ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2608–2616
Published online 1 June 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13348

SHORT COMMUNICATION

Growth differentiation factor-15, treatment with liraglutide, and clinical outcomes among patients with heart failure

Abhinav Sharma[1], Stephen Greene[2], Muthiah Vaduganathan[3], Marat Fudim[1], Andrew P. Ambrosy[4], Jie-Lena Sun[2], Steven E. McNulty[2], Adrian F. Hernandez[2], Barry A. Borlaug[5], Eric J. Velazquez[6], Robert J. Mentz[2], Adam D. DeVore[2], Brooke Alhanti[2], Kenneth Margulies[7] and G. Michael Felker[2]*

[1]*DREAM-CV Lab, McGill University Health Centre, McGill University, Montreal, Quebec, Canada;* [2]*Duke Clinical Research Institute, Duke University, 200 Morris Street, Durham, NC 27701, USA;* [3]*Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA, USA;* [4]*Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA;* [5]*Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA;* [6]*Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA; and* [7]*University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

Abstract

Aims Associations between growth differentiation factor-15 (GDF-15), cardiovascular outcomes, and exercise capacity among patients with a recent hospitalization for heart failure (HHF) and heart failure with reduced ejection fraction (HFrEF) are unknown. We utilized data from the 'Functional Impact of GLP-1 for Heart Failure Treatment' (FIGHT) study to address these knowledge gaps.

Methods and results FIGHT was a randomized clinical trial testing the effect of liraglutide (vs. placebo) among 300 participants with HFrEF and a recent HHF. Multivariable regression models evaluated associations between baseline GDF-15 and change in GDF-15 (per 1000 pg/mL increase from baseline to 30 days) with clinical outcomes (at 180 days) and declines in exercise capacity (6 min walk distance $\geq$ 45 m). At baseline (n = 249), median GDF-15 value was 3221 pg/mL (interquartile range 1938–5511 pg/mL). Participants in the highest tertile of baseline GDF-15 were more likely to be male and have more comorbidities. After adjustment, an increase in GDF-15 over 30 days was associated with higher risk of death or HHF [hazard ratio 1.35, 95% confidence interval (CI) 1.11–1.64]. In addition, higher baseline GDF-15 (per 1000 pg/mL until 6000 pg/mL) and an increase in GDF-15 over 30 days were associated with declining 6 min walk distance (odds ratio 1.26, 95% CI 1.02–1.55 and odds ratio 1.37, 95% CI 1.12–1.69, respectively). GDF-15 levels remained stable among participants randomized to liraglutide.

Conclusions An increase in GDF-15 over 30 days among patients in HFrEF was independently associated with an increased risk of cardiovascular events and declining exercise capacity. These results support the value of longitudinal GDF-15 trajectory in informing risk of heart failure disease progression.

Keywords GDF-15; Heart failure; Liraglutide; GLP-1 receptor agonist

Received: 16 February 2021; Revised: 8 March 2021; Accepted: 26 March 2021
**Correspondence to: G. Michael Felker, Duke Clinical Research Institute, Duke University, 200 Morris Street, Durham, NC 27701, USA. Email: michael.felker@duke.edu*

Introduction

Patients with recent hospitalization for heart failure (HHF) and heart failure with reduced ejection fraction (HFrEF) are at high risk for readmission and mortality.[1–3] Strategies to identify disease progression and increased risk of adverse outcomes in this patient group remain a clinical priority. Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β family and is secreted from multiple cell groups including adipocytes and myocytes in response to oxidative stress, mechanical strain, and ischaemia.[4] There is little information on the prognostic role of a single value or a change in GDF-15 in patients with HFrEF with recent HHF. Furthermore, prior studies have demonstrated

conflicting associations of GDF-15 and exercise capacity in chronic stable HFrEF.[5,6] The association of GDF-15 with exercise capacity and clinical outcomes has not been explored in the high-risk population of people with HFrEF with worsening heart failure (HF). Recent evidence suggests that GDF-15 may interact with the glucagon-like peptide-1 (GLP-1) signalling pathway.[7,8] GLP-1 receptor agonists reduce risk of adverse cardiovascular (CV) outcomes in patients with type 2 diabetes and are safe in patients with HF.[9,10] There is now potential to determine whether direct therapeutic modulation of this pathway impacts GDF-15 levels and HF risk.[11–15] To address these knowledge gaps, we used data from the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study[16] to identify (i) whether GDF-15 is associated with an increased risk of subsequent CV outcomes; (ii) whether GDF-15 is associated with declining exercise capacity, change in echocardiographic parameters, and change in HF symptoms; and (iii) whether liraglutide, a GLP-1 receptor agonist, impacts circulating GDF-15 levels in people with HFrEF with recent HF hospitalization.

