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ORIGINAL RESEARCH

Relationship of Fibroblast Growth Factor 23 With Hospitalization for Heart Failure and Cardiovascular Outcomes in Patients Undergoing Cardiac Surgery

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BACKGROUND: Fibroblast growth factor 23 (FGF-23) is crucial in regulating phosphate and vitamin D metabolism and is moreover associated with an increased cardiovascular risk. The specific objective of this study was to investigate the influence of FGF-23 on cardiovascular outcomes, including hospitalization for heart failure (HHF), postoperative atrial fibrillation, and cardiovascular death, in an unselected patient population after cardiac surgery.

METHODS AND RESULTS: Patients undergoing elective coronary artery bypass graft and/or cardiac valve surgery were prospectively enrolled. FGF-23 blood plasma concentrations were assessed before surgery. A composite of cardiovascular death/HHF was chosen as primary end point. A total of 451 patients (median age 70 years; 28.8% female) were included in the present analysis and followed over a median of 3.9 years. Individuals with higher FGF-23 quartiles showed elevated incidence rates of the composite of cardiovascular death/HHF (quartile 1, 7.1%; quartile 2, 8.6%; quartile 3, 15.1%; and quartile 4, 34.3%). After multivariable adjustment, FGF-23 modeled as a continuous variable (adjusted hazard ratio for a 1-unit increase in standardized log-transformed biomarker, 1.82 [95% CI, 1.34–2.46]) as well as using predefined risk groups and quartiles remained independently associated with the risk of cardiovascular death/HHF and the secondary outcomes, including postoperative atrial fibrillation. Reclassification analysis indicated that the addition of FGF-23 to N-terminal pro-B-type natriuretic peptide provides a significant improvement in risk discrimination (net reclassification improvement at the event rate, 0.58 [95% CI, 0.34–0.81]; $P<0.001$; integrated discrimination increment, 0.03 [95% CI, 0.01–0.05]; $P<0.001$).

CONCLUSIONS: FGF-23 is an independent predictor of cardiovascular death/HHF and postoperative atrial fibrillation in individuals undergoing cardiac surgery. Considering an individualized risk assessment, routine preoperative FGF-23 evaluation may improve detection of high-risk patients.

Key Words: cardiac surgery ■ cardiovascular death ■ fibroblast growth factor 23 ■ hospitalization for heart failure ■ postoperative atrial fibrillation

The onset of heart failure (HF) is a feared complication in individuals undergoing heart valve and/or coronary artery bypass grafting (CABG) surgery. Despite major improvements in preserving perioperative myocardial function, medical treatment, and postoperative patient management, it still remains a common issue

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CLINICAL PERSPECTIVE

What Is New?

- In cardiac surgery, preoperative elevated fibroblast growth factor 23 levels predicted hospitalization for heart failure, cardiovascular death, and new onset of postoperative atrial fibrillation.

What Are the Clinical Implications?

- Assessment of fibroblast growth factor 23 may extend risk stratification, to allow early identification of patients at risk for adverse cardiovascular events, who require in-depth clinical attention throughout the perioperative and postoperative phase after cardiac surgery.
- Vulnerable patients may benefit from early interventions (conservative or interventional) to prevent adverse events and reduce both mortality and morbidity.

Nonstandard Abbreviations and Acronyms

FGF-23	fibroblast growth factor 23
HHF	hospitalization for heart failure
POAF	postoperative atrial fibrillation

after cardiac surgery.[1] One predominant clinical attribute of postoperative HF is its association with an elevated risk for acute cardiovascular events, which are the primary cause of death within these individuals.

Besides HF, postoperative atrial fibrillation (POAF) represents a common entity after cardiac surgery, with an observed incidence ranging from 15% to 45% of all individuals undergoing cardiac surgical interventions.[2] POAF is associated with thromboembolic events, prolonged hospital stay, and adverse long-term outcomes.[3]

In this regard, cardiovascular risk prediction tools in patients undergoing cardiac surgery are of great interest, to allow precise risk assessment in susceptible patients. In the era of personalized medicine and individualized prognostication, the assessment of risk markers represents an attractive concept for risk stratification in clinical practice. Thus, the identification of novel markers reflecting different aspects of the underlying pathophysiologic process may improve diagnostic evaluation and provide additional prognostic information.

Fibroblast growth factor 23 (FGF-23) plays a crucial role in regulating phosphate and vitamin D metabolism.[4,5] Beyond its involvement in physiological processes, the molecule FGF-23 proved to be associated with an increased risk for fatal events in individuals presenting with cardiovascular disease, and moreover it yields prognostic value as an independent risk factor for new-onset HF and hospitalization for HF (HHF).[6,7]

Furthermore, previous research has found an association between preoperative FGF-23 levels and both surgical mortality and long-term outcome in a population who underwent elective cardiac surgery.[8] However, what remains unknown is if FGF-23 is able to predict common complications after cardiac surgery, particularly readmission for HF and development of POAF.

Therefore, we aimed to investigate the association of FGF-23 with HHF or cardiovascular death, POAF, and other major cardiovascular events (ie, the individual components of the composite end point and all-cause death) in an unselected patient population who underwent elective heart valve and/or CABG surgery.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

In this prospective observational study, a total of 451 participants undergoing elective cardiac valve and/or bypass surgery were recruited. All patients were enrolled at the time of hospital admission before elective surgical intervention at the Department of Cardiac Surgery, Medical University of Vienna (Vienna, Austria), a university-affiliated tertiary care center, in the period between May 2013 and August 2018. All participants gave written informed consent at the time of enrollment. Patients had to be at least 18 years old at the time of study inclusion. ECG analysis of all individuals was assessed at the time of hospitalization. For inclusion in this study, patients had to present with sinus rhythm at the time of recruitment, and they had to be free of any atrial fibrillation episodes for at least 6 months before and at the time of surgery. The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee of the Medical University of Vienna (No. 1110/2013). Data reporting was performed according to the Strengthening the Reporting of Observational studies in Epidemiology and Meta-analyses Of Observational Studies in Epidemiology guidelines.

Data Acquisition and FGF-23 Measures

At the time of enrollment, patient data were assessed using a predefined record abstraction form. Peripheral venous blood samples of all participants were taken at the day before surgery. Routine laboratory blood samples were processed following the laboratory standards

of the Department of Laboratory Medicine (General Hospital of Vienna–Medical University of Vienna). Blood plasma was harvested after centrifugation at 3000 rounds per minute for 20 minutes at 4 °C (Allegra X-12R Centrifuge; Beckman Coulter) and subsequently stored at −80 °Celsius. Plasma FGF-23 concentrations were assessed via a sandwich enzyme immunoassay (Biomedica Medizinprodukte GmbH, Vienna, Austria). The intra-assay and interassay precision values were ≤12% and ≤10%, respectively. The assay limit of detection (0 pmol/L+3 SDs) was 0.08 pmol/L. For better clinical evaluation, FGF-23 was converted to units of pg/mL, with a conversion factor of 1 pg/mL=0.133 pmol/L.

Outcomes and Follow-Up

The primary outcome of interest was a composite of cardiovascular death and HHF. Secondary outcomes were the development of POAF during the postoperative hospital stay, the individual components of the primary composite end point, and death from any cause. After surgical intervention, all individuals were continuously followed up and screened for the development of cardiac arrhythmias during the total hospital stay. Furthermore, patients were continuously monitored via ECG-telemetry for at least 9 days after the surgical intervention as a standard operating procedure at the study center. ECG-telemetry consisted of a standard 3-lead portable device that transmitted and recorded data on centrally positioned monitors, including storage of telemetry data of all patients. If an arrhythmic episode was detected, a >30-second 12-lead ECG was performed to diagnose POAF, according to European Society of Cardiology guidelines. The patients' cause and date of death were assessed by screening the national registry of death until September 2020 via the Austrian Registry of Death (Statistics Austria, Vienna, Austria). HHF was determined by patient interviews during follow-up visits and subsequent verification by a search through the Vienna Healthcare Group hospitalizations database ("Wiener Gesundheitsverbund"). All outcomes were defined according to the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*).

