Chapter 30
Use of New Vitamin D Analogs in Chronic Kidney Disease

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Abstract Vitamin D is a common treatment against secondary hyperparathyroidism in renal patients. However, the rationale for the prescription of vitamin D sterols in chronic kidney disease (CKD) is rapidly increasing due to the coexistence of growing expectancies close to unsatisfactory evidences, such as the lack of randomized controlled trials (RCTs) proving the superiority of any vitamin D sterol against placebo on patient-centered outcomes, the scanty clinical data on head-to-head comparisons between the multiple vitamin D sterols currently available, the absence of RCTs confirming the crescent expectations on nutritional vitamin D pleiotropic effects even in CKD patients and the promising effects of vitamin D receptors activators (VDRA) against proteinuria and myocardial hypertrophy in diabetic CKD cohorts. The present chapter arguments these issues focusing on the opened questions that nephrologists should consider dealing with the prescription and the choice of a VDRA.

Keywords VDRA • Alfacalcidol • Doxercalciferol • Paricalcitol • Cinacalcet • Secondary hyperparathyroidism • Albuminuria • Left ventricular hypertrophy • Left atrial dimension • Bone histology • Bone mineral density • Kidney transplantation

30.1 Introduction

Secondary hyperparathyroidism (SHPT) is recognized as a major complication of chronic kidney disease (CKD). Over the past decades, nephrologists have been encouraged to effectively control PTH due to the reported worrisome consequences

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of SHPT as pruritus, bone pain, severe bone demineralization, skeletal fractures, brown tumors, severe cardiac hypertrophy, and calciphylaxis. Although repeated observational data described an independent association between serum PTH levels and unfavorable outcomes in CKD stage 3–5 as well as in end-stage renal disease (ESRD) patients, no randomized controlled trial (RCT) has still proven that an active reduction of PTH values could improve patient-centered outcomes as hospitalizations, cardiovascular events (CVE), CKD progression, and survival. Furthermore, the optimal targets of PTH levels are still uncertain in CKD as well as in ESRD cohorts. Thus, Kidney Disease-Improving Global Outcomes (KDIGO) guidelines provide a low-grade suggestion to maintain serum PTH levels into the range of normality in CKD 3–5 and between two and nine times the upper limit of normal range in ESRD.

Active vitamin D receptor activators (VDRA) (Table 30.1) are one of the classic therapies suggested to achieve those PTH targets. Emerging evidence of several pleiotropic effects related to the activation of the vitamin D receptor (VDR) is transforming the original world of vitamin D into a more complex scenario and affecting the use of vitamin D sterols among nephrologists. Different forms of vitamin D analogs are currently available in several countries, but clinical data on head-to-head comparisons between them are still scanty. Nonetheless, promising data suggest some beneficial effects of vitamin D analogs on proteinuria, myocardial hypertrophy in diabetic CKD cohorts, inflammation, and cardio-renal syndromes. Nutritional vitamin D replenishment is also receiving a growing interest for its potential autocrine-paracrine effects even in CKD patients, although its use is still based on observational rather than RCT data.

Table 30.1 Vitamin D sterols currently available as medical treatments in nephrology field

	Nutritional vitamin D		VDRA	
		Hydroxylation required to activate VDR		Hydroxylation required to activate VDR
Vitamin D2 and its analogs	Ergocalciferol	25-hydroxylation and 1-hydroxylation	Paricalcitol 19-nor1,25$(OH)_2D_2$	–
			Doxercalciferol 1α$(OH)D_2$	25-hydroxylation
Vitamin D3 and its analogs	Cholecalciferol	25-hydroxylation and 1-hydroxylation	Calcitriol 1,25$(OH)_2D_3$	–
			Alfacalcidol 1α$(OH)D_3$	25-hydroxylation
	Calcifediol	1-hydroxylation		
			Oxacalcitriol 22oxa1,25$(OH)_2D_3$	–

All the VDRA reported in the table are considered analogs with the exception of calcitriol, which corresponds to the natural form of 1,25$(OH)_2D_3$
VDRA vitamin D receptor activators, *VDR* vitamin D receptor

30.2 Alfacalcidol

30.2.1 Non-dialysis CKD: Effects on Bone Histology and Bone Mineral Density

A multicenter, prospective, double-blind, randomized, placebo-controlled trial was conducted on 176 non dialysis CKD patients (GFR 15–50 ml/min) with no baseline clinical, radiographic or biochemical signs of bone disease to test efficacy of a 2 year oral Alfacalcidol treatment (dose range 0.25 μg every other day to 1 μg a day) on bone histological pattern and quantitative changes in histomorphometric parameters [1]. Oral Alfacalcidol was administered in order to maintain serum calcium concentration at the upper limit of the normal laboratory reference range; calcium supplements were allowed (maximum 500 mg a day of elemental calcium), phosphorus restriction and phosphate binders were allowed to keep serum phosphate below 6.8 mg/dl.

All 176 patients underwent baseline bone biopsy, while only 134 (76 %) received a second bone biopsy at the end of treatment (n = 124) or after premature withdrawal because of starting dialysis (n = 10). Reasons for premature withdrawal included need to start dialysis, default and death, while no patients withdrew for adverse events.

By definition, all 176 patients had normal serum calcium and alkaline phosphatase at baseline, while serum phosphate levels were high in 50 patients and PTH levels were high in 72 patients. Prevalence of histological abnormalities was high at baseline (132/176 patients), with those patients with no subclinical bone disease having a higher mean GFR. After randomization, no difference in baseline biochemical and bone disease pattern was found between treatment groups, except for PTH levels (93.6 pg/ml VS 58.2 pg/ml in Alfacalcidol group versus placebo, respectively).

Among 134 patients, 72 taking Alfacacidol and 62 taking placebo, whom paired bone biopsy specimens were available for analysis, 76 % and 73 % respectively had significant bone abnormalities at baseline. At the end of the study, proportion of patients with bone disease decreased to 54 % in Alfacacidol group, while it increased to 82 % in placebo group. When considering only patients with bone abnormalities at baseline, 42 % of patients receiving Alfacalcidol treatment showed normal bone histology at the end of the study compared to only 4 % receiving placebo. Among patients with apparently normal bone at baseline, no difference in bone histology was found between groups at the end of the study. When compared to placebo, Alfacalcidol treatment among patients with subclinical bone disease caused a statistical significant decrease in bone marrow fibrosis, bone turnover (bone resorption and bone formation) and osteomalacia indexes. Four of the six patients in Aflacalcidol group resolved adynamic bone disease (ABD) by the end of the study versus two out of the three patients taking placebo; by contrast eight versus four patients in Alfacalcidol and placebo group respectively developed ABD.

