

# Cardiovascular, Kidney and Safety Outcomes with GLP-1 Receptor Agonists Alone and in Combination with SGLT2 Inhibitors in Type 2 Diabetes: A Systematic Review and Meta-Analysis

**Running title:** *Neuen et al.; GLP-1 RA with and without SGLT2i*

Brendon L. Neuen, MBBS, MSc, PhD<sup>1,2</sup>; Robert A. Fletcher, MSc<sup>1</sup>; Lauren Heath, MBBS<sup>2</sup>; Adam Perkovic, MD<sup>2</sup>; Muthiah Vaduganathan, MD, MPH<sup>3</sup>; Sunil V. Badve, MBBS, PhD<sup>1,4,5</sup>; Katherine R. Tuttle, MD<sup>6</sup>; Richard Pratley, MD<sup>7</sup>; Hertzel Gerstein, MD, MSc<sup>8</sup>; Vlado Perkovic, MBBS, PhD<sup>1,9</sup>; Hiddo JL Heerspink PhD<sup>1,10</sup>

<sup>1</sup>The George Institute for Global Health, University of New South Wales, Sydney, Australia;

<sup>2</sup>Department of Renal Medicine, Royal North Shore Hospital, Sydney, Australia; <sup>3</sup>Division of Cardiovascular Medicine, Center for Cardiometabolic Implementation Science, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; <sup>4</sup>Faculty of Medicine and Health, University of New South Wales, Sydney, Australia; <sup>5</sup>Department of Renal Medicine, St George Hospital, Sydney, Australia; <sup>6</sup>Kidney Research Institute and Nephrology Division, University of Washington School of Medicine Seattle, WA; Providence Medical Research Center, Providence Inland Northwest Health, Spokane, WA; <sup>7</sup>AdventHealth Translational Research Institute, Orlando, FL; <sup>8</sup>Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada; <sup>9</sup>University of New South Wales, Sydney, Australia; <sup>10</sup>Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

## Address of Correspondence:

Dr Brendon L Neuen and Professor Hiddo JL Heerspink

The George Institute for Global Health  
International Towers Three, Level 18  
300 Barangaroo Avenue, Barangaroo  
Sydney NSW 2000, Australia

Email: [bneuen@georgeinstitute.org.au](mailto:bneuen@georgeinstitute.org.au); [h.j.lambers.heerspink@umcg.nl](mailto:h.j.lambers.heerspink@umcg.nl)

\*This article is published in its accepted form, it has not been copyedited and has not appeared in an issue of the journal. Preparation for inclusion in an issue of *Circulation* involves copyediting, typesetting, proofreading, and author review, which may lead to differences between this accepted version of the manuscript and the final, published version.

\*\*This work was presented as an abstract at ESC Congress 2024; August 30–September 2, 2024; London, England.

## Abstract

**Background:** Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors both improve cardiovascular and kidney outcomes in persons with type 2 diabetes. We conducted a systematic review and meta-analysis to assess the effects of GLP-1 receptor agonists on clinical outcomes with and without SGLT2 inhibitors.

**Methods:** We searched MEDLINE and Embase databases from inception until July 12, 2024 for randomized, double-blind, placebo-controlled outcome trials of GLP-1 receptor agonists in type 2 diabetes that reported treatment effects by baseline use of SGLT2 inhibitors, with findings supplemented by unpublished data. We estimated treatment effects by baseline SGLT2 inhibitor use using inverse variance weighted meta-analysis. The main cardiovascular outcomes were major adverse cardiovascular events ([MACE] nonfatal myocardial infarction, stroke or cardiovascular death) and hospitalization for heart failure. Kidney outcomes included a composite of  $\geq 50\%$  reduction in estimated glomerular filtration rate (eGFR), kidney failure or death due to kidney failure, and annualized rate of decline in eGFR (eGFR slope). Serious adverse events and severe hypoglycemia were also evaluated. This meta-analysis was registered on PROSPERO (CRD42024565765).

**Results:** We identified three trials with 1,743/17,072 (10.2%) participants with type 2 diabetes receiving an SGLT2 inhibitor at baseline. GLP-1 receptor agonists reduced the risk of MACE by 21% (HR 0.79, 95% CI 0.71-0.87), with consistent effects in those receiving and not receiving SGLT2 inhibitors at baseline (HR 0.77, 95% CI 0.54-1.09 and HR 0.79, 95% CI 0.71-0.87, respectively; P-heterogeneity=0.78). The effect on hospitalization for heart failure was similarly consistent regardless of SGLT2 inhibitor use (HR 0.58, 95% CI 0.36-0.93 and HR 0.73, 95% CI 0.63-0.85; P-heterogeneity=0.26). Effects on the composite kidney outcome (RR 0.79, 95% CI 0.66-0.95) and eGFR slope (0.78 mL/min/1.73m<sup>2</sup>/year, 95% CI 0.57-0.98) also did not vary according to SGLT2 inhibitor use (P-heterogeneity=0.53 and 0.94, respectively). Serious adverse effects and severe hypoglycemia were also similar regardless of SGLT2 inhibitor use (P-heterogeneity=0.29 and 0.50, respectively).

**Conclusion:** In persons with type 2 diabetes, the cardiovascular and kidney benefits of GLP-1 receptor agonists are consistent regardless of SGLT2 inhibitor use.

**Key Words:** Glucagon-like peptide-1 receptor agonists; cardiovascular diseases; diabetes mellitus, type 2; glomerular filtration rate; kidney; renal insufficiency, chronic; sodium glucose cotransporter 2; treatment outcome

**Non-standard Abbreviations and Acronyms:** GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose cotransporter 2; CKD, chronic kidney disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO International Prospective Register of Systematic Reviews; MACE, major adverse cardiovascular events; eGFR, estimated glomerular filtration rate; AMPLITUDE-O, Effect of efpeglenatide on cardiovascular outcomes; FLOW, Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease; REWIND Researching cardiovascular events with a weekly incretin in diabetes

## Clinical Perspective

### What is new?

- This systematic review and meta-analysis pooled three GLP-1 receptor agonist clinical outcome trials in patients with type 2 diabetes (n=17,072) reporting treatment effects by baseline use of SGLT2 inhibitors (n=1,743[10.2%] using SGLT2 inhibitors at baseline)
- The effects of GLP-1 receptor agonists on cardiovascular and kidney outcomes, including estimated glomerular filtration rate slope, were consistent regardless of baseline use of SGLT2 inhibitors
- Effects on serious adverse events and severe hypoglycemia also did not vary by use of SGLT2 inhibitors at baseline

### What are the clinical implications?

- The totality of the worldwide randomized evidence indicates independent effects with GLP-1 receptor agonists and SGLT2 inhibitors in type 2 diabetes
- Combination treatment with both classes of agents is likely to provide additional benefits on cardiovascular and kidney outcomes for patients with type 2 diabetes



## Introduction

Large clinical outcome trials have indicated that glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular events and chronic kidney disease (CKD) progression in persons with type 2 diabetes.<sup>1, 2</sup> As a result, clinical practice guidelines from major cardiovascular, endocrinology, and nephrology organizations recommend both classes of agents to people with type 2 diabetes to reduce cardio-kidney-metabolic risk.<sup>3-5</sup>

Because of their distinct and complementary mechanisms of action, there has been substantial interest in using both classes of agents in combination to further improve clinical outcomes in persons with type 2 diabetes. Small trials of short duration suggest that combined use of GLP-1 receptor agonists and SGLT2 inhibitors improve glycemia, blood pressure, body weight and albuminuria to a greater extent than either alone.<sup>6, 7</sup> In a 2024 collaborative meta-analysis of 12 completed SGLT2 inhibitor outcome trials, the cardiovascular and kidney benefits of SGLT2 inhibitors were consistent regardless of background use of GLP-1 receptor agonists.<sup>8</sup>

Whether the effects of GLP-1 receptor agonists are similarly independent of SGLT2 inhibitor use across outcomes trials remains unresolved. While subgroup analyses of the AMPLITUDE-O trial suggest that the effects of GLP-1 receptor agonists might be consistent irrespective of SGT2 inhibitor use,<sup>9</sup> the background use of SGLT2 inhibitors in any single trial was too infrequent and the number of events too limited to reliably assess the effects of GLP-1 receptor agonists on clinical outcomes in those receiving and not receiving an SGLT 2 inhibitor.

