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- **Dr. Block is the Director of Clinical Research at Colorado Kidney Care, a department he created to further enhance the care and treatment of patients suffering from Chronic Kidney Disease (CKD) and its effects.**
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KDIGO 2016 Clinical Practice Guideline Update

UPDATE ON MANAGEMENT OF PTH AND VITAMIN D IN CKD

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CKD-MBD GUIDELINE UPDATE 2016

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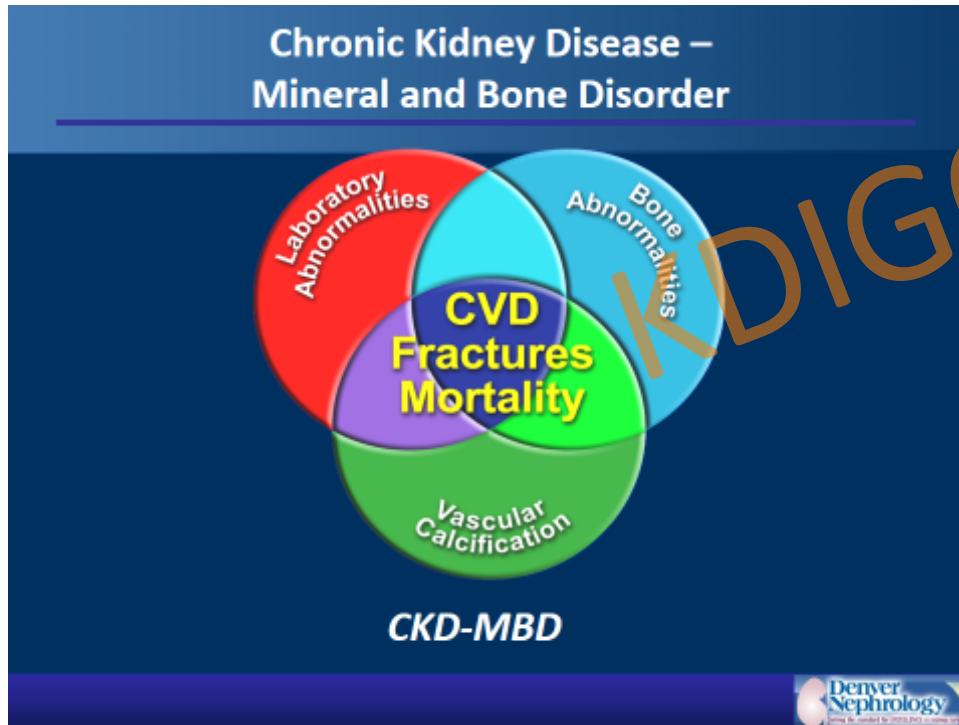


KDIGO CONTROVERSIES CONFERENCE ON CKD-MBD, 2013 (MADRID, SPAIN)

- **74 attendees** from **5 continents** and **19 countries**
- Represented experts in adult, pediatric and transplant nephrology, endocrinology, cardiology, bone histomorphometry, and epidemiology
- Divided into 4 Breakout Groups-12 Items Rec. for Review
 - Bone Quality
 - Calcium and Phosphate
 - Vitamin D and PTH
 - Vascular Calcification



ARE WE ACHIEVING OUR DESIRED OUTCOMES?



We should care about treating

PATIENTS, NOT their lab values!



EVIDENCE BASED

- Working Group Recognized that many large areas with evidence gap remain
- Existing Guidelines for which there were no new evidence based outcomes were not modified or addressed (e.g. PTH assay)



CHAPTER 4.2:

TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD



ASSESSMENT

4.2.1: In patients with CKD Stages 3a-5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. (2C)



RATIONALE

- Since the 2009 KDIGO guideline there are still no RCTs that define an optimal PTH level for patients with CKD stages 3a-5, or clinical endpoints of hospitalization, fracture or mortality.
- The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and have revised this statement to include “persistently” above the upper normal PTH level as well as “progressively rising” PTH levels, rather than “above the upper normal limit.” That is, treatment should not be based on a single elevated value.



RATIONALE

- Although the optimal PTH is not known, the Work Group felt that rising PTH levels in CKD stages 3a-5 warrant examination of modifiable factors:
 - Vitamin D insufficiency/deficiency
 - Hypocalcemia
 - Hyperphosphatemia
 - High phosphate intake
- Work Group also added ‘high phosphate intake,’ because of the increasing recognition that excess phosphate intake does not always result in hyperphosphatemia, especially in early stages of CKD, and that high phosphate could promote SHPT.