Mild hypercalcemia occurred in three patients given placebo versus ten patients given Alfacalcidol, severe hypercalcemia occurred only in one patient taking Alfacalcidol. Serum phosphate levels increased in both groups in a similar way. Serum PTH levels rapidly decreased among patients taking Alfacalcidol and then returned toward baseline levels by 24 month, while progressive increase of serum PTH levels was observed in placebo group. Serum total alkaline phosphatase levels showed a similar trend. Serum 25(OH) vitamin D levels were not assessed. There was a similar decline in glomerular filtration rate (GFR) decline between groups (P = 0.94).

These results strongly support precocious use of Alfacalcidol among CKD patients in order to improve subclinical bone disease: benefits seem to overwhelm hazards in terms of developing ABD, hypercalcemia risk and fastening GFR decrease.

Results from this study were corroborated by another small prospective double blind placebo-controlled study which examined the effect of 18-month low dose Alfacalcidol treatment on bone mineral density (BMD) and markers of bone metabolism in early CKD (GFR 10–60 ml/min) [2]. Starting dose of 0.25 μg a day was increased in a 3-month period up to a maximum of 0.75 μg a day, while maintaining ionized serum calcium below 1.35 mmol/l and serum phosphate below 6.2 mg/dl. BMD was assessed in five sites: lumbar spine, femoral neck, total femur, distal forearm, and total body. ANOVA analysis with BMD as the dependent variable and treatment and time as independent variables suggested a significant effect of Alfacalcidol treatment on BMD in the hip, spine and total body sites. During treatment period, only one episode of hypercalcemia occurred among Alfacalcidol-treated subjects, serum phosphate levels were unaffected and a between-group difference in serum PTH levels was evident from week 3 onward, with lower levels among Alfacalcidol-treated subjects. Alfacalcidol-treated group showed a significant decrease over time of serum osteocalcin and bone alkaline phosphatase levels compared to placebo, while no statistical differences was observed in propeptide of type I collagen (PICP) – a marker of bone formation – and telopeptide of type I collagen (ICTP) – a marker of bone resorption. No difference in GFR decline rate was also found between groups.

30.2.2 Kidney Transplant Recipients: Effects on Bone Mineral Density

Bone disease after kidney transplantation is a complex matter with multiple contributing factors, including corticosteroid treatment, duration of prior chronic renal disease and dialysis, metabolic acidosis, vitamin D insufficiency/deficiency, hyperparathyroidism, hypophosphatemia, diabetes mellitus, etc. A few studies suggest beneficial effects of Alfacalcidol treatment among kidney transplant recipients.

A randomized study examined the effect of a 12 months course of low dose Alfacalcidol plus calcium versus calcium supplementation alone in pediatric

renal transplant recipients with low baseline BMD at lumbar spine, femoral neck and for the whole body (z-score < −1.0 by DEXA) and a transplant vintage of more than 1 year [3]. High proportion of patients in both groups showed high serum PTH, low osteocalcin and elevated alkaline phosphatase levels at baseline. Alfacalcidol treatment was shown to significantly improve BMD at the lumbar spine, femoral neck and whole body and to reduce serum PTH and alkaline phosphatase levels.

Data from the same authors seem to suggest equal or superior efficacy of Alfacalcidol plus calcium treatment on BMD compared to alendronate or nasal spray calcitonin in a similar kidney transplant pediatric population [4].

Among adult population, De Sevaux et al. [5] found a beneficial effect of Alfacalcidol plus calcium (0.25 μg + 1,000 mg daily) versus placebo during the first 6 months after renal transplantation in terms of reduction of BMD loss in the lumbar spine and femoral neck.

Trabulus et al. [6] compared 1 year treatment with calcium plus either Alfacalcidol (0.5 μg daily), Alendronate (10 mg/daily) or a combination of both drugs on transplant recipients with a T-score equal or less than −1.0 at either lumbar spine (LS) or femoral neck (FN). The range of time since renal transplantation was 1–179 months. Combination therapy lead to an increase of BMD in the LS and FN of about 8 % from baseline. Alfacalcidol treatment alone failed to show significant effects in BMD of the LS, while it gave a small advantage in terms of lesser decrease in BMD of the FN compared to control group.

30.2.3 Comparison with Other VDRAs

Comparison studies of Alfacalcidol with other active forms of vitamin D are scanty.

El-Reshaid et al. [7] demonstrated comparable effects of i.v. Calcitriol and i.v. Alfacalcidol in terms of PTH suppression. Moe et al. [8] found that Calcitriol was superior to Alfacalcidol in a 6 week crossover study of PTH suppression in hemodialysis patients when both drugs were given orally at equal doses (PTH reduction 26.2 % in Calcitriol arm versus 6.2 % in Alfacalcicol arm). In contrast, Kiattisunthorn et al. [9] compared both drugs given orally after hemodialysis session for 24 weeks to control SHPT when administered Alfacalcidol dose was 1.5–2.0 times that of Calcitriol: both drugs gave analogous PTH suppression, with no significant difference in episodes of hypercalcemia and hyperphosphatemia.

Hansen et al. [10] conducted a multicenter randomized open label trial to compare i.v. Paricalcitol to i.v. Alfacalcidol in the treatment of SHPT in hemodialysis patient. The original study had a crossover design, but after first treatment period and a 6-week washout period, PTH values were significantly lower than at study baseline, suggesting a biological effect of both drugs lasting more than 6 weeks after treatment discontinuation. This fact led to decision of excluding data from crossover period from being analyzed.

Among 80 patients who concluded the first treatment period, baseline serum PTH levels were 571 ± 210 pg/ml versus 528 ± 176 pg/ml in Alfacalcidol and Paricalcitol group, respectively; there was no difference in biochemical and dialytic parameters at baseline. Paricalcitol and Alfacalcidol were administered at a starting dose of 9 μg/week and 3 μg/week, respectively, and subsequently titrated to reach a >30 % reduction of baseline serum PTH levels, while keeping serum ionized calcium concentration <1.35 mmol/l and serum phosphate levels <6.2 mg/dl. Hyperphosphatemia was treated by means of administration of calcium-free intestinal phosphate binders, dietary intervention and reevaluation of dialysis dose. After 16 weeks treatment, similar proportion of patients reached a 30 % reduction of baseline PTH (82 % and 93 %, for Alfacalcidol and Paricalcitol groups, respectively, P = 0.18) and serum PTH levels less than 300 pg/ml (68 % and 83 %, respectively, P = 0.188). Serum calcium, phosphate, total alkaline phosphatase at week 16 did not significantly differ; single episodes and repeated episodes of hypercalcemia were comparable. When correcting for baseline serum PTH levels, a significant interaction was found between baseline PTH values and effect of treatment, with Alfacalcidol effectively suppressing PTH throughout the entire range of PTH values, while Paricalcitol having a better efficacy on lower serum PTH levels than higher ones.

