# GDF 15 - A Novel Biomarker in the Offing for Heart Failure

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**Abstract: *Background*:** Several diagnostic and prognostic biomarkers are being explored in heart failure. GDF-15 belongs to the transforming growth factor β (TGF-β) cytokine family that is highly up regulated in inflammatory conditions. We undertook this systematic review to summarize the current evidence on the utility of GDF-15 as a biomarker in heart failure.

***Design and Methods*:** Multiple electronic databases for studies that reported the association between GDF- 15 and heart failure were searched using different electronic databases such as MEDLINE, Science Direct, Springer Link, Scopus, Cochrane Reviews, and Google Scholar using pre-defined inclusion-exclusion criteria.

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***Results*:** Twenty one original studies were identified that included data from 20,920 study participants. GDF 15 was found to be a strong prognosticator of all-cause mortality in heart failure patients. Several studies found the benefit of using GDF-15 as a component of a multi-biomarker strategy in prognosticating patients with heart failure.

***Conclusion*:** More studies are warranted to elucidate the molecular pathways involving GDF-15 and to see how knowledge about GDF-15 can be used to make therapeutic decisions in the clinic.

**Keywords:** All-cause mortality, cardiac biomarker, GDF -15, heart failure, novel biomarker, prognosis.

## INTRODUCTION

Heart Failure (HF) is a syndrome which is characterized by a diminished ability of the heart to pump optimum amount of blood to meet the body's demand [1]. Improvements in medical and device therapy in the last few decades among patients with coronary artery heart disease have resulted in a steep rise in HF hospitalizations and deaths attributable to HF and expanding costs. Around 23 million people are affected by HF globally. In United States, the prevalence of HF is 4.7 million (1.5% - 2% of the total population) with approximately 550,000 incident cases of HF diagnosed annually. The scenario is not different in Europe, with the prevalence ranging from 0.4% to 2%. The prevalence of HF continues to rise with age and affects 6-10% of people older than 65 years [2]. According to National Health Services, total annual mortality ranges from 10-50% depending on severity [1]. Regrettably, till date, there is no accurate method to prognosticate patients with HF.

The field of biomarkers has attracted intensive investigation in the last decade in the management and care of HF patients. Circulating cardiac biomarkers, reflecting different aspects of the orchestral molecular interplay involved in HF have been sought after, with the prospect that these markers in combination would reveal the signature of the disease [3]. The natriuretic peptides, which include B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), are the approved biomarkers for HF [4]. ST-2, Growth differentiation factor-15 (GDF-15), Pentraxin-3, Galectin-3, Osteopontin [5], are some of the novel biomarkers that have been investigated alone or in combination in the context of HF.

Growth-differentiation factor-15 is a distant member of the transforming growth factor-β (TGF-β) cytokine super family that is constantly expressed in the liver. It is also known as Prostate derived factor (PDF), Macrophage inhibitory cytokine-1(MIC-1), NSAID-activated gene (NAG-1) and Placental TGF-Beta (PTGFB) [6].While the exact function of GDF-15 is still not completely understood, it has been shown to be weakly expressed in all tissue types under normal physiological states [7]. The increased expression of GDF-15 has been observed during pulmonary, cardiac or renal diseases [8, 9].

Experimental studies suggest that various forms of cardiac stress including pressure overload increase the concentration of GDF-15. Animal studies indicate that GDF-15 is protective against cardiac injury by virtue of its anti-hypertrophic [7], anti-inflammatory and anti-apoptotic properties [10]. However, clinical studies in humans indicate that higher concentration of GDF-15 is associated with increased mortality. For example, studies by Lok *et al*. and Kempf *et al*. observe GDF-15 to be a marker of increased mortality in CHF [11, 12]. Furthermore, Lok *et al*. observe GDF-15 to be an even stronger predictor than NTproBNP [12]. Therefore, GDF-15 seems to display an array of different functions, rendering protection at some instances, while simultaneously being associated with poor outcomes. As there is a fair degree of uncertainty with respect to GDF-15's role in HF, we performed this systematic review.

