FGF23 Genotype and Cardiovascular Disease in Patients Undergoing Hemodialysis

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Abstract

Background: Elevated serum concentrations of fibroblast growth factor 23 (FGF23) are associated with cardiovascular mortality in patients with chronic kidney disease (CKD) and those undergoing dialysis.

Objectives: We tested the hypotheses that polymorphisms in FGF23, its co-receptor alpha-klotho (KL), and/or FGF23 receptors (FGFR) are associated with cardiovascular events and/or mortality.

Methods: We used 1,494 DNA samples collected at baseline from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial, in which patients were randomized to the calcimimetic cinacalcet or placebo for the treatment of secondary hyperparathyroidism. We analyzed European and African Ancestry samples separately and then combined summary statistics to perform a meta-analysis. We evaluated single nucleotide polymorphisms (SNPs) in FGF23, KL, and FGFR4 as the key exposures of interest in proportional hazards (Cox) regression models using adjudicated end-points (all-cause and cardiovascular mortality, sudden cardiac death and heart failure) as the outcomes of interest.

Results: rs11063112 in FGF23 was associated with cardiovascular mortality (risk allele = A, hazard ratio (HR) = 1.32, meta-p value = 0.004) and heart failure (HR=1.40, meta-p value=0.007).

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No statistically significant associations were observed between FGF23 rs13312789 and SNPs in FGFR4 or KL genes and the outcomes of interest.

Conclusions: rs11063112 was associated with heart failure and cardiovascular mortality in patients receiving dialysis with moderate to severe secondary hyperparathyroidism.

Keywords
Dialysis; Cardiovascular Disease; Mortality; Fibroblast growth factor-23 (FGF23); CKD-Mineral Bone Disorder (CKD-MBD)

Introduction:
Chronic kidney disease-mineral bone disorder (CKD-MBD) is a systemic syndrome characterized by derangements in mineral metabolism, extra osseous calcification, and bone fragility[1]. Fibroblast growth factor 23 (FGF23) is produced in bone osteoblasts, with a primary effect on renal tubules through FGF receptor 1 (FGFR1) to increase phosphate excretion and enhance synthesis of 1,25(OH)2-vitamin D in conjunction with its co-receptor α-klotho. In the heart, FGF23 binds to FGF receptor 4 (FGFR4) in a klotho-independent manner and directly induces left ventricular hypertrophy in animal models[2, 3]. Serum concentrations of FGF23 become markedly elevated in patients with CKD and are associated with progression of left ventricular hypertrophy[4, 5] and mortality[6, 7]. Cinacalcet-induced reduction in serum FGF23 was associated with a lower risk of cardiovascular death, adjudicated heart failure events and sudden cardiac death[7]. These data suggest that DNA polymorphisms in the genes encoding FGF23 (FGF23), FGFR4 (FGFR4), or α-klotho (KL) may contribute to cardiovascular disease in patients with CKD.

To explore the potential role of genetic polymorphisms in the FGF23-klotho pathway on cardiovascular disease in patients receiving hemodialysis, we utilized DNA samples from the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial[8, 9]. In EVOLVE, 3,883 patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism (sHPT; baseline PTH ≥600 μg/mL and serum calcium ≥8.4 mg/dL) were randomized to receive either cinacalcet or placebo, in addition to standard of care treatments that generally included phosphate binders and calcitriol or vitamin D analogs. Mortality and cardiovascular events were assessed and adjudicated by an independent Clinical Events Committee. Patients were followed for up to 64 months, and DNA was collected in a subset of these subjects. The present study sought to determine if known single nucleotide polymorphisms (SNPs) in FGF23, FGFR4 or KL are associated with mortality and/or cardiovascular events.

