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GLP1 Receptor Agonist Therapy with and without SGLT2 inhibitors in Patients with Type 2 Diabetes

Short title: GLP1 Agonists with SGLT2 Inhibitors

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Short tweet: In T2D with cardiovascular disease, treatment with GLP-1 RA reduced cardiovascular events independently of SGLT2i use. The combined use of GLP-1 RA with SGLT2i should be tested in randomized trials. @UnIC_cardiovasc #T2D #SGLT2i #GLP1-RA

Abstract

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1 RA) reduce adverse cardiovascular outcomes in type 2 diabetes (T2D). However, the efficacy of combination therapy is unclear.

Objectives: Our aim was to evaluate the effects of GLP-1 RA on cardiovascular outcomes in patients with T2D treated with or without SGLT2i.

Methods: Post hoc analysis of Harmony Outcomes evaluating the effect of albiglutide in T2D with cardiovascular disease by background SGLT2i use. Additionally, a trial-level meta-analysis of Harmony Outcomes and AMPLITUDE-O (which evaluated T2D with cardiovascular or renal disease) was performed combining the treatment effect estimates according to SGLT2i use.

Results: From the 9462 participants in Harmony outcomes, 575 (6.1%) were treated with SGLT2i at baseline. The effect of albiglutide on reducing the composite of cardiovascular death, myocardial infarction or stroke (MACE) was consistent with or without SGLT2i (p-interaction=0.70). The effect of albiglutide on secondary outcomes and adverse events was not modified by SGLT2i. Meta-analysis of Harmony Outcomes and AMPLITUDE-O included 13538 patients, of whom 1193 (8.8%) used SGLT2i. Compared to placebo, GLP1-RA reduced MACE without effect modification by SGLT2i use: HR 0.77, 95%CI 0.76-0.92 without SGLT2i and HR 0.78, 95%CI 0.49-1.24 with SGLT2i (p-interaction=0.95); and reduced heart failure hospitalization: HR 0.72, 95%CI 0.55-0.92 versus HR 0.34, 95%CI 0.12-0.96 (p-interaction=0.18).

Conclusions: In patients with T2D and cardiovascular disease, GLP-1 RA reduced cardiovascular events independently of SGLT2i use. These findings suggest that the

combination of GLP-1 RA with SGLT2i may further reduce cardiovascular risk. Clinical trials with combination therapy are needed.

Keywords: GLP-1 receptor agonist, SGLT2 inhibitor, type 2 diabetes, cardiovascular disease; heart failure

Condensed abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1 RA) reduce adverse cardiovascular outcomes in type 2 diabetes (T2D). In a post hoc analysis of Harmony Outcomes, and in a meta-analysis with AMPLITUDE-O (13538 patients), we evaluated the effect of GLP-1 RA on cardiovascular outcomes by SGLT2i use (1193 patients, 8.8%, with baseline SGLT2i use in the meta-analysis). Treatment with GLP-1 RA reduced major adverse cardiovascular events (MACE) and heart failure hospitalization independently of SGLT2i use. These findings suggest that combining GLP-1 RA with SGLT2i may further reduce cardiovascular risk in T2D. Clinical trials with combination therapy are needed.

Abbreviations

AMPLITUDE-O, Effect of Efglenatide on Cardiovascular Outcomes

ASCVD, atherosclerotic cardiovascular disease

GLP-1 RA, glucagon-like peptide 1 receptor agonists

Harmony Outcomes, Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease

HbA1c, glycated hemoglobin

HF, heart failure

HR, hazard ratio

RCT, randomized clinical trials

SGLT2i, sodium-glucose cotransporter-2 inhibitors

T2D, type 2 diabetes

Introduction

Cardiovascular diseases are among the main causes of death and morbidity in people with type 2 diabetes (T2D).¹ Both sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RA) reduce the cardiovascular risk of patients with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD).^{2,3} Current guidelines recommend treatment of people with type 2 diabetes and ASCVD with either SGLT2i or GLP-1 RA, but the prioritization of combination routinely in this population is less clear.⁴

Whether the protection from cardiovascular outcomes in people with type 2 diabetes is greater with the combined use of SGLT2i and GLP1-RA (vs either treatment alone) is still uncertain. In an exploratory analysis of the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial that included 618 (15.2%) participants receiving SGLT2i treatment at baseline, the benefits of using GLP1-RA were similar regardless of background SGLT2i use.⁵ To date, this subgroup analysis is the sole report from a large clinical trial analyzing the effect of GLP-1 RA added to an SGLT2i.

