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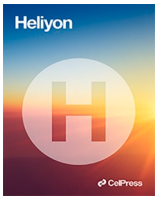

Research article

Association between growth differentiation factor-15 and adverse outcomes among patients with heart failure: A systematic literature review

Ali Javaheri [a,b,*], Mualla Ozcan [a], Lauren Moubarak [c], Karen E. Smoyer [d], Michelle I. Rossulek [e], James H. Revkin [e], John D. Groarke [e], Lisa C. Tarasenko [f], Mikhail N. Kosiborod [g]

[a] *Department of Medicine, Washington University School of Medicine in St. Louis, St. Louis, MO, USA*
[b] *John J. Cochran Veterans Affairs Medical Center, St. Louis, MO, USA*
[c] *Envision Pharma Group, London, UK*
[d] *Envision Pharma Group, Philadelphia, PA, USA*
[e] *Pfizer Inc, Cambridge, MA, USA*
[f] *Pfizer Inc, New York, NY, USA*
[g] *Saint Luke's Mid America Heart Institute and University of Missouri–Kansas City, Kansas City, MO, USA*

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ABSTRACT

Growth differentiation factor-15 (GDF-15) is an emerging biomarker in several conditions. This SLR, conducted following PRISMA guidelines, examined the association between GDF-15 concentration and range of adverse outcomes in patients with heart failure (HF). Publications were identified from Embase® and Medline® bibliographic databases between January 1, 2014, and August 23, 2022 (congress abstracts: January 1, 2020, to August 23, 2022). Sixty-three publications met the eligibility criteria (55 manuscripts and 8 abstracts; 45 observational studies and 18 post hoc analyses of randomized controlled trials [RCTs]). Of the 19 outcomes identified, the most frequently reported longitudinal outcomes were mortality (n = 32 studies; all-cause [n = 27] or cardiovascular-related [n = 6]), composite outcomes (n = 28; most commonly mortality ± hospitalization/rehospitalization [n = 19]), and hospitalization/re-hospitalization (n = 11). The most common cross-sectional outcome was renal function (n = 22). Among longitudinal studies assessing independent relationships with outcomes using multivariate analyses (MVA), a significant increase in risk associated with higher baseline GDF-15 concentration was found in 22/24 (92 %) studies assessing all-cause mortality, 4/5 (80 %) assessing cardiovascular-related mortality, 13/19 (68 %) assessing composite outcomes, and 4/8 (50 %) assessing hospitalization/rehospitalization. All (7/7; 100 %) of the cross-sectional studies assessing the relationship with renal function by MVA, and 3/4 (75 %) assessing exercise capacity, found poorer outcomes associated with higher baseline GDF-15 concentrations. This SLR suggests GDF-15 is an independent predictor of mortality and other adverse but nonfatal outcomes in patients with HF. A better understanding of the prognostic role of GDF-15 in HF could improve clinical risk prediction models and potentially help optimize treatment regimens.

* Corresponding author. Washington University School of Medicine in St. Louis, St. Louis, MO, USA.
E-mail address: ali.javaheri@wustl.edu (A. Javaheri).

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1. Introduction

Heart failure (HF) is a complex clinical syndrome caused by structural and functional defects that impair the ability of the heart to provide sufficient blood flow to the body [1]. Despite improvements in the understanding of progressive HF, it remains a life-limiting condition [1]. Several biomarkers including N-terminal pro B-type natriuretic peptide (NT-proBNP), cardiac troponins T and I, and soluble ST2, are commonly used to measure disease severity in patients with HF and predict prognosis [2–4]. Some emerging biomarkers may also provide insight into the underlying mechanisms of HF [5–9]. One emerging biomarker is growth differentiation factor-15 (GDF-15), a stress-inducible member of the transforming growth factor-β cytokine family that exerts various physiological actions, including modulation of inflammatory pathways, immunity, and apoptosis [10,11]. Serum and tissue GDF-15 concentrations are low when a person is in a healthy state, but several cell types, including cardiomyocytes, upregulate expression during injury and disease [10,12,13]. Consequently, the association between GDF-15 concentration and clinical outcomes has been evaluated in many life-changing conditions, such as cancer, diabetes mellitus, and cardiovascular (CV) diseases (including chemotherapy-induced cardiotoxicity) [14–18]. An elevated GDF-15 concentration has been found in clinical studies of patients with HF, and this positively correlates with symptom severity and left ventricular (LV) remodeling [5,19–23]. Previous meta-analyses and systematic literature reviews (SLRs) have found elevated levels of GDF-15 to be a strong prognostic indicator of all-cause mortality and hospitalization in patients with HF [24–26]. Further characterization of the relationship between GDF-15 concentration and other outcomes in patients with HF is warranted, including evaluation of the contemporary evidence. Here we report findings from an SLR summarizing the relationship between GDF-15 and a variety of adverse outcomes in patients with HF, including mortality, hospitalization, and renal dysfunction. This SLR was designed to build on that previously conducted by George et al. by summarizing the findings in a narrative synthesis of studies published since 2014 [25].

2. Methods

This SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [27]. The protocol was developed following the PRISMA Protocol guidelines [28], and the SLR was prospectively registered with PROSPERO, the International Prospective Register of Systematic Reviews (registration number: CRD42022355215).

2.1. Search strategy, eligibility criteria, and information sources

The search strategy was developed to capture the most relevant publications by utilizing prespecified inclusion and exclusion criteria. Publications reporting any outcome associated with GDF-15 in adult patients with HF were included. Any publications where the outcomes were not specific to GDF-15, or that reported only on the association between GDF-15 and biomarkers of HF, were excluded. The full inclusion and exclusion criteria according to population, intervention, comparator, outcomes, and study design are shown in Table S1.

Searches were run in Medline® and Embase® databases on August 23, 2022, initially with no date restriction. Only publications in English were sought, and any duplicated references were removed prior to screening. All studies published prior to January 1, 2014, were removed before screening to avoid summarizing evidence previously captured in the SLR published by George et al. (2016) [25]. Congress abstracts published from January 1, 2020, to August 23, 2022, were identified in Embase® and included.

2.2. Selection process

Using a rigorous, 2-stage screening process, 2 independent reviewers first assessed the titles and abstracts of identified studies for eligibility according to the inclusion/exclusion criteria. The same 2 reviewers conducted a full-text review of all publications selected at the first screening. Any discrepancies were discussed until a consensus was reached or, if necessary, a third reviewer made the final determination. Reasons for exclusion at full-text screening were provided and cross-checked between reviewers. In addition to database screening, reference lists from relevant reviews and papers selected for inclusion in the SLR were screened by a single researcher to identify any publications that may not have appeared in the pre-defined database searches.