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We have thus collected the evidence from various clinical studies to understand the prognostic utility of GDF-15 as a novel biomarker in CHF. We also looked at the value of GDF-15 in predicting HF in post MI patients and in the community setting.
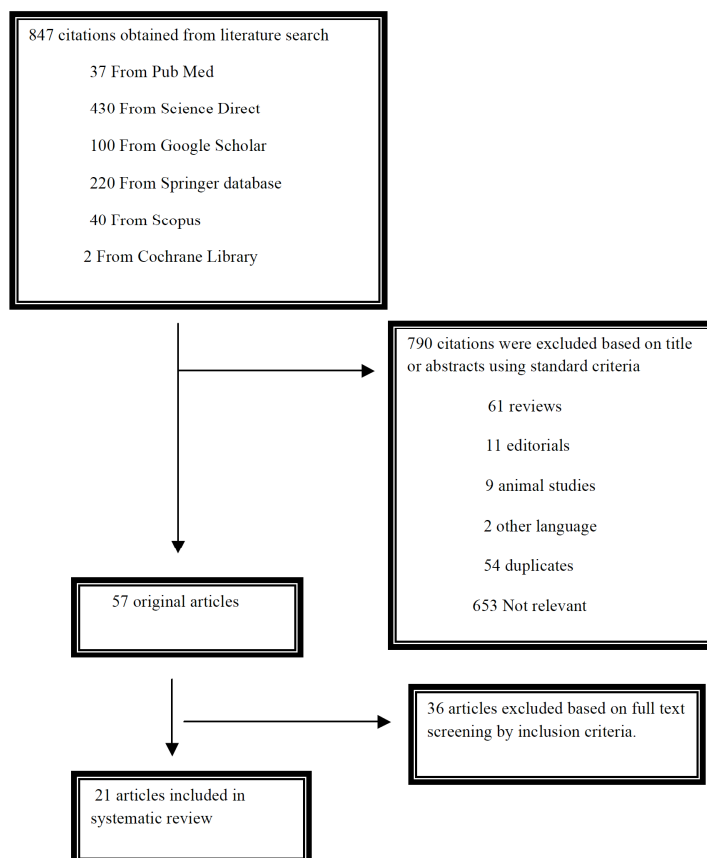
## METHODS

### Literature Search and Selection of Articles

We performed an electronic search using databases such as MEDLINE, ScienceDirect, Cochrane Library, Scopus, Google Scholar and Springer Database. The search term used was "GDF-15 AND heart failure" and we limited our search to human studies in the adult population. We included original studies, describing the association between GDF-15 and HF. We excluded pediatric studies, studies looking at GDF-15 as a sole prognosticator in ACS without incorporating HF as one of the outcomes, studies assessing GDF-15 assay methods, studies done in other populations such as Non-ST elevation myocardial infarction (NSTEMI), valvular heart disease, coronary atherosclerosis, stable coronary artery disease, congenital heart disease, acute pulmonary embolism, idiopathic pulmonary arterial hypertension, diabetic nephropathy, anemia, hypertrophic cardiomyopathy and HF with concomitant conditions such as renal dysfunction and obesity. Furthermore, in-vitro studies, device therapy, cardiac resynchronization therapy, and studies looking at GDF-15 genetic polymorphisms were removed from the final list of selected articles. We also excluded abstracts and poster presentations. References of included studies were also examined in order to ensure that no potential eligible studies

in order to ensure that no potential eligible studies were missed. Three investigators independently extracted information from the title and abstracts of the identified studies and relevant articles were selected for full-text review. Any discrepancies were resolved by consensus.

## RESULTS

We retrieved 847 citations, of which 790 citations were excluded based on title or abstracts. Out of 57 original articles, we identified 21 studies that fulfilled inclusion criteria (Fig. **1**). The studies comprised a total of 20,920 participants, and had 1863 cardiovascular events and 2052 cardiovascular deaths. The baseline characteristics of the studies have been displayed (Table **1**). There were 16 studies with a prospective cohort study design, three with a randomized controlled trial design and two with a cross sectional design. Only 12 studies reported the follow-up duration; the mean of which was 3.87 years. A total of nine studies reported the association between GDF-15 and all-cause mortality. It was found that in all the studies, higher GDF-15 levels independently predicted all-cause mortality (Table **2**). Among the nine studies that assessed the power of GDF-15 to predict mortality, four were performed in HF populations, two in MI and two in community dwelling elderly population. All studies showed the association between elevated GDF-15 levels and increased risk for all-cause mortality even after adjustment with clinical risk factors such as age, sex, body mass index, diabetes mellitus, hypertension, smoking, left ventricular ejection fraction (LVEF), eGFR, BNP, hs-CRP, NYHA, β-blocker, aspirin, & diuretic use.

| 847 citations obtained from literature search |
| --- |
| 37 From Pub Med |
| 430 From Science Direct |
| 100 From Google Scholar |
| 220 From Springer database |
| 40 From Scopus |
| 2 From Cochrane Library |

| 790 citations were excluded based on title or abstracts using standard criteria |
| --- |
| 61 reviews |
| 11 editorials |
| 9 animal studies |
| 2 other language |
| 54 duplicates |
| 653 Not relevant |

| 57 original articles |
| --- |

| 36 articles excluded based on full text screening by inclusion criteria. |
| --- |