We therefore conducted a systematic review and meta-analysis to evaluate the effects of GLP-1 receptor agonists on cardiovascular, kidney, mortality and key safety outcomes in people with type 2 diabetes according to use of SGLT2 inhibitors.

## Methods

This systematic review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.<sup>10</sup> The protocol for this meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42024565765). We confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

We searched MEDLINE and Embase databases from inception to July 12, 2024 for English language publications using the search term “glucagon-like peptide-1 receptor agonist” and related phrases, including individual drug names and terms related to randomized controlled trials. Full details of the search strategy are provided in Table S1. We included all randomized, double-blind, placebo-controlled, event-driven randomized trials in persons with type 2 diabetes evaluating a GLP-1 receptor agonist versus placebo on a primary clinical outcome where subgroup data were available for clinical outcomes by baseline use of SGLT2 inhibitors. Two authors (LH and AP) independently screened and reviewed titles, abstracts and full texts where required to identify studies eligible for inclusion. Any discrepancies resolved through consensus discussion with a third author (BLN).

Two authors (BLN and RF) independently extracted data using a standardized form and assessed risk of bias using version 2 of the Cochrane risk of bias tool. Any discrepancies were resolved through consensus discussion with a third author (HJLH).



We assessed the effects of GLP-1 receptor agonists with and without SGLT2 inhibitors on a range of adjudicated cardiovascular, kidney, and mortality outcomes as well as key safety outcomes. These included: major adverse cardiovascular events ([MACE] nonfatal myocardial infarction or cardiovascular death); hospitalization for heart failure; cardiovascular death; and all-cause mortality. We evaluated two kidney outcomes: a composite outcome of sustained  $\geq 50\%$  reduction in eGFR, kidney failure, or cardiovascular or kidney failure-related death, as well as the annualized rate of decline in eGFR (total eGFR slope). For total eGFR slope, a validated surrogate outcome for CKD progression, we annualized reported changes in eGFR from baseline to follow-up, obtained from mixed effects models for repeat measures. Because total eGFR slope is an absolute measure of effect which is dependent on the background rate of eGFR decline that varies depending on the population studied, we also calculated the relative treatment effect on eGFR slope by dividing the absolute effect and its 95% CI by the mean slope in the placebo group, as done in previous trials and meta-analyses reporting this outcome.<sup>8, 11</sup> Key safety outcomes assessed were serious adverse events and severe hypoglycemia. Findings from database review were supplemented by unpublished data obtained by contacting the relevant investigators wherever possible.

### **Statistical analysis**

To compared characteristics of participants receiving and not receiving SGLT2 inhibitors at baseline across the included trials, we calculated the weighted mean and standard deviations for continuous variables using the weighted inverse variance method and pooled categorial variables as has been done previously.<sup>8</sup>

We undertook two-stage inverse variance weighted meta-analysis, with summary effect estimates obtained by pooling log-transformed hazards ratios and risk ratios using inverse-variance weighted averages as was done in large-scale collaborative meta-analyses

undertaken by the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium.<sup>2,8</sup> We used hazards ratios (HR) and supplemented these with risk ratios (RR) based on the number of events and participants where HRs were not available. We pooled treatment effects on total eGFR slope as aforementioned. Heterogeneity in treatment effects by baseline SGLT2 inhibitor use was assessed using p-values for heterogeneity obtained from random-effects meta-regression with restricted maximum likelihood (REML), assuming a normal distribution for the random effects with constant variance across the range of the outcome. All analyses were performed with R version 4.3.1.

## Results

From 3,361 records identified, we identified six publications of three trials assessing three GLP-1 receptor agonists: albiglutide, efpeglenatide, and semaglutide (Figure S1).<sup>9,12-16</sup> Two trials (Harmony Outcomes and AMPLITUDE-O) evaluated the effect of a GLP-1 receptor agonist on a primary outcome of MACE and one trial (FLOW) evaluated the effect of a GLP-1 receptor agonist on a primary outcome of sustained  $\geq 50\%$  reduction in eGFR, kidney failure or cardiovascular or kidney-failure-related death. Median follow-up ranged from 1.6 years (Harmony Outcomes) to 3.4 years (FLOW) (**Table 1**). SGLT2 inhibitor use at baseline was 6.1% in Harmony Outcomes, 15.2% in AMPLITUDE-O and 15.6% in FLOW (**Table 1**). In two trials (AMPLITUDE-O and FLOW), randomization was stratified by SGLT2 inhibitor use at baseline (**Table 1**). Risk of bias was low for all three trials (Table S2). Outside of these three trials, use of SGT2 inhibitors at baseline was  $\leq 1\%$  in almost all other GLP-1 receptor agonist outcome trials.<sup>1</sup>

Across the three trials 1,743/17,072 (10.2%) participants were receiving an SGLT2 inhibitor at baseline. Those receiving an SGLT2 inhibitor at baseline were younger, more likely to be men, and less likely to have a history of heart failure. They were also more likely to have a higher baseline eGFR (**Table 2**).



Overall, 1,538 participants experienced a MACE outcome, 132 (8.6%) and 1,406 (91.4%) receiving and not receiving an SGLT2 inhibitor at baseline, respectively. GLP-1 receptor agonists reduced the risk of MACE by 21% (HR 0.79, 95% CI 0.71-0.87), with consistent effects in those receiving and not receiving an SGLT2 inhibitor at baseline (HR 0.77, 95% CI 0.54-1.09 and HR 0.79, 95% CI 0.71-0.87; P-heterogeneity=0.78; **Figure 1A**).

There were 775 first hospitalizations for heart failure, including 75 (9.7%) and 700 (90.3%) receiving and not receiving SGLT2 inhibitors at baseline, respectively. GLP-1 receptor agonists consistently reduced the risk of hospitalization for heart failure in participants receiving and not receiving SGLT2 inhibitors at baseline (HR 0.58, 95% CI 0.36-0.93 and HR 0.73, 95% CI 0.63-0.85; P-heterogeneity=0.26; **Figure 1B**).

Overall, 669 (3.9%) and 1,087 (6.4%) participants died due to cardiovascular disease or due to any cause, respectively. The effect of GLP-1 receptor agonists on cardiovascular death was consistent in participants receiving and not receiving an SGLT2 inhibitor (HR 0.57, 95% CI 0.31-1.04 and HR 0.81, 95% CI 0.69-0.95, respectively; P-heterogeneity=0.31; **Figure 2A**). A similarly consistent pattern of effect was observed for all-cause mortality (HR 0.67, 95% CI 0.42-1.06 and HR 0.85, 95% CI 0.76-0.96; P-heterogeneity=0.31; **Figure 2B**).