30.2.4 Doxercalciferol

30.2.4.1 Secondary Hyperparathyroidism Treatment in Non-dialysis CKD Patients

Couburn et al. [11] conducted a multicenter double-blinded randomized placebo-controlled trial to test efficacy and safety of Doxercalciferol treatment on SHPT in non-dialysis CKD patients.

After an 8-week washout period, 55 CKD patients (GFR range 13–47 ml/min) with a baseline PTH above 85 pg/ml received 24 week treatment with oral Doxercaciferol or placebo. Starting dose was 1 μg daily, subsequently titrated to reach 30 % of baseline PTH suppression while keeping serum calcium, serum phosphate and urinary calcium within the normal range. Moderate hypercalcemia (serum calcium >10.7 mg/dl), hypercalciuria (urinary calcium >200 mg/day) and PTH oversuppression (iPTH <15 pg/ml) lead to temporary discontinuation of study drug, while mild hypercalcemia (Ca 10.3–10.7 mg/dl) or hyperphosphatemia (serum phosphate >5.0 mg/dl) lead to the prescription of calcium-based intestinal phosphate binder or Doxecracliferol dose adjustment.

During treatment, serum PTH levels decreased from 219 ± 22 to 118 ± 17 pg/ml (−43 ± 7.6 %) at week 24 in Doxercalciferol group, while they remained unchanged in placebo group. Seventy-four percent of patients in Doxercalciferol group reached a 30 % or more reduction of baseline serum PTH levels during week 20–24, compared to only 7 % in placebo group. Serum calcium levels increased slightly in Doxercalciferol-treated patients from baseline, but no between-groups difference was found except than at week 20. Significant higher serum phosphate levels were

also found in Doxercalciferol group compared to placebo at weeks 4 and 24. Doxercalciferol group experienced an increase in 24-h urinary calcium excretion from baseline onward, but no significant difference was found between groups at any time during treatment. Prevalence of hypercalcemia, defined as Ca >10.5 mg/dl, was not different between groups (2.6 % versus VS 1.9 % in Doxercalciferol and placebo groups, respectively, P = 0.27), as no difference was found in prevalence of hyperphosphatemia defined as P > 5.0 mg/dl (8.8 % versus 6.5 %, respectively, P = 0.47). Mean GFR decline rate was similar between groups. Doxercalciferol leads to reduction of serum total alkaline phosphatase by 12 % (P < 005), bone-specific alkaline phosphatase by 27.9 % (P < 0.001) and osteocalcin by 22 % (P < 0.001) from baseline to week 24, compared to no reduction of either marker in the placebo group.

30.2.4.2 Secondary Hyperparathyroidism Treatment in Dialysis Patients

Oral intermittent Doxercalciferol administration for PTH suppression in hemodialysis patients was evaluated in a study conducted by Frazão et al. [12]. This study consisted in an 8-week washout period from previously calcitriol administration and a 24-week period, divided in a 16 week open-label treatment with Doxercalciferol for all patients and an 8-week randomized double-blind placebo-controlled Doxercalciferol administration.

After washout, patients should have baseline serum PTH levels above 400 pg/ml with no upper limit of severity, serum phosphate levels between 2.9 and 6.9 mg/dl and serum calcium levels below 10.6 mg/dl. Calcium based phosphate binders administration was allowed.

One hundred thirty-eight patients entered in the treatment period. During open-label treatment, Doxercalciferol was administered at a starting dose of 10 mg a day, subsequently titrated up to a maximum dose of 20 mg thrice weekly to reach serum PTH levels between 150 and 300 pg/ml, while avoiding development of hypercalcemia (Ca >11.2 mg/dl), repeated hyperphosphatemia (P > 8.0 mg/dl) or elevated calcium x phosphorus product. During double-blind treatment, 50 % of patients were switched to placebo with unchanged pill dose. Patients who developed serum phosphate levels above 6.9 mg/dl were excluded from primary efficacy analysis, which was conducted as per-protocol analysis.

Mean serum PTH levels decreased rapidly during open-label treatment and reached 44.7 % reduction from baseline to week 16 (P < 0.001). After switching to placebo, serum PTH levels remained suppressed only in Doxercalciferol-treated patients, while placebo-receiving patients experienced an increase in serum PTH levels, which did not differ from baseline by week 20. During blinded treatment the prevalence of hypercalcemia (defined as serum calcium >10.5 mg/dl) was 5.5 % versus 15 % in placebo and Doxercalciferol group, respectively. Prevalence of hyperphosphatemia (serum phosphate >6.9 mg/dl) was 9.7 % versus 16.9 % respectively. Efficacy analysis was also conducted after splitting patients into three groups depending on the baseline serum PTH levels: patients with more severe hyperparathyroidism needed a longer treatment with higher Doxercalciferol doses, in spite of comparable calcium and phosphate baseline levels.

Patients who completed open-label oral treatment were subsequently enrolled in another trial [13] aimed at comparing oral to intravenous (IV) administration route.

After an 8-week washout period, patients underwent a 12 week open-label Doxercalciferol treatment with the drug administered IV at the end of each hemodialysis session at 40 % of the oral dose previously received. Drug titration and/or temporary suspension followed the same rules of the oral administration trial [12].

Following washout period, only 70 patients entered the IV trial. Mean baseline serum PTH levels in this trial were slightly but significantly lower than in the oral trial (748 versus 950 pg/ml, $p < 0.05$), thus suggesting a prolonged treatment effect of Doxercalciferol previously administered orally.

Oral and IV routes gave comparable effects in terms of absolute PTH suppression, the proportion of patients achieving 30 and 50 % baseline PTH suppression, and PTH oversuppression (PTH <150 pg/ml). The average increase in serum calcium levels calculated over the 12 weeks treatment period was significantly greater during oral than IV Doxercalciferol therapy (+0.5 mg/dl versus +0.3 mg/dl, respectively, $P < 0.02$). Similar results were found with respect to the increase in serum phosphate levels (+0.89 mg/dl versus +0.5 mg/dl, respectively, $P < 0.02$). Proportion of patients experiencing hypercalcemia and hyperphosphatemia were not statistically different between the two trials, but absolute number of episodes of hypercalcemia and hyperphosphatemia were greater with the oral route of administration.

