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ORIGINAL ARTICLE

Fibroblast Growth Factor-23, Heart Failure Risk, and Renin–Angiotensin–Aldosterone-System Blockade in Hypertension: The MESA Study

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BACKGROUND
Higher fibroblast growth factor-23 (FGF23) concentrations have been found to be associated with incident heart failure (HF). Experimental data suggest FGF23 directly stimulates myocardial hypertrophy. FGF23 may also enhance renin–angiotensin–aldosterone system activity. Whether FGF23 is associated with increased HF risk in populations with hypertension and whether this association is weaker in the presence of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy is unknown.

METHODS
We studied 2,858 adults with hypertension free of cardiovascular disease at baseline (65.6 ± 9.5 years, 46.2% male) participating in the Multi-Ethnic Study of Atherosclerosis (MESA). We investigated the association of baseline serum intact FGF23 with incident HF over a 14-year median follow-up and whether ACEI/ARB therapy modified this risk. We also investigated the relationship of FGF23 with aldosterone and plasma renin activity in a random subgroup of the entire MESA cohort with available assays ($N = 1,642$).

RESULTS
In adjusted Cox regression models, higher FGF23 was associated with a 63% greater hazard of incident HF (hazard ratio: 1.63, 95% confidence interval: [1.13–2.36] per 1-unit increase in log-transformed FGF23), which persisted after exclusion of participants with chronic kidney disease (hazard ratio: 1.94 [1.10–3.43]). There was no heterogeneity by ACEI/ARB use ($P_{interaction} = 0.438$). FGF23 improved model fit over covariables (likelihood ratio $\chi^2 = 6.67$, $P = 0.010$). In multivariable linear regression models, there was no association between FGF23 and aldosterone or plasma renin activity.

CONCLUSIONS
Higher FGF23 concentrations are associated with a significantly increased risk of HF in hypertension but this risk did not differ by ACEI/ARB treatment status. FGF23 may be a useful biomarker for HF risk in hypertensive populations.

Keywords: aldosterone; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; blood pressure; fibroblast growth factor 23; heart failure; hypertension; renin; renin–angiotensin system.

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Fibroblast growth factor-23 (FGF23) is an endocrine hormone that acts on the kidney to increase urinary phosphate excretion and decrease calcitriol synthesis.[1] Serum FGF23 concentrations increase in chronic kidney disease (CKD) to maintain phosphate balance but elevated FGF23 is associated with higher mortality and worse cardiovascular outcomes.[1–4] Higher FGF23 levels have been associated with incident heart failure (HF) in general populations,

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independent of kidney function.[5–9] In addition, some studies suggest that higher FGF23 is associated with an increased risk of hypertension, a well-known risk factor for HF.[10,11] Although experimental data suggest that FGF23 directly stimulates myocardial hypertrophy,[12,13] the mechanisms behind the association between FGF23 and HF risk are not well-characterized.

The renin–angiotensin–aldosterone system (RAAS) is involved in the pathophysiology of HF and RAAS antagonists are integral to HF treatment.[14–16] Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are also commonly used antihypertensive medications. Experimental evidence suggests that there are mechanisms by which FGF23 may enhance RAAS activity.[17] A previous study of patients with stable ischemic heart disease found that ACEI therapy decreased the risk of a composite endpoint of HF and cardiovascular death associated with elevated FGF23 levels.[8] Whether FGF23 is an independent predictor of HF in hypertensive populations free of cardiovascular disease at baseline and whether there is heterogeneity in this risk based on treatment with ACEI or ARB antihypertensive therapy is unknown. Therefore, in this study of a large multiethnic population of community-dwelling adults, we tested the hypotheses that in populations with hypertension, higher FGF23 concentrations are associated with increased risk of incident HF and that this association is weaker in the presence of ACEI or ARB therapy. We also investigated whether there was an association between higher FGF23 concentrations and increased markers of RAAS activity in the blood as a potential indicator of possible mechanisms behind the association between FGF23 and HF.

