

# The Effect of Insulins, GLP-1 and GIP Receptor Agonists, and Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events in Diabetic Patients



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## Aim

- Assess and evaluate the efficacy and safety of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) receptor agonists (RAs), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and insulins through a model-based meta-analysis.
- Explore and investigate drug effects on inflammatory biomarkers: low-density lipoprotein cholesterol (LDL), triglyceride and c-reactive protein (CRP) levels, and their impact on cardiovascular (CV) risk in patients with type 2 diabetes through model-based techniques.
- Quantify the effect of the effective dose of various GLP-1 and GIP RAs and SGLT2is on the CV risk to provide valuable insight to this nuanced relationship.

## Introduction

- Cardiovascular diseases (CVDs) are of the most prevalent complications for individuals with diabetes, reflecting a complex interplay between risk factors and pathogenesis (1).
- The efforts needed to identify CV benefits of antidiabetic therapies are massive, with historical CV outcome trials (CVOTs) enrolling 3.183-17.160 participants for a duration of over 2 years (2,3).
- Model-based tools supporting early safety and efficacy assessments of diabetic medications are of high value.
- Current meta-analyses have investigated the effects of GLP-1 RAs and SGLT2is on glycated hemoglobin (HbA1c) and body weight in relation to major adverse cardiovascular events (MACE) risk.
- For development of CVD in any population, dyslipidemia and hypertriglyceridemia are known risk factor; however, the effects of GLP-1 RAs and SGLT2is have not yet been investigated in model-based analyses in the literature (2,4-6).
- The effects on inflammatory biomarkers, LDL, triglycerides, and CRP, were in focus in this project.

## Methods

- Systematic literature review using the PECOS (population, exposure, comparator, outcome, and study design) framework with following criteria:
  - Randomized phase 3 studies of GLP-1 and GIP RAs, SGLT2is, and insulin-based therapies comparing with placebos.
  - Adult patients (≥18 years) with type 2 diabetes.
  - Reporting measures of three-point MACE (MACE-3), LDL, triglycerides, and CRP at baseline and the change from baseline, including the mean and variation.
- Model-based meta-analysis was performed to investigate multiple responses in terms of differences between placebo and drug effects.
- Firstly, effects were investigated by forest plots for each measured variable. For studies with multiple treatment arms, only those with the recommended maintenance dose were included.
  - Forest plots were based on the random-effects models.
  - Publication bias was assessed using funnel plots for LDL, triglycerides, and log-scaled hazard ratio (HR).
- Modelling involved investigation of biomarkers and MACE risk relationships through univariate meta-regression models for GLP-1 RAs and SGLT2is separately.
  - Using the inverse variance method for random-effects meta-regression.
  - Examined the placebo-adjusted percentage change from baseline of glycated hemoglobin (HbA1c), body weight, LDL, triglycerides and CRP.
- The effect of different drugs and drug levels were investigated as well.
- Based on HbA1c and body weight placebo-adjusted change from baseline, the effective dose was identified within each drug class, except for insulins.
  - Emax models were fitted for each drug class for each biomarker. Drug specific ED50 scaling parameters were estimated with semaglutide and dapagliflozin as reference drugs.
  - Doses across drug classes were adjusted based on a combined ED50 scaling estimate calculated based on weighted mean of estimates obtained from HbA1c and body weight Emax models.
  - If ED50 scaling estimate could not be obtained for a drug, it was excluded.
- The MACE risk within each drug class, HR, versus adjusted doses for relative potency of semaglutide and dapagliflozin was investigated through model-based techniques.
  - Linear model.
  - Log-log linear model.
  - Emax model with a Hill factor of 1.
  - Log-log Emax model with a Hill factor of 1.

- Prior to this, outlier detection of studies based on their MACE risk was conducted and considered for exclusion. Outliers were identified based on visual inspection and a two-tailed test with a significance level ( $\alpha$ ) of 0.025 for standardized residuals from linear meta-regressions.
- Best model was determined based on log-likelihood and AIC measures.

