

Supplementary Material

Figure S1. Cohort flow diagram (screening, eligibility, enrolment, missing information), based on STROBE guidelines.

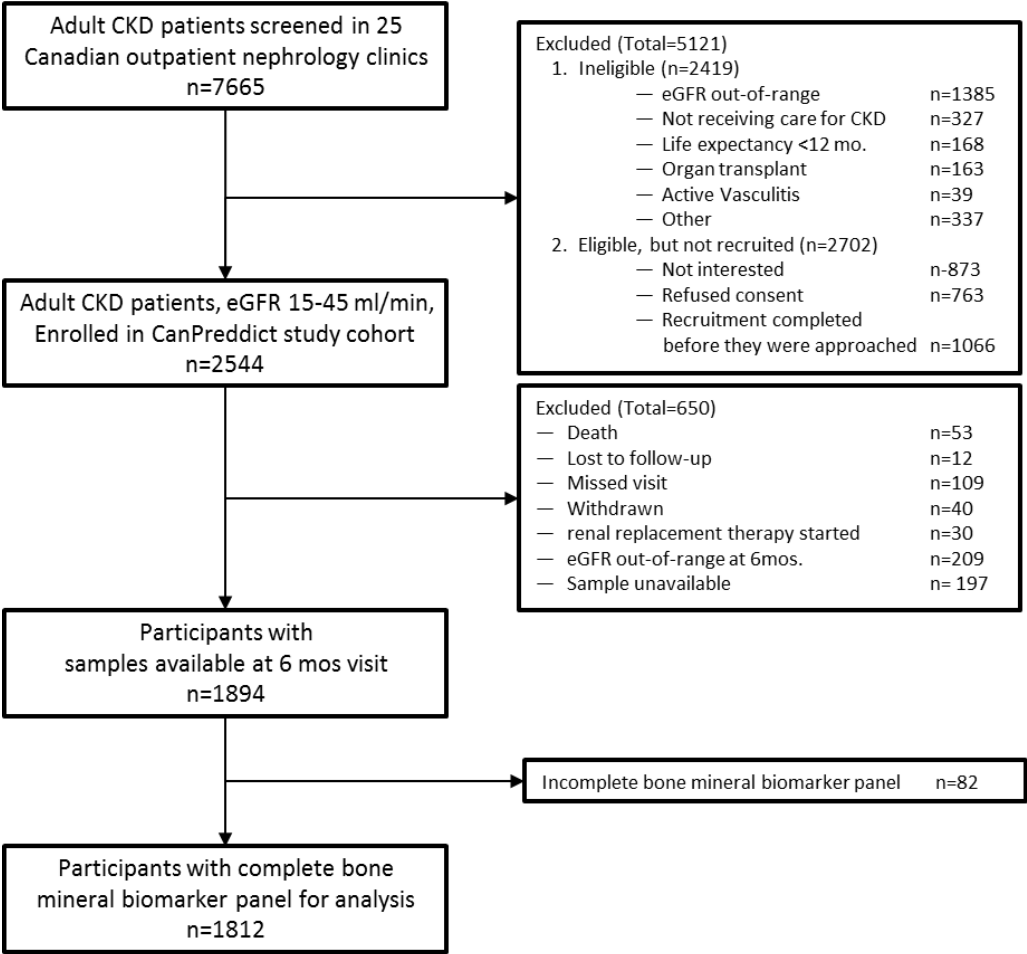


Figure S2. Boxplots illustrating the distribution of PTH1-84 (a) and FGF-23 (b) overall and by category of estimated GFR.

