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Effects of liraglutide on cardiovascular outcomes by heart failure history in the LEADER randomized trial

Short title: **Effects of liraglutide by heart failure history**

Steven P. Marso, MD[a], Florian M.M. Baeres, MD[b], Stephen C. Bain, MD[c], Bryan Goldman, MS[b], Mansoor Husain, MD[d], Michael A. Nauck, MD[e], Neil R. Poulter, F.Med.Sci[f], Richard E. Pratley, MD[g], Anne Bloch Thomsen, MD PhD[b*], John B. Buse, MD PhD[h]; on behalf of the LEADER Trial Investigators

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[a]Midwest Heart and Vascular Institute, HCA Midwest Health, Overland Park, KS, USA;
[b]Novo Nordisk A/S, Søborg, Denmark;
[c]Swansea University Medical School, Swansea, Wales, UK;
[d]Ted Rogers Centre for Heart Research, Toronto General Hospital Research Institute, Toronto, ON, Canada;
[e]Diabetes Center Bochum-Hattingen, St. Josef-Hospital (Ruhr University), Bochum, Germany;
[f]Faculty of Medicine, School of Public Health, Imperial College London, London, UK;
[g]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA;
[h]University of North Carolina School of Medicine, Chapel Hill, NC, USA.
*At the time of the study

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Address for correspondence: Steven P. Marso, Midwest Heart and Vascular Institute, HCA Midwest Health, 12200 West 106th St Ste 320, Overland Park, KS 66215, USA; Tel: +1 816 276 4800; Fax: +1 816 276 4800; Email: Steve.Marso@HCAHealthcare.com; Twitter handle: @Steve_Marso

Summary for Twitter: This LEADER analysis showed fewer major cardiovascular events with liraglutide vs placebo in adults with diabetes with/without heart failure (NYHA class I–III).

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Abstract:

Background: More data regarding effects of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes (T2D) and heart failure (HF) are required.
Objectives: To investigate effects of liraglutide on cardiovascular events and mortality in LEADER participants, by HF history.
Methods: In the multinational, double-blind, randomized LEADER trial (ClinicalTrials.gov: NCT01179048), 9340 patients with T2D and high cardiovascular risk were assigned 1:1 to liraglutide (1.8 mg daily or maximum tolerated dose up to 1.8 mg daily) or placebo plus standard care, and followed for 3.5–5 years. New York Heart Association (NYHA) class IV HF was an exclusion criterion. The primary composite major adverse cardiovascular events (MACE) outcome was time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. *Post hoc* Cox regression analyses of outcomes by baseline HF history were conducted.
Results: At baseline, 18% of patients had a history of NYHA class I–III HF (liraglutide, N = 835/4668; placebo: N = 832/4672). Effects of liraglutide versus placebo on MACE were consistent in patients with (hazard ratio [HR; 95% confidence interval CI]: 0.81 [0.65; 1.02]) and without (0.88 [0.78; 1.00]) a history of HF (*p*-interaction = 0.53). In both subgroups, fewer deaths were observed with liraglutide (0.89 [0.70; 1.14] with HF; 0.83 [0.70; 0.97] without HF; *p*-interaction = 0.63), versus placebo. No increased risk of HF hospitalization was observed with liraglutide, regardless of HF history (0.98 [0.75; 1.28] with HF; 0.78 [0.61; 1.00] without HF; *p*-interaction = 0.22). Effects of liraglutide on the composite of HF hospitalization or cardiovascular death were consistent in patients with (0.92 [0.74; 1.15]) and without (0.77 [0.65; 0.91]) a history of HF (*p*-interaction = 0.19).
Conclusions: Based on these findings, liraglutide should be considered suitable for patients with T2D with or without a history of NYHA class I–III HF.

Condensed abstract:
Different glucose-lowering therapies have varying effects on heart failure (HF) outcomes. This analysis investigated effects of the glucagon-like peptide-1 analog liraglutide on cardiovascular events and mortality in LEADER trial participants with/without New York Heart Association (NYHA) class I–III HF at baseline (class IV excluded). Its results showed fewer major adverse cardiovascular events, fewer deaths and no increased risk of HF hospitalization with liraglutide versus placebo, regardless of baseline HF status. This analysis indicates that liraglutide should be considered a suitable treatment option for patients with type 2 diabetes, with/without a history of NYHA class I–III HF.

Keywords: heart failure; GLP-1 receptor agonist; liraglutide; major adverse cardiovascular events; mortality; type 2 diabetes

Abbreviations list:
CI = confidence interval
DPP-4is = dipeptidyl peptidase-4 inhibitors
GLP-1RAs = glucagon-like peptide-1 receptor agonists
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MACE = major adverse cardiovascular events
MI = myocardial infarction
NYHA = New York Heart Association
T2D = type 2 diabetes

Introduction

Different glucose-lowering therapies have varying effects on heart failure (HF) outcomes. Studies of the thiazolidinediones rosiglitazone and pioglitazone and the dipeptidyl peptidase-4 inhibitor (DPP-4i) saxagliptin have indicated an increase in the risk of HF events or HF hospitalization in patients with type 2 diabetes (T2D) (1-3), whereas the sodium-glucose cotransporter-2 inhibitors empagliflozin, canagliflozin and dapagliflozin reduce this risk (4-6).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used to treat patients with T2D (7). Cardiovascular outcomes trials have demonstrated cardiovascular safety of the GLP-1RAs lixisenatide, once-weekly exenatide and oral semaglutide (which showed non-inferiority versus placebo for major adverse cardiovascular events [MACE]), and cardiovascular risk reduction with liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide versus placebo in patients with T2D (8-15). Albiglutide reduced the risk of HF hospitalization versus placebo in the Harmony Outcomes trial (15); in the remaining trials, no significant differences in risk of HF hospitalization were reported with GLP-1RAs versus placebo (8-15). More data are required to establish whether these benefits are observed in patients with HF or whether these patients are at a higher risk of such events when treated with a GLP-1RA. While some previous small studies with liraglutide in patients with HF showed improvements in left ventricular function (16,17), others indicated potential safety concerns in patients with HF with reduced ejection fraction (18,19).