Materials and Methods
DNA was collected at baseline from those patients in the EVOLVE trial who signed a separate consent (n=1,919). EVOLVE was an international study in 22 countries, and not all countries allowed the collection of DNA for research purposes. Blood samples were processed by the central study laboratory (Covance, Princeton NJ) and de-identified samples sent to Indiana University. The study was deemed not subject to the Common Rule by the
Indiana University Institutional Review Board. After DNA extraction, 1,852 samples were genotyped using the Sequenom MassArray system. DNA and genotyping quality assessment have been described previously\[10\]. We categorized ancestry group by self-reported race. For this report, we only included patients of European Ancestry (EA; n=1,083) and African Ancestry (AfAn, n=411) due to small numbers of patients in other self-reported race groups (i.e., Asians, Aboriginal and other Native persons, and persons of mixed race). Based on previously published literature reporting an association of SNPs in genes in the FGF23-klotho pathway, we genotyped five SNPs in FGFR4, two SNPs in FGF23, and two SNPs in KL[11, 12, 13, 14, 15]. There was no significant deviation from Hardy-Weinberg equilibrium for any SNP in either ancestry group (all p>0.21).

**Statistical Analyses**

Descriptive statistics to characterize the groups are provided in Table 1. As primary analysis, association between 9 SNPs and four EVOLVE outcomes relevant to the known biologic effects of FGF23 on the heart (all-cause mortality, cardiovascular mortality, sudden cardiac death (SCD) and heart failure (HF)) were tested using proportional hazards regression (Cox) models, or the Fine-Gray modification of the Cox model when accounting for competing risks (i.e., non-cardiovascular death). All models were stratified by site and presence of diabetes. Study participants were followed for up to 64 months. We included age, sex, vintage (number of years since starting dialysis), history of smoking (current or past), and treatment assignment (placebo/cinacalcet in addition to standard treatment) as covariates[8]. A global test combining zero-slope tests on the scaled Schoenfeld residuals plotted against time was used to examine the proportional hazards assumption for each covariate in the model. We considered death as a competing risk in the evaluation of non-fatal events. For the analyses including competing risks, we constructed cumulative incidence rather than survival plots for each genotype, and calculated sub-distribution hazards.

We utilized an additive genetic model, which assumed a similar increase (or decrease) in the hazard ratio for each copy of the coded allele. Our primary analysis of interest was a meta-analysis across the two ancestry groups, EA and AfAn, in order to account for the known differences in cardiovascular risk[16, 17] and minor allele frequencies. To compare results across groups in the meta-analysis, we assigned the minor alleles of the EA group as the reference alleles in both EA and AfAn samples. All meta-analysis heterogeneity p-values were greater than 0.06, suggesting there was no significant heterogeneity between the two population groups, and meta-analysis of the EA and AfAn summary statistics was performed using R package “r-meta” (https://cran.r-project.org/web/packages/rmeta/index.html, 2.16). The inverse standard errors were implemented as weights. We accounted for sample heterogeneity by using a random effects model. We performed all analyses using SAS 9.4 (SAS Institution Inc, Cary, NC) and R.

Due to the correlation among the outcomes, and the correlation among the SNPs, the number of independent tests in this study was not simply the product of the number of outcomes times the number of SNPs. The Matrix Spectral Decomposition method (MatSpD, https://gump.qimr.edu.au/general/daleN/matSpD/) was used to estimate the number of independent tests, based on the correlation matrix of the outcomes (Supplemental Table 1)
and on the correlation matrix of the SNPs (D’ values of LD; Figure 1). The MatSpD method was applied separately in the EA and AfAn samples. As the SNPs had lower linkage disequilibrium in the AfAn individuals, this sample was estimated to have a larger number of independent tests compared with the EA sample. Hence the AfAn MaTSpD results included 6.21 independent tests (=1.6 independent outcomes × 3.88 independent SNPs) and this factor was used to correct for multiple testing for both populations. This corresponded to a corrected alpha threshold of 0.008. To aid the interpretation of survival analysis results, secondary analyses tested for association between the 9 SNPs and the following biochemical measurements: baseline serum calcium, phosphate, parathyroid hormone (PTH), 1,25(OH)₂-vitamin D, and FGF23, along with percentage change in serum concentrations between baseline and 20 week follow-up. Due to non-normal distributions of the traits, which can inflate type I error rates, we adjusted all baseline and percentage change in serum concentrations for covariates reported in a previous publication[10] and using the same method, obtained residuals and tested associations with the SNPs. As with survival analyses, all analyses linking SNPs to laboratory tests were conducted separately in EA and AfAn samples followed by meta-analysis using summary statistics from the two groups.

