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,[*1] Brendon L Neuen,[2,3*] Robert A Fletcher[2], Niels Jongs[1], Stefan D Anker,[4] Deepak L Bhatt,[5] Javed Butler,[6,7] David ZI Cherney,[8] William G Herrington,[9] Silvio E Inzucchi,[10] Meg J Jardine,[2,11,12] Kenneth W Mahaffey,[13] Darren K McGuire,[14] John JV McMurray,[15] Bruce Neal,[2] Milton Packer,[16] Vlado Perkovic,[2] Marc S Sabatine,[17,18] Scott D Solomon,[18] Natalie Staplin,[9] Muthiah Vaduganathan,[18] Christoph Wanner,[19] David C Wheeler,[20] Stephen D Wiviott,[17,18] Faiez Zannad,[21] Yujie Zhao,[22] Hiddo J.L. Heerspink[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. Stanford Center for Clinical Research (SCCR), Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA.
14. University of Texas Southwestern Medical Center and Parkland Health, Dallas, TX, USA.
15. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom.
16. Baylor University Medical Center, Dallas TX, USA and Imperial College, London United Kingdom.
17. TIMI Study Group.
18. Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
19. Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center (CHFC), University Hospital, Würzburg, Germany.
20. Department of Renal Medicine, University College London, London, United Kingdom
21. 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.
22. Merck & Co., Inc., Rahway, NJ, USA.

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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 (250/250 words)

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. Whether the benefits of SGLT2i are consistent in patients receiving and not receiving GLP-1RA is unknown.

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 (≥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; P-heterogeneity=0.31). Effects on hospitalisation for HF or cardiovascular death (HR 0.76, 95%CI 0.57-1.01 vs. HR 0.78, 95%CI 0.74-0.82; 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; P-heterogeneity=0.81) were also consistent irrespective of GLP-1RA use. Fewer

serious adverse events occurred with SGLT2i compared with placebo, regardless of GLP-1RA use (P-heterogeneity=0.41).

Interpretation

The effects of SGLT2i on cardiovascular and kidney outcomes are similar regardless of background use of GLP-1RA, suggesting independent effects of these evidence-based therapies in patients with diabetes.

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, 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. 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 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 ≥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 cardiovascular events, slow chronic kidney disease (CKD) progression, and extend overall survival 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 participating SMART-C trials 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 SMART-C trials 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: ≥40% decline in estimated glomerular filtration rate (eGFR), kidney failure (eGFR<15 mL/min/1.73m^2, 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. 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/1.73m^2/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. Among the 72,970 participants with diabetes, 3065 (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). 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, 7,270 (9.5%) participants experienced a MACE event, including 268 who were receiving a GLP-1RA at baseline. The incidence of MACE was highest in the HF trials, driven by cardiovascular death (**Figure 1**). The effect of SGLT2i on MACE 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, 6,471 (8.9%) participants were hospitalised for HF or died due to cardiovascular disease, of whom 211 were receiving a GLP-1RA at baseline. 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 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 0.87; **Figure 2**). The effect of SGLT2i on hospitalisation for HF did not differ by baseline GLP-1RA use (HR 0.76, 95% CI 0.57-1.01 and HR 0.78, 95% CI 0.74-0.82; P-heterogeneity=0.90; **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 who were receiving a GLP-1RA at baseline (**Figure 3**). SGLT2i reduced the risk of CKD progression (≥40% decline in GFR, kidney failure or death due to kidney failure) 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. Treatment effects on cardiovascular and kidney outcomes by individual trial are summarised in Tables S1-3.

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/1.73m^2/year in participants receiving GLP-1RA and by 1.21 [95% CI 1.14 to 1.28] mL/min/1.73m^2/year) in participants not receiving GLP-1RA at baseline (P-heterogeneity=0.55; **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/1.73m^2/year and 0.66 [95% CI 0.61 to 0.71] mL/min/1.73m^2/year, respectively; P-heterogeneity=0.92; **Figure 4**). Treatment effects on eGFR slope in individual trials are summarised in Table S4.

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 S5.

