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Albiglutide in patients with type 2 diabetes and heart failure: a post-hoc analysis from Harmony Outcomes

Short title: Albiglutide and heart failure

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Abstract

Background: Glucagon-like peptide-1 receptor agonists (GLP1-RA) improve cardiovascular outcomes in patients with type 2 diabetes (T2D). However, some studies suggest that their effects in patients with heart failure (HF) may be attenuated. We aim to explore the effects of the GLP1-RA albiglutide on HF outcomes in patients with and without HF history enrolled in the Harmony Outcomes trial.

Methods: Harmony Outcomes enrolled patients with T2D and cardiovascular disease randomized to either albiglutide or placebo over a median follow-up of 1.6 years.

Results: 9462 patients were included, of whom 1922 (20%) had HF history. Patients with HF had more cardiovascular comorbidities, poorer renal function, and had a 3 to 4-fold higher risk of HF events compared to patients without HF. Compared to placebo, the effect of albiglutide on the composite of cardiovascular death or HF hospitalization was more pronounced among patients without HF (HR=0.73, 95%CI=0.56-0.95) than in patients with HF (HR=1.06, 95%CI=0.79-1.43), interaction P=0.062. A similar pattern was observed for HF hospitalizations (interaction P=0.025). The effect of albiglutide on cardiovascular death, sudden death or “pump failure” death, and all-cause mortality was also attenuated among patients with HF history, but without significant interaction (P>0.1). The benefit of albiglutide to reduce atherosclerotic events was consistent regardless of HF history.

Conclusions: In patients with T2D and cardiovascular disease, albiglutide appeared to have no effect in reducing HF-related events among patients with HF history. These findings, placed in the context of other trials, suggest that GLP1-RA may not improve HF outcomes in patients with HF.

Key-words: albiglutide; GLP1 receptor agonists; type 2 diabetes; heart failure.

Introduction

Glucagon-like peptide receptor agonists (GLP1-RA) reduced the incidence of cardiovascular events in patients with type 2 diabetes (T2D) and constitute a preferential drug class for reducing the cardiovascular risk of patients with T2D.^{1,2}

Despite the robust evidence supporting the use of GLP1-RA to reduce the risk of atherosclerotic events in patients with T2D, the impact of GLP1-RA on heart failure (HF) outcomes is less well-established.² Furthermore, the effect of GLP1-RA in patients with overt HF is uncertain.³ Dedicated outcome trials with GLP1-RA in HF are scarce, and those performed enrolled a few hundred of patients having limited power to study the effect of GLP1-RA on morbidity and mortality of HF patients.⁴ Moreover, among patients with heart failure and a reduced ejection fraction (HFrEF), GLP1-RA have no clear benefit and may even be harmful.^{5,6} Also, an analysis by HF subgroups from the EXSCEL study (Exenatide Study of Cardiovascular Event Lowering) suggested that the benefit of exenatide to reduce mortality and HF hospitalizations was present only in patients without prior HF, with no benefit (for any of the studied outcomes) among patients with HF.⁷ The existing evidence with GLP1-RA in patients with HF contrasts with that using sodium glucose co-transporter 2 inhibitors (SGLT2i), a drug class that showed a consistent benefit to reduce HF hospitalizations in patients with T2D with or without established HF, regardless of ejection fraction.⁸⁻¹⁰

Generating further evidence around the use of GLP1-RA in HF patients is extremely important since 10-20% of the patients with T2D suffer from HF (and a high proportion may be undiagnosed) and 40-50% of the patients with HF have T2D.¹¹⁻¹³

The present study aims to assess the effect of the GLP1-RA albiglutide according to HF history in patients with T2D and cardiovascular disease enrolled in the Harmony Outcomes (albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease) trial.¹⁴

Methods

Study design, participants, and procedures

The design and baseline characteristics of Harmony Outcomes have been previously published.¹⁵ In short, Harmony Outcomes was a double-blind, randomized, placebo-controlled, event-driven trial including patients with T2D with a glycated hemoglobin (HbA1c) above 7.0%, aged 40 years or older, with established cardiovascular disease (coronary: myocardial infarction, at least 50% stenosis in one coronary artery or more, or previous coronary revascularisation; cerebrovascular: ischaemic stroke, at least 50% carotid artery stenosis, or a previous carotid vascular procedure; and/or peripheral arterial: intermittent claudication and an ankle to brachial index <0.9, non-traumatic amputation, or a previous peripheral vascular procedure), randomized in a 1:1 ratio to either once a week subcutaneous injections of albiglutide or matching placebo. The starting dose of the study medication was 30 mg in 0.5 mL once a week, with possibility to increase to 50 mg once a week after 5 weeks if glucose-lowering intensification was required. Patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m², previous pancreatitis or risk factors for pancreatitis were excluded from the trial.¹⁴

The protocol was approved by the ethics committee at each participating site and all patients provided written informed consent. An independent data and safety

monitoring committee, with access to unblinded data, performed regular safety surveillance.

Outcomes

The primary outcome of Harmony Outcomes was a composite of cardiovascular death, myocardial infarction, or stroke, analysed as time-to-first event according to the intention-to-treat principle.

The median follow-up time was 1.6 (percentile₂₅₋₇₅ 1.3 to 2.0) years.

In the present post-hoc analysis of Harmony Outcomes, the main outcome was a composite of cardiovascular death or HF hospitalization. Cardiovascular death, HF hospitalization (first and total), sudden death or HF (“pump failure”) death, and all-cause death were also studied, as well as the addition of unstable angina to the composite of cardiovascular death, myocardial infarction, or stroke. All outcomes were studied in patients with and without HF history.

