Received: 22 July 2022 | Revised: 25 August 2022 | Accepted: 4 September 2022

DOI: 10.1111/dom.14862

ORIGINAL ARTICLE

WILEY

# Risk of adverse events with liraglutide in heart failure with reduced ejection fraction: A post hoc analysis of the FIGHT trial

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**Funding information**
This study was supported by national funds through FCT Fundação para a Ciência e Tecnologia, I.P., under the scope of the Cardiovascular R&D Center – UnIC (UIDB/00051/2020 and UIDP/00051/2020.

## Abstract

**Aim:** To perform a post hoc analysis of the FIGHT trial, evaluating the effect of liraglutide (vs. placebo) on the totality of events in patients with heart failure with reduced ejection fraction (HFrEF).

**Materials and Methods:** FIGHT was a double-blind randomized controlled trial (RCT) that studied liraglutide versus placebo in 300 recently hospitalized patients with HFrEF followed for 180 days. The main outcome of the present analysis was total events of hospitalizations for heart failure (HF) or all-cause death. Secondary outcomes included total arrhythmic events and prespecified total events of interest (arrhythmias, sudden cardiac death, acute coronary syndrome, worsening HF, cerebrovascular event, venous thromboembolism, lightheadedness, presyncope/syncope or worsening renal function). Treatment effect was evaluated with negative binomial regression.

**Results:** Compared to placebo, there was a trend towards increased risk with liraglutide of total HF hospitalizations or all-cause deaths (96 vs. 143 events, incidence rate ratio [IRR] 1.41, 95% confidence interval [CI] 0.98-2.04; $P = 0.064$) and total arrhythmias (21 vs. 39, IRR 1.76, 95% CI 0.92-3.37; $P = 0.088$). Total prespecified events of

interest were increased with liraglutide compared to placebo (196 vs. 295, IRR 1.43, 95% CI 1.06-1.92; $P = 0.018$). The risk of HF hospitalizations or all-cause deaths with liraglutide was higher among patients in New York Heart Association (NYHA) Class III to IV (IRR 1.86, 95% CI 1.21-2.85) than in those in NYHA Class I to II (IRR 0.62, 95% CI 0.31-1.23; interaction $P = 0.008$), and among patients with diabetes (interaction $P = 0.051$). The risk of arrhythmic events was higher among those without an implanted cardiac device (interaction $P = 0.047$).

**Conclusions:** In patients with HFrEF, liraglutide might increase the risk of cardiovascular adverse effects, an effect possibly driven by excess risk of arrhythmias and worsening HF events. As this was a post hoc analysis, these results should be interpreted as exploratory and hypothesis-generating. Further RCTs must be conducted before drawing definitive conclusions.

**KEYWORDS**

adverse events, arrhythmia, GLP-1 receptor agonists, heart failure hospitalizations, heart failure with reduced ejection fraction, liraglutide

## 1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a drug class that promote glycaemic control and weight loss, lower blood pressure and improve lipid profile.[1] In randomized controlled trials (RCTs), GLP-1RAs decreased the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes (T2D) with a high cardiovascular risk,[2] and current guidelines for treatment of T2D propose GLP-1RAs as a preferential class for those patients at high risk of atherosclerotic cardiovascular events.[3,4]

Despite these beneficial effects, GLP-1RAs are known for increasing heart rate and activating cyclic adenosine monophosphate (cAMP)-dependent pathways,[5] which have been associated with detrimental effects in patients with heart failure with reduced ejection fraction (HFrEF).[6]

Despite the reduction in MACE in RCTs with patients with T2D, these trials included only a small fraction of heart failure (HF) patients without measuring ejection fraction or natriuretic peptides;[7] thus, the efficacy and safety of GLP-1RAs among patients with HF, particularly those with HFrEF, is not well established.

In two small RCTs with the GLP-1RA liraglutide in HFrEF, namely, the Heart Failure Network Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT)[8] and the Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients with and without Diabetes (LIVE) studies,[9] treatment with liraglutide was not associated with beneficial effects and there was a higher number of hospitalizations for worsening HF and arrhythmia-related events in the group treated with liraglutide compared to placebo, albeit not reaching statistical significance. The analysis of both trials focused on the evaluation of first events which may have limited their power to detect potential adverse effects of GLP-1RAs. The effect of the GLP-1RA albiglutide was also evaluated in patients with stable HFrEF.[10] In that small RCT (82 participants, 12 weeks follow-up), albiglutide did not improve cardiac function or myocardial glucose use. Although albiglutide was well tolerated in the RCT, the number of participants and the short follow-up may have limited the detection of potential adverse effects (no hospitalizations for worsening HF were reported during this period).

In the present analysis, we aimed to evaluate the effect of the GLP-1RA liraglutide (vs. placebo) on the totality of events of HF hospitalization or all-cause death in patients with HFrEF enrolled in the FIGHT trial.

