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Association of Fibroblast Growth Factor 23 With Recurrent Cardiovascular Events in Patients After an Acute Coronary Syndrome

A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Elevated fibroblast growth factor 23 (FGF-23) concentrations are associated with myocardial fibrosis and renin-angiotensin system upregulation, potentially providing prognostic information distinct from standard cardiovascular (CV) biomarkers.

OBJECTIVE To evaluate the association of FGF-23 with recurrent CV events in patients after an acute coronary syndrome (ACS).

DESIGN, SETTING, AND PARTICIPANTS C-terminal FGF-23 was measured in plasma samples using an established enzyme-linked immunosorbent assay system for 4947 patients within 30 days of ACS (median, 14 days) and with 1 additional CV risk factor in the Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial of the lipoprotein-associated phospholipase A_2 inhibitor darapladib vs placebo performed from December 1, 2009, to April 24, 2014 (median follow-up, 2.5 years). Analyses were adjusted for clinical risk factors, renal function, and established cardiorenal biomarkers. This secondary analysis was performed from September 25, 2014, to October 1, 2017.

EXPOSURE The FGF-23 concentration at baseline.

MAIN OUTCOMES AND MEASURES The primary end point for this post hoc analysis was the composite of CV death or hospitalization for heart failure.

RESULTS In this study, baseline FGF-23 concentrations were available for 4947 patients (median age, 64.0 years; interquartile range, 59.0-71.0 years; 1276 [25.8%] female). Patients with higher FGF-23 concentrations were older and more likely female, with a greater proportion of hypertension, diabetes, and previous myocardial infarction. After multivariable adjustment for baseline clinical characteristics and established biomarkers (high-sensitivity troponin I, brain-type natriuretic peptide, and high-sensitivity C-reactive protein), FGF-23 concentration in the top quartile was independently associated with an increased risk of CV death or heart failure hospitalization (adjusted hazard ratio [HR], 2.35; 95% CI, 1.82-3.02; $P < .001$) and its individual components. Elevated FGF-23 concentration was also associated with an increased risk of all-cause mortality (adjusted HR, 2.27; 95% CI, 1.73-2.97; $P < .001$) and CV death, myocardial infarction, or stroke (adjusted HR, 1.42; 95% CI, 1.17-1.71; $P < .001$). When analyses were stratified by patient sex, the association between FGF-23 and CV risk, including CV death or heart failure, appeared to be attenuated in women (adjusted HR, 1.11; 95% CI, 0.70-1.76; $P = .67$) compared with men (HR, 3.11; 95% CI, 2.29-4.22; $P < .001$; $P < .001$ for interaction).

CONCLUSIONS AND RELEVANCE In patients stabilized after ACS, elevated FGF-23 concentrations may be associated with recurrent major CV events and all-cause mortality, providing information independent of established clinical risk factors and cardiorenal biomarkers. A potential sex difference in these findings deserves further study.

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Supplemental content

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Fibroblast growth factor 23 (FGF-23) is a protein hormone that was first described for its role in mineral metabolism.[1] Produced most abundantly by osteocytes, FGF-23 prevents reabsorption of phosphate in the renal proximal convoluted tubule and inhibits conversion of 25-hydroxyvitamin D to its active form.[1,2] These effects limit hyperphosphatemia in renal failure, a disease associated with elevated concentrations of FGF-23.[1,2] Prior work has suggested a possible causal link between FGF-23 and adverse cardiovascular (CV) remodeling, in particular to the development of left ventricular hypertrophy,[3-5] alterations in myocyte calcium handling,[6] renin-angiotensin system upregulation,[7] and promotion of vascular calcification.[8]

Given these pleotropic effects on CV structure and function, FGF-23 might be expected to provide prognostic value independent of established biomarkers. Previous observations have found elevated FGF-23 concentrations to be associated with adverse CV outcomes in patients without established CV disease[9-15] and in patients with stable coronary artery disease and preserved left ventricular ejection fraction.[16]

The prognostic utility of FGF-23 in patients stabilized after a recent acute coronary syndrome (ACS) remains unknown, however. We therefore examined the association of FGF-23 with recurrent CV events in patients after ACS in the Stabilization of Plaques Using Darapladib-Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial.[17]

Key Points

Question Is fibroblast growth factor 23 associated with recurrent cardiovascular events in patients stabilized after an acute coronary syndrome?

