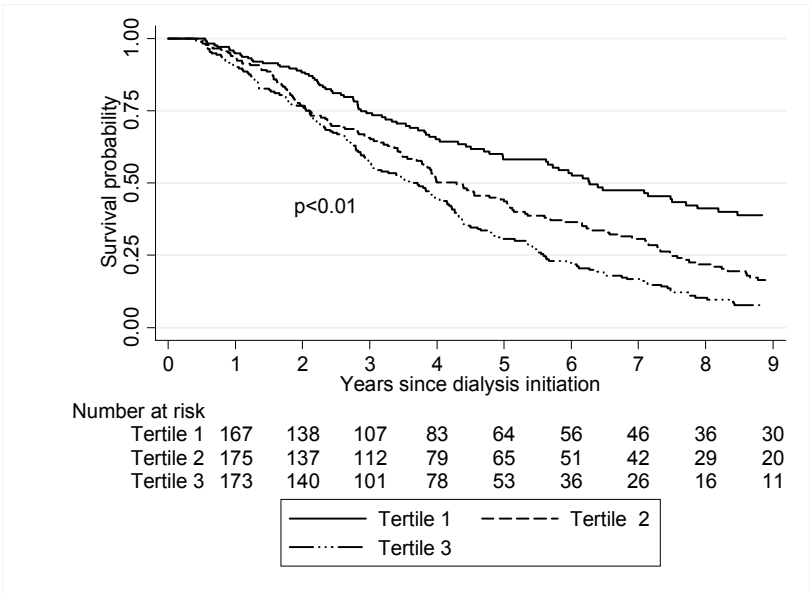


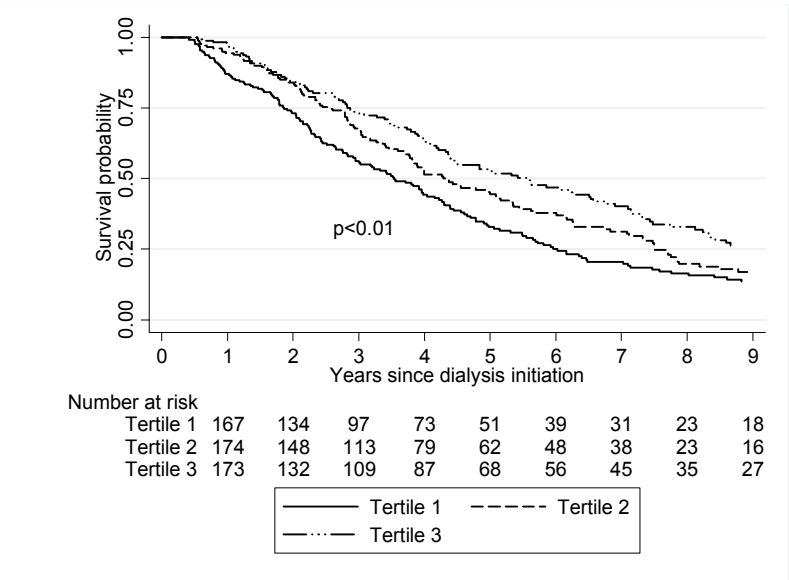
Biomarkers of Vascular Calcification and Mortality in Patients with ESRD

Supplemental Data

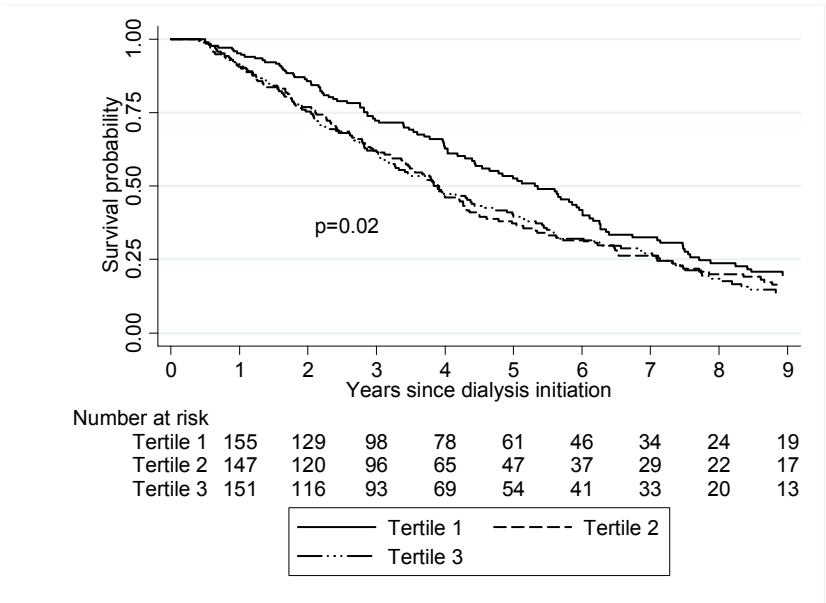
Supplemental Figure 1A. Unadjusted Kaplan Meier survival curves by tertiles of osteoprotegerin



