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The association of circulating fibroblast growth factor 21 levels with incident heart failure: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Fibroblast growth factor 21 (FGF21) levels are often elevated in heart failure (HF), although this has not been assessed using a longitudinal study design. Therefore, we investigated the association between baseline plasma FGF21 levels and incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: A total of 5408 participants, free of clinically apparent cardiovascular disease, were included in the analysis, of which 342 developed HF over a median follow-up period of 16.7 years. Multivariable Cox regression analysis was performed and the additive value of FGF21 in the performance of risk prediction over other well-established cardiovascular biomarkers was assessed.

Results: The mean age of the participants was 62.6 years with 47.6 % male. Regression spline analysis demonstrated a significant association of FGF21 levels with incident HF among participants with FGF21 levels ≥239.0 pg/mL (hazard ratio = 1.84 [95 % confidence interval 1.21, 2.80] per SD increase in ln-transformed levels) after adjustment for traditional cardiovascular

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CRediT authorship contribution statement

William Tucker: Conceptualization, Methodology, Data curation, Software, Formal analysis, Writing – original draft. **Robyn L. McClelland:** Methodology, Writing – review & editing. **Matthew A. Allison:** Conceptualization, Methodology, Writing – review & editing. **Moyses Szklo:** Methodology, Writing – review & editing. **Kerry-Anne Rye:** Methodology, Supervision, Writing – review & editing. **Kwok Leung Ong:** Conceptualization, Validation, Methodology, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2023.155535.

risk factors and biomarkers, but not in participants with FGF21 levels <239.0 pg/mL (p for heterogeneity = 0.004). Among participants with FGF21 levels ≥239.0 pg/mL, FGF21 levels were associated with HF with preserved ejection fraction (HR [95 % CI] = 2.57 [1.51, 4.37]), but not HF with reduced ejection fraction.

Conclusions: The present study suggests baseline FGF21 levels could predict the development of incident HF with preserved ejection fraction, among participants with elevated FGF21 levels at baseline. This study may suggest a pathophysiological role of FGF21 resistance in HF with preserved ejection fraction.

Keywords

Fibroblast growth factor 21; Heart failure; Heart failure with preserved ejection fraction; Biomarker; Multi-Ethnic Study of Atherosclerosis

1. Introduction

Heart failure (HF) is a chronic, progressive clinical syndrome characterised by an inability to generate a cardiac output sufficient to meet physiologic demands [1]. Clinically, HF is a major global health problem with a 5-year mortality rate of 45 % [2] and a prevalence that is predicted to rise with ageing. The progressive nature of the condition results in a significant economic burden, with the average annual healthcare costs for a patient with HF amounting to approximately $27,000 in the Western world [3]. As such, it is paramount that individuals at increased risk or in the early stages of HF be identified to facilitate early intervention.

Recent studies have suggested fibroblast growth factor 21 (FGF21) as a promising biomarker candidate for HF. FGF21 is a peptide hormone that is involved in energy homeostasis. It protects against various pathophysiologic processes intrinsically related to HF development, namely cardiac oxidative stress [4], hypertrophy [5] and inflammation [5] as demonstrated in animals and in vitro cell culture studies. In clinical studies, however, FGF21 levels are often elevated in cardiovascular diseases, including HF [6,7]. The paradoxical increase reported in these conditions has been suggested to be due to FGF21 resistance [8,9].

Previous studies have assessed the relationship between FGF21 levels and prevalent HF using cross-sectional study designs. The majority of such studies confirm an association between elevated FGF21 levels and HF, however, conclusions are limited by small sample sizes, a lack of information on cohort ethnicity and differing baseline characteristics [10]. As such, this study aimed to investigate the prospective association between baseline FGF21 levels and incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA), a large, ethnically diverse cohort of participants free of clinically apparent cardiovascular disease (CVD) at baseline [11]. In this study, we additionally assessed the association of FGF21 levels with HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).

2. Materials and methods

2.1. Study participants

MESA is a prospective cohort study of participants free of clinically apparent CVD at baseline, designed to assess risk factors, prevalence, and progression of subclinical CVD. Details regarding the MESA study design have been described previously [11]. Briefly, the cohort is comprised of 6814 men and women, aged 45–84 years from four major racial/ethnic groups, namely non-Hispanic Whites, African Americans, Hispanic Americans, and Chinese Americans. Participants were recruited in 2000–2002 from six field centers across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY, and St. Paul, MN) and were followed up for CVD events, including HF, up to 31 December 2018. Sampling was performed to provide balanced recruitment across strata defined by gender, ethnicity, and age group (45–54, 55–64, 65–74, and 75–84 years). The study was approved by institutional review boards at all participating centres. Informed written consent was obtained from participants upon arrival at the relevant field center. A random subgroup of approximately 1000 participants had limited availability of plasma samples for FGF21 measurement, leaving 5792 participants in the final population with valid data on plasma FGF21 levels. After further excluding 23 participants with missing data on incident HF, 4 participants with pre-existing peripheral vascular disease at baseline and 357 with self-reported liver/kidney disease at baseline, a total of 5408 participants were included in this analysis (Supplementary Fig. 1). To avoid potential confounding, participants with baseline liver and kidney diseases were excluded from the analysis. This is because FGF21 is primarily secreted by the liver, and both liver and renal functions are closely related to cardiac function, with the circulating FGF21 levels often elevated in participants with both these conditions [12,13].

2.2. FGF21 measurement

At baseline exam, using standard venepuncture technique, peripheral venous blood samples were collected from participants following a 12-h fast. FGF21 levels were measured in plasma samples using enzyme-linked immunosorbent assay kits (Antibody and Immunoassay Services, University of Hong Kong, Hong Kong) as previously described [14]. These samples were stored at −70 °C for >14–16 years before FGF21 measurement. Intra-assay and inter-assay coefficients of variation were both <10 %. Technicians that performed the analyses were blinded to participant information and identity.