The Harmony Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease) evaluated the effect of albiglutide on cardiovascular outcomes among people with type 2 diabetes and cardiovascular disease. This trial included 575 (6.1%) participants treated with SGLT2i at baseline and, as such, represents an important contribution to the evaluation of the effects of GLP-1 RA in patients with and without background SGLT2i treatment. Furthermore, meta-analysis of Harmony outcomes and AMPLITUDE-O allows the evaluation of the effect of GLP-1 RA in more than 1000 similar patients treated with a SGLT2i at baseline. This represents the largest experience of participants treated with SGLT2i in randomized clinical trials (RCTs) testing the effect of GLP-1 RA on cardiovascular outcomes of patients with T2D. The remaining GLP1-RA trials

included few participants with baseline SGLT2i use.⁶ We hypothesized that the effects of GLP1-RA on cardiovascular outcomes would be independent of SGLT2i use.

Methods

Harmony Outcomes trial

The design and the main results of the Harmony Outcomes have been previously published.^{7,8} Briefly, Harmony Outcomes was a double-blind RCT that included patients aged 40 years or older with type 2 diabetes with established cardiovascular disease and a glycated hemoglobin (HbA1c) >7.0%, randomized in a 1:1 ratio to once a week subcutaneous injection of albiglutide or matching placebo. The starting dose of the study medication was 30 mg once a week, with possibility to increase to 50 mg once a week after 5 weeks if glucose-lowering intensification was needed. Main exclusion criteria included an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m², previous pancreatitis or risk factors for pancreatitis.⁸ The trial was conducted between July 2015 and March 2018. GlaxoSmithKline discontinued the marketing of albiglutide in 2018 due to commercial reasons and not related to any safety issues.

The primary outcome of Harmony Outcomes trial was a composite of cardiovascular death, myocardial infarction (MI), or stroke. The median follow-up time was 1.6 (percentile₂₅₋₇₅ 1.3 to 2.0) years. Albiglutide significantly reduced the rate of the primary composite outcome: 338/4731 (7%) events in the albiglutide group vs. 428/4732 (9%) events in the placebo group, HR 0.78 (95% CI 0.68-0.90, P <0.001).

The protocol of the Harmony Outcomes trial was approved by the ethics committee at each participating site and all patients provided written informed consent. Data for this post-hoc analysis was accessed through the Vivli® (Center for Global Clinical Research Data) platform with the Vivli ID: 00008542.

Trial Outcomes

In the present analysis of Harmony Outcomes, we used as main outcome the primary composite outcome of the original trial. We also analyzed as secondary outcomes the following events: the composite of cardiovascular death or heart failure (HF) hospitalization; the composite of cardiovascular death, MI, unstable angina, or stroke; the composite of all-cause mortality, MI or stroke; the individual components of the primary outcome; and all-cause mortality. All outcomes were studied in patients with and without SGLT2i use at baseline.

Body weight, heart rate, systolic blood pressure (SBP), HbA1c, and estimated glomerular filtration rate (eGFR) were used for longitudinal analysis.

Other events were evaluated in Harmony Outcomes, including serious adverse events (any), adverse events leading to permanent drug discontinuation, severe hypoglycemia, diabetic ketoacidosis, urinary tract infection, renal failure, hypersensitivity reaction, pneumonia and pancreatitis.

For the trial-level meta-analysis of Harmony Outcomes with AMPLITUDE-O, we used the published outcomes reported in AMPLITUDE-O SGLT2i subgroup post hoc analysis,⁵ also assessed in the present analysis.

Statistical analysis

The Harmony Outcomes population was divided into two subgroups according to SGLT2i use at baseline (with vs. without SGLT2i), and their characteristics were described as mean (standard deviation) or medians (percentile₂₅₋₇₅) for normal and non-normal continuous variables respectively. Categorical variables were described as numbers and percentage. Baseline characteristics of the trial population were compared with t-test or Mann-Whitney

test for normal and non-normal continuous variables respectively, and with chi-square test for categorical variables.