2.3. Data extraction and quality assessment

Full papers were obtained and underwent detailed examination; a single researcher extracted relevant data, including study design, region, and patient characteristics and a second reviewer validated all data entries against the source publications. No assumptions were made for missing data. Each outcome was categorized as either cross-sectional (i.e., assessed at the same timepoint as GDF-15 concentration) or longitudinal (i.e., through repeated observations). Risk of bias was assessed for full-text publications using the Cochrane Risk of Bias tool (version 2) for randomized controlled trials (RCTs), the Newcastle-Ottawa Scale for observational longitudinal studies and nonrandomized studies, and the modified Newcastle-Ottawa Scale for cross-sectional studies [29–31]. Results of the included studies were qualitatively synthesized.

3. Results

3.1. Study selection

The number of publications identified at each stage of the search strategy are shown in Tables S2–S4. A PRISMA flow diagram of the screening process is shown in Fig. 1. In total, 756 records (709 publications; 47 conference abstracts) were identified from the database searches. After removal of duplicates (n = 199) and studies published before 2014 (n = 101), the remaining records were screened based on title and abstract, and 383 were excluded. Full texts were retrieved and screened for 73 studies. Overall, 63 publications (55 full papers and 8 congress abstracts) met the pre-defined eligibility criteria and were included in this SLR.

3.2. Study characteristics

Of the 63 publications that met eligibility criteria, 45 were observational and the remaining 18 were post hoc analyses or biomarker sub studies of RCTs. Among observational studies, 29/45 were conducted in Europe and 13/45 in Asia, while most post hoc analyses were from multinational RCTs (13/18).

Among the 35 full-text longitudinal studies assessed for bias, all scored ≥5/9 using the Newcastle-Ottawa Scale, indicating a medium or low risk of bias (Table S5). The most common cause of potential bias was a single-center design. Each of the 3 full-text cross-sectional studies assessed using the modified Newcastle-Ottawa Scale scored ≥6/8, also indicating medium or low risk of bias (Table S6). Of RCTs with reported blinding, this was double in all but 1 study (Table S7).

3.3. Patient characteristics

A summary of relevant patient characteristics from each of the 63 studies is shown in Table S8. Per the inclusion criteria, all publications reported studies that were conducted in adults. The number of patients included in each study varied widely, from 15 to 4548 [32,33]. With the exception of 1 study, with mean age of 39 years [32], mean patient age ranged from 53 to 80 years [34,35]. Sex ratios also varied widely (7 %–82 % female [32,36]), and few studies (17/63) reported race/ethnicity [22,36–51]. Average body mass

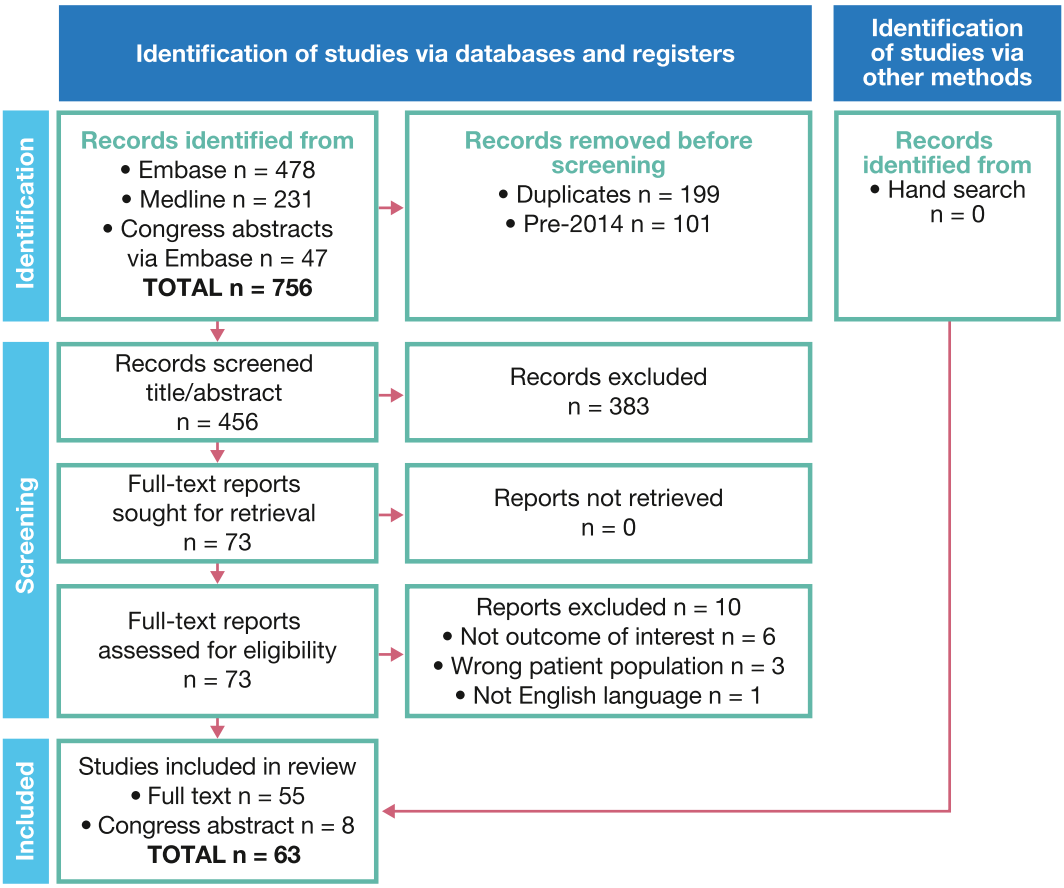

Fig. 1. PRISMA flow diagram.

index (BMI) skewed towards the overweight or obese categories (≥25 kg/m^2), with mean BMI ranging from 20 kg/m^2 to 40.6 kg/m^2 across the 45 studies that included data [10,52]. Only 3 studies reported an average BMI within the healthy range (18.5–25 kg/m^2) [52–54].

Among publications that reported on mean LV ejection fraction (LVEF), this ranged from 22 % to 69 % [32,34,48]. The most frequent cut-off for HF with reduced ejection fraction (HFrEF) was <40 %, which is consistent with the European (2021) and US (2022) guidelines for the management of HF [55,56]. Baseline characteristics were reported separately for patients with preserved ejection fraction (HFpEF; LVEF ≥50%) and mildly reduced ejection fraction (HFmrEF; LVEF 40–49 %) in 21 (33 %) and 4 (6 %) studies, respectively; 32 publications (51 %) reported separate baseline data for patients with HFrEF. The remaining studies reported data for mixed populations or did not provide LVEF status. Over three-quarters of all studies (49/63; 78 %) reported some detail on patient's New York Heart Association (NYHA) class. In most studies, the highest proportions of patients were NYHA class II or III. There was a large range in the proportion of patients with comorbidities, such as ischemic or congestive heart disease (0 %–100 %) [46,57] and diabetes (0 %–58 %) [37,58], and of the 35 studies reporting baseline estimated glomerular filtration rate (eGFR), the mean value ranged from 47 to 89 mL/min/1.73 m^2 [35,59].