VITAMIN D

4.2.2: In adult patients with CKD Stages 3a-5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used.

(2C) It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism. *(Not Graded)*

In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. *(Not Graded)*

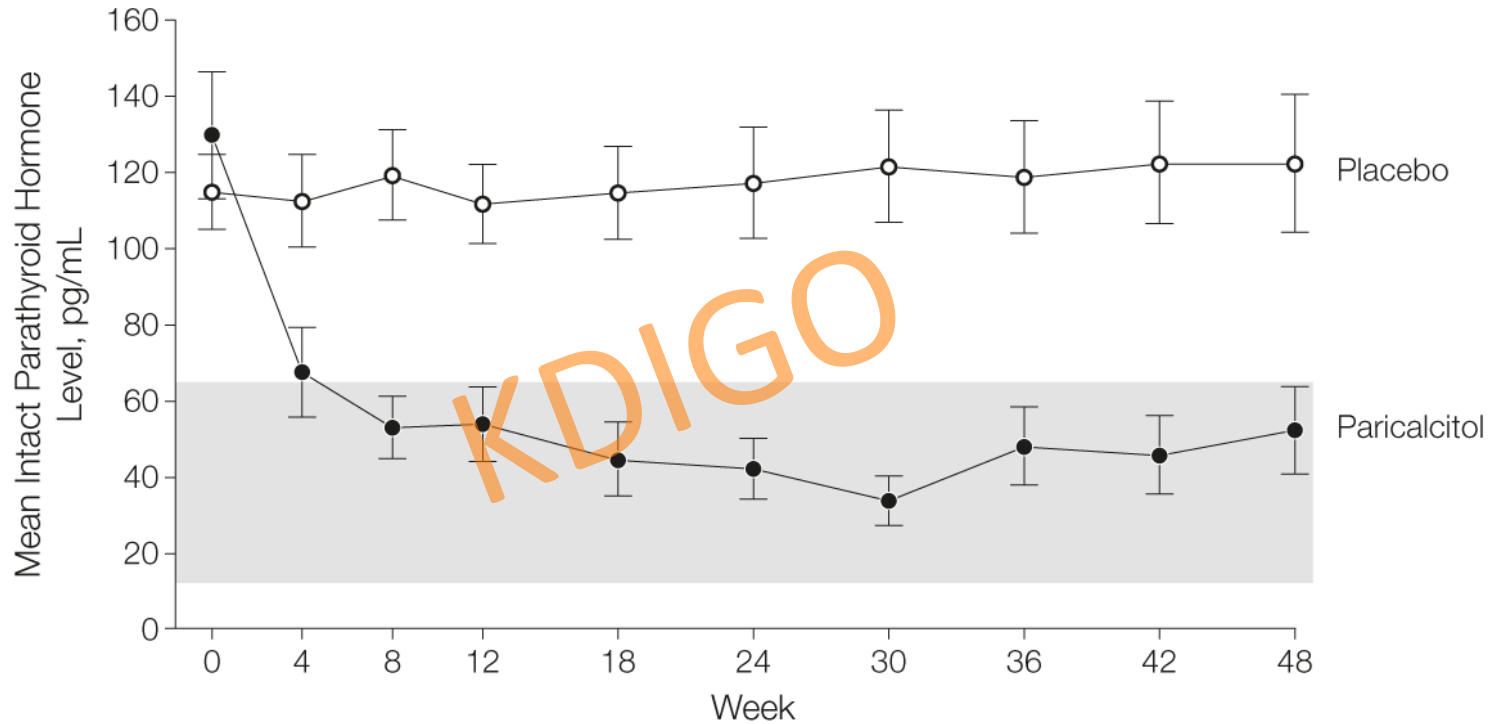


RATIONALE

- Suppression of PTH via calcitriol and other vitamin D analogs have been the therapeutic mainstay for the treatment of SHPT. Multiple RCTs cited in the 2009 Guideline reported benefits of these agents on improving biochemical endpoints and adverse effects of hypercalcemia were also noted.
- Two trials, PRIMO and OPERA, demonstrated significantly increased risk of hypercalcemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints.