30.2.4.3 Comparison with Other VDRAs

Two small trials were conducted among HD patients to evaluate dose equivalency between Doxercalciferol and Paricalcitol in SHPT treatment.

Zisman et al. [14] switched 27 patients on stable Paricalcitol treatment to a 6-week Doxercalciferol treatment at three different doses, and found comparable PTH inhibition at a Doxercalciferol dose of 55–60 % previous Paricalcitol dose. Fadem et al. [15] converted 42 HD patients receiving a fixed Paricalcitol dose to Doxercalciferol treatment, at a starting dose of either 50 or 65 % of Paricalcitol dose, which was subsequently titrated to reach a serum PTH level between 150 and 300 pg/ml. Authors found comparable efficacy of both regimens on PTH suppression, with significant cost-saving effect with Doxercalciferol treatment compared to Paricalcitol.

30.3 Paricalcitol

30.3.1 Secondary Hyperparathyroidism Treatment in Non-dialysis CKD Patients

Coyne et al. [16] evaluated results from three independently performed prospective, double-blinded, multicenter trials in which 220 stage 3 and 4 CKD patients were randomized to receive either oral Paricalcitol ($n = 107$) or placebo ($n = 113$) to control SHPT (PTH >120 pg/ml). Paricalcitol was administered either daily (initial

dose of 1 μg or 2 μg according to baseline PTH <500 pg/ml or >500 pg/ml) or thrice-weekly (2 μg or 4 μg according to the same baseline PTH cut-off). Mean baseline estimated GFR (eGFR) and PTH levels were 23.1 ml/min/1.73 m^2 and 265 pg/ml in Paricalcitol group and 23.0 ml/min/1.73 m^2 and 280 pg/ml in placebo group, respectively. After 24 weeks, 91 % of patients receiving Paricalcitol versus 13 % of patients receiving placebo ($P < 0.001$) had two consecutive serum PTH levels reductions <30 % under the baseline levels. Both the regimens of Paricalcitol administration were equally effective in achieving PTH reduction; average daily Paricalcitol dose in either regimen was between 1.3 and 1.4 μg. Hypercalcemia (defined as two consecutive corrected calcium values >10.5 mg/dl [2.62 mmol/l]) was observed in 2 % of patients receiving Paricalcitol, but in none receiving placebo; hyperphosphatemia (serum phosphorus >5.5 mg/dl on two consecutive determinations) occurred similarly in both groups (10 % for Paricalcitol versus 12 % for placebo); urinary calcium excretion increased slightly in patients receiving Paricalcitol (from 39.6 mg/day to 42.0 mg/day) although no significant differences were observed between groups from baseline to final visit. Paricalcitol-treated subjects had also a significant reduction in serum levels of bone formation markers (bone-specific alkaline phosphatase and osteocalcin).

Only one randomized trial [17] compared efficacy and safety of Paricalcitol versus Calcitriol treatment in stage 3 and 4 CKD patients with SHPT. In this study 107 patients with a baseline PTH value >120 pg/ml were randomized to receive a starting daily dose of either Paricalcitol 1 μg ($n = 53$) or Calcitriol 0.25 μg ($n = 54$), subsequently titrated to reach PTH suppression of 40–60 % below baseline. Primary end point was the rate of confirmed hypercalcemia (calcium >10.5 mg/dl), and this was similar between treatment groups (5.7 % for Paricalcitol and 1.9 % for Calcitriol, $P = 0.36$). Percentage 24 week reduction of PTH was similar between groups (−52 % in Paricalcitol group versus −46 % in Calcitriol group, $P = 0.17$) even if baseline PTH values were slightly different, being higher in Calcitriol group (176 pg/ml [IQR 142–221] versus 209 pg/ml [IQR 158–287], respectively). After 24 weeks, a significant greater proportion of patients reached a >40 and >60 % percentage reduction of baseline PTH in Paricalcitol-treated compared to Calcitriol-treated subjects (98 % versus 87 %, $P = 0.03$ and 83 % versus 52 %, $P < 0.001$, respectively). Average daily Paricalcitol dose administered was 1.3 μg, while average daily Calcitriol dose was 0.5 μg. The study showed also a similar small increase in serum calcium levels, phosphate levels and reduction in total alkaline phosphatase between treatment groups (P = NS for all). Both drugs increased in a similar way urinary calcium excretion.

30.3.2 Albuminuria Reduction

GFR and albuminuria are important independent risk factors for kidney failure, acute kidney injury, and all-cause or cardiovascular mortality [18]. RAAS inhibitors, such as ACE inhibitors or angiotensin receptor blockers, are the treatment of choice in albuminuric CKD, because they may delay cardiovascular and renal

disease as well as mortality. However, residual CV and renal risk can be high in patients treated with RAAS inhibitors, and this residual risk is positively associated to residual albuminuria [19, 20]: this underlines the role of albuminuria as a surrogate marker and a potential target for intervention in CKD patients.

Paricalcitol anti-albuminuric effect was first demonstrated in humans in a post hoc analysis [21] of a trial, which investigated Paricalcitol role in SHPT suppression in non-dialysis CKD patients. This antiproteinuric effect may be not specific for Paricalcitol, but it could be a class-effect of vitamin D compounds [22].

The VITAL study [23] was a multinational, placebo-controlled, double-blind trial specifically designed to test the anti-albuminuric effect of incremental doses of Paricalcitol on top of Renin-Angiotensin-Aldosterone System (RAAS) inhibition in patients affected by type 2 diabetes, albuminuria and CKD. Eligible patients had type 2 diabetes, a urinary albumin-to-creatinine ratio (UACR) 11–339 mg/mmol [100–3,000 mg/g], eGFR 15–90 ml/min and serum PTH concentration 35–500 pg/ml.

