KDIGO 2017 CLINICAL PRACTICE GUIDELINE UPDATE FOR THE DIAGNOSIS, EVALUATION, PREVENTION AND TREATMENT OF CKD-MBD

EVIDENCE SUMMARY TABLES

REVISED SEPTEMBER 2017: Previous Supplemental Table 21 erroneously stated calcium acetate (rather than calcium carbonate) as the comparator against sevelamer in two studies authored by Di Iorio. Supplemental Table 21 has now been corrected and the conclusions from the Work Group remain unchanged.

KDIGO: CKD-MBD Update
Summary of Results for Bisphosphonates and Other Bone Treatments

Research question 3.2.1: In patients with CKD G3a-G5D, what is the effect on bone quality of bisphosphonates, teriparatide, denosumab and raloxifene?

Research question 4.3.4: In patients with CKD G4-G5D, what is the effect on bone quality of bisphosphonates, teriparatide, denosumab and raloxifene?

Supplemental Table 1. Summary table of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5 – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Bisphosphonates vs. placebo						
Coco, 2003[1]	USA	72	Post-transplant	NR NR	12 mo	NR
Walsh, 2009[2]	UK	125	Post-transplant	NA	24 mo	Industry
Jamal, 2007[3]	USA	581	G3a-G3b	NR NR	Mean 36 mo[a]	NR
Toussaint, 2010[4]	Australia	51	G3a-G4	NA	18 mo	Industry
Smerud, 2012[5]	Norway	129	Post-transplant	NA	12 mo	Industry, non-profit
Torregrosa, 2010[6]	Spain	101	Renal transplant	NA	12 mo	Industry
Raloxifene vs. placebo						
Haghverdi, 2014[7]	Iran	60	51 on dialysis and 9 with G5	HD NR	8 mo	NR
Hernandez, 2003[8]	Venezuela	50	G5D	HD NR	12 mo	Industry, government
Ishani, 2008[9]	Multi-national	3493	G3a-G3b	NA NA	36 mo	NR
		1480	G3a-G5	NA NA	36 mo	NR
Teriparatide vs. placebo						
Miller, 2007[10]	USA	648	G2-G3b	NA NA	Median 21 mo	Industry
		83	G3a-G3b	NA NA	Median 21 mo	Industry
Denosumab vs. placebo						
Jamal, 2011[11]	NR	7808	G1-G4	NA NA	36 mo	Industry
Ibandronate vs. Risedronate						
Sanchez-Escuredo, 2015[12]	NR	69	Post-transplant	NA	12 mo	NR

CKD = chronic kidney disease; HD = hemodialysis; mo = months; NA = not applicable; NR = not reported; UK = United Kingdom; USA = United States of America

a. Women with and without existing vertebral fracture were followed for 3 and 4 y, respectively.

Bolded studies were included in the previous evidence report.

Supplemental Table 2. Summary table of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5 – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
Bisphosphonates vs. placebo									
Coco, 2003[1]	Pamidronate N=31	44	39	Black 32% Hispanic 39% White 23% Asian 7%	NR 3.5 years (total sample)	NR NR NR	Ca 7.9 mg/dL P 5.4 mg/dL iPTH 395 pg/dl Vitamin D 25 15 ng/ml Vitamin D1,25 24 ng/ml ALP 49 U/L	Vertebral BMD	NR
								Hip BMD	NR
	Control N=28	44	68	Black 32% Hispanic 46% White 18% Asian 4%	NR 3.5 years (total sample)	NR NR NR	Ca 8.2 mg/dL P 5.3 mg/dL iPTH 280 pg/dl Vitamin D 25 20 ng/dl Vitamin 1, 25 25 ng/dl ALP 41 U/L	Vertebral BMD	NR
								Hip BMD	NR
Walsh, 2009[2]	Pamidronate N = 46	46	76	White 76 Black 11 Asian 2 Other 11	NR NA	7 13 NR	Ca 9.8 mg/dL P 6.8 mg/dL iPTH 29 pg/mL ALP 32 IU/L	BMD, femoral neck (g/cm^2)	0.847
								BMD, femoral neck (z-score)	-0.586
								BMD, lumbar spine (g/cm^2)	1.066
								BMD, lumbar spine (z-score)	-0.550
								BMD, total hip (g/cm^2)	0.924
								BMD, total hip (z-score)	-0.602
								BMD, Ward's area (g/cm^2)	0.708
								BMD, Ward's area (z-score)	-0.409
	Control N = 47	46	72	White 81 Black 9 Asian 0 Other 11	NR NA	4 13 NR	Ca 9.8 mg/dL P 6.9 mg/dL iPTH 33 pg/mL ALP 37 IU/L	BMD, femoral neck (g/cm^2)	0.869
								BMD, femoral neck (z-score)	-0.34
								BMD, lumbar spine	1.134

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
								(g/cm^2)	
								BMD, lumbar spine (z-score)	0.089
								BMD, total hip (g/cm^2)	0.971
								BMD, total hip (z-score)	-0.209
								BMD, Ward's area (g/cm^2)	0.731
								BMD, Ward's area (z-score)	-0.156
Jamal, 2007[3]	Total N = 581	75	0	White 97	<45 mL/min/1.73 m^2	NR NR NR	Ca 2.4 mmol/L P 1.13 mmol/L PTH 3.8 pmol/L Allegro-intact PTH [ref: NR] ALP 83.3 U/L	BMD, femoral neck (g/cm^2)	0.54
								BMD, lumbar spine (g/cm^2)	0.78
								BMD, total hip (g/cm^2)	0.63
								% vertebral fracture	42%
Toussaint, 2010[4]	Alendronate N=25	66	68	NR	33.8 mL/min/1.73 m^2	56 92 NR	Ca 9.32 mg/dL P 3.93 mg/dL iPTH 15.3 pmol/L ALP 98.0 U/L	BMD, lumbar spine, t-score	0.40
								BMD, lumbar spine, z-score	0.84
								BMD, right femoral neck, t-score	-1.28
								BMD, right femoral neck, z-score	-0.31
	Placebo N=25	59	64	NR	35.6 mL/min/1.73 m^2	60 100 NR	Ca 9.36 mg/dL P 3.77 mg/dL iPTH 14.6 pmol/L ALP 93.6 U/L	BMD, lumbar spine, t-score	0.37
								BMD, lumbar spine, z-score	0.54
								BMD, right femoral neck, t-score	-1.26
								BMD, right femoral neck, z-score	-0.55
Smerud, 2012[5]	Ibandronate	50	73	NR	64.45	NR	Ca NR	BMD, lumbar spine	1.175 (0.18)

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
	N=66				mL/min/1.73 m²	NR NR	P NR iPTH 79.6 pg/mL 25-OH vitamin D 60.7 nM bALP 37.8 U/L	(L2-L4) (g/cm²)	
								BMD, lumbar spine (L2-L4), T-score	-0.56 (1.38)
								BMD, lumbar spine (L2-L4), Z-score	-0.25 (1.29)
								BMD, total femur (g/cm²)	0.911 (0.13)
								BMD, total femur (t-score)	-1.19 (0.96)
								BMD, total femur (z-score)	-0.74 (0.89)
								BMD, ultradistal radius (g/cm²)	0.381 (0.07)
								BMD, ultradistal radius (t-score)	-0.75 (1.57)
								BMD, ultradistal radius (z-score)	-0.46 (1.51)
								BMD, proximal 1/3 radius (g/cm²)	0.726 (0.10)
								BMD, proximal 1/3 radius (t-score	-0.68 (1.16)
								BMD, proximal 1/3 radius (z-score)	-0.37 (1.14)
								Total body (g/cm²)	1.136 (0.11)
								Total body (t-score)	-0.71 (1.28)
								Total body (z-score)	-0.51 (1.21)
	Placebo N=63	53	81	NR	64.15 mL/min/1.73 m²	NR NR NR	Ca NR P NR iPTH 91.7 pg/mL 25-OH vitamin D 59.4 nM bALP 31.7 U/L	BMD, lumbar spine (L2-L4) (g/cm²)	1.193 (0.17)
								BMD, lumbar spine (L2-L4), T-score	-0.44 (1.36)
								BMD, lumbar spine (L2-L4), Z-score	-0.23 (1.52)
								BMD, total femur (g/cm²)	0.913 (0.16)
								BMD, total femur (t-	-1.23 (1.21)

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
								score)	
								BMD, total femur (z-score)	-0.81 (1.21)
								BMD, ultradistal radius (g/cm²)	0.394 (0.07)
								BMD, ultradistal radius (t-score)	-0.49 (1.52)
								BMD, ultradistal radius (z-score)	-0.12 (1.60)
								BMD, proximal 1/3 radius (g/cm²)	0.738 (0.08)
								BMD, proximal 1/3 radius (t-score	-0.62 (0.88)
								BMD, proximal 1/3 radius (z-score)	-0.25 (1.01)
								Total body (g/cm²)	1.153 (0.09)
								Total body (t-score)	-0.56 (1.08)
								Total body (z-score)	-0.54 (1.15)
Torregrosa, 2010[6]	Risedronate N = 52	47	65	NR	NR NA	NR NR NR	Ca 8.9 mg/dL P 4.0 mg/dL iPTH 323.2 pg/mL ALP NR 25-OH vitamin D 24.6 ng/mL 1,25-OH vitamin D 18.6 ng/mL	BMD, lumbar spine (L1-L4) t-score	-0.80
								BMD, femoral neck t-score	-1.06
	Placebo N = 49	51	71	NR	NR NA	NR NR NR	Ca 8.7 mg/dL P 4.2 mg/dL iPTH 465.4 pg/mL ALP NR 25-OH vitamin D 20.9 ng/mL 1,25-OH vitamin D 22.3 ng/mL	BMD, lumbar spine (L1-L4), t-score	-1.19
								BMD, femoral neck t-score	-1.14
Raloxifene vs. placebo									
Haghverdi, 2014[7]	Raloxifene N=30	64	0	NR	NR NR	NR NR	Ca 9.2 mg/dL P 6.2 mg/dL	BMD, lumbar spine (mg/cm²)	728.0

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
						NR	iPTH 510 pg/dL ALP 445.9 IU/L		
								T score lumbar spine	-2.9
								BMD, femoral neck (mg/cm^2)	508.8
								T score femoral neck	-3.0
	Placebo N=30	62	0	NR	NR NR	NR NR NR	Ca 8.9 mg/dL P 6.6 mg/dL iPTH 462.2 pg/dL ALP 483.4 IU/L	BMD, lumbar spine (mg/cm^2)	773.8
								T score lumbar spine	-2.4
								BMD, femoral neck (mg/cm^2)	544.8
								T score femoral neck	-2.7
Hernandez, 2003[8]	Raloxifene N = 25	63	0	NR	NR 75 months	0 NR NR	Ca 2.31 mmol/L P 1.65 mmol/L iPTH 34.0 pmol/L Nichols Allegro IRMA [ref: NR]	BMD, femoral neck (g/cm^2)	0.722 [a]
								BMD, L2-L4 (g/cm^2)	0.942[b]
	Placebo N = 25	62	0	NR	NR 69 months	0 NR NR	Ca 2.26 mmol/L P 1.52 mmol/L iPTH 40.6 pmol/L Nichols Allegro IRMA [ref: NR]	BMD, femoral neck (g/cm^2)	0.745[a]
								BMD, L2-L4 (g/cm^2)	0.952[b]
Ishani, 2008[9]	Raloxifene[c] N=2323	67	0	White 97	CrCl 45-59 mL/min NA	3 NR NR	Ca NR P NR PTH 3.6 pmol/L NR 25(OH) Vit D 72	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, trochanter (g/cm^2) % with prevalent vertebral fractures	0.62 0.81 0.55 0: 65 1: 20 2: 16
	Placebo[c] N=1170	67	0	White 97	CrCl 45-59 mL/min NA	4 NR NR	Ca NR P NR PTH 3.6 pmol/L	BMD, femoral neck (g/cm^2)	0.62

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
							NR 25(OH) Vit D 72	 BMD, lumbar spine (g/cm^2) BMD, trochanter (g/cm^2) % with prevalent vertebral fractures	 0.81 0.55 0: 60 1: 21 2: 19
	Raloxifene[d] N=970	72	0	White 97	CrCl <45 mL/min NA	3 NR NR	Ca NR P NR PTH 3.7 pmol/L NR 25(OH) Vit D 75	BMD, femoral neck (g/cm^2)	0.59
								BMD, lumbar spine (g/cm^2)	0.79
								BMD, trochanter (g/cm^2)	0.52
								% with prevalent vertebral fractures	0: 54 1: 22 2: 25
	Placebo[d] N=510	72	0	White 96	CrCl <45 mL/min NA	4 NR NR	Ca NR P NR PTH 3.9 pmol/L NR 25(OH) Vit D 73	BMD, femoral neck (g/cm^2)	0.59
								BMD, lumbar spine (g/cm^2)	0.79
								BMD, trochanter (g/cm^2)	0.52
								% Pts with prevalent vertebral fractures	0: 58 1: 20 2: 22
Teriparatide vs. placebo									
Miller, 2007[10]	Teriparatide 20 µg/d[e] N = 208	72	0	NR	68 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 3.3 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.63
								BMD, lumbar spine (g/cm^2)	0.81
								% with prevalent	89%

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
								vertebral fractures	
	Teriparatide 40 µg/d[e] N = 214	72	0	NR	68 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 3.5 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.61
								BMD, lumbar spine (g/cm^2)	0.79
								% with prevalent vertebral fractures	88%
	Placebo[e] N = 226	71	0	NR	67 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 3.5 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.62
								BMD, lumbar spine (g/cm^2)	0.79
								% with prevalent vertebral fractures	86%
	Teriparatide 20 µg/d[f] N = 29	77	0	NR	43 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 3.7 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.55
								BMD, lumbar spine (g/cm^2)	0.77
								% with prevalent vertebral fractures	86%
	Teriparatide 40 µg/d[f] N = 34	78	0	NR	44 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 3.2 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.63
								BMD, lumbar spine (g/cm^2)	0.84
								% with prevalent vertebral fractures	77%
	Placebo[f] N = 20	78	0	NR	44 mL/min/1.73 m^2	NR NR NR	Ca NR P NR PTH 2.9 pmol/L Assay: NR	BMD, femoral neck (g/cm^2)	0.54
								BMD, lumbar spine (g/cm^2)	0.73
								% with prevalent vertebral fractures	85%

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	DXA score/ fractures
Denosumab vs. placebo									
Jamal, 2011[11]	CKD G3a-G3b N = 2817	75	0	NR	eGFR 30-59 mL/min NA	NR NR NR	Ca 9.8 mg/dL Vit D 63.1 nmol/L	Lumbar spine, BMD T-score	-2.83
								Femoral neck, BMD T-score	-2.38
								Total-hip, BMD T-score	-2.17
	CKD G4 N = 73	80	0	NR	eGFR 15-29 mL/min NA	NR NR NR	Ca 9.9 mg/dL Vit D 61.8 nmol/L	Lumbar spine, BMD T-score	-2.48
								Femoral neck, BMD T-score	-2.80
								Total-hip, BMD T-score	-2.79
Ibandronate vs. Risedronate									
Sanchez-Escuredo, 2015[12]	Ibandronate N=35	63	20	NR	NR	0 NR NR	Ca 9.7 mg/dl ALP 118 IU/l iPTH 114 pg/ml	BMD, trabecular bone T-score	-1.7
								BMD, corticol bone T-score	-2.1
	Risendronate N=34	64	12	NR	NR	0 NR NR	Ca 9.8 mg/dl ALP 121 IU/l iPTH 121 pg/ml	BMD, trabecular bone T-score	-1.9
								BMD, corticol bone T-score	-2.2

ALP = alkaline phosphatase; bALP = bone-specific alkaline phosphatase; BMD = bone mineral density; Ca = calcium; CrCl = creatinine clearance; DM = diabetes mellitus; DXA = dual-energy X-ray absorptiometry; g/cm² = grams/centimeter squared; HC = hypercholesterolemia; HTN = hypertension; iPTH = intact parathyroid hormone; MBD = mineral bone disorder; mg/dL = miligram per deciliter; mL/min = milliliters per minute; mmol/L = millimoles per liter; ng/mL = nanogram per milliliter; NR = not reported; P = phosphate; pg/dL = picogram/deciliter; ug/d^{e} = micrograms per deciliter; u/L = units per liter; pmol/L = picomole per liter; 25 (OH) Vit D = 25-hydroxyvitamin D

a. Z-score: -0.800 (-0.630); T-score: -2.15 (-1.99).

b. Z-score: -0.64 (-0.61); T-score: -2.51 (-2.52).

c. Among those with a creatinine clearance of 45 to 59 mL/min

d. Among those with a creatinine clearance less than 45 mL/min

e. Among those with mild renal impairment (GFR 50 to 79 ml/min)

f. Among those with moderate renal impairment (GFR 30 to 49 ml/min)

Bolded studies were included in the previous evidence report.

Supplemental Table 3. Summary table of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5 – results

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Bisphosphonates vs. placebo					
Coco, 2003[1]	Pamidronate 60 mg followed by 30 mg at months 1, 2 ,3, and 6	Placebo	Calcitriol and calcium carbonate to maintain serum calcium between 8.5 and 10.5 mg/dL	Change in vertebral BMD at 12 months	0.0105 g/cm² [P<0.033] vs. -0.39 g/cm² [P<0.01]
				Change in hip BMD at 12 months	0.8933 g/cm² vs. 0.8216 g/cm² (P NS)
				Vertebral fractures diagnosed by x-ray, n	1 vs. 2
				Hip fractures diagnosed by x-ray, n	0 vs. 0
Walsh, 2009[2]	Pamidronate 1 mg/kg, intravenous infusion at baseline, 1, 4, 8, and 12 months	No bisphosphonates	Calcichew D_3 Forte, 1 Tablet daily Calcium carbonate 500 mg 400 units cholecalciferol	Femoral neck	Final at 24 mos: 0.86 vs. 0.80 g/cm^2 Percentage change: 1.95 vs. -2.62
				Lumbar spine	Final at 24 mos: 1.11 vs. 1.00 g/cm^2; P<0.05 Percentage change: 3.56 vs. -6.37; P<0.05
				Total hip	Final at 24 mos: 0.93 vs. 0.86 g/cm^2; P<0.05 Percentage change: 0.58 vs. -3.65; P<0.05
				Ward's area	Final at 24 mos: 0.72 vs. 0.64 g/cm^2; P<0.05 Percentage change: 2.05 vs. -7.71; P<0.05
				Fractures, %	4% vs. 13% Risk difference = 8.4% (95% CI, -3.7 to 22.2; P=0.3)
Jamal, 2007[3]	Alendronate 5 mg/d, increased to 10 mg/d in year 2	Placebo	500 mg/d elemental Ca and 250 IU/d of vitamin D, if necessary	Clinical fractures	OR 0.78 (95% CI 0.51-1.2)[e]
				Vertebral fractures by X-ray	OR 0.72 (95% CI 0.31-1.7)[e]
				%Δ BMD, femoral neck, compared with placebo	+5.0% (95% CI 4.0%-5.9%)[e]
				%Δ BMD, spine, compared with placebo	+6.7 (95% CI 5.7%-7.8%)[e]
				%Δ BMD, total hip, compared with placebo	+5.6% (95% CI 4.8%-6.5%)[e]
Toussaint, 2010[4]	Alendronate 70 mg/week orally	Placebo	Allowed phosphate binders and vitamin D supplements	Between-arm difference in lumbar spine t-score	0.4 (95% CI, -0.04 to 0.7)
				Between-arm difference in lumbar spine BMD, g/cm²	0.02 (95% CI, -0.009 to 0.04)
				Between-arm difference in femoral neck t-score	0.006 (95% CI, -0.02 to 0.03)
				Between-arm difference in femoral neck BMD, g/cm²	0.005 (95% CI, -0.03 to 0.04)
				Fractures, %	0% vs. 8%

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Smerud, 2012[5]	Ibandronate 3 mg i.v. as an infusion over 3 min every 3 months	Placebo	Daily oral calcitriol 0.25 mcg/day Calcium Carbonate 1260 mg	Change in BMD lumbar spine (L2-L4), g/cm^2	0.017 (0.06) vs. 0.004 (0.08) Tx Diff: 0.013 (95% CI, -0.01, 0.04) (P = 0.28)
				Change in BMD lumbar spine (L2-L4), t-score	0.13 (0.45) vs. 0.05 (0.62) Tx Diff: 0.067 (95% CI, -0.13, 0.26) (P = 0.50)
				Change in BMD lumbar spine (L2-L4), z-score	0.01 (0.43) vs. -0.03 (0.68) Tx Diff: 0.043 (95% CI, -0.16, 0.25) (P = 0.67)
				Change in BMD total femur, g/cm^2	0.011 (0.04) vs. -0.007 (0.04) Tx Diff: 0.017 (95% CI, 0.004, 0.030) (P = 0.013)
				Change in BMD total femur, t-score	0.07 (0.28) vs. -0.07 (0.32) Tx Diff: 0.135 (95% CI, 0.03, 0.239) (P = 0.012)
				Change in BMD total femur, t-score	0.01 (0.31) vs. -0.10 (0.35) Tx Diff: 0.114 (95% CI, 0.004, 0.224) (P = 0.043)
				Change in BMD ultradistal radius, g/cm^2	0.002 (0.03) vs. -0.008 (0.03) Tx Diff: 0.010 (95% CI, 0.001, 0.019) (P=0.039)
				Change in BMD ultradistal radius, t-score	0.01 (0.69) vs. -0.24 (0.66) Tx Diff: 0.237 (95% CI, -0.005, 0.478) (P = 0.055)
				Change in BMD ultradistal radius, z-score	0.06 (0.69) vs. -0.22 (0.64) Tx Diff: 0.260 (95% CI, 0.022, 0.498) (P=0.032)
				Change in BMD proximal 1/3 radius, g/cm^2	0.005 (0.03) vs. 0.000 (0.03) Tx Diff: 0.004 (95% CI, -0.005, 0.014) (P=0.35)
				Change in BMD proximal 1/3 radius, t-score	0.04 (0.41) vs. -0.01 (0.33) Tx Diff: 0.046 (95% CI, -0.086, 0.178) (P=0.49)
				Change in BMD proximal 1/3 radius, z-score	0.07 (0.43) vs. 0.01 (0.37) Tx Diff: 0.046 (95% CI, -0.093, 0.185) (P=0.51)
				Change in BMD total body, g/cm^2	0.008 (0.03) vs. -0.001 (0.03) Tx Diff: 0.007 (95% CI, -0.003, 0.182) (P=0.17)
				Change in BMD total body, t-score	0.08 (0.40) vs. -0.04 (0.34) Tx Diff: 0.098 (95% CI, -0.003, 0.230)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
					(P=0.14)
				Change in BMD total body, z-score	-0.08 (0.46) vs. -0.13 (0.40) Tx Diff: 0.057 (95% CI, -0.091, 0.206) (P=0.45)
				Withdrawn due to fractures in the thoracic spine, n	0 vs. 1
				Low-energy vertebral fractures, self-reported, n	2 vs. 1
				Thoraco-lumbar x-ray verified fracture, n	1 vs. 1
Torregrosa, 2010[6]	Risedronate 35 mg/week, orally	Placebo	400 IU cholecalcipherol 1500 mg $CaCO_3$ daily	BMD, lumbar spine (L1-L4) at 12 months	T-Score -0.72 vs. -1.46 (P<0.05)
				BMD, femoral neck at 12 months	T-Score -1.10 vs. -1.37 (ns)
				Vertebral fracture, n	4 vs. 6 (P ns)
Raloxifene vs. placebo					
Haghverdi, 2014[7]	Raloxifene 60 mg/d	Placebo	NR	T-score, lumbar spine	-2.8 (p=0.01 vs. baseline) vs. -2.5 (p=0.59 vs baseline)
				T-score, femoral neck	-3.0 (p=0.11 vs. baseline) vs. -2.7 (p>0.99 vs. baseline)
				BMD, lumbar spine	742.4 (p=0.01 vs. baseline) vs. 755.2 (p=0.08 vs. baseline)
				BMD, femoral neck	517.9 (p=0.06 vs. baseline) vs. 535.9 (p=0.09 vs. baseline)
				Lumbar spine fracture, n	0 vs. 1
Hernandez, 2003[8]	Raloxifene 60 mg/d	Placebo	NR	%Δ T-score, L2-L4	+2.3% vs. -0.3% (<0.01)[a]
				T-score, femoral neck	-2.11 vs. -2.0 (NR)[b]
Ishani, 2008[9]	Raloxifene 60 or 120 mg/d[c]	Placebo	Daily Ca 500 mg and 400-600 IU Vit D	Incident vertebral fracture by CrCl	OR 0.45 (95% CI 0.34-0.59)
				Incident nonvertebral fracture by CrCl	OR 1.02 (95% CI 0.8-1.3)
				%Δ BMD, lumbar spine	1.2% vs. 0.3% (NR)[e]
				%Δ BMD, femoral neck	0.41% vs. -0.36 (NR)[e]
	Raloxifene 60 or 120 mg/d[d]	Placebo	Daily Ca 500 mg and 400-600 IU Vit D	Incident vertebral fracture	OR 0.78 (95% CI 0.54-1.11)
				Incident nonvertebral fracture	OR 0.84 (95% CI 0.6-1.17)
				%Δ BMD, lumbar spine	1.35% vs. 0.31% (NR)[e]
				%Δ BMD, femoral neck	0.55% vs. -0.45% (NR)[e]
Teriparatide vs. placebo					
Miller, 2007[10]	Teriparatide 20 mcg/day	Placebo	Daily calcium 1,000 mg Vitamin D 400-1200 IU	% change in BMD, lumbar spine[f]	9.5% vs. 2% (P<0.05)[g]

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				% change in BMD, femoral neck[f]	1.5% vs. 0% (P<0.05)[g]
				% change in BMD, lumbar spine[h]	12% vs. 2.5% (P<0.05)[g]
				% change in BMD, femoral neck[h]	2.2% vs. -0.7% (P=NS)[g]
	Teriparatide 40 mcg/day	Placebo	Daily calcium 1,000 mg Vitamin D 400-1200 IU	% change in BMD, lumbar spine[f]	16% vs. 2% (P<0.05)[g]
				% change in BMD, femoral neck[f]	3.% vs. 0% (P<0.05)[g]
				% change in BMD, lumbar spine[h]	15.5% vs. 2.5% (P<0.05)[g]
				% change in BMD, femoral neck[h]	2.3% vs.-0.7% (P=NS)[g]
	Teriparatide 20 or 40 mcg/day	Placebo	Daily calcium 1,000 mg Vitamin D 400-1200 IU	Vertebral fractures, %[f]	4% vs. 18% (P<0.01)
				Nonvertebral fractures, %[f]	3% vs. 7% (P<0.01)
				Vertebral fractures, %[h]	6% vs. 24% (P=0.05)
				Nonvertebral fractures, %[h]	0% vs. 0%
Denosumab vs. placebo					
Jamal, 2011[11]	Denosumab, G3a-G3b N = 1332	Placebo, G3a-G3b N = 1309	NR	Vertebral fracture	38 vs. 92 (OR, 0.38; 95% CI, 0.26 to 0.59)
	N = 1418	N = 1399		Nonvertebral fracture	93 vs. 106 (OR, 0.88; 95% CI 0.66 to 1.16)
	Denosumab, G3a-G3b Total N = 2817	Placebo, G3a-G3b Total N = 2817		Lumbar spine BMD, difference in % change[i]	8.9 (95% CI, 8.4 to 9.3), p ≤ .0002
				Femoral neck BMD, difference in % change[i]	5.1 (95% CI, 4.7 to 5.5), p ≤ .0002
				Total-hip BMD, difference in % change[i]	6.4 (95% CI, 6.1 to 6.7), p ≤ .0002
Jamal, 2011[11]	Denosumab, G4 N = 31	Placebo, G4 N = 33	NR	Vertebral fracture	1 vs. 3 (OR, 0.31; 95% CI, 0.02 to 5.08)
	N = 36	N = 37		Nonvertebral fracture	1 vs. 2 (OR, 0.51; 95% CI, 0.04 to 7.26)
	Denosumab, G4 Total N = 73	Placebo, G4 Total N = 73		Lumbar spine BMD, difference in % change[i]	5.0 (95% CI, -0.8 to 10.8)
				Femoral neck BMD, difference in % change[i]	5.9 (95% CI, 3.3 to 8.5), p ≤ 0.0002
				Total-hip BMD, difference in % change[i]	5.9 (95% CI, 3.0 to 8.7), p ≤ 0.0002
Ibandronate vs. Risedronate					
Sanchez-Escuredo, 2015[12]	Ibandronate 150 mg monthly	Risedronate 35 mg weekly	Vitamin D (800 IU cholecalciforal) Calcium (2500 mg $CaCO_3$)	Trabecular (lumbar) BMD T-score at 12 months	-1.4 (SD, 0.6; P < 0.01 vs. baseline) vs. -1.5 (SD, 0.8; P < 0.01 vs. baseline)
				Cortical (proximal femur) BMD T-score at 12 months	-1.8[g] (P >0.05 vs. baseline) vs. -1.8[g] (P >0.05 vs. baseline)

BMD = bone mineral density; Ca = calcium; CaCO3 = calcium carbonate; CI = confidence interval; CrCl = creatinine clearance; g/cm² = grams per centimeter squared; IU/d = international unit per deciliter; mcg = micrograms; mg = milligram; mg/dL = milligrams per deciliter; mg/kg = milligram per kilogram; NR = not reported; OR = odds ratio; SD = standard deviation; Tx Diff = treatment difference

a. BMD (g/cm2): 0.973 vs. 0.949 (NR); Z-score: -0.56 vs. -0.63 (NR), within-arm changes P <0.01 for raloxifene and NS for placebo for both measurements.

b. BMD (g/cm2): 0.727 vs. 0.743 (NR); Z-score: -0.761 vs. -0.649 (NR), within-arm changes are all NS for both measurements.
c. Among those with creatinine clearance 45 to 59 ml/min
d. Among those with creatinine clearance less than 45 ml/min
e. Results in subgroup with osteoporosis at baseline (N = NR) Clinical fractures: OR 0.84 (95% CI 0.45-1.54); vertebral fractures by X-ray: 1.01 (95% CI 0.29-3.6); %Δ total hip BMD compared with placebo: +4.9% (95% CI 3.7%-6.3%); %Δ femoral neck BMD compared with placebo 4.5% (95% CI 3.2%-5.8%); %Δ spine BMD compared with placebo 5.9% (95% CI 4.3%-7.5%).
f. Among those with mild renal impairment (GFR 50 to 79 ml/min).
g. Estimated from graph.
h. Among those with moderate renal impairment (GFR 30 to 49 ml/min)
i. Differences greater than 0 favor denosumab.

Supplemental Table 4. Summary table of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5 – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bisphosphonates vs. placebo								
Coco, 2003[1]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Walsh, 2009[2]	Yes	Yes	No	No	Yes	Yes	Unclear	Yes
Jamal, 2007[3]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Toussaint, 2010[4]	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes
Smerud, 2012[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Torregrosa, 2010[6]	No	Yes	No	No	No	Unclear	Unclear	Yes
Raloxifene vs. placebo								
Haghverdi, 2014[7]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Hernandez, 2003[8]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ishani, 2008[9]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Teriparatide vs. placebo								
Miller, 2007[10]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Ibandronate vs. Risedronate								
Sanchez-Escuredo, 2015[12]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear
Denosumab vs. placebo								
Jamal, 2011[11]	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear

Supplemental Table 5. Evidence matrix of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N* (on agent)	Followup	Author	*N* (on agent)	Followup	Author	*N* (on agent)	Followup
Bisphosphonates vs. placebo									
TMV (bone turnover, mineralization, volume as measured by bone biopsy)									
Bone mineral density/bone mineral content				Coco (2003) Walsh (2009) Jamal (2007) Toussaint (2010) Smerud (2012) Torregrosa (2010)	59 (31) 93 (46) 581 (NR) 50 (25) 129 (66) 101 (52)	12 mo. 24 mo. 36 mo. 18 mo. 12 mo. 12 mo.			
Fracture				Coco (2003) Walsh (2009) Jamal (2007) Toussaint (2010) Smerud (2012) Torregrosa (2010)	59 (31) 93 (46) 581 (NR) 50 (25) 129 (66) 101 (52)	12 mo. 24 mo. 36 mo. 18 mo. 12 mo. 12 mo.			
Raloxifene vs. placebo									
TMV									
Bone mineral density/bone mineral content							Haghverdi (2014) Hernandez (2003) Ishani (2008)	60 (30) 50 (25) 4973 (3293)	8 mo. 12 mo. 36 mo.
Fracture							Haghverdi (2014) Ishani (2008)	60 (30) 4973 (3293)	8 mo. 36 mo.
Teriparatide vs. placebo									
TMV									
Bone mineral density/bone mineral content							Miller (2007)	731 (485)	21 mo.
Fracture							Miller (2007)	731 (485)	21 mo.
Denosumab vs. placebo									
TMV									
Bone mineral density/bone mineral content							Jamal (2011)	G3a-G3b: 2817 (1418) G4: 73 (36)	36 mo
Fracture							Jamal (2011)	G3a-G3b: 2641-2817 (1332-1418) G4: 64-73 (31-36)	36 mo
Ibandronate vs. Risedronate									
TMV									

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N* (on agent)	Followup	Author	*N* (on agent)	Followup	Author	*N* (on agent)	Followup
Bone mineral density/bone mineral content							Sanchez-Escuredo (2015)	69 (35)	12 mo
Fracture									

Supplemental Table 6. Evidence profile of randomized controlled trials examining the treatment of CKD-MBD with bisphosphonates in CKD G3a-G5

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Bisphosphonates vs. placebo									
TMV (bone turnover, mineralization, volume as measured by bone biopsy)	0								
Bone mineral density/bone mineral content	6 (RCTs)	1106 (>266)	Moderate	Consistent	Direct	Results are not consistent across all sites measured	Moderate	Bisphosphonates may help with bone mineral density, but the results are not consistent across sites.	Moderate
Fracture	6 (RCTs)	1106 (>266)	Moderate	Consistent	Direct	Few events	Low	No difference in fracture incidence.	High
Raloxifene vs. placebo									
TMV (bone turnover, mineralization, volume as measured by bone biopsy)	0								
Bone mineral density/bone mineral content	3 (RCTs)	5083 (3348)	High	Inconsistent	Direct		Moderate	We are unable to draw conclusions.	Moderate
Fracture	2 (RCTs)	5033 (3323)	High	Inconsistent	Direct		Moderate	We are unable to draw conclusions.	High
Teriparatide vs. placebo									
TMV (bone turnover, mineralization, volume as measured by bone biopsy)	0								
Bone mineral density/bone mineral content	1 (RCT)	731 (485)	High	NA	Direct		Very low	Teriparatide may help with bone mineral density.	Moderate
Fracture	1 (RCT)	731 (485)	High	NA	Direct		Very low	Teriparatide may reduce the number of fractures.	High
Denosumab vs. placebo									
TMV (bone turnover,	0								

Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings: Quality of evidence for outcome	Summary of findings: Qualitative and quantitative description of effect	Summary of findings: Importance of outcome
mineralization, volume as measured by bone biopsy)									
Bone mineral density/bone mineral content	1 (RCT)	G3a-G3b: 2817 (1418) G4: 73 (36)	High	NA	Direct		Very low	We are unable to draw conclusions	Moderate
Fracture	1 (RCT)	G3a-G3b: 2641-2817 (1332-1418) G4: 64-73 (31-36)	High	NA	Direct		Very low	We are unable to draw conclusions	High
Ibandronate vs. Risedronate									
TMV (bone turnover, mineralization, volume as measured by bone biopsy)	0								
Bone mineral density/bone mineral content	1 (RCT)	69 (35)	High	NA	Direct		Very low	We are unable to draw conclusions	Moderate
Fracture	0								

NA = not applicable; RCT = randomized controlled trial; ROB = risk of bias

REFERENCES

1. Coco M, Glicklich D, Faugere MC, Burris L, Bognar I, Durkin P, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol. 2003 Oct;14(10):2669-76.

2. Walsh SB, Altmann P, Pattison J, Wilkie M, Yaqoob MM, Dudley C, et al. Effect of pamidronate on bone loss after kidney transplantation: a randomized trial. Am J Kidney Dis. 2009 May;53(5):856-65.

3. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res. 2007 Apr;22(4):503-8.

4. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. Am J Kidney Dis. 2010 Jul;56(1):57-68.

5. Smerud KT, Dolgos S, Olsen IC, Asberg A, Sagedal S, Reisaeter AV, et al. A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. Am J Transplant. 2012 Dec;12(12):3316-25.

6. Torregrosa JV, Fuster D, Gentil MA, Marcen R, Guirado L, Zarraga S, et al. Open-label trial: effect of weekly risedronate immediately after transplantation in kidney recipients. Transplantation. 2010 Jun 27;89(12):1476-81.

7. Haghverdi F, Mortaji S, Soltani P, Saidi N, Farbodara T. Effect of raloxifene on parathyroid hormone in osteopenic and osteoporotic postmenopausal women with chronic kidney disease stage 5. Iran J Kidney Dis. 2014 Nov;8(6):461-6.

8. Hernandez E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F, et al. Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. Kidney Int. 2003 Jun;63(6):2269-74.

9. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD. J Am Soc Nephrol. 2008 Jul;19(7):1430-8.

10. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. Osteoporos Int. 2007 Jan;18(1):59-68.

11. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res. 2011 Aug;26(8):1829-35.

12. Sanchez-Escuredo A, Fuster D, Rubello D, Muxi A, Ramos A, Campos F, et al. Monthly ibandronate versus weekly risedronate treatment for low bone mineral density in stable renal transplant patients. Nucl Med Commun. 2015 Aug;36(8):815-8.

KDIGO: CKD-MBD Update
Summary of Results for BMD Results Predicting Fractures/Renal Osteodystrophy

Research question 3.2.2 (a): In patients with CKD G3a-G5D, how well do BMD results predict fractures?

Research question 3.2.2 (b): In patients with CKD G3a-G5D, how well do BMD results predict renal osteodystrophy?

Research question 5.5: In patients with CKD G1T-G3bT, how well do BMD results predict fractures?

Research question 5.7: In patients with CKD G4T-G5T, how well do BMD results predict fractures?

Supplemental Table 7. Summary table of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5 – study characteristics

Author, year	Region of study	N	CKD GFR category	Follow up duration	Funding source
Denburg, 2013[1]	United States	171	G2-G5, G5D	1 year	Government, Industry, Non-profit
West, 2014[2]	Canada	131	G3a-G5	2 years	Government, non-profit
Yenchek, 2012[3]	United States	2754 (587 with CKD)	G3a-G5	Median time 11.3 years[a]	Government
Iimori, 2012[4]	Japan	485	G5D	Median: 39.9 months	Not stated
Naylor, 2015[5]	Canada	2107 (320 with CKD)	G3a-G5	4.8 years	Non-profit, industry

CKD = chronic kidney disease

a. This includes both patients with and without CKD. The authors did not report a median followup time just patients with CKD.

Supplemental Table 8. Summary table of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5 – study population characteristics

Author, year	Interven-tion group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
Denburg, 2013[1]	Total N=171	5-8: 18 (11%) 9-11: 33 (19%) 12-14: 41 (24%) 15-21: 79 (46%)	59	White: 68 Black: 26 Other: 6 Hispanic: 5	CKD GFR category G2-G3b: 68 (40%) G4-G5: 51 (30%) Dialysis: 52 (30%) Duration on dialysis NR	NR NR NR	Corrected Ca mg/dL: CKD 2-3: 9.4 CKD 4-5: 9.3 Dialysis: 9.4 P mg/dL CKD 2-3: 4.2 CKD 4-5: 5.2 Dialysis: 5.5 iPTH pg/mL: CKD 2-3: 46 CKD 4-5: 140 Dialysis: 252 Total 25(OH)D, ng/mL: CKD 2-3: 31.4 CKD 4-5: 22.0 Dialysis: 14.4 $1,25(OH)_2$ D pg/mL: CKD 2-3: 36.5 CKD 4-5: 30.5 Dialysis: 18.6	Cort BMD Z-score CKD 2-3: 0.27 CKD 4-5: -0.56 Dialysis: 0.00 CortBMD: peripheral quantitative tomography, midshaft tibia, 38% proximal to the distal growth plate. CortBMD in healthy children increased with age and greater in females and in black children, sex and race effects vary with age. CortBMD results were converted to sex-and race-specific Z-scores relative to age using LMS method.