METHODS

Source population

Full details about the design of the Multi-Ethnic Study of Atherosclerosis (MESA) have been previously published.[18] Briefly, MESA is a longitudinal cohort study that enrolled 6,814 White (38%), African-American (28%), Hispanic (22%), and Asian (12%) individuals aged 45–84 free of known cardiovascular disease from six field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN) between July 2000 and July 2002. The study was designed to investigate subclinical cardiovascular disease and the risk factors for its progression to clinical cardiovascular disease. After the aforementioned baseline examination, 4 additional follow-up visits have been completed at approximately 2- to 5-year intervals. The 5th examination was completed in January 2012 and follow-up is ongoing. The institutional review board at each study site approved the study and all study participants provided informed consent.

Study sample

Serum FGF23 concentration was measured at the baseline exam and available for 6,654 (97.7%) participants. Participants with no follow-up examinations (n = 212) or missing baseline covariates of interest (n = 71) were excluded. From the remaining sample (n = 6,371), we excluded participants without hypertension at baseline (n = 3,513), which we defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment with an antihypertensive medication. The final study sample for the primary analysis (analytic subcohort 1) was composed of 2,858 participants with hypertension (Supplementary Figure).

We derived an additional study sample (analytic subcohort 2) for the purposes of the secondary analyses investigating the association of FGF23 with serum RAAS markers. From the aforementioned set of participants with a FGF23 measurement, follow-up and no missing covariates of interest (n = 6,371 as above), we included individuals with serum aldosterone and plasma renin activity measurements (N = 1,642, Supplementary Figure). Renin and aldosterone had been measured as part of a previous ancillary study in a random subset of the full MESA cohort at exam 2 (over 18 months from September 2002 to February 2004) or exam 3 (over 18 months from March 2004 to September 2005).

Blood pressure measurement

Trained MESA staff measured blood pressure in the seated position after 5 minutes at rest with Dinamap automated oscillometric sphygmomanometers using a standardized protocol.[18] Participants had three blood pressure readings performed and the average of the second and third readings were taken.

Measurement of FGF23, aldosterone, and plasma renin activity

MESA staff collected and stored blood samples in a standardized protocol that has been previously described.[18] Serum intact FGF23 was measured using an enzyme-linked immunosorbent assay (ELISA) which recognizes the intact FGF23 molecule (Kianos Laboratories, INC, Tokyo, Japan). The coefficient of variation for high and low control samples used for each assay run for quality control purposes was 6.7% and 12.4%, respectively.[6]

Aldosterone was measured using a radioimmunoassay (DiaSorin, Stillwater, MN). The intra-assay coefficients of variation ranged from 6.3% to 8.9%. Plasma renin activity was measured via a radioimmunoassay that determines the quantity of angiotensin I produced in 1 ml of sample per hour (DiaSorin). The coefficients of variation ranged from 6.9% to 18.4%.[19]

Ascertainment of incident HF

To date, MESA events have been adjudicated through 31 December 2015. MESA participants were screened for possible events during regularly scheduled telephone interviews every 9–12 months, and medical records were obtained for incident hospitalizations. MESA categorized HF events as either probable or definite. Probable HF required a physician diagnosis and medical treatment for HF. Definite HF required evidence of pulmonary congestion by chest x-ray

and/or cardiac imaging demonstrating abnormal systolic or diastolic function. Events were determined by at least 2 independent MESA physician reviewers and in the case of discrepancy by a MESA Morbidity and Mortality Committee.[18,20]

Other study variables

MESA personnel determined demographic, personal, and medical history using standardized questionnaires. Participants were asked to bring their medications to their visits and an inventory was determined by interview via standardized questionnaire and review of the medications. MESA-defined diabetes at the baseline exam was based on the 2003 American Diabetes Association fasting criteria algorithm or being on medication for diabetes. Current smoking within 30 days was self-reported. Estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation.[21]