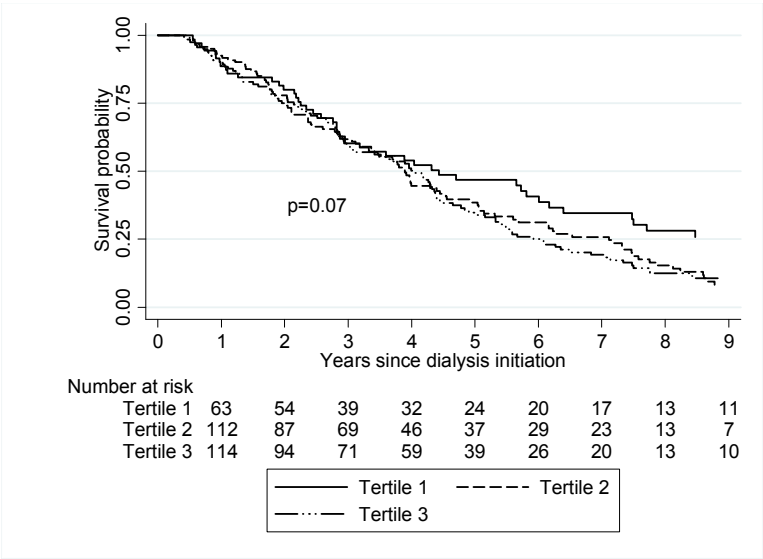
Supplemental Figure 1B. Unadjusted Kaplan Meier survival curves by tertiles of fetuin-A



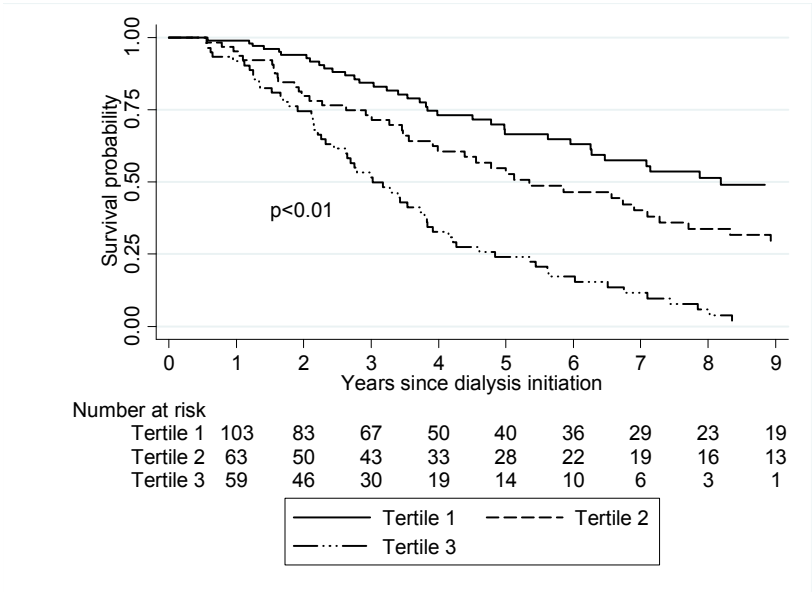
Supplemental Figure 1C. Unadjusted Kaplan Meier survival curves by tertiles of osteopontin



Supplemental Figure 2A. Unadjusted Kaplan Meier survival curves by tertiles of osteoprotegerin among diabetics