Results

Baseline demographic, cardiovascular and CKD-MBD laboratory data for individuals genotyped for at least one of the SNPs are provided in Table 1. A total of 1,494 patients were analyzed (1,083 EA and 411 AfAn samples). Patients who were analyzed in this cohort were, in general, similar to the overall EVOLVE cohort with multiple risk factors for cardiovascular disease (Table 1). Alleles and minor allele frequency (MAF) for the analyzed SNPs in FGF23, FGFR4, and KL are shown in Supplemental Table 2 and the LD plots in Figure 1.

Rs11063112 was associated with cardiovascular mortality (Hazard Ratio (HR) = 1.32, meta-p value = 0.004, A allele increased risk) and heart failure (HR=1.40, meta-p value=0.007, A allele increased risk). (Table 2 and Figure 2). No significant associations were observed between the other SNPs in FGF23, FGFR4 or KL genes and the four tested cardiovascular/mortality outcomes (Supplemental Table 3). In order to understand the potential mechanism of our association between the FGF23 SNP and cardiovascular mortality, we determined if rs11063122 was also associated with the baseline biochemical measures of CKD-MBD. We tested for the association between rs11063122 and serum calcium (corrected for albumin), phosphate, intact PTH, 1,25(OH)₂-vitamin D, and intact FGF23. No statistically significant associations were observed (Supplemental Table 4). We further tested if rs11063112 modified the treatment (cinacalcet or placebo) effect on the percent change of CKD-MBD laboratory values from baseline to 20 weeks. There was no significant effect modification (Supplemental Table 5).

Discussion/Conclusion:

Cardiovascular disease is the leading cause of death in patients with CKD. Among patients with more advanced CKD the predominant cardiovascular diseases are those related to poorly controlled hypertension and left ventricular hypertrophy (LVH) – heart failure,
stroke, and sudden cardiac death\textsuperscript{18, 19}. In patients receiving dialysis, LVH is present in more than 75% of patients\textsuperscript{20, 21}. Multiple studies have demonstrated that the highest serum concentrations of FGF23 are associated with LVH and mortality in CKD and in patients receiving dialysis \textsuperscript{2, 4, 22, 23, 24}. Herein we report the novel observation that one SNP in FGF23, rs11063112, is associated with adjudicated cardiovascular mortality and heart failure events in participants from the EVOLVE trial.

We previously reported that a 30% or more reduction in serum intact FGF23 induced by cinacalcet was associated with lower rates of heart failure, sudden cardiac death, and cardiovascular mortality\textsuperscript{17}. These results are consistent with the known cardiotoxic effects of FGF23. In rodent models, FGF23 induces cardiac hypertrophy mediated by FGF receptor 4\textsuperscript{2, 25, 26}. Genetic ablation of FGFR4 can prevent the induction of LVH by FGF23 in rodent models of CKD and aging\textsuperscript{27}. In autopsy studies of children with advanced CKD, the upregulation of FGF23 and FGFR4 expression in heart tissue was associated with fibrosis\textsuperscript{24}, a known precursor of diastolic dysfunction, heart failure, and arrhythmia. In addition, FGF23 can induce a spike in intracellular calcium in cardiomyocytes and alter contractility, physiology predisposing to sudden cardiac death\textsuperscript{27}. Thus, the findings in the present study support the biologic effects of FGF23.

In the current report, we did not find associations among either SNP in FGF23 with serum FGF23 concentrations. A recent report by Robinson-Cohen et al. also reported a lack of association between variants in FGF23 region and serum FGF23 concentrations in patients without CKD\textsuperscript{28}. This may indicate that currently tested SNPs in FGF23 do not modulate serum levels of FGF23. Furthermore, serum concentrations of intact FGF23 in patients receiving dialysis can increase 400-fold from CKD stage 2 to 5, due not only to increased secretion from bone, but also altered regulation and clearance\textsuperscript{7, 30, 31}. The striking elevations and wide distribution of FGF23 among patients receiving dialysis may have masked associations of any of the FGF23 SNPs and serum concentrations of FGF23.