Statistical Analysis

Categorical data are presented as counts and percentages and were compared between subgroups using the χ^2 test. Continuous data are shown as median and interquartile range (IQR) and were analyzed using Mann-Whitey-*U* test. Differences between FGF-23 quartiles were analyzed using Kruskal-Wallis test. Correlations between continuous variables and FGF-23 values were calculated using Spearman correlation coefficient. The 4-year Kaplan-Meier event rates were compared using the log-rank test. Classification and regression tree analysis was used to determine different FGF-23 risk groups (low risk, intermediate risk, and high risk). FGF-23 was modeled as a continuous standardized log-transformed variable, as well as using quartiles and evaluated risk groups. An FGF-23 threshold was delineated using the maximally selected log-rank statistic. Binary logistic regression analysis was used to assess the influence of FGF-23 on the development of POAF. Data were presented as odds ratios, including their respective 95% CIs. Cox proportional hazard models were applied to assess the impact of FGF-23 on cardiovascular death, HHF, and all-cause death. Results were presented as hazard ratio (HR) and the respective 95% CI. The multivariate model was adjusted for potential confounders, such as age, sex, hypertension, HF, chronic kidney disease, diabetes, coronary artery disease, and body mass index.

Category-free net reclassification improvement and integrated discrimination increment were calculated to estimate an improvement in individual risk prediction for the addition of FGF-23 to NT-proBNP (N-terminal pro-B-type natriuretic peptide). We further used receiver operating characteristic curve analysis to assess discriminatory performance of FGF-23 and NT-proBNP. Considering the purpose of the present analysis, the discrimination and calibration of the presented data have been validated by net reclassification improvement and integrated discrimination increment, which is recommended for the detection of prognostic biomarkers and illustrated by Cook.[9] Calibration was ensured by visually inspecting the calibration plot and the Hosmer-Lemeshow test. A 2-sided $P<0.05$ was defined as statistically significant. Statistical analysis was performed using R (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Detailed baseline characteristics for the entire study population, stratified by quartiles of FGF-23, are summarized in Table 1. In short, 451 patients were included in the present analysis and followed over a median of 3.9 years. The patients' median age was 69.8 years (IQR, 60.4–75.4 years), 322 (71.4%) patients were men, and the median body mass index was 27.2 kg/m^2 (IQR, 24.3–30.2 kg/m^2). Most patients presented with New York Heart Association classification II (43.9%) and New York Heart Association classification III (42.0%). The median left ventricular ejection fraction (LVEF) was 60.0% (IQR, 50.2%–60.0%).

Overall, 15.5% of patients showed a reduced LVEF (LVEF 50%–40%, 8.6%; LVEF 40%–30%, 2.2%; and LVEF <30%, 4.7%).

Single-valve replacement surgery was the most commonly performed surgical intervention within the study population (41.2%; n=186), followed by CABG

Table 1. Baseline Characteristics, Stratified by FGF-23 Quartiles

Characteristic		Quartiles of FGF-23						
	Overall (n=451)	Quartile 1 (n=113)	Quartile 2 (n=113)	Quartile 3 (n=112)	Quartile 4 (n=113)	*P* value	R value	*P* value*
FGF-23, median (IQR), pg/mL	14.4 (8.9–26.7)	6.0 (4.0–7.5)	11.7 (10.0–12.8)	18.8 (16.6–22.3)	44.9 (31.8–83.0)	<0.001†	/	/
Clinical presentation								
Age, median (IQR), y	69.8 (60.4–75.4)	66.0 (58.0–74.7)	68.8 (59.4–74.1)	70.9 (61.2–76.5)	71.5 (63.5–76.8)	0.027†	0.071	0.131
Sex, male, n (%)	322 (71.4)	85 (75.2)	88 (77.9)	78 (69.6)	71 (62.8)	0.061	/	/
Heart rate, median (IQR), bpm	70.0 (62.0–80.0)	70.0 (62.0–75.0)	70.0 (60.0–80.0)	70.0 (62.0–77.0)	73.0 (65.0–80.0)	0.293	0.058	0.437
Systolic BP, median (IQR), mm Hg	130.0 (119.0–143.0)	131.0 (118.5–143.0)	130.0 (118.0–142.0)	130.0 (120.0–143.3)	128.0 (117.0–142.8)	0.824	−0.029	0.550
Diastolic BP, median (IQR), mm Hg	71.0 (62.7–80.3)	74.0 (65.5–83.5)	72.0 (65.0–83.0)	71.0 (62.8–80.0)	68.0 (57.3–75.8)	<0.001†	−0.150	0.002†
NYHA classification, n (%)								
I	24 (9.2)	6 (10.2)	9 (12.9)	6 (10.7)	3 (3.9)	0.267	/	/
II	115 (43.9)	28 (47.5)	34 (48.8)	27 (48.2)	26 (33.9)	0.207	/	/
III	110 (42.0)	23 (39.0)	26 (37.1)	19 (33.9)	42 (54.5)	0.061	/	/
IV	13 (5.0)	2 (3.4)	1 (1.4)	4 (7.1)	6 (7.8)	0.258	/	/
LVEF, median (IQR), %	60.0 (50.0–60.0)	60.0 (60.0–60.0)	60.0 (55.0–60.0)	60 (50–60)	60.0 (45.0–60.0)	0.046†	−0.162	0.001†
BMI, median (IQR), kg/m^2	27.2 (24.3–30.2)	26.6 (24.1–30.0)	27.5 (24.5–29.9)	27.4 (24.7–29.7)	27.7 (24.4–31.3)	0.491	0.108	0.022†
Type of surgery, n (%)								
CABG	151 (33.5)	41 (36.3)	50 (44.2)	39 (34.8)	21 (18.6)	<0.001†	/	/
Valve	186 (41.2)	47 (41.6)	42 (37.2)	46 (41.1)	51 (45.1)	0.686	/	/
CABG+valve	114 (25.3)	25 (22.1)	21 (18.6)	27 (24.1)	41 (36.3)	0.014†	/	/
Comorbidities, n (%)								
Diabetes	132 (29.3)	24 (21.2)	29 (25.7)	33 (29.5)	46 (40.7)	0.010†	/	/
Hypertension	366 (81.2)	83 (73.5)	98 (86.7)	88 (78.6)	97 (85.8)	0.032†	/	/
Prior MI	119 (26.4)	31 (27.4)	22 (19.5)	31 (27.7)	35 (31.0)	0.244	/	/
Coronary artery disease	278 (61.6)	72 (63.7)	70 (61.9)	68 (60.7)	68 (60.2)	0.950	/	/
Heart failure	262 (58.1)	59 (52.2)	70 (61.9)	56 (50.0)	77 (68.1)	0.019†	/	/
Medication, n (%)								
β-Blocker	251 (55.7)	59 (52.2)	55 (48.7)	56 (50.0)	81 (71.7)	0.001†	/	/
ACE inhibitors	136 (30.2)	37 (32.7)	25 (22.1)	35 (31.3)	39 (34.5)	0.179	/	/
Statins	289 (64.1)	74 (65.5)	76 (67.3)	71 (63.4)	68 (60.2)	0.714	/	/

(*Continued*)

Table 1. Continued

Characteristic	Overall (n=451)	Quartiles of FGF-23						
		Quartile 1 (n=113)	Quartile 2 (n=113)	Quartile 3 (n=112)	Quartile 4 (n=113)	*P* value	R value	*P* value*
Laboratory variables, median (IQR)								
NT-proBNP, pg/mL	457.8 (189.4–1222.0)	339.8 (142.8–737.4)	305.1 (151.8–681.3)	471.2 (184.2–1088.0)	926.7 (459.5–3212.5)	<0.001†	0.424	<0.001†
eGFR, mL/min per 1.73 m^2	79.7 (61.9–94.7)	86.5 (71.6–99.2)	83.4 (68.4–97.6)	81.9 (62.8–96.6)	63.9 (47.5–83.5)	<0.001†	−0.348	<0.001†
CRP, mg/dL	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.3 (0.1–0.8)	0.012†	0.074	0.121

Categorical data are presented as counts and percentages and analyzed using χ^2 test. Continuous data are presented as median and the respective IQR and analyzed using Mann-Whitney *U* test. ACE indicates angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and R, Spearman Rho coefficient.