Findings Among 4947 patients with recent acute coronary syndrome enrolled in the SOLID-TIMI 52 trial, fibroblast growth factor 23 was independently and significantly associated with an increased risk of cardiovascular death or heart failure hospitalization and its individual components after adjustment for baseline clinical characteristics and established biomarkers (high-sensitivity troponin I, brain-type natriuretic peptide, and high-sensitivity C-reactive protein). Although this association was robust in men, C-terminal fibroblast growth factor 23 did not appear to be useful for risk stratification in women.

Meaning In patients stabilized after acute coronary syndrome, elevated fibroblast growth factor 23 concentrations may be associated with recurrent major cardiovascular events independent of established clinical risk factors and cardiorenal biomarkers; however, this association may be attenuated in women.

Methods

Study Design and Participants

The study design, baseline patient characteristics, and primary results of the SOLID-TIMI 52 trial (NCT01000727)[18] have been previously described.[17,19] In brief, SOLID-TIMI 52 was a multinational, double-blind, placebo-controlled trial performed from December 1, 2009, to April 24, 2014, that randomized 13 026 patients within 30 days of ACS (median, 14 days) to the lipoprotein-associated phospholipase A_2 inhibitor darapladib or placebo, with a median follow-up of 2.5 years. In addition to the recent ACS, patients were required to have 1 additional CV risk factor for inclusion in the trial. Major exclusion criteria relevant to the current analysis included coronary artery bypass graft surgery completed or planned for the index ACS, liver disease, estimated glomerular filtration rate (eGFR) less than 30 mL/min /1.73 m^2 by the Modification of Diet in Renal Dysfunction formula, New York Heart Association class III or IV heart failure, poorly controlled hypertension, and life expectancy less than 2 years because of a non-CV condition. Written informed consent was provided by all participants, and the study protocol was approved by all relevant institutional review boards (see the full list of all participating institutions in SOLID-TIMI 52 in eAppendix 1 in Supplement 1 in the report by O'Donoghue et al[17]). The SOLID-TIMI 52 trial and this post hoc secondary analysis (performed from September 25, 2014, to October 1, 2017) comply with the Declaration of Helsinki.[20] All data were deidentified.

End Points

On the basis of prior work[16] showing the prognostic value of an elevated FGF-23 concentration for CV death or heart failure hospitalization but not atherothrombotic events in patients with stable ischemic heart disease, the primary prespecified outcome of interest for the current analysis was the composite of CV death or heart failure hospitalization. Other end points captured in the SOLID-TIMI 52 trial were also examined, including the primary trial end point of major coronary events (coronary heart disease death, myocardial infarction [MI], or urgent revascularization for myocardial ischemia) and the key secondary end point of major adverse CV events (MACE), defined as CV death, MI, or stroke. All deaths, heart failure hospitalizations, cardiac ischemic events, and cerebrovascular events were adjudicated by an independent and blinded clinical events committee according to prespecified criteria.[17,19] Atrial fibrillation was captured as a term in the safety database but was not adjudicated.

Measurement of Biomarkers

The FGF-23 concentrations were analyzed at baseline in 4947 patients randomly selected from the overall trial cohort. Patients included in the biomarker subgroup had baseline characteristics similar to the overall trial population (eTable 1 in the Supplement). The FGF-23 concentration was measured in duplicate using a C-terminal human enzyme-linked immunosorbent assay (Immutopics)[21] with a median coefficient of variation of 3.86% (eTable 2 in the Supplement). Mean (SD) normal values for this assay in adults with preserved renal function were 55 (50) reference units (RU)/mL.[21] All assays for FGF-23 and other biomarkers, including high-sensitivity troponin I (hsTnI) (Architect i2000SR, Abbott Laboratories), high-sensitivity C-reactive protein (hsCRP) (cobas 6000, Roche Diagnostics), brain-type natriuretic peptide (BNP) (Architect i2000SR, Abbott Laboratories), and cystatin-C (Randox), were performed in the TIMI Clinical Trials Laboratory (Boston, Massachusetts) by laboratory personnel masked to treatment allocation and clinical outcome.

Statistical Analysis

All patients with FGF-23 concentrations were included in this exploratory analysis and categorized by quartile of baseline FGF-23 concentration. Baseline characteristics by FGF-23 quartile were described with median and interquartile range (IQR) for continuous variables and number and percentage for categorical variables. Comparisons of baseline characteristics across FGF-23 quartiles were made with analysis of variance (linear trend) for continuous variables and the Cochran-Armitage trend test for categorical variables.