Discussion

In 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, we observed that the relative risk reductions in cardiovascular and kidney outcomes conferred with SGLT2i were similar regardless of baseline use a GLP-1RA. Additionally, the safety and tolerability of SGLT2i appeared consistent in those receiving and not receiving a GLP-1RA. These data suggest that the cardiovascular and kidney protective effects of both drug classes are likely independent and additive, supporting their combined use 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 in small trials of relatively short duration.[23] Our findings, which represent the most comprehensive evaluation of the effects of SGLT2i with and without baseline use of GLP-1RA on clinical outcomes, provide support for 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.[24,25] 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. However, these effects are unlikely to fully explain the magnitude of benefit observed on clinical outcomes for either class.[26] While SGLT2i reduce measures of glomerular pressure which may contribute to their kidney protective effects,[27,28] effects on tubular energy expenditure, nutrient deprivation signalling, autophagy and inflammation are also likely to be important.[29] 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.[30] 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,[31] 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 combined use of these agents to slow CKD progression in patients with type 2 diabetes.

There are some limitations to acknowledge when interpreting these findings. While this work represents the largest and most comprehensive assessment of the effects of SGLT2i on clinical outcomes by baseline use of GLP-1RA, 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,[31,32] 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.[33] 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. 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, which 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.

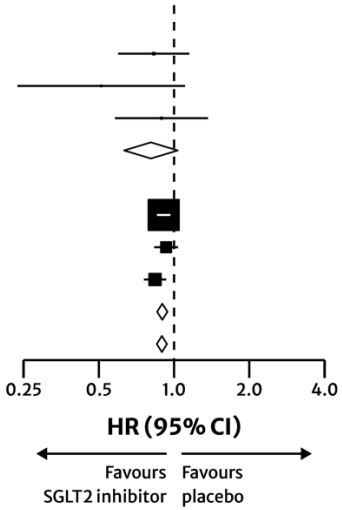
Table 1. Characteristics of participants stratified by study population and use of GLP-1RA at baseline.

	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)
Female sex, n (%)	269 (28.7)	207 (29.9)	7922 (33.5)	6138 (35.5)
History of CV disease, n (%)	602 (64.3)	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/m2 (SD)	34.9 (5.8)	35.0 (6.8)	31.5 (5.7)	31.5 (5.8)
HbA1c, % (SD)	8.2 (1.0)	8.1 (1.0)	8.2 (1.0)	8.2 (1.1)
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 (%)	312 (33.7)	228 (33.3)	8034 (34.2)	5680 (33.1)
Insulin use, n (%)	477 (50.9)	349 (50.4)	10788 (45.7)	7781 (45.0)
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)
Female sex, 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/m2 (SD)	35.4 (6.8)	35.7 (7.6)	31.2 (6.4)	31.2 (6.3)
HbA1c, % (SD)	8.1 (2.2)	8.2 (2.0)	8.2 (2.0)	8.2 (2.0)
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)
Insulin use, n (%)	454 (71.5)	496 (77.5)	6024 (61.2)	5893 (60.0)
Heart failure trials				
Participants, n	88	72	4699	4724
Age, years (SD)	67.7 (8.9)	70.4 (9.1)	69.1 (9.6)	69.0 (9.7)
Female sex, n (%)	23 (26.1)	28 (38.9)	1598 (34.0)	1654 (35.0)
History of CV disease, n (%)	63 (71.6)	55 (76.4)	3179 (67.7)	3159 (66.9)
History of heart failure, n (%)	88 (100.0)	72 (100.0)	4699 (100.0)	4724 (100.0)
Systolic BP, mmHg (SD)	127.9 (17.4)	126.9 (16.7)	127.5 (16.5)	127.6 (16.6)
Body mass index, kg/m2 (SD)	31.3 (6.8)	31.3 (7.1)	29.9 (6.0)	30.0 (6.0)
HbA1c, % (SD)	8.0 (1.5)	7.5 (1.7)	7.4 (1.6)	7.4 (1.6)
eGFR, mL/min/1.73m^2 (SD)	53.3 (20.3)	56.2 (20.2)	60.8 (20.5)	60.9 (20.5)
uACR ≥30 mg/g, n (%)*	26 (60.5)	14 (40.0)	1223 (52.0)	1201 (50.8)
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.