Author, year	Interven-tion group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
West, 2014[2]	Total N = 131 Fracture: 35 Without Fracture 96	Fracture: 66.1 Without Fracture: 60.6	Fracture: 31 Without Fracture: 72	Fracture: White: 69 Without Fracture: White: 72	With Fracture G3a-G3b: 11 (31%) G4:15 (43%) G5: 9 (26%) No patients on dialysis Mean eGFR 23.6 mL/min/1.73 m^2 Without Fracture G3a-G3b: 34 (35%) G4: 37 (39%) G5: 25 (26%) No patients on dialysis Mean eGFR 27.2 mL/min/1.73 m^2	With Fracture 49% 29% NR Without Fracture 55% 8% NR	With Fracture Ca 2.4 mmol/L P 1.3 mmol/L ALP 91 U/L PTH 27.3 pmol/L 25-hydroxyVitD 65.0 nmol/L 1,25, dihydroxy VitD 58 pmol/L Without fracture: Ca 2.4 mmol/L P 1.3 mmol/L ALP 90.4 U/L PTH 25.7 pmol/L 25-hydroxyVitD 86.6 nmol/L 1,25, dihydroxy VitD 91.2 pmol/L	BMD by DXA: (95%CI) *Subjects w/o incident fractures at 2 years:* Total Hip (g/cm^2): 0.95 (0.92,0.98) Lumbar Spine (g/cm^2): 1.13 (1.09,1.18) Ultradistal radius (g/cm^2):0.46 (0.45, 0.48) 1/3 Radius (g/cm^2): 0.74 (0.73,0.76) *Subjects w/ incident fractures at 2 years* Total Hip (g/cm^2): 0.77 (0.73,0.80) Lumbar Spine (g/cm^2): 0.90(0.85,0.94) Ultradistal radius (g/cm^2):0.34(0.32,0.35) 1/3 Radius (g/cm^2):0.63(0.60,0.66) HRpQCT at Distal Radius (95% CI) *Subjects w/o incident fractures at 2 years:* Volumetric BMD (mg HA/cm^3): 317.6(306,329.1) Cortical Area (mm^2): 62.6 (59.3, 65.9) Trabecular Area (mm^2): 260.1 (243.5, 276.7) Cortical Density (mg HA/cm^3):822.2 (807.1, 837.3) Cortical Thickness (mm) : 0.79 (0.75,0.84) Trabecular Density (mg HA/cm^3): 162.5 (154.9,170.2) Trabecular Thickness (mm) : 0.069 (0.067,0.071) Trabecular Separation (mm): 0.45 (0.43, 0.47) *Subjects w/incident fracture at 2 years.* Volumetric BMD (mg HA/cm^3): 232.0(213.0,251.0) Cortical Area (mm^2): 36.7 (33.1, 40.1) Trabecular Area (mm^2): 239.0 (217.1, 26 Cortical Density (mg HA/cm^3): 656.8 (724.7,789.0) Cortical Thickness (mm) : 0.52 (0.46,0.59) Trabecular Density (mg HA/cm^3): 115.9 (103.1,128.7) Trabecular Thickness (mm) : 0.057(0.054,0.060) Trabecular Separation (mm): 0.59 (0.50,0.67)
Yenchek, 2012[3]	CKD N=587	74	45	Black: 30	eGFR 45-59.9: 83% eGFR 30 - 44.5: 13% eGFR 15-29.9: 3% eGFR <15: 1%	NR NR NR	PTH 37.8 pg/mol 25 hydroxy VitD 27.5±13.1 ng/ml	Femoral Neck BMD: 0.74 Total Hip BMD: 0.89

Author, year	Interven-tion group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
Iimori, 2012[4]	Hemodialysis N=485	Fracture: 61 No fracture: 60	Fracture: 54 No fracture: 65	NR	Dialysis vintage (month) Fracture: 68 No fracture: 19	Fracture: 32.6 No : 39.2%	Ca, mg/dL Fracture: 9.3 No: 9.0 P, mg/dL Fracture: 5.8 No: 5.7 PTH, pg/mL Fracture: 172 No: 220 ALP: NR	Fracture: 1/3 Distal Radius BMD (g/cm^2) : 0.566± 0.148 Lumbar Spine BMD (g/cm^2): 0.571±0.164 Femoral neck BMD (g/cm^2): 0.567±0.164 Femoral trochanter BMD (g/cm^2) : 0.480± 0.128 Total Hip BMD (g/cm^2) : 0.646 ± 0.176 Whole Body BMD (g/cm^2) : 0.917±0.106 No Fracture: 1/3 Distal Radius BMD (g/cm^2) : 0.635±0.124 Lumbar Spine BMD (g/cm^2): 0.614±0.174 Femoral neck BMD (g/cm^2): 0.636±0.141 Femoral trochanter BMD (g/cm^2) : 0.556±0.137 Total Hip BMD (g/cm^2) :0.743±0.163 Whole Body BMD (g/cm^2) : 0.970±0.119
Naylor, 2015[5]	CKD=320	76	29	NR	Mean eGFR 49.5 ml/min/1.73 m^2 G3a: 231 (72%) G3b: 76 (24%) G4/G5: 13 (4%)	13 58 NR	Ca 9.6 mg/dl P 3.7 gm/dl PTH 62.6 pg/ml 25-hydroxy VitD 28.2 ng/ml	Femoral neck BMD by DXA T-score -1.27 +/- 0.96

ALP = alkaline phosphatase; BMD = bone mineral density; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; CortBMD = cortical bone mineral density; DM = diabetes mellitus; DXA = dual-energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; g/cm² = grams per centimeter squared; HC = hypercholesterolemia; HRpQCT = high resolution peripheral computer tomography; HTN = hypertension;
iPTH = intact parathyroid hormone; LMS = least mean squares; MBD = mineral bone disorder; mg/dL = milligrams per deciliter; mg HA/cm^3 = milligrams hectares per centimeter cubed; mm^2 = millimeter squared; ng/mL = nanograms per milliliter; NR = not reported; P = phosphate; pg/mL = pictograms per milliliter; 25(OH)D = 25-hydroxyvitamin D

Supplemental Table 9. Summary table of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5 – results

Author, year	Patients w/ and w/o fracture	Predictors	Outcomes Number of fractures/Kinds	Covariates	Results
Denburg, 2013[1]	11 of 170 participants sustained fracture after baseline visits (incidence of 556 per 10,000)	CortBMD	Fracture: clavicle (1), tibia (3), foot (3), tibia (3), toes (2), radius/ulna (2). Activities: snowboarding, dancing, running, soccer, scooter racing, fall with foot caught in chair, football, struck by slow moving car tire, roughhousing, car accident and fall down stairs. 24 fractures in total: all were included in primary analysis	Difference in CortBMD-Z, 95% CI, p value Calcium (per 1mg/dL) 0.31, (0.08, 0.54), .01 PTH, (per 10%) -0.02, (-0/04,-0.01), .002 25(OH)D, (per10ng/mL) 0.18, (0.008, 0.34), .04 $1,25(OH)_2D$ (per 10%) -0.07, (-0/10,-0.04), <.001 Glucocorticoid therapy 0.76, (0.23, 1.30), .006	Fracture HR associated with each SD decrease in CortBMD: 1.75 (95% CI 1.15,2.67 p=0.009) HR excluding 2 events involving cars: 1.89 per SD increase in CortBMD (95% CI 1.19, 2.99; p=0.007) Mean CortBMD Z score in those that did fracture: -0.93 Mean CortBMD Z score in those that did not: 0.08
West, 2014[2]	32 of 131 subjects sustained 52 fractures	DXA (total hip, lumbar spine, ultradistal, 1/3 radius) HRpQCT (at radius)	Low trauma fractures as defined by WHO, confirmed self reported by independent blinded review of radiographs or radiographic reports	Odds of morphometric spine fractures and/or clinical non-spine and spine fractures per standard deviation decrease in the predictor for continuous variables and for affirmative response to dichotomous variables , 95% CI eGFR : 1.47 (1.23, 1.71) Weight 1.59 (1.31,1.87) Serum 25-hydroxy-vitamin D: 0.98 (0.95, 1.01) Current alcohol use: 0.74 (0.70, 0.78) Falls in past year: 1.22 (1.09,1.35) Self reported fracture since age 40: 1.27 (1.13, 1.41) Prevalent morphometric spine fracture: 1.33 (1.21, 1.45)	Odds of morphometric spine fractures and/or clinical non-spine and spine fractures per standard deviation decrease in the Total Hip BMD by DXA Fully adjusted (VitD, EtOH, falls in past year, fracture after 40, prevalent morphometric spine fracture, weight, CKD-EPI formula) : OR: 1.75 (95%, 1.30, 2.20) Odds of morphometric spine fractures and/or clinical non-spine and spine fractures per standard deviation decrease in the Lumbar Spine BMD by DXA Fully adjusted (VitD, EtOH, falls in past year, fracture after 40, prevalent morphometric spine fracture, weight, CKD-EPI formula) : OR: 1.65 (95%, 1.20, 2.10) BMD by DXA; AUC (95% CI) Total Hip 0.68 (0.57, 0.79) Lumbar Spine 0.62 (0.50, 0.74) Ultradistal Radius 0.74 (0.65, 0.83) 1/3 Radius 0.70 (0.59, 0.81) HRpQCT at Radius; AUC (95% CI) Volumetric BMD 0.70 (0.57,0.83)

Author, year	Patients w/ and w/o fracture	Predictors	Outcomes Number of fractures/Kinds	Covariates	Results
					Cortical Area 0.73 (0.60, 0.86) Trabecular Area 0.65 (0.52 , 0.78) Cortical Density 0.72 (0.59, 0.84) Cortical Thickness 0.72 (0.59, 0.84) Trabecular Density 0.62 (0.47, 0.77) Trabecular Thickness 0.59 (0.47, 0.71) Trabecular Separation 0.61 (0.48 , 0.74)
Yenchek, 2012[3]	384 fractures /3075 98 in CKD group /587 286 in non-CKD group /2167	DXA	Primary: all nonspine fragility fractures Secondary: fragility, hip fracture. Identified by self-report and verified by radiology reports. All reports adjudicated. Fracture: first nonspine fracture event of any cause Fragility fractures: spontaneous or with modest trauma, such as a fall from standing height Time to fracture: initial clinic visit to fracture event date	Femoral neck BMD (per SD decrease) with risk of fracture Positive parathyroid status and Vitamin D status p=.68 No CKD 2.15 (1.80, 2.57) CKD 2.74 (1.99, 3.77)	Hazard ratio for femoral neck BMD, per SD decrease, with risk of fracture (95% CI) Adjusted for age, race sex, BMI CKD: 2.69 (1.96, 3.69) P value for CKD BMD Interaction=0.70 Hazard ratio for total hip BMD, per SD decrease, with risk of fracture (95% CI) 2.59 (1.86, 3.61) Hazard ratio for osteoporosis with risk of fracture (95% CI) CKD 2.10 (1.24, 3.59)

Author, year	Patients w/ and w/o fracture	Predictors	Outcomes Number of fractures/Kinds	Covariates	Results
Iimori 2012 [4]	46 fractures/ 485 hemodialyzed patients	DXA	46 new incident fractures (10 rib or clavicle, 2 spine: traumatic, 3 humerus, 6 wrist, 11 hip, 5 tibia or fibula, 6 ankle, 3 other sites. Prevalent spine fracture in 29 patients)	Adjusted HR for any type of fracture History of fracture: 2.71 (1.20-6.11) p=.002	Adjusted HR (95% CI) for any fracture Femoral neck BMD per 10 mg/cm^2: 0.96 (0.94, 0.99) p=.01 Femoral neck BMD per SD: 0.65 (0.47, 0.90) p=.009 Femoral trochanter BMD per 10mg/cm^2: 0.95 (0.92, 0.98) p =.003 Total hip BMD per 10 mg/cm^2: 0.97 (0.94, 0.99) p =.005 Total hip BMD per SD: 0.65 (0.49, 0.87) p =.004) Lumbar spine BMD per 10mg/cm^2: 0.98 (0.96, 1.00) Lumbar spine per SD : 0.87 (0.73, 1.03) 1/3 distal radius per 10mg/cm^2: 0.97 (0.94, 1.01) 1/3 distal radius per SD 0.87 (0.73, 1.04) Whole Body BMD per 10mg/cm^2: 0.97 (0.94, 1.00) AUC Femoral neck: 0.827, p=.00001 Femoral trochanter: 0.776, P=.0001 Total hip: 0.808, p<.0001 Lumbar spine: 0.674, p=.001 1/3 distal radius: 0.724, p=.0001 Whole body: 0.680, p=.008
Naylor, 2015[5]	Out of 320, there were 16 fractures during the follow up period	Femoral neck T score	Fracture defined as a composite of incident clinical spine, hip, forearm/wrist & humerus fractures that resulted from low trauma	None	AUC for incident fracture prediction (AUC, 95% CI) Femoral neck T score 0.65 (0.52 to 0.80)

AUC = area under the curve; BMD = bone mineral density; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; cortBMD = cortical bone mineral density; DXA = dual-energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; HR = hazard ratio; HRpQCT = high resolution peripheral computer tomography; mg/cm^2; OR = odds ratio; PTH = parathyroid hormone; SD = standard deviation; WHO = World Health Organization; 25(OH)D = 25-hydroxyvitamin D

Supplemental Table 10. Summary table of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5 – quality

Author, year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall quality
Denburg, 2013[1]	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
West, 2014[2]	Moderate	Moderate	Low	Low	Low	Low	Moderate
Yenchek, 2012[3]	Low	High	Low	Low	Low	Low	Moderate
Iimori 2012[4]	Moderate	Moderate	Low	Low	Low	Low	Moderate
Naylor, 2015[5]	Low	Moderate	Low	Moderate	Low	Low	Moderate

Supplemental Table 11. Evidence matrix of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N*	Followup	Author	*N*	Followup	Author	*N*	Followup
Fracture				Denburg, 2013 West, 2014 Yenchek, 2012 Iimori, 2012 Naylor, 2015	171 131 587 485 320	1 year 2 years 11.3 years 39.9 months 4.8 years			
TMV (bone turnover, mineralization, volume)				Iimori, 2012 Denburg, 2013	485 171	39.9 mo 1 year			
Renal osteodystrophy									

Supplemental Table 12. Evidence profile of studies evaluating the ability of bone mineral density results to predict fracture or renal osteodystrophy among patients with CKD G3a-G5

							Summary of findings		
Outcome	No. of studies and study design	Total *N*	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Fracture	5 Observational	3860	Moderate	Consistent	Direct		Low	Tendency toward BMD scores to be predictive of fracture risk	High
TMV (bone turnover, mineralization, volume)	2 Observational	655	Moderate	Consistent	Direct		Low	Volumetric CortBMD associated with fracture risk	Moderate

BMD = bone mineral density; CortBMD = cortical bone mineral density; ROB = risk of bias

REFERENCES

1. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, et al. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. J Clin Endocrinol Metab. 2013 May;98(5):1930-8.

2. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, et al. Bone mineral density predicts fractures in chronic kidney disease. J Bone Miner Res. 2014 Nov 15.

3. Yenchek RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, et al. Bone mineral density and fracture risk in older individuals with CKD. Clin J Am Soc Nephrol. 2012 Jul;7(7):1130-6.

4. Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrol Dial Transplant. 2012 Jan;27(1):345-51.

5. Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. Clin J Am Soc Nephrol. 2015 Apr 7;10(4):646-53.

KDIGO: CKD-MBD Update
Summary of Results for Dialysate Calcium Concentrations

Research question 4.1.3: In patients with CKD G5D, what is the evidence for benefit or harm in using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) compared with other concentrations of dialysate calcium in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 13. Summary table of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality	Follow up duration	Funding source
Ok, 2015[1]	NR	425	Dialysis	HD	24 months	Industry
Spasovski, 2007[2]	NR (presumably Macedonia)	60	Dialysis	HD	6 months	Industry

CKD = chronic kidney disease; HD = hemodialysis; NR = not reported

Supplemental Table 14. Summary table of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
Ok, 2015[1]	1.25 calcium dialysate n = 212	59.3	59	NR	NR 51.2 months	24% NR NR	P 4.31 mg/dl Ca 9.18 mg/dl PTH 84 pg/ml ALP 104 U/L	Bone biopsy	587
	1.75 calcium dialysate n = 213	59.9	54	NR	NR 50.5 months	27% NR NR	P 4.40 mg/dl Ca 9.12 mg/dl PTH 86 pg/ml ALP 103 U/L		551
Spasovski, 2007[2]	Low calcium dialysate n=26	61	54%	NR	NR 74.7 months	31% NR NR	P 1.50 mmol/L Ca* 1.09 mmol/L Ca x P 3.68 $mmol^2/L^2$ iPTH 38.6 pg/mL TAP 59.5 U/L BAP 23.4 U/L	Serum TAP, BAP	NA
	High calcium dialysate n=26	57	54%	NR	NR 59.3 months	23% NR NR	P 1.30 mmol/L Ca* 1.20 mmol/L Ca x P 3.05 $mmol^2/L^2$ iPTH 43.5 pg/mL TAP 58.0 U/L BAP 25.4 U/L		

ALP = alkaline phosphatase; BAP = bone alkaline phosphatase; Ca x P = calcium x phosphate product; DM = diabetes mellitus; HC = hypercholesterolemia; HTN = hypertension; MBD = mineral and bone disorder; NR = not reported; PTH = parathyroid hormone; TAP = total alkaline phosphatase; U/L = units per liter

* Calcium = ionized, post-hemodialysis calcium

Supplemental Table 15. Summary table of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D – results

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Ok, 2015[1]	1.25 mmol/L calcium dialysate	1.75 mmol/L calcium dialysate	None	Fractures, n/N (%)	1/212 (0.4%) vs. 1/213 (0.4%)
				Hypercalcemia, episodes per 100 patient-months	4.4 vs. 11.3; P < 0.001
				CAC score – Agatston, mean (SD) at 24 months Mean between-group difference in CAC score change (95% CI)	616 (1086) vs. 803 (1412); P=0.25 -138 (-265 to -12); P=0.03
				CAC score – volume, mean (SD) at 24 months Mean between-group difference in CAC score change (95% CI)	466 (821) vs. 617 (1089) -118 (-214 to -22); P=0.01
				Bone turnover, bone formation rate/bone surface (normal: 1.80-3.80 mm^3/cm^2 per year), mean (SD) at 24 months	3.24 (2.77; P < 0.001 vs. baseline) vs. 1.93 (1.37; P = 0.07 vs. baseline); P = 0.03
				Bone turnover, activation frequency (normal: 0.49-0.72 per year), mean (SD) at 24 months	0.67 (0.56; P < 0.001 vs. baseline) vs. 0.41 (0.28; P = 0.06 vs. baseline); P = 0.03
				Bone turnover, osteoblast no./bone perimeter (normal: 10-200/100 mm), mean (SD) at 24 months	144 (199; P < 0.01 vs. baseline) vs. 66.7 (124; P = 0.12 vs. baseline); P = 0.01
				Bone turnover, osteoclast no./bone perimeter (normal: 1-53/100 mm), mean (SD) at 24 months	48 (44.8; P < 0.01 vs. baseline) vs. 39.8 (42.4; P = 0.01 vs. baseline); P > 0.05
				Mineralization, osteoid thickness (normal: <20 µm), mean (SD) at 24 months	13.1 (5.5; P < 0.001 vs. baseline) vs. 11.0 (6.1; P = 0.87 vs. baseline); P > 0.05
				Mineralization, mineralization lag time (normal: < 100 d), mean (SD) at 24 months	126 (127; P = 0.09 vs. baseline) vs. 83 (73; P = 0.17 vs. baseline); P > 0.05
				Mineralization, osteoid maturation time (normal: <35 d), mean (SD) at 24 months	17.25 (7.35; P < 0.001 vs. baseline) vs. 15.21 (8.39; P < 0.001 vs. baseline); P > 0.05
				Volume, bone volume/tissue volume (normal: 16.8%-22.9%), mean (SD) at 24 months	21.3 (6.6; P = 0.02 vs. baseline) vs. 18 (7.1; P = 0.43 vs. baseline); P = 0.01
				Volume, trabecular thickness (normal: 99-142 µm), mean (SD) at 24 months	98.5 (24.7; P = 0.05 vs. baseline) vs. 88.4 (25.9; P = 0.26 vs. baseline); P = 0.04
				Volume, cortical thickness (normal: 0.52-1.65 µm), mean (SD) at 24 months	550 (350; P = 0.14 vs. baseline) vs. 540 (560; P = 0.33 vs. baseline); P > 0.05
				Volume, cortical porosity (normal: 1.9%-10%), mean (SD) at 24 months	14.78 (14.78; P < 0.001 vs. baseline) vs. 10.88 (6.27; P < 0.001 vs. baseline); P > 0.05
				Mortality, n/N (%) Incidence per 100 patient-yrs	31/212 (14.6%) vs. 37/213 (17.3%); P = 0.44 7.86 vs. 9.84; P=0.29
				Cardiovascular mortality, n/N (%)	13/212 (6.1%) vs. 15/213 (7.0%); P = 0.70
				Nonfatal cardiovascular events, n/N (%)	3/212 (1.4%) vs. 6/213 (2.8%); P = 0.31

				Hospitalization, %	12.7% vs. 11.2%
				Calcium, mg/dL time-averaged during 24-mo study	8.96 vs. 9.40; P<0.001
Spasovski, 2007[2]	Low calcium dialysate (1.25 mmol/L)	High calcium dialysate (1.75 mmol/L)	Calcium carbonate (no difference between groups)	Ionized calcium* at follow-up	1.12 vs. 1.18 mmol/L, p<0.05
				Hypotension (%)	17% vs. 16%, NS
				Cramps (%)	8% vs. 6%, NS
				Mortality (%)	0% vs. 0%
				Corrected total calcium* at follow-up	2.59 vs. 2.73 mmol/L, p<0.05
				Total calcium at follow-up	2.48 vs. 2.63 mmol/L, p<0.05

AE = adverse event; CAC = calcium artery calcification; cm = centimeter; mg/dl = milligrams per deciliter; mm = millimeter; mmol/L = millimoles per liter; NS = not statistically significant at p<0.05; µm = micrometre

* Post-hemodialysis calcium

Supplemental Table 16. Summary table of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Ok, 2015[1]	Unclear	Unclear	Unclear	No	Yes	No	No	Unclear
Spasovski, 2007[2]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes

Supplemental Table 17. Evidence matrix of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D

	Risk of Bias											
	Low			Moderate			High			Adverse events (no grade)		
Outcome	Author	*N*	Follow up	Author	*N*	Follow up	Author	*N*	Follow up	Author	*N*	Follow up
Mortality							Ok 2015 Spasovski, 2007	425 60	24 mo. 6 mo.			
Cardiovascular and cerebrovascular events							Ok 2015	425	24 mo.			

ALP = alkaline phosphatase; Ca = calcium; P = phosphate; PTH = parathyroid hormone

Supplemental Table 18. Evidence profile of randomized controlled trials examining the treatment of CKD-MBD with varying dialysate calcium concentration levels in CKD G5D

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs	485 (238)	High	Consistent	Direct		Very low	No effect on mortality	Critical
Cardiovascular and cerebrovascular events	1 RCT	425 (212)	High	NA	Direct		Very low	No effect on cardiovascular mortality or morbidity	Critical

NA = not applicable; RCT = randomized controlled trial; ROB = risk of bias

REFERENCES

1. Ok E, Asci G, Bayraktaroglu S, et al. Reduction of Dialysate Calcium Level Reduces Progression of Coronary Artery Calcification and Improves Low Bone Turnover in Patients on Hemodialysis. J Am Soc Nephrol. 2015 Dec 23doi: 10.1681/asn.2015030268. PMID: 26701977.

2. Spasovski G, Gelev S, Masin-Spasovska J, et al. Improvement of bone and mineral parameters related to adynamic bone disease by diminishing dialysate calcium. Bone. 2007 Oct;41(4):698-703. doi: 10.1016/j.bone.2007.06.014. PMID: 17643363.

KDIGO: CKD-MBD Update
Summary of Results for Phosphate Binders

Research question 4.1.4: In patients with CKD G3a-G5 or G5D with hyperphosphatemia, what is the evidence for benefit or harm in using calcium-containing phosphate-binding agents to treat hyperphosphatemia compared with calcium-free phosphate-binding agents in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 19. Summary table of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Sevelamer vs. other treatment						
Barreto, 2008[1]	Brazil	101	Dialysis	HD 3.5 mEq/L[a]	12 mo	NR
Block, 2005[2] Block, 2007[3]	USA	148	G5D	Incident HD 2.5 mmol/L	18 mo (44 mo median for mortality)	Industry
Block, 2012[4]	USA	148	GFR 20-45 mg/dl	NA NA	9 mo	Industry
Braun, 2004[5] Asmus, 2005[6]	Austria, Germany	114 (93 overlap with Chertow, 2002[7]	G5D (25, history of transplant)	HD 1.5 mmol/L	12 mo (24 mo for subgroup)	NR (1 author had industry COI)
Chertow, 2002[7]	Austria, Germany, USA	200	Dialysis	HD NR	12 mo	Industry
De Francisco, 2010[8]	Germany, Poland, Portugal, Romania, Spain	255	G5D	HD or online haemodiafiltration 3x/week 1.25 or 1.5 mmol/L	25 weeks	NR
Di Iorio, 2012[9]	Italy	239	G3a-G4	NA NA	36 mo	NR
Di Iorio, 2013[10]	Italy	466	Dialysis	HD NR	24-36 mo	Government
Ferreira, 2008[11]	Portugal	119	Dialysis	HD NR	13.5 mo	Industry
Kakuta, 2011[12]	Japan	183	Hemodialysis	HD 2.5 mEq/L	12 mo	Unclear (Japan Dialysis Outcomes Research Group)
Qunibi, 2008[13]	USA	203	Dialysis	HD 1.25 mmol/L (2.5 mEq/L)	12 mo	Industry
Russo, 2007[14]	Italy	90	G3a-G5	NA NA	Mean 24 mo	None
Suki, 2007[15] Suki, 2008[16]	USA	2103	Dialysis	HD NR	Mean 20 mo	Industry
Yubero-Serrano, 2015[17]	USA	117	G2-G4 (DKD)	NA NA	6 mo	Industry
Lanthanum carbonate vs. other treatment						
D'Haese, 2003[18]	"12 countries"	98	Dialysis	HD or peritoneal dialysis (CAPD)	12 mo	NR
Finn, 2006[19]	Poland, Puerto Rico, South Africa, USA	1359	Dialysis	HD NR	24 mo	Unclear
Hutchison, 2005[20]	Belgium, Germany,	800	Dialysis	HD	6 mo	Industry

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Hutchison, 2006[21]	Netherlands, UK					
Malluche, 2008[22]	Poland, Puerto Rico, South Africa, USA	211	Dialysis	HD 2.5 mEq/L	24 mo	Industry
Wilson, 2009[23]	USA, Puerto Rico, Poland, South Africa	1354	Dialysis	NR	40 mo maximum	Industry
Ferric citrate vs. (calcium acetate &/or sevelamer carbonate)						
Lewis, 2015[24] Van Buren, 2015[25]	USA, Israel	441	G5D	HD & PD NR	52 weeks	Industry

CAPD = continuous ambulatory peritoneal dialysis; CKD = chronic kidney disease; CKD-MBD = chronic kidney disease-mineral bone disorder; COI = conflict of interest; DKD = diabetic kidney disease; GFR = glomerular filtration rate; HD = hemodialysis; mEg/L = milliequivalents of solute per liter of solvent; mg/dl = milligrams per deciliter; mmol/L = millimoles per liter; NA = not applicable; NR = not reported; PD = peritoneal dialysis; UK = United Kingdom; USA = United States of America

Supplemental Table 20. Summary table of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders– study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
Sevelamer vs. other treatments									
Barreto, 2008[1]	Sevelamer	47	66	White 58	NR 36 mo	15 66	iCa 1.23 mmol/L P 2.3 mmol/L iPTH 494 pg/mL b-ALP 34 U/L 25(OH)D 33 ng/mL	Bone biopsy	Median CAC 190 CAC Score >30[a]: 66%
	Calcium carbonate	47	70	White 63	NR 38 mo	13 73	iCa 1.23 mmol/L P 2.3 mmol/L iPTH 343 pg/mL b-ALP 27 U/L 25(OH)D 31 ng/mL	Bone biopsy	Median CAC 50 CAC Score >30[a]: 53%
Block, 2005[2]	Sevelamer-HCl (non-calcium phosphate binder)	57	59	White 43 Black 26 Other 31	NR 2.9 mo	63 96 31	Ca 9.3 mg/dL corrected P 5.2 mg/dL Ca x P 48 mg^2/dL^2 iPTH 293 pg/dL ALP NR	NR	% with no CAC: 37%
	Calcium-containing phosphate binder	59	67	White 40 Black 36 Other 24	NR 3.0 mo	56 98 35	Ca 293 mg/dL corrected P 5.4 mg/dL Ca x P 49 mg^2/dL^2 iPTH 319 pg/dL ALP NR	NR	% with no CAC: 31%
Block, 2012[4]	Sevelamer N=30	66	50	White 80 Black 7	32 NA	53 97 97	Ca 9.3 mg/dl P 4.2 mg/dL Median iPTH 70 pg/mL $1,25(OH)_2D$ 24.7	Mean L2-L4 BMD 111 g/cm^2	Median CAC 362.5 Median TAC 536 Median AAC 1367
	Calcium acetate N=28	68	47	White 80 Black 17	30 NA	57 97 83	Ca 9.3 gm/dl P 4.2 mg/dl iPTH 76 pg/ml (median) $1,25(OH)_2D$ 25.5	L2-L4[f] BMD (Mean) 120	Median CAC[e] 130 Median TAC[e] 511 Median AAC[e] 1468
	Lanthanum N=30	70	54	White 82 Black 7	33 NA	57 100 86	Ca 9.2 mg/dl P 4.2 mg/dl iPTH 87 pg/ml (median) $1,25(OH)_2D$ 26.9	L2-L4 [f] BMD (Mean) 99	Median CAC[e] 216.5 Median TAC[e] 1609 Median AAC[e] 4035

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
	Placebo N=57	65	49	White 79 Black 11	30 NA	58 100 93	P 4.2 mg/dl iPTH 91 pg/ml (median) $1,25(OH)_2D$ 27.2	L2-L4 [f] BMD (Mean) 108	Median CAC[e] 225 Median TAC[e] 496 Median AAC[e] 1693
Braun, 2004[5] Asmus, 2005[6]	Sevelamer (calcium-free phosphate binder)	55	64	White 100	NR 69 mo	16 82 NR	Ca 2.34 mmol/L P 2.45 mmol/L iPTH 17.1 pmol/L ALP NR	NR	Mean CAC 1784 % with no CAC: 11%
									Mean AoC 4694 % with no AoC: 18%
									Mean MVC 1711 % with no MVC: NR
									Mean AVC 367 % with no AVC: NR
	Calcium carbonate	58	61	White 98	NR 58 mo	21 75 NR	Ca 2.32 mmol/L P 2.29 mmol/L iPTH 13.9 pmol/L ALP NR	NR	Mean CAC 1466 % with no CAC: 11%
									Mean AoC 5267 % with no AoC: 10%
									Mean MVC 1118 % with no MVC: NR
									Mean AVC 70 % with no AVC: NR
Chertow, 2002[7]	Sevelamer N=99	57	64	White 71 Black 17 Other 12	NR 43 mo	32 86 NR	Ca 9.4 mg/dL corrected P 7.6 mg/dL Ca x P 71 mg^2/dL^2 iPTH 232 pg/mL	NR	Mean CAC 1712 Mean AoC 3874 Mean MVC 4[a] % with no MVC: 50% Mean AVC 0 [a] % with no AVC: 59% Mean Both Valves 56 [a] % with no MVC or AVC: 36%
	Calcium acetate or calcium carbonate N=101	56	66	White 66 Black 23 Other 11	NR 35 mo	33 83 NR	Ca 2.32 mmol/L corrected P 2.39 mmol/L iPTH 21.2 pmol/L nd ALP nd	NR	Mean CAC 1125 Mean AoC 3233 Mean MVC 0[a] % with no MVC: 57% Mean AVC 0[a] % with no AVC: 70% Mean Both Valves 25[a] % with no MVC or AVC: 46%

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
De Francisco, 2010[8]	Calcium Acetate,105	59.2	53.3	NR	4.9 years	24.8	P 2.464 mmol/L Ca ionized 1.071 mmol/L Ca total serum 2.148 mmol/L iPTH 450.84 pg/mL	NA	NA
	Sevelamer-HCL, 99	55.9	51.5	NR	5.1 years	20.2	P 2.480 mmol/L Ca ionized 1.076 mmol/L Ca total serum 2.185 mmol/L iPTH 438.97 pg/mL	NA	NA
Di Iorio, 2012[9]	Sevelamer N=107	57	61	NR NR NR	NR NA	27 73 NR	Ca 9.0 mg/dl P 4.82 mg/dl iPTH 200 pg/dl (median) ALP NR	NR	Median CAC[b]: 122 % With CAC[b]: 62.6 % with CAC[b] score > 100: 53.3
	Calcium Carbonate N=105	59	61	NR NR NR	NR NA	29 76 NR	Ca 8.8 mg/dl P 4.87 mg/dl iPTH 188 pg/dl (median) ALP NR	NR	Median CAC[b]: 0 % With CAC[b]: 47.6% % with CAC[b] score > 100: 38.1
Di Iorio, 2013[10]	Sevelamer N=232	67	50	NR NR NR	< 3 mo	30 78 NR	Ca 9.0 mg/dl P 5.6 mg/dl iPTH 265 pg/dl ALP NR	NR	Median CAC: 19
	Calcium carbonate N=234	65	48	NR NR NR	< 3 mo	29 81 NR	Ca 8.8 mg/dl P 4.8 mg/dl iPTH 283 pg/dl ALP NR	NR	Median CAC: 30
Ferreira, 2008[11]	Sevelamer hydrochloride	56	67	White 97 Black 3	NR 23 mo	6 73 NR	Ca 9.6 mg/dL P 5.8 mg/dL iPTH 167 pg/mL b-ALP 11.5 µg/L 25(OH)D 16.3 ng/dL $1,25(OH)_2D$ 6.4 pg/mL	Bone biopsy	NR

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
	Ca carbonate	54	51	White 97 Black 3	NR 25 mo	23 71 NR	Ca 9.8 mg/dL P 5.7 mg/dL iPTH 113 pg/mL b-ALP 10.6 µg/L 25(OH)D 16.6 ng/mL $1,25(OH)_2D$ 11.8 pg/mL	Bone biopsy	NR
Kakuta, 2011[12]	Sevelamer, 91	59	57	NR	NR 105 mo	NR	Ca corrected 9.79 mg/dL P 5.65 mg/dL	CT	Coronary Artery Calcification Score 879
	Calcium Carbonate, 92	57	51	NR	NR 119 mo	NR	Ca corrected 9.71 mg/dL P 5.75 mg/dL	CT	Coronary Artery Calcification Score 872
Qunibi, 2008[13]	Sevelamer	60	46	Black 39	NR 22 mo	NR	Ca 8.8 mg/dL P 6.6 mg/dL Ca x P 58 mg^2/dL^2 iPTH 509 pg/mL ALP 93.9 U/L b-ALP 19.7 U/L	NR	Mean CAC 969 % of total population with no AoC 14 % of total population with AVC 60 % of total population with MVC 45
	Calcium acetate	59	57	Black 34	NR 23 mo	NR	Ca 8.8 mg/dL P 6.5 mg/dL Ca x P 58 mg^2/dL^2 iPTH 466 pg/mL ALP 88.9 U/L b-ALP 19.0 U/L	NR	Mean CAC 1098
Russo, 2007[14]	Sevelamer N=27	54	89	NR NR NR	26 NA	0 NR NR	Ca 9.2 mg/dl P 4.5 mg/dl Mean CaXP (mg^2/dl^2) 41.7 PTH pg/ml 136.5 ALP mg/dl 134.2	NR	5% without CAC
	Calcium carbonate N=28	55	82	NR NR NR	26 NA	0 NR NR	Ca 9.1 mg/dl P 4.6 mg/dl Mean CaXP (mg^2/dl^2) 42.3 PTH pg/ml 172.1 ALP mg/dl 148.0	NR	5% without CAC

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
	Control N=29	54	86	NR NR NR	33 NA	0 NR NR	Ca 9.2 mg/dl P 3.9 mg/dl Mean CaXP (mg^2/dl^2) 35.8 PTH pg/ml 140.7 ALP mg/dl 113.7	NR	5% without CAC
Suki, 2007[15] Suki, 2008[16d]	Sevelamer	60	55	White 49 Black 47 Asian 1 Other 4	NR 39 mo	51 NR NR	Ca 9.2 mg/dl P 5.8 mg/dl iPTH 278 pg/dl (mean) ALP NR	NR	None
	Calcium	60	54	White 47 Black 47 Asian 1 Other 5	NR 38 mo	50 NR NR	Ca 9.5 mg/dl P 5.7 mg/dl iPTH 226 pg/dl (mean) ALP NR	NR	None
Yubero-Serrano, 2015[17]	Sevelamer carbonate N=57	64	51	Caucasian 49	50.1 ml/min/1.73 m^2	100 NR NR	NR NR NR	NR	NR
	Calcium carbonate N=60	63	62	Caucasian 38	47.2 ml/min/1.73 m^2	100 NR NR	NR NR NR	NR	NR
Lanthanum carbonate vs. other treatments									
D'Haese, 2003[18]	Lanthanum carbonate	Total 55	Total 60	NR	NR NR	Total 26 Total 14 NR	***in Figure 1	Bone biopsy	NR
	Ca carbonate							Bone biopsy	
Finn, 2006[19]	Lanthanum Carbonate N=682	54	57	Caucasian 44 Black 44 Hispanic 8 Asian/ Pacific <1 Native American 1 Other 2	NR 3.9 years	NR NR NR	Ca 2.30 mmol/L[e] P 2.58 mmol/L[e] PTH 17.2 pmol/Le ALP(U/l) 97	NR	NR

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
	Standard therapy (78% were using calcium containing binders) N=677	55	61	Caucasian 46 Black 41 Hispanic 8 Asian/ Pacific 2 Native American 1 Other 2	NR 3.8 years	NR NR NR	Ca 2.27 mmol/L[e] P 2.58 mmol/L[e] PTH 14.6 pmol/L[e] ALP(U/l) 95.6	NR	NR
Hutchison, 2005[20] Hutchison, 2006[21]	Lanthanum carbonate	57	67	NR	NR 43 mo	NR NR NR	Ca 0.57 mmol/L 25(OH)D_3 43.7 ng/mL PTH 127 ng/L	Bone biopsy	NR
	Calcium carbonate	58	64	NR	NR 44 mo	NR NR NR	Ca 0.56 mmol/L 25(OH)D_3 37.4 ng/mL PTH 163 ng/L	Bone biopsy	NR
Malluche, 2008[22]	Lanthanum carbonate	49	73	Black 49 Caucasian 33 Hispanic 8 Asian/Pacific Islander 0 Native American 0 Other 10	NR 3.5 yrs	28 37 NR	cCa 8.8 mg/dL P 7.6 mg/dL PTH 318 pg/mL b-ALP 27.3 ng/mL	Bone biopsy	NR
	Prestudy P binder reinstituted at prestudy dose	51	77	Black 52 Caucasian 29 Hispanic 6 Asian/Pacific Islander 2 Native American 0 Other 10	NR 5.1 yrs	17 40 NR	cCa 9.2 mg/dL P 8.1 mg/dL PTH 211 pg/mL b-ALP 20.8 ng/mL	Bone biopsy	NR

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc/Valv Calcification by EBCT in Agatston units
Wilson, 2009[23]	Lanthanum Carbonate, 680	53.8	57.2	White 44.6 Black 44.3 Hispanic 7.9 Asian 0.4 Native American 0.9 Other 1.9	NR 3.4 years	34.4 31.2	NR	Bone biopsy	NR
	Standard therapy (P binder), 674	54.9	61.4	White 46.4 Black 40.7 Hispanic 40.7 Asian 1.9 Native American 0.9 Other 1.9	NR 3.3 years	34.6 28.5	NR	Bone Biopsy	NR
Ferric citrate vs. (Calcium acetate &/OR Sevelamer carbonate)									
Van Buren, 2015[25] Lewis, 2015[24]	Ferric citrate N=292	55	63	Caucasian 43 Black 53 Hispanic NR Other 5	NR ≥3mo	NR NR NR	Ca 9.0 mg/dl P 7.2 mg/dl iPTH 514 pg/ml CaXP 63.5 mg^2/dl^2 ALP NR	NR	NR
	Active control (78 used sevelamer only, 41 used calcium acetate only and 30 used both) N=149	54	58	Caucasian 42 Black 52 Other 6	NR ≥3mo	NR NR NR	Ca 9.0 mg/dl P 7.4 mg/dl iPTH 479 pg/dl CaXP 66.2 mg^2/dl^2 ALP NR	NR	NR

AoC, aortic calcification; ALP, alkaline phosphatase; AVC, aortic valve calcification; b-ALP, bone-specific alkaline phosphatase; BMD: bone mineral density; Ca: calcium; CAC, coronary artery calcification; TVC, Thoracic aorta calcification; AAC Abdominal Aorta Calcification; CaXP, calcium-phosphate product; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; EBCT, electron-beam CT; g/cm^2: grams per centimeter squared; HC = hypercholesterolemia; HTN = hypertension; iPTH, intact parathyroid hormone; MBD, mineral and bone disease; mg.dL: milligrams per deciliter; mmol/L: millimoles per liter; MVC, medial vascular calcification; ng/mL, nanograms per milliliter; N, number of subjects; nd, not documented; NR = not reported; P: phosphate; pg/dL: picogram per deciliter; pmol/L: picomole per liter; PTH, parathyroid hormone; TVC, Time varying covariates; U/L, units per liter; 25(OH)D: 25-hydroxyvitamin D

a. Raggi P, Bommer J, Chertow GM. Valvular calcification in hemodialysis patients randomized to calcium-based phosphate binders or sevelamer. *The Journal of Heart Valve Disease* 2004; **13:** 134-141

b. The CAC score was assessed by a multi-slice computed tomography (CT) scan (GE Medical Systems) at study entry as well as scans at 6, 12, 18, and 24 months. CAC score was reported in Agatston units (AUs).

c. CAC score was assessed by multislice lightspeed (GE Medical Systems) equipment at one center (Solofra, AV)
d. Randomization is stratified by age (>55 vs <55), DM & race (black vs. Non-black)
e. Estimated from the graph
f. We used the GE-Imatron C150 scanner at baseline and month 9 using a standard protocol as previously described. We defined atherosclerotic calcium as a plaque area$1 mm2 with a density of $130 Hounsfield units. The thoracic aorta was de- fined as the segment from the aortic root to the diaphragm, whereas the abdominal aorta was the segment from the diaphragm to the iliac bifurcation. A single experienced investigator, blinded to treatment assignment, performed all image assessments.
g. Lumbar BMD was determined using abdominal computed tomography scans with a calibrated phantom of known density (Image Analysis QCT 3D PLUS, Columbia, KY). Measurements of BMD were performed in a 5-mm-thick slice of trabecular bone from each vertebra (L2 to L4) at baseline and month 9.