3.4. Association between GDF-15 and outcomes

The range of outcomes of interest evaluated in the 63 studies is shown in Fig. 2. Several publications reported more than one outcome, with the most common being mortality, a composite outcome, renal function, and BMI. Pathophysiological measures of HF (e.g., LV mass, left atrial volume, and measures of fibrosis) were reported in 33/63 publications, of which 7 (6 observational and 1 post hoc analysis of an RCT) did not report any other outcomes (for brevity, these studies are not discussed in detail).

The most frequently evaluated outcomes in longitudinal studies were all-cause mortality and a composite outcome of multiple endpoints (all included mortality, most commonly with hospitalization; Fig. 3A). More than half of studies evaluating all-cause mortality, composite outcomes, hospitalization or rehospitalization, cardiac-specific mortality, arrhythmic event, exercise capacity or cognitive found a significant association with baseline GDF-15 concentration in either univariate (UVA) or multivariate analyses (MVA). A number of longitudinal studies also evaluated the association between change in GDF-15 and adverse outcomes, though over a wide variety of timepoints. Among these, 7/8 studies evaluating a composite outcome found a significant association in MVA, 3/4 for all-cause mortality, 2/2 for hospitalization or rehospitalization, 4/4 for cardiac-specific mortality, 1/1 for exercise capacity, and 0/1 for dyspnea.

The most frequently evaluated outcomes in cross-sectional studies were renal function, BMI, and exercise capacity (Fig. 3B). These outcomes showed a significant association with baseline GDF-15 in the majority of studies.

3.5. Outcomes in longitudinal observational studies

A summary of all outcomes, excluding physiological measures, evaluated in the longitudinal observational studies is provided in Table S9. The findings are further described below.

3.5.1. Mortality

The association between GDF-15 and any form of mortality was reported in 32 studies (22 longitudinal and 10 post hoc analyses of RCTs) [5,20–23,33,37–40,42,43,46,48,49,53,57,60–74]. Two studies were congress abstracts that did not describe the type of mortality evaluated and are not discussed for this outcome [73,74]. The most frequently reported mortality outcome was all-cause mortality, which was reported in 27 studies (20 longitudinal and 7 post hoc analyses of RCTS [5,20–23,33,37–40,48,49,53,57,60–72]) while 6 reported on cardiac-specific mortality (5 post hoc and 1 case-control analyses of RCTs [40,42,43,46,49,63]). Of the 27

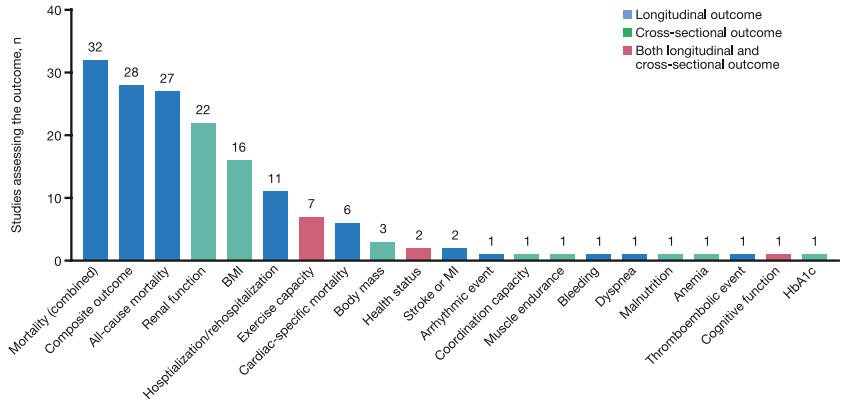

Fig. 2. Number of publications of each type reporting on specific outcomes. Number of publications (n = 33) reporting physiological parameters are not shown. BMI = body mass index; HbA1c = hemoglobin A1c; MI = myocardial infarction.

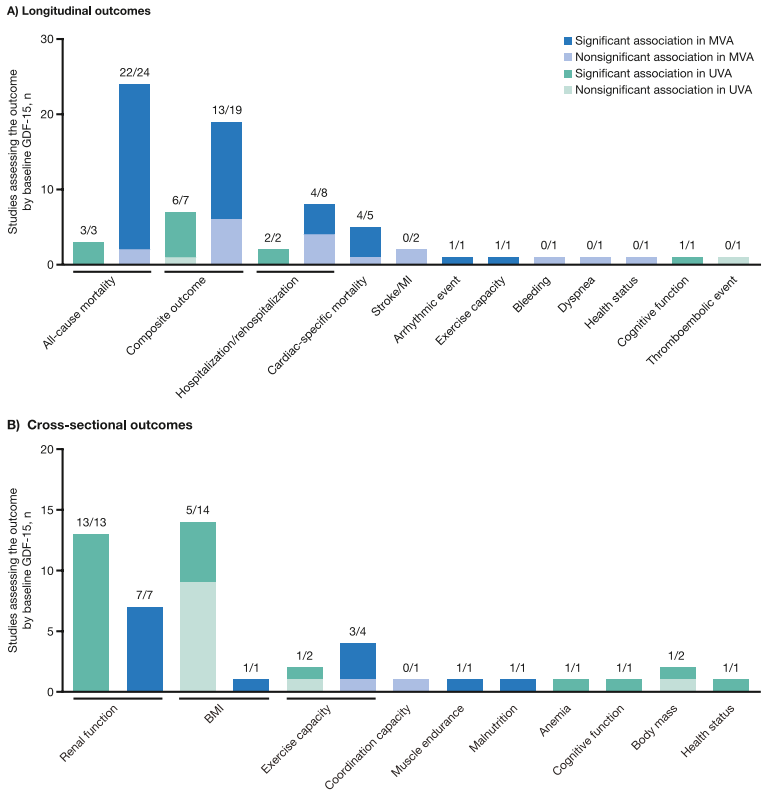

Fig. 3. Significant associations with baseline GDF-15 in observational studies. Panel **A** shows outcomes in longitudinal studies and panel **B** shows outcomes in cross-sectional studies. BMI = body mass index; GDF-15 = growth differentiation factor-15; MI = myocardial infarction; MVA = multivariate analysis; UVA = univariate analysis.

studies reporting on all-cause mortality, 13/27 reported all-cause mortality outcomes in patients with HFrEF [20,22,33,38,40,48,49,57,62,63,67,70,72], 5 in patients with HFpEF [33,60,62,64,67], and 1 in patients with either HFmrEF or HFpEF [21].

Twenty-four of the 27 studies reported mortality associations with baseline GDF-15 concentration using an MVA, in which 22/24 found statistical significance in at least 1 of the cohorts or timepoints (Fig. 4A) [5,20–23,37–40,48,49,53,57,61–65,67–72]. Significant associations with mortality were observed when GDF-15 was assessed both as a continuous variable, as well as by specific cutoff thresholds.