A total of 281 patients were randomly assigned to receive Paricalcitol 1 μg/day (n = 93), Paricalcitol 2 μg/day (n = 95), or placebo (n = 93) for 24 weeks. Mean baseline eGFR and UACR were similar between groups being 40, 42 and 39 ml/min/1.73 m^2 and 101, 92 and 94 mg/mmol [894, 814 and 832 mg/g] for 1 μg Paricalcitol, 2 μg Paricalcitol and placebo, respectively. All patients, except 2 in 2 μg Paricalcitol group, received some form of RAAS inhibition (ACE inhibitors, ARB, other RAAS inhibitors or a combination of these drugs); as a rule, this regimen could not be changed after randomization. Patients in this trial were generally 25OH-vitamin D depleted, being mean baseline serum levels 40, 42 and 42 nmol/L [16, 17 and 17 ng/ml] for 1 μg Paricalcitol, 2 μg Paricalcitol and placebo, respectively.

The primary efficacy point was the percentage change in geometric mean UACR from baseline to the last measurement during treatment. When compared to placebo, combined Paricalcitol groups showed a trend to reduction of UACR (between-group difference −15 %, 95 % CI −28 % to +1 %; P = 0.071). Further analysis of data suggested that UACR reduction could be dose-dependent, being difference between placebo and 2 μg Paricalcitol group closer to statistical significance (between-group difference −18 %, 95 % CI −32–0, P = 0.053), while that between placebo and 1 μg Paricalcitol being not (P = 0.23).

Secondary efficacy analysis seemed to confirm dose-dependency of Paricalcitol anti-albuminuric effect: a significant 24 urinary albumin reduction in 2 μg Paricalcitol group compared to placebo (between-group difference −28 %; 95 % CI −43 to −8, P = 0.009) and a higher proportion of patients achieving a change in UACR of at last 15 % between baseline and the last measurement (55 % versus 40 %, P = 0.038) were observed. UACR reduction (2 μg Paricalcitol versus placebo) was sustained during treatment, and reversible after treatment discontinuation. Degree of PTH reduction and rate of hypercalcemia reported were similar to previously published trials.

In a post-hoc analysis patients were stratified in tertiles according to their baseline 24 h urinary sodium excretion (<121 mmol; 121–178 mmol; >178 mmol). The greatest efficacy in UACR reduction was found in patients with the highest sodium intake receiving Paricalcitol 2 μg/day (−40 % versus placebo, P = 0.005).

Interestingly, 43 % of patients in the study were receiving maximal recommended dose of RAAS inhibition but no interaction was found with UACR reduction during Paricalcitol treatment, suggesting the efficacy of this regimen irrespective to the degree of RAAS inhibition. No significant changes were found between treatment groups in plasma renin activity and aldosterone levels.

A recent randomized, double blinded, placebo-controlled, crossover study was conducted to investigate whether antialbuminuric Paricalcitol effect could be due to plasma renin suppression [24]. Twenty-six non diabetic stage 3 and 4 CKD patients with urinary albumin >30 mg/l received a 6 weeks treatment with either Paricalcitol 2 μg/day or placebo, while discontinuing all RAAS inhibitors. Patients received a standardized diet during the last 4 days of each 6 weeks period, before assessment of plasma renin concentration (PRC). Etiology of CKD included polycystic kidney disease (n = 3), glomerulonephritis (n = 6), chronic interstitial nephritis (n = 2) or was unknown (n = 15); average baseline albuminuria was 169 mg/l (IQR 59–489).

No difference was found in PRC at the end of 6 weeks treatment with Paricalcitol compared to placebo, no significant difference was also found in 24 h urinary albumin excretion during Paricalcitol treatment (−7 % versus placebo, 95 % CI −20–7, P = 0.12).

With a complex experimental procedure, investigators wanted also to test Paricalcitol effect on hemodynamic and biochemical parameters before and during infusion of L-NMMA, a nitric-oxide synthase (NOS) inhibitor, supposing a modulatory effect of Paricalcitol on renal nitric oxide bioavailability. They observed that while acute NOS inhibition induced an albuminuric effect in patients taking placebo, the albuminuric response was blunted in Paricalcitol-treated subjects.

30.3.3 Cardiac Structure and Function, Cardiovascular End-Points

Vitamin D deficiency is associated with hypertension, left ventricular hypertrophy (LVH) and heart failure, and animal models demonstrated that vitamin D therapy prevents the progression of LVH [25, 26]. Retrospective data suggested a beneficial role of Paricalcitol treatment in humans on diastolic function and LVH [27]. These suggestions were explored in some specifically designed prospective trials.

The PRIMO study [28] was a multinational, randomized, placebo-controlled trial to test Paricalcitol ability to reduce left ventricular mass index (LVMI) and ameliorate cardiac diastolic parameters in stage 3 and 4 CKD patients with echocardiographic evidence of mild to moderate LVH and preserved systolic function, with baseline PTH values 50–300 pg/ml.

Patients were randomized to receive either Paricalcitol 2 μg/day or placebo for 48 weeks, with pre-specified dose reduction to 1 μg/day in case of hypercalcemia (serum calcium >11 mg/dl). At 24 and 48 weeks patients underwent cardiovascular magnetic resonance (CMR) to assess LVMI and transthoracic echocardiography (TTE) to measure diastolic cardiac parameters (peak early diastolic lateral mitral

annular tissue velocity (E′), isovolumetric relaxation time, ratio of early mitral inflow wave velocity E-wave (E) to E′, E-wave deceleration time). PTH and B-natriuretic peptide (BNP) were measured throughout the study period. Cardiovascular hospitalization and deaths were also recorded.

Baseline mean GFR and albuminuria were similar between groups, diabetics accounted for about one-half of sample size (54.8 % in Paricalcitol versus 50.9 % in placebo-treated patients), blood pressure was well controlled in both groups (mean 135/76 mmHg in Paricalcitol versus 135/75 mmHg in placebo group). Baseline LVMI normalized to height to the 2.7th power and E′ were similar between groups, consistent with mild to moderate LVH and diastolic dysfunction (LVMI 23.7 ± 7.3 g/m$^{2.7}$ versus 23.5 ± 8.3 g/m$^{2.7}$ and E′8.2 ± 2.5 versus 8.4 ± 2.4 cm/s in Paricalcitol and placebo-treated subjects, respectively).

One hundred two patients receiving Paricalcitol and 94 patients receiving placebo were included in primary intention-to-treat efficacy analysis. No cardiac parameter was significantly different between groups after 24 and 48 weeks. A trend was observed towards LVMI reduction in placebo-treated subjects compared to Paricalcitol-treated ones. In a pre-specified analysis considering patients with more severe baseline LMVI (the upper three quartile of baseline LVMI, named "LVH population") LVMI increased slightly in the Paricalcitol group with borderline statistical significance (P = 0.5).