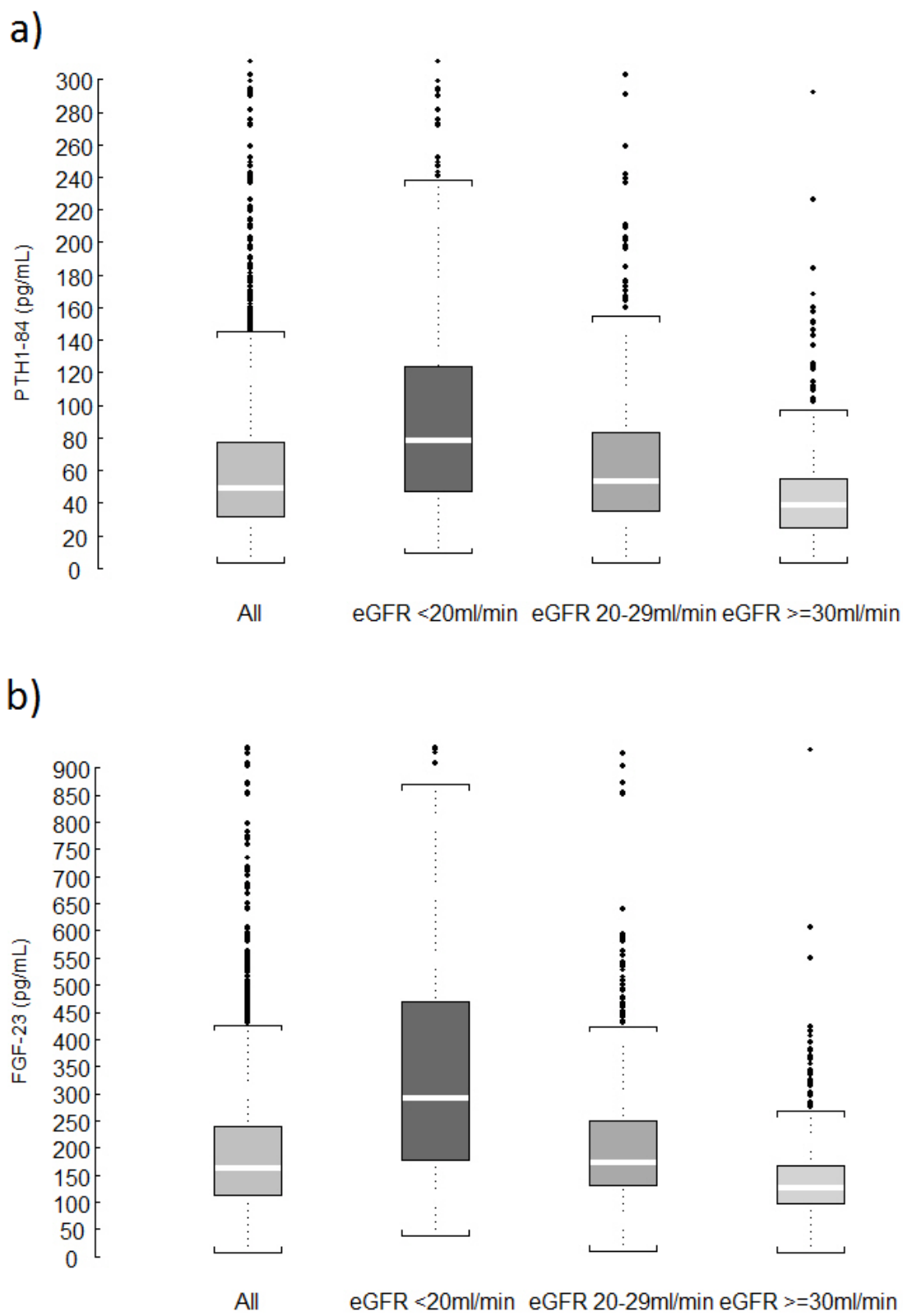


Table S1. Distribution of biomarkers by prescribed supplement use

	Overall			eGFR <20mL/min			eGFR 20-29mL/min			eGFR ≥30mL/min		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Vitamin D												
n	643	1161		173	176		265	460		205	525	
PTH1-84	46.4 [30.8, 77.3]	51.5 [32.5, 77.1]	0.1	74.4 [40.9, 114.0]	87.2 [56.6, 137.5]	0.02	46.9 [31.9, 74.8]	56.6 [36.9, 84.6]	0.004	34.9 [23.0, 49.7]	39.7 [25.4, 56.5]	0.02
FGF-23	177.7 [128.6, 291.1]	153.4 [107.9, 225.3]	<0.001	305.4 [185.4, 448.3]	278.7 [172.8, 497.5]	0.6	177.7 [136.4, 265.8]	168.7 [128.9, 242.8]	0.2	137.3 [106.5, 177.9]	123.4 [93.1, 161.7]	<0.001
Calcium												
n	487	1317		132	217		209	516		146	584	
PTH1-84	43.6 [27.1, 73.6]	51.5 [33.4, 78.7]	<0.001	72.9 [39.2 ,108.5]	84.9 [54.5 ,136.0]	0.004	45.1 [30.4 ,69.9]	56.6 [36.7 ,87.3]	<0.001	31.1 [19.2 ,46.1]	40.35 [27.0 ,56.6]	<0.001
FGF-23	173.3 [120.5, 283.7]	157.7 [112.7, 233.8]	<0.001	288.9 [176.1 ,454.8]	291.1 [184.5 ,471.2]	0.5	174.4 [128.9 ,272.2]	171.1 [130.3 ,244.2]	0.6	130.1 [99.2 ,172.0]	125.7 [96.6 ,166.7]	0.5
Iron												
n	476	1336		113	238		206	524		157	574	
PTH1-84	48.1 [30.8, 78.0]	49.3 [32.0, 76.9]	0.7	72.5 [40.6 ,126.0]	82.2 [52.1 ,120.0]	0.2	54.2 [35.6 ,83.1]	166.9 [127.6 ,233.8]	0.2	38.0 [23.1 ,55.3]	38.6 [25.2 ,55.2]	0.5
FGF-23	179.7 [124.7, 297.0]	154.5 [111.0, 230.3]	<0.001	318.6 [179.4 ,545.4]	278.7 [178.9 ,450.5]	0.3	192.9 [142.3 ,292.9]	691 [525 ,912]	0.001	135.5 [104.4 ,187.2]	123.8 [94.1 ,164.0]	0.009

eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone
Among patients who were prescribed vitamin D, the majority (59.8%) were receiving a nutritional supplement compared to an active sterol such as alfacalcidol (30.8%) or calcitriol (9.4%)

Table S2. Association between PTH1-84 or FGF-23 and each outcome in the overall cohort and within strata of eGFR. Estimates are hazard ratios (95% confidence intervals) per standard deviation of the log-transformed continuous biomarker.

PTH1-84									
Outcome	eGFR Level	N Events	% Events	Unadjusted			Multivariable adjusted		
				HR	95% CI	P	HR	95% CI	P
CV Event	All	341/1812	18.8%	1.33	1.20-1.48	<.001	1.11	0.99-1.26	0.08
	< 20 mL/min	93/351	26.5%	1.36	1.11-1.67	0.003	1.36	1.08-1.72	0.01
	20-29 mL/min	154/730	21.1%	1.11	0.94-1.32	0.23	1.05	0.89-1.25	0.55
	≥30 mL/min	94/731	12.9%	1.16	0.90-1.48	0.25	0.99	0.76-1.31	0.97
RRT	All	307/1812	16.9%	2.03	1.81-2.28	<.001	1.23	1.08-1.39	0.001
	< 20 mL/min	147/351	41.9%	1.39	1.17-1.65	0.001	1.19	1.00-1.41	0.049
	20-29 mL/min	120/730	16.4%	1.51	1.24-1.84	<.001	1.15	0.93-1.42	0.20
	≥30 mL/min	40/731	5.5%	2.12	1.42-3.16	<0.001	1.72	1.13-2.63	0.012

FGF-23									
Outcome	eGFR Level	Events per 1000 person-years		Unadjusted			Multivariable adjusted		
		Rate	95% CI	HR	95% CI	P	HR	95% CI	P
CV Event	All	59.1	53.2 - 65.6	1.41	1.30-1.54	<.001	1.21	1.08-1.37	0.002
	< 20 mL/min	93.6	76.4 - 114.7	1.29	1.09-1.51	0.002	1.28	1.05-1.56	0.016
	20-29 mL/min	67.1	57.3 - 78.6	1.26	1.09-1.47	0.002	1.13	0.94-1.36	0.20
	≥30 mL/min	37.8	30.9 - 46.2	1.64	1.21-2.22	0.001	1.42	1.02-1.98	0.04
RRT	All	53.0	47.4 - 59.3	1.87	1.74-2.01	<.001	1.31	1.17-1.46	<.001
	< 20 mL/min	174.1	148.1 – 204.7	1.45	1.28-1.65	<.001	1.26	1.07-1.48	0.005
	20-29 mL/min	51.0	42.7 – 61.0	1.54	1.34-1.77	<.001	1.23	1.03-1.47	0.02
	≥30 mL/min	15.4	11.3 - 21.0	2.75	1.73-4.35	<.001	1.54	0.96-2.47	0.076

CV model adjusted for: age, sex, diabetes, cardiac disease, eGFR, ACR, hemoglobin, albumin, bicarbonate and phosphate.

RRT model adjusted for: age, sex, diabetes, systolic blood pressure, eGFR, ACR, hemoglobin, albumin, phosphate and bicarbonate

Table S3. Multivariable-adjusted association between risk-based cut-offs for PTH1-84 and FGF-23 and each outcome. The reference group consists of individuals whose biomarker values were greater than the uniform cut-off and below the risk-based cut-off identified for their specific eGFR category.