## 2 | MATERIALS AND METHODS

### 2.1 | FIGHT trial

FIGHT was a multicentre, double-blind RCT, designed to determine if the use of the GLP-1RA liraglutide improved clinical stability in recently hospitalized patients with HFrEF.[11] The trial was conducted between August 2013 and March 2015 at 24 sites in the United States, and participants were identified based on hospital admission records. Participants, aged 18 years or older, were required to have an established diagnosis of HF and a left ventricular ejection fraction (LVEF) of 40% or lower during the preceding 3 months. Additional inclusion criteria included: (i) a recent (within 14 days) hospitalization for acute HF and (ii) a preadmission oral diuretic dose of at least 40 mg of furosemide or an equivalent per day. Key exclusion criteria were: (i) a recent acute coronary syndrome or coronary intervention; (ii) known intolerance of GLP-1RA therapy; and (iii) severe renal, hepatic or pulmonary disease. Subjects with and without T2D were enrolled in the trial. In total, 300 patients were randomized. A permuted block randomization scheme, stratified by clinical site and T2D status, was performed. Of these, 154 were randomized to liraglutide and 146 to placebo. Liraglutide and placebo were packaged identically

to maintain blinding to patients and investigators. Study drug dosage was uptitrated 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. In the primary analysis, the main outcome was a global rank score in which patients were ranked across three hierarchical tiers (with higher values indicating better health): time to death, time to rehospitalization for HF, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level from baseline to 180 days. There was no significant between-group difference in the global rank scores (146 for the liraglutide group vs. 156 for the placebo group; $P = 0.31$).

The FIGHT trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The study protocol was approved by the institutional review board and ethics committee at each participating centre. Access to the FIGHT database was provided through NHLBI/BioLINCC (https://biolincc.nhlbi.nih.gov/studies/hfn_fight/) with ethical approval from the *Centro Hospitalar Universitário São João / Faculdade de Medicina da Universidade do Porto* (process number #432/21).

## 2.2 | Study outcomes

The main outcome of this analysis was total events (first and recurrent) of HF hospitalizations or all-cause death. As secondary outcomes we evaluated: (i) total HF hospitalizations; (ii) all-cause death; (iii) total events of HF hospitalizations; urgent HF visits requiring intravenous diuretic treatment or all-cause death; (iv) total events of urgent HF visit requiring intravenous treatment; (v) total arrhythmic events (investigator reported); and (vi) prespecified total events of interest (predefined by the study investigators as any of the following: arrhythmias, sudden cardiac death, acute coronary syndrome, worsening HF, cerebrovascular event, venous thromboembolism, lightheadedness, presyncope or syncope, or worsening renal function).

## 2.3 | Statistical analysis

The main analyses of this study were conducted using the intention-to-treat principle and included all randomized participants during the study follow-up of approximately 180 days. The main and secondary outcomes were analysed by a negative binomial regression model with count of events as outcome and treatment group as independent variable. The results of the negative binomial test for the treatment effect of liraglutide versus placebo are described as incidence rate ratios (IRRs) with the respective 95% confidence intervals (CIs). Andersen-Gill models for recurrent events were also performed for internal consistency assessment. The introduction of anti-arrhythmic drugs during the follow-up period was assessed by mixed-effects logistic regression as an exploratory analysis.

Subgroup analyses were performed according to age (≥65 years vs. <65 years), sex (female vs. male), diagnosis of T2D (yes vs. no), LVEF (≤25% vs. >25%), body mass index (BMI; ≥30 kg/m$^2$ vs. <30 kg/m$^2$), NT-proBNP levels (≥2000 pg/mL vs. <2000 pg/mL), New York Heart Association (NYHA) class (Class III-IV vs. Class I-II), HF aetiology (ischaemic vs. non-ischaemic), use of cardiac resynchronization therapy or implantable cardioverter-defibrillator (yes vs. no), use of digoxin (yes vs. no), and use of amiodarone or other anti-arrhythmic drugs (yes vs. no), with differences in the effect of liraglutide versus placebo assessed using subgroup analyses with interaction terms.

A two-sided $P$ value of <0.05 was taken to indicate statistical significance. No correction for multiple testing was performed due to the exploratory nature of this work. All analyses were performed using Stata® (StataCorp. 2021. Stata Statistical Software: Release 17; StataCorp LLC College Station, Texas).

# 3 | RESULTS

## 3.1 | Baseline patient characteristics by number of total events

The median (percentile$_{25\text{-}75}$) age of the patients was 61 (52-68) years, the median LVEF was 25 (19–33)%, and 64 (21%) were women. Compared to patients alive and without HF hospitalizations during the 180-day follow-up (N = 156), those who had only one (N = 56) and particularly those who had two or more HF hospitalizations or a fatal event (N = 88) presented more frequently with severely symptomatic HF (NYHA Class III or IV: 63.8% vs. 69.1% vs. 79.1%; $P = 0.050$), had lower LVEF (median: 23% vs. 25% vs. 20%; $P = 0.016$), had more frequent previous HF hospitalizations (two or more: 40.4% vs. 60.7% vs. 69.3%; $P < 0.001$), used cardiac devices more often (78.2% vs. 73.2% vs. 88.6%; $P = 0.048$), had lower haemoglobin levels (median: 13 g/dL vs. 12 g/dL vs. 12 g/dL; $P = 0.041$), and used angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers less frequently (76.9% vs. 75.0% vs. 61.4%; $P = 0.029$ [Table 1]). The distribution of total HF hospitalizations or death is shown in Figure 1A. The distribution of total investigator-reported events of interest is shown in Figure 1B.