2.3. Other covariates of interest

A standardized questionnaire was used to ascertain information on participant demographics, socioeconomic status, medical and family history, medication use, smoking status, smoking pack-years, alcohol consumption, and physical activity. Resting blood pressure (BP) was assessed at the baseline exam utilizing a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) along with height and weight for calculation of body mass index (BMI). Seated blood pressure was measured three times with the final two readings averaged for use in the analysis. Coronary artery calcium (CAC) was measured with either electron-beam computed tomography or multidetector computed tomography. The extent of calcification was quantified using the

Agatston scoring method [15]. Cardiac magnetic resonance imaging (MRI) was used for measurement of left ventricular (LV) mass, LV end diastolic and systolic volume and LV ejection fraction [16]. Of the 6814 participants, 5098 participants underwent cardiac MRI of which 5004 had valid data [17].

Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were assayed as described previously [18]. The Friedewald equation was utilized to estimate low-density lipoprotein (LDL) cholesterol in plasma samples with a triglyceride value <400 mg/dL. LDL cholesterol in samples with a triglyceride value >400 mg/dL were not measured. Serum fasting glucose was determined by reflectance spectrophotometry with the Vitros analyser (Johnson & Johnson Clinical Diagnostics, Rochester, NY). The estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration Eq. [19]. The homeostasis model assessment of insulin resistance index (HOMA2-IR) was calculated as described previously [20]. Interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, N-terminal pro-brain natriuretic peptide (NT-proBNP), and γ-glutamyl transferase (GGT) levels were measured as previously described [21–23].

2.4. HF and coronary heart disease determination

Participants were contacted at 9–12-month intervals to identify CVD events, including HF and coronary heart disease (CHD). Self-reported cardiovascular events were confirmed by requesting hospital or outpatient medical record documentation. Trained personnel abstracted medical records indicating any possible CVD events which were then reviewed independently by two physicians for event classification [18]. Disagreements between physicians were adjudicated by a third reviewer for final endpoint classification. HF diagnosis was defined as probable or definite HF. Probable HF included participants who had been diagnosed as having HF by a physician and were receiving treatment. HF was classified as definite if one or more of the following criteria were also present: evidence of pulmonary edema/congestion on chest X-ray, dilated ventricle, poor left ventricular (LV) function on echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction. Definite and probable HF were combined as the endpoint in this study. In patients with a recorded ejection fraction, the first HF event was classified as HFrEF or HFpEF, which were defined as ejection fraction <45 % and ≥ 45 % respectively [24]. CHD was defined as the composite endpoint of myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina, and CHD death.

2.5. Statistical analysis

Statistical analysis was conducted using SPSS 28 (IBM, Armonk, NY), STATA 17 (StataCorp, College Station, TX) and R 4.2.1 (The R Core Team, Vienna, Austria). Comparison of baseline clinical characteristics between participants with and without incident HF was performed by chi-square test for categorical variables and independent *t*-test for continuous variables. Adjustment for age, sex, and race/ethnicity was performed using Cox regression analysis. Variables with highly skewed distributions were transformed using natural logarithms (ln) prior to analysis. Participants with missing data for a variable

were excluded from the analysis of that variable. Unless otherwise stated, a p value <0.05 was considered statistically significant.

The correlates of ln-transformed plasma FGF21 levels were assessed by multivariable linear regression analysis. Regression coefficients (B) were expressed as the percentage change in FGF21 levels per one standard deviation (SD) increment in continuous variables. Data were presented as unadjusted and then subsequently adjusted for age, sex, and race/ethnicity in model 1. In order to decrease the beta error, variables with $p < 0.2$ in model 1 were then used as covariates for adjustment in model 2. In the full adjustment model, no multicollinearity was identified based on variance inflation factors (<3.0 for all variables).

Cumulative survivals across FGF21 quartiles were estimated by the Kaplan-Meier method and compared by the log-rank test. The association of baseline FGF21 levels with incident HF and its two sub-types (HFpEF and HFrEF) was assessed by Cox regression analysis. The proportional hazard assumption was checked by using Schoenfeld residuals. Hazards ratio (HR) and 95 % confidence interval (CI) were expressed per one SD increase in ln-transformed FGF21 levels. In model 1, data was adjusted for demographic and socioeconomic variables, including age, sex, race/ethnicity, education, and family income. Model 2 was further adjusted for traditional cardiovascular risk factors, including body mass index (BMI), physical activity, smoking, smoking pack-years, alcohol consumption, LDL cholesterol, HDL cholesterol, triglycerides, lipid-lowering medications, eGFR, systolic blood pressure (SBP), anti-hypertensive medications, diabetes, and HOMA2-IR. In model 3, the data were further adjusted for well-established CVD risk biomarkers, including CRP, IL-6, fibrinogen, and NT-proBNP. NT-proBNP and FGF21 levels were highly skewed and were ln-transformed in the Cox regression analysis to prevent unstable estimates given extreme values may impact estimation of the regression coefficient. CRP and IL-6 were also skewed however to a lesser extent and therefore not ln-transformed in the analysis. In a separate analysis, similar results were obtained when using ln-transformed CRP and IL-6. The relationship of FGF21 levels with incident HF were assessed for potential nonlinearity using restricted cubic regression splines by the “mvrs” program in STATA. The relationship was allowed to be nonlinear with a maximum of 4 knots and knot positions being determined according to equally spaced percentiles of the continuous FGF21 distribution. We assumed a linear relationship of all other covariates with incident HF. When nonlinearity was detected, the approximate knot positions were used to fit regression analyses within strata defined by these thresholds.

All analyses were assessed for potential interactions by sex and race/ethnicity. The p for heterogeneity was estimated by including the multiplicative interaction term in the regression models in the full sample after adjusting for the main effects of the covariates. In a separate analysis, a time-dependent Cox regression model was used to account for the possibility that interim incident CHD might have been a confounder. A sensitivity analysis was performed with further adjustment for GGT levels and CAC score to assess the potential confounding effect of liver function and subclinical atherosclerosis, respectively. In a separate analysis, data was further adjusted for health insurance status to minimize the confounding effect of access to health care. In a separate sensitivity analysis, the analysis was repeated after removing the first 3 and 5 years of follow-up separately to reduce

potential reverse causality. Furthermore, given FGF21 levels can be affected by heavy drinking and are related to alcohol appetite [25], a subgroup analysis was performed with participants categorised by the number of alcoholic drinks per week. Finally, the incremental value of the addition of ln-transformed FGF21 levels in risk prediction model for HF was assessed by the change in Harrell's C-statistic using the likelihood ratio test and the category-free net reclassification improvement (NRI > 0) as previously described [26,27]. The May and Hosmer test was used to assess the goodness-of-fit of the risk prediction models [28].