Supplemental Table 21. Summary table of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders– results

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (p-value)
Sevelamer vs. other treatments					
Barreto, 2008[1]	Sevelamer Monthly adjustments to a maximum of 12 g daily to achieve P 1.13– 1.78 mmol/L, Ca 1.11–1.40 mmol/L and iPTH 15.9 and 31.8 pmol/L	Ca acetate Monthly adjustments to a maximum of 2.028g of elemental Ca to achieve P 1.13– 1.78 mmol/L, Ca 1.11–1.40 mmol/L and iPTH 15.9 and 31.8 pmol/L	Adjustments to dialysate Ca and Vit D based on bone biopsy diagnosis	Bone Overall Summary by WG	Overall no clinically important differences between the two treatments.[a]
				Bone Turnover	Not different
				Bone Mineralization	Same
				Bone Volume	Slightly worse (-1.6)
				Absolute increase in CAC score	139 vs. 182 (NS)
				Relative increase in CAC score	45 vs. 55 (NS)
				iCa (mmol/L)	1.28 vs. 1.27 (NS)
				P (mmol/L)	1.71 vs. 1.87 (NS)
				iPTH (pg/mL)	498 vs. 326 (<.005)
				b-ALP (U/L)	38 vs. 28 (<.005)
				25(OH)D (ng/mL)	28 vs. 29 (NS)
Block, 2005[2]	Sevelamer-HCl Protocol per routine care, Ca supplement allowed	Ca-containing binder no specific protocol, changing between types allowed Average elemental Ca: 2300 mg/d	Dialysate Ca 2.5 mmol/L, Vitamin D used but no specific protocol, No calcimimetics	*Mortality (*N = 127)*:* Block 2007, Spiegel 2007	
				All-cause Mortality (N)	11 vs. 23 (nd)
				All-cause Mortality (per 100 patient-year)	5.3 vs. 10.6 (P=.05) HR 0.5 (P=.02)
				Vascular calcification: Block 2005	
				‡ Δ Mean CAC at 12 mo (N = 92)	+87 vs. +169 (.056)
				Δ Mean CAC at 18 mo (N = 85)	+138 vs. +338 (.015)
				Laboratory (mean on treatment values) F/U time unclear Block 2005	
				Corrected Ca (mmol/L)	2.27 vs. 2.40 (≤.05)
				P (mmol/L)	1.68 vs. 1.65 (NS)

				CaXP ($mmol^2/L^2$)	3.79 vs. 3.95 (NS)
				iPTH (pmol/L)	31.6 vs. 25.8 (≤.05)
Block, 2012[4]	All active Mean dose for 5.9 g calcium acetate, 2.7 g lanthanum carbonate & 6.3 g of sevelamer	Placebo	Cholecalciferol 1000 IU daily	Δ Mean P (mg/dl)	-0.3 vs. -0.1 (P=0.03)
				Δ Mean $1,25(OH)_2D$	Reduced with active treatment (P=0.004)
				Δ Mean iPTH	Stable vs. 21% increase (P=0.002)
				Δ Mean cFGF23	(P=0.67)
				Δ Mean iFGF23	(P=0.42)
				Median annual % Δ calcium score	Increased in active group Coronary artery (P=0.05) Abdominal aorta (P=0.03)
				CAC progression	38% vs. 17% (P=0.03)
				Thoracic aorta calcium score	NS
				Annual Δ BMD	(P=0.03)
				AEs	35% vs. 21%
	Lanthanum	Placebo	Same	Δ Mean P (mg/dl)	(P=0.04)
				Mean iFGF23	(P=0.30)
	Sevelamer	Placebo	Same	Δ Mean P (mg/dl)	NS
				Median iFGF23 (pg/ml)	Decrease by 24 in active group (P=0.002)
	Calcium	Placebo	Same	Δ Mean P (mg/dl)	NS
				Median iFGF23 (pg/ml)	Increase by 28 in active group (P=0.03)
Braun, 2004[5] Asmus, 2005[6]	Sevelamer titrated to P 1.0-1.6 mmol/L Ca <2.6 mmol/L and (after 3 mo) iPTH 150-300 pg/mL	Calcium carbonate titrated to P 1.0-1.6 mmol/L Ca <2.6 mmol/L and (after 3 mo) iPTH 150-300 pg/mL Average elemental Ca in year 1: 1560 mg/d	After 3 mo, vitamin D, Ca supplement, dialysate Ca titrated to P 1.0-1.6 mmol/L Ca <2.6 mmol/L and iPTH 150-300 pg/mL Al as rescue binder	*Vascular Calcification at 21 mo, N = 52:* Asmus 2005	
				Δ Mean CaC	+142 vs. +637 (.02)
				Δ Mean AoC	-425 vs. +1697 (.004)
				Valvular Calcification at 21 mo, N = 52: Asmus 2005	
				Δ Mean MVC	-912 vs. +370 (NS)
				Δ Mean AVC	+232 vs. +230 (NS)
				Bone Attenuation by EBCT	

				at 21 mo, N = 50: Asmus 2005	
				Δ Cortical Density (HU)	+0.3 vs. -9.0 (NS)
				Δ Trabecular Density (HU)	+8.0 vs. -12.3 (.0015)
				Laboratory at 24 mo, N = 54: Asmus 2005	
				Mean Ca (mmol/L)	2.2 vs. 2.4 (NS)
				Mean P (mmol/L)	2.0 vs. 1.9 (NS)
				Mean CaXP ($mmol^2/L^2$)	4.0 vs. 4.5 (NS)
				Mean iPTH (pg/mL)	497 vs. 256 (<.001)
Chertow, 2002[7]	Sevelamer titrated to P 3.0-5.0 mg/dL Ca 8.5-10.5 mg/dL and (after 3 mo) iPTH 150-300 pg/mL[a]	USA: Calcium acetate Europe: Calcium carbonate titrated to P 3.0-5.0 mg/dL Ca 8.5-10.5 mg/dL and (after 3 mo) iPTH 150-300 pg/mL[a] Average elemental Ca: USA: 1165 mg/d Europe: 1560 mg/d	After 3 mo, vitamin D, Ca supplement, dialysate Ca titrated to P 3.0-5.0 mg/dL Ca 8.5-10.5 mg/dL and iPTH 150-300 pg/mL Al as rescue binder[a]	Δ Mean MVC	-655 vs. +98 (NS)
				Δ Mean AVC	24 vs. 24 (NS)
				Bone Attenuation by EBCT at 12 mo (N = 111): Raggi, 2005[b]	
				Δ Cortical Density (g/cm^3)	-1 vs. -7 (NS)
				Δ Trabecular Density (g/cm^3)	+3 vs. -6 (.01)
				Laboratory at end of treatment: Chertow 2002	
				Mean Ca (mg/dL)	9.5 vs. 9.7 (.002)
				Hypercalcemia (%)	5% vs. 16% (.04)
				Mean P (mg/dL)	5.1 vs. 5.1 (NS)
				‡ Mean Ca x P (mg^2/dL^2)	48 vs. 49 (NS)
				Median iPTH (pg/mL)	224 vs. 138 (NS)
				Δ CAC	-46 vs. 151 (.04)
				Δ AoC	-532 vs. 185 (.01)
				Laboratory (mean during study): (N = 111) Raggi[b]	
				Mean ALP (mg/dL)	103.0 vs. 81.7 (.002)
				Mean b-ALP (mg/dL)	42.3 vs. 26.8 (<.0001)
De Francisco, 2010[8]	Calcium Acetate 435 mg containing 110 mg elemental calcium combined with magnesium carbonate 235 mg containing 60 mg elemental magnesium (OsvaRen®)	Sevelamer-HCL 800 mg (Renagel®)		P (mmol/L)	Change from baseline: -0.761 (SD 0.5805) vs. -0.711 (SD 0.5850) Treatment difference (LS-Means) -0.0693 mmol/L (97.5% CI: -∞ to 0.0692)
				Ionized Ca (mmol/L)	Change from baseline: 0.036 (SD 0.1702) vs. 0.036 (SD 0.1369) Treatment difference (LS-Means) -0.0015 mmol/L (97.5% CI -0.0294 to 0.0264)

				Total serum Ca (mmol/L)	Change from baseline: 0.071 (SD 0.1790) vs. 0.004 (SD 0.1522) Treatment difference (LS-Means) 0.0477 mmol/L (97.5% CI 0.0162 to 0.0793; P = 0.0032)
				Adverse event	4 vs. 9 (leading to study withdrawal); no difference regarding occurrence of adverse events between groups
				Related gastrointestinal adverse events	13.6% vs. 23.6%
				Related metabolism disorders adverse event	8.8% vs. 2.4%
Di Iorio, 2012[9]	Sevelamer titrated to P 2.7-4.6 mg/dl (G3a-G3b, G4) P 3.5-5.5 mg/dl (G5) Minimum start dose: 1600 mg/dl	Ca carbonate titrated to P 2.7-4.6 mg/dl (G3a-G3b, G4) P 3.5-5.5 mg/dl (G5) Minimum start dose: 2000 mg/dl	NR	Mean Ca (mg/dl)	8.5 vs. 9.6 (NR)
				Mean P (mg/dl)	4.16 vs. 4.72 (<0.01)
				Median iPTH (pg/ml)	180 vs. 250 (<0.01)
				All-cause mortality [HR (95% CI) adjusted for baseline & TVC][c]	0.36 (0.15-0.83)
				Dialysis inception [HR (95% CI) adjusted for baseline & TVC][c]	0.77 (0.45-1.34)
				Composite end-point (death & dialysis)[c] – HR (95% CI)	0.62 (0.40-0.97)
Di Iorio, 2013[10]	Sevelamer titrated to P 2.7-5.5 mg/dl Ca 8.0-9.9 mg/dl iPTH 150-300 pg/ml	Ca carbonate titrated to P 2.7-5.5 mg/dl Ca 8.0-9.9 mg/dl iPTH 150-300 pg/ml	Al as rescue therapy	Mean DID Ca (mg/dl)	-1.37 +/- 0.09 (<0.001)
				Mean DID P (mg/dl)	-0.65 +/- 0.12 (< 0.001)
				Mean DID iPTH (pg/ml)	-173.7 +/- 15.85 (<0.001)
				CV mortality, arrhythmia – HR (95% CI) (p-value)[d]	0.08 (0.02-0.34) (<0.001)
				All-cause CV mortality – HR (95% CI) (p-value)[d]	0.11 (0.05-0.22) (<0.001)
				All-cause mortality – HR (95% CI) (p-value)[d]	0.26 (0.17-0.41) (<0.001)
				Non-CV mortality – HR (95% CI) (p-value)[d] f/u < 24 months f/u ≥ 24 months	2.74 (0.81-9.30) (0.3) 0.19 (0.06-0.61) (0.01)
Ferreira, 2008[11]	Sevelamer Starting dose individualized by substituting prior P binder gram for gram. Dose titrated to achieve serum P of 1.03-	Ca carbonate Starting dose individualized by substituting prior P binder gram for gram. Dose titrated to achieve serum P of 1.03-	Calcitriol or its analog could be titrated to maintain levels of PTH at 15.9-31.8 pmol/L. Choice of Vit D not specified. No parent Vit D/calcidiol was	Bone Overall Summary by WG	Turnover improved more often in placebo biopsies without much difference in mineralization or volume.

	1.61 mmol/L	1.61 mmol/L Average elemental Ca at study completion: 600-2600 mg/d	given.		
				Bone Turnover	Worse (-9.4)
				Bone Mineralization	Same
				Bone Volume	Almost same (+0.9)
				Laboratory	
				Ca (mg/dL)	9.1 vs. 9.3 (NS)
				P (mg/dL)	5.4 vs.5.3 (NS)
				iPTH (pg/mL)	275 vs. 227 (NS)
				25(OH)D (ng/mL)	20.0 vs. 17.4 (NS)
				$1,25(OH)_2D$ (pg/mL)	8.1 vs. 13.7 (NS)
				Bicarbonate (mmol/L)	20.4 vs. 21.2 (NS)
				b-ALP (µg/L)	19.1 vs. 12.7 (NS)
Kakuta, 2011[12]	Sevelamer HCl 250 mg tablets	Calcium carbonate	when serum P level could not be controlled to < 5.6 mg/dL in sevelamer arm, 9 g/day sevelamer and up to 1.5 g/d of precipitated calcium carbonate allowed	Ca corrected (mg/dL)	Mean change from baseline Arm 1: -0.18 (95% CI -0.33 to -0.03; P=0.02) Mean change from baseline Arm 2: 0.14 (95% CI -0.003 to 0.28; P=0.06) Difference in Mean change -0.32 (95% CI -0.52 to -0.12; P=0.002)
				P (mg/dL)	Mean change from baseline Arm 1: -0.50 (95% CI -0.69 to -0.31; P=<0.001) Mean change from baseline Arm 2: -0.61 (95% CI -0.81 to -0.41; P<0.001) Difference in Mean change 0.11 (95% CI -0.17 to 0.38; P=0.08)
				Coronary Artery Calcification Score	Mean change from baseline Arm 1: 81.8 (95% CI 42.9 to 120.6; P<0.001) Mean change from baseline Arm 2: 194.0 (95% CI 139.7 to 248.4; P<0.001) Difference in Mean change -112.3 (95% CI -178.8 to -45.8; P<0.001) OR for >/= 15% increase in

					CACS: Arm 2: 1.00 (Ref); Arm 1: 0.38 (95% CI 0.21 to 0.69; P=0.02)
				Death	0 vs. 0
				Constipation	2 vs. 0
				Persistent increases in serum Ca levels (> 11 mg/dL)	0 vs. 5
Qunibi, 2008[13]	Sevelamer Starting dose was based on P levels and the package inserts and titrated to achieve P level of 1.13-1.78 mmol/L	Ca acetate Starting dose was based on P levels and the package inserts and titrated to achieve P level of 1.13-1.78 mmol/L Average elemental Ca: 1375 mg/d	Atorvastatin Starting dose was 20 mg/d but was subsequently increased to achieve the LDL-C goal of <1.81 mmol/L	*Vascular Calcification:*	
				CAC	1.01 (95% CI 0.86-1.18)[e]
				AoC	1.09 (95% CI 0.87-1.35)[e]
				AVC	1.41 (95% CI 0.92-2.13)[e]
				MVC	1.19 (95% CI 0.79-1.82)[e]
				Δ Mean CAC at 6 mo (N = 139)	97 vs. 109 (NS)
				Δ Mean CAC at 12 mo (N = 126)	227 vs. 228 (NS)
				Mean CAC at 6 mo (N = 139)	996 vs. 1197 (NS)
				% increase in CAC at 6 mo (N = 139)	24 vs. 71
				Mean CAC at 12 mo (N = 126)	1116 vs. 1297 (NS)
				% increase in CAC at 12 mo (N = 126)	57 vs. 52
				Laboratory (N = 129)	
				Ca (mmol/L)	2.25 vs. 2.35 (*)
				P (mmol/L)	1.74 vs. 1.61 (NS)
				Ca x P ($mmol^2/L^2$)	3.87 vs. 3.71 (NS)
				PTH (pmol/L)	46.0 vs. 33.5 (*)
				Bicarbonate (mmol/L)	22 vs. 23 (NS)
				ALP (U/L)	124 vs. 95.1 (NS)
				b-ALP (U/L)	27.2 vs. 18.8 (NS)
Russo, 2007[14]	Sevelamer (Baseline vs. Final)			Mean TCS	415+/-115 vs. 453+/-127 (NS)
				Annualize increase in TCS	36+/-32
				Mean P (mg/dl)	4.5 vs. 4.8 (NS)
				Mean Ca (mg/dl)	9.2 vs. 9.0 (<0.05)
				Mean PTH	136.2vs. 134.9 (NS)
				Mean CaXP (mg^2/dl^2)	41.7 vs. 43.1 (NS)
				ALP(mg/dl)	134.2 vs. 103.4(<0.001)
	Ca carbonate (Baseline vs. Final)			Δ Mean TCS	340+/-38 vs. 473+/-69(NS)
				Annualize increase in TCS	178+/-40
				Mean P (mg/dl)	4.6 vs. 4.7 (NS)

				Mean Ca (mg/dl)	9.0 vs. 9.1 (NR)
				Mean PTH	172.1 vs. 176.1 (NR)
				Mean CaXP (mg^2/dl^2)	42.3 vs. 40.3 (NR)
				ALP(mg/dl)	148 vs. 143 (NS)
	Control (Baseline vs. Final)			∆ Mean TCS	369+/-115 vs. 547+/- (P<0.001)
				Annualize increase in TCS	205+/-82
				Mean P (mg/dl)	3.9 vs. 3.9 (NS)
				Mean Ca (mg/dl)	9.2 vs. 9.3(NS)
				Mean PTH	140.7 vs. 146.9 (NS)
				Mean CaXP (mg^2/dl^2)	35.8 vs. 36.0 (NS)
				ALP(mg/dl)	113.7 vs 85.1 (<0.05)
	Sevelamer / Calcium carbonate	Control		Absolute TCS & Annualized progression of TCS	NS
Suki, 2008[16] Suki, 2007[15]	Sevelamer (N=549, completed study) Mean dose: 6.9 g for sevelamer	Ca acetate or Ca carbonate (N=516, completed study) Mean dose: 5.3 g for calcium acetate, 4.9 g for calcium carbonate	NR	Mean Ca (mg/dl)[f]	9.2 vs. 9.5 (<0.0001)
				Mean P (mg/dl)[f]	5.8 vs. 5.7 (<0.01)
				Median iPTH (pg/ml)[f]	278 vs. 226 (<0.0001)
				Mean Ca x P (mg^2/dl^2)	53.7 vs. 53.6 (0.60)
				All-cause mortality [HR (95% CI)] ≥65 years of age <65 years of age	0.92 (0.78-1.09) (0.40) 0.77 (0.62-0.97) (0.02) 1.16 (0.88-1.49) (0.21)
				CV mortality [HR (95% CI)] ≥65 years of age	0.92 (0.73-1.16) (0.53) 0.79 (0.59-1.07) (0.10)
				Mortality due to infections (Rates/100 person year)	2.6 vs. 2.4 (0.68)
				Number of hospitalizations, mean Number of hospitalizations ≥65 years of age, mean Duration (days) of hospitalizations, mean Duration (days) of hospitalizations ≥65 years of age, mean	2.1 +/- 4.4 vs 2.3+/-4.9 (P=0.06) 2.1+/-2.8 vs 2.9+/-6.7 (P=0.03) 14.8 +/-27.9 vs. 17.4 +/- 32.0 (P=0.09) 16.6+/-27.9 vs. 21.8+/-36.0 (P=0.08)
Yubero-Serrano, 2015[17]	Sevelamer carbonate (1600 mg three times daily)	Calcium carbonate (1200 mg three times daily)	Cholecalciferol	Mean differences after treatment, eGFR ($ml/min/1.73m^2$)	-0.048 (95% CI: -0.16 to 0.07) (p=0.40)
Lanthanum carbonate vs. other treatments					
D'Haese, 2003[18]	Lanthanum carbonate	Ca carbonate		Nausea	10% vs. 4%
				Vomiting	14% vs. 10%
				Diarrhea	8% vs. 8%
				Constipation	10% vs. 16%

				Hypercalcemia (>2.65 mmol/L)	6% vs. 49%
				Hypocalcemia	24% vs. 10%
				All AE	96% vs. 96%
				Gastrointestinal	53% vs. 49%
				SAE	64 events vs. 64 events
				Mean bone La:	1.77 µg/g vs. 0.06 µg/g
				Total discontinued due to AE	24% vs. 22%
				Adynamic bone disease	4% vs. 26%
Finn, 2006[19]	Lanthanum carbonate initiated at 750 or 1500 mg/d, adjusted[a]	Pre-study phosphate binder(s) and dosing regimen[b]	Ca supplementation for hypocalcemic patients. No maximum daily dose of Ca was specified.	% with *P* ≤1.90 mmol/L (≤5.9 mg/dL)	46% vs. 49% (P=0.5)
				Mean Ca (mmol/L)	2.35 vs. 2.40 (NR)[g]
				Mean P (mmol/L)	1.97 vs. 1.94 (NR)[g]
				Median PTH (pmol/L)	21.3 vs. 14.5 (NR)[g]
				ALP (U/L)	117.5 vs. 108.6 (NR)
				b-ALP (ng/mL)	25.2 vs. 20.3 (NR)
				Gastrointestinal AE Nausea Vomiting Diarrhea Abdominal pain	 37% vs. 29% 27% vs. 22% 24% vs. 24% 17% vs. 18%
				Hypercalcemia	4.3% vs. 8.4%
				Total D/C due to AE	14% vs. 4%
				Deaths	6% vs. 14%
Hutchison, 2005[20] Hutchison, 2006[21]	Lanthanum carbonate	Ca carbonate		Nausea	16% vs. 13%
				Vomiting	18% vs. 11%
				Diarrhea	13% vs. 10%
				Constipation	6% vs. 7%
				Hypercalcemia	<1% vs. 20%[b]
				1 measurement > upper limit of normal	6% vs. 38%
				All AE	78% vs. 80%
				AE reported in ≥5% of pts	
				Mean plasma La	0.55 ng/mL vs. 0.01-0.03 ng/mL
				Modality change	2% vs. 4%
Malluche, 2008[22]	Lanthanum carbonate at 750 or 1500 mg/d to achieve P ≤1.91 mmol/L	Prestudy P binder reinstituted at prestudy dose	Calcitriol or Vit D analog supplementation allowed in both groups according to the investigator discretion to maintain serum PTH levels within the KDOQI guidelines. Ca supplementation allowed	Bone overall summary by WG	Overall no change seen at year one. At year two results favor lanthanum with better turnover.

			for hypocalcemic patients in La arm.		
				Bone Turnover Year 1 Year 2	 Same (+2) Better (+35)
				Bone Mineralization Year 1 Year 2	 Same Same
				Bone Volume Year 1 Year 2	 Same Slightly better (+1.3)
				Mean Ca (mmol/L)	2.4 vs. 2.0 (nd)
				Mean P (mmol/L)	1.49 vs. 2.03 (nd)
				Median PTH (pmol/L)	25.5 vs. 8.5 (nd)
				b-ALP (ng/mL)	33.6 vs. 8.3 (nd)
				Osteocalcin (ng/mL)	451.9 vs. 241.6 (nd)
Wilson, 2009[23]	Lanthanum carbonate at 750 or 1500 mg/d to achieve P ≤1.91 mmol/L	Prestudy P binder reinstituted at prestudy dose	Calcitriol or Vit D analog supplementation allowed in both groups according to the investigator discretion to maintain serum PTH levels within the KDOQI guidelines. Ca supplementation allowed for hypocalcemic patients in La arm.	Overall Mortality	19.9% vs. 23.3% (log-rank p = 0.18; HR 0.86; 95% CI 0.68 to 1.08)
				Hypercalcaemia	3.8% vs. 7.5%
Ferric citrate vs. (Calcium acetate &/OR Sevelamer carbonate)					
Van Buren, 2015[25] Lewis, 2015[24]	Ferric citrate 210 mg	Active control Calcium, 667 mg or Sevelamer, 800 mg	Vitamin D & its analogs, fasting calcium supplements, variations in dialysate calcium concentration were permitted during the study at the discretion of the treating physician	Mean (SD) phosphate at 52 weeks, mg/dL Ferric citrate vs. sevelamer Ferric citrate vs. calcium acetate	 5.4 (1.6) vs. 5.4 (1.7) (P=0.94) 5.4 (1.6) vs. 5.3 (1.4) (P=0.84)
				Δ Mean P (mg/dL) Adjusted between-group difference	-2.04 vs -2.18 (p=0.9) 0.01 (95% CI: -0.30 to 0.33) (P=0.95)
				Δ Mean C (mg/dL) Adjusted between-group difference	0.22 vs 0.31 (p=0.2) -0.12 (95% CI: -0.28 to 0.04) (P=0.16)
				Δ Mean iPTH (mg/dL) Adjusted between-group difference	-167.1 vs -146.5 (p=0.9) 4.3 (95% CI: -61.5 to 70.0) (P=0.90)
				Deaths	13 (4.5%) vs. 8 (5.4%)

				Hospitalization	34.6% vs 45.6%
				Fractures	0 vs 0
				Cardiac events	7.3% vs 12.1 % (p=0.1)
				Kidney transplant	4.2% vs 4.0% (p=0.9)
				Gastrointestinal events	6.9% vs 12.8% (p=0.05)

AE, adverse event; AoC, aortic calcification; ALP, alkaline phosphatase; AVC, aortic valve calcification; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; Ca, calcium; CAC, coronary artery calcification; CI, confidence interval; TAC, Thoracic aorta calcification; AAC Abdominal Aorta Calcification; CaXP, calcium-phosphate product; CKD-MBD, chronic kidney disease-mineral and bone disorder; DID, difference in differences; DM, diabetes mellitus; EBCT, electron-beam CT; eGFR, estimated glomerular filtration rate; g/cm^3, grams per centimeter cubed; g, grams; HCL, hydrochloride; NR, not reported; IU, international unit; iPTH, intact parathyroid hormone; MBD, mineral and bone disease; mg/dL, milligrams per deciliter; mmol/L, millimoles per liter; ml/min, milliliters per minute; mg, milligrams; MVC, medial vascular calcification; N, number of subjects; nd, not documented; ng/mL, nanograms per milliliter; NS, not specified; pmol/L, picomoles per liter; P, phosphate; pg/mL, picogram per milliliter; PTH, parathyroid hormone; SD, standard deviation; SAE, serious adverse event; TVC, Time varying covariates; U/L, units per liter; ug/g, microgram per gram; f/u, follow up; HR, hazard ratio; CV, Cardiovascular; TCS, Total Calcium Score; USA, United State of America; 25(OH)D, 25-hydroxyvitamin D

a. During the first 12 weeks dose of study drug [sevelamer-HCl in 800 mg tablets or Ca acetate (US patients) in 667 mg tablets or Ca carbonate (European patients) in 500 mg tablets] are titrated every 3 wk to achieve P 1.0-1.6 mmol/L and Ca 2.12-2.6 mmol/L. After titration phase, study drug, vitamin D, vitamin D analogs, or dialysate Ca were titrated every 4 wk to P and Ca targets as well as PTH 15.9-31.8 pmol/L. Aluminum allowed as rescue binder if CaXP >5.81 mmol^2/L^2.
b. Raggi P, James G, Burke SK, *et al.* Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. *J Bone Miner Res* 2005; **20:** 764-772.
c. Baseline time invariant covariates were age, sex, diabetes, hypertension, basal creatinine clearance, and baseline coronary artery calcification (CAC) score. Time-varying covariates (TVC) were serum concentration of calcium, phosphate, intact parathyroid hormone, cholesterol (total and LDL), triglycerides, C-reactive protein, creatinine clearance, systolic and diastolic BP, and CAC score. These variables were measured every 6 months during the follow-up. Covariates included in the final model were age, sex, diabetes, hypertension, basal and time-varying values of creatinine clearance, CAC score, calcium, intact parathyroid hormone, cholesterol, and C-reactive protein.
d. Adjusted model was adjusted for C-reactive protein level, serum phosphate level and coronary artery calcification at baseline and time-varying C-reactive protein level; serum phosphate level and coronary artery calcification.
e. Values are the geometric mean of the sevelamer to calcium acetate ratio of day-360 to screening ratio in electron-beam computed tomography calcification scores.
f. The lab values are reported weighted average of post baseline
g. Estimated from the graph

Supplemental Table 22. Summary table of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Sevelamer vs. other treatment								
Barreto, 2008[1]	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes
Block, 2005[2]	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Block, 2012[4]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Braun, 2004[5] Asmus, 2005[6]	Unclear	Unclear	No	No	Yes	Yes	Unclear	Yes
Chertow, 2002[7]	Yes	No	No	No	Yes	Yes	Unclear	Yes
De Francisco, 2010[8]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Di Iorio, 2012[9]	Yes	Yes	No	No	Yes	Yes	Unclear	Yes
Di Iorio, 2013[10]	Unclear	Yes	No	No	Yes	Yes	Yes	Yes
Ferreira, 2008[11]	Yes	Unclear	No	No	Unclear	Yes	Yes	Unclear
Kakuta, 2011[12]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Qunibi, 2008[13]	Yes	Unclear	No	No	Yes	Yes	Yes	Unclear
Russo, 2007[14]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes
Suki, 2007[15] Suki, 2008[16]	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	Unclear
Yubero-Serrano, 2015[17]	Unclear	Unclear	No	No	No	No	Unclear	Unclear
Lanthanum carbonate vs. other treatment								
D'Haese, 2003[18]	Yes	Unclear	No	No	Unclear	Unclear	Unclear	Unclear
Finn, 2006[19]	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	Unclear
Hutchison, 2005[20] Hutchison, 2006[21]	Yes	Yes	No	No	Unclear	Yes	Yes	Yes
Malluche, 2008[22]	Unclear	Yes	No	No	Yes	Yes	Yes	Unclear
Wilson, 2009[23]	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear
Ferric citrate vs. (calcium acetate &/or sevelamer carbonate)								
Van Buren, 2015[25]	Unclear	Unclear	No	No	Unclear	No	Unclear	Unclear
Lewis, 2015[24]	Yes	No	No	No	No	Yes	No	Unclear

CKD-MBD = chronic kidney disease-mineral bone disorder

Supplemental Table 23. Evidence matrix of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U
Mortality				Di Iorio 2012 Di Iorio 2013	239 (105) 466 (234)	36 mo 36 mo	Suki 2008 Finn 2006 Van Buren 2015	2103 (1050) 1359 (677) 441 (292)	45 mo 24 mo 12 mo
Cardiovascular and cerebrovascular events				Di Iorio 2013	466 (234)	36 mo	Suki 2008 Van Buren 2015	2103 (1050) 441 (292)	45 mo 12 mo

CKD-MBD = chronic kidney disease-mineral bone disorder; F/U = follow-up

Supplemental Table 24. Evidence profile of randomized controlled trials examining the treatment of CKD-MBD with calcium-containing phosphate binders vs. calcium-free phosphate binders

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	5 RCTs	4608 (2358)	Moderate	Consistent	Direct	One of the studies compared ferric citrate with sevelamer or calcium acetate.	Moderate	Possibly lower mortality with non-calcium-containing phosphate binders	Critical
Cardiovascular and cerebrovascular events	3 RCTs	3010 (1576)	Moderate	Inconsistent	Direct	One of the studies compared ferric citrate with sevelamer or calcium acetate.	Low	Two of the studies evaluated CVD mortality. One showed significantly less CVD mortality due to arrhythmias, but the other study suggested no difference. The third study reported no difference in cardiac events.	Critical

CKD-MBD = chronic kidney disease-mineral bone disorder; CVD = cardiovascular disease; RCT = randomized controlled trial; ROB = risk of bias

REFERENCES

1. Barreto DV, Barreto Fde C, de Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Phosphate binder impact on bone remodeling and coronary calcification--results from the BRiC study. Nephron Clin Pract. 2008;110(4):c273-83.

2. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005 Oct;68(4):1815-24.

3. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int. 2007 Mar;71(5):438-41.

4. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol. 2012 Aug;23(8):1407-15.

5. Braun J, Asmus HG, Holzer H, Brunkhorst R, Krause R, Schulz W, et al. Long-term comparison of a calcium-free phosphate binder and calcium carbonate--phosphorus metabolism and cardiovascular calcification. Clin Nephrol. 2004 Aug;62(2):104-15.

6. Asmus HG, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, et al. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant. 2005 Aug;20(8):1653-61.

7. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002 Jul;62(1):245-52.

8. de Francisco AL, Leidig M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrol Dial Transplant. 2010 Nov;25(11):3707-17.

9. Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. Clin J Am Soc Nephrol. 2012 Mar;7(3):487-93.

10. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. Am J Kidney Dis. 2013 Oct;62(4):771-8.

11. Ferreira A, Frazao JM, Monier-Faugere MC, Gil C, Galvao J, Oliveira C, et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. J Am Soc Nephrol. 2008 Feb;19(2):405-12.

12. Kakuta T, Tanaka R, Hyodo T, Suzuki H, Kanai G, Nagaoka M, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. Am J Kidney Dis. 2011 Mar;57(3):422-31.

13. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis. 2008 Jun;51(6):952-65.

14. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int. 2007 Nov;72(10):1255-61.

15. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int. 2007 Nov;72(9):1130-7.

16. Suki WN. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. J Ren Nutr. 2008 Jan;18(1):91-8.

17. Yubero-Serrano EM, Woodward M, Poretsky L, Vlassara H, Striker GE. Effects of sevelamer carbonate on advanced glycation end products and antioxidant/pro-oxidant status in patients with diabetic kidney disease. Clin J Am Soc Nephrol. 2015 May 7;10(5):759-66.

18. D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int Suppl. 2003 Jun(85):S73-8.

19. Finn WF. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. Clin Nephrol [serial on the Internet]. 2006; (3): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/486/CN-00563486/frame.html.

20. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract. 2005;100(1):c8-19.

21. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al. Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. Nephron Clin Pract [serial on the Internet]. 2006; (2): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/537/CN-00552537/frame.html.

22. Malluche HH, Siami GA, Swanepoel C, Wang GH, Mawad H, Confer S, et al. Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clin Nephrol. 2008 Oct;70(4):284-95.

23. Wilson R, Zhang P, Smyth M, Pratt R. Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. Curr Med Res Opin. 2009 Dec;25(12):3021-8.

24. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol. 2015 Feb;26(2):493-503.

25. Van Buren PN, Lewis JB, Dwyer JP, Greene T, Middleton J, Sika M, et al. The Phosphate Binder Ferric Citrate and Mineral Metabolism and Inflammatory Markers in Maintenance Dialysis Patients: Results From Prespecified Analyses of a Randomized Clinical Trial. Am J Kidney Dis. 2015 Sep;66(3):479-88.

26. De Sevaux RG, Hoitsma AJ, Corstens FH, Wetzels JF. Treatment with vitamin D and calcium reduces bone loss after renal transplantation: a randomized study. J Am Soc Nephrol. 2002 Jun;13(6):1608-14.

27. Fishbane S, Shapiro WB, Corry DB, Vicks SL, Roppolo M, Rappaport K, et al. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol. 2008 Nov;3(6):1718-25.

28. Mose FH, Vase H, Larsen T, Kancir AS, Kosierkiewic R, Jonczy B, et al. Cardiovascular effects of cholecalciferol treatment in dialysis patients--a randomized controlled trial. BMC Nephrol. 2014;15:50.

29. Wissing KM, Broeders N, Moreno-Reyes R, Gervy C, Stallenberg B, Abramowicz D. A controlled study of vitamin D3 to prevent bone loss in renal-transplant patients receiving low doses of steroids. Transplantation. 2005 Jan 15;79(1):108-15.

30. Wetmore JB, Gurevich K, Sprague S, Da Roza G, Buerkert J, Reiner M, et al. A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM). Clin J Am Soc Nephrol. 2015 Apr 22.

KDIGO: CKD-MBD Update
Summary of Results for Limiting Dietary Phosphate

Research question 4.1.7: In patients with CKD G3a-G5D with hyperphosphatemia, what is the evidence for benefit or harm in limiting dietary phosphate compared with a standard diet in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 25. Summary table of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality	Follow up duration	Funding source
Lou, 2012[1]	Spain	91	Dialysis	HD	6 months	NR
Karavetian, 2015[2]	Lebanon	570	Dialysis	HD	6 months	Government

CKD = chronic kidney disease HD = hemodialysis; NR = not reported

Supplemental Table 26. Summary table of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs
Lou, 2012[1]	Intensive dietary education n=41	61	51	NR	NR (serum creatinine – 8.6 mg/dL) NR	20 NR NR	P 7.1 mg/dL Ca 9.5 mg/dL Ca X P 67.9 mg^2/dL^2 iPTH 428 pg/mL
	Usual dietary recommendations (control) n=39	63	54	NR	NR (serum creatinine – 8 mg/dL) NR	22 NR NR	P 6.8 mg/dL Ca 9.4 mg/dL Ca X P 63.8 mg^2/dL^2 iPTH 491 pg/mL
Karavetian, 2015[2a]	Dietitian dedicated n=133	57	55	NR	NR NR	39 64 NR	Serum P 5.6 mg/dl PTH 401 pg/ml Dietary P 796 mg/d
	Usual care (control) n=138	60	57	NR	NR NR	36 69 NR	Serum P 5.4 mg/dl PTH 382 pg/ml Dietary P 786 mg/d
	Trained hospital dietitian n=299	60	58	NR	NR NR	34 67 NR	Serum P 5.2 mg/dl PTH 345 pg/ml Dietary P 756 mg/d

Ca X P = calcium-phosphate product; Ca = calcium; DM = diabetes mellitus; HC = hypercholesterolemia; HTN = hypertension; MBD = mineral bone disorder; NR = not reported; mg/dL = milligrams per deciliter; pg/mL = picogram per milliliter; P = phosphate; PTH = parathyroid hormone

a. Baseline characteristics are reported in Karavetian M, De Vries N, El Zein H. Nutritional education for management of osteodystrophy in hemodialysis patients (NEMO) trial program, Lebanon: design and patient characteristics. Nutr Res Pract 2014;8:103–11.

