and NewAmsterdam; and honoraria for consultancy from Lilly USA, Boehringer Ingelheim, , Merck & Co., Inc., Rahway, NJ, USA, Novo Nordisk, Applied Therapeutics, CSL Behring, Bayer, Altimune, Intercept, Alynlam, and Pfizer.

Dr. McMurray has received payments through Glasgow University from work on clinical trials, consulting, and other activities from Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis; has received personal consultancy fees from Alynlam Pharma, Bayer, BMS, George Clinical PTY Ltd, Ionis Pharma, Novartis, Regeneron Pharma, and River 2 Renal Corporation; has received personal lecture fees from Abbott, Alkem Metabolics, AstraZeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharma. Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharma. Ltd, Lupin Pharma, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharma., The Corpus, Translation Research Group, and Translational Medicine Academy; and he is a director of Global Clinical Trial Partners Ltd. Dr Nunez has received personal fees from or is on the advisory boards for

Alleviant, AstraZeneca, Boehringer Ingelheim, Bayer, Cytokinetics, Novartis, Novo Nordisk, Rovi, and Vifor Pharma.

Dr. Neal has received grants for CANVAS and CREDENCE, advisory board, honoraria, travel reimbursement all from Janssen and all paid to his institution. He has received research support from the Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen, and has served on advisory boards and/or has had involvement in continuing medical education programs for Janssen, with any consultancy, honoraria, or travel support paid to his institution. He also notes institutional relationships with AbbVie, Actelion and Janssen.

Dr. Packer reports consulting to 89bio, Abbvie, Altimune, Alnylam, Amarin, Amgen, Ardelyx, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Medtronic, MSD, Novartis, Reata, Relypsa, and Salamandra.

Dr. Perkovic serves as a Board Director for St. Vincent's Health Australia, George Clinical and several Medical Research Institutes. He has received honoraria for Steering Committee roles, scientific presentations and/or advisory board attendance from Abbvie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier and Tricida.

Dr. Sabatine reports research grant support through Brigham and Women's Hospital from Abbott; Amgen; Anthos Therapeutics, Inc.; AstraZeneca; Boehringer Ingelheim; Daiichi-Sankyo; Ionis; Merck; Novartis; Pfizer; Saghmos Therapeutics; Verve Therapeutics, and consulting for Amgen; Anthos Therapeutics, Inc.; AstraZeneca; Beren Therapeutics; Boehringer Ingelheim; Dr. Reddy's Laboratories; Merck; Moderna; Novo Nordisk; Precision BioSciences; Silence Therapeutics.

Dr. Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta.

Dr. Staplin reports institutional grant support from Boehringer Ingelheim, Lilly, and Novo Nordisk.

Dr Szarek reports serving as a consultant or receiving research support, or both, from CiVi, Resverlogix, Lexicon, Baxter, Esperion, Amarin, NewAmsterdam, Sanofi, and Regeneron Pharmaceuticals, Inc.

Dr. Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics.

Dr. Wanner reports personal fees from Boehringer Ingelheim, AstraZeneca, Eli Lilly and Company, MSD, and Bayer.

Dr. Wheeler reports honoraria and/or consultancy fees from Amgen, AstraZeneca (ongoing), Astellas, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Mundipharma, MSD, Napp, and Dohme, Takeda, Vifor Fresenius, and Zydus.

Dr. Wiviott reports research grants from Amgen, AstraZeneca, Janssen, Merck, and Pfizer, Consulting Fees or Honoraria from Icon Clinical and Novo Nordisk, Varian and Harvard Medical School. Dr. Wiviott's spouse, Dr. Caroline Fox is an employee of Vertex, and former employee of Flagship Pioneering and Merck.

Drs. Sabatine and Wiviott are members of the TIMI Study Group, which has received institutional grant support through Brigham and Women's Hospital from Abbott, Abiomed, Inc., Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sagmos Therapeutics, Inc., Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc., Zora Biosciences.

Dr. Zannad reports personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, NovoNordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, USa2, having stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, Eshmoun Clinical research and being the founder of Cardiovascular Clinical Trialists.

Dr. Heerspink has received grants or contracts from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Dimerix, Eli Lilly, Gilead, Janssen, Novo Nordisk, Novartis, and Traverre Therapeutics; payment or honoraria for speaking from AstraZeneca and Novo Nordisk.

All other authors have no relevant disclosures.

References

1. The Nuffield Department of Population Health Renal Studies Group and the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *The Lancet* 2022; **400**(10365): 1788-801.
2. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2024. *Diabetes Care* 2023; **47**(Supplement_1): S179-S218.
3. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023; **44**(39): 4043-140.
4. Levin A, Ahmed SB, Carrero JJ, et al. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: known knowns and known unknowns. *Kidney International* 2024; **105**(4): 684-701.
5. Sattar N, Lee MM, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *The lancet Diabetes & endocrinology* 2021; **9**(10): 653-62.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022; **45**(11): 2753-86.
7. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus: systematic review and meta-analysis of cardiovascular outcomes trials. *Circulation* 2019; **139**(17): 2022-31.
8. Rossing P, Caramori ML, Chan JC, et al. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney International* 2022; **102**(5): S1-S127.
9. Patel S, Kang YM, Neuen BL, et al. Sodium Glucose Co-transporter 2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis. *Circulation* 2024.
10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New England Journal of Medicine* 2015; **373**(22): 2117-28.
11. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *New England Journal of Medicine* 2017; **377**(7): 644-57.
12. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine* 2019; **380**(4): 347-57.
13. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *New England Journal of Medicine* 2020; **383**(15): 1425-35.
14. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *New England Journal of Medicine* 2019; **380**(24): 2295-306.
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine* 2020; **383**(15): 1436-46.
16. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *New England Journal of Medicine* 2021; **384**(2): 129-39.
17. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine* 2022; **388**(2): 117-27.

18. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *New England Journal of Medicine* 2019; **381**(21): 1995-2008.
19. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine* 2020.
20. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *New England Journal of Medicine* 2021; **385**(16): 1451-61.
21. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine* 2022; **387**(12): 1089-98.
22. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *New England Journal of Medicine* 2021; **384**(2): 117-28.
23. Mantsiou C, Karagiannis T, Kakotrichi P, et al. Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Diabetes, Obesity and Metabolism* 2020; **22**(10): 1857-68.
24. Sivalingam S, Wasehuus VS, Rotbain Curovic V, et al. Albuminuria-lowering effect of adding semaglutide on top of empagliflozin in individuals with type 2 diabetes: A randomized and placebo-controlled study. *Diabetes Obes Metab* 2024; **26**(1): 54-64.
25. Vernstrøm L, Gullaksen S, Sørensen SS, Funck KL, Laugesen E, Poulsen PL. Separate and combined effects of empagliflozin and semaglutide on vascular function: A 32-week randomized trial. *Diabetes Obes Metab* 2024; **26**(5): 1624-35.
26. van Ruiten CC, Veltman DJ, Wijdeveld M, et al. Combination therapy with exenatide decreases the dapagliflozin-induced changes in brain responses to anticipation and consumption of palatable food in patients with type 2 diabetes: A randomized controlled trial. *Diabetes Obes Metab* 2022; **24**(8): 1588-97.
27. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine* 2023; **389**(24): 2221-32.
28. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *New England Journal of Medicine* 2023; **389**(12): 1069-84.
29. Staplin N, Haynes R, Judge P, et al. Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the EMPA-KIDNEY trial. *The Lancet Diabetes & Endocrinology* 2024; **12**(1): 39-50.
30. Li J, Neal B, Perkovic V, et al. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney International* 2020.
31. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; **129**(5): 587-97.
32. Kidokoro K, Cherney DZ, Bozovic A, et al. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. *Circulation* 2019; **140**(4): 303-15.
33. Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis. *Circulation* 2022; **146**(18): 1383-405.
34. Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. *Diabetologia* 2023; **66**(10): 1765-79.
35. Inker LA, Collier W, Greene T, et al. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. *Nat Med* 2023; **29**(7): 1867-76.

36. Neuen BL, Jun M, Wick J, et al. Estimating the population-level impacts of improved uptake of SGLT2 inhibitors in patients with chronic kidney disease: a cross-sectional observational study using routinely collected Australian primary care data. *Lancet Reg Health West Pac* 2024; **43**: 100988.
37. Lamprea-Montealegre JA, Madden E, Tummalapalli SL, et al. Prescription Patterns of Cardiovascular- and Kidney-Protective Therapies Among Patients With Type 2 Diabetes and Chronic Kidney Disease. *Diabetes Care* 2022; **45**(12): 2900-6.
38. Grams ME, Sang Y, Ballew SH, et al. Evaluating glomerular filtration rate slope as a surrogate end point for ESKD in clinical trials: an individual participant meta-analysis of observational data. *Journal of the American Society of Nephrology* 2019; **30**(9): 1746-55.
39. Neves JS, Borges-Canha M, Vasques-Nóvoa F, et al. GLP-1 Receptor Agonist Therapy With and Without SGLT2 Inhibitors in Patients With Type 2 Diabetes. *Journal of the American College of Cardiology* 2023; **82**(6): 517-25.

Supplementary Appendix: Efficacy and safety of sodium glucose co-transporter 2 inhibitors with and without glucagon-like peptide-1 receptor agonists: A SMART-C collaborative meta-analysis of randomized controlled trials

Table of Contents:

	Page
Table S1. Details of included trials.	2
Table S2. Effects of SGLT2 inhibitors on major adverse cardiovascular events by baseline use of GLP-1RA in individual trials.	3
Table S3. Effects of SGLT2 inhibitors on (A) heart failure hospitalisation or cardiovascular death and (B) hospitalisation for heart failure by baseline use of GLP-1RA in individual trials.	4
Table S4. Effects of SGLT2 inhibitors on CKD progression by baseline use of GLP-1RA in individual trials.	6
Table S5. Effects of SGLT2 inhibitors on chronic and total eGFR slope by baseline use of GLP-1RA in individual trials.	7
Table S6. Number of participants experiencing (A) serious adverse events; (B) hypoglycaemia (C) volume depletion by baseline GLP-1RA in individual trials.	9

Table S1. Details of included trials.