3. Results

3.1. Baseline characteristics

A total of 5408 participants were included in the analysis, of which 342 developed HF over a median follow-up period of 16.7 years. Compared to 1406 excluded participants, those included in the study were older and a higher proportion were African American (Supplementary Table 1).

The baseline characteristics of the included participants are shown in Table 1. Participants with incident HF were older, and more likely to be male, have diabetes and take anti-hypertensive medications at baseline. Such participants had higher BMI, number of pack-years of smoking, triglycerides, BP, HOMA2-IR, IL-6, CRP, NT-proBNP, FGF21 and fibrinogen levels, and lower HDL cholesterol and eGFR. Among participants with incident HF, there was a larger proportion of African Americans and Non-Hispanic Whites. Those that developed HF also had a lower education attainment level and family income. There were also significant differences in cardiac MRI parameters, with higher LV end diastolic mass, LV end diastolic volume, LV end systolic volume and LV stroke volume, and a lower LV ejection fraction among incident HF patients.

As shown in Supplementary Table 2, participants who developed HFpEF were older, more likely to be female and Chinese American, and less likely to be African American as compared to those who developed HFrEF.

The association between each covariate and FGF21 levels are illustrated in Table 2. In the final multivariable model, FGF21 levels were higher with higher age, triglycerides, systolic BP, HOMA2-IR, IL-6 and CRP levels. The levels were also higher in current smokers and participants with diabetes. FGF21 levels were lower in former drinkers, as well as in Chinese and African American ethnicities. In addition, the levels were lower with higher physical activity, eGFR and fibrinogen levels.

3.2. FGF21 and incident HF

As shown in Fig. 1, HF incidence increased from the lowest to the highest FGF21 quartile. Table 3 shows the association of baseline FGF21 levels with incident HF. In model 1, higher baseline FGF21 levels were associated with HF development. However, the association became non-significant after adjustment for traditional CVD risk factors in model 2. Similar non-significant results were obtained when assessing FGF21 quartile levels (Supplementary Table 3). However, when assessing the non-linear relationship of FGF21 levels with

incident HF, an approximate knot position of 5.48 in ln-transformed FGF21 levels, which corresponded to an FGF21 level of 239.0 pg/mL (i.e. 74th percentile), was found (Fig. 2). In participants with an FGF21 level ≥ 239.0 pg/mL, a significant association of ln-transformed FGF21 levels with incident HF was observed (HR [95 % CI] = 1.84 [1.21, 2.80]) even after adjustment for traditional CVD risk factors and CVD risk biomarkers, but not in those with FGF21 level < 239.0 pg/mL (p for heterogeneity = 0.004). No significant heterogeneity with sex and race/ethnicity was found. Supplementary Table 4 shows the baseline characteristics of the participants with FGF21 levels <239.0 and ≥ 239.0 pg/mL.

3.3. FGF21 levels in HFpEF and HFrEF

As shown in Table 3, there was a significant association between baseline FGF21 levels and HFpEF in model 1 that became non-significant with adjustment for traditional CVD risk factors. However, a significant association was found with HFpEF in the full adjustment models (HR [95 % CI] = 2.57 [1.51, 4.37]) in participants with FGF21 levels ≥239.0 pg/mL, but not in those with FGF21 level < 239.0 pg/mL (p for heterogeneity <0.001). No association was found between baseline FGF21 levels and HFrEF in any of the analyses. No significant heterogeneity with sex and race/ethnicity was found.

3.4. Sensitivity analyses

In sensitivity analyses, the association of baseline FGF21 levels with incident HF and HFpEF among participants with FGF21 levels ≥239.0 pg/mL remained significant after further adjustment for GGT levels and/or CAC score, or health insurance status, as well as after removing the first 3 and 5 years of follow-up separately (Supplementary Table 5). As shown in Supplementary Table 6, among 3912 participants with data on cardiac MRI parameters, the associations of FGF21 levels with incident HF and HFpEF among participants with FGF21 levels ≥239.0 pg/mL at baseline remained statistically significant after further adjustment for cardiac MRI parameters. In a separate analysis, the association of baseline FGF21 levels with incident HF and HFpEF among participants with FGF21 levels ≥239.0 pg/mL remained statistically significant after further adjustment for incident CHD as a time-dependent variable (Supplementary Table 7). Moreover, there were no statistically significant differences between the observed association with HF across alcohol consumption levels (Supplementary Table 8).

3.5. Incremental predictive performance of elevated FGF21 levels for HFpEF

As FGF21 levels predicted incident HFpEF, but not HFrEF, we assessed the incremental predictive performance of elevated FGF21 levels for HFpEF among all participants using a piecewise Cox regression model with two slopes and a change point at a FGF21 level of 239.0 pg/mL. As shown in Table 4, among the 5 biomarkers, including FGF21, only NT-proBNP increased the HF risk prediction performance when compared to a base model with only demographic factors and traditional CVD risk factors as assessed by both C-statistics and NRI. Nevertheless, FGF21 could further improve the predictive performance of a model containing NT-proBNP, regardless of the presence or absence of the other three biomarkers. All the examined models exhibited a high goodness of fit.

4. Discussion

To our knowledge, the present study was the first to investigate the relationship of circulating FGF21 levels with incident HF with a longitudinal study design. Our study showed a threshold for the relationship of FGF21 levels with incident HF, in which FGF21 levels were significantly associated with incident HF exclusively in participants with elevated baseline FGF21 levels. Stratifying HF into its respective subtypes, we observed that FGF21 levels were related to incident HFpEF, but not HFrEF. No significant heterogeneity was found with sex and racial/ethnic groups in all the analyses. Additionally, FGF21 could improve the risk prediction of HFpEF over a model with traditional CVD risk factors and NT-proBNP.

The finding of raised circulating FGF21 levels in HF in humans is paradoxical to preclinical evidence where FGF21 attenuated cardiac oxidative stress [4], hypertrophy and inflammation [5] in animal and in vitro studies, therefore potentially protecting against the development of HF. This suggests that the elevated circulating FGF21 levels could be due to a compensatory response to comorbid metabolic conditions which precipitated HF. Alternatively, it may be due to the presence of FGF21 resistance which is caused by the impaired expression and downstream signalling pathways of the FGF21 receptor complex, leading to the need for a higher FGF21 level to exert its normal physiological function [8,29,30]. The phenomenon of FGF21 resistance was first discovered in relation to the liver and adipose tissue [8], however, impaired cardiac expression of the FGF21 receptor complex has since been reported in obese rats [31]. This suggests that FGF21 resistance occurs in the heart and in response to obesity, a risk factor for HF.