All outcomes were independently adjudicated by an adjudication committee blinded to treatment allocation. A HF hospitalization was adjudicated only when HF was the primary cause of hospitalization, lasting more than 24h along with signs and symptoms of HF.¹⁴

Statistical analysis

Harmony Outcomes population was divided into two subgroups according to prior HF history (with vs. without HF history), and their characteristics were described as medians (percentile₂₅₋₇₅) for continuous variables and number (%) for categorical variables and compared through means of Mann-Whitney and Chi² tests, as appropriate. Normality testing was performed using Kolmogorov Smirnov tests. The associations of HF history with outcomes were assessed using Cox models for time-

to-first event analyses and negative binomial models for total HF event analysis, adjusting for age, sex, race, coronary artery disease (CAD), body mass index (BMI), systolic blood pressure (SBP), HbA1c, and eGFR. The choice of these covariates was based on their established association with HF and cardiovascular outcomes.¹⁶

The effect of albiglutide vs. placebo was tested using Cox models for time-to-first event analyses and negative binomial models for total HF event analysis with treatment group as explanatory variable and HF history as stratification variable, with treatment-by-HF history interaction term in the model. The results are presented separately for patients with and without HF history, along with the respective interaction P-value. Analyses were performed according to the intention-to-treat principle and, additionally, including patients who received at least one dose of the study treatment. 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, HF history, baseline value of the variable of interest, treatment-by-time, and treatment-by-HF history interaction terms in the model; random effects were set at the patient id level using an unstructured covariance matrix. Adverse events were studied among patients who received at least one dose of the study drug using logistic regression models with treatment group as explanatory variable and HF history as stratification variable, with treatment-by-HF history interaction term in the model. No data imputation was performed. No adjustment for multiplicity was performed given the exploratory nature of this work. A two-sided P-value <0.05 was considered statistically significant for main effects, and a two-sided P-value <0.10 was considered statistically significant for interaction tests, which have less statistical power. These statistical thresholds were used solely for data interpretation and

hypothesis generation and were placed in the clinical context along with the work from others in the discussion. Analyses were performed using Stata® (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Data access

All data packages were assessed through the Vivli® (Center for Global Clinical Research Data) platform with the Vivli ID: 00007609.

Results

Main report summary

As shown in the main report of Harmony Outcomes,¹⁴ in the overall population albiglutide reduced the composite of cardiovascular death, myocardial infarction, or stroke: 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); and the composite of cardiovascular death, unstable angina, myocardial infarction, or stroke: 373/4731 (8%) events in the albiglutide group vs. 468/4732 (10%) events in the placebo group (HR 0.78, 95%CI 0.69-0.90, P =0.001). Albiglutide did not reduce the composite of cardiovascular death or HF hospitalization: 188/4731 (4%) events in the albiglutide group vs. 218/4732 (5%) events in the placebo group (HR 0.85, 95%CI 0.70-1.04, P =0.11); cardiovascular death: 122/4731 (3%) events in the albiglutide group vs. 130/4732 (3%) events in the placebo group (HR 0.93, 95%CI 0.73-1.19, P =0.58); nor all-cause mortality: 196/4731 (4%) events in the albiglutide group vs. 205/4732 (5%) events in the placebo group (HR 0.95, 95%CI 0.79-1.16, P =0.64).

Patient's characteristics by HF history status

From the 9462 patients randomized into the trial, 1922 (20.3%) had HF history. Compared to patients without HF history, those with HF were more frequently women (34.9 vs. 29.5%), White (83.4 vs. 66.0%), had more frequent history of CAD (81.4 vs. 67.8%), atrial fibrillation/flutter (19.5 vs. 6.2%), and diabetic eye disease (32 vs. 17.5%), had higher BMI (32.6 vs. 31.2 Kg/m²), lower eGFR (72 vs. 78 ml/min/1.73m²), and used angiotensin converting enzyme/angiotensin receptor blockers (ACEi/ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), loop diuretics and statins more frequently (all P-values <0.05). Most patients with HF history were in NYHA class I/II (86.8%) at the time of inclusion. *Table 1*. The patient's description with further splitting by randomized treatment is presented in the *Supplemental Table 1*.

Association of HF history with events

Compared to patients without HF history, those with HF history had a higher risk of cardiovascular events and all-cause mortality. For example, the risk of cardiovascular death or HF hospitalization was 2.6-fold higher (HR 2.64, 95%CI 2.15-3.23), the risk of HF hospitalizations was 3.6-fold higher (HR 3.59, 95%CI 2.67-4.81), the risk of cardiovascular death, MI, or stroke was 1.7-fold higher (HR 1.66, 95%CI 1.42-1.94), and the risk of all-cause mortality 1.9-fold higher (HR 1.92, 95%CI 1.55-2.37). *Table 2*. The breakdown of event-rates by NYHA class is presented in the *Supplemental Table 2* and shows a gradual increase in risk with higher NYHA classes.