The effect of albiglutide vs. placebo was tested using Cox models for time-to-first event analyses with treatment group as an explanatory variable and baseline SGLT2i use as a stratification variable, with treatment-by-SGLT2i use interaction term in the model. The results are presented separately for patients with and without baseline SGLT2i use, along with the respective interaction P-value. Analyses were performed according to the intention-to-treat principle. The Kaplan-Meier method was used to estimate event rates.

The effect of treatment on body weight, heart rate, SBP, HbA1c, and eGFR over time, was studied using mixed random effects models with treatment, time, SGLT2i use, baseline value of the variable of interest, treatment-by-time, and treatment-by- SGLT2i interaction terms in the model; random effects were set at the patient id level using an unstructured covariance matrix.

We evaluated adverse events in Harmony Outcomes among patients who received at least one dose of the study drug, using logistic regression models with the treatment group as an explanatory variable and SGLT2i as a stratification variable, and including a treatment-by-SGLT2i interaction term in the model.

For the meta-analysis of Harmony Outcomes with AMPLITUDE-O, we used a random-effect meta-analysis approach with heterogeneity assessed using the Cochran Q test statistic and Higgins and Thompson I^2 .⁹ Heterogeneity was considered to be low, moderate, or high if I^2 was <25%, 25% to 75%, or >75%, respectively.¹⁰ The hazard ratio (HR) and respective 95% confidence intervals (95%CI) were extracted from the treatment effect estimates of SGLT2i subgroup analyses reported in each trial. Estimates from each trial were combined by the use of inverse variance-weighted averages of logarithmic HR in random-effects analysis.

A two-sided P-value of <0.05 was considered statistically significant. P-values and 95% confidence intervals presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. All analyses were performed using Stata® (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Data and Resource Availability

The Harmony Outcomes database can be fully available from Vivli upon reasonable request.

Results

Baseline patient characteristics

Of the 9462 participants randomized in the Harmony outcomes, 575 (6.1%) were treated with a SGLT2i at baseline. Compared to patients without SGLT2i use at baseline, those using SGLT2i use were younger (62.9 vs 64.2 years), more frequently men (75.7 vs 69.0%), had higher body mass index (BMI) (33.6 vs 32.2 kg/m²), lower HbA1c (8.5 vs 8.8%), more frequent history of coronary artery disease (CAD) (78.6 vs. 70.0%), and less frequent history of HF (15.1 vs 20.6%) and peripheral artery disease (19.5 vs 25.2%). Participants treated with an SGLT2i at baseline, were also more frequently treated with metformin (79.3 vs 73.3%), DPP4i (24.2 vs 14.6%), beta-blockers (71.1 vs 66.4%) and statins (89.6 vs 83.7%), and less frequently treated with sulfonylureas (21.9 vs 29.2%) and anticoagulants (5.9 vs 8.6%) than those not receiving an SGLT2i at baseline (*Table 1*).

The baseline characteristics of patients with and without baseline SGLT2i use were well balanced within albiglutide and placebo groups (*Supplemental Table 1*). During the trial period, more participants in the placebo group started SGLT2i than in the albiglutide group (361 vs 240 participants).

Effects of albiglutide vs. placebo on outcomes according to SGLT2 inhibition

The effect of albiglutide (vs. placebo) on the primary outcome was consistent regardless of SGLT2i use at baseline: HR 0.78, 95%CI 0.67-0.90 in patients without baseline SGLT2i use and HR 0.89, 95%CI 0.45-1.77 in patients with baseline SGLT2i use, interaction P =0.70. A similar pattern was observed for cardiovascular death or HF hospitalization: HR 0.87, 95%CI 0.71-1.06 in patients without baseline SGLT2i use and HR 0.68, 95%CI 0.28-1.64 in patients with baseline SGLT2i use, interaction P =0.60. The effect of albiglutide on cardiovascular

death, HF hospitalization, the composite of cardiovascular death, MI, unstable angina, or stroke, the composite of all-cause mortality, MI or stroke, and all-cause mortality was also not modified by baseline SGLT2i use (interaction $P > 0.1$ for all) (*Table 2*).