Although all-cause hospitalization rate was similar between groups, Paricalcitol-treated patients had fewer cardiovascular hospitalizations compared to placebo (1 versus 8, P = 0.03). Plasma brain natriuretic peptide (BNP) levels increased in both groups, with no difference after 48 weeks in the ITT population, while Paricalcitol showed a blunting effect on BPN increase among patients in LHV population: Paricalcitol +15 % VS Placebo +50 % from baseline, P = 0.04).

As already seen in other studies, Paricalcitol treatment effectively decreased PTH levels compared to placebo, but in this study a higher rate of confirmed hypercalcemia during Paricalcitol treatment was observed than previously reported (prevalence of serum calcium >10.5 mg/dl in two consecutive determinations: 22.6 % VS 0.9 %, P < 0.001).

The OPERA trial [29] was a randomized-controlled trial with a study design similar to PRIMO study. Sixty patients from Hong Kong population were included in this RCT to test efficacy of Paricalcitol on LVMI reduction and amelioration of diastolic cardiac indices in a stage 3–5 non dialysis CKD population with echocardiographic documented LVH. Patients received Paricalcitol (1 or 2 μg/day, depending on baseline PTH value <500 pg/ml or >500 pg/ml, subsequently titrated to avoid hypercalcemia) or placebo for 52 weeks. LVMI was assessed by means of CMR and diastolic function by means of TTE.

Patients had an overall good blood pressure control (mean Paricalcitol group 131/76 mmHg; mean placebo group 135/74 mmHg). Compared to PRIMO study, patients in this trial had a more severe LVH and worse diastolic dysfunction at baseline (LVMI 39.2 ± 7.3 g/m$^{2.7}$ versus 38.0 ± 8.5 g/m$^{2.7}$ and E′6.8 ± 1.5 versus 6.7 ± 1.8 cm/s in Paricalcitol and placebo-treated subjects, respectively).

As already seen in PRIMO trial, there was no difference was found between groups in LVMI and diastolic parameters after 52 weeks. All-cause hospitalizations were fewer in Paricalcitol treated subjects (7 % versus 33 %, P = 0.02), with all cardiovascular-hospitalization being in placebo group. Hypercalcemia was higher in Paricalcitol group (43.3 % versus 3.3 %, P < 0.001), with a high proportion of patients being treated with calcium-based phosphate binders during hypercalcemic episodes (69.2 %). PTH suppression was similar to previously reported studies, even with a smaller daily Paricalcitol dose. No significant difference was found in 24 h urinary protein excretion between groups after 52 weeks treatment.

A post-hoc analysis of the PRIMO study [30] considered Paricalcitol effect on left atrium volume (LAV), which is considered a sensitive indicator of diastolic dysfunction severity, with added prognostic value above left ventricular morphology and function [31, 32].

LAV, assessed by biplane 2D echocardiography and indexed to body surface area (LAVi), at baseline showed a similar moderate enlargement in both groups (32.8 ± 9.8 ml/m^2 versus 35.4 ± 11.4 ml/m^2 in Paricalcitol group compared to placebo). Over the study period, LAVi demonstrated a significant decrease in Paricalcitol-treated patients compared with placebo-treated (−2.79 ml/m^2; 95 % CI −4.00 to −1.59 VS −0.7 ml/m^2; 95 % CI −1.93 to 0.53; P = 0.002), which paralleled corresponding attenuation in the rise in plasma levels of BNP. Given the fact that diuretic use and body weight changes were similar between groups, Paricalcitol effect on LAVi seems to be independent from extracellular volume reduction, even if Paricalcitol-induced BNP-mediated natriuresis or increase in urinary calcium concentration could have a contributory role in subclinical extracellular volume reduction.

30.3.4 Secondary Hyperparathyroidism Treatment in Dialysis Patients

In 2003 Sprague et al. [33] conducted the first multicenter, prospective, controlled, double-blind, randomized study to compare the safety and effectiveness of intravenous Calcitriol and intravenous Paricalcitol in medically stable hemodialysis patients with SHPT (PTH >300 pg/ml after SHPT-controlling drugs suspension).

It is important to emphasize that investigators used a very high threshold to define hypercalcemia (serum calcium >11.5 mg/dl), reflecting nephrologists' practice of the early-to-mid 1990s: this level was used to initially define patients suitable to active vitamin D therapy and to manage vitamin D dose titration. Furthermore, except from aluminium-containing phosphate binders, which were a priori excluded from the trial, the only intestinal phosphate binders available at time were calcium-containing ones. All these aspects should be considered when analyzing these results and trying to translate them in today's clinical practice.

Two hundred sixty-three patients were randomized to receive either Paricalcitol 0.04 μg/kg (n = 130) or Calcitriol 0.01 μg/kg (n = 133) thrice weekly. Dose could be increased every 4 weeks to reach a 50 % reduction from baseline PTH without PTH oversuppression (PTH <150 pg/ml), dose reduction could be done at 1 week intervals in case of hypercalcemia or two consecutive elevated Ca × P products (>75 mg^2/dl^2). Investigators were instructed not to change phosphate binder prescription.

After a pre-treatment phase, in which previous SHPT-controlling drugs were discontinued and phosphate binder doses and dialysate bath calcium were adjusted, mean baseline PTH were 648 pg/ml VS 645 pg/ml, mean serum calcium 9.0 mg/dl VS 9.0 mg/dl, mean serum phosphorus 5.9 mg/dl VS 5.8 mg/dl for Paricalcitol and Calcitriol-treated patients, respectively. Dialysis vintage was variable, including subjects with 5 years or more in both groups (prevalence in both groups about 30 %). Treatment phase lasted 12–32 weeks for each patient.

Both treatment groups achieved the primary end point of 50 % reduction of mean PTH, although Paricalcitol-treated subjects reached the end point earlier (15 weeks versus 23 weeks). Proportion of patients achieving a 50 % reduction from baseline PTH at least once during treatment period was more than 80 % in both groups, while 4 weeks-sustained PTH suppression was more frequently achieved in Paricalcitol-treated patients (64 % versus 54 %).

Proportion of patients who experienced a single episode of hypercalcemia or elevated Ca × P product was comparable between groups (64 % versus 68 %, P = 0.52, for Paricalcitol and Calcitriol respectively), while incidence of confirmed hypercalcemia or elevated Ca × P product was higher in Calcitriol group (38 % versus 50 %, P = 0.034, respectively). Hyperphosphatemia was very common and comparable between groups; similar reduction in total alkaline phosphatase levels was observed with both drugs.