Methods

The results of the FIGHT trial have been previously reported.[16] FIGHT was a double-blind, placebo-controlled, randomized clinical trial designed to test the efficacy, safety, and tolerability of liraglutide (vs. placebo) among 300 participants with HFrEF and a recent HHF (within the prior 2 weeks). The primary endpoint was a composite global rank score of time to death, time to rehospitalization for HF, and change in N-terminal pro-brain natriuretic peptide (NT-proBNP) level at 180 days compared with baseline.

Biomarker assessment

Blood samples were obtained at baseline, 30, 90, and 180 days. Samples were collected from the peripheral vein into EDTA-containing tubes, centrifuged immediately, and stored at −70°C for subsequent analysis. GDF-15 concentrations were measured in a core laboratory from samples using sensitive sandwich-immunoassay monoclonal antibodies (Elecsys GDF-15 assay, Roche Diagnostics, Indianapolis, Indiana).[17]

Study endpoints

This is a post hoc and hypothesis-generating analysis of the FIGHT trial. The primary endpoint of interest for the present analysis was 180 day death or HF hospitalization. Secondary endpoints included a decrease in exercise capacity, defined as a ≥45 m decrease in 6 min walk distance (6MWD); improvement in patient-reported quality of life, defined as an increase in Kansas City Cardiomyopathy Questionnaire (KCCQ) ≥ 5 points; and worsening left ventricular (LV) function, defined as either a 5% decrement in left ventricular ejection fraction (LVEF) or a 5% increase in LV volumes. The changes in secondary endpoints were assessed between baseline and 180 days.

Statistical analysis

The associations between GDF-15 tertile and baseline characteristics were described (*Table 1*). Categorical variables were presented as counts (percentages), and differences between the two groups were assessed using the Pearson χ^2 test or the Fisher exact test. Continuous variables were presented as median, 25th and 75th percentiles, and differences between the three groups were assessed using the Kruskal–Wallis test. Modelling was performed with complete case analysis. There were 249 patients at baseline with GDF-15 measurements. The biomarker subset population was demographically similar to the overall clinical trial population. For the clinical outcomes of interest, Cox proportional hazard models were used (the proportional hazards assumption was assessed and met). Logistic regression assessed the relationship between baseline and a change in GDF-15 (from baseline to 30 days) and a decrease in KCCQ ≥ 5 points, a decrease in 6MWD ≥ 45 m, and worsening LV function (defined as either a 5% decrement in LVEF or a 5% increase in LV volumes).

Regression models were adjusted for age, sex, diabetes mellitus, LVEF, estimated glomerular filtration rate, NT-proBNP, troponin, history of myocardial infarction, body mass index, and atrial fibrillation (with baseline GDF-15 added to the models assessing the association between change in GDF-15 and outcomes). All continuous variables were tested for linearity assumption, and the log transformation or two-piece linear splines were applied to some variables that violated the assumption. An interaction term of GDF-15 and randomized treatment evaluated whether GDF-15 modified the relationship between randomized treatment and outcomes. In addition, we evaluated an expanded model that included all the variables as indicated earlier and added history of myocardial infarction, body mass index, and history of atrial fibrillation. Data were analysed using SAS Version 9.4 software (SAS, Cary, North Carolina). Statistical significance was based on a *P*-value of ≤0.05.

Results

Baseline demographics

Among 300 participants enrolled in FIGHT, 249 (83%) had data for baseline GDF-15 concentration. Median baseline