490 participants experienced the composite kidney outcome, including 63 (12.9%) and 427 (87.1%) receiving and not receiving SGLT2 inhibitors at baseline, respectively. GLP-1 receptor agonists reduced the composite kidney outcome overall (RR 0.79, 95% CI 0.66-0.95), with no statistical evidence of heterogeneity, although there were few kidney outcomes in the SGLT2 inhibitor subgroup (P-heterogeneity=0.53; **Figure 3A**). GLP-1 receptor agonists improved total eGFR slope by 0.76 mL/min/1.73m<sup>2</sup>/year in participants receiving an SGLT2 inhibitor and 1.25 mL/min/1.73m<sup>2</sup>/year in those not receiving an SGLT2 inhibitor (P-heterogeneity for absolute difference 0.94; **Figure 3B**). In relative terms, this translated into a

35% (95% CI 9-61) and 26% (95% CI 20-34) improvement in total eGFR slope, respectively (P-heterogeneity for relative difference 0.99; **Figure 3B**).

Overall, the incidence of serious adverse events was lower with GLP-1 receptor agonists compared to placebo (RR 0.93, 95% CI 0.89-0.97), an effect consistent regardless of SGLT2 inhibitor use at baseline (P-heterogeneity=0.29; **Figure 4**). The effect on severe hypoglycemia (RR 0.78, 95% CI 0.58-1.03) was also similar regardless of baseline SGLT2 inhibitor use (P-heterogeneity=0.50; **Figure 4**).

## Discussion

In this meta-analysis of three large-scale randomized GLP-1 receptor agonist clinical outcome trials, the effects on cardiovascular, kidney and mortality outcomes were consistent regardless of SGLT2 inhibitor use at baseline. With 1,743 participants receiving an SGLT2 inhibitor at baseline, these analyses include data from the three completed GLP-1 receptor agonists outcome trials that included the largest numbers of participants receiving SGLT2 inhibitors. As a result, these data represent the most comprehensive analysis of the effects of GLP-1 receptor agonists on cardiovascular, kidney and safety outcomes with and without SGLT2 inhibitors. The available randomized evidence indicates that combining GLP-1 receptor agonists and SGLT2 inhibitors offers the potential to further improve cardiovascular and kidney outcomes in persons with type 2 diabetes.

Inconsistent statements from major clinical practice guidelines on the combined use of GLP-1 receptor agonists and SGLT2 inhibitors reflect the previously limited evidence regarding effects on clinical outcomes. European Society of Cardiology guidelines for the management of cardiovascular disease in diabetes identifies the combined use of SGLT2 inhibitors and GLP-1 receptor agonists as an evidence gap.<sup>17</sup> In contrast, the American Diabetes Association Standards of Care recommends that combined use may be considered for additive cardio-kidney protection.<sup>4</sup> Since the publication of these guidelines, a 2024



collaborative meta-analysis of 12 SGLT2 inhibitor trials enrolling 73,000 participants of whom over 3000 participants receiving a GLP-1 receptor agonist concluded that the effects of SGLT2 inhibitors are consistent irrespective of GLP-1 receptor agonists.<sup>8</sup> Together with our findings that the effects of GLP-1 receptor agonists are consistent regardless of SGLT2 inhibitor use, the totality of the worldwide placebo-controlled randomized evidences indicates that combination GLP-1 receptor agonists and SGLT2 inhibitors are likely to have independent and additive effects on clinical outcomes in persons with type 2 diabetes.

The clear evidence of benefit on hospitalization for heart failure with GLP-1 receptor agonists, regardless of SGLT2 inhibitor use, is noteworthy since heart failure is one of the most frequent first manifestation of cardiovascular disease in people with diabetes.<sup>18</sup> While SGLT2 inhibitors are strongly guideline recommended to reduce the risk of heart failure outcomes in persons with diabetes, CKD or heart failure,<sup>5, 19, 20</sup> the effect of GLP-1 receptor agonists on this outcome has been less clear. Meta-analyses of GLP-1 receptor agonist cardiovascular outcome trials identified potential benefits on heart failure hospitalization.<sup>1</sup> In pooled analyses of the STEP-HFpEF trials, semaglutide improved functional status and reduced hospitalization for heart failure or cardiovascular death in persons with heart failure with preserved ejection fraction.<sup>21</sup> In the SELECT and FLOW trials, semaglutide reduced heart failure events in people with obesity or overweight and established cardiovascular disease who did not have diabetes and in people with CKD and type 2 diabetes, respectively.<sup>12, 22</sup> Thus, emerging evidence suggests that GLP-1 RA may reduce worsening heart failure across the spectrum of cardio-kidney-metabolic diseases, including when used in addition to SGLT2 inhibitors.

The data on eGFR slope, a validated surrogate outcome for CKD progression,<sup>23</sup> is particularly important, given that the number of composite kidney outcomes observed in participants receiving SGLT2 inhibitors was low. In the FLOW trial, semaglutide reduced the

risk of CKD progression, kidney failure or cardiovascular or kidney failure-related death by 24% in people with established CKD and type 2 diabetes, supporting a GLP-1 receptor agonist as a key evidence-based therapy to prevent kidney failure.<sup>12</sup> While evidence for kidney protection is clearest for semaglutide, benefits on kidney outcomes have also been observed with other GLP-1 receptor agonists, most notably dulaglutide in the REWIND trial.<sup>24, 25</sup> Importantly, the magnitude of benefit on total eGFR slope (~0.75 mL/min/1.73m<sup>2</sup>/year) in participants receiving and not receiving SGLT2 inhibitors is clinically meaningful, and consistent with an effect size that is highly likely to translate to benefit on clinical kidney endpoints, based on the work of the CKD-Epidemiology Clinical Trials Consortium.<sup>26</sup> The eGFR slope data in this analysis provide the clearest evidence yet that GLP-1 receptor agonists attenuate the rate of GFR decline, independent of SGLT2 inhibitor use, and suggest that GLP-1 receptor agonists should be used alongside SGLT2 inhibitors and other evidence-based kidney therapies to reduce loss of kidney function in people with type 2 diabetes.

GLP-1 receptor agonists and SGLT2 inhibitors have distinct and separate mechanisms of action that have made the concept of combination therapy inherently attractive to clinicians and patients. Both classes of agents improve cardiometabolic risk factors, although the magnitude of benefit on glycemia and body weight is greater with GLP-1 receptor agonists. However, the mechanisms contributing to end-organ protection with both classes of agents are likely to be multifactorial and extend beyond improvements in cardiometabolic risk factors. Experimental models have indicated that GLP-1 receptor agonists exert direct anti-atherosclerotic and anti-inflammatory effects that appear independent of weight loss, which may contribute to their more prominent effects on myocardial infarction and stroke which have not been as clearly demonstrated with SGLT2 inhibitors.<sup>27, 28</sup> On the other hand, SGLT2 inhibitors reduce glomerular hyperfiltration and tubular energy expenditure and may



also have important effects on cellular metabolism, contributing to substantial benefits on heart failure and kidney failure.<sup>29, 30</sup> The observed consistency of benefit on cardio-kidney outcomes with GLP-1 receptor agonists regardless of SGLT2 inhibitor use further strengthens the rationale for combination therapy with both classes of agents.