Effect of albiglutide on the study outcomes by HF history status

Compared to placebo, the effect of albiglutide on the composite of cardiovascular death or HF hospitalization was more pronounced among patients without HF history: HR 0.73, 95%CI 0.56-0.95 in patients without HF history and HR 1.06,

95%CI 0.79-1.43 in patients with HF history, interaction P =0.062. A similar pattern was observed for HF hospitalizations: HR 0.49, 95%CI 0.31-0.77 in patients without HF history and HR 0.97, 95%CI 0.66-1.42 in patients with HF history, interaction P =0.025. The effect of albiglutide on cardiovascular death, sudden death or “pump failure” death, and all-cause mortality also showed an attenuated effect among patients with HF history, although without significant treatment-by-HF history interaction (interaction P >0.1). The benefit of albiglutide to reduce the composite of cardiovascular death, MI, or stroke (including the extended composite incorporating unstable angina) was consistent regardless of HF history (interaction P >0.1). *Table 3, Figure 1 & Supplemental Figure 1 for Kaplan-Meier curves.*

The treatment effect remained similar when considering only the patients who received at least one dose of study drug. *Supplemental Table 3.*

Effect of albiglutide on longitudinal measures by HF history status

On average, albiglutide increased heart rate by 1 to 2 bpm, decreased weight by 1 to 2 Kg, and decreased HBA1c by 0.5 to 1%, without significant differences according to HF history. In addition, the effect of albiglutide on eGFR and SBP was of small magnitude without differences according to HF history (interaction P >0.1 for all).

Figure 2.

Adverse events by HF history status

Overall, albiglutide was well-tolerated regardless of HF history status. *Table 4.*

Permanent drug discontinuation was more frequent among patients taking albiglutide, without difference by HF history (interaction P =0.73). Incidence of pneumonia and atrial fibrillation/flutter might have been less frequent among patients

with HF history taking albiglutide (interaction P =0.062 and 0.072, respectively).

Table 4.

Discussion

The present study shows that among almost 9500 patients with T2D and established cardiovascular disease, around 20% had HF history. These were more frequently women, had more frequent cardiovascular comorbidities (e.g., coronary artery disease, atrial fibrillation/flutter, diabetic eye disease), poorer renal function, and were more frequently treated with RAAS inhibitors and loop diuretics. Patients with HF history were mildly symptomatic with the vast majority in NYHA classes I or II. Despite mildly symptomatic, compared to patients without HF history, those with HF had an increased risk of cardiovascular events and mortality, including a 3.6-fold higher risk of subsequent HF hospitalization, 2.6-fold higher risk of sudden or “pump failure” death, 1.7-fold higher risk of cardiovascular death, MI or stroke, and 1.9-fold higher risk of death. Notwithstanding the high risk of events, particularly HF-related, albiglutide (compared to placebo) appeared to have no effect in reducing cardiovascular death and HF hospitalizations among patients with HF history, but appeared to reduce HF hospitalizations in patients without HF history, who had a low risk for such events (placebo group: 1.0 events per 100 person-years in patients without HF vs. 3.4 events per 100 person-years in patients with HF history), with a significant treatment-by-HF history interaction P-value of 0.025. Interestingly, the differences in treatment effect observed for HF outcomes contrast with the effect seen on atherosclerotic cardiovascular events such as MI, unstable angina, or stroke with a similar event reduction irrespective of HF history status. In addition, albiglutide reduced weight regardless of HF status. Overall, albiglutide was well-tolerated

without major differences between patients with and without HF history. These results are of clinical importance, because they suggest that in patients with T2D and HF history, GLP1-RA may not be the ideal drugs for reducing HF-related events, albeit that may still be considered to reduce atherosclerotic events regardless of HF. However, as the risk of HF-related events is highly increased in patients with concomitant T2D and HF, SGLT2i may constitute a better option for treating patients with T2D and HF, as SGLT2i have consistently shown to improve HF outcomes, including in patients with severe HF.^{8,9,17-19}

Our findings replicate to a great extent those from the EXSCEL study (Exenatide Study of Cardiovascular Event Lowering) in 14752 patients with T2D with and without cardiovascular disease of whom 16% had HF history,⁷ where the effect of exenatide to reduce the composite of cardiovascular death or HF hospitalization and all-cause death or HF hospitalization was more pronounced among patients without HF history (HR 0.86, 95%CI 0.74 to 1.01 and HR 0.81, 95%CI 0.71 to 0.93, respectively) than in patients with HF history in whom the effect was neutral (HR 1.05, 95%CI 0.86 to 1.29 and HR 1.07, 95%CI 0.89 to 1.29; interaction P values of 0.13 and 0.015, respectively). The benefit of exenatide to reduce MI or stroke events was similar in patients with and without HF history.

Our findings also align with the results from the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) in 9370 patients with T2D and a high cardiovascular risk of whom 18% had HF history,²⁰ where the effect of liraglutide to reduce the composite of cardiovascular death or HF hospitalization was more pronounced among patients without HF history (HR 0.77, 95%CI 0.65 to 0.91) than in patients with HF history in whom the effect was neutral (HR 0.92, 95%CI 0.74 to 1.15; interaction P value 0.19). Again, the effect to reduce

cardiovascular death, MI, or stroke was similar in patients with and without HF history.²¹

In the SUSTAIN-6 trial (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes) HF outcomes according to HF history status have not been reported yet; however, and in contrast with Harmony Outcomes, EXSCEL and LEADER, the effect of semaglutide to reduce the primary composite outcome of cardiovascular death, MI, or stroke was more pronounced in patients without HF history (HR 0.64, 95%CI 0.48 to 0.86) than in patients with HF history in whom the effect was neutral (HR 1.03, 95%CI 0.64 to 1.66; interaction P value 0.09).²² These findings were reinforced in the individual patient combined analysis of SUSTAIN-6 and PIONEER-6 (Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes), where the HRs for the composite of cardiovascular death, MI, or stroke were <1.0 in all subgroups, except for those with HF history (HR 1.06, 95%CI 0.72 to 1.57; interaction P value 0.046). Moreover, in the combined trials semaglutide did not reduce HF hospitalizations (HR 1.03, 95%CI 0.75 to 1.40).²³

No HF outcomes by HF history status or HF subgroup analysis have been reported in AMPLITUDE-O (Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes), with only 71 patients experiencing an HF event in this trial.²⁴

Together, these findings suggest that GLP1-RA do not improve HF-related outcomes among patients with HF history i.e., those who are at highest risk for HF events.