The LEADER cardiovascular outcomes trial evaluated effects of liraglutide (1.8 mg daily or maximum tolerated dose up to 1.8 mg daily) versus placebo in patients with T2D and high cardiovascular risk who were followed for up to 5 years (12). Presence of New York Heart

Association (NYHA) class II–III chronic HF was one of several possible cardiovascular risk enrichment criteria and was used to define pre-specified subgroups (with/without chronic HF) (12). HF requiring hospitalization was among the adjudicated endpoints captured during treatment exposure and follow-up (12).

This analysis investigated effects of liraglutide versus placebo on cardiovascular events (including HF hospitalization), all-cause death, nephropathy and heart rate in LEADER trial participants, stratified by HF history (NYHA class I–III). We also investigated the influence of prior atherosclerotic events on risk of HF hospitalization with liraglutide versus placebo.

Methods

The design of the multinational, double-blind, LEADER cardiovascular outcomes trial (NCT01179048) has been detailed elsewhere (12). The protocol was approved by the relevant independent ethics committee or institutional review board for each study site. The protocol and details of the 410 study sites have been published previously (12). All participants provided written informed consent.

LEADER included patients with T2D aged ≥50 years with either established cardiovascular disease or chronic kidney disease, or aged ≥60 years with ≥1 cardiovascular risk factor. Chronic NYHA class IV HF was an exclusion criterion. HF history and NYHA class were based on medical history as reported by the trial investigator for each patient. Information relating to inclusion/exclusion criteria and to HF, including NYHA class, was recorded in a case report form at the screening visit.

Participants were randomized 1:1 to receive once-daily, subcutaneous liraglutide 1.8 mg (or maximum tolerated dose up to 1.8 mg) or placebo, both plus standard care, and followed for 3.5–5 years. For patients not meeting their glycated hemoglobin target, the addition of glucose-lowering medications was permitted after randomization, except for GLP-1RAs, DPP-4is or pramlintide. A global expert panel developed standard of care treatment guidelines to encourage investigators to manage individual participant's blood glucose, blood pressure and lipid levels, and to guide concomitant therapy. Use of concomitant medications (e.g. for management of cardiovascular risk factors and events such as HF hospitalization) was at the investigator's discretion, according to local practices and regulations.

The primary endpoint was time from randomization to the first occurrence of a composite MACE outcome consisting of cardiovascular death, non-fatal (including silent) myocardial infarction (MI) or non-fatal stroke. Pre-specified secondary endpoints included time from randomization to the first occurrence of: an expanded composite outcome that additionally included coronary revascularization or hospitalization for unstable angina pectoris or HF (expanded MACE); individual components of the expanded MACE outcome; all-cause death; and a composite nephropathy endpoint (new-onset macroalbuminuria, persistent doubling of serum creatinine level and creatinine clearance $\leq$45 mL/min/1.73m^2 per Modification of Diet in Renal Disease equation, need for continuous renal-replacement therapy [in the absence of an acute reversible cause], or death due to renal disease). An external, independent, blinded event adjudication committee adjudicated all potential cardiovascular events (including HF requiring hospitalization) and all deaths. The definitions used for these events have been published previously (12). The definition of adjudicated HF hospitalization is provided in the Online Appendix. The composite outcomes of time to first HF hospitalization or all-cause death and of time to first HF hospitalization or cardiovascular death were analyzed *post hoc*.

Statistical methods

Exploratory analyses of the primary and secondary outcomes by chronic HF subgroups were pre-specified (12), but the present analyses were conducted *post hoc*. Presence or absence of HF at screening was recorded for all randomized participants (N = 9340). We evaluated the risk of cardiovascular events, all-cause death and nephropathy observed with liraglutide versus placebo in LEADER participants with or without a history of HF (NYHA class I–III) at baseline. The analysis used the full analysis set and a Cox regression model with treatment, HF history and the interaction between these variables as covariates.

Sensitivity analyses were performed in which patients were censored at the time of first non-fatal MI/stroke (including hemorrhagic stroke), to investigate the influence of prior atherosclerotic events on risk of HF hospitalization with liraglutide versus placebo.

The interaction between trial treatment, HF history and heart rate was also assessed. Change in heart rate from baseline at 3 years was analyzed using a mixed model for repeated measures, which included treatment group (liraglutide or placebo), HF history at baseline, baseline heart rate, sex, region, antidiabetic therapy at baseline, age at baseline, the interaction between each of these variables and study visit, and the interaction between treatment group and HF history.

Statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics

At baseline, 18% of patients had a history of HF (NYHA class I–III) (12); these patients were similarly distributed across the two treatment groups in each NYHA class (Table 1). Overall, most patients with HF had NYHA class II HF (Table 1). Fourteen patients with HF at baseline had missing NYHA category information and were included in the 'with NYHA I–III HF at baseline' group (NYHA class IV HF was an exclusion criterion) (Table 1).

Baseline characteristics were generally comparable between treatment arms, both among patients with and without a history of HF at baseline (Table 1). Higher proportions of patients with a history of HF at baseline were female and White, versus patients without a history of HF (Table 1). Patients with a history of HF also had a numerically shorter mean diabetes duration and numerically higher mean body weight, body mass index, low density lipoprotein cholesterol and triglycerides than those without HF (Table 1).

Table 2 summarizes the use of cardiovascular medications (including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, loop diuretics and aldosterone antagonists) at baseline by history of HF and randomized treatment. The use of cardiovascular medications was generally balanced between treatment groups at baseline, with expectedly greater use of diuretics and antithrombotic medication in participants with, versus without, a history of HF at baseline (Table 2). The distribution of new types of concomitant cardiovascular medications added after baseline is also shown in Table 2. A numerically higher proportion of patients with, versus without, a history of HF at baseline initiated new antithrombotic therapy (Table 2). There was also slightly less initiation of new antihypertensives and diuretics in participants with a history of HF, but this may be reflective of higher baseline use: most patients in this group were receiving these medication classes, which can be used to treat HF, at baseline (Table 2). Similar proportions of patients with and without HF at baseline initiated new loop diuretics (Table 2). Sodium-glucose cotransporter-2 inhibitors had not been approved at the time of randomization and were introduced for

relatively small proportions of patients in the overall population (liraglutide arm: 2.1%; placebo arm: 2.8%), as previously reported (12).