| 21 articles included in systematic review |
| --- |

**Fig. (1).** Flow chart of the systematic review.

**Table 1.     Baseline characteristics of patients in selected studies.**

| S.No | Author | Year | Sample size | Study population | Type of Study | Age | Male (%) | e GFR | BMI | GDF-15[*] | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Anand *et al.* | 2010 | 3251 | Symptomatic HF | RCT | 63.2 ±11.6 | 79 | 57.3±17.1 | 27.5± 5.1 | 2040 ng/L | [16] |
| 2 | Kempf *et al.* | 2007 | 455 | CHF | PC | 64 | 90.5 | NM | 25.9 | 1 st quartile- 184–602 ng/L; 2nd quartile-603–763 ng/L; 3rd quartile-764–959 ng/L; 4th quart 960–2241 ng/L | [11] |
| 3 | Lok *et al.* | 2013 | 209 | Chronic HF | PC | 71±10 | 73 | 52±14 | 26±5 | 1606 ng /L | [12] |
| 4 | Peeters *et al.* | 2014 | 622 | Chronic HF | RCT | 76.9±7.6 | 59 | NM | 25.6±4.44 | NM | [33] |
| 5 | Gaggin *et al.* | 2013 | 151 | Chronic HF | PC | GDF)-≤2,000 ng/l ( n = 53) 15-54.2 ±9.9 GDF-15 >2,000 ng/l(n =97)-68.1 ±13.3 | GDF-15-≤2,000 ng/l(n = 53)-43 (81.1) GDF-15 >2,000 ng/l (n =97)-84 (86.6) | GDF-15-≤2,000 ng/l(n = 53)-69.7 ±15.7 GDF-15 >2,000 ng/l(n =97)-55.8 ±21.7 | GDF-15-≤2,000 ng/l (n = 53)-30.3 ±6.8 GDF-15 >2,000 ng/l(n =97)-27.7 ±5.8 | ≤2,000 ng/L | [42] |
| 6 | Richter *et al.* | 2013 | 349 | Advanced HF | PC | 75 | 66.2 | 50.9 | 26.1 | 2600 ng/L | [35] |
| 7 | Wang F *et al.* | 2010 | 208 | HF and controls | CS | 62.37±11.57 | 71.6 | NM | NM | Stage A - 697.5±324.3 ng/L, Stage B - 978.9±278.5 ng/L, Stage C -1302.3± 324.4 ng /L Control - 245.2±101.7ng /L | [37] |
| 8 | Santhanakrishnan *et al.* | 2012 | 151 | HFpEF HFrEF Controls | PC | 63.66±10.47 | 63.4 | 66.6±25.4 | 25.9±4.7 | Controls- 540.09 ng/L (421.23, 840.16) HFpEF- 2528.98 ng/L (1247.14, 349.34) HFrEF- 2672.45 ng/L (1552.48, 493.08) | [39] |
| 9 | Stahrenberg *et al.* | 2010 | 416 | HFpEF HFrEF Controls | PC | HFnEF-73, HFrEF-71, Controls-56 | 45 | HFnEF-60 HFrEF-61 controls-80 | HFnEF-30.1, HFrEF-29.1 controls-25.3 | HFnEF-1660 ng/L, HFrEF-1810 ng/L controls-900 ng/L | [41] |
| 10 | Dinh *et al.* | 2011 | 119 | Mild LVDD, HFnEF, Normal DF. | Cohort | Normal DF-51, Mild LVDD 67, HFnEF-73 | 71.4 | NM | Normal DF- 26, Mild LVDD-28, HFnEF-27 | normal diastolic function - 600 ng/L[500-710], mild LVDD- 780 [620-1040] HFnEF patients 1080 ng/L [880-1300] | [40] |
| 11 | Izumiya *et al.* | 2014 | 149 | LVDD | PC | 69.9 ± 10.0 | 48 | 62.2 ± 17.6 | 24.8 ± 4.1 | 3690 ng/L | [17] |
| 12 | Manhenke *et al.* | 2013 | 236 | AMI and evidence of HF | PC | 67.7±10 | 70 | 72±17 | 26±4 | 2855.59±1785.45 | [3] |

