KDIGO CLINICAL PRACTICE GUIDELINE FOR THE DIAGNOSIS, EVALUATION, PREVENTION, AND TREATMENT OF CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDER (CKD-MBD)

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Supplemental Table 1. Literature search strategy

KDIGO - Bone and Kidney Original
1. exp Kidney Glomerulus/
2. exp Kidney Diseases/
3. exp Kidney Function Tests/
4. renal.mp.
5. nephro$.mp.
6. kidney.mp.
7. ur?emia.tw.
8. exp Renal Replacement Therapy/
9. h?emodialysis.tw.
10. or/1-9
11. limit 10 to human
12. exp "Bone and Bones"/
13. exp Renal Osteodystrophy/
14. exp Calcification, Physiologic/
15. exp Hyperparathyroidism/
16. exp Phosphorus Metabolism Disorders/
17. hyperphosphatemia.mp.
18. exp Calcium Metabolism Disorders/
19. or/12-18
20. exp Parathyroid Hormone/
21. calcium/
22. Phosphorus/
23. exp Alkaline Phosphatase/
24. exp Vitamin D/
25. exp Osteocalcin/
26. or/20-25
27. (cinacalcet or Calcimimetic or sensipar or "AMG 073" or KRN 1493).mp. or 364782-34-3.rn.
28. (sevelamer or renagel).mp. or 182683-00-7.rn.
29. exp Calcium Carbonate/
30. calcium acetate.mp.
31. phoslo.mp.
32. exp Calcium Citrate/
33. exp Bone Density Conservation Agents/
34. (doxercalciferol or rocaltrol or paricalcitriol or ergocalciferol or cholecalciferol or calciferol or dihydrotachysterol or calcifediol or calcidiol or faldecalcitrol or maxicalcitriol or hydroxycholecalciferols).mp.
35. Lanthanum.mp.
36. or/27-35
37. 19 or 26 or 36
38. pulse pressure.mp.
39. pulse wave velocity.mp.
40. arterial stiffness.mp.
41. vascular stiffness.mp.
42. vascular calcification.mp.
43. or/38-42
44. exp Bone Density/ or exp Densitometry, X-ray/ or DXA.mp.
45. exp Tomography, X-ray Computed/
46. exp Ultrasonography/
47. exp Magnetic Resonance Imaging/
48. Bone scan.mp.
49. EBCT.mp.

50. MSCT.mp.
51. or/44-50
52. exp Cardiovascular Diseases/
53. 37 or 52
54. 51 and 53
55. exp biopsy/
56. exp histology/
57. 55 or 56
58. 37 and 57
59. 11 and 37
60. 11 and 43
61. 11 and 54
62. 11 and 58
63. or/59-62
64. limit 63 to (addresses or bibliography or biography or comment or dictionary or directory or editorial or festschrift or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review" or review, academic or review, tutorial)
65. 63 not 64
66. limit 65 to yr="1995 - 2006"
67. limit 65 to yr="2001 - 2006"

Supplemental Table 2. Use of other relevant systematic reviews and meta-analyses

Review Name	Reference	Cut-off Dates of Literature Search	Use in Work Group deliberation
Calcimimetics			
Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients Strippoli, GFM; Tong, A; Palmer, SC; Elder, G; Craig, JC	1	Cochrane CENTRAL (The Cochrane Library-Issue 4, 2005) MEDLINE 1966-11/2005 EMBASE 1980-11/2005	References used to check and supplement reference list of ERT systematic review.
Phosphate Binders			
Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F, Manns B	2	Cochrane CENTRAL Cochrane Database of Systematic Reviews DARE MEDLINE 1966-1/19/2007 EMBASE 1988-1/19/2007 The National Health Service Economic Evaluation Database TOXNET BIOSIS Previews	References used to check reference list of ERT systematic review.
Transplant			
Interventions for preventing bone disease in kidney transplant recipient Palmer SC, McGregor DO, Strippoli GFM	3	Cochrane CENTRAL (The Cochrane Library-Issue 3, 2004) MEDLINE 1996-2004 EMBASE 1980-8/2004	References used to check and supplement reference list of ERT systematic review.
Bone disease after renal transplantation Weisenger JR, Carlini RG, Rojas E, Bellorin-Font E	4		References used to check reference list of ERT systematic review.
Vitamin D			
Meta-analysis: vitamin D compounds in chronic kidney disease Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GFM	5	Cochrane CENTRAL (no dates) MEDLINE 1966- July 2007 EMBASE 1980- July 2007	References used to check and supplement reference list of ERT systematic review. Use of systematic review of comparison of PO vs. IV vitamin D.
Growth hormone for children with chronic kidney disease Vimalachancdra D, Hodson EM, Willis NS, Craig JC, Cowell C, Knight JF	6	Cochrane CENTRAL, in The Cochrane Library Issue 3, 2005) MEDLINE 1966-Apr 2000 EMBASE 1988- Apr 2000	Use of systematic review. ERT search yielded no additional references

ERT, evidence review team; IV, intravenous; PO, oral.

Supplemental Table 3. Key features of the guideline

Topic	Description	Discussed in KDIGO CKD-MBD Guideline
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Executive Summary.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Definition of CKD-MBD provided in Chapter 1. Guideline addresses evaluation and treatment of CKD-MBD.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for patients with CKD-MBD in their evaluation and in selecting treatments (among the different options) to improve patient survival and quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Providers: Nephrologists (adult and pediatric), bone specialists, dialysis providers (including nurses), dietitians. Patients: Adult and pediatric patients with CKD-MBD, CKD Stages 3-5, 5D, CKD Stages 1-5 T and their relatives and friends. Policy Makers: Those in related health fields.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Patients, adult and pediatric, with CKD-MBD, CKD Stages 3-5, 5D or CKD Stages 1-5T.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in the Work Group Biographic and Disclosure Information.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest (see section on Biographic and Disclosure Information).	Funding per KDIGO from a consortium including: Abbott, Amgen, Belo Foundation, Coca-Cola Company, Dole Food Company, Genzyme, JC Penney, NATCO-The Organization for Transplant Professionals, National Kidney Foundation-Board of Directors, Novartis, Robert and Jane Cizik Foundation, Roche, Shire, Transwestern Commercial Services, and Wyeth. No role of funding source in development or reporting of this guideline. Stakeholders could participate in the public review.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	The evidence collection started with the reference list from the KDOQI Bone Guidelines for Adults and Children,[7,8] which was based on a systematic search of MEDLINE (1966-Dec 31, 2000). This was supplemented by a MEDLINE search going forward for relevant terms including kidney, kidney disease, renal replacement therapy, bone, calcification and specific treatments. The search was limited to English language publications since Jan 1, 2001 (See through December 2008 and supplemented by articles identified by Work Group members.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance if adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harm.	Quality of individual studies was graded in a three-tiered grading system. Quality of evidence and strength of recommendations were graded following the GRADE approach. The Work Group could provide general guidance in ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	1) Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic review topics, summary tables and evidence profiles were generated. 2) For recommendations on treatment interventions, the steps outlined by GRADE were followed.

Topic	Description	Discussed in KDIGO CKD-MBD Guideline
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline underwent internal and external peer review and revision in response to the review.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, expiration date for this version of the guideline.	The updating of the guideline will depend on the publication of new data that would change the quality of the evidence or the estimates for net benefit. Results from registered ongoing trials (see table of ongoing studies) and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	See Chapter 1, Definition of CKD-MBD, and list of Abbreviations and acronyms.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in 9.	Recommendations are provided in Chapter 3: Diagnosis of CKD-MBD, Chapter 4: Treatments of CKD-MBD and Chapter 5: Evaluation and Treatment of Kidney Transplant Bone Disease. Each recommendations builds on a chain of logic and a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence is provided in parenthesis at the end of each recommendation.
15. Potential benefits and harm	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each intervention are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the guideline recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Level 2 recommendations inherently indicate a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	These were not provided in the guideline, but may be developed later as implementation tools by Kidney Learning System®
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These guideline recommendations are global. Review criteria were not suggested because most recommendations are weak (level 2) and implementation with prioritization and development of review criteria has to proceed locally. Suggestions for future research were provided.

CKD-MBD, chronic kidney disease-mineral and bone disorder; GRADE, Grades of Recommendations Assessment, Development, and Evaluation; KDOQI, Kidney Disease Outcomes Quality Initiative; NATCO, North American Transplant Coordinators Association.
Key features are summarized according to the Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines.[9]

Supplemental Table 4. Prevalence and incidence of fractures in patients with CKD 5D

Author, Year	N	Patients	Prevalence			Incidence (%/y)		
			Any	Hip	Spine	Any	Hip	Spine
Pendras, 1966[10]	19	first HD patients	47%					
Rubini, 1969[11]	29	HD	27%					
Parfitt, 1972[12]	16	HD	44%		25%			
Piraino, 1988[13]	16	HD: Fibrosis				4.8		
Yamaguchi, 1996[14]	124	HD	10%		11%			
Atsumi, 1999[15]	187	HD			21%			
Gerakis, 2000[16]	62	HD	11%					
Alem, 2000[17]	182493	Males					0.74	
Alem, 2000[17]	143971	Females					1.36	
Coco, 2000[18]	1272	HD all in unit					1.39	
Stehman-Breen, 2000[19]	4952	HD					0.69	
Ball, 2002[20]	101039	USRDS on Tx list					0.29	
Jamal, 2002[21]	104	HD>55yrs	52%		33%			
Kaji, 2002[22]	183	HD		7.60%				
Urena, 2003[23]	70	HD	30%		7%			
Block, 2004[24]	40538	HD, Fresenius				0.52		
Inaba, 2005[25]	114	PD >65yrs			18%			
Danese, 2006[26]	9007	USRDS					0.65	0.28
Elder, 2006[27]	242	Pre-Tx			28%			
Ersoy, 2006[28]	292	PD	10%					
Jadoul, 2006[29]	12782	HD, DOPPS, international		2.60%		2.56	0.89	
Jamal, 2006[30]	52	HD >50yrs	52%					
Kaneko, 2006[31]	7159	USRDS					1	
Mitterbauer, 2007[32]	1777	HD				4.1		

DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis; N, number of subjects; PD, peritoneal dialysis; Tx, transplant; USRDS, United States Renal Data System.

Supplemental Table 5. Fractures in patients with CKD Stages 3-4

Author, Year	N	Population	Study Design	Age	% with CKD 3-4	Hip Fractures in CKD	Odds Ratio
Nickolas, 2006[33]	6270	US adults NHANES	xs	>50	14%	5%	2.32
Dukas, 2005[34]	5313	German people with osteoporosis	xs	elderly	61%	7.80%	1.57
Ensrud, 2007[35]	9704 149 cases	SOF	case cohort	>65	47%		1.57 eGFR 45-59 2.32 eGFR <45
Fried, 2007[36]	4699	CardiovascHealth	prospective x 7yr	adults>65		0.97%/y women 0.59%/y men	1.26 per SD cystatin
Jassal, 2007[37]	1023	Rancho Bernardo	cohort	elderly	50%	2%/y (All fx)	Not related
Dooley,2008[38]	33 091	Male veterans>50	retrospective cohort	adults	41%	0.24%/y stage 3 0.47%/y stage 4	1.23 stage 3 3.65 stage 4
LaCroix, 2008[39]	39 795 404 cases	WHI	nested case cohort	women>50	18%		2.51

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; fx, fracture; N, number of subjects; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; SOF, study of osteoporotic fractures; WHI, Women's Health Initiative; xs, cross-sectional.

Notes: Odds Ratio compares risk of hip fracture in patients with CKD Stages 3-4 to patients with CKD Stages 0-1 or CKD Stages 0-2.

Supplemental Table 6. Overview Table of selected studies of the natural history of bone disorders

Author, Year	N Population	Study Design Country	Test (s)	Follow-up
Changes in bone histology in CKD Stages 3-5				
Hamdy, 1995[40]	62 CKD Stage 3-4	RCT (placebo arm) Belgium, France, Netherlands, UK	Transiliac bone biopsy	24 mo
Changes in BMD in CKD Stages 3-5				
Miller, 2005[41]	CrCl<30 mL/min (N = 271) CrCl 30-50 (N = 2037)	MA of RCTs (placebo arm) Asia, Australia, Europe, North America	DXA at lumbar spine	Mean 25 mo
Jassal, 2007[37]	488 CKD Stage ≥3	Prospective USA	DXA, total hip	Up to 84 mo
Changes in bone histology in CKD Stages 1-5T				
Cruz, 2004[42]	20 At KTx	Prospective Brazil	Iliac crest bone biopsy	1.3 mo before and 6 mo after KTx
Changes in BMD in CKD Stages 1-5T				
Grotz, 1995[43]	115 KTR (0-237 mo post-KTx)	Unclear Germany	DXA, L1-L4	12 mo
Pichette, 1996[44]	70 KTR (>2 y post-KTx)	Prospective Canada	DXA, average of L2- L4	Mean 22 mo
Brandenburg, 2004[45]	63 At KTx	Prospective Germany	DXA, average of L2- L4	Yearly for 24-72 mo
Cruz, 2001[46]	62 KTR (>1 y post-KTx)	Prospective USA	DXA at lumbar spine, at hip, and at wrist	12 mo
de Sevaux, 2003[47]	61 At KTx	Prospective Netherlands	DXA at L1-L4, femoral neck, trochanter, ward's triangle	3, 6, 12, 24 mo

BMD, bone mineral density; CKD, chronic kidney disease; CrCl, creatinine clearance; DXA, dual-energy X-ray absorptiometry; KTR, kidney transplant recipients; KTx, kidney transplant; MA, meta-analysis; N, number of subjects; RCT, randomized controlled trial.

Supplemental Table 7. Overview Table of selected studies demonstrating the risk relationship between bone measurements and mortality in CKD Stage 5D

Author, Year Study Design Country	N Population Follow-up	Technique	Categorization	Mortality Categorization
Fracture				
Mittalhenkle, 2004[48] USRDS USA	30 532 HD nd	Inpatient diagnosis codes	-Hip fracture -None (matched controls)	-All cause -Cardiovascular
Danese 2006[26] DMMS Waves 1-4 USA	9007 HD/PD 36 mo	Inpatient diagnosis codes	-Hip, vertebral or pelvic fracture -None	-All cause
Kaneko, 2007[31] DMMS Waves 3&4 USA	7179 HD 39 mo	Hospital discharge diagnosis codes	-Long-bone fracture -None	-All cause
Coco, 2000[18] Registry USA	1272 HD 120 mo	Medical record review	-Hip fracture -None	-All cause
Rodriguez-Garcia, 2009[49] Prospective Spain	193 HD 24 mo	X-ray of thoracic, lumbar spine, pelvis and hands	-Vertebral fraction	-All cause
BMD				
Taal, 2003[50] Prospective UK	88 HD 42 mo	DXA	Osteopenia or osteoporosis defined by -total hip bone mass T score -lumbar spine bone mass T score	-All cause

BMD, bone mineral density; DMMS, Dialysis Morbidity and Mortality Study (US Renal Data System); DXA, dual energy x-ray absorptiometry; HD, hemodialysis; iPTH, intact parathyroid hormone; N, number of subjects; nd, not documented; PD, peritoneal dialysis; USRDS, United States Renal Data System.

Supplemental Table 8. Overview Table of selected studies demonstrating the risk relationships between hormonal parameter, PTH, and fractures in CKD Stage 5D

Author, Year Database	N Follow-up Country	Fracture Ascertainment & Categorization	Categorization or Comparison[Measurement technique] PTH (pmol/L)
Block, 2004[24] Fresenius	40 538 12 to 18 mo USA	Hospitalization due to fracture by diagnosis code[a]	<15.9, 15.9-31.8, 31.8-63.6, >63.6 (*a priori*) [nd]
Jadoul, 2006[29] DOPPS II	12782 Up to 24 mo 12 Countries[b]	Diagnoses and procedures[c] -Hip -Any	<15.9, 15.9-31.8, 31.9-63.6, 63.7-79.5, 79.6-95.4, >95.4 [intact] Continuous [intact]
Danese, 2006[26] DMMS 1-4	9007 36 mo USA	Diagnosis codes[d] -Hip -Vertebral -Pelvic[e]	<5.3, 5.3-15.8, 15.9-31.7, 31.8-84.8, ≥84.8 per 10.6 pmol/L within groups: 1-31.8, 31.8-84.8, >84.8 [nd]
Stehman-Breen, 2000[19] DMMA Wave 1	4952 34 mo USA	Diagnosis codes[f] -Cervical, intertrochanteric, or subtrochanteric hip	<10.6, 10.6-31.8, >31.8 [intact]
Mitterbauer, 2007[32] OEDTR	1777 nd Austria	Clinical or radiological evidence of fractures or decrease in any vertebral height of >20%[g]	iPTH <7.4 vs. 7.4 ≤iPTH≤17, 17 ≤iPTH ≤31.8vs. 7.4 ≤iPTH≤17, iPTH >31.8 vs. 7.4 ≤iPTH≤17
Coco, 2000[18] Montefiore	1272 Mean 38 mo USA	Diagnosed by radiologist -Intertrochanteric or proximal femoral neck	Quartiles (<6.9, 7.0-20.7, 20.8-53.0, >53.1) [intact]

DOPPS II, Dialysis Outcomes and Practice Patterns Study, Phase 2; DMMS 1-4, Dialysis Morbidity and Mortality Study Waves 1-4 (US Renal Data System); iPTH, intact parathyroid hormone; N, number of subjects; nd; not documented; OEDTR, Austrian dialysis and transplant registry; PTH, parathyroid hormone.

Annotations:

a. Unadjusted, case-mix adjusted and multivariate adjusted analyses were reported. For all analyses, case mix adjustment refers to adjustment for age, gender, race or ethnicity, diabetes, and vintage. Multivariable adjustment refers to case mix plus body weight, URR, serum albumin, creatinine, predialysis BUN, bicarbonate, cholesterol, hemoglobin, ferritin, and aluminum. Phosphorus models simultaneously adjusted for calcium + PTH, calcium models simultaneously adjusted for phosphorus + PTH, PTH models simultaneously adjusted for phosphorus + calcium.

b. Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, UK, and US.

c. Models accounted for facility clustering effects using robust standard error estimates and were adjusted for age, sex, race, BMI, years since ESRD onset, prior renal transplant, prior PTx, inability to walk without assistance, residency in a nursing home, serum phosphorus, albumin-corrected serum calcium, serum albumin, intact PTH, serum bicarbonate, history of carpal tunnel syndrome or b2 microglobulin disorder, 13 summary comorbid conditions (coronary artery disease, cerebrovascular disease, congestive heart failure, other CVD, cancer other than of the skin, diabetes mellitus, gastrointestinal bleeding, hypertension, lung disease, psychiatric disorder, neurologic disorder other than dementia, peripheral vascular disease, and recurrent cellulitis or gangrene), dementia, and country.

d. Adjustments were made using continuous (age, hematocrit, and predialysis systolic blood pressure) and dichotomous variables (sex, race, history of diabetes, current smoking status, previous smoking status, and history of any fracture). Because Wave 2 was conducted several years after Waves 1, 3, and 4, Wave 2 cohort status also was included as a categorical covariate. For the proportional hazards model, left truncation of data was performed to account for variation in dialysis vintage (i.e., time since initiation of dialysis therapy) when serum markers were obtained. Dialysis vintage was included as a continuous covariate in companion analyses.

e. Open fractures excluded. Pelvic fracture included areas of the acetabulum, ilium, and ischium. Hip fracture is defined as located primarily at the neck of the femur.

f. PTH was adjusted for age, gender, and race.

g. Variables included in predictive model besides iPTH were age, sex, albumin, ALP, serum Ca, serum P, extraosseal calcifications, DM, number of previous transplants, Vitamin D analogs, cumulative time on renal replacement therapy.

Supplemental Table 9. Overview Table of selected studies of diagnostic tests: studies for vascular and valvular calcification techniques in CKD

Author, Year Study Design Country	N Population	Test (s)	Reference Standard
Bellasi, 2006[51] Prospective USA	140 CKD 5D on HD	Pulse pressure Valve calcification by Echo Abdominal X-ray	CAC by EBCT
Sigrist, 2006[52] Prospective UK	134 CKD 4, 5D on HD/PD	Pulse wave velocity Pulse pressure Augmentation index	Arterial calcification by MSCT
Raggi, 2007[53] Prospective USA	131 CKD 5D on HD	Pulse wave velocity	CAC by EBCT Thoracic aorta calcium by EBCT
Kobayashi, 2008[54] Cross-sectional Japan	111 CKD 3-5, 5D	CAC by CT	CAC by EBCT
Shroff, 2007[55] Retrospective UK	85 Children aged 5-18 y CKD 5D	Carotid IMT Pulse Wave Velocity	CAC by MSCT
Stompor, 2006[56] Prospective Poland	61 CKD 5D on PD	Pulse wave velocity Carotid IMT	Total CAC by MSCT
Haydar, 2004[57] Prospective UK	55 CKD 3-5, 5D, 1-5T	Pulse wave velocity	Total CAC by EBCT
Nitta, 2004[58] Prospective Japan	53 CKD 5D on HD	Aortic calcification by CT Pulse wave velocity	CAC by MSCT

CAC, Coronary artery calcification; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron-beam CT; HD, hemodialysis; IMT, intima-media thickness; MSCT, multislice spiral computed tomography; N, number of subjects; PD, peritoneal dialysis.

Supplemental Table 10. Overview Table of selected studies presenting data on calcification prevalence

Author, Year Study Design Country	N Population	Representative Test (s)	Prevalence of Calcification
Hernandez, 2005[59] Chart Review Spain	1117 CKD 5D, At transplant	Plain X-ray of abdomen and pelvis	24.4%
Honkanen, 2008[60] Cross-sectional Belgium, Netherlands, Sweden, Denmark, Finland, Norway	933 CKD 5D on HD/PD	Abdominal aorta calcification by lumbar (L1-L4) radiographs	81%
Ix, 2007[61] Cross-sectional USA	653 CKD 3-5	Valvular calcification by MSCT/EBCT	20/25%
Okuno, 2007[62] Prospective Japan	515 CKD 5D, HD	Plain X-ray	56.5%
Adeney, 2008[63] Retrospective US	439 CKD Stage 3-5	CAC and Valvular calcifications by EBCT or multi-detector CT	67% coronary 49% aortic 20% mitral valve 25% aortic valve
Panuccio, 2004[64] Prospective Italy	202 CKD 5D, HD	Valvular calcification by echocardiography	23.3%
London, 2003[65] Prospective France	202 CKD 5D, HD	Calcification score by ultrasound and conventional X-ray	63.9%
Wang, 2003[66] Prospective Hong Kong	193 CKD 5D, PD	Valvular calcification by echocardiography	32.3%
Rodriguez-Garcia, 2009[49] Prospective Spain	193 CKD 5D, HD	Vascular calcifications by thoracic, lumbar spine, pelvic and hand X-rays	79%
Jean, 2009[67] Prospective France	161 CKD 5D on HD	Vascular calcification by plain radiograph	83%
Kronenberg, 2003[68] Prospective Austria	155 CKD 5D on Incident HD and PD	Conventional X-ray of pelvis and calves	67%

Author, Year Study Design Country	N Population	Representative Test (s)	Prevalence of Calcification
Sharma, 2007[69] Prospective UK	140 CKD 4-5D, Predialysis, HD and PD on transplant waiting list	Valvular calcification by echocardiography	40%
Varma, 2005[70] Chart review USA	137 CKD 5D, HD	Valvular calcification by echocardiography	47%
Sigrist, 2006[52] Sigrist, 2007[71] Prospective UK	134 CKD 4, 5D on HD/PD	Arterial calcification by MSCT	CKD 4: 47% PD: 71% HD 73% + higher scores
Adragao, 2004[72] Prospective Portugal	123 CKD 5D, HD	Calcification score by conventional X-ray	61% iliac 60% femoral 36% radial 5% digital
Garland, 2008[73] Cross-sectional Canada	119 CKD 3-5	CAC by MSCT	83.2%
Blacher, 2001[74] Prospective France	110 CKD 5D, HD	Calcification score by ultrasound and conventional X-ray	66.4%
Matsuoka, 2004[75] Prospective Japan	104 CKD 5D, HD	CAC by EBCT	81.7%
Russo, 2007[76] Prospective Italy	90 CKD Stage 3-5	CAC by MSCT	83%
Shroff, 2007[55] Retrospective USA	85 Children aged 5-18 y CKD 5D	CAC by MSCT	20%
Chertow, 2002[77] Raggi 2004[78] RCT USA, Germany, Austria	70 CKD Stage 5D on HD	CAC by EBCT Valvular calcification by EBCT	83% coronary 80% aortic 46% mitral valve 33% aortic valve
Stompor, 2006[56] Prospective Poland	61 CKD 5D on PD	Total CAC by MSCT	>51% (51% w/ a CAC score of <10, median 0)

Author, Year Study Design Country	N Population	Representative Test (s)	Prevalence of Calcification
Russo, 2007[79] Prospective Italy	53 CKD Stage 3-5	CAC by MSCT	51%
Block, 2005[80] RCT USA	53 CKD 5D on Incident HD	CAC by EBCT	63%/69%
Nitta, 2004[58] Prospective Japan	53 CKD 5D on HD	CAC by MSCT	92.5%

CAC, coronary artery calcification; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron-beam CT; HD, hemodialysis; MSCT, multislice spiral computed tomography; N, number of subjects; PD, peritoneal dialysis; RCT, randomized controlled trial.

Supplemental Table 11. Overview Table of selected studies demonstrating the natural history of vascular and valvular calcifications in CKD

Author, Year Study Design Country	N Population	Test (s)	Follow-up
CKD Stages 3-5			
Sigrist, 2007[71] Prospective UK	134 CKD Stage 4-5	CAC by MSCT	12 & 24 mo
Russo, 2007[76] RCT Italy	90 CKD Stage 3-4	CAC by MSCT	24 mo
Russo, 2007[79] Prospective Italy	53 CKD Stage 3-5	CAC by MSCT	24 mo
Bursztyn, 2003[81] Side study of RCT Israel	53 CKD Stage 3-5 Hypertensive	CAC by MSCT	36 mo
CKD Stage 5D			
Kronenberg, 2003[68] Prospective Austria	149 CKD 5D on Incident HD and PD	X-ray of pelvis and calves	12 mo
Chertow, 2002[77] Raggi, 2004[78] Control arm of RCT USA, Germany Austria	70 CKD Stage 5D on HD	CAC, AoC, MVC, AVC by EBCT	12 mo
Block, 2005[80] Control arm of RCT USA	53 CKD 5D on Incident HD	CAC by EBCT	6, 12, 18 mo
CKD Stages 1-5T			
Suwelack, 2001[82] Prospective Germany	55 CKD Stage 5T (Post-transplant)	Carotid IMT by US	3, 6, 12 mo

AoC, aortic calcification; AVC, aortic valve calcification; CAC, coronary artery calcification; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron-beam CT; HD, hemodialysis; IMT, intima-media thickness; MSCT, multislice spiral computed tomography; MVC, medial vascular calcification; N, number of subjects; PD, peritoneal dialysis; RCT; randomized controlled trial.

