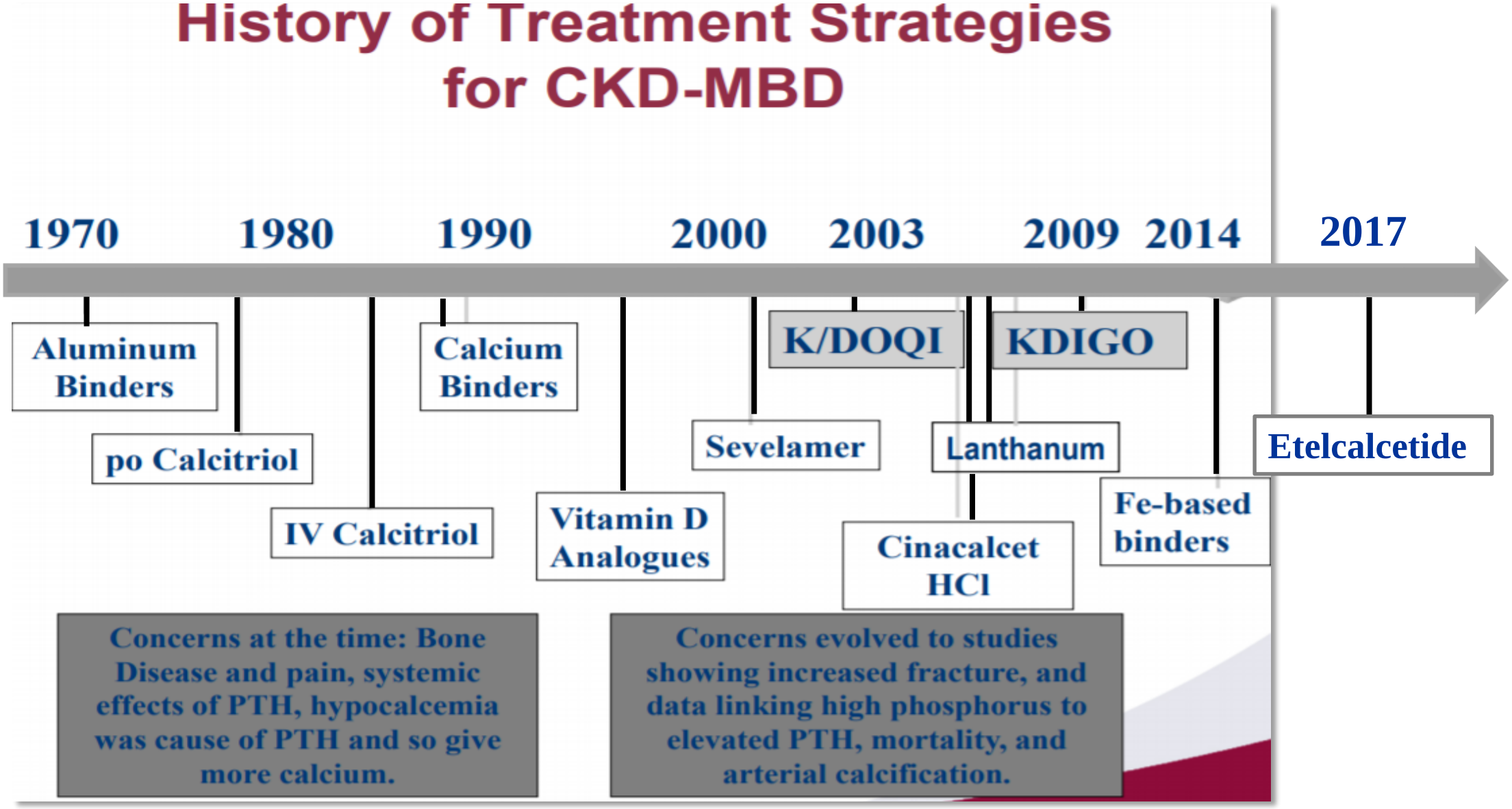
Farmaci "vecchi e nuovi" disponibili per il controllo della malattia metabolica dell'osso

Maurizio Gallieni



Modificata da Sharon M. Moe

Obiettivi terapeutici e potenziali esiti clinici nella CKD-MBD

• Riduzione dell'assorbimento dietetico di fosforo, del sovraccarico di fosforo e della fosfatemia	• Rallentamento progressione CKD, riduzione della massa ventricolare sinsitra; riduzione eventi CV, riduzione mortalità.
• Controllo PTH	• Riduzione eventi CV, riduzione anomalie del rimaneggiamento osseo e fratture
• Riduzione FGF23 ??	• Riduzione eventi CV, riduzione mortalità
• Evitare sovraccarico di calcio e ipercalcemia	• Riduzione calcificazioni vascolari ed eventi CV

Obiettivi terapeutici: livello di PTH in emodialisi

The recently updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines* on CKD-MBD do not identify a specific serum PTH level for patients with CKD receiving hemodialysis, but instead recommend maintaining PTH levels in the range of two to nine times the upper limit of normal for the assay and state that trending elevations in PTH should be addressed prior to reaching the threshold of nine times the upper limit of normal

* KDIGO Workgroup. KDIGO 2017 Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2017; 7: 1–59

Terapia della CKD-MBD

Chelanti del fosforo

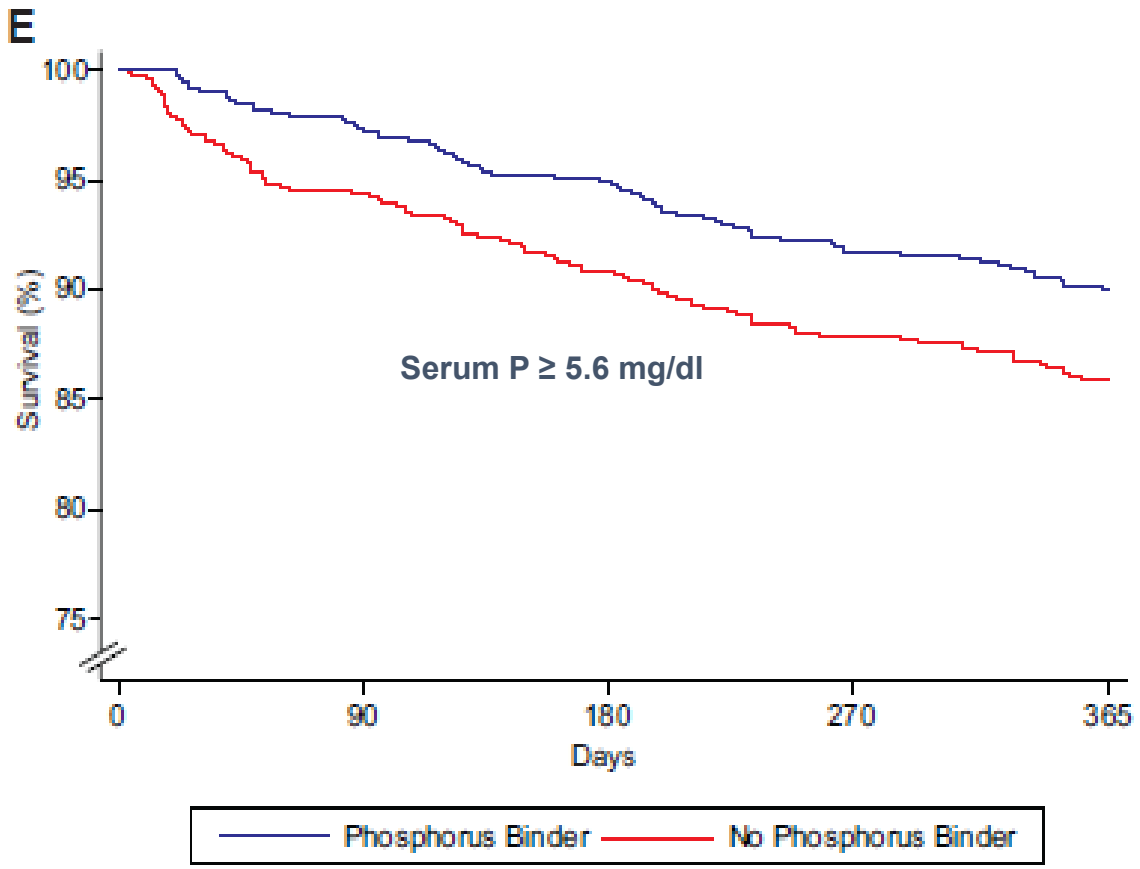
Vitamina D e attivatori del recettore della vitamina D

Calciomimetici

Etelcalcetide

Meccanismo d’azione

P-binders and survival on Hemodialysis



T. Isakova JASN 2008

P-binders and survival on Hemodialysis

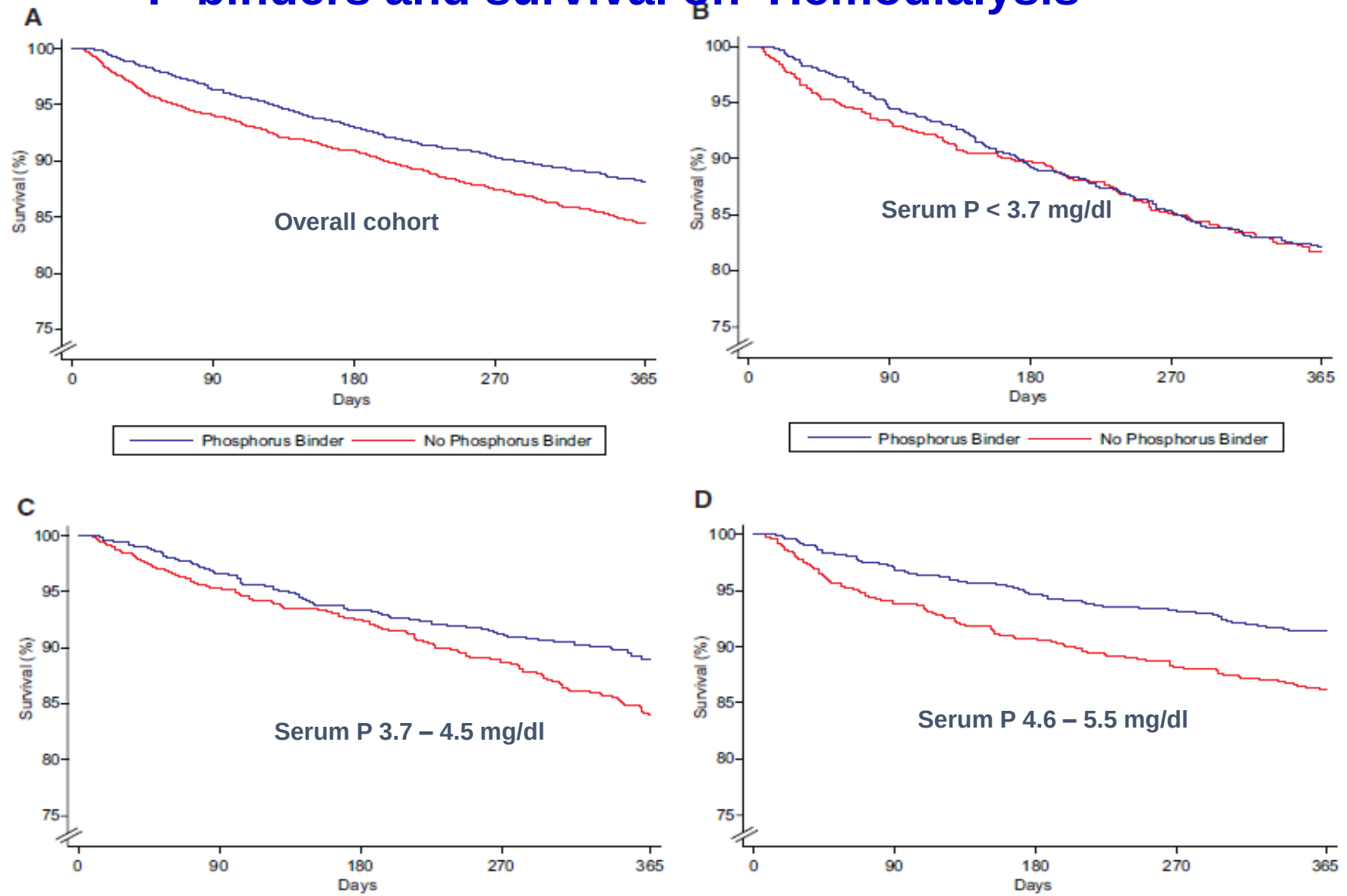


Figure 2. (A through E) Survival of treated and untreated patients in the overall propensity score–matched cohort (A) and according to quartiles of baseline serum phosphate: <3.7 mg/dl (B), 3.7 to 4.5 mg/dl (C), 4.6 to 5.5 mg/dl (D), and ≥5.6 mg/dl (E).

T. Isakova JASN 2008

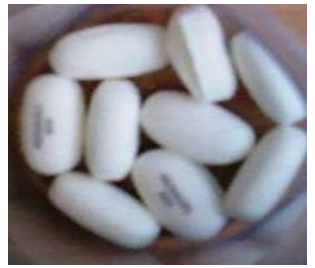
Therapeutic options for hyperphosphatemia in SHPT

1. Restriction of dietary phosphorus
2. Administration of phosphorus binders
   - Calcium-containing binders
     - Calcium carbonate
     - Calcium acetate
     - Calcium acetate/magnesium carbonate
   - Calcium-free binders
     - Sevelamer hydrochloride/carbonate
     - Lanthanum carbonate
     - Iron-based compounds
     - Colestilan
     - Niacine/niacinamide
3. Increase frequency of dialysis sessions

Rodríguez M, et al. Expert Opin Pharmacother 2015;16:1703–1716.

Phosphate binders: Use and mode of action

- Administered when dietary phosphate restrictions are inadequate to control serum levels of phosphorus
- Bind to phosphate in the gastrointestinal tract to prevent absorption of phosphate molecules contained in food
- Administered with meals. Number of pills directly proportional to the size of meals
- Phosphate binders do not influence the phosphorus that is already absorbed or released from bone



Rodríguez M, et al. Expert Opin Pharmacother 2015;16:1703–1716.
National Kidney Foundation. Am J Kidney Dis 2003;42(suppl 3):S1–S201.