Study	Population	Year	NCT ID	Participants, n	Diabetes, n (%)	GLP-1RA, n (%)	SGLT2i, dose	Median F/U (years)
EMPA-REG OUTCOME	Diabetes at high ASCVD risk	2015	NCT01131676	7020	7020 (100.0)	196 (2.8)	Empagliflozin, 10/25mg	3.1
CANVAS Program	Diabetes at high ASCVD risk	2017	NCT01032629	10142	10142 (100.0)	407 (4.0)	Canagliflozin 100mg	3.6
DECLARE-TIMI 58	Diabetes at high ASCVD risk	2019	NCT01730534	17160	17160 (100.0)	750 (4.4)	Canagliflozin 10mg	4.2
VERTIS CV	Diabetes at high ASCVD risk	2020	NCT01986881	8238	8238 (100.0)	277 (3.4)	Ertugliflozin 5/15mg	3.5
CREDENCE	CKD	2019	NCT02065791	4401	4401 (100.0)	183 (4.2)	Canagliflozin 100mg	2.6
DAPA-CKD	CKD	2020	NCT03036150	4304	2906 (67.5)	122 (4.2)	Dapagliflozin 10mg	2.4
SCORED	CKD	2021	NCT03315143	10584	10584 (100.0)	633 (6.0)	Sotagliflozin 400mg	1.3
EMPA-KIDNEY	CKD	2023	NCT03594110	6609	2936 (44.4)	337 (5.1)	Empagliflozin 10mg	2.0
DAPA-HF	HF	2019	NCT03036124	4744	1983 (41.8)	21 (1.1)	Dapagliflozin 10mg	1.5
EMPEROR-REDUCED	HF	2020	NCT03057977	3730	1856 (49.8)	19 (1.0)	Empagliflozin 10mg	1.3
EMPEROR-PRESERVED	HF	2021	NCT03057951	5988	2938 (49.1)	59 (2.0)	Empagliflozin 10mg	2.2
DELIVER	HF	2022	NCT03619213	6263	2806 (44.8)	61 (2.2)	Dapagliflozin 10mg	2.3
Total				89183	72970 (81.8)	3065 (4.2)		

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; HF: heart failure; NCT ID: national clinical trial identification number; F/U: follow-up.

Table S2. Effects of SGLT2 inhibitors on major adverse cardiovascular events by baseline use of GLP-1 in individual trials.

	Events/patients (%)		Event rate /100 patient years		HR (95% CI)
	SGLT2i	Placebo	SGLT2i	Placebo	
Baseline use of GLP-1 RA					
EMPA-REG OUTCOME	15/126 (11.9)	10/70 (14.3)	4.32	5.42	0.83 (0.37 to 1.84)
CANVAS Program	18/222 (8.1)	15/185 (8.1)	2.64	3.1	0.73 (0.36 to 1.46)
DECLARE-TIMI 58	31/397 (7.8)	32/353 (9.1)	1.9	2.3	0.84 (0.51 to 1.38)
VERTIS CV	21/192 (10.9)	9/85 (10.6)	3.54	3.79	0.94 (0.43 to 2.05)
CREDENCE	11/89 (12.4)	11/94 (11.7)	4.65	4.23	1.13 (0.49 to 2.64)
DAPA-CKD	8/63 (12.7)	6/59 (10.2)	5.91	4.78	1.31 (0.42 to 4.09)
SCORED	17/310 (5.5)	18/323 (5.6)	3.9	4.2	0.90 (0.46 to 1.74)
EMPA-KIDNEY	6/173 (3.5)	11/164 (6.7)	1.8	3.6	0.46 (0.17 to 1.26)
DAPA-HF	1/11 (9.1)	3/10 (30)	6.1	33.3	0.23 (0.02 to 2.92)
EMPEROR-REDUCED	2/13 (15.4)	1/6 (16.7)	12.19	11.54	1.12 (0.1 to 12.36)
EMPEROR-PRESERVED	5/30 (16.7)	5/29 (17.2)	7.59	9.03	0.85 (0.24 to 2.93)
DELIVER	4/34 (11.8)	8/27 (29.6)	5.5	17.1	0.32 (0.1 to 1.08)
No baseline use of GLP1-RA					
EMPA-REG OUTCOME	475/4561 (10.4)	272/2263 (12)	3.72	4.36	0.86 (0.74 to 1.00)
CANVAS Program	567/5573 (10.2)	411/4162 (9.9)	2.69	3.15	0.86 (0.76 to 0.98)
DECLARE-TIMI 58	734/8185 (9)	788/8225 (9.6)	2.3	2.5	0.93 (0.84 to 1.03)
VERTIS CV	632/5301 (11.9)	318/2660 (12)	3.91	4.02	0.97 (0.85 to 1.11)
CREDENCE	206/2113 (9.7)	258/2105 (12.3)	3.84	4.9	0.78 (0.65 to 0.94)
DAPA-CKD	105/1392 (7.5)	112/1392 (8)	3.49	3.75	0.93 (0.71 to 1.21)
SCORED	269/4982 (5.4)	316/4969 (6.4)	4.1	4.9	0.84 (0.72 to 0.99)
EMPA-KIDNEY	85/1352 (6.3)	96/1351 (7.1)	3.2	3.6	0.89 (0.66 to 1.19)
DAPA-HF	156/1064 (14.7)	173/1054 (16.4)	10.3	11.7	0.88 (0.71 to 1.1)
EMPEROR-REDUCED	124/914 (13.6)	126/923 (13.7)	10.4	10.35	1.01 (0.78 to 1.29)
EMPEROR-PRESERVED	166/1436 (11.6)	171/1443 (11.9)	5.71	5.79	0.98 (0.79 to 1.21)
DELIVER	168/1367 (12.3)	191/1378 (13.9)	5.7	6.4	0.88 (0.72 to 1.08)

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval. Major adverse cardiovascular events was defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.