Effects on Heart Rate, Blood Pressure, HbA1c, Body Weight, and eGFR

During the trial period, compared to placebo, albiglutide increased heart rate by 1 to 2 bpm, decreased weight by 1 to 2 kg, and decreased HbA1c by approximately 0.5%, without significant differences by baseline SGLT2i use. The effects of albiglutide on eGFR and SBP were small and did not differ by baseline SGLT2i use (interaction $P > 0.1$ for all) (*Supplemental Figure 1*).

Adverse events with albiglutide vs. placebo by baseline SGLT2i use

Overall, albiglutide was well-tolerated regardless of baseline SGLT2i use (*Table 3*). Treatment with albiglutide was not associated with an increased risk of serious adverse events but was associated with more permanent drug discontinuation than placebo, without no difference according to baseline SGLT2i use. Severe hypoglycemia, diabetic retinopathy, renal failure, atrial fibrillation/flutter, hypersensitivity reactions, pneumonia, pancreatitis, urinary tract infection and diabetic ketoacidosis were not significantly different between treatment groups, and did not vary according to baseline SGLT2i use (interaction $P > 0.1$ for all) (*Table 3*).

Meta-analysis of Harmony Outcomes and AMPLITUDE-O

A total of 13538 patients with type 2 diabetes from the Harmony outcomes and AMPLITUDE-O were included in this analysis, of whom 1193 (8.8%) were using SGLT2i at baseline. Compared to placebo, GLP1-RA reduced the composite of cardiovascular death, MI, or stroke (HR 0.77, 95%CI 0.76-0.92) without significant interaction between participants with and without baseline SGLT2i use (interaction P =0.95): HR 0.77, 95%CI 0.76-0.92, in patients without baseline SGLT2i use, and HR 0.78, 95%CI 0.49-1.24, in patients with baseline SGLT2i use. A similar pattern was observed for the composite outcomes of cardiovascular death, MI, unstable angina or stroke, and the composite of all-cause death, MI or stroke (*Central illustration*).

Similarly, compared to placebo, GLP1-RA reduced the risk of HF hospitalization (HR 0.69, 95%CI 0.54-0.88) without significant interaction between participants with and without baseline SGLT2i use (interaction P =0.18): HR 0.72, 95%CI 0.55-0.92, in patients without baseline SGLT2i use, and HR 0.34, 95%CI 0.12-0.96, in patients with baseline SGLT2i use (*Central illustration*).

Discussion

In Harmony Outcomes, treatment with albiglutide reduced the composite of cardiovascular death, MI or stroke, and the risk of heart failure hospitalization, and this benefit was not modified by baseline treatment with an SGLT2i. Meta-analysis of Harmony Outcomes and AMPLITUDE-O showed consistent findings.

A previous meta-analysis of RCTs with GLP-1 RA in type 2 diabetes showed that treatment with GLP-1 RA decreased the risk of MI, stroke or cardiovascular death by 14%, the risk of cardiovascular death by 12%, and the risk of HF hospitalization by 12%.³ These benefits appeared to be independent of whether the GLP-1 RA had structural homology with the human GLP-1 (e.g. albiglutide) or exendin-4 (e.g. efpeglenatide).³

Previous RCTs had shown that the combination of GLP-1 RA with SGLT2i was associated with additive benefits on metabolic outcomes. In the DURATION-8 (Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy),¹¹ AWARD-10 (Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes),¹² and SUSTAIN 9 (Semaglutide once weekly as add on to SGLT-2 inhibitor therapy in type 2 diabetes) trials,¹³ the combination of a GLP-1 RA with an SGLT2i led to additional reductions in HbA1c, weight and blood pressure. The fact that GLP-1 RA and SGLT2i have complementary mechanisms of action supports the hypothesis that their combination may also have additive effects on cardiovascular events.¹⁴ The cardiovascular benefits of SGLT2i may be related to renal, hemodynamic, and metabolic effects.¹⁵ SGLT2i positively influence cardiac function and metabolism, enhance erythropoiesis, and reduce inflammation.^{15,16} The cardiovascular benefits of GLP-1 RA may be related to the improvement of cardiovascular risk factors, such as HbA1c, body weight, blood pressure, and lipid profile, as well as direct anti-atherosclerotic effects.^{17,18}