Biomarker	eGFR <20mL/min				eGFR 20-29mL/min				eGFR ≥30mL/min			
	Biomarker Level	HR	95% CI	P value	Biomarker Level	HR	95% CI	P value	Biomarker Level	HR	95% CI	P value
PTH1-84 (pg/mL)	CV Risk Cut-off=134.3 pg/mL				CV Risk Cut-off=104.6 pg/mL				CV Risk Cut-off=42.9 pg/mL			
	< 39.4	0.72	0.37-1.39	0.3	< 39.4	1.24	0.86-1.80	0.3	< 39.4	6.00	0.82-43.9	0.08
	39.4-134.3	Reference			39.4-104.6	Reference			39.4-42.9	Reference		
	>134.3	1.94	1.20-3.13	0.007	>104.6	1.63	1.06-2.53	0.03	>42.9	6.63	0.91-48.4	0.06
	RRT Risk Cut-off=93.7 pg/mL				RRT Risk Cut-off=49.4 pg/mL				RRT Risk Cut-off=53.5 pg/mL			
	< 39.4	1.05	0.62-1.76	0.9	< 39.4	1.04	0.48-2.27	0.9	< 39.4	0.79	0.30-2.08	0.6
FGF-23 (pg/mL)	39.4-93.7	Reference			39.4-49.4	Reference			39.4-53.5	Reference		
	>93.7	1.37	0.94-2.00	0.1	>49.4	1.32	0.65-2.69	0.4	>53.5	1.39	0.57-3.41	0.5
	CV Risk Cut-off=528.5 pg/mL				CV Risk Cut-off=228.1 pg/mL				CV Risk Cut-off=177.7 pg/mL			
	< 95.4	0.39	0.05-3.01	0.4	< 95.4	0.98	0.52-1.87	0.9	< 95.4	0.98	0.51-1.79	0.9
	95.4-528.5	Reference			95.4-228.1	Reference			95.4-177.7	Reference		
	>528.5	2.34	1.41-3.89	0.001	>228.1	1.56	1.08-2.25	0.02	>177.7	1.76	1.10-2.80	0.02
	RRT Risk Cut-off=311.1 pg/mL				RRT Risk Cut-off=192.5 pg/mL				RRT Risk Cut-off=141.2 pg/mL			
	< 95.4	0.91	0.27-3.04	0.9	< 95.4	0.96	0.37-2.49	0.9	< 95.4	0.88	0.26-2.93	0.8
	95.4-311.1	Reference			95.4-192.5	Reference			95.4-141.2	Reference		
	>311.1	1.77	1.20-2.61	0.004	>192.5	1.71	1.13-2.60	0.01	>141.2	1.30	0.56-2.99	0.5

CV model adjusted for: age, sex, diabetes, cardiac disease, GFR, ACR, hemoglobin, albumin, bicarbonate and phosphate.

RRT model adjusted for: age, sex, diabetes, systolic blood pressure, GFR, ACR, hemoglobin, albumin, phosphate and bicarbonate

Table S4. Event NRI, non-event NRI and overall NRI at 4 years of follow-up for PTH1-84 and FGF-23 in a univariate analysis, comparing GFR-specific cut-offs to uniform cut offs.

eGFR Level	Event NRI	Non-event NRI	NRI
PTH1-84 Cardiovascular Events			
< 20 mL/min	-0.150	0.241	0.091
20-29 mL/min	-0.539	0.736	0.197
≥ 30 mL/min	0.111	0.188	0.299
PTH1-84 Renal Events			
< 20 mL/min	0.263	-0.049	0.213
20-29 mL/min	0.389	-0.016	0.373
≥ 30 mL/min	0.705	-0.586	0.119
FGF-23 Cardiovascular Events			
< 20 mL/min	-0.319	0.592	0.274
20-29 mL/min	-0.028	0.241	0.213
≥ 30 mL/min	0.109	0.124	0.233
FGF-23 Renal Events			
< 20 mL/min	0.246	0.221	0.466
20-29 mL/min	0.242	0.008	0.249
≥ 30 mL/min	0.525	-0.273	0.252

Table S5. Added prognostic value of different biomarker cut-offs for cardiovascular events