Four studies also reported on the association between a change in GDF-15 and all-cause mortality using MVA, with 3/4 finding a significantly higher risk with higher concentrations. All 4 studies were in patients with HFrEF, and 3 were post hoc analyses of RCTs [20,40,48,49].

The association between GDF-15 and cardiac-specific mortality was reported in 6 studies, all utilizing MVA [40,42,43,46,49,63]. The most common outcome was CV death; however, sudden cardiac death, HF-specific death, and CV non-HF death were also assessed. Four of the 5 studies that looked at the association with baseline GDF-15 concentration found statistical significance (Fig. 4B; one study showing a significant association is not plotted as it reported odds ratio by doubling of GDF-15 concentration: 1.736 [95 % CI: 1.265–2.380]) [40,42,46,49,63]. All four of the studies that looked for an association with change in GDF-15 found statistical significance in MVA at one or more timepoints [40,42,43,49].

3.5.2. Composite outcome

The association between GDF-15 and a composite outcome of multiple endpoints was reported in 28 studies [5,20,22,23,32,37,39–42,45,46,48,49,52,54,57,59,62,63,69,72,75–80]. Of these, 17 were longitudinal studies and 11 were post hoc analyses of RCTs. Death or cardiac-specific mortality was a component of the composite outcome in all studies. The most common composite outcome was mortality and a form of hospitalization/rehospitalization (19/28) [5,22,23,37,39–42,48,49,52,59,62,69,72,76,78–80]. Two of these studies included rehospitalizations related to renal failure/renal causes in their composite outcomes [42,62]. Other endpoints alongside mortality were an urgent heart transplantation or ventricular assist device implantation [75]; a heart transplantation, ventricular assist device implantation, or hospitalization for HF [77]; a lifesaving CV intervention or hospitalization for worsening HF [63]; MI or stroke [46]; MI or rehospitalization for HF [20]; non-fatal MI, stroke, or hospitalization for decompensated HF [54]; severe arrhythmic events [57]; severe primary graft dysfunction [32]; and composite endpoints of multiple (6) CV-related outcomes [45]. Fourteen studies reported composite outcomes in patients with HFrEF [20,22,32,40,45,46,48,49,57,63,72,75,76,80]; 3 in patients

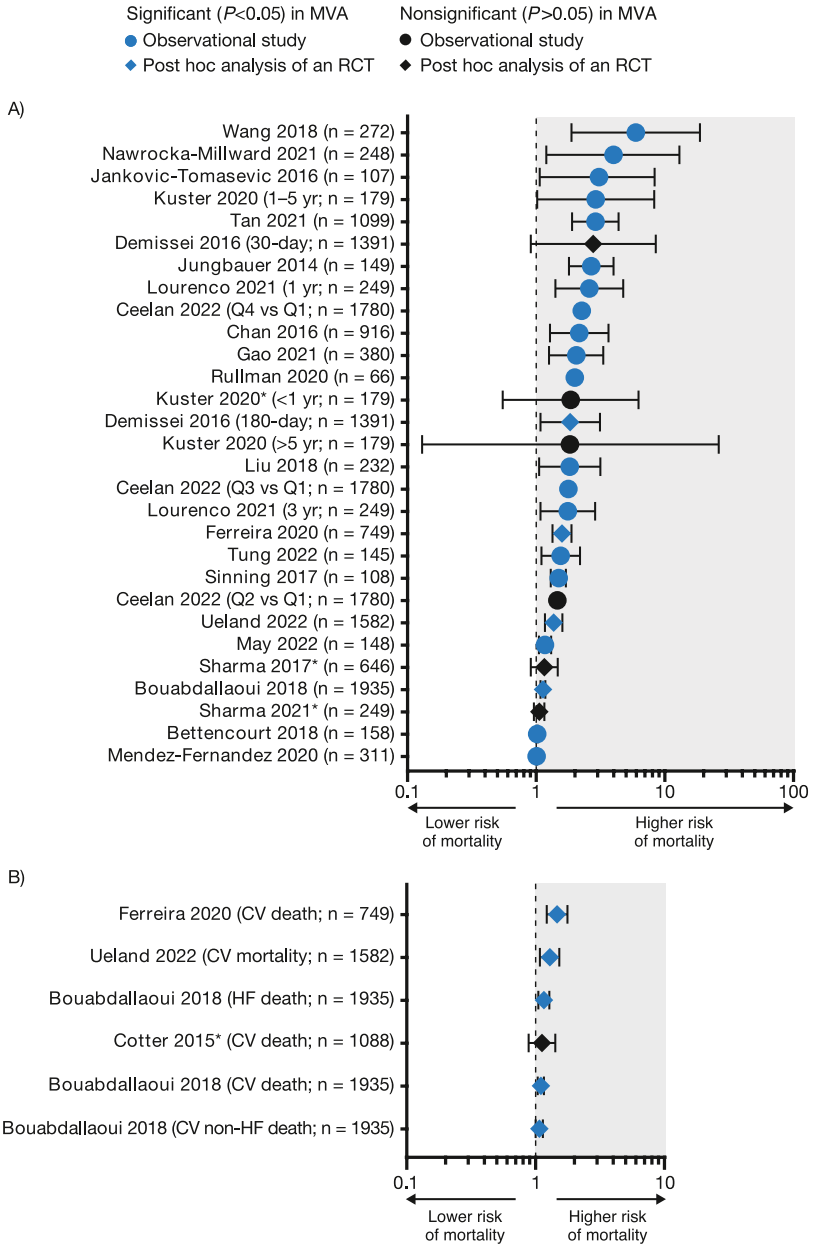

Fig. 4. Hazard ratio for (A) all-cause mortality and (B) cardiac-specific mortality by baseline GDF-15 concentration.
*P < 0.05 in UVA only (data not shown).
Only studies with adjusted HR from MVA analysis are presented. In **A**), findings from 23/24 studies utilizing MVA are plotted. The other publication included GDF-15 alongside N-terminal pro B-type natriuretic peptide concentration in the outcome. In **B**), findings from 4/5 studies utilizing MVA are plotted. The other publication reported odds ratio only. Where relevant data are reported for multiple time points, data are presented as Author, year (mortality timepoint). Where data for both continuous and cut-offs of GDF-15 concentration are reported, only continuous has been presented. CV = cardiovascular; GDF-15 = growth differentiation factor-15; HF = heart failure; HR = hazard ratio; MVA = multivariate analysis; Q = quartile; RCT = randomized controlled trial; UVA = univariate analysis.

with HFpEF [41,54,79]; 1 stratified by HFrEF, HFmEF, and HFpHF [59]; and another stratified by HFrEF and HFpEF [62].