THE PRIMO TRIAL



No. of patients

Placebo	112	105	106	104	100	93	94	91	92	85
Paricalcitol	115	111	112	108	104	101	96	92	88	84

Thadani R et al. JAMA. 2012;307:674-684

Kidney Disease: Improving Global Outcomes

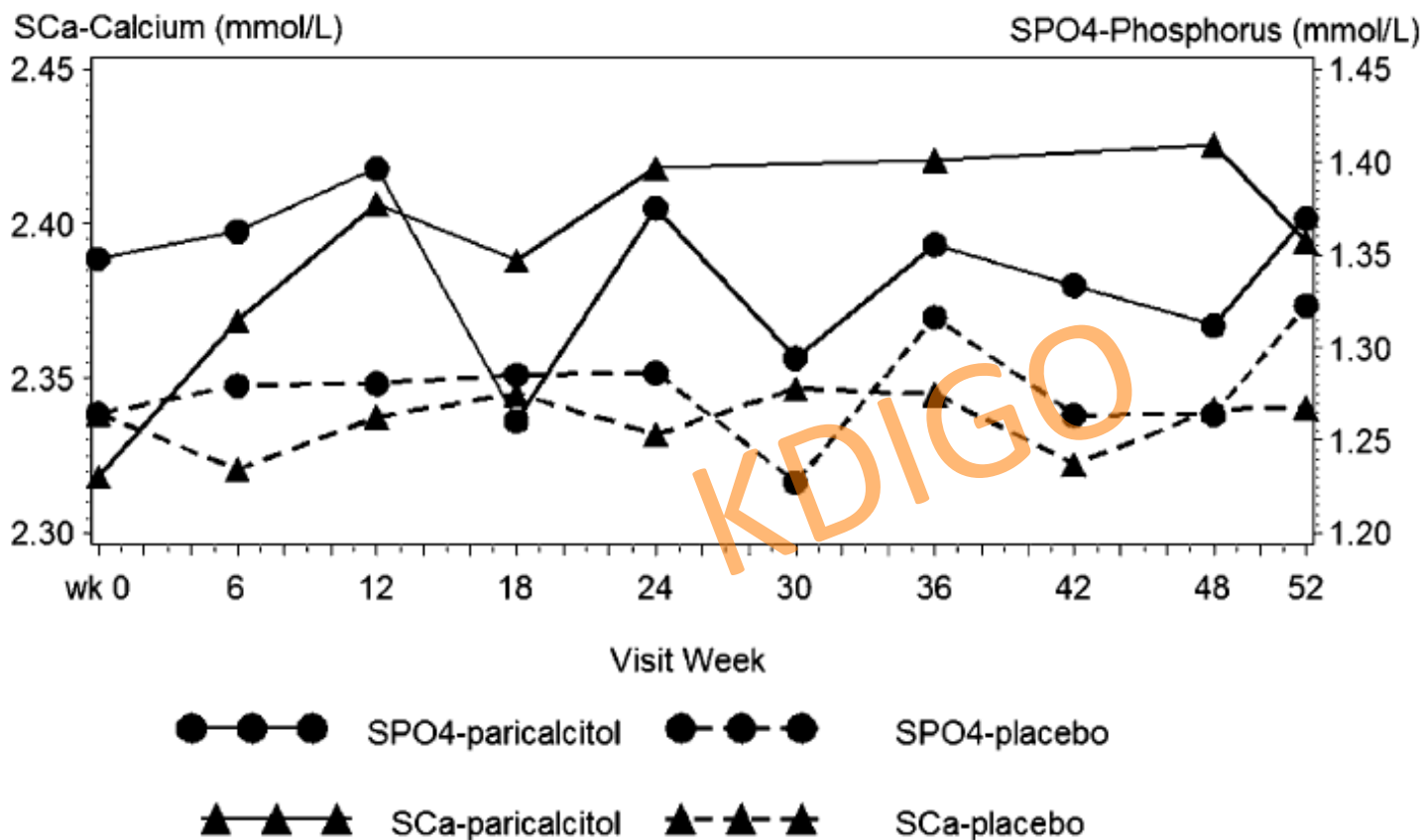


PARICALCITOL EFFECT ON CALCIUM AND PHOSPHATE

- Serum calcium levels increased a mean of 0.32 mg/dL (95% CI, 0.19-0.45 mg/dL) in the paricalcitol group and decreased 0.25 mg/dL (95% CI, -0.37 to -0.12 mg/dL) in the placebo group (between-group difference, $P < .001$).
- Serum phosphorus levels increased 0.23 mg/dL (95% CI, 0.07-0.39 mg/dL) in the paricalcitol group and increased 0.04 mg/dL (95% CI, -0.12 to 0.20 mg/dL) in the placebo group (between-group difference, $P = .05$).
- Hypercalcemia-paricalcitol 22.6% versus placebo 0.9%, $p < .001$
- eGFR decrease (creatinine) paricalcitol -4.1 ml/min versus placebo -0.1 ml/min, $p < .001$
- No significant effect on measures of LV size or function