**(Table 1) contd…**

| S.No | Author | Year | Sample size | Study population | Type of Study | Age | Male (%) | e GFR | BMI | GDF-15[*] | Ref. |
|------|--------|------|-------------|------------------|---------------|-----|----------|-------|-----|-----------|------|
| 13 | Khan *et al.* | 2009 | 1142 | Post AMI | PC | 67 | 71.8 | 66.2 | NM | 1470 ng/L | [14] |
| 14 | Dominguez Rodriguez *et al.* | 2011 | 97 | STEMI | PC | 62.8±11.3 | 80.4 | NM | 33.5±7.3 | With LVR-3,439 ng/L (2,391–6,168) Without LVR-1,998 ng/L(1,204–3,067) | [15] |
| 15 | Lin *et al.* | 2013 | 216 | STEMI | PC | GDF <median (N =108)-58.5 (49.2±66.0) GDF >median (N = 108)-61.0 (53.0±73.0) | GDF <median (N =108) -99 (91.7%) GDF >median (N = 108) -92 (85.2%) | NM | NM | NM | [43] |
| 16 | Lind *et al.* | 2009 | 1004 | Elderly individuals | CS | NM | 50 | 74.2 | 26.6 | Quartiles of GDF 15 (<948 ng/L), (948–1134 ng/L), (1135–1390 ng/L), (>1390 ng/L) | [38] |
| 17 | Eggers *et al.* | 2013 | 1,016 | Healthy elderly population | PC | NM | 50 | 79.0 | 27.0 ± 4.4 | 1135 ng/L | [19] |
| 18 | Xanthakis *et al.* | 2013 | 2460 | Healthy individuals (Framingham offspring) | PC | 58±9.44 | 43.2 | NM | 27.4±4.6 | Men - 1016 ng/L, Women -991 ng/ml | [44] |
| 19 | Daniels *et al.* | 2011 | 1740 | Community dwelling adults with no heart disease | PC | 71 ±11 | 39 | NM | 25.4± 4.0 | Quartiles (962 ng/L), (962–1268 ng/L), (1269–1780 ng/L), (1780 ng/L) | [13] |
| 20 | Wang TJ *et al.* | 2012 | 3428 | Framingham cohort | PC | 59±10 | 46.9 | NM | 27.9±5.1 | Men- 1066 ng/L, Women-1022 ng/L | [34] |
| 21 | Bonaca *et al.* | 2011 | 3501 | ACS | RCT | 58.1 ±11.1 | 78.9 | NM | 29.50±5.66 | GDF-15 Cut off point (1200, 1200–1800, and 1800 ng/L) | [36] |

Data are presented as mean±standard deviation, percentage or as median.
HF, heart failure; AMI, acute myocardial infarction; STEMI, ST elevated myocardial infarction; ACS, acute coronary syndrome; LVDD, left ventricular diastolic dysfunction; CHF, chronic heart failure; HFnEF, heart failure with normal ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; DF, diastolic function; LVR, Left ventricular remodelling; PC, prospective cohort; RCT, randomized controlled trial; CS, cross sectional study; eGFR, estimated glomerular filtration rate; NM, Not mentioned;*GDF – mean, median and cut off.

**Table 2. Studies which link GDF-15 and mortality.**

| Author (year) | Study population | Sample size | Outcome measures | Follow- up period (years) | Total Deaths | Findings | Ref. |
|---------------|------------------|-------------|------------------|---------------------------|--------------|----------|------|
| Anand *et al.* (2010) | HF | 1734 | Mortality | 1 | 367 | Baseline GDF-15 remained independently associated with an increased risk of mortality (adjusted HR, 1.010; 95% CI, 1.006 to 1.015; P< 0.001) | [16] |
| Kempf *et al.* (2007) | CHF | 455 | All-cause mortality | 3.33 (IQR: (1.16- 6.5) | 117 | GDF-15 remained an independent predictor of mortality (adjusted hazard ratio for1Unit in the Ln scale 2.26; 95% CI- 1.52 to 3.37; p < 0.001) | [11] |

| Author (year) | Study population | Sample size | Outcome measures | Follow-up period (years) | Total Deaths | Findings | Ref. |
|---|---|---|---|---|---|---|---|
| Lok *et al.* (2013) | Chronic HF | 209 | All-cause mortality | 8.4 (7.8-9.8) | 151 | Elevated concentrations of GDF-15 (HR: 1.41, CI 1.1 to 178, p <0.005) were independently related to mortality | [12] |
| Eggers *et al.* (2013) | Healthy elderly population | 1,817 | All-cause mortality | 8.0 (7.1-8.9) | 111 | Adjusting for established cardiovascular risk indicators GDF-15 independently predicted all-cause mortality with a HR of 4.0 (95% CI 2.7– 6.0), P < 0.001 | [19] |
| Daniels *et al.* (2011) | Community dwelling older adults without heart disease | 1391 | All-cause mortality & CVD and non CVD | 11 | 436 | GDF-15 was a stronger predictor of all-cause mortality than either NT-proBNP or C-reactive protein (HR [95% confidence interval] per SD logunits 1.5[1.3 to 1.8], *P*<0.0001 for GDF-15 versus 1.3 [1.2 to 1.5], *P*<0.0001 for NT-proBNP; C-reactive protein was not a significant predictor | [13] |
| Khan *et al.* (2008) | Post AMI | 1142 | Death or HF | 1.38 | 140 | GDF-15 (ln [GDF-15]) (HR: 1.77; 95% CI: 1.03-3.05; p=0.039) is an independent predictor of death or heart failure post-acute myocardial infarction | [14] |
| Izumiya *et al.* (2013) | LVDD | 149 | All-cause mortality | 1.89 | 31 | GDF-15 (ln [GDF-15]) (HR: 4.74; 95% CI: 1.26-17.88; p=0.022) is an independent predictors of risk of death and cardiovascular events. | [17] |
| Bonaca *et al.* (2011) | ACS | 3501 | Death or recurrent MI | 2 | NM | After adjustment for important clinical covariates, patients with a GDF-15 >1800 ng/L were at significantly higher risk of death or MI (adjusted HR: 1.66 [95% CI, 1.16 to 2.38]; P <0.005;) | [36] |
| Lin *et al.* (2013) | STEMI | 216 | all-cause death and readmission to hospital for HF | 2.33 | 7 | The independent predictors of all-cause death and HF were age (hazard ratio [HR], 1.06; 95%confidence interval [CI], 1.01–1.12, P = 0.014), ln GDF-15 levels (HR: 13.39, 95% CI, 2.80–63.89,P = 0.001) and diabetes mellitus (HR: 9.77, 95% CI, 2.87–33.30, P < 0.001) | [43] |