Table 1 Baseline demographics by tertile of growth differentiation factor-15

Characteristic	Overall (*N* = 249)	Tertile 1 (*N* = 83)	Tertile 2 (*N* = 83)	Tertile 3 (*N* = 83)	*P*-value
Demographics					
Age, years: *n*, median (25th–75th)	249, 61 (53–68)	83, 54 (43–62)	83, 63 (55–69)	83, 65 (59–72)	<0.001
Female	53/249 (21.3%)	23/83 (27.7%)	17/83 (20.5%)	13/83 (15.7%)	0.2
White	147/249 (59.0%)	31/83 (37.3%)	52/83 (62.7%)	64/83 (77.1%)	<0.001
Weight, kg (median, 25th–75th)	209 (171–252)	217 (178–265)	213 (168–246)	202 (163–238)	0.08
Body mass index, (median, 25th–75th)	31.5 (25.2–36.4)	33.2 (27.3–37.9)	31.1 (25.5–36.4)	29.8 (23.9–35.6)	0.07
Ejection fraction: *n*, median (25th–75th)	249, 22.0 (17.0–25.0)	83, 20.0 (15.0–25.0)	83, 25.0 (17.0–27.0)	83, 23.0 (18.0–25.0)	0.2
Systolic blood pressure, mmHg: *n*, median (25th–75th)	248, 108 (99–118)	83, 110 (100–118)	83, 106 (98–118)	82, 108 (98–118)	0.7
Heart rate, b.p.m.: *n*, median (25th–75th)	249, 75 (68–86)	83, 77 (69–88)	83, 72 (67–80)	83, 75 (66–87)	0.1
Jugular venous pressure					0.07
Not elevated/not distended	131/242 (54.1%)	52/82 (63.4%)	43/81 (53.1%)	36/79 (45.6%)	
Elevated/distended	111/242 (45.9%)	30/82 (36.6%)	38/81 (46.9%)	43/79 (54.4%)	
Not done	0/242 (0.0%)	0/82 (0.0%)	0/81 (0.0%)	0/79 (0.0%)	
Co-morbidities					
Hypertension	199/248 (80.2%)	67/83 (80.7%)	65/83 (78.3%)	67/82 (81.7%)	0.9
Heart failure aetiology: ischaemic	209/249 (83.9%)	67/83 (80.7%)	77/83 (92.8%)	65/83 (78.3%)	0.03
Atrial fibrillation history	118/247 (47.8%)	26/82 (31.7%)	38/82 (46.3%)	54/83 (65.1%)	<0.001
Diabetes	146/249 (58.6%)	39/83 (47.0%)	53/83 (63.9%)	54/83 (65.1%)	0.03
Obstructive sleep apnoea	92/233 (39.5%)	37/78 (47.4%)	27/77 (35.1%)	28/78 (35.9%)	0.2
Orthopnoea	105/240 (43.8%)	34/82 (41.5%)	32/81 (39.5%)	39/77 (50.6%)	0.5
COPD	52/249 (20.9%)	15/83 (18.1%)	17/83 (20.5%)	20/83 (24.1%)	0.6
NYHA class					0.1
I	5/246 (2.0%)	2/82 (2.4%)	3/82 (3.7%)	0/82 (0.0%)	
II	77/246 (31.3%)	24/82 (29.3%)	31/82 (37.8%)	22/82 (26.8%)	
III	153/246 (62.2%)	55/82 (67.1%)	43/82 (52.4%)	55/82 (67.1%)	
IV	11/246 (4.5%)	1/82 (1.2%)	5/82 (6.1%)	5/82 (6.1%)	
Medications at enrolment					
ACE inhibitor or ARB	176/247 (71.3%)	73/83 (88.0%)	61/81 (75.3%)	42/83 (50.6%)	<0.001
Beta-blockers	232/249 (93.2%)	78/83 (94.0%)	81/83 (97.6%)	73/83 (88.0%)	0.05
Aldosterone antagonist	149/247 (60.3%)	57/83 (68.7%)	54/82 (65.9%)	38/82 (46.3%)	0.006
Any furosemide equivalent diuretic	247/249 (99.2%)	83/83 (100.0%)	82/83 (98.8%)	82/83 (98.8%)	1.0
Laboratory values					
Sodium, mEq/L: *n*, median (25th–75th)	247, 137 (134–139)	81, 137 (135–139)	83, 136 (134–138)	83, 137 (134–139)	0.1
Blood urea nitrogen, mg/dL: *n*, median (25th–75th)	247, 31.0 (22.0–47.0)	81, 24.0 (17.0–31.0)	83, 32.0 (24.0–46.0)	83, 42.0 (29.4–56.0)	<0.001
Creatinine (mg/dL): *n*, median (25th–75th)	247, 1.5 (1.1–1.9)	81, 1.2 (1.0–1.4)	83, 1.5 (1.2–1.8)	83, 1.8 (1.5–2.3)	<0.001
Core lab NT-proBNP (pg/mL): *n*, median (25th–75th)	248, 1927 (1046–4280)	83, 1296 (918.6–2085)	83, 1936 (1140–4685)	82, 3414 (1504–8393)	<0.001
eGFR (mL/min/1.73 m^2): *n*, median (25th–75th)	247, 49.2 (36.2–66.4)	81, 66.5 (52.2–84.7)	83, 47.3 (37.5–59.1)	83, 36.4 (28.3–49.2)	<0.001
Baseline hs-TnT (mg/L): *n*, median (25th–75th)	248, 29.9 (16.2–53.5)	82, 17.4 (10.0–34.7)	83, 31.5 (17.8–51.9)	83, 38.6 (25.0–68.6)	<0.001
Liraglutide treatment	126/249 (50.6%)	42/83 (50.6%)	46/83 (55.4%)	38/83 (45.8%)	0.5

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

DOI: 10.1002/ehf2.13348

GDF-15 value was 3221 pg/mL (interquartile range 1938–5511 pg/mL). Participants in the highest tertile of baseline GDF-15 were more likely to be older and male and tended to have higher concentrations of NT-proBNP and troponin and lower estimated glomerular filtration rate (*Table 1*).