While SGLT2i are effective for prevention and treatment of HF in patients with T2D, GLP1-RA may prevent the development of HF in T2D but do not reduce HF events in those with established HF. The mechanisms underlying the effect attenuation of GLP1-RA in patients with HF history are not well-established, but they may be

related to an increase in heart rate which may be particularly deleterious to HF patients.²⁵ Furthermore, the GLP-1 receptor, expressed in cardiomyocytes and sinoatrial node cells, signals through a cAMP-dependent pathway which may induce intracellular calcium overload that may be deleterious in HF patients, particularly those with advanced HFrEF (which were excluded from Harmony Outcomes).^{3,26,27} In this regard, in the FIGHT trial (the Heart Failure Network Functional Impact of GLP-1 for Heart Failure Treatment) liraglutide might have increased the risk of emergency department visit, HF hospitalization, or all-cause death compared to placebo (HR 1.36, 95%CI 0.99 to 1.85, P =0.05).⁵ Still, it is important to highlight that patients with symptomatic HFrEF were most likely not included (or only in residual numbers) in T2D trials, where most patients with HF history were mildly symptomatic outpatients, likely with preserved ejection fraction. On the other hand, atherosclerotic events may be reduced regardless of HF history, because these may be more dependent on glycemic control, weight reduction and improvements in metabolic profile, mechanisms that may also contribute to reduce the incidence of new-onset HF.²⁸

Limitations

Several limitations should be acknowledged in this study. First, this is a post-hoc analysis of a randomized trial without adjustment for test multiplicity and these findings should be regarded as exploratory. Second, details about HF were incomplete and not standardized across T2D trials. Third, natriuretic peptide values were not available and left ventricular ejection fraction or other echocardiographic parameters not reported. Fourth, in the main Harmony Outcomes publication,¹⁴ a total of 9463 patients were included in the intention-to-treat analysis, whereas in our dataset 9462 patients were available. Moreover, in the main Harmony Outcomes

publication 766 primary outcome events (composite of cardiovascular death, MI, or stroke) were reported, whereas we found 758 events. Numbers regarding HF and mortality outcomes, and all estimates of treatment effects were similar in the two datasets. Fifth, only 13% (n =287) patients had reported NYHA III HF, which does not allow to provide reliable estimates within this subgroup. Most patients with HF history were White and these findings cannot be generalized to other ethnicities. Discontinuation of concomitant treatments (such as ACEi/ARBs and beta-blockers) was not consistently reported throughout the follow-up; thus, we cannot speculate about their potential association with HF risk. Finally, the extensive replication of the results suggests that there is a true attenuation of GLP1-RA effect among patients with HF, particularly regarding HF-related outcomes; still, dedicated large-scale outcome trials with GLP1-RA in patients with HF are warranted.

Conclusions

In patients with T2D and cardiovascular disease enrolled in Harmony Outcomes, albiglutide appeared to reduce HF-related events among patients without HF history but not among those with HF history in whom the effect was neutral. These findings placed in the context of other trials, suggest that GLP1-RA may not improve HF outcomes in patients with HF, although they may be used to reduce atherosclerotic events regardless of HF history. Dedicated trials with GLP1-RA in HF patients are necessary.

Declarations

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Table 1. Baseline patient's characteristics by HF history status