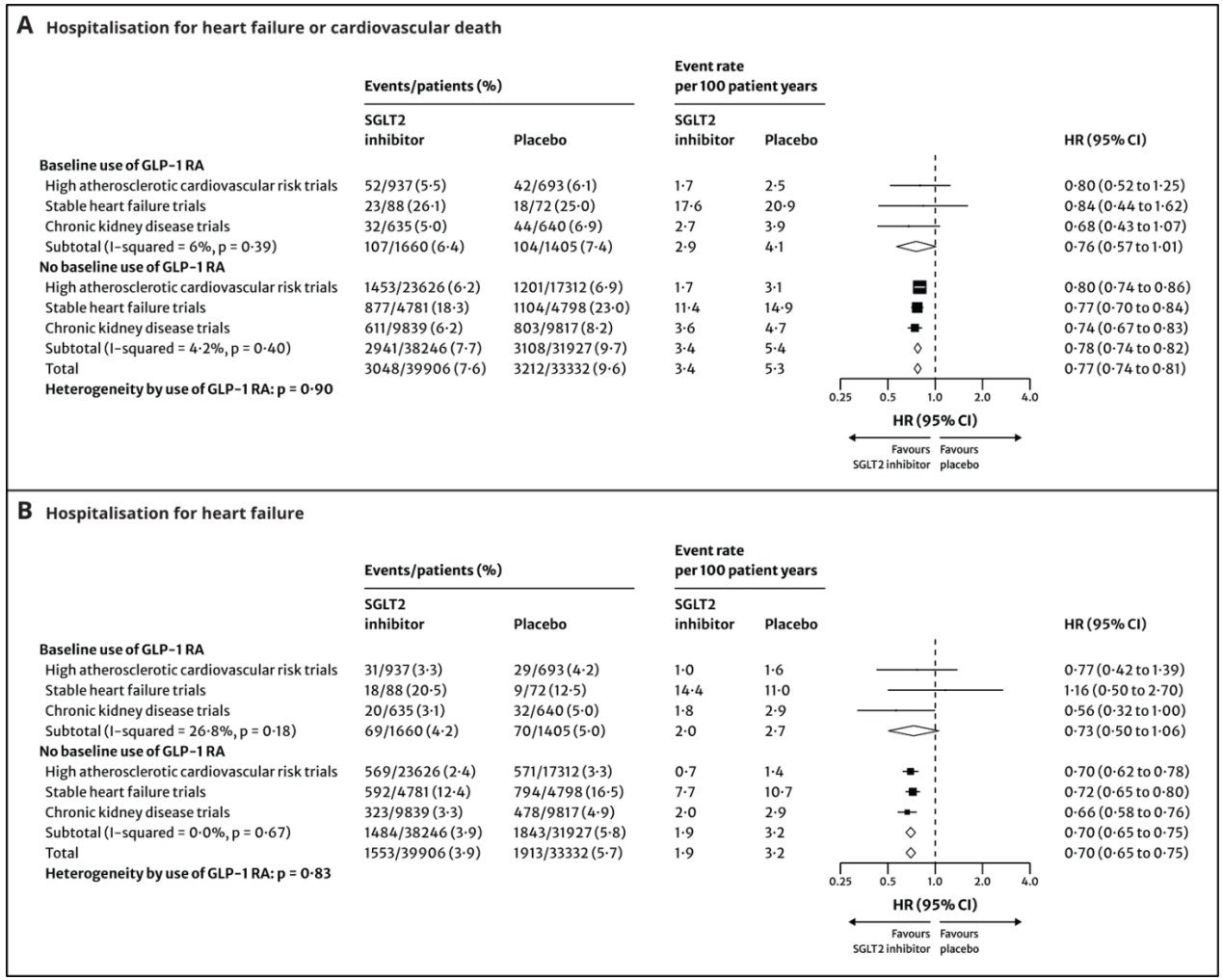
Figure 1. Effect of SGLT2 inhibitors on major adverse cardiovascular events (myocardial infarction, stroke or cardiovascular death) with and without GLP-1 receptor agonists use at baseline.