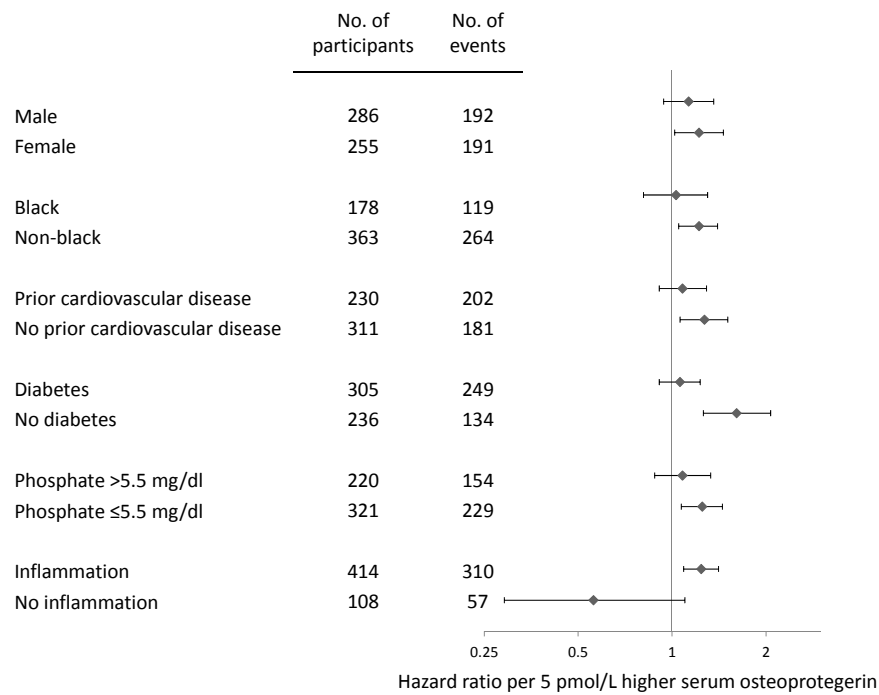


Supplemental Figure 2B. Unadjusted Kaplan Meier survival curves by tertiles of osteoprotegerin among non-diabetics

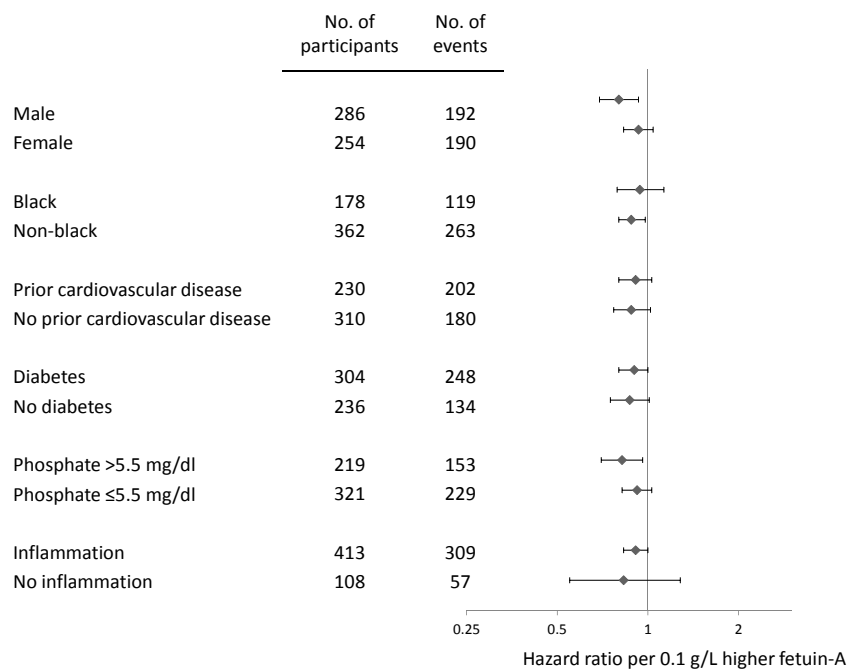


Supplemental Figure 3. Adjusted log hazard ratio of all-cause mortality among subgroups and by levels of: A) osteoprotegerin per 5 pmol/l; and B) fetuin-A per 0.1 g/l. Dots represent log hazard ratio and lines represent 95% confidence interval. Models adjusted for age, sex, race, index of coexistent disease, diabetes, cardiovascular disease, body mass index, serum phosphate and corrected serum calcium. CVD, cardiovascular disease and inflammation defined as serum albumin <3.6 g/dl, C-reactive protein ≥ 10 mg/l, or interleukin-6 ≥ 3.09 pg/ml.

Supplemental Figure 3A.