Table S3. Effects of SGLT2 inhibitors on (A) heart failure hospitalisation or cardiovascular death and (B) hospitalisation for heart failure by baseline use of GLP-1RA in individual trials.

A.	Events/patients (%)		Event rate per 100 patient years		
	SGLT2i	Placebo	SGLT2i	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
EMPA-REG OUTCOME	5/126 (4.0)	3/70 (4.3)	1.39	1.59	0.85 (0.2 to 3.56)
CANVAS Program	13/222 (5.9)	5/185 (2.7)	1.89	1.01	1.85 (0.65 to 5.27)
DECLARE-TIMI 58	4/397 (1.0)	18/353 (5.1)	0.2	1.3	0.2 (0.07 to 0.6)
VERTIS CV	9/192 (4.7)	3/85 (3.5)	1.32	1.01	1.30 (0.35 to 4.80)
CREDENCE	4/89 (4.5)	8/94 (8.5)	1.67	3.1	0.54 (0.16 to 1.08)
DAPA-CKD	2/63 (3.2)	5/59 (8.5)	1.39	3.98	0.29 (0.05 to 1.54)
SCORED	9/310 (2.9)	14/323 (4.3)	2	3.3	0.58 (0.25 to 1.35)
EMPA-KIDNEY	5/173 (2.9)	5/164 (3)	1.5	1.6	0.79 (0.23 to 2.72)
DAPA-HF	5/11 (45.5)	1/10 (10)	41.3	10.2	4.39 (0.45 to 43.19)
EMPEROR-REDUCED	4/13 (30.8)	1/6 (16.7)	29.15	13.07	1.81 (0.2 to 16.24)
EMPEROR-PRESERVED	4/30 (13.3)	2/29 (6.9)	6.29	3.71	1.59 (0.29 to 8.68)
DELIVER	5/34 (14.7)	5/27 (18.5)	7.1	11.7	0.58 (0.17 to 2.01)
No baseline use of GLP1-RA					
EMPA-REG OUTCOME	121/4561 (2.7)	92/2263 (4.1)	0.92	1.44	0.65 (0.49 to 0.85)
CANVAS Program	110/5573 (2)	115/4162 (2.8)	0.51	0.86	0.62 (0.48 to 0.81)
DECLARE-TIMI 58	208/8185 (2.5)	268/8225 (3.3)	0.6	0.8	0.77 (0.64 to 0.92)
VERTIS CV	130/5307 (2.4)	96/2662 (3.6)	0.71	1.05	0.68 (0.52 to 0.88)
CREDENCE	85/2113 (4.0)	133/2105 (6.3)	1.56	2.51	0.62 (0.47 to 0.81)
DAPA-CKD	29/1392 (2.1)	59/1392 (4.2)	0.95	1.97	0.48 (0.31 to 0.75)
SCORED	149/4982 (3.0)	211/4969 (4.2)	2.3	3.3	0.70 (0.57 to 0.86)
EMPA-KIDNEY	60/1352 (4.4)	75/1351 (5.6)	2.2	2.8	0.78 (0.55 to 1.09)
DAPA-HF	133/1064 (12.5)	171/1054 (16.2)	9.1	12.3	0.74 (0.59 to 0.93)
EMPEROR-REDUCED	136/914 (14.9)	200/923 (21.7)	12.15	18.66	0.66 (0.53 to 0.82)
EMPEROR-PRESERVED	151/1436 (10.5)	213/1443 (14.8)	5.36	7.65	0.68 (0.55 to 0.84)
DELIVER	172/1367 (12.6)	210/1378 (15.2)	6	7.5	0.80 (0.66 to 0.98)