GDF 15, growth differentiation factor; HF, heart failure; AMI, acute myocardial infarction; HR, hazard ratio; MI, myocardial infarction; CI, confidence interval; CVD, cardiovascular death; LVDD, left ventricular diastolic dysfunction; CHF, chronic heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACS, acute coronary syndrome; NM, Not mentioned;

Eight studies compared GDF-15 with other biomarkers (Table **3**). NTproBNP was most commonly used to ascertain the incremental utility of GDF-15. In addition to this, other established biomarkers used for comparison included TnT, TnI and hsCRP. A gamut of novel biomarkers such as Galectin-3, ST2, Fractalkin, Monocyte chemo attractant protein-1 (MCP-1) C-terminal pro-endothelin-1 (CT-pro-ET-1), C-terminal telopeptide of type I collagen (ICTP), C-terminal provasopressin (CT-pro-AVP), to name a few were also used for comparison.

The ability of GDF-15 to predict LV remodeling (Supplementary Table **1**) was also investigated in 3 studies, with a strong correlation being observed in two of these studies, suggesting GDF-15 as an independent marker for LV remodeling. Both the studies observed the correlation of LV remodeling through echocardiography. The diagnostic ability of GDF-15 was observed in two studies, with a combination of GDF-15 and NTproBNP being able to differentiate Heart Failure with Preserved Ejection Fraction (HFpEF) and Heart Failure with Reduced Ejection Fraction (HFrEF) from controls better than either of the biomarkers alone.

## DISCUSSION

GDF-15, a cytokine belonging to the TGF-β family [10] has been investigated in various populations to determine its utility as a marker of adverse outcomes especially in the context of HF. In the HF, Acute Coronary Syndrome (ACS), and community based populations considered in this review, GDF-15 demonstrated its ability to predict mortality and cardiovascular events such as HF hospitalization [11, 13, 14]. GDF-15 was also found to be associated with deteriorating cardiovascular function, as measured by echocardiographic indices [15]. These studies have also ascertained its incremental ability to traditional cardiovascular risk factors and established biomarkers to predict outcomes of mortality and HF.

## GDF-15 and Mortality

High levels of GDF-15 were predictive of all-cause mortality in HF, ACS and healthy populations. The Rancho-Bernado study, a community based study observed that high GDF-15 levels were predictive of cardiovascular mortality, a