Terapia della CKD-MBD

Chelanti del fosforo

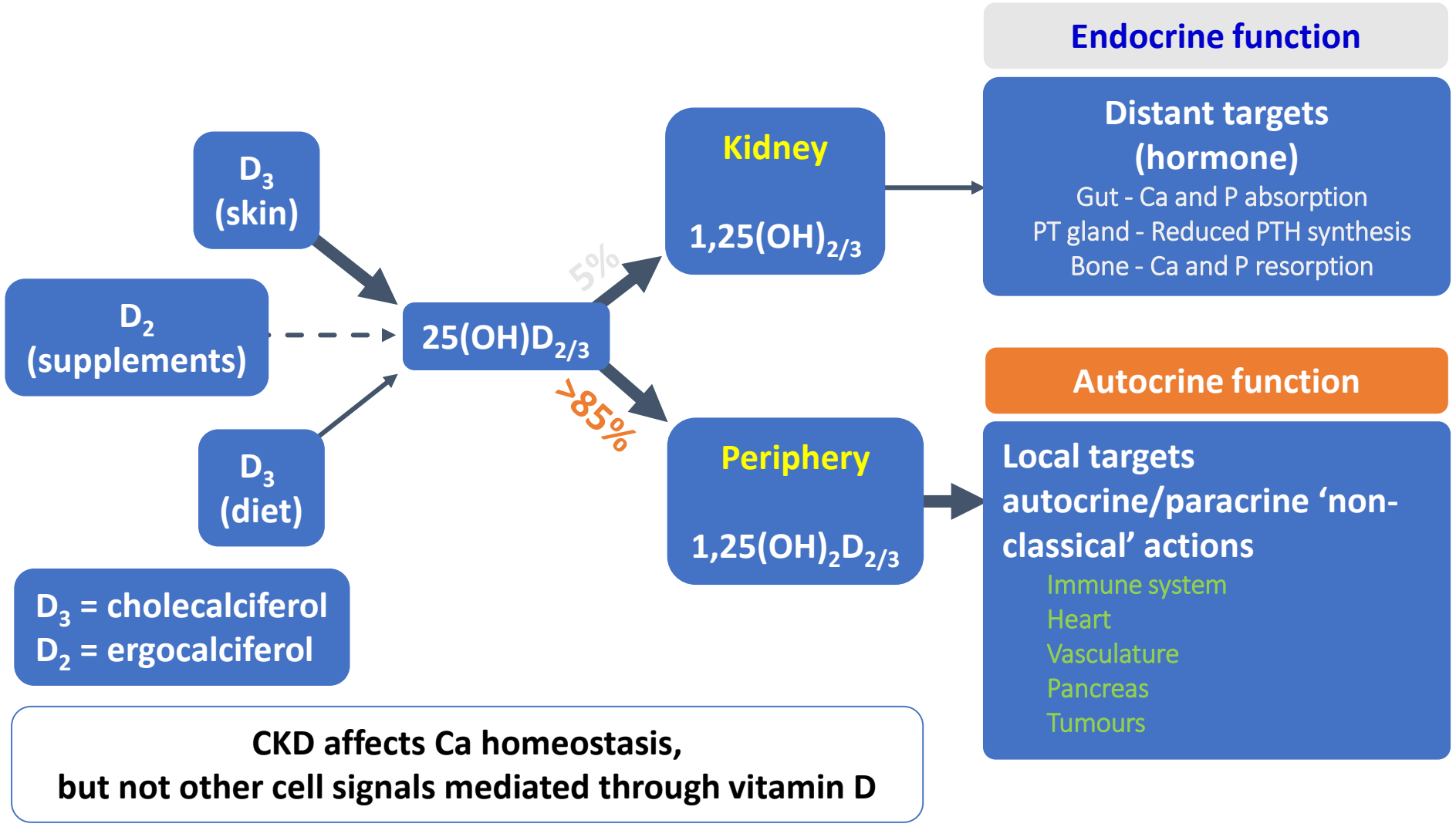
Vitamina D e attivatori del recettore della vitamina D

Calciomimetici

Etelcalcetide

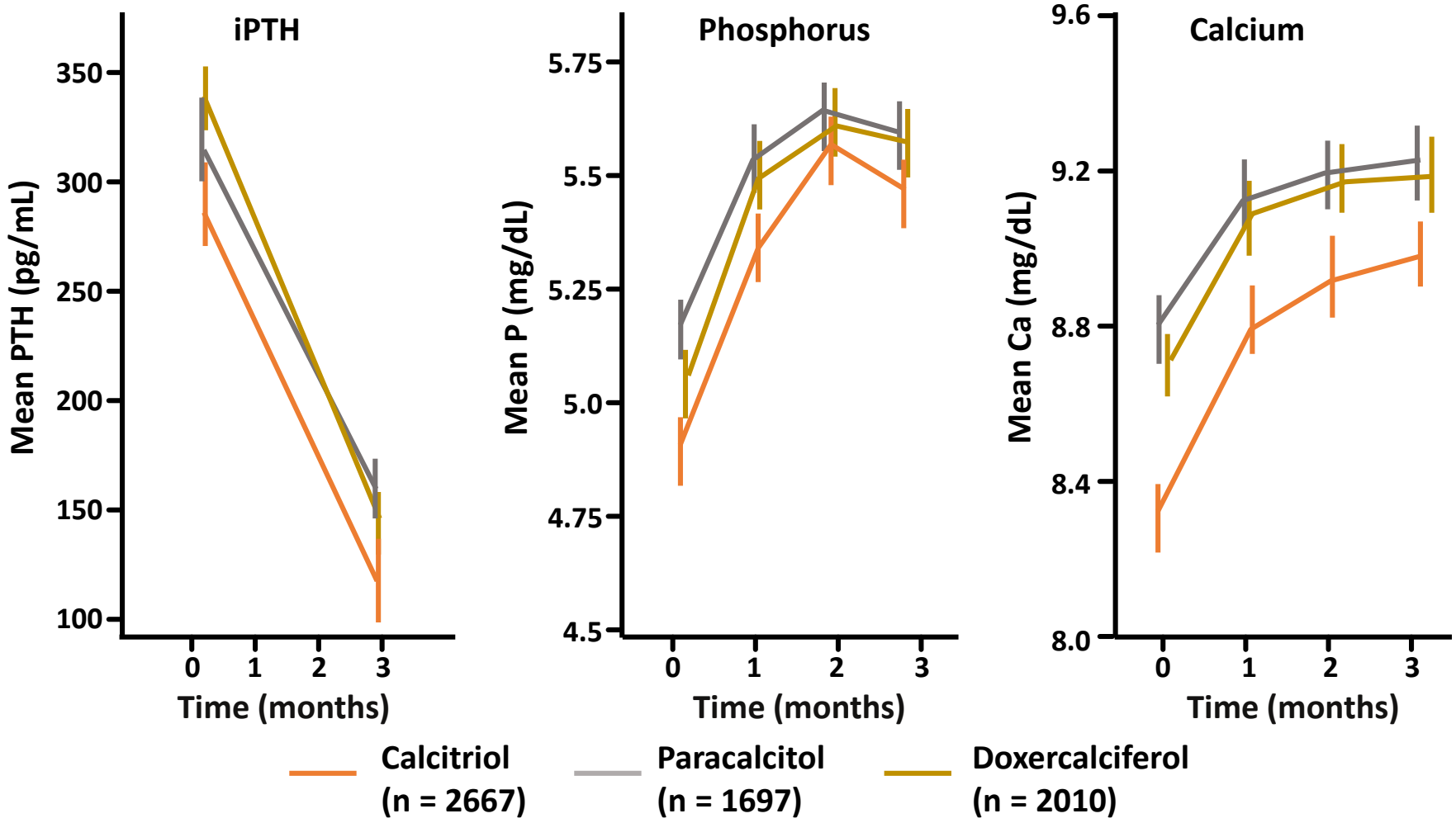
Meccanismo d’azione

Mode of action of 1,25-dihydroxyvitamin D



Redrawn from: Heaney RP. Clin J Am Soc Nephrol 2008;3:1535-1541; K/DOQI Clinical Practice Guidelines Am J Kindey Dis 2003;42(Suppl 3).

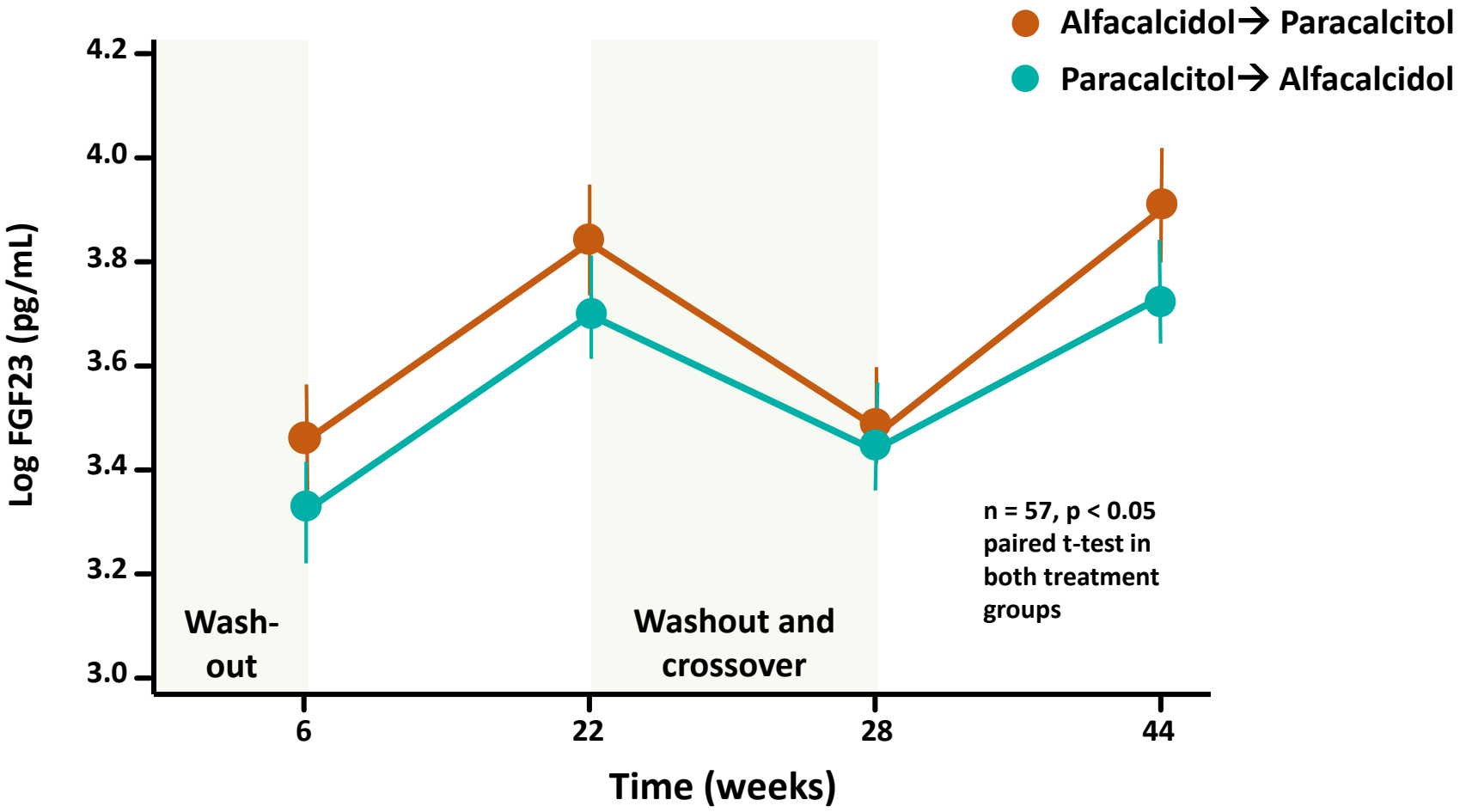
Vitamin D analogs lower PTH and raise serum Ca and P



Error bars represent 95% confidence intervals

Tentori F, et al. Kidney Int 2006;70:1858–1865.

Vitamin D analogues increase plasma FGF23 in hemodialysis patients

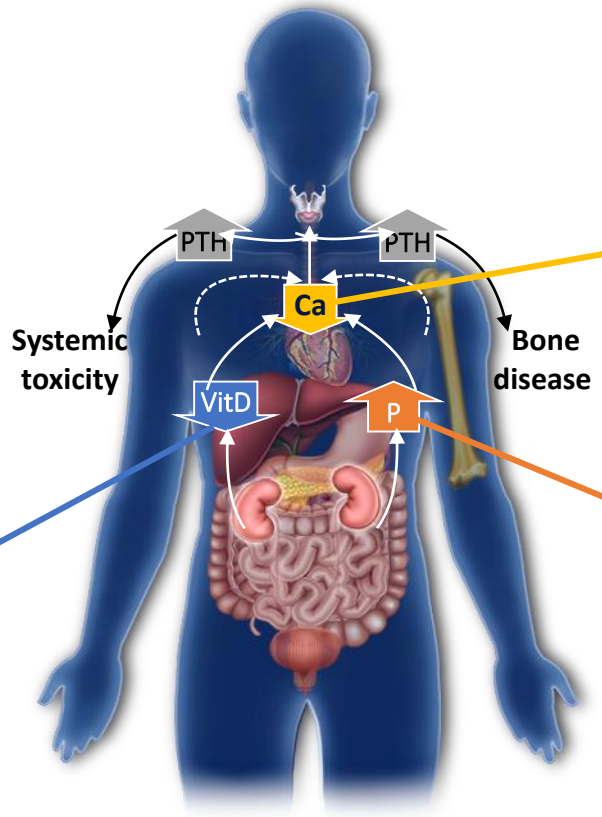


Serum samples were collected at the beginning (6 and 22 weeks) and at the end (28 and 44 weeks) of each treatment period, interrupted by a 6-week washout period.

Adapted from: Hansen D, et al. Nephrol Dial Transplant 2012;27:2263–2269.

Summary of traditional treatment approaches to the management of SHPT

The combined use of vitamin D and phosphate binders often does not adequately control PTH levels



Control calcium
- Control intake
- Adjust dialysate calcium
- Use calcium supplements or vitamin D therapy (if calcium low)

Increase vitamin D levels
- Administer vitamin D sterols to reduce PTH

Lower elevated serum phosphate
- Control dietary intake
- Use phosphate binders

Treatment approach = vitamin D + phosphate binders as first-line therapy; cinacalcet later in the course of therapy.

Adapted from: Tomasello S. Diabetes Spectrum 2008;21:19–25.

Limitations of vitamin D and phosphate binders

- **Vitamin D**
  - Parathyroid gland hyperplasia leads to reduced vitamin D receptor and calcium receptor expression which may limit efficacy of vitamin D[1]
  - Hypercalcemia and hyperphosphatemia
    - High phosphorus increases PTH[2]
    - Risk for vascular calcification[3,4]
- **Phosphate binders**
  - Effective, but can be associated with poor compliance[5]
  - No effect on bone-released phosphorus[5]
  - High-dose calcium-containing binders increase Ca^{2+} load and could raise risk of cardiovascular calcifications[4]

1. Fukuda N, et al. J Clin Invest 1993;92:1436–1443; 2. Tallon S, et al. Kidney Int 1996;49:1441–1446;
3. Jono S, et al. Circulation 1998;98:1302–1306; 4. Goodman WG, et al. N Engl J Med 2000;342:1478–1483;
5. National Kidney Foundation. Am J Kidney Dis 2003;42(suppl 3):S1–S201.