Supplemental Table 12. Overview Table of selected studies demonstrating the risk relationship between vascular calcification and mortality in CKD

Author, Year Study Design Country	N Population Follow-up	Vascular Calcification		Mortality Categorization
		Technique	Categorization	
Hernandez, 2005[59] Chart Review Spain	1117 At transplant Median 49 mo	Plain X-ray of abdomen and pelvis	-Vascular calcification -None	-All cause -Cardiovascular
Okuno, 2007[62] Prospective Japan	515 HD 51 mo	Plain	-Abdominal aortic calcification -None	-All cause -Cardiovascular
London, 2003[65] Prospective France	202 HD Up to ~100 mo	B-mode US	-Arterial medial -Arterial intimal -None	-All cause -Cardiovascular
Rodriguez-Garcia, 2009[49] Prospective Spain	193 HD 24 mo	X-ray of thoracic, lumbar spine, pelvis and hands	-Vascular calcifications -Abdominal aortic calcifications	-All-cause
Block, 2007[83] RCT USA	127 HD Median 44 mo	EBCT	CAC score 0, 1-400, >400	-All cause
Adragao, 2004[84] Prospective Portugal	123 HD 37 mo	Plain X-ray of pelvis and hands	Vascular calcification score <or ≥ 3	-Cardiovascular
Blacher, 2001[74] Prospective France	110 HD 53 mo	US	Arterial calcification score 0-4	-All cause -Cardiovascular
Matsuoka, 2004[75] Prospective Japan	104 HD 44 mo	EBCT	CAC score <or ≥ 200	-Cardiac -Stroke -Infection -Other
Adragao, 2009[72] Prospective Portugal	101 HD 43 mo	Plain X-ray of pelvis and hands	Vascular calcification score < or ≥3	-All-cause
Kushiya, 2005[85] Prospective Japan	84 HD 24 mo	CT	ACI > or <0.3	-All cause

ACI, aortic calcification index; AVC, aortic valve calcification; CAC, coronary artery calcification; CKD, chronic kidney disease; CT, computed tomography; EBCT, electron-beam CT; HD, hemodialysis; N, number of subjects; PD, peritoneal dialysis; RCT, randomized controlled trial; US, ultrasound.

Supplemental Table 13. Overview Table of selected studies demonstrating the risk relationship between valvular calcification and mortality in CKD Stage 5D

Author, Year Study Design Country	N Population Follow-up	Valvular Calcification		Mortality Categorization
		Technique	Categorization	
Panuccio, 2004[64] Prospective Italy	202 HD 44 mo	Echo	-Either mitral or aortic -None	-All cause -Cardiovascular
Wang, 2003[66] Prospective Hong Kong	193 PD 16 mo	Echo	-Calcification -None -Both mitral and aortic -Either mitral or aortic -None -Calcification + AVC -AVC only -Calcification only -Neither	-All cause -Cardiovascular
Sharma, 2007[69] Prospective UK	140 Predialysis, HD and PD on transplant waiting list 26 mo	Echo	-Mitral annular -No mitral annular	-All cause -Cardiac mortality or cardiac event
Varma, 2005[70] Chart review USA	137 HD 42 mo	Echo	-Mitral -Mitral annular -Aortic -Any	-All cause
Sigrist, 2007[71] Prospective UK	134 CKD Stage 4, HD, PD 24 mo	MSCT	-Femoral artery	-All cause

AVC, aortic valve calcification; ACI, aortic calcification index; CKD, chronic kidney disease; Echo, echocardiogram; HD, hemodialysis; MSCT, multislice spiral computed tomography; N, number of subjects; PD, peritoneal dialysis.

Supplemental Table 14. Overview Table of selected studies demonstrating the risk relationships between biochemical parameters of Ca, P, CaXP, and mortality in CKD Stages 3-5 and 5D

Author, Year Database	N Follow-up Country	Mortality Ascertainment Categorization	Categorization or Comparison [Measurement technique] P (mmol/L)	Ca (mmol/L)	CaXP ($mmol^2/L^2$)
CKD Stage 5D on HD					
Kalantar-Zadeh, 2006[86] DaVita	58 349 24 mo USA	nd[a] nd	<0.97 to ≥2.91 in 0.32 mmol/L increments (*a priori*)	<2.0 to ≥2.74 in 0.12 mmol/L increments (*a priori*) [adjusted]	<2.42 to ≥6.46 in 0.40 $mmol^2/L^2$ increments (*a priori*) [nd]
Block, 2004[24] Fresenius	40 538 12 to 18 mo USA	nd[b] nd	<0.97 to ≥2.91 in 0.32 mmol/L increments (*a priori*)	<2.0 to ≥2.74 in 0.12 mmol/L increments (*a priori*) [measured] <2.0 to ≥2.74 in 0.12 mmol/L increments (*a priori*) [adjusted]	<2.42 to ≥6.46 in 0.40 $mmol^2/L^2$ increments (*a priori*) [nd]
Tentori, 2008[87] DOPPS I, DOPPS II, DOPPS III	25 588 17 mo Multicenter, International	nd[c] -All-cause -Cardiovascular	<0.52 to >3.23 in 0.16 mmol/L increments	<1.90 to >2.99 in 0.12 mmol/L increments	—
Young, 2005[88] DOPPS	17 236 nd France, Germany, Italy, Japan, Spain, UK, USA	Standardized questionnaires of medical records[d] -All-cause -Cardiovascular	<0.81 to >2.26 in 0.16 mmol/L increments Continuous	<1.95 to ≥2.84 in 0.10 -0.15 mmol/L increments [corrected] Continuous [corrected]	<3.23 to >5.65 in 0.40 $mmol^2/L^2$ increments [unadjusted] Continuous [unadjusted]
Ganesh, 2001[89] CMAS & DMMS Waves 1, 3, 4	12 833 24 mo USA	HCFA[e] -All-cause -Coronary artery disease -Other cardiac -Sudden death -Cerebrovascular -Infection -Other -Unknown -Missing	Continuous >2.10 vs. 0.77-2.10	—	0.81 $mmol^2/L^2$ higher [nd]
Block, 1998[90] CMAS & DMMS Wave 1	6407 24 mo USA	nd[f] nd	Quintiles (0.36-1.45, 1.42-1.78, 1.81-2.10, 2.13-2.52, 2.55-5.46) >2.10 vs. 0.77-2.10 Continuous	Quintiles (0.92-2.15, 2.17-2.27, 2.30-2.37, 2.40-2.52, 2.54-4.37) [uncorrected] Quintiles (nd) [corrected]	Quintiles (1.13-3.39, 3.47-4.20, 4.28-4.48, 4.92-5.81, 5.89-10.65) [uncorrected] Quintiles (nd) [corrected]
Kimata, 2007[91] J-DOPPS 1, 2	5041 Mean 19 mo Japan	nd[g] -All-cause -Cardiovascular	Continuous	Continuous [corrected]	Continuous [uncorrected]

Author, Year Database	N Follow-up Country	Mortality Ascertainment Categorization	Categorization or Comparison [Measurement technique] P (mmol/L)	Ca (mmol/L)	CaXP ($mmol^2/L^2$)
CKD Stage 5D on HD/PD					
Noordzij, 2005[92] NECOSAD	1629 Up to 90 mo[h] Netherlands	nd[i] nd	Less than, at, or greater than KDOQI target (1.13-1.78 mmol/L)	Less than, at, or greater than KDOQI target (2.10-2.37) mmol/L) [corrected]	At or greater than KDOQI target (4.44 $mmol^2/L^2$) [corrected]
CKD Stages 2-5					
Kestenbaum, 2005[93] VA CHIPS	6730 CKD 2-5[j] Median 25 mo USA	nd[k] nd	<0.81 to ≥1.61 in 0.16 mmol/L increments Continuous	—	—
Menon, 2005[94] MDRD	840 CKD 3-4 Median 124 mo USA	National Death Index[l] -All-cause -Cardiovascular	Continuous	—	Continuous [nd]
CKD Stages 2-5T					
Schaeffner, 2007[95] OeDTR	733 Median 73 mo Austria	nd[m] - All-cause	Quintiles (≤0.84, 0.85-0.96, 0.97-1.08, 1.09-1.22, ≥1.23)	Quintiles (≤2.25, 2.26-2.32, 2.33-2.40, 2.41-2.49, ≥2.50)	Quintiles (≤2.00, ,2.00-2.29, 2.29-2.57, 2.57-2.89 ≥2.90)
Egbuna, 2007[96] SMH	303 64 mo USA	nd[n] -All-cause	≤0.81 to >1.45 in 0.16 mmol/L increments at 3, 6, 12 mo post-transplant	≤2.12 to >2.74 in 0.12 mmol/L increments at 3, 6, 12 mo post-transplant	<2.02 to >3.63 in 0.40 $mmol^2/L^2$ increments at 3, 6, 12 mo post-transplant

CaXP, calcium-phosphorus product; CMAS, Case Mix Adequacy Study (US Renal Data System); DMMS, Dialysis Morbidity and Mortality Study (US Renal Data System); DOPPS, Dialysis Outcomes and Practice Patterns Study; HCFA, Health care Financing Administration ESRD Death Notification Form (HCFA-2746-U3); HD, hemodialysis; J-DOPPS 1, 2 , DOPPS conducted in Japan Phase I and Phase II; KDOQI, Kidney Disease Outcomes Quality Initiative; MDRD, Modification of Diet in Renal Disease Study; N, number of subjects; nd, not documented; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; OeDTR, Austrian Dialysis and Transplant Registry; SMH, Strong Memorial Hospital solid organ transplant program; VA CHIPS, Veterans' Affairs Consumer Information and Performances Sets data system.

Annotations:

a. Case-mix–adjusted models included additional covariates: age, gender, race and ethnicity, diabetes mellitus, vintage, primary insurance, marriage status, and standardized mortality ratio of the dialysis clinic during entry quarter, continuous values of Kt/V, dialysate Ca concentration, and administered doses of each of vitamin D analogs within each calendar quarter. Case-mix and MICS-adjusted models included all of the above-mentioned covariates plus 11 indicators of nutritional status and inflammation, including the time-varying body mass index, averaged dose of rHuEPO in each calendar quarter, and the nine above-mentioned time-varying laboratory values.

b. Unadjusted, case-mix–adjusted and multivariate-adjusted analyses were reported. For all analyses, case-mix adjustment refers to adjustment for age, gender, race or ethnicity, diabetes, and vintage. Multivariable adjustment refers to case mix plus body weight, URR, serum albumin, creatinine, predialysis BUN, bicarbonate, cholesterol, hemoglobin, ferritin, and aluminum. P models simultaneously adjusted for Ca + PTH, Ca models simultaneously adjusted for P + PTH, PTH models simultaneously adjusted for P + Ca.

c. Models were adjusted for case mix, comorbidities, baseline hemoglobin, albumin, normalized protein catabolic rate, single-pool Kt/V, prior PTx, and the other mineral metabolism markers. To test the relationship between facilities' control of mineral metabolism markers and mortality, models were adjusted for the percentage of patients at a facility with values of other markers in each risk category for Ca, P, and PTH.

d. Stratified by country and adjusted for dialysate Ca concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and the following comorbid conditions: coronary artery disease, congestive heart failure, other cardiac disease, HTN, cerebrovascular disease, peripheral vascular disease, DM, lung disease, cancer (excluding skin), HIV/AIDS, GI bleeding, neurologic disease, psychiatric disease, and recurrent cellulitus. P analysis adjusted for serum concentrations of Ca and PTH; Ca analysis adjusted for serum concentrations of P and PTH; CaXP analysis adjusted for serum concentrations of PTH; PTH analysis adjusted for serum concentrations of P and Ca.

e. The main analyses were adjusted for patient age at study start, duration of ESRD, gender, race, cause of ESRD, and noncardiovascular comorbid conditions.

f. Main analyses were adjusted for age at onset of ESRD, race, sex, active smoking, and the presence of diabetes, neoplasm, or AIDS.

g. Cox survival models were adjusted for age, sex duration of ESRD, Kt/V, albumin, hemoglobin, dialysate Ca concentration, and the following comorbid conditions present at study entry: coronary artery disease, congestive heart failure, other cardiac disease, HTN, cerebrovascular disease, peripheral vascular disease, DM, lung disease, cancer (excluding skin), HIV/AIDS, GI bleeding, neurologic disease, psychiatric disease, and recurrent cellulitus.
h. Median 2.3 y (HD), 2.4 y (PD).
i. Adjustment for the possible confounding effects of age, Davies comorbidity score, primary kidney disease, SGA, albumin level, Kt/V_{urea} per week, and hemoglobin level. Supplementary adjustments for laboratory parameters related to mineral metabolism were made for P and iPTH in analyses on the effects of Ca. Similarly, we made additional adjustments for Ca and iPTH levels in analyses of P, for iPTH levels in analyses of CaXP, and for Ca and P levels in analyses of iPTH.
j. CKD was defined by two abnormal outpatient SCr measurements at least 6 mo but no more than 2 y apart, without normal intervening SCr measurements. Abnormal SCr were defined as ≥106.1 µmol/L (1.2 mg/dL) for women and ≥132.6 µmol/L (1.5 mg/dL) for men. Patients were classified by CKD stage using calculated CrCl using the Cockcroft and Gault formula.
k. Potential confounders that were chosen before the analyses included age, race, gender, previous medical conditions, total elemental Ca intake from medications, hemoglobin, Ca, and the baseline serum creatinine; a second model included time-averaged creatinine, rate of creatinine change, and the maximal value for creatinine during the baseline period; a third model added BP, body mass index, cardiovascular medications, albumin, bicarbonate, and triglycerides.
l. The first multivariable model, model 1, included serum P level or CaXP with age, race, sex, and randomization assignments to different blood pressure goals and protein diets. Model 2 adjusted for traditional CVD risk factors: smoking status, diabetes, history of coronary artery disease, body mass index, systolic blood pressure, and LDL-C and HDL-C levels, in addition to variables in model 1. Model 3 adjusted for variables in model 2 and cause of kidney disease and proteinuria.
m. Age, gender, and eGFR were forced into all multivariate models.
n. The Cox proportional hazard model for time to all-cause recipient death included acute rejection within the first year of transplant, history of pretransplant DM, age over 60 years, serum Ca >2.62 mmol/L at 3, 6, and 12 mo post-transplant, CaXP >2.82 $mmol^2/L^2$ at 3, 6, and 12 mo post-transplant and serum *P* ≤0.81 mmol/L at 3, 6, and 12 mo post-transplant and delayed graft function and type of graft.

Supplemental Table 15. Summary Table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs. calcium-containing phosphate binders in CKD Stage 5D—description of population at baseline

Author, Year	N Country of Study	Age* % Male*	% Race	Dialysis Vintage* Dialysate Calcium	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	Vasc./Valv. Calcification by EBCT in Agatston units*
Suki, 2007[97] St Peter, 2008[98]	2103 US	60 (60) 55 (54)	49 (47) White 47 (47) Black 1(1) Asian 4 (5) Other	39 (38) mo nd	51 (50) nd	Ca nd P nd PTH nd ALP nd	nd	None
Qunibi, 2008[99]	203 US	60 (59) 46 (57)	39 (34) Black	22 (23) mo 1.25 mmol/L	nd nd	Ca 2.20 (2.20) mmol/L P 2.13 (2.10) mmol/L iPTH 54.0 (49.3) pmol/L Bayer Advia Centaur Intact PTH [ref:nd] ALP 93.9 (88.9) U/L b-ALP 19.7 (19.0) U/L	nd	Mean CAC 969 (1098) % of total population with no AoC 14 % of total population with AVC 60 % of total population with MVC 45
Chertow, 2002[77]	200 Austria, Germany, US	57 (56) 64 (66)	71 (66) White 17 (23) Black 12 (11) Other	43 (35) mo nd	32 (33) nd	Ca 2.35 (2.32) mmol/L corrected P 2.45 (2.39) mmol/L iPTH 24.6 (21.2) pmol/L nd ALP nd	nd	Mean CAC 1712 (1125) % with no CAC: 17% Mean AoC 3874 (3233) % with no AoC: 20% Mean MVC 4 (0) % with no MVC: 50% (57%)[78] Mean AVC 0 (0) % with no AVC: 59% (70%)[78] Mean Both Valves 56 (25) % with no MVC or AVC: 36% (46%)[78]
Braun, 2004[100] Asmus, 2005[101] *Patient overlap with Chertow, 2002*[77]	114 (93 overlap with[77]) Austria, Germany	55 (58) 64 (61)	100 (98) White	69 (58) mo 1.5 mmol/L	16 (21) ≥36 (≥28)	Ca 2.34 (2.32) mmol/L P 2.45 (2.29) mmol/L iPTH 17.1 (13.9) pmol/L nd ALP nd	nd	Mean CAC 1784 (1466) % with no CAC: 11% (11%) Mean AoC 4694 (5267) % with no AoC: 18% (10%) Mean MVC 1711 (1118) % with no MVC: nd Mean AVC 367 (70) % with no AVC: nd
Block, 2005[80]	148 US	57 (59) 59 (67)	43 (40) White 26 (36) Black 31 (24) Other	2.9 (3.0) mo 2.5 mmol/L	63 (56) nd	Ca 2.32 (2.32) mmol/L corrected P 1.68 (1.74) mmol/L iPTH 31.1 (33.8) pmol/L Allegro-intact PTH [ref: nd] ALP nd	nd	Mean CAC 648 (667) % with no CAC: 37% (31%)

Author, Year	N Country of Study	Age* % Male*	% Race	Dialysis Vintage* Dialysate Calcium	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	Vasc./Valv. Calcification by EBCT in Agatston units*
Barreto, 2008[102]	101 Brazil	47 (47) 66 (70)	White 58 (63)	36 (38) mo 3.5 mEq/L[a]	15 (13) nd	Ca 1.23 (1.23) mmol/L P 2.3 (2.3) mmol/L iPTH 42.8 (36.4) pmol/L two-site 2nd gen PTH assay b-ALP 34 (27) U/L 25 (OH) Vit D 82 (77) nmol/L	Bone biopsy	Median CAC 123 (150) CAC Score >30[b]: 66% (53%)
Ferreira, 2008[103]	91 Portugal	≥18 67 (51)	97 (97) White 3 (3) Black	23 (25) mo nd	6 (23) nd	Ca 2.40 (2.45) mmol/L P 1.87 (1.84) mmol/L PTH 17.7 (12.0) pmol/L nd ALP 11.5 (10.6) µg/L	Bone biopsy	None
Pediatrics								
Salusky, 2005[104]	42 USA	15 (11) 53 (71)	nd	13 (15) mo 2.5 mEq/L	nd nd	Ca 2.25 (2.25) mmol/L P 1.81 (1.91) mmol/L PTH 103.4 (103.9) pmol/L Allegro-intact PTH [ref:nd]	Bone biopsy	None

AoC, aortic calcification; ALP, alkaline phosphatase; AVC, aortic valve calcification; b-ALP, bone-specific alkaline phosphatase; CAC, coronary artery calcification; CaXP, calcium-phosphorus product; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; EBCT, electron-beam CT; iPTH, intact parathyroid hormone; MBD, mineral and bone disease; MVC, medial vascular calcification; N, number of subjects; nd, not documented; PTH, parathyroid hormone.

Symbols: *Arm 1 (Arm 2).

Note: No study reported DXA or bone histology at baseline.

Annotations:

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

b. By MSCT.

Supplemental Table 16. Summary Table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs. calcium-containing phosphate binders in CKD Stage 5D—intervention and results

Author, Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Suki, 2007[97] St Peter, 2008[98]	2103 Mean 20 mo HD	Sevelamer Protocol not specified	Ca acetate or Ca carbonate Protocol not specified[a] Average elemental Ca at study completion: Ca acetate: 1342 mg/d Ca carbonate: 1960 mg/d	Standard of care	*Mortality* St Peter 2008[98] (N = 2102, mean F/U: 28 mo)		
					‡All-cause Mortality (N)	431 vs. 426 (nd)	B
					‡All-cause Mortality (per 100 pt-y)	17.7 vs. 17.4 (NS) HR 1.01 (CI 0.89-1.16)[b]	B
					CV Mortality (per 100 pt-y)	9.0 vs. 8.2 (NS)[c] HR 1.09 (CI 0.90-1.33)[b]	B
					Hospitalizations St Peter 2008[98] (N = 1947, mean F/U: 25 mo)		
					All-cause Hospitalizations (N)	3439 vs. 3782 (nd)	C
					Mean Hospitalizations (per pt-y)	1.7 vs. 1.9 HR 0.89 (CI 0.82-0.98) (.02)[d,b]	C
					Hospital days (per pt-y)	12.3 vs. 13.9 HR 0.88 (CI 0.78 – 0.99)	C
					Hospitalizations Suki 2007[97] (N = 2103, Mean F/U: 20 mo)		
					Mean Hospitalizations (per pt-y)	2.1 vs. 2.3 (.07)[e]	C
					All-cause Mortality in subjects ≥65 y old (per 100 pt-y)	18.2 vs. 23.4 HR 0.77 (CI 0.61-0.96)	C
					Hospital days (per pt-y)	14.8 vs. 17.4 (NS)	C
					Laboratory (mean on treatment values)F/U unclear: Suki 2007[97]		
					Ca (mmol/L) [N = 1672]	2.30 vs. 2.38 (<.0001)	C
					P (mmol/L) [N = 1686]	1.87 vs. 1.84 (<.01)	C
					CaXP ($mmol^2/L^2$) [N = 1668]	4.33 vs. 4.33 (NS)	C
					Median iPTH (pmol/L) [N = 1542]	29.5 vs. 24.0 (<.0001)	C
					Total Chol. (mmol/L) [N = 1055]	3.77 vs. 4.16 (<.0001)	C
					LDL-C (mmol/L) [N = 399]	1.78 vs. 2.20 (<.0001)	C
					HDL-C (mmol/L) [N = 495]	1.17 vs. 1.15 (NS)	C
Qunibi, 2008[99]	203	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	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[f]	1.01 (CI 0.86-1.18)	B
					AoC[f]	1.09 (CI 0.87-1.35)	B
					AVC[f]	1.41 (CI 0.92-2.13)	B
					MVC[f]	1.19 (CI 0.79-1.82)	B
					Δ Mean CAC at 6 mo (N = 139)	97 vs. 109 (NS)[g]	B
					Δ Mean CAC at 12 mo (N = 126)	227 vs. 228 (NS)[g]	B

Author, Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
			mg/d		Mean CAC at 6 mo (N = 139)	996 vs. 1197 (NS)[g]	B
					% increase in CAC at 6 mo (N = 139)	24 vs. 71	B
					Mean CAC at 12 mo (N = 126)	1116 vs. 1297 (NS)[g]	B
					% increase in CAC at 12 mo (N = 126)	57 vs. 52	B
					Laboratory (N = 129)		
					Ca (mmol/L)	2.25 vs. 2.35 (*)	B
					P (mmol/L)	1.74 vs. 1.61 (NS)	B
	12 mo				CaXP ($mmol^2/L^2$)	3.87 vs. 3.71 (NS)	B
					PTH (pmol/L)	46.0 vs. 33.5 (*)	B
					Bicarbonate (mmol/L)	22 vs. 23 (NS)	B
					Total Cholesterol (mmol/L)	3.18 vs. 3.47 (*)	B
					LDL-C (mmol/L)	1.61 vs. 1.78 (NS)	B
					HDL-C (mmol/L)	1.0 vs. 1.0 (NS)	B
	HD				Triglycerides (mmol/L)	1.68 vs. 1.77 (NS)	B
					ALP (U/L)	124 vs. 95.1 (NS)	B
					b-ALP (U/L)	27.2 vs. 18.8 (NS)	B
Chertow, 2002[77]/Raggi, 2005[105]/Raggi, 2004[78]		Sevelamer titrated to P 1.0-1.6 mmol/L Ca 2.12-2.6 mmol/L and (after 3 mo) iPTH 15.9-31.8 pmol/L[h]	USA: Ca acetate Europe: Ca carbonate titrated to P 1.0-1.6 mmol/L Ca 2.12-2.6 mmol/L and (after 3 mo) iPTH 15.9-31.8 pmol/L[h] Average elemental Ca: USA: 1165 mg/d Europe: 1560 mg/d	After 3 mo, vitamin D, Ca supplement, dialysate Ca titrated to P 1.0-1.6 mmol/L Ca 2.12-2.6 mmol/L and iPTH 15.9-31.8 pmol/L. Al as rescue binder[h]	*Vascular Calcification at 12 mo (N = 132):* Chertow 2002[77]		
					Δ Mean CAC	-46 vs. +151 (.04)	B
					Δ Mean AoC	-532 vs. +185 (.01)	B
					Valvular Calcification at 12 mo (N = 132): Raggi 2004[78]		
					Δ Mean MVC	-655 vs. +98 (NS)	B
					Δ Mean AVC	24 vs. 24 (NS)	B
					Bone Attenuation by EBCT at 12 mo (N = 111): Raggi, 2005[105]		
					Δ Cortical Density (g/cm^3)	-1 vs. -7 (NS)[i]	C
					Δ Trabecular Density (g/cm^3)	+3 vs. -6 (.01)[i]	C
					Laboratory at end of treatment: Chertow 2002[77]		
					Mean Ca (mmol/L)	2.37 vs. 2.42 (.002)	B
	12 mo				Mean P (mmol/L)	1.65 vs. 1.65 (NS)	B
					‡ Mean CaXP ($mmol^2/L^2$)	3.87 vs. 3.95 (NS)	B
					Median iPTH (pmol/L)	23.7 vs. 14.6 (NS)	B
					Mean Total Chol. (mmol/L)	3.65 vs. 4.71 (<.0001)	B
	HD				Mean LDL-C (mmol/L)	1.68 vs. 2.66 (<.0001)	B
					Mean HDL-C (mmol/L)	1.1 vs. 1.2 (NS)	B
					Median Triglycerides (mmol/L)	1.55 vs. 1.69 (NS)	B
					Mean Bicarbonate (mmol/L)	19.2 vs. 22.1 (.0003)	B