Interaction between treatment group and HF history for cardiovascular events and all-cause death

Based on pooled data for both treatment groups, higher proportions of patients with a history of HF at baseline experienced cardiovascular events (except non-fatal stroke) and all-cause death during the trial than patients without a history of HF (Figure 1 and Table 3).

Overall, no statistically significant interaction was detected between treatment group (liraglutide or placebo) and HF history for cardiovascular events or all-cause death (Figure 1).

Effects of liraglutide versus placebo on MACE observed in the overall population (Figure 2A) (12) were consistent in patients with a history of HF at baseline (Figures 1 and 2B) and those without a history of HF at baseline (*p*-interaction = 0.53; Figures 1 and 2C). Similar results were obtained for expanded MACE (*p*-interaction = 0.72; Figure 1).

The risks of the three individual components of the primary composite outcome (namely non-fatal MI, non-fatal stroke and cardiovascular death) in these patient subgroups are displayed in Figure 1. There was no increase in non-fatal MI or non-fatal stroke in either subgroup (*p*-interaction for non-fatal MI = 0.29; *p*-interaction for non-fatal stroke = 0.99; Figure 1). Furthermore, fewer patients experienced cardiovascular death with liraglutide versus placebo, regardless of whether they had a history of HF at baseline or not (*p*-interaction = 0.50; Figure 1).

No increased risk of HF hospitalization was observed with liraglutide versus placebo in the overall population (Figure 2D) (12) or in either HF subgroup (*p*-interaction = 0.22; Figures 1, 2E and 2F).

Effects of liraglutide versus placebo on the composite outcome of HF hospitalization or cardiovascular death observed in the overall population (Figure 2G) were consistent in patients with a history of HF at baseline (Figures 1 and 2H) and those without HF at baseline (*p*-interaction = 0.19; Figures 1 and 2I). Similar results were observed for all-cause death (*p*-interaction = 0.63; Figures 1 and 3) and for the composite outcome of HF hospitalization or all-cause death (*p*-interaction = 0.31; Figure 1).

Rates of MACE, HF hospitalization, all-cause death and two composite outcomes are presented by baseline NYHA class in Table 4. Due to the small number of patients in some of these subgroups, no statistical analyses were performed.

Influence of atherosclerotic events on risk of HF hospitalization

In the overall population, there were 275 and 304 first non-fatal MI events with liraglutide and placebo, respectively. There were 152 and 163 first non-fatal stroke events with liraglutide and placebo, respectively. Separate sensitivity analyses were conducted in which patients were censored at the time of first non-fatal MI/stroke, to assess whether the risk of HF hospitalization with liraglutide versus placebo was influenced by prior atherosclerotic events. In these sensitivity analyses, 396 first events of HF hospitalization were analyzed (compared with 466 first events of HF hospitalization in the main analyses). Results of these analyses were consistent with the main analyses without censoring at the time of first non-fatal MI/stroke. Specifically, in the overall population, the HR (95% CI) for liraglutide versus placebo in the sensitivity analysis was 0.86 (0.71; 1.05). In patients with a history of HF (N = 193 first events), the corresponding HR (95% CI) was 0.94 (0.71; 1.24) and in those without a history of HF (N = 203 first events), it was 0.79 (0.60; 1.04). Results of the main analyses are displayed in Figure 1.

Interaction between treatment group, HF history and nephropathy

Based on estimated glomerular filtration rate, renal function at baseline was similar in patients with and without a history of HF at baseline (Table 1).

Incidence of the pre-specified nephropathy endpoint was numerically lower in patients with a history of HF at baseline versus those without HF at baseline (5.2% vs 6.8%, respectively).

There was a significantly lower risk of nephropathy with liraglutide versus placebo in the overall population (12). There was no statistically significant interaction between treatment group and history of HF at baseline for confirmed nephropathy (*p*-interaction = 0.95). The HR for confirmed nephropathy with liraglutide versus placebo was 0.77 (95% CI: 0.51; 1.18) in patients with a history of HF at baseline and 0.78 (95% CI: 0.66; 0.93) in patients without HF at baseline.

Interaction between treatment group, HF history and heart rate

Liraglutide was associated with an increase in heart rate versus placebo in the overall population (12). No statistically significant interaction was observed between treatment group and history of HF at baseline for change in heart rate (*p*-interaction = 0.16). The estimated treatment difference for the change in heart rate from baseline to 3 years was 2.3 beats per minute (95% CI: 1.2; 3.4) in patients with a history of HF at baseline and 3.1 beats per minute (95% CI 2.6; 3.6) in patients without HF at baseline.

Discussion

Recent European Society of Cardiology guidelines developed in collaboration with the European Association for the Study of Diabetes refer to cardiovascular outcomes trials of glucose-lowering therapies and provide recommendations based on their findings (20). The guidelines recognize that GLP1-RAs (liraglutide, semaglutide, lixisenatide, exenatide and

dulaglutide) had a neutral effect on the risk of HF hospitalization in their placebo-controlled randomized trials and state that these medications may be considered for diabetes treatment in patients with HF (20). Liraglutide is also recommended in patients with T2D and cardiovascular disease, or very high/high cardiovascular risk, to reduce cardiovascular events and the risk of death (20).