Twenty-six of the 28 studies reported on the association between a composite outcome and baseline GDF-15 concentration: 19 used MVA, and 13 had ≥1 significant finding [5,20,22,23,32,37,39–42,45,46,48,49,52,54,57,59,62,63,69,72,75,77–79]. Several studies found significance after partial adjustment, but this was lost in fully adjusted models. The results from the 13 studies evaluating the risk of mortality or hospitalization/rehospitalization by baseline GDF-15 concentration in MVA are presented in Fig. 5A [5,22,37,39–42,

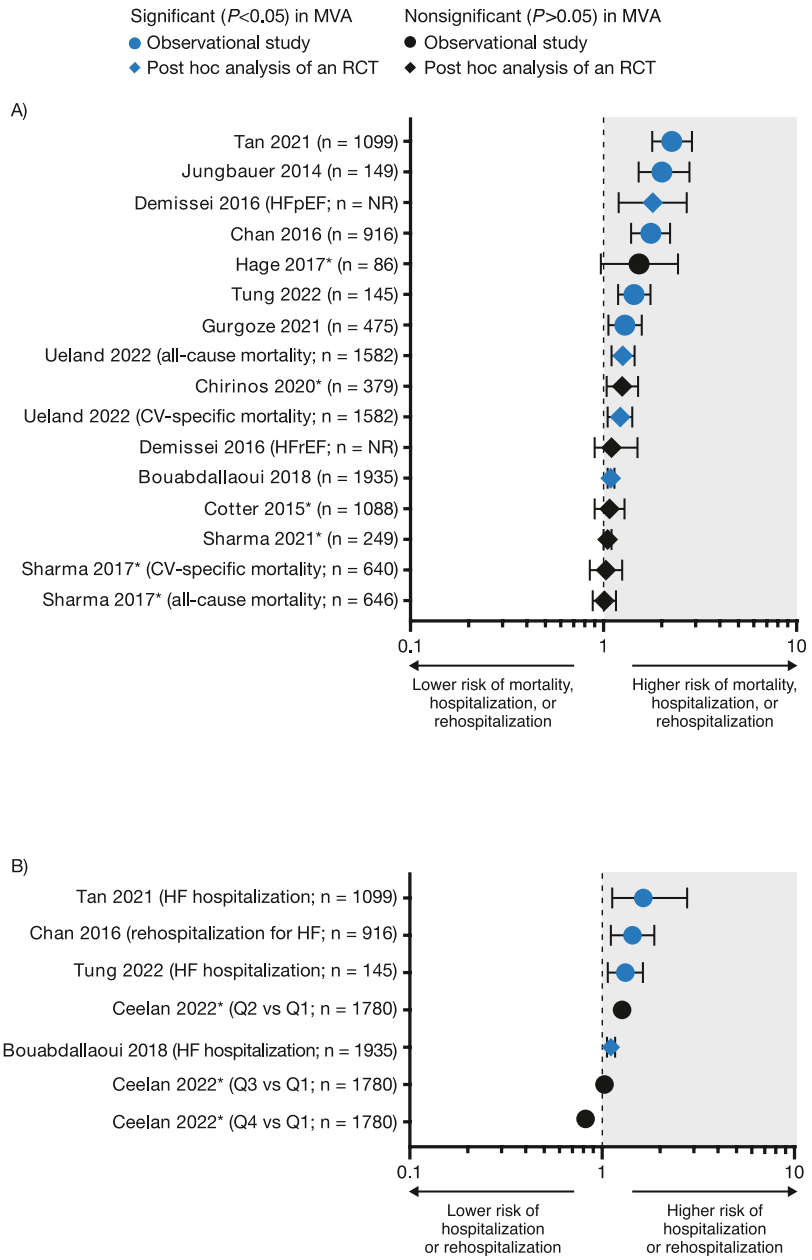

Fig. 5. Hazard ratio for a (A) composite outcome of mortality or hospitalization/rehospitalization and (B) hospitalization/rehospitalization alone by baseline GDF-15 concentration.
*P < 0.05 in UVA only (data not shown).
Only studies with adjusted HR from MVA analysis are presented. In **B**), findings from 5/8 studies utilizing MVA to examine the relationship between hospitalization and baseline GDF-15 concentration are plotted. The other 3 studies did not report a HR, and all associations were non-significant. Where relevant data are reported for multiple time points, data are presented as Author, year (mortality timepoint). Where data for both continuous and cut-offs of GDF-15 concentration are reported, only continuous has been presented.CV = cardiovascular; GDF-15 = growth differentiation factor-15; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; MVA = multivariate analysis; Q = quartile; RCT = randomized controlled trial; UVA = univariate analysis.

48,49,62,72,78,79]. All significant associations showed an increased risk of a composite outcome with higher GDF-15 concentrations. In 1 other study, GDF-15 concentration was found to be a stronger predictor of death, urgent heart transplantation, or ventricular assist device implantation in patients with chronic kidney disease compared with the conventionally used brain natriuretic peptide (BNP) [75]. When GDF-15 was added into the multivariate model, it replaced BNP, which was no longer significant [75].

Eleven of the 28 studies reported the association between a composite outcome and change in GDF-15 concentration, of which 6

reported on a short-term change (<6 weeks), 5 on a long-term change (>6 weeks), and 2 assessed over multiple timepoints [20,37,40,42,48,49,59,76–78,80]. All studies evaluating a defined short-term change in GDF-15 concentration using MVA (n = 4) found a significant association [37,40,42,48]. In the studies evaluating a defined long-term change in GDF-15 using MVA (n = 4), 3 found a significant association [20,37,40,49]. In all studies showing significance, an increase in GDF-15 concentration was associated with an increased risk of reaching the composite outcome.

3.5.3. Hospitalization or rehospitalization

The association between hospitalization or rehospitalizations was reported in 11 studies [23,33,37–40,46,65,66,72,73]. Of these, 8 were longitudinal studies and 3 were post hoc or case-control analyses of RCTs. Hospitalization/rehospitalizations were HF-related in all but one study, where the reason was not specifed [73]. Two studies included separate analyses for non–cardiac-specific hospitalizations [40,66]. Four studies reported the association with hospitalization/rehospitalization in patients with HFrEF [38,40,46,72] and 1 in patients stratified by HFrEF and HFpEF [33], while the others were mixed or did not report LVEF.

Ten of the 11 studies reported on the association between hospitalization/rehospitalization and baseline GDF-15 concentration, of which 8 utilized MVA, and 4 found statistical significance (Fig. 5B; 3 studies that did not report HR are not plotted [all nonsignificant association]) [23,33,37–40,46,65,72,73]. Three studies found significance for HF-related hospitalization/rehospitalization in UVA that was lost in MVA [38,46,65]. All studies showing significance found a higher GDF-15 concentration to be associated with an increased risk of hospitalization/rehospitalization. Two studies assessed hospitalization outcomes based on the change in GDF-15 over time [40,66]. One study found a short-term reduction in GDF-15 levels from admission to discharge in patients with acute HF was associated with a significantly lower risk of rehospitalization over 30 days [66]. The other study found each 20 % increase in GDF-15 was associated with a higher risk of hospitalization, including HF-specific, CV non-HF, and non-CV hospitalization [40].