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	85/937 (9·1)	66/693 (9·5)	2·7	4·3	0·83 (0·60 to 1·15)
Stable heart failure trials	12/88 (13·6)	17/72 (23·6)	7·3	19·0	0·51 (0·24 to 1·11)
Chronic kidney disease trials	42/635 (6·6)	46/640 (7·2)	3·6	4·1	0·89 (0·58 to 1·37)
Subtotal (I-squared = 0·0%, p = 0·86)	139/1660 (8·4)	129/1405 (9·2)	3·3	5·0	0·81 (0·63 to 1·03)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	2408/23620 (10·2)	1789/17310 (10·3)	3·0	4·6	0·91 (0·85 to 0·97)
Stable heart failure trials	614/4781 (12·8)	661/4798 (13·8)	7·6	8·1	0·93 (0·83 to 1·04)
Chronic kidney disease trials	665/9839 (6·8)	782/9817 (8·0)	3·8	4·6	0·84 (0·76 to 0·93)
Subtotal (I-squared = 0·0%, p = 0·80)	3687/38240 (9·6)	3232/31925 (10·1)	3·8	5·1	0·90 (0·86 to 0·94)
Total	3826/39900 (9·6)	3361/33330 (10·1)	3·8	5·1	0·89 (0·85 to 0·94)
Heterogeneity by use of GLP-1 RA: p = 0·31					



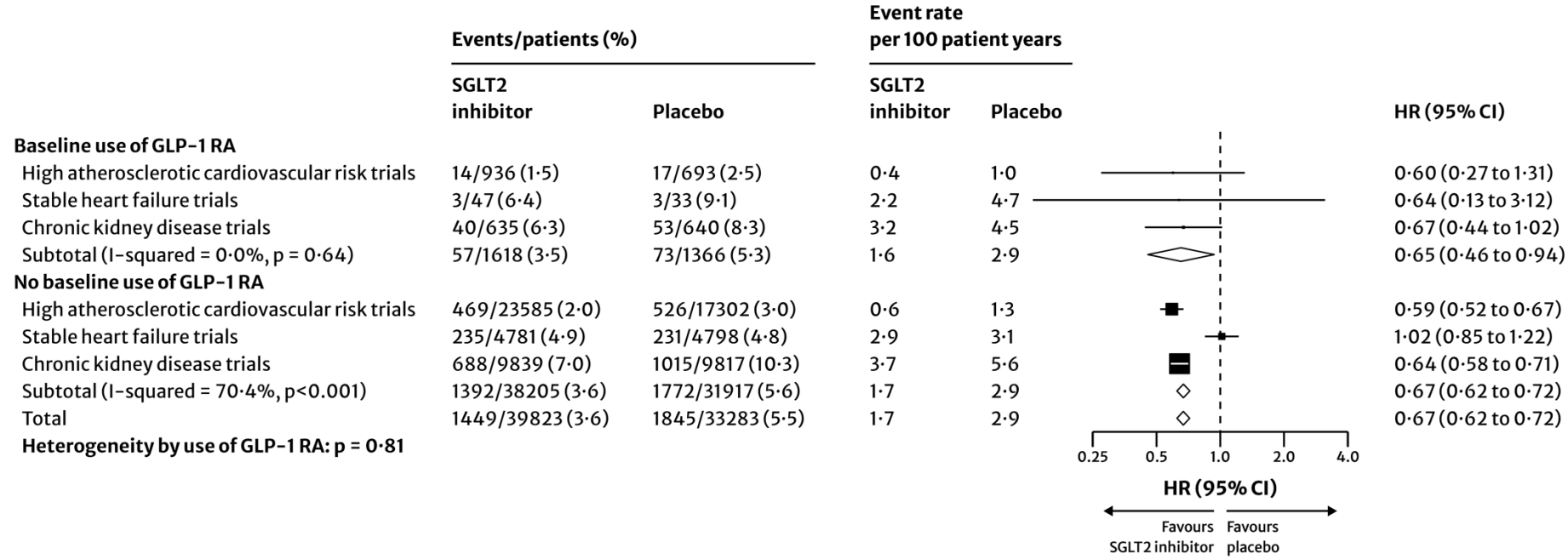
Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