## Results

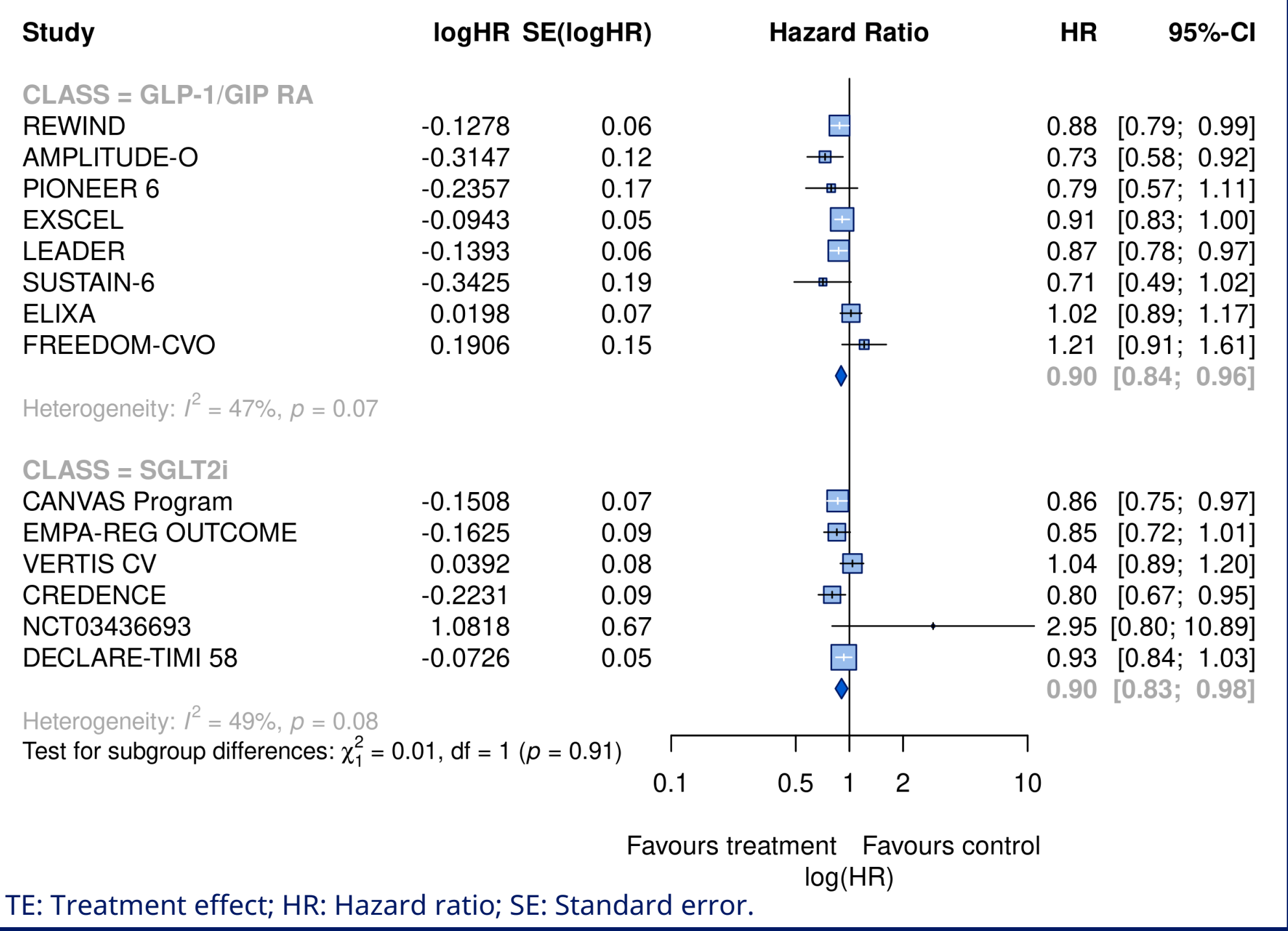
- 45 among 5.007 articles were selected based on eligibility criteria.
  - 15 of the 45 studies were concerning CV safety and benefits in terms of MACE risk.
  - 35 studies reported on LDL, 28 on triglycerides, and 3 on CRP.
- Only one study, ORIGIN, concerned the use of insulin versus placebo. Results with and without this study were of interest. In the forest plots for MACE risk and triglycerides this study was assigned the largest weight, influencing the overall summary effect sizes.
- No statistical heterogeneity of analysis including all studies were present for LDL, triglycerides or CRP changes (Table 1).
- No differences in overall MACE risk between GLP-1 RAs and SGLT2is were found in subgroup analysis (Figure 1).