Author, Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
					Laboratory (mean on treatment values): (N = 111) Raggi[105]		
					Mean ALP (mg/dL)	103.0 vs. 81.7 (.002)	C
					Mean b-ALP (mg/dL)	42.3 vs. 26.8 (<.0001)	C
Braun, 2004[100]/Asmus, 2005[101] *Patient overlap with Chertow, 2002*[77]	114 (93 from[77]) 12 mo (24 mo for subgroup) HD	Sevelamer titrated to P 1.0-1.6 mmol/L Ca <2.6 mmol/L and (after 3 mo) iPTH 15.9-31.8 pmol/L[j]	Calcium carbonate titrated to P 1.0-1.6 mmol/L Ca <2.6 mmol/L and (after 3 mo) iPTH 15.9-31.8 pmol/L[j] 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 15.9-31.8 pmol/L Al as rescue binder[j]	*Vascular Calcification at 21 mo, N = 52:* Asmus 2005[101]		
					Δ Mean CaC	+142 vs. +637 (.02)	C
					Δ Mean AoC	-425 vs. +1697 (.004)	C
					Valvular Calcification at 21 mo, N = 52: Asmus 2005[101]		
					Δ Mean MVC	-912 vs. +370 (NS)	C
					Δ Mean AVC	+232 vs. +230 (NS)	C
					Bone Attenuation by EBCT at 21 mo, N = 50: Asmus 2005[101]		
					Δ Cortical Density (g/cm^3)	+0.3 vs. -9.0 (NS)	C
					Δ Trabecular Density (g/cm^3)	+8.0 vs. -12.3 (.0015)	C
					Laboratory at 24 mo, N = 54: Asmus 2005[101]		
					Mean Ca (mmol/L)	2.2 vs. 2.4 (NS)	C
					Mean P (mmol/L)	2.0 vs. 1.9 (NS)	C
					Mean CaXP (mmol^2/L^2)	4.0 vs. 4.5 (NS)	C
					Mean iPTH (pmol/L)	52.7 vs. 27.1 (<.001)	C
					Median Total Chol. (mmol/L)	3.75 vs. 4.53 (<.001)	C
Block, 2005[80]/ Block, 2007[83]/ Spiegel, 2007[106]	148 18 mo (44 mo median for mortality) Incident HD	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[83], Spiegel 2007[106]		
					All-cause Mortality (N)	11 vs. 23 (nd)	B
					All-cause Mortality (per 100 pt-y)	5.3 vs. 10.6 (.05) HR 0.5 (.06)[k]	B
					Vascular calcification: Block 2005[80]		
					‡ Δ Mean CAC at 12 mo (N = 92)	+87 vs. +169 (.056)[l]	B
					Δ Mean CAC at 18 mo (N = 85)	+138 vs. +338 (.015)	B
					Laboratory (mean on treatment values) F/U time unclear Block 2005[80]		
					Corrected Ca (mmol/L)	2.27 vs. 2.40 (≤.05)	B
					P (mmol/L)	1.68 vs. 1.65 (NS)	B
					CaXP (mmol^2/L^2)	3.79 vs. 3.95 (NS)	B
					iPTH (pmol/L)	31.6 vs. 25.8 (≤.05)	B
					Total Chol (mmol/L)	3.47 vs. 4.14 (≤.05)	B
					LDL-C (mmol/L)	1.55 vs. 2.09 (≤.05)	B
					Triglycerides (mmol/L)	1.93 vs. 2.16 (NS)	B

Author, Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Barreto, 2008[102]	101 12 mo HD	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[o]	Bone Overall Summary by WG[m]	Overall no clinically important differences between the two treatments.[p]	A
					Bone Turnover	Not different	
					Bone Mineralization	Same	
					Bone Volume	Slightly worse (-1.6)	
					Absolute increase in CAC score	139 vs. 182 (NS)	C
					Relative increase in CAC score	45 vs. 55 (NS)	C
					Ca (mmol/L)	1.28 vs. 1.27 (NS)	C
					P (mmol/L)	1.71 vs. 1.87 (NS)	C
					iPTH (pmol/L)	52.8 vs. 34.6 (<.005)	C
					b-ALP (U/L)	38 vs. 28 (<.005)	C
					25 (OH) Vit D (nmol/L)	70 vs. 72 (NS)	C
					LDL-C (mmol/L)	1.91 vs. 2.35 (<.005)	C
					HDL-C (mmol/)	1.1 vs. 1.0 (NS)	C
					Triglycerides (mmol/L)	1.66 vs. 1.82 (NS)	C
Ferreira, 2008[103]	91 13.5 mo HD	Sevelamer Starting dose individualized by substituting prior P binder gram for gram. Dose titrated to achieve serum P of 1.03-1.61 mmol/L	Ca carbonate Starting dose individualized by substituting prior P binder gram for gram. Dose titrated to achieve serum P of 1.03-1.61 mmol/L Average elemental Ca at study completion: 600-2600 mg/d	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 given.	‡Bone Overall Summary by WG[m]	Turnover improved more often in placebo biopsies without much difference in mineralization or volume.	A
					Bone Turnover	Worse (-9.4)	
					Bone Mineralization	Same	
					Bone Volume	Almost same (+0.9)	
					Laboratory		
					Ca (mmol/L)	2.27 vs. 2.32 (NS)	B
					P (mmol/L)	1.74 vs. 1.71 (NS)	B
					iPTH (pmol/L)	29.2 vs. 24.1 (NS)	B
					25(OH) D (nmol/L)	50 vs. 43 (NS)	B
					$1,25(OH)_2$ D (pmol/L)	21 vs. 36 (NS)	B
					Total Cholesterol (mmol/L)	3.62 vs. 4.29 (0.03)	B
					LDL-C (mmol/L)	1.76 vs. 2.59 (<0.01)	B
					HDL-C (mmol/L)	1.42 vs. 1.27 (NS)	B
					Bicarbonate (mmol/L)	20.4 vs. 21.2 (NS)	B
					b- ALP (µg/L)	19.1 vs. 12.7 (NS)	B

Author, Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Pediatrics							
Salusky, 2005[104]	42[n] 8 mo PD	Sevelamer Initial dose had comparable P-binding capacity to previous dose of calcium carbonate. Plus 1000 mg of elemental Ca when Ca <205 mmol/L.	Ca carbonate Initial dose based on previous prescription and the 1250mg tablets (500 mg elemental Ca) given with each meal and snack. Average elemental Ca from medication: 2800-3200 mg/d	PO Calcitriol or doxercalciferol TIW Target values: Ca 2.10-2.54 mmol/L P 1.29-1.94 mmol/L PTH 31.8-42.4 pmol/L Dialysate Ca 2.5 mEq/L	Bone Overall Summary by WG[m]	Overall not much difference between groups.	B
					Bone Turnover (N = 29)	Not different (+6)	
					Bone Mineralization	Same	
					Bone Volume (N = 29)	Slightly worse (-3.4)	

AoC, aortic calcification; ALP, alkaline phosphatase; AVC, aortic valve calcification; b-ALP, bone-specific alkaline phosphatase; CAC, coronary artery calcification; CaXP, calcium-phosphorus product; CI, confidence interval; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; Δ, change; EBCT, electron-beam CT; F/U, followup; HD, hemodialysis; iPTH, intact parathyroid hormone; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MVC, medial vascular calcification; N, number of subjects; nd, not documented; NS, not significant; PTH, parathyroid hormone; pt-y, patient-year; TIW, three times weekly; WG, work group.

Symbols: ‡ Primary outcome; **P* <0.05, but unclear whether value is within or between arm.

Annotations:

a. 70% began study on Ca acetate of which 94% remained on drug. 30% began study on Ca carbonate of which 87% remained on drug. Other subjects switched formulations but remained on Ca-based P binders.
b. Data for HR and CI for mortality and hospitalizations in St. Peter are adjusted for baseline CVD covariates.
c. Additional cause-specific mortality outcomes (per 100 pt-y): Infection HR 1.38 (0.94-2.04) (NS); Other causes HR 0.83 (0.67-1.04) (NS).
d. Other-cause hospitalizations had a HR 0.87 (0.77-0.98) (0.02).
e. Nonparametric test.
f. Ratio of the ratios of geometric means of day 360 to screening calcification scores for sevelamer-HCl vs. Ca acetate, adjusted for covariates (baseline calcification scores, age, sex, race, body weight, PTH). For CAC, study aimed to show noninferiority of Ca acetate with an upper bound of the 95% CI <1.8. Numbers in the table are the inverse of ratios reported for calcium vs. sevelamer-HCl. For aortic valve calcification, the unadjusted ratio was 1.20 (CI 0.75-1.94) and thus crossed the upper boundary of noninferiority There was imbalance at baseline with greater calcification in the sevelamer-HCl arm.
g. *P*-values are for statistical comparison of medians.
h. 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 $mmol^2/L^2$.
i. Estimated from graph.
j. During year 1, same protocol as Chertow 2002.[77] During year 2, optimal study conditions with strict control by pill counts and frequent interviews were suspended so that the patients were treated under standard conditions of daily practice.
k. Multivariate analysis using 10 variables with 34 events: HR 3.1 (CI 1.23-7.61).
l. ΔCAC at 6 mo [N = 104]: +16 vs. +4 (NS).
m. See Supplemental Table 17.
n. Twenty-nine pediatric patients had reported bone biopsy results. Fifteen were from Arm 1 and 14 were from Arm 2.
o. In patients with low-turnover bone disease, vitamin D treatment was withdrawn and the calcium dialysate concentration was set at a level of 2.5 mEq/L, regardless of iPTH levels.
p. 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.

Supplemental Table 17. Summary Table of RCTs examining the treatment of CKD-MBD with sevelamer-HCl vs. calcium-containing phosphate binders in CKD Stage 5D—bone biopsy results

Author, Year	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients			% of TV
Barreto, 2008[102]	Sevelamer	nd	nd	nd	nd	nd	nd	-2.3	-0.3
	Calcium	nd	nd	nd	nd	nd	nd	5.3	1.3
Ferreira, 2008[103]	Sevelamer	12	9	15	0	6	0	Mlt: 8d	1.4
	Calcium	2.8	17	17	8.6	3	0	Mlt: 14d	2.3
Salusky, 2005[104]	Sevelamer	0	7	0	67	0	nd	OW: -3.2 µm	-2.5
	Calcium	0	7	0	61	0	nd	OW: -5.5 µm	+0.9

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Mlt, mineralization lag time; nd, not documented; OW, osteoid width; TV, trabecular volume.

Supplemental Table 18. Adverse events of sevelamer-HCl vs. calcium-containing phosphate binders in CKD Stages 3-5 and 5D

Author, Year Follow-up	N	Arm 1 / Arm 2	CV Events % Pts	CV Events D/C	Gastrointestinal AE % Pts	Gastrointestinal AE D/C	Hypercalcemia % Pts	Hypercalcemia D/C	Hypocalcemia % Pts	Hypocalcemia D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths	Modality Change
CKD Stage 5D															
Suki, 2007[97] Up to 45 mo	1053	Sevelamer	—	—	D/C due to AE mostly due to GI	—	—	—	—	—	—	—	8%	25%	8%
	1050	Ca Acetate or Ca Carbonate	—	—	—	—	D/C due to AE mostly due to hypercalcemia	—	—	—	—	—	5%	26%	7%
Qunibi, 2008[99] 12 mo	103	Sevelamer	—	—	Abdominal pain: 8%, Constipation: 10%, Diarrhea: 16%, Reflux: 6%, Nausea: 17%, Vomiting: 18%	—	Adjusted Ca>2.54 mmol./L ≥1study visit: 19%[a] Persistent hypercalcemia (Ca >2.54 mmol/L for 3 consecutive study time points): 3.0%	—	Persistent hypocalcemia: 21%[a]	—	Asthenia: 4%, Fatigue: 4%, Malaise: 7%, Pruritus: 11%, Arthralgia: 12%, Back Pain: 10%, Muscle Spasms: 19%, Myalgia: 4%	—	8%	3%	—
	100	Ca Acetate	—	—	Abdominal pain: 4%, Constipation: 5%, Diarrhea: 16%, Reflux: 5%, Nausea: 17%, Vomiting: 17%	—	Adjusted Ca>2.54mmol./L ≥1study visit: 31%[a] Persistent hypercalcemia (Ca >2.54 mmol/L for 3 consecutive study time points): 2.9%	—	Persistent hypocalcemia: 14%[a]	—	Asthenia: 11%, Fatigue: 9%, Malaise: 10%, Pruritus: 5%, Arthralgia: 8%, Back Pain: 10%, Muscle Spasms: 12%, Myalgia: 7%	—	6%	7%	—
Chertow, 2002[77] 12 mo	99	Sevelamer	—	—	—	—	§Undefined: 17% †CaXP >5.81 mmol^2/L^2: 4%	—	—	—	§iPTH <15.9 pmol/L: 30% Pts hospitalized: 37%[b]	—	—	6%	—
	101	Ca Acetate or Ca Carbonate	—	—	—	—	§Undefined: 43% †CaXP >5.81 mmol^2/L^2: 12%	—	—	—	§iPTH <15.9 pmol/L: 57% Pts hospitalized: 48%[b]	—	—	5%	—
Chertow, 2003[107] 12 mo (USA only)	54	Sevelamer	—	—	Vomiting: 17% Nausea 19% Diarrhea 19% Constipation 11%	—	*Undefined: 13%	—	—	—	*Headache: 4% Pts hospitalized: 37% Other AE observed in >10% Pts[c]	—	—	—	—
	54	Ca Acetate	—	—	Vomiting 26% Nausea 24% Diarrhea 24% Constipation 17%	—	*Undefined: 36%	—	—	—	*Headache: 20% Pts hospitalized: 48% Other AE observed in >10% Pts[c]	—	—	—	—
Braun, 2004[100] 12 mo (Germany, Austria only)	55	Sevelamer	CV events: 13% CV events requiring hospitalization: 4%	—	*GI AE: 74% *Dyspepsia: 26%	—	*Ca >2.6 mmol/L: 16% *Ca >2.8 mmol/L: 0% CaXP >5.8 mmol^2/L^2: 7%	—	Undefined: 0%	—	Pts hospitalized: 29%	—	25%	4%	—
	59	Ca Carbonate	CV events: 14% CV events requiring hospitalization: 7%	—	*GI AE: 53% *Dyspepsia: 5%	—	*Ca >2.6 mmol/L: 46% *Ca >2.8 mmol/L: 19% CaXP >5.8 mmol^2/L^2: 17%	—	Undefined: 2%	—	Pts hospitalized: 42%	—	10%	2%	—
Block, 2005[80] 18 mo	73	Sevelamer	—	—	—	—	§Ca >2.54 mmol/L: 22% *Ca >2.74 mmol/L: 5%	—		—	§PTH <15.9 pmol/L: 18%[d]	—	1%	1%[e]	3%
	75	Ca-containing P binders	—	—	—	—	§Ca >2.54 mmol/L: 54% *Ca >2.74 mmol/L: 24%	—		—	§PTH <15.9 pmol/L: 29%[d]	—	1%	1%[e]	3%

Author, Year Follow-up	N	Arm 1 / Arm 2	CV Events % Pts	CV Events D/C	Gastrointestinal AE % Pts	Gastrointestinal AE D/C	Hypercalcemia % Pts	Hypercalcemia D/C	Hypocalcemia % Pts	Hypocalcemia D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths	Modality Change
Barreto, 2008[102] 12 mo	41	Sevelamer	Death attributed to CV disease 17%	17%	—	—	—	—	—	—	PTx 3%	3%	—	2%	—
	30	Ca acetate	Death attributed to CV disease 2%	2%	—	—	—	—	—	—	PTx 2%	2%	—	27%	—
Ferreira, 2008[103] 13.5 mo	44	Sevelamer	—	—	—	—	—	—	—	—	"AEs": 5%	5%	5%	—	—
	47	Ca-based binders	—	—	—	—	—	—	—	—	"AEs": 4%	4%	4%	—	—
Pediatrics															
Salusky, 2005[104] 8 mo	21[f]	Sevelamer	—	—	—	—	Hypercalcemia episodes (Ca >2.54 mmol/L): 5	—	—	—	Hyperphosphatemic episodes (*P* >1.94 mmol/L): 43	—	—	—	—
	21[f]	Ca Carbonate	—	—	—	—	Hypercalcemia episodes (Ca >2.54 mmol/L): 22	—	—	—	Hyperphosphatemic episodes (*P* >1.94 mmol/L): 34	—	—	—	—
CKD Stages 3-4															
Russo, 2007[76] Mean 24 mo	30	Sevelamer	—	0%	—	0%	—	0%	—	0%	—	0%	0%	0%	0%
	30	Ca Carbonate	—	0%	—	0%	—	0%	—	0%	—	0%	0%	0%	0%
	30	Control	Acute MI 3%	3%	—	0%	—	0%	—	0%	—	0%	3%	0%	0%

AE, adverse event; CaXP, calcium-phosphorus product; CV, cardiovascular; D/C, discontinued; GI, gastrointestinal; iPTH, intact parathyroid hormone; MI, myocardial infarction; N, number of subjects; PTH, parathyroid hormone; Pts, patients; PTx, parathyroidectomy.

Symbols: "—" indicates data not documented; § *P* <0.001 between groups, if documented; * *P* <0.05 between groups, if documented; † 0.05< *P* <0.1 between groups, if documented.

Annotations:

a. Between group comparisons of adjusted Ca >2.54mmol/L had a *P*-value of 0.053 and persistent hypocalcemia had a *P*-value of 0.056.

b. Hospital days 567 vs. 980 (NS), for arm 1 vs. arm 2.

c. Sevelamer-HCl vs. Ca acetate, all comparisons are NS: pain in limb 15% vs. 19%, pruritus 13% vs. 6%, arthralgia 13% vs. 15%, dyspnea 15% vs. 19%, insomnia 9% vs. 11%, cough 9% vs. 13%, chest pain 7% vs. 11%, mechanical complication of implant 9% vs. 15%, upper respiratory tract infection 9% vs. 20%, hypertension aggravated 4% vs. 15%.

d. No difference between arms in episodes of hyperphosphatememia. Data not provided.

e. Deaths reported within study period (18 mo). See Intervention/Results table for mortality at 44 mo (median).

f. Twenty-nine pediatric patients had reported bone biopsy results. Fifteen were from Arm 1 and 14 were from Arm 2.

Supplemental Table 19. Ongoing RCTs examining the effect of phosphate binders on CKD-MBD

Name of study (PI) Sponsor: Clinical Trial ID	Patient Population/ Inclusion Criteria	F/U	N	Experimental Group	Control Group	CKD-MBD Outcomes	Start Date	Status
Ca-containing P binders vs. placebo								
EPIC (Qunibi) Nabi: NCT00211978	Stages 4-5 elevated P	nd	nd	Ca acetate	Placebo	‡P, CaXP	nd	No longer recruiting
Sevelamer-HCl vs. Ca-containing P binders								
Arterial Stiffness Sevelamer-HCl vs. Calcium[a] (Covic and Mircescu) Romanian Soc Nephrol: NCT00364000	Stage 5D on HD iPTH 21.2-84.8 pmol/L Ca 2.2-2.6 mmol/L	12 mo	240	Sevelamer	Ca acetate	‡PWV, ‡AIX, ‡Radiological calcification score, Mortality and CV events, iPTH, Ca, P, CaXP	2006	Not yet recruiting
Sevelamer-HCl administration								
Sevelamer-HCl Powder vs. Tablets[b] (Blair) Genzyme: NCT00268957	Stage 5D on HD P binder therapy P 1.0-2.1 mmol/L iPTH ≤85 pmol/L	6 mo	207	Sevelamer-HCl powder QD	Sevelamer-HCl tablets TID	‡P, CaXP, Lipids, Harm	2006	Completed
Lanthanum vs. placebo								
Safety and Efficacy of Lanthanum Carbonate (PI: nd) Shire: NCT00234702	Stages 3-4 P ≥1.52 mmol/L	2 mo	84	Lanthanum carbonate	Placebo	‡P, PTH, CaXP	2005	No longer recruiting
Lanthanum vs. sevelamer								
Lanthanum vs. Sevelamer[c] (Sprague) Shire: NCT00441545	Stage 5D	nd	128	Lanthanum carbonate	Sevelamer	‡ΔP, Ca, P, PTH	2007	Recruiting
Other P binders								
Alpharen for Reduction of P in HD Patients[d] (PI: nd) Ineos: NCT00317694	Stage 5D on HD Stable P binder dose	nd	160	Alpharen	Placebo	‡% Pts achieving P target , P, Ca, CaXP, PTH, Harm	2006	Completed
ACT 3[e] (Taal) Ineos: NCT00436683	Stage 5D on HD Stable P binder dose	nd	60	Alpharen	Sevelamer	‡Harm, PTH	2007	Recruiting
Colestilan Phase III[f] (PI: nd) Mitsubishi: NCT00451295	Stage 5D Ca-based P binder	3 mo	200	Colestilan + Ca-containing P binder	Placebo + Ca-containing P binder	‡P, Ca, CaXP, PTH, Lipids, Harm	2007	Recruiting
Colestilan Withdrawal[g] (PI: nd) Mitsubishi: NCT00506441	Stage 5D Stable P	4 mo	200	Colestilan	Placebo	‡ΔP, Ca, P, CaXP, PTH, Lipids, Harm	nd	Not yet recruiting

ACT 3, Dose Ranging Study of Magnesium Iron Hydroxycarbonate in HD Subjects with Hyperphosphatemia (ACT 3); AIX, augmentation index; CaXP, calcium-phosphorus product; CV, cardiovascular; CARE-2, Calcium Acetate (PhosLo)/Sevelamer-HCl (Renagel) Evaluation Study 2; CKD-MBD, chronic kidney disease-mineral and bone disorder; EPIC, Effect of PhosLo on Phosphorus Levels in Chronic Kidney Disease; F/U, followup; HD, hemodialysis; iPTH, intact parathyroid hormone; N, number of subjects; nd, not documented; PI, principal investigator; PTH, parathyroid hormone; pts, patients; PWV, pulse wave velocity; QD, once daily; TID, three times daily.

Notes: www.clinicaltrials.gov accessed September 2007.

Shaded rows indicate trials known to not meet inclusion criteria for this systematic review.

See also Cochrane review in development.[108]

Symbols: ‡ Designated primary outcome(s).

Annotations:

a. Arterial Stiffness and Arterial Calcifications Evolution in ESRD Hemodialysis Patients Treated by Sevelamer-HCl or Calcium Acetate.
b. Randomized, Parallel, Open-Label Study to Compare Once Per Day Sevelamer Carbonate Powder Dosing With Three Times Per Day Sevelamer-HCl Tablet Dosing in Chronic Kidney Disease Patients on Hemodialysis.
c. A Prospective, Multicenter, Open-Label, Randomized, Cross-Over Study to Compare the Efficacy and Safety of Fosrenol® and Sevelamer-HCl in Patients Receiving Hemodialysis for End-Stage Renal Disease.
d. A Multicentre Phase II Study With Alpharen: an Open-Label, Dose-Ranging Phase Followed by a Placebo-Controlled, Double-Blind, Parallel-Group Comparison in Hemodialysis Subjects with Hyperphosphataemia.
e. An Open Label, Dose-Ranging Study to Establish the Tolerability of Alpharen in Haemodialysis Subjects with Hyperphosphataemia.
f. A Phase III, Double-Blind, Multi-Centre, Randomised, Parallel Group Design, Placebo-Controlled, Flexible Dose Study of MCI-196 in Combination With a Ca-Based Phosphate Binder in CKD Stage V Subjects on Dialysis with Hyperphosphatemia.
g. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Withdrawal Study Comparing MCI-196 vs. Placebo Following A 12-Week Dose Titration Period With MCI-196 in Stage V Subjects on Dialysis with Hyperphosphatemia.

Supplemental Table 20. Summary Table of the treatment of CKD-MBD with lanthanum carbonate vs. other phosphate binders in CKD Stage 5D—description of population at baseline

Author Year	N / Country of Study	Age* / % Male*	Race (%)	Dialysis Vintage* / Dialysate Calcium	% DM* / % Prior Al Exposure*	Baseline MBD Labs*	Bone Evaluation Technique
Finn 2006[109]	1359 Poland, Puerto Rico, South Africa, USA	54 (55) 57 (61)	44 (46) Caucasian 44 (41) Black 8 (8) Hispanic <1 (2) Asian/ Pacific 1 (1) Native American 2 (2) Other	49 (46) mo nd	nd nd[a]	Ca 2.30 (2.27) mmol/L[b] P 2.58 (2.58) mmol/L[b] PTH 17.2 (14.6) pmol/L[b] nd ALP nd	None
Hutchison 2005[110c]	800 Belgium, Germany, Netherlands, UK	57 (58) 67 (64)	nd	43 (44) mo nd	nd nd	Ca 0.57 (0.56) mmol/L P 2.67 (2.69) mmol/L PTH 13.5 (17.3) pmol/L nd ALP nd	None
Malluche 2007[111]	211 Poland, Puerto Rico, South Africa, USA	49 (51) 73 (77)	49 (52) Black 33 (29) Caucasian 8 (6) Hispanic 0 (2) Asian/Pacific Islander 0 (0) Native American 10 (10) Other	42 (61) mo nd	nd nd	Ca 2.20 (2.30) mmol/L P 2.45 (2.62) mmol/L PTH 33.7 (22.4) pmol/L 2nd gen assay DiaSorin SpA [ref: nd] b-ALP 27.3 (20.8) ng/mL	Bone biopsy
Freemont 2005[112]	98 Europe, South Africa	56 (54) 63 (57)	92 (94) Caucasian 4 (4) Mixed race 2 (2) Asian 2 (0) Other[d]	<3 mo nd	nd nd	Ca 2.24 (2.29) mmol/L P 1.72 (1.87) mmol/L iPTH 24.21 (20.20) pmol/L nd ALP nd Calcitriol 67.7 (52.8) pmol/L	Bone biopsy
Spasovski 2006[113]	24 Macedonia	55 (57) 60 (60)	nd	<3 mo nd	nd nd	Ca 2.13 (2.27) mmol/L P1.58 (1.76) mmol/L iPTH 35.6 (27.7) pmol/L nd ALP nd 25(OH) Vit D 48.3 (43.5) nmol/L 1,25(OH) Vit D 126 (133) pmol/L	Bone biopsy

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CaXP, calcium-phosphorus product; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; iPTH, intact parathyroid hormone; MBD, mineral and bone disease; N, number of subjects; nd, not documented; PTH, parathyroid hormone.