Cumulative rates of all outcomes and their components were calculated for each quartile using the Kaplan-Meier method reported at 3 years and tested for significance with the trend test. The association between FGF-23 concentration and trial end points was examined using Cox proportional hazards regression models to produce hazard ratios (HRs) and 95% CIs for elevation in FGF-23 concentrations, which were analyzed as categorical and continuous variables (as restricted cubic splines). Clinical risk predictors were included in the risk adjustment model (age, sex, body mass index [BMI], current smoker, race/ethnicity [white vs nonwhite], geographic region, hypertension, hyperlipidemia, diabetes, MI before qualifying event, index diagnosis, days from qualifying event, baseline low-density lipoprotein cholesterol concentration, and randomized treatment arm), in addition to eGFR (Modification of Diet in Renal Dysfunction formula), cystatin-C, hsTnI, hsCRP, and BNP measurements. On the basis of inspection of the distribution of continuous variables, the following variables were log-transformed: BMI, low-density lipoprotein cholesterol, cystatin-C, hsTnI, hsCRP, BNP, and FGF-23. Additional restricted cubic splines were used for age and biomarker data (hsTnI, hsCRP, and BNP) in which nonlinear associations were still significant after transformation. Cystatin-C and eGFR were highly correlated (Spearman correlation coefficient $r = -0.68$) with each other; thus, only eGFR was retained in the final model.

We also explored the FGF-23 cut point for CV death or heart failure by the Youden index in the context of receiver operating curve analysis because descriptive data showed evidence of a threshold effect.[22] We observed that an FGF-23 concentration of 92.8 RU/mL was an optimal cutoff value that maximized discrimination between those who had a clinical event (CV death or heart failure hospitalization) and those who did not, and this value was close to the third quartile of FGF-23 distribution (93.5 RU/mL). On the basis of an apparent threshold in risk between the third and fourth quartiles, categorical FGF-23 data were further analyzed as a binary variable (quartile 4 vs quartiles 1-3). There was no interaction by treatment arm, and all analyses were therefore performed in the full biomarker subgroup (n = 4947).

Metrics of discrimination (C-statistic, categoryless net reclassification improvement, and integrated discrimination improvement) were calculated for the adjusted multivariable models with and without FGF-23. To evaluate the incremental value of FGF-23 for prediction over an adjusted multivariable model based on clinical risk factors alone, *P* values were also calculated based on the likelihood ratio test.[23] A test for FGF-23 concentration interaction by sex was performed by including an interaction term in the adjusted Cox proportional hazards regression model.

All analyses were performed by the TIMI Study Group with a commercial statistical software package (SAS, version 9.4; SAS Institute Inc). Assessment of all trial outcomes was performed on an intention-to-treat basis. A 2-sided, unpaired $P<.05$ was considered to be significant for all tests.

Results

Baseline FGF-23 concentrations were available for 4947 patients (median age, 64.0 years; IQR, 59.0-71.0 years; 1276 [25.8%] female). The median FGF-23 concentration was 63.1 RU/mL (IQR, 46.0-93.5 RU/mL). Patients with higher FGF-23 concentrations tended to be older (67 years [IQR, 60-74 years] vs 63 years [IQR, 58-69 years]), more likely female (499 [40.4%] vs 183 [14.8%]), more likely to present with a non-ST-elevation MI (636 [51.5%] vs 467 [37.8%]), and more likely to have a history of hypertension (987 [79.9%] vs 853 [69.0%]), diabetes (463 [37.5%] vs 398 [32.2%]), and prior MI (478 [38.7%] vs 346 [28.0%]) (**Table 1**). The FGF-23 concentrations were moderately correlated with eGFR ($r = -0.29$) and cystatin-C ($r = 0.39$) and weakly with hsTnI ($r = 0.05$), hsCRP ($r = 0.14$), and BNP ($r = 0.20$) (eTable 3 in the Supplement).

Unadjusted Risk of CV Outcomes

During a median follow-up period of 2.5 years, 205 CV deaths and 183 hospitalizations for heart failure occurred. There were 648 MACE, including 404 fatal or nonfatal MIs and 118 fatal or nonfatal strokes.