## 3.2 | Effect of liraglutide versus placebo on total events

During the 6-month follow-up period, in participants treated with liraglutide, compared to placebo, there was a trend towards increased number of total HF hospitalizations or all-cause deaths (96 vs. 143 events, IRR 1.41, 95% CI 0.98-2.04; $P = 0.064$), total HF hospitalizations (80 vs. 124 events, IRR 1.47, 95% CI 0.98-2.20; $P = 0.061$), intravenous diuretic therapy, HF hospitalizations or all-cause deaths (102 vs. 153 events, IRR 1.48, 95% CI 1.00-2.19; $P = 0.056$) and total investigator-reported arrhythmias (21 vs. 39, IRR 1.76, 95% CI 0.92-3.37; $P = 0.088$). Total prespecified investigator-reported events of interest were increased with liraglutide compared to placebo (196 vs. 295, IRR 1.43, 95% CI 1.06-1.92; $P = 0.018$ [Table 2]). The Andersen-Gill model provided similar results: hazard ratio [HR] 1.53, 95% CI 1.02 to 2.31 ($P = 0.040$) for total HF hospitalizations or all-cause deaths and HR 1.41, 95% CI 1.01 to 1.97 ($P = 0.043$) for total prespecified investigator-reported events of interest (Figure 2).

**TABLE 1** Baseline characteristics of the patients by the number of events of heart failure hospitalization or all-cause mortality

| | Number of events of HF hospitalization or all-cause mortality | | | |
|---|---|---|---|---|
| | None (N = 156) | 1 event (N = 56) | 2 or more events (N = 88) | *P* value* |
| Age, years | 61.0 (53.0, 68.5) | 62.5 (50.5, 68.0) | 61.0 (51.0, 66.0) | 0.57 |
| Women, n (%) | 27 (17.3) | 12 (21.4) | 25 (28.4) | 0.13 |
| Race, n (%) | | | | 0.42 |
| White | 94 (60.3) | 30 (53.6) | 48 (54.5) | |
| Black | 53 (34.0) | 25 (44.6) | 37 (42.0) | |
| Other | 9 (5.8) | 1 (1.8) | 3 (3.4) | |
| BMI, kg/m$^2$ | 31.6 (26.1, 35.6) | 32.1 (25.5, 36.6) | 30.8 (26.0, 36.9) | 0.96 |
| NYHA Class III-IV, n (%) | 97 (63.8) | 38 (69.1) | 68 (79.1) | 0.050 |
| Systolic BP, mmHg | 107.0 (98.0, 120.0) | 110.0 (96.0, 120.5) | 108.0 (100.0, 117.0) | 0.97 |
| Diastolic BP, mmHg | 66.0 (59.0, 75.0) | 67.0 (59.5, 79.0) | 66.0 (59.0, 74.0) | 0.67 |
| Heart rate, bpm | 76.0 (68.0, 86.0) | 76.0 (66.5, 89.5) | 75.5 (69.0, 86.0) | 0.61 |
| LVEF, % | 23.0 (18.0, 25.0) | 25.0 (17.8, 30.0) | 20.0 (15.0, 25.5) | 0.016 |
| HF of ischaemic aetiology, n (%) | 125 (80.1) | 47 (83.9) | 74 (84.1) | 0.68 |
| Time from HF diagnosis, years | 6.5 (3.3, 11.1) | 5.1 (3.0, 9.6) | 7.3 (3.3, 12.5) | 0.63 |
| HHF within past year, n (%) | | | | <0.001 |
| 0 | 22 (14.1) | 6 (10.7) | 10 (11.4) | |
| 1 | 71 (45.5) | 16 (28.6) | 17 (19.3) | |
| 2+ | 63 (40.4) | 34 (60.7) | 61 (69.3) | |
| Type 2 diabetes, n (%) | 93 (59.6) | 29 (51.8) | 56 (63.6) | 0.37 |
| Hypertension, n (%) | 122 (78.2) | 45 (81.8) | 68 (77.3) | 0.80 |
| Atrial fibrillation / flutter, n (%) | 78 (50.0) | 34 (60.7) | 42 (47.7) | 0.28 |
| History of sustained VT, VF or resuscitated cardiac arrest, n (%) | 23 (14.7) | 6 (10.7) | 19 (21.6) | 0.18 |
| Pacemaker or ICD, n (%) | 122 (78.2) | 41 (73.2) | 78 (88.6) | 0.048 |
| Stroke of TIA, n (%) | 23 (14.8) | 7 (12.5) | 11 (12.8) | 0.86 |
| Chronic kidney disease, n (%) | 54 (34.6) | 22 (40.0) | 42 (48.3) | 0.11 |
| Sodium, mEq/L | 137.0 (135.0, 140.0) | 136.5 (134.0, 139.0) | 136.0 (134.0, 139.0) | 0.080 |
| Potassium, mEq/L | 4.1 (3.8, 4.5) | 4.0 (3.7, 4.3) | 4.2 (3.8, 4.4) | 0.11 |
| eGFR, mL/min/1.73 m$^2$ | 51.1 (38.8, 69.4) | 55.5 (38.4, 72.2) | 49.4 (34.1, 65.9) | 0.38 |
| Cystatin C, mg/L | 1.3 (1.1, 1.7) | 1.5 (1.2, 1.8) | 1.4 (1.1, 1.9) | 0.23 |
| Glucose, mg/dL, mmol/L | 108.0 (95.0, 143.0) mg/dL = 6.0 (5.3, 7.9) mmol/L | 109.0 (94.5, 137.5) mg/dL = 6.1 (5.3, 7.6) mmol/L | 115.0 (96.0, 148.0) mg/dL = 6.4 (5.3, 8.2) mmol/L | 0.38 |
| HbA1c, %, mmol/mol | 6.6 (6.0, 7.6) % = 49 (42, 60) mmol/mol | 6.6 (5.8, 7.9) % = 49 (40, 63) mmol/mol | 6.8 (6.0, 8.0) % = 51 (49, 64) mmol/mol | 0.42 |
| Haemoglobin, g/dL | 13.0 (11.5, 14.5) | 12.0 (11.2, 13.8) | 12.3 (11.0, 13.5) | 0.041 |
| NT-proBNP, pg/mL | 2150.5 (1016.5, 4271.5) | 1908.5 (1153.0, 3944.0) | 1982.5 (1141.0, 4754.0) | 0.80 |
| ACE inhibitors or ARBs, n (%) | 120 (76.9) | 42 (75.0) | 54 (61.4) | 0.029 |
| Beta-blockers, n (%) | 149 (95.5) | 52 (92.9) | 81 (92.0) | 0.51 |
| Aldosterone antagonists, n (%) | 87 (56.5) | 37 (66.1) | 53 (60.2) | 0.45 |
| Loop diuretics, n (%) | 156 (100.0) | 54 (96.4) | 87 (98.9) | 0.070 |
| Digoxin, n (%) | 52 (33.3) | 17 (30.4) | 33 (37.5) | 0.66 |
| Amiodarone or other antiarrhythmic drugs, n (%) | 38 (24.4) | 18 (32.1) | 26 (29.9) | 0.44 |