A key strength of this meta-analysis is the inclusion of data from the three GLP-1 receptor agonists trials with the largest number of participants receiving an SGLT2 inhibitor at baseline; use of SGT2 inhibitors at baseline was  $\leq 1\%$  in most other GLP-1 receptor agonist outcome trials. Other important features of this work are the use of unpublished data from both AMPLITUDE-O and FLOW, two trials that stratified randomization by SGLT2 inhibitor use, as well as a harmonized composite kidney outcome definition, which has not been available in previous meta-analyses of GLP-1 receptor agonists.<sup>1</sup>

However, there are some important limitations of this work. FLOW was the only dedicated kidney outcome trial included and thus the number of kidney outcomes in the SGLT2 inhibitor subgroup was low, limiting our ability to explore heterogeneity in effects on this outcome. However, the continuous eGFR slope outcome provided substantially greater statistical power to evaluate effects of CKD progression, with clear evidence of benefit regardless of SGLT2 inhibitor use. While the number of hospitalizations for heart failure in the SGLT2 inhibitor subgroup was also relatively modest, we were able to detect clear benefit in these individuals. These analyses did not account for SGLT2 inhibitor initiation during the trials, however such analyses introduce bias through the evaluation of post-randomization subgroups. Finally, we were not able to evaluate other GLP-1 receptor agonists such as dulaglutide and liraglutide because trials of these agents included very few, if any, participants receiving SGLT2 inhibitors at baseline.



In summary, in persons with type 2 diabetes, the effects of GLP-1 receptor agonists on cardiovascular, kidney and safety outcomes are consistent regardless of SGLT2 inhibitor use. The totality of the randomized evidence therefore indicates independent effects of these therapies and supports their combined use to further improve clinical outcomes in type 2 diabetes.

## Sources of funding

None.

## Disclosures

BLN 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 Travers Therapeutics with all honoraria paid to The George Institute for Global Health. RAF has received studentship awards from the HDR-UK-Turing Wellcome Programme in Health Data Science. MV has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, 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. SVB reports consulting fees from Bayer, AstraZeneca, GlaxoSmithKline, and Vifor Pharma; speaking fees from Bayer, AstraZeneca, Pfizer, and Vifor Pharma (all honoraria paid to his institution); and nonfinancial research support from Bayer. KRT is supported by NIH research grants R01MD014712, U2CDK114886, UL1TR002319, U54DK083912,



U01DK100846, OT2HL161847, UM1AI109568, OT2OD032581, and CDC project numbers 75D301-21-P-12254 and 75D301-23-C-18264. She has also received investigator-initiated grant support from Travere Therapeutics Inc, Bayer, and the Doris Duke Charitable Foundation. She reports consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Travere Therapeutics Inc, and Pfizer; and speaker fees from Novo Nordisk. REP declares speaker fees from Lilly and Novo Nordisk; consulting fees from Bayer AG, Bayer HealthCare Pharmaceuticals, Endogenex, Gasherbrum Bio, Genprex, Getz Pharma, Intas Pharmaceuticals, Lilly, Novo Nordisk, Pfizer and Sun Pharmaceutical Industries; and research grants from Biomea Fusion, Carmot Therapeutics, Dompe, Endogenex, Fractyl, Lilly, Novo Nordisk and Sanofi. HCG holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, AstraZeneca, Novo Nordisk, Hanmi, and Merck; continuing education grants from Eli Lilly, Abbott, Sanofi, Novo Nordisk and Boehringer Ingelheim; honoraria for speaking from AstraZeneca, Eli Lilly, Novo Nordisk, DKSH, Zuellig, Sanofi, Carbon Brand, and Jiangsu Hanson; and consulting fees from Abbott, Bayer, Eli Lilly, Novo Nordisk, Pfizer, Sanofi, Kowa, and Hanmi. VP serves as a board director for St Vincent's Health Australia, Victor Chang Cardiac Research Institute, and Mindgardens; and has received honoraria for Steering Committee roles, scientific presentations, or advisory board attendance, or a combination, 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. HJLH 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 Travere



Therapeutics; and payment or honoraria for speaking from AstraZeneca and Novo Nordisk.

EMA and NJ declare no competing interests. All other authors have nothing to declare.

### Acknowledgements

BLN is supported by 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). These funders had no role in the design, analysis or writing of the manuscript or decision to submit for publication.

### Supplemental Materials

Tables S1 - 2

Figures S1



Circulation

## References

1. Sattar N, Lee MM, Kristensen SL, Branch KR, Del Prato S, Khurmi NS, Lam CS, Lopes RD, McMurray JJ and Pratley RE. 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;9:653-662.
2. 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;400:1788-1801.
3. Rossing P, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K, Liew A, Michos ED, Navaneethan SD and Olowu WA. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney International*. 2022;102:S1-S127.
4. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2024. *Diabetes Care*. 2023;47:S179-S218.
5. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C and Mingrone G. 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;45:2753-2786.
6. Mantsiou C, Karagiannis T, Kakotrichi P, Malandris K, Avgerinos I, Liakos A, Tsapas A and Bekiari E. 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;22:1857-1868.
7. van Ruiten CC, van der Aart-van der Beek AB, IJzerman RG, Nieuwdorp M, Hoogenberg K, van Raalte DH and Heerspink HJL. Effect of exenatide twice daily and dapagliflozin, alone and in combination, on markers of kidney function in obese patients with type 2 diabetes: A prespecified secondary analysis of a randomized controlled clinical trial. *Diabetes, Obesity and Metabolism*. 2021;23:1851-1858.
8. Apperloo EM, Neuen BL, Fletcher RA, Jongs N, Anker SD, Bhatt DL, Butler J, Cherney DZI, Herrington WG, Inzucchi SE, Jardine MJ, Liu C-C, Mahaffey KW, McGuire DK, McMurray JJV, Neal B, Packer M, Perkovic V, Sabatine MS, Solomon SD, Staplin N, Szarek M, Vaduganathan M, Wanner C, Wheeler DC, Wiviott SD, Zannad F and Heerspink HJL. 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;12:545-557.
9. Lam CS, Ramasundarahettige C, Branch KR, Sattar N, Rosenstock J, Pratley R, Del Prato S, Lopes RD, Niemoeller E and Khurmi NS. Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation*. 2022;145:565-574.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA and Brennan SE. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372.
11. The EMPA-KIDNEY Collaborative Group. Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empagliflozin trial. *The Lancet Diabetes & Endocrinology*. 2024;12:39-50.
12. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL and Pratley R. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2024;391:109-121.

