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Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

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IMPORTANCE Abnormal cardiac metabolism contributes to the pathophysiology of advanced heart failure with reduced left ventricular ejection fraction (LVEF). Glucagon-like peptide 1 (GLP-1) agonists have shown cardioprotective effects in early clinical studies of patients with advanced heart failure, irrespective of type 2 diabetes status.

OBJECTIVE To test whether therapy with a GLP-1 agonist improves clinical stability following hospitalization for acute heart failure.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, double-blind, placebo-controlled randomized clinical trial of patients with established heart failure and reduced LVEF who were recently hospitalized. Patients were enrolled between August 2013 and March 2015 at 24 US sites.

INTERVENTIONS The GLP-1 agonist liraglutide (n = 154) or placebo (n = 146) via a daily subcutaneous injection; study drug was advanced to a dosage of 1.8 mg/d during the first 30 days as tolerated and continued for 180 days.

MAIN OUTCOMES AND MEASURES The primary end point was a global rank score in which all patients, regardless of treatment assignment, were ranked across 3 hierarchical tiers: time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days. Higher values indicate better health (stability). Exploratory secondary outcomes included primary end point components, cardiac structure and function, 6-minute walk distance, quality of life, and combined events.

RESULTS Among the 300 patients who were randomized (median age, 61 years [interquartile range {IQR}, 52-68 years]; 64 [21%] women; 178 [59%] with type 2 diabetes; median LVEF of 25% [IQR, 19%-33%]; median N-terminal pro-B-type natriuretic peptide level of 2049 pg/mL [IQR, 1054-4235 pg/mL]), 271 completed the study. Compared with placebo, liraglutide had no significant effect on the primary end point (mean rank of 146 for the liraglutide group vs 156 for the placebo group, *P* = .31). There were no significant between-group differences in the number of deaths (19 [12%] in the liraglutide group vs 16 [11%] in the placebo group; hazard ratio, 1.10 [95% CI, 0.57-2.14]; *P* = .78) or rehospitalizations for heart failure (63 [41%] vs 50 [34%], respectively; hazard ratio, 1.30 [95% CI, 0.89-1.88]; *P* = .17) or for the exploratory secondary end points. Prespecified subgroup analyses in patients with diabetes did not reveal any significant between-group differences. The number of investigator-reported hyperglycemic events was 16 (10%) in the liraglutide group vs 27 (18%) in the placebo group and hypoglycemic events were infrequent (2 [1%] vs 4 [3%], respectively).

CONCLUSIONS AND RELEVANCE Among patients recently hospitalized with heart failure and reduced LVEF, the use of liraglutide did not lead to greater posthospitalization clinical stability. These findings do not support the use of liraglutide in this clinical situation.

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Group Information: Lists of the clinical sites and principal investigators participating in the NHLBI (National Heart, Lung, and Blood Institute) Heart Failure Clinical Research Network appear in Supplement 1.

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Heart failure is the leading cause of hospitalization in the United States with more than 4 million admissions per year from 2003-2009.[1] Abnormal cardiac metabolism, including reduced fatty-acid oxidation and myocardial insulin resistance, contributes to the syndrome of heart failure.[2] As heart failure progresses, these abnormalities become more pronounced and are observed in both patients with and without type 2 diabetes.[3,4] No current heart failure therapy targets these metabolic derangements. In this context, agents that improve glucose metabolism could be repurposed as new therapies for patients with advanced heart failure.

Agents that increase glucagon-like peptide 1 (GLP-1) signaling have shown potential in preclinical and early clinical studies. Glucagon-like peptide 1 is an endogenous incretin hormone that improves insulin sensitivity with minimal risk of hypoglycemia. Recombinant GLP-1 increases myocardial insulin sensitivity[5] and is cardioprotective during ischemia in model systems.[6]

In a pilot study,[7] recombinant GLP-1 was associated with favorable effects on myocardial function and exercise tolerance in patients with advanced heart failure and reduced left ventricular ejection fraction (LVEF), and GLP-1 agonists reduced rates of hospitalization for patients with heart failure in a single-center, retrospective analysis.[8] Together, these data suggest potential benefit of GLP-1 agonists for patients with advanced heart failure.

We performed the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study to test the hypothesis that sustained therapy with a GLP-1 agonist initiated during the postacute hospital discharge period is associated with greater clinical stability through 180 days in patients with advanced heart failure and reduced LVEF. Furthermore, we hypothesized that the treatment effects would be greater in patients with type 2 diabetes.

Methods

Study Design

The FIGHT trial was a multicenter, double-blind, placebo-controlled randomized clinical trial of patients with established heart failure and reduced LVEF. The trial was conducted by the NHLBI (National Heart, Lung, and Blood Institute) Heart Failure Clinical Research Network, which is funded by the NHLBI, with approval by the research network's protocol review committee and monitored by an independent data and safety monitoring board. The ethics committee at each participating site approved the trial design (the full protocol appears in Supplement 2).

At 24 sites in the United States, patients with heart failure and reduced LVEF were identified based on hospital admission records. All participants provided written informed consent and were enrolled during either the last 24 hours of his or her hospitalization for heart failure or the 2-week interval after the hospitalization.