*Note*: Results are presented as median (IQR) unless otherwise stated.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate (CKD-EPI creatinine formula); HbA1c, glycated haemoglobin; HF, heart failure; HHF, heart failure hospitalizations; ICD, implantable cardioverter-defibrillator, IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TIA, transient ischaemic attack, VF, ventricular fibrillation; VT, ventricular tachycardia.
**P* value for trend.

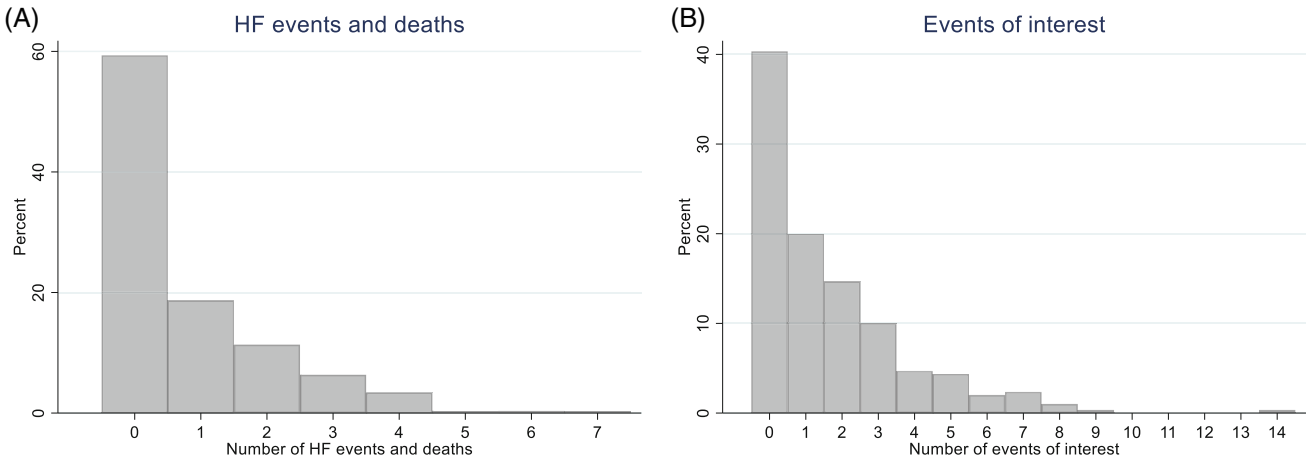


**FIGURE 1** Total number of events of heart failure (HF) hospitalizations or all-cause mortality (A). Total number of events of interest, predefined by the study investigators as any of the following: arrhythmias, sudden cardiac death, acute coronary syndrome, worsening HF, cerebrovascular event, venous thromboembolism, lightheadedness, presyncope or syncope, or worsening renal function (B)