*P value according to Spearman correlation.

†Statistically significant.

/Not applicable.

(33.5%; n=151) and combined CABG+valve replacement surgery (25.3%; n=114).

The median FGF-23 level was 14.4 pg/mL (IQR, 8.9–26.7 pg/mL), and the median NT-proBNP level was 457.8 pg/mL (IQR, 189.4–1222.0 pg/mL). Patients with higher FGF-23 quartiles were more likely to be older (P=0.027), had diabetes (P=0.010), showed higher NT-proBNP (P<0.001) levels and lower estimated glomerular filtration rates (P<0.001), and received significantly more frequent combined CABG+valve replacement surgery (P=0.014) (Table 1).

Furthermore, FGF-23 showed, as expected, strong and significant correlations with NT-proBNP (r=0.424; P<0.001) and estimated glomerular filtration rate (r=−0.348; P<0.001) (Table 1).

Relationship of FGF-23 With Cardiovascular Death/HHF

Classification and regression tree analysis determined an FGF-23 cutoff value of <15 pg/mL as low risk for cardiovascular death/HHF, a value between 15 and 31 pg/mL as intermediate risk, and a value of >31 pg/mL as high risk for cardiovascular death/HHF. On the basis of these cutoff values, the present patient population was stratified into 3 risk groups. Detailed baseline characteristics for distribution of conventional risk factors and laboratory parameters, stratified by evaluated risk groups of FGF-23 values, are presented in Table S1.

Patients in higher FGF-23 risk groups had higher rates of cardiovascular death/HHF (low risk, 7.7%; intermediate risk, 15.4%; high risk, 39.7%; P<0.001 by log-rank test; Figure 1A). A similar pattern was observed for HHF (Figure 1B), cardiovascular death (Figure 1C), and all-cause death (Figure 1D).

Similarly, a significant gradient of risk was observed when FGF-23 was stratified into quartiles (quartile 1, 7.1%; quartile 2, 8.6%; quartile 3, 15.1%; and quartile 4, 34.3%; P<0.001 by log-rank test; Figure S1 and Table S2). An FGF-23 cut point of 21 pg/mL yielded the maximum selected log-rank statistic, thus offering the best separation (8.3% versus 32.3%; P<0.001 by log-rank test; Figure S2).

Within a multivariate model, FGF-23 modeled as a continuous variable (adjusted HR for a 1-unit increase in standardized log-transformed biomarker 1.82, 95% CI, 1.34–2.46; Figure 2) as well as using risk groups remained independently associated with the risk of cardiovascular death/HHF (Figure 2). This relationship was similar for the individual components of the composite end point and all-cause death (Figure 2). A sensitivity analysis with further adjustment for NT-proBNP and aortic clamp time (indirect measure of operative challenges/complications) yielded similar results for cardiovascular death/HHF (FGF-23 continuous: adjusted HR, 1.61; intermediate risk: adjusted HR, 2.04; and high risk:

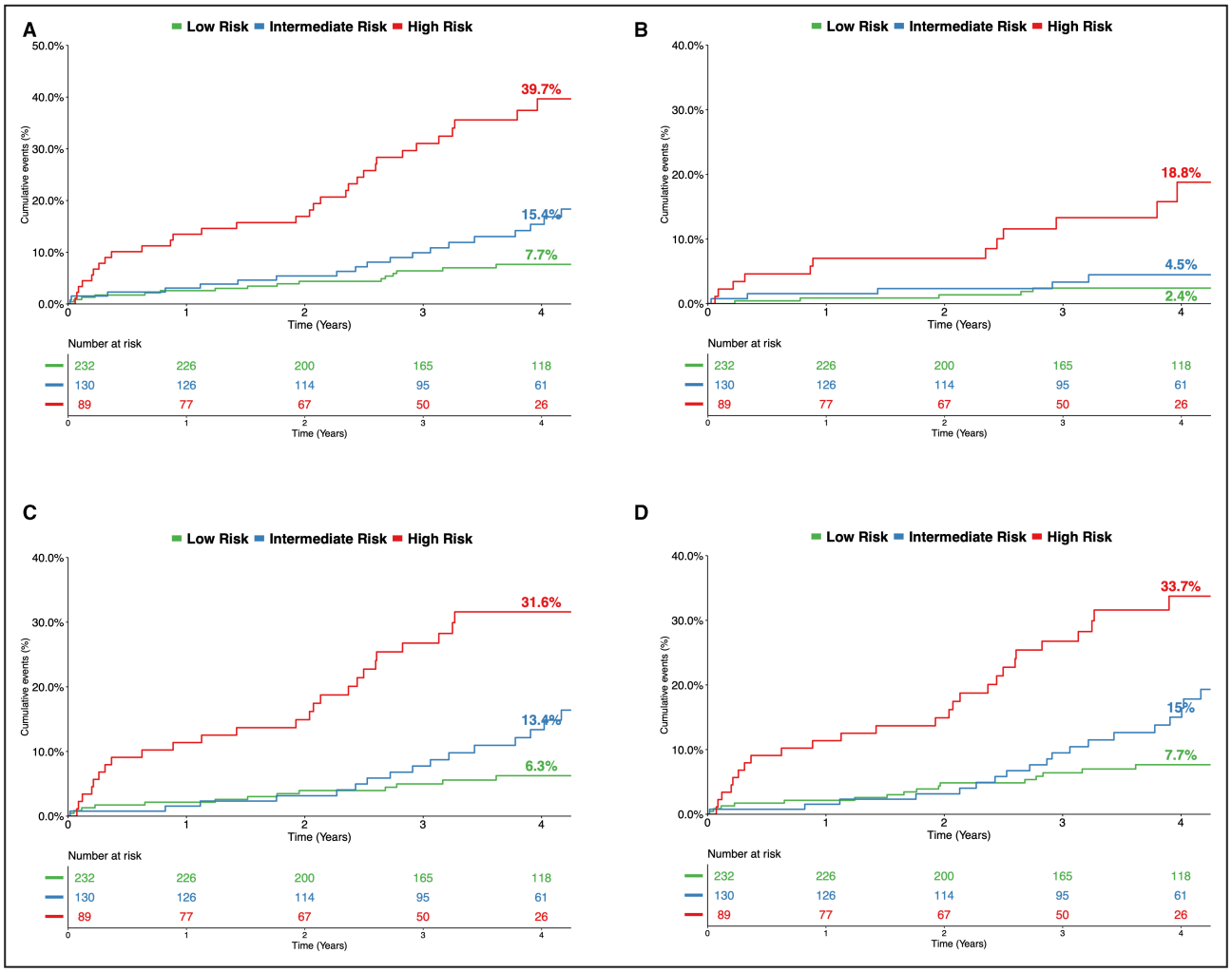

Figure 1. Kaplan-Meier curves and the corresponding 4-year Kaplan-Meier event rates for the composite of cardiovascular death or hospitalization for heart failure (HHF) (A), HHF (B), cardiovascular death (C), and all-cause death (D), stratified by fibroblast growth factor 23 (FGF-23) risk groups.
A, Cardiovascular death/HHF. Low-risk FGF-23 levels, <15 pg/mL; intermediate-risk FGF-23 levels, 15 to 31 pg/mL; and high-risk FGF-23 levels, >31 pg/mL. **B**, HHF. Low-risk FGF-23 levels, <15 pg/mL; intermediate-risk FGF-23 levels, 15 to 31 pg/mL; and high-risk FGF-23 levels, >31 pg/mL. **C**, Cardiovascular death. Low-risk FGF-23 levels, <15 pg/mL; intermediate-risk FGF-23 levels, 15 to 31 pg/mL; and high-risk FGF-23 levels, >31 pg/mL. **D**, All-cause death. Low-risk FGF-23 levels, <15 pg/mL; intermediate-risk FGF-23 levels, 15 to 31 pg/mL; and high-risk FGF-23 levels, >31 pg/mL.

adjusted HR, 3.24). In a further sensitivity analysis in patients with reduced ejection fraction, our results also remained similar.