A recent small study compared oral Paricalcitol versus oral Calcitriol for SHPT treatment in a Malaysian population of dialysis patients [34], a small percentage of peritoneal dialysis patients was also included. Patients eligibility criteria included PTH >300 pg/ml and absence of hypercalcemia (defined as serum calcium above 11 mg/dl).

Initial doses of either drug were calculated from baseline PTH obtained after a 3 weeks wash out period from previous drugs. Starting doses were PTH/120 for Paricalcitol and PTH/360 for Calcitriol. Drugs were titrated every 3 week to achieve a 30 % reduction of baseline PTH, while keeping it in the range 150–300 pg/ml. If hypercalcemia or elevated Ca × P occurred, dose reduction was required. No change in phosphate binder dose or calcium concentration in the dialysate bath was allowed.

Thirty-six and 30 patients received Paricalcitol and Calcitriol treatment, respectively. Mean dialysis vintage was 8.7 VS 7.8 years and baseline PTH levels were 495.0 VS 558.5 pg/ml, in Paricalctol group and Calcitriol group respectively.

At the end of 24 weeks 61.1 % of Paricalcitol-treated subjects and 73.3 % of Calcitriol-treated subjects (P = 0.29) achieved the primary end point of 30 % PTH reduction from baseline. No difference in time of primary end point achievement was observed between groups. Median percentage PTH reduction from baseline to weeks 12 and 24 was similar between groups (54.3 % versus 57.4 % at 12 weeks, 48.4 % versus 41.9 % at 24 weeks, for Paricalcitol and Calcitriol, respectively).

Average weekly dose of Paricalcitol administered was 20.7 μg, average Calcitriol dose was 7.1 μg/week, with a ratio of about 3:1, similar to starting dose.

Serum calcium increased in a similar way in both groups, while serum phosphorus was minimally reduced in Paricalcitol-treated subjects compared to Calcitriol-treated ones (–0.37 mg/dl versus +0.47 mg/dl, $P<0.01$). Proportion of patients experiencing hypercalcemia was similar between groups (16.7 %); if the threshold for hypercalcemia definition had been lowered down to 10.2 mg/dl, incidence of hypercalcemia would have been significantly higher: 27.8 % for Paricalcitol and 33.3 % for Calcitriol. Both treatments reduced serum alkaline phosphatase, with greater reduction obtained by Calcitriol.

30.3.5 Treatment of Secondary Hyperparathyroidism: Comparison Between a Paricalcitol-Based and a Cinacalcet-Based Regimen

Hypercalcemia and hyperphosphatemia are known risk factors for vascular and soft tissue calcification. Acceptable levels of serum calcium and phosphate while treating CKD mineral and bone disease in dialysis patients were re-evaluated in 2003 NKF/K-DOQI (National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative) guidelines, which suggested to keep serum calcium and phosphate concentrations as close as possible to their normal range and to maintain Ca × P product below 55 mg^2/dl^2. Those levels were considerably lower than previously accepted in everyday clinical practice.

Moreover, 2009 KDIGO (Kidney Disease-Improving Global Outcomes) CKD-mineral bone disease (CKD-MBD) guidelines suggested to keep PTH between two and nine times the upper normal limit of the assay used, widening the range of previously accepted serum PTH levels of 150–300 pg/ml. While previous guidelines suggested tight PTH control to avoid low and high bone turnover disease, subsequent studies showed poor predictive value of this range with respect to bone histology in dialysis patients. Moreover, observational data suggested that a wider PTH range could be acceptable when considering patient-level outcomes (mortality, cardiovascular death and bone fractures).

After 2003 guidelines release, two trials were conducted to assess whether a Cinacalcet-based or a Vitamin D-based therapy was better to achieve the new targets advocated while treating CKD-MBD. These two trials gave somewhat conflicting results.

The ACHIEVE study [35] was a multicenter, open-label, RCT. Eligible subjects included HD patients already receiving vitamin D therapy (Paricalcitol or Doxercalciferol) without attaining PTH target levels (150–300 pg/ml) or Ca × P target levels (<55 mg^2/dl^2).

Patients were randomly assigned to receive either Cinacalcet plus low fixed doses of VDRA (Doxercalciferol 1 μg or Paricalcitol 2 μg i.v. thrice weekly) – named “Cinacalcet-D group” – or escalating doses of VDRA – named “Flexi-D

group". Very tight rules were given to manage drug dosing, with respect to calcium, phosphate and PTH levels.

Cinacalcet-D patients (n = 87) received a starting dose of 30 mg Cinacalcet, raised every 4 weeks up to 180 mg/day, if needed. Criteria for Cinacalcet reduction were hypocalcemia (Ca <7.5 mg/dl) and PTH oversuppression (<150 pg/ml) with low serum calcium. Criterion for VDRA suspension was oversuppression of PTH with a serum calcium level >8.4 mg/dl. VDRA was reduced if serum calcium exceeded 9.5 mg/dl or serum phosphate exceeded 5.5 mg/dl.

Flexi-D patients (n = 86) received escalating doses of either Paricalcitol (starting dose 2 μg thrice weekly) or Doxercalciferol (1 μg thrice weekly): upwards titration was accomplished every 4 weeks. Criteria for vitamin D suspension were PTH oversuppression, hypercalcemia (Ca >10.2 mg/dl), hyperphosphatemia (P > 5.5 mg/dl) or elevated Ca × P product. Vitamin D therapy could be subsequently resumed at a lower dose.

Dialysate calcium and phosphate binder doses could be adjusted throughout the study. Doxercalciferol and Paricalcitol were considered biologically equivalent with a 2:1 dosing ratio. The study had a 16-week titration phase and a 11 week efficacy assessment phase, during which no escalation of VDRA or Cinacalcet could be made.

Patients enrolled had a mean dialysis vintage of 46 months in both groups, with similar median baseline PTH levels (Cinacalcet-D 597 pg/ml, IQR 471–775 versus Flexi-D 621 pg/ml, IQR 463–883). Baseline calcium and phosphate levels were also similar. During assessment phase, Flexi-D patients received mean weekly dose of 13.9 ± 10.4 μg Paricalcitol equivalents, while Cinacalcet-D patients received a Cinacalcet mean daily dose of 68.5 ± 41.1 mg). Phosphate binder use (either calcium-free, calcium-containing or a combination of both) did not differ between study groups.

Notably, a high dropout rate (25 % overall) should be considered when analyzing study results.

