Challenges in Treatment of Secondary Hyperparathyroidism

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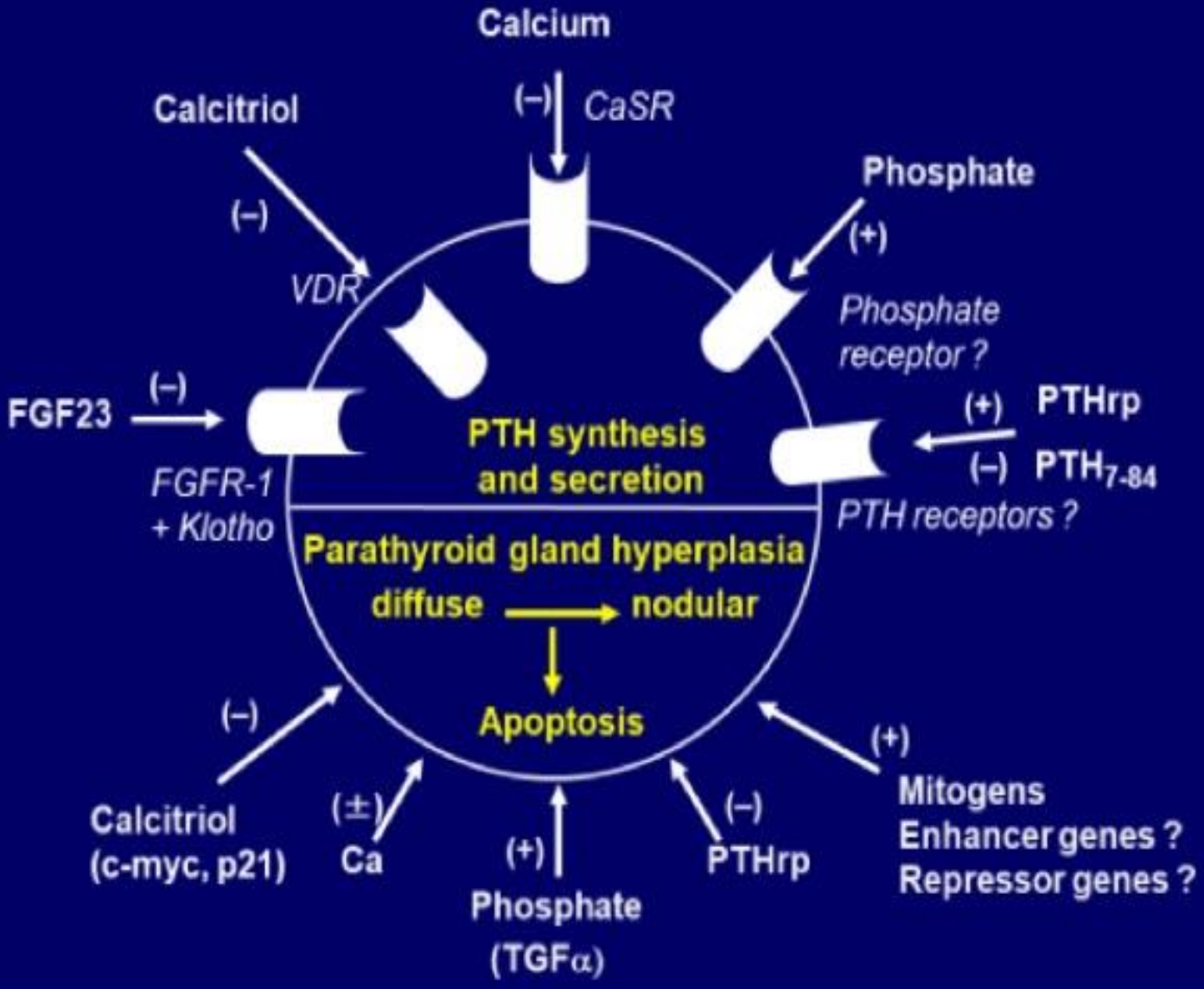
Defination

- Chronic kidney disease mineral and bone disorder (CKD-MBD) is characterized by:
  - Biochemical abnormalities (calcium, phosphate, parathyroid hormone [PTH], and vitamin D)
  - Abnormalities in bone turnover, mineralization, volume linear growth, or strength
  - Extraskeletal calcification.

Secondary Hyperparathyroidism

- Secondary hyperparathyroidism occurs in response to the following series of abnormalities that initiate and maintain increased parathyroid hormone (PTH) secretion
  - Phosphate retention
  - Decreased free ionized calcium concentration
  - Decreased 1,25-dihydroxyvitamin D (calcitriol) concentration
  - Increased fibroblast growth factor 23 (FGF23) concentration
  - The reduced expression of vitamin D receptors (VDRs), calcium-sensing receptors (CaSRs), fibroblast growth factor receptors, and klotho in the parathyroid glands

Pathogenesis of Secondary Hyperparathyroidism



Strategies of Treatment of CKD-MBD

- Treat hyperphosphatemia
- Maintain normocalcemia
- Treat vitamin D deficiency
- Calcitriol and synthetic vitamin D analogs
- Calcimimetics
- parathyroidectomy

Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis

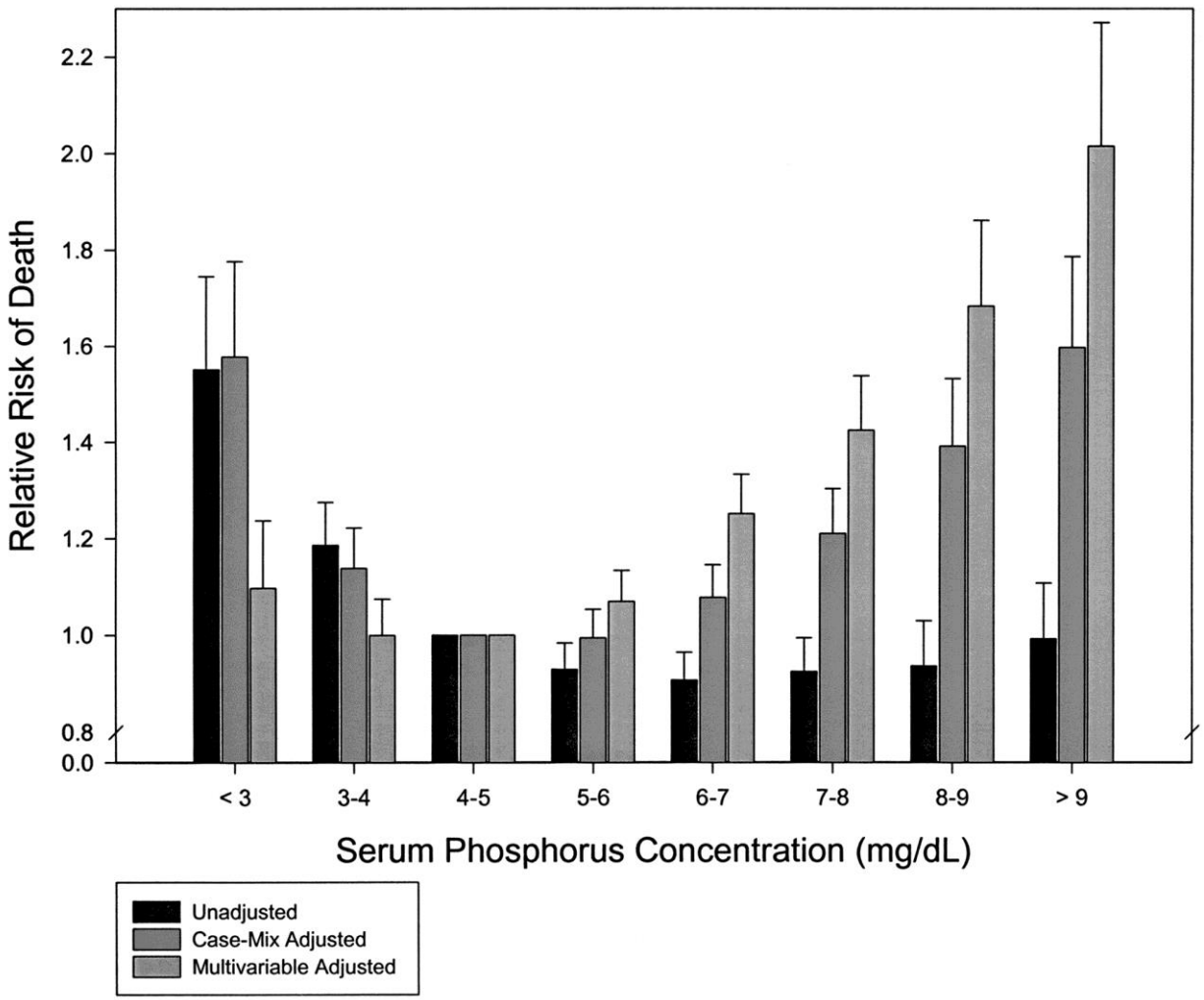
- For determining associations among disorders of mineral metabolism, mortality, and morbidity in hemodialysis patients, data on 40,538 hemodialysis patients with at least one determination of serum phosphorus and calcium during the last 3 mo of 1997 were analyzed.
- Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks of death were calculated for categories of serum phosphorus, calcium, calcium × phosphorus product, and intact parathyroid hormone (PTH) using proportional hazards regression.

J Am Soc Nephrol 2004; 15(8), 2208-18

Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis

- After adjustment for case mix and laboratory variables, serum phosphorus concentrations >5.0 mg/dl were associated with an increased relative risk of death (1.07, 1.25, 1.43, 1.67, and 2.02 for serum phosphorus 5.0 to 6.0, 6.0 to 7.0, 7.0 to 8.0, 8.0 to 9.0, and ≥9.0 mg/dl).
- Higher adjusted serum calcium concentrations were also associated with an increased risk of death, even when examined within narrow ranges of serum phosphorus.
- Moderate to severe hyperparathyroidism (PTH concentrations ≥600 pg/ml) was associated with an increase in the relative risk of death.
- Whereas more modest increases in PTH were not.

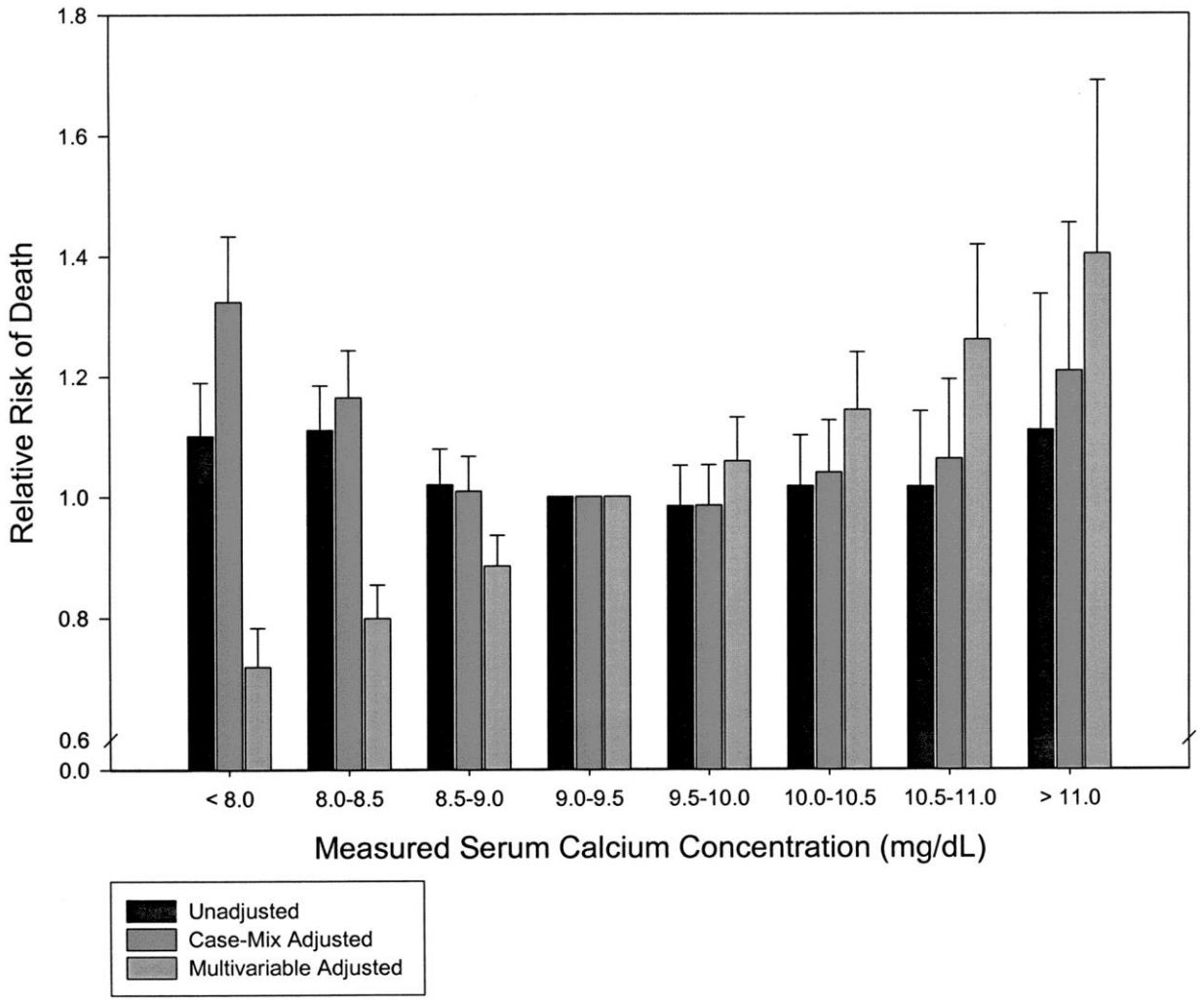
Figure 1. Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks (RR; of death) and 95% confidence intervals (CI) for eight categories of serum phosphorus (referent range, 4.0 to 5.0 mg/dl)



Geoffrey A. Block et al. JASN 2004;15:2208-2218

JASN Journal of the American Society of Nephrology

Figure 2. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of measured serum calcium (referent range, 9.0 to 9.5 mg/dl).