Note: No study reported vascular or valvular calcification. -- Symbols: *Arm 1 (Arm 2)

Annotations:

a. 4% (4%) on "other" binders including aluminum and magnesium at prior to study.

b. Estimated from graph.

c. Safety outcomes only.

d. Does not include any patients classified as Black, Oriental, or Hispanic.

Supplemental Table 21. Summary Table of the treatment of CKD-MBD with lanthanum carbonate vs. other phosphate binders in CKD Stage 5D—intervention and results

Author Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Finn, 2006[109]	1359 24 mo HD	Lanthanum carbonate initiated at 750 or 1500 mg/d, adjusted[a]	Prestudy phosphate binder(s) and dosing regimen[b]	Ca supplementation for hypocalcemic patients. No maximum daily dose of Ca was specified.	% with *P* ≤1.91 mmol/L	46% vs. 49% (NS)	C
					Mean Ca (mmol/L)	2.35 vs. 2.40 (nd)[c]	C
					Mean P (mmol/L)	1.97 vs. 1.94 (nd)[c]	C
					Median PTH (pmol/L)	21.3 vs. 14.5 (nd)[c]	C
					ALP (IU/L)	107.5 vs. 108.6 (NS)	C
					b-ALP (mg/mL)	0.000025 vs. 0.000020 (nd)	C
					Bicarbonate	nd (NS)	C
Malluche, 2007[111]	211 24 mo HD	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.	Bone overall summary by WG[d]	Overall no change seen at year one. At year two results favor lanthanum with better turnover.	B
					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)[c]	B
					Mean P (mmol/L)	1.49 vs. 2.03 (nd)[c]	B
					Median PTH (pmol/L)	25.5 vs. 8.5 (nd)[c]	B
					b-ALP (ng/mL)	33.6 vs. 8.3 (nd)[c]	B
					Osteocalcin (ng/mL)	451.9 vs. 241.6 (nd)[c]	B
Freemont, 2005[112]	98 12 mo nd	Lanthanum carbonate up to 3750 mg/d, adjusted[e]	Ca carbonate up to 9000 mg/d, adjusted[e]	No restriction on Vitamin D	Bone overall summary by WG[d] [N = 63]	Overall profile favors lanthanum due to better turnover	B
					‡Bone Turnover	Better (+35)	
					‡Bone Mineralization	Same	
					Bone Volume	nd	
					Mean Ca (mmol/L)	2.33 vs. 2.39 (nd)	B
					Mean P (mmol/L)	1.79 vs. 1.65 (nd)	B
					Mean CaXP ($mmol^2/L^2$)	4.19 vs. 3.95 (nd)	B
					Mean iPTH (pmol/L)	23.68 vs. 14.65 (nd)	B

Author Year	N Follow-up Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Spasovski, 2006[113]	24	Lanthanum carbonate up to 3000 mg/d, adjusted to P ≤1.8 mmol/L	Ca carbonate up to 4000 mg/d, adjusted to P ≤1.8 mmol/L	Vitamin D Protocol: nd	Bone overall summary by WG[d]	The data in this paper primarily showed that bone formation did not significantly deteriorate with lanthanum (unlike aluminum)	B
	12 mo				Bone Turnover	nd	
	nd				Bone Mineralization	Same	
					Bone Volume	nd	

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CaXP, Calcium-phosphorus product; KDOQI, CKD-MBD, chronic kidney disease-mineral and bone disorder; Kidney Disease Outcomes Quality Initiative; La, lanthanum; N, number of subjects; nd, not documented; NS, not significant; PTH, parathyroid hormone; WG, work group.

Symbols: ‡ Primary outcome.

Annotations:

a. Dose adjusted to P ≤1.91 mmol/L.

b. In control arm, patients were permitted to switch from one conventional treatment to another, including to aluminum-based agents or to a combination of agents, in the event of intolerance or failure to achieve P ≤1.91 mmol/L.

c. Estimated from graph.

d. See Supplemental Table 22.

e. Median lanthanum dose 1250 mg/d and median Ca carbonate dose 2000 mg/d; doses adjusted to optimal P levels (undefined).

Supplemental Table 22. Summary Table of the treatment of CKD-MBD with lanthanum carbonate vs. other phosphate binders in CKD Stage 5D—bone biopsy results

Study	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ in Mlt	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients		d	% of TV
Malluche, 2007 [111]	Year 1 Lanthanum	32	10	6	6	0	0	15	-0.6
	Standard	29	16	3	0	0	0	-40	-1.2
	Year 2 Lanthanum	17	23	10	3	6	0	-16	3.1
	Standard	43	29	0	10	0	0	1	1.8
Freemont, 2005 [112]	Lanthanum	6	6	33	12	0	3	-4	nd
	Ca carbonate	10	20	13.5	6.5	0	3	-35	nd
Spasovski, 2006 [113]	Lanthanum	nd	0	nd	nd	nd	nd	-50%	nd
	Ca Carbonate	nd	30	nd	nd	nd	nd	-50%	nd

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Mlt, mineralization lag time; nd, not documented; TV, trabecular volume.

Supplemental Table 23. Adverse events of lanthanum carbonate vs. other phosphate binders in CKD Stage 5D

Author, Year Follow-up	N	Arm 1 / Arm 2	Gastrointestinal AE % Pts	Gastrointestinal AE D/C	Hypercalcemia/Hypocalcemia % Pts	Hypercalcemia/Hypocalcemia D/C	Cognitive Function % Pts	Cognitive Function D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths	Modality Change
Finn 2006[109] 24 mo	682	Lanthanum carbonate	Nausea: 37% Vomiting: 27% Diarrhea: 24% Abdominal pain: 17%	—	Hypercalcemia: 4%[b]	<1%	MMSE: no change[c]	—	All drug related AE: 22% SAE: 58%[d] Abnormal PTH: 15% Abnormal lab values: 40%[e] AE reported in ≥15% of pts[f] Mean plasma La: 0.5 ng/mL	2 measurements of P >3.23 mmol/L: 5% of P <0.65 mmol/L: 0% of CaXP >7.26 mmol^2/L^2: 2% Increase in PTH ≥52 pmol/L: 1%	14%	6%	8%
	677	Other P binder(s)[a]	Nausea: 29% Vomiting: 22% Diarrhea: 24% Abdominal pain: 18%	—	Hypercalcemia: 8%[b]	<1%	MMSE: no change[c]	—	All drug related AE: 13% SAE:73%[d] Abnormal PTH: 16% Abnormal lab values: 42%[e] AE reported in ≥15% of pts[f]	2 measurements of P >3.23 mmol/L: 3% of P <0.65 mmol/L: <1% of CaXP >7.26 mmol^2/L^2: 1% Increase PTH ≥52 pmol/L: <1%	4%	14%	11%
Hutchison 2005[110] 1.25 mo or 6 mo	533	Lanthanum carbonate	Nausea: 16% Vomiting: 18% Diarrhea: 13% Constipation: 6%	—	Hypercalcemia: <1%[b] §1 measurement > upper limit of normal: 6%	—	—	—	All AE: 78% AE reported in ≥5% of pts[g] Mean plasma La: 0.55 ng/mL[h]	—	—	—	2%
	267	Ca carbonate	Nausea: 13% Vomiting: 11% Diarrhea: 10% Constipation: 7%	—	Hypercalcemia: 20%[b] §1 measurement > upper limit of normal: 38%	—	—	—	All AE: 80% AE reported in ≥5% of pts[g] Mean plasma La: 0.01-0.03 ng/mL[h]	—	—	—	4%
Malluche, 2008[111] 24 mo	51	Lanthanum carbonate	—	—	Hypercalcemia (serum Ca >2.87 mmol/L): 2%	—	—	—	Serum P >3.23 mmol/L: 4% PTH >53 pmol/L over screening value: 4% Mean Δbone La[i] (µg/g) Year 1: 0.99 Year 2: 1.68	—	6%	20%	20%
	48	Standard therapy	—	—	Hypercalcemia (serum Ca >2.87 mmol/L): 0%	—	—	—	Serum P >3.23 mmol/L: 2% PTH >53 pmol/L over screening value: 2% Mean Δbone La[i] (µg/g) Year 1: 0.16 Year 2: 0.16	—	6%	33%	21%
Freemont 2005[112] D'Haese 2003[149] 13 mo	49	Lanthanum carbonate	Nausea: 10% Vomiting: 14% Diarrhea: 8% Constipation: 10%	—	1 measurement >2.65 mmol/L: 6% Hypocalcemia: 24%[a]	—	—	—	All AE: 96%, SAE: 64 events[j] Mean bone La: 1.77 µg/g	—	24%	—[k]	—[k]
	49	Ca carbonate	Nausea: 4% Vomiting: 10% Diarrhea: 8% Constipation: 16%	—	1 measurement >2.65 mmol/L: 49% Hypocalcemia: 10%[a]	—	—	—	All AE: 96%, SAE: 64 events[j] Mean bone La: 0.06 µg/g	—	22%	—[k]	—[k]

Author, Year Follow-up	N	Arm 1 / Arm 2	Gastrointestinal AE % Pts	Gastrointestinal AE D/C	Hypercalcemia/Hypocalcemia % Pts	Hypercalcemia/Hypocalcemia D/C	Cognitive Function % Pts	Cognitive Function D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths	Modality Change
Spasovski 2006[113] 12 mo	12	Lanthanum carbonate	—	0%	*1 measurement >2.6 mmol/L: 0%	0%	—	0%	*Mean plasma La: 0.59 ng/mL *Mean bone La: 2.3 μg/g	—	0%	0%	0%
	12	Ca carbonate	—	0%	*1 measurement >2.6 mmol/L: 50%	0%	—	0%	*Mean plasma La <0.03 ng/mL *Mean bone La 0.1 μg/g	—	0%	8%	0%

AE, adverse event; CaXP, calcium-phosphorus product; D/C, discontinued; Δ, change; La, lanthanum; MMSE, mini-mental state examination; PTH, parathyroid hormone; pts, patients; SAE, serious adverse event.
Note: No CV events were reported.
Symbols: "—" indicates data not documented; § P <0.001; * P <0.05 between groups, if documented.
Annotations:

a. AE rates in standard therapy arm were exposure-corrected using a factor of 0.74.
b. Undefined.
c. MMSE: mini-mental state examination a 30-point computerized assessment, no differences seen between arms. Using the Cognitive Drug Research tool, lanthanum arm was similar to standard therapy arm in deterioration of cognitive function as assessed by the Cognitive Drug Research tool. (Lanthanum arm was slightly better in numeric working memory—response time parameter).[114]
d. Three considered likely secondary to lanthanum: one pancreatitis, one GI bleed, one constipation. No SAE considered secondary to drug in standard therapy arm.
e. Includes Ca, PTH, osteocalcin, albumin, glucose, bicarbonate, urea nitrogen, potassium, creatinine, transferrin, ALP, γ-glutamyltransaminase, b-ALP, hemoglobin, hematocrit, red blood cells, platelets and white blood cells.
f. Statistical significance not documented. General: chest pain 21% vs. 19%, influenza-like symptoms 16% vs. 17%, pain 18% vs. 19%; CV: peripheral edema 16% vs. 20%, hypotension 16% vs. 18%; Nervous system: dizziness 21% vs. 20%, headache 22% vs. 21%; Dialysis complications: catheter complication 17% vs. 18%, graft complication 25% vs. 24%, graft occlusion 21% vs. 21%; Musculoskeletal system: myalgia 21% vs. 20%; Respiratory system: coughing 20% vs. 20%, dyspnea 23% vs. 24%, upper respiratory tract infection 16% vs. 14%.
g. Statistical significance not documented. General: Surgical intervention 1% vs. 1%; CV: Hypotension measured during dialysis 8% vs. 9%; angina pectoris: 1% vs. <1%; Nervous system: headache 5% vs. 6%; Dialysis complications: graft occlusion 4% vs. 6%; catheter complication: 1% vs. 1%; Musculoskeletal system: cramps: 7% vs. 6%; Respiratory system: bronchitis 5% vs. 6%, rhinitis: 7% vs. 6%; Resistance mechanism: sepsis 0% vs. 1%; Vision: cataract <1% vs. 1%.
h. Data at 7 wk, N ≤289 and 154 for La and Ca arms, respectively; at 5 mo, 0.49 ng/mL and 0.0-0.01 ng/mL, respectively.
i. Calculated from table.
j. Most common serious AEs: dialysis graft creation, dialysis graft occlusion; dialysis catheter complication, peritonitis, renal transplant.
k. Ten patients received kidney transplant and 11 patients died, arms not reported.

Supplemental Table 24. Overview Table of selected studies demonstrating the risk relationships between hormonal parameters of PTH, vitamin D, and mortality in CKD Stages 3-5 and 5D

Author, Year Database	N Follow-up Country	Mortality Ascertainment	Categorization or Comparison [Measurement technique]		
		Categorization	PTH (pmol/L)	25 Vit D (nmol/L)	1, 25 Vit D (pmol/L)
CKD Stage 5D on HD					
Kalantar-Zadeh, 2006[86] DaVita	58 349 24 mo USA	nd[a] nd	<10.6 to ≥74.2 in 10.6 pmol/L increments (*a priori*) [Nichols intact 1st gen. IRMA]	—	—
Block, 2004[24] Fresenius	40 538 12 to 18 mo USA	nd[b] nd	<15.9, 15.9-31.8, 31.8-63.6, >63.6 (*a priori*) [nd]	—	—
Tentori, 2008[87] DOPPS I, DOPPS II, DOPPS III	25 588 17 mo Multicenter, International	nd[c] -All-cause -Cardiovascular	<5.4 to >68.9 in 5.3 pmol/L increments	—	—
Young, 2005[88] DOPPS	17 236 nd France, Germany, Italy, Japan, Spain, UK, USA	Standardized questionnaires of medical records[d] -All-cause -Cardiovascular	Continuous [nd]	—	—
Ganesh, 2001[89] CMAS & DMMS Waves 1, 3, 4	12 833 24 mo USA	HCFA[e] -All-cause -Coronary artery disease -Other cardiac -Sudden death -Cerebrovascular -Infection -Other -Unknown -Missing	Quintiles (0-3.4, 3.5-9.5, 9.6-20.9, 21.0-52.5, 52.6-1004.5) [nd]	—	—
Block, 1998[90] CMAS & DMMS Wave 1	6407 24 mo USA	nd[f] nd	Quintiles (0-3.5, 3.6-9.6, 9.8-21.9, 22.0-54.1, 54.2-1007.0) [nd] Continuous (log PTH) [nd]	—	—
Kimata, 2007[91] J-DOPPS 1, 2	5041 Mean 19 mo Japan	nd[g] -All-cause -Cardiovascular	Continuous [intact]	—	—
Wolf, 2007[115] ArMORR	825 3 mo USA	nd[h] nd	—	<25, 25-75, >75 [nd] Continuous	<13, 16-34, >34 [nd] Continuous
Wang, 2008[116]	230 36 mo China	nd[i] -All-cause -Cardiovascular	—	≤45.7 or >45.7	—

Author, Year Database	N Follow-up Country	Mortality Ascertainment Categorization	Categorization or Comparison [Measurement technique] PTH (pmol/L)	25 Vit D (nmol/L)	1, 25 Vit D (pmol/L)
Inaguma, 2008[117]	226 Up to 72 mo Japan	nd[j] -All-cause	—	—	<52 or ≥52
CKD Stage 5D on HD/PD					
Noordzij, 2005[92] NECOSAD	1629 Up to 90 mo[k] Netherlands	nd[l] nd	Less than, at, greater than KDOQI target (15.9-31.8) [intact]	—	—
Melamed, 2007[118] CHOICE	515 35 mo (median) USA	nd[m] -All-cause	Total PTH: <15.9, 15.9-31.8, >31.8 1-84 PTH: <8.5, 8.5-17.0, >17.0 7-84 PTH: <7.4, 7.4-14.8, >14.8 1-84 PTH/7-84 PTH Ratio: <1.0, 1.0-1.3, >1.4	—	—
Melamed, 2008[119] NHANES III	743 104 mo (median) US	nd[n] -All-cause		<44, 44-61, 61-80, >80 [Diasorin RIA kit]	

ArMORR, Accelerated Mortality on Renal Replacement; CHOICE, Choices for Healthy Outcomes in Caring for End-Stage Renal Disease; CMAS, Case Mix Adequacy Study (US Renal Data System); CKD, chronic kidney disease; DMMS, Dialysis Morbidity and Mortality Study (US Renal Data System); DOPPS, Dialysis Outcomes and Practice Patterns Study; HCFA, Health care Financing Administration ESRD Death Notification Form (HCFA-2746-U3); HD, hemodialysis; J-DOPPS 1, 2 , DOPPS conducted in Japan Phase I and Phase II; IRMA, immunoradiometric assay; KDOQI, Kidney Disease Outcomes Quality Initiative; N, number of subjects; nd, not documented; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; PD, peritoneal dialysis; PTH, parathyroid hormone; RIA, radioimmunoassay.

Annotations:

a. Case-mix adjusted models included additional covariates: age, gender, race and ethnicity, diabetes mellitus, vintage, primary insurance, marriage status, and standardized mortality ratio of the dialysis clinic during entry quarter, continuous values of Kt/V, dialysate calcium concentration, and administered doses of each of vitamin D analogs within each calendar quarter. Case-mix and MICS adjusted models included all of the above-mentioned covariates plus 11 indicators of nutritional status and inflammation including the time-varying body mass index, averaged dose of rHuEPO in each calendar quarter, and the nine above-mentioned time-varying laboratory values.

b. Unadjusted, case-mix adjusted and multivariate adjusted analyses were reported. For all analyses, case mix adjustment refers to adjustment for age, gender, race or ethnicity, diabetes, and vintage. Multivariable adjustment refers to case mix plus body weight, URR, serum albumin, creatinine, predialysis BUN, bicarbonate, cholesterol, hemoglobin, ferritin, and aluminum. Phosphorus models simultaneously adjusted for calcium + PTH, calcium models simultaneously adjusted for phosphorus + PTH, PTH models simultaneously adjusted for phosphorus + calcium.

c. Models were adjusted for case-mix, comorbidities, baseline hemoglobin, albumin, normalized protein catabolic rate, single-pool Kt/V, prior PTx, and the other mineral metabolism markers. Vitamin D prescription was added as an additional covariate to the PTH models in sensitivity analysis. To test the relationship between facilities' control of mineral metabolism markers and mortality, models were adjusted for the percentage of patients at a facility with values of other markers in each risk category for calcium, phosphorus, and PTH.

d. Stratified by country and adjusted for dialysate calcium concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and the following comorbid conditions: coronary artery disease, congestive heart failure, other cardiac disease, HTN, cerebrovascular disease, peripheral vascular disease, DM, lung disease, cancer (excluding skin), HIV/AIDS, GI bleeding, neurologic disease, psychiatric disease, and recurrent cellulitus. Phosphorus analysis adjusted for serum concentrations of calcium and PTH; calcium analysis adjusted for serum concentrations of phosphorus and PTH; CaXP analysis adjusted for serum concentrations of PTH; PTH analysis adjusted for serum concentrations of phosphorus and calcium.

e. The main analyses were adjusted for patient age at study start, duration of ESRD, gender, race, cause of ESRD, and noncardiovascular comorbid conditions.

f. Main analyses were adjusted for age at onset of ESRD, race, sex, active smoking, and the presence of diabetes, neoplasm, or AIDS.

g. Cox survival models were adjusted for age, sex, duration of ESRD, single-pool Kt/V, serum albumin, hemoglobin, dialysate Ca concentration, and the following comorbid conditions present at study entry: coronary artery disease, congestive heart failure, other cardiac disease, HTN, cerebrovascular disease, peripheral vascular disease, DM, lung disease, cancer (excluding skin), HIV/AIDS, GI bleeding, neurologic disease, psychiatric disease, and recurrent cellulitus.

h. The reference groups were subjects receiving therapy in the highest vitamin D groups (25D>30ng/mL; 1,25D > 13pg/mL.). Other covariates included age, sex, race, etiology of renal failure, standardized mortality rates, blood pressure, vascular access, albumin, creatinine, PTH, calcium phosphorus, hemoglobin, and a past medical history of coronary artery disease, stroke, malignancy, or congestive heart failure.

i. Covariates adjusted in stepwise multivariable Cox regression models were age, sex, diabetes mellitus, coronary artery disease, duration of dialysis, residual GFR, biochemical [hemoglobin, LDL cholesterol, C-reactive protein, serum phosphorus] and nutritional [serum albumin, subjective global assessment], echocardiographic markers [left ventricular mass index and left ventricular volume index].

j. Multivariate model for all-cause mortality was adjusted for age, diabetes, hemoglobin, albumin, BUN, estimated GFR, total cholesterol, use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

k. Median 2.3 y (HD), 2.4 y (PD).

l. Adjustment for the possible confounding effects of age, Davies comorbidity score, primary kidney disease, SGA, albumin level, Kt/Vurea per week, and hemoglobin level. Supplementary adjustments for laboratory parameters related to mineral metabolism were made for phosphorus and iPTH in analyses on the effects of calcium. Similarly, we made additional adjustments for calcium and iPTH levels in analyses of phosphorus, for iPTH levels in analyses of CaXP product, and for calcium and phosphorus levels in analyses of iPTH.

m. Adjustment for the potential confounders: age, race, sex, baseline modality, smoking, diabetes mellitus, index of coexistent diseases, referral time, employment, IV calcitriol use, BMI, log C-reactive protein, albumin, hemoglobin, Ca and P.

n. Because serum 25(OH)D levels vary by season, all multivariate analyses were adjusted for season of examination. Inclusion in the final model was based on the variable of interest being associated with both 25(OH)D levels and mortality (P <0.20) and on a priori determination of confounders of the association between 25(OH)D levels and mortality. Covariates included in the final model were age, sex, race, season, hypertension, history of CVD, diabetes mellitus, smoking, body mass index (BMI), high density lipoprotein cholesterol, total cholesterol, the use of cholesterol-lowering medications, eGFR categories, serum albumin level, log urinary albumin to creatinine ratio, log C-reactive protein, physical activity level, vitamin D supplementation, and low SES.

Supplemental Table 25. Summary Table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs. placebo in CKD Stages 3-5—description of population at baseline

Author, Year	N Country of Study	Age* % Male*	% Race*	CKD Stage(s)	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique
Coyne, 2006[120] 3 RCTs	220 Poland, USA	64 (62) 68 (67)	69 (73) White 26 (26) Black 5 (1) Other	3-4	60 (58) nd	Ca 2.32 (2.34) mmol/L corrected P 1.29 (1.28) mmol/L iPTH 28.1 (29.7) pmol/L Allegro-intact PTH [ref 10-65 pg/mL] b-ALP 17.1 (18.8) µg/L	None
Hamdy, 1995[40]	176 Belgium, France, Netherlands, UK	53 (51) 61 (61)	nd	3-4	nd nd[a]	Ca 2.36 (2.37) mmol/L corrected P 1.29 (1.33) mmol/L iPTH 10.3 (6.4) pmol/L MagicLite chemiluminescent assay [ref 0.8 – 5.4 pmol/L] ALP 154 (152) IU/L	Bone biopsy
Coburn, 2004[121]	55 USA	64 (65) 78 (86)	44 (36) African American 48 (54) Caucasian 4 (11) Hispanic 4 (0) Other	3-4	nd nd	Ca 2.19 (2.21) mmol/L P 1.30 (1.26) mmol/L iPTH 23.2 (18.2) pmol/L Allegro-intact PTH [ref nd] 25 Vit D 46 (46) nmol/L 1,25 Vit D 88 (91) pg/mL HPLC method ALP 113.9 (106.9) U/L	None
Nordal 1988[122]	30 Norway	48 (47) 60 (73)	nd	3-5	6 (6) 60 (60)	Ca 2.30 (2.40) mmol/L[b] P 1.6 (1.4) mmol/L PTH 1.33 (0.94) µg/L nd [ref <0.60][c] ALP 201 (209) U/L	Bone biopsy
Kooienga, 2009[123] Posthoc analysis	222 France	86 0	nd	3	nd nd	Ca 2.32 mmol/L P 1.03 mmol/L b-ALP 15.3 ng/mL 2-site radioimmunoassay 25(OH) Vit D 23 nmol/L iPTH 7.7 pmol/L 2-site 2nd gen PTH assay	None
	100 France	87 0	nd	3-4	nd nd	Ca 2.30 mmol/L P 1.07 b-ALP 15.8 ng/mL 2-site radioimmunoassay	None

						25(OH) Vit D 22 nmol/L iPTH 9.4 pmol/L 2-site 2nd gen PTH assay

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CaXP, Calcium-phosphorus product; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; iPTH, intact parathyroid hormone; MBD, mineral and bone disease; N, number of subjects; nd, not documented; PTH, parathyroid hormone.

Symbols: * Overall or Arm 1 (Arm 2).

Note: No study reported vascular or valvular calcification at baseline.

Annotations:

a. Two patients in Arm 1 and no patients in Arm 2 had aluminum staining of bone at baseline.

b. Ionized Ca: 1.25 (1.27) mmol/L.

c. Immunoreactive PTH measured with an antibody directed against the midregion of the hormone.