In this study, an association between baseline FGF21 levels and incident HF was found exclusively among participants with elevated FGF21 levels at baseline. One possible explanation may relate to the presence of FGF21 resistance. We hypothesize that an increase in FGF21 levels beyond the cut-off value of 239.0 pg/mL may represent more severe FGF21 resistance and therefore a greater extent of underlying metabolic/cardiac dysfunction related to HF development such as oxidative stress and inflammation. At a level below this cut-off value, FGF21 and its downstream signalling pathways may function normally with minimal or absent FGF21 resistance, and therefore increases in FGF21 within this range may reflect its normal physiological and metabolic properties. Further studies are needed to validate our hypothesis and assess whether the relationship of FGF21 with other cardiometabolic conditions would be stronger beyond a particular FGF21 level and whether such observations could be replicated in other independent cohorts.

In concordance with previous studies, higher FGF21 levels were associated with an adverse CVD risk profile [32]. However, our study results do not support an association of higher FGF21 levels with higher physical activity as reported previously [33]. Our study additionally reported an association of lower fibrinogen levels with a higher FGF21 level which is also not consistent with results in previous studies [34,35]. However, this association is not appear well-established [14] and may vary depending on patient characteristics.

In the present study of participants with elevated FGF21 at baseline, higher FGF21 levels were associated with incident HFpEF but not HFrEF. This suggests that FGF21 levels may potentially be able to identify people at risk of different HF subtypes. This is important considering the substantial differences between HFpEF and HfrEF. The identification of FGF21 as an effective biomarker would assist in the early detection of high-risk patients, hence improving early treatment decisions and outcomes. Our study suggests that FGF21 is likely better suited to a multi-biomarker panel where it can further improve the performance of a model with traditional risk factors and NT-proBNP for prediction of incident HfpEF. The natriuretic peptides are the gold standard for biomarkers for HF in clinical practice. However, as they are limited by low specificity [36], FGF21 may be of value in improving its diagnostic capabilities. Further studies are needed to investigate the clinical value of FGF21 levels in the prognosis and management of patients with HF.

In previous cross-sectional studies, FGF21 has been shown to be elevated in both HFrEF and HFpEF [10]. The underlying mechanism for FGF21 elevation in HFpEF may relate to the presence of congestive hepatopathy, which may act as a signal for FGF21 production in a hepatic to cardiac signalling loop [37] that feeds back to the heart where it exerts its cardioprotective functions. Given liver pathologies such as non-alcoholic liver disease and complications such as congestive hepatopathy are more prevalent in HFpEF than in HFrEF [38,39], raised FGF21 levels in HFpEF may reflect this compensatory protective feedback loop. As such, it was hypothesised that congestive hepatopathy may be responsible for the elevation in FGF21 in those who developed HFpEF. Although participants with self-reported liver disease were excluded in the present study, the presence of subclinical or undiagnosed congestive hepatopathy may contribute to the relationship between FGF21 and incident HFpEF. GGT is a cell surface enzyme widely used to diagnose hepatobiliary pathologies and is often elevated in patients with congestive hepatopathy [40]. However, further adjustment for GGT did not attenuate the association in a sensitivity analysis. Nevertheless, GGT is not a well-established specific marker for congestive hepatopathy. Furthermore, congestive hepatopathy does not exclusively occur in HFpEF and may also be present in HFrEF if there is right-sided ventricular involvement. Another potential reason for the elevation of FGF21 levels in HFpEF may be due to the recognised central role of metabolic disturbances and inflammatory pathways to the pathophysiology of HFpEF [41]. This is in contrast to HFrEF where the involvement of metabolic dysregulation in the development of HFrEF is less pronounced than that in HFpEF [42]. Given FGF21 levels are related to glucose and lipid metabolism, in the setting of FGF21 resistance, the prevalence of metabolic dysregulation in HFpEF may account for the elevation in FGF21 levels. Nonetheless, BMI, triglycerides and cholesterol levels as well as diabetes status were variables that were adjusted for in this study. In summation, further research is required to elucidate the pathophysiologic role of FGF21 in HFpEF.

FGF21 in its native form has poor pharmacological properties and hence various analogues have been developed. Current clinical trials on FGF21 have focused predominantly on non-alcoholic steatohepatitis [43] and hypertriglyceridemia due to its potent lipid-lowering effects, despite the elevation of endogenous FGF21 levels in humans under these conditions [13,44]. FGF21 analogues have not yet met the endpoints of glycaemic control for type 2 diabetes, however, the combination of such drugs with antidiabetic medications has

produced potent antidiabetic effects. Despite these efforts, there have not yet been any clinical trials on the application of FGF21-based treatments to CVDs [45]. The findings from the present study may provide valuable insights regarding the future therapeutic potential of FGF21 for HF. Interestingly, the effects of sodium-glucose co-transporter 2 inhibitors, the first medication to improve cardiovascular outcomes in patients with HFpEF, are, in part, mediated by FGF21 [46–48]. Nevertheless, a recent study using Mendelian randomization did not support a causal role of FGF21 in HF [49]. However, it should be noted that this previous study was performed in the general populations of European ancestry and there was no data on the individual subtype of HF, whereas the association between baseline FGF21 and incident HFpEF observed in the present study was found only in participants with elevated FGF21, which may indicate the presence of FGF21 resistance. Additionally, Mendelian randomization is limited by the unknown functional status of the measured genes on other variables of interest. Further studies are needed to elucidate the potential pathophysiological role of FGF21 in HF.

This study benefits from utilizing data from the well-established MESA cohort, a large, multi-ethnic study with standardized protocols for measurement of sociodemographic, clinical characteristics and outcome events. Moreover, data on several important CVD risk biomarkers, namely CRP, fibrinogen, IL-6, and NT-proBNP, were available as covariates in the adjustment model. However, this study also has some limitations. FGF21 levels were measured at baseline only which precluded longitudinal analysis of the relationship between change in FGF21 levels and incident HF. Moreover, local tissue expression of FGF21 in the heart was not ascertained as in previous studies, only its circulating levels. We also could not exclude the possibility of residual confounding due to unmeasured confounding variables, as well as selection bias due to missing data in some covariates and HF subtype. Finally, the small number of incident HF cases also limited the further study of the two HF subtypes. Although the large sample size and the multi-ethnic study design of the MESA cohort as well as the use of different sensitivity analyses should enhance the generalisability of our findings, further studies in an independent cohort with similar participant characteristics are needed to validate the current findings.