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

B.	Events/patients (%)		Event rate per 100 patient years		
	SGLT2i	Placebo	SGLT2i	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
EMPA-REG OUTCOME	11/126 (8.7)	6/70 (8.6)	3.06	3.18	0.96 (0.36 to 2.61)
CANVAS Program	17/222 (7.7)	8/185 (4.3)	2.47	1.61	1.38 (0.59 to 3.23)
DECLARE-TIMI 58	10/397 (2.5)	24/353 (6.8)	0.6	1.7	0.37 (0.18 to 0.78)
VERTIS CV	14/192 (7.3)	4/85 (4.7)	2.05	1.35	1.51 (0.50 to 4.60)
CREDENCE	9/89 (10.1)	11/94 (11.7)	3.76	4.26	0.96 (0.39 to 2.35)
DAPA-CKD	3/63 (4.8)	6/59 (10.2)	2.09	4.78	0.4 (0.1 to 1.67)
SCORED	13/310 (4.2)	18/323 (5.6)	2.9	4.2	0.65 (0.32 to 1.34)
EMPA-KIDNEY	7/173 (4)	9/164 (5.5)	2.1	2.9	0.63 (0.24 to 1.7)
DAPA-HF	5/11 (45.5)	3/10 (30)	41.3	30.7	1.62 (0.33 to 7.85)
EMPEROR-REDUCED	5/13 (38.5)	1/6 (16.7)	36.44	13.07	2.46 (0.29 to 21.07)
EMPEROR-PRESERVED	6/30 (20)	5/29 (17.2)	9.43	9.27	0.94 (0.29 to 3.1)
DELIVER	7/34 (20.6)	9/27 (33.3)	9.9	21.1	0.47 (0.17 to 1.26)
No baseline use of GLP1-RA					
EMPA-REG OUTCOME	269/4561 (5.9)	203/2263 (9)	2.05	3.18	0.65 (0.54 to 0.78)
CANVAS Program	347/5573 (6.2)	280/4162 (6.7)	1.6	2.1	0.76 (0.65 to 0.9)
DECLARE-TIMI 58	407/8185 (5)	472/8225 (5.7)	1.2	1.5	0.86 (0.75 to 0.98)
VERTIS CV	430/5307 (8.1)	246/2662 (9.2)	2.35	2.7	0.87 (0.75 to 1.02)
CREDENCE	170/2113 (8)	242/2105 (11.5)	3.12	4.56	0.68 (0.56 to 0.83)
DAPA-CKD	82/1392 (5.9)	113/1392 (8.1)	2.68	3.78	0.71 (0.53 to 0.94)
SCORED	270/4982 (5.4)	339/4969 (6.8)	4.1	5.2	0.78 (0.67 to 0.92)
EMPA-KIDNEY	89/1352 (6.6)	109/1351 (8.1)	3.3	4.1	0.8 (0.61 to 1.07)
DAPA-HF	208/1064 (19.5)	265/1054 (25.1)	14.2	19	0.74 (0.62 to 0.89)
EMPEROR-REDUCED	195/914 (21.3)	264/923 (28.6)	17.43	24.63	0.72 (0.59 to 0.86)
EMPEROR-PRESERVED	233/1436 (16.2)	286/1443 (19.8)	8.27	10.27	0.79 (0.66 to 0.94)
DELIVER	241/1367 (17.6)	289/1378 (21)	8.5	10.4	0.82 (0.69 to 0.97)

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

Table S4. Effects of SGLT2 inhibitors on CKD progression by baseline use of GLP-1RA in individual trials.

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2i	Placebo	SGLT2i	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
EMPA-REG OUTCOME	4/125 (3.2)	2/70 (2.9)	1.21	1.13	1.19 (0.22 to 6.51)
CANVAS Program	1/222 (0.5)	3/185 (1.6)	0.14	0.6	0.37 (0.04 to 3.56)
DECLARE-TIMI 58	4/397 (1)	10/353 (2.8)	0.2	0.7	0.36 (0.11 to 1.15)
VERTIS CV	5/192 (2.6)	2/85 (2.4)	0.74	0.67	1.10 (0.21 to 5.67)
CREDENCE	12/89 (13.5)	11/94 (11.7)	5.18	4.17	1.21 (0.53 to 2.76)
DAPA-CKD	2/63 (3.2)	9/59 (15.3)	1.52	7.58	0.21 (0.04 to 0.97)
SCORED	8/310 (2.6)	9/323 (2.8)	1.8	2.1	0.82 (0.32 to 2.14)
EMPA-KIDNEY	18/173 (10.4)	24/164 (14.6)	5.4	8	0.53 (0.29 to 0.98)
DAPA-HF	0/11 (0)	2/10 (20)	N/A	20.7	N/A
EMPEROR-REDUCED	1/13 (7.7)	1/6 (16.7)	7.93	15.46	0.45 (0.03 to 7.36)
EMPEROR-PRESERVED	0/30 (0)	2/29 (6.9)	N/A	4.58	N/A
DELIVER	2/34 (5.9)	2/27 (7.4)	2.8	4.0	0.76 (0.11 to 5.37)
No baseline use of GLP1-RA					
EMPA-REG OUTCOME	104/4520 (2.3)	85/2253 (3.8)	0.84	1.43	0.57 (0.43 to 0.76)
CANVAS Program	123/5573 (2.2)	122/4162 (2.9)	0.57	0.91	0.61 (0.47 to 0.78)
DECLARE-TIMI 58	128/8185 (1.6)	232/8225 (2.8)	0.4	0.7	0.55 (0.44 to 0.68)
VERTIS CV	114/5307 (2.1)	87/2662 (3.3)	0.63	0.95	0.66 (0.5 to 0.87)
CREDENCE	237/2113 (11.2)	361/2105 (17.1)	4.48	7.11	0.62 (0.53 to 0.73)
DAPA-CKD	101/1392 (7.3)	164/1392 (11.8)	3.59	5.96	0.59 (0.46 to 0.75)
SCORED	186/4982 (3.7)	254/4969 (5.1)	2.8	3.9	0.72 (0.60 to 0.87)
EMPA-KIDNEY	164/1352 (12.1)	236/1351 (17.5)	6.2	9.1	0.63 (0.52 to 0.77)
DAPA-HF	32/1064 (3)	37/1054 (3.5)	2.2	2.6	0.84 (0.52 to 1.34)
EMPEROR-REDUCED	21/914 (2.3)	38/923 (4.1)	2.22	4.09	0.52 (0.30 to 0.88)
EMPEROR-PRESERVED	75/1436 (5.2)	72/1443 (5)	3.16	3.01	1.03 (0.74 to 1.42)
DELIVER	107/1367 (7.8)	84/1378 (6.1)	3.7	2.8	1.30 (0.98 to 1.73)

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval. N/A: Not applicable. CKD progression defined as $\geq 40\%$ decline in eGFR, kidney failure or death due to kidney failure.