The primary end point was the proportion of patients simultaneously reaching a PTH in the range 150–300 pg/ml and Ca × P product >55 mg^2/dl^2 during the assessment phase. Only a small minority of patients achieved the combined end point, with no statistical difference between groups (Cinacalcet-D 21 % versus Flexi-D 14 %, P = 0.231), mainly for PTH oversuppression in Cinacalcet-D group. Patients simultaneously achieving serum calcium, phosphate, PTH and Ca × P product target levels suggested by KDOQI guidelines were even a smaller group (8 % versus 0 %, respectively, P = 0.017).

When considering single parameters, PTH suppression was more pronounced in patients receiving Cinacalcet-based therapy with respect to median values achieved in assessment phase (Cinacalcet-D 320 pg/ml, IQR 211–589 versus Flexi-D 559 pg/ml, IQR 314–768). Median calcium levels significantly decreased in Cinacalcet-D patients compared to Flexi-D grop (assessment phase 8.9 mg/dl versus 9.7 mg/dl, respectively) while serum phosphate did not change appreciably (5.3 mg/dl for both).

The IMPACT SHPT study was a multicenter, international, RCT [36, 37]. Paricalcitol-based therapy was compared to Cinacalcet-based therapy in terms of

efficacy of PTH suppression in HD patients. Vitamin D route of administration defined two strata (oral, in non-US sites, and intra-venous, in US and Russian sites), which were considered separately for randomization and efficacy analysis.

Patients eligible for the study were HD patients with a serum PTH between 300 and 800 pg/ml, normal serum calcium levels and phosphate levels below 6.5 mg/dl after discontinuation of previous assumed PTH suppressing drugs.

Paricalcitol group received a starting dose of 0.07 μg/kg IV thrice weekly or daily oral dose calculated from PTH/60 μg, according to stratum. It was subsequently titrated every 2 weeks, first according to Ca × P product (which must be maintained below 75 –IV stratum – or 70 – oral stratum mg^2/dl^2), then to serum calcium levels (<10.5 mg/dl), then to serum PTH levels to reach a value between 150 and 300 pg/ml. Cinacalcet could be co-administered as supplemental medication in case of confirmed hypercalcemia.

Cinacalcet group received oral drug plus small fixed doses of VDRA (either Doxercalciferol 1 μg thrice weekly – IV stratum – or Alfacalcidol 0.25 μg daily – oral stratum). Starting Cinacalcet dose was 30 mg, subsequently titrated according first to serum calcium levels and then to serum PTH levels, with the same target of 150–300 pg/ml. Oral calcium could be administered to maintain serum calcium between 8.4 and 10.5 mg/dl.

Two hundred seventy-two patients were randomized and 268 received one or more dose of study drug. Among 126 patients who constituted the IV stratum 62 received Paricalcitol and 64 received Cinacalcet, among 142 in the oral stratum 72 received Paricalcitol and 70 received Cinacalcet. Mean dialysis vintage was 3.7 ± 3.4 years and mean baseline PTH was 509 pg/ml. PTH, duration of dialysis and demographic characteristics were similar across treatment groups and strata.

Study design included a treatment period and an evaluation period (from week 21 to week 28). Only patients with two or more PTH assessments during evaluation period were included in primary efficacy analysis. Discontinuation rates, mainly due to adverse events, were quite high and ranged from 19.4 % in the Paricalcitol group/IV stratum to 31.1 % in the Cinacalcet group/IV stratum.

The proportion of patients achieving a PTH in the range 150–300 pg/ml (primary end point) was higher in Paricalcitol-treated patients compared to Cinacalcet-treated in both strata, although only in the IV stratum the difference was statistically significant (IV stratum 57.7 % versus 32.7, P = 0.016; oral stratum 54.4 % versus 43.4 %, P = 0.26). When the strata were combined in a subsequent analysis Paricalcitol was proven superior to Cinacalcet (P = 0.01) in terms of achieving specific PTH target levels. Moreover the proportion of patients achieving a >30 and >50 % reduction from baseline PTH was higher in the Paricalcitol group. Average doses administered were 3.5 ± 3.5 μg/day, 5.5 ± 3.7 μg thrice weekly, 31.8 ± 28.7 mg/day and 61.6 ± 44.8 mg for oral Paricalcitol, IV Paricalcitol, Cinacalcet in the oral stratum and Cinacalcet in the IV stratum, respectively.

Only a minority of patients received Cinacalcet while being treated with Paricalcitol (five patients per stratum): sensitivity analysis conducted excluding these subjects lead to similar conclusions. Phosphate binder use and doses increased in both treatment groups, consisting primarily in calcium-containing phosphate binders for Cinacalcet-receiving group and calcium-free compounds for

Paricalcitol-receiving group. While hypocalcemia was a frequent condition during the evaluation period among patients receiving Cinacalcet (46.9% and 54.7% in the IV stratum and oral stratum, respectively), hypercalcemia rarely occurred among patients receiving Paricalcitol (7.7% and 0% in the IV stratum and oral stratum, respectively).

A subsequent analysis [38] conducted on IMPACT study markers of bone mineral disease showed a decrease in total alkaline phosphatase and bone specific AP in the Paricalcitol centered group in both strata from baseline to week 28 (for AP: IV stratum 109.2–91.7 UI/L, oral stratum 95.6–81.2 UI/L). In contrast, AP and BSAP increased from baseline to the end of the study in the Cinacalcet centered groups (for AP: IV stratum 124–153 UI/L, oral stratum 104.5–108.9 UI/L).

Paricalcitol treatment was also associated with an increase of FGF23 (fibroblast growth factor 23) levels from baseline to subsequent assessments in both strata, while Cinacalcet administration was associated with minimal FGF23 levels reduction. In addition, while phosphate levels peaked early (week 5) among Paricalcitol treated patients and subsequently declined, Cinacalced treated subjects showed a minimal decrease in phosphate levels in the IV stratum, while in the oral stratum after an initial decrease serum phosphate levels returned to baseline levels.

30.4 Conclusions

An expanding body of evidence is rapidly enriching the rationale for vitamin D use in CKD-MBD. The traditional action of VDRAs on PTH suppression is now flanked by encouraging data on their pleiotropic effects on microalbuminuria and LVH. Furthermore, nutritional Vitamin D is receiving a growing interest as a preventive and treating strategy against SHPT as well as a protective intervention on immune responses, insulin resistance, and inflammation even in renal patients. However, further RCTs are advocated to investigate the many opened questions and uncertainties on the effects of VDRA and nutritional vitamin D on hard end points and their comparison with calcimimetic in CKD.

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