In conclusion, the present study demonstrated a significant association of baseline FGF21 levels with incident HFpEF among participants with elevated baseline FGF21 levels. A larger independent longitudinal study analysing both HF subtypes will be required to validate the results of the present study given the potential limitations of residual confounding in the present study. Nevertheless, our findings may provide a good rationale for further preclinical and clinical studies to assess the potential therapeutic role of FGF21 analogues in the prevention and management of HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
CAC	coronary artery calcium
CHD	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
FGF21	fibroblast growth factor 21
FGFR	fibroblast growth factor receptor
GGT	serum γ-glutamyl transferase
HDL	high density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HOMA2-IR	homeostasis model assessment of insulin resistance index
HR	hazards ratio
IL-6	interleukin 6

LDL	low density lipoprotein
LV	left ventricular
LVEF	left ventricular ejection fraction
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	magnetic resonance imaging
NRI	net reclassification improvement
NT-proBNP	N-terminal pro-brain natriuretic peptide
ln	natural logarithm
SD	standard deviation

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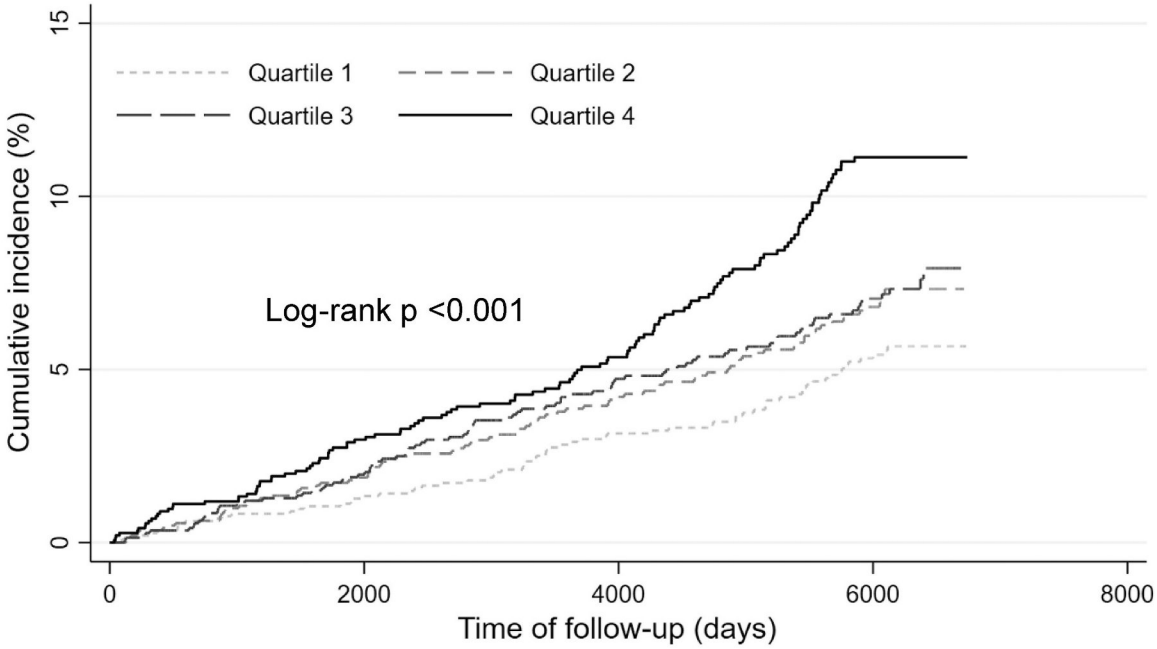

Fig. 1.
Unadjusted Kaplan-Meier curves of HF development across FGF21 quartiles.