Table S5. Effects of SGLT2 inhibitors on chronic and total eGFR slope by baseline use of GLP-1RA in individual trials.

A. Chronic slope	eGFR slope (mL/min/1.73m ² /year)			
	SGLT2i (95% CI)	Placebo (95% CI)	Mean Difference (95% CI)	SE
Baseline use of GLP-1 RA				
EMPA-REG OUTCOME	0.78 (-0.34 to 1.91)	-2.7 (-4.39 to -1)	3.48 (1.45 to 5.51)	1.04
CANVAS Program	0.11 (-0.51 to 0.73)	-1.13 (-1.98 to -0.29)	1.24 (0.2 to 2.29)	0.53
DECLARE-TIMI 58	-1.29 (-1.64 to -0.94)	-2.34 (-2.74 to -1.94)	1.05 (0.51 to 1.58)	0.27
VERTIS CV	-0.6 (-1.05 to -0.14)	-1.58 (-2.32 to -0.85)	0.99 (0.12 to 1.85)	0.44
CREDENCE	-1.86 (-2.88 to -0.85)	-4.05 (-5.07 to -3.04)	2.19 (0.75 to 3.62)	0.72
DAPA-CKD	-1.21 (-2.57 to 0.15)	-3.98 (-5.39 to -2.57)	2.77 (0.81 to 4.73)	0.08
SCORED	-0.23 (-1.01 to 0.56)	-0.64 (-1.46 to 0.17)	0.42 (-0.71 to 1.55)	0.05
EMPA-KIDNEY	-1.13 (-1.86 to -0.40)	-2.56 (-3.32 to -1.80)	1.42 (0.37 to 2.47)	0.54
DAPA-HF	-2.26 (-7.1 to 2.59)	-3.72 (-9.78 to 2.35)	1.46 (-6.31 to 9.23)	3.96
EMPEROR-REDUCED	-1.87 (-7.58 to 3.85)	-0.98 (-9.03 to 7.07)	-0.89 (-10.76 to 8.98)	5.04
EMPEROR-PRESERVED	0.08 (-2.2 to 2.36)	-6.91 (-9.39 to -4.43)	6.99 (3.62 to 10.37)	1.72
DELIVER	1.5 (-0.7 to 3.7)	-4.3 (-8.1 to -0.6)	6 (1.7 to 10.3)	2.20
No baseline use of GLP1-RA				
EMPA-REG OUTCOME	-0.39 (-0.48 to -0.17)	-1.72 (-1.97 to -1.46)	1.39 (1.09 to 1.68)	0.15
CANVAS Program	0.35 (0.25 to 0.45)	-0.73 (-0.87 to -0.6)	1.09 (0.92 to 1.26)	0.09
DECLARE-TIMI 58	-1.52 (-1.6 to -1.44)	-2.51 (-2.59 to -2.43)	0.99 (0.87 to 1.1)	0.06
VERTIS CV	-0.87 (-0.96 to -0.79)	-1.79 (-1.91 to -1.67)	0.91 (0.77 to 1.06)	0.07
CREDENCE	-1.91 (-2.17 to -1.65)	-4.61 (-4.88 to -4.35)	2.7 (2.33 to 3.07)	0.19
DAPA-CKD	-1.6 (-1.89 to -1.31)	-3.83 (-4.12 to -3.54)	2.23 (1.82 to 2.64)	0.02
SCORED	-0.06 (-0.32 to 0.2)	-2.17 (-2.43 to -1.9)	2.11 (1.73 to 2.48)	0.02
EMPA-KIDNEY	-1.23 (-1.48 to -0.98)	-2.84 (-3.09 to -2.59)	1.61 (1.25 to 1.97)	0.18
DAPA-HF	-1.5 (-1.99 to -1)	-3.73 (-4.24 to -3.22)	2.23 (1.52 to 2.95)	0.36
EMPEROR-REDUCED	-0.7 (-1.4 to 0)	-3.01 (-3.71 to -2.3)	2.3 (1.31 to 3.3)	0.51
EMPEROR-PRESERVED	-1.3 (-1.63 to -0.96)	-3.02 (-3.35 to -2.69)	1.72 (1.25 to 2.19)	0.24
DELIVER	0.1 (-0.4 to 0.5)	-1.9 (-2.3 to -1.4)	1.9 (1.3 to 2.6)	0.3

SGLT2i: sodium glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; CI: confidence interval; SE: standard error.