3.5.4. Other outcomes

Other outcomes were reported in ≤2 studies each (Fig. 2). Two studies reported on the association between GDF-15 concentration and the risk of stroke or MI [40,46]. Both were post hoc or case-control analyses of RCTs that enrolled patients with HFrEF and found a nonsignificant association in MVA [40,46]. One study also looked at the association between stroke/MI and change in GDF-15 concentration, but this was found to be statistically significant in UVA but not MVA [40]. The same study found a significant association between arrhythmic events and baseline GDF-15 in MVA [40]. Another study found a significant association by MVA between baseline and change in GDF-15 concentration, and reduction in 6-min walk test (6MWT) distance [48]. All other outcomes (dyspnea, health status, cognitive function, thromboembolic events, and bleeding) were only tested in UVA or were nonsignificant in MVA [40,42,48,72].

No longitudinal studies reporting on markers of renal function, dialysis, or kidney transplant were identified. Two studies included hospitalization for renal causes as part of the composite outcome, 1 of which also included death due to renal causes [42,62].

3.6. Outcomes in cross-sectional studies

A summary of outcomes (excluding physiological measures) evaluated in cross-sectional observational studies is provided in Table S10. The findings are further described below.

3.6.1. Renal function

The association between markers of renal function and GDF-15 concentration was reported in 22 cross-sectional studies [5,20,22,23,34,35,37,38,40,42,45,47–49,54,61,65,75,76,81–83]. Twelve were conducted in patients with HFrEF [20,22,38,40,45,47–49,75,76,82,83] and 2 in patients with HFpEF [34,54]. The other studies were conducted in mixed populations or did not specify LVEF.

The most common renal outcome was estimated glomerular filtration rate (eGFR) and was reported in 19 studies, of which 17 evaluated baseline associations and 2 used alternative timepoints [5,20,22,23,34,35,37,38,45,47–49,54,65,75,76,81–83]. Only 2/19 studies presented results of an adjusted model, and both found a significant association [5,34]. Lewis et al. reported a regression coefficient of −0.12 (95 % CI: −0.18 to −0.07) when assessing GDF-15 concentration as a predictor of eGFR in a post hoc analysis of an RCT in patients with HFpEF [34]. Jungbauer et al. evaluated the inverse relationship (eGFR as a predictor of GDF-15), finding a regression coefficient of −0.013 in an observational study of patients with HF and mixed LVEF [5]. Both suggest a higher GDF-15 concentration is associated with poorer renal function.

Twelve studies reported on the association between baseline GDF-15 and creatinine concentrations [22,23,35,37,38,40,42,48,49,61,81,83]. Of these, 4 reported findings from MVA, and all found a significant association between higher GDF-15 concentration and higher creatinine concentration, regardless of LVEF status [22,35,37,40]. Chan et al. found a regression coefficient of 0.002 (95 % CI: 0.001 to 0.003) when GDF-15 concentration was evaluated as a predictor of creatinine concentration in an observational study of patients with mixed LVEF [37]. In a post hoc analysis of an RCT that comprised patients with HFrEF, Sharma et al. found a correlation coefficient of 0.35 (0.22–0.48) for the same relationship [22]. Bouabdallaoui et al. also conducted a post hoc analysis of an RCT comprising patients with HFrEF, finding a 4 % increase in baseline GDF-15 concentration for every 10 mg/dL increase in creatinine concentration [40]. Przybylowski et al. evaluated creatinine as a predictor of GDF-15 concentration in an observational study of patients with HF and mixed LVEF, finding a correlation coefficient of 0.28 [35].

Three studies reported on the association between baseline GDF-15 and urea concentration [38,65,81]. Only one utilized MVA, finding serum urea concentration to be a significant predictor of GDF-15 concentration (regression coefficient: 0.37) [81]. One other study reported on the association between GDF-15 concentration and uric acid, and blood nitrogen urea (BUN), both using UVA. A

significant association was found between higher levels of GDF-15 and higher levels of uric acid, and BUN [42].

3.6.2. BMI and body mass

The association between GDF-15 concentration and BMI or body mass was reported in 16 studies [5,20,22,23,34,37,38,42,45,47–49,54,67,75,83]. Nine were conducted in patients with HFrEF [20,22,38,45,47–49,75,83] and 2 in patients with HFpEF [34,54].

Fifteen studies reported on the association between baseline GDF-15 concentration and BMI [5,20,22,23,34,37,38,42,45,48,49,54,67,75,83], and 1 reported on change in both over 12 weeks [47]. The single study that used MVA found patients with a higher baseline GDF-15 concentration also had lower BMI (regression coefficient: −0.02; 95 % CI: −0.008 to −0.03) [22]. In general, findings from UVA conducted in other studies supported this association.

Three studies reported on the association between baseline GDF-15, or change in GDF-15 over 12 weeks, and body mass [38,47,48]. All three studies were conducted in patients with HFrEF but none reported MVA. They found patients with a lower weight tended to have a higher GDF-15 level, and that increase in GDF-15 concentration at 12 weeks was weakly correlated a reduction in weight in UVA.

3.6.3. Exercise capacity

The association between GDF-15 concentration and exercise capacity, performance, or physical function was reported in 6 studies [22,34,36,44,82,84]. The most frequent outcome measures were 6MWT distance [22,34,36,44,82] and maximal oxygen consumption (VO_2) [22,36,44,82]. Other outcomes included the minute ventilation–carbon dioxide production relationship (VE/VCO_2 slope) [22,44], short distance walk speed [36], chair rise time [36], the Short Physical Performance Battery (SPPB) [36], peak metabolic equivalent (MET) [36], time to exhaustion [36], exercise duration [22], and ischemia in an exercise stress test [84]. Two studies were conducted in patients with HFrEF [22,82], 2 in patients with HFpEF [34,36], and 2 in patients stratified by HFrEF and HFpEF [44,84].