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



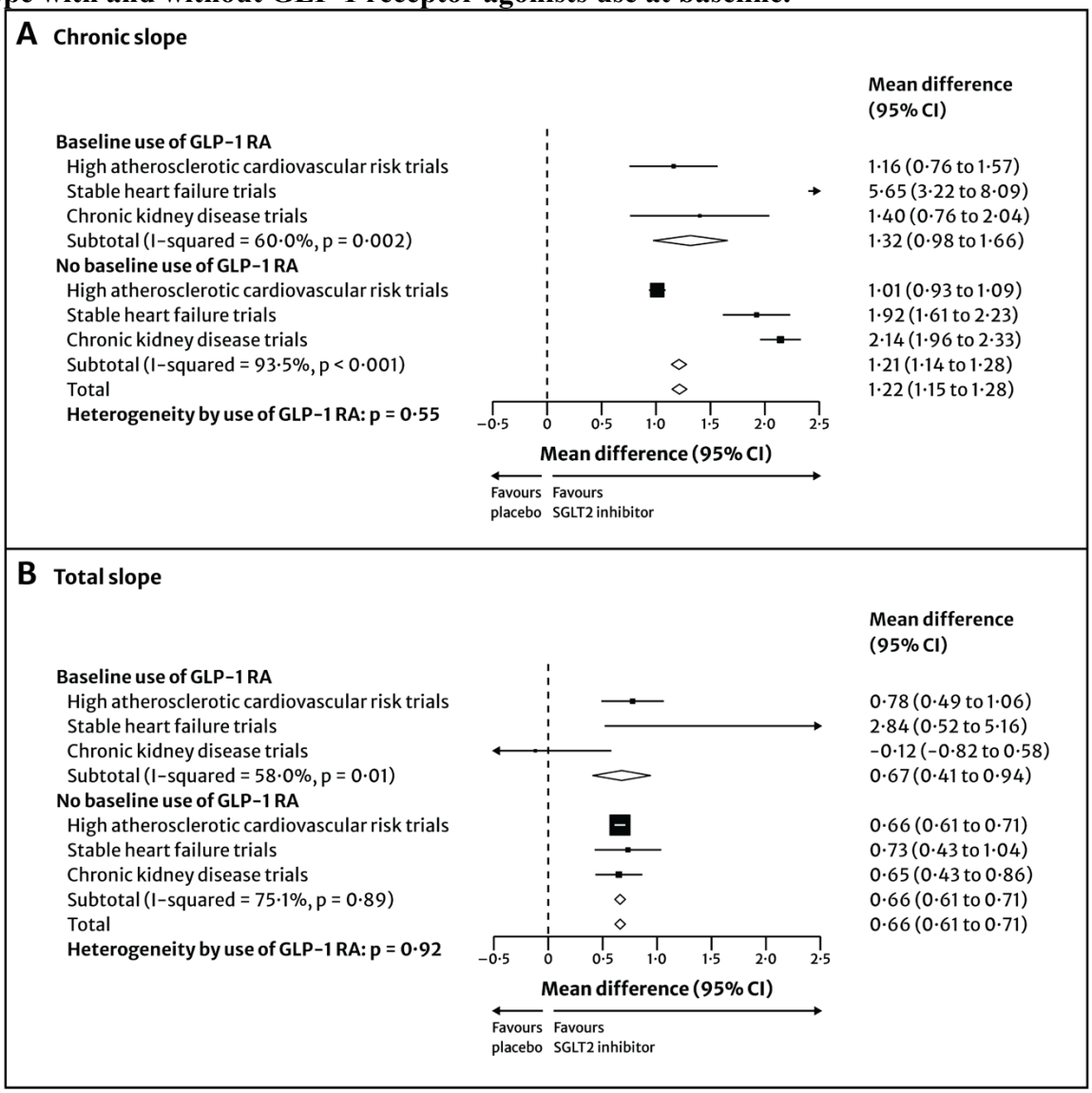
Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