Table 1: Results of random effects models comparing treatment to placebo.

|                                    | MD/HR                  | I <sup>2</sup> | P-value |
|------------------------------------|------------------------|----------------|---------|
| LDL CFB [95% CI] with insulin      | -0.63 [-1.86; 0.60]    | 0              | 0.72    |
| LDL CFB [95% CI] without insulin   | -0.63 [-1.98; 0.72]    | 0              | 0.67    |
| TG CFB [95% CI] with insulin       | -5.15 [-8.09; -2.22]   | 0              | 0.62    |
| TG CFB [95% CI] without insulin    | -10.46 [-15.07; -5.86] | 0              | 0.94    |
| CRP CFB [95% CI] with insulin      | -                      | -              | -       |
| CRP CFB [95% CI] without insulin   | -0.48 [-0.87; -0.09]   | 0              | 0.40    |
| MACE risk [95% CI] with insulin    | 0.91 [0.87; 0.96]      | 53             | <0.01   |
| MACE risk [95% CI] without insulin | 0.90 [0.86; 0.94]      | 44             | 0.04    |

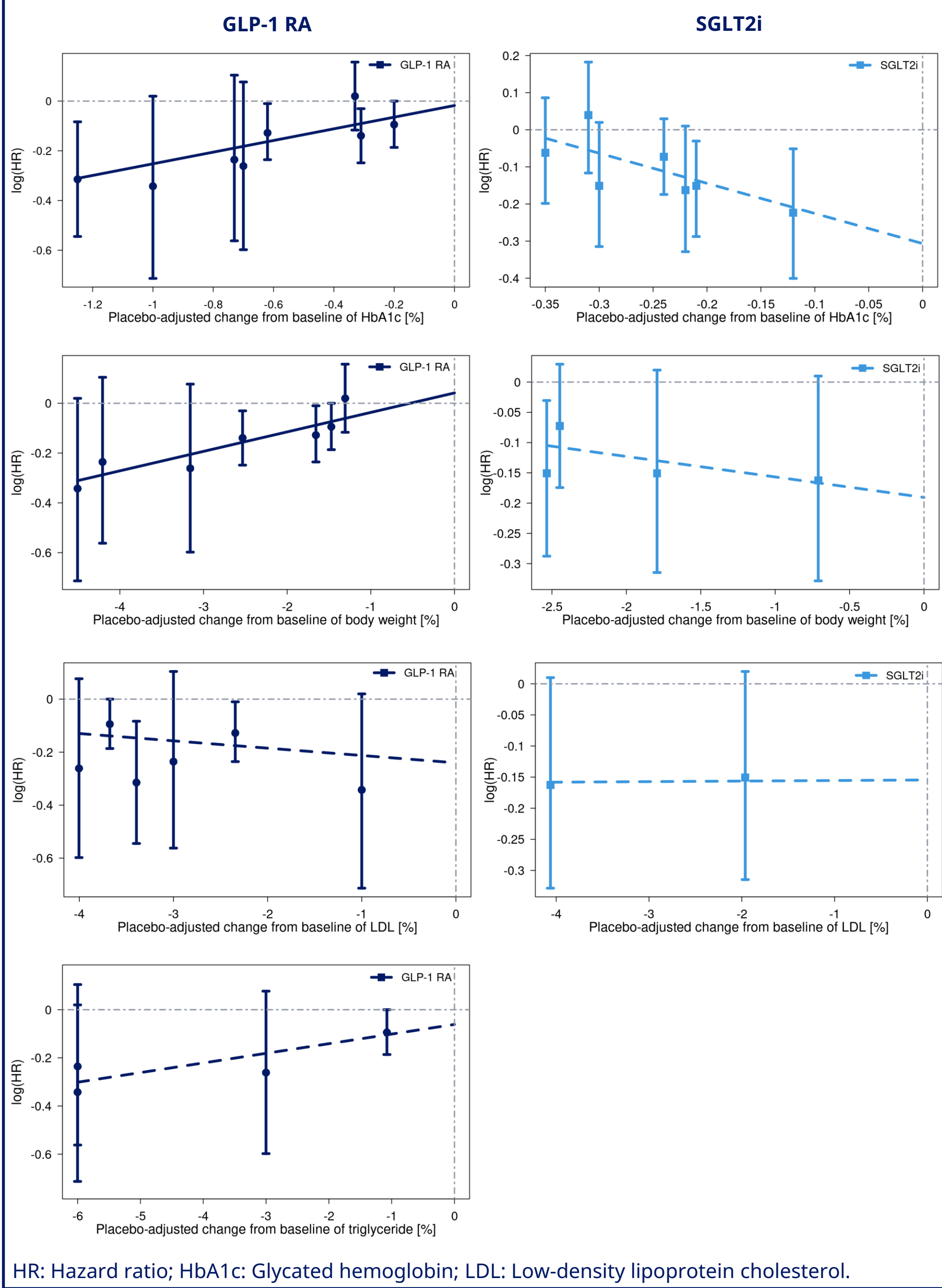
MD: Mean difference; HR: Hazard ratio; I<sup>2</sup>: Heterogeneity statistic; LDL: Low-density lipoprotein cholesterol; TG: Triglyceride; CRP: C-reactive protein; MACE: Major adverse cardiovascular event; CFB: Change from baseline; CI: Confidence interval.