When FGF-23 was modeled as a continuous variable, there was a significant 75% higher risk of CV death or heart failure hospitalization for each SD increase in log-transformed FGF-23 (HR, 1.75; 95% CI, 1.61-1.91; $P < .001$). A similar higher risk was observed for each of the individual components of the composite end point and MACE.

When the FGF-23 concentrations were categorized by quartile, patients with higher baseline FGF-23 concentrations had a significant increase in the 3-year rate of CV death or heart failure hospitalization with evidence of an apparent threshold effect between quartiles 3 and 4 (4.4% in quartile 1, 4.7% in quartile 2, 4.9% in quartile 3, and 17.5% in quartile 4; $P < .001$) (eTable 4 and eFigures 1 and 2 in the Supplement). Similar observations were seen for the rates of all-cause mortality, with a marked inflection in risk for patients with FGF-23 concentrations between the third and fourth quartiles (5.0% in quartile 1, 5.2% in quartile 2, 4.3% in quartile 3, and 14.6% in quartile 4; $P < .001$) (eTable 4 in the Supplement). As such, subsequent analyses modeled FGF-23 as a dichotomous variable by applying a threshold of quartile 4 vs quartiles 1 through 3. The observed risk of CV death or heart failure and MACE for patients with FGF-23 concentrations in the top quartile emerged early and persisted over time (**Figure 1** and eFigure 3 in the Supplement).

Adjusted Risk of CV Outcomes

After multivariable adjustment for the clinical characteristics and the renal and CV biomarkers previously described, pa-

Table 1. Baseline Patient Characteristics by FGF-23 Quartile[a]

Characteristic	FGF-23 Quartile[b] 1 (n = 1237)	2 (n = 1237)	3 (n = 1237)	4 (n = 1236)	*P* Value for Trend
Age, median (IQR), y	63 (58-69)	64 (59-69)	64 (60-71)	67 (60-74)	<.001
Female	183 (14.8)	247 (20.0)	347 (28.1)	499 (40.4)	<.001
BMI	27.3 (24.9-30.4)	27.5 (24.8-30.8)	27.7 (25.1-31.4)	28.6 (25.2-32.6)	<.001
Current smoker	205 (16.6)	238 (19.2)	222 (18.0)	243 (19.7)	.10
Race/ethnicity					
White	1082 (87.5)	1074 (86.8)	1104 (89.3)	1089 (88.1)	.30
Black	24 (1.9)	28 (2.3)	30 (2.4)	45 (3.6)	.01
Asian	105 (8.5)	116 (9.4)	86 (7.0)	86 (7.0)	.04
Other	26 (2.1)	19 (1.5)	17 (1.4)	16 (1.3)	.10
Hypertension	853 (69.0)	903 (73.0)	921 (74.5)	987 (79.9)	<.001
Hyperlipidemia	790 (63.9)	788 (63.7)	840 (67.9)	828 (67.0)	.03
Diabetes	398 (32.2)	386 (31.2)	423 (34.2)	463 (37.5)	<.01
Prior MI	346 (28.0)	359 (29.0)	379 (30.6)	478 (38.7)	<.001
Prior PCI	246 (19.9)	274 (22.2)	298 (24.1)	352 (28.5)	<.001
Index event					
STEMI	626 (50.6)	593 (47.9)	561 (45.4)	460 (37.2)	<.001
Non-STEMI	467 (37.8)	499 (40.3)	507 (41.0)	636 (51.5)	<.001
Unstable angina	144 (11.6)	145 (11.7)	169 (13.7)	140 (11.3)	.81
Catheterization performed at QE	1057 (85.5)	1081 (87.4)	1067 (86.3)	1032 (83.5)	.12
PCI performed at QE	967 (78.2)	966 (78.1)	943 (76.2)	880 (71.2)	<.001
Time from QE to randomization, median (IQR), d	15.0 (7.0-23.0)	14.0 (7.0-23.0)	15.0 (6.0-23.0)	13.0 (5.5-22.0)	.01
Aspirin	1198 (96.8)	1206 (97.5)	1201 (97.1)	1180 (95.5)	.05
P2Y12 inhibitor	1116 (90.2)	1098 (88.8)	1100 (88.9)	1057 (85.5)	<.001
Statin	1169 (94.5)	1173 (94.8)	1180 (95.4)	1169 (94.6)	.78
β-Blocker	1087 (87.9)	1080 (87.3)	1101 (89.0)	1083 (87.3)	.82
ACEI/ARB	1040 (84.1)	1038 (83.9)	1026 (82.9)	1006 (81.4)	.06
Aldosterone antagonist	790 (63.9)	788 (63.7)	840 (67.9)	828 (67.0)	.03
hsTnI, median (IQR), ng/mL	28.8 (8.3-352.7)	25.9 (7.9-309.3)	27.4 (8.7-365.2)	41.8 (11.2-511.6)	.62
BNP, median (IQR), pg/mL	83.2 (34.2-167.2)	88.6 (42.5-189.3)	106.0 (44.3-224)	149.2 (67.4-337.1)	<.001
hsCRP level, median (IQR), mg/L	3.3 (1.3-10.3)	3.4 (1.4-189.3)	4.2 (1.7-10.1)	5.9 (2.5-15.9)	<.001
Cystatin-C level, median (IQR)	0.8 (0.7-0.9)	3.4 (1.4-9.0)	0.9 (0.8-1.0)	1.0 (0.9-1.3)	<.001
eGFR<60 mL/min/1.73 m^2	39 (3.2)	78 (6.4)	127 (10.5)	346 (28.6)	<.001
Lp-PLA_2 level, median (IQR), nmol/min/mL	110.3 (90.7-132.2)	113.0 (90.7-133.4)	111.6 (93.1-133.8)	109.7 (92.0-132.4)	.68
LDL-C level, median (IQR), mg/dL	74.9 (54.8-95.0)	76.8 (57.5-96.1)	76.1 (58.7-97.7)	74.1 (56.0-97.9)	.09