After baseline evaluations, including echocardiographic measures, the 6-minute walk test, the Kansas City Cardiomyopathy Questionnaire (KCCQ), and blood tests, patients were

Key Points

Question Does therapy with the glucagon-like peptide 1 agonist liraglutide improve clinical stability in patients with advanced heart failure?

Findings In this randomized clinical trial of 300 adults with advanced heart failure, liraglutide had no significant effect on posthospitalization clinical stability based on a global rank score of time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level. There was no benefit observed among the 178 patients with type 2 diabetes.

Meaning These findings do not support the use of liraglutide for improving clinical stability in patients with advanced heart failure and reduced left ventricular ejection fraction.

randomized in a 1:1 ratio to receive either the GLP-1 agonist liraglutide or placebo as a daily subcutaneous injection. At 30-, 90-, and 180-day study visits, follow-up testing was performed. Participants were called at a mean of 210 days (SD, 7 days) to determine their adverse event status. Details of the study design have been described.[9]

Study Population

Patients were required to have an established diagnosis of heart failure and a LVEF of 40% or lower during the preceding 3 months. To target a relatively high-risk patient population, the inclusion criteria were (1) a recent (within 14 days) hospitalization for an acute heart failure syndrome despite already receiving evidence-based therapies and (2) a preadmission oral diuretic dose of at least 40 mg of furosemide or an equivalent.

Key exclusion criteria were (1) recent acute coronary syndrome or coronary intervention, (2) known intolerance of GLP-1 agonist therapy, and (3) severe renal, hepatic, or pulmonary disease. Recognizing that myocardial insulin resistance has been observed in patients with advanced heart failure but without diabetes,[3,4] this trial did not exclude patients who did not have type 2 diabetes.

Study Drug and Randomization

Active therapy in this trial consisted of a human GLP-1 analog with 97% homology to native GLP-1, liraglutide (Victoza), which has been approved for use by the US Food and Drug Administration. Patients were randomly assigned to liraglutide or placebo in a 1:1 ratio.

A permuted block randomization scheme stratified by clinical site and type 2 diabetes status was performed with an automated web-based system to ensure relatively equal distribution of patients to each group within each site. The protocol involved uptitration of study drug dosage as tolerated every 14 days from 0.6 mg/d to 1.2 mg/d to 1.8 mg/d during the first 30 days of the trial. Liraglutide and placebo were packaged identically to maintain blinding.

Concomitant Medications

The protocol allowed for adjustment of standard heart failure therapies, including attempted uptitration of neurohormonal

antagonists, during and after the participants' initial hospitalization. In patients with type 2 diabetes, plans for risk reduction of hypoglycemia included (1) adjustments to doses of insulin or insulin secretagogues (sulfonylureas or meglitinide), (2) at least daily monitoring of blood glucose, and (3) close follow-up with the treating physician managing the participant's diabetes. All participants were counseled on the signs and symptoms of hypoglycemia and the appropriate treatment.

Study End Points

End point assessments were blinded to treatment assignment. The primary end point was a global rank score in which all participants, regardless of treatment assignment, were ranked across 3 hierarchical tiers: time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level from baseline to 180 days. Higher values indicate better health (stability). Patients who died during the 180-day study period were ranked based on the time of their death with earliest death being ranked first and then later deaths. Next, patients who did not die were ranked based on the time to their first rehospitalization for heart failure, such that the individual with the earliest rehospitalization received the next lowest rank and then those with later rehospitalizations. Those patients who neither died nor were rehospitalized were ranked based on their time-averaged proportional changes in NT-proBNP levels from the least to most favorable change. The mean rank score was then compared between groups. In this scheme, a higher mean rank score indicates greater overall stability for patients with heart failure.[10]

All-cause mortality was considered an objective end point. Rehospitalization for heart failure was distinguished from rehospitalizations due to other causes by a blinded adjudication committee based on the presence of both clinical manifestations of worsening heart failure and additional or increased therapy specifically for the treatment of worsening heart failure. Levels of NT-proBNP were determined at a central core laboratory that was blinded to treatment assignment.

The key exploratory secondary end points included (1) the individual components of the primary end point, (2) time to other prespecified cardiac events (including emergency department visits), (3) changes in cardiac structure and function (by echocardiographic measures) from baseline to 180 days, (4) functional status based on 6-minute walk distances at 30, 90, and 180 days, and (5) changes in the KCCQ clinical summary score.

Comparison of treatment effects in patients by type 2 diabetes status was a prespecified subgroup analysis. Tertiary end points included changes in metabolic biomarkers (ie, hemoglobin A_{1c}, weight, and fasting lipid levels) and changes in cystatin C. Safety end points were reported by site investigators using an online system and were not adjudicated.