Figure 1: Forest plot of MACE risk grouped by drug class



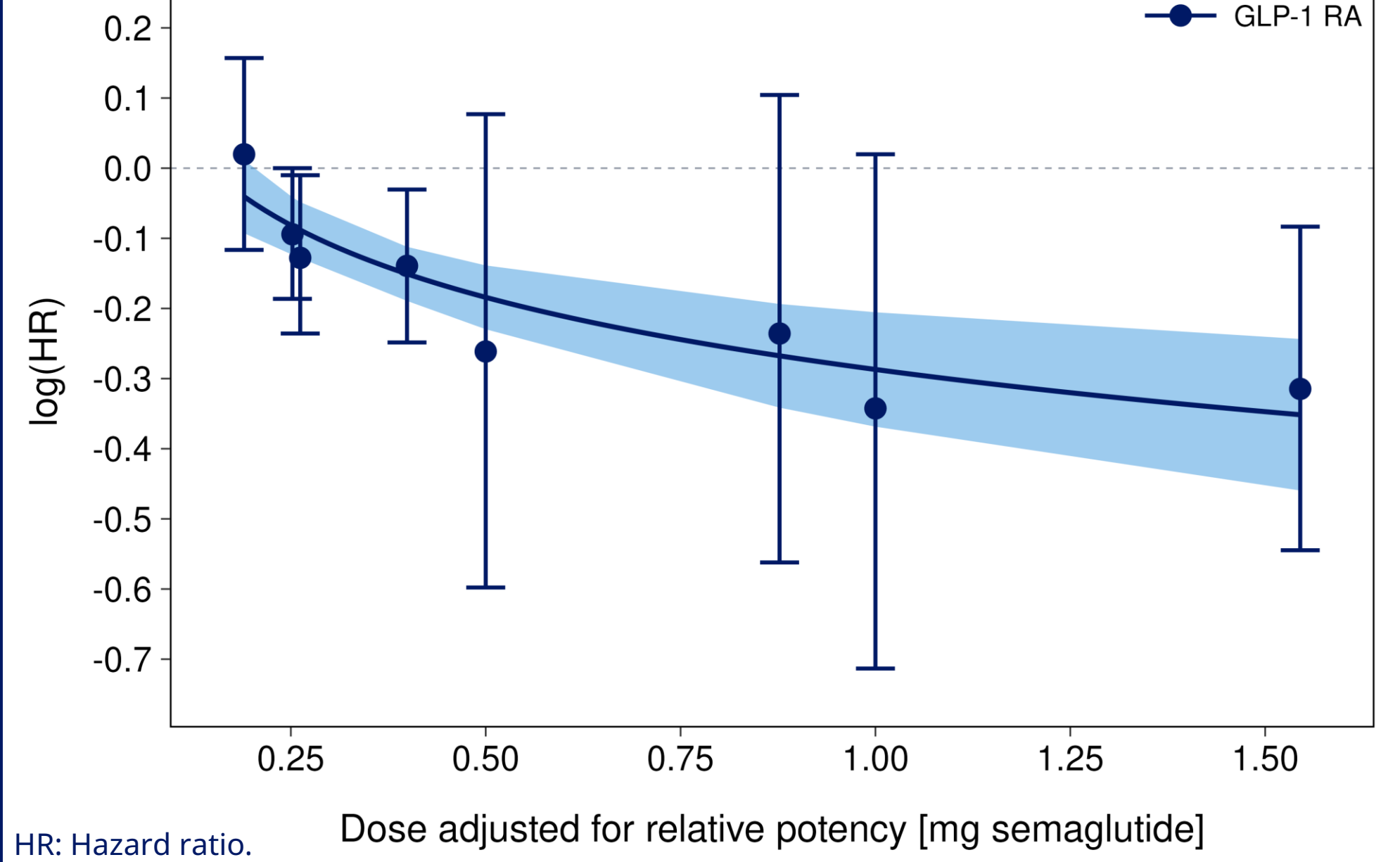
- For each drug class linear models for log(HR) and HbA1c, body weight, LDL, and triglycerides were fitted on data before and after removal of 2 outlier CVOTs.
  - FREEDOM-CVO**: Delivery of exenatide through osmotic mini-pump.
  - NCT03436693**: Small Japanese only study with extreme confidence interval around the HR estimate.
- Linear relationship models showed significance for HbA1c and body weight for GLP-1 RAs only (Figure 2).
- None of the CVOTs with SGLT2is as active treatment included estimates of triglycerides with a measure of variance.
- GLP-1 RA**: For every 1% reduction in HbA1c, body weight, and triglyceride, the relative HR is reduced by 26.4%, 8.1%, and 4.1%, respectively. For LDL, a 1% reduction results in a 2.8% increase in the relative HR.
- SGLT2i**: For every 1% reduction in HbA1c and body weight, the relative HR is increased by 55.6% and 3.3%, respectively. For LDL, a 1% reduction results in a 0.1% decrease in the relative HR.