13. Mann JFE, Rossing P, Bakris G, Belmar N, Bosch-Traberg H, Busch R, Charytan DM, Hadjadj S, Gillard P, Górriz JL, Idorn T, Ji L, Mahaffey KW, Perkovic V, Rasmussen S, Schmieder RE, Pratley RE and Tuttle KR. Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial. *Nature Medicine*. 2024.
14. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, Lam CSP, Khurmi NS, Heenan L, Prato SD, Dyal L and Branch K. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *New England Journal of Medicine*. 2021;385:896-907.
15. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *The Lancet*. 2018;392:1519-1529.
16. Neves JS, Borges-Canha M, Vasques-Nóvoa F, Green JB, Leiter LA, Granger CB, Carvalho D, Leite-Moreira A, Hernandez AF, Del Prato S, McMurray JJV and Ferreira JP. GLP-1 Receptor Agonist Therapy With and Without SGLT2 Inhibitors in Patients With Type 2 Diabetes. *Journal of the American College of Cardiology*. 2023;82:517-525.
17. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, Christodorescu RM, Crawford C, Di Angelantonio E, Eliasson B, Espinola-Klein C, Fauchier L, Halle M, Herrington WG, Kautzky-Willer A, Lambrinou E, Lesiak M, Lettino M, McGuire DK, Mullens W, Rocca B, Sattar N and Group ESD. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). *European Heart Journal*. 2023;44:4043-4140.
18. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A and Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1&#xb7;9 million people. *The Lancet Diabetes & Endocrinology*. 2015;3:105-113.
19. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International*. 2024;105:S117-S314.
20. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Skibeland AK and Group ESD. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2023;44:3627-3639.
21. Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrøm SZ, Davies MJ, Hovingh GK, Kitzman DW, Møller DV, Verma S, Einfeldt MN, Lindegaard ML, Rasmussen S, Abhayaratna W, Ahmed FZ, Ben-Gal T, Chopra V, Ezekowitz JA, Fu M, Ito H, Lelonek M, Melenovský V, Merkely B, Núñez J, Perna E, Schou M, Senni M, Sharma K, van der Meer P, Von Lewinski D, Wolf D and Kosiborod MN. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. *The Lancet*. 2024;403:1635-1648.
22. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM,

- Plutzky J, Tornøe CW and Ryan DH. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine*. 2023;389:2221-2232.
23. Inker LA, Collier W, Greene T, Miao S, Chaudhari J, Appel GB, Badve SV, Caravaca-Fontán F, Del Vecchio L, Floege J, Goicoechea M, Haaland B, Herrington WG, Imai E, Jafar TH, Lewis JB, Li PKT, Maes BD, Neuen BL, Perrone RD, Remuzzi G, Schena FP, Wanner C, Wetzel JFM, Woodward M and Heerspink HJL. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. *Nature Medicine*. 2023;29:1867-1876.
24. Botros FT, Gerstein HC, Malik R, Nicolay C, Hoover A, Turfanda I, Colhoun HM and Shaw JE. Dulaglutide and Kidney Function-Related Outcomes in Type 2 Diabetes: A REWIND Post Hoc Analysis. *Diabetes Care*. 2023;46:1524-1530.
25. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Botros FT, Riddle MC, Rydén L et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *The Lancet*. 2019;394:131-138.
26. Inker LA, Heerspink HJL, Tighiouart H, Levey AS, Coresh J, Gansevoort RT, Simon AL, Ying J, Beck GJ and Wanner C. GFR slope as a surrogate end point for kidney disease progression in clinical trials: A meta-analysis of treatment effects of randomized controlled trials. *Journal of the American Society of Nephrology*. 2019;30:1735-1745.
27. Drucker DJ. The benefits of GLP-1 drugs beyond obesity. *Science*. 2024;385:258-260.
28. Patel S, Kang YM, Neuen BL, Anker SD, Bhatt DL, Butler J, Cherney DZ, Claggett BL, Fletcher RA, Herrington WG, Inzucchi Silvio E, Jardine MJ, Mahaffey KW, McGuire DK, McMurray John JV, Neal B, Packer M, Perkovic V, Solomon Scott D, Staplin N, Vaduganathan M, Wanner C, Wheeler DC, Zannad F, Zhao Y, Heerspink Hiddo JL, Sabatine Marc S and Wiviott SD. Sodium Glucose Co-transporter 2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis. *Circulation*. 2024.
29. Cherney DZ, Perkins BA, Soleimanlou N, Maiione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE and Broedl UC. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587-597.
30. 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;146:1383-1405.

**Table 1.** Characteristics of included trials.

	<b>FLOW</b>	<b>AMPLITUDE-O</b>	<b>Harmony Outcomes</b>
<b>Number of participants</b>	3533	4076	9463
<b>Drug</b>	Semaglutide	Efpeglenatide	Albiglutide
<b>Primary outcome</b>	≥50% reduction in eGFR, kidney failure, or death due to cardiovascular or kidney failure related death	Nonfatal myocardial infarction, nonfatal stroke, cardiovascular death	Nonfatal myocardial infarction, nonfatal stroke, cardiovascular death
<b>Median follow up (years)</b>	3.4	1.8	1.6
<b>Age (mean [SD], years)</b>	66.6 (9)	64.5 (8.2)	64 (7)
<b>Women (no. [%])</b>	1069 (30.3)	1344 (33.0)	2894 (31)
<b>HbA1c (mean [SD], %)</b>	7.8 (1.3)	8.91 (1.5)	8.7 (1.5)
<b>Established cardiovascular disease (no. [%])</b>	808 (22.9)	3650 (89.6)	9463 (100)
<b>History of heart failure (no. [%])</b>	678 (19.2)	737 (18.1)	1922 (20)
<b>SGLT2i use at baseline (no. [%])</b>	550 (15.6)	618 (15.2)	575 (6.1)
<b>Randomization stratified by SGLT2i</b>	Yes	Yes	No

SD: standard deviation; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate.

**Table 2. Baseline characteristics of participants in the included trials according to SGLT2 inhibitor use at baseline.**

	FLOW		AMPLITUDE-O		Harmony Outcomes		Pooled	
	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i
<b>N (%) unless stated</b>	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i	SGLT2i	No SGLT2i
<b>Number of participants</b>	550	2983	618	3458	575	8887	1743	15328
<b>Age (mean [SD], years)</b>	64.8 (9.1)	67 (8.9)	64 (8.1)	64.6 (8.3)	62.9 (8.2)	64.2 (8.7)	64.1 (8.5)	65.6 (8.7)
<b>Women</b>	124 (22.5)	945 (31.7)	174 (28.2)	1170 (33.8)	140 (24.3)	2754 (31)	438 (25.1)	4869 (31.8)
<b>White</b>	320 (58.2)	2003 (67.1)	524 (84.7)	3010 (87)	491 (85.4)	6091 (68.5)	1335 (76.6)	11104 (72.4)
<b>HbA1c (mean [SD], %)</b>	7.8 (1.2)	7.8 (1.3)	8.6 (1.2)	9 (1.5)	8.5 (1.2)	8.8 (1.5)	8.2 (1.3)	8.3 (1.6)
<b>BMI (mean [SD], kg/m<sup>2</sup>)</b>	31.7 (6.2)	32 (6.4)	32.8 (6.2)	32.7 (6.1)	33.6 (5.8)	32.2 (5.9)	32.5 (6.1)	32.2 (6)
<b>Systolic BP (mean [SD], mmHg)</b>	134.9 (15.6)	139.3 (15.7)	131.8 (15.1)	135.4 (15.5)	132.2 (16.3)	134.9 (16.6)	133.5 (15.7)	137.3 (16.3)
<b>Diastolic BP (mean [SD], mmHg)</b>	75.3 (9.6)	76.7 (10.1)	75.6 (9.9)	76.9 (9.7)	75.3 (9.5)	76.9 (10.1)	75.3 (9.7)	76.8 (10)
<b>History of heart failure</b>	82 (14.9)	596 (20)	85 (13.8)	652 (18.9)	87 (15.1)	1835 (20.6)	254 (14.6)	3083 (20.1)
<b>eGFR (mean [SD], ml/min/1.73m<sup>2</sup>)</b>	51.1 (15.3)	46.3 (15)	73.6 (21)	72.2 (22.6)	80.1 (23.8)	79 (25.6)	59.3 (25.6)	54.4 (31.2)

N (%) unless otherwise stated. SGLT2i: sodium-glucose cotransporter-2 inhibitor; SD: standard deviation; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate.