Four of the studies reported on the association with baseline GDF-15 concentration and exercise capacity using MVA [22,34,44,84]. A higher baseline GDF-15 concentration was frequently associated with a poorer exercise capacity. In a post hoc analysis of an RCT comprising patients with HFrEF, Fudim et al. found significant associations between higher baseline GDF-15 concentration and lower peak VO_2, lower 6MWT distance, and a higher VE/VCO_2 slope in MVA [44]. Sharma et al. also completed a post hoc analysis of an RCT including patients with HFrEF, finding the same association with peak VO_2 (correlation coefficient: −0.04; 95 % CI: −0.06 to −0.03) in patients with HFrEF [22]. In their post hoc analysis of an RCT comprising patients with HFpEF, Fudim et al. found a significant association between higher baseline GDF-15 concentration and lower peak VO_2 in MVA; however, the associations with 6MWT distance and VE/VCO_2 slope were only significant in UVA [44]. A post hoc analysis of an RCT comprising patients with HFpEF by Lewis et al. reported a correlation coefficient of −0.017 (95 % CI: −0.025 to −0.009) for the relationship between GDF-15 concentration and 6MWT distance in MVA [34]. Stojanovic et al. found a significant association between higher GDF-15 concentration and increased ischemia during exercise testing using UVA in patients with HFrEF, but not HFpEF, but this association was not significant in MVA [84].

Fudim et al. also evaluated the association between exercise capacity and change in GDF-15 concentration in cohorts of patients with HFrEF and HFpEF using MVA [44]. None of the evaluated measures, including VO_2, VE/VCO_2, and 6MWT assessed at 16 weeks in patients with HFrEF and at 24 weeks in patients with HFpEF, were found to be significantly associated with change in GDF-15 concentration [44].

3.6.4. Other outcomes

The association between baseline GDF-15 concentration and other outcomes were each evaluated in a single study, namely muscle endurance, coordination capacity, health status, anemia, cognitive function, and malnutrition (Fig. 2) [34,35,72,85–87]. All found significant associations, mostly using UVA. Three studies used MVA, finding a significant association between higher GDF-15 concentration and lower muscle endurance (correlation coefficient: −54.3 for $\log_{10}$ GDF-15: 95 % CI: −106 to −2.0)[85] and increased malnutrition (odds ratio: 5.81; 95 % CI: 2.43, 17.62) [87]. The association with lower coordination capacity was not significant in MVA, only UVA [86]. One other study reported a nonsignificant association between change in GDF-15 concentration and HbA1c at 12 weeks using UVA [47].

3.7. Physiological outcomes

As previously described, 7 of the identified studies only reported on the association between GDF-15 concentration and physiological measures of HF. Of the other 56 studies included in the outcome summaries above, 26 also included data on physiological measures. The findings of these studies are shown in Table S11. These measures are not considered to be the focus of this SLR and are presented for completeness.

4. Discussion

The concentration of GDF-15 is known to be elevated in patients with HF and positively correlates with symptom severity and LV remodeling; as such, its utility as a predictive biomarker for prognosis is being investigated [5,19–23]. This SLR, which builds on a previous publication by George et al. [25], found a higher concentration of GDF-15 was consistently and significantly associated in MVA with a higher risk of mortality (both all-cause and CV-related), hospitalization/rehospitalization, composite outcomes typically comprising mortality and hospitalization/rehospitalization, and other adverse outcomes including renal dysfunction, lower BMI or

body mass, and poorer exercise capacity.

The previously published SLR by George et al. included 21 studies published between 2007 and 2014 [25]. The search strategy was initially broader than this SLR (search terms of 'GDF-15 AND heart failure') but George et al. subsequently limited the search and excluded studies in patients with specific conditions [25]. Distinct search strategies likely resulted in small differences in study types included in Geroge et al. vs the current SLR. The 21 relevant studies in George et al. included 16 prospective cohort studies, 2 cross-sectional studies, and 3 randomized controlled studies [25]. No assessments of study bias were reported [25]. Overall findings demonstrated that higher GDF-15 concentration was a statistically significant prognostic factor for all-cause mortality in all 9 studies including this outcome as either an individual or composite outcome (HR ranged from 1.0 to 13.4) [25]. Higher GDF-15 concentration was also strongly correlated with left ventricular remodeling in 2 of the 3 studies examining at this outcome [25]. Comparative evaluation against commonly utilized biomarkers for HF, such as NT-proBNP, TnT, and TnI, suggested a value in the addition of GDF-15 to the biomarker monitoring array in order to better characterize the prognosis of patients with HF [25]. Our SLR summarized studies that reported on the association between GDF-15 concentration and adverse outcomes in patients with HF published since the SLR by George et al. We collated data on a range of 19 outcomes of relevance, including mortality, composite outcomes, renal function, BMI, hospitalization/rehospitalization, exercise capacity, body mass, health status, stroke/MI, arrhythmic events, coordination capacity, muscle endurance, bleeding, dyspnea, malnutrition, anemia, thromboembolic events, cognitive function, and HbA1c. Of these, all but health status, stroke/MI, coordination capacity, bleeding, and dyspnea showed $\geq$1 statistically significant association with baseline or change in GDF-15 concentration in $\geq$1 study when assessed by MVA. Body mass, anemia, thromboembolic events, cognitive function, and HbA1c were assessed with UVA only, where all but thromboembolic events and HbA1c showed a statistically significant association with baseline or change in GDF-15 concentration in $\geq$1 study. Several studies additionally showed significance in UVA that was lost on adjustment. Overall, higher GDF-15 concentrations were generally associated with a higher risk of adverse outcomes.

GDF-15 is not a specific biomarker for HF and is expressed at high levels in several conditions such as inflammation, infection, and cancer [10,11,88]. This means it likely increases alongside comorbidity burden and could be a useful marker of overall physiological disruption and subsequent morbidity and mortality in patients with HF. The only known endogenous receptor for GDF-15, glial--derived neurotrophic factor family receptor α-like, is exclusively found in the brain, leading to a lack of knowledge around the intracellular and intercellular signaling pathways activated by GDF-15 in the heart [13]. Many potential signaling pathways have been linked to GDF-15 activities in a wide range of tissues, suggesting heterogeneity in its physiological role [13]. Understanding the potential benefits and harms of GDF-15 necessitates consideration of its role in different disease settings. Its effects may vary depending on the cell type, tissue, disease, and disease phenotype present. Further research is needed to unravel the complex, systemic actions of GDF-15.

Preclinical and clinical studies have revealed controversy surrounding the physiological actions of GDF-15 in the heart. On one hand, it is believed to exhibit cardioprotective effects against cell death, ischemic scar formation, and hypertrophy, while on the other hand it has been linked to cachexia, cardiac fibrosis, ischemia, and atrophy [18,89–95]. Upregulation of GDF-15 may be protective in the settings of acute heart stress, as some investigators have observed GDF-15 knockout mice are predisposed to ischemic injury, while others have shown GDF-15 upregulation impairs cardiac hemodynamics via exacerbated endothelial dysfunction [93,95]. In clinical studies, an elevated GDF-15 concentration has been found in patients with HF, and this positively correlates with symptom severity and left ventricular (LV) remodeling [5,19–23]. An increased understanding of the potential prognostic role of GDF-15 in HF, beyond mortality alone, could improve clinical risk prediction and identify patients with HF who may warrant additional treatment optimization or intensification. Although not a specific biomarker for HF, it is clear from this SLR that GDF-15 is a consistent prognostic biomarker in patients with HF across the LV ejection fraction spectrum. This has led to speculation that elevated GDF-15 could represent a therapeutic target for improvement of outcomes in HF. This hypothesis is now the subject of an ongoing international, multicenter, phase 2 randomized control trial of ponsegromab, a monoclonal antibody directed against GDF-15, in patients with symptomatic heart failure and elevated circulating levels of GDF-15 (NCT05492500) [96].

