Supplemental Material

Supplemental Table 1. Associations of circulating FGF-23 concentrations with left atrial diameter (A) and left ventricular end diastolic mass (B) in the Cardiovascular Health Study (CHS)

A. Left Atrial Diameter

			Adjusted difference (cm with 95% CI)		
FGF-23 (RU/mL)	No.	Mean [cm (SD)]	Model 1	Model 2	Model 3
0-52.7	339	3.8 (0.5)	0 (ref)	0 (ref)	0 (ref)
52.8-67.9	342	3.9 (0.6)	0.04 (-0.04 to 0.12)	0.02 (-0.06 to 0.10)	0.02 (-0.06 to 0.10)
68.0-93.7	322	3.9 (0.5)	0.13 (0.05 to 0.21)	0.09 (0 to 0.17)	0.08 (0 to 0.17)
93.8-14,200	253	3.9 (0.6)	0.12 (0.03 to 0.21)	0.04 (-0.06 to 0.14)	0.05 (-0.05 to 0.15)
per doubling			0.08 (0.02 to 0.13)	0.04 (-0.02 to 0.09)	0.04 (-0.02 to 0.09)
p-value			0.004	0.21	0.19

B. Left Ventricular End Diastolic Mass

			Adjusted difference (g with 95% CI)		
FGF-23 (RU/mL)	No.	Mean [g (SD)]	Model 1	Model 2	Model 3
0-52.7	262	139 (42)	0 (ref)	0 (ref)	0 (ref)
52.8-67.9	250	137 (40)	-0.85 (-7.46 to 5.76)	-3.54 (-9.48 to 2.40)	-3.89 (-9.76 to 1.98)
68.0-93.7	238	141 (38)	5.42 (-1.33 to 12.17)	1.58 (-4.81 to 7.97)	1.67 (-4.73 to 8.08)
93.8-14,200	200	145 (43)	11.14 (3.42 to 18.86)	5.90 (-1.27 to 13.06)	6.79 (-0.46 to 14.03)
per doubling			7.26 (3.06 to 11.46)	4.45 (0.63 to 8.28)	5.00 (1.11 to 8.88)
p-value			<0.001	0.023	0.012

Results from linear regression models examining associations of plasma FGF-23 with left atrial diameter (A) and left ventricular end diastolic mass (B) in CHS. Cell contents are beta coefficients (in cm (A) and in g (B)) with 95% confidence intervals. Model 1 is adjusted for age, gender, ethnicity, study site, and attained education. Model 2 is additionally adjusted for low-density lipoprotein cholesterol, use of lipid-lowering medications, smoking, diabetes, physical activity, height, height squared, weight, urine albumin-creatinine ratio, estimated glomerular filtration rate, systolic blood pressure, and use of anti-hypertensive medication. Model 3 is adjusted as per Model 2 with the addition of the serum concentrations of calcium, phosphate, 25-hydroxyvitamin D, and parathyroid hormone.

Abbreviations: FGF-23, fibroblast growth factor-23

Supplemental Table 2. Atrial fibrillation predictive modeling using clinical risk factors with and without the inclusion of FGF-23

Cohort	Model	C-statistic	p-value†	LR test p-value
MESA	RF*	0.7815		
	+ FGF-23	0.7865	0.078	0.0001
CHS	RF*	0.6170		
	+FGF-23	0.6179	0.739	0.3320

*Adjusted for components derived from the AF Framingham Risk Score and includes age, gender, race, body mass index, systolic blood pressure, use of hypertension medication, and the PR interval.

†Compared to model with RFs only

Abbreviations: FGF-23, fibroblast growth factor-23; RF, risk factors; LR, likelihood ratio

Supplemental Table 3. Predictive risks and reclassification for AF using a multivariate risk prediction model with and without inclusion of FGF-23 in the Multi-Ethnic Study of Atherosclerosis (MESA)

			10-Year Risk from Model with FGF-23[2]					
10-Year Risk from Adjusted Model[1]	<5%	5-15%	>15%	Total	Reclassified to higher risk	Reclassified to lower risk	Bias corrected NRI*	p-value**

<5%								
N	3914	140	1	4055				
AF, N	52	9	0	61	9	0		
No AF, N	3862	131	1	3994	132	0	0.031	0.498
5 - 15%								
N	159	1495	84	1738				
AF, N	5	116	11	132	11	5		
No AF, N	154	1379	73	1606	73	154	0.032	0.323
>15%								
N	0	88	459	547				
AF, N	0	9	81	90	0	9		
No AF, N	0	79	378	457	0	79	0.015	0.706
Total								
N	4073	1723	544	6340				
AF, N	57	134	92	283	20	14		
No AF, N	4016	1589	452	6057	205	233	0.026	0.210

[1]Model is derived using components from the Framingham AF Risk Score and includes age (continuous), sex, race, body mass index (continuous), systolic blood pressure (continuous), use of hypertension medication, and the PR interval (continuous).
[2]Model further includes FGF-23 (continuous).