Statistical Analysis

The full statistical analysis plan appears in Supplement 3. All analyses were conducted using the intention-to-treat principle and included all randomized patients (**Figure 1**). Analysis of the global rank end point was based on the Wilcoxon test

Figure 1. Patient Flow Diagram for the Functional Impact of GLP-1 for Heart Failure Treatment Study
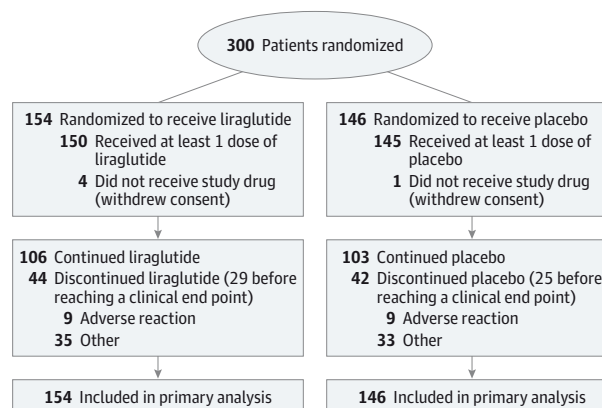
Data on patients screened for eligibility were not available. Secondary end points were analyzed with multiple imputation techniques when data were unavailable for the end point.

statistic and calculated using the NPAR1WAY procedure within SAS software (SAS Institute Inc).

To evaluate for potential clustering of treatment responses by site, a mixed model was also computed using PROC MIXED with terms for treatment effect and random effects for sites. For binary outcomes, logistic regression analysis was used for the estimated odds ratio and associated 95% CI to compare liraglutide with placebo.

Unadjusted time-to-event comparisons were conducted using Kaplan-Meier survival estimates and log-rank tests. All P values are 2-sided with a level of significance of .05 and no adjustments for multiple comparisons.

Power Calculation

We regarded a reduction of 25% in deaths or rehospitalizations for heart failure as clinically significant based on the treatment effects of neurohormonal blockade,[11] and a reduction of 0.5 SD in NT-proBNP level as clinically significant based on associations between serial natriuretic peptide levels and future events.[12] Under these assumptions, the planned sample size of 300 patients (150 participants per treatment group) provided approximately 92% power.[9] This planned sample size of 300 patients provided more than 90% power to detect differences of 0.4 SD for the continuous secondary end points; however, these secondary end points remain exploratory absent adjustment for multiple comparisons.

Missing data only affected the primary end point when patients did not die and were not rehospitalized for heart failure. Among patients who did not die or were not rehospitalized for heart failure, data were available for the time-averaged NT-proBNP levels in 136 cases and were missing in 35 cases. On these occasions, a LOESS smoother (adjusted for sex and treatment group) was used to impute missing values.

Multiple imputation was used to impute missing data for the secondary and tertiary end points. No adjustment for missing information was made for the safety end points. All statistical analyses were conducted using SAS software version 9.4.

Results

Patients and Treatment

Between August 2013 and March 2015, a total of 154 patients were randomized to receive liraglutide and 146 to receive placebo (Figure 1). Baseline characteristics were similar in the 2 groups (**Table 1**). Across the entire cohort, the median age was 61 years (interquartile range [IQR], 52-68 years), the median duration of heart failure was 6.2 years (IQR, 3.3-11.2 years), and more than 85% of participants in both groups had been hospitalized for heart failure at least once during the year prior to the hospitalization for heart failure that was required for study eligibility.

Ischemic heart disease was the primary origin of heart failure in 82% of participants, and most patients had 1 or more comorbid conditions. Fifty-nine percent of randomized participants (178 patients) had type 2 diabetes. The median body mass index (calculated as weight in kilograms divided by height in meters squared) was 32 (IQR, 26-37).

Twenty-nine percent of participants had New York Heart Association class II heart failure, 63% had class III, and 5% had class IV. Despite high rates of disease-modifying therapies for heart failure, the median NT-proBNP level at the time of enrollment was 2049 pg/mL (IQR, 1054-4235 pg/mL) and the median LVEF was 25% (IQR, 19%-33%).

At least 1 dose of study drug was received by 150 of the 154 randomized to receive liraglutide and 145 of the 146 patients randomized to receive placebo. In the liraglutide group, 60% of participants achieved the target maximal dose of 1.8 mg/d, 21% received a maximum of 1.2 mg/d, and 16% received a maximum of 0.6 mg/d, whereas the corresponding proportions were 71%, 19%, and 10% for the placebo group.

In both groups, 29% of patients permanently discontinued use of the study drug prior to study termination. Of those who discontinued the study drug prior to rehospitalization for heart failure or death, this occurred in 19% of patients in the liraglutide group and in 17% of patients in the placebo group. The median duration that participants received the study drug was 25.0 weeks (IQR, 8.6-25.9 weeks) in the liraglutide group and 25.0 weeks (IQR, 11.4-26.0 weeks) in the placebo group (eFigure 1 in Supplement 1).

Primary End Point

In the primary intention-to-treat analysis, there was no significant between-group difference in the global rank scores (mean rank of 146 in the liraglutide group vs 156 in the placebo group; Wilcoxon rank sum *P* = .31), with higher rank indicating better stability (**Table 2**). To account for possible clustering of responses by enrollment site, we conducted a sensitivity analysis with site as a covariate; the results were nearly identical to the primary analysis (eTable 1 in Supplement 1).