Geoffrey A. Block et al. JASN 2004;15:2208-2218

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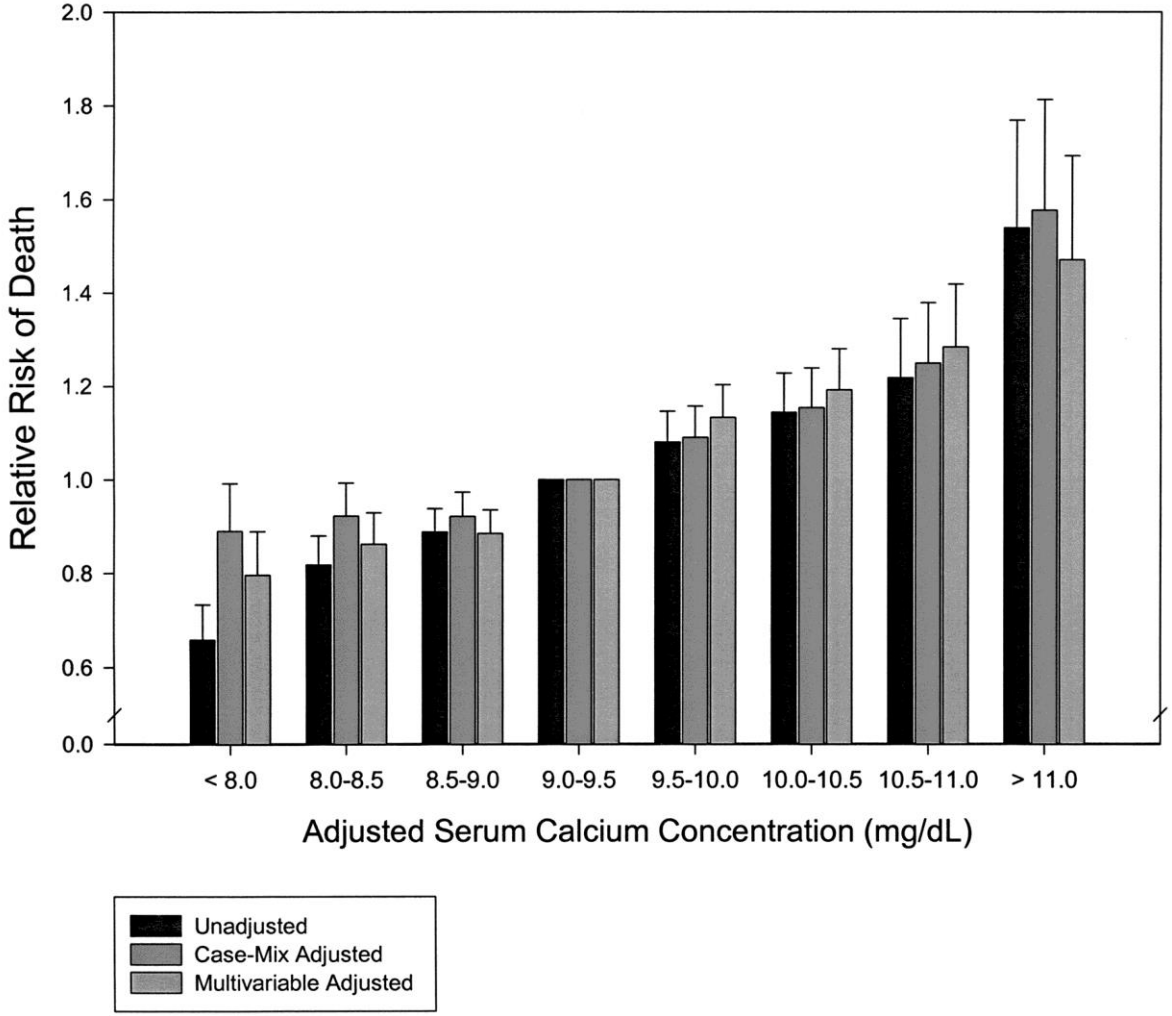
Figure 3. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of adjusted serum calcium (measured calcium adjusted for serum albumin, referent range, 9.0 to 9.5 mg/dl)



Geoffrey A. Block et al. JASN 2004;15:2208-2218

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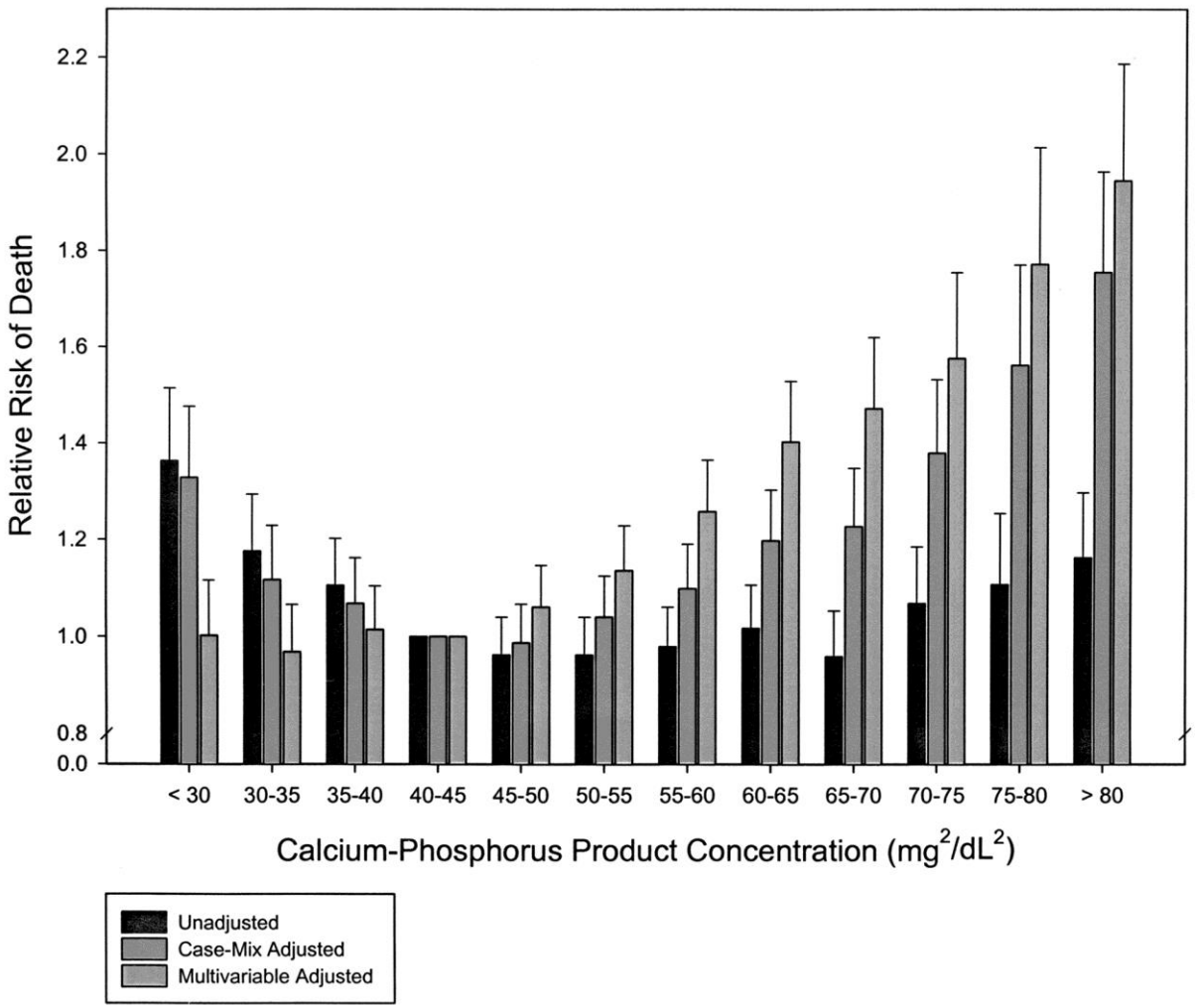
Figure 4. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for 12 categories of calcium × phosphorus product (referent range, 40 to 45 mg2/dl2).



Geoffrey A. Block et al. JASN 2004;15:2208-2218

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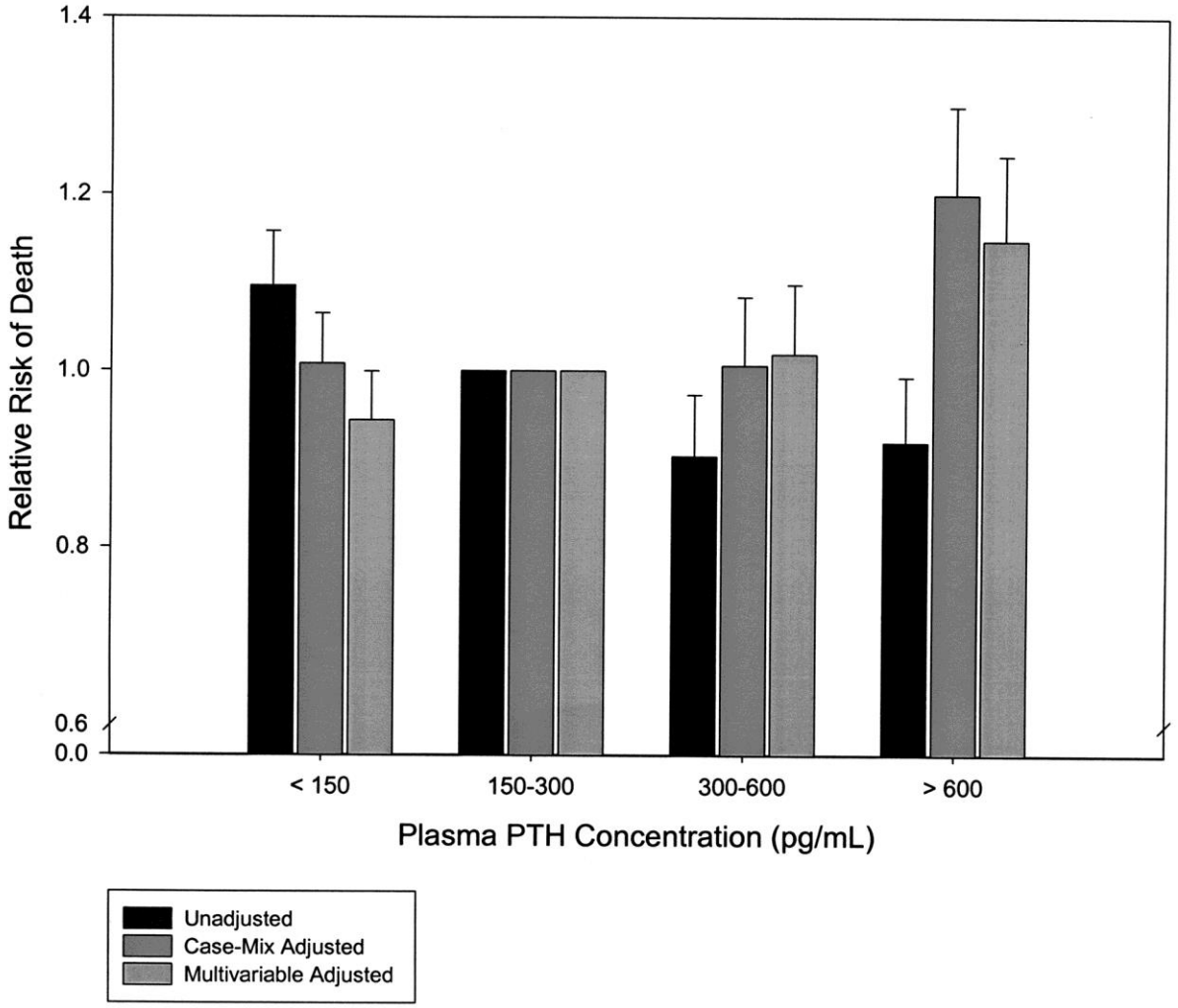
Figure 5. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for four categories of intact parathyroid hormone (referent range, 150 to 300 pg/ml).



Geoffrey A. Block et al. JASN 2004;15:2208-2218

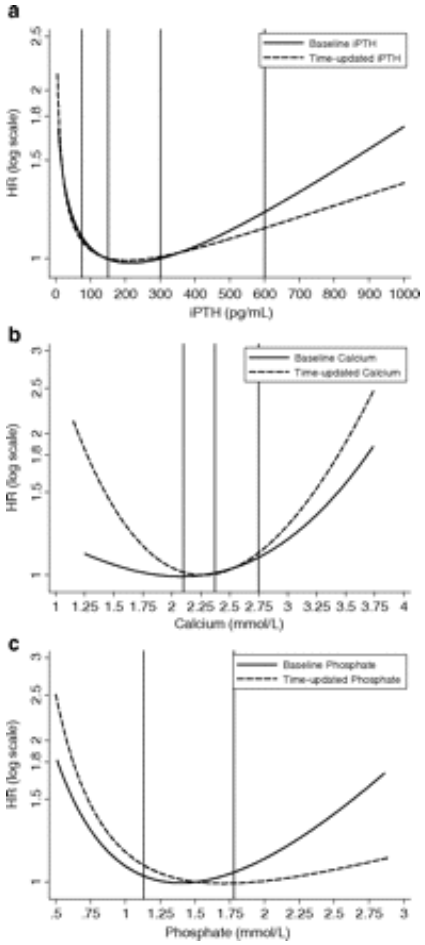
JASN Journal of the American Society of Nephrology

Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population

- The association between the markers of mineral and bone disease and clinical outcomes was examined in 7970 patients.
- **.** Hazard ratio (HR) estimates from baseline analysis for iPTH were U-shaped [>600 pg/mL, HR = 2.10, 95% confidence interval (CI) 1.62–2.73; <75 pg/mL, HR = 1.46, 95% CI 1.17–1.83]. Confirmed by TD analysis.
- Baseline analysis showed that calcium >2.75 mmol/L increased risk of death (HR = 1.70, 95% CI 1.19–2.42).
- TD analysis showed that both low (HR = 1.19, 95% CI 1.04–1.37) and high calcium (HR = 1.74, 95% CI 1.30–2.34) increased risk of death.
- Baseline analysis for phosphate showed a U-shaped pattern (<1.13 mmol/L, HR = 1.18, 95% CI 1.01–1.37; >1.78 mmol/L, HR = 1.32, 95% CI 1.13–1.55). Results confirmed by TD analysis.

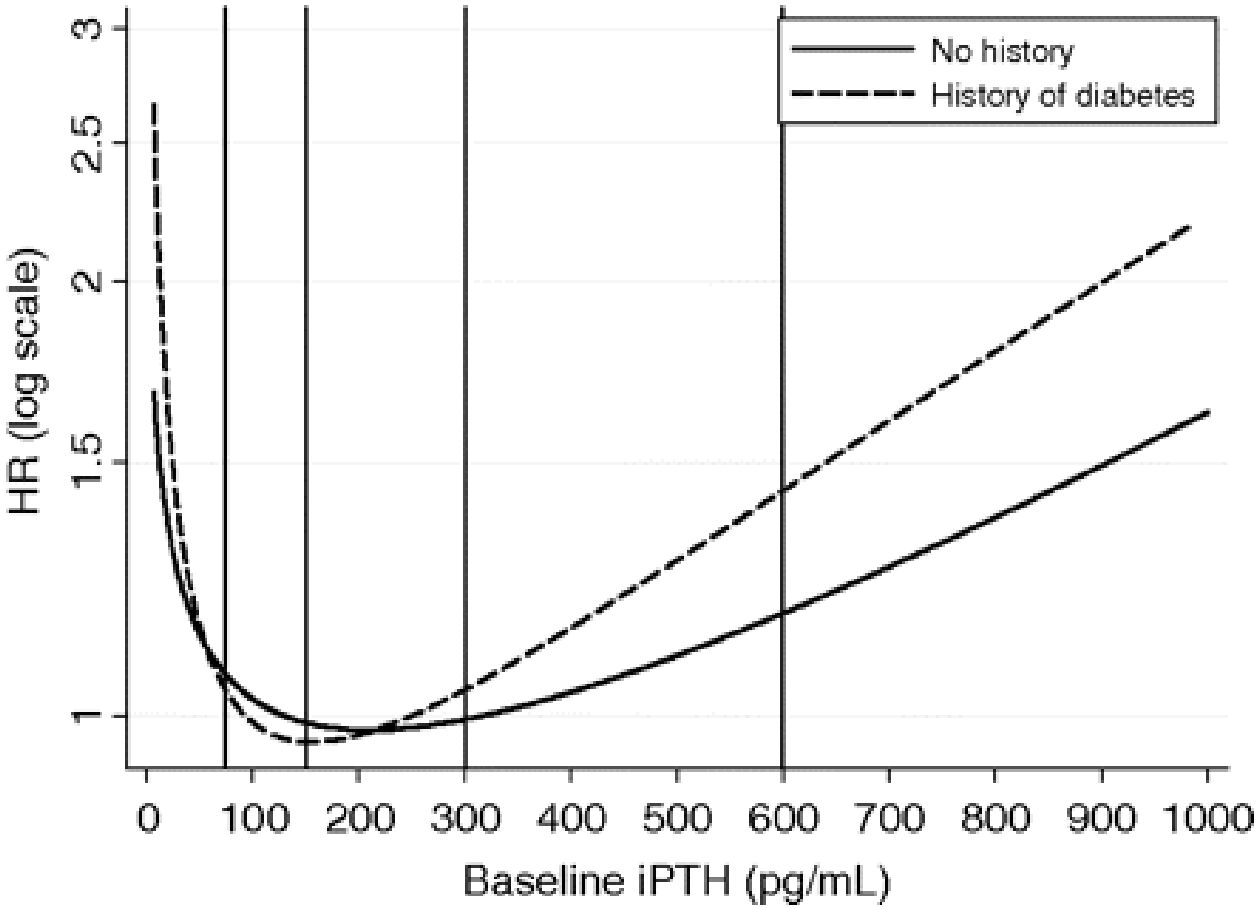
NDT 2011, 26(6), 1948-55

Fig. 1 (a) Relative risk of all-cause mortality for iPTH comparing baseline versus time-dependent Cox regression ...



Nephrology Dialysis Transplantation, Volume 26, Issue 6, June 2011, Pages 1948–1955, https://doi.org/10.1093/ndt/gfq219

Fig. 2 Relative risk of all-cause mortality for iPTH baseline Cox regression using fractional polynomials in ...