**TABLE 2** Study outcomes (results are displayed as total events)

| Outcome | Events placebo (N = 146) | Events liraglutide (N = 154) | Incidence rate ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Total HHF or death | 96 | 143 | 1.41 (0.98-2.04) | 0.064 |
| Total HHF | 80 | 124 | 1.47 (0.98-2.20) | 0.061 |
| Death | 16 | 19 | 1.13 (0.58-2.19) | 0.72 |
| Total HHF, urgent HF visit or death | 102 | 153 | 1.48 (1.00-2.19) | 0.056 |
| Urgent HF visits | 6 | 10 | 1.58 (0.52-4.81) | 0.42 |
| Total arrhythmic events[a] | 21 | 39 | 1.76 (0.92-3.37) | 0.088 |
| Total events of interest[a,b] | 196 | 295 | 1.43 (1.06-1.92) | 0.018 |

Abbreviations: HF, heart failure; HHF, hospitalizations for heart failure.
[a]Investigator-reported.
[b]Events of interest, predefined by the study investigators as any of the following: arrhythmias, sudden cardiac death, acute coronary syndrome, worsening HF, cerebrovascular event, venous thromboembolism, lightheadedness, presyncope or syncope, or worsening renal function.

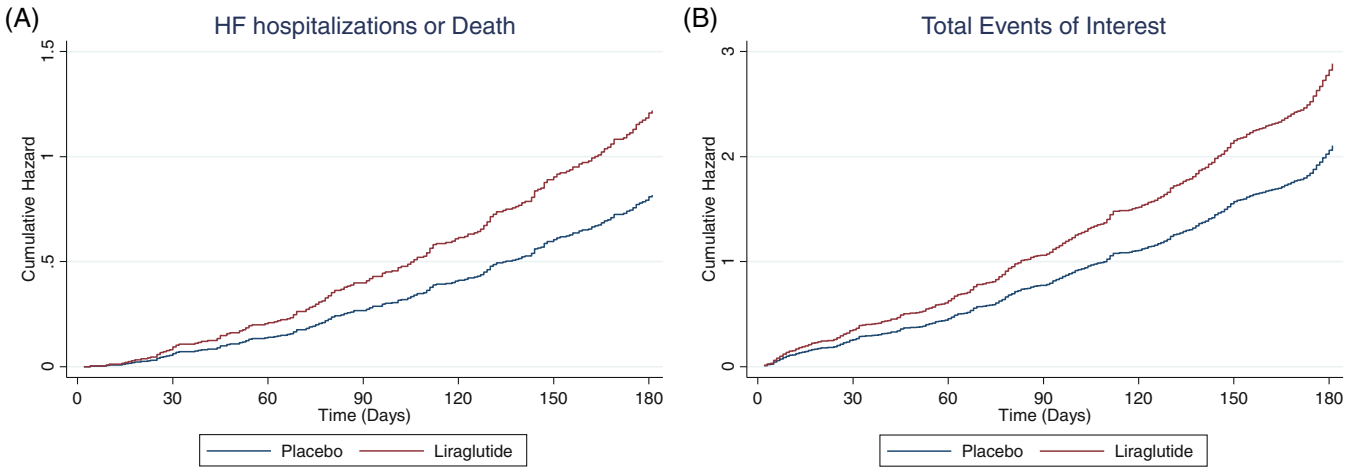


**FIGURE 2** Cumulative hazard (Andersen-Gill model) of total events of heart failure (HF) hospitalization or all-cause mortality: hazard ratio [HR] 1.53, 95% confidence interval [CI] 1.02-2.31, $P = 0.040$ (A) and total events of interest: HR 1.41, 95% CI 1.01-1.97, $P = 0.043$ (B)