	AUC	AUC Difference	IDI
PTH 1-84 Cut-off values for eGFR < 20 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (134.3 pg/mL)	36.2 (33.6 – 37.6) vs. 42.6 (38.1 - 44.2)	6.4 (1.0 - 8.1)	0.020 (0.014 - 0.025)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	78.3 (75.2 - 85.5) vs. 78.7 (75.5 - 85.9)	0.4 (-0.1 – 1.9)	0.006 (-0.002 - 0.036)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	78.3 (75.2 - 85.5) vs. 79.1 (75.3 - 85.9)	0.8 (0.1 – 2.3)	0.012 (0.001 - 0.037)
PTH 1-84 Cut-off values for eGFR 20-29 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (104.6 pg/mL)	36.4 (35.9 – 38.7) vs. 36.7 (31.7 - 39.3)	0.3 (-5.1 – 0.9)	0.011 (-0.000 - 0.021)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	76.1 (73.9 - 80.8) vs. 76.0 (73.9 – 80.8)	-0.1 (-0.1 – 0.5)	-0.001 (-0.001 - 0.009)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	76.1 (73.9 – 80.8) vs. 76.9 (74.0 - 81.1)	0.8 (0.0 – 1.5)	0.014 (0.001 - 0.024)
PTH 1-84 Cut-off values for eGFR ≥ 30 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (42.9 pg/mL)	40.9 (37.5 – 44.9) vs. 43.8 (39.5 – 48.2)	2.9 (1.1 – 3.3)	0.005 (0.001 - 0.011)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	77.2 (74.7 – 81.0) vs. 77.2 (75.2 - 81.1)	-0.00 (-0.00 – 0.61)	-0.000 (-0.003 - 0.009)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	77.2 (74.7 – 81.0) vs. 77.4 (75.4 - 81.3)	0.1 (-0.0 – 0.9)	0.003 (-0.002 - 0.012)
FGF-23 Cut-off values for eGFR < 20 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (528.5 pg/mL)	28.5 (27.3 - 30.0) vs. 42.7 (37.4 - 53.0)	14.2 (8.4 - 23.0)	0.029 (0.005 - 0.089)
Base Model ¹ vs. Base Model + FGF-23 with Uniform Cut-off	78.3 (75.2 - 85.5) vs. 78.3 (75.3 - 85.8)	0.04 (-0.01 – 0.64)	0.001 (-0.001 - 0.009)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	78.3 (75.2 - 85.5) vs. 79.9 (75.5 - 85.5)	1.6 (0.1 – 3.0)	0.030 (0.003 - 0.055)
FGF-23 Cut-off values for eGFR 20-29 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (228.1 pg/mL)	31.2 (29.2 – 33.2) vs. 44.4 (41.7 – 50.5)	13.2 (8.8 – 18.6)	0.019 (0.003 - 0.049)
Base Model ¹ vs. Base Model + FGF-23 with Uniform Cut-off	76.1 (73.9 - 80.8) vs. 76.1 (73.9 – 80.8)	0.02 (-0.00 – 0.17)	0.000 (-0.001 - 0.001)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	76.1 (73.9 - 80.8) vs. 76.6 (74.2 - 82.0)	0.4 (0.3 – 2.3)	0.007 (0.004 - 0.044)
FGF-23 Cut-off values for eGFR ≥ 30 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (177.7 pg/mL)	37.5 (34.1 – 42.8) vs. 43.4 (40.5 – 48.6)	5.9 (0.5 – 10.2)	0.015 (-0.005 - 0.034)
Base Model ¹ vs. Base Model + FGF-23 with Uniform Cut-off	77.2 (74.7 – 81.0) vs. 77.3 (74.7 - 82.2)	0.08 (-0.00 – 1.20)	0.001 (0.000 - 0.013)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	77.2 (74.7 – 81.0) vs. 77.7 (75.0 - 81.4)	0.5 (0.1 – 1.0)	0.011 (0.002 - 0.021)

AUC, area under the receiver operating characteristic curve; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; IDI, integrated discrimination improvement; PTH, parathyroid hormone

¹Base Model includes: age, sex, diabetes, cardiac disease, GFR, ACR, hemoglobin, albumin, phosphate and bicarbonate

Table S6. Added prognostic value of different biomarker cut-offs for renal events