Figure 2: Biomarker-driven meta-regression for MACE effect



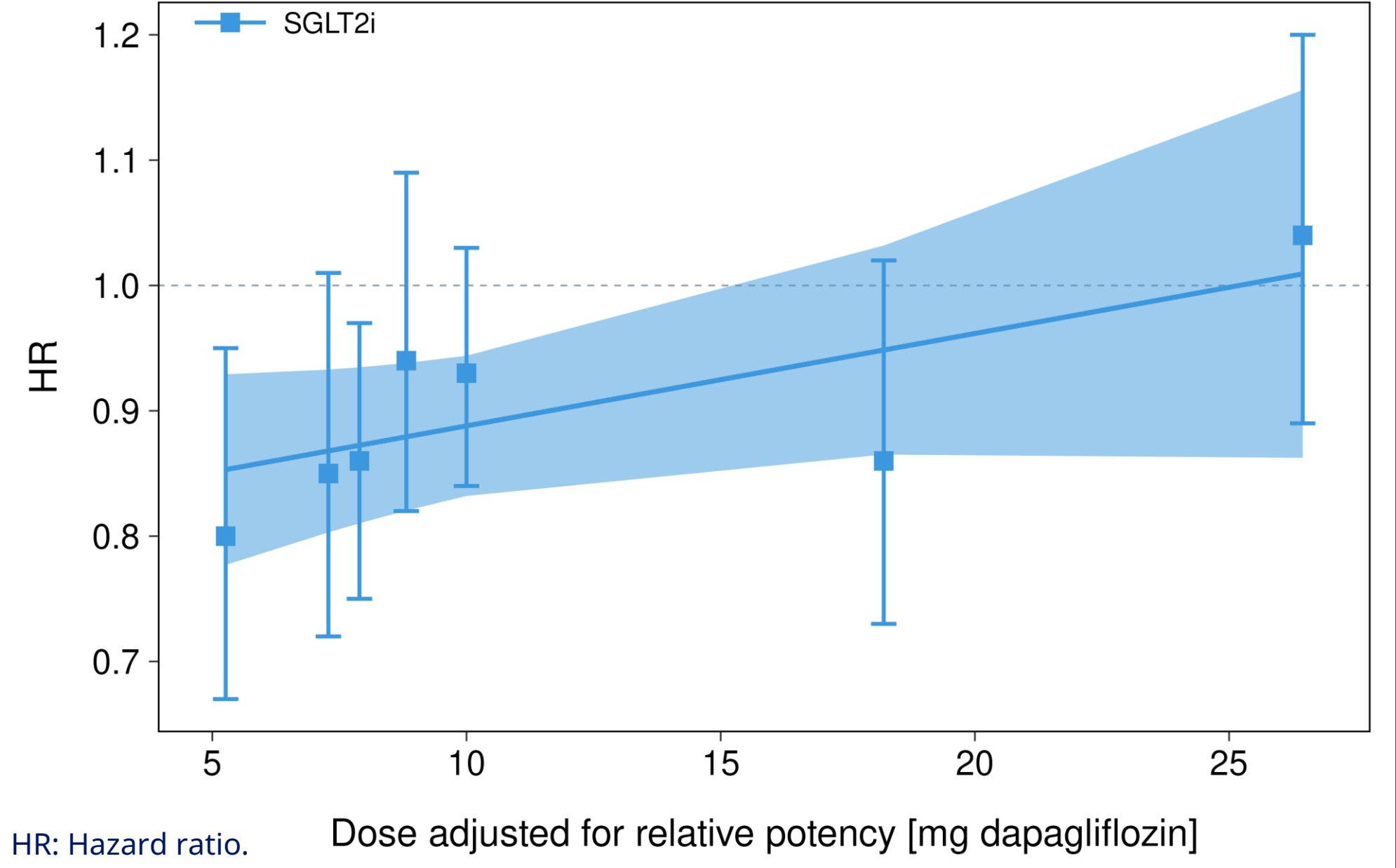
- Within each drug class, the dose was investigated as a mediator for MACE risk combining HbA1c and body weight mediated effects.
- Individual drug dose adjustments were made to match the relative potency of semaglutide and dapagliflozin.
  - The relationship between doses adjusted to semaglutide, obtained from HbA1c and body weight, is described by Emax models with Emax and ED<sub>50</sub> of -1.55 [%-points] and 0.37 [mg], and -11.73 [%] and 1.6 [mg], respectively.
  - For SGLT2is adjusted to dapagliflozin the Emax and ED<sub>50</sub> for the HbA1c and body weight models were -0.58 [%-points] and 2.03 [mg], and -2.88 [%] and 1.58 [mg], respectively.
- Four models were created to describe the relationship between HR for MACE risk and adjusted doses.
  - GLP-1 RA**: Log-log linear model was superior (Figure 3).
  - SGLT2i**: Linear model was superior (Figure 4).