Supplemental Table 27. Summary table of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate – results

Author, year	Arm 1	Arm 2	Arm 3	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Lou, 2012[1]	Intensive dietary education	Usual dietary recommendations (control)		Phosphate binders (100% in arm 1 and 100% in arm 2), vitamin D (61% in arm 1 and 63% in arm 2)	Change in mean serum phosphate between baseline and follow-up	-1.67 vs. -0.58 mg/dL; adjusted* mean between-group difference 0.93 mg/dL (95% CI 0.34 to 1.52; p=0.003)
					Serum phosphate <5.5 mg/dL at follow-up	51% vs. 18%, p=0.002; adjusted* OR 11 (95% CI 2.7 to 44.2, p=0.001)
					Serum phosphate <5 mg/dL at follow-up	31.7% vs. 15.4%, p=0.08; adjusted* OR 4.1 (95% CI: 1.06 to 16.3, p=0.04)
Karavetian, 2015[2]	Dietitian dedicated N=133	Usual care (control) N=138	Trained hospital dietitian N=299	NR	Serum P, baseline (mmol/L)	1.79 vs 1.72 vs 1.67
					Serum P, post 6 months (mmol/L)	1.70 vs 1.82 vs 1.65 Change from baseline in dietitian dedicated arm significant, p=0.012

CI, confidence interval; CKD-MBD, chronic kidney disease-mineral and bone disorder; mg/dL, milligrams per deciliter; mmol/L, millimoles per liter; NA, not applicable; NR, not reported; OR, odds ratio; P, phosphate

* Adjusted for age, gender, change in phosphate binder treatment at follow-up, initial phosphate intake, and baseline serum phosphate levels.

Supplemental Table 28. Summary table of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Lou, 2012[1]	No	Unclear	No	Unclear	Unclear	Yes	Unclear	Yes
Karavetian, 2015[2]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear

Supplemental Table 29. Evidence matrix of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate

	Risk of Bias											
	Low			Moderate			High			Adverse events (no grade)		
Outcome	Author	*N* (on agent)	Follow up	Author	*N* (on agent)	Follow up	Author	*N* (on agent)	Follow up	Author	*N*	Follow up
Mortality												
Cardiovascular and cerebrovascular events												
Vascular and valvular calcification												
Bone histology, bone mineral density												
Measures of glomerular filtration rate												
Hospitalizations												
Quality of life												
Kidney or kidney graft failure												
Fracture												
Parathyroidectomy												
Growth, skeletal deformities, bone accrual												
Calciphylaxis/ calcific uremic arteriolopathy												
Serum phosphate							Lou, 2012 Karavetian 2015	91 (41) 570 (133)	6 months 6 months			

Supplemental Table 30. Evidence profile of randomized controlled trials examining the treatment of CKD-MBD with dietary phosphate

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0						Very low		
Cardiovascular and cerebrovascular events	0						Very low		
Vascular and valvular calcification imaging	0						Very low		

ROB = risk of bias

REFERENCES

1. Lou LM, Caverni A, Gimeno JA, Moreno R, Perez J, Alvarez R, et al. Dietary intervention focused on phosphate intake in hemodialysis patients with hyperphosphoremia. Clin Nephrol. 2012 Jun;77(6):476-83.

2. Karavetian M, de Vries N, Elzein H, Rizk R, Bechwaty F. Effect of behavioral stage-based nutrition education on management of osteodystrophy among hemodialysis patients, Lebanon. Patient Educ Couns. 2015 Sep;98(9):1116-22.

KDIGO: CKD-MBD Update
Summary of Results for Treatments for High PTH

Research question 4.2.1: In patients with CKD G3a-G5 with levels of intact PTH above the upper normal limit of the assay, what is the evidence for benefit or harm in reducing dietary phosphate intake or treating with phosphate-binding agents, calcium supplements, or native vitamin D in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 31. Summary table of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Phosphate binding agents vs. other treatment						
Block, 2012[1]	USA	148	GFR 20-45 mg/dl	NA NA	9 mo	Industry
Chue, 2013[2]	UK	109	G3a-G3b (eGFR = 30 to 59 ml/min per 1.73 m^2)	NR	36 weeks (after 4 weeks open label run in)	Industry
Lemos, 2013[3]	Brazil	117	eGFR mean 35.6 ml/min/1.73 m^2	NR	24 mo	Industry
Cholecalciferol vs. other treatment						
Oksa, 2008[4]	Slovakia	87	G2 to G4	NR	12 mo	Government

CKD = chronic kidney disease; COI = conflict of interest; eGFR = estimated glomerular filtration rate; HD = hemodialysis; ml/min = milliliters per minute; m = meters; NR = not reported; PD = peritoneal dialysis; UK = United Kingdom; USA = United States of America

a. In almost half of the patients enrolled, the dialysate concentration had been reduced to 2.5 mEq/L at 12 mo.

Supplemental Table 32. Summary table of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function (mean baseline eGFR) Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
Phosphate binding agents vs. other treatments									
Block, 2012[1]	Sevelamer N=30	66	50	White 80 Black 7	32 NA	53 97 97	Ca 9.3 mg/dl P 4.2 mg/dL Median iPTH 70 pg/mL $1,25(OH)_2D$ 24.7	Mean L2-L4 BMD 111 g/cm^2	Median CAC 362.5 Median TAC 536 Median AAC 1367
	Calcium acetate N=28	68	47	White 80 Black 17	30 NA	57 97 83	Ca 9.3 gm/dl P 4.2 mg/dl iPTH 76 pg/ml (median) $1,25(OH)_2D$ 25.5	L2-L4[f] BMD (Mean) 120	Median CAC[e] 130 Median TAC[e] 511 Median AAC[e] 1468
	Lanthanum N=30	70	54	White 82 Black 7	33 NA	57 100 86	Ca 9.2 mg/dl P 4.2 mg/dl iPTH 87 pg/ml (median) $1,25(OH)_2D$ 26.9	L2-L4 [f] BMD (Mean) 99	Median CAC[e] 216.5 Median TAC[e] 1609 Median AAC[e] 4035
	Placebo N=57	65	49	White 79 Black 11	30 NA	58 100 93	P 4.2 mg/dl iPTH 91 pg/ml (median) $1,25(OH)_2D$ 27.2	L2-L4 [f] BMD (Mean) 108	Median CAC[e] 225 Median TAC[e] 496 Median AAC[e] 1693
Chue, 2013[2]	Sevelamer, 55	55	58	NR	49 ml/min per $1.73m^2$	NR	Ca 8.88 mg/dl corrected P 3.16 mg/dl PTH 52 pg/ml log transformed before analysis LV mass index 52 g/m^2	DXA	NR
	Placebo, 54	54	52	NR	49 ml/min per $1.73m^2$	0	Ca 8.80 mg/dl corrected P 3.25 mg/dl PTH 54 pg/ml log transformed before analysis LV mass index 51 g/m^2	DXA	NR
Lemos, 2013[3]	Rosuvastatin, 22	58.4	45	NR	39.7	18	P 3.7 mg/dl Ca ionized 1.31 mmol/L iPTH 100.0 pg/mL	Multi-slice computer tomography scanner	Baseline calcium score 170.5 AU

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function (mean baseline eGFR) Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
	Sevelamer HCl, 26	58.2	65	NR	39.8	27	P 3.6 mg/dl Ca ionized 1.29 mmol/L iPTH 74.0 pg/mL	Multi-slice computer tomography scanner	Baseline calcium score 266.7 AU
	Control, 29	57.4	69	NR	37.2	17	P 3.6 mg/dl Ca ionized 1.28 mmol/L iPTH120 pg/mL	Multi-slice computer tomography scanner	Baseline calcium score 371.7 AU
Cholecalciferol vs. other treatments									
Oksa, 2008[4]	Cholecalciferol low dose, 44	66	43	NR	43 ml/min/1.73 m^3 CKD G2: 8 G3a-G3b: 24 G4: 11	NR	Ca 2.32 mmol/L P 1.14 mmol/L 25(OH)D 15 ng/ml $1,25(OH)_2$ 21 pg/ml iPTH 63 pg/ml		
Oksa, 2008[4]	Cholecalciferol high dose, 43	66	33	NR	51 ml/min/1.73 m^3 CKD G2: 17 G3a-G3b: 20 G4: 6	NR	Ca 2.29 mmol/L P 1.13 mmol/L 25(OH)D 16 ng/ml $1,25(OH)_2$ 29 pg/ml iPTH 50 pg/ml		

ALP = alkaline phosphatase; AoC = aortic calcification; AU = Agatson units; AVC = aortic valve calcification; BMD = bone mineral density; Ca = calcium; CAC = coronary artery calcification; CKD = chronic kidney disease; DM = diabetes mellitus; DXA = dual-energy x-ray absorptiometry; EBCT = electron-beam computed tomography; HC = hypercholesterolemia; HCl = hydrochloride; HTN = hypertension; iPTH = intact parathyroid hormone; LV = left ventricular; MBD = mineral bone disorder; ml/min = milliliters per minute; mmol/L = millimoles per liter; MVC = mitral valve calcification; NA = not applicable; NR = not reported; P = phosphate; 25(OH)D = 25-hydroxyvitamin D

a. By MSCT.
b. Estimated from graph.
c. T-score: -0.71 (-1.20); Z-score: -0.30 (-0.81) [P <0.05].
d. P ≤0.01.
e. T-score: -0.55 (-1.45) [P <0.01]; Z-score: -0.22 (-1.14) [P <0.01].
f. based on baseline (post-washout) and as medians

Supplemental Table 33. Summary table of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD – results

Author, year	Arm 1	Arm 2	Arm 3	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (p-value)
Phosphate binding agents vs. other treatments						
Block, 2012[1]	All active Mean dose for 5.9 g calcium acetate, 2.7 g lanthanum carbonate & 6.3 g of sevelamer	Placebo		Cholecalciferol 1000 IU daily	Δ Mean P (mg/dl)	-0.3 vs. -0.1 (P=0.03)
					Δ Mean $1,25(OH)_2D$	Reduced with active treatment (P=0.004)
					Δ Mean iPTH	Stable vs. 21% increase (P=0.002)
					Δ Mean cFGF23	(P=0.67)
					Δ Mean iFGF23	(P=0.42)
					Median annual % Δ calcium score	Increased in active group Coronary artery (P=0.05) Abdominal aorta (P=0.03)
					CAC progression	38% vs. 17% (P=0.03)
					Thoracic aorta calcium score	NS
					Annual Δ BMD	(P=0.03)
					AEs	35% vs. 21%
	Lanthanum	Placebo		Same	Δ Mean P (mg/dl)	(P=0.04)
					Mean iFGF23	(P=0.30)
	Sevelamer	Placebo		Same	Δ Mean P (mg/dl)	NS
					Median iFGF23 (pg/ml)	Decrease by 24 in active group (P=0.002)
	Calcium	Placebo		Same	Δ Mean P (mg/dl)	NS
					Median iFGF23 (pg/ml)	Increase by 28 in active group (P=0.03)
Chue, 2013[2]	Sevelamer 1600 mg with meals; dose reduced to 800 mg with meals if persistent adverse effects of hypophosphatemia occurred. All patients received 1600 mg for 4 week run in	Placebo With meals All patients received 1600 mg for 4 week run in			LV mass index (g/m^2)	52 vs. 51 (Mean difference in change between groups -0.07; 95% CI: -1.71 to 1.58; P= 0.58)
					Corrected Ca (mg/dl)	8.84 vs. 8.76 (Mean difference in change between groups 0.00; 95% CI: -0.14 to 0.15)
					P (mg/dl)	3.16 vs. 3.31 ((Mean difference in change between groups 0.06;

Author, year	Arm 1	Arm 2	Arm 3	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (p-value)
						95% CI: -0.18 to 0.30)
					PTH (pg/ml)	52 vs. 51 (Mean difference in change between groups -3.1; 95% CI: -10.4 to 4.3)
					Mean GFR (mL/min/1.73 m^2)	48 vs. 50 (Mean difference in change between groups 1.2; 95% CI: -1.3 to 3.6)
					BMD lumbar spine (g/cm^2)	1.06 vs. 1.14 (Mean difference in change between groups 0.00; 95% CI: -0.01 to 0.01)
					BMD hips (g/cm^2)	1.00 vs. 10.3 (Mean difference in change between groups 0.01; 95% CI: -0.04 to 0.05)
					Hypophosphatemia requiring dose reduction (n)	4 vs. 3 (P = 0.70)
					Persistent hypophosphatemia, n	3 vs. 1
					Hospitalization, n	6 vs. 4
					Deaths, n	0 vs. 0
					Aortic Calcification	48% total patients (not specified; written in text p. 848)
Lemos, 2013[3]	Rosuvastatin 10 mg tablets fixed dose per day	Sevelamer HCl 800 mg tablets dose 2,400 mg/day (800 mg 3x/day)	Control	Pts in all groups were using ACE inhibitors, diuretics, Beta-blockers, calcitriol, and calcium channel blockers; in Arm 1 and 3, some patients using Ca Carbonate	Mean eGFR (ml/min/1.73 m^3) at 24 months	37.4 vs. 36.8 vs. 32.2
					Mean P (mg/dl) at 24 months	3.5 vs. 3.5 vs. 3.3
					Mean Ca ionized (mmol/L) at 24 months	1.33 vs. 1.32 vs. 1.30 (all NS vs. baseline control)
					Mean iPTH (pg/ml) at 24 months	94.0 vs. 75.5 vs. 116.0
					Mean CAC (AU) at 24 months	269.8 vs. 413.8 vs. 462.4 (P = 0.59 between groups); drug effect p = 0.85; time effect p>0.001; interaction p=0.76 for drug regimens impact on progression of CAC
					Hypocalcemia, n	0 vs. 0 vs. 0
					Hypophosphatemia, n	0 vs. 0 vs. 3
					Hyperphosphatemia	13.2% vs. 7.9% vs. 17.1 % (p = 0.47)

Author, year	Arm 1	Arm 2	Arm 3	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (p-value)
					Hypercalcemia	5.3% vs. 2.4% vs. 0% (p=0.34)
Cholecalciferol vs. other treatments						
Oksa, 2008[4]	Cholecalciferol 5,000 IU/week	Cholecalciferol 20,000 IU/week		Lower dose (approximately 700 IU/day) common supplementary dose for prevention of vitamin D deficiency	Median Ca (mmol/L) at 12 months	2.31 vs. 2.30
					Median P (mmol/L) at 12 months	1.20 vs. 1.18 (p<0.01 for comparison to baseline Arm 2)
					Median 25(OH)D (ng/ml) at 12 months	28 vs. 37 (p<0.01 for between group and p<0.0001 for comparison to baseline in Arm 1 and Arm 2)
					Median $1,25(OH)_2D$ (pg/ml) at 12 months	25 vs. 25
					Median iPTH (pg/ml) at 12 months	48 vs. 40 (p<0.0001 for comparison with baseline for Arm 1 and Arm 2)

ACE = angiotensin-converting enzyme; AE = adverse events; Al = aluminum; ALP = alkaline phosphatase; AoC = aorta calcification; AVC = aortic valve calcification; BMD = bone mineral density; Ca = calcium; CaC = coronary artery calcification; CI = confidence interval; CV = cardiovascular; EBCT = electron-beam computed tomography; g/m = grams per meter; GFR = glomerular filtration rate; HR = hazard ratio; HRQOL = health-related quality of life; HU = Hounsfield units; iPTH = intact parathyroid hormone; IU = international unit; LV = left ventricular; mg = milligrams; mg/dL = milligrams per deciliter; mmol/L = millimoles per liter; MVC = mitral valve calcification; ng/mL = nanograms per milliliter; NS = not significant; OR = odds ratio; P = phosphate; pg/mL = picogram per milliliter; SD = standard deviation

a. No significant change in bone mineralization in either group overall, but improvement in low turnover group that was similar in both treatments. Significant but slight improvement in bone volume with calcium. There was no change with sevelamer-HCl.

b. Estimated from graph.

c. Calculated from table.

Supplemental Table 34. Summary table of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD– quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Phosphate binding agents vs. other treatments								
Block, 2012[1]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Chue, 2013[2]	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear
Lemos, 2013[3]	No	Yes	No	No	No	Yes	Yes	Unclear
Cholecalciferol vs. other treatments								
Oksa, 2008[4]	Unclear	Yes	No	No	No	Yes	No	No

CKD-MBD = chronic kidney disease-mineral bone disorder

Supplemental Table 35. Evidence matrix of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U
Phosphate binding agents vs. other treatments									
Mortality				Chue, 2013	109 (55)	36 weeks			
Cardiovascular and cerebrovascular events									
GFR Decline				Chue, 2013	109 (55)	36 weeks	Lemos, 2013	117 (38)	24 mos
Cholecalciferol vs. other treatments									
Mortality									
Cardiovascular and cerebrovascular events									
GFR Decline									

CKD-MBD = chronic kidney disease-mineral bone disorder; F/U = follow-up

Supplemental Table 36. Evidence profile of randomized controlled trials examining the treatment of parathyroid hormone in CKD-MBD

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Phosphate binding agents vs. other treatments									
Mortality	1 (RCT)	109 (55)	Moderate	NA	Direct	There was only one small, short-term study evaluating this outcome.	Low	We are unable to draw a conclusion.	Critical
Cardiovascular and cerebrovascular events									
GFR decline	2 (RCT)	226 (93)	High	Consistent	Direct		Very low	We are unable to draw a conclusion.	Moderate
Cholecalciferol vs. other outcomes									
Mortality	0								
Cardiovascular and cerebrovascular events	0								
GFR decline	0								

CKD-MBD = chronic kidney disease-mineral bone disorder; GFR = glomerular filtration rate; NA = not applicable; RCT = randomized controlled trial; ROB = risk of bias

REFERENCES

1. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol. 2012 Aug;23(8):1407-15.

2. Chue CD, Townend JN, Moody WE, Zehnder D, Wall NA, Harper L, et al. Cardiovascular effects of sevelamer in stage 3 CKD. J Am Soc Nephrol. 2013 Apr;24(5):842-52.

3. Lemos MM, Watanabe R, Carvalho AB, Jancikic AD, Sanches FM, Christofalo DM, et al. Effect of rosuvastatin and sevelamer on the progression of coronary artery calcification in chronic kidney disease: a pilot study. Clin Nephrol. 2013 Jul;80(1):1-8.

4. Oksa A, Spustova V, Krivosikova Z, Gazdikova K, Fedelesova V, Lajdova I, et al. Effects of long-term cholecalciferol supplementation on mineral metabolism and calciotropic hormones in chronic kidney disease. Kidney Blood Press Res. 2008;31(5):322-9.

KDIGO: CKD-MBD Update
Summary of Results for Calcitriol Activated Vitamin D Analogues

Research question 4.2.2: In patients with CKD G3a-G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, what is the evidence for benefit or harm in treating with vitamin D analogs compared with placebo or active control in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 37. Summary table of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis– study characteristics

Author, year	Region of study	N	CKD GFR category	Follow up duration	Funding source
Vitamin D vs. placebo					
Coburn, 2004[1]	USA	55	G3a-G4	6 mo	Industry
Coyne, 2006[2]	USA, Poland	220	G3a-G4	24 weeks	Industry
Fishbane, 2009[3]	USA	61	G2-G4	6 mo	Industry, non-profit
Hamdy, 1995[4]	Belgium, France, Netherlands, UK	176	G3a-G4	24 mo	NR
Thadhani, 2012[5] Tamez, 2012[6]	Asia, Australia, Europe, USA	227	G3a-G4	48 weeks	Industry
Wang, 2014[7]	Hong Kong	60	G3a-G5 (non-dialysis)	52 weeks	Industry
Paricalcitol vs. calcitriol					
Riccio, 2015[8]	Italy	60	G3b-G5	6 mo	None
Coyne, 2015[9]	USA	110	G3a-G4	6 mo	Industry

CKD = chronic kidney disease; HD = hemodialysis; NA = not applicable; NR = not reported

a. All patients were randomized day 3 of post renal transplantation

Supplemental Table 38. Summary table of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function	% DM % HTN % HC	Baseline MBD labs
Vitamin D vs. placebo							
Coburn, 2004[1]	Doxercalciferol N = 27	64	78	African American 44 Caucasian 48 Hispanic 4 Other 4	eGFR ml/min/1.73m^2 Measured 33.5 Calculated 25.2	NR NR NR	Ca 8.79 mg/dl corrected P 4.02 mg/dl iPTH 219.1 pg/ml 25 Vit D 18.5 ng/ml 1,25 Vit D 33.9 pg/mL ALP 113.9 U/L
	Placebo N = 28	65	86	African American 36 Caucasian 54 Hispanic 11 Other 0	eGFR ml/min/1.73m^2 Measured 36.9 Calculated 24.7	NR NR NR	Ca 8.87 mg/dl corrected P 3.89 mg/dl iPTH 171.4 pg/ml 25 Vit D 18.4 ng/ml 1,25 Vit D 34.9 pg/mL ALP 106.9 U/L
Coyne, 2006[2]	Paracalcitol N = 107	64	68	White 69 Black 26 Other 5	eGFR 23.1 mL/min/1.73m²	60 NR NR	cCa 9.28 mg/dL P 3.99 mg/dL iPTH 265 pg/mL Ca x P 36.7 mg^2/dL^2
	Placebo N = 113	62	67	White 73 Black 26 Other 1	eGFR 23.0 mL/min/1.73m²	58 NR NR	cCa 9.39 mg/dL P 3.97 mg/dL iPTH 280 pg/mL Ca x P 36.9 mg^2/dL^2
Fishbane, 2009[3]	Paricalcitol N=28	55	75	African American 14 White 61 Hispanic 14 Other 11	eGFR ml/min/1.73m^2 39.8	65 77 NR	Ca 9.0 mg/dl P 3.8 mg/dl iPTH 72.7 pg/ml 25 Vit D 23.6ng/ml 1,25 Vit D 19.5 pg/mL
	Placebo N=27	61	74	African American 8 White 83 Hispanic 4 Other 4	eGFR ml/min/1.73m^2 34.7	50 83 NR	Ca 9.0 mg/dl P 3.8 mg/dl iPTH 72.5 pg/ml 25 Vit D 20.8 ng/ml 1,25 Vit D 21.3 pg/mL
Hamdy, 1995[4]	Alfacalcidol N=89	53	61	NR	NR	NR NR NR	Ca 2.36 mmol/L corrected P 1.29 mmol/L iPTH 10.3 pmol/L MagicLite chemiluminescent assay [ref 0.8 – 5.4 pmol/L]

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function	% DM % HTN % HC	Baseline MBD labs
							ALP 154 IU/L
	Placebo N=87	51	61	NR	NR	NR NR NR	Ca 2.37 mmol/L corrected P 1.33 mmol/L iPTH 6.4 pmol/L MagicLite chemiluminescent assay [ref 0.8 – 5.4 pmol/L] ALP 152 IU/L
Thadhani, 2012[5] Tamez, 2012[6]	PO Paricalcitol N=115	64	69	Whites 73 Africa American 11 Asian 12 Others 4	eGFR 31 ml/min/1.73m^2	55 97 NR	Ca 9.6 mg/dl P 3.7 mg/dl iPTH 100 pg/ml ALP 24.1 U/L
	Placebo N=112	66	71	Whites 75 Africa American 11 Asian 14 Others 1	eGFR 36 ml/min/1.73m^2	51 96 NR	Ca 9.6 mg/dl P 3.5 mg/dl iPTH 106.0 pg/ml ALP 23.0 U/L
Wang, 2014[7]	Paricalcitol N=30	61	60	NR	eGFR 19.7 ml/min/1.73m^2	27 100 NR	Ca 2.32 mmol/L P 1.35 mmol/L PTH 156 pg/m ALP 74 IU/L
	Placebo N=30	62	47	NR	eGFR 23.9 ml/min/1.73m^2	43 100 NR	Ca 2.34 mmol/L P 1.26 mmol/L PTH 129 pg/m ALP 85 IU/L
Paricalcitol vs. calcitriol							
Riccio, 2015[8]	Paricalcitol N=30	60	50	NR	25.4 mL/min/1.73 m^2	10 NR NR	Ca 9.4 mg/dl P 3.6 mg/dl PTH 116 pg/ml
	Calcitriol N=30	55	83	NR	27.4 mL/min/1.73 m^2	30 NR NR	Ca 9.3 mg/dl P 3.6 mg/dl PTH 114 pg/ml
Coyne, 2015[9]	Paracalitol N=54	67	NR	Caucasian 33 Black 61 Other 6	27.8 mL/min/1.73 m^2	NR NR NR	Ca 9.3 mg/dl P 3.66 mg/dl PTH 176 pg/ml ALP 80 U/L
	Calcitriol N=56	65	NR	Caucasian 25 Black 73 Other 2	27.0 mL/min/1.73 m^2	NR NR NR	Ca 9.4 mg/dl P 3.74 mg/dl PTH 209 pg/ml ALP 77.5 U/L

ALP = alkaline phosphatase; b-ALP = bone-specific alkaline phosphatase; BMD = bone mineral density; CaXP = calcium-phosphate product; DM = diabetes mellitus; DXA = dual-energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; HC = hypercholesterolemia; HTN = hypertension; iPTH = intact parathyroid hormone; IRMA = immunoradiometric assay; MBD = mineral bone disease; NA = not applicable; NR = not reported; PO = oral; PTH = parathyroid hormone

a. Estimated from graphs
b. Solid-phase, two-site chemiluminescent enzyme immunometric assay on DPC-Immulite.
c. P <0.05 between arms.

Supplemental Table 39. Summary table of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis – results

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Vitamin D vs. placebo					
Coburn, 2004[1]	Doxercalciferol Initial dose 1µg/d, adjusted up to 5µg/d[a]	Placebo	Ca-based P binder, if necessary	Δ GFR (mL/min/1.73 m^2)	-4.7 vs. -2.5 (NS)[b]
				Mean corrected Ca (mmol/L)	2.30 vs. 2.25 (NS)
				Mean P (mmol/L)	1.38 vs. 1.27 (.047)
				Mean iPTH (nmol/L)	12.5 vs. 17.7 (<.05)
				% with 1 measurement of iPTH ≥30% decrease from baseline	74% vs. 7% (NR)
				%Δ b-ALP	-27.9% vs. NR (<.05)
				Ca > 2.67 mmo/L	4% vs. 4%
				iPTH < 1.6 pmol/L	4%[b]
				Congestive heart failure MI Neuromuscular symptoms Unable to tolerate drug Death 2° to cardiac arrest:	4% vs. NR NR vs. 4% NR vs. 4% NR vs. 4% NR vs. 4%
				Total discontinued due to adverse events	4% vs. 12%
				Mortality	0% vs. 4%
Coyne, 2006[2]	Paracalcitol (N=107) Thrice-weekly studies: initial dose of 2 µg thrice weekly if iPTH level ≤ 500 pg/mL or 4 µg thrice-weekly if iPTH >500 pg/mL. Uptitrated by 2 µg based on serum calcium, phosphate, and iPTH levels. Once-daily study: initial dose of 1 µg if iPTH was ≤ 500 pg/mL and 2 µg if > 500 pg/mL. Uptitrated by 1 µg based on serum calcium, phosphate, and iPTH levels	Placebo (N=113)	Phosphate binders	Bone-specific alkaline phosphatase, final (µg/L)	9.20 vs. 17.4
				Bone-specific alkaline phosphatase, change from baseline (µg/L)	-7.89 vs. -1.44; P < 0.001
				P, final (mmol/L)	1.38 vs. 1.36
				Ca, final (mmol/L)	2.37 vs. 2.32
				iPTH pg/mL, maximum mean decrease	-45.2% vs. 13.9%
				iPTH, 2 consecutive decreases ≥ 30%	91% vs. 13%; *P* < 0.001
				iPTH, 4 consecutive decreases ≥ 30%	74% vs. 0%; *P* < 0.001
				iPTH < 110 pg/mL	75% vs. 12%; *P* < 0.05
				Hypercalcemia (at least 2 consecutive corrected Ca values > 10.5 mg/dL), %	2% vs. 0%; *P* = 0.237
				eGFR, change from baseline (mL/min/1.73 m^2)	-2.52 vs. 1.57; *P* = 0.187
				Nausea, %	6% vs. 4%
				Vomiting, %	6% vs. 4%

				Mortality, n	2 vs. 1
Fishbane, 2009[3]	Paricalcitol (N=28) Initial dose of 1 µg/d, increased to a max of 2 µg/d if iPTH > 200pg/ml & decreased if iPTH <20pg/ml	Placebo (N=27)	NR	Mean Ca at 6 months, mg/dl	9.1 vs. 8.8 (NS)
				Mean P at 6 months, mg/dl	3.8 vs. 3.6 (NS)
				Hypercalcemia, N (%)	1 (4%) vs. 0
				Mean iPTH at 6 months, pg/ml	50 vs. 70[b] (P=0.01)
				Mean eGFR	NS from baseline to final in either group and NS between groups
				Adverse events (N)	7 vs. 9
				Hospitalizations	1 (for pneumonia) vs. 2 (for congestive heart failure)
				Atrial fibrillation	1 vs. NR
Hamdy, 1995[4]	Alfacalcidol (N=89) Initial dose 0.25µg/d, Adjusted[c]	Placebo (N=87)	Ca supplements Other P binders, if necessary[d]	Bone overall summary by WG	Overall slightly favoring calcitriol because turnover better, mostly caused by improvement of HPT.
				Bone Turnover (N = 134)	Better (+30)
				Bone Mineralization	NR
				Bone Volume	Same
				Δ CrCl (mL/min)	-5.7 vs. -4.0 (NS)
				Δ Corrected Ca (mmol/L)	+0.07 vs. -0.01 (<.001)
				Δ P (mmol/L)	+0.13 vs. -0.06 (NS)
				Δ iPTH (pmol/L)	+0.6 vs. +8.1 (.001)
				Δ ALP (IU/L)	-5.7 vs. +19.8 (<.001)
				†Ca 2.63-3.00 mmol/L, %	11% vs. 3%
				Ca >3.00 mmol/L, %	4% vs. 0%
				Gastrointestinal adverse events, N (%)	6 (7%) vs. 1 (1%)
				Hypocalcemia, n (%)	0 (0%) vs. 1 (1%)
				Total discontinued due to adverse events	0% vs. 0%
				Mortality, n (%)	4 (4%) vs. 1 (1%)
Thadhani, 2012[5]	Paricalcitol (n = 82) Initial dose 2 µg/d	Placebo (n = 80)	Nutritional Vitamin D (Cholecalciferol & Ergocalciferol) dose was limited to 400 IU	Decrease in iPTH of greater than 30% by week 48	85.7% vs. 16.5% (P <0.001)
				Δ Mean Ca change (mg/dl)	0.32 vs -0.25 (<0.001)
				Δ Mean Phosphate	0.23 vs. 0.04 (P = .05)
				Hospitalization from any cause	15.7% vs. 17.0% (P = .86)
				Hospitalization from CV cause, N/number of events	1/1 vs. 7/8 (P=0.003)
				LV mass index, g/m$^{2.7}$ at 48 weeks	0.34 (−0.14 to 0.83) vs. -0.07 (−0.55 to 0.42) (P=.0.15)
				Overall incidence of adverse events	80.0% vs. 77.7% (P=0.75)

				Hypercalcemia	22.6% vs. 0.9% (P <.001)
				Mean GRF decline mL/min/1.73 m2	−4.1 vs. −0.1 (P <.001)
				Mortality, n	0 vs. 0
Wang, 2014[7]	Paricalcitol Initial dose 1 µg/day if iPTH < 500 pg/mL or 2 µg/day if iPTH ≥ 500 pg/ml Titrated based on calcium level	Placebo	NR	Δ in LV mass index by BSA, g/m2 (95% CI)	-2.59 (-6.13 to +0.32) vs. -4.85 (-9.89 to -1.10) (P=0.40)
				Δ in LV mass index by height$^{2.7}$, g/m$^{2.7}$ (95% CI)	-1.75 (-3.35 to +0.19) vs. -2.28 (-5.51 to -0.34) (P=0.60)
				Median (IQR) Δ in calcium, mmol/L	+ 0.01 (-0.06 to +0.05) vs. +0.08 (+0.02 to +0.16) (P=0.03)
				Median (IQR) Δ in phosphate, mmol/L	+0.08 (-0.07 to +0.18) vs.+0.07 (-0.08 to +0.21)
				Median (IQR) Δ in alkaline phosphatase, U/L	-12 (-21 to -1) vs. +2 (-6 to +10) (P=0.001)
				Median (IQR) Δ in iPTH, pg/ml	-86 (-131 to -43) vs. +21 (-25 to +134) (P<0.001)
				Patients with ≥50% reduction in iPTH, n (%)	19 (63.3%) vs. 1 (3.3%) (P<0.001)
				Patients with hospitalizations, n (%)	2 (0.07) vs. 10 (0.33) (P=0.02)
				Total hospitalization episodes	5 vs. 14 (NR)
				Patients with hypercalcemia, n (%)	13 (43.3) vs. 1 (3.3) (<0.001)
				Cardiovascular events, number of episodes	0 vs. 6 (5 patients)
				Mortality	0 vs. 0
Paricalcitol vs. calcitriol					
Riccio, 2015[8]	Paricalcitol (1 mcg/day) N=30	Calcitriol (0.5 mcg/every other day) N=30	All patients were maintained at same dietary and pharmacological therapies. No calcium supplements to both groups during the duration of the studies	Mean calcium at 6 months (mg/dl)	9.5 vs. 9.4 (NS)
				Mean phosphate at 6 months (mg/dl)	3.7 vs. 3.8 (NS)
				Mean PTH at 6 months (pg/ml)	103 vs. 104 (NS)
				Mean GFR at 6 months (mL/min)	23.0 (P<0.05 vs. baseline) vs. 25.4
Coyne, 2015[9]	Paracalcitol 1 µg/d; dose was titrated up if PTH < 40% from baseline and cCa < 10.5 mg/dL; 4 µg/d maximum dose N=53	Calcitriol 0.25 µg/d; dose was titrated up if PTH < 40% from baseline and cCa < 10.5 mg/dL; 1 µg/d maximum dose N=54	NR	Hypercalcemia (confirmed cCa > 10.5 mg/dL)	5.7% vs 1.9% (p=0.36)
				Hypercalcemia (any cCa >10.5 mg/dL)	13.2% vs 7.4% (p=0.36)
				Δ Mean PTH (%)	-52 vs -46 (p=0.17)
				>40% PTH reduction	98% vs. 87% (p=0.03)
				>60% PTH reduction	83% vs. 52% (p<0.001)
				Δ Mean cCa (mg/dL)	0.38 vs 0.28 (p=0.27)
				Δ Mean P (mg/dL)	0.2 vs 0.3 (p=0.88)

				Δ Mean ALP (U/L)	-9.0 vs -13.0 (p=0.32)
				Any P >4.5 mg/dl	40% vs 52% (p=0.21)
				eGFR (ml/min/1.73m^2), 24 wks	24.0 vs 22.6 (p=0.45)
				Mortality	0 vs. 0
				Cardiac events, n	9 vs 7
				Dermatologic AE, n	7 vs 7
				Neurologic AE, n	11 vs 6
				Gastrointestinal AE, n	10 vs 4
				Genitourinary AE, n	10 vs 4
				Endocrine AE, n	4 vs 10
				Respiratory AE, n	7 vs 7
				Musculoskeletal AE, n	15 vs 12
				Psychiatric AE, n	2 vs 2
				Other AE, n	6 vs 6

AE, adverse events; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphate product; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; DM, diabetes mellitus; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; HPLC, high-performance liquid chromatography; iPTH, intact parathyroid hormone; IRMA, immunoradiometric assay; KT, kidney transplant; MBD, mineral bone disease; MLT, mineralization lag time; N, number of subjects; NA, not applicable; nd, not documented; NR = not reported; PO, oral; PTH, parathyroid hormone; SCr, serum creatinine; SXA: single-energy X-ray absorptiometry; TMV, turnover, mineralization, volume; LAVi, Left atrial volume index; LA, left atrial area; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; EF, ejection fraction; MRI, magnetic resonance imaging; LV, left ventricle; EDV, end diastolic volume; ESV, end systolic volume; E/A, ratio of early filling velocity to atrial filling velocity; E', early diastolic mitral annular velocity; S', systolic mitral annular velocity; A', late diastolic mitral annular velocity; E/E', ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity.

a. The initial dose was 1 μg/d. The dosage was increased by 0.5 μg/d monthly PTH level was not reduced >30% from baseline and if Ca <2.4 mmol/L, P <1.6 mmol/L, urine Ca <5.0 mmol/d and fasting urine Ca-Cr ratio ≤0.71 mmol/mmol. The maximum dosage permitted was 5 μg/d or 35 μg/wk. Treatment was suspended temporarily if iPTH <1.6 pmol/L, corrected >2.7 mmol/L, urinary Ca >5.0 mmol/d, or a fasting urine Ca-Cr ratio >0.71 mmol/mmol. When Ca and urine Ca levels normalized, treatment resumed at a dose reduced by 0.5 μg/d.
b. Calculated.
c. Dose adjusted to between 0.25 μg every other day and 1 μg/d to maintain Ca at the upper limit of normal of the laboratory reference range.
d. Ca supplements if previously taken were continued up to 500 mg elemental Ca daily. Other phosphate binders allowed when dietary restrictions failed to keep P <2.2 mmol/L.

Supplemental Table 40. Summary table of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Vitamin D vs. placebo								
Coburn, 2004[1]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Coyne, 2006[2]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Fishbane, 2009[3]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Hamdy, 1995[4]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes
Thadhani, 2012[5] Tamez, 2012[6]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes
Wang, 2014[7]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Paricalcitol vs. calcitriol								
Riccio 2015[8]	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Coyne, 2015[9]	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear

Supplemental Table 41. Evidence matrix of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U
Vitamin D vs. placebo									
LV hypertrophy	Wang 2014	60 (30)	52 wks	Thadhani 2012	162 (82)	48 wks			
Hypercalcemia	Fishbane 2009 Coyne 2006 Wang 2014	55 (28) 220 (107) 60 (30)	6 mos 24 wks 52 wks						
Mortality	Coburn 2004 Coyne 2006 Wang 2014	55 (27) 220 (107) 60 (30)	6 mos 24 wks 52 wks	Hamdy 1995 Thadhani 2012	176 (89) 162 (82)	24 mo 48 wks			
Cardiovascular and cerebrovascular events	Coburn 2004 Fishbane 2009 Wang 2014	55 (27) 55 (28) 60 (30)	6 mo 6 mos 52 wks	Thadhani 2012	162 (82)	48 wks			
Paricalcitol vs. calcitriol									
LV hypertrophy									
Hypercalcemia				Coyne 2015	107 (53)	6 mo			
Mortality				Coyne 2015	107 (53)	6 mo			
Cardiovascular and cerebrovascular events				Coyne 2015	107 (53)	6 mo			

Supplemental Table 42. Evidence profile of randomized controlled trials examining the treatment of high levels of PTH with calcitriol or activated vitamin D analogues in CKD G3a-G5 not on dialysis

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Vitamin D vs. placebo									
LV hypertrophy	2 RCTs	222 (112)	Moderate	Consistent	Direct		Moderate	No difference in LV mass index	High
Hypercalcemia	3 RCTs	335 (165)	Low	Inconsistent	Direct		Low	Only one study showed significantly more hypercalcemic events with paracalcitol than with placebo.	High
Mortality	5 RCTs	673 (335)	Moderate	Consistent	Direct	Few events with most studies having 1 year or shorter follow up duration	Low	No difference in short-term mortality rates	Critical
Cardiovascular and cerebrovascular events	4 RCTs	332 (167)	Moderate	Consistent	Direct	Few events with all studies having 1 year or shorter follow up duration	Low	Trend towards fewer cardiovascular events with vitamin D therapy	Critical
Paricalcitol vs. calcitriol									
LV hypertrophy	0								
Hypercalcemia	2 RCTs	329 (169)	Low	Consistent	Direct		Moderate	No significant differences between therapies	High
Mortality	1 RCT	66 (36)	Low	NA	Direct		Moderate	No significant differences between therapies	Critical
Cardiovascular and cerebrovascular events	1 RCT	66 (36)	Low	NA	Direct		Moderate	No significant differences between therapies	Critical

NA = not applicable; RCT = randomized controlled trial; ROB = risk of bias

REFERENCES

1. Coburn JW, Maung HM, Elangovan L, Germain MJ, Lindberg JS, Sprague SM, et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis. 2004 May;43(5):877-90.