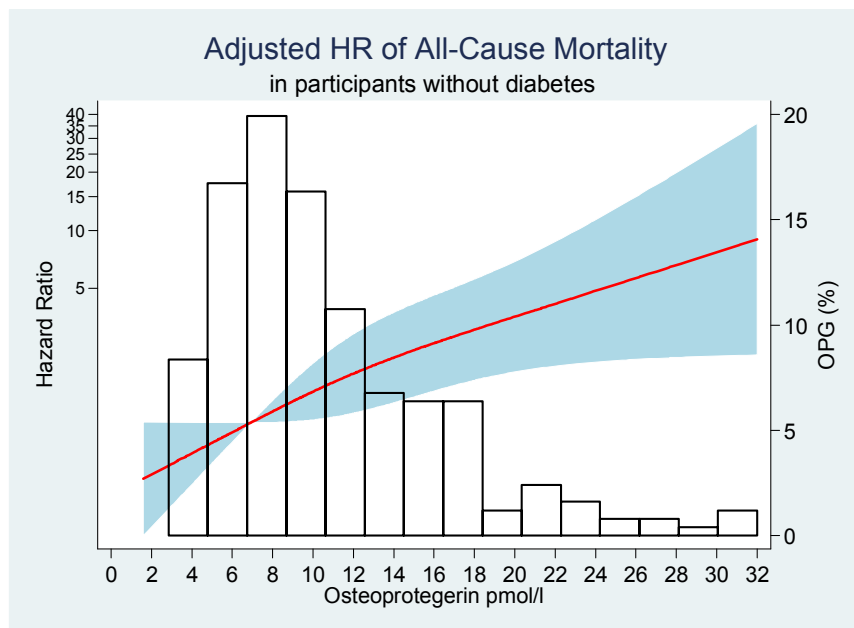


Supplemental Figure 3b.

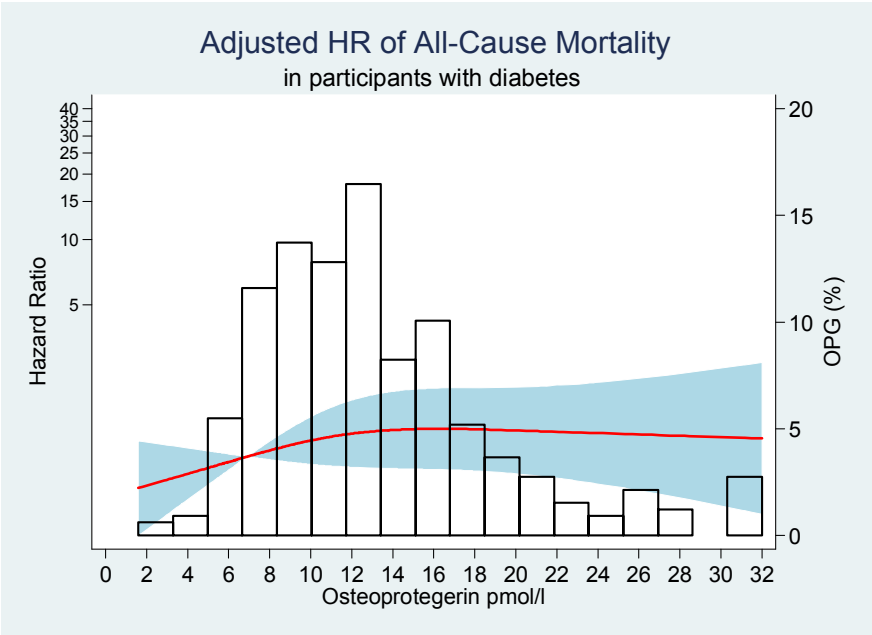


Supplemental Figure 4. Adjusted hazard ratio of all-cause mortality by levels of calcification biomarkers using restricted cubic spline with knots at the 10th, 50th and 90th percentile: A) serum osteoprotegerin among participants without diabetes; B) serum osteoprotegerin among participants with diabetes; and, C) fetuin-A in the overall study population. Hazard ratio is graphed on a logarithmic scale. Blue shaded area represents the 95% confidence interval. Histogram presents percentage of participants with corresponding biomarker levels in the study population. Models adjusted for age, sex, race, index of coexistent disease, diabetes, cardiovascular disease, body mass index, serum phosphate and corrected serum calcium and were created using the unimputed data.