When considering the effect of other glucose-lowering therapies on HF, the sodium-glucose cotransporter-2 inhibitors empagliflozin, canagliflozin and dapagliflozin have been associated with early and significant decreases in the risk of HF outcomes versus placebo in people with T2D (5,6,21-23). These medications are recommended to lower the risk of HF hospitalization in patients with diabetes (20). In some studies, other glucose-lowering medications have been associated with an increased risk of HF events or HF hospitalization in people with T2D (1,3,20,24,25). For this reason, thiazolidinediones (rosiglitazone and pioglitazone) and the DPP-4i saxagliptin are not recommended for diabetes treatment in patients at risk of HF or with previous HF (20). Results from the TECOS and CARMELINA cardiovascular outcomes trials of sitagliptin and linagliptin, respectively, do not support a class effect of DPP-4is on HF hospitalization, however (26,27). Sitagliptin and linagliptin have a neutral effect on HF hospitalization and can be considered for diabetes treatment in patients with HF (20). Overall, there is a need to manage cardiovascular risk in patients with T2D in an individualized manner.

In this study, we investigated effects of liraglutide versus placebo on cardiovascular events, including HF hospitalization, all-cause death, nephropathy and heart rate, in LEADER trial participants, stratified by history of HF at baseline. Consistent with published results for the overall LEADER population (12), we report lower observed frequencies of MACE, expanded MACE, several individual cardiovascular endpoints, nephropathy and death with liraglutide versus placebo in patients with or without a history of HF (NYHA class I–III). No increased

risk of HF hospitalization was observed in patients randomized to liraglutide versus placebo, regardless of baseline HF status. No statistically significant interaction was observed between treatment group and history of HF at baseline for change in heart rate. Our findings support the recommendation that liraglutide may be considered for diabetes treatment in patients with HF (20).

In other subgroup analyses of GLP-1RAs by history of HF at baseline, there were no significant differential treatment effects of lixisenatide, once-weekly exenatide, semaglutide or albiglutide on MACE (8,9,11,13). However, reductions in all-cause death and the composite of all-cause death or HF hospitalization with once-weekly exenatide were only observed in patients without baseline HF (*p*-interaction for the HF subgroups = 0.031 and 0.015, respectively) (28).

Increases in mean heart rate (generally <10 beats per minute) have been observed following treatment with liraglutide or other GLP-1RAs (12,29,30), which theoretically may be detrimental in HF (31). No increased risk of MACE or HF hospitalization was observed with liraglutide versus placebo in patients with heart rate increases of <10 or ≥10 beats per minute from baseline to 6 months in the LEADER trial (32). In the present analysis, the increase in heart rate with liraglutide did not seem to raise the risk for MACE or HF hospitalization, even in those patients with HF at baseline.

Taken together, results from previous small studies with liraglutide in patients with HF were inconclusive: some showed improvements in left ventricular function (16,17), while others indicated potential safety concerns (18,19). For example, in the LIVE study, which assessed 241 patients with chronic HF with reduced left ventricular ejection fraction (LVEF) with or without T2D, more patients experienced serious cardiac adverse events in the liraglutide group than in the placebo group, when serious cardiac adverse events of different etiologies

were pooled (19). However, these events were experienced by few patients in both treatment groups (19). The FIGHT trial, which included 300 patients with or without T2D, who were recently hospitalized with HF and reduced LVEF, showed a non-significant increase in re-hospitalization for HF with liraglutide versus placebo (18). The LIVE and FIGHT trial populations differed from the LEADER population, which only included patients with T2D and had a relatively low prevalence of HF at baseline (12). Furthermore, the LEADER population with HF (most of whom had NYHA class II HF) does not represent a more advanced HF population than the LIVE and FIGHT populations, which recruited patients based on LVEF criteria (≤45% and ≤40%, respectively). With a substantively larger dataset and much longer treatment duration compared with LIVE and FIGHT, the present analysis shows no increase in HF hospitalization with liraglutide versus placebo in patients with a history of NYHA class I–III HF and T2D.

The risk of total (first and recurrent) HF hospitalization events occurring with liraglutide versus placebo in LEADER has been analyzed using three different models (33). Results from each of the models were consistent with the analysis of first HF hospitalization events (33).

A recent meta-analysis of cardiovascular outcomes trials showed that GLP-1RAs reduced the risk HF hospitalization by 9%, although this reduction was not considered statistically robust (15). It was noted that the largest reductions in HF hospitalization were observed in the two trials with the greatest reductions in MI (Harmony Outcomes and LEADER), and hypothesized that the favorable effect in the meta-analysis could be secondary to reduction in MI (15). However, results of our sensitivity analyses in which patients were censored at the time of first non-fatal MI/stroke suggest that any effect of liraglutide to reduce HF hospitalization cannot be solely explained by reductions in atherosclerotic events (non-fatal MI/stroke).

Mechanisms underlying the observed numeric reduction in HF hospitalization with liraglutide versus placebo in the LEADER population are unknown, but could involve weight loss and/or less nephropathy with liraglutide (12). Weight reduction from baseline was 2.3 kg (95% CI: 2.5; 2.0) greater with liraglutide versus placebo at 36 months (12). Another randomized clinical trial, involving participants with obesity and clinically stable HF with preserved ejection fraction, showed that caloric restriction or aerobic exercise training can lead to weight loss and increased exercise capacity (measured as peak oxygen consumption), representing improvement in the primary HF symptom of exercise intolerance (34). With caloric restriction, improvements were observed in some, but not all, measures of cardiac function, suggesting that favorable 'non-cardiac' peripheral adaptations may accompany weight loss in these individuals (34). In the current analysis, liraglutide was associated with a lower occurrence of nephropathy versus placebo in patients with and without a history of HF at baseline. Whether or not these results are related to the natriuretic effects of liraglutide (35) is unclear.

Finally, anti-inflammatory effects associated with GLP-1RAs, including liraglutide, may also have an impact on cardiac function and the pathophysiology of HF (36).