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; hsCRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; IQR, interquartile range; LDL-C, low-density lipoprotein protein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A_2; MI, myocardial infarction; PCI, percutaneous coronary intervention; QE, qualifying event; RU, reference unit; STEMI, ST-elevation myocardial infarction.

SI conversion factors: To convert hsTnI to micrograms per liter, multiply by 1; BNP to nanograms per liter, multiply by 1; hsCRP to nanomoles per liter, multiply by 9.524; and LDL-C to millimoles per liter, multiply by 0.0259.

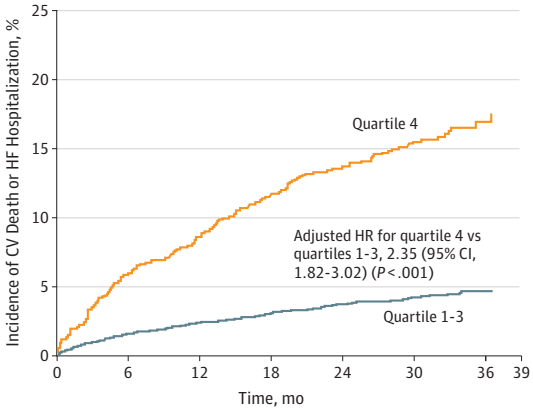
[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Quartile 1 represents an FGF-23 concentration ≤45.97 RU/mL; 2, 45.97-63.05 RU/mL; 3, 63.05-93.53 RU/mL; and 4, >93.53 RU/mL.

tients with FGF-23 concentrations in quartile 4 had more than a 2-fold higher risk of CV death or heart failure hospitalization than patients with FGF-23 concentrations in quartiles 1 through 3 (adjusted HR, 2.35; 95% CI, 1.82-3.02; $P < .001$), including increased risks of CV death and heart failure hospitalization individually (**Figure 2**). The FGF-23 concentrations in quartile 4 were also associated with an increased risk of all-cause mortality, CV death, MI or stroke, fatal or nonfatal stroke, and atrial fibrillation (Figure 2). The association with MI was directionally consistent but of lesser magnitude.

Inclusion of baseline left ventricular ejection fraction (available in 4163 patients) in the multivariable model yielded simi-

Figure 1. Observed 3-Year Incidence of the Composite of Cardiovascular (CV) Death or Heart Failure (HF) Hospitalization for Quartile 4 vs Quartiles 1 Through 3 Fibroblast Growth Factor 23 Concentration



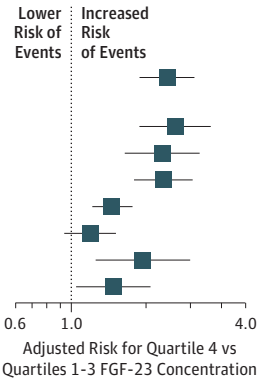
No. at risk

Quartiles 1-3	3711	3613	3563	3513	3245	1178
Quartile 4	1236	1145	1097	1049	951	532

HR indicates hazard ratio.