Statistical analysis

Baseline characteristics of the study population were summarized by FGF23 tertile. For the purposes of primary analyses, FGF23 was log-transformed as its distribution is known to be substantially skewed. The primary analysis was conducted in the subset of participants with hypertension (analytic subcohort 1). To investigate the association of FGF23 at baseline with incident HF, we constructed Cox proportional hazard models. Follow-up time for incident HF was defined as time-to-first HF event, date of last follow-up telephone contact, death or end of follow-up on 31 December 2015. We constructed multivariable models sequentially. Model 1 adjusted for age, sex, race/ethnicity, and education level. Model 2 adjusted for model 1 variables and body mass index, smoking, diabetes, systolic blood pressure, eGFR, urine albumin-to-creatinine ratio (ACR), serum 25-hydroxy vitamin D, urine sodium, and incident cardiovascular disease (defined as any of the following prior to and not including incident HF: myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina if followed by revascularization, stroke, or related death from these cardiovascular disease events). Additional models adjusted for ACEI or ARB treatment status at the last exam prior to incident cardiovascular disease, incident HF or end of follow-up, or their time-varying use (years). Because previous data have shown differences in the association of FGF23 with HF based on ACEI treatment status, we examined heterogeneity of the association of FGF23 with the time to incident HF risk based on ACEI or ARB status, by entering an interaction term between continuous log-transformed FGF23 and last known ACEI/ARB treatment status into the multivariable models. Significant multiplicative interaction was deemed to be present if the P value for the interaction term in the multivariable model was <0.05.

Since CKD is associated with higher FGF23 and HF, we repeated all analyses excluding patients with underlying kidney disease at baseline ($n = 829$), which we defined as a urine ACR ≥30 mg/g or eGFR <60 ml/min/1.73 m². Additional sensitivity analyses added adjustment for serum parathyroid hormone, serum phosphorus, urine phosphorus, and serum calcium individually to multivariable models including and excluding CKD participants.

Finally, to investigate whether FGF23 added predictive value for HF over covariables alone, we used likelihood ratio tests to compare multivariable models with and without FGF23 to evaluate if addition of FGF23 improved overall model fit. We deemed there to be a statistically significant improvement in model fit with addition of FGF23 if the P value associated with the calculated chi-squared value (with 1 degree of freedom with FGF23 as a continuous variable and 2 degrees with FGF23 as a categorical variable in tertiles) from the likelihood ratio test was <0.05.

Our secondary analysis was conducted in the subset of MESA participants with aldosterone and plasma renin activity levels (analytic subcohort 2). Because aldosterone and plasma renin activity are not normally distributed values, they were log-transformed. To investigate the association of FGF23 at baseline with serum aldosterone, we constructed linear regression models with FGF23 as the primary exposure and aldosterone as the dependent variable. Multivariable models adjusted for age, sex, race/ethnicity, education level, body mass index, smoking, diabetes, systolic blood pressure, eGFR, urine ACR, serum 25-hydroxy vitamin D, urine sodium and treatment with an ACEI, ARB, or aldosterone receptor antagonist at the time of the aldosterone and plasma renin activity measurements. Additional models adjusted for other antihypertensives. In sensitivity analyses, we excluded individuals with CKD and performed analyses stratified by the presence of RAAS antagonist use at the time of the assay. We replicated these models with plasma renin activity in place of aldosterone as the outcome. Percent change in aldosterone and plasma renin activity was calculated by exponentiation of beta coefficients obtained from the linear regression models.

RESULTS

Association of FGF-23 with HF among participants with hypertension and interaction with ACEI or ARB therapy

In the hypertensive cohort (analytic subcohort 1, $N = 2,858$), the mean age was 65.6 (±9.5) years; 46.2% were male, 34.3% were Black, 20.1% were Hispanic and 9.9% were Chinese (Table 1). There were higher proportions of older and White participants along with individuals on antihypertensive therapy among participants with higher FGF23. Mean body mass index was also greater in participants with higher FGF23. Urine ACR was greater and eGFR lower among participants with higher FGF23.

