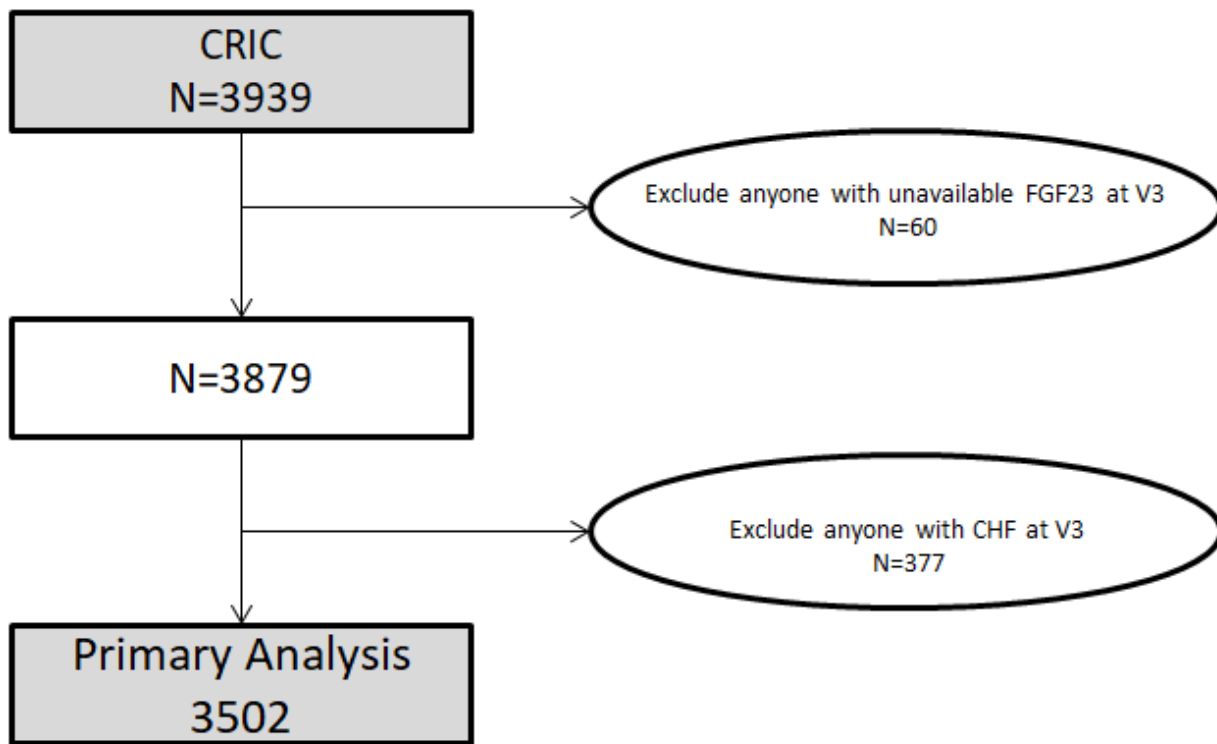


**Figure S1. Inclusion Flow Chart**



Inclusion flowchart for primary analysis to determine incident heart failure events. Visit 3 is the initial study visit.