Supplemental Table 26. Summary Table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs. placebo in CKD Stages 3-5 —intervention and results

Author, Year	N Follow-up CKD Stage	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Coyne, 2006[120] 3 RCTs	220	Paricalcitol Initial dose 2 or 4µg TIW or 1 or 2µg daily, depending on iPTH level, adjusted[a]	Placebo	Stable P binder regimen, if necessary[b]	%Δ eGFR[c]	-10.40% vs. -6.95% (NS)	C
					Mean Corrected Ca (mmol/L)	2.37 vs. 2.32 (nd)	A
					Mean P (mmol/L)	1.38 vs. 1.36 (NS)	A
	6 mo				‡ % with 2 consecutive measurements with iPTH >30% decrease from baseline	91% vs. 13% (<.001)	A
	3-5				Δ b-ALP (IU/L)	-8 vs. -1.5 (<.001)	A
Hamdy, 1995[40]	176	Alfacalcidol Initial dose 0.25µg/d, adjusted[d]	Placebo	Ca supplements Other P binders, if necessary[e]	Bone overall summary by WG[f]	Overall slightly favoring calcitriol because turnover better, mostly caused by improvement of HPT.	C
					Bone Turnover (N = 134)	Better (+30)	
	24 mo				Bone Mineralization	nd	
					Bone Volume	Same	
					Δ CrCl (mL/min)	-5.7 vs. -4.0 (NS)	C
					Δ Corrected Ca (mmol/L)	+0.07 vs. -0.01 (<.001)	C
	3-4				Δ P (mmol/L)	+0.13 vs. -0.06 (NS)	B
					Δ iPTH (pmol/L)	+0.6 vs. +8.1 (.001)	B
					Δ ALP (IU/L)	-5.7 vs. +19.8 (<.001)	B
Coburn, 2004[121]	55	Doxercalciferol Initial dose 1µg/d, adjusted up to 5µg/d[g]	Placebo	Ca-based P binder, if necessary[h]	Δ GFR (mL/min/1.73 m^2)	-4.7 vs. -2.5 (NS)[i]	C
					Mean corrected Ca (mmol/L)	2.30 vs. 2.25 (NS)	A
					Mean P (mmol/L)	1.38 vs. 1.27 (.047)	A
					Mean CaXP ($mmol^2/L^2$)	3.16 vs. 2.82 (<.05)	A
	6 mo				‡ iPTH (nmol/L)	12.5 vs. 17.7 (<.05)	A
					‡ % with 1 measurement of iPTH ≥30% decrease from baseline	74% vs. 7% (nd)	A
	3-4				%Δ b-ALP	-27.9% vs. nd (<.05)	B
Nordal, 1988[122]	30	Calcitriol For 1st 2 wk: 0.25µg/d, then 0.5µg/d[j]	Placebo	Al-containing P binders as needed to maintain P < 1.7 mmol/L	Bone overall summary by WG[f]	Bone formation increased in placebo group (many worsened) and decreased in calcitriol (some better, others developed adynamic). Mineralization and volume similar	C
	8 mo				Bone Turnover	nd	
					Bone Mineralization	Same	
	3-5				Bone Volume	Same	

	322 24 mo 3-4	Ca-Vit D Active comparator	Placebo	nd	In pts with GFR <60, proportion of patients with ≥30% reduction in PTH	42% vs. 5% (<.001)	B
	149 24 mo 3	Ca-Vit D fixed-combination (1 tablet 1200 mg of elemental Ca in the form of tricalcium phosphate and 800 IU of Vit D_3)	Placebo	nd	Δ iPTH (pmol/L) Δ 25(OH) Vit D (nmol/L) Δ Ca (mmol/L) Δ P (mmol/L) Δ b-ALP(ng/mL)	-0.2 vs. +0.1 (0.02) +50 vs. -10 (<.001) +0.02 vs. -0.05 (NS) +0.03 vs. +0.03 (NS) -1.2 vs. +3.6 (NS)	B B B B C
Kooienga, 2009 [123]	143 24 mo 3	Ca-Vit D separate (1 tablet 1200 mg elemental Ca in the form of tricalcium phosphate, and 2 tablets Vit D_3 400IU each)	Placebo	nd	Δ iPTH (pmol/L) Δ 25(OH) Vit D (nmol/L) Δ Ca (mmol/L) Δ P (mmol/L) Δ b-ALP (ng/mL)	-0.2 vs. +0.1 (0.02) +65 vs. -10 (<.001) +0.02 vs. -0.05 (<.05) 0.0 vs. +0.03 (NS) -1.6 vs. +3.6 (NS)	B B B B C
	64 24 mo 3-4	Ca-Vit D fixed-combination (1 tablet 1200 mg of elemental Ca in the form of tricalcium phosphate and 800 IU of Vit D_3)	Placebo	nd	Δ iPTH (pmol/L) Δ 25(OH) Vit D (nmol/L) Δ Ca (mmol/L) Δ P (mmol/L) Δ b-ALP (ng/mL)	-0.2 vs. +0.6 (0.02) +50 vs. -7 (<.001) 0.0 vs. 0.0 (NS) 0.0 vs. +0.03 (NS) -2.4 vs. +1.7 (NS)	B B B B C
	74 24 mo 3-4	Ca-Vit D separate (1 tablet 1200 mg elemental Ca in the form of tricalcium phosphate, and 2 tablets Vit D_3 400IU each)	Placebo	nd	Δ iPTH (pmol/L) Δ 25(OH) Vit D (nmol/L) Δ Ca (mmol/L) Δ P (mmol/L) Δ b-ALP (ng/mL)	-0.2 vs. +0.6 (0.02) +55 vs. -7 (<.001) +0.05 vs. 0.0 (<.05) +0.06 vs. +0.03 (NS) -2.0 vs. +1.7 (<.05)	B B B B C

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CaXP, Calcium-phosphorus product; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; Δ, change; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HPT, hyperparathyroidism; iPTH, Intact parathyroid hormone; IU, international units; N, number of subjects; nd, not documented; NS, not significant; PTH, parathyroid hormone; WG, work group.

Symbols: ‡ Primary outcome.

Annotations:

a. Initial dose dependent on iPTH level (> or ≤53 pmol/L). Either 2 µg or 4 µg, respectively for TIW dosing or 1 µg or 2 µg, respectively, for daily dosing. Dose titrated by 2 µg (TIW) or 1 µg (daily) according to Ca, P, and iPTH levels. Dose decreased if iPTH >60% from baseline, dose withheld if Ca >2.74 mmol/L. Patients were discontinued if iPTH >106 pmol/L on 2 consecutive measurements or if iPTH increased to >3 times baseline.

b. Calcitonin, bisphosphonates, and aluminum-containing phosphate binders were not allowed for more than 3 wk during the study.

c. Of patients with baseline dipstick proteinuria (N = 118), % with reductions in dipstick proteinuria were 51% vs. 25% (P = 0.004) [124].

d. 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.

e. 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.

f. See Supplemental Table 27.

g. 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.

h. No active vitamin D sterol other than doxercalciferol. Ca-based phosphate binders as needed and dose adjusted if Ca 2.6-2.7mmol/L or P >1.6 mmol/L. Dose increased if Ca ≤2.2 mmol/L.

i. Calculated.

j. Treatment suspended for 3 d if Ca ≥2.7 mmol/L. Dose was reduced by half until Ca <2.4 mmol/L.

Supplemental Table 27. Summary Table of the treatment of CKD-MBD with calcitriol or vitamin D analogs vs. placebo in CKD Stages 3-5—bone biopsy results

Author, Year	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ in Mlt	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients		d	% of TV
Hamdy, 1995[40]	Alfacalcidol	0	10	5	26	nd	nd	-1.7	1
	Placebo	6.5	6.5	3.2	0	*	*	*	0.9
Nordal, 1988[122]	Calcitriol	nd	~25	nd	nd	nd	nd	2	-3
	Placebo	nd	nd	nd	nd	nd	nd	1	0

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Mlt, mineralization lag time; nd, not documented; TV, trabecular volume.

Supplemental Table 28. Adverse events of calcitriol or vitamin D analogs in CKD Stages 3-5D

Author, Year Follow-up	N	Arm 1 / Arm 2	Hypercalcemia % Pts[a]	Hypercalcemia D/C	Hyperphosphatemia/Elevated CaXP % Pts[a]	Hyperphosphatemia/Elevated CaXP D/C	Other Reported AE (% Pts)	D/C due to Other Reported AE (% Pts)	Total D/C due to AE	Deaths	Modality Change
Stages 3-5											
Calcitriol or Vitamin D Analogs vs. Placebo											
Coyne, 2006[120] 6 mo	107	Paricalcitol	2 consecutive measurements Ca >2.62 mmol/L: 2%	—	2 consecutive measurements CaXP >4.44 mmol^2/L^2: 12%[b]	—	Any AE: 82%, SAE: 20%, Nausea: 6%, Vomiting: 6%, Rash: 2%	Bradycardia and elevated liver enzymes: 1%, Rash: 1%, nd: 4%	6%	2%	—
	113	Placebo	2 consecutive measurements Ca >2.62 mmol/L: 0%	—	2 consecutive measurements CaXP >4.44 mmol^2/L^2: 6%[b]	—	Any AE: 76%, SAE: 16%, Nausea 4%, Vomiting: 4%	nd: 4%	4%	1%	—
Hamdy, 1995[40] 24 mo	89	Alfacalcidol	†Ca 2.63-3.00 mmol/L: 11% Ca >3.00 mmol/L: 4%	0%	—	0%	GI: 7%, Pseudogout: 2%	Hypocalcemia: 0%	0%	4%	9%
	87	Placebo	†Ca 2.63-3.00 mmol/L: 3% Ca >3.00 mmol/L: 0%	0%	—	0%	GI: 1%	Hypocalcemia: 1%	0%	1%	11%
Coburn, 2004[121] 6 mo	27	Doxercalciferol	Ca >2.67 mmol/L: 4%[c]	0%[d]	CaXP ≥5.25 mmol^2/L^2: 0%[e]	0%	iPTH <1.6 pmol/L: 4%[f]	Congestive heart failure: 4%	4%	0%	4%
	28	Placebo	Ca >2.67 mmol/L: 4%[c]	0%	CaXP ≥5.25 mmol^2/L^2: 4%[e]	0%	—	MI: 4%, Neuromuscular symptoms: 4%, Unable to tolerate drug: 4%, Death 2° to cardiac arrest: 4%	12%	4%	4%
Nordal, 1998[122] 8 mo	15	Calcitriol	—[g]	0%	—	0%	—	Unilateral nephrectomy due to bleeding from polycystic kidney: 6%	6%	0%	0%
	15	Placebo	—[g]	0%	—	0%	—	—	0%	0%	7%
Stage 5D											
Calcitriol vs. Placebo											
Baker, 1986[125] 60 mo	38	Calcitriol	—	16%	—	—	PTx: 13%[h]	Unrelated diseases: 11%	26%	0%	29%
	38	Placebo	—	5%	—	—	PTx: 5%[h]	Unrelated diseases: 8%	13%	0%	24%
Calcitriol vs. Vitamin D Analogs											
Sprague, 2003[126] 3-8 mo	133	Calcitriol	Ca >2.87 mmol/L and/or CaXP >6.05 mmol^2/L^2: 64%	—	—[b]	—	—	—	—	—	—
	130	Paricalcitol	Ca >2.87 mmol/L and/or CaXP >6.05 mmol^2/L^2: 68%	—	—[b]	—	—	—	—	—	—
Hayashi, 2004[146] 12 mo	47	Calcitriol	Ca >2.87 mmol/L: 2%[i]	0%	P >1.94 mmol/L: 64%[j]	0%	—	—	0%	2%	0%
	44	Maxacalcitiol	Ca >2.87 mmol/L: 5%[i]	0%	P >1.94 mmol/L: 68%[j]	0%	—	—	0%	5%	2%
Intraperitoneal vs. PO-Pediatrics											
Salusky, 1998[127] 12 mo	16	IP Calcitriol	Ca >2.74 mmol/L: 50%	—	P >2.26 mmol/L: 13%	—	—	—	—	—	—
	17	PO Calcitriol	Ca >2.74 mmol/L: 29%	—	P >2.26 mmol/L: 18%	—	—	—	—	—	—

AE, adverse event; CaXP, Calcium-phosphorus product; D/C, discontinued; GI, gastrointestinal; IP, intraperitoneal; iPTH, intact parathyroid hormone; MI, myocardial infarction; N, number of subjects; nd, not documented; PTH, parathyroid hormone; PO, oral; pts, patients; PTx, parathyroidectomy; SAE, serious adverse event.

Symbols: "—" indicates data not documented; † 0.05< *P* <0.1 between groups, if documented.

Annotations:

a. Percentage of patients with one measurement above stated range unless otherwise noted.
b. Incidence of hyperphosphatemia not statistically significantly different between groups. Data not provided.
c. Hypercalcemia: doxercalciferol arm: two measurements in one patient; placebo arm: one measurement in one patient.
d. One patient had treatment suspended twice due to hypercalcemia.
e. Elevated CaXP: placebo arm: one measurement in one patient. % of measurements with elevated P: >2.10 mmol/L: 0.4% vs. 0.5%, >1.94 mmol/L: 2.6% vs. 0.5%, >1.61 mmol/L: 8.5% vs. 63.5%.
f. One measurement in one patient. Three additional patients received a reduction in treatment due to low PTH.
g. Seven patients completed the study without a hypercalcemic episode, arms not provided.
h. In calcitriol arm, five patients had parathyroid hyperplasia. In the placebo arm, one patient had parathyroid hyperplasia and one patient had parathyroid adenoma.
i. Maxacalcitol arm: two measurements in two patients; calcitriol arm: two measurements in one patient.
j. Maxacalcitol arm: 121 measurements in 30 patients; calcitriol arm: 112 measurements in 30 patients.

Supplemental Table 29. Ongoing RCTs examining the effect of vitamin D, calcitriol, or vitamin D analogs on CKD-MBD in CKD Stages 3-5

Name of Study (PI) Sponsor: Clinical Trial ID	Patient Population/ Inclusion Criteria	F/U	N	Experimental Group	Control Group	CKD-MBD Outcomes	Start Date	Status
Vitamin D Analogs vs. placebo								
Doxercalciferol in CKD[a] (Duggal) Genzyme: NCT00123461	Stages 3-4 iPTH >11.7 (stage 3) or >15.9 pmol/L (stage 4), 25(OH)D ≥75 nmol/L	6 mo	70	Doxercalciferol	Placebo	‡iPTH, Serum bone markers	2005	No longer recruiting
Fall prevention by Alfacalcidol (Pientka) Teva Pharm Ind./ Ruhr Univ. of Bochum: NCT00483275	Stage 3 Age >65 y, Nonsyncopal movement related falls	12 mo	484	Alfacalcidol	Placebo	Fractures, Hypercalcemia	2007	Not yet recruiting
VITAL[b] (Blakesley) Abbott: NCT00421733	Stages 2-4 GFR 25-75, Type II DM ACR 200-800 mg/g Ca ≤2.37 mmol/L iPTH 5.3-53 pmol/L	nd	258	Paricalcitol	Placebo	None listed	2007	Recruiting
Paricalcitol on proteinuria[c] (Schoen) Winthrop Univ. Hospital: NCT00469625	Stages 2-4 PCR >0.4 iPTH 2.1-26.5 pmol/L	6 mo	60	Paricalcitol	Placebo	Kidney disease progression	2006	Recruiting
PRIMO (Thadhani) Abbot/MGH: NCT00497146	Stages 3B-4[d] iPTH 3.7-37.1 pmol/L LVH by echo	12 mo	266	Paricalcitol	Placebo	Mortality, Hospitalizations	2007	Not yet recruiting
$1,25(OH)_2$ Vit D on the CV system[e] (Ivarsen) Univ. Aarhus: NCT00175149	SCr 150 – 600 µmol/L PTH 3-8X upper limit of normal	6 mo	40	1,25 dihydroxy-cholecalciferol	Placebo	None listed	2002	Recruiting
Paricalcitol on vessels-pilot[f] (Agarwal) Indiana Univ. School Med/ Abbott: NCT00428246	Stages 1-3	1.75 mo	24	Paricalcitol	Placebo	Kidney function	2006	Recruiting
Vitamin D Analogs vs. Native Vitamin D								
Cholecalciferol vs. Doxercalciferol[g] (Moe) Indiana U School of Med: NCT00285467	Stages 3-4 iPTH >10.6 (Stage 3) or >15.9 pmol/L (Stage 4), calcidiol ≤ 50 nmol/L	nd	58	Doxercalciferol	Cholecalciferol	‡ Pain and QOL, % reduction in PTH	2006	Recruiting

ACR, albumin to creatinine ratio; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; F/U, followup; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; LVH, left ventricular hypertrophy; MGH, Massachusetts General Hospital; N, number of subjects; nd, not documented; PCR, urine protein:creatinine ratio; PI, principal investigator; PTH, parathyroid hormone; PRIMO, Paricalcitol benefits in Renal failure Induced cardiac Morbidity; VITAL, Selective VITamin D Receptor Activator (Paricalcitol) for Albuminuria Lowering Study; QOL, quality of life; SCr, serum creatinine.

Notes: www.clinicaltrials.gov accessed September 2007.

Shaded rows indicate trials known to not meet inclusion criteria for this systematic review.

Symbols: ‡ Designated primary outcome(s).

Annotations:

a. A Phase 4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Assess the Safety and Efficacy of Doxercalciferol Capsules in Vitamin D-Replete Subjects With Chronic Kidney Disease (CKD) Stages 3 or 4 With Secondary Hyperparathyroidism (SHPT).
b. Selective VITamin D Receptor Activator (Paricalcitol) for Albuminuria Lowering Study: A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Paricalcitol Capsules on Reducing Albuminuria in Type 2 Diabetic Nephropathy Subjects Who Are Currently Being Treated With Renin-Angiotensin System Inhibitors.
c. A Study Of Oral Paricalcitol To Treat Proteinuric Renal Disease.
d. Stage 3B is undefined in www.clinicaltrials.org protocol but is usually defined as GFR 30-44 mL/min/1.73 m2.
e. The efficacy of 1,25 dihydroxycholecalciferol on the Cardiovascular System in Patients with Renal Dysfunction.
f. Anti-Inflammatory and Endothelial Protectant Effects of Paricalcitol.
g. Comparison of Cholecalciferol Versus Doxercalciferol in the Treatment of Secondary Hyperparathyroidism in Chronic Kidney Disease Stage Three and Four.

Supplemental Table 30. Summary Table of the treatment of CKD-MBD with calcitriol vs. placebo or vitamin D analogs in CKD Stage 5D—description of population at baseline

Author Year	N Country of Study	Age* % Male*	% Race*	Dialysis Vintage* Dialysate Calcium*	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	TMV Classification/ DEXA Score
Calcitriol vs. placebo/control								
Baker 1986[125a]	76 UK	42 nd	nd	20 mo 1.65 mmol/L	nd ~100%	Ca 2.48 (2.47) mmol/L[b] corrected P nd PTH 18.6 (26.5) pmol/L[b] Amino-terminal PTH IRMA [ref nd] ALP 66.3 (67.2) U/L[b]	Bone biopsy	See below
Calcitriol vs. Vitamin D Analogs								
Sprague 2003[126]	266 The Netherlands, Spain, Switzerland, USA	57 (57) 60 (54)	30 (26) Caucasian, 57 (62) African American, 13 (12) Other	0 to ≥12 mo[c] 2.5 mEq/L	nd nd	Ca 2.25 (2.25) mmol/L P 1.87 (1.91) mmol/L iPTH 71.6 (68.7) pmol/L Allegro-intact PTH [ref nd]	None	—
Hayashi, 2004[146]	91 Japan	56 (55) 87 (71)	nd	103 (77) mo 3.0 mEq/L	nd nd	Ca 2.27 (2.24) mmol/L corrected P 1.86 (1.83) mmol/L iPTH 63.5 (63.2) pmol/L Allegro-intact PTH [ref nd] b-ALP 30.0 (26.8) IU/L	None	—
Intraperitoneal vs. PO-Pediatrics								
Salusky, 1998[127]	46 US	13 (13) 56 (53)	nd	21 (27) mo 3.5 mEq/L	nd nd	Ca 2.27 (2.12) mmol/L P 2.00 (2.07) mmol/L PTH 68.7 (71.0) pmol/L Allegro-intact PTH [ref: nd] ALP 344 (354) IU/L	Bone biopsy	

ALP, Alkaline phosphatase; b-ALP, Bone-specific alkaline phosphatase; CKD-MBD, chronic kidney disease-mineral and bone disorder; DEXA, dual energy X-ray absorptiometry; DM, diabetes mellitus; iPTH, Intact parathyroid hormone; MBD, mineral bone disease; N, number of subjects; nd, not documented; PTH, Parathyroid hormone; PO, oral; TMV, Turnover, mineralization, volume.

Symbols: *Overall or Arm 1 (Arm 2).

Note: No study reported vascular or valvular calcifications at baseline.

Annotations:

a. Study conducted from 1977 to 1982.

b. Estimated from graph.

c. <1 y: 24% (24%); 1-5 y: 40% (45%); 5-10 y: 29% (16%); ≥10 y 7% (15%).

Supplemental Table 31. Summary Table of the treatment of CKD-MBD with calcitriol vs. placebo or vitamin D analogs in CKD Stage 5D—intervention and results

Author, Year	N / Follow-up / Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Calcitriol vs. placebo/control							
Baker, 1986[125a]	76 / 60 mo / HD	PO Calcitriol 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	Aluminum-based P binder adjusted to P 1.2-1.8 mmol/L	New Fractures	Rib: 1 vs. 1 Hand, feet, pelvis: 0 vs. 0	C
					Bone Histology N = 20 F/U=12-62 mo		
					Bone Overall Summary by WG[b]	Biopsy results somewhat favored calcitriol with better turnover and mineralization. Aluminum toxicity may have played an important role.[c]	C
					Bone Turnover	Better (+10)	
					Bone Mineralization	Better (+10)	
					Bone Volume	nd	
					Calcification by X-ray [N = nd]		
					Pts with increased CAC	0 vs. 2 (NS)	C
					Pts with increased calcification of vessels of the hands, feet, pelvis	14 vs. 20 (NS)	C
					Laboratory at 18 mo:		
					Median Corrected Ca (mmol/L)	2.59 vs. 2.50 (<.05)[d]	B
					Median PTH (pmol/L)	12.2 vs. 25.4 (<.05)[d]	B
					Median ALP (IU)	54 vs. 70 (<.05)[d]	B
Calcitriol vs. Vitamin D Analogs							
Sprague, 2003[126]	266 / 3-8 mo / HD	IV Calcitriol: Initial dose 0.01 µg/kg, adjusted up to 0.06 µg/kg[e]	IV Paricalcitol: Initial dose 0.4 µg/kg, adjusted up to 0.24 µg/kg[e]	Stable P binder[f]	‡[g] % Pts with ≥50% reduction in PTH from baseline	>80% vs. >80% (nd)	B
					Time to ≥50% reduction in PTH from baseline (days)	108 vs. 87 (.025)[h]	B
					Hypercalcemic and/or CaXP >75 at least once during treatment	68% vs. 64% (NS)	B
					Hypercalcemic and/or CaXP >75 for at least 2 consecutive blood draws	50% vs. 38% (.034)	B
					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%	B
Hayashi, 2004[146]	91 / 12 mo / HD	IV Calcitriol Initial dose 1 µg each HD session, adjusted[i]	IV Maxacalcitol Initial dose 5 or 10 µg depending on iPTH, adjusted[i,j]	Ca carbonate adjusted to P <1.94 mmol/L	‡ # pts with PTH <15.9 pmol/L[k]	13 vs. 18 (NS)	C
					Mean adjusted Ca (mmol/L)	2.37 vs. 2.42 (nd)[d,l]	C
					Mean P (mmol/L)	1.91 vs. 2.00 (NS)[d]	C
					Mean CaXP ($mmol^2/L^2$)	4.52 vs. 4.84 (NS)[d]	C
					Mean b-ALP (IU/L)	0.0136 vs. 0.0096 (NS)[d]	C

Author, Year	N / Follow-up / Modality	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
IP vs. PO-Pediatrics							
Salusky, 1998[127]	46 12 mo PD	IP Calcitriol Initial dose 1.0µg TIW. Increased in increments of 0.5µg each month if Ca levels remained <2.5mmol/L and P levels <1.94mmol/L	PO Calcitriol Initial dose 1.0µg TIW. Increased in increments of 0.5µg each month if Ca levels remained <2.5mmol/L and P levels <1.94mmol/L	Ca carbonate was primary P binder. Dose was adjusted monthly. Dietary intake of Ca, P and other nutrients was determined each month using 3-day diet diaries[m]	Bone Overall Summary by WG[b]	Overall not very many differences between these routes with slightly better turnover in the oral route.	C
					Bone Turnover	Better (+11)	
					Bone Mineralization	Same	
					Bone Volume	nd	

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CAC, cornary artery calcification; CaXP, calcium-phosphorous product; CKD-MBD, chronic kidney disease-mineral and bone disorder; F/U, followup; HD, hemodialysis; IP, intraperitoneal; iPTH, intact parathyroid hormone; IV, intravenous; N, number of subjects; nd, not documented; NS, not significant; PD, peritoneal dialysis; PO, oral; PTH, parathyroid hormone; QOL, quality of life; TIW, three times a week; WG, work group.

Symbols: ‡ Primary outcome.

Annotations:

a. Study conducted from 1977-1982.
b. See Supplemental Table 32.
c. Placebo group had worsening due to HPT but calcitriol worsened from adynamic bone disease.
d. Estimated from graph.
e. 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.
f. Predominantly Ca carbonate or Ca acetate (not sevelamer-HCl or aluminum containing binders).
g. PTH was designated as the primary outcomes; however, the power analysis was calculated for hypercalcemia.
h. Additional analyses regarding proportions are not statistically significant.
i. If Ca <2.87 mmol/L and iPTH >15.9 pmol/L, dose increased to 1.5 µg per HD session for calcitriol or 20 µg per HD session for maxacalcitiol. Dose discontinued or adjusted if Ca >2.87 mmol/L. Treatment stopped and restarted at lower dose if iPTH <15.9 pmol/L.
j. Initial dose of maxacalcitol 5 or 10 µg per HD session for iPTH < or >53 pmol/L, respectively.
k. Additional PTH outcomes: %Δ iPTH: 60.8% vs. 67.4% (NS). Estimated from graph: Mean iPTH (pmol/L): 36 vs. 36 (NS); Mean whole (1-84) PTH (pmol/L): 17.0 vs. 15.4 (NS); Ratio whole/whole-intact PTH: 2.4 vs. 2.25 (NS).
l. Time course of changes in Ca were significantly different.
m. Patients who developed persistent hypercalcemia with serum Ca >2.74 mmol/L during concurrent therapy with calcitriol and calcium carbonate were changed to dialysate containing 2.5 mEq/L of calcium. For those remaining hypercalcemic despite the use of low-calcium dialysate and reduced doses of calcium carbonate, aluminum hydroxide was added as an alternative phosphate-binding agent. Subjects were withdrawn from study if hypercalcemia persisted despite these maneuvers.