## Figure Legends

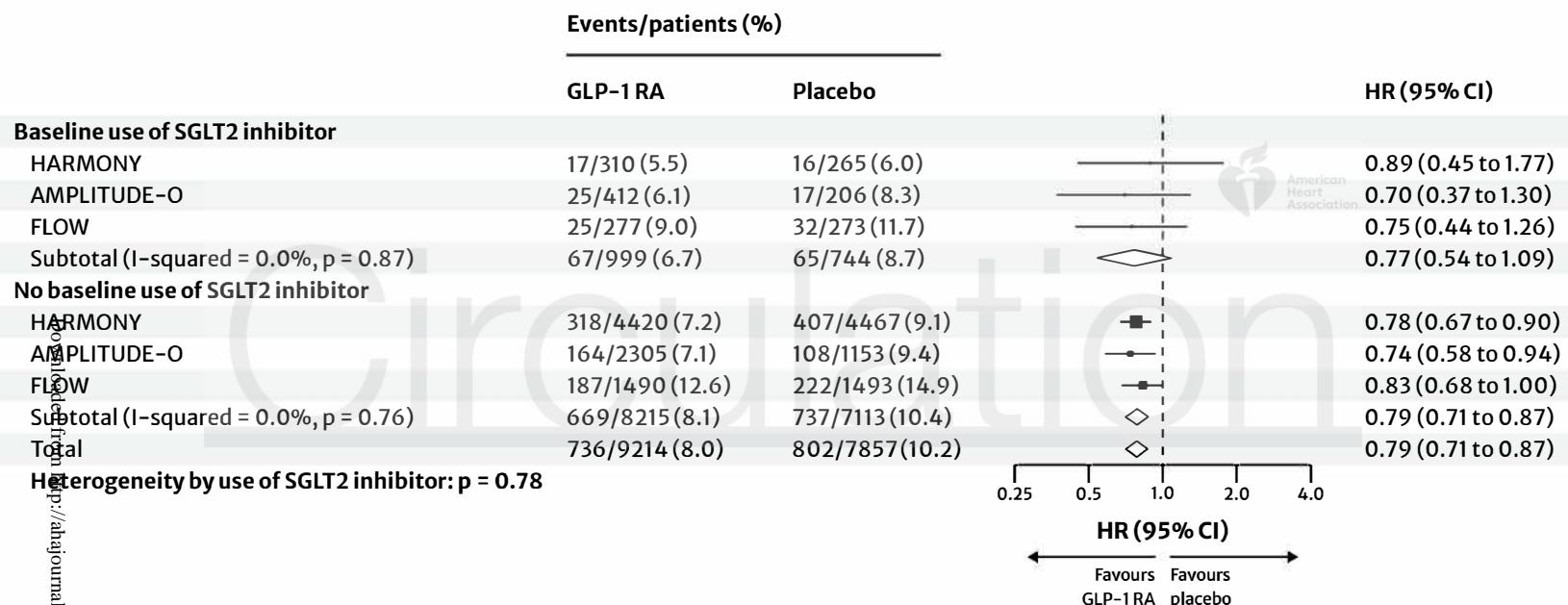
**Figure 1. Effects of GLP-1 receptor agonists on (A) major adverse cardiovascular events and (B) hospitalization for heart failure by baseline SGLT2 inhibitor use.** GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2: sodium glucose cotransporter-2; HR: hazard ratio; CI: confidence interval.

**Figure 2. Effects of GLP-1 receptor agonists on (A) cardiovascular death and (B) all-cause death by baseline SGLT2 inhibitor use.** GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2: sodium glucose cotransporter-2; HR: hazard ratio; CI: confidence interval.

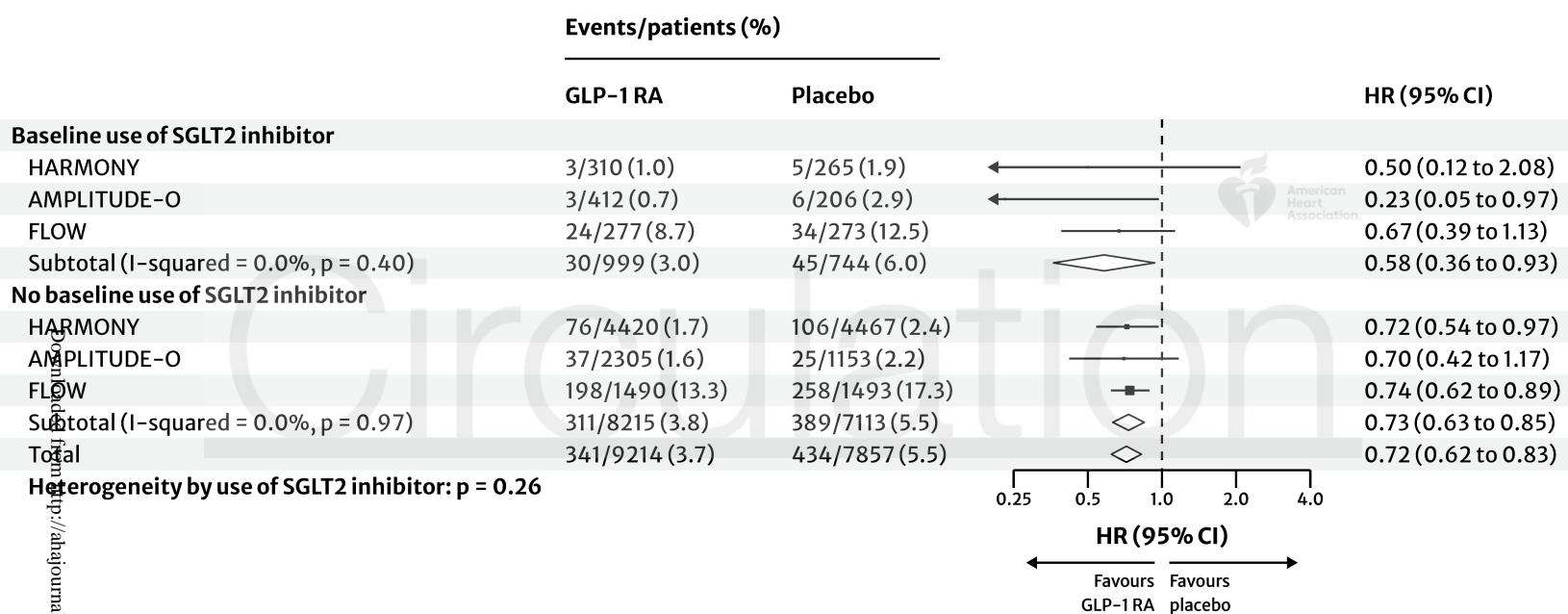
**Figure 3. Effects of GLP-1 receptor agonists on (A) 50% decline in eGFR, kidney failure or kidney failure-related death and (B) total eGFR slope by baseline SGLT2 inhibitor use.** GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2: sodium glucose cotransporter-2; RR: risk ratio; CI: confidence interval. \*Heterogeneity between trials for absolute difference.

**Figure 4. Effects of GLP-1 receptor agonists on (A) serious adverse events and (B) severe hypoglycemia by baseline SGLT2 inhibitor use.** GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2: sodium glucose cotransporter-2; RR: risk ratio; CI: confidence interval.