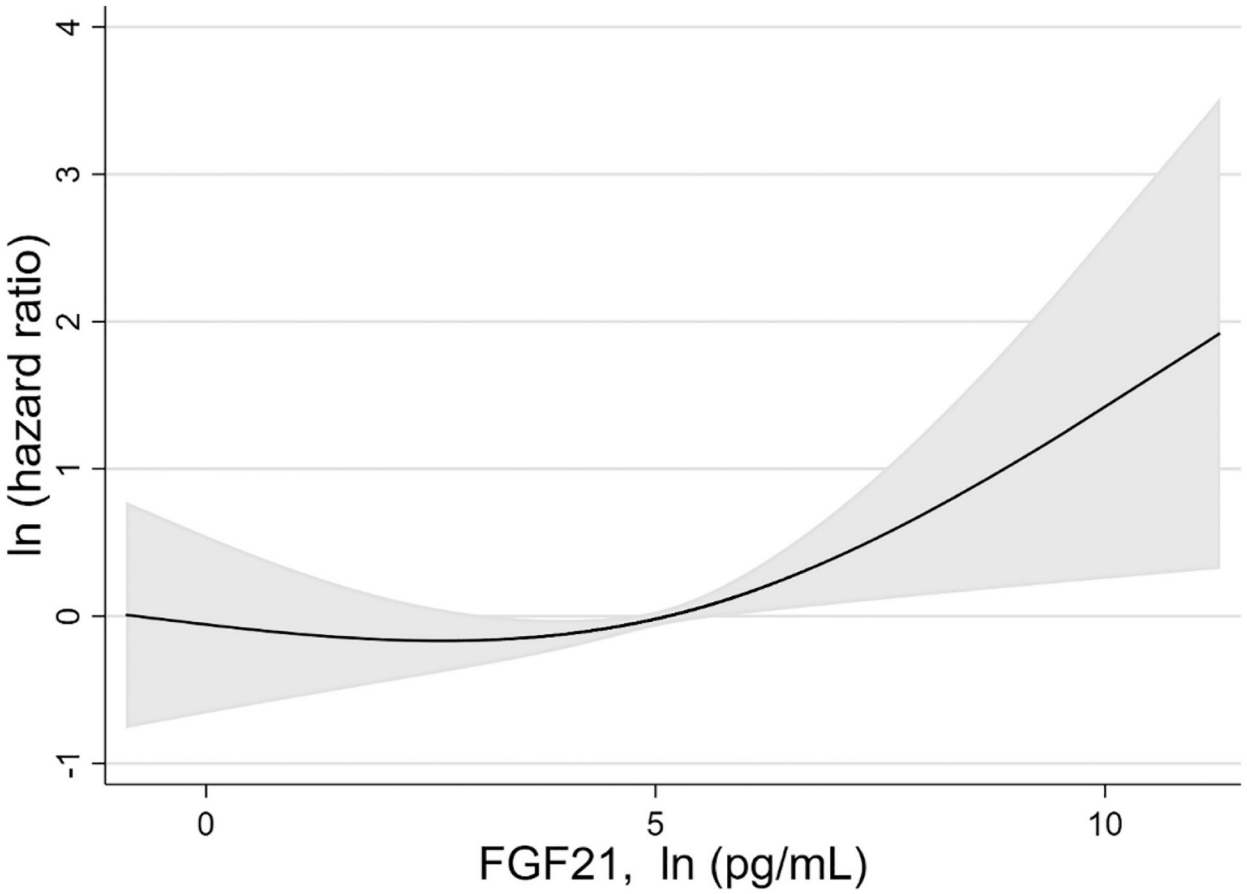

Fig. 2.

A plot of ln-transformed hazards ratio versus ln-transformed FGF21. The curve illustrates a cut-off value in ln-transformed FGF21 levels of approximately 5.48 (i.e. a FGF21 level of 239.0 pg/mL) for HF risk prediction following which the hazards ratio increases. The gray area indicates the 95 % CI.

Table 1

Baseline characteristics of the MESA participants included in the study.

Characteristics	n	No HF (*n* = 5066)	FH (*n* = 342)	p	Adjusted p[b]
Age (years)	5408	62.3 (10.2)	68.3 (9.2)	<0.001	<0.001
Male (%)	5408	47.0 (2380)	56.1 (192)	0.001	<0.001
Race/ethnicity (%)	5408				
Non-Hispanic White	2043	37.7 (1908)	39.5 (135)	0.073	0.009
African American	1600	29.4 (1488)	32.7 (112)		
Hispanic American	1149	21.3 (1079)	20.5 (70)		
Chinese American	616	11.7 (591)	7.3 (25)		
Education (%)	5391				
<high school	971	17.7 (896)	22.0 (75)	0.011	0.028
High school	2274	42.0 (2119)	45.5 (155)		
>high school	2146	40.3 (2035)	32.6 (111)		
Family income (%)	5177				
<$30,000	1940	36.8 (1788)	46.9 (152)	<0.001	0.006
$30,000–$75,000	2057	39.9 (1936)	37.3 (121)		
>$75,000	1180	23.3 (1129)	15.7 (51)		
Body mass index (kg/m^2)	5408	28.2 (5.4)	29.6 (5.9)	<0.001	<0.001
Physical activity[a] (MET-hour/week)	5393	67.3 (32.8–125.0)	58.3 (25.3–108.9)	0.042	0.133
Smoking (%)	5391				
Never	2704	50.6 (2554)	44.0 (150)	0.019	0.053
Former	2007	36.8 (1856)	44.3 (151)		
Current	680	12.7 (640)	11.7 (40)		
Pack years of smoking	5333	11.0 (20.1)	15.5 (26.3)	0.002	0.001
Alcohol use (%)	5367				
Never	1090	20.4 (1025)	19.1 (65)	<0.001	<0.001
Former	1283	23.2 (1165)	34.6 (118)		
Current	2994	56.4 (2836)	46.3 (158)		
Lipid-lowering medications (%)	5397	16.7 (844)	21.7 (74)	0.017	0.681
LDL cholesterol (mg/dL)	5336	117.8 (31.5)	114.0 (32.4)	0.032	0.101
HDL cholesterol (mg/dL)	5398	51.2 (15.0)	49.5 (14.0)	0.049	0.024
Triglycerides[a] (mg/dL)	5401	109 (77–160)	117 (76–161)	0.222	0.010
eGFR (mL/min/1.73 m^2)	5399	78.0 (15.9)	71.8 (17.7)	<0.001	0.042
Systolic BP (mmHg)	5407	126 (21)	137 (23)	<0.001	<0.001
Diastolic BP (mmHg)	5407	72 (10)	73 (12)	0.031	0.012
Anti-hypertensive medications (%)	5406	36.0 (1821)	59.1 (202)	<0.001	<0.001
Diabetes (%)	5399	11.7 (592)	27.5 (94)	<0.001	<0.001
HOMA2-IR[a]	5385	0.91 (0.66–1.36)	1.07 (0.73–1.50)	<0.001	<0.001
IL-6[a] (pg/mL)	5269	1.2 (0.7–1.9)	1.5 (1.0–2.4)	<0.001	<0.001
CRP[a] (mg/L)	5378	1.9 (0.8–4.2)	2.4 (1.0–5.0)	0.004	<0.001

Characteristics	n	No HF (*n* = 5066)	FH (*n* = 342)	p	Adjusted p[b]
Fibrinogen (mg/dL)	5380	346 (73)	365 (77)	<0.001	<0.001
NT-proBNP[a] (pg/mL)	5402	51.2 (23.2–102.5)	109.2 (52.7–232.9)	<0.001	<0.001
FGF21[a] (pg/mL)	5408	145.0 (81.1–241.3)	170.3 (97.1–313.0)	<0.001	0.001
LV end diastolic mass (g)	3912	144.1 (38.4)	172.3 (51.0)	<0.001	<0.001
LV end diastolic volume (mL)	3912	125.3 (30.6)	140.0 (39.5)	<0.001	<0.001
LV end systolic volume (mL)	3912	39.3 (15.9)	50.7 (29.3)	<0.001	<0.001
LV stroke volume (mL)	3912	85.9 (19.6)	89.2 (20.0)	0.016	<0.001
LV ejection fraction (%)	3912	69.2 (7.2)	65.5 (10.5)	<0.001	<0.001

Data are expressed as mean (SD), percent (n), or median (interquartile range). Data was compared by chi square test for categorical variables and independent t-test for continuous variables.