| Characteristic | HF | No HF | P-value |
|------------------------------------|--------------------|--------------------|---------|
| N. | 1922 | 7540 | |
| Age, years | 65.0 (58.0, 70.0) | 65.0 (58.0, 70.0) | 0.40 |
| Women | 671 (34.9%) | 2223 (29.5%) | <0.001 |
| NYHA I/II | 1635 (86.8%) | 0 | <0.001 |
| Race | | | |
| Asian | 88 (4.6%) | 382 (5.1%) | <0.001 |
| Hispanic | 171 (8.9%) | 1822 (24.2%) | |
| Black or African American | 35 (1.8%) | 190 (2.5%) | |
| White | 1603 (83.4%) | 4979 (66.0%) | |
| Other | 25 (1.3%) | 167 (2.2%) | |
| Region | | | |
| Asia Pacific | 74 (3.9%) | 302 (4.0%) | <0.001 |
| Eastern Europe | 930 (48.4%) | 1117 (14.8%) | |
| Latin America | 111 (5.8%) | 1592 (21.1%) | |
| North America | 283 (14.7%) | 1661 (22.0%) | |
| Western Europe | 524 (27.3%) | 2868 (38.0%) | |
| Current Smoker | 258 (13.4%) | 1230 (16.3%) | <0.001 |
| CAD | 1564 (81.4%) | 5113 (67.8%) | <0.001 |
| CABG | 433 (22.5%) | 1299 (17.2%) | <0.001 |
| PAD | 395 (20.6%) | 1959 (26.0%) | <0.001 |
| Cerebrovascular disease | 499 (26.0%) | 1843 (24.4%) | 0.17 |
| Atrial fibrillation/flutter | 374 (19.5%) | 468 (6.2%) | <0.001 |
| Weight, kg | 93.0 (81.0, 107.2) | 89.7 (78.0, 102.8) | <0.001 |
| BMI, Kg/m ² | 32.6 (29.0, 37.0) | 31.2 (28.0, 35.2) | <0.001 |
| Heart rate, bpm | 72 (65, 78) | 72 (65, 79) | 0.82 |
| Systolic BP, mmHg | 134 (123, 143) | 135 (124, 145) | 0.005 |
| Diastolic BP, mmHg | 79 (70, 85) | 78 (70, 83) | <0.001 |
| HbA1c, % | 8.5 (7.7, 9.6) | 8.3 (7.6, 9.4) | <0.001 |
| eGFR, ml/min/1.73m ² | 72 (56, 89) | 78 (62, 95) | <0.001 |
| eGFR <60 ml/min/1.73m ² | 593 (30.9%) | 1564 (20.7%) | <0.001 |
| Diabetic eye disease | 615 (32.0%) | 1322 (17.5%) | <0.001 |
| Diabetes duration, years | 12.4 (7.1, 18.4) | 13.0 (7.8, 19.5) | <0.001 |
| Insulin | 1176 (61.2%) | 4420 (58.6%) | 0.041 |
| Metformin | 1309 (68.1%) | 5659 (75.1%) | <0.001 |
| DPP4i | 231 (12.0%) | 1206 (16.0%) | <0.001 |
| Sulfonylureas | 608 (31.6%) | 2117 (28.1%) | 0.002 |
| SGLT2i | 87 (4.5%) | 488 (6.5%) | 0.001 |
| Thiazolidinediones | 20 (1.0%) | 174 (2.3%) | <0.001 |
| ACEi/ARBs | 1647 (85.7%) | 5877 (77.9%) | <0.001 |
| Beta-blockers | 1572 (81.8%) | 4738 (62.8%) | <0.001 |
| MRAs | 394 (20.5%) | 414 (5.5%) | <0.001 |
| CCBs | 624 (32.5%) | 2235 (29.6%) | 0.016 |
| Nitrates | 417 (21.7%) | 1138 (15.1%) | <0.001 |
| Thiazides | 425 (22.1%) | 1701 (22.6%) | 0.67 |
| Loop diuretics | 728 (37.9%) | 1066 (14.1%) | <0.001 |
| Statins | 1692 (88.0%) | 6263 (83.1%) | <0.001 |

| | | | |
|---------------------|--------------|--------------|--------|
| Fibrates | 124 (6.5%) | 591 (7.8%) | 0.040 |
| Ezetimibe | 78 (4.1%) | 538 (7.1%) | <0.001 |
| Antiplatelet agents | 1521 (79.1%) | 5769 (76.5%) | 0.015 |
| Anticoagulants | 291 (15.1%) | 506 (6.7%) | <0.001 |

Legend: CAD, coronary artery disease; CABG, coronary artery bypass grafting; 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; CCBs, calcium channel blockers.

Continuous variables are reported as medians and respective 25th to 75th percentiles.

Table 2. Associations of HF history with cardiovascular events and mortality

| Event | HF n. (%) Inc.-rate per 100py | No HF n. (%) Inc.-rate per 100py | HR (95%CI) * P-value |
|--|--|---|---------------------------------|
| Cardiovascular death or HF hospitalization | 179/1922 (9.3) IR =5.9 | 227/7540 (3.0) IR=1.9 | 2.64 (2.15-3.23) P <0.001 |
| Cardiovascular death | 96/1922 (5.0) IR =3.1 | 156/7540 (2.1) IR =1.3 | 2.11 (1.62-2.74) P <0.001 |
| Sudden death or “pump failure” death | 60/1922 (3.1) IR =1.9 | 78/7540 (1.0) IR =0.6 | 2.58 (1.82-3.65) P <0.001 |
| HF hospitalization (first) | 103/1922 (5.4) IR =3.4 | 87/7540 (1.2) IR =0.7 | 3.59 (2.67-4.81) P <0.001 |
| HF hospitalizations (total) ** | 153/1922 | 106/7540 | 4.41 (3.17-6.15) P<0.001 |
| Cardiovascular death, MI, or stroke | 246/1922 (12.8) IR =8.3 | 512/7540 (6.8) IR =4.4 | 1.66 (1.42-1.94) P <0.001 |
| Cardiovascular death, MI, unstable angina, or stroke | 284/1922 (14.8) IR =9.6 | 628/7540 (8.3) IR =5.4 | 1.56 (1.35-1.80) P <0.001 |
| All-cause mortality | 141/1922 (7.3) IR =4.5 | 260/7540 (3.4) IR =2.2 | 1.92 (1.55-2.37) P <0.001 |

*Hazard ratio adjusted for age, sex, race, coronary artery disease, body mass index, systolic blood pressure, HbA1c, and eGFR. **Total events and incidence rate ratio obtained from a negative binomial model.

Legend: IR, incidence-rate per 100 person-years; HF, heart failure; MI, myocardial infarction.