**Table 3.** **Studies which compare GDF-15 with other biomarkers.**

| Author | Study population | Sample size | Comparitive biomarkers | Findings | Ref. |
|---|---|---|---|---|---|
| Khan *et al.* (2008) | Post AMI | 1142 | NT-proBNP | GDF-15 levels were correlated with NT-proBNP (r =0.47, P, 0.001). Combining these markers yielded an AUC of 0.81 (95% CI: 0.77–0.85), which exceeded that of GDF-15 (P, 0.001) and NT-proBNP (P, 0.004) alone | [14] |
| Lok *et al.* (2013) | Chronic HF | 209 | NT-proBNP, hs-CRP, galectin-3, and hs-TnT | GDF-15 was significantly better than NT-proBNP in predicting mortality (p<0.001). GDF-15 and showed to be of significant additive value when combined with NT-proBNP (p<0.001) | [12] |
| Manhenke *et al.* (2011) | AMI and evidence of HF | 236 | 37 circulating markers | A combination of GDF 15 with MR-proADM, sTNFR 1, CT-pro-ET-1, ICTP, CT-pro-AVP, Uric acid, CGA, PIIINP are strongest predictors of total mortality, CV deaths & myocardial re-infarction | [3] |
| Gaggin *et al.* | Chronic HF | 151 | sST2, GDF-15, and hsTnT | sST2 biomarker concentrations added incremental prognostic information to baseline (p = 0.01); such findings were not seen with GDF-15 (p = 0.19) or hsTnT (p =0.91) | [42] |
| Richter *et al.* (2012) | Advanced HF | 349 | Fractalkin, HGF, sFAS, sTRAIL, MCP-1, sTWEAK, PEDF, Myeloperoxidase, hsTNF-α, M-CSF, hsG-CSF | A multibiomarker score combination of chemokine Fractalkin, HGF, GDF-15 ,the 2 pro-apoptotic molecules sFAS and sTRAIL had strong discrimination power for 5years mortality with AUC of 0.81 (95% CI: 0.76–0.85; p<0.001) | [35] |
| Santhanankrishnan *et al.* (2012) | Controls, HF with preserved EF, HF with Reduced EF | 151 | ST2, hs-TnT, and NT-proBNP | The combination of NT-proBNP and GDF-15 gave an AUC of 0.956 [95% CI 0.919–0.994; P <0.001). This was not different from that of GDF-15 alone (p=0.31) or NT-proBNP alone (p=0.33) | [39] |
| Wang TJ *et al.* (2012) | Ambulatory individuals | 3428 | sST2, hs-TnI, BNP, and hs-CRP | The multi marker score comprising of soluble ST2 and the high-sensitivity troponins. The highest quartile had 3-fold risk of death (p<0.001), 6-fold risk of heart failure (p<0.001), and 2-fold risk of cardiovascular events (p=0.001). Addition of the multimarker score to clinical variables led to significant increases in the c-statistic (p=0.007 or lower) and net reclassification improvement (p=0.001) | [34] |
| Xanthakis *et al.* (2013) | Healthy individuals (Framingham offspring) | 2460 | sST2, hsTnI and BNP | The C-statistic for the composite outcome increased from 0.765 with risk factors to 0.770 adding BNP, to 0.774 adding novel bio-markers. NRI was 0.212 (95% CI: 0.119 to 0.305, P<0.0001) after adding the novel biomarkers to risk factors plus BNP | [44] |

GDF 15, growth differentiation factor; HF, heart failure; AMI, acute myocardial infarction; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide ; AUC, area under curve; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T ; MR-proADM , Mid-regional pro-adrenomedullin; sTNFR 1, Soluble tumor necrosis factor receptor; CT-pro-ET-1, C-terminal pro-endothelin-1; ICTP, C-terminal telopeptide of type I collagen; CT-pro-AVP, C-terminal provasopressin (co-peptin); CGA, Chromogranin A; PIIINP, Procollagen type III N-terminal; sFAS, soluble apoptosis-stimulating fragment; HGF, the angiogenic and mitogenic hepatocyte growth factor; sTRAIL, soluble tumor necrosis factor-related apoptosis-inducing ligand; MCP-1, monocyte chemoattractant protein 1; sTWEAK, soluble tumor necrosis factor-like weak inducer of apoptosis; PEDF, pigment epithelium-derived factor ; hsTNF-α, high sensitive tumor necrosis factor-alpha; M-CSF, macrophage colony-stimulating factor; hsG-CSF, high sensitive granulocyte colony-stimulating factor; sST2, Soluble ST-2; hsTnI, high-sensitivity troponin I; BNP, B-type natriuretic peptide; NYHA, New York Heart Association.

decade after measurement in populations with no CV-risk. The authors deliberate whether elevated levels indicate the involvement of GDF-15 in the long pathobiological processes that eventually result in cardiovascular events [13]. Similar findings were observed in the Womens Health study, where elevated GDF-15 levels contributed a two-fold greater risk in the development of CV events [16-18]. Serial measurements of GDF-15 have also shown to predict all-cause mortality, enhancing the predictive ability of the marker. This has been observed in both HF and community based studies [16, 19]. In a large community based study, it was found that >40% change in GDF-15 levels was associated with a four-fold increased risk of mortality [19].

While GDF-15 emerged as a predictor of all-cause mortality and CVD, it was also associated with non-cardiac conditions. There is abundant evidence to show that GDF-15 is highly expressed in several malignancies such as pancreatic, breast, ovarian, colorectal and gastric cancers, melanoma and glioblastoma [20-24]. Therefore, one has to be wary while interpreting endpoints of all-cause mortality. As a consequence, GDF-15 is not considered to be a cardiac specific marker. In agreement with this, expression studies have shown that cardiac mRNA and protein expression of GDF-15 are very low [25]. While this may pose as an impediment to its application in the clinic, the argument lies in its utility in HF populations. HF being a systemic condition, a multi-

marker panel including markers reflecting cardiac and systemic abnormalities might prove useful in prognosticating this patient population, providing information that is incremental to cardiac specific markers [16].