However, before the present analysis, only the AMPLITUDE-O trial provided information on the effects of a GLP-1 RA (exendin-4-based) on cardiovascular outcomes according to baseline SGLT2i use.⁵ Thus, our results from the Harmony Outcomes trial with a different GLP-1 RA (human GLP-1-based) and the meta-analysis of both Harmony Outcomes and AMPLITUDE-O, almost doubling the number of SGLT2i treated participants, supports and extends the evidence that GLP-1 RA are efficacious when added to an SGLT2i. Importantly, with individual participant data from Harmony Outcomes we were also able to examine the safety of combining these therapies, finding no significant cause for concern. Specifically, the safety profile of GLP-1 RA was similar among those with and without SGLT2i treatment. Of note, the risk of serious adverse events, hypoglycemia and diabetic retinopathy was not increased by albiglutide and the risk of urinary tract infections and diabetic ketoacidosis was very low overall.

Current guidelines from the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD),¹⁹ and from the American Heart Association (AHA)/American College of Cardiology (ACC)²⁰ recommend that all patients with type 2 diabetes and established cardiovascular disease should be treated with a GLP-1 RA or an SGLT2i. The ADA/EASD consensus algorithm recommends the combination of a GLP-1 RA and an SGLT2i if HbA1c is above target after the initiation of one of these classes.¹⁹ The ACC consensus recommends reassessing patients after treatment with a GLP-1 RA or an SGLT2i and considering the addition of the alternative class if the benefits outweigh the risks.²⁰ However, both guidelines do not recommend routinely adding a GLP-1 RA to those already on an SGLT2i for further reduction of the risk of adverse cardiovascular outcomes. The approach used in these recommendations is in disagreement with the recommendation for other conditions with a high risk of adverse cardiovascular outcomes (e.g. treatment of acute myocardial infarction or treatment of HF with reduced ejection fraction), where the

concomitant use of all interventions with clear evidence of benefit on major outcomes is recommended.²¹⁻²³ Clearly, cost considerations are relevant here but each of these treatments, individually, is cost-effective in high-risk patients, in part because prevention of cardiovascular events offsets the cost of therapy.

Our study has limitations that we should acknowledge. This analysis was not pre-specified and the randomized treatment assignment in the Harmony Outcomes was not stratified according to baseline SGLT2i use. Given the exploratory nature of this study, we did not perform statistical correction for test multiplicity. The small proportion of participants in the subgroup with baseline SGLT2i use (6.1% in Harmony Outcomes and 8.8% in the meta-analysis) reduced the precision of the treatment effect estimates and the statistical power of the interaction tests. However, it is important to note that this still represents a sample of more than 1000 patients who were treated with an SGLT2i at baseline, and the consistency of the point estimates for all outcomes suggests that the benefits of GLP-1 RA on cardiovascular outcomes are independent of the use of SGLT2i. Harmony Outcomes did not collect data on albuminuria and, as such, we could not evaluate the effects of albiglutide on composite renal outcomes according to baseline SGLT2i use. Albiglutide and efpeglenatide are not currently available for clinical use. However, as the ASCVD risk reduction with GLP-1 RA was also observed with other drugs in the class (liraglutide, semaglutide and dulaglutide),³ our findings are likely to apply to other GLP-1 RA. Our findings do not apply to patients with advanced HF with reduced ejection fraction (HFrEF) where GLP-1 RA may increase the risk of adverse cardiovascular events.²⁴⁻²⁶ Despite these limitations, our meta-analysis describes the largest number of patients with baseline SGLT2i use randomized to treatment with a GLP-1 RA or placebo and thus the best evidence to date on the effects of the addition of GLP-1 RA to patients treated with SGLT2i.³

Conclusions

In patients with type 2 diabetes and cardiovascular disease enrolled in Harmony Outcomes, and in a meta-analysis of Harmony Outcomes and AMPLITUDE-O, treatment with a GLP-1 RA reduced the risk of adverse cardiovascular events independently of background SGLT2i use without increased risk of serious adverse events. These findings suggest that the benefits of a GLP-1 RA in patients with type 2 diabetes and cardiovascular disease were consistent in patients receiving or not background treatment with an SGLT2i. Randomized trials are needed to evaluate the potential added value of combining these treatments.

Clinical perspectives

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS

In patients with type 2 diabetes and cardiovascular disease, treatment with GLP-1 receptor agonists reduce cardiovascular events independently of treatment with SGLT2 inhibitors, supporting combination therapy.