Association between baseline growth differentiation factor-15 and outcomes

After multivariable adjustment, higher baseline GDF-15 (per 1000 pg/mL increase) was not associated with 180 day clinical outcomes including death or HHF [adjusted hazard ratio 1.05, 95% confidence interval (CI) 1.00–1.11] (*Table 2*). The association between baseline GDF-15 and 6MWD was non-linear: a higher baseline GDF-15 (per 1000 pg/mL) was associated with a 45 m lower 6MWD [adjusted odds ratio (aOR) 1.26, 95% CI 1.02–1.55] until 6000 pg/mL, where higher GDF-15 values were not associated with 6MWD (aOR 0.92, 95% CI 0.80–1.05). Baseline GDF-15 was not associated with decreases in KCCQ (aOR 1.00, 95% CI 0.91–1.08) or worsening LV function (aOR 1.07, 95% CI 0.95–1.19).

Association between 30 day change in growth differentiation factor-15 and outcomes

A 30 day increase in GDF-15 was associated with higher risk of death or HHF at 180 days (per 1000 pg/mL GDF-15 above a change of −500 pg/mL; adjusted hazard ratio 1.35, 95% CI 1.11–1.64) (*Table 2*). An increase in GDF-15 over 30 days (per 1000 pg/mL from baseline to 30 days) was associated with an increased risk of declining 6MWD of more than 45 m (aOR 1.37, 95% CI 1.12–1.69). Change in GDF-15 was not associated with change in KCCQ score. The results from the expanded model were consistent with these findings (*Tables A1* and *A2*).

Interaction of liraglutide and growth differentiation factor-15

Neither baseline GDF-15 nor 30 day change in GDF-15 modified the association between randomization to liraglutide versus placebo and changing KCCQ score, 6MWD, worsening LV function, or clinical outcomes at 180 days (all interaction *P*-values > 0.05). Randomization to liraglutide versus placebo did not change GDF-15 across follow-up, with no statistical difference between changes in GDF-15 from baseline to 30, 90, and 180 days ($P > 0.05$ at all time points; *Figure 1*).

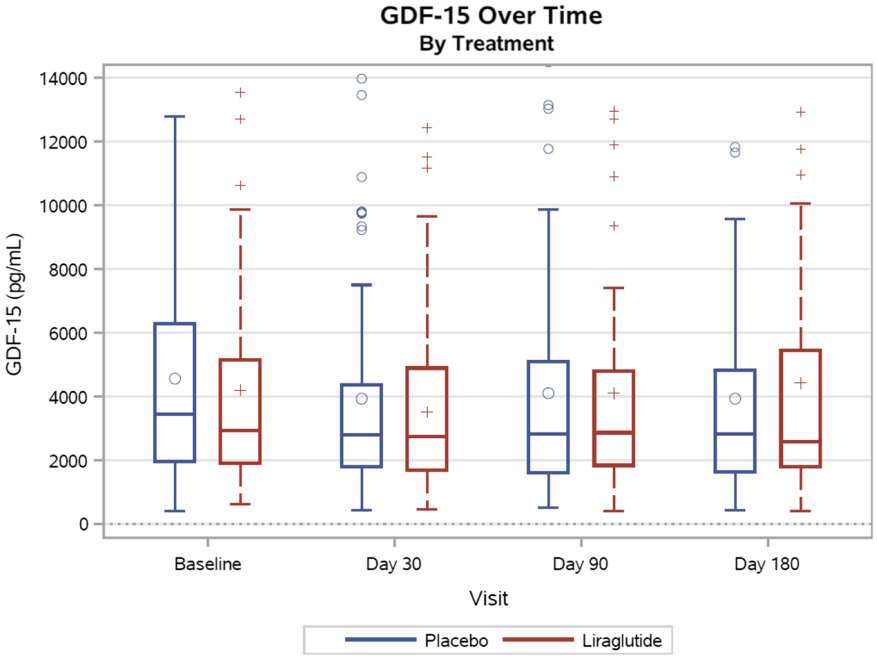
Table 2 Associations of baseline and change in growth differentiation factor-15 and clinical outcomes from Cox models