Components of the Primary End Point

For the components of the primary end point, there was no significant between-group difference in the number of deaths (19 [12%] in the liraglutide group vs 16 [11%]) in the placebo group; hazard ratio [HR], 1.10 [95% CI, 0.57-2.14]; *P* = .78) (**Figure 2**A),

rehospitalizations for heart failure (63 [41%] in the liraglutide group vs 50 (34%) in the placebo group; HR, 1.30 [95% CI, 0.89-1.88]; *P* = .17), or the composite of death or rehospitalization for heart failure (72 [47%] in the liraglutide group vs 57 [39%] in the placebo group; HR, 1.30 [95% CI, 0.92-1.83]; *P* = .14) (Figure 2B). Among participants who were alive and not rehospitalized for heart failure, the time-averaged proportional change in NT-proBNP level was 1.52 (SD, 1.71) times the baseline levels in the liraglutide group and 1.44 (SD, 1.22) times the baseline levels in the placebo group (*P* = .94; Figure 2C).

Exploratory Secondary End Points

Compared with placebo, there was no significant effect of liraglutide on any of the prespecified secondary end points including changes in cardiac structure and function from baseline to 180 days, 6-minute walk test distances, the KCCQ clinical summary score, emergency department visits, and the composites of death and rehospitalization for heart failure with or without emergency department visits (Table 2).

Exploratory Tertiary End Points

Compared with placebo, liraglutide treatment was associated with greater weight decreases at 30 days (intergroup difference, −1.7 kg [95% CI, −2.9 to −0.5 kg]; *P* = .004) and 90 days (intergroup difference, −1.9 kg [95% CI, −3.4 to −0.4 kg]; *P* = .01), with no significant difference at 180 days (intergroup difference, −1.8 kg [95% CI, −3.9 to 0.3 kg], *P* = .09). Increases in cystatin C (a marker of renal dysfunction) were significantly greater at 180 days in patients in the liraglutide group compared with those in the placebo group (between-group difference, 0.16 mg/L [95% CI, 0.04 to 0.28] mg/L; *P* = .009). An exploratory analysis limited to patients who continued taking the study drug was not significant (eFigure 2 in Supplement 1).

Diabetes Subgroup Analysis

Among the 178 patients with diabetes (baseline characteristics appear in eTable 2 in Supplement 1), there was no statistically significant between-group difference in global rank score (mean rank of 85 for the liraglutide group vs 94 for the placebo group; *P* = .27) (eTable 3 in Supplement 1). The *P* value for interaction was 0.60 for treatment based on type 2 diabetes status.

Similar to the overall study population, the findings for the secondary clinical outcomes were not significantly different between the liraglutide and placebo groups. However, the point estimates consistently suggested higher risk of heart failure–related events with liraglutide and were higher in magnitude in patients with diabetes than in the overall study population (Table 2, **Figure 3**, and eTable 3 in Supplement 1).

Investigator-Reported Safety Events

Severe adverse events observed with liraglutide and placebo are reported in eTable 4 in Supplement 1. The number of investigator-reported hyperglycemic events was 16 (10%) in the liraglutide group vs 27 (18%) in the placebo group and hypoglycemic events were infrequent (2 [1%] in the liraglutide group vs 4 [3%] in the placebo group). The study was not adequately powered for statistical comparisons of the rates of adverse events between groups.

Table 1. Baseline Characteristics

	Liraglutide (n = 154)	Placebo (n = 146)
Age, median (IQR), y	62 (52-68)	61 (51-67)
Female sex, No. (%)	31 (20)	33 (23)
White race, No. (%)[a]	82 (53)	90 (62)
Hispanic, No. (%)[a]	4 (3)	11 (8)
Body mass index, median (IQR)[b]	31 (26-36)	33 (25-38)
Functional Measures		
New York Heart Association Classification, No. (%)		
II	49 (32)	36 (25)
III	93 (60)	96 (66)
IV	8 (5)	6 (4)
Kansas City Cardiomyopathy Questionnaire summary scores, median (IQR)[c]		
Clinical[d]	46 (32-65)	44 (29-65)
Overall[e]	43 (30-61)	41 (28-61)
6-min walk distance, median (IQR), m	234 (143-313)	212 (141-311)
Physical Examination		
Weight, median (IQR), kg	93 (79-113)	96 (76-117)
Systolic blood pressure, median (IQR), mm Hg	108 (99-120)	108 (99-118)
Heart rate, median (IQR), beats/min	75 (68-85)	76 (68-88)
Elevated jugular venous pressure, No. (%)	72 (47)	66 (45)
Edema, No. (%)	82 (53)	88 (60)
Duration since diagnosis of heart failure, median (IQR), y	6.6 (3.3-12.5)	6.1 (3.2-10.8)
Medical History, No. (%)		
Prior hospitalization for heart failure within past year	137 (89)	125 (86)
Ischemic heart disease	133 (86)	113 (77)
Hypertension	121 (79)	114 (78)
Atrial fibrillation	74 (48)	70 (48)
Type 2 diabetes mellitus	91 (59)	87 (60)
Stage ≥3 chronic kidney disease[f]	65 (42)	53 (36)
Heart Failure Medications at Enrollment, No. (%)		
β-Blocker	143 (93)	139 (95)
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	112 (73)	104 (71)
Hydralazine	51 (33)	47 (32)
Long-acting nitrates	60 (39)	53 (36)
Aldosterone antagonist	88 (57)	89 (61)
Loop diuretic	151 (98)	146 (100)
Digoxin	51 (33)	51 (35)
Calcium-channel blocker	12 (8)	5 (3)
Lipid-lowering agent	110 (71)	110 (75)
Antiplatelet agent	114 (74)	102 (70)
Anticoagulant agent	79 (51)	80 (55)
Laboratory or Echocardiographic Measures, median (IQR)		
Creatinine, mg/dL	1.5 (1.1-1.8)	1.5 (1.2-1.9)
Hemoglobin A_{1c}, %	6.6 (6.0-7.6)	6.7 (5.9-7.9)
Total cholesterol, mg/dL	132 (110-161)	131 (108-164)
High-density lipoprotein cholesterol, mg/dL	36 (28-47)	35 (29-47)
Low-density lipoprotein cholesterol, mg/dL	72 (54-96)	68 (57-92)
Triglycerides, mg/dL	97 (72-138)	97 (73-145)
N-terminal pro-B-type natriuretic peptide, pg/mL[g]	1936 (1075-4231)	2083 (1020-4333)
Cystatin C, mg/L[g]	1.3 (1.0-1.7)	1.5 (1.1-1.9)
Left ventricular ejection fraction, %	25 (20-33)	25 (19-32)
Left ventricular end-diastolic volume index, mL/m²	140 (112-173)	137 (115-174)
Left ventricular end-systolic volume index, mL/m²	104 (78-130)	100 (80-133)
Ratio of early mitral inflow velocity to early diastolic medial mitral annular velocity	22 (17-28)	23 (18-30)