We did not find associations among SNPs in FGFR4 or KL and cardiovascular events in the present study. Alpha-klotho is a required co-receptor for the kidney effects of FGF23 mediated through FGFR1, but not the cardiac effects mediated through FGFR4. Friedman et al. found an association with 1-year mortality in patients on dialysis with the KL polymorphism rs577912 in a cohort of 1,307 white and Asian patients on hemodialysis (RR, 1.76; 95% CI, 1.19--2.59; p = 0.003)\textsuperscript{12}. Interestingly, they found a more robust association in patients who were not receiving treatment for sHPT with calcitriol or its analogues, raising the possibility that treatment of sHPT with cinacalcet may have masked this association in our sample.

This study has several strengths. It is the largest genetic study in patients receiving dialysis to date with follow-up of up to 64 months. In addition, the cardiovascular end-points were adjudicated, which is critically important in studies of heart failure. In EVOLVE, nearly half of the investigator-designated heart failure events were adjudicated negative (Chertow, unpublished data) due to the difficulty in clinically diagnosing heart failure in patients receiving dialysis. Limitations include the modest sample size. Although large by dialysis clinical trial standards, we had fewer than 2,000 samples and only 747 primary composite events.
cardiovascular endpoint events; therefore, we believe that we had insufficient power to
detect other possible genetic associations or outcomes. Furthermore, patients in EVOLVE
were enrolled because of moderate to severe secondary hyperparathyroidism despite therapy
with phosphate binders and calcitriol or active vitamin D analogs; thus these findings are not
generalizable to all patients receiving hemodialysis or to other patients with ESKD,
including patients treated with peritoneal dialysis, patients treated with non-dialytic
(conservative) therapy, or to kidney transplant recipients. Finally, there is strong LD between
the two tested SNPs in FGF23 (chosen based upon prior literature\cite{11,15}) and many, but not
all, ungenotyped variants in that gene. Thus, the associated SNP might not be the functional
one, and it is possible we missed an association with SNPs that are not in high LD with the
tested SNPs. Finally our genotype coverage of FGF23, FGFR4 or KL was not complete and
thus possibly missed associations that were not in LD with the genotyped SNPs.

In conclusion, we report a novel association between rs11063112 and cardiovascular
mortality and heart failure events utilizing stored samples and adjudicated cardiovascular
event data from EVOLVE. Although the mechanistic link between our findings of a
significant association with rs11063112 in FGF23 is not yet known, the finding is important
in pointing out a target for future research. If validated, these results may help to recognize
those patients receiving dialysis who are at increased risk for these events, or to identify
persons who might be better suited for participation in clinical trials with FGF23-lowering
therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:
The Authors dedicate this manuscript to the memory of Dr. Brian Decker, who passed away during the manuscript’s
final stage of editing but contributed to the planning and analyses of the study. Dr. Decker was a true scholar who
had established a brilliant career dedicated to pharmacology and pharmacogenomics in CKD. His keen intellect and
the resilience he exhibited during his illness will continue to inspire his co-authors, other colleagues, trainees, and
students.

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Statement of Ethics: The collection of DNA was under a separate consent during the primary trial, approved at
each Institution. For the purposes of this use of the DNA samples, all data was de-identified and considered not
subject to the Common Rule by the Indiana University Institutional Review Board.

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other from Ardelyx, personal fees from Astra Zeneca, personal fees from Baxter, personal fees from Gilead,
personal fees from Keryx, other from Cricket Health, other from Durect, other from Outset Medical, other from
Physiowave, other from PuraCath Medical, outside the submitted work. The other authors report no disclosures.

REFERENCES:

Figure 1: Linkage Disequilibrium (LD) in *FGF23*, *KL*, and *FGFR4*:
LD plots for the *FGF23*, *KL*, and *FGFR4* SNPs examined in the European Ancestry (EA), and the African Ancestry (AfAn) samples. For each gene and ancestry combination, left panel shows LD measured in $D'$ and right panel shows LD measured in $r^2$. 