Figure 2. Adjusted Risk for Quartile 4 vs Quartiles 1 Through 3 Fibroblast Growth Factor 23 (FGF-23) Concentration

End Point	Adjusted HR (95% CI)
CV death or heart failure hospitalization	2.35 (1.82-3.02)
CV death	2.53 (1.81-3.52)
Heart failure hospitalization	2.26 (1.60-3.19)
All-cause mortality	2.27 (1.73-2.97)
CV death, MI, or stroke	1.42 (1.17-1.71)
MI	1.15 (0.91-1.47)
Stroke	1.96 (1.28-3.01)
Atrial fibrillation	1.58 (1.12-2.23)



Covariates in the adjustment model were age, sex, current smoker, diabetes, body mass index, race/ethnicity, hypertension, hyperlipidemia, region, prior myocardial infarction (MI), index diagnosis (non–ST-elevation MI vs ST-elevation MI, unstable angina vs ST-elevation MI), low-density lipoprotein cholesterol level, days from qualifying event, randomized treatment arm, estimated glomerular filtration rate (Modification of Diet in Renal Dysfunction), high-sensitivity troponin I concentration, brain-type natriuretic peptide concentration, and high-sensitivity C-reactive protein concentration.
CV indicates cardiovascular; HR, hazard ratio.

lar findings (CV death or heart failure: adjusted HR, 2.39; 95% CI, 1.81-3.15; $P < .001$ for quartile 4 vs quartiles 1-3).

Furthermore, FGF-23 provided an incremental value for risk stratification when analyses were stratified by baseline eGFR (≤60 or >60 mL/min/1.73 m^2) (eFigure 4 in the Supplement). In the described risk model including clinical variables, established biomarkers, eGFR, and FGF-23, the adjusted HR for CV death or heart failure hospitalization was 1.51 (95% CI, 1.18-1.93) for low eGFR (≤60 mL/min/1.73 m^2) and 2.44 (95% CI, 1.92-3.09) for elevated FGF-23 concentration (quartile 4). When dividing patients into 4 groups with high eGFR (>60 mL/min/1.73 m^2) and low FGF-23 concentration (quartiles 1-3) as the reference, the adjusted HR of CV death or heart failure hospitalization was 1.56 (95% CI, 1.07-2.27) for patients with low eGFR and low FGF-23 concentration, 2.61 (95% CI, 1.95-3.50) for patients with high eGFR and high FGF-23 concentration, and 2.88 (95% CI, 2.10-3.95) for patients with the highest-risk combination of low eGFR and high FGF-23 concentration (**Figure 3**A and **Table 2**). A similar association was seen with triple stratification by FGF-23, hsTnI, and BNP, with an adjusted HR of 15.40 (95% CI, 8.87-26.73) for patients with elevated concentrations of each biomarker compared with patients with low FGF-23, hsTnI, and BNP concentrations (Figure 3B and Table 2).

Discrimination and Reclassification

Compared with the base model of clinical variables, inclusion of FGF-23 (restricted cubic spline) significantly improved the model for risk of CV death or heart failure hospitalization (likelihood ratio test $P < .001$), with an improvement in the C statistic from 0.72 (95% CI, 0.69-0.75) to 0.76 (95% CI, 0.73-0.79). The FGF-23 (restricted cubic spline) was also associated with better net reclassification improvement (0.53; 95% CI, 0.42-0.64), with positive event net reclassification improvement (0.19; 95% CI, 0.09-0.30) and nonevent net reclassification improvement (0.34; 95% CI, 0.31-0.37) and the integrated discrimination improvement indicator (0.05; 95% CI, 0.03-0.06). Additional discrimination and reclassification values are provided in eTable 5 in the Supplement.