2. Coyne D, Acharya M, Qiu P, Abboud H, Batlle D, Rosansky S, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. American journal of kidney diseases [serial on the Internet]. 2006; (2): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/583/CN-00554583/frame.html.

3. Fishbane S, Chittineni H, Packman M, Dutka P, Ali N, Durie N. Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. Am J Kidney Dis. 2009 Oct;54(4):647-52.

4. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. BMJ. 1995 Feb 11;310(6976):358-63.

5. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA. 2012 Feb 15;307(7):674-84.

6. Tamez H, Zoccali C, Packham D, Wenger J, Bhan I, Appelbaum E, et al. Vitamin D reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease. Am Heart J. 2012 Dec;164(6):902-9 e2.

7. Wang AY, Fang F, Chan J, Wen YY, Qing S, Chan IH, et al. Effect of paricalcitol on left ventricular mass and function in CKD--the OPERA trial. J Am Soc Nephrol. 2014 Jan;25(1):175-86.

8. Riccio E, Sabbatini M, Bruzzese D, Capuano I, Migliaccio S, Andreucci M, et al. Effect of paricalcitol vs calcitriol on hemoglobin levels in chronic kidney disease patients: a randomized trial. PLoS One. 2015;10(3):e0118174.

9. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM. A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. Clin J Am Soc Nephrol. 2014 Sep 5;9(9):1620-6.

KDIGO: CKD-MBD Update
Summary of Results for Treatments for High PTH on Dialysis

Recommendation 4.2.4: In patients with CKD G5D what is the what is the evidence for benefit or harm in treating with calcitriol, vitamin D analogs, calcimimetics or combination thereof compared with placebo or active control in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 43. Summary table of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D – study characteristics

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Vitamin D analogs vs. placebo						
Baker, 1986[1]	UK	76	G5D	HD 1.65 mmol/L	60 mo	NR
Vitamin D analogs head-to-head comparisons						
Hayashi, 2004[2]	Japan	91	G5D	HD 3.0 mEq/L	12 mo	Industry
Ong, 2013[3]	Malaysia	73	G5D	HD & PD 2-3 mEq/L	24 weeks	NR
Sprague, 2003[4]	The Netherlands, Spain, Switzerland, USA	266	G5D	HD 2.5 mEq/L	32 weeks	NR
Cinacalcet vs. placebo						
Block, 2004[5]	Australia, Europe, N. America	741	G5D	HD NR	6 mo	Industry
Chertow, 2012[6] Floege, 2015[7] Wheeler, 2014[8] Parfrey, 2015[9] Moe, 2014[10] Moe, 2015[11]	USA, Australia, Russia, Canada, Europe, Latin America	3883	G5D	HD NR	64 mo	Industry
El-Shafey, 2011[12]	Kuwait, Saudi Arabia	82	G5	HD NR	36 wk	NR
Lindberg, 2005[13]	Australia, Canada, USA	395	G5D	HD 88%; PD 12% NR	26 wk	Industry
Cinacalcet vs. vitamin D						
Fishbane, 2008[14]	USA	173	Dialysis	HD 2 micrograms of paricaclitrol or 1 microgram doxercalciferol	27 weeks	Industry
Ketteler, 2012[15]	Europe, Russia, USA	272	G5D	HD NR	28 weeks	Industry
Raggi, 2014[16]	North America, Europe, Australia	360	G5D	HD NR	52 wk	Industry
Sprague, 2015[17]	Multinational	312	G5D	HD 2.5 mEq/L (Median)	52 wk	Industry
Urena-Torres, 2013[18] Rodriguez, 2013[19]	USA, Russia, Europe	304	G5D	HD 3.5 mEq/L	56 wk	Industry
Wetmore, 2015[20]	USA, Russia, Canada, Australia	540	Dialysis	HD Median 2.50 mEq/L	12 mo	Industry

Author, year	Region of study	N	CKD GFR category	Dialysis modality Dialysate calcium	Follow up duration	Funding source
Native vitamin D vs. placebo						
Bhan, 2015[21]	USA	105	5D	HD	52 wk[a]	Government
Hewitt, 2013[22]	Australia and New Zealand	60	Dialysis	HD 2.6 or 3 mEq/L (1.3 or 1.5 mmol/L)	6 mo	Industry
Mose, 2014[23]	Denmark	64	Dialysis	HD	6 mo	Unclear
Studies conducted among transplant patients						
Amer, 2013[24]	USA	100	Immediate post transplant[a]	NA NA	1 year	Industry
Torres, 2004[25]	Spain	90	At transplant	NA NA	12 mo	Government, non-profit
Jeffery, 2003[26]	Canada	117	85 – 115 mo post-transplant	NA NA	12 mo	NR
Evenepoel, 2014[27]	Multinational	114	Kidney transplant	NA NA	56 wk	Industry
Wissing, 2005[28]	Belgium	90	Transplant	NA	12 mo	NR
De Sevaux, 2002[29]	The Netherlands	113	Post-transplant	NR	24 weeks	NR

CKD = chronic kidney disease; HD = hemodialysis; NA = not applicable; NR = not reported; PD = peritoneal dialysis

a. Only mortality was assessed through 1 year; all other outcomes were assessed for 16 weeks.

Supplemental Table 44. Summary table of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D – study population characteristics

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
Vitamin D analogs vs. placebo									
Baker, 1986[1]	Calcitriol N=38	NR	NR	NR	NR	NR	Ca 2.48 mmol/L[a] corrected P nd PTH 18.6 pmol/L[a] Amino-terminal PTH IRMA [ref NR] ALP 66.3 U/L[a]	Bone biopsy	NR
	Placebo N=38	NR	NR	NR	NR	NR	Ca 2.47 mmol/L[a] corrected P nd PTH 26.5 pmol/L[a] Amino-terminal PTH IRMA [ref NR] ALP 67.2 U/L[a]	Bone biopsy	NR
	Total N=76	42	NR	NR	NR 20 mo	NR	NR	Bone biopsy	NR
Vitamin D analogs head-to-head comparisons									
Hayashi, 2004[2]	Calcitriol N=38	56	87	NR	NR 103 mo	NR NR NR	Ca 2.27 mmol/L corrected P 1.86 mmol/L iPTH 63.5 pmol/L Allegro-intact PTH [ref nd] b-ALP 30.0 IU/L	None	None
	Maxacalcitol N=35	55	71	NR	NR 77 mo	NR NR NR	Ca 2.24 mmol/L corrected P 1.83 mmol/L iPTH 63.2 pmol/L Allegro-intact PTH [ref nd] b-ALP 26.8 IU/L	None	None
Ong, 2013[3]	Paricalcitol N=36	46	67	NR	NA 8.7 years	NR NR NR	Ca 2.17 mmol/L P 1.87 mmol/L CaXP 4.04 ($mmol^2/L^2$) iPTH 495.0 pmol/L ALP 151 IU/L	None	NA
	Calcitriol N=30	45	57	NR	NA 7.8 years	NR NR	Ca 2.12 mmol/L P 1.72 mmol/L	None	NA

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
						NR	CaXP 3.64 ($mmol^2/L^2$) iPTH 558.5 pmol/L ALP 173.5 IU/L		
Sprague, 2003[4]	IV calcitriol N=130	57	60	Caucasian 30 African American 57 Other 13	NR 0 to ≥12 mo[c]	NR NR NR	Ca 2.25 mmol/L P 1.87 mmol/L iPTH 71.6 pmol/L Allegro-intact PTH [ref NR]	None	NA
	IV paricalcitol N=133	57	54	Caucasian 26 African American 62 Other 12	NR 0 to ≥12 mo[c]	NR NR NR	Ca 2.25 mmol/L P 1.91 mmol/L iPTH 68.7 pmol/L Allegro-intact PTH [ref NR]	None	NA
Cinacalcet vs. placebo									
Block, 2004[5]	Cinacalcet N = 371	54	61	White 56 Black 35 Other 9	NR 72 mo	30 NR NR	Ca 2.47 mmol/L P 2.00 mmol/L PTH 68.2 pmol/L Allegro-intact PTH b-ALP 23.3 ng/mL	None	None
	Placebo N = 370	55	62	White 61 Black 32 Other 7	NR 72 mo	29 NR NR	Ca 2.47 mmol/L P 2.00 mmol/L PTH 68.1 pmol/L Allegro-intact PTH b-ALP 24.2 ng/mL	None	None
Chertow, 2012[6]	Cinacalcet N=1948	Median 55	58	White 58 Black 21 Other 21	NR Median 45.4 mo	34% 93% NR	Ca 9.8 P 6.3 PTH 694.5	None	None
	Placebo N=1935	Median 54	60	White 58 Black 22 Other 20	NR Median 45.1 mo	34% 92% NR	Ca 9.8 P 6.2 PTH 690.0	None	None
El-Shafey, 2011[12]	Cinacalcet N=55	52	50	NR	NR 48 mo	42 NR NR	Ca 2.39 mmol/L P 1.81 mmol/L iPTH 70.52 pmol/L Ca-P 4.32 $mmol^2/L^2$	Dual energy X-ray absorptiometry	None
	Conventional therapy N=27	52	52	NR	NR 44 mo	41 NR NR	Ca 2.39 mmol/L P 1.76 mmol/L iPTH 74.88 pmol/L Ca-P 4.25 $mmol^2/L^2$	Dual energy X-ray absorptiometry	None
Lindberg, 2005[13]	Cinacalcet	52	62	White 39	NR	NR	Ca 2.44 mmol/L	None	None

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
	N=294			Black 39 Other 22	56 mo	NR NR	P 1.97 mmol/L iPTH 89.9 pmol/L Allegro-intact PTH ALP NR		
	Placebo N=101	54	63	White 39 Black 35 Other 26	NR 64 mo	NR NR NR	Ca 2.50 mmol/L P 1.97 mmol/L iPTH 88.2 pmol/L Allegro-intact PTH ALP NR	None	None
Cinacalcet vs. vitamin D									
Fishbane, 2008[14]	Cinacalcet-D, 87	57.7	60	NR	NR 46.3 mo	56 93	Ca 9.6[f] mg/dl P 5.1[f] mg/dl iPTH 597[f] pg/mL	NA	NA
	Flex-D, 86	59.0	52	NR	NR 46.8 mo	71 100	Ca 9.7[f] mg/dl P 5.2[f] mg/dl iPTH 621[f] pg/mL	NA	NA
Ketteler, 2012[15]	IV Paricalcitol N=62	61	61	NR	NR 4 years	69 NR NR	Ca 9.0 mg/dl P 4.9 mg/dl iPTH 526.3 pg/ml 25 Vit D 22.1 ng/ml ALP 111.2 IU/L	None	NA
	IV Cinacalcet N=64	60	60	NR	NR 4.1 years	55 NR NR	Ca 9.0 mg/dl P 4.9 mg/dl iPTH 521.1 pg/ml 25 Vit D 23.2 ng/ml ALP 123.8 IU/L	None	NA
	PO Paricalcitol N=72	66	68	NR	NR 3.8 years	40 NR NR	Ca 9.0 mg/dl P 4.9 mg/dl iPTH 494.8 pg/ml 25 Vit D 15.6 ng/ml ALP 100.1 IU/L	None	NA
	PO Cinacalcet N=70	65	61	NR	NR 4 years	16 NR NR	Ca 9.0 mg/dl P 4.4 mg/dl iPTH 509.5 pg/ml 25 Vit D 17.1 ng/ml ALP 105.7 IU/L	None	NA
Raggi, 2014[16]	Cinacalcet + VitD N=180	61	62	White 64 Black 25 Hispanic 6 Other 4	NR Median 38 mo	42 93 NR	PTH, median 432 pg/ml Ca 9.4 mg/dl P 6.0 mg/dl CaxP 55.8 mg^2/L^2	None	Total coronary artery 695 Thoracic aorta 2114 Aortic valve 2 Mitral valve 0

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
	Flexible VitD N=180	62	53	White 67 Black 22 Hispanic 8 Other 3	NR Median 37 mo	45 94 NR	PTH, median 424 pg/ml Ca 9.4 mg/dl P 5.6 mg/dl CaxP 52.5 mg^2/L^2	None	Total coronary artery 590 Thoracic aorta 1552 Aortic valve 0 Mitral valve 6
Sprague, 2015[17]	Cinacalcet N=155	53 (median)	60	White 43 Black 49 Asian 5 Other 3	NA 33 mo (median)	NR NR NR	Ca 9.55 mg/dl P 5.73 mg/dl PTH 845.7 pg/L Vitamin D 25.59	None	None
	Vitamin D analogue N=157	55 (median)	61	White 55 Black 38 Asian 3 Other 4	NA 38 mo (median)	NR NR NR	Ca 9.49 mg/dl P 5.77 mg/dl PTH 815.7 pg/L Vitamin D 26.13	None	None
Urena-Torres, 2013[18] Rodriguez, 2013[19]	Cinacalcet + vitamin D sterols N=153	58	54	White 78 Black 18 Hispanic 1 Asian 2 Aborigine 0 Other 1	NR 7.3 mo	32 20 NR	Ca 9.30 mg/dl P 5.55 mg/dl Plasma PTH 559.2 pg/ml bs-ALP 20.95 pg/L	None	None
	Calcitriol (or a synthetic analog to Calcitriol) N=151	57	63	White 74 Black 21 Hispanic 1 Asian 3 Aborigine 1 Other 1	NR 7 mo	31 17 NR	Ca 9.14 mg/dl P 5.49 mg/dl Plasma PTH 511.6 pg/ml bs-ALP 20.69 pg/L	None	None
Wetmore, 2015[20]	Cinacalcet, 155	Median 53	60	Asian 5 Black 49 White 43 Other 5	NR Median 32.9 mo	40 26	PTH 845.7 pg/ml Ca 9.5 mg/dl P 5.7 mg/dl ALP 112.1 U/L		
	Vitamin D analogs, 157	Median 55	61	Asian 3 Black 38 White 55 Other 4	NR Median 32.9 mo	37 28	PTH 815.7 pg/ml Ca 9.7 mg/dl P 5.6 mg/dl ALP 107.6 U/L		
Native vitamin D vs. placebo									
Bhan, 2015[21]	Monthly ergocalciferol N=33	58	85	White 64 Black 27 Asian 6 Multiple 3	NA <=2 mo	NR NR NR	Ca 8.7 mg/dl P 4.2 mg/dl PTH 253 pg/L ALP 75.5 IU/L	None	None
	Weekly ergocalciferol N=36	53	69	White 64 Black 36 Asian 0	NA <=2 mo	NR NR NR	Ca 8.8 mg/dl P 4.2 mg/dl PTH 265 pg/L	None	None

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
				Multiple 0			ALP 77.5 IU/L		
	Placebo N=36	59	81	White 61 Black 25 Asian 11 Multiple 3	NA <=2 mo	NR NR NR	Ca 8.8 mg/dl P 4.1 mg/dl PTH 249 pg/L ALP 87.0 IU/L	None	None
Hewitt, 2013[22]	Cholecalciferol, 30	60 (median)	53	White 50.0	NR	15	Ca 9.4 mg/dl P 5.4 mg/dl ALP 147 U/L iPTH 335 U/L $1,25(OH)_2D$ 18 pg/ml 25(OH)D 18 ng/ml	NA	NA
	Placebo, 30	67 (median)	43	White 36.7	NR	18	Ca 9.4 mg/dl P 4.8 mg/dl ALP 116 U/L iPTH 222 U/L $1,25(OH)_2D$ 18 pg/ml 25(OH)D 16 ng/ml	NA	NA
Mose, 2014[23]	Cholecalciferol, 25	68	68	NR	NR	T1DM: 8 T2DM: 8	25(OH)D 28 nmol/L PTH 13.5 pmol/L Ca 1.21 mg/dL P 1.59 nmol/L ALP 70 U/L	Echocardiography	Left ventricular mass index 116 g/m^2
	Placebo, 25	67	60	NR	NR	T1DM: 16 T2DM: 20	25(OH)D 28 nmol/L PTH 18.0 pmol/L Ca 1.20 mg/dL P 1.66 nmol/L ALP 67 U/L	Echocardiography	Left ventricular mass index 123 g/m^2
Studies conducted among transplant patients									
Amer, 2013[24]	Paricalcitol N=51	49	65	White 96	eGRF=45 ml/min/1.73m^2 0 months	19.6 NR NR	Ca 9.8 mg/dl corrected P 3.0 mg/dl PTH 171 pg/ml Total 25-hydroxyvitamin D 35	BMD (T score) Lumbar spine Hip	 -0.82 -0.96
	Control N=49	48	67	White 86	eGFR=45.3 ml/min/1.73m^2 0 months	24.5 NR NR	Ca 9.8 mg/dl corrected P 3.1 mg/dl PTH 233 pg/ml Total 25-hydroxyvitamin D 36	BMD (T score) Lumbar spine Hip	 -0.63 -0.69
Torres, 2004[25]	Calcitriol	47	82	NR	NA[d]	31	Ca 2.40 mmol/L	BMD, femoral neck	0.81[f]

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
	N=45				18.5 mo	NR NR	P 1.65 mmol/L PTH 20.9 pmol/L DPC IRMA[b] [ref 1.3-7.6] ALP 140 IU/L	(g/cm^2)	
								BMD, intertrochanteric region (g/cm^2)	1.06[f]
								BMD, lumbar spine (g/cm^2)	1.02
								BMD, total hip (g/cm^2)	0.91
								BMD, trochanteric region (g/cm^2)	0.70
								BMD, ward's triangle (g/cm^2)	0.64
	Placebo N=41	51	73	NR	NA[d] 18.8 mo	20 NR NR	Ca 2.42 mmol/L P 1.65 mmol/L PTH 20.3 pmol/L DPC IRMA[b] [ref 1.3-7.6] ALP 145 IU/L	BMD, femoral neck (g/cm^2)	0.76[f]
								BMD, intertrochanteric region (g/cm^2)	1.03[f]
								BMD, lumbar spine (g/cm^2)	0.98
								BMD, total hip (g/cm^2)	0.87
								BMD, trochanteric region (g/cm^2)	0.66
								BMD, ward's triangle (g/cm^2)	0.57
Jeffery, 2003[26]	Alendronate N=46	52	74	NR	71 mL/min/1.72m[2b]	15	Ca nd P nd iPTH 15.6 pmol/L NR [ref 0.7-5.3] ALP nd	BMD, lumbar spine (g/cm^2)	0.984
								BMD, total proximal femur (g/cm^2)	0.809

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
								% with T score < -2.5	43.5%
	Calcitriol N=51	56	73	NR	83 mL/min/1.72m^{2b}	22	Ca nd P nd iPTH 12.2 pmol/L NR [ref 0.7-5.3] ALP nd	BMD, lumbar spine (g/cm^2)	1.014
								BMD, total proximal femur (g/cm^2)	0.830
								% with T score < -2.5	39.2%
Evenepoel, 2014[27]	Cinacalcet N=57	53	54	White 83 Black 9 Other 9	eGFR 57.0 ml/min/1.73,^{2} 62 mo	NR NR NR	Ca 11.28 mg/dl iPTH 327.7 pg/ml P 2.66 mg/dl	Dual energy X-ray absorptiometry	None
	Placebo N=57	52	56	White 81 Black 7 Black 12	eGFR 54.68 ml/min/1.73,^{2} 63 mo	NR NR NR	Ca 11.31 mg/dl iPTH 307.5 pg/ml P 2.48 mg/dl	Dual energy X-ray absorptiometry	None
Wissing, 2005[28]	Cholecalciferol (25,000 IU vitamin D) + 400 mg calcium	43	61	NR	NR NA	NR NR NR	Ca 10.2 mg/dL P 5.1 mg/dL iPTH 127 pg/mL 25(OH)D 24.5 ng/mL 1,25(OH)$_2$D 9.9 pg/mL	BMD, femoral neck (g/cm^2)	0.8[c]
								BMD, lumbar spine (g/cm^2)	1.04[d, e]
								BMD, midfemoral shaft (g/cm^2)	1.63
	400 mg calcium	43	54	NR	NR NA	NR NR NR	Ca 10.0 mg/dL P 5.6 mg/dL iPTH 222 pg/mL 25(OH)D 19.5 ng/mL 1,25(OH)$_2$D 9.8 pg/mL	BMD, femoral neck (g/cm^2)	0.74[c]
								BMD, lumbar spine (g/cm^2)	0.94[d, e]
								BMD, midfemoral shaft (g/cm^2)	1.53
De Sevaux, 2002[29]	Ca plus D, 65	46	62	NR	NR 31 mo	9	Ca adjusted 2.38 mmol/L P 1.68 mmol/L Alkaline phosphatase	BMD, lumbar spine (g/cm^2) BMD, femoral neck (g/cm^2)	0.955 0.731

Author, year	Intervention group	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Bone evaluation technique	Vasc./Valv. Calcification by EBCT in Agatston units*
							88 IU/L 25-OH Vitamin D 24 ng/mL	BMD, Ward's triangle (g/cm^2) BMD, Trochanteric region (g/cm^2) BMD, Total hip (g/cm^2)	0.552 0.619 0.819
	No treatment, 46	49	54	NR	NR 30 mo	2	Ca adjusted 2.42 mmol/L P 1.79 mmol/L Alkaline phosphatase 64 IU/L 25-OH Vitamin D 32 ng/mL	BMD, lumbar spine (g/cm^2) BMD, femoral neck (g/cm^2) BMD, Ward's triangle (g/cm^2) BMD, Trochanteric region (g/cm^2) BMD, Total hip (g/cm^2)	1.007 0.799 0.591 0.681 0.880

ALP = alkaline phosphatase; Ca = calcium; DM = diabetes mellitus; EBCT = electron-beam computed tomography; eGFR = estimated glomerular filtration rate; MBD = mineral bone density; NR = not reported; P = phosphate; PTH = parathyroid hormone

Supplemental Table 45. Summary table of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D – results

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
Vitamin D analogs vs. placebo					
Baker, 1986[1]	PO Calcitriol (N=38) Initial dose 0.25 µg/d, adjusted to Ca ≤2.75 mmol/L. First 18 mo, maximum dose 1 µg/d, then maximum reduced to 0.5 µg/d.	Placebo (N=38)	Aluminum-based P binder adjusted to P 1.2-1.8 mmol/L	Discontinued due to hypercalcemia, n (%)	6 (16%) vs. 2 (5%)
				Parathyroidectomy, n (%)	5 (13%) vs. 2 (5%)
				Discontinued due to adverse events	26% vs. 13%
				Mortality	0% vs. 0%
				Modality change	29% vs. 24%
				New Fractures	Rib: 1 vs. 1 Hand, feet, pelvis: 0 vs. 0
				Bone Histology N = 20 F/U=12-62 mo	
				Bone Overall Summary by WG	Biopsy results somewhat favored calcitriol with better turnover and mineralization. Aluminum toxicity may have played an important role.[a]
				Bone Turnover (% Patients) Worsened (Higher, Lower) Improved (Higher, Lower)	 (10,30) vs. (50,0) (0,0) vs. (0,0)
				Bone Mineralization Worse Better	 30 vs. 40 0 vs. 0
				Bone Volume	NR
				Calcification by X-ray [N = nd]	
				Pts with increased CAC	0 vs. 2 (NS)
				Pts with increased calcification of vessels of the hands, feet, pelvis	14 vs. 20 (NS)
				Laboratory at 18 mo:	
				Median Corrected Ca (mmol/L)	2.59 vs. 2.50 (<.05)[b]
				Median PTH (pmol/L)	12.2 vs. 25.4 (<.05)[b]
				Median ALP (IU)	54 vs. 70 (<.05)[b]
Vitamin D analogs head-to-head comparisons					
Hayashi, 2004[2]	Calcitriol 1 µg per HD session	Maxacalcitol 10 µg for basal	Ca carbonate adjusted to P <1.94 mmol/L	Ca > 2.87 mmol/L	2% vs. 5%

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
		iPTH ≥ 500 pg/ml or 5 µg for basal iPTH < 500 pg/ml per HD session			
				P > 1.94 mmol/L	64% vs. 68%
				Mortality, n (%)	1 (3%) vs. 2 (6%)
				# pts with PTH <15.9 pmol/L	13 vs. 18 (NS)
				Mean adjusted Ca (mmol/L)	2.37 vs. 2.42 (nd)[b]
				Mean P (mmol/L)	1.91 vs. 2.00 (NS)[b]
				Mean b-ALP (IU/L)	0.0136 vs. 0.0096 (NS)[b]
Ong, 2013[3]	PO Paricalcitol (N=36) titrated to achieve at least 30% reduction in iPTH and a range of 150-300 pg/mL	PO Calcitriol (N=30) titrated to achieve at least 30% reduction in iPTH and a range of 150-300 pg/mL	Phosphate binders, dialysate calcium	% with iPTH decrease by >30%	61.1% vs. 73.3% (P=0.29)
				Median maximal iPTH reduction	77.1% vs. 83.7% (NS)
				Mean (SD) calcium at 24 weeks, mmol/L Mean change from baseline in serum calcium	2.36 (0.25) vs. 2.31 (0.17) (NS) 0.20 vs. 0.19 (NS)
				Mean (SD) phosphate at 24 weeks, mmol/L	1.86 (0.52) vs. 1.99 (0.56) (NS)
				Mean (SD) alkaline phosphatase at 24 weeks, U/L Median change from baseline in ALP, IU/L	113.5 (62.3) vs.134.72 (151.9) (NS) 67.5 vs. 46.5 (P=0.038)
				Serious adverse event episodes	25% vs. 16%
				Hypercalcemia (serum Ca > 2.74 mmol/L), %	16.7% vs. 16.7% (NS)
				GI disorders, N (%)	3 (8) vs. 0 (0)
				CVD disorders, N (%)	4 (11) vs. 4 (13)
				Mortality, N (%)	2 (6) vs. NR
Sprague, 2003[4]	IV Calcitriol: Initial dose 0.01 µg/kg, adjusted up to 0.06 µg/kg[c]	IV Paricalcitol: Initial dose 0.4 µg/kg, adjusted up to 0.24 µg/kg[c]	Stable P binder[d]	Ca >2.87 mmol/L and/or CaXP >6.05 $mmol^2/L^2$	64% vs. 68%
				% Pts with ≥50% reduction in	>80% vs. >80% (nd)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				PTH from baseline	
				Time to ≥50% reduction in PTH from baseline (days)	108 vs. 87 (.025)[l]
				Hypercalcemic and/or CaXP >75 at least once during treatment	68% vs. 64% (NS)
				Hypercalcemic and/or CaXP >75 for at least 2 consecutive blood draws	50% vs. 38% (.034)
				Hyperccalcemic for at least 2 consecutive blood draws and/or CaXP >75 for a t least one period of 4 consecutive blood draws	33% vs. 18%
Cinacalcet vs. placebo					
Block, 2004[5]	Cinacalcet 30-180 mg/d PO, adjusted if iPTH >21.2 pmol/L and Ca >1.95 mmol/L[e]	Placebo	Current standards of care concerning P binder and vitamin D use, dialysate Ca unadjusted[f]	% pts with PTH ≤26.5 pmol/L	43% vs. 5% (<.001) OR 7.3 (95% CI 4.8-11.1)
				% pts with ≥30% decrease PTH	64% vs. 11% (<.001) OR 15.38 (95% CI 10.31-22.95)
				% Δ iPTH	–43% vs. +9% (<.001)
				% Δ Ca	–6.8% vs. +0.4% (<.001)
				% Δ P	–8.4% vs. +0.2% (<.001)
				% Δ CaXP	–14.6% vs. +0.5% (<.001)
				% Δ b-ALP	–35.1% vs. -4.0% (<.001)
				Mortality	2% vs. 2%
				Nausea	32% vs. 19% (P<0.001)
				Vomiting	30% vs. 16% (P<0.001)
Chertow, 2012[6] Floege, 2015[7] Wheeler, 2014[8] Parfrey, 2015[9] Moe, 2014[10] Moe, 2015[11]	Cinacalcet 30-180 mg/d PO, adjusted for iPTH and Ca	Placebo	Dialysis, P binders, vitamin D sterols, calcium supplements and other medications prescribed by treating physicians	All-cause mortality	703 vs. 718 deaths HR 0.94 (95% CI 0.85-1.04) (p=0.25)
				Death, or first nonfatal cardiovascular event, n (%)	938 (48%) vs. 952 (49%) aRH, 0.88 (95% CI, 0.79 to 0.97; p=0.008)
				Death by cardiovascular events	377 vs. 391 Relative Hazard 0.92 (95% CI 0.80-1.07) (p=0.28)
				Cumulative cardiovascular events	25.3 (95% CI 24.1-26.5) vs. 27.3 (26.0-28.5) per 100 patients (p=0.02)
				Myocardial infarction	187 vs. 183 HR 0.97 (95% CI 0.79-1.19) (p=0.80)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				Hospitalization for unstable angina	56 vs. 66 HR 0.82 (95% CI 0.58-1.18) (p=0.28)
				Heart failure, episodes	206 vs. 236 HR 0.82 (95% CI 0.68-0.99) (p=0.03)
				Peripheral vascular events	184 vs. 200 HR 0.87 (95% CI 0.72-1.07) (p=0.19)
				Stroke	115 vs. 102 Relative Hazard 1.07 (95% CI 0.82-1.40) (p=0.61)
				Parathyroidectomy, n (%)	140 (7%) vs. 278 (14%) Relative hazard 0.44 (95% CI, 0.36 to 0.54)
				Fracture, n (%)	238 (12%) vs. 255 (13%) Relative hazard 0.85 (95% CI, 0.71 to 1.01)
				Vertebral fracture, HR (95% CI)	0.71 (0.40 to 1.27)
				Non-vertebral fracture, HR (95% CI)	0.91 (0.76 to 1.09)
				Hypocalcemia (serum Ca <8.0 mg/dL [2.0 mmol/L]), %	49% vs. 13%
				Hypocalcemia (serum Ca <7.5 mg/dL [1.87 mmol/L]), %	25% vs. 7%
				Hypercalcemia (serum Ca ≥ 10.5 mg/dL [2.62 mmol/L]), %	33% vs. 51%
				Hypercalcemia (serum Ca ≥ 11.0 mg/dL [2.75 mmol/L]), %	14% vs. 24%
				Severe, unremitting hyperparathyroidism, n (%)	143 (7%) vs. 304 (16%)
				Nausea, n (%)	563 (29%) vs. 299 (16%)
				Vomiting, n (%)	497 (26%) vs. 264 (14%)
				Diarrhea, n (%)	397 (21%) vs. 360 (19%)
				Calcific uremic arteriolopathy incidence, N (%) aHR (95% CI)	6 (0.3%) vs 18 (0.9%) HR 0.25 (0.10 to 0.67) (p<0.01)
				Time to first cardiovascular event, HR (95% CI)	0.89 (0.80 to 0.99) (p=0.029)
				Occurrence of first clinical fracture, relative hazard (95% CI)	0.84 (0.69 to 1.01) (p=0.07)
				Median FGF-23 values at wk 20, pg/mL	2255 vs. 5580 (*P*<0.001)
El-Shafey, 2011[12]	Cinacalcet 30-180 mg/d PO, adjusted so	Conventional therapy	Calcium-based phosphate binders, calcium supplements	iPTH level post-treatment, pmol/L	38.12 (SD 21.51) vs 67.78 (SD 25.63) (p<0.001)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
	iPTH <10.5 pmol/L and Ca <1.87 mmol/L	IV alfacalcidol 3x per week at end of dialysis session and phosphate binders	or vitamin D sterols		
				Change in iPTH level from baseline, pmol/L	-32.4 (SD 3.74) vs -7.09 (SD 6.23)
				Serum Ca level post treatment, mmol/L	2.22 (SD 0.18) vs 2.41 (SD 0.12) (P<0.001)
				Change in serum Ca level from baseline, mmol/L	-0.17 (SD 0.03) vs 0.13 (SD 0.04)
				Serum P level post treatment, mmol/L	1.47 (SD 0.28) vs 1.71 (SD 0.22) (p<0.001)
				Change in serum P level from baseline, mmol/L	-0.34 (SD 0.06) vs -0.05 (SD 0.07)
				Parathyroidectomy, N (%)	1 (1.9%) vs 4 (15.4%) (p<0.05)
				Fractures (femur and tibia), N (%)	2 (3.8%) vs 5 (19.2%) (p<0.05)
				Lumbar spine BMD, before vs after (in cinacalcet patients who achieved K/DOQI targets)	0.92 (SD 0.16) vs 0.92 (SD 0.17) (p=0.956)
				Lumbar spine T-score, before vs after (in cinacalcet patients who achieved K/DOQI targets)	-1.59 (SD 1.26) vs -1.59 (SD 1.28) (p=0.914)
				Femur BMD, before vs after (in cinacalcet patients who achieved K/DOQI targets)	0.84 (SD 0.19) vs 0.85 (SD 0.18) (p=0.029)
				Femur T-score, before vs after (in cinacalcet patients who achieved K/DOQI targets)	-1.43 (SD 1.02) vs -1.29 (SD 0.94) (p=0.014
				Mortality, %	2% vs. 4%
				Nausea, n (%)	7 (13%) vs. 1 (4%)
				Vomiting, n (%)	5 (9%) vs. 2 (8%)
				Diarrhea, n (%)	3 (6%) vs. 1 (4%)
				Dyspepsia, n (%)	5 (9%) vs. 2 (8%)
				Hypocalcemia, n (%)	6 (11%) vs. 0 (0%)
Lindberg, 2005[13]	Cinacalcet 30-180 mg/d adjusted at 4 wk intervals if iPTH >21.2 pmol/L and Ca >1.95 mmol/L[g]	Placebo	Previously prescribed P binders and/or vitamin D, dialysate Ca adjusted[h]	% pts with mean iPTH ≤26.5 pmol/L[i]	39% vs. 7% (<.001)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				%pts with a reduction in iPTH ≥30%[j]	65% vs. 13% (<.001)
				%Δ iPTH	–40.3% vs. +4.1% (<.001)
				%Δ Ca	–6.5% vs. +0.9% (<.001)
				%Δ P	–7.2% vs. –2.2% (<.05)
				%Δ CaXP[k]	–12.8% vs. –1.4% (<.001)
				Mortality, %	1% vs. 2%
				Withdrawn due to parathyroidectomy, %	0% vs. 2%
				Nausea, %	30% vs. 22%
				Vomiting, %	23% vs. 12%
				Diarrhea, %	24% s. 19%
				Abdominal pain, %	12% vs. 18%
Cinacalcet vs. vitamin D					
Fishbane, 2008[14]	Cinacalcet-D Initial dose 30 mg/d and; Cinacalcet dosage raised incrementally at 4-wk intervals to 60, 90, 120, or 180 mg/d to achieve PTH level between 150 and 300 pg/mL. Cinacalcet withheld if PTH was >150 pg/mL	Flex-D Flexible, escalating doses of 2 micrograms paricalcitol or 1 microgram doxercalciferol with thrice weekly dialysis; Vitamin D dosage according to KDOQI guidelines	Either 2 micrograms of paricalcitol or 1 microgram doxercalciferol by IV thrice weekly with dialysis; vitamin D dosage could not be reduced if calcium levels were <7.5 mg/dl or hypocalcemia persisted; 98% subjects received a phosphate binder during study	Adverse events leading to withdrawal	6% vs. 1%
				Death	2% vs. 2% (n=3 in each group, not considered treatment related)
				Median PTH (pg/mL)	320 vs. 559
				Median Ca (mg/dl)	8.9 vs. 9.8
				Median P (mg/dl)	5.3 vs. 5.3 (NS)
				Proportion of subjects in each group who achieved KDOQI target ranges for PTH and P	No difference between groups
				Proportion of subjects who achieved KDOQI target range for CA of 8.5 to 9.5 mg/dl	63% vs. 25% (P< 0.001)
				Subjects who experienced at least 1 Adverse Event	71% vs. 71%
				Diarrhea	8% vs. 11%