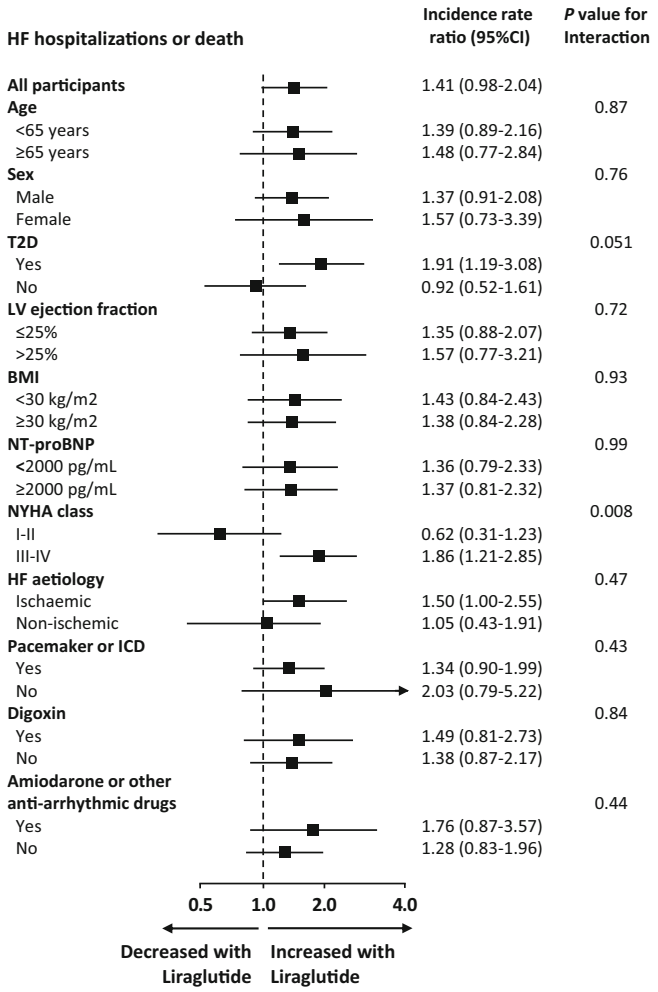


**FIGURE 3** Subgroup analyses for the total events of heart failure (HF) hospitalization or all-cause mortality. CI, confidence interval; T2D, type 2 diabetes; LV, left ventricular; BMI, body mass index; NYHA New York Heart Association; ICD, implantable cardioverter-defibrillator

Liraglutide increased the new use of anti-arrhythmic drugs (amiodarone, propafenone, digoxin): 75 versus 115 (odds ratio 4.01, 95% CI 0.78-20.6; $P = 0.097$).

### 3.3 | Subgroup analyses

The risk of total HF hospitalizations or all-cause deaths with liraglutide was higher among patients in NYHA Class III or IV (IRR 1.86, 95% CI 1.21-2.85) than in those in NYHA Class I or II (IRR 0.62, 95% CI 0.31-1.23; interaction $P = 0.008$) and among patients with T2D (IRR 1.91, 95% CI 1.19-3.08) than in those without diabetes (IRR 0.92, 95% CI 0.52-1.61; interaction $P = 0.051$ [Figure 3]). The risk of total arrhythmic events with liraglutide was higher among those without an implantable cardioverter-defibrillator (IRR 12.57, 95% CI 1.42-111.54) than in those with an implantable cardioverter-defibrillator (IRR 1.23, 95% CI 0.61-2.48; interaction $P = 0.047$) and in those not using digoxin (IRR 3.11, 95% CI 1.26-7.68) than in those using digoxin (IRR 0.92, 95% CI 0.34-2.50; interaction $P = 0.076$ [Figure S1]). A similar pattern was found for total investigator-reported events of interest (Figure S2).

## 4 | DISCUSSION

Our re-analysis of the FIGHT trial found a consistent pattern of increased risk of adverse events with liraglutide compared to placebo. Although it did not reach the statistical significance threshold of 0.05 for many of the studied endpoints, the consistency of the pattern across all outcomes strongly suggests that there is a potential risk associated with the use of liraglutide (and probably other GLP-1RAs) in patients with HFrEF. This risk is possibly driven by an excess of arrhythmias and worsening HF events with liraglutide use. A potentially increased risk of arrhythmic and worsening HF events with the use of GLP-1RAs in HFrEF is biologically plausible and has been externally replicated. In the small LIVE trial that enrolled 241 stable HFrEF patients randomized to either liraglutide or placebo (a lower-risk population compared to that in FIGHT), an excess risk of serious cardiac events was seen in the liraglutide group, driven by ventricular tachycardias (including one death) and atrial fibrillation (10% vs. 3%; $P = 0.04$).[9]

Despite its modest size and short follow-up (300 patients followed for 180 days), the FIGHT trial included a remarkably high-risk population due to the requirement for high natriuretic peptide levels and recent HF hospitalization prior to inclusion. Thus, the FIGHT trial was able to provide many "hard" events to assess the effect of liraglutide among patients with advanced HFrEF. Contrary to the original analysis, we evaluated not only time to first event, but the total number of events, which may more fully capture the total burden of disease in HF.[12] Potentially harmful effects of liraglutide could already be seen in the primary report of the FIGHT trial, with a time-to-first-event analysis, where the risk of: hospitalization for cardiovascular reasons (HR 1.33, 95% CI 0.95-1.85; $P = 0.09$); emergency department visit, hospitalization for cardiovascular reasons, or all-cause death (HR 1.34, 95% CI 1.00-1.80; $P = 0.05$); and emergency department visit, HF hospitalization, or all-cause death (HR 1.36, 95% CI 0.99-1.85; $P = 0.05$) all increased with liraglutide compared to placebo.[8] These findings are reinforced and expanded by the present total event analysis, highlighting the risk of HF re-hospitalizations, arrhythmias (supported by the introduction of anti-arrhythmic agents), and total events of interest (including arrhythmias, sudden cardiac death, acute coronary syndrome, worsening HF, cerebrovascular event, venous thromboembolism, lightheadedness, presyncope or syncope, or worsening renal function). The heightened risk among patients with severe symptoms (NYHA III-IV), and those not treated with cardiac devices or anti-arrhythmic agents such as digoxin, suggests that liraglutide may be particularly harmful among unstable HFrEF patients who are not protected against arrhythmias, including potentially fatal ventricular arrhythmias.