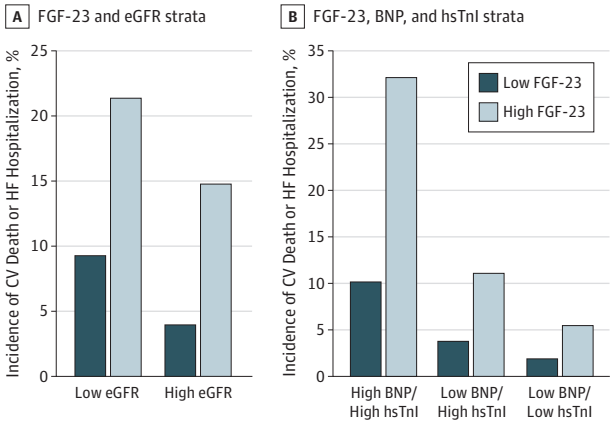
Interaction by Sex

Women had significantly higher baseline median FGF-23 concentrations than men (77.7 RU/mL [IQR, 55.5-125.5 RU/mL] vs 59.1 RU/mL [IQR, 44.0-84.7 RU/mL]; $P < .001$). After multivariable adjustment, the HR of CV death or heart failure hospitalization for each 1-SD increase in log-transformed FGF-23 concentration was 1.01 (95% CI, 0.82-1.25; $P = .93$) in women compared with 1.58 (95% CI, 1.38-1.80; $P < .001$) in men ($P<.001$ for interaction). Similar findings were observed for results stratified by sex when modeled by quartile of FGF-23 concentration, with an attenuated association in women (quartile 4 vs quartiles 1-3: HR, 1.11; 95% CI, 0.70-1.76; $P = .67$) compared with men (HR, 3.11; 95% CI, 2.29-4.22; $P < .001$; $P<.001$ for interaction). The association appeared similarly attenuated in women for additional CV outcomes of interest (eTable 6 in the Supplement).

Discussion

In a large, contemporary cohort of patients with recent ACS, we found that an elevated FGF-23 concentration was associated with the risk of adverse CV outcomes, including CV death or heart failure hospitalization. Furthermore, FGF-23, a protein reflective of physiologic axes separate from those affecting traditional CV biomarkers, provided prognostic information that was incremental to established clinical predictors and multiple biomarkers, including eGFR, BNP, hsCRP, and hsTnI.

Figure 3. Observed 3-Year Incidence of Cardiovascular (CV) Death or Hospitalization for Heart Failure (HF)



Biomarker stratifications are as follows: for fibroblast growth factor 23 (FGF-23) and brain-type natriuretic peptide (BNP), quartile 4 was high and quartiles 1 through 3 were low; for estimated glomerular filtration rate (eGFR), greater than 60 mL/min/1.73 m^2 was high and 60 mL/min/1.73 m^2 or less was low; and for high-sensitivity troponin I (hsTnI), quartiles 2 through 4 were high and quartile 1 was low.

Table 2. Observed 3-Year Adjusted HR of Cardiovascular Death or Hospitalization for Heart Failure[a]

	Adjusted HR, % (95%CI)	
Biomarker	Low FGF-23	High FGF-23
Low eGFR	1.6 (1.1-2.3)	2.9 (2.1-4.0)
High eGFR	1 [Reference]	2.6 (2.0-3.5)
High BNP and high hsTnI	5.6 (3.2-9.7)	15.4 (8.9-26.7)
Low BNP and high hsTnI	1.8 (1.0-3.2)	4.5 (2.5-8.0)
Low BNP and low hsTnI	1 [Reference]	2.1 (0.9-4.7)

Abbreviations: BNP, brain-type natriuretic peptide; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; HR, hazard ratio; hsTnI, high-sensitivity troponin I.

[a] Biomarker stratifications are as follows: for FGF-23 and BNP, quartile 4 was high and quartiles 1 through 3 were low; for eGFR, greater than 60 mL/min/1.73 m^2 was high and 60 mL/min/1.73 m^2 or less was low; and for hsTnI, quartiles 2 through 4 were high and quartile 1 was low.

To our knowledge, this is the first time this association has been explored in patients stabilized after recent ACS. An apparent attenuation of this association in women additionally merits further investigation.

The median FGF-23 concentration of 63.1 RU/mL (IQR, 46.0-93.5 RU/mL) observed here is similar to that seen in patients with stable ischemic heart disease (50.6 RU/mL; IQR, 38.7-69.9 RU/mL)[16] but higher than concentrations in the general population[9,24] and lower than those in patients with chronic kidney disease.[3,4]

The observed correlation between FGF-23 concentration and subsequent CV risk after ACS is intriguing with respect to the protein's postulated direct and indirect CV effects. In non-ACS populations, an elevated FGF-23 concentration has been associated with mortality and heart failure but with mixed associations with atherothrombotic outcomes.[9-11,16,25-27] In the current analysis, we observed an association between FGF-23 and the risk of CV death, heart failure hospitalization, and all-cause mortality among patients after ACS. However, we also found an independent association between FGF-23 concentration and the risk of MACE with directional consistency across all components.