During follow-up (median time: 14 years), 215 participants developed HF. The crude incidence of HF overall by different FGF23 concentrations is presented in Figure 1. HF developed in more participants in higher FGF23 tertiles. This pattern was also present when excluding those with CKD ($n = 829$).

In Cox regression models fully adjusted for both demographic and clinical factors including preceding incident

Table 1. Baseline characteristics of participants with hypertension in the Multi-Ethnic Study of Atherosclerosis by FGF23 concentration

| Characteristic | Overall | Serum intact FGF23, pg/ml | | | P value |
		<33.0	33.0–42.9	≥43.0	
N	2,858	870	919	1,069	
Age, years	65.6 (9.5)	64.2 (9.6)	66.2 (9.2)	66.3 (9.5)	<0.001
Male	1321 (46.2)	383 (44.0)	431 (46.9)	507 (47.4)	0.288
Race/ethnicity					<0.001
White	1,021 (35.7)	245 (28.2)	311 (33.8)	465 (43.5)	
Black	980 (34.3)	337 (38.7)	315 (34.3)	328 (30.7)	
Hispanic	574 (20.1)	203 (23.3)	202 (22.0)	169 (15.8)	
Chinese	283 (9.9)	85 (9.8)	91 (9.9)	107 (10.0)	
Education college or higher	898 (31.4)	262 (30.1)	277 (30.1)	359 (33.6)	0.157
Current alcohol	1,460 (51.4)	454 (52.7)	434 (47.4)	572 (53.7)	0.014
Current smoking	294 (10.3)	117 (13.4)	95 (10.3)	82 (7.7)	0.001
Body mass index, kg/m^2	29.3 (5.5)	28.9 (5.5)	29.2 (5.3)	29.7 (5.6)	0.003
Diabetes	520 (18.2)	152 (17.5)	170 (18.5)	198 (18.5)	0.803
Systolic blood pressure, mm Hg	138.8 (21.5)	139.5 (21.3)	139.4 (21.6)	137.7 (21.6)	0.101
Any hypertension medication	2187 (76.5)	620 (71.3)	689 (75.0)	878 (82.1)	<0.001
ACEI or ARB	1053 (36.8)	292 (33.6)	322 (35.0)	439 (41.1)	0.001
ACEI/ARB or aldosterone antagonist	1066 (37.3)	295 (33.9)	325 (35.3)	446 (41.7)	<0.001
Beta blockers	559 (19.6)	163 (18.7)	175 (19.0)	221 (20.7)	0.503
Diuretic	785 (27.5)	185 (21.3)	241 (26.2)	359 (33.6)	<0.001
Calcium channel blocker	724 (25.3)	202 (23.2)	239 (26.0)	283 (26.5)	0.222
Lipid-lowering medication	670 (23.5)	178 (20.5)	211 (23.0)	281 (26.3)	0.001
eGFR, ml/min per 1.73 m^2	78.8 (18.3)	79.7 (15.8)	75.7 (15.0)	69.2 (17.2)	<0.001
Urine ACR, mg/g	7.1 (3.9, 16.6)	6.9 (4.0, 15.6)	7.1 (3.9, 15.7)	7.5 (3.9, 18.9)	0.008
Urine sodium, mmol/l	101.0 (50.3)	103.5 (52.3)	101.9 (51.8)	98.2 (47.2)	0.060
High-density lipoprotein, mg/dl	50.7 (14.6)	52.4 (14.6)	50.6 (15.0)	49.5 (14.1)	<0.001
Low-density lipoprotein, mg/dl	114.4 (30.9)	114.9 (30.1)	114.4 (30.3)	114.0 (32.0)	0.818
Serum 25-hydroxy vitamin D, ng/ml	25.1 (11.6)	23.2 (11.2)	24.9 (10.5)	26.8 (12.5)	<0.001
Serum calcium, mg/dl	9.7 (0.4)	9.6 (0.4)	9.7 (0.4)	9.7 (0.4)	<0.001
Serum parathyroid hormone, pg/ml	47.7 (22.6)	46.7 (20.1)	47.0 (19.8)	49.0 (26.3)	0.048
Serum phosphorus, mg/dl	3.6 (0.5)	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)	<0.001
Urine phosphorus, mg/dl	49.6 (34.4)	48.5 (33.3)	48.8 (33.1)	51.1 (36.1)	0.183