**Table S1. FGF23 and Risk of Incident Heart Failure in Kidney Failure-censored models**

| FGF23 and incident HFpEF<br>Hazard Ratio (95%CI)  |               |                    |           |                    |                     |                    |                   |
|---|---------------|--------------------|-----------|--------------------|---------------------|--------------------|-------------------|
|   |               | ln(FGF23)          | FGF23 Q1  | FGF23 Q2           | FGF23 Q3            | FGF23 Q4           | p-value for trend |
| <b>N, events</b>                                  | 3502<br>(239) | 239                | 32        | 42                 | 70                  | 95                 |                   |
| <b>Unadjusted</b>                                 | 3502<br>(239) | 1.84 (1.66 – 2.04) | Reference | 1.47 (0.93 – 2.32) | 3.04 (2.00 – 4.62)  | 5.35 (3.57 – 8.01) | <0.001            |
| <b>Model 1</b>                                    | 3502<br>(239) | 1.91 (1.70 – 2.15) | Reference | 1.33 (0.84 – 2.11) | 2.76 (1.80 – 4.23)  | 5.05 (3.32 – 7.69) | <0.001            |
| <b>Model 2</b>                                    | 3336<br>(230) | 1.65 (1.44 – 1.88) | Reference | 1.20 (0.75 – 1.92) | 1.97 (1.25 – 3.09)  | 3.11 (1.96 – 4.96) | <0.001            |
| <b>Model 3</b>                                    | 3214<br>(223) | 1.49 (1.28 – 1.74) | Reference | 0.99 (0.61 – 1.59) | 1.41 (0.89 – 2.23)  | 1.92 (1.18 – 3.11) | 0.0015            |
| <b>Model 4</b>                                    | 3079<br>(214) | 1.54 (1.31 – 1.81) | Reference | 1.13 (0.68 – 1.85) | 1.62 (0.995 – 2.64) | 2.17 (1.29 – 3.64) | 0.0007            |
| FGF23 and incident HFrfEF<br>Hazard Ratio (95%CI) |               |                    |           |                    |                     |                    |                   |
|   |               | ln(FGF23)          | FGF23 Q1  | FGF23 Q2           | FGF23 Q3            | FGF23 Q4           | p-value for trend |
| <b>N, events</b>                                  | 3502<br>(178) | 178                | 31        | 38                 | 49                  | 60                 |                   |
| <b>Unadjusted</b>                                 | 3502<br>(178) | 1.56 (1.36 – 1.79) | Reference | 1.39 (0.87 – 2.24) | 2.28 (1.45 – 3.58)  | 3.74 (2.41 – 5.80) | <0.001            |
| <b>Model 1</b>                                    | 3502<br>(178) | 1.68 (1.44 – 1.96) | Reference | 1.28 (0.79 – 2.06) | 2.23 (1.41 – 3.53)  | 4.02 (2.55 – 6.35) | <0.001            |
| <b>Model 2</b>                                    | 3336<br>(169) | 1.36 (1.13 – 1.63) | Reference | 1.11 (0.68 – 1.81) | 1.58 (0.97 – 2.58)  | 2.26 (1.35 – 3.79) | <0.001            |

| <b>Model 3</b>                                   | 3214<br>(160)    | 1.27 (1.05 –<br>1.55) | Reference           | 1.02 (0.61 –<br>1.71) | 1.36 (0.81 –<br>2.28) | 1.76 (1.01 –<br>3.07)            | 0.0214 |
|--|------------------|-----------------------|---------------------|-----------------------|-----------------------|----------------------------------|--------|
| <b>Model 4</b>                                   | 3079<br>(156)    | 1.31 (1.06 –<br>1.62) | Reference           | 1.03 (0.61 –<br>1.72) | 1.46 (0.86 –<br>2.48) | 1.94 (1.09 –<br>3.46)            | 0.0104 |
| FGF23 and incident HFuEF<br>Hazard Ratio (95%CI) |                  |                       |                     |                       |                       |                                  |        |
|  | <b>ln(FGF23)</b> | <b>FGF23<br/>Q1</b>   | <b>FGF23<br/>Q2</b> | <b>FGF23<br/>Q3</b>   | <b>FGF23<br/>Q4</b>   | <b>p-value<br/>for<br/>trend</b> |        |
| <b>N, events</b>                                 | 3502<br>(102)    | 102                   | 19                  | 18                    | 23                    | 42                               |        |
| <b>Unadjusted</b>                                | 3502<br>(102)    | 1.81 (1.53 –<br>2.15) | Reference           | 1.06 (0.56 –<br>2.02) | 1.74 (0.95 –<br>3.20) | 4.33 (2.50 –<br>7.47)            | <0.001 |
| <b>Model 1</b>                                   | 3502<br>(102)    | 1.82 (1.51 –<br>2.20) | Reference           | 0.96 (0.50 –<br>1.84) | 1.58 (0.85 –<br>2.93) | 3.94 (2.23 –<br>6.96)            | <0.001 |
| <b>Model 2</b>                                   | 3336<br>(98)     | 1.76 (1.44 –<br>2.14) | Reference           | 0.96 (0.50 –<br>1.84) | 1.40 (0.72 –<br>2.69) | 3.65 (1.96 –<br>6.81)            | <0.001 |
| <b>Model 3</b>                                   | 3214<br>(96)     | 1.65 (1.32 –<br>2.06) | Reference           | 0.79 (0.40 –<br>1.57) | 1.08 (0.55 –<br>2.11) | 2.50 (1.28 –<br>4.86)            | 0.002  |
| <b>Model 4</b>                                   | 3079<br>(90)     | 1.61 (1.25 –<br>2.07) | Reference           | 0.71 (0.36 –<br>1.43) | 0.96 (0.48 –<br>1.93) | 2.10 (1.03 –<br>4.27)            | 0.018  |