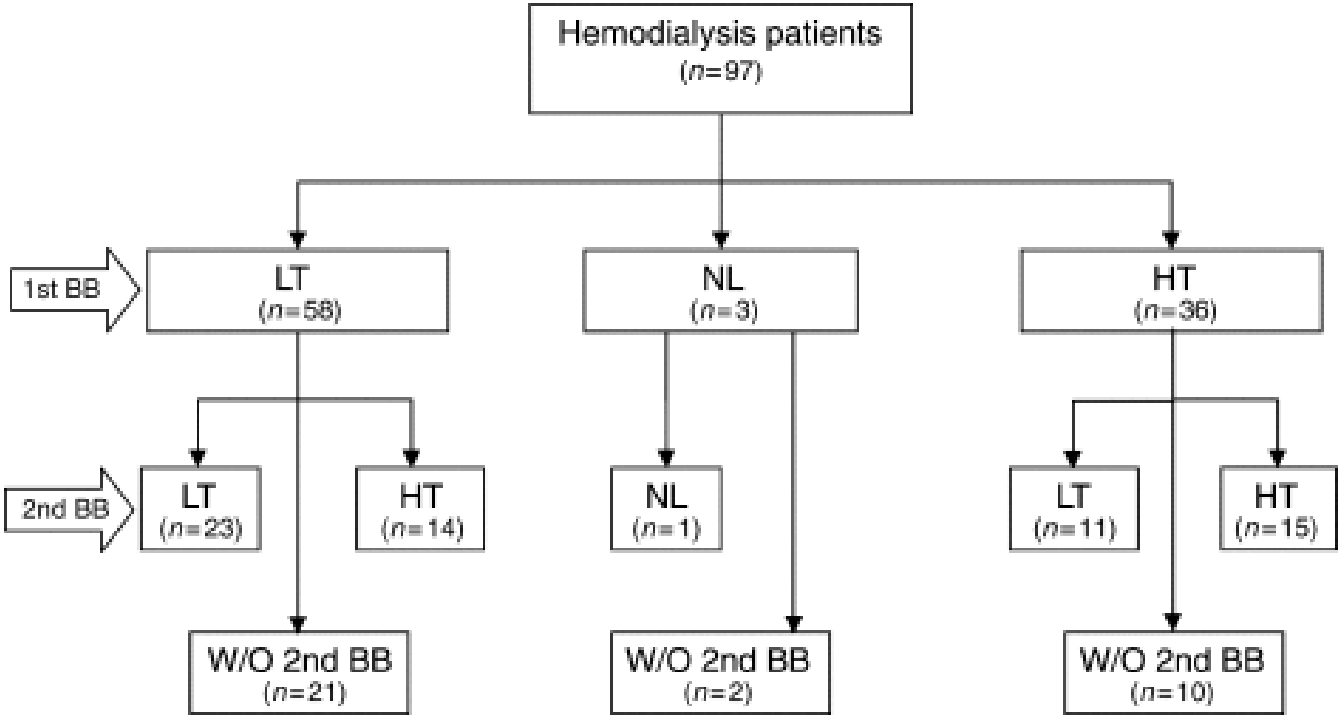


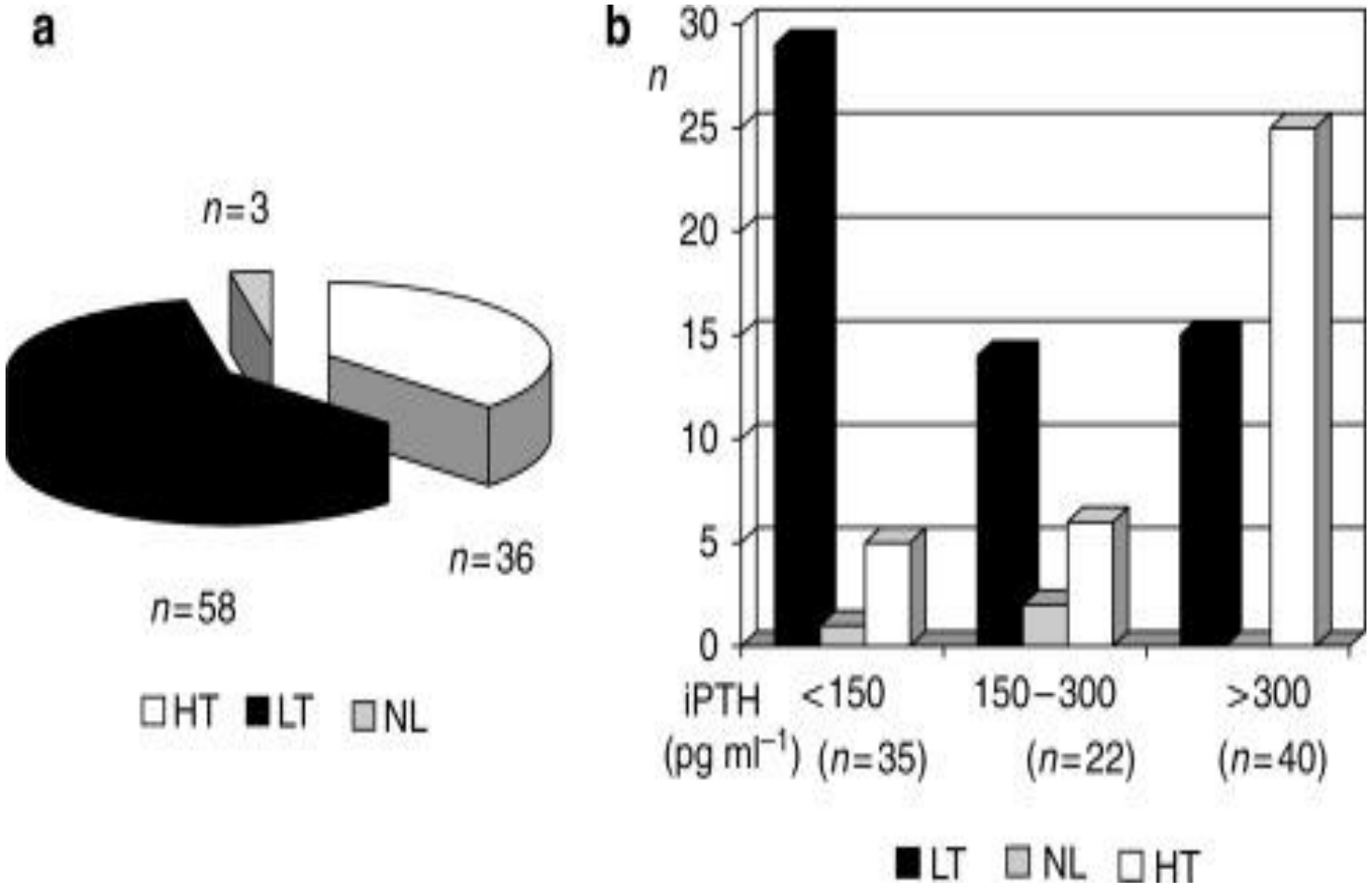
Nephrology Dialysis Transplantation, Volume 26, Issue 6, June 2011, Pages 1948–1955, https://doi.org/10.1093/ndt/gfq219

K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients

- serum markers of bone turnover have been used to evaluate bone turn over in CKD patients. Measurement of intact parathyroid hormone (iPTH) has long been considered the principal biochemical marker for diagnosis and monitoring therapy of ROD.
- A target range of plasma iPTH for stage 5 CKD patients has been suggested to be between 150 and 300 pg ml.
- A total of 101 patients were enrolled in the study. Ninety-seven patients provided adequate bone samples for histomorphometric analysis.
- LT was the most common finding (64%) in the ideal range of iPTH.
- an association between LT and being of white race and a trend toward an association with older age (P=0.07) and diabetes (P=0.07) was noticed.

KI 2008, VOL 73, ISSUE 6, 771- 777


Hemodialysis patients
(n=97)
1st BB
LT
(n=58)
NL
(n=3)
HT
(n=36)
2nd BB
LT
(n=23)
HT
(n=14)
NL
(n=1)
LT
(n=11)
HT
(n=15)
W/O 2nd BB
(n=21)
W/O 2nd BB
(n=2)
W/O 2nd BB
(n=10)


a
n=3
n=36
n=58
HT
LT
NL
b
n
30
25
20
15
10
5
0
iPTH (pg ml−1)
<150 (n=35)
150–300 (n=22)
>300 (n=40)
LT
NL
HT

K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients

- Despite not using aluminum-based phosphate binder and strictly controlling water quality in the dialysis centers involved in this study, aluminum intoxication (Al.S/BS>25%) was present in 41% of the entire population.
- However, one should notice that the amount of aluminum bone surface was not that high (Al.S/BS=24.3±28.6%).
- Other aluminum exposure source that may be important in patients with CKD, such as aluminum kitchen utensils.
- NKF K/DOQI guidelines. LT was quite frequent in the recommended iPTH range. Thus, the so-called ideal range of iPTH does not seem to guarantee a healthy bone.
- Additionally, one might conclude that the upper cut-off of iPTH (300 pg ml^{-1}) should be revised.

Effects of Calcium on Cardiovascular Events in Patients with Kidney Disease and in a Healthy Population

- A key risk factor for CVD in patients with ESRD is vascular calcification.(typically medial calcification)
- Vascular calcification is not a passive deposition of Ca and phosphate but rather a well organized active process.
- The first critical step involves transformation of vascular smooth muscle cell to osteoblast like cells.
- Elevated serum level of Ca and P facillitate this transformation.

clin J Am Soc Nephrol 5:S41-S47, 2010

Effects of Calcium on Cardiovascular Events in Patients with Kidney Disease and in a Healthy Population

- Measurement of serum Ca is not a good surrogate for overall calcium balance.
- In healthy subject, bone mass measurement and fracture rate is the most commonly used indirect measure of Ca adequacy.
- Bone mass and fracture rate in CKD patients associated with different factors.
- Because of alteration in mineral metabolism , the recommendation of Ca intake in healthy subjects can not be directly applied to patients with CKD.

clin J Am Soc Nephrol 5:S41-S47,2010

Effects of Calcium on Cardiovascular Events in Patients with Kidney Disease and in a Healthy Population

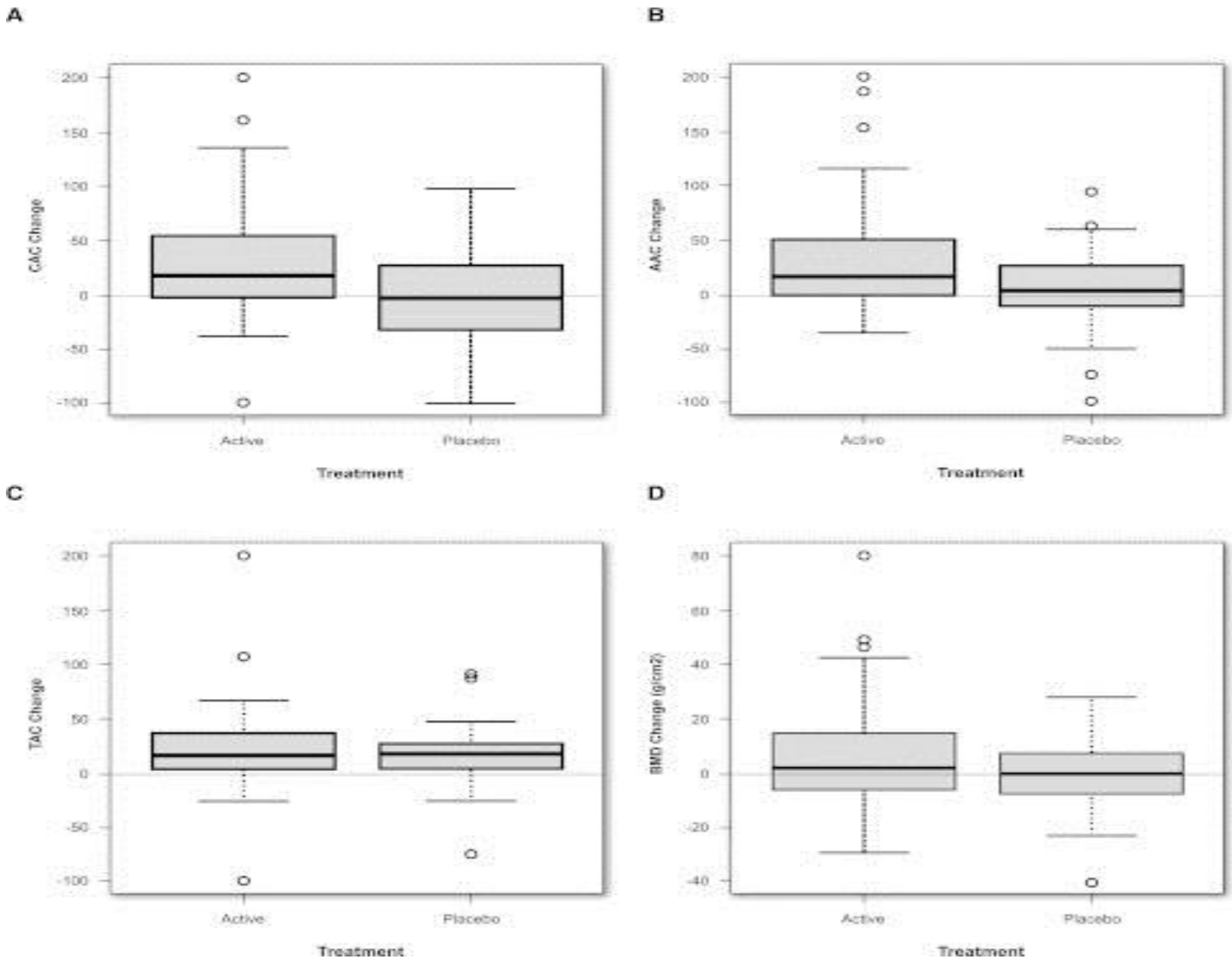
- It seems 3 factor must be considered before perscribing Ca or Ca based phosphate binder:
  - Calcium based phosphate binders are a substantial source of elemental Calcium
  - Elevated PTH in CKD caused by hyperphosphatemia rather than hypocalcemia
  - There are no data to support a benefitial effect of calcium supplementation in patients with CKD.
- There is no data showing that giving calcium reduce risk of osteoporotic fractures, among patients with CKD.

clin J Am Soc Nephrol 5: S41-S47, 2010

Effects of Phosphate Binders in Moderate CKD

- randomly assigned 148 patients with estimated GFR=20–45 ml/min per 1.73 m^2 to calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo.
- Serum phosphorus decreased from a baseline mean of 4.2 mg/dl in both active and placebo arms to 3.9 mg/dl with active therapy and 4.1 mg/dl with placebo (*P*=0.03).
- Median serum intact parathyroid hormone remained stable with active therapy and increased with placebo (*P*=0.002).
- Active therapy did, however, significantly increase calcification of the coronary arteries and abdominal aorta (coronary: median increases of 18.1% versus 0.6%, *P*=0.05; abdominal aorta: median increases of 15.4% versus 3.4%, *P*=0.03).
- It is possible that noncalcium-containing phosphate binders also enhance the availability of free intestinal calcium and result in a positive calcium balance.

J Am Soc Nephrol, 23(8),1407-15

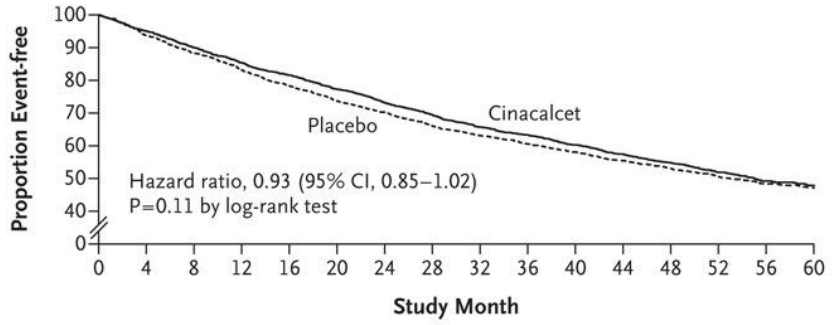

A
CAC Change
200
150
100
50
0
-50
-100
Active
Placebo
Treatment
B
AAC Change
200
150
100
50
0
-50
-100
Active
Placebo
Treatment
C
TAC Change
200
150
100
50
0
-50
-100
Active
Placebo
Treatment
D
BMD Change (g/cm2)
80
60
40
20
0
-20
-40
Active
Placebo
Treatment

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

- The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event.
- Secondary end points included the time to the individual components of the primary composite end point, death from cardiovascular causes, stroke, bone fracture, and parathyroidectomy.
- The primary composite end point was reached in 938 of1948 patients(48.2%) in the cinacalcet group and 952 of 1935 patients(49.2%) in placebo group(relative hazard in cinacalcet group versus placebo, 0.93)
- Hypocalcemia and gastrointestinal adverse events more frequent in patients receiving cinacalcet.
- Cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate to severe secondary hyper parathyroidism who were undergoing hemodialysis.