Data shown are n (%) for categorical and mean (SD) or median (25th, 75th) for continuous variables. Abbreviation: ACEI, angiotensin-converting enzyme inhibitors; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; FGF23, Fibroblast Growth Factor-23.

cardiovascular disease (model 2), higher FGF23 was associated with a 63% greater hazard of incident HF for every 1-unit increase in log-transformed FGF23 (Table 2: hazard ratio, 1.63, 95% confidence interval [1.13, 2.36]). The risk of HF also increased in higher FGF23 tertiles relative to the lowest tertile (Table 2). Findings were similar with CKD participants excluded from the population. The association of higher FGF23 with HF was unaltered in models which further adjusted for last ACEI or ARB treatment status or time-varying use of ACEI or ARBs. Finally, there was no significant interaction by ACEI or ARB use (P = 0.438).

The association of higher FGF23 with HF was minimally altered in sensitivity analyses which additionally adjusted for parathyroid hormone, serum phosphorus, urine phosphorus, and serum calcium in models including and excluding CKD participants (Supplementary Table 1).

Addition of FGF23 to covariables alone (from model 2) led to a statistically significant improvement in the model fit [For log-transformed FGF23: χ^2(1 degree of freedom) = 6.67, P = 0.010; for categorical FGF23 in tertiles: χ^2(2 degrees-of-freedom) = 12.4, P = 0.002] suggesting that FGF23 added significant predictive value for HF.

Association of FGF-23 with aldosterone and plasma renin activity

The mean age of the study sample with aldosterone and renin measurements (analytic subcohort 2, N = 1,642) was 61.9 years (±9.8); 49.8% were male, 19.2% were Black, 25.8% were Hispanic, and 13.9% were Chinese (Supplementary Table 2). Participants with higher FGF23 were older and more likely to be White and have hypertension. Mean body mass index was greater and eGFR lower among participants with higher FGF23.

In linear regression analyses, higher FGF23 concentrations were not associated with a statistically significant change
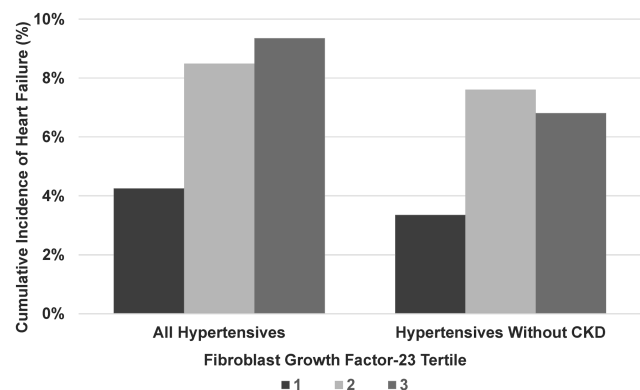

Figure 1. Cumulative Incidence of Heart Failure by Intact Fibroblast Growth Factor 23 (FGF23) Tertile in Participants with Hypertension at Baseline Including and Excluding Those with Chronic Kidney Disease (CKD). During follow-up, heart failure developed in more participants with higher FGF23 concentrations.

in serum aldosterone concentration (Table 3: β = 0.021 or +2.1% change per 1-unit increase in log-transformed FGF23, 95% confidence interval [−0.052, 0.093]). There was also no statistically significant association between FGF23 and plasma renin activity concentrations (Table 3). Additional adjustment for treatment with other classes of antihypertensives aside from RAAS antagonists did not significantly alter results. No association was also present in sensitivity analyses excluding individuals with CKD and in analyses stratified by RAAS antagonist use at the time of the aldosterone and plasma renin activity assays.