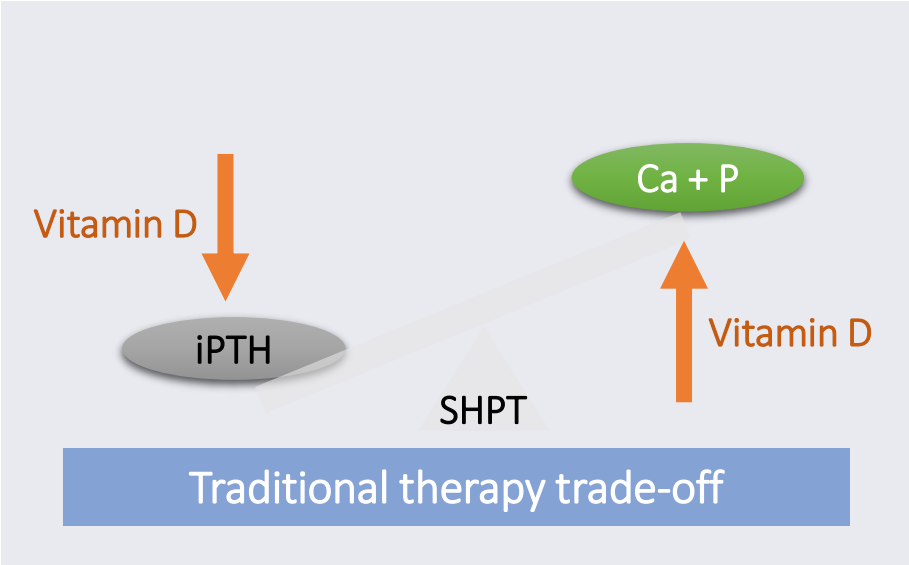
- Terapia della CKD-MBD
  - Chelanti del fosforo
  - Vitamina D e attivatori del recettore della vitamina D
  - Calciomimetici
- Etelcalcetide
  - Meccanismo d’azione

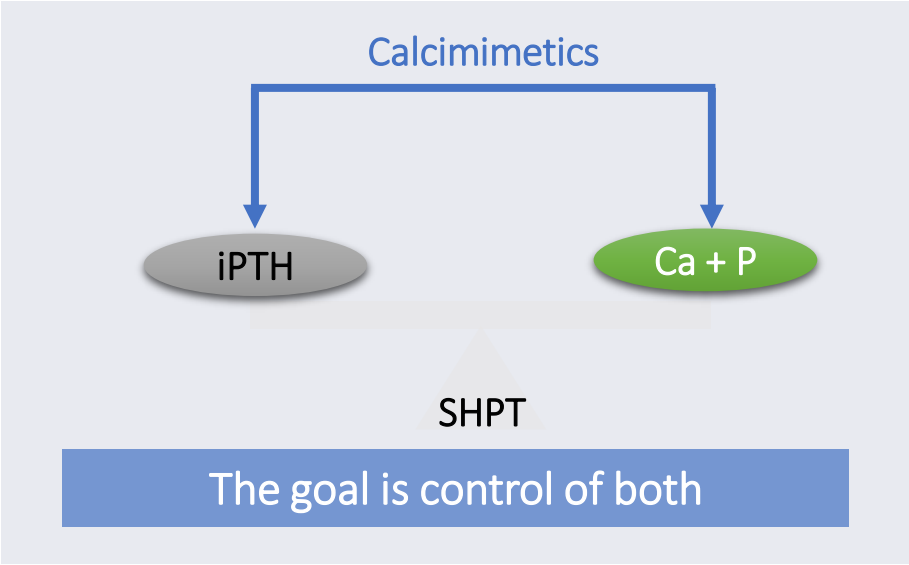
Calcimimetics specifically activate the CaSR

- Inhibit PTH secretion
  - Promptly lower plasma PTH levels, the main biochemical feature of HPT
  - Effective in all types of HPT
- Diminish PTH gene expression (mRNA)
  - Reduce PTH production
  - Less hormone available for secretion
  - Potentially important in patients with enlarged parathyroid glands
- Retard development of parathyroid gland hyperplasia
  - Key determinant of the severity of SHPT
  - May alter disease progression over time
  - Reduce the need for surgical parathyroidectomy

Rodriguez M, et al. Am J Physiol Renal Physiol 2005;288:F253–F264; Goodman WG, et al. Adv Ren Replace Ther 2002;9:200–208; Poon G. BUMC Proc 2005;18:181–184; Walter S, et al. J Pharmacol Exp Ther 2013;346:229–240.

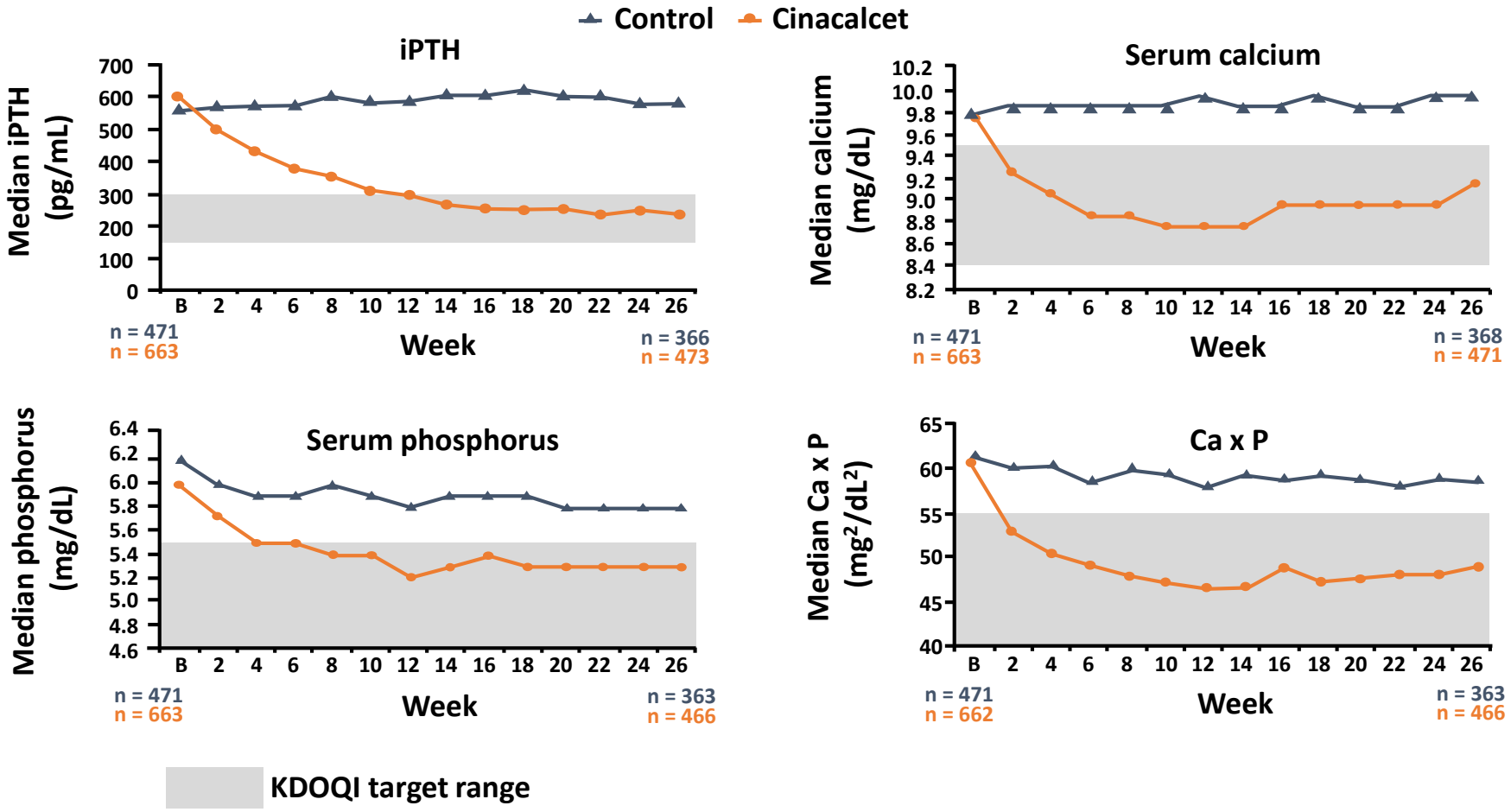
Calcimimetics can simultaneously reduce PTH, Ca and phosphate compared with vitamin D therapy





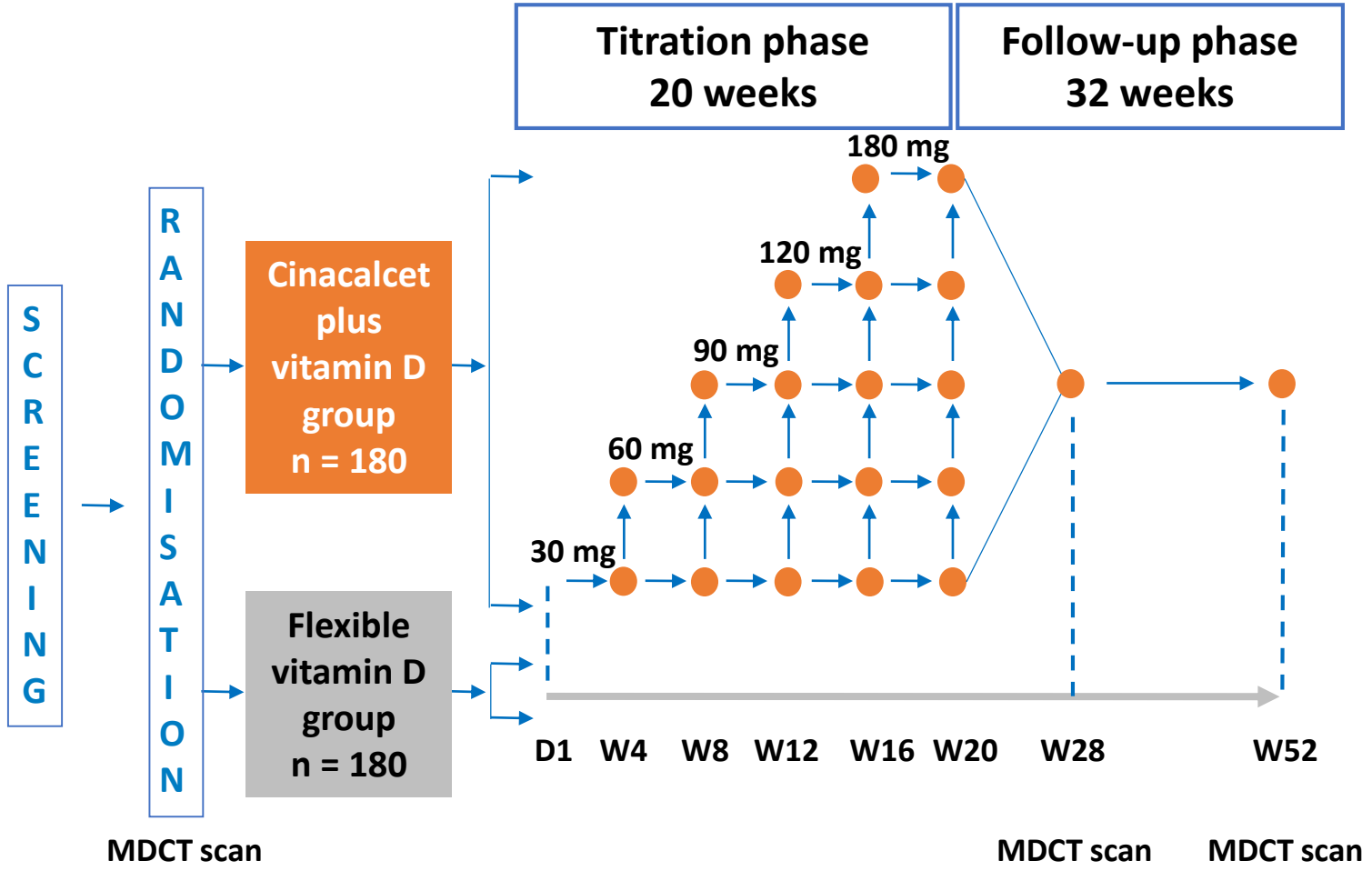
Moe SM, et al. Kidney Int 2005;67:760–771.

Cinacalcet reduced PTH, calcium, phosphorus and Ca x P



Adapted from: Moe SM, et al. Kidney Int 2005;67:760–771 and National Kidney Foundation. Am J Kidney Dis 2003;42:S1–S201

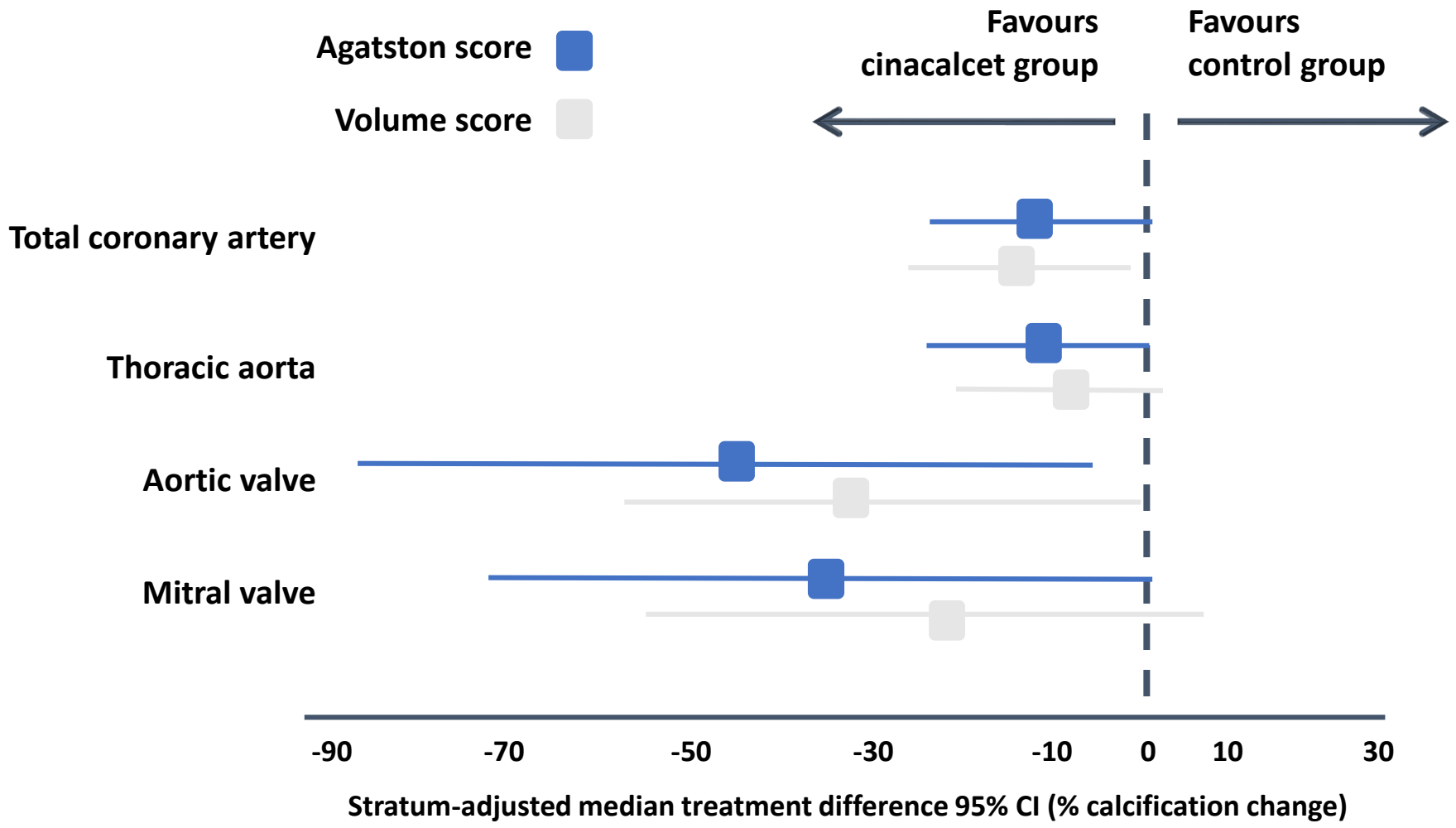
ADVANCE study: Impact of cinacalcet on vascular / valvular calcification in hemodialysis patients



D: study day; MDCT: multi detector computerised tomography; W: study week

Raggi P, et al. Nephrol Dial Transplant 2011;26:1327–1339.