Relationship of FGF-23 With POAF

Baseline characteristics of the study population, stratified by the occurrence of POAF, are summarized in Table 2. In short, patients with POAF were more likely to be older, to be women, receive combined CABG+valve replacement surgery, and have higher NT-proBNP levels (all $P<0.05$; Table 2). More important, plasma levels of FGF-23 were significantly elevated in the POAF group compared with non-POAF counterparts (16.9 versus 12.9 pg/mL; $P=0.001$).

After multivariable adjustment, FGF-23 modeled as a continuous variable (adjusted OR for a 1-unit increase in standardized log-transformed biomarker, 1.25 [95% CI, 1.01–1.55]; $P=0.040$) as well as using quartiles remained independently associated with the risk of POAF (Table 3). Notably, a sensitivity analysis with further adjustment for NT-proBNP and aortic clamp time yielded similar results.

Discrimination and Reclassification Analysis

Because NT-proBNP represents a routinely available and powerful prognostic marker for outcome and furthermore its measurement augments the prognostic

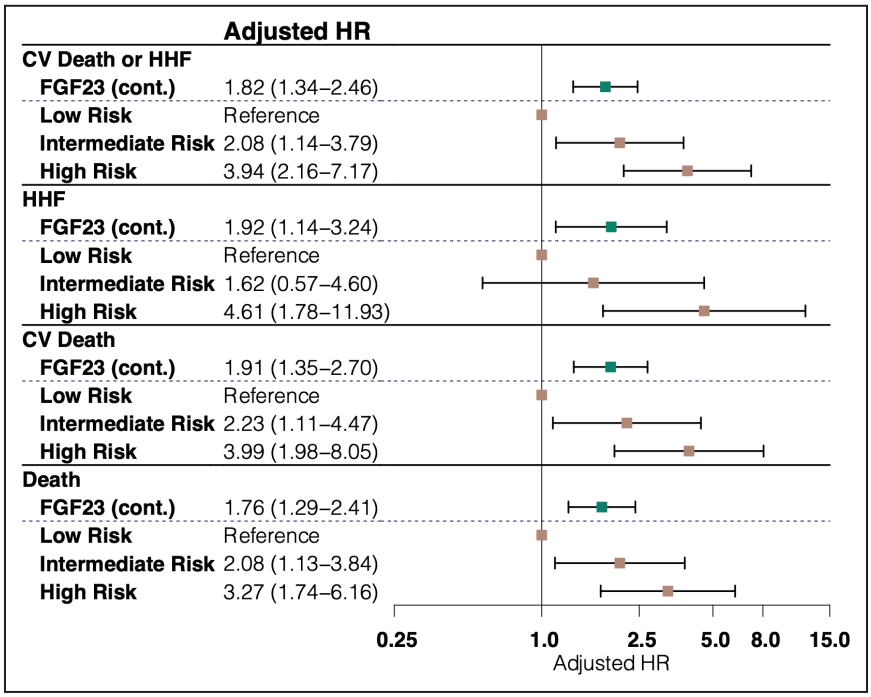

Figure 2. Relationship between fibroblast growth factor 23 (FGF-23), FGF-23 risk groups, and cardiovascular (CV) outcomes.
Cox regression models were adjusted for age, sex, hypertension, chronic kidney disease, diabetes, heart failure, coronary artery disease, and body mass index. Low-risk FGF-23 levels, <15 pg/mL; intermediate-risk FGF-23 levels, 15 to 31 pg/mL; and high-risk FGF-23 levels, >31 pg/mL. Cont. indicates continuous; HHF, hospitalization for heart failure; and HR, hazard ratio.

information of clinical risk scores, it was chosen as a marker for comparison.

The discriminatory performance evaluated by receiver operating characteristic curve analysis showed moderate performance of FGF-23 for the discrimination of cardiovascular death/HHF (area under the curve, 0.68 [95% CI, 0.62–0.75]; Figure S3) and was comparable to the discriminatory performance of NT-proBNP for cardiovascular death/HHF, with an area under the curve of 0.68 (95% CI, 0.62–0.75; Figure S4). The addition of FGF-23 to NT-proBNP significantly increased the discriminatory power, as demonstrated by improvements in net reclassification improvement and integrated discrimination increment (net reclassification improvement at the event rate, 0.58 [95% CI, 0.34–0.81]; $P<0.001$; integrated discrimination increment, 0.03 [95% CI, 0.01–0.05]; $P<0.001$; Table 4).

DISCUSSION

This study represents, to the best of our knowledge, the largest prospective trial in literature that is describing the clinical utility of FGF-23 as a prognostic tool for the prediction of cardiovascular death/HHF, POAF, and death in patients after cardiac valve and/or CABG surgery. The present data highlight that FGF-23 improves risk stratification for HHF, cardiovascular death, and POAF in an unselected patient population undergoing cardiac surgery and fosters individualized patient care in this highly vulnerable patient population. Within our investigation, FGF-23 showed identical discriminatory power as the well-established biomarker NT-proBNP. Interestingly, within a subgroup analysis, FGF-23 tended to be a more powerful predictor of cardiovascular outcomes in patients undergoing CABG surgery or combined CABG/valve surgery compared with lone valve surgery. However, sample size was too low to draw a definite conclusion. Overall, a combined approach of both biomarkers showed promising results in terms of elevated discriminatory power, which could augment the reach of clinical prognostication.

In line with previous reports, we observed high rates of HHF and adverse cardiovascular outcomes in this patient population. These findings emphasize the need for a personalized and integrated prevention strategy to improve cardiovascular outcomes in patients undergoing cardiac surgery.