DISCUSSION

In this study, we investigated whether FGF23 was associated with incident HF in a large multiethnic population of middle- and older-age adults with hypertension without cardiovascular disease at baseline and whether this risk was modified by antihypertensive therapy with ACEIs or ARBs. We demonstrated that higher FGF23 levels were associated with a significantly greater risk of developing HF in participants with hypertension even in the absence of underlying kidney disease and after adjustment for potential confounders including incident cardiovascular disease and other risk factors. We also found that there was no heterogeneity in this risk based on treatment for hypertension with an ACEI or ARB.

Experimental evidence suggests that there are mechanisms by which FGF23 may interact with the RAAS system. Increased FGF23 may contribute to RAAS activation through suppression of angiotensin-converting enzyme II[22–24] in addition to other theoretical indirect mechanisms by which

Table 2. Association of FGF23 with incident heart failure in hypertensives at baseline including and excluding CKD

All (N = 2,858)	Heart failure rate per 1,000 person years (events)	Hazard ratio (95% confidence interval)	
		Model 1	Model 2
Total heart failure events = 215			
FGF23, pg/ml			
LogFGF23		2.05 (1.45–2.88)	1.63 (1.13–2.36)
Tertile 1	3.42 (37)	Referent	Referent
Tertile 2	6.99 (78)	1.90 (1.28–2.81)	1.85 (1.25–2.75)
Tertile 3	7.89 (100)	2.10 (1.44–3.08)	1.86 (1.25–2.76)
Without CKD (N = 2,029)			
Total heart failure events = 120			
FGF23, pg/ml			
LogFGF23		2.01 (1.17–3.45)	1.94 (1.10–3.43)
Tertile 1	2.63 (23)	Referent	Referent
Tertile 2	6.15 (53)	2.10 (1.29–3.43)	2.04 (1.24–3.34)
Tertile 3	5.48 (44)	1.86 (1.12–3.10)	1.80 (1.07–3.03)

Model 1 adjusted for age, sex, race/ethnicity, and education level. Model 2 adjusted for body mass index, smoking, diabetes, systolic blood pressure, estimated glomerular filtration rate, urine albumin-to-creatinine ratio, 25OH vitamin D, urine sodium and incident cardiovascular disease (prior to and other than heart failure). Chronic kidney disease was defined as a urine albumin-to-creatinine ratio ≥30 mg/g or estimated glomerular filtration rate <60 ml/min per 1.73 m^2 at baseline. Abbreviation: CKD, chronic kidney disease; FGF23, fibroblast growth factor-23.

Table 3. Linear regression models for association of FGF23 with aldosterone and plasma renin activity levels

FGF23, pg/ml	Aldosterone (log)		Plasma renin activity (log)	
	Mean aldosterone,[a] pg/ml (SD)	Adjusted model, β [CI][b]	Mean PRA, ng/mL/h (SD)	Adjusted model, β [CI][b]
LogFGF23		0.021 (−0.052, 0.093)		−0.036 (−0.193, 0.121)
<33.0	147.2 (83.2)	Referent	1.45 (3.4)	Referent
33.0–42.9	150.4 (86.3)	0.013 (−0.049, 0.076)	1.26 (2.6)	0.017 (−0.152, 0.118)
≥43.0	154.1 (85.3)	0.017 (−0.047, 0.082)	1.65 (3.9)	−0.010 (−0.149, 0.133)

Fully adjusted model: adjusted for age, sex, race/ethnicity, education, body mass index, smoking, diabetes, systolic blood pressure, estimated glomerular filtration rate, urine albumin-to-creatinine ratio, Serum 25-hydroxy vitamin D, urine sodium, and treatment with an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker or aldosterone antagonist. Abbreviations: CI, confidence interval; FGF23, fibroblast growth factor-23; PRA, plasma renin activity.

[a]Aldosterone assay was measured in pg/ml. Clinical units of ng/dl can be obtained by dividing by 10.