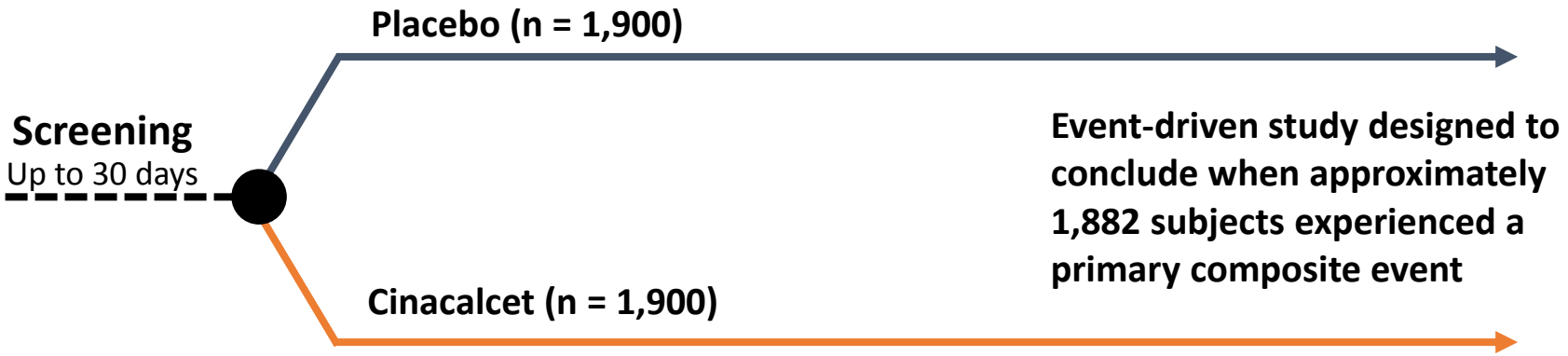
ADVANCE: Cinacalcet may attenuate vascular / valvular calcification in haemodialysis patients



Raggi P, et al. Nephrol Dial Transplant 2011;26:1327–1339.

EVOLVE study design
Impact of cinacalcet on cardiovascular events

Primary composite endpoint:
Time to death or the first nonfatal cardiovascular event

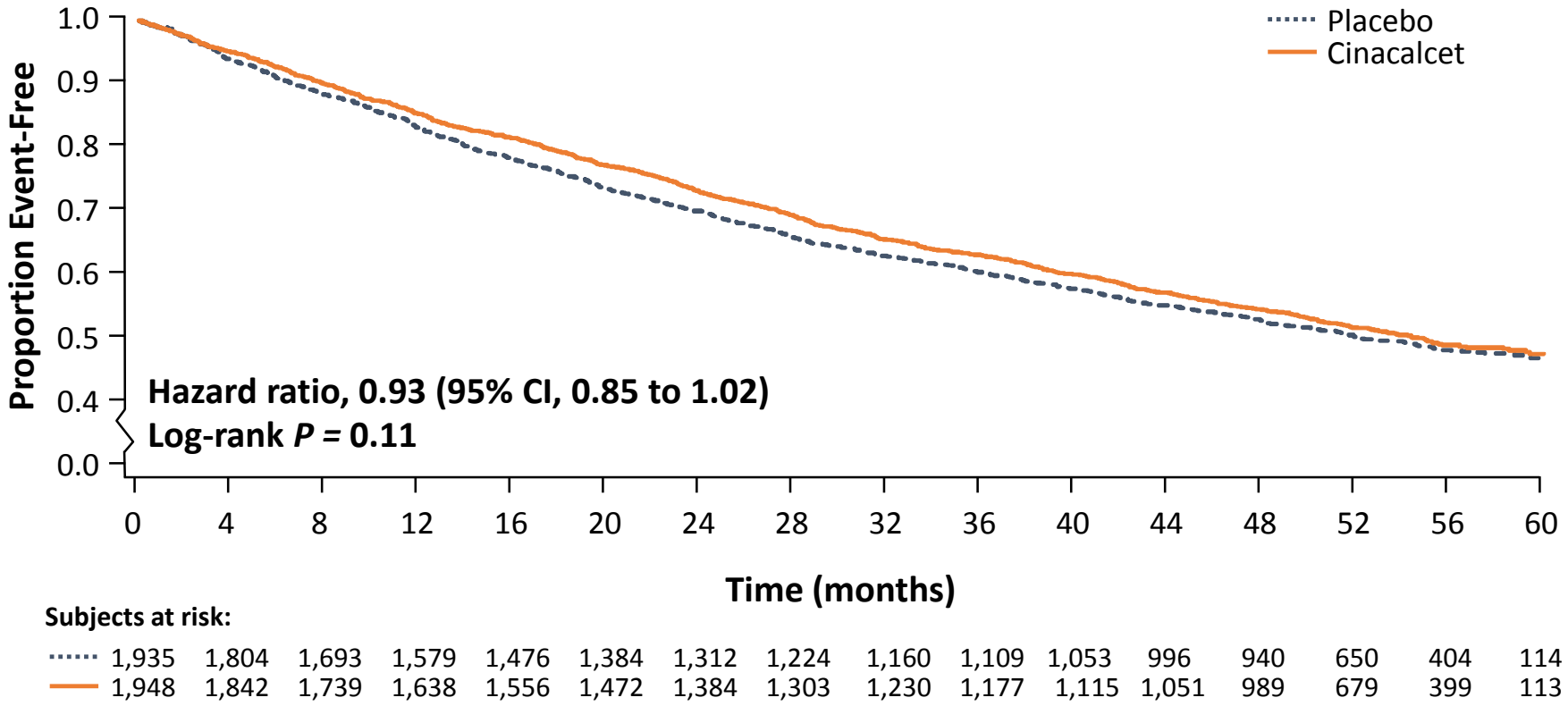


- Multicentre, prospective, randomised, double-blind, placebo-controlled trial
- Starting dose of 30 mg once daily
- Possible sequential doses of cinacalcet or placebo included 60, 90, 120, and 180 mg
- All patients could receive vitamin D sterols and phosphate binders, as necessary, at the discretion of the physician
- Anticipated study duration = 4 years
- Actual study duration > 5 years

The EVOLVE Trial Investigators. *N Engl J Med*. 2012;367:2482–2494
Adapted from: The EVOLVE Trial Investigators [Supplementary Appendix]. N Engl J Med 2012;1-54.

Time to the primary composite endpoint in EVOLVE was not significant: ITT Analysis

Primary composite endpoint: death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event



Adapted from The EVOLVE Trial Investigators. *N Engl J Med*. 2012;367:2482-2494.
The cinacalcet and placebo groups included vitamin D and phosphate binders, if prescribed.
The EVOLVE Trial Investigators. *N Engl J Med*. 2012;367:2482-2494.

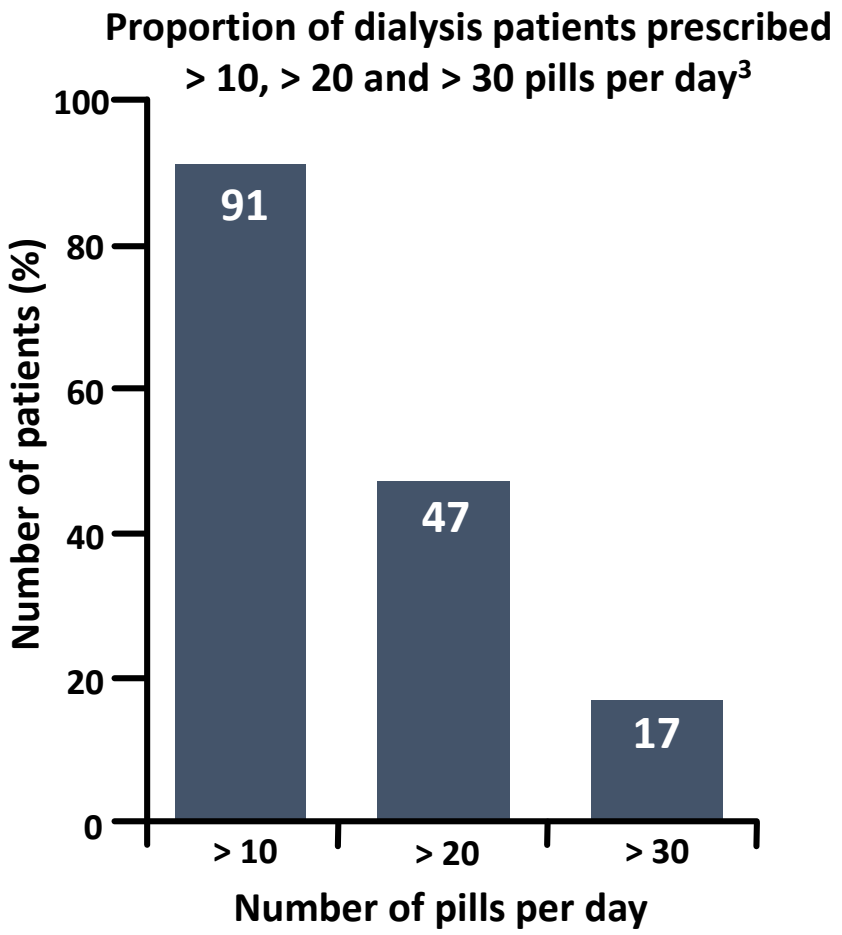
Limitations of cinacalcet

Side effects

- Gastrointestinal problems including nausea and vomiting are very common[1]
- GI problems are the predominant reason for discontinuation due to undesirable effects
- Cinacalcet treatment may result in hypocalcaemia in some patients[1]

Pill burden

- **Pill burden of patients undergoing dialysis is high, and patients are at high risk of non-adherence[2-4]**
- **Adherence to cinacalcet[5-7]: 29–54%**



1. Mimpara® (cinacalcet) Summary of Product Characteristics, Amgen; 2. Chiu YW, et al. Clin J Am Soc Nephrol 2009;4:1089–1096; 3. Neri L, et al. Am J Nephrol 2011;34:71–76; 4. Ghimire S, et al. Am J Nephrol 2016;43:318–324; 5. Gincherman Y, et al. Hemodial Int 2010;14:68–72; 6. Lee A, et al. J Med Econ 2011;14:798–804; 7. Park H, et al. J Manag Care Spec Pharm 2014;20:862–876.

Terapia della CKD-MBD

Chelanti del fosforo

Vitamina D e attivatori del recettore della vitamina D

Calciomimetici

Etelcalcetide

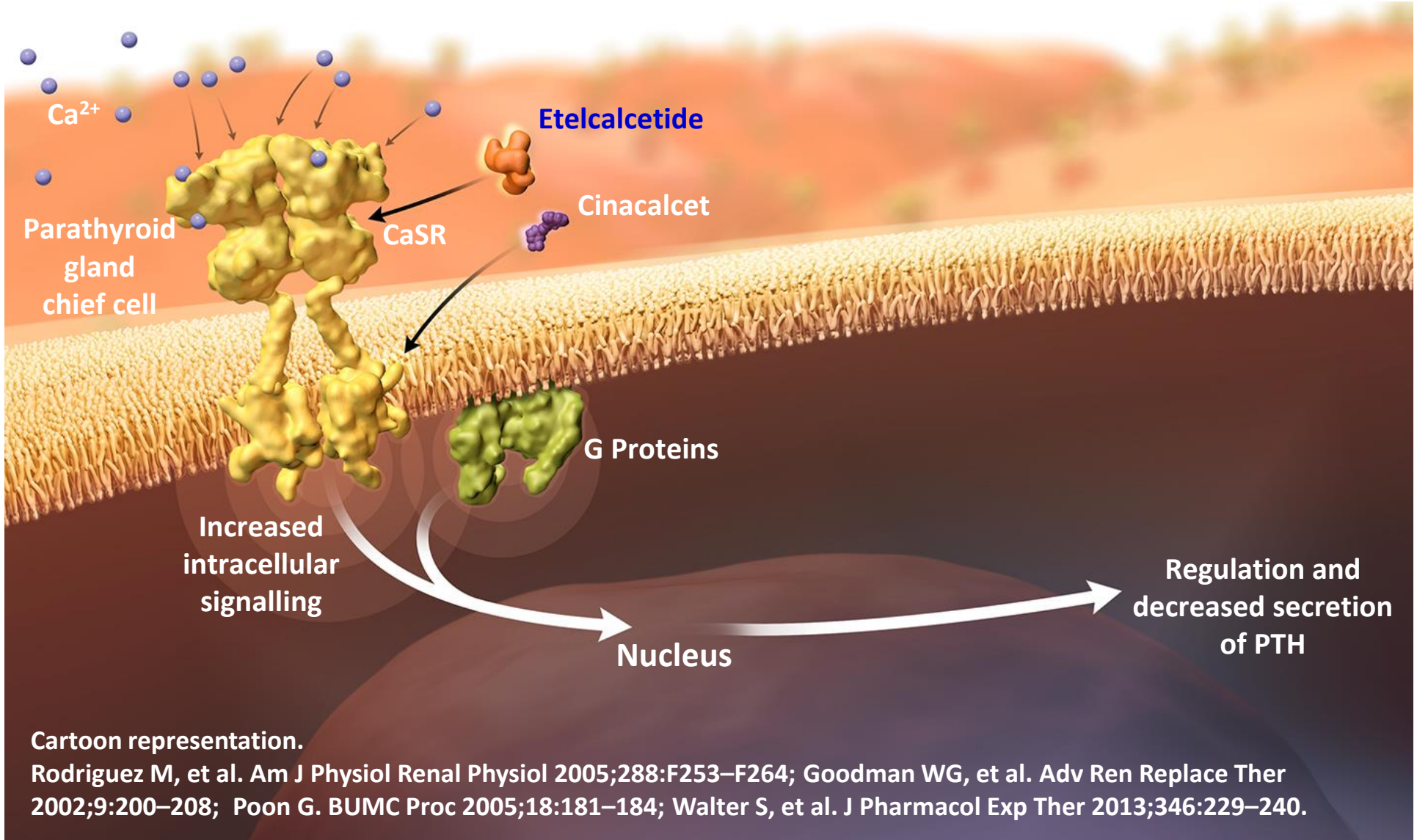
Meccanismo d’azione

Comparison of the modes of action of cinacalcet and etelcalcetide

	Cinacalcet[1-3]	Etelcalcetide[4-10]
Class	Calcimimetic	Calcimimetic
Compound	Small organic molecule; molecular weight = 393.9 g/mol	Synthetic 8-amino acid peptide (comprised primarily of D amino acids)
Mode of action	Interacts with membrane-spanning segments of CaSR and enhances signal transduction, thereby reducing PTH secretion	Interacts with the extracellular domain of CaSR to enhance signal transduction, thereby reducing PTH secretion
Duration of action	Short acting	Long acting