In-vivo studies suggest that GDF-15 is cardioprotective, and that its expression reflects the onset of cardiac damage and its participation in the mitigation of damage [7, 10]. Infusion of recombinant GDF-15 in GDF-15 gene targeted mice under the stress of ischemia or reperfusion injury prevent cardiomyocyte cell death [10]. In addition, overexpression of heart-specific GDF-15 induced pressure overload induced hypertrophy in mice [7]. Counter intuitively, elevated GDF-15 levels are accurate predictors of mortality in humans, raising the question whether elevated GDF-15 levels mediate myocardial damage or do they reflect the body's protective but unsuccessful attempt at mitigating damage. GDF-15 acts via the SMAD dependent and SMAD independent pathways with SMAD dependent pathways being implicated in a number of pathological conditions of the heart. Knockout of SMAD4 (Transcriptional mediator of SMAD dependent pathways) in mice resulted in hypertrophy and HF suggestive of its cardio-protective role. However, owing to its affinity to Type I and II TGF-β receptors and the SMAD receptors, GDF-15's function may indeed depend on the presence of these receptors thereby contributing to the heterogeneity in GDF-15's role [7, 26].

GDF-15 is expressed in a variety of cell types and tissues, and its expression is regulated by the p53 enzyme system [27]. GDF-15 has been implicated in cardiovascular and cancer mortality and its expression has been shown to be reflective of oxidative stress, inflammation, and repair [8, 27, 28]. Since the p53 enzyme system is a mediator in cardiovascular and cancer pathobiology, elevated levels of the biomarker may be indicative of the requirement of repair even before organ-specific damage has occurred, thereby providing the opportunity of early intervention in diseases with high mortality such as CVD and cancer [29].

## GDF-15 and other Biomarkers

The natriuretic peptides, markers of myocardial strain, have surfaced as efficient prognostic and diagnostic biomarkers [30, 31]. However, their measurements have broad intra-individual variability [32], making it a significant hurdle in its utilization. Moreover, natriuretic peptides are produced in response to wall stress, and their elevated levels do not give information about the etiology and intensity of myocardial distress [12, 32]. Till date most scientific societies have not included natriuretic peptide measurement in clinical practice guidelines. In the context of HF, there is increasing consensus that a multi-marker panel, with each marker reflecting distinct patho-physiological processes that occur during HF will be incremental to one cardiac-specific marker [16]. Therefore, studies performed in cardiovascular disease populations and in the community have explored the additional prognostic value offered by GDF-15, incremental to conventional markers of CV risk, clinical signs and symptoms, NTproBNP, hsCRP, troponins, and a gamut of other novel biomarkers.

Most studies evaluate the incremental ability of GDF-15 to NTproBNP. Studies observed that the addition of GDF-15

improves the C-statistic of NTproBNP, thus offering additional value [12, 13, 19]. A combination of NTproBNP and GDF-15 surpassed the ability of either of the biomarkers alone in predicting all-cause mortality [14]. Addition of GDF-15 also improved the Net Reclassification Index [19]. In a community study, participants who had elevated levels of both GDF-15 and NTproBNP had a higher risk of mortality. Participants with elevated levels of either of the biomarkers had an intermediate risk, while those with low levels of both biomarkers had significantly low risk of mortality indicating the utility of these two biomarkers in risk-stratification [13]. The additional value provided by GDF-15 to other conventional biomarkers such as troponins and hsCRP were also documented by these studies [12].

Exploratory factor analysis of a panel of 37 biomarkers to predict adverse events in the post MI population was conducted. GDF-15 along with Midregionalpro-adrenomedullin (MR-proADM), Soluble tumor necrosis factor receptor (sTNFR), C-terminal pro-endothelin-1 (CT-pro-ET-1), C-terminal telopeptide of type 1 collagen (ICTP), C-terminal provasopressin (CT-proAVP) , Uric acid, Chromogranin A (CGA), Procollagen type III N-terminal (PIIINP) were clustered as one factor, indicating high collinearity between them. This group of biomarkers emerged to be strongest in predicting all-cause mortality and the combined end point of CV death and myocardial reinfarction. Their incremental ability was observed even after adjustment with several clinical covariates in multivariate analysis mirroring the ability of this set of biomarkers to accurately reflect several pathophysiological processes following MI [3]. A panel of biomarkers NTproBNP, hsTnT, cystatin-C, GDF-15 and CRP did not correlate with clinical signs and symptoms of NYHA class, oedema, rales, jugular venous distention and orthopnoea showing that the information provided by biomarkers is distinct to that available from clinical signs and symptoms, and their measurement would positively influence clinical judgement [33]. In addition to this, multi biomarker scores integrating biomarker information for efficient patient prognosis have been studied, demonstrating the practical applicability of the biomarker tests [34, 35].

Unlike other markers of myonecrosis which follow a rise and fall pattern, GDF-15 is relatively stable, presenting few difficulties to bring the marker into clinical use [36]. Although, GDF-15 and NTproBNP together predict CV death/ all-cause mortality, GDF-15 has emerged as a significant predictor of non-cardiovascular death and cancer, independent of other biomarkers [13] possibly because GDF-15 acts as a downstream mediator in pathways common to these conditions. Pathobiological pathways of oxidative stress and inflammation, common to cardiac and non-cardiac diseases probably elicit GDF-15 expression via p53 pathways [29]. Due to the diverse information provided by the markers encompassing different aspects of HF, a multi-marker panel might prove to be clinically useful for the prognosis of HF.