[b]Beta coefficients represent change in aldosterone and PRA per 1-unit increase in continuous log-transformed FGF23 or difference for each upper FGF23 tertile relative to tertile 1. Percentage change presented in the text was obtained by exponentiation of beta coefficients.

FGF23 may modulate the RAAS system.[17] Experimental data also suggest that angiotensin II downregulates production of klotho, the renal co-receptor for FGF23, thus potentially leading to secondary increases in FGF23. Previous clinical trial data have demonstrated that ACEI therapy with trandolapril decreased the risk of HF and cardiovascular death associated with high FGF23 levels in a population with stable ischemic heart disease, regardless of CKD status.[8] Our study extends this previous analysis in 2 significant ways. First, we investigated whether ACEI or ARB therapy as a class modified the association of FGF23 with incident HF in a hypertensive population of community-dwelling adults without known cardiovascular disease at baseline. Secondly, we examined whether higher FGF23 was associated with differences in aldosterone and renin concentrations in a general population of adults. To date, previous data investigating whether FGF23 interacts with the RAAS system have primarily only been in animal models with CKD.

Given the high prevalence of hypertension in the United States and around the world along with increasing evidence of an association of FGF23 with HF,[5–8] our findings may have potential significant implications. The differing risk of HF based on differing concentrations of FGF23 in an adult population with underlying hypertension—a well-known risk factor for HF—is notable. Our study also suggests FGF23 may add predictive value to traditional HF risk factors. Further prospective study is necessary to help elucidate mechanisms by which FGF23 may increase HF risk. Experimental evidence suggests that at least some of the cardiotoxic effects of FGF23 are direct.[12,13] Whether there are indirect mechanisms via other pathways remains uncertain.

Strengths of our study include the use of a large well-characterized prospective cohort of community-dwelling adults. However, our findings should be viewed with several limitations in mind. Our study was significantly limited in its investigation of an association between FGF23 and RAAS markers due to the differing timing of when the FGF23 and RAAS markers were assayed. FGF23 was measured at baseline while aldosterone and renin activity were measured later at exam 2 or 3 (~2–4 years later). Although FGF23 would not be expected to change significantly in the absence of significant renal dysfunction[25] and RAAS antagonist therapy at the time of the assays was taken into account, it is possible that other factors affecting aldosterone and renin may have developed during the interval between the baseline and subsequent blood sampling. Furthermore, the previously reported coefficients of variability for the plasma renin activity assay had a fairly wide range, which could have resulted in misclassification, which if nondifferential could have masked a possible association. Medication data were only available at the time of each exam so we could not assess treatment in between exams. Thus, our use of last ACEI/ARB status prior to end of follow-up time or time-varying use in our cox proportional hazard models were approximations of actual use. Although the baseline group of participants was diverse and a random sample of individuals was chosen to have renin and aldosterone assays performed, MESA participants were not randomized to any particular antihypertensive therapies. Thus, it is possible that there are other factors that may explain the lack of heterogeneity by ACEI or ARB status in the association of FGF23 with incident HF which we did not account for. Although we focused on a population with hypertension, performed analyses excluded participants with CKD and accounted for other incident cardiovascular disease, residual confounding related to alternative indications for ACEI or ARB therapy is possible. Our results nonetheless suggest that FGF23 is a strong predictor of HF in hypertensive adults.

In conclusion, higher FGF23 concentrations were independently associated with a significantly increased risk of HF in a multiethnic cohort of adults with hypertension but this risk did not differ based on the presence of antihypertensive therapy that antagonizes the RAAS system. Additionally, we also did not observe associations between baseline FGF23 and markers of RAAS activity. Our findings suggest that FGF23 may be an important biomarker for HF risk in adults with hypertension. Further research is necessary to determine the mechanisms by which FGF23 leads to increased HF risk and whether therapy with RAAS antagonism reduces this risk among adults with hypertension and in general populations.

SUPPLEMENTARY DATA

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURES

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