The glycoprotein FGF-23 belongs to the family of fibroblast growth factors, which exert pleiotropic functions in the human organism, such as controlling metabolic functions and regulation of organogenesis in

Table 2. Baseline Characteristics, Stratified by POAF

Characteristic	Overall (n=451)	POAF (n=184)	No POAF (n=267)	*P* value
Clinical presentation				
Age, median (IQR), y	69.8 (60.4–75.4)	72.4 (65.7–76.7)	67.4 (57.9–74.2)	<0.001*
Sex, female, n (%)	129 (28.6)	63 (34.2)	66 (24.7)	0.028*
Heart rate, median (IQR), bpm	70.0 (62.0–78.0)	70.0 (63.0–77.8)	70.0 (62.0–80.0)	0.952
Systolic BP, median (IQR), mm Hg	131.0 (120.0–142.0)	131.0 (121.0–142.0)	131.0 (118.0–142.0)	0.968
Diastolic BP, median (IQR), mm Hg	72.0 (64.0–80.0)	72.0 (62.0–80.0)	72.0 (64.8–81.0)	0.242
NYHA classification, n (%)				
I	24 (9.2)	10 (8.8)	14 (9.5)	0.848
II	115 (43.9)	46 (40.4)	69 (46.6)	0.311
III	110 (42.0)	53 (46.5)	57 (38.5)	0.195
IV	13 (5.0)	5 (4.4)	8 (5.4)	0.706
LVEF, median (IQR), %	60.0 (54.2–60.0)	60.0 (54.2–60.0)	60.0 (54.2–60.0)	0.862
BMI, median (IQR), kg/m^2	27.3 (24.4–30.1)	27.0 (24.2–30.9)	27.4 (24.5–29.8)	0.913
Type of surgery, n (%)				
Bypass	151 (33.5)	52 (28.3)	99 (37.1)	0.051
Valve	186 (41.2)	72 (39.1)	114 (42.7)	0.450
Bypass+valve	114 (25.3)	60 (32.6)	54 (20.2)	0.003*
Comorbidities, n (%)				
Diabetes	132 (29.3)	59 (32.1)	73 (27.3)	0.278
Hypertension	366 (81.2)	156 (84.8)	210 (78.7)	0.102
Prior MI	119 (26.4)	49 (26.6)	70 (26.2)	0.922
Coronary artery disease	278 (61.6)	116 (63.0)	162 (60.7)	0.611
Heart failure	262 (58.1)	114 (62.0)	148 (55.4)	0.167
Medication, n (%)				
β-Blocker	251 (55.7)	107 (58.2)	144 (53.9)	0.375
ACE inhibitors	136 (30.2)	59 (32.1)	77 (28.8)	0.463
Statins	289 (64.1)	114 (62.0)	175 (65.5)	0.435
Laboratory variables, median (IQR)				
FGF-23, pg/mL	14.4 (8.9–26.7)	16.9 (10.6–30.4)	12.9 (7.8–24.2)	0.001*
NT-proBNP, pg/mL	457.8 (189.4–1222.0)	640.1 (297.1–1757.0)	355.3 (144.4–905.9)	<0.001*
eGFR, mL/min per 1.73 m^2	79.7 (61.9–94.7)	75.0 (57.5–90.7)	82.6 (65.7–97.8)	0.001*
CRP, mg/dL	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.08–0.5)	0.146

Categorical data are presented as counts and percentages and analyzed using χ^2 test. Continuous data are presented as median and the respective IQR and analyzed using Mann-Whitney *U* test. ACE indicates angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and POAF, postoperative atrial fibrillation.
*Statistically significant.

the embryonic state transmitted via binding on the respective FGF receptor with intracellular tyrosine kinase activity.[10] As a bone-derived hormone, FGF-23 is predominately secreted by osteoblasts and osteocytes; nonetheless, under pathologic conditions or excessive strain, FGF-23 can also be synthesized by various tissues, in particular the myocardium.[11] The respective FGF receptors are ubiquitously expressed, and appear in 4 isoforms (FGF receptors 1–4).[12] In the heart, FGF-23 binds independently to FGF receptor 4.[12–14] FGF-23 is crucially involved in regulating phosphate and vitamin D metabolism, and is therefore an essential part of the bone-kidney-parathyroid axis.[5] In physiologic conditions, the parathyroid glands stimulate via parathyroid hormone calcium and phosphate release from osseous tissue into the circulatory system. Subsequently, elevated phosphate plasma levels promote FGF-23 synthesis, which leads to greater renal phosphate excretion and downregulation of vitamin D synthesis (because there is sufficient calcium in the bloodstream).

It is well known that this axis is severely out of balance in chronic kidney disease, and this fosters adverse cardiovascular events. As the renal function decays, phosphate excretion capacity and vitamin D

Table 3. Unadjusted and Adjusted Effects of FGF-23 on POAF

Variable	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	POAF, n/N (%)
FGF-23 continuous	1.40 (1.12–1.76)	0.004*	1.25 (1.01–1.55)	0.040*	
Quartile 1 (reference)	1		1		31/113 (27.4)
Quartile 2	1.88 (1.08–3.29)	0.026*	1.87 (1.04–3.36)	0.037*	47/113 (41.6)
Quartile 3	2.13 (1.22–3.72)	0.008*	1.93 (1.07–3.48)	0.029*	50/112 (44.6)
Quartile 4	2.60 (1.49–4.52)	<0.001*	1.89 (1.02–3.51)	0.043*	56/113 (49.6)

Binary logistic regression models were adjusted for age, sex, hypertension, heart failure, chronic kidney disease, diabetes, coronary artery disease, and body mass index. FGF-23 indicates fibroblast growth factor 23; OR, odds ratio; and POAF, postoperative atrial fibrillation.
*Statistically significant.

synthesis diminish, causing an increase in parathyroid hormone (low calcium) and FGF-23 (high phosphate). This then results in left ventricular hypertrophy, HF, and other adverse cardiovascular events.[5,15,16] Circulatory FGF-23 levels are already recommended for routine assessment within this group of patients, as a predicting biomarker.[17]

Numerous studies have shown that high FGF-23 levels are associated with cardiovascular diseases (ie, HF, atrial fibrillation, myocardial infarction, and stroke) along with elevated risk for both cardiovascular and noncardiovascular mortality.[8,17,18] Furthermore, in a prospective cohort study of 859 patients undergoing cardiac surgery, Speer and colleagues demonstrated that preoperatively measured FGF-23 levels have the same prognostic value as the established European System for Cardiac Operative Risk Evaluation in terms of predicting postoperative complications (ie, acute kidney injury and nonocclusive mesenteric ischemia) and outcome.[8]

Results of the present study are consistent with previous findings, illustrating that patients with high FGF-23 levels show greater cardiovascular and all-cause mortality. It was additionally observed that higher FGF-23 levels are associated with higher risk for the composite of cardiovascular death/HHF.

Concerning patients with HF with reduced ejection fraction, it has been previously demonstrated that FGF-23 independently possesses diagnostic potential to predict worse outcome.[6] Furthermore, a recent study has demonstrated that FGF-23 is a feasible outcome predictor in individuals with HF and preserved ejection fraction.[7]

In this regard, FGF-23 positively correlates with well-established biomarkers, such as NT-proBNP, troponin T, and CRP (C-reactive protein).[6,8,18,19] Given that most studies have found an association between FGF-23 and reduced ejection fraction (EF), elevated FGF-23 plasma levels are thought to be directly linked to systolic dysfunction. In addition, there is an association between patients with a more severe New York Heart Association score and higher FGF-23 levels.[6,18] Participants of the present study showed overall preserved left ventricular systolic function, with a median ejection fraction of 60%.