B. Total Slope	eGFR slope (mL/min/1.73m ² /year)			
	SGLT2i (95% CI)	Placebo (95% CI)	Mean Difference (95% CI)	SE
Baseline use of GLP-1 RA				
EMPA-REG OUTCOME	-0.39 (-1.47 to -0.68)	-2.63 (-4.24 to -1.02)	2.24 (0.3 to 4.17)	0.99
CANVAS Program	-0.06 (-0.63 to 0.5)	-0.97 (-1.73 to -0.2)	0.9 (-0.05 to 1.85)	0.48
DECLARE-TIMI 58	-1.55 (-1.76 to -1.33)	-2.22 (-2.47 to -1.97)	0.67 (0.34 to 1.01)	0.17
VERTIS CV	-0.63 (-1.03 to -0.22)	-1.65 (-2.31 to -0.99)	1.02 (0.25 to 1.8)	0.39
CREDENCE	-1.36 (-7.81 to 5.09)	-4.85 (-12.54 to 2.84)	3.49 (-6.54 to 13.53)	5.11
DAPA-CKD	-2.87 (-4.24 to -1.49)	-4.14 (-5.56 to -2.71)	1.27 (-0.71 to 3.25)	0.08
SCORED	-3.02 (-3.82 to -2.23)	-1.32 (-2.13 to -0.51)	-1.7 (-2.83 to -0.57)	0.05
EMPA-KIDNEY	-2.09 (-2.78 to -1.40)	-2.83 (-3.56 to -2.10)	0.73 (-0.27 to 1.73)	0.51
DAPA-HF	-3.23 (-7.93 to 1.48)	-4.19 (-10.01 to 1.63)	0.96 (-6.53 to 8.45)	3.82
EMPEROR-REDUCED	-3.87 (-9.22 to 1.47)	-2 (-9.62 to 5.61)	-1.87 (-11.16 to 7.43)	4.74
EMPEROR-PRESERVED	-2.71 (-4.98 to -0.44)	-5.53 (-7.94 to -3.13)	2.83 (-0.48 to 6.14)	1.69
DELIVER	0.1 (-1.9 to 2.1)	-4.1 (-7.3 to -0.9)	4.2 (0.3 to 8)	2.00
No baseline use of GLP1-RA				
EMPA-REG OUTCOME	-1.12 (-1.27 to -0.97)	-1.74 (-1.98 to -1.49)	0.62 (0.33 to 0.91)	0.15
CANVAS Program	-0.19 (-0.28 to -0.09)	-0.83 (-0.96 to -0.7)	0.64 (0.48 to 0.8)	0.08
DECLARE-TIMI 58	-1.78 (-1.83 to -1.73)	-2.41 (-2.46 to -2.36)	0.63 (0.57 to 0.7)	0.03
VERTIS CV	-0.87 (-0.94 to -0.8)	-1.71 (-1.81 to -1.6)	0.84 (0.71 to 0.97)	0.07
CREDENCE	0.77 (-1.19 to 2.73)	-5.05 (-6.82 to -3.28)	5.82 (3.18 to 8.46)	1.35
DAPA-CKD	-2.83 (-3.12 to -2.54)	-4 (-4.3 to -3.71)	1.17 (0.76 to 1.59)	0.02
SCORED	-1.86 (-2.12 to -1.61)	-1.9 (2.16 to -1.64)	0.04 (-0.33 to 0.4)	0.02
EMPA-KIDNEY	-2.12 (-2.36 to -1.88)	-2.87 (-3.12 to -2.62)	0.75 (0.4 to 1.09)	0.18
DAPA-HF	-3.04 (-3.52 to -2.54)	-3.95 (-4.44 to -3.46)	0.91 (0.22 to 1.61)	0.35
EMPEROR-REDUCED	-2 (-2.66 to -1.34)	-3.38 (-4.04 to -2.71)	1.38 (0.44 to 2.31)	0.48
EMPEROR-PRESERVED	-2.72 (-3.05 to -2.39)	-3.1 (-3.43 to -2.78)	0.38 (-0.08 to 0.84)	0.24
DELIVER	-1.2 (-1.6 to -0.8)	-2.1 (-2.5 to -1.7)	0.9 (0.3 to 1.5)	0.30

Table S5. Number of participants experiencing (A) serious adverse events; (B) hypoglycaemia (C) volume depletion by baseline GLP-1RA in individual trials.

A. Serious adverse events	Events/Participants (%)	
	SGLT2i	Placebo
Baseline use of GLP-1RA		
EMPA-REG OUTCOME	60/126 (47.6)	40/70 (57.1)
CANVAS Program	79/222 (35.6)	67/185 (36.2)
DECLARE-TIMI 58	145/397 (36.5)	134/352 (38.1)
VERTIS CV	70/192 (36.5)	38/85 (44.7)
CREDENCE	34/89 (38.2)	39/94 (41.5)
DAPA-CKD	18/63 (28.6)	27/59 (45.8)
SCORED	86/310 (27.7)	89/323 (27.6)
EMPA-KIDNEY	70/173 (40.5)	79/164 (48.2)
DAPA-HF	7/10 (70)	5/10 (50)
EMPEROR-REDUCED	7/13 (53.8)	6/6 (100)
EMPEROR-PRESERVED	21/29 (72.4)	16/29 (55.2)
DELIVER	23/34 (67.6)	17/27 (63)
No baseline use of GLP-1RA		
EMPA-REG OUTCOME	1729/4561 (37.9)	948/2263 (41.9)
CANVAS Program	1842/5568 (33.1)	1289/4159 (31)
DECLARE-TIMI 58	2780/8177 (34)	2966/8217 (36.1)
VERTIS CV	1825/5301 (34.4)	952/2660 (35.8)
CREDENCE	703/2111 (33.3)	767/2103 (36.5)
DAPA-CKD	435/1390 (31.3)	494/1391 (35.5)
SCORED	1150/4981 (23.1)	1242/4963 (25)
EMPA-KIDNEY	577/1352 (42.7)	626/1351 (46.3)
DAPA-HF	440/1063 (41.4)	508/1053 (48.2)
EMPEROR-REDUCED	390/914 (42.7)	451/920 (49)
EMPEROR-PRESERVED	711/1436 (49.5)	782/1442 (54.2)
DELIVER	637/1367 (46.6)	684/1378 (49.6)