Outcomes	Description	Unadjusted		Adjusted[a]	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Baseline GDF-15					
180 day death or HF hospitalization	Baseline GDF-15 per 1000 pg/mL	1.05 (1.01, 1.10)	0.029	1.05 (1.00, 1.11)	0.069
180 day death or CV hospitalization	Baseline GDF-15 per 1000 pg/mL	1.03 (0.98, 1.08)	0.234	1.02 (0.97, 1.08)	0.458
180 day death or any hospitalization	Baseline GDF-15 per 1000 pg/mL	1.05 (1.00, 1.09)	0.037	1.04 (0.99, 1.09)	0.114
180 day death	Baseline GDF-15 per 1000 pg/mL	1.11 (1.03, 1.20)	0.005	1.06 (0.96, 1.16)	0.226
Change in GDF-15					
180 day death or HF hospitalization	Change in GDF-15 per 1000 pg/mL increase up to −500 pg/mL	0.95 (0.83, 1.09)	0.472	1.09 (0.87, 1.36)	0.439
	Change in GDF-15 per 1000 pg/mL increase above −500 pg/mL	1.39 (1.15, 1.68)	<0.001	1.35 (1.11, 1.64)	0.003
180 day death or CV hospitalization	Change in GDF-15 per 1000 pg/mL: baseline to 30 days	1.14 (0.99, 1.32)	0.060	1.22 (1.06, 1.40)	0.006
180 day death or any hospitalization	Change in GDF-15 per 1000 pg/mL: baseline to 30 days	1.10 (0.97, 1.25)	0.134	1.25 (1.08, 1.44)	0.003
180 day death	Change in GDF-15 per 1000 pg/mL: 30 days to baseline	1.12 (0.91, 1.38)	0.280	1.16 (1.00, 1.34)	0.052

CI, confidence interval; CV, cardiovascular; GDF-15, growth differentiation factor-15; HF, heart failure.
The hazard ratio is for 1 k increase in the change of GDF-15.
[a]Adjusted for baseline GDF-15, age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, N-terminal pro-brain natriuretic peptide, and troponin.

DOI: 10.1002/ehf2.13348

Figure 1 Growth differentiation factor-15 (GDF-15) over time by baseline randomization arm.



Discussion

Among participants with HFrEF who had a recent HHF in the FIGHT trial, we identified the following major findings: (i) an increase in GDF-15 over time was associated with an increased risk of subsequent CV events; (ii) higher baseline and increasing GDF-15 over 30 days were both associated with declining exercise capacity as measured by the 6MWD; and (iii) treatment with liraglutide did not impact GDF-15 levels. These results suggest that short-term changes in GDF-15 have a role in identifying HF disease progression in people with HFrEF with a recent HHF.

The prognostic role of GDF-15 in stable people with HFrEF has been demonstrated in several studies.[5,18–21] Our results are unique and extend on prior results as they demonstrate the prognostic value of short-term changes in GDF-15 beyond the baseline value. Furthermore, the prognostic role of a change in GDF-15 in people with HFrEF with recent HHF had not been previously described. These results reinforce prior data identifying associations between 1 year changes in GDF-15 and CV outcomes and support the incremental value of GDF-15 trajectory beyond results of a singular measurement.[18] Our findings contrast with prior analyses in ambulatory HFrEF and people with HF with preserved ejection fraction, where GDF-15 and other novel biomarkers (ST-2 and galectin-3) were only mildly associated with a change in functional parameters.[6]

Identifying people with HFrEF who may functionally decline overtime remains a clinically important endeavour, yet identifying a biomarker that can serve as a surrogate for exercise capacity remains challenging.[6] The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial suggested that among participants with chronic stable HFrEF, higher baseline GDF-15 was associated with greater baseline impairments in exercise capacity.[5] Similar results were seen in the 'Iron Repletion effects On Oxygen UpTake in Heart Failure' (IRONOUT) trial.[6] The current results extend these prior data by suggesting that both baseline and 30 day change in GDF-15 are associated with a subsequent decline in 6MWD, highlighting the potential role of serial GDF-15 in identifying people at high risk for worsening functional status following HHF. This aligns with prior analysis demonstrating the strength of serial biomarker measurement in HF.[22] Furthermore, ongoing trials are now evaluating the role of GDF-15-based titration of HF therapies.[23]