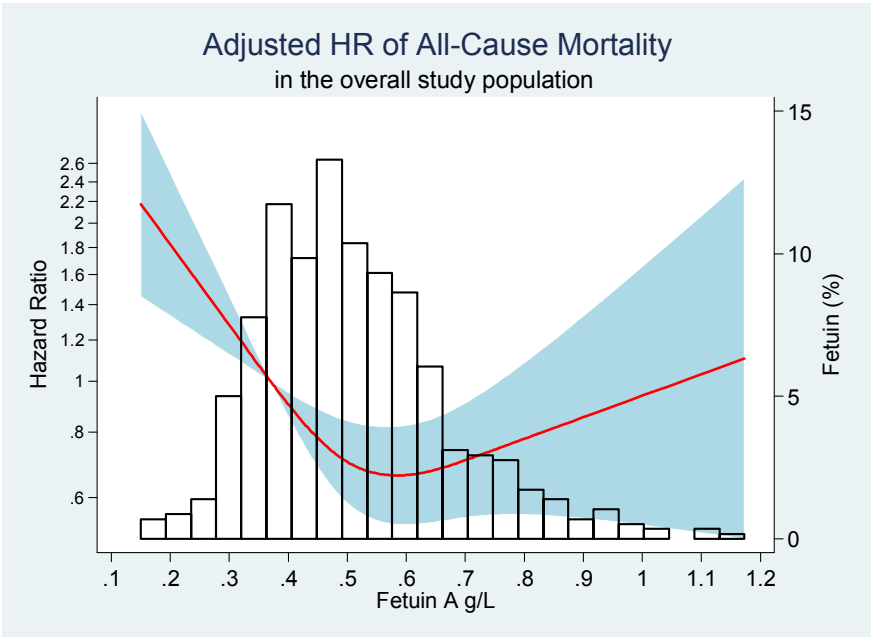
Supplemental Figure 4A.



Supplemental Figure 4B.



Supplemental Figure 4C.



Supplemental Table 1. Multivariable adjusted hazard ratio (Model 1) of all-cause mortality by calcification biomarkers in the unimputed data

	Multivariable Adjusted*		
	All (n=602)	Diabetics [†] (n=340)	Non-diabetics (n=261)
<u>Osteoprotegerin</u> (n=541)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.39 (1.02-1.89)	1.16 (0.77-1.77)	1.57 (0.88-2.80)
Tertile 3	1.53 (1.10-2.14)	1.19 (0.77-1.84)	2.84 (1.52-5.30)
Continuous (per 5 pmol/l)	1.16 (1.04-1.30)	1.06 (0.91-1.23) [‡]	1.61 (1.26-2.07) [‡]
<u>Fetuin-A</u> (n=540)			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.93 (0.71-1.22)	1.14 (0.80-1.61)	0.78 (0.45-1.32)
Tertile 3	0.70 (0.52-0.94)	0.68 (0.46-1.00)	0.56 (0.33-0.95)
Continuous (per 0.1 g/l)	0.91 (0.84-0.99)	0.90 (0.80-1.00)	0.87 (0.75-1.01)
<u>Osteopontin</u> (n=479)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.23 (0.90-1.66)	1.27 (0.84-1.90)	1.17 (0.62-2.18)
Tertile 3	1.30 (0.95-1.77)	1.13 (0.75-1.71)	2.25 (1.19-4.24)
Continuous (per 50 ng/ml)	1.02 (0.97-1.08)	1.02 (0.95-1.10)	1.08 (0.98-1.20)
<u>Bone morphogenic protein 7</u> (n=466)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.04 (0.77-1.40)	1.15 (0.77-1.71)	0.94 (0.52-1.70)
Tertile 3	1.15 (0.86-1.54)	1.16 (0.79-1.71)	1.87 (1.02-3.46)
Continuous (per ln) [§]	1.15 (0.95-1.40)	1.13 (0.87-1.47)	1.36 (0.90-2.04)

*Multivariable model adjusted for age, sex, race, index of coexistent disease, diabetes, cardiovascular disease, body mass index, serum phosphate and corrected serum calcium

[†] Diabetic status was unknown in 1 participant

[‡] P-interaction<0.01 from model using biomarker as a continuous variable

[§]Natural log (ln) transformed prior to continuous modeling due to highly skewed distribution

^{||}p<0.05

Supplemental Table 2. Adjusted hazard ratio in model 2, additionally adjusted for inflammation and fibroblast growth factor 23 (FGF23), by calcification biomarker in the unimputed data