The mechanisms by which liraglutide and other GLP-1RAs may increase the risk of adverse cardiovascular events in patients with HFrEF are not fully understood but might relate to altered intracellular cAMP dynamics. GLP-1 receptors are expressed in cardiomyocytes and sinoatrial node cells, signalling through a cAMP-dependent pathway.[13] Preclinical data have already shown an increase in cardiac intracellular cAMP levels with GLP-1RA treatment.[14-16] Furthermore, extensive mechanistic data have shown that increased intracellular cAMP raises the risk of arrhythmia and leads to myocardial dysfunction in HF.[17-19] Importantly, the macromolecular complexes responsible for restricting cAMP action have been shown to be disrupted in HF,[20] extending cAMP-dependent signalling activation in time and space within the cardiomyocyte, causing calcium overload and predisposing to myocardial dysfunction and fatal arrhythmic events.[17,21] This is in accordance with data from clinical trials, showing that drugs that increase cAMP levels (eg, milrinone) increase the risk of arrhythmic events and mortality in HFrEF,[22] while drugs that decrease cAMP levels (e.g. beta-blockers) are associated with decreased risk.[23] GLP-1RAs increase cAMP levels by pathways independent of beta-adrenergic receptors.[24-26] The increased risk of cardiovascular adverse effects in the FIGHT trial, despite more than 90% of participants being treated with beta-blockers, suggests that beta-blockers do not protect from arrhythmic events and worsening HF events with GLP-1RAs in HFrEF.

While in populations without myocardial dysfunction and with low risk of arrhythmias, the myocardial effects of GLP-1RAs may not significantly increase the risk of HF events or arrhythmias,[27] in patients with HFrEF, the lower cardiac reserve and the higher pro-arrhythmogenic potential may make this population particularly susceptible to adverse cardiac effects with GLP-1RAs. In agreement with this hypothesis, some RCTs with GLP-1RAs in T2D showed significant interactions of the treatment arm with baseline HF status on study endpoints, with event rate reductions seen only in patients without HF at baseline. In the EXSCEL trial with exenatide, all-cause mortality was not reduced in the subgroup with HF (HR 1.05, 95% CI, 0.85-1.29) but was significantly reduced in those without HF at baseline (HR 0.79, 95% CI, 0.68-0.92; interaction $P = 0.03$).[28] Also, in a combined analysis of the SUSTAIN-6 and PIONEER-6, semaglutide reduced MACE among participants without HF (HR 0.79, 95% CI 0.68-0.92), but not in those with HF at baseline (HR 1.06, 95% CI 0.72-1.57; interaction $P = 0.03$).[29] In the LEADER trial, liraglutide reduced the composite of HF hospitalization or cardiovascular death in the subgroup without baseline HF history (HR 0.77, 95% CI 0.65-0.91) but not in the subgroup with baseline HF (HR 0.92, 95% CI, 0.74-1.15), even though the interaction was not significant (interaction $P = 0.19$).[30] In all these trials, HF subgroup included patients with HFrEF and patients with HF with preserved ejection fraction (HFpEF), which may explain the differences compared to the FIGHT trial. From the RCTs with GLP-1RAs in T2D, only the EXSCEL reported LVEF and, among participants with baseline HF and documented ejection fraction, only 22% had reduced ejection fraction.[28] Furthermore, some trials of GLP-1RAs versus placebo in patients with T2D have reported an excess of risk of ventricular fibrillation/tachycardia or cardiovascular conduction disorders with GLP-1RAs (EXCSEL: 41/7356 vs. 26/7396; LEADER 18/4668 vs. 8/4672; REWIND: 216/4949 vs. 192/4952).[31-33]

The findings reported here have important clinical consequences and further trials are needed to confirm the potential excess risk with GLP-1RAs in patients with HFrEF. Until such trials are conducted, GLP-1RAs should be avoided in patients with HFrEF.

Whether this increased risk is also observed in patients with HFpEF is uncertain; no RCTs have specifically evaluated GLP-1RAs in this population. Given the contribution of metabolic dysfunction and obesity to the pathophysiology of HFpEF,[34] the systemic effects of GLP-1RAs may counterweight, at least partially, the potential direct increased risk of arrhythmogenic effects. The Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF; clinicaltrials.gov identifier: NCT04788511) and the Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes (STEP HFpEF DM; clinicaltrials.gov identifier: NCT04916470) are evaluating the effect of the GLP-1RA semaglutide on the function and symptoms of patients with HFpEF.

It is important to distinguish the effects of GLP-1RAs in patients with T2D without HF from the effects in patients with established HF. While our results suggest that, in those with established HFrEF, treatment with GLP-1RAs may increase the risk of adverse effects, and in those without HF, GLP-1RAs may prevent the development of HF. A recent meta-analysis of RCTs in T2D showed that treatment with GLP-1RAs significantly reduced hospitalizations for HF.[35] Observational data also suggest that GLP-1RAs may decrease HF events in primary prevention.[36] The improvement of metabolic control and the prevention of coronary atherosclerotic disease with GLP-1RAs may explain the primary prevention of HF development in T2D. Furthermore, GLP-1RAs decrease epicardium fat,[37] which likely plays a role in the pathogenesis of HFpEF.[38] It is plausible that HF events prevented by GLP-1RAs in diabetes are predominantly HFpEF events.