THE OPERA TRIAL



Hypercalcemia > 2.55 mmol/L:

Paricalcitol
43.3%

Placebo
3.3%

No significant effect on measures of LV size or function

Wang A et al. J Am Soc Nephrol. 2014;25:175-186

Kidney Disease: Improving Global Outcomes



CONCLUSIONS

- Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Recent meta-analyses were largely confirmatory and supported the hypercalcemia risk association with calcitriol and vitamin D analogs.
- These results, combined with the opinion that moderate PTH elevations may represent an appropriate adaptive response, led the Work Group to conclude that the risk-benefit ratio of treating moderate PTH elevations was no longer favorable and that the use of calcitriol or vitamin D analogs should be reserved for only severe and progressive SHPT.



CONCLUSIONS

- There are still no RCTs demonstrating beneficial effects of calcitriol or vitamin D analogs on patient-level outcomes, such as cardiac events or mortality, and the optimal level of PTH in CKD stages 3a-5 is not known.
- Therapy with these agents may have additional harmful effects related to increases in serum phosphate and FGF23 levels.
- If initiated for severe and progressive SHPT, calcitriol or vitamin D analogs should be started with low doses, independent of the initial PTH concentration, and then titrated based on the PTH response.
- Hypercalcemia should be avoided.



VITAMIN D

4.2.2: In adult patients with CKD Stages 3a-5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used. (2C) It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism. *(Not Graded)*

In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. *(Not Graded)*



RATIONALE

- A recent Cochrane review examined vitamin D therapy for bone disease in children with CKD stages 2–5 and on dialysis. Bone disease, as assessed by changes in PTH levels, was improved by all vitamin D preparations regardless of preparation or route or frequency of administration. The Cochrane review has not shown any significant difference in hypercalcemia risk with vitamin D preparations compared with placebo, but one study showed a significantly greater risk of hypercalcemia with intravenous calcitriol administration.



CONCLUSIONS

- No difference in growth rates was detected between different vitamin D analogs or use of oral or intravenous vitamin D treatments.
- The Work Group recommended that serum calcium should be maintained within age-appropriate reference range in children, and given the association of high PTH levels with reduced bone mineralization and increased vascular calcification, children are likely to require calcitriol or other active vitamin D analog therapy.



LOWERING PTH

4.2.4: In patients with CKD Stage 5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs. (2B)

KDIGO



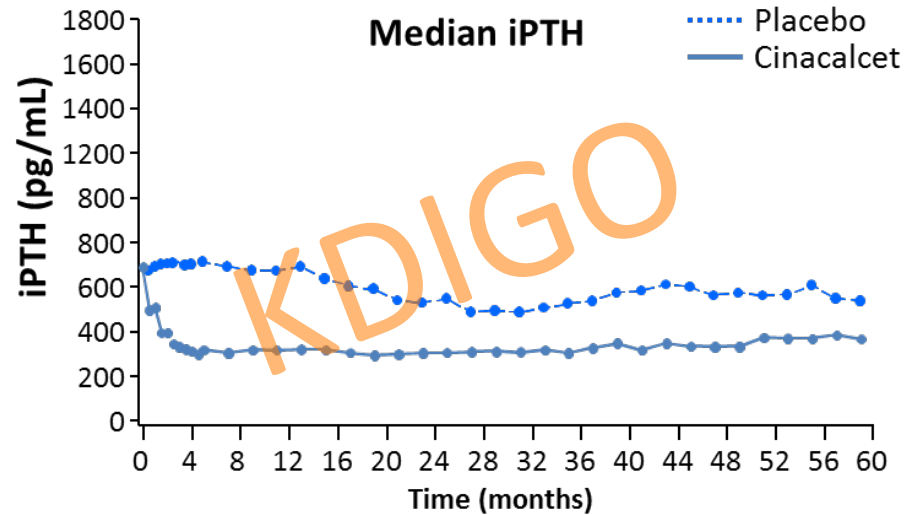
RATIONALE

- This recommendation originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate Rec. 4.2.4 as well.