Supplemental Table 32. Summary Table of the treatment of CKD-MBD with calcitriol vs. placebo or vitamin D analogs in CKD Stage 5D—bone biopsy results

Study	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ in MIt	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients		d	% of TV
Baker, 1986[125]	Calcitriol	10	30	0	0	30	0	nd	nd
	Placebo	50	0	0	0	40	0	nd	nd
Salusky, 1998[127]	IP Calcitriol	0	44	0	37	0	0	nd	nd
	PO Calcitriol	12	29	0	23	6	0	nd	nd

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; IP, intraperitoneal; MIt, mineralization lag time; nd, not documented; PO, oral; TV, trabecular volume.

Supplemental Table 33. Ongoing RCTs examining the effect of vitamin D, calcitriol, or vitamin D analogs on CKD-MBD in CKD Stage 5D

Name of Study (PI) Sponsor: Clinical Trial ID	Patient Population/ Inclusion Criteria	F/U	N	Experimental Group	Control Group	CKD-MBD Outcomes	Start Date	Status
Native vitamin D vs. placebo								
Cholecalciferol on bone, function and QoL[a] (Lund) Creighton Univ/DCI: NCT00511225	Stage 5D	3.75 mo	60	Cholecalciferol	Placebo	‡Physical performance, Bone pain , Neuromuscular function, QOL	2007	Not yet recruiting
Active vitamin D sterols vs. Calcitriol or Vitamin D Analogs								
Zemplar vs. Calcijex[b] (PI: nd) Abbott: NCT00062699	Stage 5D on HD requiring Vit D therapy	nd	2200	Paricalcitol	Calcitriol	‡Time to death, time to CV mortality, Hospitalizations,	2003	Terminated
Zemplar vs. Hectorol[c] (Lund) Abbott: NCT00257920	Stage 5D on HD iPTH ≥21.2 pmol/L; Ca <2.54 mmol/L; P <2.10 mmol/L; CaXP <5.25 $mmol^2/L^2$	nd	42	Paricalcitol	Doxercalciferol	‡Ca absorption fraction, Harms, iPTH	2006	Recruiting
Alfacalcidol vs. paricalcitol in uremic pts[d] (Hansen) Roskilde County Hospital: NCT00469599	Stage 5D on HD iPTH >37.1 pmol/L P <1.8 mmol/L Ca <1.25 mmol/L Max dose Ca-containing P binder	16 wk	117	Paricalcitol	Alfacalcidol	‡iPTH, CaXP, 25 (OH) Vit D, ALP, PTx	2007	Recruiting
Dose Comparison Studies								
Vitamin D on CAC[e] (Tumlin) Southeast Renal Research Institute: NCT00502268	Stage 5D on HD CAC >130 Hounsfield units iPTH 10.6-106 pmol/L Stable P binder dose	12 mo	50	Vitamin D_2	Dose comparison	‡%Δ CAC	2007	Not yet recruiting
Paricalcitol on Markers of Inflammation[f] (Kaplan) Fresenius/Abbott: NCT00294866	Stage 5D on HD iPTH 15.9-42.4 pmol/L Ca <2.54 mmol/L P <2.26 mmol/L	4wk	50	Paricalcitol	Dose comparison	PTH, Ca, P	2006	No longer Recruiting
Hectorol dosing[g] (Duggal) Genzyme: NCT00463021	Stage 5D on HD Stable paricalcitol dose iPTH 15.9-63.6 pmol/L Ca <2.50 mmol/L P <2.26 mmol/L	2.5 mo	36	Doxercalciferol	Dose comparison	None listed	2007	Recruiting

ALP, alkaline phosphatase; CAC, coronary artery calcification; CaXP, calcium-phosphorus product; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; Δ, change; F/U, followup; HD, hemodialysis; iPTH, intact parathyroid hormone; N, number of subjects; nd, not documented; PI, principal investigator; PTH, parathyroid hormone; PTx, parathyroidectomy; QOL, quality of life

Notes: www.clinicaltrials.gov accessed September 2007.

Shaded rows indicate trials known to not meet inclusion criteria for this systematic review.

Symbols: ‡ Designated primary outcome(s).

Annotations:

a. Effects of Oral Cholecalciferol (Vitamin D3) on Bone Health, Neuromuscular Function, and Quality of Life in Adults With Chronic Kidney Disease.

b. A Phase IV, Prospective, Randomized, Active-Controlled, Double-Blind, Double-Dummy, Multi-Center Study to Evaluate the Survival Benefits of Zemplar Relative to Calcijex in Subjects With Stage V Chronic Kidney Disease on Hemodialysis.
c. A Phase 4, Single-Center, Open-Label, Randomized, Active-Controlled, Cross-Over Pilot Study to Evaluate the Effects of Two Vitamin D Analogs, Zemplar Injection and Hectorol Injection, on Intestinal Absorption of Calcium in CKD Stage 5 Subjects on Hemodialysis.
d. Treatment of Secondary Hyperparathyroidism in the Uremic Patient. A Study Comparing Alfacalcidol and Paricalcitol.
e. A Prospective, Randomized, Open-Label Trial Investigating the Effect of 1α Hydroxy Vitamin D2 on the Development of Coronary Calcification in New ESRD Patients Using the 1-84/7-84 PTH Ratio to Determine Dosing.
f. An Open Label, Multi-Center Study of the Effect of Paricalcitol on Markers of Inflammation in Patients With Stage 5 Chronic Kidney Disease on Hemodialysis.
g. A Phase 4, Multi Center, Open-Label, Randomized Study to Determine Clinically Appropriate Doses of Hectorol® (Doxercalciferol Capsules) When Converting From Zemplar® (Paricalcitol Injection) for the Treatment of Secondary Hyperparathyroidism in Stage 5 Chronic Kidney Disease (CKD) Subjects on Hemodialysis.

Supplemental Table 34. Summary Table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD Stage 5D—description of population at baseline

Author, Year	N Country of Study	Age* % Male*	% Race*	Dialysis Vintage* Dialysate Calcium*	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation	Vasc. / Valv. Calcification Imaging
Block, 2004[128] 2 RCTs	741 Australia, Europe, N. America	54 (55) 61 (62)	White: 56 (61) Black: 35 (32) Other: 9 (7)	72 (72) mo nd	30 (29) nd	Ca 2.47 (2.47) mmol/L P 2.00 (2.00) mmol/L PTH 68.2 (68.1) pmol/L Allegro-intact PTH b-ALP 23.3 (24.2) ng/mL	None	None
Lindberg, 2005[129] 1 RCT	395 Australia, Canada, USA	52 (54) 62 (63)	White: 39 (39) Black: 39 (35) Other: 22 (26)	56 (64) mo nd	nd nd	Ca 2.44 (2.50) mmol/L P 1.97 (1.97) mmol/L iPTH 89.9 (88.2) pmol/L Allegro-intact PTH ALP nd	None	None
Cunningham, 2005[130] 4 RCTs Block[128] + Lindberg[129]	1136 as above + 48 Australia, Europe, N. America	53 (55) 61 (63)	White: 48 (55) Black: 38 (34) Other: 14 (10)	66 (70) mo nd	31 (32) nd	Ca 2.47 (2.47) mmol/L P 2.00 (2.00) mmol/L PTH 77.5 (72.3) pmol/L nd ALP nd	None	None
Malluche, 2008[131]	48 Europe, US	50 (52) 63 (69)	White: 37 (38) Black: 53 (62) Other: 11 (0)	nd nd	nd nd	Ca 2.45 (2.42) mmol/L P 2.20 (2.13) mmol/L iPTH 75.6 (74.5) pmol/L Allegro-intact PTH biPTH 43.6 (43.1) pmol/L Bio-Intact PTH (Nichols) ALP 34.6 (43.1) ng/mL	Bone biopsy	None

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; biPTH, bio-intact parathyroid hormone; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; iPTH, intact parathyroid hormone; MBD, mineral bone disease; N, number of subjects; nd, not documented; PTH, parathyroid hormone; RCT, randomized controlled trial.
Symbols: *Overall or Arm 1 (Arm 2).

Supplemental Table 35. Summary Table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD Stage 5D—intervention and results

Author, Year	N / Follow-up / Modality	Arm 1 / Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Block, 2004 [128] *2 RCTs* [Extension study Sterrett, 2007[1320]]	741 / 6 mo / HD	Cinacalcet 30-180 mg/d PO, adjusted if iPTH >21.2 pmol/L and Ca >1.95 mmol/L[a] / Placebo	Current standards of care concerning P binder and vitamin D use, dialysate Ca unadjusted[b]	‡ %pts with PTH ≤26.5 pmol/L	43% vs. 5% (<.001) OR 7.3 (CI 4.8-11.1)[c]	B
				%pts with ≥30% decrease PTH	64% vs. 11% (<.001) OR 15.38 (CI 10.31-22.95)[d]	B
				%Δ iPTH	–43% vs. +9% (<.001)[e]	B
				%Δ Ca	–6.8% vs. +0.4% (<.001)	B
				%Δ P	–8.4% vs. +0.2% (<.001)	B
				%Δ CaXP	–14.6% vs. +0.5% (<.001)	B
				%Δ b-ALP	–35.1% vs. -4.0% (<.001)	B
Lindberg, 2005[129] *1 RCT*	395 / 6 mo / HD 91% PD 9%	Cinacalcet 30-180 mg/d adjusted at 4 wk intervals if iPTH >21.2 pmol/L and Ca >1.95 mmol/L[f] / Placebo	Previously prescribed P binders and/or vitamin D, dialysate Ca adjusted[g]	‡ %pts with mean iPTH ≤26.5 pmol/L[h]	39% vs. 7% (<.001)	B
				%pts with a reduction in iPTH ≥30%[i]	65% vs. 13% (<.001)	B
				%Δ iPTH	–40.3% vs. +4.1% (<.001)	B
				%Δ Ca	–6.5% vs. +0.9% (<.001)	B
				%Δ P	–7.2% vs. –2.2% (<.05)	B
				%Δ CaXP[j]	–12.8% vs. –1.4% (<.001)	B
Moe, 2005[148] *3 RCTs: Block[128] + Lindberg[129]*	1136 as above / 6 mo / 96% HD 4% PD	See above	See above	%pts with iPTH <31.8 pmol/L	56% vs. 10% (<.001)	B
				%pts with iPTH 15.9-31.8 pmol/L	33% vs. 9% (nd)	B
				% pts with Ca 2.10-2.37 mmol/L	49% vs. 24% (<.001)	B
				% pts with P 1.13-1.78 mmol/L	46% vs. 33% (<.001)	B
				% with CaXP <4.44 mmol^2/L^2	65% vs. 36% (<.001)	B
				%pts with iPTH <31.8 pmol/L AND CaXP <4.44 mmol^2/L^2	41% vs. 6% (<.001)	B
Cunningham, 2005[130] *4 RCTs: Block[128] + Lindberg[129]*	1136 as above + 48 / 6 mo (12 mo for up to N=314) / 96% HD 4% PD	See above	See above	Mortality (per 100 pt-yr)	5.2 vs. 7.4 (NS) HR 0.81 (CI 0.45-1.45)	C
				All cause Hospitalizations (per 100 pt -yr)	67.0 vs. 71.0 (NS) HR 1.03 (CI 0.87-1.22)	C
				CV Hospitalizations (per 100 pt-yr)[k]	15.0 vs. 19.7 (0.005) HR 0.61(CI 0.43-0.86)	C
				Quality of Life (N=876)		C
				ΔSF-36 Physical component summary	+0.5 vs. –0.8 (.01)	C
				ΔSF-36 Bodily pain	+0.6 vs. –1.0 (.03)	C
				ΔSF-36 General health perception	+0.2 vs. –1.0 (.02)	C
				ΔAll Other SF-36 domains[l]	NS	C
				ΔKDQOL Cognitive functioning	+0.2 vs. –0.8 (NS)	C
				Fracture (per 100 pt-yr)	3.2 vs. 6.9 (.04) HR 0.46 (CI 0.22-0.95)	C
				PTx (per 100 pt-yr)	0.3 vs. 4.1 (.009) HR 0.07 (CI 0.01-0.55)	C

Author, Year	N Follow-up Modality	Arm 1 Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Malluche, 2008[131]	48 12 mo HD	Cinacalcet Initial dose of 30 mg/d increasing incrementally to 50, 70, 90, 120 and 180 mg/d to achieve PTH ≤21.2 pmol/L[m] Placebo Initial dose of 30 mg/d increasing incrementally to 50, 70, 90, 120 and 180 mg/d to achieve PTH ≤21.2 pmol/L	No restrictions on P binder. Vitamin D also permitted with guidelines to maintain constant dose but changes were permitted if safety thresholds were met.	Bone Overall Summary by WG[n] Bone Turnover Bone Mineralization Bone Volume	Turnover improved more often in the placebo patients Worse (–27) Same Better (+4.3)	C

b-ALP, bone-specific alkaline phosphatase; CaXP, calcium-phosphorus product; CI, confidence interval; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; Δ, change; HD, hemodialysis; HR, hazard ratio; iPTH, intact parathyroid hormone; KDQOL, Kidney Disease Quality of Life Instrument; N, number of subjects; nd, not documented; NS, not significant; OR, odds ratio; PD, peritoneal dialysis; PTH, parathyroid hormone; PTx, parathyroidectomy; pt-yr, patient-year; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36; WG, work group.

Symbols: ‡ Primary outcome.

Annotations:

a. 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.

b. 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).

c. Adjusted for baseline PTH and CaXP.

d. Statistical adjustments not documented.

e. %Δ bio-intact PTH (N = 410 in N. American centers): -38% vs. +23% (<.001).

f. 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.

g. 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.

h. % of patients with mean iPTH ≤31.8 pmol/L (300 pg/mL): 46% vs. 9% (p<.001).

i. % of patients with reduction of iPTH ≥20%: 74% vs. 21% (p<.001); ≥40%: 60% vs. 10% (p<.001); ≥50%: 48% vs. 6% (p<.001).

j. % 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).

k. Non-CV hospitalizations (per 100 pt-yr): HR 1.16 (0.96-1.39); hospitalizations unrelated to CVD, Fracture or PTx (per 100 pt-yr): HR 1.18 (0.98-1.42).

l. ΔMental component summary, ΔPhysical functioning, ΔRole limitations – physical, Δ Social functioning, ΔVitality, ΔRole limitations – emotional, and ΔEmotional well being.

m. Dosage of study medication could be increased every 4 weeks unless PTH from the preceding visit was ≤21.2 pmol/L, maximum dosage of 180 mg had been reached, serum Ca <1.95 mmol/L, or patient experienced symptoms of hypocalcemia or an adverse event precluded increase in dosage. Reduction in the dosage was made if PTH <10.6 pmol/L on two consecutive study visits, serum Ca <1.87 mmol/L, or patient reported symptoms of hypocalcemia when vitamin D could not be increased.

n. See Supplemental Table 36.

o. 543 patients completed 6 months of parent study. Of those, 266 participated in the extension study for a total of 52 weeks. Rates of treatment discontinuation in extension study due to AEs were 10% in cinacalcet group and 0% in control group. Treatment with cinacalcet was associated with sustained clinically significant reduction in PTH.

Supplemental Table 36. Summary Table of RCTs examining the treatment of CKD-MBD with calcimimetics in CKD Stage 5D—bone biopsy results

Study	Arm	Bone Turnover				Bone Mineralization			Bone Volume
		Worsened		Improved		Worse	Better	Mean Δ in Mlt	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients		d	% of TV
Malluche, 2008[131]	Cinacalcet	10	16	0	21	0	0	9	+3.9
	Placebo	23	0	7	38	nd	0	9	–0.4

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Mlt, mineralization lag time; nd, not documented; RCT, randomized controlled trial; TV, trabecular volume.

Supplemental Table 37. Adverse events of calcimimetics vs. placebo in CKD Stage 5D

Author, Year Follow-up	N	Arm 1 / Arm 2	Gastrointestinal AE % Pts	Gastrointestinal AE D/C	Transient Hypocalcemia % Pts	Transient Hypocalcemia D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths	Modality Change
Block, 2004[128] 6 mo	371	Cinacalcet	§Nausea: 32% §Vomiting: 30%[a]	<5%	§2 consecutive measurements Ca <1.9 mmol/L: 5%	<1%	*Upper respiratory tract infection: 7% *Hypotension: 6%, All AE: 91%	—	15%	2%	4%
	370	Placebo	§Nausea: 19% §Vomiting: 16%	<1%	§2 consecutive measurements Ca <1.9 mmol/L: 1%	<1%	*Upper respiratory tract infection: 13% *Hypotension: 12%, All AE: 94%	—	7%	2%	4%
Lindberg, 2005[129] 6 mo	294	Cinacalcet	Nausea: 30% Vomiting: 23% Diarrhea: 24%	9%	% of measurements Ca <1.9 mmol/L: 5%	0%	Upper respiratory tract infection: 18% PTx: 0%, Headache: 17%, Asthenia: 8% Abdominal pain: 12%, Hypotension: 7%, All AE: 91%, SAE: 27%, Treatment related SAE: 2%	—	13%	1%	3%
	101	Placebo	Nausea: 22% Vomiting: 12% Diarrhea: 19%	3%	% of measurements Ca <1.9 mmol/L: <1%	0%	Upper respiratory tract infection: 13% PTx: 2%, Headache: 12%, Asthenia: 2% Abdominal pain: 18%, Hypotension: 12% All AEs 93%, SAE: 26%, Treatment related SAE: 2%	—	8%	2%	6%
Malluche, 2008[131] 24 mo	32	Cinacalcet	Dyspepsia, Nausea and Vomiting: 13%	13%	—	—	—	—	>13%	9%	—
	16	Placebo	0%	0%	—	—	—	—	nd	13%	—

AE, adverse event; D/C, discontinued; N, number of subjects; nd, not documented; pts, patients; PTx, parathyroidectomy; SAE, serious adverse event.
Symbols: "—" indicates data not documented; § *P* <0.001 between groups, if documented; * *P* <0.05 between groups, if documented.
Annotations:
a. Vomiting, but not nausea, occurred more frequently at higher doses of cinacalcet.

Supplemental Table 38. Ongoing RCTs examining the effect of calcimimetics on CKD-MBD

Name of Study (PI) Sponsor: Clinical Trial ID	Patient Population/ Inclusion Criteria	F/U	N	Experimental Group	Control Group	CKD-MBD Outcomes	Start Date	Status
CKD Stages 3-5								
Cinacalcet in CKD 3-4[a] (nd) Amgen: NCT00094484	Stages 3-4 iPTH >10.6 (Stage 3) or >17.0 pmol/L (Stage 4) Ca ≥2.25 mmol/L	32 wk	400	Cinacalcet	Placebo	‡% pts with reduction in iPTH ≥ 30%, Δ iPTH, Harms	2004	Completed
CKD Stage 5D								
EVOLVE (nd) Amgen: NCT00345839	Stage 5D on HD PTH ≥31.8 pmol/L Ca ≥2.1 mmol/L CaXP ≥3.63 $mmol^2/L^2$	nd	3800	Cinacalcet	Placebo	‡All-cause mortality and nonfatal CV events, Mortality, CV events, Fracture, PTx	2006	Recruiting
ACHIEVE (nd) Amgen: NCT00135304	Stage 5D on HD iPTH 150-800 pmol/L Ca >2.10 mmol/L	nd	170	Cinacalcet + vitamin D	Placebo + vitamin D	‡% of pts achieving KDOQI targets for iPTH and CaXP, Ca, P, CaXP	2005	No longer recruiting
ADVANCE (nd) Amgen: NCT00379899	Stage 5D on HD	1 y	330	Cinacalcet + low dose vitamin D	Vitamin D	‡ΔCAC, AVC, PTH, Ca, P, CaXP, Harm	2006	Recruiting

ACHIEVE, Optimizing the Treatment of Secondary Hyperparathyroidism: A Comparison of Sensipar and Low Dose Vitamin D vs. Escalating Doses of Vitamin D Alone; ADVANCE, A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects With Chronic Kidney Disease (CKD) Receiving Hemodialysis; AVC, aortic valve calcification; CaXP, calcium-phosphorus product; CAC, coronary artery calcification; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; Δ, change; EVOLVE, Evaluation Of Cinacalcet HCl Therapy to Lower CardiVascular Events; F/U, followup; HD, hemodialysis; iPTH, intact parathyroid hormone; KDOQI, Kidney Disease Outcomes Quality Initiative; N, number of subjects; nd, not documented; PI, principal investigator; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.

Note: www.clinicaltrials.gov accessed Sept 2007.

Symbols: ‡ Designated primary outcome(s).

Annotations:

a. A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Chronic Kidney Disease Subjects With Secondary Hyperparathyroidism Not Receiving Dialysis.

Supplemental Table 39. Summary Table of the treatment of CKD-MBD with bisphosphonates in CKD Stages 3-5—description of population at baseline

Author, Year Study Type	N Country of Study	Age* % Male*	% Race*	CKD Stage Kidney Function	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	DXA Score/Fractures*
Jamal, 2007[133] Posthoc analysis[a]	581 USA	75 0	97 White	3 <45 mL/min/1.73 m^2	nd nd	Ca 2.4 mmol/L P 1.13 mmol/L PTH 3.8 pmol/L Allegro-intact PTH [ref: nd] ALP 83.3 U/L	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, total hip (g/cm^2) % vertebral fracture	0.54 0.78 0.63 42%
Miller, 2005[41] Posthoc analysis of 9 trials[b]	572[c] Asia, Australia, Europe, N. America	83 (83) 0	nd	4-5 26.4 (27.2) mL/min/1.73 m^2	nd nd	nd	BMD, femoral T Score BMD, lumbar spine T score >1 prevalent vertebral fracture by X-ray	-3.15 (-3.10) -3.23 (-2.93) 57% (64%)
	4071[d] As above	77 (78) 0	nd	3 41.5 (41.4) mL/min/1.73 m^2	nd nd	nd	BMD, femoral T Score BMD, lumbar spine T score >1 vertebral fracture by X-ray	-2.74 (-2.74) -2.78 (-2.75) 58% (54%)

ALP, alkaline phosphatase; BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; DM, diabetes mellitus; DXA: dual-energy x-ray absorptiometry; GN, glomerulonephritis; MBD, mineral bone disease; N, number of subjects; nd, not documented; PTH, parathyroid hormone; Pts, Patients; SCr, serum creatinine.

Symbols: *Overall or Arm 1 (Arm 2).

Notes: No studies report imaging of vascular or valvular calcifications.

Annotations:

a. Exclusion criteria for original studies included SCr ≥1.1 or ALP or >1.5 times the upper limit of normal.

b. Exclusion criteria included SCr >122 μmol/L, PTH >9.0 pmol/L in isolation, or PTH >6.9 pmol/L in combination with abnormal Ca, ALP, or P.

c. Severe renal impairment group.

d. Moderate renal impairment group.

Supplemental Table 40. Summary Table of the treatment of CKD-MBD with bisphosphonates in CKD Stages 3-5—intervention and results

Author, Year Study Type	N Follow-up CKD Stage	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
Jamal, 2007[133] Posthoc analysis	581 Mean 36 mo[a] 3[b]	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)[c]	C
					Vertebral fractures by X-ray	OR 0.72 (95% CI 0.31-1.7)[c]	C
					%Δ BMD, femoral neck, compared with placebo	+5.0% (95% CI 4.0%-5.9%)[c]	C
					%Δ BMD, spine, compared with placebo	+6.7 (95% CI 5.7%-7.8%)[c]	C
					%Δ BMD, total hip, compared with placebo	+5.6% (95% CI 4.8%-6.5%)[c]	C
Miller, 2005[41] Posthoc analysis of 9 trials[d]	572 Mean 22 mo 4-5	Risedronate 5 mg/d	Placebo	≤1000 mg/d elemental Ca and 500 IU/d of vitamin D, if necessary[e]	New vertebral fractures by X-ray (N = 232)	14% vs. 28% (unclear)[f]	C
					%Δ BMD, lumbar spine	+4.23% vs. -1.37% (<.001)	C
					%Δ Ca, compared with placebo	-0.3% (NS)[f]	C
					%Δ P, compared with placebo	-3.5% (<0.05)[f]	C
					%Δ SCr, compared with placebo	+0.4% (NS)[f]	C
	4071 Mean 25 mo 3	Risedronate 5 mg/d	Placebo	≤1000 mg/d elemental Ca and 500 IU/d of vitamin D, if necessary[e]	New vertebral fractures by X-ray (N = 2426)	13% vs. 19% (unclear)[f]	C
					%Δ BMD, lumbar spine	+4.33% vs. -0.47% (<.001)	C
					%Δ Ca, compared with placebo	-0.4% (NS)[f]	C
					%Δ P, compared with placebo	-1.3% (NS)[f]	C
					%Δ SCr, compared with placebo	+0.3% (NS)[f]	C

BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; Δ, change; DXA, dual-energy x-ray absorptiometry; iPTH, intact parathyroid hormone; N, number of subjects; NS, not significant; OR, odds ratio; PTH, parathyroid hormone; Pts, patients; SCr, serum creatinine.

Note: *P*-value is designated as "unclear" if the reporting of the data is unclear.

Annotations:

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

b. 581 patients were in the severely reduced GFR <45 mL/min/1.73 m2 category. Only this group is summarized in the table. eGFRs were obtained using the Cockcroft-Gault formula where lean body mass was obtained from whole-body DXA.

c. Results in subgroup with osteoporosis at baseline (N = nd) 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%).

d. Risedronate was evaluated in the treatment of postmenopausal osteoporosis in six studies, in the prevention of postmenopausal osteoporosis in one study, and in the prevention and treatment of glucocorticoid-induced osteoporosis in one study each.

e. Up to 1 g of elemental Ca daily. In seven of nine studies, if 25(OH)D <40 nmol/L at baseline, then patients received 500 IU/d of vitamin D.

f. Estimated from graph.