Abbreviation: IQR, interquartile range.

SI conversion factors: To calculate creatinine to μmol/L, multiply by 88.4; low-density lipoprotein, high-density lipoprotein, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

[a] Race and ethnicity were self-reported.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Range from 1 to 100; higher scores indicate better function.

[d] A composite score for functional status, quality of life, and social limitation.

[e] Derived from the physical function, symptom (frequency and severity), social function, and quality-of-life domains.

[f] Determined by enrollment site.

[g] Determined at a central core laboratory that was blinded to treatment assignment.

Table 2. Study End Points

	Liraglutide (n = 154)	Placebo (n = 146)	Treatment Effect (95% CI)[a]	P Value
Primary End Point				
Mean global rank score[b]	146	156		.31[c]
Secondary End Points				
Change from baseline to 180 d, mean (95% CI)				
Left ventricular end-diastolic volume index, mL/m^2	3.4 (−3.7 to 10.4)	−2.9 (−9.7 to 3.9)	6.7 (−2.6 to 16.0)	.16
Left ventricular end-systolic volume index, mL/m^2	1.2 (−4.6 to 6.9)	−3.5 (−9.0 to 2.1)	5.0 (−2.6 to 12.7)	.19
Left ventricular ejection fraction, %	1.1 (−0.7 to 2.8)	1.4 (−0.4 to 3.2)	−0.1 (−2.3 to 2.1)	.95
6-min walk distance, m	56 (30 to 81)	55 (29 to 81)	5 (−29 to 39)	.79
Kansas City Cardiomyopathy Questionnaire summary scores[d]				
Clinical[e]	14 (10 to 18)	13 (9 to 17)	1.3 (−4.0 to 6.5)	.64
Overall[f]	13 (10 to 17)	13 (9 to 17)	0.6 (−4.5 to 5.8)	.81
Events from baseline to 180 d, No. (%)[g]				
Death	19 (12)	16 (11)	1.10 (0.57 to 2.14)[h]	.78
Rehospitalization for heart failure	63 (41)	50 (34)	1.30 (0.89 to 1.88)[h]	.17
Death or rehospitalization for heart failure	72 (47)	57 (39)	1.30 (0.92 to 1.83)[h]	.14
N-terminal pro-B-type natriuretic peptide level from baseline to 180 d, mean (95% CI)				
Total change, pg/mL	1055 (201 to 1909)	1216 (336 to 2096)	−155 (−1368 to 1058)	.80
Time-averaged proportional change expressed as ratio vs baseline value	1.9 (1.4 to 2.3)	1.8 (1.4 to 2.1)	0.1 (−0.4 to 0.7)	.65
Tertiary End Points				
Change from baseline to 180 d, mean (95% CI)				
Cystatin C, mg/L	0.08 (−0.01 to 0.17)	−0.09 (−0.18 to 0)	0.16 (0.04 to 0.28)	.009
Hemoglobin A$_{1c}$, %	−0.21 (−0.45 to 0.03)	0.10 (−0.14 to 0.34)	−0.33 (−0.67 to 0)	.05
Total cholesterol, mg/dL	8 (0 to 15)	17 (9 to 24)	−9.9 (−19.9 to 0.1)	.05
High-density lipoprotein cholesterol, mg/dL	4 (2 to 7)	3 (1 to 5)	2 (−2 to 5)	.37
Low-density lipoprotein cholesterol, mg/dL	0.3 (−6 to 6)	7 (0 to 13)	−7 (−15 to 1)	.08
Triglycerides, mg/dL	15 (−1 to 32)	39 (20 to 57)	−22 (−47 to 3)	.08
Weight, kg	−1.5 (−3.0 to 0)	0.3 (−1.2 to 1.8)	−1.8 (−3.9 to 0.3)	.09
Other Clinical End Points				
Events from baseline to 180 d				
Rehospitalization for cardiovascular reasons, No. (%)	78 (51)	62 (42)	1.33 (0.95 to 1.85)[h]	.09
ED visit, No. (%)	39 (25)	28 (19)	1.41 (0.87 to 2.30)[h]	.16
Death, rehospitalization for cardiovascular reasons, or ED visit, No. (%)	97 (63)	81 (55)	1.34 (1.00 to 1.80)[h]	.05
Death, rehospitalization for heart failure, or ED visit, No. (%)	89 (58)	72 (49)	1.36 (0.99 to 1.85)[h]	.05
Change in heart rate (95% CI), beats/min	1.0 (−1.72 to 3.63)	1.2 (−1.5 to 3.8)	−1.6 (−4.8 to 1.6)	.33