FGF-23 is able to induce structural changes in the myocardium, by prompting left ventricular hypertrophy and therefore causing greater atrial filling pressure.[20] Over time, this higher strain will lead to enlarged atrial size, which mirrors a major risk factor for atrial fibrillation.[20] Furthermore, results from cell culture and animal models indicate that FGF-23 is involved in abnormal intracellular calcium handling and cardiac fibrosis, which are both related to atrial fibrillation.[17] Several clinical studies have shown that elevated FGF-23 levels are associated with the onset of atrial arrhythmias.[20–22] The proposed pathologic mechanisms for these structural changes are direct interaction of FGF-23 via the FGF 4 receptor, which induces a growth stimulus for cardiac myocytes, and subsequent cardiac fibrosis through upregulation of β-catenin and transforming growth factor-β.[23,24] Moreover, it was observed that FGF-23 is capable of inhibiting angiotensin-converting enzyme 2, and therefore stimulates the renin-angiotensin-aldosterone system, which further promotes cardiac fibrosis and additionally increases fluid retention that might lead to HHF.[23,25,26]

Concerning POAF and FGF-23, plasma levels of FGF-23 were significantly elevated in the POAF group compared with non-POAF individuals within the present study. A crucial aspect of POAF reflects its effect on increased postoperative mortality rates

Table 4. Reclassification Analyses for the Composite Outcome of Cardiovascular Death or HHF

Variable	IDI (95% CI)	*P* value	NRI at the event rate (95% CI)	*P* value
NT-proBNP				
NT-proBNP+FGF-23	0.03 (0.01–0.05)	<0.001*	0.58 (0.34–0.81)	<0.001*

NT-proBNP and FGF-23 were included as log-transformed variables. FGF-23 indicates fibroblast growth factor 23; HHF, hospitalization for heart failure; IDI, integrated discrimination increment; NRI, net reclassification index; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*IDI and NRI and the corresponding *P* values are reported for the comparisons between NT-proBNP and NT-proBNP with FGF-23.

and susceptibility for subsequent atrial fibrillation episodes. Interestingly, the risk of POAF is constant in the upper FGF-23 quartiles, suggesting a threshold effect, whereas the risk of cardiovascular death/HHF increases with increasing quartile. Beyond contributing to the patients' worse outcome, POAF is a financial burden, because it commonly leads to a prolonged intensive care unit and hospital stay. Previous studies report POAF incidence rates in cardiothoracic surgery ranging from 40% to 60% in relation to type of procedure, with higher rates in more complex interventions. Within this regard, a POAF rate of nearly 41% in the entire cohort has been observed in the present investigation. In consideration of these high incidence rates of POAF and the associated consequences on morbidity, this commonly observed complication represents a significant threat on both a patient and a socioeconomic level.[27]

Therefore, a preoperative diagnostic workup that includes relevant biomarkers for an extended POAF risk prediction might be beneficial and may allow detection of vulnerable patients along with prophylactic measures to improve outcome. This early identification of predisposed individuals is of utmost importance to prevent POAF-associated consequences.

Considering the results of the present study, preoperative FGF-23 evaluation provides significant diagnostic yield for identifying patients undergoing cardiac surgery who are at risk for HHF, POAF, and mortality.

In an approach of personalized risk assessment via a preoperative biomarker-based workup, FGF-23 could extend standard clinical evaluation. As consequence, vulnerable patients may benefit from intensified care and prophylactic measures to prevent HF-associated adverse effects, which otherwise may substantially influence the patients' long-term survival.

In this regard, FGF-23 should be considered as an additional diagnostic tool for the prediction of cardiovascular death/HHF, POAF, and all-cause death in patients undergoing cardiac surgery.

Limitations

Despite the prospective study design and the extended follow-up, several limitations should be addressed. First, patients were included from a single tertiary academic site, and therefore, these results might not be generalizable to the general population. In addition, the potential impact of surgical complications might interfere with study outcomes, and because of the nature of the study design, a possible selection bias may be introduced. Furthermore, some cases of HHF might have been underreported because of recall bias. Finally, despite multivariable adjustment for clinical variables and biomarkers, residual confounding is possible.

CONCLUSIONS

Beyond its involvement in physiological processes, FGF-23 proved to be an independent predictor for HHF, POAF, cardiovascular mortality, and all-cause mortality in individuals undergoing elective cardiac valve and/or CABG surgery. Considering these results, circulating plasma FGF-23 analysis extends risk stratification, to allow early identification of patients at risk for adverse cardiovascular events, who might need in-depth clinical attention to prevent worse outcome. Consequently, vulnerable patients may benefit from early interventions to prevent adverse events and reduce both mortality and morbidity.

ARTICLE INFORMATION

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None.

Supplemental Material

Tables S1–S2
Figures S1–S4

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Supplemental Material

Table S1. Baseline characteristics stratified by evaluated risk groups.

	Low risk (n=232)	Intermediate risk (n=130)	High risk (n=89)	p -value
FGF-23, pg/mL (IQR)	9.0 (6.0-11.8)	20.4 (17.3-25.1)	54.6 (40.5-104.0)	**<0.001**
Clinical presentation				
Age, years (IQR)	68.0 (58.8-74.2)	71.1 (61.5-76.1)	71.4 (64.1-76.9)	**0.010**
Sex (male), n (%)	178 (76.7)	86 (66.2)	58 (65.2)	**0.036**
Heart rate, bpm (IQR)	70.0 (61.3-78.5)	70.0 (62.0-78.0)	71.0 (65.0-79.0)	0.245
Systolic BP, mmHg (IQR)	131.0 (120.0-141.0)	130.0 (120.0-143.3)	131.0 (119.3-141.0)	0.951
Diastolic BP, mmHg (IQR)	72.0 (66.0-83.0)	71.0 (61.0-79.0)	68.5 (59.3-75.0)	**0.001**
NYHA, n (%)				
I	15 (11.5)	7 (10.0)	2 (3.2)	0.168
II	62 (47.7)	32 (45.7)	21 (33.9)	0.184
III	49 (37.7)	27 (38.6)	34 (54.8)	0.063
IV	4 (3.1)	4 (5.7)	5 (8.1)	0.312
LVEF, % (IQR)	60.0 (55.0-60.0)	60.0 (50.0-60.0)	60.0 (45.0-60.0)	**0.020**
BMI, kg/m^2 (IQR)	26.9 (24.2-30.1)	27.6 (24.6-30.1)	27.6 (24.3-31.0)	0.672
Type of surgery				
CABG, n (%)	141 (60.8)	73 (56.2)	51 (57.3)	0.660
Valve, n (%)	139 (59.9)	89 (68.5)	72 (80.9)	**0.001**
CABG+Valve, n (%)	48 (20.7)	32 (24.6)	34 (38.2)	**0.005**
Comorbidities				
Diabetes, n (%)	56 (24.1)	37 (28.5)	39 (43.8)	**0.002**
Hypertension, n (%)	186 (80.2)	104 (80.0)	76 (85.4)	0.521
Prior MI, n (%)	55 (23.7)	33 (25.4)	31 (34.8)	0.123
Coronary artery disease, n (%)	146 (62.9)	75 (57.7)	57 (64.0)	0.538
Heart failure, n (%)	130 (56.0)	70 (53.8)	62 (69.7)	**0.044**
Medication				
Beta-blocker, n (%)	117 (50.4)	69 (53.1)	65 (73.0)	**0.001**
ACE-inhibitors, n (%)	64 (27.6)	39 (30.0)	33 (37.1)	0.252
Statins, n (%)	155 (66.8)	84 (64.6)	50 (56.2)	0.204
Laboratory values				
NT-proBNP, pg/ml (IQR)	358.5 (162.7-940.5)	530.8 (229.4-1136.8)	1129.0 (495.2-4424.5)	**<0.001**
eGFR, ml/min/1.73m^2 (IQR)	84.4 (70.1-98.5)	80.9 (63.1-95.6)	59.3 (43.6-79.7)	**<0.001**
CRP, mg/dl (IQR)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.3 (0.1-0.8)	**0.010**

Categorical data are presented as counts and percentages and analyzed using Chi-square-test. Continuous data are presented as median and the respective interquartile range and analyzed using Kruskal Wallis Test.

ACE, angiotensin converting enzyme; BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Classification.

Table S2. Relationship between quartiles of FGF-23 and the risk of death and hospitalization for heart failure.

	CV death/HHF Adj. HR (IQR)	HHF Adj. HR (IQR)	CV death Adj. HR (IQR)	All-cause death Adj. HR (IQR)
Q1 (Reference)	1	1	1	1
Q2	1.01 (0.43-2.65)	1.56 (0.37-6.57)	1.12 (0.37-3.35)	0.85 (0.34-2.12)
Q3	2.32 (1.07 -5.05)	1.87 (0.45-7.67)	2.58 (1.02-6.55)	2.01 (0.94-4.31)
Q4	3.51 (1.64-7.51)	5.02 (1.39-18.21)	3.78 (1.52-9.40)	2.77 (1.31-5.87)

Cox regression models were adjusted for age, sex, hypertension, chronic kidney disease, diabetes, heart failure, coronary artery disease, body mass index.

CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; IQR, interquartile range; Q, quartile.

Figure S1. Kaplan Meier curves and the corresponding 4-year Kaplan-Meier event rates for CV death/HHF stratified by quartiles of FGF-23.

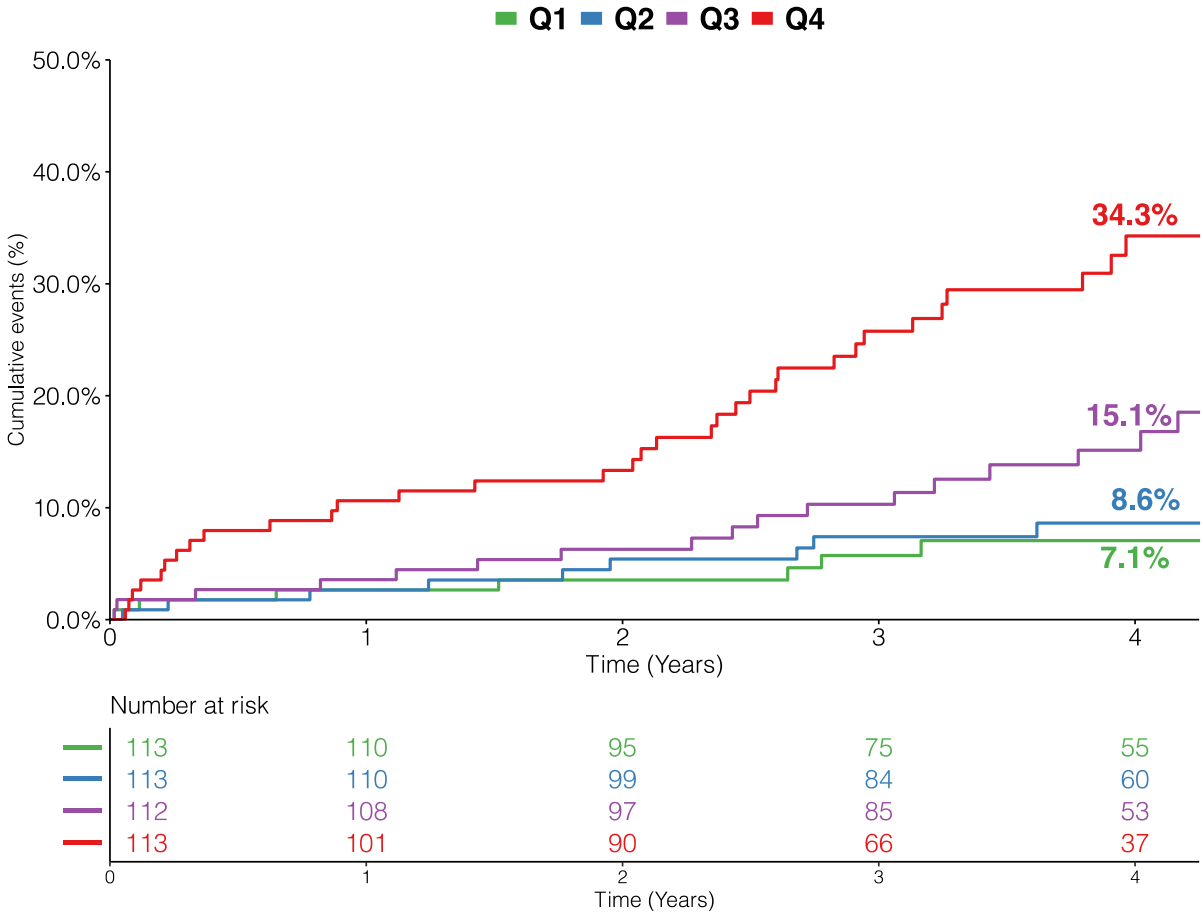


Figure S2. Kaplan Meier curves and the corresponding 4-year Kaplan-Meier event rates for CV death/HHF stratified by an FGF-23 cut-off value of 21 pg/mL.