Pathophysiologic and Clinical Considerations

The renin-angiotensin system is a central mediator of the CV effects of FGF-23. Klotho, the FGF-23 coreceptor in the kidney and vasculature, is a renin-angiotensin system inhibitor,[28-30] and FGF-23 suppresses renal expression of angiotensin-converting enzyme 2,[7] a negative renin-angiotensin system regulator.[31] Elevation of FGF-23 concentration is associated with left ventricular hypertrophy independent of blood pressure and renal function,[3,4,32] whereas FGF receptor blockade appears to reverse murine left ventricular hypertrophy and myocardial fibrosis.[33]

It has previously been demonstrated that patients with stable coronary artery disease in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial derived enhanced benefit from the angiotensin-converting enzyme inhibitor trandolapril if they had an elevated baseline concentration of FGF-23.[16] In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, significant reductions in CV death and heart failure were reported among patients undergoing hemodialysis whose FGF-23 concentrations decreased by at least 30% with cinacalcet.[34] Together, FGF-23 elevation and Klotho deficiency support renin-angiotensin system activation[29,30] and its known deleterious downstream effects, including cardiac remodeling and heart failure.

The association between FGF-23 and ischemic events is less clear. In the arterial system, FGF-23 prevents vascular calcification via Klotho,[8,28,35] and FGF-23 knockout mice have developed rapid vascular calcification and died by 12 weeks of age.[36,37] However, a study[9] in patients did not find consistent associations between FGF-23 and vascular events. Our results in a post-ACS population show an independent association between FGF-23 and the risk of subsequent stroke and a weaker association with MI. The Multi-Ethnic Study of Atherosclerosis (MESA) found an elevated FGF-23 concentration to be associated with incident coronary heart disease events in the general population,[32] whereas other nontrial cohorts of lower-risk patients did not find statistically significant associations between increased stroke and/or MI.[9] In a cohort of patients enrolled 6 to 12 months after ACS, elevated FGF-23 concentration was associated with higher incidence of a composite outcome, including ischemic events, heart failure, and all-cause mortality.[38]

The statistically significant interaction with patient sex was unexpected. Higher concentrations of FGF-23 in women compared with men have been reported in observational cohorts irrespective of FGF-23 assay used,[11,16] although differential prognostic value of this biomarker in women has not previously been shown. Estrogen is known to influence concentrations of FGF-23–modifying compounds, including parathyroid hormone, phosphate, and vitamin D,[24] and may contribute to an observed sex difference in the association between serum phosphorus concentration and CV outcomes.[39]

Because the current study enrolled patients after ACS, most women were likely to have been postmenopausal. Menopause results in urine phosphorus retention, which in turn is believed to increase FGF-23 concentration.[40] In fact, postmenopausal women not receiving exogenous estrogen have higher FGF-23 concentrations than postmenopausal women receiving estrogen therapy or men.[40] Conceivably, low FGF-23 concentrations in this context may reflect intrinsically low FGF-23 concentrations or low FGF-23 concentrations related to exogenous estrogen.

One cannot exclude that the observed difference by patient sex could have occurred by chance. Of note, the prognostic utility of FGF-23 previously appeared to be broadly comparable in men and women in the Atherosclerosis Risk in Communities (ARIC) study and MESA.[11,32] However, the current study measured the C-terminal fragment of FGF-23 as opposed to the intact peptide that was previously measured in the older studies. As such, it remains unclear whether the observed findings may reflect differences between men and women in the posttranslational processing of FGF-23. Further study will be useful in that regard.

Limitations

Although the present analysis benefits from a well-characterized trial cohort, a large sample size and number of events, and adjudicated outcomes, it has several limitations. First, the analysis is observational and does not allow for causal inference. Second, left ventricular ejection fraction was only assessed in 84% of patients; however, the findings remained consistent after inclusion of left ventricular ejection fraction in the adjustment model. Finally, any clinical cut points for FGF-23 will require prospective validation in a separate cohort in addition to validation of the observed interaction by patient sex.

Conclusions

In a large, contemporary cohort of patients with recent ACS, we found elevated FGF-23 concentrations to be associated with a higher risk of adverse CV outcomes independent of established risk predictors and cardiorenal markers. A potential sex difference in these findings deserves further study.

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