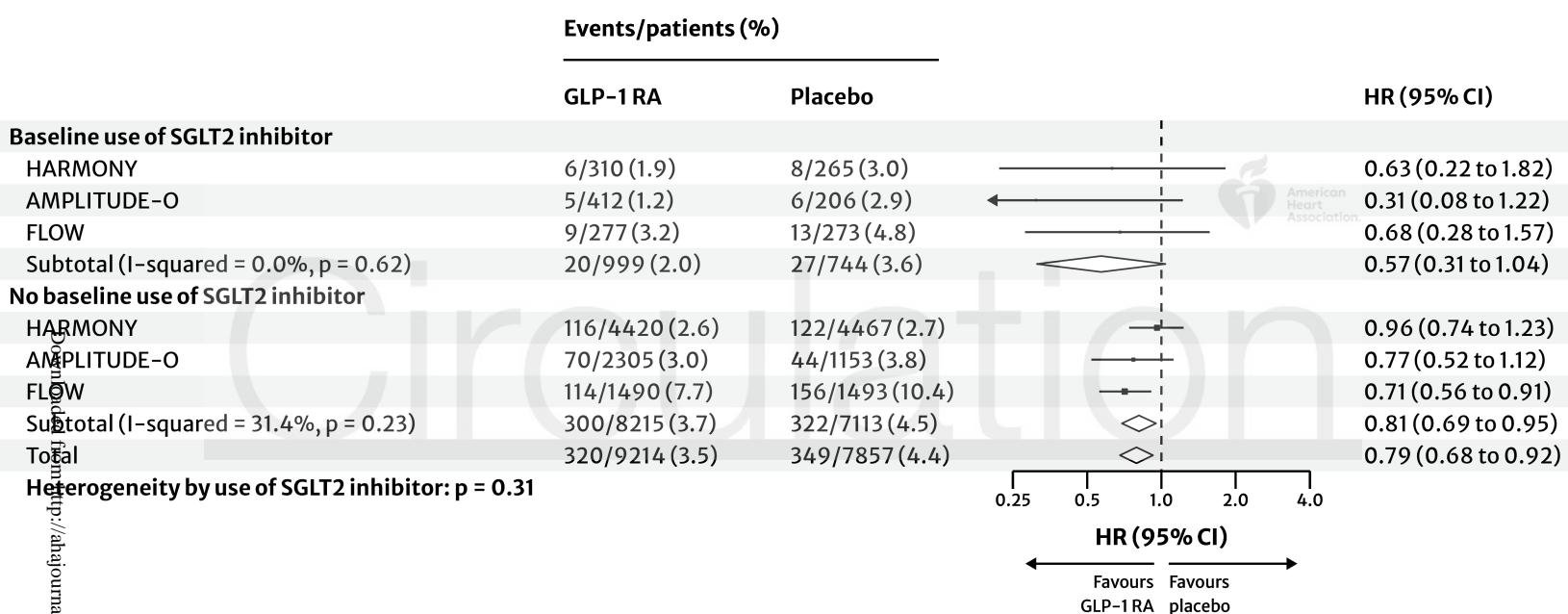
**Figure 1A**



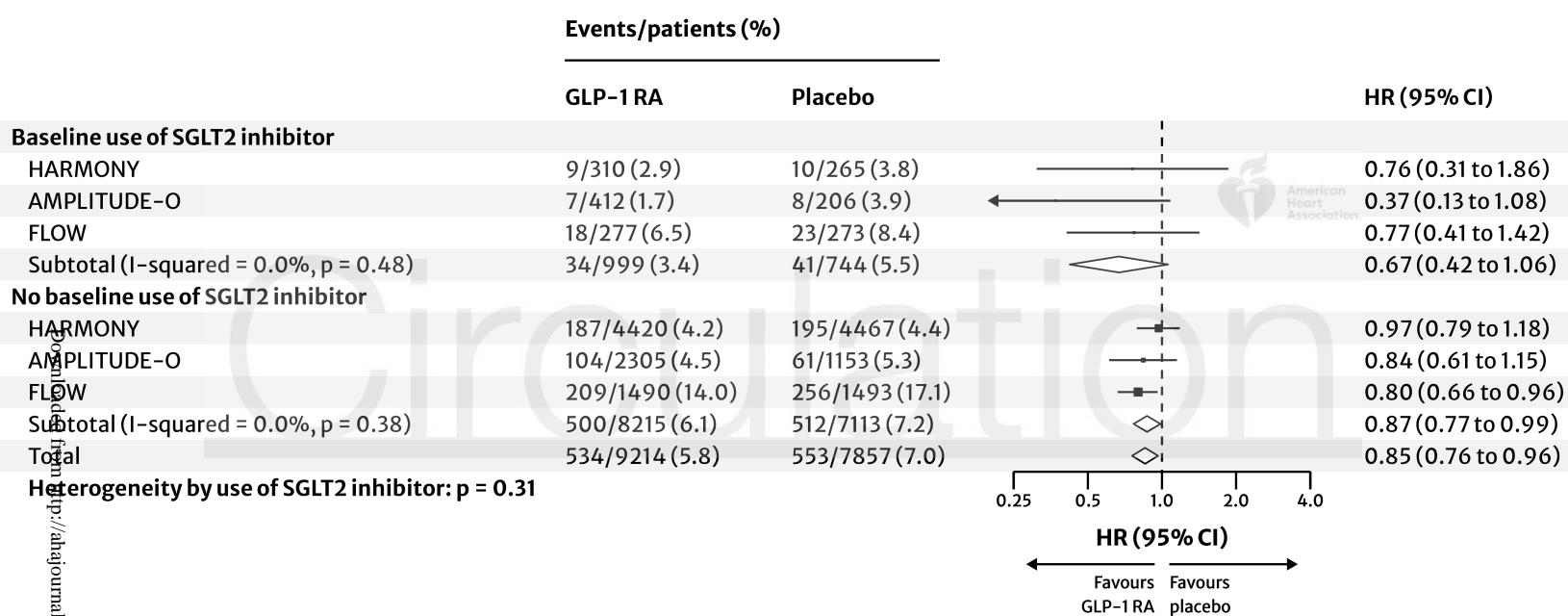
**Figure 1B**



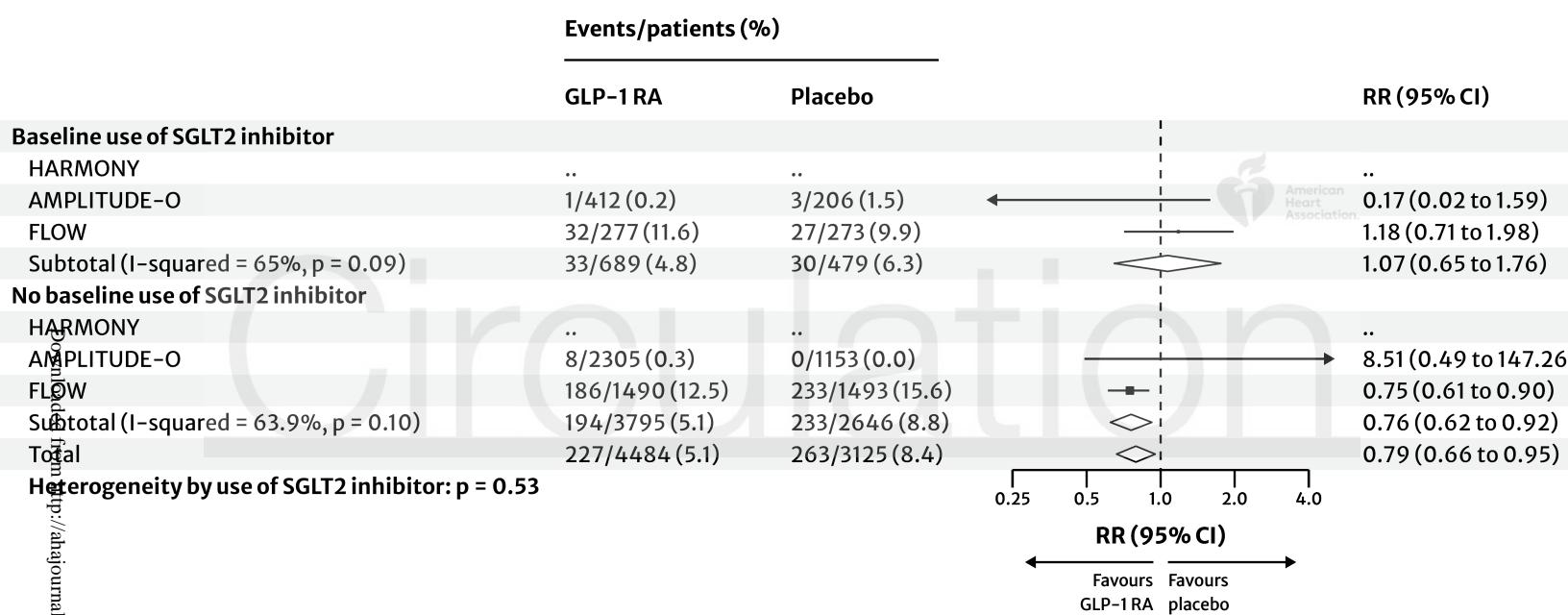