KDIGO



EVOLVE: LOWERING PTH



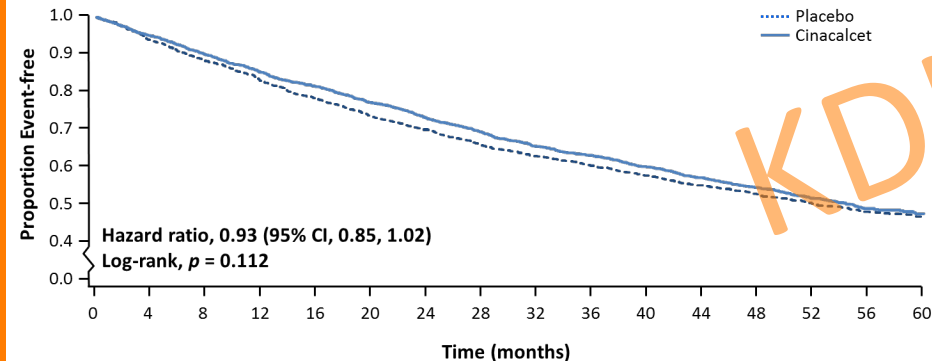
Chertow GM, et al. N Engl J Med. 2012;367:2482-2494



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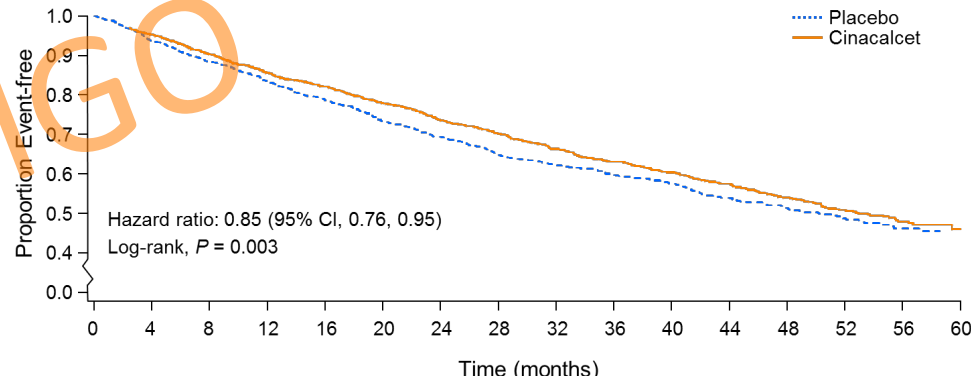
EVOLVE STUDY: CINACALCET

KDIGO



Subjects at risk:

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



Subjects at risk:

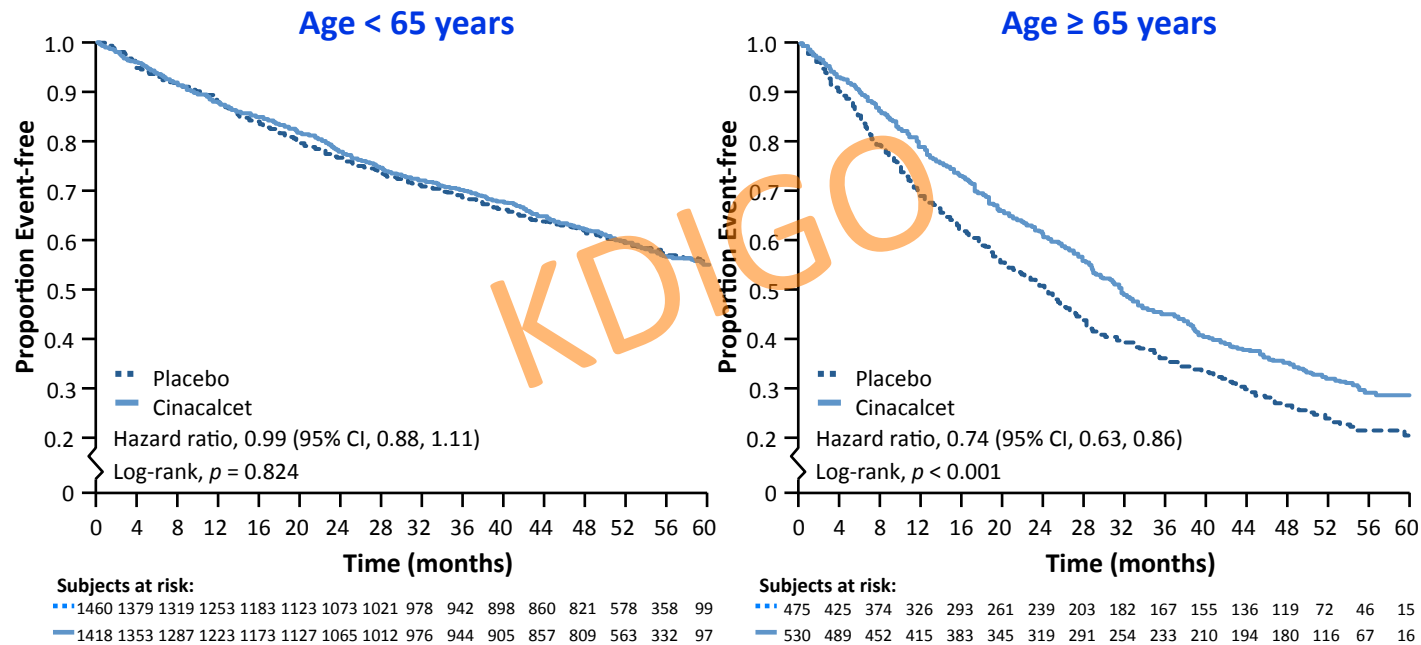
1935	1789	1615	1299	1080	875	739	625	525	474	419	353	303	180	93	26
1948	1835	1627	1376	1179	1002	847	731	632	551	491	425	362	239	130	28

Chertow GM, et al. N Engl J Med. 2012;367:2482-2494



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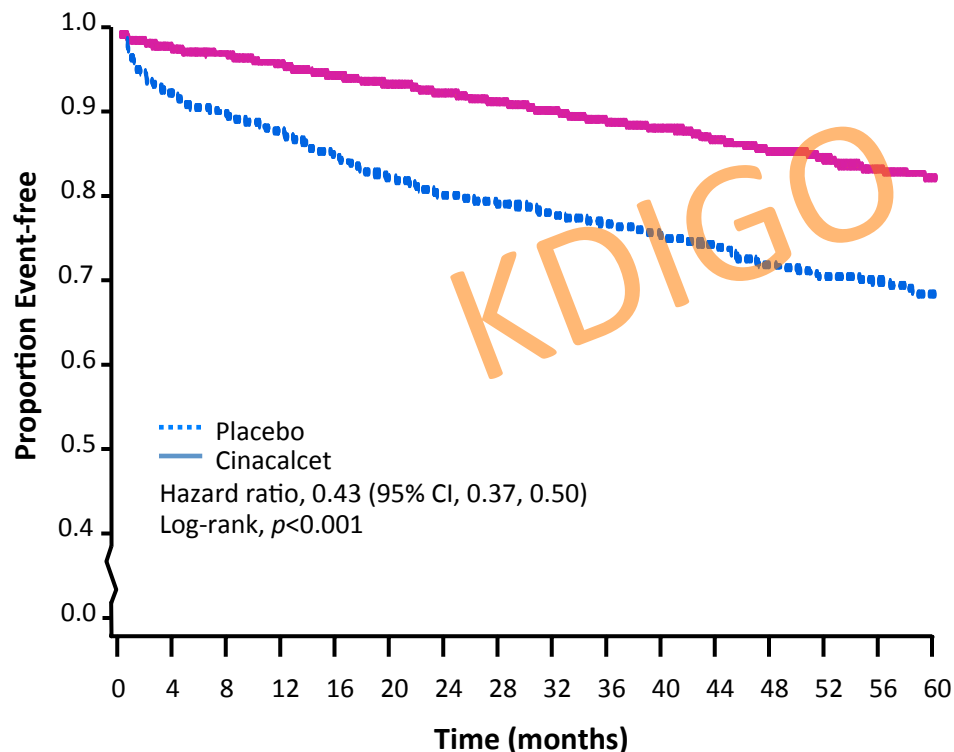
TIME TO PRIMARY COMPOSITE ENDPOINT