Table 3. Effect of albiglutide vs. placebo on the study outcomes by HF history

| Outcome/HF history status | Albiglutide n. (%) Inc.-rate per 100py | Placebo n. (%) Inc.-rate per 100py | HR (95%CI) | Inter.P |
|---|---|---|-------------------|----------------|
| Cardiovascular death or HF hospitalization | | | | |
| No HF | 97/3776 (2.6) IR =1.6 | 130/3764 (3.5) IR =2.2 | 0.73 (0.56-0.95) | 0.062 |
| HF | 91/954 (9.5) IR =6.1 | 88/968 (9.1) IR =5.7 | 1.06 (0.79-1.43) | |
| Cardiovascular death | | | | |
| No HF | 74/3776 (2.0) IR =1.2 | 82/3764 (2.2) IR =1.4 | 0.89 (0.65-1.21) | 0.54 |
| HF | 48/954 (5.0) IR =3.1 | 48/968 (5.0) IR =3.0 | 1.04 (0.70-1.55) | |
| Sudden death or “pump failure” death | | | | |
| No HF | 32/3776 (0.8) IR =0.5 | 46/3764 (1.2) IR =0.8 | 0.69 (0.44-1.08) | 0.32 |
| HF | 29/954 (3.0) IR =1.9 | 31/968 (3.2) IR =2.0 | 0.97 (0.58-1.61) | |
| HF hospitalization (first) | | | | |
| No HF | 29/3776 (0.8) IR =0.5 | 58/3764 (1.5) IR =1.0 | 0.49 (0.31-0.77) | 0.025 |
| HF | 50/954 (5.2) IR =3.3 | 53/968 (5.5) IR =3.4 | 0.97 (0.66-1.42) | |
| HF hospitalizations (total) * | | | | |
| No HF | 33/3776 | 71/3764 | 0.47 (0.30-0.75) | 0.096 |
| HF | 72/954 | 81/968 | 0.85 (0.51-1.40) | |
| Cardiovascular death, MI, or stroke | | | | |
| No HF | 234/3776 (6.2) IR =4.0 | 278/3764 (7.4) IR =4.8 | 0.82 (0.69-0.98) | 0.30 |
| HF | 101/954 (10.6) IR =6.8 | 145/968 (15.0) IR =9.8 | 0.70 (0.54-0.90) | |
| Cardiovascular death, MI, unstable angina, or stroke | | | | |
| No HF | 282/3776 (7.5) IR =4.8 | 346/3764 (9.2) IR =6.0 | 0.80 (0.68-0.93) | 0.64 |
| HF | 121/954 (12.7) IR =8.2 | 163/968 (16.8) IR =11.0 | 0.75 (0.59-0.94) | |
| All-cause mortality | | | | |
| No HF | 125/3776 (3.3) IR =2.1 | 135/3764 (3.6) IR =2.3 | 0.91 (0.71-1.16) | 0.48 |
| HF | 71/954 (7.4) IR =4.6 | 70/968 (7.2) IR =4.4 | 1.06 (0.76-1.47) | |

*Total events and incidence rate ratio obtained from a negative binomial model.

Legend: IR, incidence-rate per 100 person-years; HF, heart failure; MI, myocardial infarction.

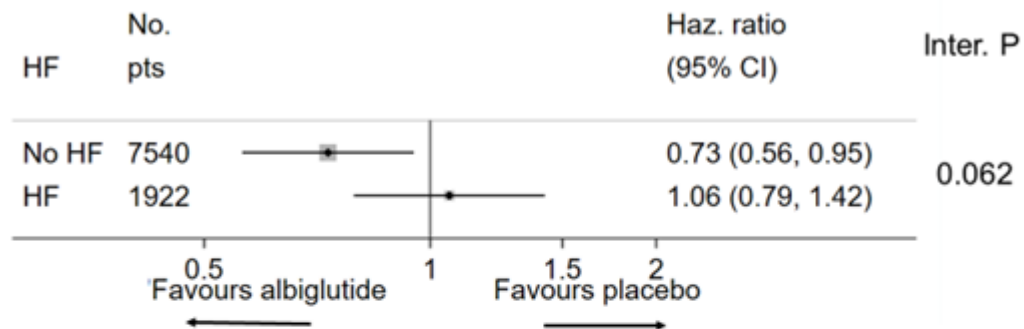
Table 4. Adverse events with albiglutide vs. placebo by HF history status

| AE/HF history status | Albiglutide n. (%) | Placebo n. (%) | OR (95%CI) | Inter.P |
|--|--------------------|-----------------|------------------|---------|
| Serious adverse event (any) | | | | |
| No HF | 756/3764 (20.1) | 812/3749 (21.7) | 0.91 (0.81-1.02) | 0.52 |
| HF | 264/952 (27.7) | 302/966 (31.3) | 0.84 (0.69-1.03) | |
| Adverse event leading to permanent drug discontinuation | | | | |
| No HF | 324/3764 (8.6) | 258/3749 (6.9) | 1.27 (1.07-1.51) | 0.73 |
| HF | 105/952 (11.0) | 81/966 (8.4) | 1.35 (1.00-1.84) | |
| Severe hypoglycemia | | | | |
| No HF | 32/3764 (0.9) | 47/3749 (1.3) | 0.68 (0.43-1.06) | 0.71 |
| HF | 9/952 (0.9) | 16/966 (1.7) | 0.57 (0.25-1.29) | |
| Diabetic retinopathy | | | | |
| No HF | 717/3764 (19.0) | 699/3749 (18.6) | 1.03 (0.91-1.15) | 0.59 |
| HF | 325/952 (34.1) | 311/966 (32.2) | 1.09 (0.90-1.32) | |
| Renal failure | | | | |
| No HF | 170/3764 (4.5) | 178/3749 (4.7) | 0.95 (0.77-1.18) | 0.12 |
| HF | 72/952 (7.6) | 101/966 (10.5) | 0.70 (0.51-0.96) | |
| Hypersensitivity reaction | | | | |
| No HF | 36/3764 (1.0) | 40/3749 (1.1) | 0.90 (0.57-1.41) | 0.65 |
| HF | 10/952 (1.1) | 9/966 (0.9) | 1.13 (0.46-2.79) | |
| Pneumonia | | | | |
| No HF | 115/3764 (3.1) | 104/3749 (2.8) | 1.10 (0.84-1.45) | 0.062 |
| HF | 37/952 (3.9) | 54/966 (5.6) | 0.68 (0.45-1.05) | |
| Pancreatitis | | | | |
| No HF | 13/3764 (0.3) | 11/3749 (0.3) | 1.18 (0.53-2.63) | 0.80 |
| HF | 11/952 (1.2) | 11/966 (1.1) | 1.01 (0.44-2.35) | |
| Atrial fibrillation/flutter (new onset) | | | | |
| No HF | 57/3531 (1.6) | 55/3518 (1.6) | 1.03 (0.71-1.50) | 0.072 |
| HF | 21/767 (2.7) | 37/778 (4.8) | 0.56 (0.33-0.97) | |