Given the potential adverse effects of GLP-1RAs in HFrEF, in patients with T2D or obesity with symptoms suggestive of or clinical suspicion of HF, an echocardiogram and natriuretic peptides may be considered before starting the treatment. On the other hand, in those without HFrEF, our results should not discourage clinicians from using GLP-1RAs, given their well-established atherosclerotic cardiovascular benefit in T2D[2] and their potential cardiovascular benefits in obesity.[39]

Our study has some limitations. This was a post hoc analysis of an RCT and some studied endpoints did not reach the statistical significance threshold of 0.05; however, the consistent trend for increased risk of adverse events across different outcomes, the biological plausibility, and the finding of similar results in the LIVE trial provide robustness to our analyses.[9] This RCT had a short follow-up (6 months) and a modest size sample (300 participants); however, the remarkably high-risk population included led to a high number of "hard" outcomes during the trial. The increased risk observed in this high-risk population with a recent hospitalization may not apply to other groups of patients with HFrEF. The FIGHT trial was conducted

between August 2013 and March 2015, and new therapeutic interventions have been introduced since then in the management of HFrEF (including ARNI and SGLT2 inhibitors); although the potential detrimental effects of GLP-1RAs are not expected to be modified by the current management of HFrEF, we cannot exclude this possibility. We could not determine the cause of HF decompensation that led to hospitalization, but it is possible that arrythmias could have contributed to some of these HF events. No correction for multiplicity of tests was made, which may increase the risk of chance findings and type I error.

Despite these limitations, this analysis is an important addition to what was already known from the original analysis. In the original analysis, the global rank score did not differ between groups, and the study was interpreted as neutral. Although there was already a trend towards worse outcomes with liraglutide in the original analysis (Table S1), the use of totality of events allowed a clearer assessment of the effects of liraglutide in advanced HFrEF. The identification that the risk of HF hospitalizations or death with liraglutide was higher in patients in NYHA Class III to IV is clinically relevant. Furthermore, the higher risk of HF hospitalizations or death with liraglutide in patients with T2D is also relevant as this is the population most commonly treated with GLP-1RAs. Arrhythmic events were not specifically evaluated in the original analysis and our analysis showed a trend towards an increased risk of arrhythmias, particularly among those without an implanted cardiac device. As with any post hoc analysis, our study must be interpreted as exploratory and hypothesis-generating, and further RCTs must be conducted before drawing definitive conclusions.

In conclusion, in patients with HFrEF, treatment with liraglutide might increase the risk of cardiovascular adverse effects, an effect possibly driven by an excess risk of arrhythmias and worsening HF events. Further trials with GLP-1RAs should be performed to better assess the risks versus benefit of GLP-1RAs in patients with HFrEF; until then, the use of liraglutide, and possibly other GLP-1RAs, should be avoided in patients with advanced HFrEF.

## ACKNOWLEDGMENTS

This study was supported by national funds through FCT Fundação para a Ciência e Tecnologia, I.P., under the scope of the Cardiovascular R&D Center – UnIC (UIDB/00051/2020 and UIDP/00051/2020).

## CONFLICT OF INTERESTS

Dr Neves has received consulting or speaker fees from AstraZeneca, BIAL, Boehringer Ingelheim, Lilly, Merck and Novo Nordisk. Dr Sharma is supported by the McGill University Health Centre (MUHC) Foundation, Montreal General Hospital (MGH) Foundation, Sarah Louise King Award, Marjorie Cadham Award, Inez and Willena Beaton Award, *Fonds de Recherche Santé Quebec* (FRSQ) Junior 1 clinician scholars' program, and Canada Institute for Health Research grant – 175 095. Dr Sharma reports receiving support from the European Society of Cardiology young investigator grant, Roche Diagnostics, Boehringer-Ingelheim, Novartis and Takeda. Dr Carvalho has received consultancy fees from Novo-Nordisk and Eli-Lilly, and has held lectures Novo-Nordisk, Eli-Lilly and Astra-Zeneca. Dr Packer has received personal fees from Abbvie, Actavis, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Moderna, Novartis, Reata, Relypsa and Salamandras. Dr Zannad reports personal fees from Boehringer Ingelheim, Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer and Cellprothera, outside the submitted work, and other support from CVCT and Cardiorenal, outside the submitted work. Dr Ferreira is a consultant for Boehringer-Ingelheim, and receives research support from AstraZeneca and Novartis. All other authors have no potential conflicts of interest to disclose.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14862.

## DATA AVAILABILITY STATEMENT

The FIGHT database can be fully available from NHLBI/BioLINCC upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Neves JS, Vasques-Nóvoa F, Borges-Canha M, et al. Risk of adverse events with liraglutide in heart failure with reduced ejection fraction: A post hoc analysis of the FIGHT trial. *Diabetes Obes Metab*. 2023;25(1):189-197. doi:10.1111/dom.14862