TRANSLATIONAL OUTLOOK

Randomized trials are needed to evaluate the potential advantages and disadvantages of combining GLP1 receptor agonists with SGLT2 inhibitors.

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Table 1. Baseline patient characteristics by baseline SGLT2i use

	No SGLT2i at baseline n=8887	SGLT2i at baseline n=575	P-value
Age, years	64.2 ± 8.7	62.9 ± 8.2	<0.001
Male sex	6133 (69.0%)	435 (75.7%)	<0.001
Race			<0.001
Asian	457 (5.1 %)	13 (2.3 %)	
Hispanic	1936 (21.8%)	57 (9.9 %)	
Black or African American	214 (2.4 %)	11 (1.9 %)	
White	6091 (68.5%)	491 (85.4%)	
Other	189 (2.1 %)	3 (0.5 %)	
Region			<0.001
Asia Pacific	368 (4.1 %)	8 (1.4 %)	
Eastern Europe	1974 (22.2%)	73 (12.7%)	
Latin America	1684 (18.9%)	19 (3.3 %)	
North America	1765 (19.9%)	179 (31.1%)	
Western Europe	3096 (34.8%)	296 (51.5%)	
Smoking			<0.001
Current smoker	1398 (15.7%)	90 (15.7%)	
Former smoker	3788 (42.6%)	293 (51.0%)	
Never smoked	3699 (41.6%)	192 (33.4%)	
Hypertension	7673 (86.3%)	511 (88.9%)	0.09
CAD	6225 (70.0%)	452 (78.6%)	<0.001
Myocardial infarction	4160 (46.8%)	298 (51.8%)	0.02
Heart failure	1835 (20.6%)	87 (15.1%)	0.001
PAD	2242 (25.2%)	112 (19.5%)	0.002
Stroke	1592 (17.9%)	89 (15.5%)	0.14
Atrial fibrillation/flutter	802 (9.0 %)	40 (7.0 %)	0.09
BMI, kg/m²	32.2 ± 5.9	33.6 ± 5.8	<0.001
Heart rate, bpm	72.3 ± 10.6	72.0 ± 10.7	0.52
Systolic BP, mmHg	134.9 ± 16.6	132.2 ± 16.3	<0.001
Diastolic BP, mmHg	76.9 ± 10.1	75.3 ± 9.5	<0.001
HbA1c, %	8.8 ± 1.5	8.5 ± 1.2	<0.001
eGFR, ml/min/1.73m²	79.0 ± 25.6	80.1 ± 23.8	0.28

Nephropathy	1641 (18.5%)	97 (16.9%)	0.34
Diabetic eye disease	1820 (20.5%)	117 (20.3%)	0.94
Diabetes duration, years	14.1 ± 8.7	14.7 ± 8.3	0.08
Insulin	5261 (59.2%)	335 (58.3%)	0.66
Metformin	6512 (73.3%)	456 (79.3%)	0.001
DPP4i	1298 (14.6%)	139 (24.2%)	<0.001
Sulfonylureas	2599 (29.2%)	126 (21.9%)	<0.001
Thiazolidinediones	174 (2.0 %)	20 (3.5 %)	0.013
ACEi/ARBs	7056 (79.4%)	468 (81.4%)	0.25
Beta-blockers	5901 (66.4%)	409 (71.1%)	0.02
MRAs	765 (8.6 %)	43 (7.5 %)	0.35
Statins	7440 (83.7%)	515 (89.6%)	<0.001
Antiplatelet agents	6836 (76.9%)	454 (79.0%)	0.26
Anticoagulants	763 (8.6 %)	34 (5.9 %)	0.025

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. CAD, coronary artery disease; PAD, peripheral artery disease; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; DPP4i, dipeptidyl peptidase 4 inhibitors; SGLT2i, sodium-glucose co-transporter 2 inhibitors; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Table 2. Effect of albiglutide vs. placebo on the trial outcomes by baseline SGLT2i use