N Engl J Med 2012; 367: 2482-94

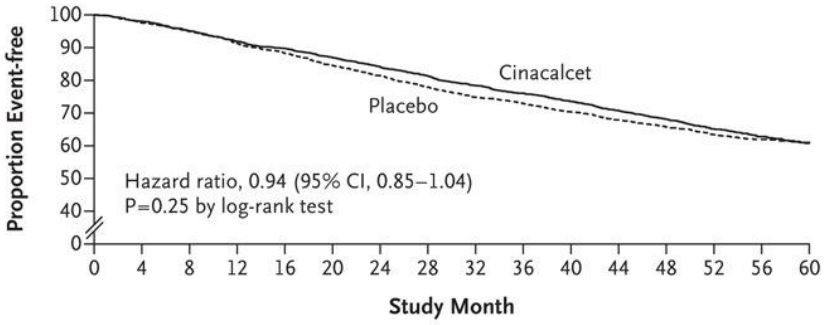
A Primary Composite End Point



No. at Risk

Placebo	1935	1804	1693	1579	1476	1384	1312	1224	1160	1109	1053	996	940	650	404	114
Cinacalcet	1948	1842	1739	1638	1556	1472	1384	1303	1230	1177	1115	1051	989	679	399	113

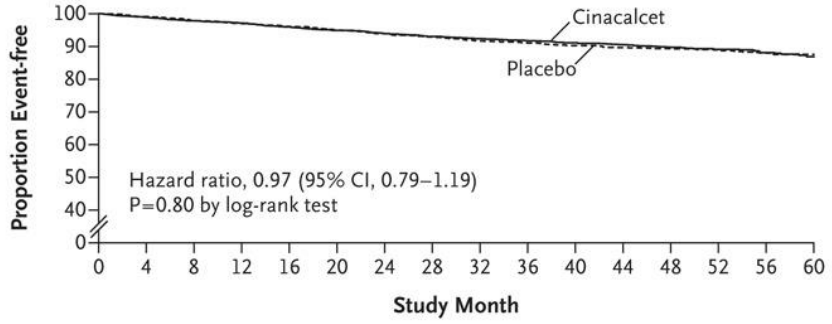
B Death



No. at Risk

Placebo	1935	1882	1828	1754	1694	1622	1559	1486	1426	1388	1334	1283	1232	886	537	162
Cinacalcet	1948	1903	1845	1779	1736	1680	1621	1565	1507	1462	1412	1354	1292	899	546	167

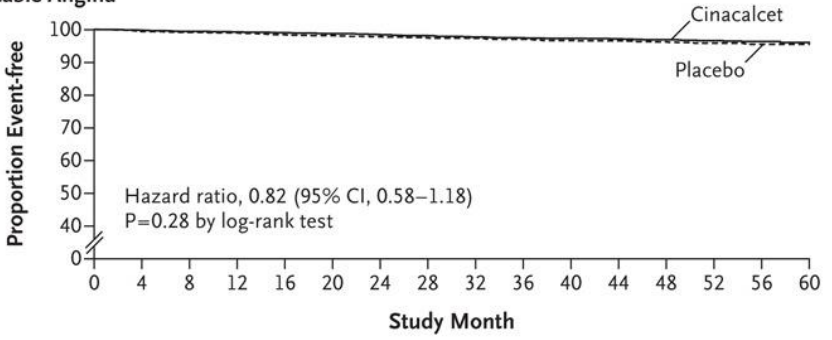
C Myocardial Infarction



No. at Risk

Placebo	1935	1857	1780	1684	1603	1521	1443	1366	1298	1254	1193	1136	1089	754	463	133
Cinacalcet	1948	1877	1799	1715	1648	1579	1512	1439	1377	1326	1268	1204	1139	785	466	137

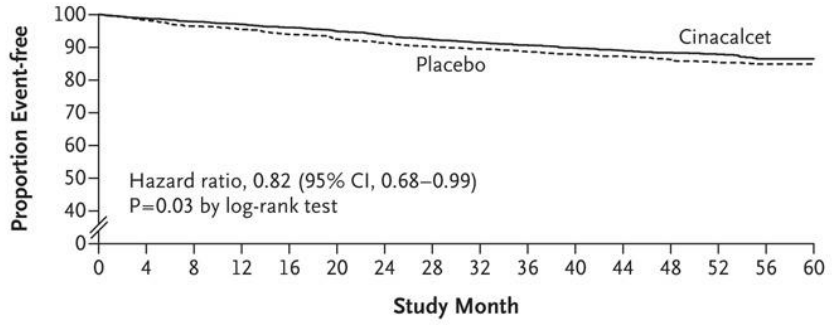
D Unstable Angina



No. at Risk

Placebo	1935	1858	1792	1703	1621	1548	1476	1400	1335	1293	1233	1181	1129	787	485	138
Cinacalcet	1948	1891	1822	1742	1686	1624	1556	1484	1423	1371	1317	1252	1187	812	482	140

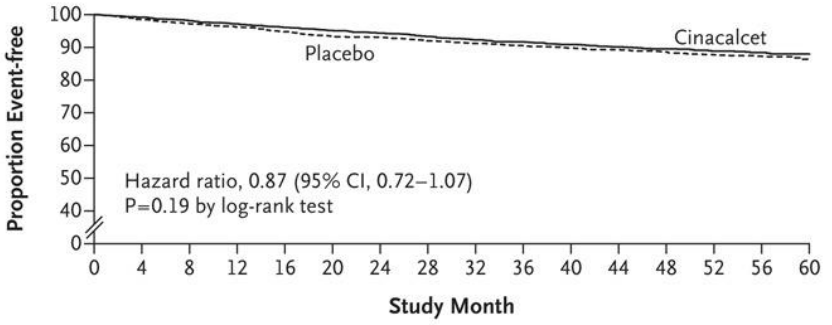
E Heart Failure



No. at Risk

Placebo	1935	1842	1753	1652	1565	1478	1404	1333	1264	1216	1159	1110	1054	737	464	129
Cinacalcet	1948	1873	1798	1712	1649	1579	1499	1422	1357	1301	1242	1176	1115	769	452	128

F Peripheral Vascular Event



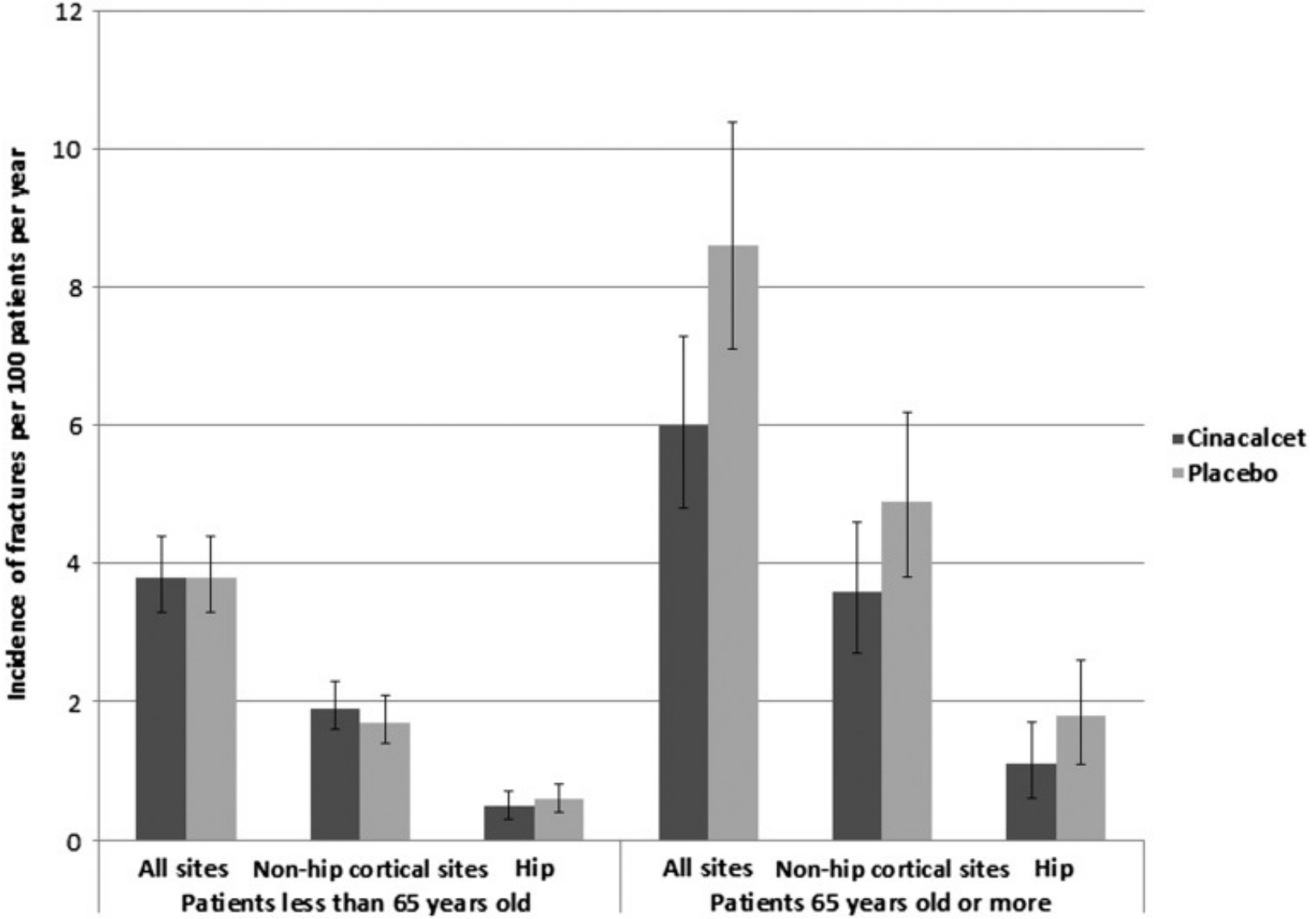
No. at Risk

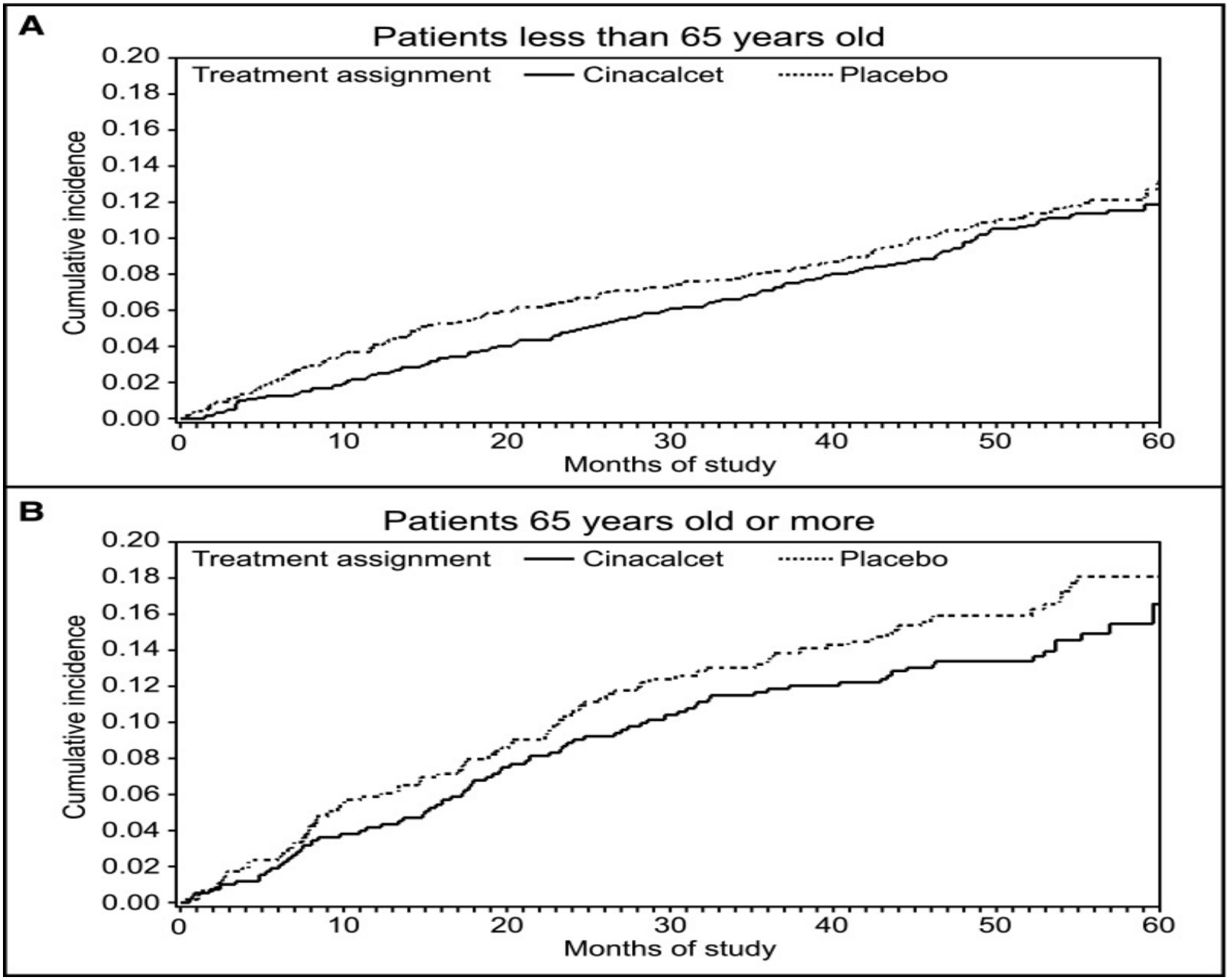
Placebo	1935	1843	1766	1667	1575	1491	1433	1348	1279	1236	1184	1129	1077	750	470	137
Cinacalcet	1948	1882	1802	1711	1647	1586	1513	1438	1376	1326	1266	1196	1137	776	465	137