	AUC	AUC Difference	IDI
PTH 1-84 Cut-off values for eGFR < 20 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (93.7 pg/mL)	36.0 (33.3 – 41.4) vs. 48.4 (41.8 – 53.9)	12.3 (5.4 – 16.9)	0.039 (-0.006 - 0.077)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	75.9 (73.5 - 81.3) vs. 75.9 (75.7 – 81.8)	-0.0 (-0.2 – 1.1)	-0.000 (-0.003 - 0.018)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	75.9 (73.5 - 81.3) vs. 76.1 (73.9 – 82.0)	0.2 (-0.1 – 0.3)	0.003 (-0.002 - 0.056)
PTH 1-84 Cut-off values for eGFR 20-29 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (49.4 pg/mL)	42.8 (40.9 – 45.5) vs. 47.4 (43.3 – 51.0)	4.7 (1.2 – 8.2)	0.010 (-0.007 - 0.022)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	83.6 (78.8 – 87.9) vs. 83.7 (79.0 – 85.7)	-0.0 (-0.0 – 0.2)	-0.001 (-0.003 - 0.024)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	83.6 (78.8 – 87.9) vs. 83.6 (78.9 – 87.9)	0.0 (0.0 – 0.4)	-0.001 (-0.004 - 0.009)
PTH 1-84 Cut-off values for eGFR ≥ 30 mL/min			
Unadjusted PTH 1-84 Uniform Cut-off (39.4 pg/mL) vs. Risk-based Cut-off (53.5 pg/mL)	48.7 (38.5 – 57.0) vs. 50.2 (42.7 – 61.2)	1.5 (-5.4 – 11.3)	0.007 (-0.007 - 0.032)
Base Model ¹ vs. Base Model + PTH 1-84 with Uniform Cut-off	86.3 (81.9 – 92.4) vs. 86.7 (83.0 – 93.3)	0.5 (-0.3 – 1.8)	0.006 (-0.023 - 0.052)
Base Model vs. Base Model + PTH 1-84 with Risk-based Cut-off	86.3 (81.9 – 92.4) vs. 87.2 (82.3 – 92.8)	0.8 (0.1 – 3.8)	0.022 (-0.003 - 0.084)
FGF-23 Cut-off values for eGFR < 20 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (311.1 pg/mL)	28.6 (26.5 – 31.4) vs. 53.3 (49.9 - 59.0)	24.6 (20.5 - 31.8)	0.080 (0.044 – 0.157)
Base Model vs. Base Model + FGF-23 with Uniform Cut-off	75.9 (75.6 - 81.8) vs. 76.0 (75.6 – 82.1)	0.1 (-0.1 – 7.7)	0.001 (-0.001 - 0.012)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	75.9 (75.6 - 81.8) vs. 76.9 (76.9 – 82.5)	0.9 (0.3 – 3.3)	0.014 (0.005 - 0.058)
FGF-23 Cut-off values for eGFR 20-29 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (192.5 pg/mL)	32.4 (30.0 – 34.8) vs. 51.8 (45.2 – 57.8)	19.3 (12.4 – 24.8)	0.035 (0.002 - 0.076)
Base Model vs. Base Model + FGF-23 with Uniform Cut-off	83.6 (78.8 – 87.9) vs. 83.8 (79.2 – 85.6)	0.1 (-0.0 – 3.9)	0.001 (-0.001 - 0.006)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	83.6 (78.8 – 87.9) vs. 84.3 (80.2 – 87.4)	0.7 (0.1 – 1.4)	0.012 (0.002 - 0.025)
FGF-23 Cut-off values for eGFR ≥ 30 mL/min			
Unadjusted FGF-23 Uniform Cut-off (95.4 pg/mL) vs. Risk-based Cut-off (141.2 pg/mL)	40.0 (34.5 – 44.7) vs. 52.4 (43.2 – 64.5)	12.4 (6.3 – 21.7)	0.011 (0.001 - 0.052)
Base Model vs. Base Model + FGF-23 with Uniform Cut-off	86.3 (81.9 – 92.4) vs. 86.4 (81.9 – 92.4)	0.2 (-0.0 – 1.5)	0.002 (-0.006 - 0.029)
Base Model vs. Base Model + FGF-23 with Risk-based Cut-off	86.3 (81.9 – 92.4) vs. 86.9 (82.1 – 93.3)	0.6 (-0.1 – 3.3)	0.015 (-0.005 - 0.071)

AUC, area under the receiver operating characteristic curve; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; IDI, integrated discrimination improvement; PTH, parathyroid hormone

¹Base Model includes: age, sex, diabetes, systolic blood pressure, GFR, ACR, hemoglobin, albumin, phosphate and bicarbonate.