Abbreviation: ED, emergency department.

SI conversion factors: To calculate low-density lipoprotein, high-density lipoprotein, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

[a] Defined as between-group difference, adjusted for baseline value.

[b] Ranked across 3 hierarchical tiers: time to death, time to rehospitalization for heart failure, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days. Higher values indicate better health (range, 1 [an early death] to 300 [a patient who survived free from rehospitalization and had an improvement in N-terminal pro-B-type natriuretic peptide level]). This nonparametric analysis does not provide an informative estimate of variability.

[c] Determined using a Wilcoxon test statistic for the primary end point.

[d] Range from 1 to 100; higher scores indicate better function.

[e] A composite score for functional status, quality of life, and social limitation.

[f] Derived from the physical function, symptom (frequency and severity), social function, and quality-of-life domains.

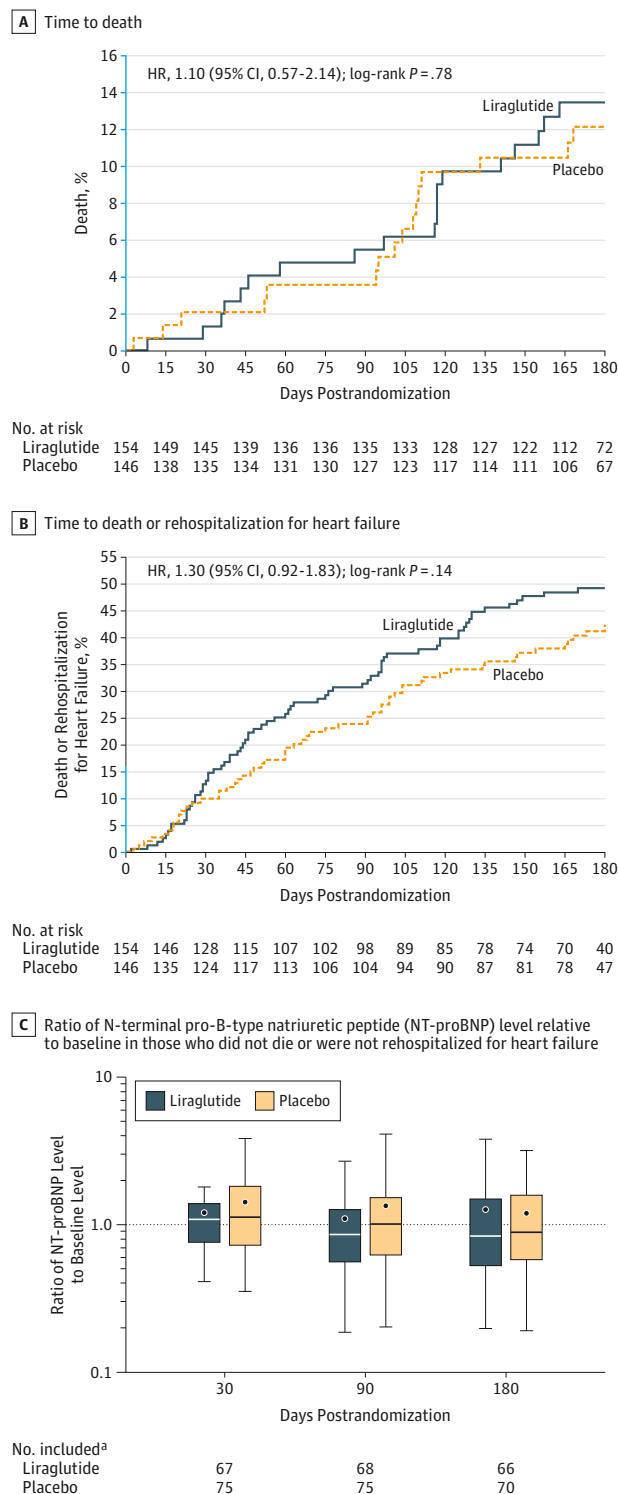[g] Patients with a left ventricular assist device or heart transplantation were not included.

[h] Data are expressed as hazard ratio (95% CI).