Supplemental Table 41. Adverse Events of bisphosphonates in CKD Stages 3-5

Author, Year Follow-up	CKD Stage	N	Arm 1 / Arm 2	Kidney Function % Pts	Kidney Function D/C	Gastric Discomfort % Pts	Gastric Discomfort D/C	Other Reported AE (% Pts)	D/C due to Other Reported AE (% Pts)	Total D/C due to AE	Deaths
Miller, 2005[41a] 25 mo	4-5	301	Risedronate	Kidney function related AE: 3%[b]	—	—	—	All AE: 87% Urinary/kidney AE: 19%[c]	—	—	—
		271	Placebo	Kidney function related AE: 3%[b]	—	—	—	All AE: 91% Urinary/kidney AE: 20%[c]	—	—	—
	3	2034	Risedronate	Kidney function related AE: 1%[b]	—	—	—	All AE: 91% Urinary/kidney AE: 18%[c]	—	—	—
		2037	Placebo	Kidney function related AE: 2%[b]	—	—	—	All AE: 90% Urinary/kidney AE: 18%[c]	—	—	—

AE, adverse event; CKD, chronic kidney disease; D/C, discontinued; N, number of subjects; Pts, patients.
Note: Jamal 2007[133]: No AEs reported by treatment arm in CKD subgroup.
Symbols: "—" indicates data not documented.
Annotations:
a. Posthoc analysis of nine trials.
b. Specific kidney function–related AEs include hematuria, hydronephrosis, kidney failure, acute kidney failure, abnormal kidney function, uremia, oliguria, polyuria, glomerulitis, and nephritis.
c. Includes AEs included specific kidney function–related AEs plus other events from the COSTART urogenital body system that were related to urinary function or kidney disease.[134] Most common urinary- and kidney-related AE was urinary tract infection.

Supplemental Table 42. Ongoing RCTs examining the effect of bisphosphonates on CKD-MBD

Name of Study (PI) Sponsor: Clinical Trial ID	Patient Population/ Inclusion criteria	F/U	N	Experimental Group	Control Group	CKD-MBD Outcomes	Start Date	Status/Projected End Date
CKD Stages 3-5								
Alendronate on calcification[a] (Kerr) Monash Univ: NCT00395382	Stage 3 No recent fractures	12 mo	50	Alendronate	Control	‡Calcification of superficial femoral artery and aorta by CT, CV events, ΔBMD, Ca, P, PTH, Fractures, Hypocalcemia, Harms	2007	Recruiting
Ibandronate and Alendronate in postmenopausal women[b] (nd) Hoffmann-La Roche: NCT00503113	Stages 3-5 Female, >65 y Osteoporosis	3-12 mo	500	Ibandronate	Alendronate	‡Kidney function	2007	Recruiting
CKD Stage 5D								
Alendronate in PD pts[c] (Kao) Nat. Taiwan Univ. Hospital: NCT00261625	Stage 5D on PD CaXP ≥4.04 $mmol^2/L^2$ AoC or CAC by MSCT	6 mo	50	Alendronate	Control	‡CAC, ‡AoC, ‡BMD P, Ca, iPTH, ALP, Lipids, Harms	2005	Not yet recruiting
Alendronate on Vascular Calcification[d] (Lai) Far Eastern Memorial Hospital: NCT00299572	Stage 5D on PD CaXP >4.44 $mmol^2/L^2$ AoC or CAC by X-ray	4 mo	50	Alendronate	Control	‡ΔCAC, ‡ΔAoC, ‡ΔBMD, PTH, Ca, P, ALP, Lipids, Harms	2006	Not yet recruiting
CKD Stages 1-5T								
Risedronate to prevent bone loss in CKD-T[e] (Coco) Montefiore Med. Ctr: NCT00266708	KTR at transplant	12 mo	60	Risedronate	Placebo	‡Bone turnover by biopsy and BMD	2002	No longer recruiting
Ibandronate in KTR[f] (Smerud) Smerud Med Research Int.: NCT00423384	Stages 1-3T Ca <2.55 mmol/L	12 mo	130	Ibandronate + Ca and Active Vit D	Placebo + Ca and Active Vit D	‡Δ BMD at lumbar, ΔBMD at hip, radius and femur, Height, Biochemistries, QOL, Harms	2007	Recruiting

AoC, aortic calcification; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; AVC, aortic valve calcification; BMD, bone mineral density; CAC, coronary artery calcification; CKD-MBD, chronic kidney disease-mineral and bone disorder; CT, computed tomography; CV, cardiovascular; Δ, change; F/U, followup; iPTH, intact parathyroid hormone; KTR, kidney transplant recipient; MVC, medial vascular calcification; MSCT, multislice spiral computed tomography; N, number of subjects; nd, not documented; PD, peritoneal dialysis; PI, principal investigator; PTH, parathyroid hormone; QOL, quality of life.

Notes: www.clinicaltrials.gov accessed September 2007.

Shaded rows indicate trials known to not meet inclusion criteria for this systematic review.

Symbols: ‡ Designated primary outcome(s).

Annotations:

a. Randomized Controlled Trial of the Effect of Alendronate on Vascular Calcification and Arterial Stiffness in Chronic Kidney Disease: A Pilot Study.
b. A Randomized, Open Label Study Evaluating the Effect on Renal Function of Intravenous Bonviva Given by Injection or Infusion, Compared With Oral Alendronate, in Postmenopausal Women With Osteoporosis at High Risk for Renal Disease.
c. Can Alendronate Suppress Aortic and Coronary Artery Calcification and Improve Bone Mineral Density in Chronic Peritoneal Dialysis Patients?
d. Can Alendronate Suppress Aortic and Coronary Artery Calcification and Improve Bone Mineral Density in Chronic Peritoneal Dialysis Patients?
e. Randomized Trial of Risedronate to Prevent Bone Loss in Renal Transplant.
f. Ibandronate Versus Placebo as Add-on to Active Vitamin D and Calcium in the Prevention of Bone Loss After Renal Transplantation.

Supplemental Table 43. Summary Table of the treatment of CKD-MBD with other bone treatments in CKD Stages 3-5 and 5D—description of population at baseline

Author, Year	N Country of Study	Age* % Male*	% Race*	CKD Stage Kidney Function	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	DXA Score/Fractures*
CKD Stage 5D								
Hernández, 2003[135]	50 Venezuela	63 (62) 0	nd	5D on HD —	0% nd	Ca 2.31 (2.26) mmol/L P 1.65 (1.52) mmol/L iPTH 34.0 (40.6) pmol/L Nichols Allegro IRMA [ref: nd]	BMD, femoral neck (g/cm^2) BMD, L2-L4 (g/cm^2)	0.722 (0.745)[a] 0.942 (0.952)[b]
CKD Stages 3-5								
Ishani, 2008[136]	3493 Canada	67 (67) 0	White 97 (97)	Stage 3 CrCl 45-59 mL/min	3 (4) nd	Ca nd P nd PTH 3.6 (3.6) pmol/L nd 25(OH) Vit D 72 (72)	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, trochanter (g/cm^2) % Pts with prevalent vertebral fractures	0.62 (0.62) 0.81 (0.81) 0.55 (0.55) 0: 65 (60) 1: 20 (21) 2: 16 (19)
	1480 Canada	72 (72) 0	White 97 (96)	Stages 3-5 CrCl <45	3 (4) nd	Ca nd P nd PTH 3.7 (3.9) pmol/L nd 25(OH) Vit D 75 (73)	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, trochanter (g/cm^2) % Pts with prevalent vertebral fractures	0.59 (0.59) 0.79 (0.79) 0.52 (0.52) 0: 54 (58) 1: 22 (20) 2: 25 (22)
Miller, 2007[137] Posthoc analysis[c]	648 USA	72 (72) [71] 0	nd	Stages 2-3 68 (68) [67] mL/min/1.73 m^2	nd nd	Ca nd P nd PTH 3.3 (3.5) [3.5] pmol/L Assay: nd	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) % Pts with prevalent vertebral fractures	0.63 (0.61) [0.62] 0.81 (0.79) [0.79] 89% (88%) [86%]
	83 USA	77 (78) [78] 0	nd	Stage 3 43 (44) [44]	nd nd	Ca nd P nd PTH 3.7 (3.2) [2.9] pmol/L Assay: nd	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) % Pts with prevalent vertebral fractures	0.55 (0.63) [0.54] 0.77 (0.84) [0.73] 86% (77%) [85%]

BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; DM, diabetes mellitus; DXA, dual-energy x-ray absorptiometry; HD, hemodialysis; iPTH, intact parathyroid hormone; MBD, mineral bone disease; N, number of subjects; nd, not documented; PTH, parathyroid hormone; Pts, patients.

Note: No studies report imaging of vascular or valvular calcifications.

Symbols: * Overall or Arm 1 (Arm 2) [Arm 3].

Annotations:

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. Exclusion criteria included SCr ≤ 177 µmol/L (2 mg/dL), or PTH or 25(0H)D less than lower limit of normal or greater than 3X upper limit of normal or HPT as diagnosed by investigator.

Supplemental Table 44. Summary Table of the treatment of CKD-MBD with other bone treatments in CKD Stages 3-5 and 5D—intervention and results

Author, Year	N / Follow-up	CKD Stage / Baseline GFR	Arm 1	Arm 2	Cointerventions	Outcomes	Results Arm 1 vs. Arm 2 (*P*-value)	Quality
CKD Stage 5D								
Hernández, 2003[135]	50 / 12 mo	5D on HD / —	Raloxifene 60 mg/d	Placebo	nd	%ΔT-score, L2-L4	+2.3% vs. -0.3% (<0.01)[a]	B
						T-score, femoral neck	-2.11 vs. -2.0 (nd)[b]	B
						Total Cholesterol (mmol/L)	4.89±0.76 vs. 4.89 ±1.42 (NS)	C
						LDL (mmol/L)	3.13 ±0.78 vs. 3.83±0.91	C
						HDL (mmol/L)	1.2±0.2 vs. 0.9±0.3	C
						Triglycerides (mmol/L)	2.15±0.92 vs. 2.25±0.6	C
CKD Stages 3-5								
Ishani, 2008[136]	3493 / 36 mo	Stage 3 / CrCl 45-59 mL/min/1.73 m^2	Raloxifene 60 or 120 mg/d	Placebo	Daily Ca 500 mg and 400-600 IU Vit D	Incident vertebral fracture by CrCl	OR 0.45 (CI0.34-0.59)	B
						Incident nonvertebral fracture by CrCl	OR 1.02 (CI 0.8-1.3)	B
						%ΔBMD, lumbar spine	1.2% vs. 0.3% (nd)[c]	B
						%ΔBMD, femoral neck	0.41% vs. -0.36 (nd)[c]	B
	1480 / 36 mo	Stage 3-5 / CrCl <45 mL/min/1.73 m^2	Raloxifene 60 or 120 mg/d	Placebo	Daily Ca 500 mg and 400-600 IU Vit D	Incident vertebral fracture	OR 0.78 (CI 0.54-1.11)	B
						Incident nonvertebral fracture	OR 0.84 (CI 0.6-1.17)	B
						%ΔBMD, lumbar spine	1.35% vs. 0.31% (nd)[c]	B
						%ΔBMD, femoral neck	0.55% vs. -0.45% (nd)[c]	B
Miller, 2007[137] Posthoc analysis	83 / Median 21 mo	Stages 3 / GFR 30-49	Teriparatide 20 or 40 µg/d	Placebo	Elemental Ca 1000 mg/d Vit D 400-1200 IU/d	Incident vertebral fracture by X-ray	6.4% vs. 23.5% (.05)[d]	C
						Incident nonvertebral fragility fractures by X-ray	0% vs. 0%[e]	C
	49 / See above	Stage 3[f] / GFR 30-49	Teriparatide 20 µg/d	Placebo	Elemental Ca 1000 mg/d Vit D 400-1200 IU/d	%ΔBMD, lumbar spine at 18 mo	+11.2% vs. +1.9% (<.05)[c]	C
						%ΔBMD, femoral neck at 12 mo	+2.2% vs. -0.7% (NS)[c]	C
						ΔGFR (mL/min/1.73 m^2)	+7.1 vs. +6.2 (NS)	C
	54 / See above	Stage 3[f] / GFR 30-49	Teriparatide 40 µg/d	Placebo	Elemental Ca 1000 mg/d Vit D 400-1200 IU/d	%ΔBMD, lumbar spine at 18 mo	+15.4% vs. +1.9% (<.05)[c]	C
						%ΔBMD, femoral neck at 12 mo	+2.2% vs. -0.7% (NS)[c]	C
						ΔGFR (mL/min/1.73 m^2)	+5.6 vs. +6.2 (NS)	C

BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; Δ, change; GFR, glomerular filtration rate; HD, hemodialysis; HDL, high-density lipoprotein; IU, international units; LDL, low-density lipoprotein; N, number of subjects; nd, not documented; NS, not significant; OR, odds ratio.

Annotations:

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

b. BMD (g/cm2): 0.727 vs. 0.743 (nd); Z-score: -0.761 vs. -0.649 (nd), within-arm changes are all NS for both measurements.

c. Estimated from graph.

d. Vertebral fractures by subgroup: GFR 50-79 mL/min/1.73 m2 3.9% vs. 18.1% (P <0.01). For those patients with GFR ≤80 mL/min/1.73 m2, the RR of vertebral fracture is 0.22 (CI 0.13-0.39).

e. Nonvertebral fractures by subgroup: GFR 50-79 mL/min/1.73 m2 2.6% vs. 6.6% (P <0.01). For those patients with GFR ≤80 mL/min/1.73 m2, the RR of vertebral fracture is 0.37 (CI 0.17-0.80).

f. Of the 731 patients in the study, 648 had CKD stage 2-3 (GFR 50-79 mL/min/1.73 m2). For the comparison of teriparatide 20 µg/d vs. placebo (N = 434), %ΔBMD, lumbar spine at 18 mo: +9.4% vs. +1.2% (P <0.05), %ΔBMD, femoral neck at 12 mo: +1.2% vs. 0% (P <0.05), and ΔGFR: +4.2% vs. +3.1% (NS). For the comparison of teriparatide 40 µg/d vs. placebo (N = 440), %ΔBMD, lumbar spine at 18 mo: +16.1% vs. +1.2% (P <0.05), %ΔBMD, femoral neck at 12 mo: +3.3% vs. 0% (P <0.05), and ΔGFR: +6.0% vs. +3.1% (P <0.05). All numbers were estimated from graph.

Supplemental Table 45. Adverse events of other bone treatments in CKD Stages 3-5 and 5D

Author, Year Follow-up	CKD Stage GFR	N	Arm 1 / Arm 2 / Arm 3	Kidney Function % Pts	Kidney Function D/C	Hypercalcemia % Pts	Hypercalcemia D/C	Other Reported AE % Pts	Other Reported AE D/C	Total D/C due to AE	Deaths
Hernández, 2003[135] 12 mo	5D on HD	25	Raloxifene	—	—	—	—	No side-effects[a]	—	—	—
	—	25	Placebo	—	—	—	—	—	—	—	—
Ishani, 2008[136] 36 mo	3	2323	Raloxifene	—	—	—	—	23%	—	10%	[b]
	45-59	1170	Placebo	—	—	—	—		—		
	3-5	970	Raloxifene	—	—	—	—	30%	—	11%	[b]
	<45	510	Placebo	—	—	—	—		—		
Miller, 2007[137] Median 21 mo	3[c]	29	Teriparatide 20 µg/d	Kidney-related AE[d]: 4%	—	*Ca >2.64 mmol/L: 24% Ca >2.74 mmol/L: 3%	—	All AE: 76% Gout, arthalgia: 4%	—	—	—
	30-49 mL/min/1.73 m^2	34	Teriparatide 40 µg/d	Kidney-related AE[d]: 6%	—	*Ca >2.64 mmol/L: 18% Ca >2.74 mmol/L: 12%	—	All AE: 85% Gout, arthalgia: 6%	—	—	—
		20	Placebo	Kidney-related AE[d]: 5%	—	Ca >2.64 mmol/L: 0% Ca >2.74 mmol/L: 0%	—	All AE: 95% Gout, arthalgia: 5%	—	—	—

AE, adverse event; CKD, chronic kidney disease; D/C, discontinued; GFR, glomerular filtration rate; HD, hemodialysis; N, number of subjects; Pts, patients.

Note: No study reported gastric discomfort.

Symbols: "—" indicates data not documented; statistical comparisons with placebo arm, if documented § P <0.01; * P <0.05; † 0.05< P <0.1.

Annotations:

a. Including thrombophlebitis, venous thromboembolism, clotting problems with the vascular accesses or increased vasomotor symptoms.

b. % Discontinued due to AE or death: Stage 3: 11%; Stage 3-5: 13%.

c. For the 648 patients with CKD Stages 2-3, kidney-related AEs were 1% in the teriparatide group (both 20 and 40 µg/d) and 2% in the placebo group. Hypercalcemia, defined as Ca>2.64 mmol/L was 8% in teriparatide 20 µg/d, 26% in teriparatide 40 µg/d, and 2% in the placebo group. Hypercalcemia defined as Ca >2.74 mmol/L was 2% in teriparatide 20 µg/d, 11% in teriparatide 40 µg/d, and <1% in placebo groups. All other AEs were reported as follows: teriparatide 20 µg/d: all AE 82%, gout, arthalgia 9%; teriparatide 40 µg/d: all AE 88%, gout arthalgia 8%; placebo: all AE 85%, gout, arthalgia 9%, nephrolithiasis <1%.

d. Hematuria, hydronephrosis, abnormal kidney function, uremia, polyuria, glomerulitis, kidney failure, acute kidney failure, oliguria, and nephritis.

Supplemental Table 46. Summary Table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD Stages 1-5T—description of population at baseline

Author, Year	N Country of Study	Age* % Male*	% Race*	Time Post-KT Kidney Function	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	TMV Classification/ DXA Score*
Prevention								
Calcitriol or alphacalcidol vs. control								
De Sévaux, 2002[138]	113 Netherlands	46 (49) 62 (54)	nd	At transplant NA[a]	9 (2) nd	Ca 2.38 (2.42) mmol/L corrected P 1.68 (1.79) mmol/L iPTH 25.9 (23.0) pmol/L Allegro-intact PTH [ref 1.0-6.5] ALP 88 (64) IU/L 25 VitD 60 (80) nmol/L[b] HPLC method [ref 25-85]	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, total hip (g/cm^2) BMD, trochanteric region (g/cm^2) BMD, ward's triangle (g/cm^2)	0.731 (0.799)[b,c] 0.995 (1.007)[c] 0.819 (0.880)[b,c] 0.619 (0.681)[b,c] 0.552 (0.591)[c]
Torres, 2004[139]	90 Spain	47 (51) 82 (73)	nd	At transplant NA[d]	31 (20) nd	Ca 2.40 (2.42) mmol/L P 1.65 (1.65) mmol/L PTH 20.9 (20.3) pmol/L DPC IRMA[e] [ref 1.3-7.6] ALP 140 (145) IU/L	BMD, femoral neck (g/cm^2) BMD, intertrochanteric region (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, total hip (g/cm^2) BMD, trochanteric region (g/cm^2) BMD, ward's triangle (g/cm^2)	0.81 (0.76)[f] 1.06 (1.03)[f] 1.02 (0.98) 0.91 (0.87) 0.70 (0.66) 0.64 (0.57)
Josephson, 2004[140]	64 USA	nd nd	nd	At transplant NA	41% nd	nd	BMD, femoral neck Z-score	Non-DM men -0.60 Non-DM women -1.10 DM men -1.27 DM women -1.59
Cholecalciferol vs. Control								
Wissing, 2005[141]	90 Belgium	43 (43) 61 (54)	nd	At transplant NA[g]	nd nd	Ca 2.54 (2.50) mmol/L P 1.65 (1.81) mmol/L iPTH 13.5 (23.5) pmol/L DiaSorin IRMA [ref nd] ALP nd 25 VitD 61 (49) nmol/L DiaSorin IRMA [ref nd] 1,25 VitD 26 (25) pmol/L DiaSorin IRMA [ref nd]	BMD, femoral neck (g/cm^2) BMD, lumbar spine (g/cm^2) BMD, midfemoral shaft (g/cm^2)	0.8 (0.74)[i] 1.04 (0.94)[f, h] 1.63 (1.53)

Author, Year	N Country of Study	Age* % Male*	% Race*	Time Post-KT Kidney Function	% DM* % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	TMV Classification/ DXA Score*
Long-Term								
Calcitriol vs. control								
Cuento-Manzano, 2000[142]	45[j] UK	52 (44) 69 (36)	nd	119 (133) mo CrCl 64 (63) mL/min	nd nd[k]	Ca 2.27 (2.40) mmol/L corrected P 0.77 (0.81) mmol/L iPTH 5.1 (6.7) pmol/L Allegro-intact PTH [ref 1.1-6.4] ALP 154 (146) IU/L 25 VitD 61 (58) nmol/L IRMA [ref 12-87] 1,25 VitD 80 (78) pmol/L IRMA [ref 52-130]	Bone biopsy BMD, distal radius by SXA BMD, femoral neck by DXA BMD, L1-L4 by DXA	— Z score -1.0 (-0.8) T score -1.9 (-1.3)[c] Z score -0.5 (-0.9) T score -1.3 (-1.4) Z score -0.1 (+0.1) T score -0.8 (-0.3)

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphorus 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; PO, oral; PTH, parathyroid hormone; SCr, serum creatinine; SXA: single-energy X-ray absorptiometry; TMV, turnover, mineralization, volume.

Symbols: * Overall or Arm 1 (Arm 2).

Note: No studies report imaging of vascular or valvular calcifications.

Annotations:

a. At 1 month, SCr 151 (144) µmol/L.
b. P <0.05
c. Z-scores: lumbar spine: -0.60 (-0.03) [P = 0.043], femoral neck: -1.03 (-0.26) [P = 0.0025], ward's triangle: -0.91 (-0.37) [P = 0.049], trochanteric region: -1.00 (-0.31) [P = 0.006], total hip: -1.14 (-0.56) [P = 0.014].
d. At 3 mo, CrCl 71.6 (69.2) mL/min.
e. Solid-phase, two-site chemiluminescent enzyme immunometric assay on DPC-Immulite.
f. P ≤0.01.
g. At 3 mo, GFR 53 (56) mL/min/1.73 m2.
h. T-score: -0.55 (-1.45) [P <0.01]; Z-score: -0.22 (-1.14) [P <0.01].
i. T-score: -0.71 (-1.20); Z-score: -0.30 (-0.81) [P <0.05].
j. Baseline data provided for N = 30 patients who completed the study protocol.
k. No AI deposits found on biopsy.

Supplemental Table 47. Summary Table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD Stages 1-5T—intervention and results

Author, Year	N / Follow-up	Arm 1	Arm 2	Cointerventions: Immunosuppressive Regimen	Outcomes	Results: Arm 1 vs. Arm 2 (*P*-value)	Quality
Prevention							
Calcitriol or alphacalcidol vs. control							
De Sévaux, 2002[138]	113 / 6 mo	Alphacalcidol 0.25 µg/d + elemental Ca 1000 mg/d[a]	No treatment	Bisphosphonates if persistent hypercalcemia[b]	% ΔBMD, femoral neck	-0.22% vs. -4.0% (<.001)	C
					% ΔBMD, L1-L4	-2.6% vs. -5.0% (.02)	C
					% ΔBMD total proximal femur	-0.97% vs. -3.0% (<.01)	C
					% ΔBMD, trochanteric region	-2.2% vs. -4.3% (<.05)	C
					% ΔBMD, ward's triangle	+0.3% vs. -2.3%[d] (NS)	C
					Mean CrCl (mL/min)	65 vs. 64 (NS)	C
				During the first 6 mo after transplant, CsA, prednisone, and MMF[c]	Mean adjusted Ca (mmol/L)	2.45 vs. 2.43 (NS)	B
					Mean P (mmol/L)	0.92 vs. 0.89 (NS)	B
					Mean iPTH (pmol/L)	9.3 vs. 9.3 (NS)	B
					Mean ALP (IU/L)	96 vs. 97 (NS)	B
Torres, 2004[139]	90 / 12 mo	Calcitriol 0.5 µg every other day for 1st 3 mo	Placebo	500 mg/d elemental Ca for 12 mo[e]	BMD, femoral neck (g/cm^2)	0.82 vs. 0.74 (≤.01)	B
					BMD, intertrochanteric area (g/cm^2)	1.07 vs. 1.01 (<.05)	B
					BMD, lumbar spine (g/cm^2)	0.99 vs. 0.93 (<.05)	B
					BMD, total hip (g/cm^2)	0.91 vs. 0.85 (<.05)	B
					BMD, trochanter (g/cm^2)	0.68 vs. 0.63 (<.05)	B
					BMD, ward's triangle (g/cm^2)	0.64 vs. 0.54 (≤.01)	B
				Induction: ATG Maintenance: prednisone, CsA and MMF or AZA[f]	CrCl (mL/min)	83.7 vs. 76 (NS)	C
					Mean Ca (mmol/L)	2.48 vs. 2.45 (NS)	B
					Mean P (mmol/L)	1.19 vs. 1.23 (NS)	B
					Mean iPTH (pmol/L)	7.1 vs. 8.8 (<.01)	B
					Mean ALP (IU/L)	205.5 vs. 188 (NS)	B
					Bicarbonate (mEq/L)	27.3 vs. 27.6 (NS)	B
Josephson, 2004[140]	64	Calcitriol 0.25-1 µg/d Ca carbonate 1 g/d	Placebo + Ca carbonate 1 g/d	—	Δ BMD, femoral neck	0.43 vs. 0.005 (nd)	C
					Δ BMD, distal radius	0.011 vs. -0.022 (nd)	C
					ΔBMD, L2-L4	-0.001 vs. 0.017 (nd)	C
	12 mo	Calcitriol 0.25-1 µg/d Ca carbonate 1 g/d	Double Placebo	CsA	ΔBMD, femoral neck	0.43 vs. 0.012 (nd)	C
					ΔBMD, distal radius	0.011 vs. -0.008 (nd)	C
					ΔBMD, L2-L4	-0.001 vs. -0.025 (nd)	C
Cholecalciferol vs. control							
Wissing, 2005[141]	90 / 12 mo	Cholecalciferol 25 000 IU PO once per mo	No treatment	400 mg/d elemental Ca[g]	‡Mean BMD femoral neck (g/cm^2)	0.78 vs. 0.74 (NS)[h]	B
					‡Mean BMD femoral shaft (g/cm^2)	1.57 vs. 1.53 (NS)	B
					‡BMD lumbar spine (g/cm^2)	1.01 vs. 0.92 (NS)[i]	B
				Tac or CsA and 2 g/d MMF; low dose steroids[j]	Mean GFR (mL/min/1.73 m^2)	60 vs. 64 (NS)	C
					Mean Ca (mmol/L)	2.52 vs. 2.52 (NS)	B
					Mean P (mmol/dL)	1.07 vs. 1.03 (NS)	B
					Mean iPTH (pmol/L)	5.7 vs. 9.4 (.018)	B

Author, Year	N / Follow-up	Arm 1	Arm 2	Cointerventions: Immunosuppressive Regimen	Outcomes	Results: Arm 1 vs. Arm 2 (*P*-value)	Quality
Long-Term							
Calcitriol vs. control							
	45			—		Net turnover was worse, calcitriol caused more adynamic. The mineralization was much better because more calcitriol treated patients improved the mixed lesion whereas more placebo patients developed mixed lesion. The actual measurement of Mlt was not reported. The overall results are therefore complicated and it is difficult to say whether these patterns would improve the bone strength.	
Cuento-Manzano, 2000[142]	12 mo	Calcitriol 0.25 μg/d + 500 mg/d elemental Ca[k]	No treatment	CsA monotherapy or AZA + prednisolone or CsA+AZA+ prednisolone[l]	Bone overall summary by WG[m]		C
					Bone Turnover (N = 30)	Worse (-53)	
					Bone Mineralization	Better (+73)	
					Bone Volume	Better (NS)	

ALP, alkaline phosphatase; ATG, antithymocyte globulin; AZA, azathioprine; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphorus product; CKD-MBD, chronic kidney disease-mineral and bone disorder; CrCl, creatinine clearance; CsA, cyclosporin A; Δ, change; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone; IU, international units; MLT, mineralization lag time; MMF, mycophenolate mofetil; N, number of subjects; nd, not documented;NS, not significant; PO, oral; PTH, parathyroid hormone; SCr, serum creatinine; Tac, tacrolimus; WG, work group.