[a] ln-transformed before analysis.

[b] Adjusted for age, sex, and race/ethnicity in Cox regression analysis.

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Table 2

Correlates of ln-transformed plasma FGF21 levels in multivariable linear regression analysis.

Characteristics	Unadjusted		Model 1		Model 2	
	% change (95 % CI)	p	% change (95 % CI)	p	% change (95 % CI)	p
Age (years)	22.2 (17.9, 26.6)	<0.001	22.4 (18.1, 26.8)	<0.001	11.4 (6.1, 17.0)	<0.001
Male (%)	−10.5 (−16.7, −3.8)	0.003	−10.6 (−16.8, −4.0)	0.002	−7.2 (−14.9, 1.3)	0.096
Race/ethnicity (%)						
Non-Hispanic White	reference	–	reference	–	reference	–
African American	−14.7 (−21.9, −6.8)	<0.001	−14.1 (−21.3, −6.2)	<0.001	−14.5 (−22.6, −5.5)	0.002
Hispanic American	11.8 (1.4, 23.2)	0.025	13.9 (3.4, 25.4)	0.008	−5.8 (−15.9, 5.5)	0.298
Chinese American	−17.3 (−26.7, −6.6)	0.002	−17.9 (−27.2, −7.4)	0.001	−14.0 (−25.0, −1.4)	0.030
Education (%)						
<high school	reference	–	reference	–	reference	–
High school	−4.2 (−13.4, 6.1)	0.412	3.5 (−6.9, 15.2)	0.521	9.7 (−1.9, 22.7)	0.104
>high school	−26.6 (−33.8, −18.8)	<0.001	−16.0 (−25.0, −5.9)	0.003	2.8 (−9.3, 16.5)	0.665
Family income (%)						
<$30,000	reference	–	reference	–	reference	–
$30,000–$75,000	−11.7 (−18.8, −3.9)	0.004	−4.2 (−12.3, 4.7)	0.345	−2.0 (−10.6, 7.5)	0.672
>$75,000	−31.3 (−37.3, −24.2)	<0.001	−23.5 (−31.4, −14.7)	<0.001	−9.0 (−19.1, 2.3)	0.114
Body mass index (kg/m^2)	20.5 (16.3, 24.9)	<0.001	24.9 (20.3, 29.7)	<0.001	3.8 (−1.2, 9.0)	0.137
Physical activity[a] (MET-hour/week)	−11.4 (−14.6, −8.2)	<0.001	−7.9 (−11.3, −4.4)	<0.001	−3.9 (−7.5, −0.1)	0.045
Smoking (%)						
Never	reference	–	reference	–	reference	–
Former	8.2 (0.0, 17.0)	0.049	7.6 (−0.6, 16.5)	0.070	5.6 (−3.9, 16.0)	0.259
Current	21.1 (8.1, 35.7)	<0.001	35.9 (21.2, 52.4)	<0.001	19.5 (4.4, 36.8)	0.010
Pack years of smoking	10.4 (6.4, 14.4)	<0.001	10.1 (6.2, 14.3)	<0.001	3.1 (−1.3, 7.8)	0.169
Alcohol use (%)						
Never	reference	–	reference	–	reference	–
Former	−14.3 (−23.2, −4.4)	0.006	−12.4 (−21.8, −1.7)	0.024	−18.2 (−27.4, −7.9)	<0.001
Current	−13.4 (−21.1, −4.9)	0.003	−9.6 (−18.4, 0.2)	0.053	−7.8 (−17.3, 2.7)	0.140
Lipid-lowering medications (%)	26.1 (14.6, 38.8)	<0.001	16.8 (6.2, 28.6)	0.001	9.3 (−1.3, 21.0)	0.089

Characteristics	Unadjusted		Model 1		Model 2	
	% change (95 % CI)	p	% change (95 % CI)	p	% change (95 % CI)	p
LDL cholesterol (mg/dL)	−3.4 (−6.9, 0.1)	0.060	−3.0 (−6.4, 0.5)	0.094	−3.1 (−6.7, 0.7)	0.109
HDL cholesterol (mg/dL)	−14.4 (−17.4, −11.3)	<0.001	−19.7 (−22.7, −16.6)	<0.001	−0.5 (−5.1, 4.4)	0.847
Triglycerides[a] (mg/dL)	40.7 (35.9, 45.7)	<0.001	42.2 (37.2, 47.3)	<0.001	30.4 (24.5, 36.6)	<0.001
eGFR (mL/min/1.73 m^2)	−15.4 (−18.4, −12.3)	<0.001	−7.9 (−11.7, −4.0)	<0.001	−6.6 (−10.6, −2.5)	0.002
Systolic BP (mmHg)	19.6 (15.4, 24.0)	<0.001	14.5 (10.2, 19.0)	<0.001	4.4 (0.3, 8.8)	0.037
Diastolic BP (mmHg)	4.1 (0.4, 8.0)	0.028	10.1 (6.0, 14.4)	<0.001	–	–
Anti-hypertensive medications (%)	37.7 (27.9, 48.3)	<0.001	28.9 (19.3, 39.2)	<0.001	6.9 (−1.7, 16.3)	0.120
Diabetes (%)	47.2 (32.2, 64.0)	<0.001	42.4 (27.8, 58.7)	<0.001	10.6 (−1.7, 24.5)	0.094
HOMA2-IR[a]	30.5 (25.9, 35.2)	<0.001	31.7 (27.1, 36.4)	<0.001	9.9 (4.9, 15.2)	<0.001
IL-6[a] (pg/mL)	31.2 (26.6, 35.9)	<0.001	27.4 (22.7, 32.2)	<0.001	17.2 (11.9, 22.8)	<0.001
CRP[a] (mg/L)	24.4 (20.0, 28.9)	<0.001	23.7 (19.2, 28.4)	<0.001	6.4 (1.3, 11.7)	0.013
Fibrinogen (mg/dL)	9.5 (5.7, 13.6)	<0.001	5.3 (1.4, 9.3)	0.007	−9.7 (−13.7, −5.5)	<0.001
NT pro-BNP[a] (pg/mL)	12.2 (8.2, 16.3)	<0.001	−0.6 (−4.7, 3.8)	0.796	–	–

Regression coefficient B (95 % confidence interval) were expressed as percentage change in FGF21 levels per one SD unit increase in continuous variables. The percentage change was estimated by the exponentiation of coefficients from linear regression analysis, in which ln-transformed FGF21 was the dependent variable. Model 1 was adjusted for age, sex, and race/ethnicity. Variables with $p < 0.2$ in Model 1 were entered into the multivariable regression analysis for model 2. Diastolic BP was not entered into the model due to multi-collinearity with systolic BP.