Median follow-up years 8.4 years. Risks modeled separately for each heart failure type with the use of cause-specific Cox models. Results are reported as hazard ratio per 1 standard deviation increase in natural log of fibroblast growth factor 23 (FGF23) or hazard ratio in relation to the reference quartile.

Model 1: adjusted for age, sex, race, ethnicity and study site. (N=3502)

Model 2: Model 1 plus estimated glomerular filtration rate, and 24H urine protein (N=3336 due to missing covariates)

Model 3: Model 2 plus BMI, diabetes, smoking, systolic blood pressure, any cardiovascular disease, total cholesterol, statins, number of blood pressure medications, phosphate, parathyroid hormone. (N= 3214 due to missing covariates)

Heart failure with preserved ejection fraction, HFpEF; Heart failure with reduced ejection fraction, HFrEF; Heart failure with unknown ejection fraction, HFuEF.

Model 4: Model 3 plus calcium, CRP (log transformed), TSAT and Ferritin (log transformed)

**Table S2. FGF23 and Risk of Incident Heart Failure (40% EF Cutoff)**

| <b>FGF23 and incident HFpEF<br/>Hazard Ratio (95%CI)</b>  |                |                     |                 |                    |                    |                    |                          |
|---|----------------|---------------------|-----------------|--------------------|--------------------|--------------------|--------------------------|
|   | <b>Total N</b> | <b>ln(FGF23)</b>    | <b>FGF23 Q1</b> | <b>FGF23 Q2</b>    | <b>FGF23 Q3</b>    | <b>FGF23 Q4</b>    | <b>p-value for trend</b> |
| <b>N, events</b>  | 3502<br>(387)  | 387                 | 46              | 83                 | 111                | 147                |                          |
| <b>Unadjusted</b>   | 3502<br>(387)  | 1.68 (1.54 – 1.83)  | Reference       | 1.92 (1.34 – 2.75) | 2.91 (2.06 – 4.11) | 4.69 (3.36 – 6.54) | <0.001                   |
| <b>Model 1</b>  | 3502<br>(387)  | 1.75 (1.59 – 1.92)  | Reference       | 1.74 (1.21 – 2.50) | 2.67 (1.88 – 3.79) | 4.48 (3.18 – 6.31) | <0.001                   |
| <b>Model 2</b>  | 3336<br>(369)  | 1.44 (1.29 – 1.62)  | Reference       | 1.44 (0.99 – 2.09) | 1.72 (1.19 – 2.49) | 2.30 (1.57 – 3.38) | <0.001                   |
| <b>Model 3</b>  | 3214<br>(354)  | 1.35 (1.19 – 1.54)  | Reference       | 1.25 (0.86 – 1.82) | 1.24 (0.84 – 1.81) | 1.56 (1.04 – 2.33) | 0.038                    |
| <b>Model 4</b>  | 3079<br>(343)  | 1.38 (1.20 – 1.58)  | Reference       | 1.36 (0.92 – 2.01) | 1.35 (0.90 – 2.01) | 1.66 (1.09 – 2.54) | 0.030                    |
| <b>FGF23 and incident HFrfEF<br/>Hazard Ratio (95%CI)</b> |                |                     |                 |                    |                    |                    |                          |
|   | <b>Total N</b> | <b>ln(FGF23)</b>    | <b>FGF23 Q1</b> | <b>FGF23 Q2</b>    | <b>FGF23 Q3</b>    | <b>FGF23 Q4</b>    | <b>p-value for trend</b> |
| <b>N, events</b>  | 3502<br>(148)  | 148                 | 30              | 24                 | 45                 | 49                 |                          |
| <b>Unadjusted</b>   | 3502<br>(148)  | 1.43 (1.23 – 1.67)  | Reference       | 0.87 (0.51 – 1.48) | 1.87 (1.18 – 2.97) | 2.55 (1.61 – 4.03) | <0.001                   |
| <b>Model 1</b>  | 3502<br>(148)  | 1.56 (1.32 – 1.84)  | Reference       | 0.81 (0.47 – 1.39) | 1.90 (1.18 – 3.04) | 2.92 (1.82 – 4.70) | <0.001                   |
| <b>Model 2</b>  | 3336<br>(134)  | 1.34 (1.10 – 1.64)  | Reference       | 0.76 (0.43 – 1.33) | 1.41 (0.83 – 2.38) | 1.99 (1.13 – 3.50) | 0.004                    |
| <b>Model 3</b>  | 3214<br>(128)  | 1.23 (0.991 – 1.53) | Reference       | 0.68 (0.38 – 1.22) | 1.24 (0.71 – 2.15) | 1.55 (0.84 – 2.85) | 0.046                    |