	Multivariable + Inflammation + FGF23 Adjusted*		
	All	Diabetics	Non-diabetics
<u>Osteoprotegerin</u> (n=429)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.39 (0.97-1.99)	1.36 (0.84-2.22)	1.25 (0.59-2.63)
Tertile 3	1.15 (0.78-1.71)	0.86 (0.51-1.45)	2.23 (0.98-5.07)
Continuous (per 5 pmol/l)	1.11 (0.97-1.28)	1.00 (0.83-1.21)	1.54 (1.11-2.14)
<u>Fetuin-A</u> (n=428)			
Tertile 1	Ref	Ref	Ref
Tertile 2	0.83 (0.60-1.13)	0.92 (0.60-1.40)	0.97 (0.49-1.90)
Tertile 3	0.77 (0.55-1.10)	0.69 (0.42-1.13)	0.94 (0.47-1.87)
Continuous (per 0.1 g/l)	0.93 (0.84-1.03)	0.88 (0.76-1.02)	1.00 (0.84-1.20)
<u>Osteopontin</u> (n=450)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.29 (0.93-1.78)	1.30 (0.85-2.00)	0.91 (0.47-1.75)
Tertile 3	1.12 (0.81-1.56)	0.86 (0.55-1.36)	1.98 (0.97-4.02)
Continuous (per 50 ng/ml)	0.99 (0.93-1.04)	0.96 (0.89-1.04)	1.05 (0.93-1.19)
<u>Bone morphogenic protein 7</u> (n=424)			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.17 (0.83-1.63)	1.51 (0.95-2.40)	0.81 (0.42-1.55)
Tertile 3	1.05 (0.76-1.46)	1.03 (0.66-1.62)	2.74 (1.28-5.84)
Continuous (per ln) [§]	1.02 (0.81-1.28)	0.95 (0.70-1.30)	1.49 (0.86-2.55)

*Model adjusted for age, sex, race, index of coexistent disease, diabetes, cardiovascular disease, body mass index, serum phosphate, corrected serum calcium, serum albumin, log interleukin-6, log C-reactive protein and log fibroblast growth factor 23

§Natural log (ln) transformed prior to continuous modeling due to highly skewed distribution

^{||}p<0.05

Supplemental Table 3. Unadjusted and multivariable adjusted hazard ratio (Model 1) of cardiovascular mortality by levels of osteoprotegerin and fetuin-A in unimputed data

	Unadjusted				Adjusted*			
	All (n=580)	Diabetics [†] (n=328)	Non-diabetics (n=251)	P-interaction [‡]	All (n=541)	Diabetics (n=305)	Non-diabetics (n=236)	P-interaction [‡]
Osteoprotegerin (n=580)								
Tertile 1	Ref	Ref	Ref		Ref	Ref	Ref	
Tertile 2	1.80 (1.17-2.76) [§]	1.08 (0.64-1.84)	3.52 (1.46-8.47) [§]		1.32 (0.81-2.15)	0.96 (0.53-1.73)	2.85 (0.91-8.95)	
Tertile 3	2.87 (1.90-4.35) [§]	1.34 (0.80-2.26)	7.43 (3.29-16.77) [§]		1.67 (1.01-2.75) [§]	1.12 (0.62-2.00)	4.24 (1.29-13.92) [§]	
Continuous (per 5 pmol/l)	1.35 (1.19-1.53) [§]	1.02 (0.86-1.21)	1.99 (1.55-2.56) [§]	<0.01	1.11 (0.93-1.31)	0.97 (0.78-1.20)	1.55 (1.03-2.34) [§]	<0.01
Fetuin-A (n=579)								
Tertile 1	Ref	Ref	Ref		Ref	Ref	Ref	
Tertile 2	0.66 (0.46-0.94) [§]	1.06 (0.68-1.64)	0.30 (0.14-0.62) [§]		0.84 (0.56-1.25)	1.18 (0.73-1.90)	0.42 (0.17-1.08)	
Tertile 3	0.48 (0.32-0.71) [§]	0.68 (0.41-1.13)	0.34 (0.17-0.69) [§]		0.66 (0.42-1.03)	0.76 (0.43-1.33)	0.36 (0.14-0.90) [§]	
Continuous (per 0.1 g/l)	0.76 (0.67-0.86) [§]	0.86 (0.74-0.99) [§]	0.69 (0.54-0.87) [§]	0.10	0.85 (0.75-0.97) [§]	0.90 (0.77-1.05)	0.69 (0.52-0.92) [§]	0.06

* Adjusted for age, sex, race, index of coexistent disease, diabetes, cardiovascular disease, body mass index, serum phosphate and corrected serum calcium

[‡] P-interaction from model using biomarker as a continuous variable

[§] p<0.05