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Figure 2: Probability of survival and SNPs in the *FGF23* gene:
Unadjusted Kaplan-Meier Curve for survival, or being free from the end points in Table 2. Panel A is the association between the *FGF23* SNP rs11063112 and heart failure; Panel B is the association between the *FGF23* SNP rs11063112 and cardiovascular mortality. The color-shaded area represents the 95% confidence interval. EA = European Ancestry, AfAn = African Ancestry.
Table 1:
Demographic and baseline laboratory values for DNA cohort compared to the primary EVOLVE trial

<table>
<thead>
<tr>
<th></th>
<th>EA n = 1,083</th>
<th>AfAn n = 411</th>
<th>EVOLVE Cohort n = 3,883</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cinacalcet Use (%)</strong></td>
<td>558 (52%)</td>
<td>206 (50%)</td>
<td>1,938 (50%)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years; mean (SD)</td>
<td>56.3 (14.0)</td>
<td>52.3 (13.4)</td>
<td>54.4 (14.4)</td>
</tr>
<tr>
<td>Sex, n (%) female</td>
<td>420 (39%)</td>
<td>176 (43%)</td>
<td>1,578 (41%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td></td>
<td></td>
<td>2,240 (58%)</td>
</tr>
<tr>
<td>AfAn</td>
<td></td>
<td></td>
<td>837 (22%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>806 (21%)</td>
</tr>
<tr>
<td><strong>Dialysis vintage (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years, n (%)</td>
<td>319 (29%)</td>
<td>139 (34%)</td>
<td>1,098 (28%)</td>
</tr>
<tr>
<td>2 to &lt; 5 years, n (%)</td>
<td>345 (32%)</td>
<td>144 (35%)</td>
<td>1,285 (33%)</td>
</tr>
<tr>
<td>≥5 years, n (%)</td>
<td>419 (39%)</td>
<td>128 (31%)</td>
<td>1,499 (39%)</td>
</tr>
<tr>
<td>Current or previous smoker, n (%)</td>
<td>488 (45%)</td>
<td>173 (42%)</td>
<td>1,696 (44%)</td>
</tr>
<tr>
<td>Abnormal baseline ECG, n (%)</td>
<td>618 (57%)</td>
<td>288 (70%)</td>
<td>2,263 (58%)</td>
</tr>
<tr>
<td>Diabetes (Type 1 or Type 2), n (%)</td>
<td>295 (27%)</td>
<td>181 (44%)</td>
<td>1,302 (34%)</td>
</tr>
<tr>
<td>Chronic Atrial fibrillation, n (%)</td>
<td>76 (7%)</td>
<td>19 (5%)</td>
<td>227 (6%)</td>
</tr>
<tr>
<td>Arrhythmia of any type, n (%)</td>
<td>188 (17%)</td>
<td>53 (13%)</td>
<td>554 (14%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>970 (90%)</td>
<td>408 (99%)</td>
<td>3,577 (92%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft n (%)</td>
<td>87 (8%)</td>
<td>18 (4%)</td>
<td>289 (7%)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>157 (14%)</td>
<td>42 (10%)</td>
<td>483 (12%)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>242 (22%)</td>
<td>139 (34%)</td>
<td>906 (23%)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>105 (10%)</td>
<td>43 (10%)</td>
<td>355 (9%)</td>
</tr>
<tr>
<td>Peripheral arterial disease, n (%)</td>
<td>190 (18%)</td>
<td>58 (14%)</td>
<td>635 (16%)</td>
</tr>
<tr>
<td>Amputation, n (%)</td>
<td>53 (5%)</td>
<td>31 (8%)</td>
<td>250 (6%)</td>
</tr>
<tr>
<td><strong>Baseline Drug Use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Based Phosphate Binders, n (%)</td>
<td>680 (63%)</td>
<td>155 (38%)</td>
<td>2,062 (53%)</td>
</tr>
<tr>
<td>Baseline Vitamin D, n (%)</td>
<td>660 (61%)</td>
<td>318 (77%)</td>
<td>2,310 (59%)</td>
</tr>
<tr>
<td><strong>Baseline Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Ca, mean (std dev) mmol/L; [mg/dL]</td>
<td>2.45 (0.17); [9.8 (0.7)]</td>
<td>2.45 (0.15); [9.8 (0.6)]</td>
<td>2.45 (0.17); [9.8 (0.7)]</td>
</tr>
<tr>
<td>Phosphate, mean (std dev) mmol/L; [mg/dL]</td>
<td>6.6 (1.5); [2.13 (0.48)]</td>
<td>6.3 (1.4); [2.03 (0.45)]</td>
<td>6.5 (1.4); [2.10 (0.45)]</td>
</tr>
<tr>
<td>Intact PTH, mean (std dev); μg/ml</td>
<td>908 (620)</td>
<td>790 (529)</td>
<td>894 (614)</td>
</tr>
<tr>
<td>FGF23, mean (std dev); μg/mL</td>
<td>8500.7 (8623.5)</td>
<td>8374.7 (10236.0)</td>
<td>8398.9 (9098.4)</td>
</tr>
<tr>
<td>Potassium mean (std dev); mmol/L</td>
<td>5.2 (0.8)</td>
<td>4.7 (0.7)</td>
<td>5.1 (0.8)</td>
</tr>
<tr>
<td>Hemoglobin mean (std dev) g/dL</td>
<td>118 (15)</td>
<td>118 (14)</td>
<td>118 (15)</td>
</tr>
<tr>
<td>Total cholesterol, mean (std dev) mmol/L; [mg/dL]</td>
<td>4.77 (1.19); [184 (46)]</td>
<td>4.04 (1.04); [156 (40)]</td>
<td>4.33 (1.11); [167 (43)]</td>
</tr>
<tr>
<td>LDL cholesterol, mean (std dev) Mmol/L; [mg/dL]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EA n = 1,083</td>
<td>AfAn n = 411</td>
<td>EVOLVE Cohort n = 3,883&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
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<tr>
<td>HDL cholesterol, mean (std dev) mmol/L; [mg/dL]</td>
<td>1.09 (0.36); [42 (14)]</td>
<td>1.24 (0.44); [48 (17)]</td>
<td>1.11 (0.39); [43 (15)]</td>
</tr>
<tr>
<td>Triglycerides mean (std dev) mmol/L; [mg/dL]</td>
<td>1.99 (1.45); [176 (128)]</td>
<td>1.60 (1.25); [142 (111)]</td>
<td>1.92 (1.36); [170 (120)]</td>
</tr>
</tbody>
</table>