## GDF-15 and LV Remodeling

LV remodeling (LVR) refers to the process by which there is change in ventricular structure leading to altered chamber configuration and ventricular volume. This develops as a response to myocardial injury and wall stress. A

strong correlation was observed between GDF-15 and LVR using echocardiography suggesting GDF-15 could be involved in LV remodeling [15, 37]. While Wang F *et al.* considered the elevation of left ventricular mass index as an indicator of LV remodeling in HF populations [37]. Dominguez-Rodriguez *et al.* -considered>20% increase in the left ventricular end diastolic volume compared to baseline, to reflect LV remodeling in ST elevated myocardial infarction population [15]. GDF-15 was associated with LVR at 12 months follow-up in these patients, 22% of whom were successfully reperfused and/or were under secondary preventive measures [15]. GDF-15 levels have also been shown to affect LV geometry, with high levels detected in patients with abnormal LV geometry. With increasing levels of GDF-15, greater remodeling and hypertrophy were detected [38].

As mentioned before, GDF-15 was highly expressed in cardiomyocytes in conditions of mechanical stretch and ischemiain animal models. GDF-15 gene targeted mice showed enhanced hypertrophic response and a pronounced loss in ventricular performance when subjected to pressure overload suggesting its anti-hypertrophic and anti-remodeling action [7, 8]. However, in human studies, the responses observed is contrary to what is found in animals. If GDF-15 is indeed anti hypertrophic and anti-remodeling in function, increased levels of the biomarker must, intuitively, indicate improved ventricular performance and normal LV geometry. This raises the debate on whether GDF-15 is triggered post myocardial damage, and if this response is inadequate to prevent disease progression or whether GDF-15 itself is a mediator of LV damage. However it is noteworthy that the studies assessing the relationship between echocardiographic parameters and GDF-15 considered in this review have a similar limitation of a reduced sample size. As there is a dearth of data on GDF-15 and LV remodeling, it is imperative that more prospective studies are carried out to establish the suitability of GDF-15 as an independent predictor of LV remodeling.

### GDF-15 and Diastolic Dysfunction

The diagnostic capability of GDF-15 to differentiate HFpEF from HFrEF and controls was evaluated [39-41]. While the diagnostic power of GDF-15 and NTproBNP to differentiate HFpEF from control populations was equal, the ratio of NTproBNP and GDF-15 provided a superior capacity to distinguish HFpEF from HFrEF [39]. GDF -15 was also seen to correlate with structural and functional indices of diastolic function such as Left ventricular mass index (LVMI), Left arterial volume index (LAVi) and E/e. The capacity of GDF-15 to distinguish normal diastolic function from asymptomatic diastolic dysfunction (DD grade I) has also been studied, with increasing concentrations of GDF-15 observed with increasing severity of diastolic dysfunction [40].

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The concentration of GDF-15 was found to increase with the worsening stages of HF, with higher levels found in Stage B than Stage A. Since stage B HF is asymptomatic, diagnoses is made only after the patient progresses to more advanced stages of HF. Therefore, GDF-15 may be useful as

a marker of HF for patients that do not show signs and symptoms of HF yet, but will eventually progress to advanced stages of HF [37]. The etiology of HF also seemed to influence the predictive ability of GDF-15, with the biomarker being a stronger predictor of all-cause mortality in HF with non-ischemic etiology [16]. Further studies are warranted in these areas, to determine the ability of HF to diagnose Stage B HF and, to document the influence of ischemic etiology on the prognostic ability of GDF-15.

### LIMITATIONS

Our systematic review is not without limitations. The heterogeneous nature of the studies did not offer us scope for performing meta-analysis. Most of the studies available for our systematic review originally had a clinical trial design, and thus their inclusion-exclusion criteria could strongly influence the results. Almost all studies were done in Caucasian populations and their results may not be generalizable. Some of the studies had a low sample size and thus the results have to be interpreted with caution. We did not include studies dealing with the effect of interventions on the GDF-15 concentration nor did we consider all end points used in the different studies but instead focused primarily on mortality, LV remodeling and comparison with other biomarkers.

### CONCLUSION

There is reasonable evidence to suggest that GDF-15 is an independent predictor of all-cause mortality in HF. GDF-15 may offer additional value in predicting the risk of HF and death in post MI patients. A multi-biomarker strategy with GDF-15 as one of the components may be superior to the conventional risk scores especially for systemic conditions such as HF. On a biological scale, the exact role of GDF-15 in the pathophysiology of HF remains to be elucidated. It is also essential to carry out studies to see how information available about GDF-15 can be used in arriving at therapeutic decisions in HF management.

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### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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### SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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