[a]Data were ln-transformed before analysis.

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Table 3

Association of baseline ln-transformed plasma FGF21 levels with incident HF.

Heart failure	No. of events, % (n)	Model 1		Model 2		Model 3	
		HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
All HF							
All	6.3 (342)	1.23 (1.07, 1.42)	0.004	1.15 (0.99, 1.33)	0.075	1.12 (0.96, 1.31)	0.138
FGF21 < 239.0 pg/mL	5.6 (223)	1.08 (0.91, 1.28)	0.377	1.00 (0.84, 1.18)	0.967	0.99 (0.83, 1.18)	0.916
FGF21 ≥ 239.0 pg/mL	8.5 (119)	1.56 (1.10, 2.20)	0.012	1.52 (1.03, 2.25)	0.035	1.84 (1.21, 2.80)	0.004
p for heterogeneity			0.071		0.050		0.004
HFpEF							
All	48.8 (167)	1.30 (1.05, 1.60)	0.018	1.20 (0.96, 1.51)	0.112	1.15 (0.91, 1.45)	0.241
FGF21 < 239.0 pg/mL	2.5 (101)	1.01 (0.80, 1.27)	0.943	0.92 (0.73, 1.16)	0.488	0.90 (0.71, 1.14)	0.386
FGF21 ≥ 239.0 pg/mL	4.7 (66)	1.81 (1.21, 2.72)	0.004	2.02 (1.24, 3.30)	0.005	2.57 (1.51, 4.37)	<0.001
p for heterogeneity			0.011		0.002		<0.001
HFrEF							
All	40.9 (140)	1.20 (0.98, 1.48)	0.083	1.14 (0.92, 1.42)	0.239	1.12 (0.89, 1.40)	0.344
FGF21 < 239.0 pg/mL	2.4 (97)	1.18 (0.89, 1.56)	0.242	1.12 (0.84, 1.49)	0.454	1.10 (0.82, 1.46)	0.537
FGF21 ≥ 239.0 pg/mL	3.1 (43)	1.06 (0.50, 2.26)	0.876	1.01 (0.46, 2.24)	0.984	1.13 (0.49, 2.61)	0.776
p for heterogeneity			0.787		0.706		0.923

Hazards ratio (HR) was expressed per one SD increase (1.357) in ln-transformed FGF21 levels. Data is expressed as percent (n) for HF events.

Model 1: Adjusted for age, sex, race/ethnicity, education, and family income.

Model 2: Further adjusted for BMI, physical activity, smoking, pack-year of smoking, alcohol use, LDL cholesterol, HDL cholesterol, triglycerides, lipid-lowering medications, eGFR, systolic BP, anti-hypertensive medication, diabetes, and HOMA2-IR.

Model 3: Further adjusted for CRP, IL- 6, fibrinogen, and ln-transformed NT-proBNP.

Table 4

Assessment of incremental value of biomarkers in risk prediction for incident HFpEF.

Prediction Model	NRI (>0), % (95 % CI)	Event NRI (%)[a]	Non-event NRI (%)[b]	C-statistics	p	May and Hosmer test	
						Chi-square	p
Base Model	–	–	–	0.804	–	0.2	0.978
+ FGF21	14.4 (−4.5, 47.7)	−35.5	49.9	0.810	0.003	0.7	0.870
+ NT-proBNP	53.3 (30.3, 80.2) *	33.5	19.9	0.824	<0.001	2.0	0.569
+ CRP	15.1 (−16.5, 30.3)	−19.3	34.4	0.804	0.645	0.2	0.978
+ IL-6	2.3 (−17.4, 39.9)	−29.0	31.3	0.806	0.092	1.3	0.739
+ fibrinogen	5.6 (−14.1, 32.0)	−4.2	9.8	0.805	0.196	0.2	0.984
Base Model + CRP + IL-6 + fibrinogen + NT-proBNP	–	–	–	0.824	–	2.7	0.442
+ FGF21	19.6 (1.5, 51.2) *	−35.4	55.0	0.829	<0.001	0.4	0.932
Base Model + NT-proBNP	–	–	–	0.824	–	2.0	0.569
+ FGF21	17.7 (4.7, 51.6) *	−37.9	55.6	0.830	0.001	0.5	0.919

FGF21 and NT-proBNP were ln-transformed in the analysis. Estimates were calculated for the 10-year risk.

Base model includes age, sex, race/ethnicity, education, family income, BMI, physical activity, smoking, pack-year of smoking, alcohol use, LDL cholesterol, HDL cholesterol, triglycerides, lipid-lowering medications, eGFR, systolic BP, anti-hypertensive medication, diabetes, and HOMA2-IR. FGF21 and NT-proBNP were ln-transformed prior to analysis. For ln-transformed FGF21, a piecewise Cox regression model was fitted with two slopes and a change point at a FGF21 level of 239.0 pg/mL. The category-less NRI (>0) measures the improvement associated with correct upward or downward change in predicted risks and was calculated as the proportion of participant with events with correct upward or downward change minus incorrect upward or downward change plus the corresponding proportion among participants without events. A value >0 indicates improved risk prediction and discrimination associated with the addition of a biomarker as compared to the base model.

The C-statistic measures discrimination and estimates the probability that, of two randomly chosen participants, the participant with the higher predicted risk will remain event-free longer than the participant with the lower predicted risk. A C-statistic near 0.5 indicates the predicted score has an equally likely and unlikely chance in determining which participant will remain event-free longer. A value above 0.5 indicates an improved ability of the model to correctly predict the outcome, with a value of 1 indicating a perfect prediction of the event. The May and Hosmer test assesses the overall goodness of fit of a model based on grouping the subjects by their estimated risk score and comparing the number of observed and model-based estimated number of expected events within each group. A significant test result indicates differences between observed and expected numbers of events and hence lack of fit.

* $p < 0.05$.

[a] Percentage correctly reclassified among participants who had events.

[b] Percentage correctly reclassified among participants who did not have events.