1. Mimpara® (cinacalcet) Summary of Product Characteristics, Amgen; 2. Goodman WG. Adv Ren Replace Ther 2002;9:200–208; 3. Srinivas TR, et al. Clin J Am Soc Nephrol 2006;1:323–326; 4. Cunningham J, et al. Presented at the 52nd ERA-EDTA Congress; May 2015; London, UK; 5. Chen P, et al. J Clin Pharmacol 2015;55:620–628; 6. Goodman WG, et al. Kidney Int 2008;74:276–288; 7. Moallem E, et al. J Biol Chem 1998;273:5253–5259; 8. Brown EM. Rev Endocr Metab Disord 2000;1:307–315; 9. Walter S, et al. J Pharmacol Exp Ther 2013;346:229–240; 10. Parsabiv® (etelcalcetide) Summary of Product Charactersitics, Amgen.

Etelcalcetide, new i.v. calcimimetic - Mode of action



Cartoon representation.

Rodriguez M, et al. Am J Physiol Renal Physiol 2005;288:F253–F264; Goodman WG, et al. Adv Ren Replace Ther 2002;9:200–208; Poon G. BUMC Proc 2005;18:181–184; Walter S, et al. J Pharmacol Exp Ther 2013;346:229–240.

Metabolism and clearance of etelcalcetide differs substantially from cinacalcet

- Renal excretion vs hepatic metabolism
  - Cinacalcet is metabolised by multiple enzymes, predominantly CYP3A4 and CYP1A2[1]
  - Etelcalcetide is not metabolised by CYP450 enzymes[2]
  - Etelcalcetide is rapidly cleared in subjects with normal renal function[2]
- Extended half-life of etelcalcetide occurs only among subjects with marked impairments in kidney function[2]

1. Mimpara® (cinacalcet) Summary of Product Characteristics, Amgen; 2. Etelcalcetide Summary of Product Characteristics, Amgen.

Terapia della CKD-MBD

- Chelanti del fosforo
- Vitamina D e attivatori del recettore della vitamina D
- Calciomimetici

Etelcalcetide

- Meccanismo d’azione
- Studi clinici

Etelcalcetide: studi clinici

1. Etelcalcetide versus Placebo. Block et al. JAMA. 2017;317(2):146-155

2. Etelcalcetide versus Cinacalcet. Block et al. JAMA. 2017;317(2):156-164

3. Etelcacetide open-label extension (OLE) trial. Bushinsky et al. Nephrol Dial Transplant (2019)

Research

JAMA | Original Investigation

Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
Two Randomized Clinical Trials

Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn M. Chertow, MD, MPH

Block et al. JAMA. 2017;317(2):146-155

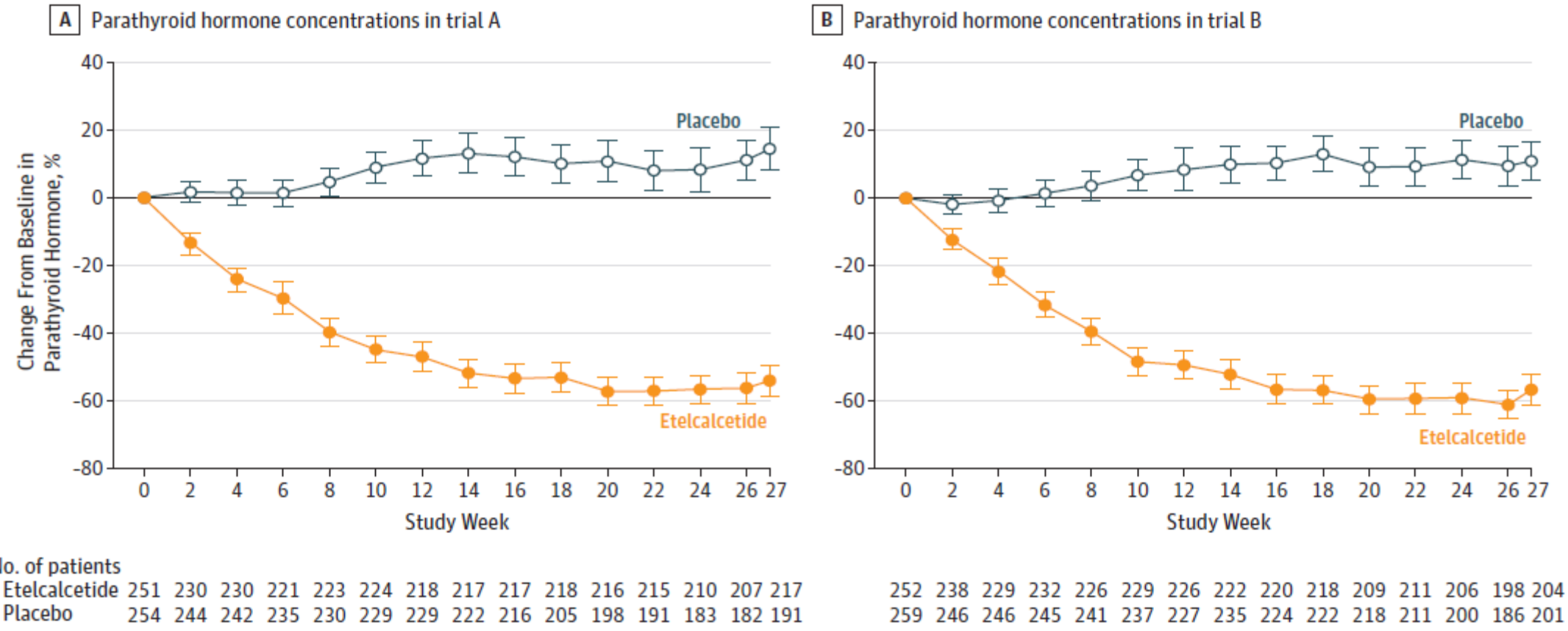
Key Points

Question What is the effect of the intravenous calcimimetic etelcalcetide compared with placebo on serum parathyroid hormone concentrations in patients receiving hemodialysis?

Findings In 2 randomized clinical trials that included 1023 adults receiving hemodialysis with moderate to severe secondary hyperparathyroidism, patients randomized to etelcalcetide compared with placebo were significantly more likely to have a greater than 30% reduction in mean parathyroid hormone concentrations over 26 weeks (74.0% vs 8.3% and 75.3% vs 9.6%).

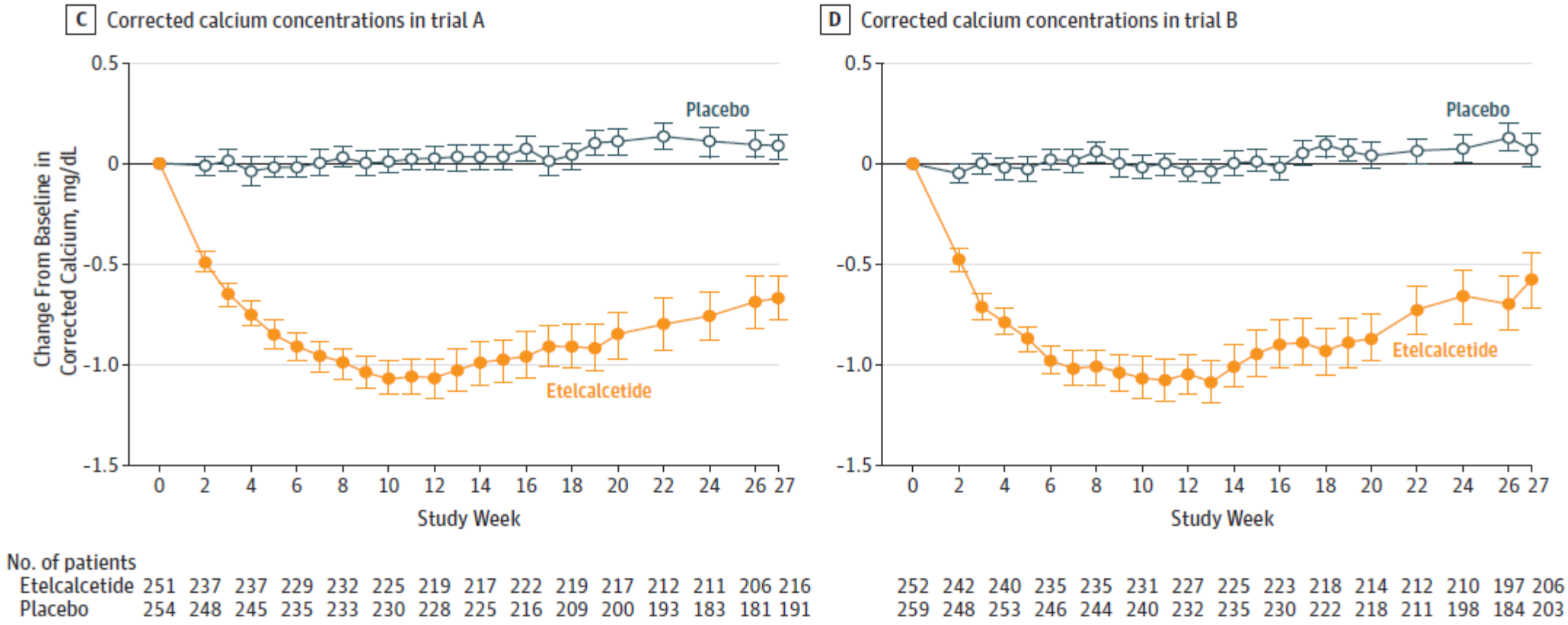
Block et al. JAMA. 2017;317(2):146-155

Mean Percentage Change From Baseline by Study Week in PTH Concentrations by Randomized Group in Each Trial



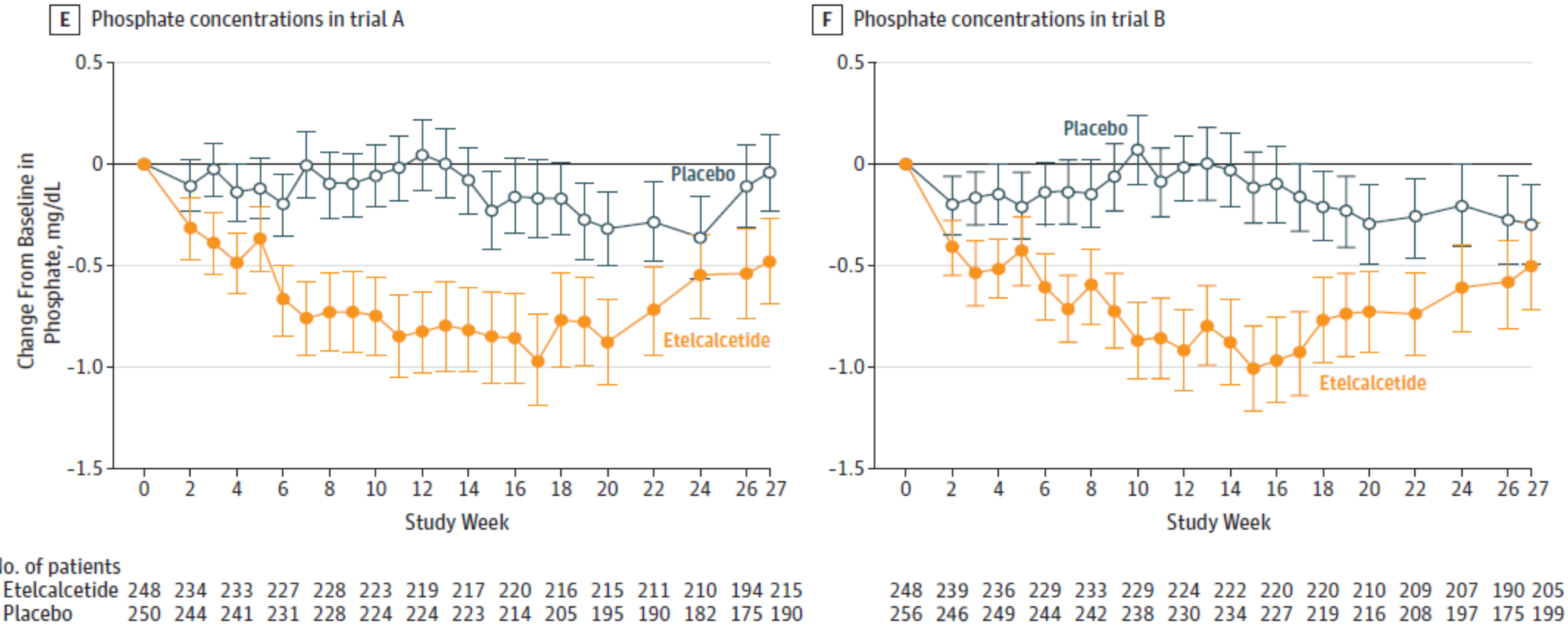
Block et al. JAMA. 2017;317(2):146-155

Mean Percentage Change From Baseline by Study Week in Corrected Calcium Concentrations by Randomized Group in Each Trial