Figure 3: HR versus potency adjusted doses relative to semaglutide



- No dose-dependency for MACE risk was observed for SGLT2is.

Figure 4: HR versus potency adjusted doses relative to dapagliflozin



## Discussion

- When looking at biomarker-driven MACE effect results, only GLP-1 RAs showed significance. Opposite relationships was observed for SGLT2is agreeing with literature analysing HbA1c reduction and body weight change (2). Data on SGLT2is suggest that other factors beyond these biomarkers influence CV risk.
- CRP was not reported in many phase 3 studies but was observed more often in phase 2 studies. Data from these earlier studies could have been included but a similar response is expected to be observed.
- Challenging to observe a relationship between LDL changes and MACE risk for SGLT2is due to lack of observations. It is not expected to see a changed pattern if more observations were available based on the results in forest plot showing no treatment effect.
- Two outlier CVOTs were removed. By keeping these, it would have changed the results seen in figure 2. If new CVOTs becomes available these could result in being identified as outliers as well due to unexplained heterogeneity not being captured by the current models.
- The drug specific potency parameters were estimated including tirzepatide, which was the main driver for body weight change. If excluded from analysis the parameters would have been adjusted differently to semaglutide resulting in another relationship to MACE risk (Figure 3).
- Drug specific potency parameters for adjusting doses to the relative potency were based on HbA1c and body weight from the 45 studies. Higher precision could be obtained if these biomarkers were included in the eligibility criteria during the literature search.

## Conclusion

- Treatment with GLP-1 and GIP RAs, and SGLT2is significantly reduce triglyceride levels. The same was seen for LDL with GLP-1 and GIP RAs.
  - SGLT2is increased LDL levels compared to placebo.
  - GLP-1 RAs significantly reduced CRP levels compared to placebo.
  - Both drug classes lowered the MACE risk.
- The effect of GLP-1 RAs on HbA1c and body weight reductions led to a significant benefit for MACE risk. Opposite trends were observed for HbA1c and body weight for SGLT2is.
- The effective dose based on clinical endpoints appeared as the best MACE risk predictor, superior to each individual biomarker for CV effects of GLP-1 RAs, offering a potentially powerful tool for understanding effects in future CVOTs. In contrast, more work is needed for SGLT2is to identify relevant biomarkers for CV effects and safety.

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(1) Wong, N. D. et al. Nature Reviews Cardiology (2023);20(10):685-695; (2) Hasebe, M. et al. Cardiovascular Diabetology (2023);22(1):62; (3) U.S. Food and Drug Administration (2008); (4) Maiorino, M. I. et al. Cardiovascular diabetology (2021);20(1):210; (5) Hansson, G. K. The New England journal of medicine (2005);352(16):1685-1695; (6) Chapman, M. J. et al. European heart journal (2011);32(11):1345-1361