4.1. Gaps in the literature

While the most frequently reported outcome was mortality or a composite outcome that included mortality, many of the 19 outcomes were only assessed in 1 study, such as arrhythmic events, thromboembolic events, and cognitive function. No studies assessed the association between change in GDF-15 and renal function. Similarly, there were few studies assessing the association between GDF-15 and CV events, such as stroke, MI, or health status. As the 2 studies reporting data on health status both used the Kansas City Cardiomyopathy Questionnaire, use of other measures would provide a more complete assessment.

Heart failure is a heterogeneous condition, arising from many distinct causes and requiring different treatment approaches. The included studies comprised a wide range of patients but most commonly those with HFrEF. Race was not reported in most studies, though the majority were conducted in European populations, which may produce different findings from those in the US, Canada, or other regions. Additional evaluation of GDF-15 concentrations in patients with HFpEF and HFmrEF from a range of racial backgrounds would better inform on the generalizability of these findings. This is particularly important noting the higher prevalence of HF and poorer CV outcomes in populations with Black ancestry [97,98].

4.2. Strengths and limitations

A particular strength of this SLR is the use of a standardized, thorough, and transparent approach to identify and appraise the

included studies, providing a robust and thorough assessment of the published evidence. We captured 63 relevant publications, which is higher than the number included in the previously published SLR by George et al. [25], showing the amount of evidence and interest in this topic is increasing.

Limitations include the considerable heterogenicity that we found between the units used to report GDF-15 concentration (e.g., log-transformed, continuous, categorical, use of cut-off points). Many outcomes were assessed at the same timepoint in cross-sectional analyses, so the temporal association and directional relationship with GDF-15 concentration could not be determined. Further, some studies looked at other outcomes as a predictor of GDF-15, which is the opposite association to that which we hoped to evaluate. Though all evidence helps to build the picture of the relationship between GDF-15 concentration and adverse outcomes in HF, these factors make assimilation of evidence more difficult.

As mentioned previously, HF is a heterogeneous condition. In addition to this, patients with HF often have multiple comorbidities that may independently influence circulating GDF-15 concentrations. While several studies conducted MVA to adjust for cofounders, these were not the same in all studies, and the applicability of these models to our question was not determined. Several studies reported on a composite outcome of multiple endpoints. It is possible the overall risk of composite outcome may have been influenced by some components more than others, which cannot be determined unless the individual endpoints were reported separately.

Finally, we assessed the risk of bias in non-interventional, non-randomized studies, using the Newcastle-Ottawa Scale. We acknowledge that a more precise tool is available (ROBINS-E). Despite all studies showing a medium or low risk of bias using the Newcastle-Ottawa Scale tool, our decision not to use ROBINS-E may have resulted in underestimation of the bias in these studies.

5. Conclusions

Findings from this SLR suggest higher GDF-15 concentration is an independent predictor of mortality and a range of other adverse outcomes in patients with HF. Identification of the role that GDF-15 plays in HF progression will help provide additional clarity around its utility as a prognostic biomarker in this patient population, and also provide further evidence on the potential value of GDF-15 modulating therapies for their treatment. Further longitudinal and mechanistic research into the role of GDF-15 in HF is warranted.

Data availability

This is a review of published literature. Although all are publicly available, some may require purchase or access through an institutional subscription. No new data were synthesized.

CRediT authorship contribution statement

Ali Javaheri: Writing – review & editing, Conceptualization. **Mualla Ozcan:** Writing – review & editing, Conceptualization. **Lauren Moubarak:** Writing – review & editing, Methodology, Conceptualization. **Karen E. Smoyer:** Writing – review & editing, Methodology, Conceptualization. **Michelle I. Rossulek:** Writing – review & editing, Conceptualization. **James H. Revkin:** Writing – review & editing, Conceptualization. **John D. Groarke:** Writing – review & editing, Conceptualization. **Lisa C. Tarasenko:** Writing – review & editing, Conceptualization. **Mikhail N. Kosiborod:** Writing – review & editing, Conceptualization.

Declaration of competing interest

Ali Javaheri, Mualla Ozcan, Lauren Moubarak, Karen E. Smoyer, Michelle I. Rossulek, James H. Revkin, John D. Groarke, Lisa C. Tarasenko, Mikhail N. Kosiborod reports administrative support, article publishing charges, and writing assistance were provided by Pfizer. Ali Javaheri reports a relationship with Mobius Scientific that includes: consulting or advisory and equity or stocks. Ali Javaheri reports a relationship with AstraZeneca that includes: funding grants. Ali Javaheri reports a relationship with Bitterroot Bio that includes: funding grants. Lauren Moubarak reports a relationship with Envision Pharma Group that includes: employment. Karen E. Smoyer reports a relationship with Envision Pharma Group that includes: employment and equity or stocks. Michelle I. Rossulek reports a relationship with Pfizer that includes: employment and equity or stocks. John D. Groarke reports a relationship with Pfizer that includes: employment and equity or stocks. James H. Revkin reports a relationship with Pfizer that includes: employment and equity or stocks. Lisa C. Tarasenko reports a relationship with Pfizer that includes: employment and equity or stocks. Mikhail N. Kosiborod reports a relationship with AstraZeneca that includes: consulting or advisory and funding grants. Mikhail N. Kosiborod reports a relationship with Boehringer Ingelheim that includes: consulting or advisory and funding grants. Mikhail N. Kosiborod reports a relationship with 35Pharma, Alnylam, Amgen, Applied Therapeutics, Bayer, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics that includes: consulting or advisory. Mikhail N. Kosiborod reports a relationship with Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, Sanofi, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, Youngene Therapeutics that includes: consulting or advisory. The study was sponsored by Pfizer. Pfizer contributed to the study design, and in their role as authors, employees of Pfizer were involved in the interpretation of data, preparation, review, and approval of the manuscript and the decision to submit for publication, along with their co-authors. The study sponsors approved the manuscript from an intellectual property perspective but had no right to veto the publication. Medical writing support was provided by Diane Hoffman, PhD, and Jennifer Bodkin, PhD, of Engage Scientific Solutions, and funded by Pfizer. Database searches, screening, data extraction and quality assessment were carried out by Lauren Moubarak, MPharm, and Karen E. Smoyer, PhD, of Envision Value & Access, funded by Pfizer. Ali Javaheri was supported by the Children's Discovery Institute of Washington University and St. Louis

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Appendix A. Supplementary data

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