Study limitations

This study has several limitations. First, it relied on the accurate reporting of medical histories of HF and NYHA class by the trial investigators at baseline. Important clinical information related to HF, including LVEF (to confirm reduced or preserved ejection fraction), etiology of HF and biomarker data (e.g. N-terminal pro-B-type natriuretic peptide or troponin), was not collected during the trial. As a result, some of the participants may have had undiagnosed HF, particularly if they had a preserved ejection fraction (37). Additionally, this limitation makes it difficult to compare the type and severity of HF observed in

LEADER to HF studied in other clinical trials. Second, this report was based on exploratory analyses, some of which were not pre-specified. Third, the analyses were not corrected for multiplicity. However, while multiple comparisons can increase the probability of obtaining a false-positive result, no interaction tests were statistically significant. Fourth, the LEADER trial was not powered to detect treatment interactions between subgroups. Fifth, our analyses may have been confounded by differences between the HF subgroups and treatment groups, e.g. in terms of concomitant medications received. Additionally, since LEADER included a patient population with T2D and high cardiovascular risk (12), our findings may not be applicable to patients with T2D who have a lower risk for cardiovascular events than the LEADER population. Finally, with NYHA class IV HF being an exclusion criterion and only 13% of the HF subgroup having NYHA class III HF, our findings are mostly based on people with NYHA class I–II HF and may not be generalizable to more advanced cases of HF. Despite these limitations, this analysis has several strengths, including its basis on data from a large, multinational, double-blind cardiovascular outcomes trial, with independent adjudication of cardiovascular events, including HF hospitalization.

Conclusions

There was no increased risk of HF hospitalization with liraglutide versus placebo in patients with or without HF at baseline. Furthermore, there were lower rates of MACE, nephropathy and mortality with liraglutide versus placebo, irrespective of baseline HF status. Overall, results from this analysis of LEADER data indicate that liraglutide should be considered a suitable treatment option for patients with T2D, either with or without a history of HF (NYHA class I–III).

Clinical perspectives

Clinical competencies in medical knowledge

Data regarding effects of the GLP-1 analog liraglutide in patients with T2D and HF have been lacking. Based on this analysis of the large LEADER patient cohort (followed for up to 5 years [median of 3.8 years]), liraglutide appears to be an appropriate therapeutic option for patients with T2D and high cardiovascular risk who have a history of HF (NYHA class I–III), as well as those who do not have a history of HF.

Translational outlook recommendations

Further studies of liraglutide in patients with T2D and a history of HF should look at HF with reduced and preserved ejection fraction and report important clinical information related to HF, including HF etiology and biomarker data (e.g. N-terminal pro-B-type natriuretic peptide or troponin), with greater control of potential confounding factors. Future studies should also evaluate mechanisms underlying the effects of liraglutide on cardiovascular outcomes, and assess whether weight loss observed with liraglutide and other GLP-1RAs could be beneficial in patients with obesity and HF with preserved ejection fraction.

Author contributions

S.P.M., F.M.M.B., S.C.B., M.A.N., N.R.P., R.E.P. and J.B.B. were members of the LEADER trial steering committee and contributed significantly to the conduct of the study and acquisition of clinical data. A.B.T. headed the Medical & Science department responsible for the clinical reporting of the LEADER trial. B.G. performed the statistical analyses. All authors reviewed and interpreted the data, and were involved in drafting and critically revising the manuscript. All authors approved the final version of the manuscript and take full responsibility for its content.

Study guarantor

S.P.M. had full access to all the study data and takes responsibility for its integrity and the data analysis.

Data sharing

The subject-level analysis data sets for the research presented in this publication are available from the corresponding author upon reasonable request.

Prior presentation

This article extends observations presented previously at the American Diabetes Association 76th Scientific Sessions (Session 3-CT-SY24; June 13 2016, New Orleans, LA, USA; available at http://professional.diabetes.org/search/site?f%5B0%5D=im_field_dbp_ct%3A7&f%5B1%5D=sm_field_wcast_sname%3Anode%3A144635) and European Association for the Study of Diabetes (EASD) 52nd Annual Meeting (Oral Presentation #S27.1; September 15, 2016, Munich, Germany; available at https://easd.org/virtualmeeting/home.html#!resources/leader-

cardiovascular-outcomes), and published by Marso and colleagues (12). The data were also presented in part at the American College of Cardiology 67th Annual Scientific Session (1318M-05; March 12, 2018, Orlando, FL, USA), the EASD 54th Annual Meeting (#1155, October 2, 2018, Berlin, Germany), and at a further eight local congresses.

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Figure legends

Figure 1 (Central Illustration). Occurrence of CV outcomes and all-cause death, stratified by history of HF at baseline.

The *p* value is for the interaction between treatment group and HF at baseline. CI, confidence interval; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; N, number of patients with at least one event; NYHA, New York Heart Association; UAP, unstable angina pectoris; % proportion of patients with a first event between randomization and follow-up.

Figure 2. First confirmed MACE (A, B and C), HF hospitalization (D, E and F) and composite outcome of HF hospitalization or CV death (G, H and I) by history of HF at baseline and randomized treatment.

Parts A and D reproduced from N Engl J Med, Marso SP et al, Liraglutide and cardiovascular outcomes in type 2 diabetes, 375:311-22. Copyright© 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society (12). Cumulative incidences estimated using the Kaplan–Meier method, and HRs using the Cox proportional-hazards regression model. Data analyses truncated at 54 months because <10% of patients had an observation time beyond 54 months. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; NYHA, New York Heart Association.

Figure 3. All-cause death by history of HF at baseline and randomized treatment. (A) Patients with NYHA I–III HF at baseline; (B) patients without NYHA I–III HF at baseline.

Cumulative incidences estimated using the Kaplan–Meier method, and HRs using the Cox proportional-hazards regression model. Data analyses truncated at 54 months because <10% of patients had an observation time beyond 54 months. CI, confidence interval; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association.

Tables

Table 1. Baseline characteristics by history of HF at baseline and randomized treatment.