Outcome/SGLT2i baseline status	Albiglutide		Placebo		HR (95%CI)	Inter. P
	n/N. (%)	Inc.-rate per 100py	n/N. (%)	Inc.-rate per 100py		
Cardiovascular death, MI, or stroke						
No SGLT2i	318/4420 (7.2)	4.6	407/4467 (9.1)	6.0	0.78 (0.67-0.90)	0.70
SGLT2i	17/310 (5.5)	3.5	16/265 (6.0)	3.9	0.89 (0.45-1.77)	
Cardiovascular death or HF hospitalization						
No SGLT2i	179/4420 (4.0)	2.5	207/4467 (4.6)	2.9	0.87 (0.71-1.06)	0.60
SGLT2i	9/310 (2.9)	1.8	11/265 (4.2)	2.6	0.68 (0.28-1.64)	
Cardiovascular death						
No SGLT2i	116/4420 (2.6)	1.6	122/4467 (2.7)	1.7	0.96 (0.74-1.23)	0.46
SGLT2i	6/310 (1.9)	1.2	8/265 (3.0)	1.9	0.63 (0.22-1.82)	
HF hospitalization						
No SGLT2i	76/4420 (1.7)	1.1	106/4467 (2.4)	1.5	0.72 (0.54-0.97)	0.62
SGLT2i	3/310 (1.0)	0.6	5/265 (1.9)	1.2	0.50 (0.12-2.08)	
Cardiovascular death, MI, unstable angina, or stroke						
No SGLT2i	364/4420 (8.2)	5.3	463/4467 (10.4)	6.8	0.78 (0.68-0.90)	0.82
SGLT2i	20/310 (6.5)	4.1	20/265 (7.5)	4.9	0.84 (0.45-1.56)	
All-cause mortality, MI or stroke						
No SGLT2i	382/4420 (8.6)	5.6	465/4467 (10.4)	6.8	0.82 (0.71-0.94)	0.57
SGLT2i	20/310 (6.5)	4.1	17/265 (6.4)	4.1	0.99 (0.52-1.89)	
All-cause mortality						
No SGLT2i	187/4420 (4.2)	2.6	195/4467 (4.4)	2.7	0.97 (0.79-1.18)	0.60
SGLT2i	9/310 (2.9)	1.8	10/265 (3.8)	2.4	0.76 (0.31-1.86)	

No corrections for multiple testing were applied. Legend: IR, incidence rate per 100 person-years; HF, heart failure; MI, myocardial infarction; SGLT2i, SGLT2 inhibitor; Inter., interaction

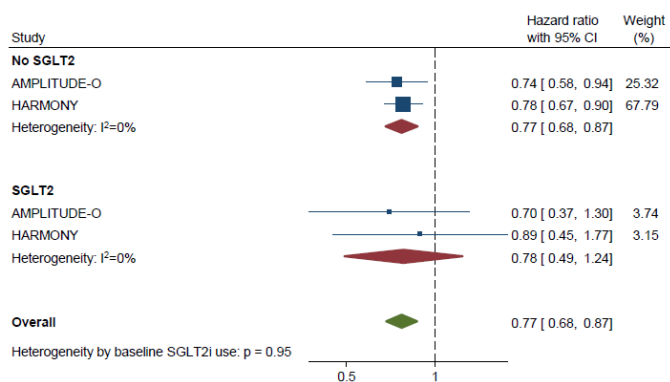
Table 3. Adverse events with albiglutide vs. placebo by baseline SGLT2i use