SGLT2i: sodium glucose cotransporter-2 inhibitor. GLP-1RA: glucagon-like peptide-1 receptor agonist.

B. Hypoglycaemia	Events/Participants (%)	
	SGLT2i	Placebo
Baseline use of GLP-1 RA		
EMPA-REG OUTCOME	0/126 (0)	1/70 (1.4)
CANVAS Program	7/156 (4.5)	5/155 (3.2)
DECLARE-TIMI 58	3/397 (0.8)	5/352 (1.4)
VERTIS CV	0/192 (0)	0/85 (0)
CREDENCE	11/89 (12.4)	7/94 (7.4)
DAPA-CKD	0/63 (0)	0/59 (0)
SCORED	28/310 (9)	15/323 (4.6)
EMPA-KIDNEY	13/173 (7.5)	10/164 (6.1)
DAPA-HF	0/10 (0)	0/10 (0)
EMPEROR-REDUCED	0/13 (0)	0/6 (0)
EMPEROR-PRESERVED	0/29 (0)	1/29 (3.4)
DELIVER	0/34	0/27
No baseline use of GLP-1 RA		
EMPA-REG OUTCOME	63/4561 (1.4)	35/2263 (1.5)
CANVAS Program	376/2820 (13.3)	163/1411 (11.6)
DECLARE-TIMI 58	55/8177 (0.7)	78/8217 (0.9)
VERTIS CV	21/5301 (0.4)	14/2660 (0.5)
CREDENCE	214/2111 (10.1)	233/2103 (11.1)
DAPA-CKD	14/1390 (1)	28/1391 (2)
SCORED	378/4981 (7.6)	401/4963 (8.1)
EMPA-KIDNEY	60/1352 (4.4)	67/1351 (5)
DAPA-HF	4/1062 (0.4)	4/1053 (0.4)
EMPEROR-REDUCED	6/914 (0.7)	7/920 (0.8)
EMPEROR-PRESERVED	22/1436 (1.5)	17/1442 (1.2)
DELIVER	4/1367 (0.3)	1/1378 (0.1)

SGLT2i: sodium glucose cotransporter-2 inhibitor. GLP-1RA: glucagon-like peptide-1 receptor agonist.

C. Volume depletion	Events/Participants (%)	
	SGLT2i	Placebo
Baseline use of GLP-1 RA		
EMPA-REG OUTCOME	0/126 (0)	1/70 (1.4)
CANVAS Program	8/156 (5.1)	5/155 (3.2)
DECLARE-TIMI 58	15/397 (3.8)	13/352 (3.7)
VERTIS CV	1/192 (0.5)	1/85 (1.2)
CREDENCE	10/89 (11.2)	10/94 (10.6)
DAPA-CKD	6/63 (9.5)	1/59 (1.7)
SCORED	25/310 (8.1)	15/323 (4.6)
EMPA-KIDNEY	10/173 (5.8)	6/164 (3.7)
DAPA-HF	1/10 (10)	1/10 (10)
EMPEROR-REDUCED	0/13 (0)	0/6 (0)
EMPEROR-PRESERVED	3/29 (10.3)	1/29 (3.4)
DELIVER	3/35 (8.6)	0/27 (0)
No baseline use of GLP-1 RA		
EMPA-REG OUTCOME	38/4561 (0.8)	15/2263 (0.7)
CANVAS Program	191/2820 (6.8)	62/1411 (4.4)
DECLARE-TIMI 58	198/8177 (2.4)	194/8217 (2.4)
VERTIS CV	50/5301 (0.9)	27/2660 (1)
CREDENCE	134/2111 (6.3)	105/2103 (5)
DAPA-CKD	86/1390 (6.2)	70/1391 (5)
SCORED	253/4981 (5.1)	198/4963 (4)
EMPA-KIDNEY	43/1352 (3.2)	30/1351 (2.2)
DAPA-HF	83/1063 (7.8)	82/1053 (7.8)
EMPEROR-REDUCED	14/914 (1.5)	13/920 (1.4)
EMPEROR-PRESERVED	28/1436 (1.9)	28/1442 (1.9)
DELIVER	14/1367 (1)	12/1378 (0.9)

SGLT2i: sodium glucose cotransporter-2 inhibitor. GLP-1RA: glucagon-like peptide-1 receptor agonist.