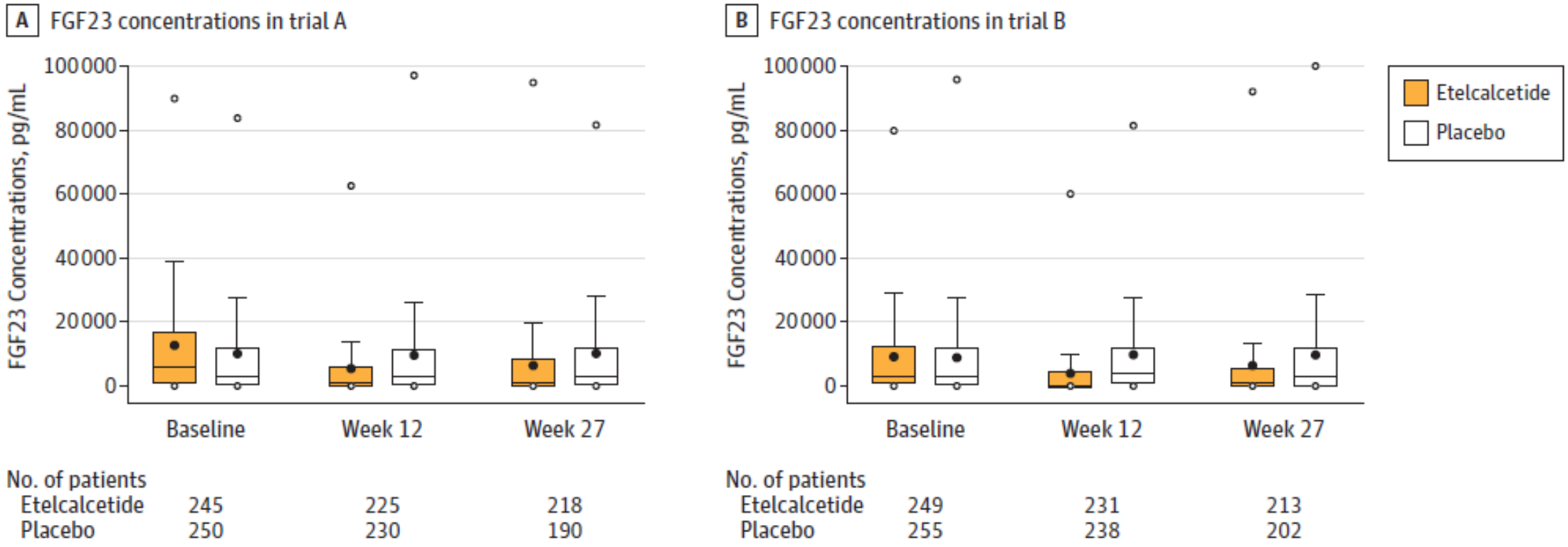
Block et al. JAMA. 2017;317(2):146-155

Mean Percentage Change From Baseline by Study Week in Phosphate Concentrations by Randomized Group in Each Trial



Block et al. JAMA. 2017;317(2):146-155

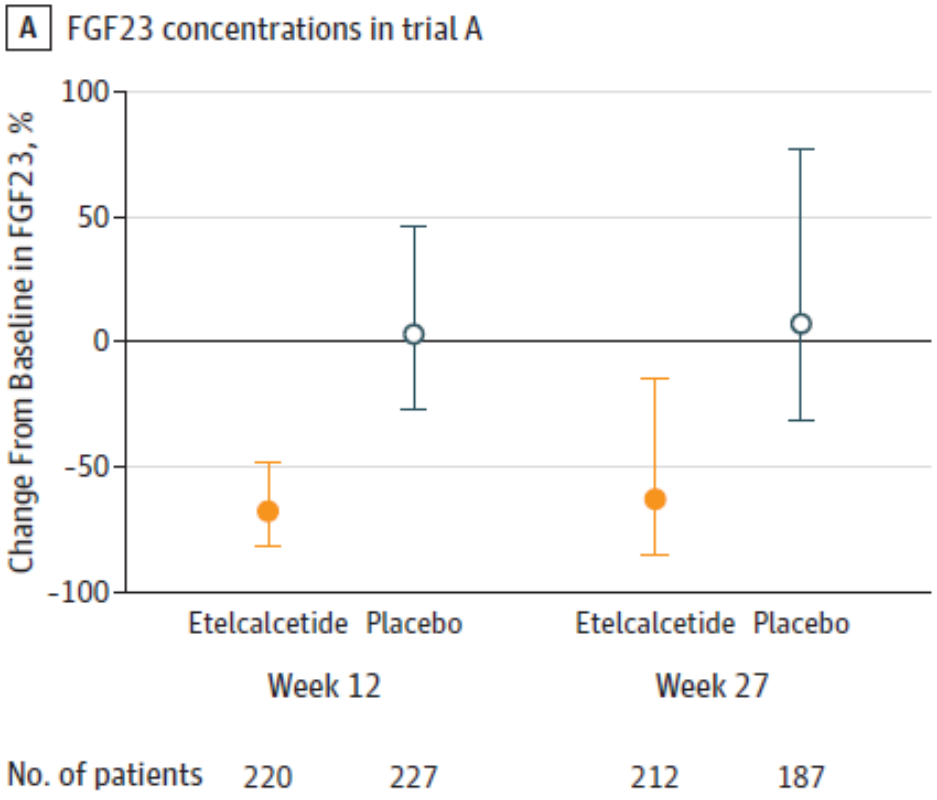
Serum Intact Fibroblast Growth Factor 23 (FGF23) Concentrations at Baseline, Week 12, and Week 27 by Randomized Group in Each Trial

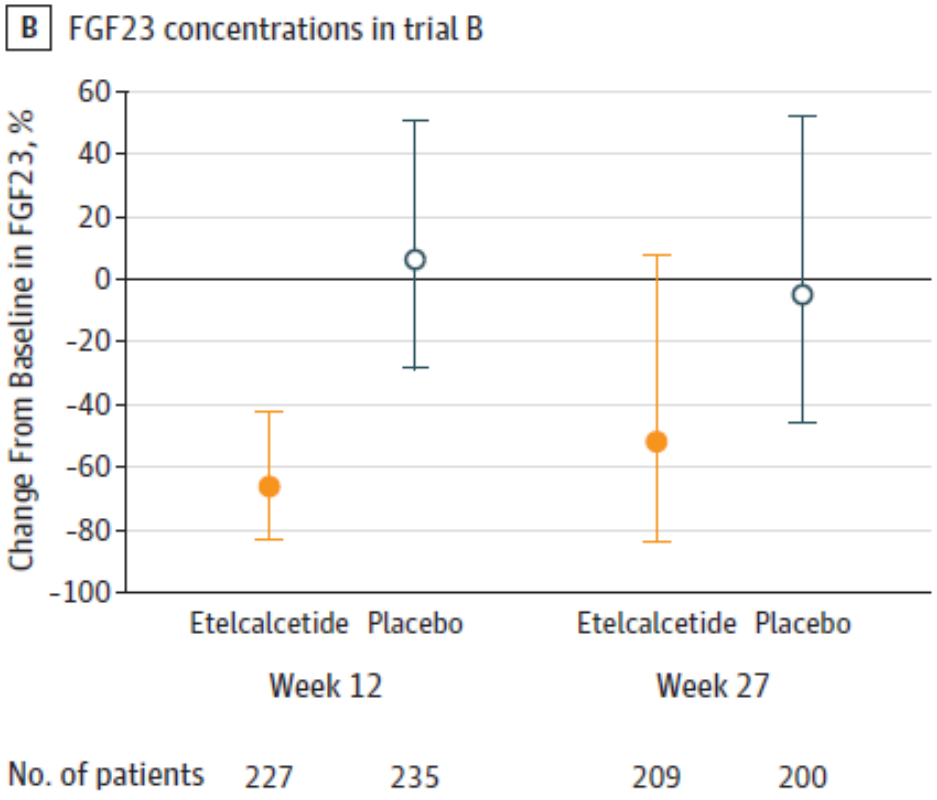


Closed circles represent means; solid lines, medians; boxes, interquartile ranges; whiskers, 1.5 times interquartile ranges; and top and bottom open circles, maximum and minimum observations.

Block et al. JAMA. 2017;317(2):146-155

Median Percentage Change From Baseline in Serum Intact Fibroblast Growth Factor 23 (FGF23) at Weeks 12 and 27 by Randomized Group in Each Trial





Error bars indicate interquartile ranges.

Block et al. JAMA. 2017;317(2):146-155

Research

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

A Randomized Clinical Trial

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

Block et al. JAMA. 2017;317(2):156-164

Key Points

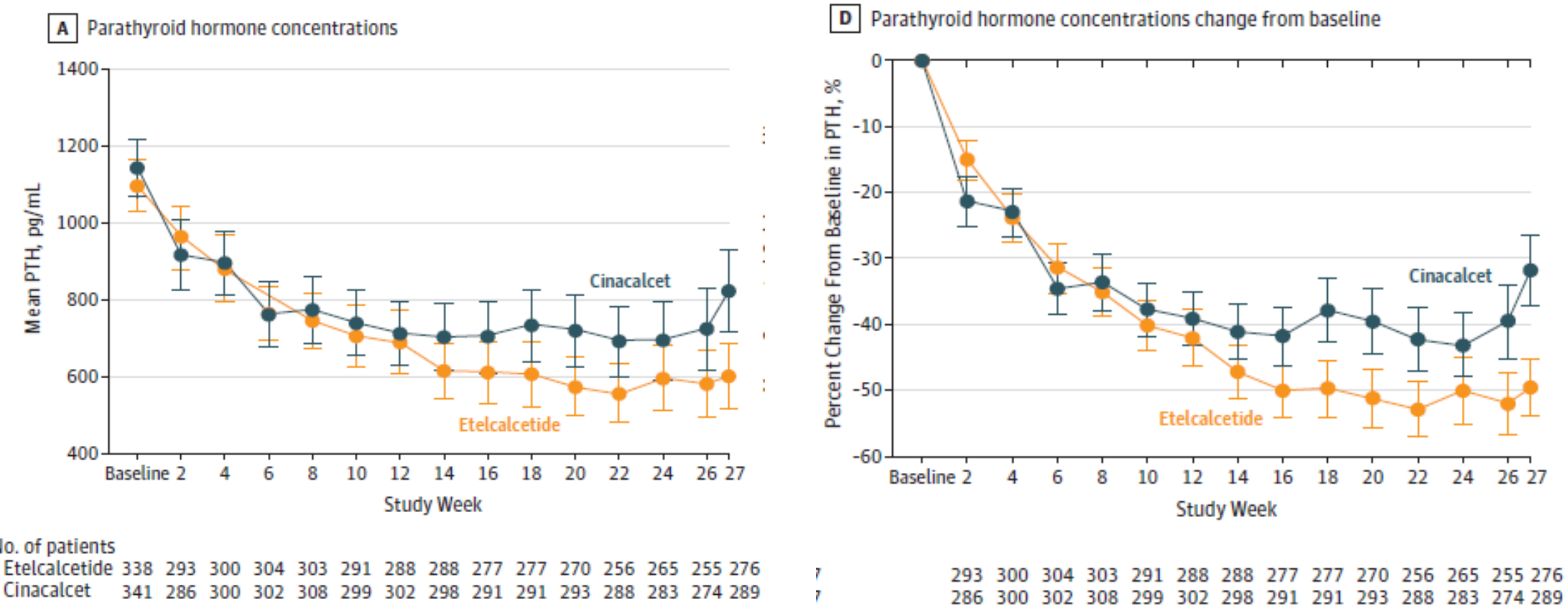
Question What is the effect of the intravenous calcimimetic etelcalcetide compared with the oral calcimimetic cinacalcet on serum parathyroid hormone (PTH) concentrations in patients receiving hemodialysis?

Findings In a randomized clinical trial that included 683 adults receiving hemodialysis with PTH levels higher than 500 pg/mL, 68.2% of patients randomized to receive etelcalcetide vs 57.7% randomized to receive cinacalcet experienced more than a 30% reduction in mean PTH concentrations over 27 weeks, a significant difference.

Meaning Etelcalcetide was more effective than cinacalcet in lowering PTH concentrations in patients receiving dialysis with secondary hyperparathyroidism receiving hemodialysis, but further research is needed to assess clinical outcomes as well as longer-term efficacy and safety.

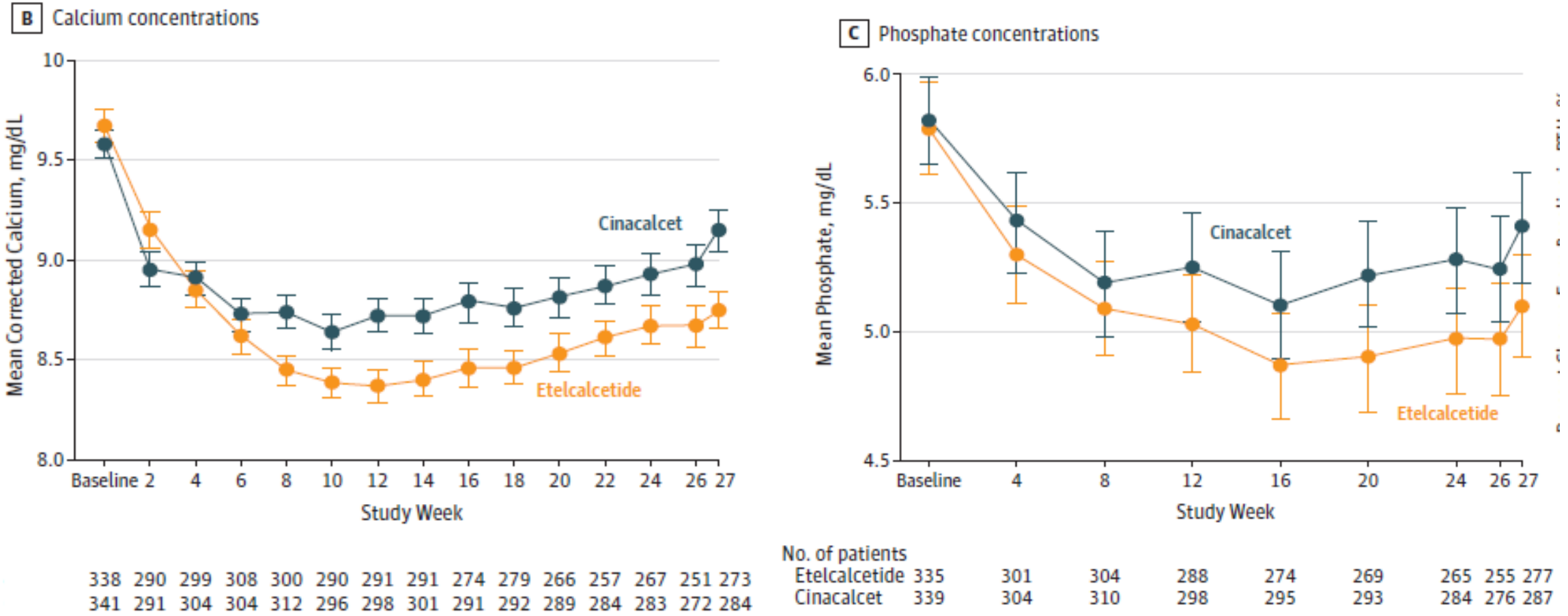
Block et al. JAMA. 2017;317(2):156-164

Parathyroid Hormone Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week



Block et al. JAMA. 2017;317(2):156-164

Calcium, and Phosphate Concentrations in Patients Receiving Cinacalcet or Etelcalcetide by Study Week



Block et al. JAMA. 2017;317(2):156-164

Etelcalcetide and Cinacalcet Dosing

The median average weekly etelcalcetide dose during the efficacy assessment phase was 15.0 mg (interquartile range [IQR], 9.2-30.0 mg) and the median average daily cinacalcet dose was 51.4 mg (IQR, 26.4-80.4 mg).