**Percent Change in Laboratory values**

|                                | EA n = 1,083 | AfAn n = 411 | EVOLVE Cohort n = 3,883<sup>a</sup> |
|                                |             |              |                              |
| Percent change in serum albumin corrected calcium (mean, std dev) | −4.6 (8.8) | −3.5 (8.4) | NA |
| Percent change in PTH (mean, std dev) | −21 (48) | −18 (52) | NA |
| Percent change in FGF23 (mean, std dev) | −5 (90) | 48 (645) | NA |
| Percent change in serum phosphate (mean, std dev) | −8.6 (22.1) | −7.4 (25.7) | NA |

<sup>a</sup> = From references (7–9, 17)
Table 2:

Association of SNPs with cardiovascular outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>Gene rsID</th>
<th>P value</th>
<th>HR (95% CI)</th>
<th>EA HR</th>
<th>AfAn HR</th>
<th>Event Number (EA/AfAn)</th>
<th>Censored Patients (EA/AfAn)</th>
<th>Competing Events (EA/AfAn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>FGF23 rs11063112</td>
<td>0.007</td>
<td>1.40 (1.10–1.79)</td>
<td>1.37</td>
<td>1.51</td>
<td>184 (100/84)</td>
<td>859 (639/220)</td>
<td>447 (340/107)</td>
</tr>
<tr>
<td>Cardio-vascular mortality</td>
<td>FGF23 rs11063112</td>
<td>0.0035</td>
<td>1.32 (1.09–1.58)</td>
<td>1.32</td>
<td>1.31</td>
<td>295 (222/73)</td>
<td>954 (678/276)</td>
<td>241 (179/62)</td>
</tr>
</tbody>
</table>

Meta-analysis results for survival analysis with cardiovascular outcome adjusted for age, sex, duration of dialysis, history (current/past) of smoking, and treatment (placebo/cinacalcet). SNP = Single Nucleotide Polymorphism. rsID = reference SNP ID number. HR = Hazard Ratio. 95% CI = 95% confidence interval. EA = European Ancestry. AfAn = African Ancestry. The HR represents the increased risk for each copy of the reference allele.