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				Muscle spasms	8% vs. 10%
				Headache	7% vs. 6%
				Hypotension during dialysis	5% vs. 7%
Ketteler, 2012[15]	IV Paricalcitol (N=62) Mean dose 5.5 µg	IV Cinacalcet (N=64) 61.6 mg	Low dose Vitamin D	% who achieved mean iPTH between 150-300 pg/ml	57.7% vs. 32.7% (P=0.016)
				Mean iPTH decrease by >=30%	84.6% vs. 49.0% (P<0.001)
				Mean iPTH decrease by >=50%	65.4% vs. 22.4% (P<0.001)
				Δ Mean iPTH, pg/mL	-244.2 ± 36.4 vs. −78.4±36.4 (<0.05)
				Δ Mean (± SE) Corrected Calcium mg/dl	0.5a ±0.1 vs. −0.7±0.1 (<0.05)
				Δ Mean (± SE) P mg/dl	0.2±0.2 vs. -0.2±0.2 (NS)
				Δ Mean (± SE) ALP (IU/L)	-19.1 ± 6.6 vs. 30.5±6.5 (<0.05)
				Hypocalcaemia (%)	0% vs. 46.9% (<0.001)
				Hypercalcemia (%)	7.7% vs. 0 (0.118)
				Any Adverse Effect (%)	80.6% vs. 84.6% (NS)
				Mortality, n (%)	1 (2) vs. 0 (0) (NS)
				Major adverse cardiac events, n (%)	6 (9.7) vs. 2 (3.1) (NS)
				CVD or cerebrovascular mortality, n (%)	1 (2) vs. 0 (0)
	PO Paricalcitol (N=72) Mean dose 3.5 µg	PO Cinacalcet (N=70) 31.8 mg	Low dose Vitamin D	% who achieved mean iPTH between 150-300 pg/ml	54.4% vs. 43.4% (P=0.260)
				Mean iPTH decrease by >=30%	68.4 % vs. 56.6% (P=0.239)
				Mean iPTH decrease by >=50%	45.6% vs. 41.5% (P=0.704)
				Δ Mean (± SE) iPTH, pg/mL	−216.3 ± 24.5 vs.−150.3 ± 24.5 (NS)
				Δ Mean (± SE) Corrected Calcium mg/dl	0.3 ±0.1 vs.−0.7±0.1 (<0.05)
				Δ Mean (± SE) P mg/dl	0.7 ±0.2 vs. 0.2±0.2 (<0.05)
				Δ Mean (± SE) ALP (IU/L)	−15.7 ± 5.1 vs. 5.4±4.6 (<0.05)
				Hypocalcaemia (%)	3.6% vs. 54.7% (<0.001)
				Hypercalcemia (%)	0% vs. 0%
				Any Adverse Effect (%)	83.3% vs. 77.1% (NS)
				Mortality, n (%)	3 (4.2) vs. 0 (0) (NS)
				Major adverse cardiac events, n (%)	6 (8.3) vs. 1 (1.4) (NS)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				CVD or cerebrovascular mortality, n (%)	2 (2.8) vs. 0 (0)
Raggi, 2014[16]	Cinacalcet + vitamin D 30-180 mg/day, plus low dose vit D sterols, adjusted so PTH <300 pg/ml N=115	Flexible Vitamin D adjusted so PTH <300 pg/ml N=120	Calcium phosphate binders	Median % change (P10, P90) in Agatston scores from baseline to week 52, Total coronary artery	24 (-22 to 19) vs 31 (-9 to 179) Treatment diff -10.3 (95% CI, -22.6 to 0.8) (p=0.073)
				Median % change (P10, P90) in volume Ca scores from baseline to week 52, Total coronary artery	22 (-12 to 105) vs 30 (-6 to 133) Treatment diff -13.3 (95% CI, -23.8 to -3.3) (p=0.009)
				Median % change (P10, P90) in Agatston scores from baseline to week 52, Thoracic aorta	19 (-11 to 103) vs 33 (-8 to 187) Treatment diff -10.4 (95% CI, -23.7 to 0.0) (p=0.055)
				Median % change (P10, P90) in volume Ca scores from baseline to week 52, Thoracic aorta	16 (-3 to 103) vs 29 (-3 to 158) Treatment diff -7.5 (95% CI, -19.6 to 1.3) (p=0.095)
				Median % change (P10, P90) in Agatston scores from baseline to week 52, Aortic valve	6 (-100 to 105) vs 52 (-86 to 200) Treatment diff -44.7 (95% CI, -85.8 to -6.1) (p=0.014)
				Median % change (P10, P90) in volume Ca scores from baseline to week 52, Aortic valve	9 (-100 to 88) vs 35 (-84 to 184) Treatment diff -31.6 (95% CI, -56.8 to -0.8) (p=0.035)
				Median % change (P10, P90) in Agatston scores from baseline to week 52, Mitral valve	12 (-39 to 443) vs 54 (-55 to 823) Treatment diff -34.8 (95% CI, -71.6 to 0.6) (p=0.053)
				Median % change (P10, P90) in volume Ca scores from baseline to week 52, Mitral valve	14 (-34 to 250) vs 42 (-31 to 439) Treatment diff -21.1 (95% CI, -54.6 to 6.3) (p=0.125)
				Proportion demonstrating >15% progression in Agatston total CAC score, N (%)	63 (55) vs 77 (65) (p=0.094)
				Adverse events, N (%)	156 (87%) vs 156 (87%)
				Deaths, N (%)	12 (7%) vs 12 (7%)
				Adverse events attributed to	Gastrointestinal: 37 (21%)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				cinacalcet	Hypocalcemia: 12 (7%)
				Adverse events attributed to Vit D	3 (2%) vs. 7 (4%) Hypocalcemia: 1 vs 5
				Mean absolute change in PTH from baseline to 52 wk, pg/mL	-120 vs. -60 (P=0.018)
				Mean absolute change in corrected Ca from baseline to 52 wk, mg/dL	-0.55 vs. 0.2 (P<0.001)
				Mean absolute change in serum P from baseline to 52 wk, mg/dL	-0.8 vs. -0.2 (P=0.025)
				Parathyroidectomy, n	0 vs. 2
Sprague, 2015[17]	Cinacalcet Started at 30 mg/dl and titrated every 4 wks up to 180 mg to achieve PTH<300 pg/ml N=155	Vitamin D analogues (paracalcitol & doxecalciferol in USA; Calcitriol & alfacalcidol in non-USA sites) Titrated to achieve PTH < 300 pg/ml N=157	Nutritional Vitamin D allowed in Cinacalcet arm but not in Vitamin D analogue arm	Mean Δ (SEM) in calcium from BL to wk 52, mg/dL Mean difference in change (95% CI) P-value	-0.86 (0.08) vs. 0.20 (0.06) -1.06 (-1.26 to -0.87) *P*<0.001
				Mean Δ (SEM) in phosphate from BL to wk 52, mg/dL Mean difference in change (95% CI) P-value	-0.617 (0.170) vs. 0.005 (0.160) -0.622 (-1.08 to -0.16) *P*<0.001
				Mean Δ (SEM) in PTH from BL to wk 52, pg/mL Mean difference in change (95% CI) P-value	-147.3 (47.2) vs. -78.9 (42.6) -68.4 (-193.6 to 56.90) P=0.28
				Mean Δ (SEM) in FGF-23 from BL to wk 52, ng/L Mean difference in change (95% CI) P-value	-107.5 (26.8) vs. 138.9 (27.8) -246.3 (-322.6 to -170.0 (0.001)
Urena-Torres, 2013[18] Rodriguez, 2013[19]	Cinacalcet + vitamin D sterols Starting dose 30 mg/day, adjusted to achieve PTH 150-300 pg/ml N=153	Calcitriol (or a synthetic analog to Calcitriol) Adjusted at discretion of independent investigators	Phosphate binders	≥30% PTH reduction from baseline at 12 months	63% vs 48% (p<0.05)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
		N=151			
				PTH ≤300 pg/ml, entire cohort	12 mo: 52% vs 44% (p NS)
				PTH <150 pg/ml at 12 months	18% vs 11% (p NS)
				Mean PTH pg/ml (95% CI), at 12 months	293.9 (262.9-328.6) vs 364.8 (325.8-408.4) (p<0.01)
				Mean % reduction in PTH (95% CI) at 12 months	34 (26-42) vs 12 (4-20) (p<0.001)
				Corrected serum Ca <10.2 mg/dl, at 12 months	95% vs 93% (p NS)
				Serum P <5.5 mg/dl, at 12 months	53% vs 53% (p NS)
				Mean corrected serum Ca mg/ml (95% CI), at 12 months	9.0 (8.8-9.1) vs 9.4 (9.3-9.5) (p<0.001)
				Mean serum P mg/dl (95% CI) , at 12 months	5.4 (5.1-5.6) vs 5.5 (5.3-5.8) (p<0.001)
				≥1 low serum Ca value (≤7.5 mg/dl) %	9% vs 2% (p<0.01)
				≥1 low serum Ca value (<8.4 mg/dl) %	38% vs. 8% (p≤0.05)
				Sustained hypocalcaemia (2 consecutive serum Ca values ≤7.5 mg/dl), entire cohort	12 mo: 3% vs 1% (p≥0.05)
				Gastrointestinal events, %	55% vs. 34%; OR 2.3 (95% CI, 1.7 to 3.7)
				Mortality, n	8 vs. 7
				Parathyroidectomy, n	1 vs. 1
Wetmore, 2015[20]	Cinacalcet Initiated at 30 mg/d titrated every 4 weeks to max 180 mg/day based on PTH and Ca assessment	Vitamin D analogs Initial dosage approximately equivalent to an intravenous dosage of 2 micrograms paricalcitol 3x/weekly. Recommended equivalent dosages 0.5 micrograms intravenous calcitriol 3x/weekly, 1 microgram	No maximum dose of vitamin D analogs; cinacalcet patients could receive vitamin D analogs for safety, nutritional D supplementation allowed, no restrictions on calcium supplements, dialysate calcium, or phosphate binders	Mean % change in PTH between baseline and efficacy assessment phase	-12.1 vs. -7.0 (p= 0.35)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
		intravenous doxercalciferol or alfacalcidol 3x/week, 0.25 micrograms/day oral calcitriol, or 0.5 micrograms per day oral alfacalcidol			
				Mean PTH (pg/ml)	689.0 vs. 708.6 (P= 0.20)
				Mean Ca (mg/dl)	8.7 vs. 9.7 (P<0.001)
				Mean P (mg/dl)	5.0 vs. 5.6 (P= 0.002)
				Treatment Adverse Events resulting in discontinuation of tx	7.8% vs. 5.8%
				Death	8.5% vs. 5.8%
				Hypocalcemia	17.6% in Arm 1
				Patients with at least one event of Ca level < 8.0 mg/dl	69.9% vs. 9.0%
				Mean change in ALP (U/L)	+51.7 vs. +17.4 (P<0.01)
Native vitamin D vs. placebo					
Bhan, 2015[21]	Ergocalciferol 50,000 IU monthly N=33	Placebo N=36	Study drug is given only for 12 weeks.	All cause mortality at end of 1 year follow up	0% (0/33) vs. 8.3% (3/33) vs. 13.9% (5/36) P=0.08
	Ergocalciferol 50,000 IU weekly N=36			All cause mortality for combined analysis of ergocalciferol at end1 year (Hazard ratio, 95% CI)	0.28 (0.07-1.19) (P=0.07)
Hewitt, 2013[22]	Cholecalciferol 10 ml oral solution medium chain triglyceride containing 50,000 IU of cholecalciferol (OsteVit D; Key Pharmaceuticals, Sydney, Australia) weekly for first 8 weeks, followed by monthly for remaining 4 months at completion of routine dialysis treatment on scheduled days	Placebo Indistinguishable medium chain triglyceride placebo taken weekly in first 8 weeks and monthly for next 4 months at completion of routine dialysis treatment on scheduled days	Patients treated with calcium based phosphate binders before study start remained unchanged in 4 weeks before study entry and could be altered if necessary to achieve acceptable levels of serum Ca or P	HRQOL using Kidney Disease Quality of Life-36 survey	No significant differences in the HRQOL domains
				Ca	Not influenced by treatment
				iPTH	Not influenced by treatment

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				ALP	Not influenced by treatment
				Mean 25(OH)D (ng/ml)	35 vs. 16 (P<0.001)
				Mean $1,25(OH)_2D$ (pg/ml)	18 vs. 12 (P=0.001)
				Falls during study period (n)	5 vs. 2 (NS)
				Fractures during study period (n)	1 vs. 0 (NS)
				Serum Ca <10.4 mg/dl on >/= 1 occasions (n)	3 vs. 2 (NS)
				Serum P >5.0 mg/dl on >/= 1 occasions (n)	17 vs. 20 (NS)
				Gastrointestinal events (n)	3 vs. 3 (NS)
				Positive blood cultures/central venous catheter sepsis (n)	1 vs. 1 (NS)
				Death; 1 cerebrovascular, 1 cardiovascular (n)	1 vs. 1 (NS)
Mose, 2014[23]	Cholecalciferol 300 IU daily	Placebo	Pts allowed on other medications	Mean left ventricular mass index at 6 months (g/m^2)	127 vs. 111 (p = 0.397)
				Median 25(OH)D (nmol/L)	84 vs. 30 (p <0.001)
				Median PTH (pmol/L)	17.4 vs. 12.9 (p=0.986)
				Mean Ca (mg/dL)	1.20 vs. 1.20 (p=0.724)
				Mean P (nmol/L)	1.73 vs. 1.59 (p=0.103)
				Median ALP (U/L)	73 vs. 72 (p=0.393)
Studies conducted among transplant patients					
Amer, 2013[24]	Paricalcitol (N=51) Initial dose 1 µg/d increased to 2 µg/d in 2 weeks if no hypercalcemia, then maximum reduced to 0.5 µg/d	Control (N=49)	Alemtuzumab 30mg, single dose 1-4 doses of Methylprednisolone (total dose<950 mg) Calcium carbonate 500mg, BID	Hyperthyroidism: either parathyroidectomy or PTH > 65 pg./ml at 1 year	15 (29%) vs. 31 (63%) (P=0.0005)
				Mean eGFR	51.2 vs. 52.7 (NS)
				Change in eGFR	6.2 vs. 7.4 (NS)
				Mean Calcium, mg/dl, at 1 yr	9.9 vs. 9.7 (<0.001)
				Mean P mg/dl	3.2 vs. 3.5 (NS)
				Total 25-hydroxyvitamin D	38 vs. 37 (NS)
				Lumbar spine (mean T score)	-0.52 vs. -0.25 (NS)
				Mean change in lumbar spine t-score	0.35 vs. 0.35 (NS)
				Hip (mean T score)	-0.74 vs. -0.52 (NS)
				Mean change in hip t-score	0.21 vs. 0.15 (NS)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
				Osteopenia of lumbar spine, n (%)	12 (29%) vs. 9 (21%) (NS)
				Osteopenia of hip, n (%)	12 (29%) vs. 9 (21%) (NS)
				Median PTH (mg/dL) at 1 yr	42 vs. 85 (p=0.0004)
				Parathyroidectomy, n	0 vs. 2
				Mortality, n	1 vs. 0
				Myocardial infarction, n	0 vs. 1
				Atrial fibrillation, n	1 vs. 1
				Orthostasis, n	1 vs. 0
				Bone fracture, n	1 vs. 0
				Mild hypercalcemia, %	20% vs. 6%
Torres, 2004[25]	Calcitriol (n=45) 0.5 µg every other day for 1st 3 mo	Placebo (n=41) every other day	500 mg/d elemental Ca for 12 mo[l] Induction: ATG Maintenance: prednisone, CsA and MMF or AZA[m]	Mean BMD, femoral neck (g/cm^2)	0.82 vs. 0.74 (≤.01)
				Mean BMD, intertrochanteric area (g/cm^2)	1.07 vs. 1.01 (<.05)
				Mean BMD, lumbar spine (g/cm^2)	0.99 vs. 0.93 (<.05)
				Mean BMD, total hip (g/cm^2)	0.91 vs. 0.85 (<.05)
				Mean BMD, trochanter (g/cm^2)	0.68 vs. 0.63 (<.05)
				Mean BMD, ward's triangle (g/cm^2)	0.64 vs. 0.54 (≤.01)
				Mean CrCl (mL/min)	83.7 vs. 76 (NS)
				Mean Ca (mmol/L)	2.48 vs. 2.45 (NS)
				Mean P (mmol/L)	1.19 vs. 1.23 (NS)
				Mean iPTH (pmol/L)	7.1 vs. 8.8 (<.01)
				Mean ALP (IU/L)	205.5 vs. 188 (NS)
				Mean Bicarbonate (mEq/L)	27.3 vs. 27.6 (NS)
				CrCl ≤ 35 mL/min	9% vs. 7%
				Graft loss	NR vs. 4%
				Irreversible rejection	0% vs. 0%[b]
				Ca > 2.74 mmo/L	5.5% vs. 8.6%
				No symptomatic fractures	0% vs. 0%
				Total discontinued due to adverse events	0% vs. 4%
				Mortality	0% vs. 0%
Jeffery, 2003[26]	Alendronate (n=46) 10 mg/d	Calcitriol (n=51) 0.25 µg/d PO	Arm 1: 1000 mg/d dietary Ca + 500 mg/d elemental Ca	Mean BMD, lumbar spine (g/cm^2)	1.025 vs. 1.034 (0.08)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
			Arm 2: Prednisone + AZA or Predinose + CsA with or without AZA or MMF		
				Mean BMD, total proximal femur (g/cm^2)	0.836 vs. 0.857 (NS)
				Mean eGFR (mL/min/1.73 m^2)	74 vs. 73 (NS)
Evenepoel, 2014[27]	Cinacalcet 30-180 mg/d adjusted at 4 wk intervals if iPTH <3.7 pmol/L and Ca <2.1 mmol/L N=57	Placebo N=57	Bisphosphonates, vit D, Ca, phosphate binders or thiazide diuretics were not allowed	Mean corrected total calcium, mg/dl	Baseline: 11.28 (SD 0.41) vs 11.31 (SD 0.50) FU (wk56): 11.04 (SD 0.69) vs 11.01 (SD 0.63)
				Mean iPTH, pg/ml	Baseline: 327.7 (SD 262.6) vs 307.5 (SD 180.5) FU (wk56): 234.2 (SD 119.0) vs 276.7 (SD 243.9)
				Mean P, mg/dl	Baseline: 2.66 (SD 0.54) vs 2.48 (SD 0.52) FU (wk56): 2.87 (SD 0.54) vs 2.71 (SD 0.47)
				Mean FGF-23, pg/ml	Baseline: 26.243 (SD 23.981) vs 23.907 (SD 14.078) FU (wk52): 17.059 (SD 10.490) vs 20.216 (22.346) % change: -7.06 (SE 2.06) vs -1.18 (SE 4.25)
				Mean 25(OH)D_3, ng/ml	Baseline: 18.49 (SD 8.92) vs 20.48 (SD 10.54) FU (wk52): 22.96 (SD 9.59) vs 22.67 (SD 8.95)
				Mean eGFR, ml/min/1.73m^2	Baseline: 57.00 (SD 17.31) vs 54.68 (14.79) FU (wk52): 55.80 (17.94) vs 54.17 (SD 15.24) Mean difference: -0.4 (95% CI: -4.37 to 3.57) (p=0.842)
				Mean BMD at femoral neck, g/cm^2	Baseline: 0.737 (SD 0.023) vs 0.732 (SD 0.022) FU (wk52): 0.751 (SD 0.024) vs 0.728 (SD 0.024) % change: 2.16 (SD 1.07) vs 0.73 (SD 0.63) Mean difference in % change: 1.41% (95% CI: -1.10 to 3.93) (p=0.266)
				Mean BMD at femoral neck, z-score	Baseline: -0.82 (SE 0.12) vs. -0.86 (SE 0.14) FU (wk52): -0.70 (SE 0.13) vs. -0.83 (SE

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
					0.14)
				Mean BMD at lumbar spine, g/cm^2	Baseline: 0.985 (SD 0.021) vs 0.966 (SD 0.29) FU (wk52): 0.991 (SD 0.021) vs 0.963 (SD 0.031) % change: 0.598 (SD 0.827) vs 1.172 (SD 0.766)
				Mean BMD at total spine, z-score	Baseline: -0.58 (SE 0.18) vs. -0.75 (SE 0.20) FU (wk52): -0.51 (SE 0.16) vs. -0.68 (SE 0.21)
				Mean BMD at distal 1/3 radius, g/cm^2	Baseline: 0.653 (SD 0.010) vs 0.622 (SD 0.016) FU (wk52): 0.641 (SD 0.012) vs 0.602 (SD 0.018) % change: -2.714 (SD 0.781) vs -1.992 (SD 0.591)
				Mean BMD at total hip, z-score	Baseline: -0.80 (SE 0.13) vs. -1.00 (SE 0.13) FU (wk 52): -0.71 (SE 0.14) vs. -0.96 (SE 0.14)
				Death, N	1 vs 0
				Foot fracture, N	1 vs 0
				Femoral neck and vertebral fracture, N	0 vs 2
				Diarrhea, n (%)	9 (16%) vs. 3 (5%)
Wissing, 2005[28]	Cholecalciferol 25 000 IU PO once per mo	No treatment	400 mg/d elemental Ca Tac or CsA and 2 g/d MMF; low dose steroids	Mean BMD femoral neck (g/cm^2)	0.78 vs. 0.74 (NS)
				Mean BMD femoral shaft (g/cm^2)	1.57 vs. 1.53 (NS)
				Mean BMD lumbar spine (g/cm^2)	1.01 vs. 0.92 (NS)
				Mean GFR (mL/min/1.73 m^2)	60 vs. 64 (NS)
				Mean Ca (mmol/L)	2.52 vs. 2.52 (NS)
				Mean P (mmol/dL)	1.07 vs. 1.03 (NS)
				Mean iPTH (pmol/L)	5.7 vs. 9.4 (.018)
De Sevaux, 2002[29]	Ca plus D 0.25 micrograms of 1-alpha-hydroxy vitamin D (Etalpha, Leo Pharmaceuticals, Weesp, The Netherlands) plus calciumlactogluconate containing 1000 mg of	No Treatment	Immunosuppressive therapy for 6 mos post-transplant: cyclosporine prednisone, mycophenolate mofetil, except for recipients of a graft from HLA-identical living related donor, who were treated with	Mean Ca adjusted (mmol/L)	2.45 (SD 0.18) vs. 2.43 (SD 0.23)

Author, year	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2
	elemental calcium (Calcium Sandoz Fortissimum, Novartis Pharma, Arnhem, The Netherlands)		cyclosporine and prednisone during the first 3 months then cyclosporine replaced by azathioprine		
				Mean P (mmol/L)	0.92 (SD 0.23) vs. 0.89 (SD 0.20)
				Mean Alkaline Phosphatase (IU/L)	96 (SD 71, P <0.0001 comparison to baseline) vs. 97 (SD 38, P<0.0001 comparison to baseline)
				Mean 25-OH Vitamin D (ng/mL)	21 (SD 11) vs. 20 (SD 9, P <0.001 comparison to baseline)
				Severe hypercalcemia (adjusted serum Ca >2.80 mmol/L on more than 1 occasion, n)	6 vs. 2 (NS)
				Avascular necrosis (n)	1 vs. 0
				Death (n)	0 vs. 0

aHR = adjusted hazard ratio; ALP = alkaline phosphatase; BMD = bone mineral density; Ca = calcium; CI = confidence interval; DID, difference in difference; eGFR = estimated glomerular filtration rate; FGF-23 = fibroblast growth factor-23; FU = followup; HD = hemodialysis; iPTH = intact parathyroid hormone; OR = odds ratio; P = phosphate; P10, P90 = tenth percentile, ninetieth percentile; PO = orally; Q1, Q3 = first quartile, third quartile; SD = standard deviation; SE = standard error

a. Placebo group had worsening due to HPT but calcitriol worsened from adynamic bone disease.
b. Estimated from graph.
c. Titrated at 4-wk intervals to ≥50% reduction of PTH. Dose reduced if PTH <10.6 pmol/L, Ca >2.87 mmol/L or if CaXP >6.05 $mmol^2/L^2$ for 2 wk.
d. Predominantly Ca carbonate or Ca acetate (not sevelamer-HCl or aluminum containing binders).
e. Initial dose 30 mg PO once daily, titrated every 3 wk to 60, 90, 120, or 180 mg/d, adjustments permitted if PTH levels were >21.2 mmol/L and Ca ≥1.95 mmol/L. No increase in case of hypocalcemic symptoms or AE precluding dose increases. Dose reductions if PTH <10.6 pmol/L on 3 consecutive visits or AE requiring dose reduction.
f. No restrictions concerning dose and type of P binder. Vitamin D: dose increase if PTH rose by ≥50% from baseline or if Ca <2.1 mmol/L or hypocalcemic symptoms; dose reduction if Ca ≥2.75 mmol/L, P ≥2.1 mmol/L, CaXP ≥5.6 $mmol^2/L^2$, or if PTH <10.6 pmol/L on 3 consecutive visits (for pts with lowest cinacalcet dose).
g. Sequential titration from a 30 mg/d starting dose to 60, 90, 120, and 180 mg/d was permitted at 4-wk intervals when iPTH was >21.2 pmol/L, Ca ≥1.95 mmol/L, symptoms of hypocalcemia were not present, the highest study dose had not been reached, and an AE that precluded a dose increase had not occurred. Patients were instructed to take cinacalcet with or shortly after a meal.
h. Previously prescribed P binders and/or vitamin D. Changes in the dose or type of P-binding agent were not restricted after the screening phase. The vitamin D dose could be reduced or withheld if the Ca ≥2.74 mmol/L, P ≥2.10 mmol/L, or CaXP ≥5.65 $mmol^2/L^2$, then resumed at the investigator's discretion. The dose of vitamin D could be increased if a patient had symptoms of hypocalcemia or Ca <2.1 mmol/L that did not respond to changes in Ca supplements and/or P binders. Dialysate Ca concentration also could be adjusted at the discretion of the investigator.
i. % of patients with mean iPTH ≤31.8 pmol/L (300 pg/mL): 46% vs. 9% (p<.001).
j. % of patients with reduction of iPTH ≥20%: 74% vs. 21% (p<.001); ≥40%: 60% vs. 10% (p<.001); ≥50%: 48% vs. 6% (p<.001).
k. % of patients with CaXP <4.44 $mmol^2/L^2$ (55 mg^2/dl^2): 65% vs. 45% (p<.001); % of patients with a mean reduction of CaXP ≥0.40 $mmol^2/L^2$: 61% vs. 39% (p<.001); ≤0.81 $mmol^2/L^2$: 47% vs. 24%. (p<.001).
l. Ca supplement given as Ca lactogluconate. If Ca >2.82 mmol/L, therapy interrupted for 1 wk. Loop diuretics allowed.
m. The dose of prednisone of 0.3 mg/kg bw/d during the first 3 mo, and then was gradually reduced to 10 mg/d by one year. Cyclosporine was started at 8 mg/kg bw/d, and then adjusted according to total blood levels. Episodes of acute rejection were initially treated with 3 X 500 mg of IV methylprednisolone. Resistant episodes were treated with a 10-d course of OKT-3 (5 mg/d).

Supplemental Table 46. Summary table of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D – quality

Author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Vitamin D analogs vs. placebo								
Baker, 1986[1]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vitamin D analogs head-to-head comparisons								
Hayashi, 2004[2]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Ong, 2013[3]	Yes	Yes	No	No	Unclear	Yes	Unclear	Yes
Sprague, 2003[4]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Cinacalcet vs. placebo								
Block, 2004[5]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Chertow, 2012[6] Floege, 2015[7] Wheeler, 2014[8] Parfrey, 2015[9] Moe, 2014[10]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
El-Shafey, 2011[12]	Unclear	Unclear	No	No	No	No	No	Yes
Lindberg, 2005[13]	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Cinacalcet vs. vitamin D								
Fishbane, 2009[30]	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes
Ketteler, 2012[15]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Yes
Raggi, 2011[16]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Sprague, 2015[17]	Unclear	Unclear	No	No	Unclear	No	Unclear	Yes
Urena-Torres, 2013[18] Rodriguez, 2013[19]	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Wetmore, 2015[20]	No	No	No	No	No	No	No	No
Native vitamin D vs. placebo								
Bhan, 2015[21]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Hewitt, 2013[22]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Mose, 2014[23]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Studies conducted among transplant patients								
Amer, 2013[24]	Yes	Unclear	No	No	No	Yes	Unclear	Yes
Torres, 2004[25]	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Jeffery, 2003[26]	Unclear	Unclear	No	No	No	Yes	Unclear	Yes
Evenepoel, 2014[27]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes
Wissing, 2005[28]	No	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear
De Sevaux, 2002[29]	Yes	Unclear	No	No	No	Yes	Yes	Unclear

Supplemental Table 47. Evidence matrix of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D

	Risk of Bias								
	Low			Moderate			High		
Outcome	Author	*N*	F/U	Author	*N*	F/U	Author	*N*	F/U
Vitamin D analogs vs. placebo									
Mortality							Baker 1986	76 (38)	60 mo
Cardiovascular and cerebrovascular events									
Fracture							Baker 1986	76 (38)	60 mo
Vascular and valvular calcification imaging							Baker 1986	76 (38)	60 mo
Vitamin D analogs head-to-head comparisons									
Mortality	-	-	-	Ong 2013	73 (46)	24 wk	Hayashi, 2004	91 (38)	12 mo
Cardiovascular and cerebrovascular events	-	-	-	Ong 2013	73 (46)	24 wk			
Fracture	-	-	-						
Vascular and valvular calcification imaging	-	-	-						
Cinacalcet vs. placebo									
Mortality	-	-	-	Lindberg, 2005	395 (294)	26 wk	Block, 2004 Chertow, 2012 El-Shafey, 2011	741 (371) 3883 (1948) 82 (55)	6 mo 64 mo 36 wk
Cardiovascular and cerebrovascular events	-	-	-	-	-	-	Chertow, 2012	3883 (1948)	64 mo
Fracture	-	-	-	-	-	-	Chertow, 2012 El-Shafey, 2011	3883 (1948) 82 (55)	64 mo 36 wk
Vascular and valvular calcification imaging	-	-	-				-	-	-
Cinacalcet vs. vitamin D									
Mortality	Fisbane 2009	173 (87)	27 wk	Raggi 2014	360 (115)	52 wk	Ketteler 2012 Urena-Torres 2013 Wetmore 2015	272 (134) 304 (153) 540 (155)	28 wk 56 wk 12 mo
Cardiovascular and cerebrovascular events	-	-	-	-	-	-	Ketteler 2012	272 (134)	28 wk
Fracture	-	-	-	-	-	-	-	-	-
Vascular and valvular calcification imaging	-	-	-	Raggi 2014	360 (115)	52 wk	-	-	-
Native vitamin D vs. placebo									
Mortality	-	-	-	-	-	-			
Cardiovascular and cerebrovascular events	-	-	-	-	-	-	-	-	-
Fracture	-	-	-	-	-	-	-	-	-
Vascular and valvular	-	-	-	-	-	-	-	-	-

calcification imaging			

Supplemental Table 48. Evidence profile of randomized controlled trials examining the treatment of high levels of PTH in CKD G5D

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Vitamin D analogs vs. placebo									
Mortality	1 (RCT)	76 (38)	High	NA	Direct	There were no events.	Very low	We are unable to draw a conclusion.	High
Cardiovascular and cerebrovascular events	0								High
Fracture	1 (RCT)	76 (38)	High	NA	Direct		Very low	We are unable to draw a conclusion.	High
Vascular and valvular calcification imaging	1 (RCT)	76 (38)	High	NA	Direct		Very low	We are unable to draw a conclusion.	Low
Vitamin D analogs vs. placebo									
Mortality	2 (RCTs)	164 (84)	High	Consistent	Direct		Low	Two small studies found no difference in mortality rates.	High
Cardiovascular and cerebrovascular events	1 (RCT)	73 (46)	Moderate	NA	Direct		Very low	We are unable to draw a conclusion.	High
Fracture	0								High
Vascular and valvular calcification imaging	0								Low
Cinacalcet vs placebo									
Mortality	4 (RCTs)	5101 (2668)	High	Consistent	Direct		Low	There is no difference in mortality rates comparing cinacalcet with placebo, but this conclusion is based on mostly short-term studies with few events.	High
Cardiovascular and cerebrovascular events	1 (RCTs)	3883 (1948)	High	Consistent	Direct		Low	Showed significant benefit of cinacalcet over placebo	High
Fracture	2 (RCTs)	3965 (2003)	High	Consistent	Direct		Low	Overall showed some benefit of cinacalcet over placebo in reducing fracture rate	High
Vascular and valvular calcification imaging									Low
Cinacalcet vs. vitamin D									
Outcome	No. of	Total *N* (*N*	ROB	Consistency	Directness of	Other	Quality of	Qualitative and quantitative	Importance

	studies and study design	on study drug)		across studies	the evidence generalizability/ applicability	considerations	evidence for outcome	description of effect	of outcome
Mortality	5 (RCTs)	1649 (644)	High	Consistent	Direct	Mostly short-term studies	Low	There is no difference in mortality rates comparing cinacalcet with vitamin D, but this conclusion is based on mostly short-term studies with few events.	High
Cardiovascular and cerebrovascular events	1 (RCT)	272 (134)	High	NA	Direct	Short-term study	Low	There was no difference in cardiovascular mortality and morbidity.	High
Fracture	0								High
Vascular and valvular calcification imaging	1 (RCT)	360 (115)	Moderate	NA	Direct		Low	The results varied depending on the measurements taken.	Low
Native vitamin D vs. placebo									
Mortality	2 (RCTs)	165 (99)	Low	Consistent	Direct		Low	There was no difference in mortality rates, based on two small, short-term studies.	High
Cardiovascular and cerebrovascular events	1 (RCT)	60 (30)	Low	NA	Direct		Very low	We are unable to draw any conclusions	High
Fracture	1 (RCT)	60 (30)	Low	NA	Direct		Very low	We are unable to draw any conclusions	High
Vascular and valvular calcification imaging	0								Low

ROB = risk of bias; RCT = randomized controlled trial

REFERENCES

1. Baker LR, Muir JW, Sharman VL, Abrams SM, Greenwood RN, Cattell WR, et al. Controlled trial of calcitriol in hemodialysis patients. Clin Nephrol. 1986 Oct;26(4):185-91.

2. Hayashi M, Tsuchiya Y, Itaya Y, Takenaka T, Kobayashi K, Yoshizawa M, et al. Comparison of the effects of calcitriol and maxacalcitol on secondary hyperparathyroidism in patients on chronic haemodialysis: a randomized prospective multicentre trial. Nephrol Dial Transplant. 2004 Aug;19(8):2067-73.

3. Ong LM, Narayanan P, Goh HK, Manocha AB, Ghazali A, Omar M, et al. Randomized controlled trial to compare the efficacy and safety of oral paricalcitol with oral calcitriol in dialysis patients with secondary hyperparathyroidism. Nephrology (Carlton). 2013 Mar;18(3):194-200.

4. Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int. 2003 Apr;63(4):1483-90.

5. Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004 Apr 8;350(15):1516-25.

6. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012 Dec 27;367(26):2482-94.

7. Floege J, Kubo Y, Floege A, Chertow GM, Parfrey PS. The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial. Clin J Am Soc Nephrol. 2015 May 7;10(5):800-7.

8. Wheeler DC, London GM, Parfrey PS, Block GA, Correa-Rotter R, Dehmel B, et al. Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: the EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial. J Am Heart Assoc. 2014 Dec;3(6):e001363.

9. Parfrey PS, Drueke TB, Block GA, Correa-Rotter R, Floege J, Herzog CA, et al. The Effects of Cinacalcet in Older and Younger Patients on Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Clin J Am Soc Nephrol. 2015 May 7;10(5):791-9.

10. Moe SM, Abdalla S, Chertow GM, Parfrey PS, Block GA, Correa-Rotter R, et al. Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial. J Am Soc Nephrol. 2014 Dec 11.

11. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, et al. Cinacalcet, Fibroblast Growth Factor-23, and Cardiovascular Disease in Hemodialysis: The Evaluation

of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Circulation. 2015 Jul 7;132(1):27-39.

12. El-Shafey EM, Alsahow AE, Alsaran K, Sabry AA, Atia M. Cinacalcet hydrochloride therapy for secondary hyperparathyroidism in hemodialysis patients. Ther Apher Dial. 2011 Dec;15(6):547-55.

13. Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol. 2005 Mar;16(3):800-7.

14. Fishbane S, Shapiro WB, Corry DB, Vicks SL, Roppolo M, Rappaport K, et al. Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone: the ACHIEVE study results. Clin J Am Soc Nephrol. 2008 Nov;3(6):1718-25.

15. Ketteler M, Martin KJ, Wolf M, Amdahl M, Cozzolino M, Goldsmith D, et al. Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. Nephrol Dial Transplant. 2012 Aug;27(8):3270-8.

16. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant. 2011 Apr;26(4):1327-39.

17. Sprague SM, Wetmore JB, Gurevich K, Da Roza G, Buerkert J, Reiner M, et al. Effect of Cinacalcet and Vitamin D Analogs on Fibroblast Growth Factor-23 during the Treatment of Secondary Hyperparathyroidism. Clin J Am Soc Nephrol. 2015 Jun 5;10(6):1021-30.

18. Urena-Torres P, Bridges I, Christiano C, Cournoyer SH, Cooper K, Farouk M, et al. Efficacy of cinacalcet with low-dose vitamin D in incident haemodialysis subjects with secondary hyperparathyroidism. Nephrol Dial Transplant. 2013 May;28(5):1241-54.

19. Rodriguez M, Urena-Torres P, Petavy F, Cooper K, Farouk M, Goodman WG. Calcium-mediated parathyroid hormone suppression to assess progression of secondary hyperparathyroidism during treatment among incident dialysis patients. J Clin Endocrinol Metab. 2013 Feb;98(2):618-25.

20. Wetmore JB, Gurevich K, Sprague S, Da Roza G, Buerkert J, Reiner M, et al. A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM). Clin J Am Soc Nephrol. 2015 Apr 22.

21. Bhan I, Dobens D, Tamez H, Deferio JJ, Li YC, Warren HS, et al. Nutritional vitamin D supplementation in dialysis: a randomized trial. Clin J Am Soc Nephrol. 2015 Apr 7;10(4):611-9.

22. Hewitt NA, O'Connor AA, O'Shaughnessy DV, Elder GJ. Effects of cholecalciferol on functional, biochemical, vascular, and quality of life outcomes in hemodialysis patients. Clin J Am Soc Nephrol. 2013 Jul;8(7):1143-9.

23. Mose FH, Vase H, Larsen T, Kancir AS, Kosierkiewic R, Jonczy B, et al. Cardiovascular effects of cholecalciferol treatment in dialysis patients--a randomized controlled trial. BMC Nephrol. 2014;15:50.

24. Amer H, Griffin MD, Stegall MD, Cosio FG, Park WD, Kremers WK, et al. Oral paricalcitol reduces the prevalence of posttransplant hyperparathyroidism: results of an open label randomized trial. Am J Transplant. 2013 Jun;13(6):1576-85.

25. Torres A, Garcia S, Gomez A, Gonzalez A, Barrios Y, Concepcion MT, et al. Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. Kidney Int. 2004 Feb;65(2):705-12.

26. Jeffery JR, Leslie WD, Karpinski ME, Nickerson PW, Rush DN. Prevalence and treatment of decreased bone density in renal transplant recipients: a randomized prospective trial of calcitriol versus alendronate. Transplantation. 2003 Nov 27;76(10):1498-502.

27. Evenepoel P, Cooper K, Holdaas H, Messa P, Mourad G, Olgaard K, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. Am J Transplant. 2014 Nov;14(11):2545-55.

28. Wissing KM, Broeders N, Moreno-Reyes R, Gervy C, Stallenberg B, Abramowicz D. A controlled study of vitamin D3 to prevent bone loss in renal-transplant patients receiving low doses of steroids. Transplantation. 2005 Jan 15;79(1):108-15.

29. De Sevaux RG, Hoitsma AJ, Corstens FH, Wetzels JF. Treatment with vitamin D and calcium reduces bone loss after renal transplantation: a randomized study. J Am Soc Nephrol. 2002 Jun;13(6):1608-14.

30. Fishbane S, Chittineni H, Packman M, Dutka P, Ali N, Durie N. Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. Am J Kidney Dis. 2009 Oct;54(4):647-52.

KDIGO: CKD-MBD Update
Summary of Results for Serum Phosphate and Serum Calcium

Recommendation 4.1.1: In patients with CKD G3a-G5 or G5D, what is the evidence for benefit or harm in maintaining serum phosphate in the normal range compared with other targets of serum phosphate in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Recommendation 4.1.2: In patients with CKD G3a-G5D, what is the evidence for benefit or harm in maintaining serum calcium in the normal range compared with other targets of serum calcium in terms of biochemical outcomes, other surrogate outcomes, and patient-centered outcomes?

Supplemental Table 49. Summary table of studies evaluating different concentrations of serum phosphate or calcium among patients with CKD G3a-G5 or G5D – study characteristics

Author, year	Region of study	N	CKD GFR category	Follow up duration	Funding source
Benavente, 2012[1]	UK	325	Post transplant	67 months (Median, after 12 months)	None
Caravaca, 2011[2]	Spain	184	G3a-G4 (47%) G5 (53%)	10 months	Not reported
Chartsrisak, 2013[3]	Thailand	466	G2-G4	25 months	Government Non profit
Chue, 2011[4]	UK	257	G2-G4	31 months	Non profit
Coen, 2010[5]	Italy	81	G5D	12-18 months	Non profit
Connolly, 2009[6]	Ireland	379	Post transplant (Median 96 month)	75 months	Non profit
De Nicola, 2014[7]	Italy	200	G3a-G3b (45%) G4 (44%) G5 (11%)	Median 31 months	Industry
Denburg, 2013[8]	USA	171	G2-3 (40%) G4-5 (30%) G5D (30%)	12 months	Government
Djukanovic, 2015[9]	Serbia	2153	G5D (HD)	3 years	NR
Eddington, 2010[10]	UK	1390	G2-G5	37 months (Median)	Industry
Fein, 2013[11]	USA	90	G5D (All PD)	31 months	NR
Fernandez-Martin, 2015[12]	Europe	6307	HD	3 years; 23.5 months (Mean); 24.0 months (Median)	Industry, government, and non profit
Fliser, 2007[13]	Germany Austria USA	227	G1 (31.7%) G2 (21.6%) G3a-G3b (27.8%) G4 &G5 (18.9%)	53 months (Median)	Non profit
Floege, 2011[14]	Europe	7970	G5D	21 months (Median)	Industry
Fouque, 2013[15]	France	8377	G5D	30 months (Median)	Industry
Fukagawa, 2014[16] Fukagawa, 2011[17]	Japan	8229	G5D	36 months	Industry
Gallieni, 2012[18]	Italy	490	G5D (All PD)	36 months	Industry
Kimata, 2007[19]	Japan	3973	Hemodialysis	8,056 patient-years	Industry
Lacson, 2009[20]	USA	78,420	G5D (HD)	1 year	None
Lim, 2014[21]	China	2144	CKD G3a-G3b CKD G4	8 years	Not reported
Lin, 2015[22]	Taiwan	94,983	G5D	3 years	None
Markaki, 2012[23]	Greece	74	G5D (47 HD and 27 PD)	Median 50 months	None
McGovern, 2013[24]	U.K.	Total: 57,832 No CKD: 24,184 CKD 1-2: 20,356	CKD G1-G5	30 months	Not reported

Author, year	Region of study	N	CKD GFR category	Follow up duration	Funding source
		CKD 3-5: 13,292			
Menon, 2005[25]	USA	840	G3a-G4	Median 123 months	NR
Miura, 2015[26]	Japan	191	G3a-G5[a]	643 days (Mean) 627 days (Median)	Government
Moore, 2011[27]	UK	270	Transplant recipients	88 months	Industry
Nakai, 2008[28]	Japan	27,404	G5D	3 years	NR
Nakano, 2012[29] Nakano, 2012[30]	Japan	738	Predialysis	Median 4.4 years	NR
Noordzij, 2009[31] Noordzij, 2011[32] Noordzij, 2005[33]	Netherlands	2004	G5D	5 years	Industry
Nowak, 2015[34]	Germany	239	G5D	1461 days (Median)	Industry
Pihlstrom, 2015[35]	Belgium, Denmark, Finland, Germany, Norway, Sweden, Switzerland, UK, Canada	1840	Renal transplant	6.7 years	Industry
Ravani, 2009[36]	Italy	168	G2-G5	Mean 48 months Median 57 months	NR
Sakaguchi, 2014[37]	Japan	142,069	G5D	1 year	NR
Schaeffner, 2007[38]	Austria	733	Renal transplant	Median 6.1 years	NR
Scialla, 2015[39]	USA	511	HD	Median 3.4 years	Industry, government
Scialla, 2013[40]	USA	809	G2, G3a, G3b, G4-G5	1 year	Government
Silva, 2013[41]	Portugal	119	G3a-G3b G4	76 months	Industry
Tentori, 2008[42]	France, Germany, Italy, Japan, Spain, the United Kingdom, United States, Australia, Belgium, Canada, New Zealand, and Sweden,	25,882	HD	1.4 years	Industry
Zhao, 2014[43]	China	1354	PD	2 years	Government

a. Patients also had heart failure.