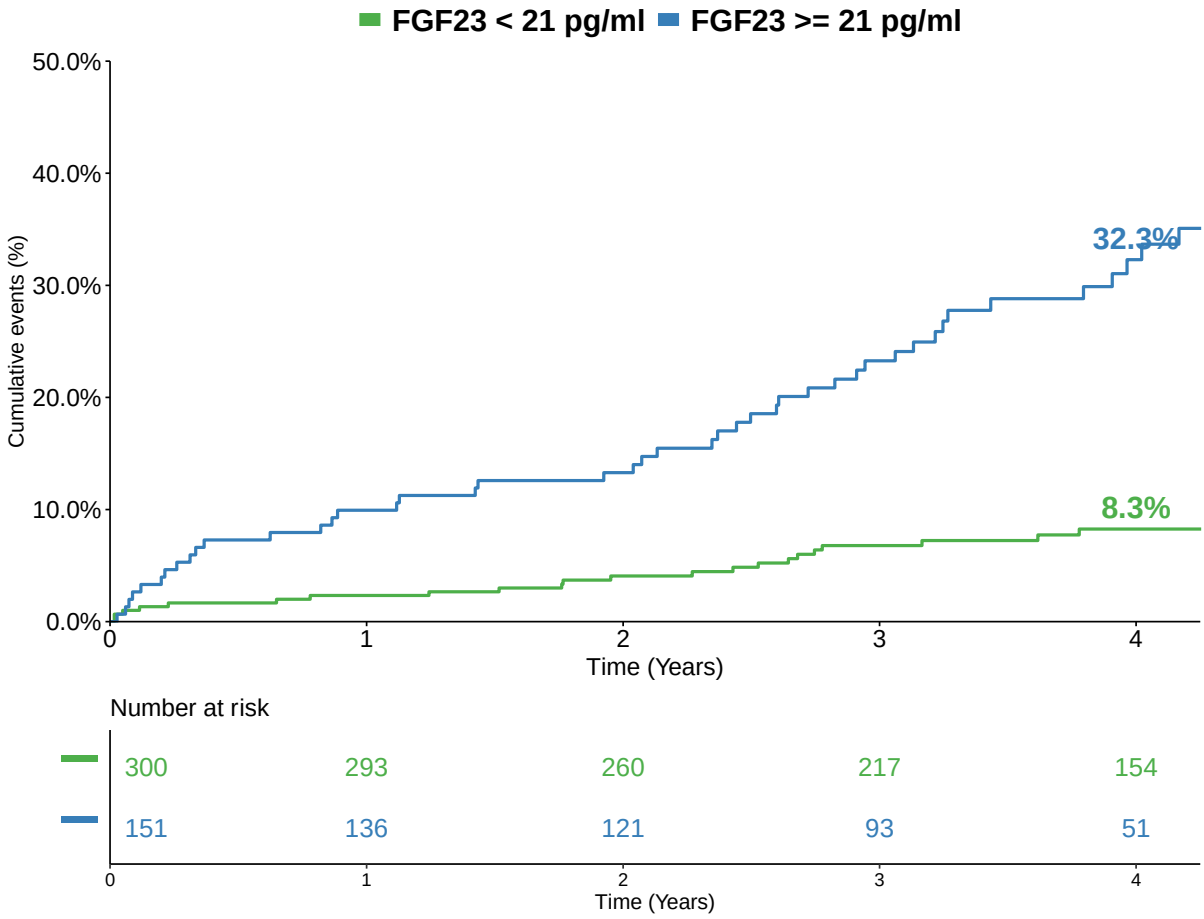
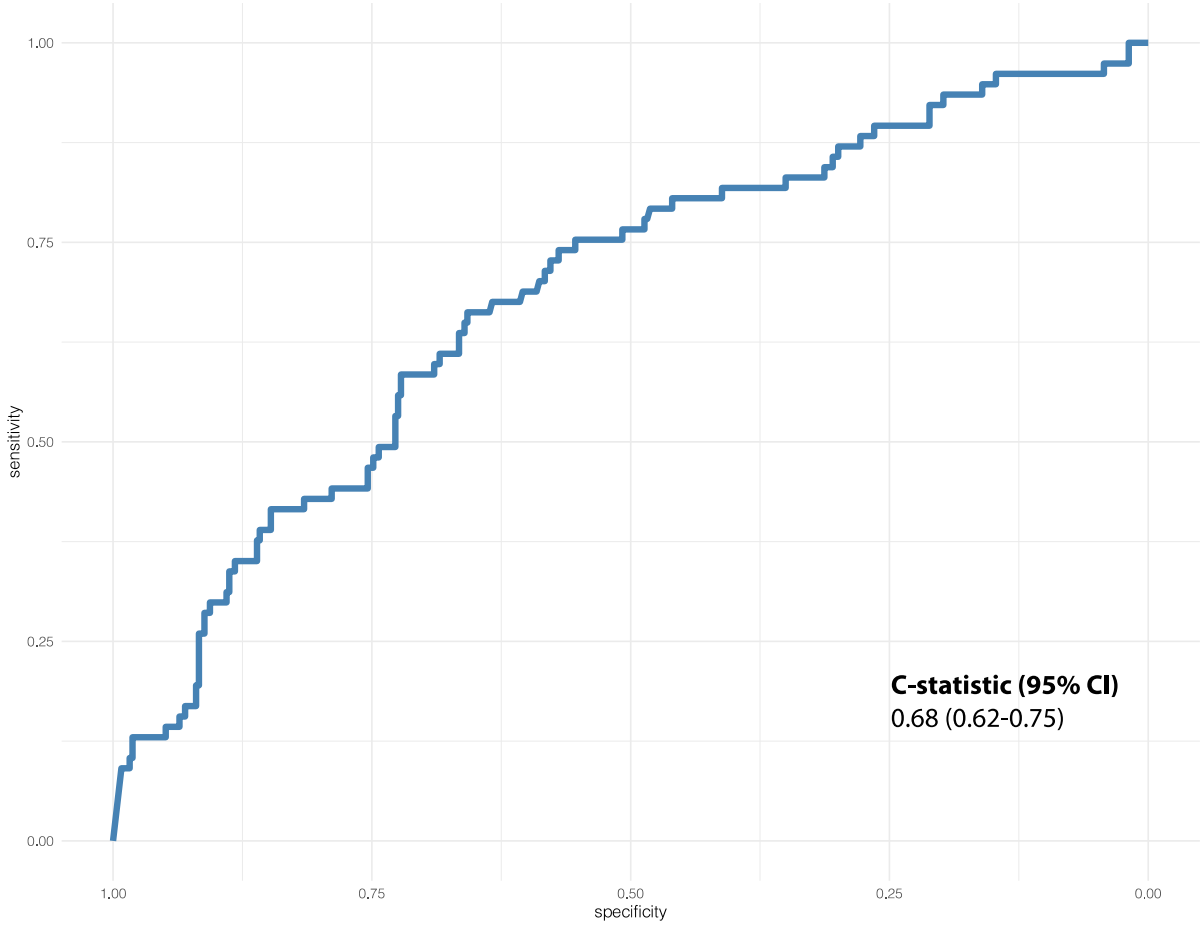
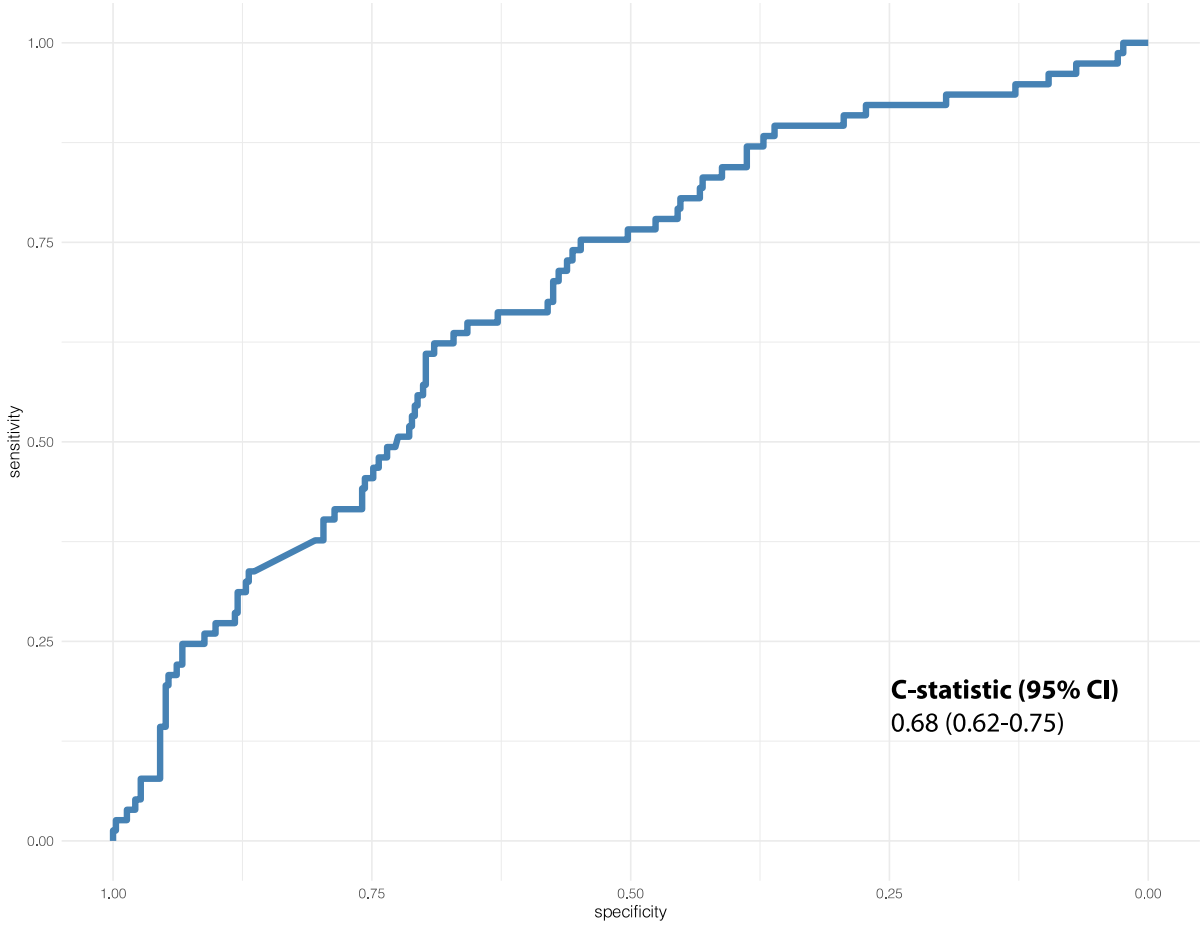


Figure S3. ROC curve of FGF-23 for the discrimination of CV death/HHF.



CV = cardiovascular; FGF-23 = fibroblast growth factor 23; HHF = hospitalization for heart failure; ROC = receiver operating characteristic

Figure S4. ROC curve of NT-proBNP for the discrimination of CV death/HHF.



CV = cardiovascular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; HHF = hospitalization for heart failure; ROC = receiver operating characteristic