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



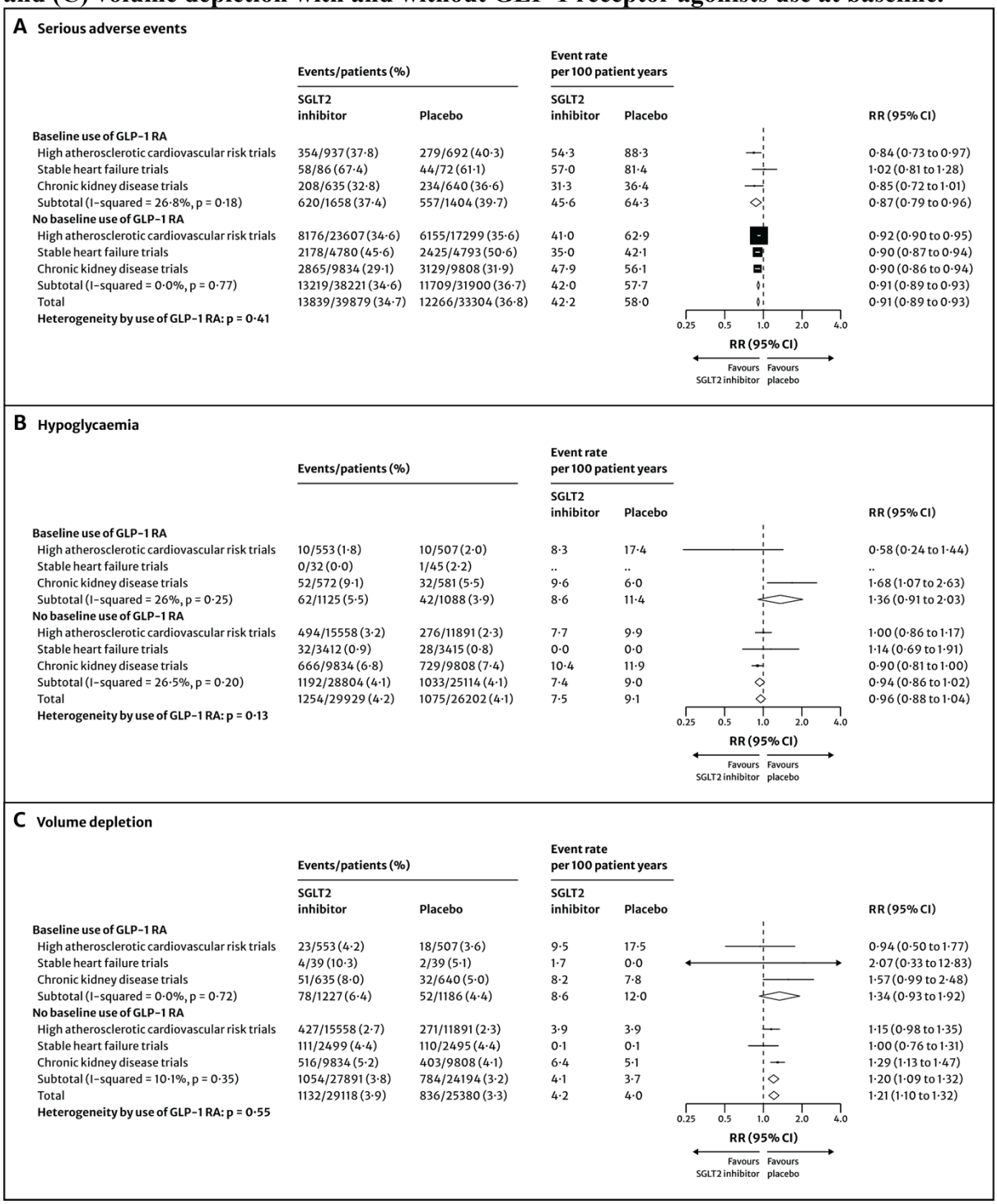
Sodium glucose cotransporter-2 (SGLT2); GLP-1 RA: glucagon-like peptide-1 receptor agonists; HR: hazard ratio; CI: confidence interval.

Figure 4. Effects of SGLT2 inhibitors on (A) chronic eGFR slope and (B) total eGFR slope with and without GLP-1 receptor agonists use 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) serious adverse events, (B) hypoglycaemia and (C) volume depletion with and without GLP-1 receptor agonists use at baseline.



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

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