Discussion

The GLP-1 agonist liraglutide did not improve posthospitalization clinical stability in patients with advanced heart failure and reduced LVEF despite prior studies indicating that GLP-1 therapy might ameliorate mechanisms of myocardial insulin resistance reported in patients with severe cardiomyopathies.[3,4] The absence of favorable effects of liraglutide on secondary end points based on echocardiographic measures, 6-minute walk distance, or quality of life based on the KCCQ clinical summary score also supports the conclusion that liraglutide did not improve heart failure status.

Figure 2. Components of the Primary End Point

A Time to death

HR, 1.10 (95% CI, 0.57-2.14); log-rank *P* = .78

No. at risk												
Liraglutide	154	149	145	139	136	136	135	133	128	127	122	112	72
Placebo	146	138	135	134	131	130	127	123	117	114	111	106	67

B Time to death or rehospitalization for heart failure

HR, 1.30 (95% CI, 0.92-1.83); log-rank *P* = .14

No. at risk												
Liraglutide	154	146	128	115	107	102	98	89	85	78	74	70	40
Placebo	146	135	124	117	113	106	104	94	90	87	81	78	47

C Ratio of N-terminal pro-B-type natriuretic peptide (NT-proBNP) level relative to baseline in those who did not die or were not rehospitalized for heart failure

No. included[a]			
Liraglutide	67	68	66
Placebo	75	75	70

HR indicates hazard ratio. A and B, y-axis scale in blue indicates range from 0% to 16%. The median duration of follow-up was 179 days (IQR, 157-182 days) in the liraglutide group and 178 days (IQR, 150-183 days) in the placebo group. In part C, the box plots were formed by the 25th and 75th percentiles and the line within the box is the median; the error bars indicate the 95% CIs and the data markers indicate the means.

[a] Without missing data.

Although the global rank end point based on a hierarchy of death, rehospitalization, and biomarker analysis does not allow definitive conclusions about the effect of liraglutide on clinical outcomes, this study effectively excludes any large favorable effects with liraglutide on the composite of time to death or rehospitalization for heart failure (Figure 2B).

To our knowledge, this is the first multicenter randomized clinical trial specifically designed to determine whether a GLP-1 agonist benefits a high-risk subset of patients with established heart failure. The high-risk features of this trial's population were evident in (1) their recent hospitalization for heart failure at entry, (2) the substantial majority with New York Heart Association class III or IV symptoms, (3) their low median LVEF (25%) and 6-minute walk distance (<240 m), and (4) the elevated baseline levels of serum creatinine (1.5 mg/dL) and NT-proBNP (2049 pg/mL) despite treatment with evidence-based medical therapies. High risk was ultimately confirmed by high rates of death (11.7%) and rehospitalization for heart failure (37.7%) during the 6-month follow-up period in the entire cohort.

There are several potential explanations for failure of liraglutide to improve heart failure status in this trial. Because GLP-1 agonists promote glucose-dependent insulin secretion, this trial raises concerns about whether enhancing endogenous insulin secretion is advantageous in the setting of heart failure. To the extent that GLP-1 agonists mitigate insulin resistance, this trial also raises questions about whether previously demonstrated[2] myocardial insulin resistance in heart failure models is a maladaptive mechanism in patients with advanced heart failure and receiving standard medical therapy. These concerns are supported by the fact that other agents that augment insulin secretion and insulin sensitivity, specifically dipeptidyl peptidase 4 inhibitors and thiazolidinediones, have generated adverse heart failure signals.[13,14]

Alternatively, differences between the results in this trial and the encouraging earlier study using recombinant GLP-1[7] could be due to the cardioprotective roles of GLP-1 metabolites, such as GLP-1(9-36)amide, which act independently of the GLP-1 receptor and are not generated by GLP-1 agonists like liraglutide.[15] It is also possible that patients with advanced heart failure, like those in this trial, are refractory to the otherwise beneficial effects of GLP-1 agonists or are prone to detrimental extracardiac actions of GLP-1, such as impairment of renal function, that are not apparent in other populations.[16] Even though most baseline parameters were equivalent in the 2 treatment groups, a slightly higher proportion of ischemic heart disease (86%) among liraglutide-treated patients (vs 77% in the placebo group) could have increased their risk of adverse outcomes.

This trial provides complementary information to an increasing number of large randomized trials that assess cardiovascular outcomes, including heart failure, associated with treatments for type 2 diabetes. These include cardiovascular safety studies of sulfonylureas, thiazolidinediones, dipeptidyl-dipeptidase inhibitors,[13,17,18] GLP-1 agonists,[19] and sodium-glucose co-transporter 2 inhibitors.[20] In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial

Figure 3. Prespecified Subgroup Analysis of Patients Who Died or Experienced Rehospitalization for Heart Failure by Type 2 Diabetes Status

A Patients with diabetes

HR, 1.54 (95% CI, 0.97-2.46); log-rank P = .07

B Patients without diabetes

HR, 1.02 (95% CI, 0.60-1.72); log-rank P = .94

No. at risk

Liraglutide	91	86	77	69	63	60	58	53	51	46	43	41	24
Placebo	87	80	75	73	72	66	64	58	57	56	52	50	31