	Patients with NYHA I–III HF at baseline			**Patients without NYHA I–III HF at baseline**		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Male, N (%)	483 (57.8)	500 (60.1)	983 (59.0)	2528 (66.0)	2492 (64.9)	5020 (65.4)
Female, N (%)	352 (42.2)	332 (39.9)	684 (41.0)	1305 (34.0)	1348 (35.1)	2653 (34.6)
Age, years	63.5 ± 7.8	64.0 ± 7.8	63.7 (7.8)	64.4 ± 7.1	64.5 ± 7.1	64.4 ± 7.1
Race, N (%)						
White	701 (84.0)	705 (84.7)	1406 (84.3)	2915 (76.1)	2917 (76.0)	5832 (76.0)
Black or African American	63 (7.5)	56 (6.7)	119 (7.1)	307 (8.0)	351 (9.1)	658 (8.6)
Asian	38 (4.6)	45 (5.4)	83 (5.0)	433 (11.3)	420 (10.9)	853 (11.1)
Other	33 (4.0)	26 (3.1)	59 (3.5)	178 (4.6)	152 (4.0)	330 (4.3)
Diabetes duration, years	11.6 ± 7.6	11.8 ± 8.1	11.7 ± 7.9	13.0 ± 8.0	13.1 ± 8.0	13.1 ± 8.0

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Glycated hemoglobin, %	8.8 ± 1.5	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.6	8.7 ± 1.5	8.7 ± 1.5
Body mass index, kg/m^2	34.2 ± 6.9	33.9 ± 6.8	34.0 ± 6.9	32.2 ± 6.1	32.2 ± 6.1	32.2 ± 6.1
Body weight, kg	96.6 ± 22.4	95.3 ± 21.6	95.9 ± 22.0	90.9 ± 20.8	90.8 ± 20.5	90.8 ± 20.6
Systolic blood pressure, mmHg	135.1 ± 18.2	134.9 ± 18.6	135.0 ± 18.4	136.1 ± 17.7	136.1 ± 17.5	136.1 ± 17.6
Diastolic blood pressure, mmHg	77.2 ± 10.6	76.9 ± 10.2	77.1 ± 10.4	77.2 ± 10.3	77.0 ± 10.1	77.1 ± 10.2
Heart rate, beats per minute	73.0 ± 11.4	73.1 ± 11.2	73.0 ± 11.3	72.6 ± 11.3	72.4 ± 11.5	72.5 ± 11.4
Low density lipoprotein cholesterol, mmol/L	2.5 ± 1.0	2.5 ± 1.0	2.5 ± 1.0	2.3 ± 0.9	2.3 ± 0.9	2.3 ± 0.9
High density lipoprotein cholesterol, mmol/L	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Total cholesterol, mmol/L	4.6 ± 1.2	4.6 ± 1.3	4.6 ± 1.2	4.4 ± 1.2	4.4 ± 1.1	4.4 ± 1.2
Triglycerides, mmol/L	2.2 ± 1.5	2.2 ± 2.0	2.2 ± 1.8	2.0 ± 1.4	2.0 ± 1.6	2.0 ± 1.5
eGFR, mL/min/1.73m^2	78.4 ± 26.7	77.8 ± 26.4	78.1 ± 26.6	80.6 ± 27.7	81.2 ± 27.3	80.9 ± 27.5
Renal function, N (%)						
Normal (eGFR $\geq$90 mL/min/1.73m^2)	274 (32.8)	268 (32.2)	542 (32.5)	1346 (35.1)	1387 (36.1)	2733 (35.6)
Mild impairment (eGFR 60 to <90 mL/min/1.73m^2)	350 (41.9)	342 (41.1)	692 (41.5)	1582 (41.3)	1633 (42.5)	3215 (41.9)
Moderate impairment (eGFR 30 to <60 mL/min/1.73m^2)	186 (22.3)	201 (24.2)	387 (23.2)	813 (21.2)	734 (19.1)	1547 (20.2)
Severe impairment (eGFR <30 mL/min/1.73m^2)	25 (3.0)	21 (2.5)	46 (2.8)	92 (2.4)	86 (2.2)	178 (2.3)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
NYHA class, N (%)*						
I	179 (21.4)	169 (20.3)	348 (20.9)	—	—	—
II	545 (65.3)	546 (65.6)	1091 (65.4)	—	—	—
III	108 (12.9)	106 (12.7)	214 (12.8)	—	—	—
Unknown	3 (0.4)	11 (1.3)	14 (0.8)	—	—	—

Full analysis set. Data are mean ± standard deviation or number of patients (percentage of patients within the relevant group). *Based on medical history as reported by the trial investigator for each patient. HF includes NYHA class I, II and III HF, and patients with HF at baseline who had missing NYHA category information. Chronic NYHA class IV HF was a LEADER trial exclusion criterion. eGFR, estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula); HF, heart failure; NYHA, New York Heart Association.

Table 2. Concomitant cardiovascular medications by history of HF and randomized treatment.