*Sum of the proportions of correctly reclassified subjects with and without AF.
**Significant *P* values indicate change in classification

Abbreviation: FGF-23, fibroblast growth factor-23; AF, atrial fibrillation; NRI, net reclassification improvement

Supplemental Table 4. Predictive risks and reclassification for AF using a multivariate risk prediction model with and without inclusion of FGF-23 **in the Cardiovascular Health Study (CHS)**

	10-Year Risk from Model with FGF-23[2]							
10-Year Risk from Adjusted Model[1]	<5%	5-15%	>15%	Total	Reclassified to higher risk	Reclassified to lower risk	Bias corrected NRI*	p-value**
<5%								
N	209	19	0	228				
AF, N	22	1	0	23	1	0		
No AF, N	187	18	0	205	18	0	-0.055	0.374
5 - 15%								
N	14	649	20	683				
AF, N	3	98	1	102	1	3		
No AF, N	11	551	19	581	19	11	-0.036	0.160
>15%								
N	0	24	387	411				
AF, N	0	6	95	101	0	6		
No AF, N	0	18	292	310	0	18	-0.025	0.288
Total								
N	223	692	407	1322				
AF, N	25	105	96	226	2	9		
No AF, N	198	587	311	1096	37	29	-0.038	0.02

[1]Model is derived using components from the Framingham AF Risk Score and includes age (continuous), sex, race, body mass index (continuous), systolic blood pressure (continuous), use of hypertension medication, and the PR interval (continuous).
[2]Model further includes FGF-23 (continuous).

*Sum of the proportions of correctly reclassified subjects with and without AF.
**Significant *P* values indicate change in classification

Abbreviation: FGF-23, fibroblast growth factor-23; AF, atrial fibrillation; NRI, net reclassification improvement

Supplemental Table 5. Mediation analysis: Associations of circulating FGF-23 concentrations with atrial fibrillation controlling for subclinical markers and biomarkers of cardiovascular disease as well as congestive heart failure events in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS).

Covariates	MESA	CHS
Model 3	1.41 (1.13 to 1.76), p = 0.003	1.30 (1.05 to 1.61), p = 0.016
LVED Mass	1.41 (1.10 to 1.80), p = 0.001	1.19 (0.91 to 1.54), p = 0.20*
LVED Size	1.40 (1.13 to 1.76), p = 0.003§	1.19 (0.92 to 1.55), p = 0.18*¶
LAD	NA	1.30 (1.03 to 1.63), p = 0.027
CHF Event	1.41 (1.05 to 1.79), p = 0.031	1.31 (1.04 to 1.62), p = 0.025
NT pro-BNP	1.43 (1.11 to 1.92), p = 0.007	1.36 (1.10 to 1.70), p = 0.005
CRP	1.41 (1.12 to 1.88), p = 0.004	1.31 (1.06 to 1.62), p =0.013
IL-6	1.40 (1.12 to 1.91), p = 0.005	NA

Cell contents are the hazard ratio (95% confidence interval) describing the association of FGF-23 and incident atrial fibrillation with additional adjustment for each covariate listed in the first column.

Results from Cox proportional hazards regression models for association of circulating FGF-23 with incident atrial fibrillation in MESA and CHS additionally adjusting for subclinical markers and biomarkers of cardiovascular disease as well as congestive heart failure events. These additional markers are added one at a time to Model 3, which is adjusted for age, gender, race/ethnicity, study site, attained education, low density cholesterol, use of lipid-lowering medications, current smoking, diabetes, physical activity, height, height squared, weight, urine albumin-creatinine-ratio, estimated glomerular filtration rate, systolic blood pressure, use of hypertension medication, serum concentrations of calcium, phosphate, 25-hydroxyvitamin D, and parathyroid hormone. Hazard ratios and p-values are derived from the models assessing FGF-23 as a continuous variable.

Abbreviations: FGF-23, fibroblast growth factor-23; LVED, left ventricular end-diastolic; CHF, congestive heart failure; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; IL-6, interleukin 6; CRP, C-reactive protein; LAD, left atrial diameter; NA, not available.

* Note LVED Mass and LVED Size in CHS represent N=950 with 155 incident atrial fibrillation events.

§ In MESA, left ventricular size was assessed by left ventricular end-diastolic volume.

¶ In CHS, left ventricular size was assessed by left ventricular end-diastolic diameter.

Supplemental Table 6. Associations of other circulating mineral metabolites with incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS).

Mineral Metabolite	MESA	CHS
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Calcium (per mg/dL)	0.82 (0.61, 1.11)	1.17 (0.80, 1.69)
Phosphorus (per 0.5 mg/dL)	1.15 (1.02, 1.31)	1.02 (0.78, 1.34)
25OHD (per 10 ng/mL)	0.92 (0.81,1.03)	1.00 (0.88, 1.14)
PTH (per doubling)	0.91 (0.75, 1.09)	0.90 (0.70, 1.15)

Results from Cox proportional hazards regression models for association of circulating mineral metabolites with incident atrial fibrillation in MESA and CHS. Models are adjusted for age, gender, race/ethnicity, study site, attained education, low density cholesterol, use of lipid-lowering medications, current smoking, diabetes, physical activity, height, height squared, weight, urine albumin-creatinine-ratio, estimated glomerular filtration rate, systolic blood pressure, and use of hypertension medication.

Abbreviations: PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D.