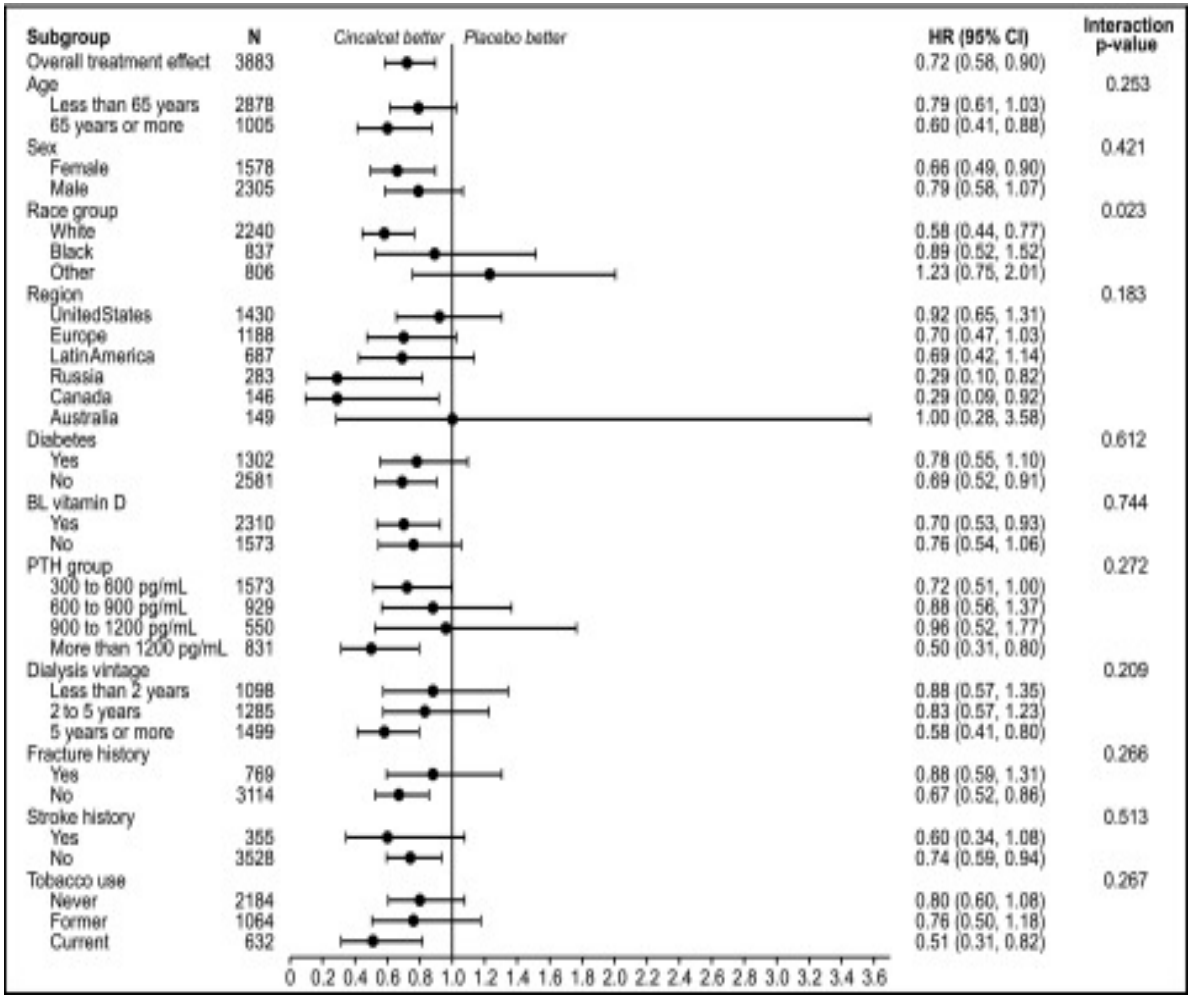
Effects of Cinacalcet on Fracture Events in Patients Receiving Hemodialysis: The EVOLVE Trial

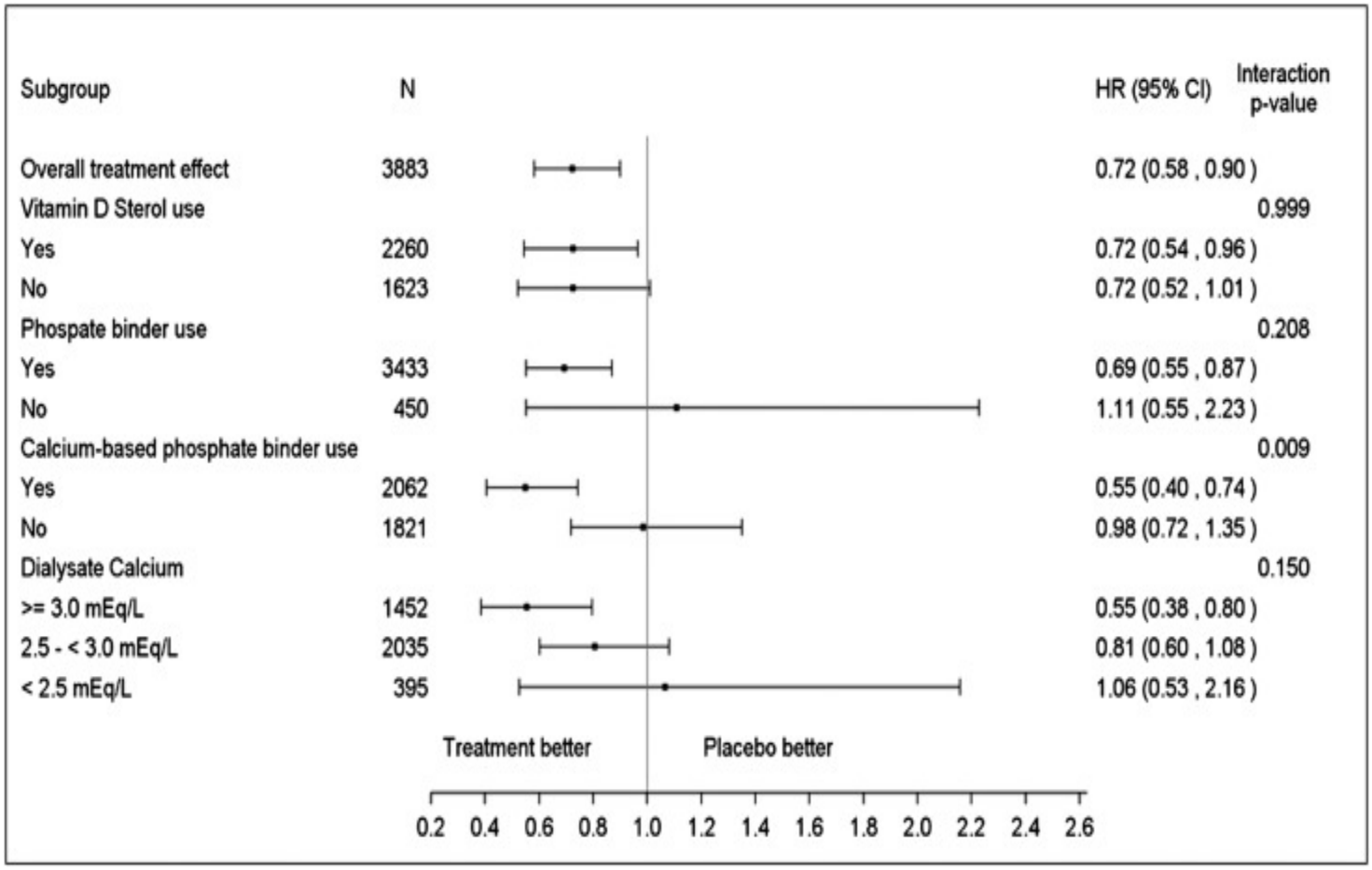
- placebo-controlled trial that randomized 3883 hemodialysis patients with secondary hyperparathyroidism to receive cinacalcet or placebo for ≤64 months.
- This study was a prespecified secondary analysis of the trial whose primary end point was all-cause mortality and non-fatal cardiovascular events, and one of the secondary end points was first clinical fracture event.
- In conclusion, using an unadjusted intention-to-treat analysis, cinacalcet did not reduce the rate of clinical fracture. However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of study drug, cinacalcet reduced the rate of clinical fracture by 16%–29%.

J Am Soc Nephro 2015, 26(6),1466-75


Incidence of fractures per 100 patients per year
12
10
8
6
4
2
0
Cinacalcet
Placebo
All sites
Non-hip cortical sites
Hip
Patients less than 65 years old
All sites
Non-hip cortical sites
Hip
Patients 65 years old or more


A
Patients less than 65 years old
Treatment assignment
Cinacalcet
Placebo
Cumulative incidence
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
0
10
20
30
40
50
60
Months of study
B
Patients 65 years old or more
Treatment assignment
Cinacalcet
Placebo
Cumulative incidence
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
0
10
20
30
40
50
60
Months of study

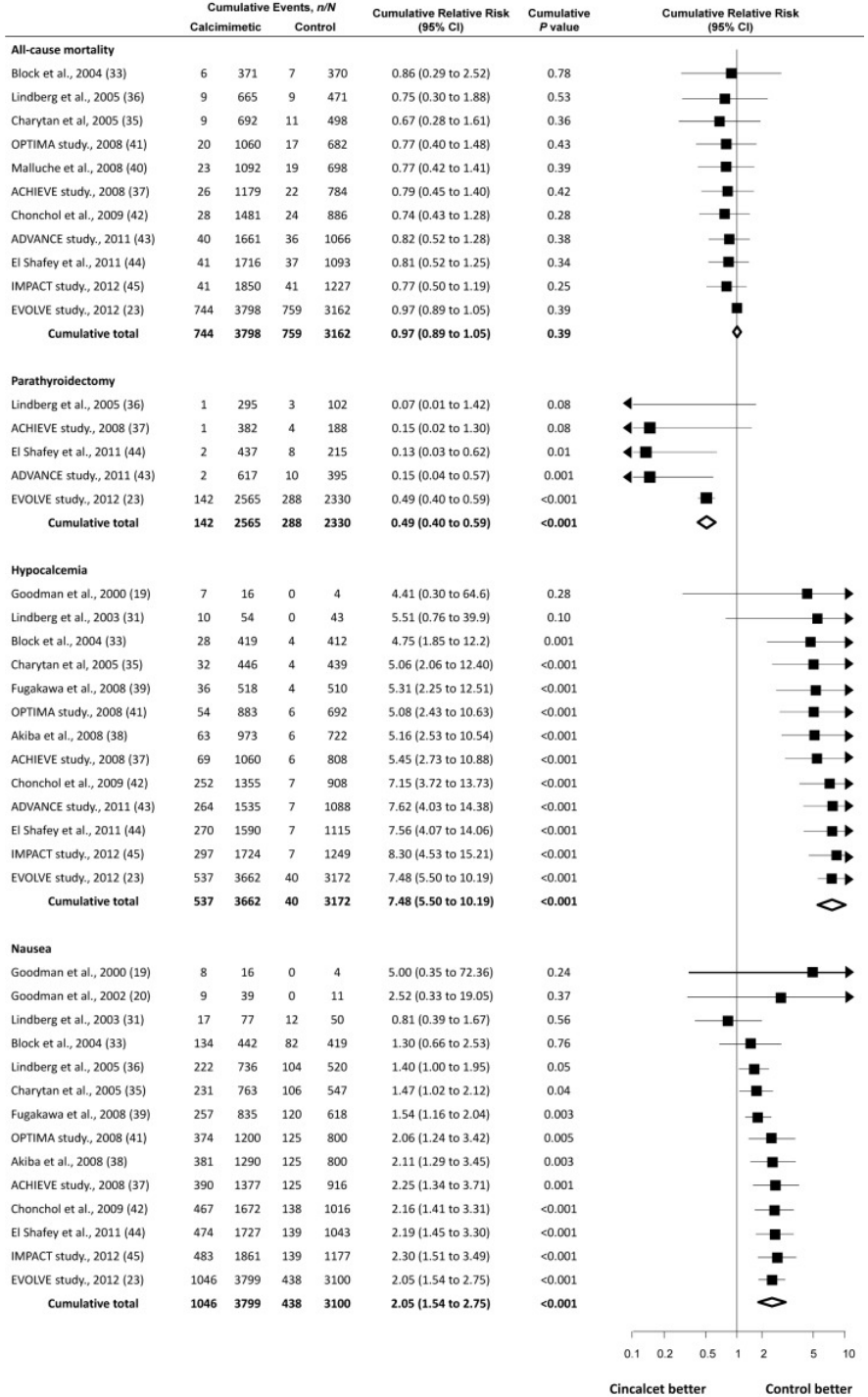

Subgroup
N
Cinacalcet better
Placebo better
HR (95% CI)
Interaction p-value
Overall treatment effect 3883 0.72 (0.58, 0.90)
Age 0.253
Less than 65 years 2878 0.79 (0.61, 1.03)
65 years or more 1005 0.60 (0.41, 0.88)
Sex 0.421
Female 1578 0.66 (0.49, 0.90)
Male 2305 0.79 (0.58, 1.07)
Race group 0.023
White 2240 0.58 (0.44, 0.77)
Black 837 0.89 (0.52, 1.52)
Other 806 1.23 (0.75, 2.01)
Region 0.183
UnitedStates 1430 0.92 (0.65, 1.31)
Europe 1188 0.70 (0.47, 1.03)
LatinAmerica 687 0.69 (0.42, 1.14)
Russia 283 0.29 (0.10, 0.82)
Canada 146 0.29 (0.09, 0.92)
Australia 149 1.00 (0.28, 3.58)
Diabetes 0.612
Yes 1302 0.78 (0.55, 1.10)
No 2581 0.69 (0.52, 0.91)
BL vitamin D 0.744
Yes 2310 0.70 (0.53, 0.93)
No 1573 0.76 (0.54, 1.06)
PTH group 0.272
300 to 600 pg/mL 1573 0.72 (0.51, 1.00)
600 to 900 pg/mL 929 0.88 (0.56, 1.37)
900 to 1200 pg/mL 550 0.96 (0.52, 1.77)
More than 1200 pg/mL 831 0.50 (0.31, 0.80)
Dialysis vintage 0.209
Less than 2 years 1098 0.88 (0.57, 1.35)
2 to 5 years 1285 0.83 (0.57, 1.23)
5 years or more 1499 0.58 (0.41, 0.80)
Fracture history 0.266
Yes 769 0.88 (0.59, 1.31)
No 3114 0.67 (0.52, 0.86)
Stroke history 0.513
Yes 355 0.60 (0.34, 1.08)
No 3528 0.74 (0.59, 0.94)
Tobacco use 0.267
Never 2184 0.80 (0.60, 1.08)
Former 1064 0.76 (0.50, 1.18)
Current 632 0.51 (0.31, 0.82)
0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6


Subgroup
N
HR (95% CI)
Interaction p-value
Overall treatment effect 3883 0.72 (0.58 , 0.90)
Vitamin D Sterol use 0.999
Yes 2260 0.72 (0.54 , 0.96)
No 1623 0.72 (0.52 , 1.01)
Phospate binder use 0.208
Yes 3433 0.69 (0.55 , 0.87)
No 450 1.11 (0.55 , 2.23)
Calcium-based phosphate binder use 0.009
Yes 2062 0.55 (0.40 , 0.74)
No 1821 0.98 (0.72 , 1.35)
Dialysate Calcium 0.150
>= 3.0 mEq/L 1452 0.55 (0.38 , 0.80)
2.5 - < 3.0 mEq/L 2035 0.81 (0.60 , 1.08)
< 2.5 mEq/L 395 1.06 (0.53 , 2.16)
Treatment better
Placebo better
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6

Cinacalcet in patients with chronic kidney disease: a cumulative meta-analysis of randomized controlled trials.

- Two independent reviewers identified trials, extracted data, and assessed risk of bias. Eighteen trials comprising 7,446 participants compared cinacalcet plus conventional therapy with placebo or no treatment plus conventional therapy in adults with CKD.
- Cinacalcet had little or no effect on all-cause mortality (relative risk, 0.97 [95% confidence interval, 0.89-1.05]), had imprecise effect on cardiovascular mortality (0.67 [0.16-2.87])
- It prevented parathyroidectomy (0.49 [0.40-0.59]) and hypercalcemia (0.23 [0.05-0.97]), but increased hypocalcemia (6.98 [5.10-9.53]), nausea (2.02 [1.45-2.81]), and vomiting (1.97 [1.73-2.24]).