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Concomitant cardiovascular medications at baseline						
Antihypertensive therapy, N (%)	812 (97.2)	798 (95.9)	1610 (96.6)	3517 (91.8)	3504 (91.3)	7021 (91.5)
Beta-blockers	635 (76.0)	576 (69.2)	1211 (72.6)	2017 (52.6)	1953 (50.9)	3970 (51.7)
Calcium channel blockers	260 (31.1)	244 (29.3)	504 (30.2)	1278 (33.3)	1235 (32.2)	2513 (32.8)
Angiotensin converting enzyme inhibitors	450 (53.9)	490 (58.9)	940 (56.4)	1967 (51.3)	1860 (48.4)	3827 (49.9)
Angiotensin receptor blockers	278 (33.3)	231 (27.8)	509 (30.5)	1210 (31.6)	1255 (32.7)	2465 (32.1)
Other antihypertensive therapies	76 (9.1)	73 (8.8)	149 (8.9)	392 (10.2)	381 (9.9)	773 (10.1)
Diuretics, N (%)	514 (61.6)	543 (65.3)	1057 (63.4)	1439 (37.5)	1410 (36.7)	2849 (37.1)
Loop diuretics	328 (39.3)	334 (40.1)	662 (39.7)	496 (12.9)	503 (13.1)	999 (13.0)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Thiazides	89 (10.7)	87 (10.5)	176 (10.6)	740 (19.3)	701 (18.3)	1441 (18.8)
Thiazide-like diuretics	102 (12.2)	128 (15.4)	230 (13.8)	223 (5.8)	227 (5.9)	450 (5.9)
Aldosterone antagonists	133 (15.9)	129 (15.5)	262 (15.7)	121 (3.2)	122 (3.2)	243 (3.2)
Lipid-lowering drugs, N (%)	605 (72.5)	598 (71.9)	1203 (72.2)	2959 (77.2)	2917 (76.0)	5876 (76.6)
Statins	582 (69.7)	567 (68.1)	1149 (68.9)	2823 (73.6)	2769 (72.1)	5592 (72.9)
Ezetimibe	21 (2.5)	17 (2.0)	38 (2.3)	144 (3.8)	152 (4.0)	296 (3.9)
Other lipid-lowering drugs	85 (10.2)	86 (10.3)	171 (10.3)	410 (10.7)	427 (11.1)	837 (10.9)
Platelet aggregation inhibitors, N (%)	550 (65.9)	520 (62.5)	1070 (64.2)	2655 (69.3)	2601 (67.7)	5256 (68.5)
Acetylsalicylic acid or acetylsalicylate lysine	517 (61.9)	494 (59.4)	1011 (60.6)	2460 (64.2)	2405 (62.6)	4865 (63.4)
Clopidogrel, ticlopidine, prasugrel, ticagrelor	105 (12.6)	101 (12.1)	206 (12.4)	615 (16.0)	644 (16.8)	1259 (16.4)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Antithrombotic medication, N (%)	130 (15.6)	123 (14.8)	253 (15.2)	179 (4.7)	191 (5.0)	370 (4.8)
Vitamin K antagonists	128 (15.3)	120 (14.4)	248 (14.9)	167 (4.4)	181 (4.7)	348 (4.5)
Direct thrombin inhibitors	2 (0.2)	3 (0.4)	5 (0.3)	15 (0.4)	9 (0.2)	24 (0.3)
Direct factor Xa inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Cardiovascular medications initiated after baseline						
Antihypertensive therapy, N (%)	14 (1.7)	15 (1.8)	29 (1.7)	141 (3.7)	147 (3.8)	288 (3.8)
Beta-blockers	6 (0.7)	7 (0.8)	13 (0.8)	60 (1.6)	58 (1.5)	118 (1.5)
Calcium channel blockers	6 (0.7)	1 (0.1)	7 (0.4)	27 (0.7)	27 (0.7)	54 (0.7)
Angiotensin converting enzyme inhibitors	5 (0.6)	8 (1.0)	13 (0.8)	73 (1.9)	84 (2.2)	157 (2.0)
Angiotensin receptor blockers	8 (1.0)	5 (0.6)	13 (0.8)	41 (1.1)	59 (1.5)	100 (1.3)
Other antihypertensive therapies	1 (0.1)	0 (0.0)	1 (<0.1)	9 (0.2)	13 (0.3)	22 (0.3)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Diuretics, N (%)	81 (9.7)	97 (11.7)	178 (10.7)	433 (11.3)	547 (14.2)	980 (12.8)
Loop diuretics	59 (7.1)	59 (7.1)	118 (7.1)	244 (6.4)	320 (8.3)	564 (7.4)
Thiazides	16 (1.9)	28 (3.4)	44 (2.6)	152 (4.0)	208 (5.4)	360 (4.7)
Thiazide-like diuretics	15 (1.8)	22 (2.6)	37 (2.2)	58 (1.5)	71 (1.8)	129 (1.7)
Aldosterone antagonists	26 (3.1)	29 (3.5)	55 (3.3)	91 (2.4)	64 (1.7)	155 (2.0)
Lipid-lowering drugs, N (%)	76 (9.1)	89 (10.7)	165 (9.9)	332 (8.7)	389 (10.1)	721 (9.4)
Statins	64 (7.7)	79 (9.5)	143 (8.6)	306 (8.0)	368 (9.6)	674 (8.8)
Ezetimibe	3 (0.4)	3 (0.4)	6 (0.4)	14 (0.4)	11 (0.3)	25 (0.3)
Other lipid-lowering drugs	16 (1.9)	18 (2.2)	34 (2.0)	44 (1.1)	46 (1.2)	90 (1.2)
Platelet aggregation inhibitors, N (%)	62 (7.4)	76 (9.1)	138 (8.3)	313 (8.2)	351 (9.1)	664 (8.7)
Acetylsalicylic acid or acetylsalicylate lysine	54 (6.5)	64 (7.7)	118 (7.1)	281 (7.3)	305 (7.9)	586 (7.6)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Clopidogrel, ticlopidine, prasugrel, ticagrelor	17 (2.0)	24 (2.9)	41 (2.5)	87 (2.3)	100 (2.6)	187 (2.4)
Antithrombotic medication, N (%)	64 (7.7)	60 (7.2)	124 (7.4)	171 (4.5)	215 (5.6)	386 (5.0)
Vitamin K antagonists	49 (5.9)	47 (5.6)	96 (5.8)	124 (3.2)	142 (3.7)	266 (3.5)
Direct thrombin inhibitors	5 (0.6)	5 (0.6)	10 (0.6)	27 (0.7)	30 (0.8)	57 (0.7)
Direct factor Xa inhibitors	18 (2.2)	15 (1.8)	33 (2.0)	39 (1.0)	57 (1.5)	96 (1.3)

Full analysis set. Includes patients with HF at baseline who had missing NYHA category information (N = 14). Data for cardiovascular medications initiated after baseline exclude patients who received a medication from the relevant class (antihypertensive therapy, diuretics, lipid-lowering drugs, platelet aggregation inhibitors or antithrombotic medications) at baseline. N, number of patients; NYHA, New York Heart Association; %, proportion of patients.

Table 3. Confirmed deaths by history of HF at baseline and randomized treatment.