Growth differentiation factor-15 is now emerging as a possible endocrine signal of nutritional stress and a target for weight loss as it potentially acts through the GLP-1 signalling pathway.[8,24] Liraglutide has also demonstrated efficacy in reducing weight.[25–27] To our knowledge, our analysis is the first to demonstrate that GDF-15 levels are not impacted by a GLP-1 receptor agonist. GDF-15 levels were not modified by valsartan (vs. placebo)[18] or sacubitril/valsartan (vs. enalapril).[20] Our results extend these prior results and provide potential insight into the role of GDF-15 in HFrEF, suggesting that GDF-15 is not modified by therapeutic regulation of the GLP-1, renin–angiotensin, or neprilysin pathways.

Limitations

Our results are subject to the limitations of a post hoc analysis. The FIGHT trial may not be representative of all people with HFrEF. Not all participants had samples, and some participants were censored after baseline due to death; therefore, the results may not be generalizable. However, the use of available samples to conduct repeated measurements of GDF-15 at baseline and 30 days in the context of a randomized trial enables a hypothesis-generating exploration of the prognostic value of GDF-15 and changes in GDF-15 with liraglutide. Our study sample size may be unable to detect small but meaningful differences in GDF-15 levels in treatment groups. The shorter duration of follow-up of the FIGHT trial may have limited our ability to identify further association between baseline GDF-15, clinical outcomes, and treatment groups. We did not provide data on use of metformin as the FIGHT trial includes both patients with and without diabetes mellitus. Hence, any adjustment of results based on metformin use at baseline would be confounded by indication and could erroneously create associations. Guideline-directed medical therapy was not optimally used in our population, which may impact biomarker levels—however, these results are reflective of the real-world use of medical therapy in patients with HFrEF and worsening HF.[28]

Conclusion

In people with HFrEF with a recent HHF, change in GDF-15 over time was significantly associated with HF disease progression including CV outcomes and declining exercise capacity. GDF-15 levels remained stable among individuals randomized to liraglutide. While future studies will be needed to confirm these results, our findings reinforce the potential role of evaluating trajectories of GDF-15 in people with HFrEF for forecasting risk of clinical events and worsening functional status.

Conflict of interest

A.S. reports receiving support from Canada Institute for Health Research - (Grant Number: 175095), the Fonds de Recherche Santé Quebec (FRSQ) Junior 1 clinician scholars programme, Alberta Innovates Health Solution, European Society of Cardiology young investigator grant, Roche Diagnostics, Boeringer-Ingelheim, Novartis, and Takeda. M. F. reports consulting fees from AxonTherapies and Daxor. R. M. reported honoraria from Roche. S.J.G. has received a Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis; has received research support from Amgen, Bristol-Myers Squibb, and Novartis; serves on advisory boards for Amgen and Cytokinetics; and serves as a consultant for Amgen and Merck. There are no additional conflicts to disclose.

Funding

Funding for this analysis and GDF-15 assays were provided by Roche Diagnostics. The FIGHT trial was funded by the National, Heart, Lung, and Blood Institute (NHLBI).

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on and Prevention Statistics Committee and Stroke Statistics Subcommittee Epidemiology. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019; **139**: e209.
2. Sharma A, Zhao X, Hammill BG, Hernandez AF, Fonarow GC, Felker GM, Yancy CW, Heidenreich PA, Ezekowitz JA, DeVore AD. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the Get With The Guidelines–Heart Failure registry. *Circ Heart Fail* 2018; **11**: e004646.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**, 2129–2200m: 2129–2200.
4. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, Heineke J, Kotlarz D, Xu J, Molkentin JD, Niessen HW, Drexler H, Wollert KC. The transforming growth factor-β superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res* 2006; **98**: 351–360.
5. Sharma A, Stevens SR, Lucas J, Fiuzat M, Adams KF, Whellan DJ, Donahue MP, Kitzman DW, Piña IL, Zannad F, Kraus WE, O'Connor CM, Felker GM. Utility of growth differentiation factor-15, a marker of oxidative stress and