Symbols: ‡Primary outcome.

Annotations:

a. Treatment begun after graft function obtained but no later than 1 mo after transplant. Ca supplement given as Ca lactogluconate. If Ca >2.8 mmol/L then treatment withheld.
b. Loop diuretics allowed.
c. Immunosuppression: During the first 6 mo after transplant, immunosuppressive therapy consisted of CsA, prednisone, and MMF, except for recipients of a graft from an HLA-identical living related donor. The latter patients were treated with CsA and prednisone during the first 3 mo, after which CsA was replaced by AZA. The dose of prednisone was 100 mg/d IV for the first 3 d and 0.35 mg/kg/d for the first month; the dose was then gradually tapered to 0.10 mg/kg/d at 3 mo. CsA was dosed to a level of 150 to 300 ng/ml during the first 3 mo and 150 ng/ml thereafter. MMF was prescribed in a fixed dose of 1000 mg twice daily. Rejection treatment consisted of 1000 mg of IV methylprednisolone for 3 consecutive days. Steroid-resistant rejections were treated with antithymocyte globulin or an extended course of oral high-dose prednisone (1500 mg within 2 wk).
d. Estimated from graph.
e. Ca supplement given as Ca lactogluconate. If Ca >2.82 mmol/L, therapy interrupted for 1 wk. Loop diuretics allowed.
f. 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 methyprednisolone. Resistant episodes were treated with a 10-d course of OKT-3 (5 mg/d).
g. For first 3 months, while on cimetidine, patients received 1600 mg Ca acetate; 1000 mg Ca carbonate thereafter.
h. T-score: –0.83 vs. –1.19 (NS); Z score: –0.37 vs. –0.76 (NS).
i. T-score: -0.86 vs. –1.61 (NS); Z score: –0.51 vs. –1.24 (NS).
j. Patients at high or intermediate risk of acute rejection received induction therapy with thymoglobulin (1.25 mg/kg/d from day 0 to day 7) or basiliximab (20 mg IV on days 0 and 4). IV methylprednisolone was administered at the dose of 500 mg on the day of transplantation and 250 mg on the first postoperative day. Subsequently, prednisolone was started at the dose of 20 mg orally and tapered to 10 mg orally during the 2nd mo, 7.5 mg orally during the 3rd mo, and 5 mg orally thereafter. Corticosteroids were completely withdrawn after 6 mo in pts at low or intermediate immunologic risk, with SCr less than 177 μmol/L (2 mg/dL), no acute rejection, and who were able to tolerate at least 1.5 g/d MMF. Immunosuppression consisted in Tac or CsA with 2 g/d MMF. CsA and Tac were concentration controlled according to standard protocols. MMF dosage was adjusted in case of intolerance. Acute rejections were treated with 3 mg/kg/d of solumedrol IV bolus on 5 consecutive days.
k. Ca supplement given as Ca carbonate.
l. 1) CsA monotherapy: CsA, 5 mg/kg, IV on days 0 and 1, continued PO at a dose of 15 mg/kg/d, and reduced according to serum levels. 2) AZA plus prednisone dual therapy: prednisone, 20 mg/d, PO for 90 d, then reduced to 5 to 10 mg/d. AZA was started at 2 mg/kg/d and reduced to 1 mg/kg/d. 3) CsA plus AZA plus prednisone Triple therapy: CsA IV initial 2 days, then 15 mg/kg/d PO, then tapered to 5 mg/kg/d (according to serum levels). AZA and prednisone are previously described. Acute rejection episodes were treated with 3 daily IV methylprednisolone boluses (1 g each). IV OKT-3 or ATG was administered in case of steroid-resistant rejection.

m. See Supplemental Table 48.
n. Reported z-scores for mineralization surfaces that were impossible. (12–43) – (50–28) = –53.

Supplemental Table 48. Summary Table of RCTs examining treatment of CKD-MBD with calcitriol or vitamin D in CKD Stages 1-5T—bone biopsy results

Author, Year	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients			Z-score[n]
Cuento-Manzano, 2000[142]	Calcitriol	6	44	0	12	0	44	nd	+0.2
	Placebo	7	21	36	7	36	7	nd	–1.1

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Mlt, mineralization lag time; nd, not documented; TV, trabecular volume.

Supplemental Table 49. Adverse events of vitamin D, calcitriol, or vitamin D analogs in CKD Stages 1-5T

Author, Year Follow-up	N	Arm 1 / Arm 2	Decreased Kidney Graft Function		Acute Rejection Episodes		Hypercalcemia/ Hyperphosphatemia		Avascular Necrosis		Other Reported AE		Total D/C due to AE	Deaths
			% Pts	D/C	% Pts	D/C	% Pts	D/C	% Pts	D/C	% Pts	D/C		
Calcitriol or alphacalcidol														
De Sévaux, 2002[138] 6 mo	65	Alphacalcidol + Ca	Graft failure: 2%[a]	nd	23%	0%	Ca >2.8 mmol/L: 9%	3%	Hip: 2%	0%	Renal calculus: 2%	—	3%	0%
	46	Control	Graft failure: 0%[a]	—	24%	—	Ca >2.8 mmol/L: 4%	—	—	—	Multiple vertebral fractures: 4%	—	—	0%
Torres, 2004[139] 12 mo	45	Calcitriol	CrCl ≤35 mL/min: 9%	0%	—	0%	Ca >2.74 mmol/L: 5.5%	0%	—	0%	No symptomatic fractures	0%	0%	0%
	45	Placebo	CrCl ≤35 mL/min: 7% Graft loss: 4%	7%	Irreversible rejection: 2%	0%[b]	Ca >2.74 mmol/L: 8.6%	0%	—	0%	No symptomatic fractures	0%	4%	0%
Josephson, 2004[140] 12 mo	26	Calcitriol + Ca	—	—	—	—	†Ca >2.74 mmol/L: 31% Ca >2.99 mmol/L: 15%	0%	—	—	—	—	—	—
	13	Placebo + Ca	—	—	—	—	Ca >2.74 mmol/L: 15% Ca >2.99 mmol/L: 0%	0%	—	—	—	—	—	—
	25	Double placebo	—	—	—	—	†Ca >2.74 mmol/L: 8% Ca >2.99 mmol/L: 0%	0%	—	—	—	—	—	—
Cuento-Manzano, 2000[142] 12 mo	23	1,25 OH Vit D3 + Ca	Kidney function loss: 4%	4%	—	0%	—	0%	No new bone symptoms	0%	Arterial fibrillation: 4%, Esophageal cancer: 4%, No new fractures	8%	13%	0%
	22	Control	—	—	—	—	—	—	No new bone symptoms	—	No new fractures	—	—	0%
Cholecalciferol														
Wissing, 2005[141] 12 mo	46	Cholecalciferol + Ca	Graft loss: 7%	7%	9%	0%	—	9%	—	0%	PTx: 4%, 1° Hyperoxaluria: 2%	7%	22%	0
	44	Ca	—	0%	9%	0%	—	15%	—	0%	—	0%	15%	0

1°, primary; CrCl, creatinine clearance; D/C, discontinued; N, number of subjects; nd, not documented; Pts, patients; PTx, parathyroidectomy.

Symbols: "—" indicates data not documented; If P-value documented: † 0.05< P <0.1 between groups.

Annotations:

a. Two additional patients lost kidney grafts before 2nd BMD measurement (3 mo) but group not reported.

b. One subject had and episode of irreversible rejection in the placebo arm and consequently lost their graft.

Supplemental Table 50. Summary Table of RCTs examining treatment of CKD-MBD with bisphosphonates vs. control or calcitriol in CKD Stages 1-5T—description of population at baseline

Author, Year	N / Country of Study	Age* / % Male*	% Race*	Time Post-KT / Kidney Function	% DM* / % Prior AI Exposure*	Baseline MBD Labs*	Bone Evaluation Technique	DXA Score*
Prevention								
Bisphosphonates vs. Control								
Grotz, 2001[143]	80 Germany	42 (44) 69 (64)	nd	At transplant NA[a]	3 (3) nd	Ca 2.49 (2.48) mmol/L P 1.88 (1.93) mmol/L iPTH 200 (232) pg/mL Allegro-intact PTH [ref 10-55] ALP 109 (126) U/L 25(OH)VitD 90 (87) nmol/L RIA IRMA [ref 50-300] 1,25(OH)VitD 31 (29) pmol/L Immunodiagnostik radioreceptor assay[ref 44-138]	BMD, lumbar spine (g/cm^2) BMD, femoral neck (g/cm^2) BMD, midfemoral neck (g/cm^2)	1.137 (1.147)[b] 0.860 (0.900)[c] 1.673 (1.720)
Coco, 2003[144]	72 USA	46 57%	Black 39% Hispanic 37% White 21% Asian 3%	At transplant NA[d]	nd nd[e]	Ca 1.97 (2.05) mmol/L P 1.74 (1.71) mmol/L iPTH 41.9 (29.7) pmol/L Immulite chemiluminescence [ref 0.5-6.9] ALP nd 25(OH)VitD 37 (50) nmol/L [ref 22-115] 1,25(OH)VitD 62 (65) pmol/L [ref 42-143]	BMD, hip (g/cm^2) # pts with vertebral fractures by X-ray # pts with hip fractures by X-ray Bone biopsy	0.91 (0.82)[f] 4 0 —
Long-Term								
Bisphosphonates vs. Calcitriol								
Jeffery, 2003[145]	117 Canada	52 (56)[g] 74 (73)	nd	85 (115) mo[h] 71 (82) mL/min/1.73 m^{2}[h]	15 (22) nd	Ca nd P nd iPTH 15.6 (12.2) pmol/L nd [ref 0.7-5.3] ALP nd	BMD, lumbar spine (g/cm^2) BMD, total proximal femur (g/cm^2) % with T score < -2.5	0.984 (1.014) 0.809 (0.830) 43.5% (39.2%)

ALP, alkaline phosphatase; BMD, bone mineral density; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; DXA, dual-energy x-ray absorptiometry; iPTH, intact parathyroid hormone; IRMA, immunoradiometric assay; KT, kidney transplant; MBD, mineral bone disease; N, number of subjects; NA, not applicable; nd, not documented; PTH, parathyroid hormone; pts, patients; RIA, radioimmunoassay.

Symbols: * Overall or Arm 1 (Arm 2) [Arm 3] .

Notes: No studies report imaging of vascular or valvular calcifications.

Annotations:

a. At 6 mo, Scr 110 (129) µmol/L.
b. Standard deviations below normal: -0.472 (-0.369).
c. Standard deviations below normal: -0.743 (-0.388).
d. At 6 mo, SCr 150 µmol/L (1.7 mg/dL) in both arms.
e. No evidence of AI on biopsy (N = 21).
f. Estimated from graph.
g. Calculated.
h. *P* <0.05 between arms.

Supplemental Table 51. Summary Table of RCTs examining the treatment of CKD-MBD with bisphosphonates vs. control or calcitriol in CKD Stages 1-5T—intervention and results

Author, Year	N Follow-up	Arm 1 Arm 2 Arm 3	Cointerventions Immunosuppressive Regimen	Outcomes	Results Arm 1 vs. Arm 2 vs. Arm 3 (*P*-value)	Quality
Prevention						
Bisphosphonates vs. Control						
Grotz, 2001[143]	80 12 mo	Ibandronate 1 mg IV immediately before and 2 mg at 3, 6, 9 mo after KT Control	Dietary intake of ≥1000 mg/d elemental Ca; cholecalciferol if Vit D <37 nmol/L[a] CsA, prednisolone, MMF[b]	New clinical fractures	1 arm vs. 1 arm (nd)	C
				New vertebral fractures by X-ray	1 vs. 1 (nd)	C
				‡% ΔBMD, femoral neck	+0.5% vs. -7.7% (<.0001)	A
				‡% ΔBMD, lumbar spine	-0.9% vs. -6.5% (<.0001)	A
				‡% ΔBMD, midfemoral neck	+2.7% vs. -4.0% (.024)	A
				ΔBody height (cm)	-0.5 vs. -1.1 (.049)	B
				New spinal deformity[c]	7 pts, 7 deformities vs. 12 pts, 23 deformities (.047)	C
				Mean SCr (μmol/L)	115 vs. 142 (NS)	C
				Mean Ca (mmol/L)	2.58 vs. 2.53 (NS)	B
				Mean P (mmol/L)	0.99 vs. 1.03 (NS)	B
				Mean iPTH (pmol/L)	6.9 vs. 9.5 (NS)	B
				Mean ALP (IU/L)	156 vs. 172 (NS)	B
				Mean b-ALP (IU/L)	31 vs. 35 (NS)	B
Coco, 2003[144]	72 12 mo	Pamidronate 60 mg IV within 48 h after KT followed by 30 mg at 1, 2, 3 and 6 mo Control	PO calcitriol and Ca carbonate to maintain Ca 2.12-2.62 mmol/L Glucocorticoids and CsA or Tac	New fractures by X-ray	1 vs. 2 (nd)[d]	C
				Bone overall summary by WG[e]	The turnover was worse because the pamidronate patients developed adynamic bone disease whereas the placebo patients improved their bone formation rates towards normal. The mineralization appeared better in the pamidronate patients based on changes from mixed category, but the measured osteoid thickness was not very different. The bone volume was slightly higher in the pamidronate group. Overall the treatment group biopsies were worse than the placebo group.	C
				Bone Turnover	Worse (-133)	
				Bone Mineralization	Better (+67)	
				Bone Volume	Slightly better (+2.3)	
				BMD, hip (g/cm^2) [N = 50]	0.8933 vs. 0.8216 (NS)	B
				‡%Δ BMD, vertebral [N = 50]	-0.39% vs. -5.81% (<.01)	B
				Mean SCr (mmol/L)	150 vs. 141 (NS)	C

Author, Year	N Follow-up	Arm 1 Arm 2 Arm 3	Cointerventions Immunosuppressive Regimen	Outcomes	Results Arm 1 vs. Arm 2 vs. Arm 3 (*P*-value)	Quality
				Mean Ca (mmol/L)	2.50 vs. 2.52 (NS)	B
				Mean P (mmol/L)	0.97 vs. 1.00 (NS)	B
				Mean iPTH (pmol/L)	10.8 vs. 12.6 (NS)	B
				Mean b-ALP (U/L)	40 vs. 54 (NS)	B
Long-Term						
Bisphosphonates vs. Vitamin D						
Jeffrey, 2003[145]	117 12 mo	Alendronate 10 mg/d Calcitriol 0.25 µg/d PO	1000 mg/d dietary Ca + 500 mg/d elemental Ca[f] Prednisone + AZA or Predinose + CsA with or without AZA or MMF	‡ BMD, lumbar spine (g/cm^2)	1.025 vs. 1.034 (0.08)	B
				‡ BMD, total proximal femur (g/cm^2)	0.836 vs. 0.857 (NS)	B
				eGFR (mL/min/1.73 m^2)	74 vs. 73 (NS)	C

ALP, alkaline phosphatase; AZA, azathioprine; b-ALP, bone-specific alkaline phosphatase; BMD, bone mineral density; CaXP, calcium-phosphorus product; CKD-MBD, chronic kidney disease-mineral and bone disorder; CsA, cyclosporin A; Δ, change; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; IV, intravenous; KT, kidney transplant; MMF, mycophenolate mofetil; N, number of subjects; nd, not documented; NS, not significant; PO, oral; PTH, parathyroid hormone; SCr, serum creatinine; Tac, tacrolimus; WG, work group.

Symbols: ‡ Primary outcome(s).

Annotations:

a. Dietary intake of ≥1000 mg/d Ca (or supplemented with 500 mg/d Ca). Patients with Vit D <37 nmol/L were treated with 10 000 U of cholecalciferol. Hormone replacement therapy continued.
b. Immunosuppressive therapy consisted of CsA dosed to a blood level of 120-180 ng/mL; prednisolone 100 mg/d for 5 d, 50 mg/d for 5 d, 25 mg/d for 10 d, and tapered to 5 mg/d after 1 y; MMF 2 g/d. Patients receiving unrelated–living-donor kidneys were treated additionally with ATG for 10 d. Acute rejections were treated with 3 x 500 mg prednisone. Refractory cases received a 10-d course of ATG.
c. Defined as reduction of the sum of anterior and posterior height of each lumbar vertebra greater than 5% between the baseline and follow-up radiographs.
d. All vertebral fractures. No new hip fractures.
e. See Supplemental Table 52.
f. Ca supplement given as Ca carbonate.

Supplemental Table 52. Summary Table of RCTs examining the treatment of CKD-MBD with bisphosphonates vs. control or calcitriol in CKD Stages 1-5T—bone biopsy results

Study	Arm	Turnover				Mineralization			Volume
		Worsened		Improved		Worse	Better	Mean Δ in Oth	Mean Δ
		Higher	Lower	Higher	Lower				
		% of Patients				% of Patients		µm	% of TV
Coco, 2003[144]	Pamidronate	0	83	0	0	0	17	0.5	-0.6
	Placebo	0	17	62	12	62	0	-0.8	-2.9

CKD-MBD, chronic kidney disease-mineral and bone disorder; Δ, change; Oth, osteoid width; TV, trabecular volume.

Supplemental Table 53. Adverse events of bisphosphonates in CKD Stages 1-5T

Author, Year Follow-up	N	Arm 1 / Arm 2	Decreased Kidney Graft Function		Acute Rejection Episodes		Hypercalcemia/ Hyperphosphatemia		Other Reported AE		Deaths	Total D/C due to AE
			% Pts	D/C	% Pts	D/C	% Pts	D/C	% Pts	D/C		
Prevention												
Grotz, 2001[143]	40	Ibandronate	Graft loss 5%	0%	*11 episodes	0%	—	0%	Temporal bone pain, flatulence 8%	0%	5%	0%
12 mo	40	Ca	Graft loss 0%	0%	*22 episodes	0%	—	0%	0%	0%	8%	0%
Coco, 2003[144] 12 mo	36	Pamidronate + Calcitriol + Ca	—[a]	—	0.27 episodes	—	—	—	0.87 AE	—	—[b]	—
	36	Calcitriol + Ca	—[a]	—	0.29 episodes	—	—	—	1.0 AE	—	—[b]	—
Long-Term												
Jeffrey, 2003[145] 12 mo	57	Alendronate + Ca	Graft loss 2%	2%	—	0	—	0	Colitis relapse 2% GI distress 3%	5%	2%	7%
	60	Calcitriol + Ca	Graft loss 0%	0%	—	0	—	0	Cardiac disease 2% Cancer 3% GI distress 3%	8%	0%	8%

1°, primary; AE, adverse event; CKD, chronic kidney disease; CVD, cardiovascular disease; D/C, discontinued; GI, gastrointestinal; N, number of subjects; pts, patients; SAE, serious adverse event.
Symbols: "—" indicates data not documented; § *P* <0.001 between groups, if documented; * *P* <0.05 between groups, if documented.
Annotations:
a. One or more patients lost kidney grafts, but arm was not specified.
b. One patient died from MI, but arm was not specified.

Supplemental Table 54. Summary of Cumulative Evidence Matrix of adverse events

Adverse Events	Intervention							TOTAL
	Bisphosphonates and Other Bone Treatments	Calcimimetics	Calcitriol	Phosphate Binders		Transplant		
				Lanthanum	Sevelamer	Bisphosphonates	Vitamin D	
Mortality	—	3	4	3	7	2	—	19
Clinical CVD	—	—	1	—	2	—	—	3
Hospitalizations	—	—	—	—	2	—	—	2
CKD Clinical Outcomes	—	—	1	—	—	3	4	8
Fractures	—	—	—	—	—	—	3	3
Other AEs	2	4	8	5	9	3	5	36
TOTAL	2	7	14	8	20	8	12	71

AE, adverse event; CKD, chronic kidney disease; CVD, cardiovascular disease.

Supplemental Table 55. Adverse event reporting

Adverse Events	Bisphosphonates and Other Bone Treatments			Calcimimetics			Calcitriol			Phosphate Binders						Transplant					
										Lanthanum			Sevelamer			Bisphosphonates			Vitamin D		
	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U
Mortality	—	—	—	Block[128]	741 (371)	6 mo	Coyne[120]	220 (107)	6 mo	Finn[109]	1359 (682)	24 mo	Suki[97]	2103 (1053)	20 mo						
				Lindberg[129]	395 (294)	6 mo	Hamdy[40]	176 (89)	24 mo				Qunibi[99]	203 (103)	12 mo	Grotz[143]	80 (40)	1 mo			
							Coburn[121]	55 (27)	6 mo	Spasovski[113]	24 (12)	12 mo	Chertow[77]	200 (99)	12 mo				—	—	—
				Malluche[131]	48 (32)	24 mo							Braun[100]	21 (11)	12 mo						
							Hayashi[146]	82 (47)	12 mo	Malluche[111]	211 (51)	24 mo	Block[104]	148 (73)	18 mo	Jeffery[145]	117 (46)	12 mo			
													Russo[76]	90 (30)	24 mo						
													Barreto[102]	101 (41)	12 mo						
Clinical CVD	—	—	—	—	—	—	Coburn[121]	55 (27)	6 mo	—	—	—	Braun[100]	21 (11)	12 mo	—	—	—	—	—	—
													Russo[76]	90 (30)	24 mo						
Hospit-alizations	—	—	—	—	—	—	—	—	—	—	—	—	Chertow[77,107]	200 (99)	12 mo	—	—	—	—	—	—
													Braun[100]	21 (11)	12 mo						
																Grotz[143]	80 (40)	12 mo	De Sevaux[138]	113 (65)	6 mo
CKD Clinical Outcomes	—	—	—	—	—	—	Nordal[122]	30 (15)	8 mo	—	—	—	—	—	—	Coco[144]	72 (36)	12 mo	Torres[139]	90 (45)	12 mo
																Jeffery[145]	117 (46)	12 mo	Cuento-Manzano[142]	45 (23)	12 mo
																			Wissing[141]	90 (46)	12 mo
Fractures	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	De Sevaux[138]	113 (65)	6 mo
																			Torres[139]	90 (45)	12 mo
																			Cuento-Manzano[142]	45 (23)	12 mo

Adverse Events	Bisphosphonates and Other Bone Treatments			Calcimimetics			Calcitriol			Phosphate Binders						Transplant					
										Lanthanum			Sevelamer			Bisphosphonates			Vitamin D		
	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U	Author	N (on Agent)	F/U
Other AEs	Miller[41]	4643 (2335)	25 mo	Block[128]	741 (371)	6 mo	Coyne[120]	220 (107)	6 mo	Freemont[112]	98 (49)	12 mo	Suki[97]	2103 (1053)	20 mo	Coco[144]	72 (36)	12 mo	Torres[139]	90 (45)	12 mo
							Hamdy[40]	176 (89)	24 mo										De Sevaux[138]	113 (65)	6 mo
							Coburn[121]	55 (27)	6 mo	Finn[109]	1359 (682)	24 mo	Qunibi[99]	203 (103)	12 mo	Grotz[143]	80 (40)	12 mo	Josephson[140]	64 (26)	12 mo
				Lindberg[129]	396 (294)	6 mo	Nordal[122]	30 (15)	8 mo										Cuento-Manzano[142]	45 (23)	12 mo
							Baker[125]	76 (38)	60 mo	Hutchison[110]	800 (533)	6 mo	Chertow[77,107]	200(99)	12 mo						
							Sprague[126]	266 (133)	3-8 mo												
													Braun[100]	21 (11)	12 mo						
	Miller[137]	731 (485)	21 mo median	Malluche[131]	48 (32)	24 mo	Hayashi[146]	82 (47)	12 mo	Spasovski[113]	24 (12)	12 mo	Block[104]	148 (73)	18 mo	Jeffery[145]	117 (46)	12 mo	Wissing[141]	90 (46)	12 mo
													Ferreira[103]	91 (44)	13.5 mo						
													Salusky[104]	42 (21)	8 mo						
							Salusky[127]	46 (16)	12 mo	Malluche[111]	211 (51)	24 mo	Russo[76]	90 (30)	24 mo						
				Choncol[147]	404 (302)	8 mo							Barreto[102]	101 (41)	12 mo						

AE, adverse event; CKD, chronic kidney disease; CVD, Cardiovascular disease; F/U, followup; N, number of subjects.
Note: All single studies of a specific comparison shown in gray.

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