**Figure 2A**



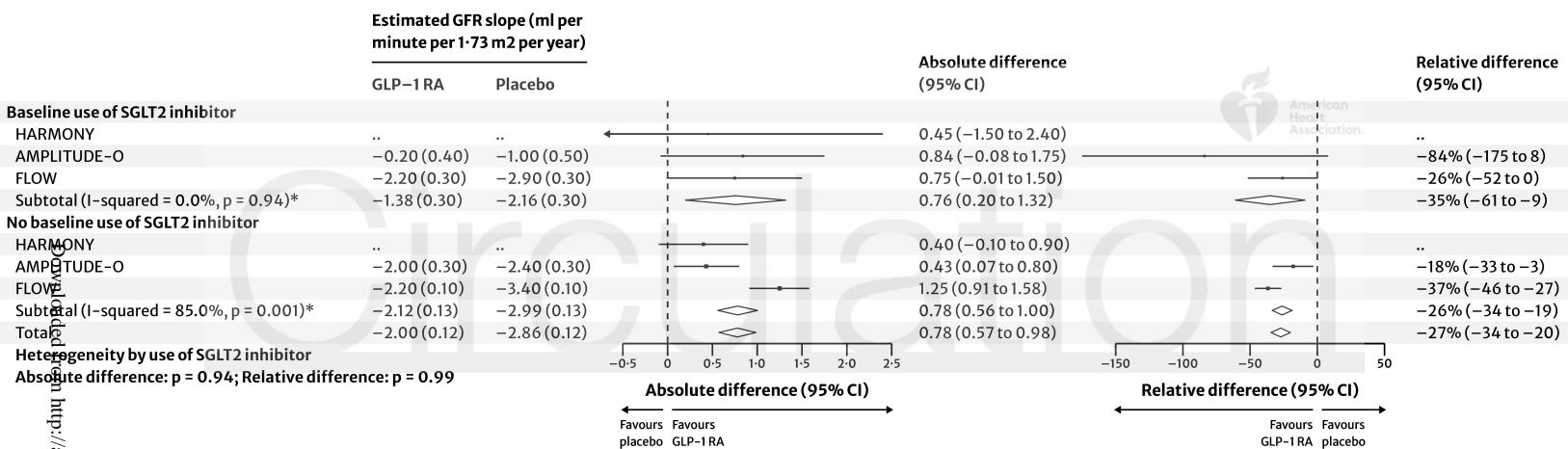
**Figure 2B**



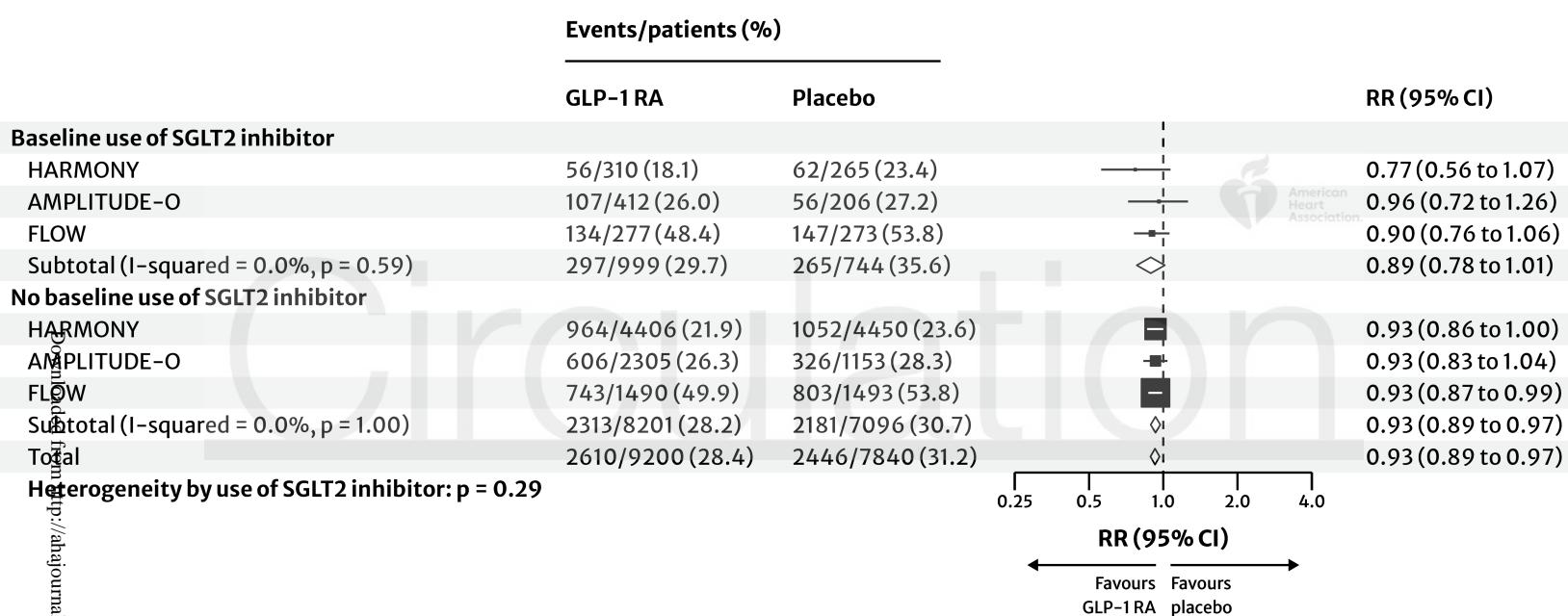
**Figure 3A**



**Figure 3B**



**Figure 4A**



**Figure 4B**