inflammation, in chronic heart failure: insights from the HF-ACTION study. *JACC Hear Fail* 2017; **5**: 724–734.
6. Fudim M, Kelly JP, Jones AD, AbouEzzeddine OF, Ambrosy AP, Greene SJ, Reddy YNV, Anstrom KJ, Alhanti B, Lewis GD, Hernandez AF, Felker GM. Are existing and emerging biomarkers associated with cardiorespiratory fitness in patients with chronic heart failure? *Am Heart J* 2020; **220**: 97–107.
7. Januzzi JL, Suchindran S, Hoffmann U, Patel MR, Ferencik M, Coles A, Tardif J-C, Ginsburg GS, Douglas PS, PROMISE Investigators. Single-molecule hsTnI and short-term risk in stable patients with chest pain. *J Am Coll Cardiol* 2019; **73**: 251–260.
8. Xiong Y, Walker K, Min X, Hale C, Tran T, Komorowski R, Yang J, Davda J, Nuanmanee N, Kemp D, Wang X. Long-acting MIC-1/GDF15 molecules to treat obesity: evidence from mice to monkeys. *Sci Transl Med* 2017; **9**: 1–12.
9. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; **7**: 776–785.
10. Redouane B, Greene SJ, Fudim M, Vaduganathan M, Ambrosy AP, Sun J-L, DeVore AD, McNulty SE, Mentz RJ, Hernandez AF, Felker GM, Cooper LB, Borlaug BA, Velazquez EJ, Margulies KB, Sharma A. Effects of liraglutide on worsening renal function among patients with heart failure with reduced ejection fraction. *Circ Heart Fail* 2020; **13**: e006758.
11. Patel S, Alvarez-Guaita A, Melvin A, Rimmington D, Dattilo A, Miedzybrodzka EL, Cimino I, Maurin A-C, Roberts GP, Meek CL, Virtue S, Sparks LM, Parsons SA, Redman LM, Bray GA, Liou AP, Woods RM, Parry SA, Jeppesen PB, Kolnes AJ, Harding HP, Ron D, Vidal-Puig A, Reimann F, Gribble FM, Hulston CJ, Farooqi IS, Fafournoux P, Smith SR, Jensen J, Breen D, Wu Z, Zhang BB, Coll AP, Savage DB, O'Rahilly S. GDF15 provides an endocrine signal of nutritional stress in mice and humans. *Cell Metab* 2019; **29**: 707–718.e8.
12. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019; **41**: 1–69.
13. Seferović PM, Coats AJ, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferović J, Sari I, Cosentino F, Ambrosio G, Metra M, Piepoli M, Chioncel O, Lund LH, Thum T, De Boer RA, Mullens W, Lopatin Y, Volterrani M, Hill L, Bauersachs J, Lyon A, Petrie MC, Anker S, Rosano GMC. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail* 2019; **4**.
14. Sharma A, Cooper LB, Fiuzat M, Mentz RJ, Ferreira JP, Butler J, Fitchett D, Moses AC, O'Connor C, Zannad F. Antihyperglycemic therapies to treat patients with heart failure and diabetes mellitus. *JACC: Heart Failure* 2018; **6**: 813–822.
15. Sharma A, Pagidipati NJ, Califf RM, McGuire DK, Green JB, Demets D, George JT, Gerstein HC, Hobbs T, Holman RR, Lawson FC, Leiter LA, Pfeffer MA, Reusch J, Riesmeyer JS, Roe MT, Rosenberg Y, Temple R, Wiviott S, McMurray J, Granger C. Impact of regulatory guidance on evaluating cardiovascular risk of new glucose-lowering therapies to treat type 2 diabetes mellitus: lessons learned and future directions. *Circulation* 2020; **141**: 843–862.
16. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP, for the NHLBI Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA - J Am Med Assoc* 2016; **316**: 500–508.
17. Wollert KC, Kempf T, Giannitsis E, Bertsch T, Braun SL, Maier H, Reim M, Christenson RH. An automated assay for growth differentiation factor 15. *J Appl Lab Med An AACC Publ* 2017; **1**: 510–521.
18. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H, Wollert KC. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the valsartan heart failure trial. *Circulation* 2010; **122**: 1387–1395.
19. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, de Berardinis B, Motiwala S, Wang TJ, Januzzi JL Jr. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *JACC Hear Fail* 2014; **2**: 65–72.
20. Bouabdallaoui N, Claggett B, Zile MR, McMurray JJV, O'Meara E, Packer M, Prescott MF, Swedberg K, Solomon SD, Rouleau JL, for the PARADIGM-HF Investigators and Committees. Growth differentiation factor-15 is not modified by sacubitril/valsartan and is an independent marker of risk in patients with heart failure and reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail* 2018; **20**: 1701–1709.
21. Suthahar N, Meems LMG, Ho JE, Boer RA. Sex-related differences in contemporary biomarkers for heart failure: a review. *Eur J Heart Fail* 2020; **22**: 775–788.
22. Israr MZ, Salzano A, Yazaki Y, Voors AA, Ouwerkerk W, Anker SD, Cleland JG, Dickstein K, Metra M, Samani NJ, Ng LL, Suzuki T, BIOSTAT-CHF Consortium (see Appendix). Implications of serial measurements of natriuretic peptides in heart failure: insights from BIOSTAT-CHF. *Eur J Heart Fail* 2020; **22**: 1486–1490.
23. Kimmoun A, Cotter G, Davison B, Takagi K, Addad F, Celutkiene J, Chioncel O, Solal AC, Diaz R, Damasceno A, Duengen HD, Filippatos G, Goncalvesova E, Merai I, Metra M, Ponikowski P, Privalov D, Sliwa K, Sani MU, Voors AA, Shogenov Z, Mebazaa A. Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study. *Eur J Heart Fail* 2019; **21**: 1459–1467.
24. Frikke-Schmidt H, Hultman K, Galaske JW, Jørgensen SB, Myers MG Jr, Seeley RJ. GDF15 acts synergistically with liraglutide but is not necessary for the weight loss induced by bariatric surgery in mice. *Mol Metab* 2019; **21**: 13–21.
25. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol* 2018; **71**: 69–84.
26. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Ortiz RV, Jensen CB, Wilding JPH, SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015; **373**: 11–22.
27. Sharma A, Ambrosy AP, DeVore AD, Margulies KB, McNulty SE, Mentz RJ, Hernandez AF, Michael Felker G, Cooper LB, Lala A, Vader J, Groake JD, Borlaug BA, Velazquez EJ. Liraglutide and weight loss among patients with advanced heart failure and a reduced ejection fraction: insights from the FIGHT trial. *ESC Hear Fail* 2018; **5**: 1035–1043.
28. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, ter Maaten JM, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *Eur J Heart Fail* 2017; **19**: 1284–1293.