Plos Med 2013; 10(4),


Cumulative Events, n/N
Calcimimetic
Control
Cumulative Relative Risk (95% CI)
Cumulative P value
Cumulative Relative Risk (95% CI)
All-cause mortality
Block et al., 2004 (33) 6 371 7 370 0.86 (0.29 to 2.52) 0.78
Lindberg et al., 2005 (36) 9 665 9 471 0.75 (0.30 to 1.88) 0.53
Charytan et al, 2005 (35) 9 692 11 498 0.67 (0.28 to 1.61) 0.36
OPTIMA study., 2008 (41) 20 1060 17 682 0.77 (0.40 to 1.48) 0.43
Malluche et al., 2008 (40) 23 1092 19 698 0.77 (0.42 to 1.41) 0.39
ACHIEVE study., 2008 (37) 26 1179 22 784 0.79 (0.45 to 1.40) 0.42
Chonchol et al., 2009 (42) 28 1481 24 886 0.74 (0.43 to 1.28) 0.28
ADVANCE study., 2011 (43) 40 1661 36 1066 0.82 (0.52 to 1.28) 0.38
El Shafey et al., 2011 (44) 41 1716 37 1093 0.81 (0.52 to 1.25) 0.34
IMPACT study., 2012 (45) 41 1850 41 1227 0.77 (0.50 to 1.19) 0.25
EVOLVE study., 2012 (23) 744 3798 759 3162 0.97 (0.89 to 1.05) 0.39
Cumulative total 744 3798 759 3162 0.97 (0.89 to 1.05) 0.39
Parathyroidectomy
Lindberg et al., 2005 (36) 1 295 3 102 0.07 (0.01 to 1.42) 0.08
ACHIEVE study., 2008 (37) 1 382 4 188 0.15 (0.02 to 1.30) 0.08
El Shafey et al., 2011 (44) 2 437 8 215 0.13 (0.03 to 0.62) 0.01
ADVANCE study., 2011 (43) 2 617 10 395 0.15 (0.04 to 0.57) 0.001
EVOLVE study., 2012 (23) 142 2565 288 2330 0.49 (0.40 to 0.59) <0.001
Cumulative total 142 2565 288 2330 0.49 (0.40 to 0.59) <0.001
Hypocalcemia
Goodman et al., 2000 (19) 7 16 0 4 4.41 (0.30 to 64.6) 0.28
Lindberg et al., 2003 (31) 10 54 0 43 5.51 (0.76 to 39.9) 0.10
Block et al., 2004 (33) 28 419 4 412 4.75 (1.85 to 12.2) 0.001
Charytan et al, 2005 (35) 32 446 4 439 5.06 (2.06 to 12.40) <0.001
Fugakawa et al., 2008 (39) 36 518 4 510 5.31 (2.25 to 12.51) <0.001
OPTIMA study., 2008 (41) 54 883 6 692 5.08 (2.43 to 10.63) <0.001
Akiba et al., 2008 (38) 63 973 6 722 5.16 (2.53 to 10.54) <0.001
ACHIEVE study., 2008 (37) 69 1060 6 808 5.45 (2.73 to 10.88) <0.001
Chonchol et al., 2009 (42) 252 1355 7 908 7.15 (3.72 to 13.73) <0.001
ADVANCE study., 2011 (43) 264 1535 7 1088 7.62 (4.03 to 14.38) <0.001
El Shafey et al., 2011 (44) 270 1590 7 1115 7.56 (4.07 to 14.06) <0.001
IMPACT study., 2012 (45) 297 1724 7 1249 8.30 (4.53 to 15.21) <0.001
EVOLVE study., 2012 (23) 537 3662 40 3172 7.48 (5.50 to 10.19) <0.001
Cumulative total 537 3662 40 3172 7.48 (5.50 to 10.19) <0.001
Nausea
Goodman et al., 2000 (19) 8 16 0 4 5.00 (0.35 to 72.36) 0.24
Goodman et al., 2002 (20) 9 39 0 11 2.52 (0.33 to 19.05) 0.37
Lindberg et al., 2003 (31) 17 77 12 50 0.81 (0.39 to 1.67) 0.56
Block et al., 2004 (33) 134 442 82 419 1.30 (0.66 to 2.53) 0.76
Lindberg et al., 2005 (36) 222 736 104 520 1.40 (1.00 to 1.95) 0.05
Charytan et al., 2005 (35) 231 763 106 547 1.47 (1.02 to 2.12) 0.04
Fugakawa et al., 2008 (39) 257 835 120 618 1.54 (1.16 to 2.04) 0.003
OPTIMA study., 2008 (41) 374 1200 125 800 2.06 (1.24 to 3.42) 0.005
Akiba et al., 2008 (38) 381 1290 125 800 2.11 (1.29 to 3.45) 0.003
ACHIEVE study., 2008 (37) 390 1377 125 916 2.25 (1.34 to 3.71) 0.001
Chonchol et al., 2009 (42) 467 1672 138 1016 2.16 (1.41 to 3.31) <0.001
El Shafey et al., 2011 (44) 474 1727 139 1043 2.19 (1.45 to 3.30) <0.001
IMPACT study., 2012 (45) 483 1861 139 1177 2.30 (1.51 to 3.49) <0.001
EVOLVE study., 2012 (23) 1046 3799 438 3100 2.05 (1.54 to 2.75) <0.001
Cumulative total 1046 3799 438 3100 2.05 (1.54 to 2.75) <0.001
0.1 0.2 0.5 1 2 5 10
Cincalcet better
Control better

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial

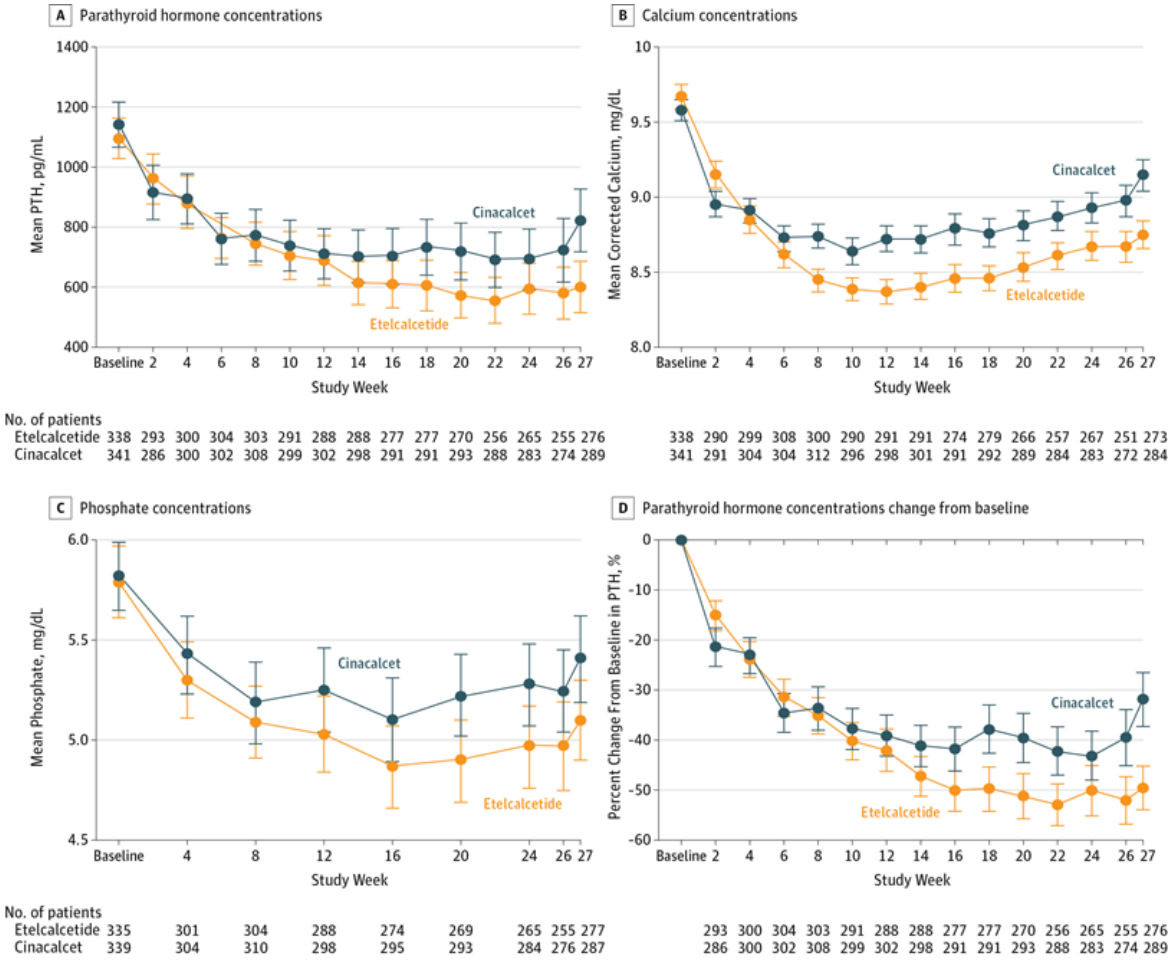
- Etelcalcetide is an octapeptide type 2 calcimimetic that interacts with the calcium sensing receptor at a site distinct from cinacalcet.
- Although the acute pharmacodynamic effects of etelcalcetide are similar to those of cinacalcet, the pharmacokinetic profile is distinct.
- Etelcalcetide is renally cleared, with a half-life allowing thrice weekly administration (concurrent with hemodialysis), yielded sustained reductions in PTH over the 48- to 72-hour dosing interval
- 680 stable patients on hemodialysis randommized 1:1 to IV etelcalcitide 5 mg 3 times weekly(each session of dialysis) and oral pelacebo (388 cases) or oral cinacalcet30 mg daily and IV pelacebo (341 cases).

JAMA 2017;317(2); 156-164

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial

- Dose titration increment 2.5 to 5 mg for etelcalcidate (2.5 -15 mg) and 30 mg for cincalcet (30-180 mg)
- The primary efficacy (noninferiority) end point was the proportion of patients with more than 30% reduction from baseline in mean PTH concentrations during the efficacy assessment phase (weeks 20-27)
- Secondary endpoint included the proportion of patients with more than a 50% and more than a 30% reduction in PTH concentrations (superiority).

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



Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial

- the estimated difference between patients randomized to cinacalcet was 57.7% (198 of 343) and to etelcalcetide was 68.2% (232 of 340) in proportions achieving the end point was −10.5% (−17.5% to −3.5%; *P* for noninferiority, <.001; *P* for superiority, .004).
- One hundred seventy-eight patients (52.4%) randomized to etelcalcetide achieved a reduction in PTH concentrations of more than 50%, whereas 138 patients (40.2%) randomized to cinacalcet achieved a reduction in PTH concentrations of more than 50% (*P* = .001, difference in proportions, 12.2%; 95% CI, 4.7% to 19.5%)
- for a reduction of more than 30%, the difference in proportions was 10.5% (95% CI, 3.3% to 17.7%). The relative proportion of patients achieving a reduction in PTH concentrations of more than 30% did not differ significantly across any of the patient subgroups examined

Subgroups	No./Total of Patients		Between-Group Difference in Proportion With >30% Decrease From Baseline in PTH Level, % (95% CI)
	Etelcalcetide	Cinacalcet	
Screening, PTH level, pg/mL			
<900	121/167	97/154	9.5 (-0.7 to 19.7)
≥900	110/171	97/182	11.0 (0.8 to 21.2)
Region			
North America	67/103	54/105	13.6 (0.3 to 26.9)
Non-North America	165/237	144/238	9.1 (0.6 to 17.7)
Time since initiation of dialysis, y			
0-≤1	33/46	36/48	-3.3 (-21.1 to 14.6)
>1-≤5	95/149	84/146	6.2 (-4.9 to 17.4)
>5	104/145	78/149	19.4 (8.5 to 30.2)
Baseline			
Dialysate calcium, mEq/L			
<3.0	128/191	104/189	12.0 (2.3 to 21.7)
≥3.0	104/149	94/154	8.8 (-1.9 to 19.4)
Vitamin D sterol use			
Yes	143/200	122/206	12.3 (3.1 to 21.5)
No	89/140	76/137	8.1 (-3.4 to 19.6)
Calcium-containing phosphate binder or calcium supplement use			
Yes	119/172	101/168	9.1 (-1.1 to 19.2)
No	113/168	97/175	11.8 (1.6 to 22.1)
Previous cinacalcet use			
Yes	53/80	49/92	13.0 (-1.5 to 27.5)
No	179/260	149/251	9.5 (1.2 to 17.8)
Race			
Black	38/54	28/52	16.5 (-1.7 to 34.7)
White or other	194/286	170/291	9.4 (1.6 to 17.2)
Sex			
Men	125/192	106/192	9.9 (0.2 to 19.6)
Women	107/148	92/151	11.4 (0.8 to 22.0)
Age, y			
<65	176/262	130/243	13.7 (5.2 to 22.1)
≥65	56/78	68/100	3.8 (-9.7 to 17.3)
Overall	232/340	198/343	10.5 (3.3 to 17.7)

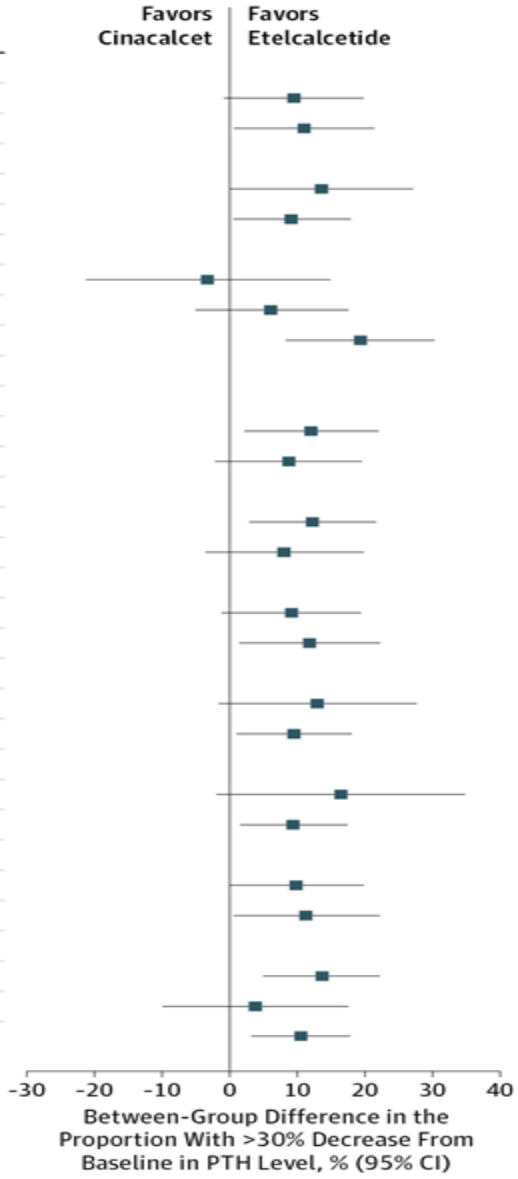


Table 2. Treatment Emergent Adverse Events[a]

Preferred Term	Patients, No. (%)	
	Etelcalcetide (n = 338)	Cinacalcet (n = 341)
Blood calcium decreased[b]	233 (68.9)	204 (59.8)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Hypotension	23 (6.8)	10 (2.9)
Headache	22 (6.5)	24 (7.0)
Muscle spasms	22 (6.5)	20 (5.9)
Diarrhea	21 (6.2)	35 (10.3)
Hypertension	21 (6.2)	23 (6.7)
Anemia	17 (5.0)	15 (4.4)
Hypocalcemia	17 (5.0)	8 (2.3)
Pain in extremity	17 (5.0)	14 (4.1)
Bronchitis	5 (1.5)	17 (5.0)

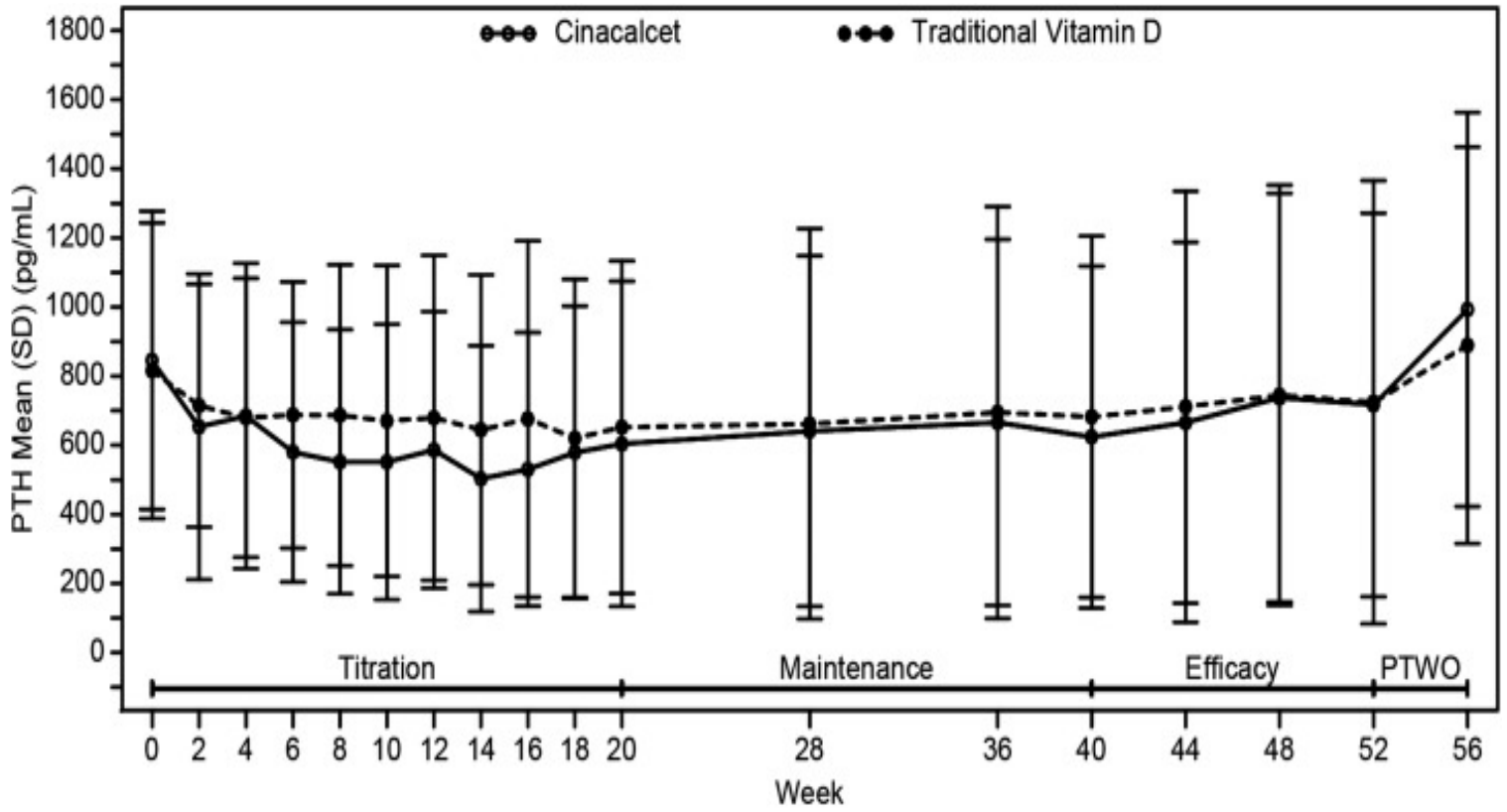
[a] Adverse events occurring among 5% or more patients in either group. The term *treatment emergent* refers to a condition either not present before exposure to a study drug that develops after drug exposure or a condition present before exposure that worsens in frequency or severity. Adverse events occurring after the first dose of study drug and up to 30 days after the last dose of study drug were included. Counts and proportions refer to patients rather than to adverse events. In other words, patients may have one or more adverse event.