Supplemental Table 50. Summary table of studies evaluating different concentrations of serum phosphate or calcium among patients with CKD G3a-G5 or G5D – study population characteristics

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
Benavente, 2012[1]	297	44	60	NR	GFR 6 mo; 46 ml/min/1.73m^2 GFR 12 mo: 48 ml/min/1.73m^2 NA	NR NR NR	P 6 mo: 1.02 mmol/L) P 12 mo; 1.06 mmol/L) Ca 6 mo; 2.49 mmol/L) Ca 12 mo; 2.47 mmol/L) ALP 6 mo; 339 IU/L ALP 12 mo; 305 IU/L PTH 6 mo; 91 ng/ml PTH 12 mo; 94 ng/ml	NR
Caravaca, 2011[2]	184	184	49	NR	GFR; 15.2 ml/min/1.73m^2 NA	NR 30 NR	P 4.43 mg/dl Ca 9.32 mg/dl PTH 372 pg/ml	NR
Chartsrisak, 2013[3]	466	65	56	NR	GFR; 42.3 ml/min/1.73m^2 NA	56 91 70	P 3.8 mg/dl Ca 9.3 mg/dl PTH 66 pg/ml (Median) ALP 73.4 IU/L 25(OH)$_2$D 22ng/ml	NR
Chue, 2011[4]	225	59	60	NR	GFR; 43 ml/min/1.73m^2 NA	12 NR NR	P 1.22 mmol/L) Ca 2.34 mmol/L) PTH 51 pg/ml	AIx$_{75}$ (%) 25 PWV (m/s) 9 PWV$_{adj}$ (m/s) 9
Coen, 2010[5]	81	59	67	NR	NA 83 months	10 47 NR	P 5.4 mg/dl Ca(corrected) 9.3 mg/dl PTH 300 pg/ml (Median) ALP 149 IU/L (Median) 25(OH)$_2$D 19.3 ng/ml	CAC time 0 481 Algastone score CAC time 1yr 528 Algastone score
Connolly, 2009[6]	397	47	64	NR	GFR; 52.5 ml/min/1.73m^2 NA	14 NR NR	P 1.03 mmol/L) Ca 2.44 mmol/L) PTH 101 pg/ml	NR
De Nicola, 2014[7]	200	66	62	White 100%	GFR; 28.6 ml/min/1.73m^2 NA		P 4.02 mg/dl Ca 9.36 mg/dl PTH 102 pg/ml	NR
Denburg, 2013[8]	171	5-8 (11%) 9-11 (19%) 12-14 (24%) 15-21 (46%)	59	White 68% Black 44% 0thers 5%	NR NR	NR NR NR	CKD 2–3 Ca, 9.4 mg/dL P 4.2 mg/dL 1,25(OH)2 D, 36.5 pg/mL iPTH, 46 pg/mL FGF-23, 52 pg/mL CKD 4–5 Ca, 9.3 mg/dL	CortBMD Z-score (Mean, SD) CKD 2–3 (0.27, 0.99) CKD 4–5 (-0.56, 1.26) Dialysis (0.00,1.57)

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
							P 5.2 mg/dL 1,25(OH)2 D, 30.5 pg/mL iPTH, 140 pg/mL FGF-23, 127 pg/mL Dialysis Ca, 9.4 mg/dL P 5.5 mg/dL 1,25(OH)2 D, 18.6 pg/mL iPTH, 252 pg/mL FGF-23, 349 pg/mL	
Djukanovic, 2015[9]	2153	59	61	NR	NR 5.3 years	NR NR NR	iPTH 407.8 pg/mL P 1.58 mmol/L C 2.31 mmol/L	NR
Eddington, 2010[10]	1203	64	64	White 98%	GFR; 32 ml/min/1.73m^2 NA	32 NR NR	P 1.2 mmol/L) Ca 2.29 mmol/L) PTH 89 pg/ml	NR
Fein, 2013[11]	90	52	39	Blacks 81%	NA	42 NR NR	ALP 135 U/L (Mean) ALP 113 U/L (Median)	NR
Fernandez-Martin, 2015[12]	6,307	61	64	NR	NR 38.9 months	31 NR NR	P 5.4 mg/dL Ca 9.1 mg/dL PTH 210.8 (pg/mL)	NR
Fliser, 2007[13]	Nonprogressor (112) [a]	45	66	Whites 100%	GFR; 79 ml/min/1.73m^2 NA	NR NR NR	P 1.04 mmol/L Ca 2.38 mmol/L PTH 6.5 pmol/L FGF 23 35 pg/ml	NR
	Progressor (65) [a]	49	68	Whites 100%	GFR; 38 ml/min/1.73m^2 NA	NR NR NR	P 1.04 mmol/L Ca 2.38 mmol/L PTH 6.5 pmol/L FGF 23 69 pg/ml	NR
Floege, 2011[14]	iPTH < 75 pg/mL (670)	67	53	NR	NA 30 % < 6 month	30 NR NR	P 1.4 mmol/L Ca 2.3 mmol/L	NR
	iPTH 75-<150 pg/mL (833)	66	61	NR	NA 33 % < 6 month	30 NR NR	P 1.4 mmol/L Ca 2.3 mmol/L	NR
	iPTH pg/mL 150-300 (1092)	66	63	NR	NA 37 % < 6 month	30 NR NR	P 1.5 mmol/L Ca 2.3 mmol/L	NR

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
	iPTH >300-600 pg/mL (890)	63	57	NR	NA 34 % < 6 month	30 NR NR	P 1.6 mmol/L Ca 2.3 mmol/L	NR
	iPTH >600 pg/mL (461)	61	52	NR	NA 27 % < 6 month	30 NR NR	P 1.7 mmol/L Ca 2.3 mmol/L	NR
	Missing (4024)	61	58	NR	NA 37 % < 6 month	30 NR NR	P 1.5 mmol/L Ca 2.2 mmol/L	NR
Fouque, 2013[15]	7700	67	59	NR	NA 36 months	27 NR NR	P 1.57 mmol/L Ca, corrected 2.29 mmol/L	NR
Fukagawa, 2014[16]	8229 (3276, sub cohort)	63	61	NR	NA 100 months	32 NR NR	P 5.5 mg/dl Ca 9.4 mg/dl PTH 265 pg/ml Dialysate Calcium 2.5 mEq/l (49%) 3.0 mEq/l (51%)	NR
Gallieni, 2012[18]	369	64	56	NR	NA 24	15 87 NR	P 5.1 mg/dl Ca 9.6 mg/dl PTH 242 pg/ml Dialysate Calcium 1.25mmol/L (68.6%) 1.5mmol/L (1.4%) 1.75mmol/L (29.8%)	No calcifications 23.4% Calcification present in one valve 26.1% Calcification present in two valves 27.8% Calcification present at ≥1 artery 65.4% Calcification present in five arteries 16.4% Calcification present at ≥1 site 76.6% Calcification present at all sites 7.5% (Done with color Doppler USG for arteries & echocardiogram for valves)
Kimata, 2007[19]	3973	60	61	NR	NR 7.3 years	27 61 NR	P 5.7 mg/dl cCa 9.4 mg/dl iPTH 194 pg/ml Dialysate Calcium 2.9 mEq/L	NR
Lacson, 2009[20]	78,420	61	53	White 49 Black 41 Other 10	NR 3.4 years	52 N4 N4	P 5.3 mg/dL Ca 9.0 mg/dL	NR
Lim, 2014[21]	2144	64.2	64.7	NR	eGFR: 33.2	43.8% 63.4% NR	Ca: 9.2 mg/dL P: 3.9 mg/dL PTH: 68.4 pg/mL	NR

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
							ALP: NR	
Lin, 2015[22]	94,983	62	50	NR	NR 3.5 years	51 NR NR	Ca 9.2 mg/dL P 4.8 mg/dL	NA
Markaki, 2012[23]	74	65	55	NR	NR 44 months for HD patients and 78 months for PD patients	19 60 NR	Ca 9.2 mg/dL P 5.1 mg/dL	NR
McGovern, 2013[24]	Total: 57,832 No CKD: 24,184 CKD 1-2: 20,356 CKD 3-5:13,292	No CKD: 52.8 CKD 1-2:56.0 CKD 3-5:72.8	No CKD: 24,184 CKD 1-2: 20,356 CKD 3-5:13,292	NR	NR NR	DM: No CKD: 8.1 CKD 1-2: 15.5 CKD 3-5: 19.1 HTN: No CKD: 18.6 CKD 1-2: 26.3 CKD 3-5: 55.6 HC: NR	No CKD: Ca: NR P: <0.75 mmol/L: 2.6% 0.75-1.00 mmol/L:27.8% 1.00-1.25mmol/L:50.5% 1.25-1.50mmol/L:17.8% >1.50mmol/L:1.4$ PTH: NR ALP: NR CKD 1-2 Ca: NR P: <0.75 mmol/L: 2.6% 0.75-1.00 mmol/L:27.0% 1.00-1.25mmol/L:51.1% 1.25-1.50mmol/L:17.9% >1.50mmol/L:1.4% PTH: ALP: NR CKD 3-5 Ca: NR P: <0.75 mmol/L: 2.1% 0.75-1.00 mmol/L:24.6% 1.00-1.25mmol/L:50.8% 1.25-1.50mmol/L:20.2% >1.50mmol/L:2.3% PTH: ALP: NR	NR
Menon, 2005[25]	840	52	61	White 85	eGFR: 33 mL/min/1.73 m^2 NA	5 NR NR	P 3.8 mg/dL Ca 9.1 mg/dL CaxP 34.7 mg^2/dL^2	NR
Miura, 2015[26]	191 Low Ca: 32	Low Ca: 71	Low Ca: 78	NR	eGFR, mL/min/1.73 m^2	Low Ca: 47 72	Low Ca: ALP 308.9 U/L	NA

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
	Normal-high Ca: 159	Normal-high Ca: 70	Normal-high Ca: 69		Low Ca: 39.8 Normal-high Ca: 41.7 NR	72 Normal-high Ca: 38 79 76	Corrected Ca 7.9 mg/dL P: 3.8 mg/dL iPTH 87.5 pg/mL Normal-high Ca: ALP: 261.0 U/L Corrected Ca: 9.2 mg/dL P 3.6 mg/dL iPTH: 58.6 pg/mL	
Moore, 2011[27]	470	48	61	NR	eGFR: 39.9	13% ACEI/ARB use: 34%	Ca: 2.40 mmol/L P:1.13 mmol/L PTH:15 ng/mL ALP:NR	NA
Nakai, 2008[28]	27,404	60	59	NR	NR 8.34 years	24 NR NR	Ca 9.5 mg/dL P 5.6 mg/dL iPTH 219 pg/mL	NR
Nakano, 2012[29]	738	64	64	NR	eGFR 35.3 mL/min/1.73 m^2 NR	19 NR NR	Corrected Ca 9.31 mg/dL P 3.49 mg/dL Whole PTH 19.6 pg/mL Bs-ALP 22.9 U/L	NR
Noordzij, 2009[31]	1468	HD: 63 PD: 52	HD: 59% PD: 67%	NR	rGFR(ml/min) HD: 4.01 PD: 4.59	DM HD: 16% PD: 16% HTN Drugs: HD: 82% PD:88% HC: NR	HD: Corrected Ca (mg/dl): 9.63 P (mg/dl): 5.74 iPTH (pg/ml): 222 PD: Corrected Ca (mg/dl): P (mg/dl): iPTH (pg/ml):	Na
Nowak, 2015[34]	239	68	64	NR	NR 59 months	38 NR NR	PTH 249 pg/ml ALP 91 U/l Ca 2.3 mmol/l P 1.6 mmol/l	NA
Pihlstrom, 2015[35]	1840	50	66	NR	eGFR 48.9 mL/min 28.3 months	19 74 NR	P 3.58 mg/dL Ca 2.42 mmol/L PTH 51.9 pg/mL	NA
Ravani, 2009[36]	168	70	63	NR	eGFR 33.5 ml/min/1.73 m^2 NA	26 NR NR	Ca 9.4 mg/dL P 3.6 mg/dL PTH 116 pg/mL	NR
Sakaguchi, 2014[37]	142,069	66	61.9	NR	NR 7	35.9 NR	Adj Ca: 9.3 mg/dL P: 5.1 mg/dL	NA

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
						NR	iPTH: 118 pg/mL ALP: IU/L	
Schaeffner, 2007[38]	733	52	60	NR	GFR 55.8 ml/min/1.73 m^2	NR NR NR	Ca 2.37 mmol/L P 1.04 mmol/L CaxP 2.46 $mmol^2/l^2$	NR
Scialla, 2015[39]	511	58	55	African American 36% Non-African American 64%	NR Median 145 days	57 NR NR	Ca 9.3 mg/dl P 5.4 mg/dl iPTH 148 pg/ml (median) ALP 89.0 IU/l (median)	NA
Scialla, 2013[40]	809	55	60.4	African American: 100%	2 (GFR≥60 ml/min per 1.73 m2) 172 (21.3%) 3a (GFR=45–59 ml/min per 1.73 m2) 239 (29.5%) 3b (GFR=30–44 ml/min per 1.73 m2) 216 (26.7%) 4–5 (GFR <30 ml/min per 1.73 m2) 179 (22.1%) NR	NR NR NR	Ca: 8.9 mg/dL P: 3.5 mg/dl iPTH: 177 pg/mL ALP: NR	NA
Silva, 2013[41]	119	62.57	54.6	NR	eGFR: 44.88	100% NR NR	Ca: 9.49 mg/dL P: 4.32 mg/dL PTH: 132.44 pg/mL ALP: NR	NR
Tentori, 2008[42]	25,529	61.7	57.4	Black: 11.1	NR 4.7 years	35 77 NR	Ca 9.3 mg/dL Adj Ca 9.5 mg/dL P 5.5 mg/dL PTH 278 pg/mL	NR
Zhao, 2014[43]	Derivation: 903	48	58	NR	NR 33.86 months	26 65 NR	Ca 2.23 mmol/L P 1.70 mmol/L iPTH 299.03 pg/mL	NR
	Validation: 451	49	59	NR	NR 34.31 momths	25 66	Ca 2.22 mmol/L P 1.68 mmol/L	

Author, year	Group Sample size	Age, mean years	Male, %	Race, %	Kidney function Duration on dialysis	% DM % HTN % HC	Baseline MBD labs	Baseline BMD and Bone evaluation technique
						NR	iPTH 290.40 pg/mL	

a. Except gender, non-progressors & progressors are statistically different for all other variables in the table.

Supplemental Table 51. Summary table of studies evaluating different concentrations of serum phosphate among patients with CKD G3a-G5 or G5D – results

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
Benavente, 2012[1]	297	Serum Phosphate at 6 mo & 12 mo (Only single measurement at both times) Analyzed as continuous variable	Donor and recipient age and sex, regraft, total human leukocyte antigen mismatch, systolic blood pressure, eGFR, serum calcium, and log-transformed PTH and urinary albumin: creatinine ratio all measured at 6 and 12 months.	Graft loss (death excluded)	Using P at 6 mo (HR, CI P value) 1.27 (1.07-1.51) (0.007) Using P at 6 mo (HR, CI P value) 1.34 (1.14-1.57) (<0.001)
				Graft loss (death included)	Using P at 6 mo (HR, CI P value) 1.22 (1.06-1.40) (0.006) Using P at 6 mo (HR, CI P value) 1.30(1.13-1.50) (<0.001)
Caravaca, 2011[2]	184	Phosphate Analyzed as continuous variable	Phosphate (averaged for multiple measurement) Proteinuria (logarithmic) Baseline GFR	Rate of decline in renal function test	Faster by 46% for each mg/dl above 4.5 mg/dl
Chartsrisak, 2013[3]	466	P (NR 2.5-4.6 mg/dl) • 0-3.7(ref) • 3.7-4.2 • >4.2	Adjusted for age, sex, DM, BMI, serum albumin and eGFR (>=45 or <45 mL/ min/1.73 m2). The final model is also adjusted for PTH & 25(OH) 2D	Developing ESRD during follow up period	P (HR, CI, P value) • 0-3.7(ref) • 3.7-4.2 1.81 (0.86-3.81) • >4.2 1.98 (0.92-4.28)
				Composite outcome of ESRD & mortality (A total of 74(16%) patients develop ESRD, 40(8.6%) developed death, 6(1.3%) developed both ESRD & death.	P (HR, CI, P value) • 0-3.7(ref) • 3.7-4.2 1.5 (0.82 -2.74) • >4.2 2.01 (1.08-3.74) (<0.005)
Chue, 2011[4]	225	Phosphate All analyzed as continuous	Age, gender, baseline eGFR, systolic BP, proteinuria, hemoglobin, & serum calcium.	Decline in eGRF	For each increment in 1 mg/dl serum phosphate, eGRF decline by 0.34 mL/min/month (P=0.01)
				Commencement of dialysis or >= 25% decline in eGFR	P (Beta=0.211, P=0.03) AI_x (Beta=0.5, P=0.1) PWV (Beta=-0.02, P=0.2) PWV_{adj} (Beta= 0.02, P=0.1)
				AUC for ROC for being highest quartile of renal function decline [a] 0.68 (0.58-0.77)(P<0.001)	Adding AI_x & PWV didn't increase AUC Adding P increase AUC 0.77 (0.61-0.79)(P<0.001)
Coen, 2010[5]	-	-	-	-	-
Connolly, 2009[6]	397	Phosphate (mmol/L) • <0.92 • 0.92-1.12 • >1.12	Cox regression analysis adjusted for graft failure, GFR, glomerular filtration rate; HDL; hsCRP, PTH	All cause mortality (HR,CI, P value) (73 deaths, no difference in serum P between CV & non-CV deaths.)	Phosphate (adj for all covariates except CV disease at enrollment) • <0.92 (ref) • 0.92-1.12 2.2 (1.1-4.4) (0.001) • >1.12 3.5 (1.8-6.8) (0.001)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
					Phosphate (adj only for CV disease at enrollment) • <0.92 (ref) • 0.92-1.12 2.1 (1.0-4.4) (0.001) • >1.12 3.8 (2.0-7.3) (0.001)
					Univariate association (deceased vs. Survivors) (Mean, SD, P values) • P 1.15 vs. 1.00 (<0.001) • Ca 2.44 vs. 2.44 (0.967) • PTH 149 vs. 97 (0.025) • CV disease at enrollment (n) 33 vs. 51 (<0.001) • Allograft loss (n) 18 vs. 36 (0.005)
De Nicola, 2014[7]	200	Phosphate (mg/dl) (continuous)	Age (5 years), male gender, Diabetes, prior CV disease, hemoglobin (g/dL), eGFR, ml/min/1.73 m2, proteinuria (g/24 h), phosphate, PTH	Renal survival (96 deaths occur over median 31 months follow up, 46 ESRD & 50 all cause mortality)	HR, CI, P value • P 1.02 (0.75-1.37) (0.924) Interaction term P*PTH (Beta, P value) • 0.035 (0.002)
Denburg, 2013[8]	-	-	-	-	-
Djukanovic, 2015[9]	2153	Serum phosphate (1.1-1.8 mmol/L)	Patient age, gender, duration of HD treatment in years, hours of HD/week, Kt/V, hemoglobin, calcium, iPTH	Mortality 577 (26.7%) patients died during the 3-year follow-up	RR, CI, P value s-phosphate 1.1-1.8 mmol/L 0.93 (0.77-1.12) (0.442)
Eddington, 2010[10]	1203	Phosphate (averaged for 12 months) (mmol/L) • <1.02 • 1.02-1.15 • 1.16-1.34 • >1.34	Adjusted for age, gender, proteinuria, diabetes, hemoglobin, systolic blood pressure, current smoking status, cardiovascular disease, eGFR, and vitamin D analog and phosphate binder use.	Mortality (Death occur in 22%=271 patients, 109 of CV causes) Using P quartiles	All cause mortality (HR, CI, P value) • <1.02 (ref) • 1.02-1.15 1.2 (0.8-1.9)(0.4) • 1.16-1.34 1.2 (0.8-1.8)(0.5) • >1.34 1.8 (1.1-2.9)(0.01) Cardiovascular mortality (HR, CI, P value) • <1.02 (ref) • 1.02-1.15 1.5 (0.8-2.9)(0.2) • 1.16-1.34 1.2 (0.6-2.3)(0.7) • >1.34 1.8 (0.9-3.9)(0.1)
				Mortality Using KDOQI target (G3a to G4: 0.87 to 1.48 mmol/L; CKD G5: 1.13 to 1.78 mmol/L)	All cause mortality (HR, CI, P value) • Below target (ref) • In target 1.8 (0.98-3.8)(0.06) • Above target 2.7 (1.3-5.7)(0.009) Cardiovascular mortality (HR, CI, P value)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
					• Below target (ref) • In target 1.8 (0.7-4.6) (0.2) • Above target 4.0(1.4-11.9) (0.01)
Fein, 2013[11]	-	-	-	-	-
Fernandez-Martin, 2015[12]	6,307	Serum phosphate <3.6 3.6-5.2 >5.2	Age, sex, body mass index, smoking habit, time on hemodialysis, etiology of chronic kidney disease, diabetes, cardiovascular disease history, parathyroidectomy, dialysis type, calcium concentration in the dialysate, hours of haemodialysis per week, treatment with erythropoietin stimulatin agents, prescription of vitamin D metabolites/analogues (calcitriol, alfacalcidol or paricalcitol), native vitamin D or calcidol, phosphate binding agents and calcimimetics, and levels of hemoglobin, albumin, phosphate, calcium and PTH	All-cause Mortality 1642 (26.0%) died during the 3-year follow-up	HR (95% CI) mg/dL <3.6: 1.34 (1.13 to 1.59) 3.6-5.2: ref >5.2: 1.34 (1.18 to 1.53)
Fliser, 2007[13]	177	Predictors with increment values Phosphate (0.1 mmol/L)	Age & gender	Progression of renal failure (Defined by doubling of serum creatinine and/or terminal renal failure) (HR, CI, P value)	Phosphate 1.052 (0.952 to 1.162) (0.322)
Floege, 2011[14]	7970	Phosphate (mmol/L) All as categorical variables	Age, gender, country, BMI, smoking status), medical history (CKD etiology, Hx of DM, CVD & Cancer), vintage, vascular access type, Kt/V, blood flow, serum albumin, CRP), antihypertensive drugs, ACE inhibitors, oral anticoagulants, anti-aggregants, vitamin D, phosphate binders, PTH, calcium, phosphate, Hb, ferritin, cholesterol, blood leucocytes, hospitalization, change in vascular access type. Note: Serum albumin, CRP, oral	All cause mortality (HR, CI) (1477, 19% died during follow up period) The values are reported adjusted for time dependent variable too.	Phosphate (mmol/L) • <1.13 1.31 (1.15–1.48) • ≥1.13–≤1.78 1.0 • >1.78 [b] 1.05 (0.91–1.22)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			vitamin D use, phosphate binder use, ferritin, hospitalization and change in vascular access type were updated over time in the time-dependent models.		
Fouque, 2013[15]	5339	Serum phosphate	Adjusted for age, gender, history of cardiovascular disease, diabetes, dialysis vintage, body mass index, serum albumin and Hgb concentrations	All cause mortality	HR of 1.1 using continuous HR analysis for P < 0.71 (0.38– 0.98) mmol/L & >1.98 (1.84–2.44) mmol/L)
					Using KDIGO recommendations (HR, CI, P value) ≤0.9 mmol/L 1.15 (0.95–1.40) (0.15) >1.4 mmol/L 1.07 (0.95–1.20) (0.29)
Fukagawa, 2014[16]	8229 (3276, sub cohort)	Serum phosphate Continuous categories	Age, sex, dialysis vintage, and cause of ESRD BMI, dialysis adequacy (Kt/V), history of cardiovascular dis- ease, creatinine, hemoglobin, albumin, total cholesterol, and VDRA use	All cause mortality (A total of 1226 deaths in the follow up 3 years)	Serum phosphate (RR,CI) < 3.0 mg/dL 1.54 (0.87-2.71) 3.0-3.9 mg/dL 1.29 (0.98-1.69) 4.0-4.9 mg/dL 0.95 (0.77-1.16) 5.0-5.9 mg/dL 1.00 (reference) 6.0-6.9 mg/dL 0.98 (0.74-1.30) 7.0-7.9 mg/dL 1.60 (0.94-2.73) 8.0-8.9 mg/dL 1.99 (1.30-3.04) >9.0 mg/dL 2.79 (1.26-6.15)
Gallieni, 2012[18]	369	Baseline Phosphate	Classes of serum Ca, P, gender, age, and the global calcification score	Progression of calcification in completers	73.0%
				Global calcification score (P values based on Kruskal–Wallis test associations)	Ca (0.828) P (0.342)
				Presence of left ventricular hypertrophy (LVH) was (Diagnosed when LVMI was > 131 g/m2 in males or >100 g/m2 in females, based on values calculated in the Framingham study	Ca (0.035) P (0.529)
				Presence of arteriosclerosis	Ca (0.014) P (0.001)
				Cardiovascular mortality (42 deaths out of 369)	Log rank test using phosphate cut offs Ph (<3.5, 3.5-5.5, >5.5) mg/dl P value=0.82
Kimata, 2007[19]	3973	Serum Phosphate	Patient demographics, comorbidities	All-Cause Mortality	P <3.5 mg/dL 1.61; *P* = 0.008 P 3.5-<4.5 mg/dL 1.21; *P* = 0.22 P 4.5-<5.5 mg/dL 1.00; Reference

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
					P 5.5-<6.5 mg/dL 1.05; *P* = 0.73 P >=6.5 mg/dL 1.33; *P* = 0.04
				Cardiovascular Mortality	P <3.5 mg/dL 0.92; *P* = 0.83 P 3.5-<4.5 mg/dL 0.62; *P* = 0.11 P 4.5-<5.5 mg/dL 1.00; Reference P 5.5-<6.5 mg/dL 1.18; *P* = 0.45 P >=6.5 mg/dL 1.24; *P* = 0.30
Lacson, 2009[20]	78,420	Phosphate (mg/dL) Continuous	Albumin, age, dialysis vintage, creatinine, phosphate, gender, body surface area, hemoglobin, access type (catheter or graft), equilibrated Kt/V, white blood cells, diabetes, bio-PTH, race (white, black other)	All-cause morality Hospitalization (all causes except for kidney transplant)	HR 1.179 (95% CI, 1.128 to 1.231) HR 1.085 (95% CI, 1.076 to 1.094)
Lim, 2014[21]	--	--	--	--	--
Lin, 2015[22]	94,983	Phosphate (mg/dL) <3.5 3.5-5.5 5.5-6.5 6.5-7.5 7.5-8.5 >8.5	Age, sex, diabetes, hematocrit, albumin, kt/V	All- cause mortality	HR (95%CI) P Value <3.5: 1.19 (1.15-1.22) (<0.01) 3.5-5.5: Reference 5.5-6.5: 1.15 (1.12-1.19) (<0.01) 6.5-7.5: 1.53 (1.45-1.62) (<0.01) 7.5-8.5: (1.80-2.20) (<0.01) >8.5: 2.46 (2.03-2.98) (<0.01)
Markaki, 2012[23]	-	-	-	-	-
McGovern, 2013[24]	57,832	Phosphate: P: <0.75 mmol/L 0.75-1.00 mmol/L 1.00-1.25mmol/L 1.25-1.50mmol/L >1.50mmol/L	Sex, Age, Smoking status (never, current, ex), DM, HTN treatment, HDL cholesterol	All-cause mortality, incident stroke, transient ischaemic attack (TIA), myocardial infarction (MI), advanced coronary artery disease, new cardiac failure or death Advanced coronary artery disease: one of : coronary artery revascularization, progressive angina, angina at rest, acute coronary syndrome not otherwise diagnosed as MI	Logistic regression: Odds ratio of CV events and mortality during 30 months of follow-up No CKD: P :<0.75 mmol/L: 0.59 (0.36-0.97) p=.049 0.75-1.00 mmol/L: 1.00 [ref] 1.00-1.25mmol/L: 1.19 (0.98-1.43) p=.077 1.25-1.50mmol/L: 1.36 (1.06-1.74) p=.016 >1.50mmol/L: 1.80(0.89-3.63) p=.100 CKD 1-2 P: <0.75 mmol/L: 0.60(0.32-1.14) p=.117 0.75-1.00 mmol/L: 1.00[ref] 1.00-1.25mmol/L: 1.12(0.92-1.36) p=.270 1.25-1.50mmol/L: 1.40(1.09-1.81) p=.010 >1.50mmol/L: 1.51(0.72-3.13) p=.272 CKD 3-5 P: <0.75 mmol/L: 1.11 (0.71-1.73) p=.647

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
					0.75-1.00 mmol/L: 1.00 [ref] 1.00-1.25mmol/L: 1.07(.0.91-1.25) p=.420 1.25-1.50mmol/L: 1.21(1.00-1.46) p=.054 >1.50mmol/L: 2.34(1.64-3.32) p<.001 Cox regression analysis: Odds ratio of CV event and mortality during 30 months of follow-up No CKD: P: <0.75 mmol/L: 0.58(0.36-0.97) p=.049 0.75-1.00 mmol/L: 1.00[ref] 1.00-1.25mmol/L: 1.19 (1.00-1.42) p=.054 1.25-1.50mmol/L: 1.38 (1.09-1.73) p=.007 >1.50mmol/L: 1.62 (0.86-3.07) p=.138 CKD 1-2 P: <0.75 mmol/L: 0.62 (0.34-1.14) p=.127 0.75-1.00 mmol/L: 1.00[ref] 1.00-1.25mmol/L: 1.09 (0.91-1.31) p=.341 1.25-1.50mmol/L: 1.31(1.03-1.66) p=.026 >1.50mmol/L: 1.44(0.73-2.83) p=.288 CKD 3-5 P: <0.75 mmol/L: 1.10(0.74-1.63) p=0.629 0.75-1.00 mmol/L: 1.00[ref] 1.00-1.25mmol/L: 1.08 (0.94-1.24) p=.303 1.25-1.50mmol/L: 1.24 (1.05-1.47) p=.014 >1.50mmol/L: 2.40 (1.82-3.16) p<.001
Menon, 2005[25]	840	Serum phosphate (per 1 mg/dL increase)	Age, sex, race, blood pressure, protein diet randomization assignment, smoking, history of coronary artery disease or diabetes, LDL, HDL, BMI, systolic blood pressure, proteinuria, cause of kidney disease, GFR	All-cause mortality Cardiovascular mortality (primary cause of death was ICD-9 codes 390 to 459 or primary cause of death was kidney disease and CVD was secondary cause of death)	HR 1.10 (95% CI, 0.86 to 1.40; P = 0.46) HR 1.27 (95% CI, 0.94 to 1.73; P = 0.12)
Miura, 2015[26]	191	-	-	-	-
Moore, 2011[27]	270	Serum phosphate (per 0.1 mmol/L)	Serum Calcium (per 0.1 mmol/L), sex, DM, age, peripheral SBP Secondary: serum calcium, male sex, baseline eGFR, serum albumin, ACEI/ARB use	Patient survival (taken from the time of data collection until death or study termination) and graft loss (taken from the time of data collection until graft loss or study termination). Graft loss was defined as the composite end-	All cause mortality hazard ratio for each 0.1mmol/L increase in phosphate HR: 1.21 (1.09, 1.35) 95% CI p<0.001 Death-uncensored graft loss Serum phosphate per 0.1 mmol/L

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
				point of patient death and re-initiation of dialysis.	increase: 1.17 (1.09, 1.27) 95% CI p<.001
Nakai, 2008[28]	27,404	Serum phosphate (mg/dL) <3.0 3.0 – 3.9 4.0 – 4.9 (ref) 5.0-5.9 6.0-6.9 7.0-7.9 8.0-8.9 ≥9.0	Sex, age, duration of dialysis, diabetes mellitus, body weight, BMI, hours of hemodialysis session, Kt/V for urea, normalized protein catabolic rate, adjusted serum calcium, hematocrit, albumin, creatinine, total cholesterol, Ipht	All-cause mortality, HR (95% CI)	<3.0: 1.142 (0.990 to 1.316; P NS) 3.0 – 3.9: 1.102 (0.999 to 1.215; P NS) 4.0 – 4.9 (ref) 5.0-5.9: 1.105 (1.1017 to 1.202; P=0.0187) 6.0-6.9: 1.172 (1.065 to 1.289; P=.0011) 7.0-7.9: 1.425 (1.265 to 1.605; P<0.0001) 8.0-8.9: 1.893 (1.620 to 2.213; P<0.0001) ≥9.0: 1.985 (1.621 to 2.432; P<0.0001)
Nakano, 2012[29]	738	Phosphate (mg/dL) Continuous	None	CVD event before start of dialysis CVD during entire followup duration	HR 1.59 (95% CI, 1.10 to 2.29; P=0.014) HR 1.72 (95% CI, 1.33 to 2.21; P<0.0001)
			Age, sex, BMI, diabetes mellitus, prior CVD, systolic blood pressure, ACE-I/ARB, hemoglobin, albumin, proteinuria, eGFR, corrected calcium, 25D, 1,25D, whole PTH, log FGF23, active vitamin D, calcium carbonate	Renal event (doubling of serum creatinine or initiation of dialysis)	HR 0.85 (95% CI, 0.62 to 1.17)
Noordzij, 2009[31]	1468 HD: 899 PD: 569	Serum Phosphate: <3.5 mg/dl 3.5-5.5 mg/dl >5.5 mg/dl	Baseline rGFR, calcium, phosphate, iPTH, age, sex, co-morbid conditions, nutritional status (SGA), systolic and diastolic blood pressure, urinary protein loss and use of anti-hypertensive drugs	Loss of residual renal function: becoming anuric during the first 3 years	Adjusted hazard ratios (HR; 95% confidence interval) for the risk of total loss of RRF in categories of plasma concentrations for HD and PD patients HD: <3.5 mg/dl: 0.7 (0.2-2.3) p=0.53 3.5-5.5 mg/dl: 1.0[ref] >5.5 mg/dl: 1.2 (0.8-1.9) p=0.31 PD: <3.5 mg/dl: 1.7 (0.7-4.3) p=0.25 3.5-5.5 mg/dl: 1.0[ref] >5.5 mg/dl: 1.3 (0.7-2.3) p=0.45
Nowak, 2015[34]	239	Phosphate, per standard deviation	Age, gender (male), dialysis center clustering, dialysis vintage, systolic and diastolic blood pressure, body-mass index, vascular access on study enrollment (fistula, graft, catheter), coexisting conditions, cause of renal failure, medication use, pooled Kt/V, albumin,	All-cause mortality	HR (95% CI) P value 1.06 (0.82-1.38) P=0.65

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			hemoglobin, C-reactive protein, cholesterol, sclerostin, FGF23, PTH, ALP, calcium, 25(OH)vitamin D		
Pihlstrom, 2015[35]	1614	Serum phosphate per mg/dL Continuous	Age, sex, smoking, coronary heart disease, diabetes mellitus, ST-T changes, high density lipoprotein, triglycerides, systolic and diastolic blood pressure, body mass index, eGFR, proteinuria, s-calcium, s-phosphate, high sensitive C-reactive protein, randomization group, time on dialysis, and time since last transplantation, serum PTH	All-cause mortality 291/1614 events	HR (95% CI) P value 1.07 (0.89-1.28) 0.488
				Graft loss (death censored) 285/1614	HR (95% CI) P value 1.52 (1.27-1.82) <0.001
Ravani, 2009[36]	168	Serum phosphate (mg/dL) Continuous	Vitamin D, CEI/ARB	ESRD and death	HR 1.57 (95% CI, 1.22 to 2.02)
Sakaguchi, 2014[37]	142,069	Serum P quartile 1 (<4.1) [ref] 2(≥4.1, <5.1) 3(≥5.1, <6.0) 4(≥6.0) Magnesium groups Lower (<2.7) Intermediate (≥2.7, <3.1) Higher (≥3.1)	Age, sex, BMI, hemodialysis vintage, duration of hemodialysis treatment, DM, serum urea nitrogen, calcium, magnesium, Alk Phos, Albumin, CRP, hemoglobin, iPTH, prescription of phos binder, cinacalcet hydrochloride, active vitD, hx of parathyroidectomy, CVD (MI, cerebral infarction, cerebral hemorrhage, and amputation), hip fracture	All cause mortality Mortality due to CVD (heart failure, pulmonary edema, ischemic heart disease, arrhythmia, and cerebrovascular disease.	Adjusted OR for all cause mortality according to phosphate quartiles(95%CI) Q1 Phosphate Lower Mg: 1.00 Intermediate Mg: 0.88 (0.77,1.01), p=.07 Higher Mg: 1.17 (1.00,1.36), p=.05 Q2 Phosphate Lower Mg: 1.00 Intermediate: 0.78 (0.67, 0.91), p=.002 Higher: 0.98 (0.80, 1.21) p=87 Q3 Phosphate Lower Mg:1.00 Intermediate: 0.81 (0.70,0.95) p=.008 Higher: 0.95 (0.77,1.17) p=0.63 Q4 Phosphate Lower Mg: 1.00 Intermediate: 0.83 (0.73, 0.96) p=.01 Higher: 0.71 (0.58, 0.86) p=.001 Adjusted OR for all cause and CVD mortality according to phosphate quartiles Q1 Phosphate Lower Mg: 1.00 Intermediate Mg: 0.89 (.73,1.07) p=.21 Higher Mg: 1.15 (0.93-1.42), p=0.19

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
					Q2 Phosphate Lower Mg: 1.00 Intermediate: 0.87 (0.70, 1.09), p=0.24 Higher: 1.14 (0.85, 1.53) p=0.37 Q3 Phosphate Lower Mg:1.00 Intermediate: 0.76 (0.61, 0.95) p=.02 Higher: 1.08 (0.82, 1.43) p=.60 Q4 Phosphate Lower Mg: 1.00 Intermediate: 0.81 (0.66-.99) p=.04 Higher: 0.74 (0.56, 0.97) p=.03
Schaeffner, 2007[38]	733	Serum phosphate quintiles (mmol/L) Q1 ≤0.84 (ref) Q2 0.85-0.96 Q3 0.97-1.08 Q4 1.09-1.22 Q5 ≥1.23	Age, gender, eGFR, C-reactive protein, total plasma homocysteine, body mass index, diabetic nephropathy, donor gender, time from first renal replacement therapy to transplantation	All-cause mortality, HR (95% CI) Kidney allograft loss or death, HR (95% CI)	Q1: (ref) Q2: 1.46 (0.83 to 2.58) Q3: 1.70 (0.99 to 2.91) Q4: 1.28 (0.72 to 2.26) Q5: 1.41 (0.78 to 2.57) Q1: (ref) Q2: 1.30 (0.81 to 2.09) Q3: 1.41 (0.89 to 2.23) Q4: 1.34 (0.84 to 2.12) Q5: 2.15 (1.36 to 3.40)
Scialla, 2015[39]	511	Serum phosphate (mg/dl) ≤4.5 4.6-5.2 5.3-6.2 ≥6.3 Continuous (per 1 mg/dl)	Age, sex, race, education, smoking, BMI, baseline ICED, baseline diabetes mellitus, baseline cardiovascular disease, serum albumin and hemoglobin	All-cause mortality, HR (95% CI) 332 events/466	≤4.5: (ref) 4.6-5.2: 1.03 (0.71-1.51) 5.3-6.2: 1.59 (1.07-2.37) ≥6.3: 1.68 (1.11-2.54) Continuous: 1.20 (1.07-1.34)
				Cardiovascular mortality, HR (95% CI) 146 events/466	≤4.5: (ref) 4.6-5.2: 0.88 (0.49-1.57) 5.3-6.2: 1.49 (0.83-2.67) ≥6.3: 1.90 (1.05-3.43) Continuous: 1.27 (1.08-1.49)
Scialla, 2013[40]	809	Serum Phosphate (mg/dL) ≤3.1 3.2-3.5 3.6-3.9 ≥4.0	Age, sex, randomized treatment assignment, 125I-iothalamate GFR, UPCR, income, prior heart disease, smoking, serum albumin, and categories of body mass index For secondary outcome: Adjusted for age, sex, income, prior heart disease, smoking,	Incident ESRD or death spanning the trial and cohort phases from 12 months postrandomization to June 30, 2007. ESRD was defined as initiation of dialysis or kidney transplantation. Secondary outcomes included death-censored ESRD and death-censored ESRD or doubling of serum creatinine from trial	Adjusted HR of ESRD or death based on serum phosphate ≤3.1: 1.13 (0.79, 1.62) 3.2-3.5: [Ref] 3.6-3.9: 0.95 (0.61, 1.46) ≥4.0: 1.46(1.19, 1.08) p=0.08 Risk of secondary renal end points, death