Self-reported Nausea and Vomiting

The adjusted mean [SE] weekly days of vomiting or nausea in the first 8 weeks of treatment were not significantly different for patients randomized to etelcalcetide (0.4 [0.04]) and cinacalcet (0.3 [0.03]), corresponding to a rate ratio of 1.20 (95% CI, 0.89-1.49).

Adverse Events

Of the 338 patients treated with etelcalcetide, 62 (18.3%) reported nausea and 45 (13.3%), vomiting. Of the 341 patients treated with cincalcet, 77 (22.6%) reported nausea and 47 (13.8%), vomiting. Death occurred in 9 patients (2.7%) in the etelcalcetide-treated group and 6 (1.8%) in the cinacalcet-treated group

Block et al. JAMA. 2017;317(2):156-164

Heart Failure in Patients Receiving Etelcalcetide or Cinacalcet

- **Heart failure events were E: 10 (3.0%) and C: 2 (0.6%), respectively, of which 5 and 1 were considered serious.**
- **Although there were numerically more episodes of heart failure in the etelcalcetide group, overall event rates were similar to rates observed in the EVOLVE trial.**
- **Initially, there were concerns that cinacalcet might lead to heart failure and sudden death owing to the effects of reduced serum calcium on myocardial contractility and the QT interval, respectively. However, rates of heart failure and sudden death were reduced in patients randomized to cinacalcet in the EVOLVE trial.**

Block et al. JAMA. 2017;317(2):156-164

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Nephrology Dialysis Transplantation

One-year safety and efficacy of intravenous etelcalcetide in patients on hemodialysis with secondary hyperparathyroidism

David A. Bushinsky[1], Glenn M. Chertow[2], Sunfa Cheng[3], Hongjie Deng[4], Nelson Kopyt[5], Kevin J. Martin[6], Anjay Rastogi[7], Pablo Ureña-Torres[8], Marc Vervloet [9] and Geoffrey A. Block[10]

Open-label extension (OLE) trial evaluated the long-term (52 wks) effects of etelcalcetide for sHPT treatment in 890 patients receiving hemodialysis.

Conclusions. Etelcalcetide effectively lowered PTH and its effect was sustained, while no new safety concerns emerged over a 1-year treatment period.

Table 1. Baseline demographics and clinical characteristics

Characteristic	Etelcalcetide ($n = 891$)
Sex, *n* (%)	
Male	550 (61.7)
Female	341 (38.3)
Race, *n* (%)	
White	567 (63.6)
Black	270 (30.3)
Asian	29 (3.3)
Other	25 (2.7)
Age, mean (SD), years	58.3 (14.4)
<65, *n* (%)	577 (64.8)
≥65, *n* (%)	314 (35.2)
≥75, *n* (%)	125 (14.0)

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Table 1. Baseline demographics and clinical characteristics

Characteristic	Etelcalcetide ($n = 891$)
Baseline PTH, *n* (%)	
<600 pg/mL	405 (45.5)
600–1000 pg/mL	221 (24.8)
>1000 pg/mL	228 (25.6)
Missing	37 (4.2)
Laboratory values, mean (SD)	
PTH, pg/mL	770 (574)
Ca, mg/dL	9.7 (0.7)
P, mg/dL	5.6 (1.8)
Ca × P, mg^2/dL^2	54.4 (17.2)

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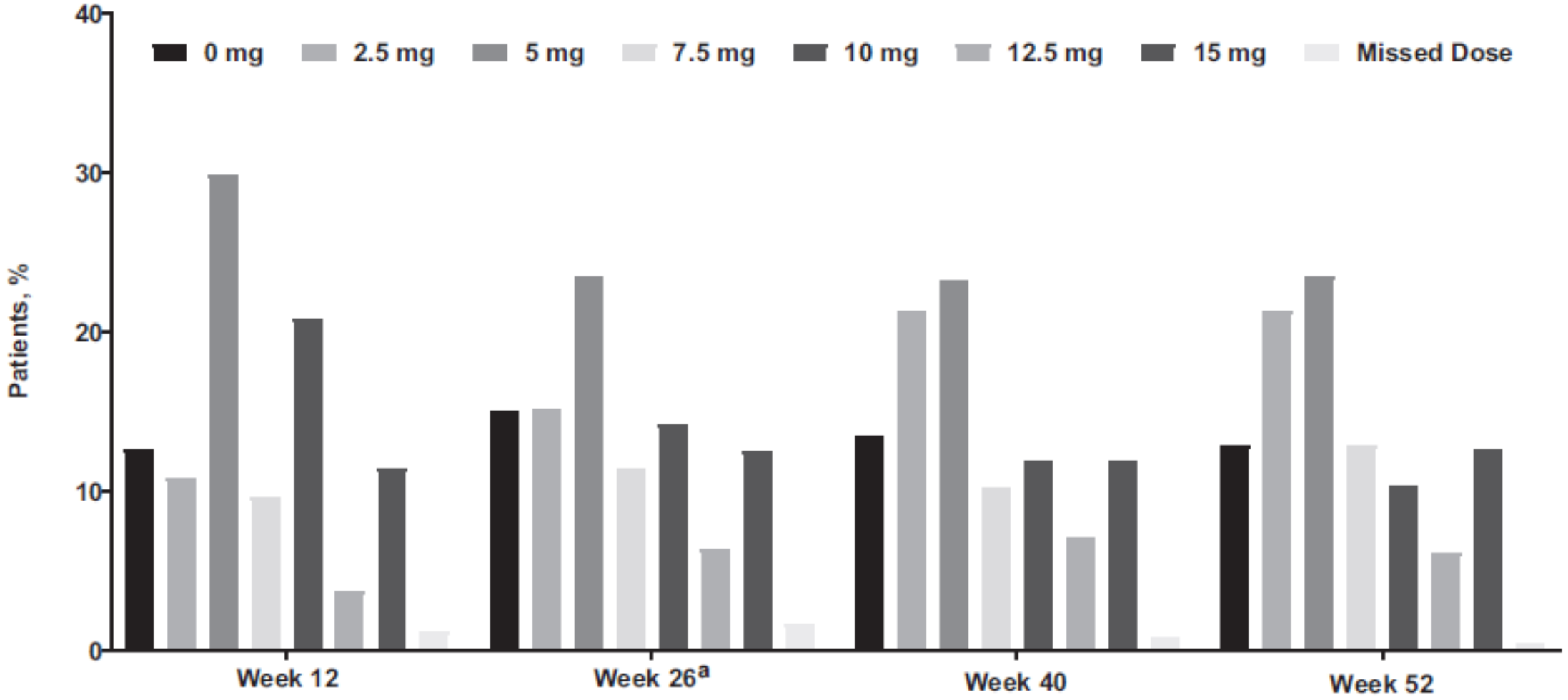
Proportion of patients receiving each dose level of etelcalcetide (mg/session) at selected visits.



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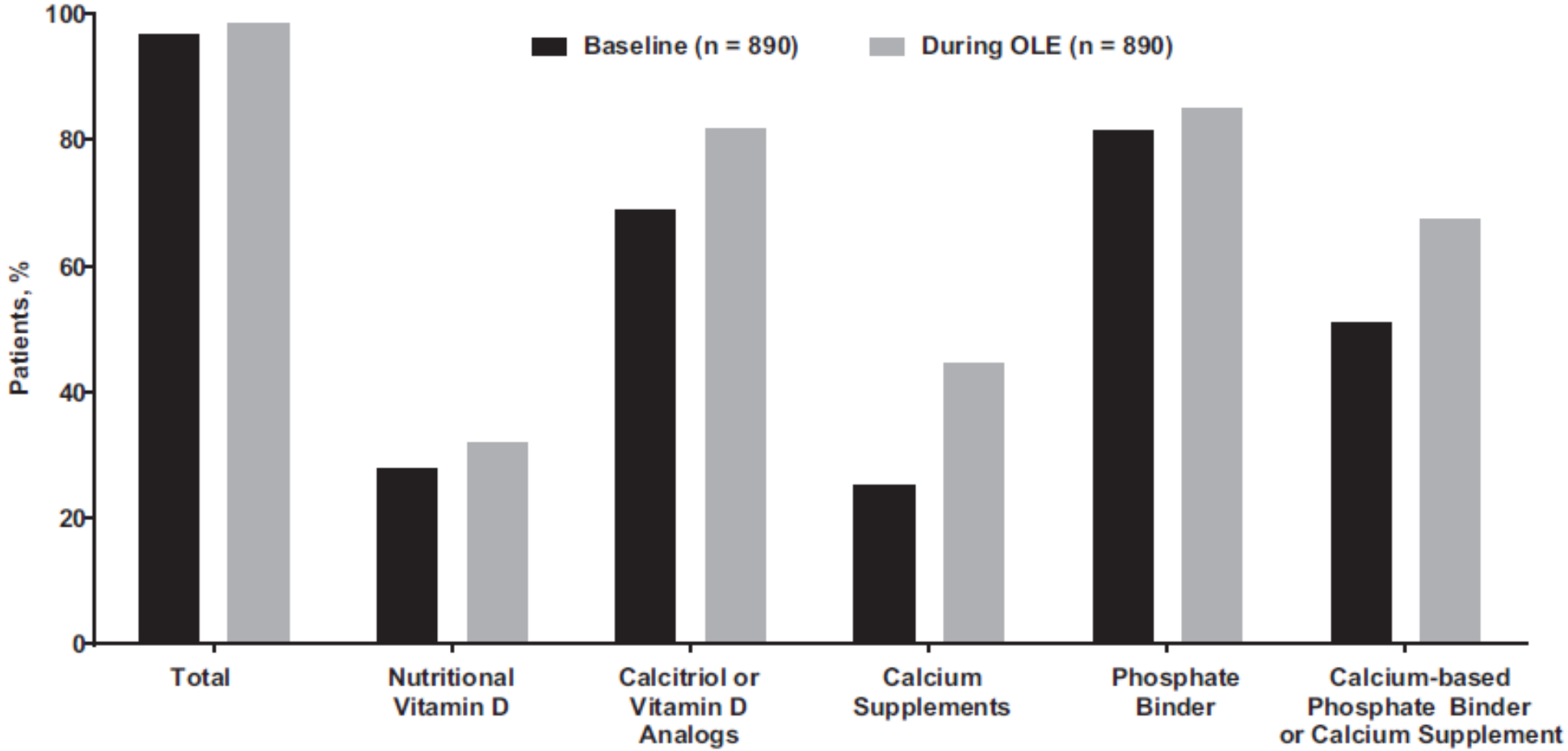
Concomitant medication use during the open-label extension (OLE) trial



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Results

- Approximately 68% of patients achieved >30% reduction in PTH, and 56% achieved PTH <300 pg/mL.
- Mean percent changes from baseline ranged from -25.4% to -26.1% for PTH, -8.3% to -9.1% for Ca, -3.6% to -4.1% for P
- Overall, 89.8% of the patients experienced one or more treatment-emergent AE:
  - decreased blood Ca (43.3%)
  - diarrhea (10.8%)
  - vomiting (10.4%) and nausea (9.6%);
  - symptomatic hypocalcemia occurred in 3.7% of the patients.

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Table 2. AEs

AEs, *n* (%) [rate per 100 patient-years]	OLE trial Etelcalcetide (*n* = 890)	Placebo-controlled trials Etelcalcetide (*n* = 503)
All treatment-emergent AEs	799 (89.8) [356.9]	461 (91.7) [712.6]
SAEs	356 (40.0) [55.4]	130 (25.8) [56.5]
Treatment-related SAE	13 (1.5) [1.6]	8 (1.6) [3.0]
AE leading to discontinuation of etelcalcetide	41 (4.6) [4.9]	9 (1.8) [3.4]
Fatal AEs	51 (5.7) [6.1]	11 (2.2) [4.1]
Common AEs (patient incidence ≥5% in either group)		
Blood calcium decreased (asymptomatic)[a]	385 (43.3) [69.1]	321 (63.8) [240.3]
Diarrhea	96 (10.8) [12.2]	54 (10.7) [21.6]
Vomiting	93 (10.4) [11.8]	45 (8.9) [17.8]
Nausea	85 (9.6) [10.7]	54 (10.7) [21.6]
Muscle spasms	79 (8.9) [9.9]	58 (11.5) [23.5]
Hypotension	75 (8.4) [9.3]	30 (6.0) [11.5]
AV fistula site complication	68 (7.6) [8.5]	29 (5.8) [11.2]
Hypertension	65 (7.3) [8.1]	31 (6.2) [12.0]
Hyperkalemia	56 (6.3) [6.9]	22 (4.4) [8.4]
Upper respiratory tract infection	56 (6.3) [6.9]	21 (4.2) [8.0]
Cough	55 (6.2) [6.8]	22 (4.4) [8.4]
Headache	53 (6.0) [6.5]	38 (7.6) [14.9]
Back pain	50 (5.6) [6.1]	22 (4.4) [8.4]
Dyspnea	50 (5.6) [6.1]	24 (4.8) [9.2]
Arthralgia	49 (5.5) [6.0]	21 (4.2) [8.0]
Pain in extremity	47 (5.3) [5.8]	24 (4.8) [9.2]
Fall	45 (5.1) [5.5]	15 (3.0) [5.7]
Hypocalcemia (symptomatic)[b]	33 (3.7) [4.0]	35 (7.0) [13.7]