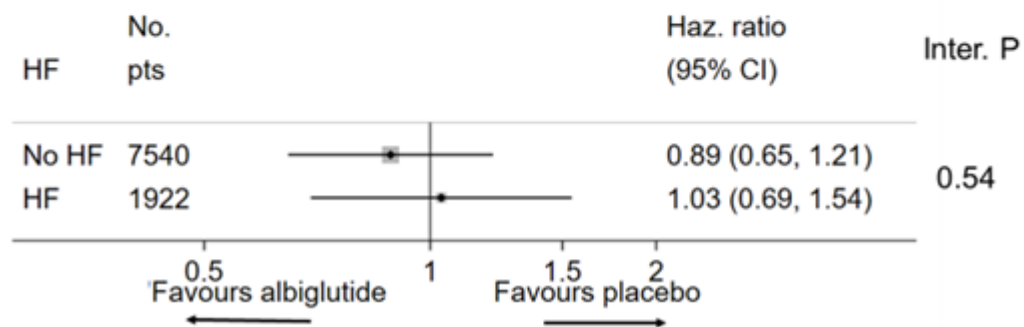
Legend: AE, adverse event; HF, heart failure; OR, odds ratio; Inter., interaction.

Figure 1. Forest plots: effect of albiglutide vs. placebo by HF history status

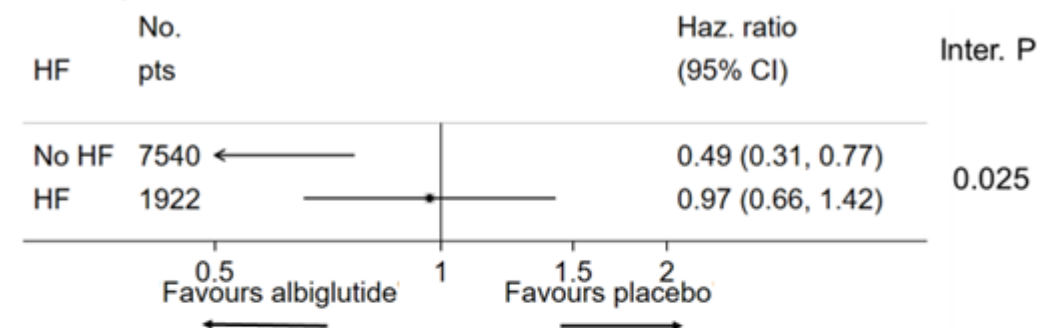
Cardiovascular death or HF hospitalization