[b] Defined as an albumin-corrected serum calcium concentrations lower than 8.3 mg/dL (to convert to mmol/L, multiply by 0.25) that resulted in a medical intervention.

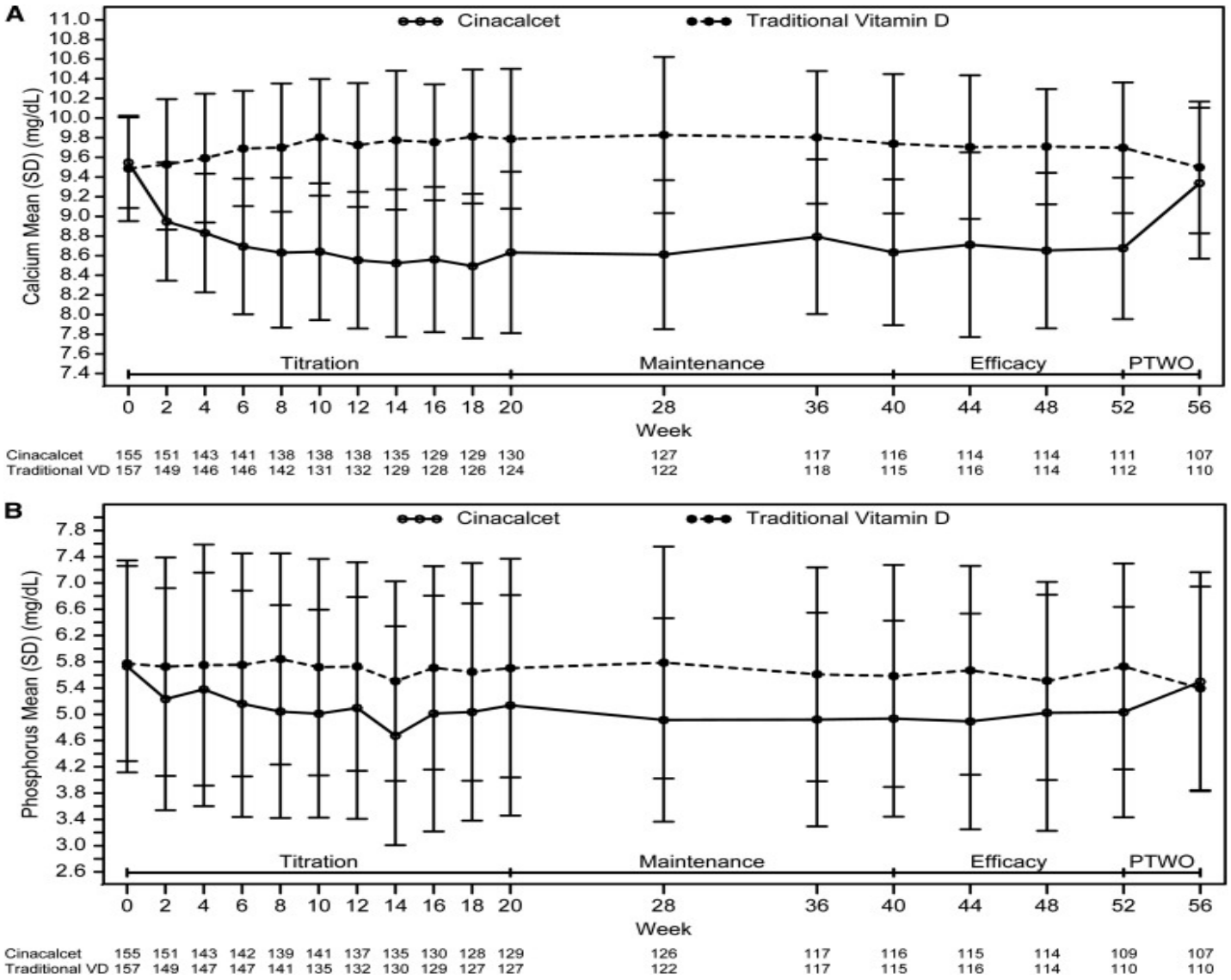
A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM)

- This was a prospective, multicenter, phase 4, randomized, open-label study that enrolled participants from 2010 to 2012. Adult participants (*n*=312) on hemodialysis with PTH >450 pg/ml were randomized 1:1 to 12 months of treatment with either cinacalcet (*n*=155) or vitamin D analogs (*n*=157)
- The mean percentage change in plasma PTH level (primary end point) and the proportion of participants achieving plasma PTH <300 pg/ml or a ≥30% decrease in PTH (secondary end points).

clin J Am Soc Nephrol 2015, 10(6), 1031-40



Cinacalcet	155	146	142	138	139	139	138	131	132	128	129	127	114	116	112	114	111	103
Traditional VD	157	150	144	146	142	134	132	132	127	124	127	122	118	116	115	114	111	110


A
Cinacalcet
Traditional Vitamin D
Calcium Mean (SD) (mg/dL)
11.0
10.8
10.6
10.4
10.2
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
Titration
Maintenance
Efficacy
PTWO
0 2 4 6 8 10 12 14 16 18 20 28 36 40 44 48 52 56
Week
Cinacalcet 155 151 143 141 138 138 138 135 129 129 130 127 117 116 114 114 111 107
Traditional VD 157 149 146 146 142 131 132 129 128 126 124 122 118 115 116 114 112 110
B
Cinacalcet
Traditional Vitamin D
Phosphorus Mean (SD) (mg/dL)
7.8
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
Titration
Maintenance
Efficacy
PTWO
0 2 4 6 8 10 12 14 16 18 20 28 36 40 44 48 52 56
Week
Cinacalcet 155 151 143 142 139 141 137 135 130 128 129 126 117 116 115 114 109 107
Traditional VD 157 149 147 147 141 135 132 130 129 127 127 122 117 115 116 114 110 110

A Randomized Trial of Cinacalcet versus Vitamin D Analogs as Monotherapy in Secondary Hyperparathyroidism (PARADIGM)

- In this study evaluating the relative efficacy of cinacalcet and vitamin D analogs as monotherapy for the treatment of SHPT in participants receiving chronic hemodialysis, there was no difference between treatment arms in the mean decrease in PTH (the primary end point), the percentage of participants achieving ≥30% reduction in PTH, or the percentage achieving a PTH<300 pg/ml.

Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney DiseaseThe PRIMO Randomized Controlled Trial

- Multinational, double-blind, randomized placebo controlled trial among 227 patients with chronic kidney disease, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries from July 2008 through September 2010
- Change in left ventricular mass index over 48 weeks by cardiovascular magnetic resonance imaging.
- At 48 weeks, the change in left ventricular mass index did not differ between treatment groups (paricalcitol group, 0.34 g/m2.7 [95% CI, −0.14 to 0.83 g/m2.7] vs placebo group, −0.07 g/m2.7 [95% CI, −0.55 to 0.42 g/m2.7]).
- Doppler measures of diastolic function including peak early diastolic lateral mitral annular tissue velocity (paricalcitol group, −0.01 cm/s [95% CI, −0.63 to 0.60 cm/s] vs placebo group, −0.30 cm/s [95% CI, −0.93 to 0.34 cm/s]) also did not differ

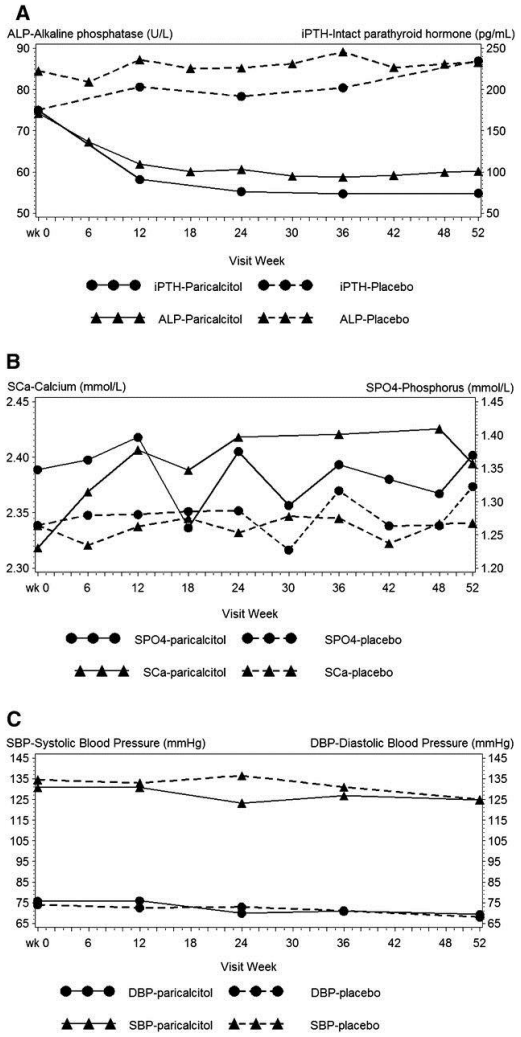
JAMA 2012, 307(7), 674-84

Effect of Paricalcitol on Left Ventricular Mass and Function in CKD—The OPERA Trial

- Subjects with echocardiographic criteria of LV hypertrophy were randomly assigned to receive either oral paricalcitol (1 μg) one time daily (*n*=30) or matching placebo (*n*=30) for 52 weeks. (60 patients)
- The primary end point was change in LV mass index over 52 weeks, which was measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volume, echocardiographic measures of systolic and diastolic function, biochemical parameters of mineral bone disease, and measures of renal function.
- Change in LV mass index did not differ significantly between groups (median [interquartile range], −2.59 [−6.13 to 0.32] g/m^2 with paricalcitol versus −4.85 [−9.89 to 1.10] g/m^2 with placebo).
- The primary analysis did not change and remained insignificant (*P*=0.90), even after adjustment was made for RAS blockers use and baseline heart failure.

J Am Soc Nephrol 2014, , 25(1), 175-186

iPTH and ALP decreased over 52-week of paricalcitol treatment but increased with placebo (A).



Angela Yee-Moon Wang et al. JASN 2014;25:175-186

JASN Journal of the American Society of Nephrology

Effect of active vitamin D on cardiovascular outcomes in predialysis chronic kidney diseases: A systematic review and meta-analysis

- Seven RCTs (five studies with paricalcitol and two studies with calcitriol, 731 patients) were included.
- Compared with control groups, active vitamin D reduced the incidence of cardiovascular events (RR, 0.27; 95% CI, 0.13–0.59), induced an increase in those with proteinuria reduction (RR, 1.9; 95% CI, 1.34–2.71), **but did not alter left ventricular mass index and systolic function** (MD, 0.42 g/m$^{2.7}$; 95% CI, −0.23–1.07 g/m$^{2.7}$, $P = 0.21$ for left ventricular mass index and MD, −0.33; 95% CI, −0.74–0.07, $P = 0.1$ for left ventricular ejection fraction).
- Neither systolic blood pressure nor diastolic blood pressure was reduced by active vitamin D (MD, 0.3 mmHg; 95% CI, −4.95–5.56 mmHg; MD, −0.24 mmHg; 95% CI: −6.21–5.72 mmHg, respectively).
- Increased probability of hypercalcaemia after paricalcitol therapy was found (RR, 7.85; 95% CI, 2.92–21.10).

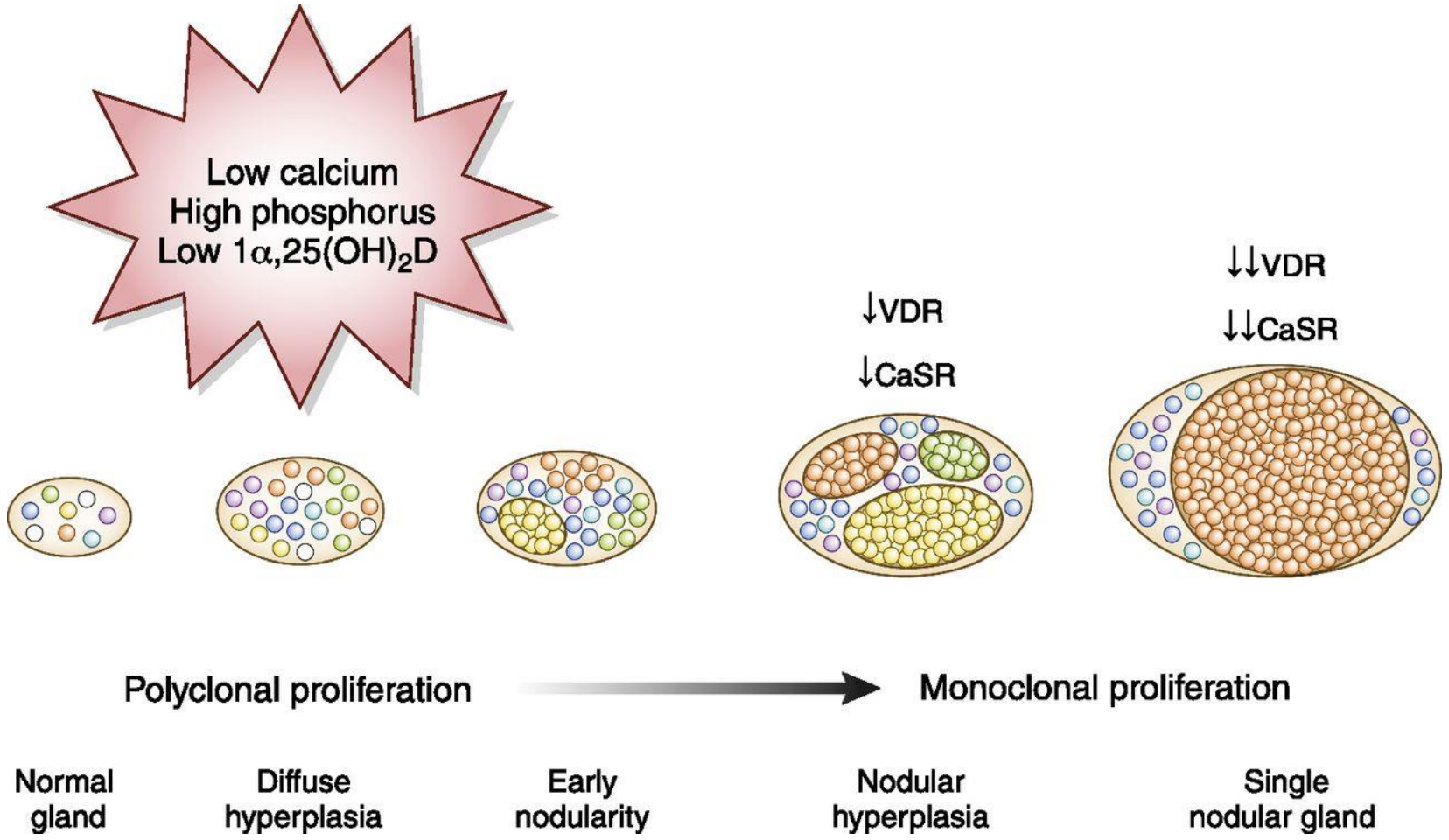
Nephrology 2015; 20, 706-14

Parathyroidectomy in the Management of Secondary Hyperparathyroidism

- Patterns of parathyroid hyperplasia in secondary hyperparathyroidism are classified into four categories:
  - Diffuse hyperplasia
  - Early nodularity in diffuse hyperplasia
  - Nodular hyperplasia
  - Single nodular gland

CJASN 2018, 13(6), 952-61

Pathophysiology of secondary hyperparathyroidism in CKD. Circulating fibroblast growth factor-23 increases early in CKD and suppresses 1α-hydroxylase in the kidney, leading to deficiency of active vitamin D [1α,25(OH)2D].