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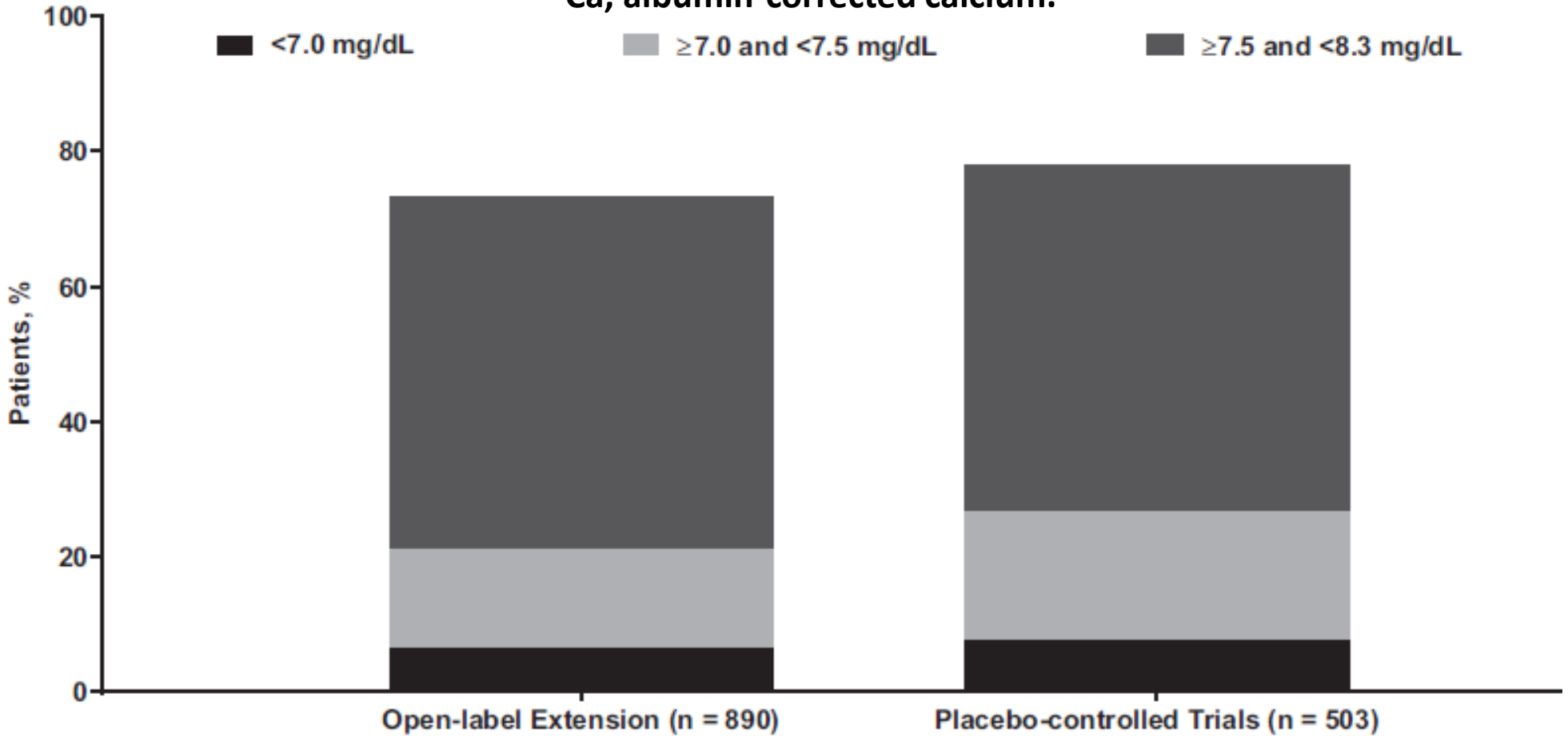
Proportion of patients with low Ca values during the trial for the current OLE study versus the active treatment arm of the placebo-controlled trials.

Ca, albumin-corrected calcium.



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Effects of etelcalcetide on PTH, Ca, P during the open-label extension (OLE) trial at 6 and 12 months of treatment

	OLE trial Etelcalcetide ($n = 891$)	
	EAP6	EAP12
>30% reduction in PTH, % (n/N_1)	68.1 (505/742)	67.5 (456/676
PTH ≤300 pg/mL, % (n/N_1)	55.5 (431/776)	56.4 (399/708
Median percentage change in PTH, % (n)	−51.6 (742)	−52.9 (676)
Mean percentage change in PTH, % (n)	−25.4 (742)	−25.6 (676)
(95% CI)	(−37.2, −13.5)	(−34.6, −16.6)
Mean percentage change in Ca, % (n)	−9.1 (774)	−8.3 (704)
(95% CI)	(−9.8, −8.4)	(−8.9, −7.6)
Mean percentage change in P, % (n)	−4.1 (743)	−3.6 (703)
(95% CI)	(−6.6, −1.5)	(−6.0, −1.2)

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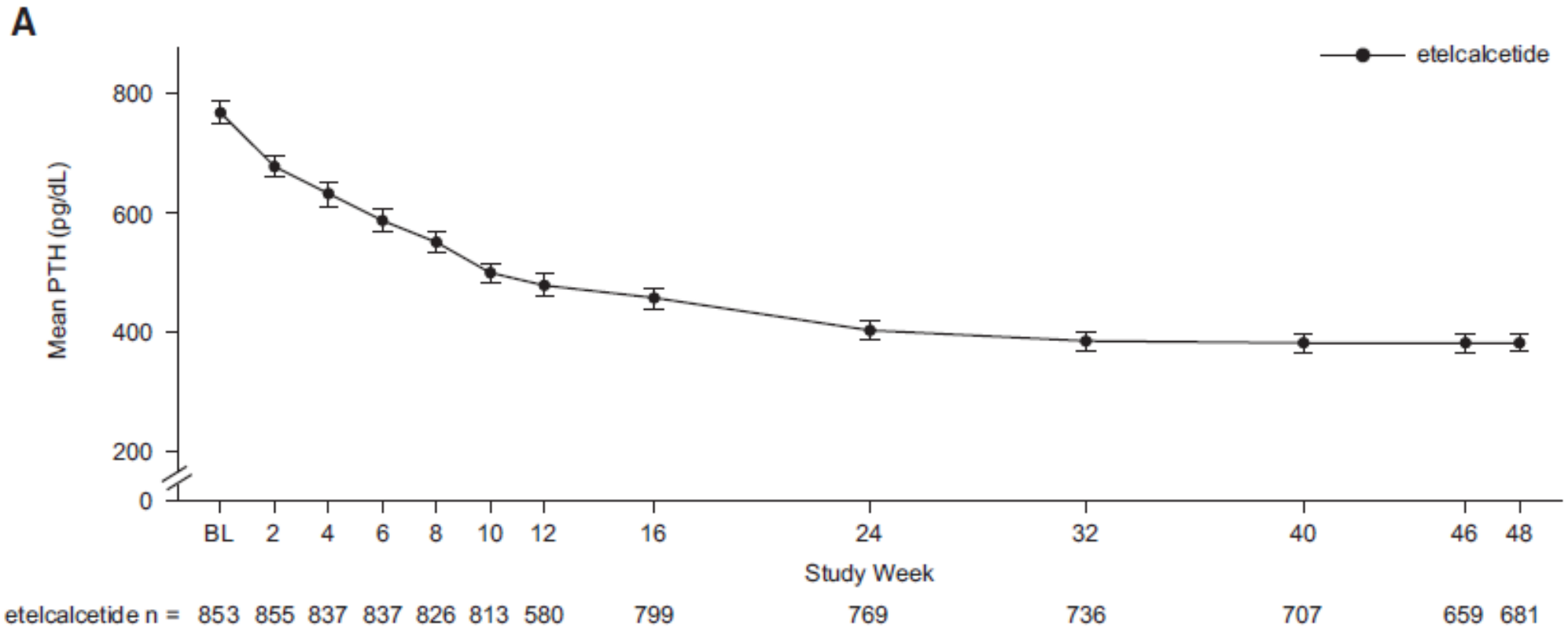
Mean (SE) predialysis PTH concentrations over time during the open-label extension (OLE) trial



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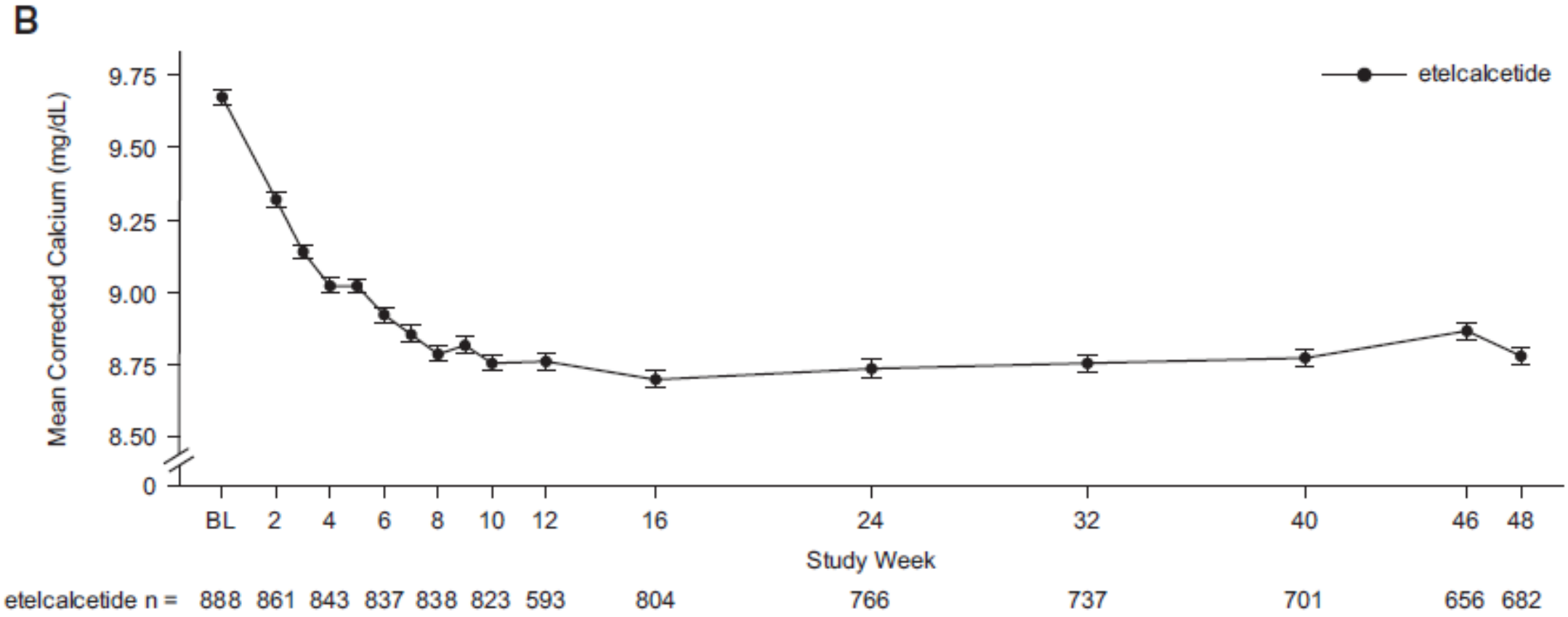
Mean (SE) predialysis calcium concentrations over time during the open-label extension (OLE) trial



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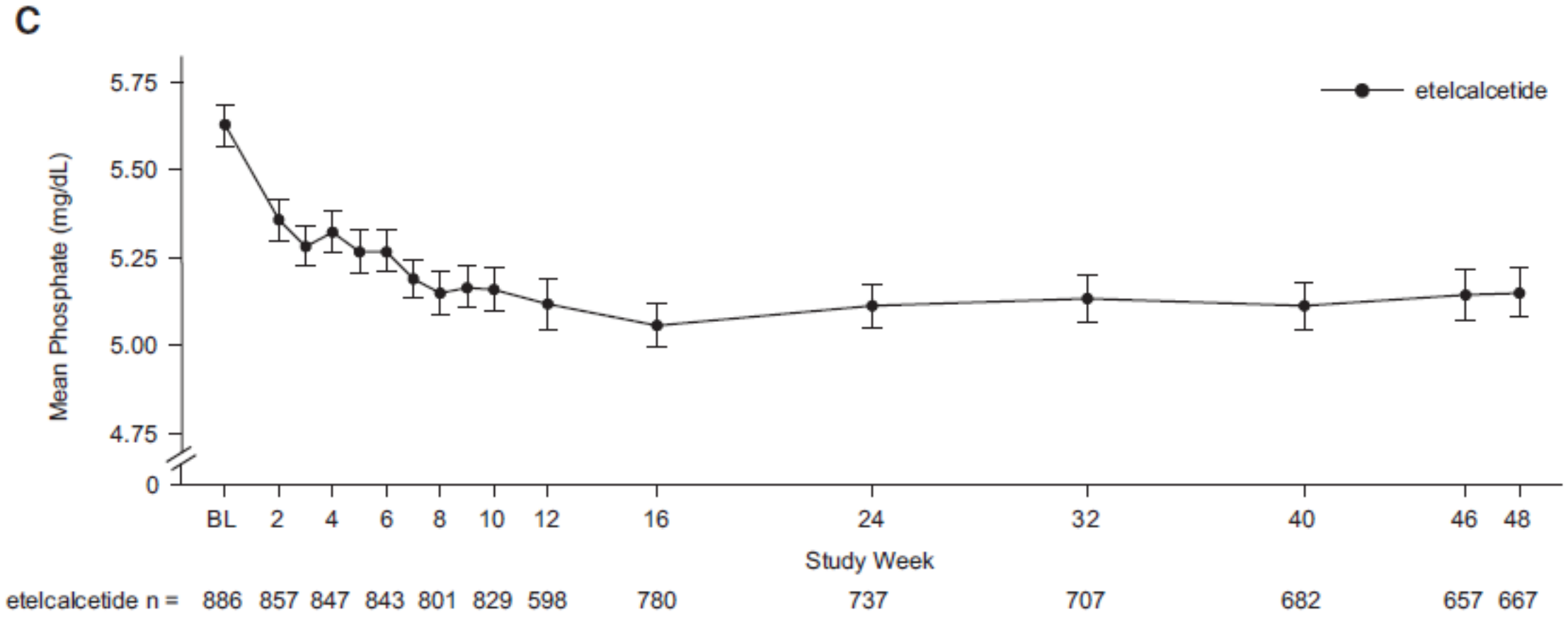
Mean (SE) predialysis phosphate concentrations over time during the open-label extension (OLE) trial



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Etelcalcetide open-label extension (OLE) trial
Conclusions

- This extension trial is the longest analysis of the use of etelcalcetide in patients receiving dialysis to date.
- The exposure-adjusted rates of serious AEs in this trial, as well as the incidence of hypocalcemia, suggest that the long-term risks associated with etelcalcetide treatment are similar to those observed in the prior shorter term studies.
- Overall, these results indicate that long-term administration of etelcalcetide exhibits a reasonable safety profile with sustained reductions in PTH, Ca and P.

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