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			categories of body mass index, 125I-iothalamate GFR, UPCR, and randomized treatment assignment and clustered by clinical center	baseline.	censored ESRD, and death censored ESRD or doubling of serum creatinine based on serum phosphate ≤3.1: 0.88 (0.55, 1.40) 3.2-3.5: [Ref] 3.6-3.9: 0.82 (0.45, 1.48) ≥4.0: 1.19 (0.93, 1.53) p=0.09
Silva, 2013[41]	119	Phosphate Group 1≤3.60 mg/dL 3.60mg/dL<Group 2≤4.60 Group 3>4.60 mg/dL	Age, sex, clearance, creatinine, PTH	Cardiovascular mortality: mortality caused by coronary artery disease, heart failure, peripheral vascular disease and cerebrovascular disease Secondary outcomes: hospitalizations due to cardiovascular causes and progression of renal failure (measurement of creatinine and estimation of GFR or hemodialysis)	Adjusted HR for mortality by Cox regression for Phosphate group 95% CI ≤3.60 mg/dL: 0.235 (0.097-0.571) 3.60mg/dL-4.60mg/dL: 0.555(0.291-1.059) >4.60 mg/dL: [Ref] Adjusted OR (95% CI) for hospitalizations by logistic regression ≤3.60 mg/dL: 0.202 (0.044-0.928) 3.60mg/dL-4.60mg/dL: 0.453 (0.124-1.660) >4.60 mg/dL: [Ref]
Tentori, 2008[42]	25,529	Phosphate (mg/dL) ≤3.5 3.6-5.0 (ref) 5.1-6.0 6.1-7.0 >7.0	Facility clustering effects, age, sex, race, body mass index, duration of end-stage renal disease, 13 comorbid conditions, hemoglobin, serum albumin, normalized protein catabolic rate, single-pool Kt/V, prior parathyroidectomy, baseline levels of serum calcium and PTH	All-cause mortality, HR (95% CI) Cardiovascular mortality, HR (95% CI) Deaths caused by acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, or congestive heart failure	≤3.5: 1.06 (0.96 to 1.16) 3.6-5.0: (ref) 5.1-6.0: 1.02 (0.94 to 1.09) 6.1-7.0: 1.18 (1.08 to 1.28; P<0.05) >7.0: 1.43 (1.32 to 1.56; P<0.001) ≤3.5: 1.08 (0.90 to 1.28) 3.6-5.0: (ref) 5.1-6.0: 1.25 (1.09 to 1.44; P<0.05) 6.1-7.0: 1.61 (1.40 to 1.85; P<0.0001) >7.0: 1.81 (1.57 to 2.09; P<0.0001)
Zhao, 2014[43]	903	Serum phosphate per 1 mmol/L increase Continuous	Age, diabetes mellitus, hypertension, cardiovascular disease, diastolic blood pressure, serum albumin, serum creatinine, phosphate, hemoglobin, triglycerides, serum uric acid, calcium, intact parathyroid hormone, high-sensitivity C-reactive protein, high-density	All-cause mortality	HR: 1.68

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			lipoprotein cholesterol		

a. For prediction of a patient being in the highest quartile of renal function decline the AUC for a ROC curve derived from a multiple logistic regression score incorporating age, gender, serum calcium, haemoglobin, systolic BP, baseline eGFR and log transformed urine albumin: creatinine ratio

b. Using the baseline covariates only, this is statistically significant at 1.32 (1.13-1.55)

Supplemental Table 52. Summary table of studies evaluating different concentrations of serum calcium among patients with CKD G3a-G5 or G5D – results

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
Benavente, 2012[1]	-	-	-	-	-
Caravaca, 2011[2]	-	-	-	-	-
Chartsrisak, 2013[3]	-	-	-	-	-
Chue, 2011[4]	-	-	-	-	-
Coen, 2010[5]	71[a]	Calcium (Mean)	Age (Mean), PTH (Median), Fetulin-A (Mean)	Δ Algastone score increment No Δ Algastone score (ref) Δ Algastone < 1000 (OR,CI,P) Δ Algastone > 1000 (OR,P)	 1 3.72 (1.09-12.68)(0.036) 1.55(0.584)
				Mortality (11 deaths, 72.7% occur in those with worsening calcification at one year)	Cumulative HR for Δ Algastone increment is significant at P=0.027
Connolly, 2009[6]	-	-	-	-	-
De Nicola, 2014[7]	-	-	-	-	-
Denburg, 2013[8]	81 (change in CortBMD Z-score) 170 (Fracture)	Change in calcium (continuous) Change in tibia length Change in calcium by change in tibia length interaction Change in PTH Baseline 1,25(OH)2D	Also adjusted for age, study site, baseline CortBMD Z-score, baseline calcium, and change in renal function.	Change in Cort BMD Z-score (Beta, CI,P value)	Change in tibia length 1.21 (-2.06, -0.37) (.006) Change in calcium -0.78(-1.58, 0.01) (.053) Change in calcium by change in tibia length interaction 0.45 (0.12, 0.79) (.009) Change in PTH -0.26 (-0.37, -0.14) (.001) Baseline 1,25(OH) 2D -0.07 (-0.13,- 0.0003) (.049)
				Fracture (7 fractures: clavicle 1, tibia 3, foot 3, toe 2, radius/ulna 2)	Lower baseline Cort BMD Z-score (HR, CI,P value) 1.79 (1.15-2.67) (0.009); per SD decrease in tBMD Mean Cort BMD Z-score (# vs. non #) -0.93 vs. 0.08 (0.02)
Djukanovic, 2015[9]	2153	Serum Calcium (2.1-2.4 mmol/L)	Patient age, gender, duration of HD treatment in years, hours of HD/week, Kt/V, hemoglobin, calcium, iPTH	Mortality 577 (26.7%) patients died during the 3-year follow-up	RR, CI, P value s-calcium 2.1-2.4 mmol/L 0.94 (0.78-1.13) (0.531)
Eddington, 2010[10]	-	-	-	-	-
Fein, 2013[11]	90	Corrected Calcium	Age, race, sex, diabetes,	All cause mortality (RR, P value)	Corrected Calcium 2.2 (0.035)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
		ALP PTH (All continuous)	hypertension, dialysis vintage at enrollment, albumin, albumin- corrected calcium, parathyroid hormone, creatinine, blood urea nitrogen, hemoglobin, iron, serum glutamic oxaloacetic transaminase, and white blood cell count, ALP		
Fernandez-Martin, 2015[12]	6,307	Serum calcium (mg/dL) <7.9 7.9-9.5 >9.5	Age, sex, body mass index, smoking habit, time on hemodialysis, etiology of chronic kidney disease, diabetes, cardiovascular disease history, parathyroidectomy, dialysis type, calcium concentration in the dialysate, hours of haemodialysis per week, treatment with erythropoietin stimulatin agents, prescription of vitamin D metabolites/analogues (calcitriol, alfacalcidol or paricalcitol), native vitamin D or calcidol, phosphate binding agents and calcimimetics, and levels of haemoglobin, albumin, phosphate, calcium and PTH	All-cause Mortality 1642 (26.0%) died during the 3-year follow-up	HR (95% CI) mg/dL <7.9: 1.13 (0.87 to 1.46) 7.9-9.5: (ref) >9.5: 1.32 (1.14 to 1.52)
Fliser, 2007[13]	177	Calcium (per 0.1 mmol/L)	Age & gender	Progression of renal failure (Defined by doubling of serum creatinine and/or terminal renal failure) (HR, CI, P value)	Calcium 1.005 (0.877 to 1.153) (0.941)
Floege, 2011[14]	7970	Total calcium (mmol/L)	Age, gender, country, BMI, smoking status), medical history (CKD etiology, Hx of DM, CVD & Cancer), vintage, vascular access type, Kt/V, blood flow, serum albumin, CRP), antihypertensive drugs, ACE inhibitors, oral anticoagulants, anti-	All cause mortality (HR, CI) (1477, 19% died during follow up period) The values are reported adjusted for time dependent variable too.	Total calcium (mmol/L) <2.10 1.19 (1.04–1.37) ≥2.10–≤2.37 1.0 >2.37–≤2.75 1.06 (0.93–1.21)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			aggregants, vitamin D, phosphate binders, PTH, calcium, phosphate, Hb, ferritin, cholesterol, blood leucocytes, hospitalization, change in vascular access type. Note: Serum albumin, CRP, oral vitamin D use, phosphate binder use, ferritin, hospitalization and change in vascular access type were updated over time in the time-dependent models.		>2.75 1.74 (1.30–2.34)
Fouque, 2013[15]	5339	Serum calcium	Adjusted for age, gender, history of cardiovascular disease, diabetes, dialysis vintage, body mass index, serum albumin and Hgb concentrations	All cause mortality	HR of 1.1 using continuous HR analysis for Calcium <1.59 (1.30– 1.79) mmol/L & >2.41 (2.31– 3.04) mmol/L
					Using KDIGO recommendations (HR, CI, P value) Serum calcium ≤2.15 mmol/L 0.96 (0.86–1.08) (0.49) >2.55 mmol/L 1.18 9 (0.84–1.68) (0.34)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
Fukagawa, 2014[16]	8229 (3276, sub cohort)	Calcium	Age, sex, dialysis vintage, and cause of ESRD BMI, dialysis adequacy (Kt/V), history of cardiovascular dis-ease, creatinine, hemoglobin, albumin, total cholesterol, and VDRA use	All cause mortality (A total of 1226 deaths in the follow up 3 years)	Serum calcium (Risk ratio, CI) < 8.0 mg/dL 1.00 (0.55-1.82) 8.0-8.4 mg/dL 0.97 (0.61-1.55) 8.5-8.9 mg/dL 0.87 (0.68-1.11) 9.0-9.4 mg/dL 1.00 (reference) 9.5-9.9 mg/dL 1.11 (0.91-1.35) 10.0-10.4 mg/dL 1.37 (1.10-1.71) 10.5-10.9 mg/dL 1.77 (1.22-2.59) >11.0 mg/dL 2.38 (1.77-3.21)
				Achieving target Ca & P based on JSDT guideline	For those PTH > 500 pg/ml (Surgical PTx vs. No surgery)(%, P value) 25.5% vs. 38.6 % (P=0.013) Those using dialysate Ca 2.5 vs. 3 mEq/l (%, P value) 43.4% vs. 38.7% (P=0.010) iPTH (pg/ml) 60-180 vs. 181-300 vs. 301-500 vs. > 500 (%, P value) 47.8% vs. 48.3% vs. 35.2% vs. 25 % (P<0.001)
Gallieni, 2012[18]	369	Baseline Calcium	Classes of serum Ca, P, gender, age, and the global calcification score	Progression of calcification in completers	73.0%
				Global calcification score (P values based on Kruskal–Wallis test associations)	Ca (0.828)
				Presence of left ventricular hypertrophy (LVH) was (Diagnosed when LVMI was > 131 g/m2 in males or >100 g/m2 in females, based on values calculated in the Framingham study	Ca (0.035)
				Presence of arteriosclerosis	Ca (0.014)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
				Cardiovascular mortality (42 deaths out of 369)	Log rank test using calcium cut offs Ca (<8.4, 8.4-9.5, >9.5) mg/dl P value=0.98
Kimata, 2007[19]	5041	Serum Albumin-Corrected Calcium Categories	Age, sex, duration of end-stage renal disease, hemoglobin, albumin, Kt/V, dialysate calcium concentration, comorbidities, other mineral metabolism markers, and facility clustering effects	All-Cause Mortality	Ca <8.4 mg/dL 0.90; *P* = 0.63 Ca 8.4-9.0 mg/dL 1.00; Reference Ca >9.0-9.5 mg/dL 0.98; *P* = 0.91 Ca >9.5-<10.4 mg/dL 1.12; *P* = 0.40 Ca >=10.4 mg/dL 1.53; *P* = 0.01
				Cardiovascular Mortality (deaths attributable to acute myocardial infarction, atherosclerotic heart disease, cardiac arrhythmia, and cardiac arrest)	Ca <8.4 mg/dL 1.20; *P* = 0.68 Ca 8.4-9.0 mg/dL 1.00; Reference Ca >9.0-9.5 mg/dL 1.16; *P* = 0.66 Ca >9.5-<10.4 mg/dL 1.78; *P* = 0.06 Ca >=10.4 mg/dL 2.29; *P* = 0.02
Lacson, 2009[20]	78,420	Calcium (mg/dL) Continuous	Albumin, age, dialysis vintage, creatinine, phosphate, gender, body surface area, hemoglobin, access type (catheter or graft), equilibrated Kt/V, white blood cells, diabetes, bio-PTH, race (white, black other)	All-cause morality Hospitalization	HR 1.141 (95% CI, 1.107 to 1.177) HR 1.107 (95% CI, 1.003 to 1.032)
Lim, 2014[21]	2144	Calcium Quartiles Q1 Ca: (<9.0) Q2 Ca: (9.0 - 9.4) Q3 Ca: (9.4 - 9.8) Q4 Ca: (>9.8) [ref]	Age, gender, eGFR, log(UPCR), DM, CVD, HbA1c, mean BP, hemoglobin, albumin, log(cholesterol, ln(CRP), BMI, phosphate, phosphate binder, PTH	Renal Replacement Therapy (Hemodialysis, peritoneal dialysis, renal transplantation) Rapid Renal Progression eGFR slope < −5 mL/min/1.73 m2 /y	Hazard ratio for renal replacement therapy according to Ca Quartile 95% CI Q1: 2.12 (1.49,3.02) p<.05 Q2: 1.50 (1.05,2.15) p<.05 Q3: 1.42 (0.95, 2.12) p value NR Q4: 1 [ref] HR for rapid renal function progression According to Ca Quartile 95% CI Q1: 1.65 (1.19,2.27) p<.05 Q2: 1.35 (0.99,1.84) p<.05 Q3: 1.11 (0.79, 1.56) p value NR Q4: 1[ref]
Lin, 2015[22]	94,983	Calcium (mg/dL) <8.5 8.5-9.5 9.5-10.5 >10.5	Age, sex, diabetes, hematocrit, albumin, kt/V	All-cause mortality	HR (95% CI) P value <8.5: 1.41 (1.36-1.45) (<0.01) 8.5-9.5: Reference 9.5-10.5: 1.05 (1.02-1.08) (<0.01) >10.5: 1.77 (1.68-1.86) (<0.01)
Markaki, 2012[23]	74	Serum Ca <9.3 mg/dL (ref) >9.3 mg/dL	Adiponectin, magnesium, peritoneal dialysis vs. hemodialysis, albumin, C-	All-cause mortality	HR 5.39 (95% CI, 1.33 to 21.87; P = 0.018)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			reactive protein, age		
McGovern, 2013[24]	---	---	---	---	---
Menon, 2005[25]	-	-	-	-	-
Miura, 2015[26]	191	Low Ca vs Normal-high Ca <8.4 mg/dL Normal-high Ca ≥8.4 mg/dL Continuous Variable Model (Ca 1 mg/dL Decrease)	Age, body mass index, presence of ischemic etiology, B-type matriuretic peptide, and sodium	Cardiovascular Mortality Low Ca: 10 (31.3%) events Normal-high Ca: 19 (11.9%)	Unadjusted HR (95% CI) P value Low Ca vs Normal-high Ca: 3.4 (1.6 to 7.4) p=0.002 Continuous Variable Model: 1.165 (1.032 to 1.505) p=0.002
				All-cause Mortality Low Ca: 16 (50.0%) events Normal-high Ca: 39 (24.5%) events	Adjusted HR (95% CI) P value Low Ca vs Normal-high Ca: 1.7 (1.0 to 3.4) P=0.045 Continuous Variable Model: 1.4 (1.0 to 1.8) P=0.021
				Rehospitalization within 1 year, n (%)	Low Ca: 2 (8.0%) Normal-high Ca: 10 (6.5%)
Moore, 2011[27]	270	Serum Ca per 0.1 mmol/L increase	Serum phosphate, male sex, DM, recipient age, peripheral SBP Secondary: serum phosphate, male sex, baseline eGFR, serum albumin, ACEI/ARB use	Patient survival (taken from the time of data collection until death or study termination) and graft loss (taken from the time of data collection until graft loss or study termination). Graft loss was defined as the composite end-point of patient death and re-initiation of dialysis.	All cause mortality hazard ratio for each 0.1mmol/L increase in calcium HR: 1.22 (1.01,1.48) 95% CI p=-0.04 Death-uncensored graft loss Serum calcium per 0.1 mmol/L increase: HR: 1.16 (1.02, 1.32) 95% CI p=0.03
Nakai, 2008[28]	27,404	Adjusted serum Ca (mg/dL) <7 7.0-7.9 8.0-8.9 9.0-9.9 (ref) 10.0-10.9 ≥11.0	Sex, age, duration of dialysis, diabetes mellitus, body weight, BMI, hours of hemodialysis session, Kt/V for urea, normalized protein catabolic rate, adjusted serum calcium, hematocrit, albumin, creatinine, total cholesterol, Ipht	All-cause mortality, HR (95% CI)	<7: 1.008 (0.835 to 1.217; P NS) 7.0-7.9: 1.067 (0.897 to 1.296; P NS) 8.0-8.9: 0.992 (0.916 to 1.074; P NS) 9.0-9.9 (ref) 10.0-10.9: 1.098 (1.020 to 1.182; P=0.0129) ≥11.0: 1.243 (1.113 to 1.388; P=0.0001)
Nakano, 2012[29]	739	Corrected Ca (mg/dL) Continuous	None	CVD event before start of dialysis CVD during entire followup duration	HR 0.62 (95% CI, 0.38 to 1.01; P=0.051) HR 0.54 (95% CI, 0.37 to 0.76; P=0.001)
			Age, sex, BMI, diabetes mellitus, prior CVD, systolic blood pressure, ACE-I/ARB, hemoglobin, albumin, proteinuria, eGFR, phosphate, 25D, 1,25D, whole PTH, log FGF23, active vitamin D,	Renal event (doubling of serum creatinine or initiation of dialysis)	HR 0.73 (95% CI, 0.49 to 1.08)

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
			calcium carbonate		
Noordzij, 2009[31]	1468 HD: 899 PD: 569	Calcium <8.4 mg/dl 8.4-9.5 mg/dl >9.5 mg/dl	Baseline rGFR, calcium, phosphate, iPTH, age, sex, co-morbid conditions, nutritional status (SGA), systolic and diastolic blood pressure, urinary protein loss and use of anti-hypertensive drugs	Loss of residual renal function: becoming anuric during the first 3 years	Adjusted hazard ratios (HR; 95% confidence interval) for the risk of total loss of RRF in categories of plasma concentrations for HD and PD patients HD: <8.4 mg/dl: 0.7 (0.3-1.6) p=0.39 8.4-9.5 mg/dl:: 1.0[ref] >9.5 mg/dl: 1.0(0.6-1.4) p=0.81 PD: <8.4 mg/dl: too few patients 8.4-9.5 mg/dl: 1.0 [ref] >9.5 mg/dl: 1.7 (0.7-4.3) p=0.18
Nowak, 2015[34]	239	Calcium per natural log increase	Age, gender (male), dialysis center clustering, dialysis vintage, systolic and diastolic blood pressure, body-mass index, vascular access on study enrollment (fistula, graft, catheter), coexisting conditions, cause of renal failure, medication use, pooled Kt/V, albumin, hemoglobin, C-reactive protein, cholesterol, sclerostin, FGF23, PTH, ALP, calcium, 25(OH)vitamin D	All-cause mortality	HR (95% CI) P value 0.38 (0.004-35.69) P=0.67
Pihlstrom, 2015[35]	1614	Serum calcium per mmol/L Continuous	Age, sex, smoking, coronary heart disease, diabetes mellitus, ST-T changes, high density lipoprotein, triglycerides, systolic and diastolic blood pressure, body mass index, eGFR, proteinuria, s-calcium, s-phosphate, s-PTH, high sensitive C-reactive protein, randomization group, time on dialysis, and time since last transplantation	All-cause Mortality 291/1614 events	HR (95% CI) P value 0.90 (0.42-1.95) 0.797
				Graft loss (death censored) 285/1614 events	HR (95% CI) P value 0.26 (0.13-0.50) <0.001
Ravani, 2009[36]	-	-	-	-	-
Sakaguchi, 2014[37]	--	--	--	--	--

Author, year	Sample size Followup	Predictors	Covariates	Outcomes	Results
Schaeffner, 2007[38]	733	Serum calcium quintiles (mmol/L) Q1 ≤2.25 Q2 2.26-2.32 Q3 2.33-2.40 Q4 2.41-2.49 Q5 ≥2.50	Age, gender, eGFR, C-reactive protein, total plasma homocysteine, body mass index, diabetic nephropathy, donor gender, time from first renal replacement therapy to transplantation	All-cause mortality, HR (95% CI) Kidney allograft loss or death	Q1: (ref) Q2: 0.87 (0.54 to 1.45) Q3: 0.95 (0.60 to 1.51) Q4: 0.85 (0.50 to 1.44) Q5: 0.65 (0.38 to 1.13) Q1: (ref) Q2: 0.89 (0.61 to 1.29) Q3: 0.68 (0.47 to 0.99) Q4: 0.75 (0.50 to 1.12) Q5: 0.61 (0.40 to 0.93)
Scialla, 2015[39]	511	Serum calcium, mg/dl ≤8.8 8.9-9.2 9.3-9.6 ≥9.7 Continuous (per 1 mg/dl)	Age, sex, race, education, smoking, BMI, baseline ICED, baseline diabetes mellitus, baseline cardiovascular disease, serum albumin and hemoglobin	All-cause mortality, HR (95% CI) 332 events/466	≤8.8: (ref) 8.9-9.2: 2.10 (1.45-3.05) 9.3-9.6: 1.30 (0.89-1.91) ≥9.7: 1.29 (0.86-1.92) Continuous: 1.04 (0.83-1.32)
Scialla, 2013[40]	--	--	--	--	--
Silva, 2013[41]	---	---	---	---	---
Tentori, 2008[42]	25,529	Serum calcium (mg/dL) ≤8.5 8.6-10.0 (ref) >10.0	Facility clustering effects, age, sex, race, body mass index, duration of end-stage renal disease, 13 comorbid conditions, hemoglobin, serum albumin, normalized protein catabolic rate, single-pool Kt/V, prior parathyroidectomy, baseline levels of serum phosphate and PTH	All-cause mortality, HR (95% CI) Cardiovascular mortality, HR (95% CI) Deaths caused by acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, or congestive heart failure	≤8.5: 1.02 (0.94 to 1.10) 8.6-10.0: (ref) >10: 1.16 (1.08 to 1.25; P<0.0001) ≤8.5: 0.95 (0.83 to 1.08) 8.6-10: (ref) >10: 1.24 (1.10 to 1.41; P<0.05)
Zhao, 2014[43]	903	Serum calcium per 1 mmol/L increase Continuous	Age, diabetes mellitus, hypertension, cardiovascular disease, diastolic blood pressure, serum albumin, serum creatinine, phosphate, hemoglobin, triglycerides, serum uric acid, calcium, intact parathyroid hormone, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol	All-cause mortality	HR: 0.62

a. Most patients had been treated with relatively limited doses of calcitriol administered orally (1,5 μg/wk) or intravenously (calcitriol 4,5 μg/wk), but had discontinued this treatment at the time of the study. However, 17 patients were on IV calcitriol treatment with weekly doses ranging from 3 to 6 μg and 8 patients were treated with paricalcitol, 10-16 μg per week. Calcitriol/Paricalcitol doses were adjusted to comply with KDIGO guidelines. 81% of the patients were on phosphate binders, mainly calcium salts (calcium carbonate 1,9 ± 0,8 g/day) and sevelamer (6200 ± 2010 mg/day). In the majority of patients, regular intravenous erythropoietin treatment was underway.

Supplemental Table 53. Summary table of studies evaluating different concentrations of serum phosphate or calcium among patients with CKD G3a-G5 or G5D – quality

Author, year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall quality
Benavente, 2012[1]	Low	Low	Moderate	Low	Moderate	Low	Moderate
Caravaca, 2011[2]	Low	Low	Low	Moderate	Moderate	Low	Moderate
Chartsrisak, 2013[3]	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Chue, 2011[4]	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Coen, 2010[5]	Low	Low	Low	Low	Moderate	Low	High
Connolly, 2009[6]	Low	Low	Low	Low	Moderate	Moderate	Moderate
De Nicola, 2014[7]	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Denburg, 2013[8]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Djukanovic, 2015[9]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Eddington, 2010[10]	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Fein, 2013[11]	High	Low	High	Moderate	Low	Moderate	Low
Fernandez-Martin, 2015[12]	Low	Moderate	Low	Low	Low	Low	High
Fliser, 2007[13]	Moderate	Low	Moderate	High	Moderate	Moderate	Moderate
Floege, 2011[14]	Moderate	High	Moderate	High	Moderate	Moderate	Low
Fouque, 2013[15]	Moderate	High	Moderate	Moderate	Moderate	Moderate	Low
Fukagawa, 2014[16]	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Gallieni, 2012[18]	Moderate	High	Moderate	Moderate	Moderate	Moderate	Low
Kimata, 2007[19]	Moderate	High	High	Moderate	Moderate	Moderate	Moderate
Lacson, 2009[20]	Low	High	Moderate	Low	Low	Low	Moderate
Lim, 2014[21]	Low	Moderate	Low	Low	Low	Low	Moderate
Lin, 2015[22]	Low	Moderate	Low	Low	Low	Low	High
Markaki, 2012[23]	Low	Low	Moderate	Low	Low	Moderate	Moderate
McGovern, 2013[24]	Low	Moderate	Moderate	Low	Low	Low	Low
Menon, 2005[25]	Low	High	Moderate	Low	Low	Moderate	Moderate
Miura, 2015[26]	Low	Low	Low	Low	Low	Low	High
Moore, 2011[27]	Low	Moderate	Low	Low	Low	Low	Moderate
Nakai, 2008[28]	Low	Low	Moderate	Low	Low	Moderate	Moderate
Nakano, 2012[29]	Low	Low	Low	Low	High	Low	Moderate
Noordzij, 2009[31]	Low	Moderate	Low	Low	Low	Low	Moderate
Nowak, 2015[34]	Low	Low	Moderate	Low	Moderate	Low	Moderate
Pihlstrom, 2015[35]	Moderate	Moderate	Low	Low	Low	Low	High
Ravani, 2009[36]	Low	Moderate	High	Low	Moderate	Low	Moderate
Sakaguchi, 2014[37]	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Schaeffner, 2007[38]	Low	Low	High	Low	Low	Low	Moderate
Scialla, 2015[39]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Scialla, 2013[40]	Low	Moderate	Low	Low	Low	Low	Moderate
Silva, 2013[41]	Low	Moderate	Low	Low	Low	Low	Moderate
Tentori, 2008[42]	Low	Moderate	Moderate	Low	Low	Low	Moderate
Zhao, 2014[43]	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate

Supplemental Table 54. Evidence matrix of studies evaluating different concentrations of serum phosphate or calcium among patients with CKD G3a-G5 or G5D

Serum phosphate - Evidence Matrix				Risk of bias					
	Low			Moderate			High		
Outcome	Author	N	F/U	Author	*N*	F/U	Author	*N*	F/U
Mortality	Fenandez-Martin 2015	6307	3 yrs	Connolly 2009	397	75 mo	Floege 2011	7970	21 mo
	Lin 2015	94,983	3 yrs	Djukanovic 2015	2153	3 yrs	Fougue 2013	5339	30 mo
	Pihlstrom 2015	1840	6.7 yrs	Eddington 2010	1203	37 mo			
				Fukagawa 2014	8229	36 mo			
				Kimata, 2007	5041	8056 py			
				Lacson 2009	78420	1 yr			
				Menon 2005	840	123 mo			
				Moore 2011	270	88 mo			
				Nakai 2008	27404	3 yrs			
				Nowak 2015	239	4 yrs			
				Sakaguchi 2014	142069	1 yr			
				Schaeffner 2007	733	6.1 yrs			
				Scialla 2015	511	3.4 yrs			
				Silva 2013	119	76 mo			
				Tentori 2008	25529	1.4 yrs			
				Zhao 2015	1354	2 yrs			
GFR decline				Benavente 2012	297	67 mo			
				Caravaca 2011	184	10 mo			
				Chartsrisak 2013	466	25 mo			
				Chue 2011	225	31 mo			
				De Nicola 2014	200	31 mo			
				Fliser 2007	177	53 mo			
				Nakano 2012	738	4.4 yrs			
				Noordzij 2009	1468	5 yrs			
Cardiovascular and cerebrovascular events				Eddington 2010	1203	37 mo	Gallieni 2012	369	36 mo
				Kimata, 2007	5041	8056 py			
				Menon 2005	840	123 mo			
				Nakano 2012	738	4.4 yrs			
				Scialla 2015	511	3.4 yrs			
				Tentori 2008	25529	1.4 yrs			
Serum calcium - Evidence Matrix				Risk of bias					
	Low			Moderate			High		
Outcome	Author	N	F/U	Author	*N*	F/U	Author	*N*	F/U
Mortality	Coen 2010	71	12-18 mo	Djukanovic 2015	2153	3 yrs	Fein 2013	90	31 mo
	Fenandez-Martin 2015	6307	3 yrs	Fukagawa 2014	8229	36 mo	Floege 2011	7970	21 mo
	Miura 2015	191	1.8 yrs	Lacson 2009	78420	1 yr	Fougue 2013	5339	30 mo
	Lin 2015	94,983	3 yrs	Kimata, 2007	5041	8056 py			

	Pihlstrom 2015	1840	6.7 yrs	Markaki 2012 Moore 2011 Nakai 2008 Nowak 2015 Schaeffner 2007 Scialla 2015 Tentori 2008 Zhao 2015	74 270 27404 239 733 511 25529 1354	50 mo 88 mo 3 yrs 4.0 yrs 6.1 yrs 3.4 yrs 1.4 yrs 2 yrs			
Cardiovascular and cerebrovascular events	Miura 2015	191	1.8 yrs	Nakano 2012 Kimata, 2007 Tentori 2008	739 5041 25529	4.4 yrs 8056 py 1.4 yrs	Gallieni 2012	369	36 mo

Supplemental Table 55. Evidence profile of studies evaluating different concentrations of serum phosphate or calcium among patients with CKD G3a-G5 or G5D

							Summary of findings		
Outcome	No. of studies and study design	Total *N*	ROB	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Serum phosphate									
Mortality	21 observational studies	410,950	Moderate	Consistent	Direct		Low	Most studies show increasing risk of death with increasing levels of serum phosphate.	Critical
GFR decline	8 observational studies	3,755	Moderate	Inconsistent	Indirect		Very low	Results are inconclusive.	Moderate
Cardiovascular and cerebrovascular events	7 observational studies	34,231	Moderate	Inconsistent	Direct		Very low	Results are inconclusive.	Critical
Serum calcium									
Mortality	20 observational studies	266,748	Moderate	Consistent	Direct		Low	Most studies show increasing risk of death with increasing levels of serum calcium.	Critical
Cardiovascular and cerebrovascular events	5 observational studies	31,869	Moderate	Consistent	Direct		Low	Most studies show increasing risk of CVD events with increasing levels of serum calcium.	Critical

GFR = glomerular filtration rate; ROB = risk of bias

REFERENCES

1. Benavente D, Chue CD, Moore J, Addison C, Borrows R, Ferro CJ. Serum phosphate measured at 6 and 12 months after successful kidney transplant is independently associated with subsequent graft loss. Exp Clin Transplant. 2012 Apr;10(2):119-24.

2. Caravaca F, Villa J, Garcia de Vinuesa E, Martinez del Viejo C, Martinez Gallardo R, Macias R, et al. Relationship between serum phosphorus and the progression of advanced chronic kidney disease. Nefrologia. 2011;31(6):707-15.

3. Chartsrisak K, Vipattawat K, Assanatham M, Nongnuch A, Ingsathit A, Domrongkitchaiporn S, et al. Mineral metabolism and outcomes in chronic kidney disease stage 2-4 patients. BMC Nephrol. 2013;14:14.

4. Chue CD, Edwards NC, Davis LJ, Steeds RP, Townend JN, Ferro CJ. Serum phosphate but not pulse wave velocity predicts decline in renal function in patients with early chronic kidney disease. Nephrol Dial Transplant. 2011 Aug;26(8):2576-82.

5. Coen G, Pierantozzi A, Spizzichino D, Sardella D, Mantella D, Manni M, et al. Risk factors of one year increment of coronary calcifications and survival in hemodialysis patients. BMC Nephrol. 2010;11:10.

6. Connolly GM, Cunningham R, McNamee PT, Young IS, Maxwell AP. Elevated serum phosphate predicts mortality in renal transplant recipients. Transplantation. 2009 Apr 15;87(7):1040-4.

7. De Nicola L, Conte G, Chiodini P, D'Angio P, Donnarumma G, Minutolo R. Interaction between phosphorus and parathyroid hormone in non-dialysis CKD patients under nephrology care. J Nephrol. 2014 Feb;27(1):57-63.

8. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, et al. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. J Clin Endocrinol Metab. 2013 May;98(5):1930-8.

9. Djukanovic L, Dimkovic N, Marinkovic J, Andric B, Bogdanovic J, Budosan I, et al. Compliance with guidelines and predictors of mortality in hemodialysis. Learning from Serbia patients. Nefrologia. 2015 May-Jun;35(3):287-95.

10. Eddington H, Hoefield R, Sinha S, Chrysochou C, Lane B, Foley RN, et al. Serum phosphate and mortality in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010 Dec;5(12):2251-7.

11. Fein PA, Asadi S, Singh P, Hartman W, Stuto S, Chattopadhyay J, et al. Relationship between alkaline phosphatase and all-cause mortality in peritoneal dialysis patients. Adv Perit Dial. 2013;29:61-3.

12. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP, Floege J, Ketteler M, London G, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrol Dial Transplant. 2015 Sep;30(9):1542-51.

13. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007 Sep;18(9):2600-8.

14. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transplant. 2011 Jun;26(6):1948-55.

15. Fouque D, Roth H, Pelletier S, London GM, Hannedouche T, Jean G, et al. Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets? Nephrol Dial Transplant. 2013 Feb;28(2):360-7.

16. Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, et al. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis. 2014 Jun;63(6):979-87.

17. Fukagawa M, Komaba H, Onishi Y, Fukuhara S, Akizawa T, Kurokawa K. Mineral metabolism management in hemodialysis patients with secondary hyperparathyroidism in Japan: baseline data from the MBD-5D. Am J Nephrol. 2011;33(5):427-37.

18. Gallieni M, Caputo F, Filippini A, Gabella P, Giannattasio M, Stingone A, et al. Prevalence and progression of cardiovascular calcifications in peritoneal dialysis patients: A prospective study. Bone. 2012 Sep;51(3):332-7.

19. Kimata N, Albert JM, Akiba T, Yamazaki S, Kawaguchi T, Fukuhara S, et al. Association of mineral metabolism factors with all-cause and cardiovascular mortality in hemodialysis patients: the Japan dialysis outcomes and practice patterns study. Hemodial Int. 2007 Jul;11(3):340-8.

20. Lacson E, Jr., Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: potentially actionable laboratory variables and vascular access. Am J Kidney Dis. 2009 Jan;53(1):79-90.

21. Lim LM, Kuo HT, Kuo MC, Chiu YW, Lee JJ, Hwang SJ, et al. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 2014;15:183.

22. Lin YC, Hsu CY, Kao CC, Chang FC, Chen TW, Chen HH, et al. Effect Modifying Role of Serum Calcium on Mortality-Predictability of PTH and Alkaline Phosphatase in

Hemodialysis Patients: An Investigation Using Data from the Taiwan Renal Registry Data System from 2005 to 2012. PLoS One. 2015;10(6):e0129737.

23. Markaki A, Kyriazis J, Stylianou K, Fragkiadakis GA, Perakis K, Margioris AN, et al. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. PLoS One. 2012;7(12):e52350.

24. McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. PLoS One. 2013;8(9):e74996.

25. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, et al. Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. Am J Kidney Dis. 2005 Sep;46(3):455-63.

26. Miura S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, et al. Association of Hypocalcemia With Mortality in Hospitalized Patients With Heart Failure and Chronic Kidney Disease. J Card Fail. 2015 Aug;21(8):621-7.

27. Moore J, Tomson CR, Tessa Savage M, Borrows R, Ferro CJ. Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation. Clin Transplant. 2011 May-Jun;25(3):406-16.

28. Nakai S, Akiba T, Kazama J, Yokoyama K, Fukagawa M, Tominaga Y, et al. Effects of serum calcium, phosphorous, and intact parathyroid hormone levels on survival in chronic hemodialysis patients in Japan. Ther Apher Dial. 2008 Feb;12(1):49-54.

29. Nakano C, Hamano T, Fujii N, Obi Y, Matsui I, Tomida K, et al. Intact fibroblast growth factor 23 levels predict incident cardiovascular event before but not after the start of dialysis. Bone. 2012 Jun;50(6):1266-74.

30. Nakano C, Hamano T, Fujii N, Matsui I, Tomida K, Mikami S, et al. Combined use of vitamin D status and FGF23 for risk stratification of renal outcome. Clin J Am Soc Nephrol. 2012 May;7(5):810-9.

31. Noordzij M, Voormolen NM, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT, et al. Disordered mineral metabolism is not a risk factor for loss of residual renal function in dialysis patients. Nephrol Dial Transplant. 2009 May;24(5):1580-7.

32. Noordzij M, Cranenburg EM, Engelsman LF, Hermans MM, Boeschoten EW, Brandenburg VM, et al. Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients. Nephrol Dial Transplant. 2011 May;26(5):1662-9.

33. Noordzij M, Korevaar JC, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease

in CKD: association with mortality in dialysis patients. Am J Kidney Dis. 2005 Nov;46(5):925-32.

34. Nowak A, Artunc F, Serra AL, Pollock E, Krayenbuhl PA, Muller C, et al. Sclerostin quo vadis? - is this a useful long-term mortality parameter in prevalent hemodialysis patients? Kidney Blood Press Res. 2015;40(3):266-76.

35. Pihlstrom H, Dahle DO, Mjoen G, Pilz S, Marz W, Abedini S, et al. Increased risk of all-cause mortality and renal graft loss in stable renal transplant recipients with hyperparathyroidism. Transplantation. 2015 Feb;99(2):351-9.

36. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, et al. Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int. 2009 Jan;75(1):88-95.

37. Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Iseki K, et al. Magnesium modifies the cardiovascular mortality risk associated with hyperphosphatemia in patients undergoing hemodialysis: a cohort study. PLoS One. 2014;9(12):e116273.

38. Schaeffner ES, Fodinger M, Kramar R, Sunder-Plassmann G, Winkelmayer WC. Prognostic associations of serum calcium, phosphate and calcium phosphate concentration product with outcomes in kidney transplant recipients. Transpl Int. 2007 Mar;20(3):247-55.

39. Scialla JJ, Parekh RS, Eustace JA, Astor BC, Plantinga L, Jaar BG, et al. Race, Mineral Homeostasis and Mortality in Patients with End-Stage Renal Disease on Dialysis. Am J Nephrol. 2015;42(1):25-34.

40. Scialla JJ, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. J Am Soc Nephrol. 2013 Jan;24(1):125-35.

41. Silva AP, Fragoso A, Pinho A, Tavares N, Camacho A, Faisca M, et al. Phosphorus as an early marker of morbidity and mortality in type 2 chronic kidney disease diabetic patients. J Diabetes Complications. 2013 Jul-Aug;27(4):328-32.

42. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2008 Sep;52(3):519-30.

43. Zhao C, Luo Q, Xia X, He F, Peng F, Yu X, et al. Risk score to predict mortality in continuous ambulatory peritoneal dialysis patients. Eur J Clin Invest. 2014 Nov;44(11):1095-103.