Wei Ling Lau et al. CJASN 2018;13:952-961

CJASN

Pharmacologic Therapies for Hyperparathyroidism and Their Limitations

- **Vitamin D Therapy**
  - Narrow therapeutic window(hypercalcemia and hyperphosphatemia may promote vascular calcification)
  - Resistance to vitamin D analogs in patients in whom severe secondary hyperparathyroidism has progressed to nodular hyperplasia with decreased vitamin D receptor expression

Pharmacologic Therapies for Hyperparathyroidism and Their Limitations

- **Calcimimetics**
  - Whether calcimimetics affect mortality, major cardiovascular events, or fracture rate remains controversial.
  - Cost-effectiveness is another consideration
- **Phosphorus Binders**
  - Are not approved for use in the predialysis population
  - use of calcium-containing salts in patients on dialysis increases the risk of hypercalcemia and vascular calcification
  - Calcium-free binders, such as sevelamer and lanthanum carbonate, as well as iron-based binders may be associated with less arterial calcification, but the effect on survival is unclear

Combination Therapy

- Both agents (Vit D or calcimimetics) must be used early in the disease when the vitamin D and calcium-sensing receptors are intact.
- There is evidence from clinical trials that more patients were able to achieve PTH targets when cinacalcet was added onto standard therapy with active vitamin D agents and phosphorus binders, and the combination therapy allowed for downtitration of vitamin D doses
- Combination therapy may also avoid blood calcium derangements, because vitamin D therapy can lead to hypercalcemia, whereas calcimimetics can induce hypocalcemia.

Indication of Parathyroidectomy

- Persistently elevated PTH values >800 pg/ml (>6 months) that remain nonresponsive to pharmacologic therapy, including maximally tolerated doses of vitamin D analogs and calcimimetics, are generally accepted as a criterion for parathyroidectomy
- Especially if nodular hyperplasia is confirmed on imaging.
- Hyperplastic parathyroid gland volume >500 mm^3 or glands >1 cm in long diameter strongly suggest nodular transformation, which is often refractory to medical therapy

Indication of Parathyroidectomy

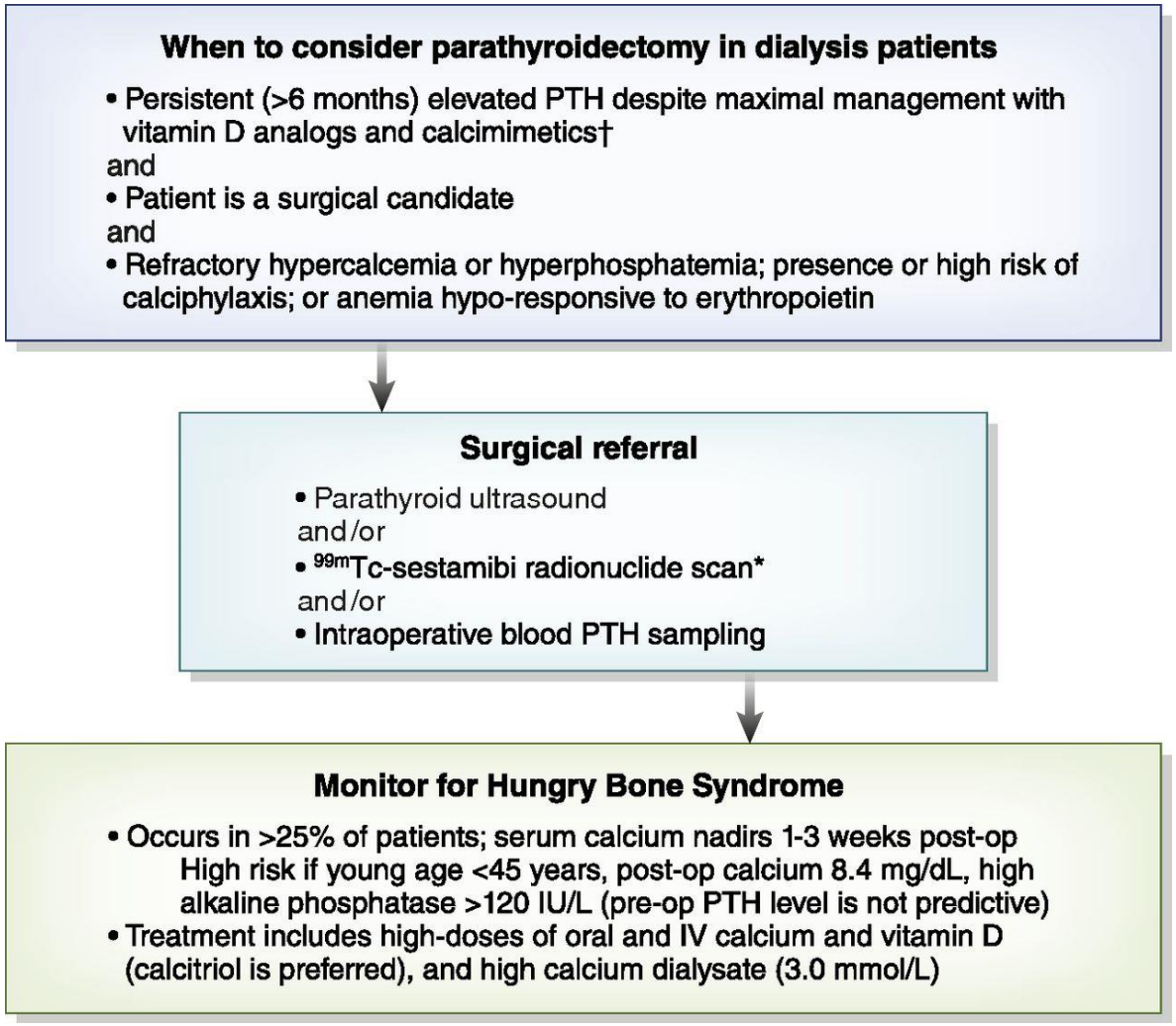
- There is no definitive lower PTH threshold
- Parathyroidectomy in patients on dialysis is reasonable when levels are in the 600- to 800-pg/ml range if there is:

  (*1*) persistent hypercalcemia or hyperphosphatemia (corrected serum calcium >10.2 mg/dl [>2.5 mmol/L] or phosphorus >5.5 mg/dl [>1.8 mmol/L]) despite patient compliance to diet and optimized vitamin D analog/calcimimetic doses

  (*2*) elevated risk or presence of calciphylaxis

  (*3*) erythropoietin-resistant anemia when other modifiable factors, such as iron deficiency or gastrointestinal bleeding, have been ruled out

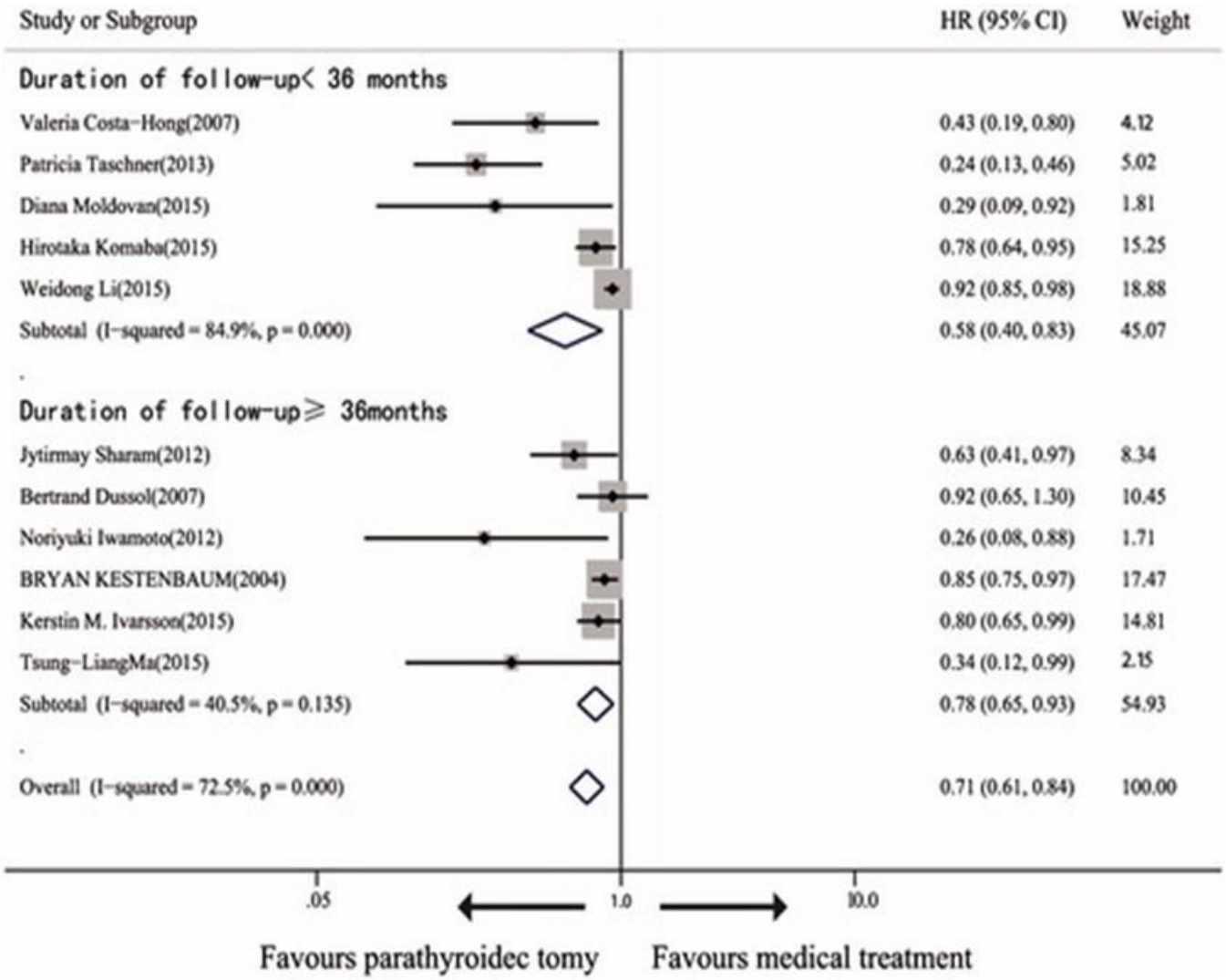
Perioperative considerations for parathyroidectomy in patients on dialysis.



Wei Ling Lau et al. CJASN 2018;13:952-961

CJASN

Long–term mortality after parathyroidectomy among chronic kidney disease patients with secondary hyperparathyroidism: a systematic review and meta-analysis

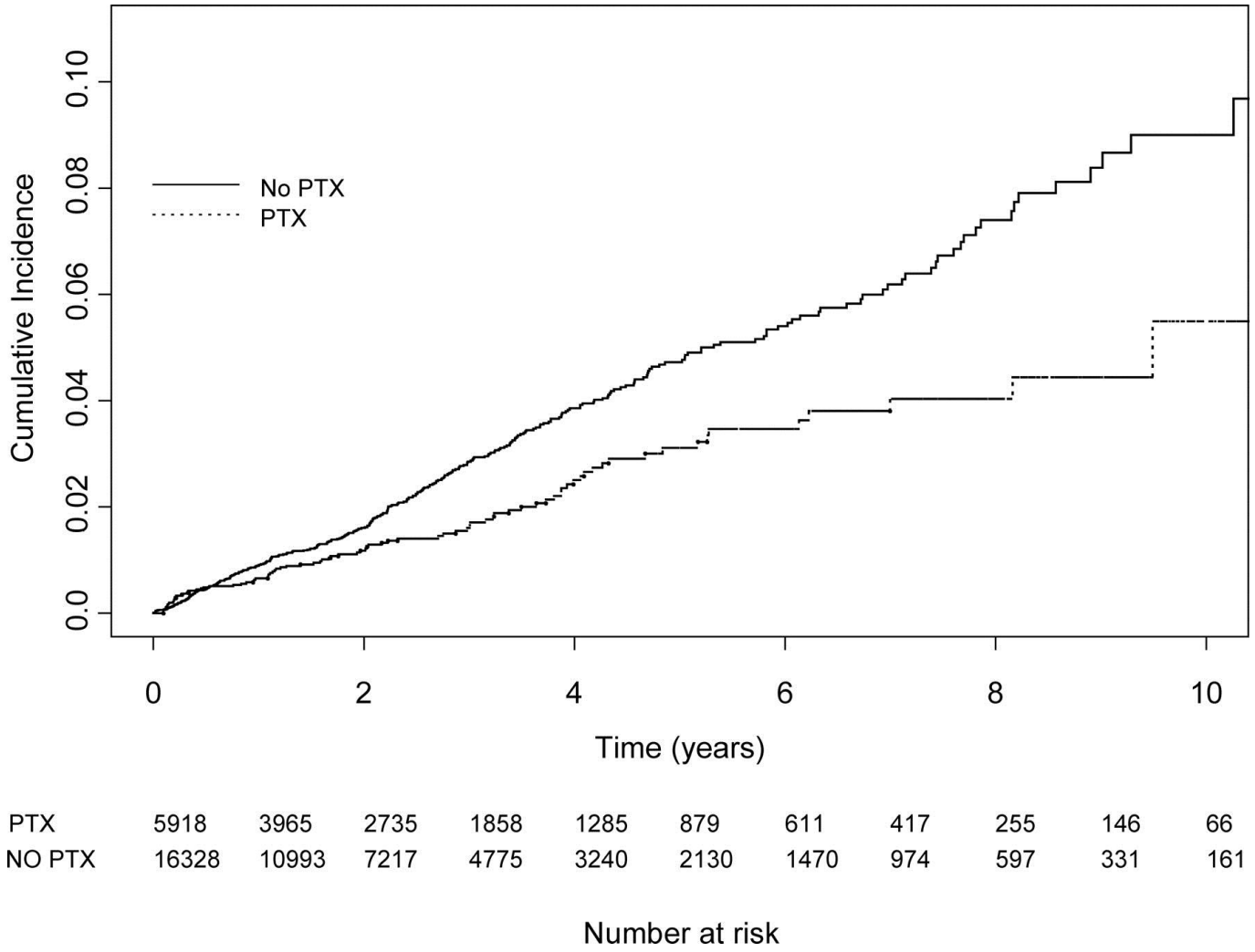


renal Failure 2016, issue 7

Long–term mortality after parathyroidectomy among chronic kidney disease patients with secondary hyperparathyroidism: a systematic review and meta-analysis

- A recent meta-analysis by Chen *et al.* extracted data from 13 cohort studies involving 22,053 patients, of whom approximately 10,000 underwent parathyroidectomy, where parathyroidectomy was associated with an overall 28% reduction in all-cause mortality and a 37% reduction in cardiovascular mortality.

Cumulative incidence of hip fracture in parathyroidectomy (PTX) and matched control groups.



Kyle D. Rudser et al. JASN 2007;18:2401-2407

JASN Journal of the American Society of Nephrology