No. at risk

Liraglutide	63	60	51	46	44	42	40	36	34	32	31	29	16
Placebo	59	55	49	44	41	40	40	36	33	31	29	28	16
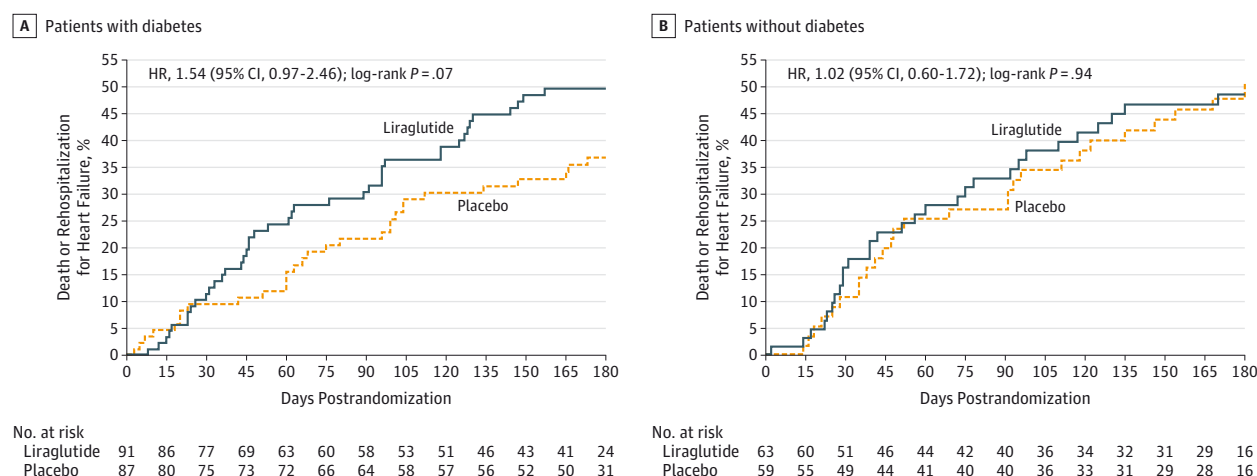
HR indicates hazard ratio. The median duration of follow-up was 179 days (interquartile range, 157-182 days) in the liraglutide group and 178 days (interquartile range, 150-183 days) in the placebo group.

Infarction 53 (SAVOR-TIMI-53) trial,[13] there was an increase in hospitalizations for heart failure in the patients with diabetes randomized to the dipeptidyl peptidase 4 inhibitor saxagliptin who had no prior diagnosis of heart failure (HR, 1.30 [95% CI, 1.03-1.65]; P = .03). Among the 234 patients with New York Heart Association class III or IV symptoms of heart failure in the SAVOR-TIMI-53 trial,[13] there was a nonstatistically significant increase in hospitalizations for heart failure in patients treated with saxagliptin (HR, 1.75 [95% CI, 0.94-3.36]). The increase in risk in SAVOR-TIMI-53 was highest among patients with elevated levels of natriuretic peptides, symptomatic heart failure, or chronic kidney disease. Similar increases in risk of heart failure were noted in patients with renal insufficiency or elevation in natriuretic peptides, which are cardinal features of advanced heart failure. To our knowledge, in trials of patients with diabetes taking GLP-1 agonists, there are no prior reports focusing on patients who already have advanced heart failure.

In the absence of a beneficial effect on heart failure status, it is important to define the efficacy and safety of liraglutide for diabetes management in patients already at high risk. In the patients with advanced heart failure and type 2 diabetes mellitus in this trial, the efficacy of liraglutide for diabetes management was supported by a reduction in hemoglobin A_{1c} and weight loss compared with the placebo-treated participants. However, nonsignificant increases in the numbers of patients with diabetes experiencing adverse heart failure outcomes, including the composite end point of time to death, rehospitalization for heart failure or emergency department visit, and signals of worsening renal function raise safety concerns about the use of liraglutide in this patient population.

Together, these nonsignificant signals of harm suggest the need for caution and close monitoring among clinicians considering initiation of liraglutide and other GLP-1 agonists for weight loss or diabetes management in patients with heart failure and reduced LVEF. Our findings are not relevant to patients already treated with GLP-1 agonists because such patients were specifically excluded from this trial. Larger safety trials[21] may provide complementary insight into the safety of liraglutide and other GLP-1 agonists in patients with less severe and earlier stages of heart failure.

This study has some important limitations. Although supported by prior work[10] and appropriate for a phase 2 trial, the global rank score end point in this trial has not been validated in patients with heart failure. In addition, this trial was not powered to detect differences in clinical events or safety end points, and it was not powered for subgroup analyses. The patients enrolled in this trial had advanced heart disease, and as expected there were missing data, especially for functional metrics such as the 6-minute walk test. It is also possible that patients seen at referral centers within the NHLBI Heart Failure Network are not representative of larger populations of patients with advanced heart failure treated outside academic medical centers.

Conclusions

Among patients recently hospitalized with heart failure and reduced LVEF, the use of liraglutide did not lead to greater posthospitalization clinical stability. These findings do not support the use of liraglutide in this clinical situation.

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