|  | Total N       | ln(FGF23)           | FGF23 Q1  | FGF23 Q2           | FGF23 Q3           | FGF23 Q4           | p-value for trend |
|--|---------------|---------------------|-----------|--------------------|--------------------|--------------------|-------------------|
| <b>Model 4</b>                                   | 3079<br>(123) | 1.26 (0.997 – 1.60) | Reference | 0.67 (0.37 – 1.23) | 1.36 (0.77 – 2.42) | 1.74 (0.91 – 3.31) | 0.023             |
| FGF23 and incident HFuEF<br>Hazard Ratio (95%CI) |               |                     |           |                    |                    |                    |                   |
|  | Total N       | ln(FGF23)           | FGF23 Q1  | FGF23 Q2           | FGF23 Q3           | FGF23 Q4           | p-value for trend |
| <b>N, events</b>                                 | 3502<br>(158) | 158                 | 21        | 29                 | 42                 | 66                 |                   |
| <b>Unadjusted</b>                                | 3502<br>(158) | 1.68 (1.46 – 1.92)  | Reference | 1.46 (0.83 – 2.57) | 2.41 (1.43 – 4.07) | 4.73 (2.89 – 7.74) | <0.001            |
| <b>Model 1</b>                                   | 3502<br>(158) | 1.69 (1.46 – 1.97)  | Reference | 1.37 (0.78 – 2.41) | 2.27 (1.33 – 3.87) | 4.41 (2.65 – 7.34) | <0.001            |
| <b>Model 2</b>                                   | 3336<br>(150) | 1.56 (1.31 – 1.85)  | Reference | 1.26 (0.71 – 2.24) | 1.72 (0.98 – 3.04) | 3.30 (1.87 – 5.83) | <0.001            |
| <b>Model 3</b>                                   | 3214<br>(148) | 1.43 (1.18 – 1.73)  | Reference | 1.11 (0.62 – 2.00) | 1.40 (0.78 – 2.51) | 2.35 (1.29 – 4.29) | 0.002             |
| <b>Model 4</b>                                   | 3079<br>(138) | 1.40 (1.13 – 1.73)  | Reference | 1.09 (0.59 – 1.99) | 1.29 (0.70 – 2.37) | 2.07 (1.10 – 3.92) | 0.012             |

Risks modeled separately for each heart failure type with the use of cause-specific Cox models. Results are reported as hazard ratio per 1 standard deviation increase in natural log (ln) of fibroblast growth factor 23 (FGF23) or hazard ratio in relation to the reference quartile.

Model 1: adjusted for age, sex, race, ethnicity, and study site.

Model 2: Model 1 plus estimated glomerular filtration rate, and 24H urine protein.

Model 3: Model 2 plus BMI, diabetes, smoking, systolic blood pressure, any cardiovascular disease, total cholesterol, statins, number of blood pressure medications, phosphate, parathyroid hormone.

Heart failure with preserved ejection fraction, HFpEF; Heart failure with reduced ejection fraction, HFrEF; Heart failure with unknown ejection fraction, HFuEF.

Model 4: Model 3 plus calcium, CRP (log transformed), TSAT and Ferritin (log transformed)