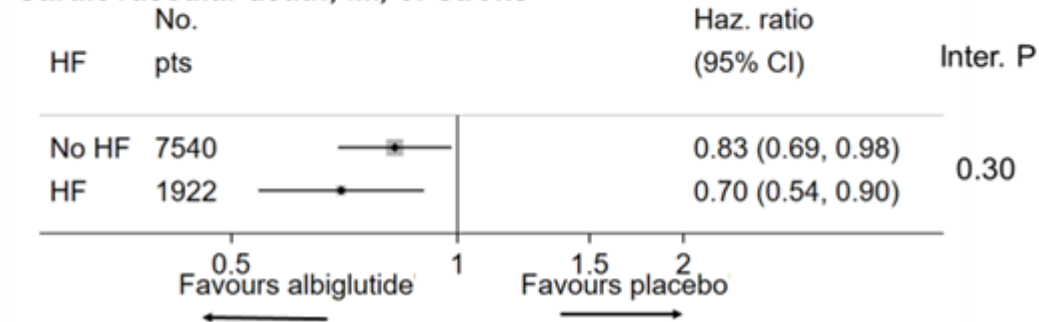
Cardiovascular death



HF hospitalization

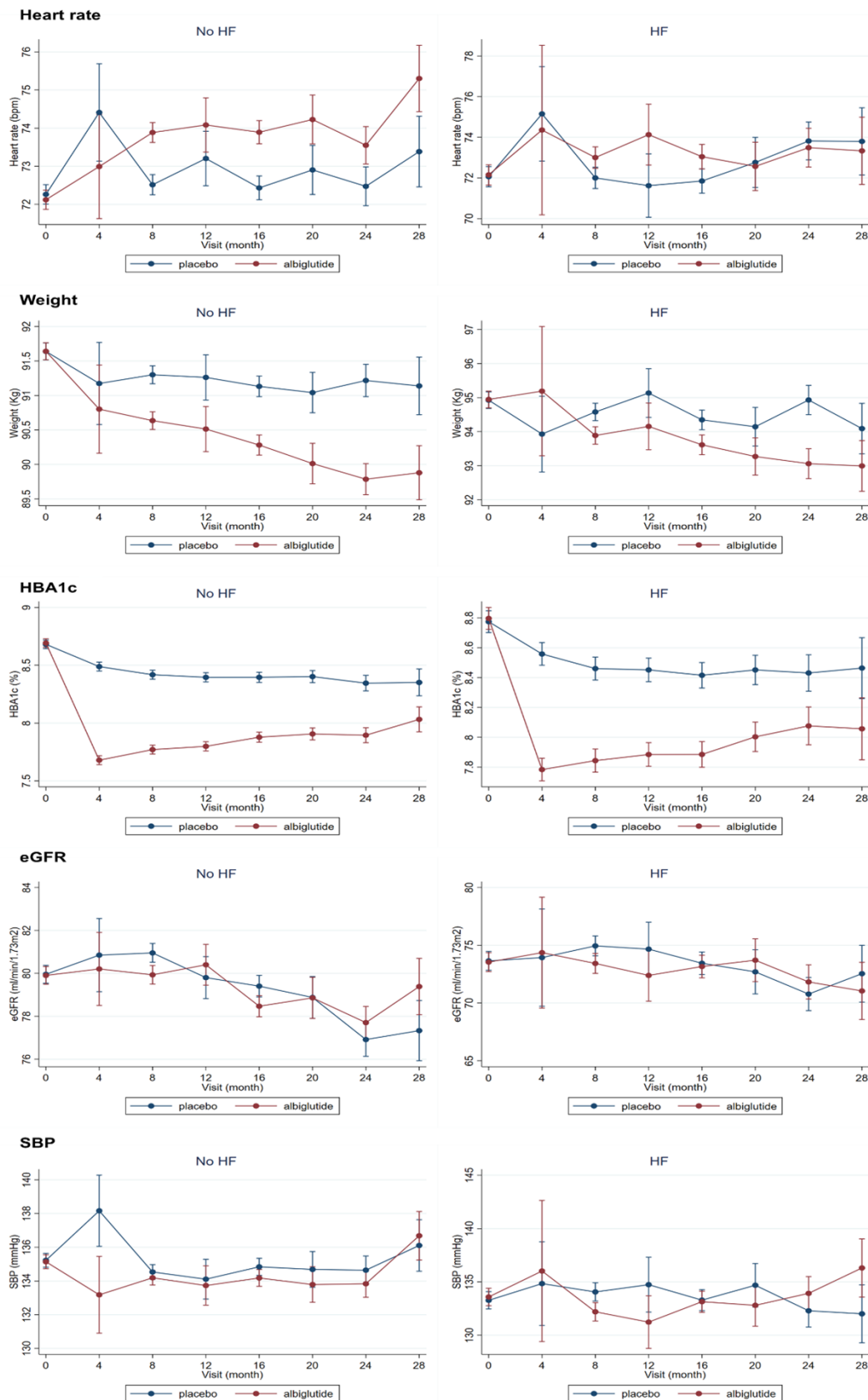


Cardiovascular death, MI, or stroke



Legend: HF, heart failure; MI, myocardial infarction; Inter., interaction; Haz., hazard.

Figure 2. Effect of albiglutide on longitudinal measures by HF history status



Legend: HF, heart failure; HBA1c%, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Caption: Difference between albiglutide and placebo: 1) heart rate: No HF: 8 months +1.4 (1.0 to 1.7) bpm, 16 months +1.5 (1.0 to 1.9) bpm, 24 months +1.1 (0.4 to 1.8) bpm; HF: 8 months +1.0 (0.3 to 1.7) bpm, 16 months +1.2 (0.3 to 2.0) bpm, 24 months -0.3 (-1.6 to 1.0) bpm; interaction P =0.56; 2) weight: No HF: 8 months -0.7 (-0.8 to -0.5) Kg, 16 months -0.9 (-1.1 to -0.6) Kg, 24 months -1.4 (-1.8 to -1.1) Kg; HF: 8 months -0.7 (-1.1 to -0.3) Kg, 16 months -0.7 (-1.1 to -0.3) Kg, 24 months -1.9 (-2.5 to -1.3) Kg; interaction P =0.92; 3) HBA1c: No HF: 8 months -0.6 (-0.7 to -0.6) %, 16 months -0.5 (-0.6 to -0.5) %, 24 months -0.5 (-0.5 to -0.4) %; HF: 8 months -0.6 (-0.7 to -0.6) %, 16 months -0.5 (-0.7 to -0.4) %, 24 months -0.4 (-0.5 to -0.2) %; interaction P =0.86; 4) eGFR: No HF: 8 months -1.0 (-1.6 to -0.4) ml/min/1.73m², 16 months -0.9 (-1.6 to -0.2) ml/min/1.73m², 24 months +0.8 (-0.3 to +1.9) ml/min/1.73m²; HF: 8 months -1.5 (-2.7 to -0.3) ml/min/1.73m², 16 months -0.3 (-1.7 to +1.1) ml/min/1.73m², 24 months +1.1 (-1.0 to +3.1) ml/min/1.73m²; interaction P =0.94; 5) SBP: No HF: 8 months -0.3 (-1.0 to +0.3) mmHg, 16 months -0.7 (-1.3 to +0.4) mmHg, 24 months -0.8 (-1.9 to +0.4) mmHg; HF: 8 months -1.9 (-3.1 to -0.6) mmHg, 16 months -0.1 (-1.5 to +1.2) mmHg, 24 months +1.6 (-0.6 to +3.8) mmHg; interaction P =0.54.