Appendix A

Table A1 Association of baseline growth differentiation factor-15 and outcomes

		Unadjusted		Adjusted[a]	
Outcomes	Description	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
180 day death or HF hospitalization	Baseline GDF-15 per 1000 pg/mL	1.05 (1.01, 1.10)	0.029	1.06 (1.00, 1.11)	0.052
180 day death or CV hospitalization	Baseline GDF-15 per 1000 pg/mL	1.03 (0.98, 1.08)	0.234	1.02 (0.97, 1.08)	0.420
180 day death or any hospitalization	Baseline GDF-15 per 1000 pg/mL	1.05 (1.00, 1.09)	0.037	1.05 (1.00, 1.10)	0.073
180 day death	Baseline GDF-15 per 1000 pg/mL	1.11 (1.03, 1.20)	0.005	1.06 (0.96, 1.16)	0.273

CI, confidence interval; CV, cardiovascular; GDF-15, growth differentiation factor-15; HF, heart failure.
The hazard ratio is for 1 k increase in GDF-15.
[a]Adjusted for age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, N-terminal pro-brain natriuretic peptide, troponin, history of myocardial infarction, body mass index, and atrial fibrillation.

DOI: 10.1002/ehf2.13348

Table A2 Association of change in growth differentiation factor-15 and outcomes

Outcomes	Description	Unadjusted		Adjusted[a]	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
180 day death or HF hospitalization	Change in GDF-15 per 1000 increase up to −500	0.95 (0.83, 1.09)	0.472	1.09 (0.87, 1.38)	0.462
	Change in GDF-15 per 1000 increase above −500	1.39 (1.15, 1.68)	<0.001	1.40 (1.13, 1.73)	0.002
180 day death or CV hospitalization	Change in GDF-15 per 1000 pg/mL: 30 days to BS	1.14 (0.99, 1.32)	0.060	1.23 (1.05, 1.43)	0.008
180 day death or any hospitalization	Change in GDF-15 per 1000 pg/mL: 30 days to BS	1.10 (0.97, 1.25)	0.134	1.30 (1.12, 1.52)	<0.001
180 day death	Change in GDF-15 per 1000 pg/mL: 30 days to BS	1.12 (0.91, 1.38)	0.280	1.15 (0.99, 1.35)	0.071

BS, baseline; CI, confidence interval; CV, cardiovascular; GDF-15, growth differentiation factor-15; HF, heart failure.
The hazard ratio is for 1 k increase in the change of GDF-15.
[a]Adjusted for baseline GDF-15, age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, N-terminal pro-brain natriuretic peptide, troponin, history of myocardial infarction, body mass index, and atrial fibrillation.

ESC Heart Failure 2021; **8**: 2608–2616
DOI: 10.1002/ehf2.13348