Parfrey et al, CJASN, 2015



TIME TO FIRST EPISODE OF SEVERE UNREMITTING HPT (INTENT-TO-TREAT ANALYSIS)



Severe, unremitting HPT

- Pre-specified and defined as
 - PTH > 1000 pg/mL (106.0 pmol/L) with serum calcium > 10.5 mg/dL (2.6 mmol/L) on 2 consecutive occasions OR
 - PTH > 1000 pg/mL with serum calcium > 10.5 mg/dL on a single occasion and subsequent commercial cinacalcet use within 2 months of the laboratory assessment OR
 - parathyroidectomy



PRIMARY COMPOSITE ENDPOINT: SENSITIVITY ANALYSES

Analysis Type	Placebo (N=1935)	Cinacalcet (N=1948)	HR (95% CI)	p-value
ITT	952 (49.2)	938 (48.2)	0.93 (0.85, 1.02)	0.112
Censor at PTX	911 (47.1)	916 (47.0)	0.90 (0.82, 0.99)	0.031
Censor at KTX	907 (46.9)	891 (45.7)	0.90 (0.82, 0.99)	0.029
Censor at Commercial Cinacalcet Use	818 (42.3)	870 (44.7)	0.90 (0.82, 0.99)	0.032
Censor at PTX or Commercial Cinacalcet Use	786 (40.6)	854 (43.8)	0.87 (0.79, 0.96)	0.006
Censor at PTX, Commercial Cinacalcet, or KTX	748 (38.7)	812 (41.7)	0.84 (0.76, 0.93)	<0.001



RATIONALE

- Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for Stage 5D patients, based on subsequent prespecified analyses.
- No PTH-lowering treatment was prioritized at this time, since calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in CKD Stage 5D patients.
- The Work Group explicitly endorses the presence of clinical equipoise and the need to conduct placebo controlled trials with calcimimetics versus standard therapy for the treatment of SHPT in patients with CKD stage 5D with emphasis on those at greatest risk (e.g., older, presence of cardiovascular disease).



PEDIATRIC PERSPECTIVE

- Studies of cinacalcet in children are limited to case reports, case series, a single center experience (with 4 to 28 patients), and an open label study of a single dose in 12 children on dialysis. In recognition of the unique calcium demands of the growing skeleton, PTH-lowering therapies should be used with caution in children to avoid hypocalcemia. Future studies are needed in children before making pediatric specific recommendations.



KEY MESSAGES

- It is important to emphasize the interdependency of serum Ca, P, and PTH for clinical therapeutic decision-making.
- The PRIMO and OPERA studies failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Accordingly, routine use of calcitriol or its analogs in CKD stages 3a–5 is no longer recommended.



KEY MESSAGES

- No consensus was reached to recommend cinacalcet as first-line therapy for lowering PTH in all patients with SHPT and CKD Stage 5D. The Work Group decided to modify the 2009 recommendation to list calcimimetic therapy now first, in alphabetical order, among acceptable treatment options while still recognizing the utility and efficacy of active vitamin D compounds.



COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

NEW 4.2.1. In patients with CKD Stages 3a-5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. (2C)

OLD 4.2.1. In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (*not graded*).



COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

Rationale: The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and have revised this statement to include 'persistently' above the upper normal PTH level as well as 'progressively rising' PTH levels, rather than 'above the upper normal limit.' That is, treatment should not be based on a single elevated value.



COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

NEW 4.2.2. In adult patients with CKD Stages 3a-5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism (*Not Graded*).

In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (*Not Graded*).

OLD 4.2.2. In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

Rationale: Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia.

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COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

NEW 4.2.4. In patients with CKD Stage 5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs. (2B)

OLD 4.2.4. In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD–MBD (*not graded*).



COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

Old 4.2.4 (cont'd)

- It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (*not graded*).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (*1B*).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (*2D*).
- We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (*2D*).
- We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (*2C*).



COMPARISON OF 2016 vs 2009 RECOMMENDATIONS

Rationale for new 4.2.4: This recommendation originally had not been for updating by the KDIGO Controversies Conference in 2013. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate Recommendation 4.2.4 as well. Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for Stage 5D patients based on subsequent pre-specified analyses. It was, however, decided not to prioritize any PTH-lowering treatment at this time since calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in Stage 5D patients.



THANK YOU

To the KDIGO staff for all of the meticulous help they have provided in creating the draft Guidelines and with the dissemination of knowledge

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