Outcome/SGLT2i baseline status	Albiglutide n. (%)	Placebo n. (%)	OR (95%CI)	Inter. P
Serious adverse event (any)				0.29
No SGLT2i	964/4406 (21.9)	1052/4450 (23.6)	0.90 (0.82-1.00)	
SGLT2i	56/310 (18.1)	62/265 (23.4)	0.72 (0.48-1.08)	
Adverse event leading to permanent study drug discontinuation				0.92
No SGLT2i	403/4406 (9.1)	322/4450 (7.2)	1.29 (1.11-1.50)	
SGLT2i	26/310 (8.4)	17/265 (6.4)	1.34 (0.71-2.52)	
Severe hypoglycemia				0.77
No SGLT2i	30/4406 (0.7)	54/4450 (1.2)	0.56 (0.36-0.87)	
SGLT2i	1/310 (0.3)	1/265 (0.4)	0.85 (0.05-13.73)	
Diabetic retinopathy				0.79
No SGLT2i	72/4406 (1.6)	84/4450 (1.9)	0.86 (0.63-1.19)	
SGLT2i	6/310 (1.9)	5/265 (1.9)	1.03 (0.31-3.40)	
Renal failure				0.57
No SGLT2i	265/4406 (6.0)	308/4450 (6.9)	0.86 (0.73-1.02)	
SGLT2i	14/310 (4.5)	11/265 (4.2)	1.09 (0.49-2.45)	
Atrial fibrillation/flutter (new onset)				0.24
No SGLT2i	99/4406 (2.2)	126/4450 (2.8)	0.79 (0.60-1.03)	
SGLT2i	9/310 (2.9)	5/265 (1.9)	1.55 (0.51-4.70)	
Hypersensitivity reaction				0.91
No SGLT2i	42/4406 (1.0)	45/4450 (1.0)	0.94 (0.62-1.44)	
SGLT2i	3/310 (1.0)	3/265 (1.1)	0.85 (0.17-4.26)	
Pneumonia				0.84
No SGLT2i	124/4406 (2.8)	131/4450 (2.9)	0.95 (0.74-1.22)	
SGLT2i	7/310 (2.3)	7/265 (2.6)	0.85 (0.29-2.46)	
Pancreatitis				_*
No SGLT2i	10/4406 (0.2)	7/4450 (0.2)	1.44 (0.55-3.80)	
SGLT2i	0/310 (0)	0/265 (0)	_*	
Urinary tract infection				_*
No SGLT2i	1/4406 (0.02)	1/4450 (0.02)	1.01 (0.06-16.16)	
SGLT2i	0/310 (0)	0/265 (0)	_*	
Diabetic ketoacidosis				_*
No SGLT2i	2/4406 (0.05)	1/4450 (0.02)	2.02 (0.18-22.30)	
SGLT2i	0/310 (0)	0/265 (0)	_*	

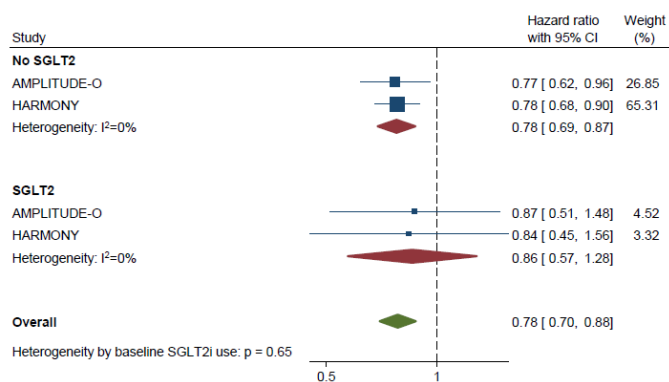
Analysis was restricted to participants that received at least one dose of the study drug. No corrections for multiple testing were applied. *OR and interaction p-value not calculated due to no events in the subgroup with baseline SGLT2i use. Legend: SGLT2i, SGLT2 inhibitor; OR, odds ratio; Inter., interaction.

Central illustration. Meta-analysis of cardiovascular outcomes of GLP-1 receptor agonist by baseline SGLT2i use. No corrections for multiple testing were applied. AMPLITUDE-O, Effect of Efpeglenatide on Cardiovascular Outcomes; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease; HF, heart failure; MI, myocardial infarction; SGLT2i, SGLT2 inhibitor.

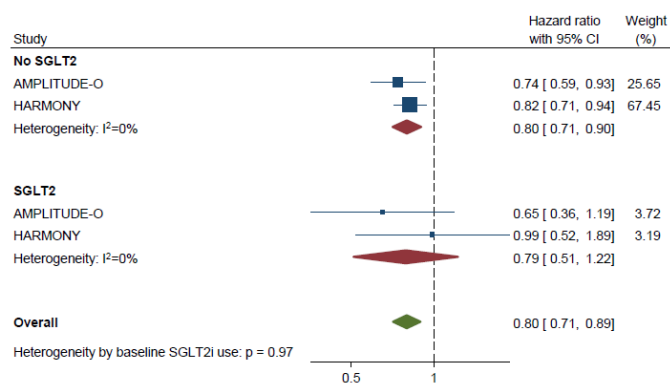
A. Cardiovascular death, MI, or stroke



B. Cardiovascular death, MI, unstable angina, or stroke



C. All-cause death, MI or stroke



D. HF Hospitalization