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
All-cause death	119 (14.3)	132 (15.9)	251 (15.1)	262 (6.8)	315 (8.2)	577 (7.5)
Unknown cause of death	20 (2.4)	23 (2.8)	43 (2.6)	50 (1.3)	58 (1.5)	108 (1.4)
Known cause of death	99 (11.9)	109 (13.1)	208 (12.5)	212 (5.5)	257 (6.7)	469 (6.1)
Cardiovascular	56 (6.7)	65 (7.8)	121 (7.3)	93 (2.4)	132 (3.4)	225 (2.9)
Death due to confirmed MI	5 (0.6)	7 (0.8)	12 (0.7)	12 (0.3)	19 (0.5)	31 (0.4)
Death due to confirmed stroke	5 (0.6)	7 (0.8)	12 (0.7)	10 (0.3)	18 (0.5)	28 (0.4)
Cardiovascular death not linked to a confirmed MI/stroke	46 (5.5)	51 (6.1)	97 (5.8)	71 (1.9)	95 (2.5)	166 (2.2)
Sudden cardiac death	17 (2.0)	22 (2.6)	39 (2.3)	34 (0.9)	52 (1.4)	86 (1.1)
Death due to acute MI	2 (0.2)	4 (0.5)	6 (0.4)	2 (<0.1)	11 (0.3)	13 (0.2)

	Patients with NYHA I–III HF at baseline			Patients without NYHA I–III HF at baseline		
	Liraglutide (N = 835)	**Placebo (N = 832)**	**Total (N = 1667)**	**Liraglutide (N = 3833)**	**Placebo (N = 3840)**	**Total (N = 7673)**
Death due to HF or cardiogenic shock	15 (1.8)	18 (2.2)	33 (2.0)	10 (0.3)	13 (0.3)	23 (0.3)
Death due to cerebrovascular event	2 (0.2)	1 (0.1)	3 (0.2)	2 (<0.1)	3 (<0.1)	5 (<0.1)
Death due to other cardiovascular cause	2 (0.2)	4 (0.5)	6 (0.4)	13 (0.3)	10 (0.3)	23 (0.3)
Unclassifiable	8 (1.0)	2 (0.2)	10 (0.6)	10 (0.3)	6 (0.2)	16 (0.2)
Non-cardiovascular	43 (5.1)	44 (5.3)	87 (5.2)	119 (3.1)	125 (3.3)	244 (3.2)

Full analysis set. Data are number of patients (percentage of patients within the relevant group). HF includes NYHA class I, II and III HF, and patients with HF at baseline who had missing NYHA category information. Chronic NYHA class IV HF was a LEADER trial exclusion criterion. Deaths with cause classified as ‘Unknown’ were considered cardiovascular deaths in the statistical analyses and hence part of the

cardiovascular mortality endpoint. Sub-classification of cardiovascular deaths not linked to a confirmed MI/stroke was performed by the sponsor. HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association.

Table 4. Confirmed events by NYHA class at baseline and randomized treatment.

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
No HF								
Full analysis set	3833				3840			
Patient-years of observation	14763				14707			
Confirmed MACE	466	12.2	567	3.84	524	13.6	656	4.46
Confirmed HF hospitalization	110	2.9	158	1.07	140	3.6	205	1.39
All-cause death	262	6.8	262	1.77	315	8.2	315	2.14
Composite of confirmed HF hospitalization and cardiovascular death	235	6.1	301	2.04	305	7.9	395	2.69
Composite of confirmed HF hospitalization and all-cause death	348	9.1	420	2.84	417	10.9	520	3.54
NYHA class I HF								

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Full analysis set	179				169			
Patient-years of observation	672				626			
Confirmed MACE	29	16.2	33	4.91	46	27.2	57	9.10
Confirmed HF hospitalization	21	11.7	27	4.02	16	9.5	28	4.47
All-cause death	21	11.7	21	3.13	22	13.0	22	3.51
Composite of confirmed HF hospitalization and cardiovascular death	27	15.1	40	5.96	26	15.4	44	7.03
Composite of confirmed HF hospitalization and all-cause death	35	19.6	48	7.15	31	18.3	50	7.98
NYHA class II HF								
Full analysis set	545				546			
Patient-years of observation	1982				1984			
Confirmed MACE	87	16.0	102	5.15	95	17.4	126	6.35

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Confirmed HF hospitalization	68	12.5	127	6.41	74	13.6	125	6.30
All-cause death	80	14.7	80	4.04	88	16.1	88	4.44
Composite of confirmed HF hospitalization and cardiovascular death	102	18.7	177	8.93	112	20.5	179	9.02
Composite of confirmed HF hospitalization and all-cause death	127	23.3	207	10.44	138	25.3	213	10.74
NYHA class III HF								
Full analysis set	108				106			
Patient-years of observation	393				387			
Confirmed MACE	25	23.1	32	8.15	24	22.6	25	6.47
Confirmed HF hospitalization	19	17.6	30	7.64	16	15.1	28	7.24
All-cause death	18	16.7	18	4.58	18	17.0	18	4.66

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Composite of confirmed HF hospitalization and cardiovascular death	28	25.9	43	10.95	24	22.6	42	10.86
Composite of confirmed HF hospitalization and all-cause death	31	28.7	48	12.22	27	25.5	46	11.90
Unknown								
Full analysis set	3				11			
Patient-years of observation	12				37			
Confirmed MACE	1	33.3	1	8.08	5	45.5	6	16.09
Confirmed HF hospitalization	0	0.0	0	0.00	2	18.2	3	8.05
All-cause death	0	0.0	0	0.00	4	36.4	4	10.73
Composite of confirmed HF hospitalization and cardiovascular death	0	0.0	0	0.00	5	45.5	7	18.77

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Composite of confirmed HF hospitalization and all-cause death	0	0.0	0	0.00	5	45.5	7	18.77

Full analysis set. Patients with HF at baseline who had missing NYHA category information (N = 14) are included in the 'unknown' group. E, number of events; HF, heart failure; MACE, major adverse cardiovascular events; N, number of patients; NYHA, New York Heart Association; R, rate of events per 100 patient-years of observation; %, proportion of patients.